TECHNICAL REPORT

for the

INTERNATIONAL EVIDENCE-BASED GUIDELINE FOR THE ASSESSMENT AND MANAGEMENT OF POLYCYSTIC OVARY SYNDROME

2023 UPDATE

For submission to NHMRC for consideration of approval under section 14A of the NHMRC Act 1992.

Please note the following considerations when reading this document:

- We recommend using the 'Bookmarks' function to navigate through this document, or ctrl + click on the relevant section in the main or chapter contents page(s).

- Evidence reviews/ summaries are systematic reviews answering a specific question or set of questions and were prepared by an evidence team with contribution from post-doctoral researchers, research assistants and clinical experts nationally and internationally.

- Narrative reviews were prepared by clinical experts allocated to a specific question or set of questions. Narrative reviews were completed where the clinical question was not well suited to a systematic review or if the systematic search did not identify any relevant evidence for a given question.

- Some reviews underwent a systematic review process, however if no evidence was identified, the results were addressed in narrative format. This has been noted at the top of the review as "No evidence identified in evidence review".

- The evidence summaries and narrative reviews in this technical report represent the steps after evidence synthesis when GDGs met to discuss and make recommendations, and are a set stage in evolution of the process of evidence synthesis and the development, refinement and consensus of recommendations in various stages of review, discussion and consultation across clinical experts, GDGs and panels. Therefore, the final recommendation (in the guideline) may not be reflected here. Final recommendations in the guideline reflect post GDG meeting follow-up, integration and response to feedback from public consultation and the latest updates in key evidence raised during public consultation, which is not encompassed or documented in these reviews. The table of responses to feedback are available as a separate document. Following these changes and evolution from the technical report to the final document, consensus was again sought with all GDG members across all recommendations.

- Each review has been completed by one or more of 60 contributors to the development of this guideline and thus, there may be minor differences in formatting or layout of detail.

- Some narrative reviews may not contain a GRADE framework. This is because the review has been considered within a GRADE framework contained in a different section. This has been noted where relevant.

- GRADE components may be formatted slightly differently across reviews given the varied nature of the questions and evidence derived.

- With respect to the methods for GDG 5, a single methods document is provided for most of the chapter (with the exception of four questions/ reviews) rather than presenting full methods for each individual review. This is because multiple clinical questions were addressed within the same search and follow the same screening process before articles are separated and allocated to their relevant questions/ reviews.

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Screening, diagnostic assessment, risk assessment and life-stage

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PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by the Evidence Team: Jillian Tay, Aya Mousa

Other Members: Loyal Pattuwage, Yanan Hu

GDG 1

Question 1.1.

In adolescents, at what time point after onset of menarche do irregular cycles indicate ongoing menstrual dysfunction?

1. STUDY SELECTION

Table 1. PICO Criteria for Inclusion	
Question	1.1 In adolescents, at what time point after onset of menarche do irregular cycles indicate ongoing menstrual dysfunction?
Clinical leads (key contacts)	Sharon Oberfield, Helena Teede
Allocation ranking	Level 2 - systematic review update

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(language, year)*
Inclusion	Females after onset of menarche, of any age, ethnicity and weight. Subgrouped by: <19 age or gynecological age group: 0-2y; 2-4y; 4+y; Note whether they are taking OCP.	No limit on time. Average interval between subsequent period/cycle lengths Note possible subgroups for: <6m – >5w oligomenorrhea >6m amenorrhea 1-3 months irregularity 1st stage: >cycles 35 days and <45 days (oligo) Note the most prominent interval as a continuous variable.	Females with irregular cycles that don't go on to develop PCOS.	Most effective method to discriminate between PCOS and normal pubertal transition. Diagnosed PCOS defined by Rotterdam or NIH criteria. Sensitivity and specificity data; and AUC data.	Evidence based guidelines, systematic reviews, health technology assessments, randomised controlled trials, prospective and retrospective cohort studies and case-control studies.	English language. Human studies
Exclusion	None	None	Not applicable	Diagnosis of WHO I/ functional hypothalamic amenorrhea and WHO III/POI/POF.	Non- evidence based guidelines, non-systematic reviews, case series, editorials, letters, commentaries.	None

2. SEARCH STRATEGY

Search details	
Search strategy source: 2018 PCOS Guideline Technical Report	
Evidence source	Date of search
Medline (Ovid)	1 January 2017 until 25 August 2022
PsychInfo (Ovid)	1 January 2017 until 25 August 2022
EMBASE	1 January 2017 until 25 August 2022
All EBM (Ovid)	1 January 2017 until 25 August 2022
CINAHL	1 January 2017 until 25 August 2022
Any subsequent updates - enter database and date: not applicable	

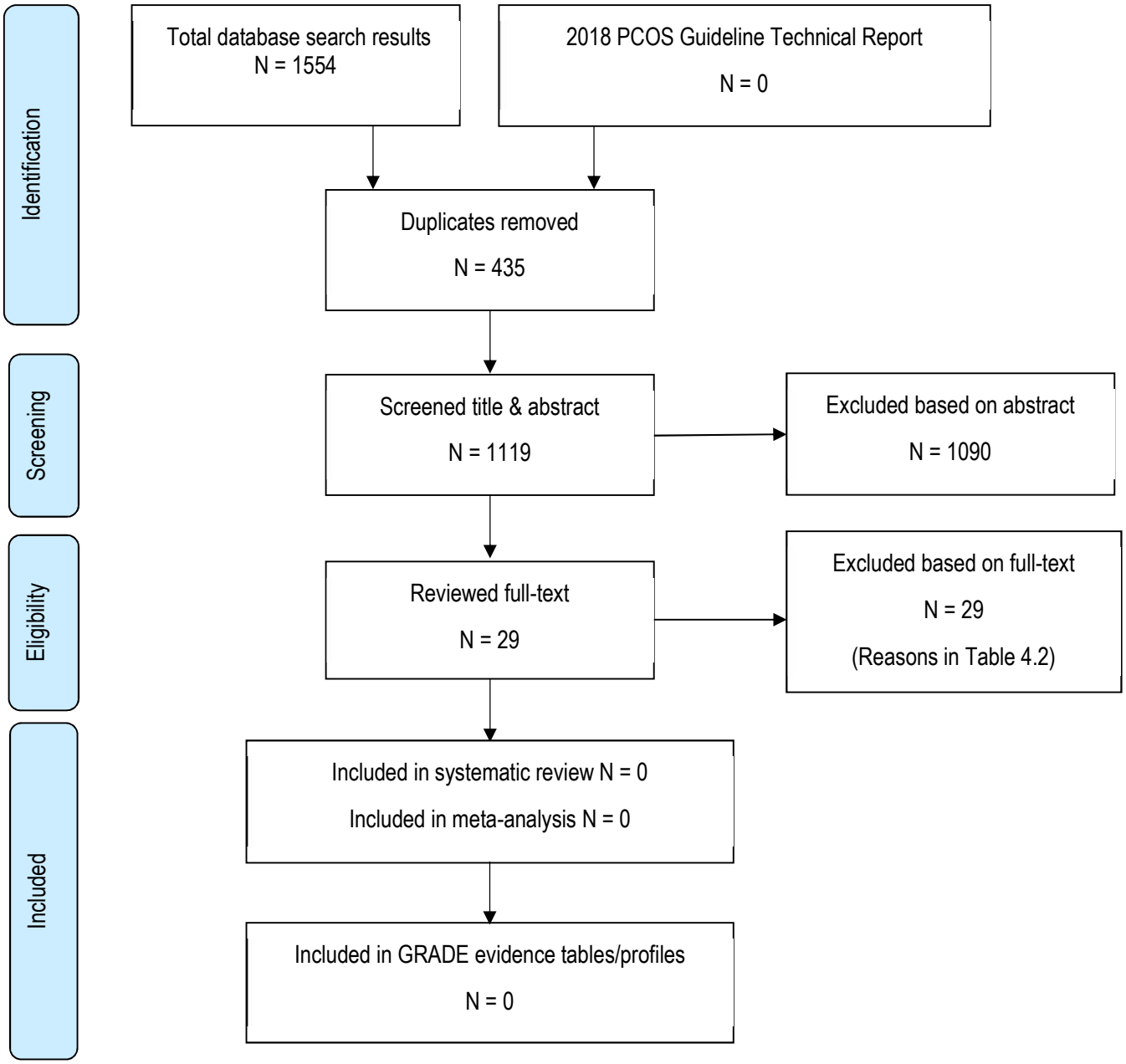
Questions addressed by this search:		
GDG	Q#	Question
1	1.1	In adolescents, at what time point after onset of menarche do irregular cycles indicate ongoing menstrual dysfunction?

OVID Medline, All EBM, EMBASE, PsychInfo	CINAHL
1 exp Menstruation Disturbances/ 2 exp Menstruation/ or exp Menstrual Cycle/ 3 mense*.tw. 4 period.tw. 5 menstrua*.tw. 6 cycl*.tw. 7 or/2-6 8 irregular*.tw. 9 dysfunction*.tw. 10 abnormal*.tw. 11 disorder*.tw. 12 disturb*.tw. 13 absen*.tw. 14 miss*.tw. 15 or/8-14 16 exp Oligomenorrhea/ 17 Oligomenorrh*.mp. 18 exp Amenorrhea/ 19 Amenorrh*.mp. 20 exp Anovulation/ 21 Anovulat*.mp. 22 or/16-21 23 exp polycystic ovary syndrome/ 24 polycystic ovar*.mp. 25 poly-cystic ovar*.mp. 26 PCO*.mp. 27 (stein-leventhal or leventhal).mp. 28 anovulation/ 29 anovulat*.mp. 30 oligo-ovulat*.mp. 31 oligoovulat*.mp. 32 (ovar* adj5 (sclerocystic or polycystic or poly-cystic or degenerate* or hyperandrogen* or hyperandrogen*)).mp. 33 or/23-32 34 1 or 15 or 22 35 7 and 33 and 34 36 Adolescen*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism	S1 MH polycystic ovary syndrome S2 TX polycystic ovar* S3 TX poly-cystic ovar* S4 TX PCO* S5 TX (stein-leventhal or leventhal) S6 MH anovulation S7 TX anovulat* S8 TX oligo-ovulat* S9 TX oligoovulat* S10 TX (ovar* N5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*)) S11 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 S12 (MH "Menstruation Disorders+") S13 (MH "Oligomenorrhea") S14 (MH "Amenorrhea+") S15 (MH "Anovulation") S16 Oligomenorrh* S17 Amenorrh* S18 Anovulat* S19 (MH "Menstruation") or (MH "Menstrual Cycle+") S20 mense* or period or menstrua* or cycl* S21 irregular* or dysfunction* or abnormal* or disorder* or disturb* or absen* or miss* S22 S19 OR S20 S23 S21 AND S22 S24 S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S23 S25 S11 AND S24 S26 S11 AND S24 Limiters - Publication Year: 2017-2022; English Language; Human; Sex: Female

supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 37 youth.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 38 young.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 39 Teenage*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 40 36 or 37 or 38 or 39 41 35 and 40 42 limit 41 to (english language and humans and yr="2017 -Current")	

Evidence processing: Studies were selected and appraised by one reviewer using study selection and appraisal criteria (PICO above) established a priori. The articles were reviewed by title and abstract by one reviewer. When a decision could not be made based on title and abstract alone, full text was retrieved. **No studies met inclusion criteria for this review.**

3. SEARCH RESULTS - PRISMA flowchart



4. STUDY INCLUSION

4.1 Included studies

None.

Table 4.2. Excluded Studies (on full text assessment)

Title	Author/Year	Journal	Volume	Pages	Notes
PCOS diagnosis in adolescents: the timeline of a controversy in a systematic review	Vassalou 2019	Journal of Pediatric Endocrinology & Metabolism	32	549-559	Exclusion reason: Wrong intervention;
Endocrine Abnormalities in Adolescents with Menstrual Disorders	Rajiwade 2018	Journal of Obstetrics and Gynecology of India	68(1)	58-64	Exclusion reason: Wrong outcomes;
American, European, and Chinese practice guidelines or consensuses of polycystic ovary syndrome: a comparative analysis	Wang 2018	Journal of Zhejiang University SCIENCE B	19	354-363	Exclusion reason: Wrong outcomes;
Polycystic ovary syndrome in adolescents	Dabadghao 2019	Best Practice & Research Clinical Endocrinology & Metabolism	33	101272	Exclusion reason: Wrong study design;
Polycystic ovarian syndrome in adolescents: Keys to diagnosis and management	Khan 2021	Pediatric Annals	50(7)	e272-e275	Exclusion reason: Wrong study design;
Adolescent polycystic ovary syndrome according to the international evidence-based guideline	Pena 2020	BMC Medicine	18	72	Exclusion reason: Wrong study design;
Standardizing diagnosis of polycystic ovarian syndrome (PCOS) and screening for metabolic disease across pediatric specialties	Olson 2017	Journal of Pediatric and Adolescent Gynecology	30(2)	299-300	Exclusion reason: No full text;
Postmenarcheal irregularities in menstrual cycle in adolescent girls	Skrenkova 2018	Casopis Lekaru Ceskych	157	343-349	Exclusion reason: No full text;
Polycystic Ovary Syndrome: Pathophysiology, Presentation, and Treatment with Emphasis on Adolescent Girls	Witchel 2019	Journal of the Endocrine Society	3(8)	1545-1573	Exclusion reason: Wrong study design;
Polycystic Ovary Syndrome: Ontogeny in Adolescence	BurtSolorzano 2021	Endocrinology and Metabolism Clinics of North America	50(1)	25-42	Exclusion reason: No full text;
Polycystic ovary syndrome in adolescents: An update	Caserta 2020	Italian Journal of Gynaecology and Obstetrics	32(2)	97-106	Exclusion reason: No full text;
Polycystic ovary syndrome in adolescents: Challenges in diagnosis and treatment	Tehrani 2019	International Journal of Endocrinology and Metabolism	17(3)		Exclusion reason: Wrong study design;
Polycystic ovary syndrome in adolescent girls	Baldauff 2017	Current Opinion in Endocrinology, Diabetes & Obesity	24	56-66	Exclusion reason: No full text;
Polycystic Ovary Syndrome in Adolescence: Challenges in Diagnosis and Management	Manique 2022	Revista Brasileira de Ginecologia e Obstetricia	44	425-433	Exclusion reason: Wrong study design;
Polycystic ovary syndrome in adolescence: Diagnostic and therapeutic strategies	Kamboj 2017	Translational Pediatrics	6(4)	248-255	Exclusion reason: Wrong study design;

Polycystic ovary morphology: age-based ultrasound criteria	Kim 2017	Fertility & Sterility	108	548-553	Exclusion reason: Wrong outcomes;
Polycystic ovarian syndrome in adolescents: From diagnostic criteria to therapeutic management	Nicolaides 2020	Acta Bio-Medica de l Ateneo Parmense	91	e2020085	Exclusion reason: Wrong study design;
Obesity, Oligomenorrhoea and PCOS in Adolescence	Venter 2018	Obstetrics and Gynaecology Forum	28(2)	27-30	Exclusion reason: Wrong study design;
The normal menstrual cycle	Itriyeva 2022	Current Problems in Pediatric & Adolescent Health Care	52	101183	Exclusion reason: Wrong study design;
Menstrual Cycle in Adolescents: Updating the Normal Pattern	Gruber 2021	Journal of Clinical Endocrinology & Metabolism	106	e372-e374	Exclusion reason: Wrong study design;
Menstrual bleeding, cycle length, and follicular and luteal phase lengths in women without known subfertility: A pooled analysis of three cohorts	Najmabadi 2020	Paediatric & Perinatal Epidemiology	34	318-327	Exclusion reason: Wrong patient population;
Hirsutism and Menstrual Irregularity in a 16-year-old Girl	Bruggeman 2021	Pediatrics in Review	42	449-452	Exclusion reason: Wrong study design;
Heavy Menstrual Bleeding in Adolescent: Normal or a Sign of an Underlying Disease?	Luiro 2022	Seminars in Reproductive Medicine	40	23-31	Exclusion reason: Wrong outcomes;
Diagnosis of adolescent polycystic ovary syndrome (PCOS) according to the 2018 international evidence-based guideline for the assessment and management of PCOS	Pena 2018	Hormone research in paediatrics	90(Supp1)	551	Exclusion reason: Wrong study design;
Diagnosis and treatment of adolescent polycystic ovary syndrome (PCOS) according to the 2018 international evidence-based guideline for the assessment and management of PCOS	Pena 2018	Australian and New Zealand Journal of Obstetrics and Gynaecology	58(Supp 1)	4-5	Exclusion reason: Wrong study design;
Development of Ovulatory Menstrual Cycles in Adolescent Girls	Carlson 2019	Journal of Pediatric and Adolescent Gynecology	32(3)	249-253	Exclusion reason: Wrong study design;
Criteria, phenotypes and prevalence of polycystic ovary syndrome	Belenkaia 2019	Minerva Ginecologica	71	211-223	Exclusion reason: No full text;
Characterization of polycystic ovary syndrome among Flo app users around the world	Jain 2021	Reproductive Biology & Endocrinology	19	36	Exclusion reason: Wrong outcomes;
Age at Onset of Metabolic Syndrome Among Women With and Without Polycystic Ovary Syndrome-Like Status	Peng 2019	Journal of Clinical Endocrinology & Metabolism	104	1429-1439	Exclusion reason: Wrong outcomes;

7. FINDINGS

After the search and screening process, no studies met the eligibility criteria for this clinical question. Therefore, the available evidence has been reviewed narratively. See Part 2 for this question.

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 1

Question 1.1.

In adolescents, at what time point after onset of menarche do irregular cycles indicate ongoing menstrual dysfunction?

BACKGROUND:

Prevalence and problem

As previously reviewed, physiologically, during the first year post-menarche, hormonal responses do not match adult patterns. During the second year about one half of the menstrual cycles range from 21-45 days in length however progesterone levels are low (1,2).

The average adult menstrual cycle is 28 days, with a normal cycle range of 24 to 35 days (2). However, during the first few years post-menarche, cycles vary considerably. Data suggests that a majority of irregular cycles may be ovulatory in girls 2 years postmenarche (3-6). In the first post-menarcheal year, around half of cycles are anovulatory. Nonetheless, 80% of cycles occur within a predictable range of 21 to 45 days and last two to seven days (5-8). By the third post-menarcheal year, 95% of cycles fall into this range and as such in the 5% without regular cycles PCOS should be considered.

Regular ovulatory cycles onset are related to age at menarche (9). In girls who begin menses at <12 years, between 12 and 13 years, and >13 years of age, 50% of cycles are ovulatory by one year, three years, and 4.5 years, respectively (9). At age 15 more than 50% of girls who are oligo-amenorrheic remain so at age 18. (10)

Hence it is variable and still remains somewhat unclear at what developmental stage irregular cycles in adolescents reflect immaturity of the reproductive system or possible PCOS. Studies assessing this have not to date yielded answers. (11)

Clinical Practice Gap: Need for guidance

Current practice defining when adolescent menstrual cycle irregularity becomes pathophysiologic is unclear. With many women reporting delayed diagnosis, it is likely that current practice involves prescription of the oral contraceptive pill without diagnosis of PCOS in adolescents. Diagnosis also allows for early intervention screening and prevention. While this may increase referral for diagnostic testing and specialist care, the benefits of early diagnosis and prevention of associated complications and infertility may be beneficial to the overall disease burden. However, in some there is a need for focused diagnostic testing even prior to 2 years post menarche to uncover treatable non-PCOS diagnosis such as NCCAH.

Summary of key information

We did not identify any evidence in our patient population to answer the question and therefore a clinical consensus recommendation has been made informed by the natural history of menstrual cycles and ovulation in adolescents (aged <18 years).

Recommendations Framework

CONSENSUS RECOMMENDATION(S)

CR: Irregular menstrual cycles are defined as:
- normal in the first year post menarche as part of the pubertal transition
- > 1 to < 3 years post menarche: < 21 or > 45 days
- > 3 years post menarche to perimenopause: < 21 or > 35 days or < 8 cycles per year
- > 1 year post menarche > 90 days for any one cycle
- Primary amenorrhea by age 15 or > 3 years post thelarche (breast development)

When irregular menstrual cycles are present a diagnosis of PCOS should be considered and assessed according to these International PCOS Guidelines.

PRACTICE POINT
The median age of menarche may fluctuate across different populations.

In adolescents with irregular menstrual cycles, the value and optimal timing of assessment and diagnosis of PCOS should be discussed with the patient, and their parent/s or guardian/s, considering diagnostic challenges at this life stage and psychosocial and cultural factors.

For adolescents who have features of PCOS but do not meet diagnostic criteria, an “increased risk” could be considered and reassessment advised at or before full reproductive maturity, 8 years post menarche. This includes those with PCOS features before combined oral contraceptive pill (COCP) commencement, those with persisting features and those with significant weight gain in adolescence.

Ovulatory dysfunction can still occur with regular cycles and if anovulation needs to be confirmed serum progesterone levels can be measured.

CONSIDERATIONS

Justifications:
See above in background.

Subgroup considerations:
Individual with obesity.
Different ethnicities.
Family history of PCOS.

Implementation considerations:
Education of paediatricians/family physicians and gynaecologists as to timing of diagnosis and normal physiologic processes.

Monitoring and evaluation considerations:
None

Research priorities:
Further longitudinal studies to identify early predictors and natural history of PCOS in adolescents would be of value and these could then be targeted to allow for timely diagnosis.
Quality and current normative data across ethnicities and BMI assessing the ongoing maturation of the pubertal axis.

Equity:
Would be important to determine if possible in all populations

Acceptability:
Likely yes

FEASIBILITY:
Likely difficult to design a meaningful study.

REFERENCES:

1. Lemarchand-Béraud T, Zufferey M, Reymond M, Rey I. Maturation of the hypothalamo-pituitary-ovarian axis in adolescent girls. Journal of Clinical Endocrinology & Metabolism. 1982;54(2):241-6.
2. Apter D, Vihko R. Serum pregnenolone, progesterone and 17-hydroxyprogesterone, testosterone and 5α-dihydrotestosterone during female puberty. J Clin Endocrinol Metab 1977;45: 1039-1048.
3. Pena AS, Doherty DA, Atkinson HC, Hickey M, Norman RJ, Hart R. The majority of irregular menstrual cycles in adolescence are ovulatory: results of a prospective study. Arch Dis Child 2017;0:1-5.
4. Treloar A, Boynton R, Behn B, Brown B. Variation of the human menstrual cycle through reproductive life. International Journal of Fertility. 1967;12:77.
5. Flug D, Largo R, Prader A. Menstrual patterns in adolescent Swiss girls: a longitudinal study. Annals of Human Biology 1984;11(6):495-508.
6. Widholm O, Kantero R. A statistical analysis of the menstrual patterns of 8,000 Finnish girls and their mothers. Acta Obstet Gynecol Scand Suppl. 1971;14(Suppl).
7. Adams Hillard P. Menstruation in young girls: a clinical perspective Obstetrics & Gynecology. 2002;99(4):655-62.
8. Slap G. Menstrual disorders in adolescence. Best Practice & Research Clinical Obstetrics & Gynaecology 2003;17(1):75-92.
9. Apter D, Vihko R. Early menarche, a risk factor for breast cancer, indicates early onset of ovulatory cycles. Journal of Clinical Endocrinology & Metabolism. 1983;57(1):82-6.
10. van Hooff MH, Voorhorst FJ, Kaptein MB, Hirasing RA, Koppenaal C, Schoemaker J. Predictive value of menstrual cycle pattern, body mass index, hormone levels and polycystic ovaries at age 15 years for oligo-amenorrhea at age 18 years. Hum Reprod 2004;19:383-392.
11. Witchel SF, Oberfield SE, Peña AS. Polycystic Ovary Syndrome: Pathophysiology, Presentation, and Treatment With Emphasis on Adolescent Girls. J Endocr Soc. 2019 Jun 14;3(8):1545-1573. doi: 10.1210/js.2019-00078. PMID: 31384717; PMCID: PMC6676075

PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by ECR Lead: Thais Rocha,
Other Members: Laura Smith, James Hawley
Supervised, edited and supported by the Evidence Team (Aya Mousa, Jillian Tay)

GDG 1

Question 1.2.

In women with suspected PCOS, what is the most effective measure to diagnose PCOS related hyperandrogenism (biochemical)?

1. SELECTION CRITERIA

Table 1. PICO Criteria for Inclusion – Not to be adapted To be used by evidence team to decide which studies will be included when screening search results.	
Question	**In women with suspected PCOS, what is the most effective measure to diagnose PCOS related hyperandrogenism (biochemical)?**
Clinical leads (key contacts)	**Prof Wiebke Arlt** **Endocrinologist** **University of Birmingham, UK** **W.Arlt@bham.ac.uk** **Prof Ricardo Azziz** **Reproductive endocrinologist** **The Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Centre, USA** **razziz67@gmail.com**
Allocation ranking	**Level 2- updated systematic review**

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(Language, year)*
Inclusion	Females with PCOS (diagnosed by Rotterdam, NIH or AES) of any age, ethnicity and weight. Note preference and subgroup for untreated or must have stopped medication for a minimum of 3 months.	Methods for assessment of androgens including: • serum and salivary testosterone (LC-MS/MS, radioimmunoassay (RIA) • calculated free androgen index, calculated free testosterone • serum SHBG • androstenedione • serum DHEAS • urinary androstandiol glucuronide	No intervention or a comparison of the biochemical assessment methods or comparison with clinical assessment methods.	Diagnosed hyperandrogenism in women with PCOS. Sensitivity and specificity data; and AUC data will be collected.	Evidence-based guidelines, systematic reviews, RCTs and comparative, prospective cohort studies.	English language. Update WHO searches.
Exclusion	Females without PCOS.	No intervention or any intervention other intervention not listed above.	The assessment method used for the intervention.	None.	Non-evidence-based guidelines or any study lower than a comparative, prospective cohort study.	

2. SEARCH STRATEGY

Table 2.1. Search details	
Search strategy source: https://www.monash.edu/__data/assets/pdf_file/0020/1412282/PCOS-Guideline_Technical-report.pdf (search date 3rd July 2017 p36)	
Evidence source	**Date of search**
Medline (Ovid)	**12/07/2022**
PsychInfo (Ovid)	**12/07/2022**
EMBASE (Ovid)	**12/07/2022**
All EBM (Ovid)	**14/07/2022**
CINAHL	**14/07/2022**
Any subsequent updates - enter database and date: NA	

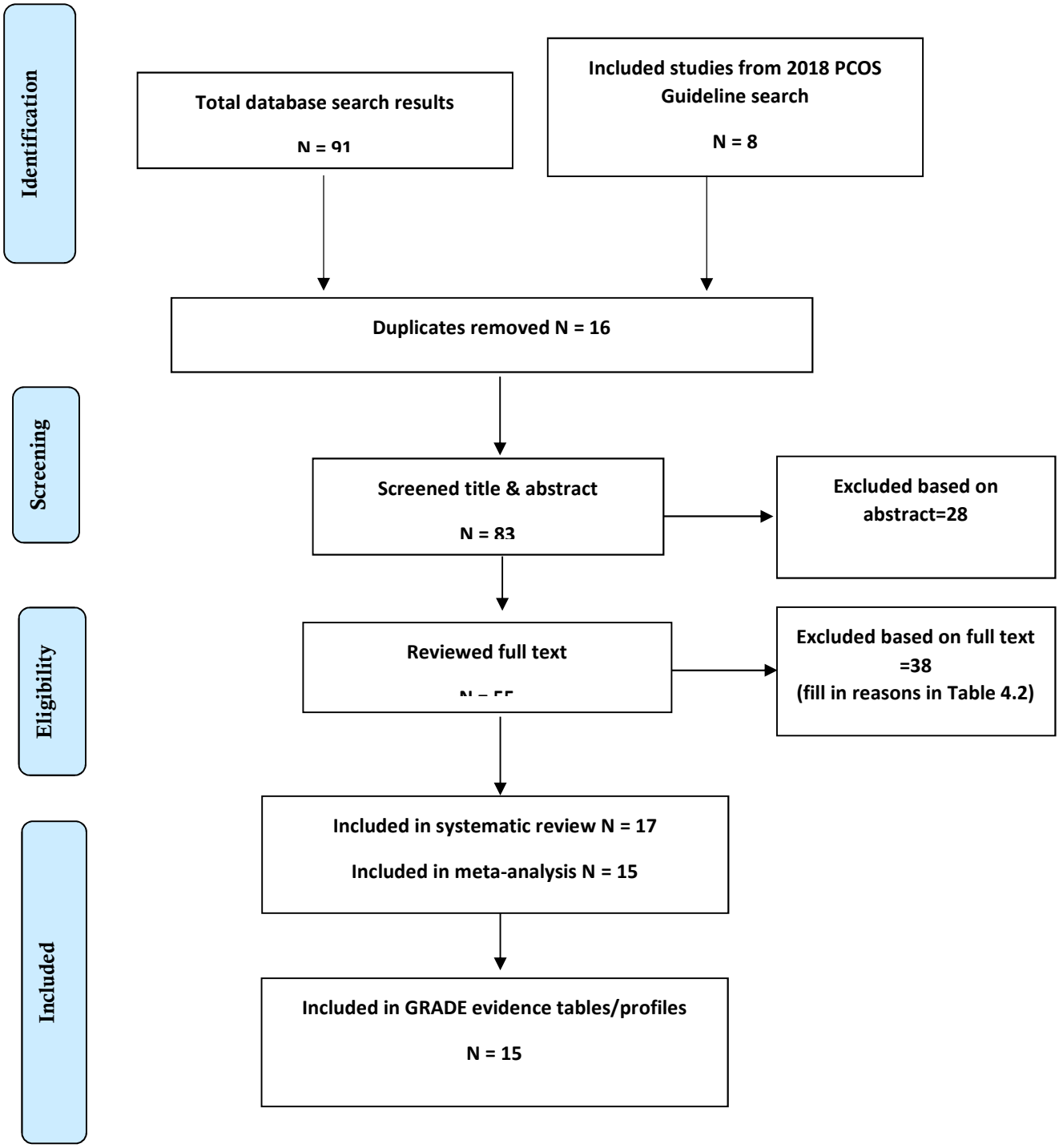
Table 2.2. Questions addressed by this search *(add more rows as needed)*:		
GDG	**Q#**	**Question**
1	1.2	In women with suspected PCOS, what is the most effective measure to diagnose PCOS related hyperandrogenism (biochemical)?

Table 2.3. Search strings used in OVID or other database/s – *please save a screenshot of search results to submit alongside this template*		
OVID Medline (41), All EBM (11), PsychInfo (0), EMBASE (19)	**CINAHL (20)**	**Other?**
	Same search	NA
1 (decision aid$ or decision tool).tw.		
2 tool$.tw.		
3 rule$.tw.		
4 measure$.tw.		
5 model.tw.		
6 assess$.tw.		
7 calculat$.tw.		
8 class$.tw.		
9 (estimate$ or estimation$).tw.		
10 equation$.tw.		
11 (score$ or scoring).tw.		
12 algorithm$.tw.		
13 chart$.tw.		
14 table$.tw.		
15 tabulat$.tw.		
16 test$.tw.		
17 screen$.tw.		
18 checklist.tw.		
19 check-list.tw.		
20 checksheet.tw.		
21 check-sheet.tw.		
22 ticklist.tw.		
23 tick-list.tw.		
24 Instrument.tw.		
25 or/1-24 16687889		
26 exp Diagnosis/		
27 diagnos$.tw.		
28 26 or 27		

29	hyperandrogen$.tw.		
30	hyper-androgen$.tw.		
31	(androgen$ adj5 (excess$ or elevat$)).mp.		
32	29 or 30 or 31		
33	testosterone.tw.		
34	LCMS.tw.		
35	assay.tw.		
36	immunoassay.tw.		
37	radioimmunoassay.tw.		
38	radio-immunoassay.tw.		
39	34 or 35 or 36 or 37 or 38		
40	33 and 39 8384		
41	Sex Hormone-Binding Globulin/an, bl, du [Analysis, Blood, Diagnostic Use]		
42	SHBG.tw.		
43	free androgen index.tw.		
44	FAI.tw.		
45	Androstenedione/an, bl, du [Analysis, Blood, Diagnostic Use]		
46	Dehydroepiandrosterone/an, bl, du [Analysis, Blood, Diagnostic Use]		
47	DHEAS.tw.		
48	exp Hydroxyprogesterones/an, bl, du [Analysis, Blood, Diagnostic Use]		
49	17 hydroxy progesterone.tw.		
50	17-OH-progesterone.tw.		
51	17-hydroxy-progesterone.tw.		
52	40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51		
53	25 and 28 and 32 and 52		
54	(sensitiv: or predictive value:).mp. or accurac:.tw.		
55	53 and 54		
56	limit 55 to (english language and female and humans)		
57	limit 56 to yr="2017 -Current"		

Evidence processing: Studies were selected and appraised by 2 reviewer/s in consultation with the evidence team/ key contact using study selection and appraisal criteria (PICO above) established a priori. The articles were reviewed by title and abstract by 2 reviewers. When a decision could not be made based on the title and abstract alone, the full text was retrieved. **Seventeen studies met the inclusion criteria for this review.**

3. SEARCH RESULTS - PRISMA flowchart



4. STUDY INCLUSION

Table 4.1.a Included studies (current update)
Sathyapalan T, Al-Qaissi A, Kilpatrick ES, Dargham SR, Adaway J, Keevil B, Atkin SL. Salivary testosterone measurement in women with and without polycystic ovary syndrome. Sci Rep. 2017 Jun 15;7(1):3589. doi: 10.1038/s41598-017-03945-w. PMID: 28620242; PMCID: PMC5472559.
Bansal, P, Sardana, K, Arora, P, Khurana, A, Garga, UC, Sharma, L. A prospective study of anti-mullerian hormone and other ovarian and adrenal hormones in adult female acne. Dermatologic Therapy. 2020; 33:e13974. https://doi.org/10.1111/dth.13974
Imran H. J, Dhaher S. A, Mansour M. A. A. Testosterone or Dehydroepiandrosterone Sulfate as A Biomarker for Hirsutism in Women with Polycystic Ovary Syndrome. Biomed Pharmacol J 2020;13(4). DOI: https://dx.doi.org/10.13005/bpj/2056
Khashchenko E, Uvarova E, Vysokikh M, Ivanets T, Krechetova L, Tarasova N, Sukhanova I, Mamedova F, Borovikov P, Balashov I, Sukhikh G. The Relevant Hormonal Levels and Diagnostic Features of Polycystic Ovary Syndrome in Adolescents. J Clin Med. 2020 Jun 11;9(6):1831. doi: 10.3390/jcm9061831. PMID: 32545404; PMCID: PMC7355484.
Chen, F., Chen, M., Zhang, W. et al. Comparison of the efficacy of different androgens measured by LC-MS/MS in representing hyperandrogenemia and an evaluation of adrenal-origin androgens with a dexamethasone suppression test in patients with PCOS. J Ovarian Res 14, 32 (2021). https://doi.org/10.1186/s13048-021-00781-5
Grassi, G.; Polledri, E.; Fustinoni, S.; Chiodini, I.; Ceriotti, F.; D'Agostino, S.; Filippi, F.; Somigliana, E.; Mantovani, G.; Arosio, M.; et al. Hyperandrogenism by Liquid Chromatography Tandem Mass Spectrometry in PCOS: Focus on Testosterone and Androstenedione. J. Clin.Med.2021,10,119. https://doi.org/10.3390/jcm10010119
Beitl K, Dewailly D, Seemann R, Hager M, Bünker J, Mayrhofer D, Holzer I and Ott J (2022) Polycystic Ovary Syndrome Phenotype D Versus Functional Hypothalamic Amenorrhea With Polycystic Ovarian Morphology: A Retrospective Study About a Frequent Differential Diagnosis. Front. Endocrinol. 13:904706. doi:10.3389/fendo.2022.904706
Kumar H, Halder A, Sharma M, Jain M, Kalsi AK.Dihydrotestosterone- A Potential Biomarker of Hyperandrogenaemia in Polycystic Ovary Syndrome: A Case-control Study from North IndiaJ Clin of Diagn Res.2022; 16(2):QC09-QC14. https://www.doi.org/10.7860/JCDR/2022/51169/15962
Diamandis EP, Stanczyk FZ, Wheeler S, Mathew A, Stengelin M, Nikolenko G, Glezer EN, Brown MD, Zheng Y, Chen YH, Wu HL, Azziz R. Serum complexed and free prostate-specific antigen (PSA) for the diagnosis of the polycystic ovarian syndrome (PCOS). Clin Chem Lab Med. 2017 Oct 26;55(11):1789-1797. doi: 10.1515/cclm-2016-1124. PMID: 28361781; PMCID: PMC5742006.

Table 4.1.b Included studies (2010, 2014 and 2017 searches)
Koskinen, P., T. A. Penttila, et al. (1996). "Optimal use of hormone determinations in the biochemical diagnosis of the polycystic ovary syndrome." Fertil Steril. 1996 Mar;65(3):517-22. doi: 10.1016/s0015-0282(16)58146-1
Escobar-Morreale, H. F., M. Asuncion, et al. (2001). "Receiver operating characteristic analysis of the performance of basal serum hormone profiles for the diagnosis of polycystic ovary syndrome in epidemiological studies." Eur J Endocrinol. 2001 Nov;145(5):619-24. doi:10.1530/eje.0.1450619
Hahn, S., W. Kuehnel, et al. (2007). "Diagnostic value of calculated testosterone indices in the assessment of polycystic ovary syndrome." Clinical Chemistry & Laboratory Medicine 45(2): 202-7. Clin Chem Lab Med. 2007;45(2):202-7. doi: 10.1515/CCLM.2007.031.
Stener-Victorin, E., G. Holm, et al. (2010). "Are there any sensitive and specific sex steroid markers for polycystic ovary syndrome?" J Clin Endocrinol Metab. 2010 Feb;95(2):810-9. doi: 10.1210/jc.2009-1908.
Bili, E., et al. (2014). "The combination of ovarian volume and outline has better diagnostic accuracy than prostate-specific antigen (PSA) concentrations in women with polycystic ovarian syndrome (PCOs)." Eur J Obstet Gynecol Reprod Biol. 2014 Aug;179:32-5. doi: 10.1016/j.ejogrb.2014.05.006
Wael A. Salameh, Mildred M. Redor-Goldman, Nigel J. Clarke, Ruchi Mathur, Ricardo Azziz, Richard E. Reitz. Specificity and predictive value of circulating testosterone assessed by tandem mass spectrometry for the diagnosis of polycystic ovary syndrome by the National Institutes of

Health 1990 criteria. Fertility and Sterility® Vol. 101, No. 4, April 2014 0015-0282. http://dx.doi.org/10.1016/j.fertnstert.2013.12.056
Villarroel, C., et al. (2015). "Hirsutism and oligomenorrhea are appropriate screening criteria for polycystic ovary syndrome in adolescents." Gynecological Endocrinology 31(8): 625-629. Gynecol Endocrinol. 2015;31(8):625-9. doi: 10.3109/09513590.2015.1025380.
Rudnicka, E., et al. (2016). "Prostate specific antigen (PSA) in diagnosis of polycystic ovarian syndrome - a new insight." Gynecol Endocrinol. 2016 Nov;32(11):931-935. doi: 10.1080/09513590.2016.1200552.

Table 4.2. Excluded studies (on 2022 search update full-text assessment)

Reference	Reason
Barrea et al. 2019	No outcomes of interest
Bouzas et al. 2019	Full text not available
Broskey et al. 2018	No outcomes of interest
Harnois-Leblanc et al. 2022	Wrong patient population
Mesinovic et al. 2020	Wrong comparator
Abbara et al. 2019	No outcomes of interest
Rackow et al. 2018	Wrong comparator
Zheng et al. 2017	Wrong comparator
Halder et al. 2018	Full text not available
Seyam et al. 2018	Wrong comparator
Bronczyk-Puzon et al. 2017	No outcomes of interest
He et al. 2021	Wrong comparator
Halder et al. 2017	Full text not available
Patlolla et al. 2018	Wrong comparator
Subramaniam et al. 2020	Wrong patient population
Qiu et al. 2020	Wrong patient population
Petta et al. 2017	No outcomes of interest
Ozkur et al. 2021	Wrong patient population
Ozegowska et al. 2020	No outcomes of interest
Ates et al. 2018	No outcomes of interest
Nadir et al. 2019	No outcomes of interest
Zhou et al. 2020	No outcomes of interest
DiStasi et al. 2021	No outcomes of interest
Shorakae et al. 2018	No outcomes of interest
deMedeiros et al. 2017	No outcomes of interest
Cai et al. 2017	No outcomes of interest
YetimSahin et al. 2019	No outcomes of interest
Rashad et al. 2019	No outcomes of interest
Garzia et al. 2022	Wrong comparator
Kaylan et al. 2018	No outcomes of interest
Elhassan et al. 2018	Wrong comparator
Tunc et al. 2021	No outcomes of interest
Sathyapalan at el. 2018	Wrong comparator
Peng et al. 2022	No outcomes of interest
Savic-Radojevic et al. 2018	No outcomes of interest
Sova et al. 2019	No outcomes of interest

5. STUDY CHARACTERISTICS

TABLE 5.1 Risk of bias, sample size, age, BMI and inclusion/exclusion criteria

Author, year	Risk of Bias/ Certainty	Sample size	Age (years)	BMI (Kg/m^2)	Inclusion criteria for PCOS	Exclusion criteria for PCOS	Inclusion criteria for controls
Koskinen et al. 1996	High/Low	Total=83 PCOS=54 Controls=29	PCOS=27±6 Controls=33±5	PCOS=27±8 Controls=29±10	Rotterdam equivalent. "All the patients in the study group were submitted to the clinic for oligomenorrhea, often jointly with hirsutism and/or infertility. The diagnosis of PCOS was based on polycystic ovary morphology assessed by vaginal ultrasonography. The criteria were an enlarged or normal sized ovary with multiple (~10) small subcortical follicles (2 to 10 mm in diameter) and increased stroma."	"All the subjects were euthyroid and normoprolactinemic."	The control group comprised 29 healthy regularly menstruating volunteers with BMI, matching the PCOS group. All the control women had normal ovarian morphology in vaginal ultrasonography.
Escobar-Morreale et al. 2001	Moderate/Moderate	Total=114 PCOS=8 Controls=106	PCOS=25.0±5.4 Controls=34.5±9.4 p<0.01	PCOS=25.5±4.2 Controls=24.2±3.1 p=0.280	NICHD. Women were diagnosed with PCOS when presenting with menstrual dysfunction, clinical and/or biochemical hyperandrogenism, and exclusion of other aetiologies. Menstrual dysfunction was considered when the women had oligomenorrhea, defined by more than 6 cycles per year with a length of more than 36 days, and/or when the patient had not had any menstrual bleeding for three consecutive months, during the last year. Clinical hyperandrogenism was defined by the presence of hirsutism, represented by a hirsutism score of 8 or more, by the persistence of acne during the third decade of life or later, or by the presence of androgenic alopecia. Hyperandrogenemia was defined by elevated circulating testosterone, FT, DHEAS and/or FAI.	"Women taking oral contraceptives were excluded"	NR

Hahn et al. 2007	Moderate/Low	Total=187 PCOS=133 Controls=54	PCOS=28 (15–45) Controls=28 (20–41)	PCOS=30 (17-58) non-PCOS=21.3* (18-29) *authors report that this is significantly different but don't provide p-value or CI.	NIHR 1990. PCOS patients (n=133) seeking medical advice for menstrual cycle abnormalities, hirsutism, acne, obesity or infertility were consecutively recruited from outpatient clinics. Diagnosis of PCOS was established when either oligomenorrhea (cycles lasting longer than 35 days) or amenorrhea (less than two menstrual cycles in the past 6 months) and clinical signs of hyperandrogenism (hirsutism and/or obvious acne and/or alopecia) were found; hyperandrogenemia was not used for the diagnosis of PCOS.	"Other pituitary, adrenal or ovarian diseases were excluded in all women by laboratory analysis of LH, FSH, estradiol, prolactin, cortisol, ACTH, TSH and androstenedione." "PCOS subjects were taking no medication known to affect either carbohydrate metabolism or endocrine parameters for at least 3 months before entering the study. Women taking contraceptive pills were also excluded from the study."	Women in the control group were recruited from a health screening program for employees of the Hospital and by public advertisement. Only women not taking contraceptive pills were included. NIH criteria were used to exclude PCOS in controls before entering the study. Other exclusionary criteria for controls were any known medical condition, except for allergy medication and occasional pain medication.
Stener-Victorin et al. 2010	High/Low	Total=105 PCOS=74 Controls=31	PCOS=30.0±4.4 Controls=27.8±3.5 p=0.018	PCOS=25.3 (22.1–33.3) Controls=23.6 (21.0 – 27.2) p=0.020	Rotterdam equivalent. Women with PCOS and controls were recruited from advertisements in two local newspapers. The criteria for PCOS were polycystic ovary morphology (12 or more 2- to 9-mm ovarian follicles or ovarian volume 10 ml in one or two ovaries by two-dimensional vaginal ultrasound), and/or clinical signs of hyperandrogenism and/or oligo/ amenorrhea.	All subjects who had physical or psychiatric disease or reported pharmacological treatment within 12 wk or breast feeding within 24 wk before enrollment were excluded.	Controls were excluded if they had PCO morphology or menstrual irregularities (cycles 28 or 35 d), hirsutism with a Ferriman-Gallwey score greater than zero and answered "yes" to the question "Do you have acne?"
Bili et al. 2014	High/Low	Total=83 PCOS=43 Controls=40	PCOS=28.9±5.0 Controls=30.8±4.3 p=0.030	PCOS=24.9±5.9 Controls=22.5±3.7 p=0.029	Rotterdam. Women with PCOS were attending the outpatient clinic for investigation of irregular menses and/or signs of androgen excess.	For the homogeneity of the PCOS group, women with regular cycles but with signs of hyperandrogenism and polycystic ultrasound morphology were excluded. Recent pregnancy or use of oral contraceptives, ovulatory agents, antidiabetic	Inclusion criteria for the control were normal ovulatory cycles, absence of clinical or biochemical hyperandrogenemia and absence of polycystic morphology on ultrasound examination. Exclusion criteria were any other cause of hyperandrogenemia

						medications and glucocorticoids, within three months prior to enrolment.	or/and anovulation, history of cardiovascular disease, chronic disease under medication and history of drug or alcohol abuse.
Salamah et al. 2014		Total=200 PCOS=100 Controls=100	PCOS=28.2±7.1 Controls=33.2±9.8	PCOS=37.0±9.1 C=27.5±6.9	NIH 1990. Hyperandrogenism was based on the presence of hirsutism or biochemical androgen excess.	PCOS and control subjects were not taking any medications that could impact hormonal levels for at least 3 months before blood collection, and all underwent a history and physical examination.	Controls were defined as healthy nonpregnant, non-hirsute, premenopausal, eumenorrheic women without personal or family history of hirsutism and/or endocrine disorders. Controls were recruited by responding to posted advertisements.
Villarroel et al. 2015	High/Low	Total=89 PCOS=26 Controls=63	PCOS=17.3 ± 1.9 Controls=16.6 ± 1.5	NR	Rotterdam.	Medications ceased at least 2 months prior to recruitment. Girls with severe acne, obesity, premature pubarche or intrauterine growth retardation were excluded	Sixty-three non-hirsute girls (FG score <6) with regular menses (cycle length between 21 and 45 days) were recruited as control group.
Rudnicka et al. 2016	High/Low	Total=205 PCOS=165 Controls=40	PCOS=25 (23-25) Controls=25 (24-27) p=0.488	PCOS=23 (21-28) Controls=22 (21.5-25) p=0.321	Rotterdam. Patients with PCOS who were referred to out-patient review at a hospital in Poland between 2010 and 2014 years due to clinical hyperandrogenism and/or menstrual irregularities.	Recent pregnancy, use of oral contraceptives,ovulatory agents, antidiabetics or glucocoritcoids within three months prior to enrollment.	Healthy women with normal ovulatory cycles and without clinical or biochemical hyperandrogenemia and absence of PCOM on US.
Sathyapalan et al. 2017	High/Low	Total=175 PCOS=110 Controls=65	PCOS=25.5 $\pm$ 10.0 Controls=32.0 $\pm$ 12.0	PCOS=33.0 (IQR 10.5) Controls=25.0 (IQR 6.2) p <0.001	Rotterdam. Women with PCOS who presented sequentially to an out-patient clinic at a hospital in the UK. Study participants had no concurrent illness, were not on any medication for the preceding 9 months and were not planning to conceive.	Non-classical 21-hydroxylase deficiency, hyperprolactinaemia, Cushing's disease, and androgen-secreting tumours were excluded by appropriate tests.	Healthy women with regular periods and no clinical or biochemical hyperandrogenemia, no significant background medical history and none of them were on any medications including oral

							contraceptive pills or over the counter medications.
Imran et al. 2020	High/Low	Total=200 All PCOS=130 PCOS w/ hirsutism=100 PCOS w/ o hirsutism=30 Controls=70	All PCOS=NR PCOS w/ hirsutism= 24±6 PCOS w/o hirsutism= 26±8 Controls=26±7 P=0.17	All PCOS=NR PCOS w/ hirsutism= 32±5.9 PCOS w/o hirsutism= 27.4±3.5 Controls=26.9 ± 5.7 p <0.001	Rotterdam. The study defined clinical hyperandrogenism by the presence of hirsutism with the mFG score ≥8. Patients with other clinical signs of androgens excess such as acne and/or female pattern alopecia were not included.	Excluded if use of medications that may affect hormone parameters during the last three months prior entering the study. Hyperprolactinemia, thyroid dysfunction, Cushing's syndrome, and NC-CAH.	Women without PCOS or hirsutism
Khashchenko et al. 2020	High/Low	Total=160 PCOS=130 Controls=30	PCOS=NR but included only girls aged 15-17 years. Controls=16.0 (15.0-17.0)	PCOS=22.4 (19.9-27.2) Controls=20.2 (18.4-21.8) p=0.0002	Rotterdam. The study included girls aged 15-17 years presenting complete Rotterdam PCOS diagnostic criteria (oligo-/amenorrhea; clinical and/or biochemical signs of HA; polycystic ovaries detected by ultrasound). The additional inclusion criteria were the onset of menarche at least 2 years prior; the absence of other endocrine diseases.	An aggravation of chronic or acute somatic and/or infectious disease; mental illnesses; inherited syndromes and congenital malformations; hyperprolactinemia; congenital dysfunction of the adrenal cortex; thyroid disorders; Cushing syndrome and disease; tumours of the pelvic organs.	30 healthy adolescent girls of normal weight with regular menstruations and without gynaecological or endocrine pathology (matched for age).
Bansal et al. 2020	Moderate/Moderate	Total=120 PCOS= 31 Controls=89	PCOS=30.43 ± 4.95 Controls=27.74 ± 4.86 p 0.010	NR	Rotterdam. This prospective study included females aged ≥25 years who presented with acne to the dermatology outpatient department of a tertiary care hospital. A Pelvic ultrasound was performed in all study participants.	Excluded if pregnant or hormonal therapy in the past 3 months	Controls were women with female adult acne without PCOS.
Chen et al. 2021	High/ Low	Total=143 PCOS=102 Controls=41	PCOS=29.02 ± 3.75 Controls=29.39 ± 4.23 p 0.628	PCOS=24.32 ± 4.52 Controls=20.30 ± 1.77 p <0.001	Rotterdam.	Diagnoses of PCOS were made after the exclusion of other aetiologies for hyperandrogenemia or ovulatory dysfunction. All individuals with PCOS	Healthy volunteers had regular menstrual cycles and normal ovarian morphology and no oclinical features of androgen excess,. In order to exclude the possible

						were newly diagnosed and treatment naïve.	
Grassi et al. 2021	Moderate/Moderate	Total=117 PCOS=93 Controls=24	PCOS=23.7 ± 6.3 Controls=23.9± 5.8 p 0.921	PCOS=23.5 ± 8.1 Controls=22.6 ± 5.4 p 0.858	Rotterdam. Age ≥18 years, clinical hyperandrogenism (hirsutism, alopecia, or acne) and/or menstrual irregularities, not interfering drugs, and not secondary forms of PCOS.	Excluded if on "interfering drugs" (i.e., estroprogestinics, glucocorticoids)	The enrolled subjects were classified as non-PCOS or PCOS initially, based on T, fT, and A levels assessed by IA.
Kumar et al. 2022	High/Low	Total=186 PCOS=137 Controls=49	PCOS=23.7 ± 4.8 Controls=26.2 ± 4.4 p<0.001	PCOS=25.23 ± 5.11 Controls: 22.6 ± 3.4 p<0.01	Rotterdam. PCOS cases were selected for the study after evaluation of reproductive and menstrual history (oligomenorrhoea/amenorrhoea), hirsutism (FG score), testosterone level and ovarian ultrasonography (polycystic and/or enlarged).	Drug induced hyperandrogenism, androgen producing tumors (ovarian neoplasm, adrenal neoplasm, thecoma), hyperprolactinemia, congenital adrenal hyperplasia, Cushing syndrome, hypothyroidism, or premature ovarian failure	Women of reproductive age with normal menstrual cycle and fertility.
Beitl et al. 2022	Moderate/ Low	Total=116 PCOS= 58 Controls=58	PCOS=25.5 ± 4.7 Controls=25.5 ± 4.7 p 1.000	PCOS=26.3 ± 6.2 Controls=26.4 ± 6.3 p 0.983	PCOS phenotype D according to Rotterdam criteria. This was a retrospective case-control study that included 58 patients with functional hypothalamic amenorrhea (FHA) having PCOM on a pelvic ultrasound and 58 PCOS phenotype D as controls.	Pregnancy, hypothyroidism, and hyperprolactinemia and any organ-related pituitary dysfunction were excluded.	58 patients with functional hypothalamic amenorrhea (FHA) matched 1:1 by age and BMI.

TABLE 5.2 Reference ranges and defined study aims and outcomes

Author, year	Reference range for androgen excess diagnosis	Aim of the Study	Outcome
Koskinen et al. 1996	**NR**	**"To investigate whether the biochemical diagnosis of PCOS could be improved by using an array of hormone measurements chosen to yield optimal and cost-effective discrimination between women with PCOS and healthy women."**	Reported outcome was diagnosis of PCOS but not HA in women with PCOS
Escobar-Morreale et al. 2001	**ROC curves were used to determine cut-off levels for androgens that characterize PCOS subjects**	**"In the present study we have performed ROC analysis considering NICHD criteria as the `gold-standard' for the diagnosis of PCOS, of the basal serum concentrations of several hormones and related parameters usually measured in these patients, in order to evaluate their potential usefulness as single diagnostic tests for screening for this disorder in epidemiological studies."**	Reported outcome was diagnosis of PCOS but not HA in women with PCOS
Hahn et al. 2007	**ROC curves were used to determine cut-off levels for androgens that characterize PCOS subjects**	**"The aim of the present study was to use ROC analysis to evaluate which androgens, including calculated variables are reliable markers of androgen excess for effective discrimination of PCOS women and healthy controls, and which cut-off values should be used in a German population."**	Reported outcome was diagnosis of PCOS but not HA in women with PCOS
Stener-Victorin et al. 2010	**NR**	**"To assess the utility of estrogens, androgen precursors, bioactive androgens, and glucuronidated androgen metabolites in the diagnosis of PCOS."**	Reported outcome was diagnosis of PCOS but not HA in women with PCOS
Bili et al. 2014	**NR**	**"To determine the performance of PSA ratio and ultrasound parameters, such as ovarian volume and outline, in the diagnosis of PCOS."**	Reported outcome was diagnosis of PCOS but not HA in women with PCOS
Salamah et al. 2014	**Local reference range**	**" We nalyzed the predictive value of TT and equilibrium dialysis–derived FT, which are determined by measuring T using either serum extraction chromatography–RIA or liquid chromatography tandem mass spectrometry (LC-MS/MS), in well-phenotyped normal and PCOS females. Furthermore, we modelled two different scenarios: one reflecting subjects seen in the clinical setting (a biased or referred population assumed to have a 70% prevalence of PCOS) and the other reflecting subjects detected in a populational study (assumed to have a 10% prevalence of PCOS).**	Reported outcome was diagnosis of PCOS but not HA in women with PCOS
Villarroel et al. 2015	**Biochemical hyperandrogenism was defined by cut-off values "that we previously demonstrated to be diagnostic for PCOS in adult women."**	**"To evaluate an adapted clinical NICHD criterion of PCOS for adolescents, as screening tools to detect biochemical hyperandrogenism (BH) and polycystic ovaries during adolescence and to determine the clinical phenotypes, threshold values of androgen levels and ultrasonographic patterns in girls with hirsutism and oligomenorrhea compared with non-obese adolescent girls."**	Reported outcome was diagnosis of PCOS but not HA in women with PCOS
Rudnicka et al. 2016	**Local laboratory reference range**	**"To assess the PSA concentration (TPSA and fPSA) in women with PCOS comparing with the healthy control group. The second goal was to determine if there is any relationship between PSA (TPSA and fPSA) and hormonal and biochemical parameters and the performance of PSA in diagnosis of PCOS."**	Reported outcome was diagnosis of PCOS but not HA in women with PCOS
Sathyapalan et al. 2017	**The threshold values (calculated using the 95th percentile of the controls for the ROC) for serum**	**To establish if salivary T and salivary androstenedione measurements had a role in diagnosing PCOS, either instead of or in addition to serum measurements.**	**Provides data on the outcome of interest for salivary testosterone** (information extracted

	T and FAI coincided exactly with the local laboratory reference range at 1.9 nmol/l and 4.0 nmol/L, respectively. Cut-off threshold value for salivary T was 19.9pmol/L. Local laboratory reference range cut-off (95% IQR) for salivary T was 31.6 pmol/L derived from a separate cohort of 91 women aged 16-74 years).		from the text was able to identify sensitivity and specificity of salivary T for detecting HA in women with PCOS).
Imran et al. 2020	**Normal androgen levels were 15-46 ng/dL for TT, 4.16-22.2 pmol/L for calculated FT, and 18-86 nmol/L for SHBG. Reference ranges for total and free testosterone and SHBG were established from a separate cohort of 161 healthy, normally cycling women (18-49 years).**	**"To investigate whether the biochemical diagnosis of PCOS could be improved by using an array of hormone measurements chosen to yield optimal and cost-effective discrimination between women with PCOS and healthy women."**	**Data for the outcome of interest (detection of HA diagnosis in women with PCOS with and without hirsutism) was extracted from the text. However, this study did not include women with other clinical signs of androgens excess such as acne and/or female pattern hair loss.**
Khashchenko et al. 2020	**Local laboratory reference values, but details of how obtained were not reported.**	"In the present study we have performed ROC analysis considering NICHD criteria as the `gold-standard' for the diagnosis of PCOS, of the basal serum concentrations of several hormones and related parameters usually measured in these patients, in order to evaluate their potential usefulness as single diagnostic tests for screening for this disorder in epidemiological studies."	Reported outcome was diagnosis of PCOS but not HA in adolescents with PCOS
Bansal et al. 2020	No report of how the RR were calculated. "We defined biochemical hyperandrogenaemia as elevated levels of any of the three parameters: TT≥1.89 nmoL/L, DHEAS >2.75 µg/mL, or FAI > 5	**"The aim of the present study was to use ROC analysis to evaluate which androgens, including calculated variables are reliable markers of androgen excess for effective discrimination of PCOS women and healthy controls, and which cut-off values should be used in a German population."**	Reported outcome was diagnosis of PCOS but not HA in women with PCOS
Chen et al. 2021	**No report of androgens RRs used to characterise biochemical hyperandrogenism in women classified as PCOS.**	**"To assess the utility of estrogens, androgen precursors, bioactive androgens, and glucuronidated androgen metabolites in the diagnosis of PCOS."**	Reported outcome was diagnosis of PCOS but not HA in women with PCOS
Grassi et al. 2021	**73 lean Caucasian women of reproductive age with regular menses, no PCOM on ultrasound and no clinical signs of hyperandrogenism served as controls to derive reference intervals**	**"To determine the performance of PSA ratio and ultrasound parameters, such as ovarian volume and outline, in the diagnosis of PCOS."**	Reported outcome was diagnosis of PCOS but not HA in women with PCOS
Kumar et al. 2022	**Total T: RR according to the manufacturer for normal females aged 21-49 years was 0.25-2.75 nmol/L (0.072-0.793 ng/mL DHT: RR according to the manufacturer 24-368 pg/mL"but reference range for North Indian female is unavailable.". DHEAS, Androstenedione, SHBG and FAI: ROC curve cut-off**	**"We analyzed the predictive value of TT and equilibrium dialysis–derived FT, which are determined by measuring T using either serum extraction chromatography–RIA or liquid chromatography tandem mass spectrometry (LC-MS/MS), in well-phenotyped normal and PCOS females. Furthermore, we modelled two different scenarios: one reflecting subjects seen in the clinical setting (a biased or referred population assumed to have a 70% prevalence of PCOS) and the other reflecting subjects detected in a populational study (assumed to have a 10% prevalence of PCOS).**	**Provides data on the outcome of interest, the detection of HA in women with PCOS.**
Beitl et al. 2022	**No report of androgens RRs used to characterise biochemical hyperandrogenism in women classified as PCOS.**	**"To evaluate an adapted clinical NICHD criterion of PCOS for adolescents, as screening tools to detect biochemical hyperandrogenism (BH) and polycystic ovaries during adolescence and to determine the clinical phenotypes, threshold values of androgen levels and ultrasonographic patterns in girls with hirsutism and oligomenorrhea compared with non-obese adolescent girls."**	Reported outcome was diagnosis of PCOS but not HA in women with PCOS

Table 5.3 Biochemical assays – characteristics and quality assessment

Author, year	Method reference	Method	Target Analyte(s)	Internal Standards	Sample Preparation	Validation	Comments
Koskinen et al. 1996	NA	RIA	A4, T, SHBG	NA	NA	Not described, no performance criteria outlined	Low grade evidence as the research is based on antibody-antigen analysis.
Escobar-Morreale et al. 2001	NA	Immunoassay (Siemens Immulite)	DHEAS, T, SHBG	NA	NA	NA	Low grade evidence as the research is based on immunoassay analysis.
Hahn et al. 2007	NA	Immunoassay (Siemens Immulite)	DHEAS, A4, T, SHBG	NA	NA	NA, some performance criteria described	Low grade evidence as the research is based on immunoassay analysis.
Stener-Victorin et al. 2010	NR	GC-MS	DHEA, A4, T, DHT	Used but not described	NR	Not described	No data available on the method just 'a validated GC-MS system' - does not reference a method paper, no mention of what internal standards were used. Free testosterone calculated without measuring albumin but assuming a fixed 43 g/L
Bili et al. 2014	NA	Immunoassay (Siemens Immulite)	DHEAS, A4, T, SHBG	NA	NA	No assurance assays are performing well - no reference to what imprecision has been achieved on their system. Also, no reference to external quality control to indicate if assay is performing similar to other users.	Low grade evidence as the research is based on immunoassay analysis.
Salamah et al. 2014	Salamah et al. 2014	LC-MS/MS	T	D5-T	Liberates T from SHBG and albumin pH adjustment	Ok for the time of original publication but the authors have not disclosed what standard they have used to validate the assay against (e.g. CLSI, FDA, EMA). This is important for defining acceptance criterai for the assay performance. They have done a range of experiments but not gone into much detail as to how these have been undertaken. They have not conducted a true recovery experiment or assessed matrix effects, instead they have assessed linearity but claim this constitutes both recovery and matrix effects. By today's standards further work would be required for validation.	From the biochemical analysis point of view, regard as scientifically sound, good grade evidence. Would make more sense to add internal standard prior to acidification to allow that to equilibrate with T.
Villarroel et al. 2015	Sir-Petermann et al.	RIA but 'traceabe' to mass spec via use of a fudge factor	A4, T, SHBG	D3-T	NR	Minimal validation data provided. The authors appear to have adapted a method described by Choi et al but have not provided enough information to conclude that the assay has been validated to a good standard.	Low grade, this is a circuitous and complicated analysis that relies on converting RIA results to a make them 'traceable' to an LC-MS/MS method by virtue of a correlation and regression analysis. (i.e. a fudge factor is applied).
Rudnicka et al. 2016	NA	Immunoassay -Abbott Architect -Siemens Immulite	DHEAS, T A4	NA	NA	No assurance assays are performing well - no reference to what imprecision has been achieved on their system. Also no reference to external quality control to indicate if assay is performing similar to other users.	Low grade evidence as the research is based on immunoassay analysis.

Sathyapalan et al. 2017	Gallagher et al. 2014 Keevil et al. 2017	LC-MS/MS LC-MS/MS	A4, T Salivary T	D2-T D5-T	Liquid-liquid extraction (MTBE) (for both assays)	The internal standards referenced can be improved upon by using C13 internal standards, but this will not have been available at the time the assays were originally published. The validation has been undertaken to a good standard for the time of original publication but by today's standards further work would be needed to investigate matrix effects quantitatively.	From the biochemical analysis point of view, regard as good grade evidence, would be further improved by using C13-T as an internal standard.
Imran et al. 2020	NA	Immunoassay (Roche)	DHEAS, T, SHBG	NA	NA	The authors do not provide any indication that the assays are performing within the criteria outlined by the manufacturer (i.e. imprecision data at various concentrations) nor that the assay is performing comparably to other users/laboratories.	Low grade evidence as the research is based on immunoassay analysis.
Khashchenko et al. 2020	NA	Immunoassay (Roche and Siemens)	DHEAS, A4, T, SHBG	NA	NA	It is unclear which system (Roche or Siemens) has been used to produce the results for each analyte. No information is provided is provided as to how the assays are performing and whether or not they are in accordance with the manufacturers' performance characteristics.	Low grade evidence as the research is based on immunoassay analysis.
Bansal et al. 2020	NA	Immunoassay -Ortho -Beckman	 T DHEAS, SHBG	NA	NA	No assurance assays are performing well - no reference to what imprecision has been achieved on their system. Also, no reference to external quality control to indicate if assay is performing similar to other users.	Low grade evidence as the research is based on immunoassay analysis.
Chen et al. 2021	NR NA	LC-MS/MS Immunoassay (Siemens)	DHEAS, DHEA, A4, T SHBG	Used but not described NA	Solid phase extraction NA	The principle of the extraction is well described but there is no information provided about the performance characteristics of the assay and what (if any) validation has been undertaken. No reference to imprecision, recovery, matrix effects.	Low grade evidence, impossible to know how good this assay is as its performance has not been described or previously published.
Grassi et al. 2021	NA - uses a commercially available LC-MS/MS kit (Chromsystems)	LC-MS/MS	DHEAS, A4, T	D6-DHEAS, C13-A4, D3-T	Solid phase extraction	This relies on the use of a commercially available LC-MS/MS kit. The calibration is traceable to certiified reference material. The authors cite imprecision which is within the manufacturers specification, thus helping to verify the method.	From the biochemical analysis point of view, regard as scientifically sound, good grade evidence. It would be improved by using C13-T internal standards.
Kumar et al. 2022	NA	Immunoassay (Abbott Architect)	T, SHBG	NA	NA	No assurance assays are performing well - no reference to what imprecision has been achieved on their system only what manufacturer recommends, there is no evidence these claims have been verified by the authors. Also, no refernce to external quality control to indicate if assay is performing similar to other users.	Low grade evidence as the research is based on immunoassay analysis.
Beitl et al. 2022	NA	Immunoassay (Roche)	A4, T, SHBG	NA	NA	No assurance how assays are performing, or in some instances (T and A4) which assay has been used for their analysis. CVs should be provided to allow the reader to ascertain assay imprecision at various concentrations.	Low grade evidence. The manuscript does not state clearly what method has been used to measure T and A4.

TABLE 5.4 Summary of the overall quality assessment of the included studies. For details on the biochemical analytical quality assessment please see Appendix I.

Author, year	Provides data on the defined outcome of interest	Method	Measured Analyte(s)	Biochemical analytical quality	Index tests	Risk of Bias/Certainty
Koskinen et al. 1996	No	Radioimmunoassay (RIA)	A4, T, SHBG	Low	A4, T, SHBG FAI	High/Low
Escobar-Morreale et al. 2001	No	Immunoassay (Siemens Immulite)	DHEAS, T, SHBG	Low	DHEAS, T, SHBG calculated free T FAI	Moderate/Moderate
Hahn et al. 2007	No	Immunoassay (Siemens Immulite)	DHEAS, A4, T, SHBG	Low	DHEAS, A4, T, SHBG calculated free T FAI	Moderate/Low
Stener-Victorin et al. 2010	No	GC-MS	DHEA, A4, T, DHT	Low	T calculated free T	High/Low
Bili et al. 2014	No	Immunoassay (Siemens Immulite)	DHEAS, A4, T, SHBG	Low	FAI	High/Low
Salamah et al. 2014	No	LC-MS/MS	T	Good	T calculated free T	High/Low
Villarroel et al. 2015	No	Radioimmunoassay (RIA)	A4, T, SHBG	Low	T, SHBG FAI	High/Low
Rudnicka et al. 2016	No	Immunoassay -Abbott Architect -Siemens Immulite	DHEAS, T A4	Low	DHEAS, A4, T FAI	High/Low
Sathyapalan et al. 2017	Yes	LC-MS/MS	A4, T Salivary A4 and T	Good	A4, T FAI Salivary T	High/Low
Imran et al. 2020	Yes	Immunoassay (Roche)	DHEAS, T, SHBG	Low	DHEAS, T, SHBG calculated free T	High/Low
Khashchenko et al. 2020	No	Immunoassay (Roche and Siemens)	DHEAS, A4, T, SHBG	Low	A4, T FAI	High/Low
Bansal et al. 2020	No	Immunoassay -Ortho -Beckman	T DHEAS, SHBG	Low	T	Moderate/Moderate
Chen et al. 2021	No	LC-MS/MS Immunoassay (Siemens)	DHEAS, DHEA, A4, T SHBG	Low	DHEAS, A4, T FAI	High/ Low
Grassi et al. 2021	No	LC-MS/MS	DHEAS, A4, T	Good	A4, T calculated free T FAI	Moderate/Moderate
Kumar et al. 2022	Yes	Immunoassay -Abbott Architect -DBC Diagnostics -DRG International	DHEAS, T, SHBG A4 DHT	Low	DHEAS, A4, T, DHT FAI	High/Low
Beitl et al. 2022	No	Immunoassay (Roche)	A4, T, SHBG	Low	T SHBG	Moderate/ Low

6. FINDINGS AND STATISTICAL ANALYSIS

COMPARISONS INCLUDED:

- **Comparison 1: PCOS versus Controls (non-PCOS)**

INDEX TESTS INCLUDED:

- **Index test 1: Serum total testosterone**
- **Index test 2: Serum androstenedione**
- **Index test 3: Serum DHEAS**
- **Index test 4: FAI**
- **Index test 5: Free testosterone**
- **Index test 6: DHT**
- **Index test 7: Serum SHBG**
- **Index test 8: Salivary testosterone**

STATISTICAL ANALYSIS:

Review Manager 5.4 (RevMan 5.4)

Meta-DiSc 2.0 is freeware software to perform Meta-analysis of studies of Diagnostic Test Accuracy (https://ciberisciii.shinyapps.io/MetaDiSc2/)

- ## EVIDENCE SUMMARY:

Serum total testosterone

Fifteen studies examined the use of serum total testosterone for diagnosing hyperandrogenism (Koskinen 1996, Escobar-Morreale 2001, Hahn 2007, Stener-Victorin 2010, Salamah 2014, Villarroel 2015, Rudnicka 2016, Sathyapalan 2017, Bansal 2020, Imran 2020, Khashchenko 2020, Chen 2021, Grassi 2021, Beitl 2022, Kumar 2022). Methods of measurement included radioimmunoassay (N=2), immunoassay (N=8) and mass spectrometry (N=5). Five studies were judged of moderate risk of bias (Escobar-Morreale 2001, Hahn 2007, Bansal 2020, Grassi 2021, Beitl 2022), the rest were all high risk of bias. Except for four studies (Escobar-Morreale 2001, Stener-Victorin 2010, Sathyapalan 2017, Khashchenko 2020), the rest were included in the meta-analysis.

Serum androstenedione

Nine studies examined the use of serum androstenedione for diagnosing hyperandrogenism (Koskinen 1996, Hahn 2007, Rudnicka 2016, Diamandis 2017, Sathyapalan 2017, Khashchenko 2020, Chen 2021, Grassi 2021, Kumar 2022). Two studies used radioummunoassay, four studies used immunoassay and three studies used mass spectrometry. Except for two studies (Hahn 2007, Grasi 2021) which were of moderate risk of bias, the rest of the studies were of high risk of bias. Five studies were included in the meta-analysis (Hahn 2007, Rudnicka 2016, Chen 2021, Grassi 2021, Kumar 2022).

Serum DHEAS

Six studies examined DHEA-S for diagnosing hyperandrogenism (Escobar-Morreale 2001, Hahn 2007, Rudnicka 2016, Imran 2020, Chen 2021, Kumar 2022). Except for Chen 2021 which used mass spectrometry, the rest of the studies used immunoassay as the method of measurement. Two studies were judged moderate risk of bias (Escobar-Morreale 2001, Hahn 2007) while the rest were of high risk of bias. Except for Grassi 2021, all the other five studies were included in the meta-analysis.

FAI

Eleven studies examined calculated FAI for diagnosing hyperandrogenism (Koskinen 1996, Escobar-Morreale 2001, Hahn 2007, Bili 2014, Villarroel 2015, Rudnicka 2016, Sathyapalan 2017, Khashchenko 2020, Chen 2021, Grassi 2021, Kumar 2022). Two studies used radioimmunoassay, six used immunoassay and the other three used mass-spectometry. Three studies were judged as moderate risk of bias (Escobar-Morreale 2001, Hahn 2007, Grassi 2021) and the rest were all high risk of bias. Except for Koskinen 1996 and Sathyapalan 2017, the other nine studies were included in the meta-analysis.

Free testosterone

Six studies examined calculated free testosterone for diagnosing hyperandrogenism (Escobar-Morreale 2001, Hahn 2007, Stener-Victorin 2010, Salamah 2014, Imran 2020, Grassi 2021) and all were included in the meta-analysis. These studies used immunoassay (N=3) and mass spectrometry (N=3) as the method of measurement. Three studies used were of high risk of bias (Stener-Victorin 2010, Salamah 2014, Imran 2020) and the other three were of moderate risk of bias.

DHT

Only one studies examined DHT for diagnosing hyperandrogenism using immunoassay (Kumar 2022). It was judged as high risk of bias and unable to have meta-analysis performed.

Serum SHBG

SHBG was examined by four studies (Koskinen 1996, Escobar-Morreale 2001, Hahn 2007, Betl 2022). Koskinen 1996 utilised radioimmunoassay and was judged as high risk of bias. The study was not included in the meta-analysis. All the other three studies used immunoassay, were of moderate risk of bias and included in the meta-analysis.

Salivary testosterone

Salivary testosterone was examined by Sathyapalan 2017 using mass spectrometry. It was judged as high risk of bias and no meta-analysis was performed.

- ## META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

Meta-analyses results showed that calculated free testosterone and calculated FAI had the best sensitivity and specificity to diagnosed biochemical hyperandrogenism compared with all other tests. For both test, their sensitivity were greater than 80%. Specificity was higher for calculated free testosterone (93.3%, 95% CI 0.799-0.980) than calculated FAI (64.0%, 95% CI 0.767-0.924). Serum total testosterone, androstenedione and DHEA-S had similar sensitivity around 70% and specificity around 75-85%. Salivary testosterone and DHT only had one study each included with no meta-analysis performed. All outcomes had very low certainty for their evidence due to their study design and high risk of bias in majority of the included studies.

6.1. Index Test: Total Testosterone (serum)

6.1.1. Individual Study Data Table

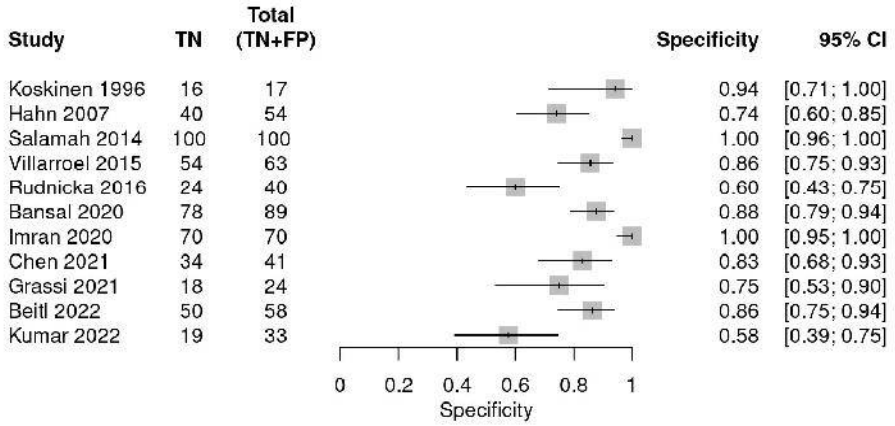
INDEX TEST: Total T			OUTCOME TYPE: Continuous											
COMPARISON (if applicable): non-PCOS														
Author, year	Unit of outcome	Method of measurement	N	PCOS	Non-PCOS	Threshold cut-off	True Pos	False Pos	True Neg	False Neg	Sensitivity (95% CI)	Specificity (95%CI)	AUC	Precision
Koskinen et al. 1996*	ng/dL	Radioimmunoassay (RIA)	74	54	20	72 ng/dL (2.50 nmol/L	38	1	16	19	70	97	0.939±0.025	NR
Escobar-Morreale et al. 2001	nmol/L	Immunoassay (Siemens Immulite)	114	8	106	NR	NR	NR	NR	NR	NR	NR	0.690 ± 0.107 (0.592 ± 0.774)	NR
Hahn et al. 2007	nmol/L	Immunoassay (Siemens Immulite)	187	133	54	2.37 nmol/L	97	14	40	36	72.9	74.1	0.799 (0.734-0.854)	NR
Stener-Victorin et al. 2010	ng/mL	GC-MS	105	74	31	NR	NR	NR	NR	NR	NR	NR	GC-MS 0.89 (0.82-0.95) / RIA 0.85 (0.77-0.93)	NR
Salamah et al. 2014	ng/dL	LC-MS/MS	200	100	100	50 ng/dL	29	0	100	71	29	100	0.765 (0.693-0.836)	NR
Villarroel et al. 2015	nmol/L	Radioimmunoassay (RIA)	89	26	63	>2.1 nmol/L	17	9	54	9	65.4	85.7	0.786	p <0.001

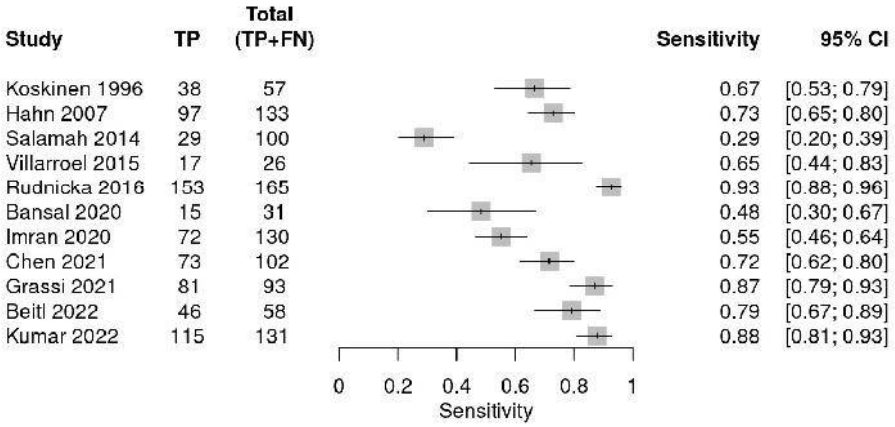
Rudnicka et al. 2016	ng/mL	Immunoassay -Abbott Architect -Siemens Immulite	205	165	40	0.54 ng/mL	153	16	24	12	92.87	59.03	0.805 (0.736–0.874)	
Sathyapalan et al. 2017	nmol/L	LC-MS/MS	175	110	65	1.9 nmol/L	NR	NR	NR	NR	NR	NR	0.684 (0.603, 0.765)	NR
Bansal et al. 2020	nmol/L	Immunoassay (Ortho)	120	31	89	>1.34 nmol/L	15	11	78	16	48.39	87.64	0.716	p=0.0002
Imran et al. 2020	ng/dL	Immunoassay (Roche)	200	130	70	NR	72	0	70	58	55.0 (46.0, 64.0)	1. (0.95, 1.00)	NR	NR
Khashchenko et al. 2020	nmol/L	Immunoassay (Roche and Siemens)	160	130	30	>1.15 nmol/L	NR	NR	NR	NR	NR	NR	0.861	NR
Chen et al. 2021	ng/mL	LC-MS/MS	143	102	41	0.337 ng/mL (1.2 nmol/L)	73	7	34	29	72.0 (62.1, 80.5)	82.93 (67.9, 92.8)	0.816 (0.742, 0.876)	p <0.001
Grassi et al. 2021	ng/mL	LC-MS/MS	117	93	24	0.24 ng/mL (0.83 nmol/L)	81	6	18	12	87	75	0.899	NR
Beitl et al. 2022	ng/mL	Immunoassay (Roche)	116	58	58	<0.31 ng/mL (<1.08 nmol/L)	46	8	50	12	79.31 (66.7, 88.8)	86.21 (74.2, 93.9)	0.886	p <0.001
Kumar et al. 2022	ng/mL	Immunoassay -Abbott Architect	186	137	49	0.28 ng/mL (0.97 nmol/L)	115	14	35	22	83.8 (77.0, 90.0)	71.4 (57.0, 83.0)	NR	NR

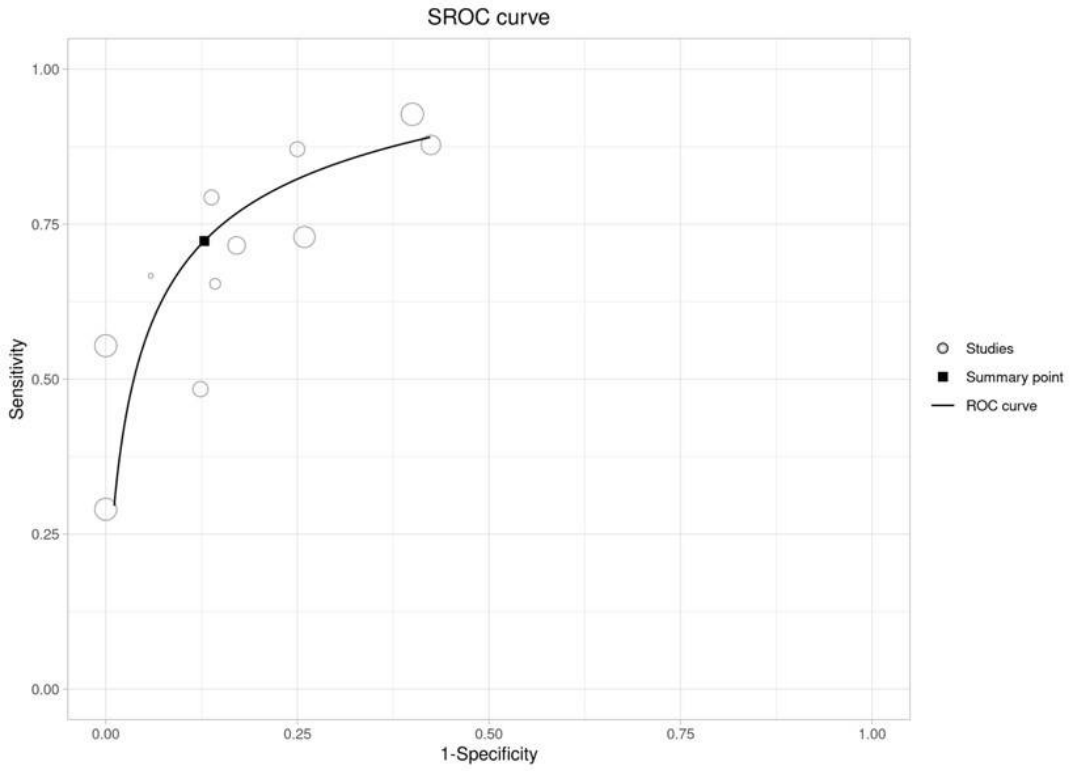
6.1.2. Summary statistics for Total Testosterone (overall – bivariate model):

Serum Total Testosterone	
Sensitivity Estimate (95% CI)	**0.723 (0.602; 0.818)**
Specificity Estimate (95% CI)	**0.871 (0.750; 0.939)**
Studies (n)	**11**
PCOS (n)	**1026**
non-PCOS (n)	**589**
Total (n)	**1615**
Prevalence	**0.64**

6.1.3. Forest Plots and SROC curve for Total Testosterone (overall– bivariate model):





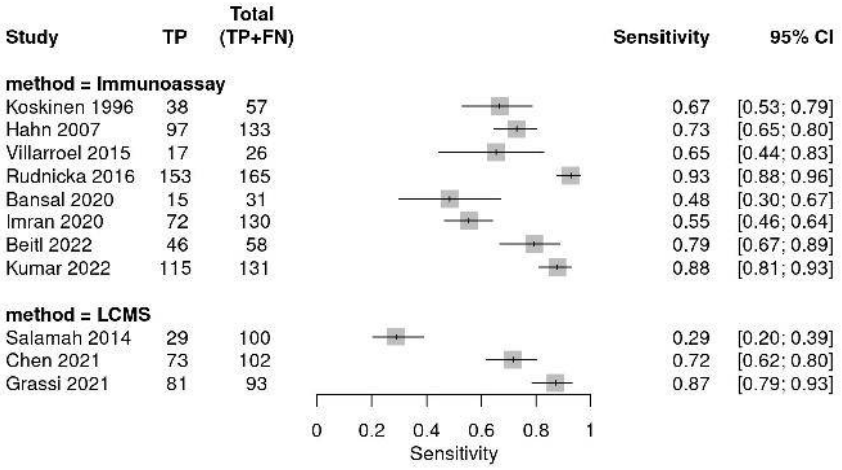


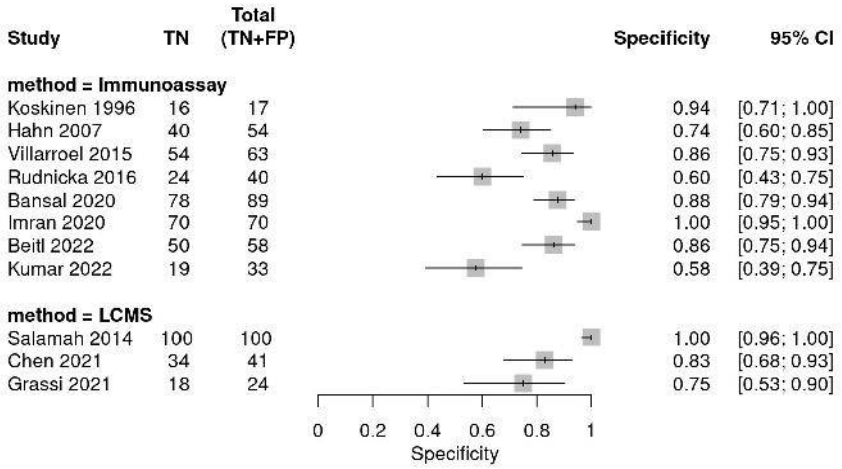
6.1.4. Summary statistics for Total Testosterone (subgroup analysis):

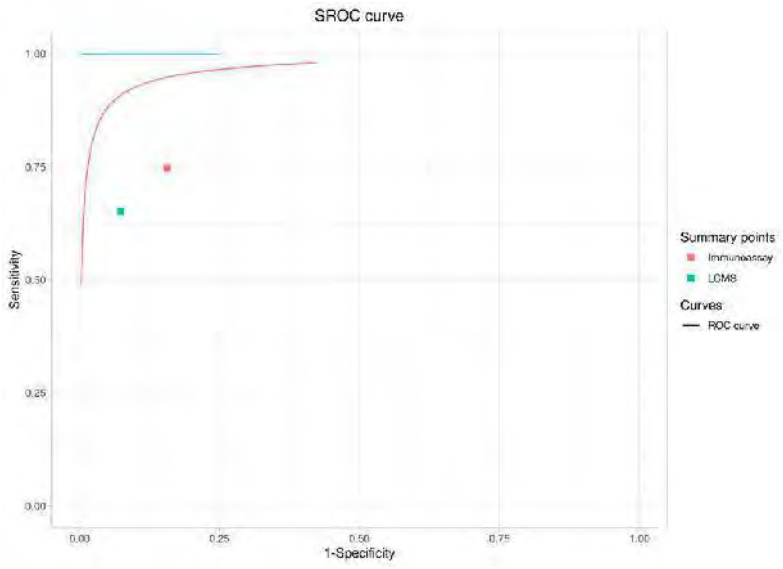
Testosterone by Immunoassays (subgroup analysis including 8 studies)	
Sensitivity Estimate (95% CI)	**0.747 (0.612; 0.847)**
Specificity Estimate (95% CI)	**0.844 (0.689; 0.929)**

Testosterone by LC-MS/MS (subgroup analysis including 3 studies)	
Sensitivity Estimate (95% CI)	**0.652 (0.406; 0.837)**
Specificity Estimate (95% CI)	**0.927 (0.730; 0.983)**

6.1.5. Forest Plots and SROC curve for Total Testosterone according to the method (subgroup analysis):







6.2. Index Test: Androstenedione (serum)

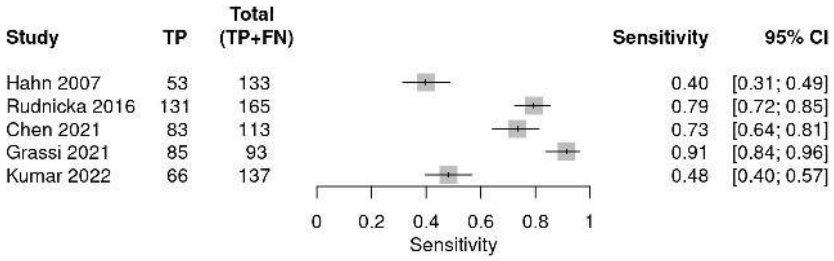
6.2.1. Individual Study Data Table

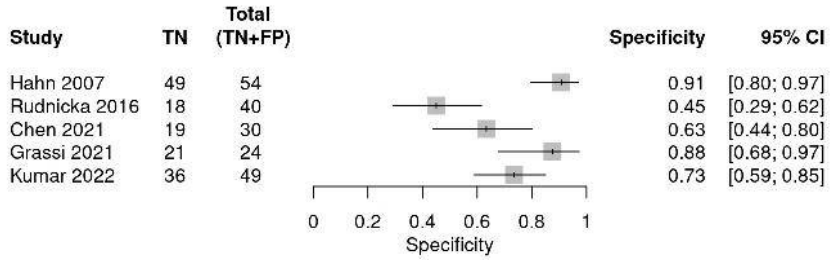
INDEX TEST: Androstenedione	OUTCOME TYPE: Continuous													
COMPARISON (if applicable): non-PCOS														
Author, year	Unit of outcome	Method of measurement	N	PCOS	non-PCOS	Threshold cut-off	True Pos	False Pos	True Neg	False Neg	Sensitivity (95% CI)	Specificity (95%CI)	AUC	Precision
Koskinen et al. 1996	ng/dL	Radioimmunoassay (RIA)	83	54	29	NR	NR	NR	NR	NR	NR	NR	0.933 ± 0.027	NR
Hahn et al. 2007	nmol/L	Immunoassay (Siemens Immulite)	187	133	54	13.79 nmol/l	53	5	49	80	39.8	90.7	0.706 (0.635-0.770)	NR
Rudnicka et al. 2016	ng/mL	Immunoassay (Siemens Immulite)	205	165	40	3.95 ng/mL	131	22	18	34	79.31	44.57	0.627	NR
Diamandis et al. 2017	ng/mL	Radioimmunoassay (RIA)	85	45	40	NR	NR	NR	NR	NR	NR	NR	0.915 (0.856, 0.974)	NR
Sathyapalan et al. 2017	nmol/L	LC-MS/MS	175	110	65	NR	NR	NR	NR	NR	NR	NR	0.662 (0.575, 0.749)	NR
Khashchenko et al. 2020	ng/mL	Immunoassay (Roche and Siemens)	160	130	30	>11.45 ng/dL (>0.40 nmol/L)	NR	NR	NR	NR	NR	NR	0.869	NR
Chen et al. 2021	ng/mL	LC-MS/MS	143	102	41	1.309 ng/mL (4.57 nmol/L)	83	11	19	30	81.0 (71.9, 88.2)	73.17 (57.1, 85.8)	0.842 (0.771, 0.898)	p <0.001
Grassi et al. 2021	ng/mL	LC-MS/MS	117	93	24	1.16 ng/mL (4.05 nmol/L)	85	3	21	8	91	88	0.957	NR
Kumar et al. 2022	ng/mL	Immunoassay (DBC Diagnostics)	186	137	49	1.19 ng/mL (4.16 nmol/L)	66	13	36	71	48	73	NR	NR

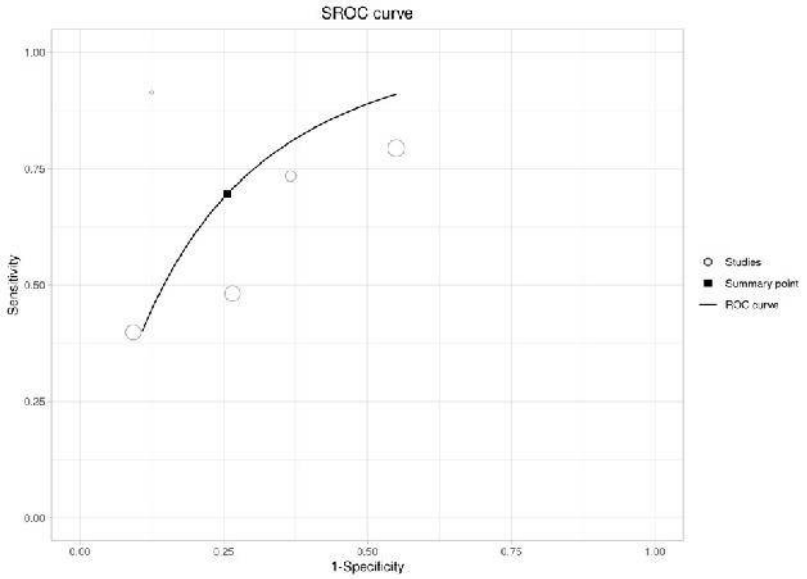
6.2.2. Summary statistics for Androstenedione (overall – bivariate analysis):

Androstenedione	
Sensitivity Estimate (95% CI)	**0.695 (0.491; 0.844)**
Specificity Estimate (95% CI)	**0.744 (0.566; 0.866)**
Studies (n)	**5**
PCOS (n)	**641**
non-PCOS (n)	**197**
Total (n)	**838**
Prevalence	**0.76**

6.2.3. Forest Plots and SROC curves for Androstenedione (overall – bivariate model):





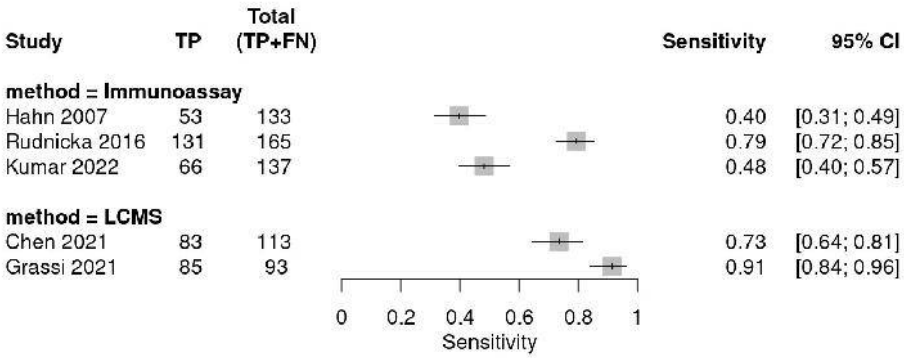


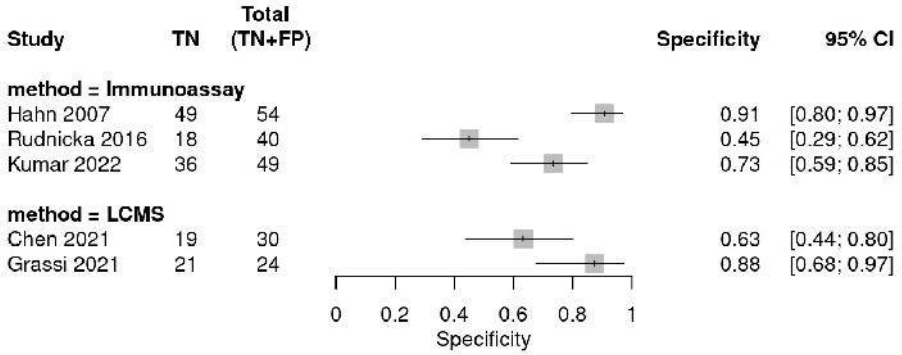
6.1.4. Summary statistics for Androstenedione (subgroup analysis):

Androstenedione by Immunoassays (subgroup analysis including 3 studies)	
Sensitivity Estimate (95% CI)	**0.571 (0.375; 0.747)**
Specificity Estimate (95% CI)	**0.733 (0.507; 0.880)**

Androstenedione by LC-MS/MS (subgroup analysis including 2 studies)	
Sensitivity Estimate (95% CI)	**0.836 (0.647; 0.934)**
Specificity Estimate (95% CI)	**0.759 (0.468; 0.919)**

6.1.5. Forest Plots and SROC curve* for Androstenedione according to the method (subgroup analysis):





**** A SROC curve for the subgroup analysis could not be computed as the LCMS category has fewer than 3 studies.***

6.3. Index Test: DHEA-S

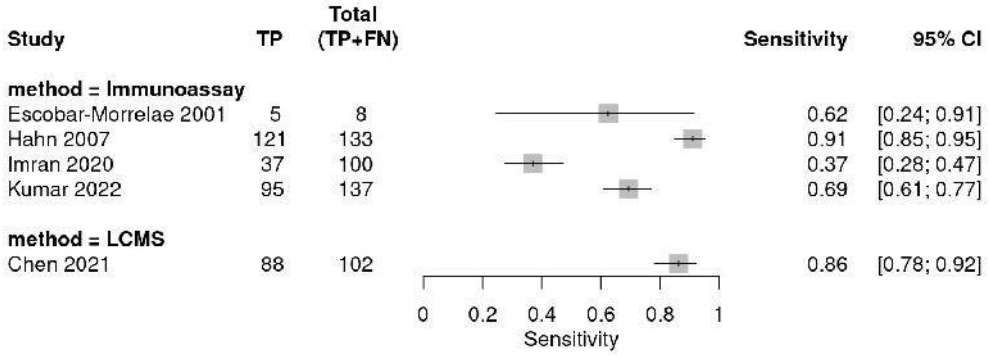
6.3.1. Individual Study Data Table

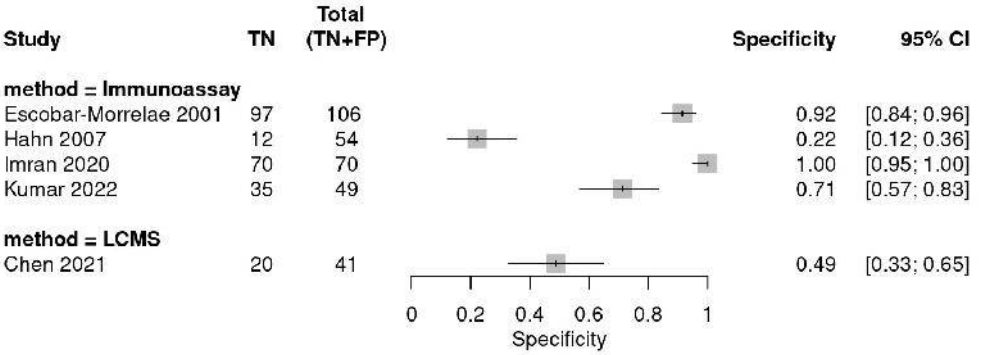
INDEX TEST: DHEA-S	OUTCOME TYPE: Continuous													
COMPARISON (if applicable): non-PCOS														
Author, year	Unit of outcome	Method of measurement	N	PCOS	non-PCOS	Threshold cut-off	True Pos	False Pos	True Neg	False Neg	Sensitivity (95% CI)	Specificity (95%CI)	AUC	Precision
Escobar-Morreale et al. 2001	µmol/L	Immunoassay (Siemens Immulite)	114	8	106	>11.6 µmol/L	5	9	97	3	62.5	91.5	0.832±0.091 (0.750-0.895)	NR
Hahn et al. 2007	µmol/L	Immunoassay (Siemens Immulite)	187	133	54	8.11 µmol/L	121	42	12	12	91	22.2	0.502	NR
Rudnicka et al. 2016	µg/dL	Immunoassay (Abbott Architect)	205	165	40	NR	NR	NR	NR	NR	NR	NR	0.561 (0.466-0.657)	NR
Imran et al. 2020	ng/dL	Immunoassay (Roche)	200	130	70	NR	37	0	70	63	0.37 (0.28-0.47)	1.00 (0.95-1.00)	NR	NR
Chen et al. 2021	ng/mL	LC-MS/MS	143	102	41	1887.057 ng/mL (188.7 µg/dL)	88	21	20	14	86.0 (77.6, 92.1)	48.78 (32.9, 64.9)	0.678	p <0.001
Kumar et al. 2022	µg/dL	Immunoassay (Abbott Architect)	186	137	49	167.5 µg/dL	95	14	35	42	69	71	NR	NR

6.3.2. Summary statistics for DHEAS (overall – bivariate model):

DHEAS	
Sensitivity Estimate (95% CI)	**0.717 (0.508; 0.862)**
Specificity Estimate (95% CI)	**0.780 (0.384; 0.953)**
Studies (n)	**5**
PCOS (n)	**480**
non-PCOS (n)	**320**
Total (n)	**800**
Prevalence	**0.6**

6.3.3. Forest Plots and SROC curves for DHEAS (overall – bivariate model):



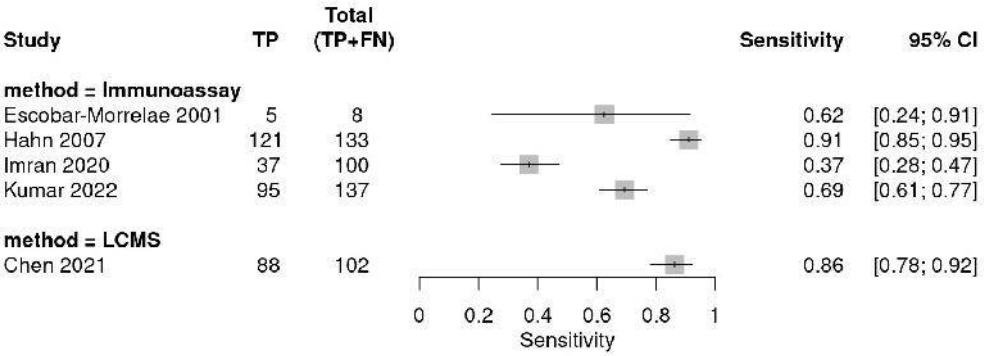


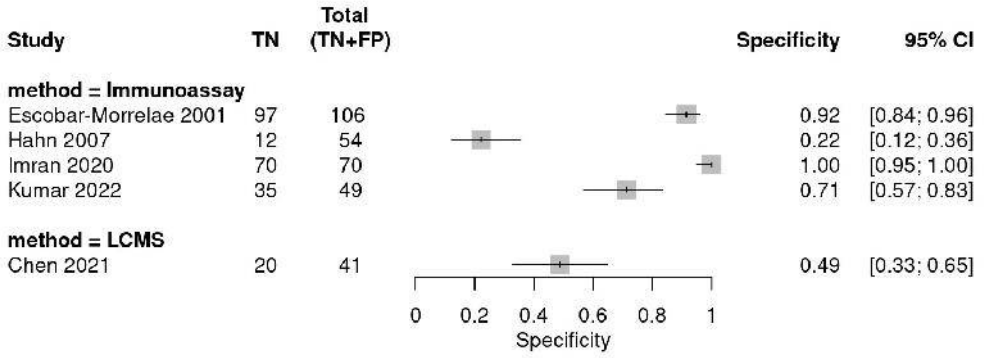
6.3.6. Summary statistics for DHEAS (subgroup analysis):

DHEAS by Immunoassays (subgroup analysis including 4 studies)	
Sensitivity Estimate (95% CI)	**0.669 (0.450; 0.833)**
Specificity Estimate (95% CI)	**0.832 (0.436; 0.970)**

DHEAS by LC-MS/MS (subgroup analysis including 1 study)	
Sensitivity Estimate (95% CI)	**0.863 (0.506; 0.975)**
Specificity Estimate (95% CI)	**0.488 (0.025; 0.973)**

6.3.7. Forest Plots and SROC curve* for DHEAS according to the method (subgroup analysis):





** A SROC curve for the subgroup analysis could not be computed as the LCMS category has fewer than 3 studies.*

6.4. Index Test: FAI (Free Androgen Index; calculated)

6.4.1. Individual Study Data Table

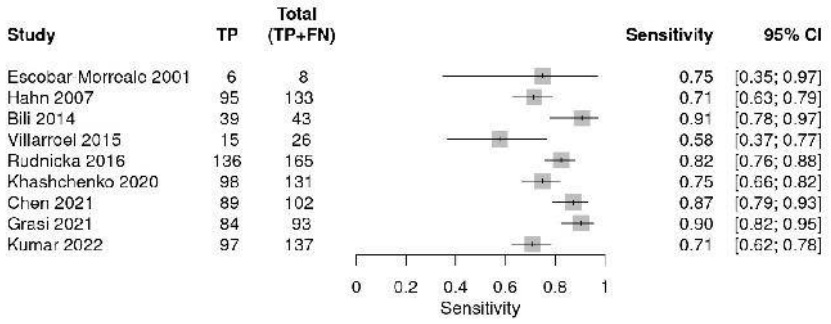
INDEX TEST: FAI	OUTCOME TYPE: Continuous													
COMPARISON (if applicable): Non-PCOS														
Author, year	Unit of outcome	Method of measurement	N	PCOS	non-PCOS	Threshold cut-off	True Pos	False Pos	True Neg	False Neg	Sensitivity (95% CI)	Specificity (95%CI)	AUC	Precision
Koskinen et al. 1996	NA	calculated from T measured by radioimmunoassay (RIA)	83	54	29	NR	NR	NR	NR	NR	NR	NR	0.831±0.044	NR
Escobar-Morreale et al. 2001	NA	calculated from T measured by Immunoassay (Siemens Immulite)	114	8	106	>3.67	6	15	91	2	75	85.8	0.867±0.083 (0.790-0.923)	NR
Hahn et al. 2007	NA	calculated from T measured by Immunoassay (Siemens Immulite)	187	133	54	4.97	95	8	46	38	71.4	85.2	0.847 (0.788-0.896)	NR
Bili et al. 2014	mIU/mL	calculated from T measured by Immunoassay (Siemens Immulite)	83	43	40	>2.20 mIU/mL	39	22	18	4	90.7	44.7	0.65 (0.52-0.78)	NR
Villarroel et al. 2015	NA	calculated from T measured by radioimmunoassay (RIA)	89	26	63	>6.1	15	4	59	11	57.7	93.7	0.832	p <0.0001
Rudnicka et al. 2016	nmol/L	calculated from T measured by Immunoassay (Abbott Architect)	205	165	40	2.56 nmol/L	136	9	31	29	82.14	77.57	0.821 (0.752-0.889)	NR
Sathyapalan et al. 2017	NA	calculated from T measured by LC-MS/MS	175	110	65	4	NR	NR	NR	NR	NR	NR	0.780 (0.723, 0.858)	NR
Khashchenko et al. 2020	NA	calculated from T measured by Immunoassay (Roche or Siemens)	160	130	30	>2.75	98	2	28	32	75	93	0.871	NR

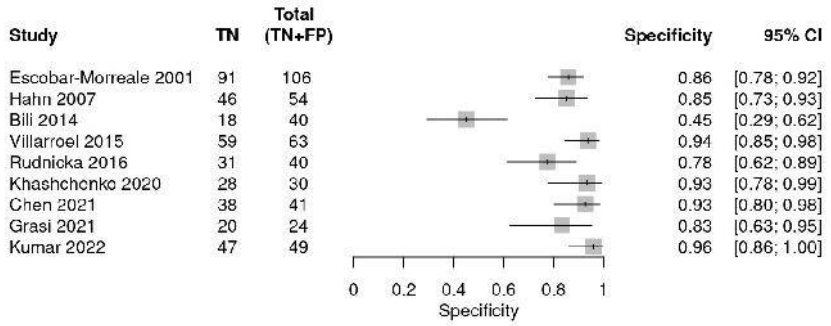
Chen et al. 2021	NA	calculated from T measured by LC-MS/MS	143	102	41	2.5	89	3	38	13	87.0 (78.8, 92.9)	92.68 (80.1, 98.4)	0.937	p <0.001
Grassi et al. 2021	NA	calculated from T measured by LC-MS/MS	117	93	24	1.67	84	4	20	9	90	83	0.951	NR
Kumar et al. 2022	NA	calculated from T measured by Immunoassay (Abbott Architect)	186	137	49	1.9	97	2	47	40	71	95.74	NR	NR

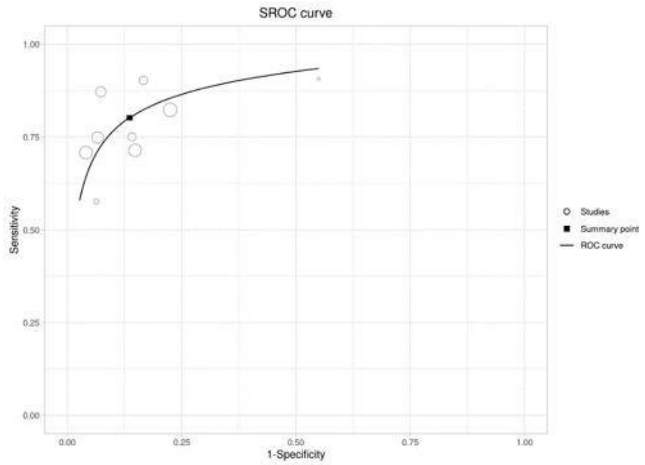
6.4.2. Summary statistics for FAI (overall – bivariate model):

FAI	
Sensitivity Estimate (95% CI)	**0.802 (0.729; 0.860)**
Specificity Estimate (95% CI)	**0.864 (0.767; 0.924)**
Studies (n)	**9**
PCOS (n)	**838**
non-PCOS (n)	**447**
Total (n)	**1285**
Prevalence	**0.65**

6.4.3. Forest Plots and SROC curves for FAI (overall – bivariate model):





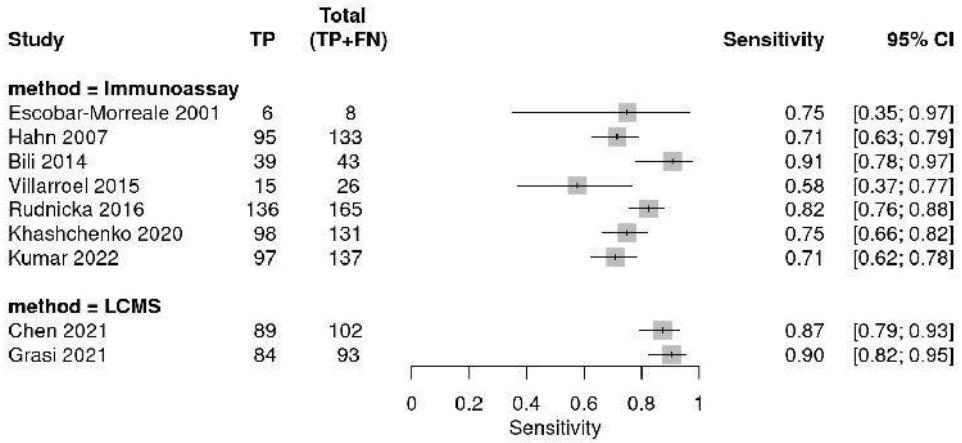


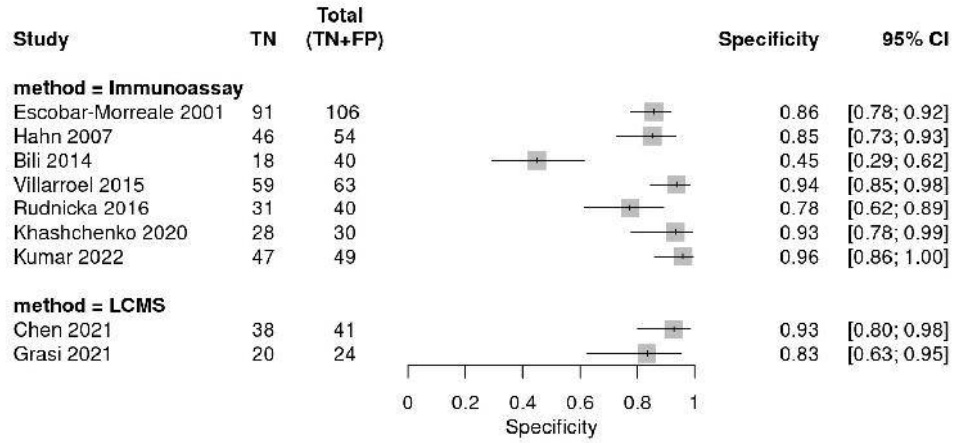
6.4.4. Summary statistics for FAI (subgroup analysis):

FAI by Immunoassays (subgroup analysis including 7 studies)	
Sensitivity Estimate (95% CI)	**0.766 (0.700; 0.821)**
Specificity Estimate (95% CI)	**0.856 (0.745; 0.924)**

FAI by LC-MS/MS (subgroup analysis including 2 studies)	
Sensitivity Estimate (95% CI)	**0.890 (0.804; 0.941)**
Specificity Estimate (95% CI)	**0.894 (0.670; 0.972)**

6.4.5. Forest Plots and SROC curve* for FAI according to the method for total T (subgroup analysis):





** A SROC curve for the subgroup analysis could not be computed as the LCMS category has fewer than 3 studies.*

6.5. Index Test: Free Testosterone (calculated)

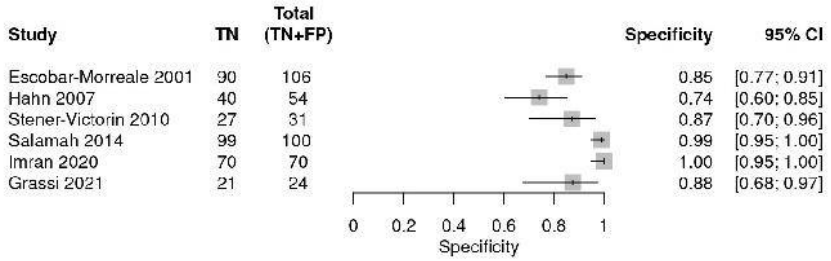
6.5.1. Individual Study Data Table

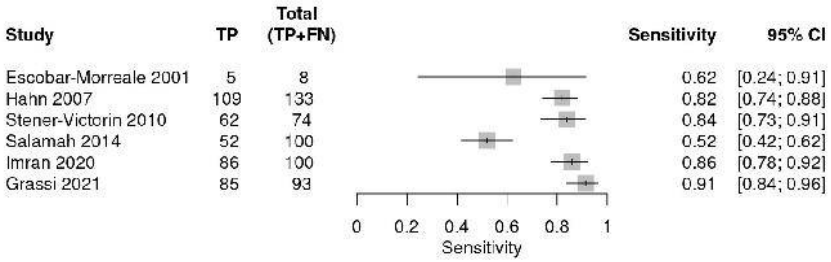
INDEX TEST: Free Testosterone	OUTCOME TYPE: Continuous													
COMPARISON (if applicable): non-PCOS														
Author, year	Unit of outcome	Method of measurement	N	PCOS	non-PCOS	Threshold cut-off	True Pos	False Pos	True Neg	False Neg	Sensitivity (95% CI)	Specificity (95%CI)	AUC	Precision
Escobar-Morreale et al. 2001	pmol/L	calculated from T measured by Immunoassay (Siemens Immulite)	114	8	106	>23 pmol/L	5	16	90	3	0.625	0.849	0.830±0.091 (0.748±0.894)	NR
Hahn et al. 2007	pmol/L	calculated from T measured by Immunoassay (Siemens Immulite)	187	133	54	25.06 pmol/L	109	14	40	24	82	74.1	0.837 (0.776-0.887)	NR
Stener-Victorin 2010	pg/mL	calculated from T measured by GC-MS	105	74	31	>3.3 pg/mL	62	4	27	12	84	87	0.91 (0.86-0.97)	NR
Salamah 2014	pg/mL	calculated from T measured by LC-MS/MS	200	100	100	5 pg/mL	52	1	99	48	52	99	0.870 (0.816-0.924)	NR
Imran et al. 2020	ng/dL	calculated from T measured by Immunoassay (Roche)	200	130	70	NR	86	0	70	14	1.00 (0.96-1.00)	0.83 (0.74-0.91)	NR	NR
Grassi et al. 2021	ng/mL	calculated from T measured by LC-MS/MS	117	93	24	0.34 ng/dL	85	3	21	8	91	89	0.954	NR

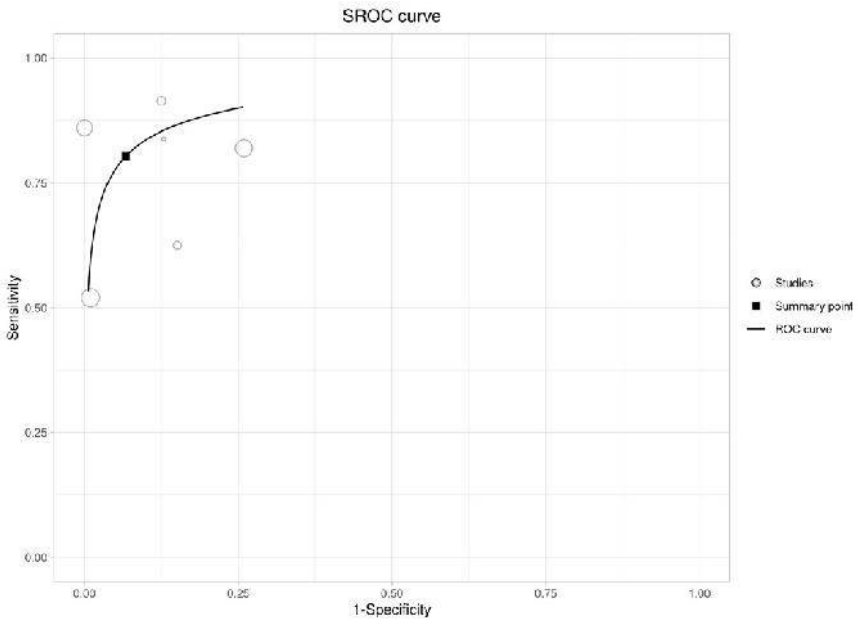
6.5.2 Summary statistics for calculated free T (overall – bivariate model):

Calculated free T	
Sensitivity Estimate (95% CI)	**0.803 (0.684; 0.885)**
Specificity Estimate (95% CI)	**0.933 (0.799; 0.980)**
Studies (n)	**6**
PCOS (n)	**508**
non-PCOS (n)	**385**
Total (n)	**893**
Prevalence	**0.57**

6.5.3. Forest Plots and SROC curves for calculated free T (overall – bivariate model)





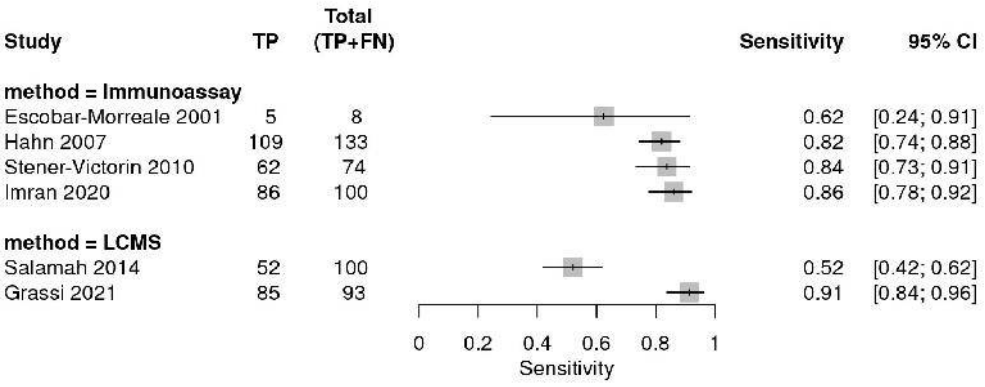


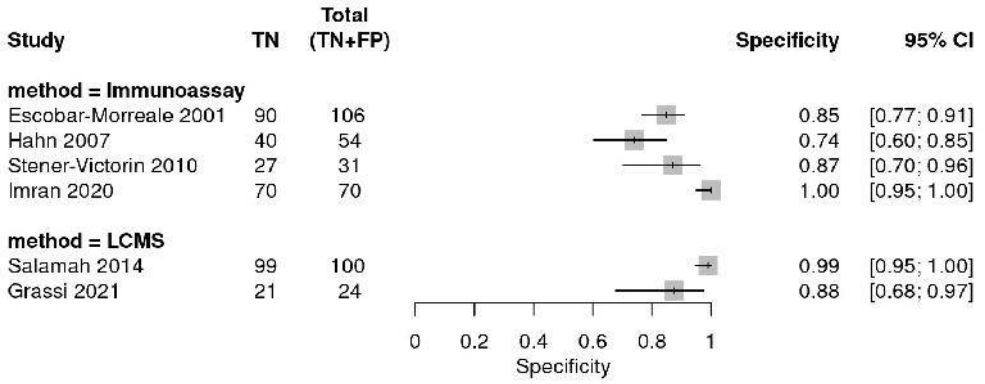
6.5.4. Summary statistics for calculated free T (subgroup analysis):

Calculated free T by total T Immunoassays (subgroup analysis including 4 studies)	
Sensitivity Estimate (95% CI)	**0.823 (0.684; 0.909)**
Specificity Estimate (95% CI)	**0.905 (0.712; 0.973)**

Calculated free T by total T LC-MS/MS (subgroup analysis including 2 studies)	
Sensitivity Estimate (95% CI)	**0.761 (0.537; 0.897)**
Specificity Estimate (95% CI)	**0.967 (0.791; 0.996)**

6.5.5. Forest Plots and SROC curve* for calculated free T according to the method for total T (subgroup analysis):





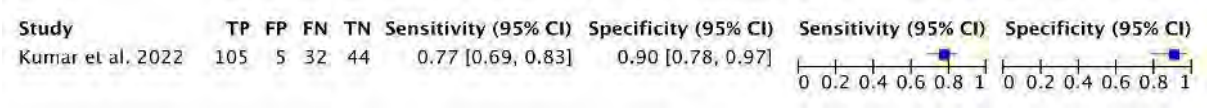
** A SROC curve for the subgroup analysis could not be computed as the LCMS category has fewer than 3 studies.*

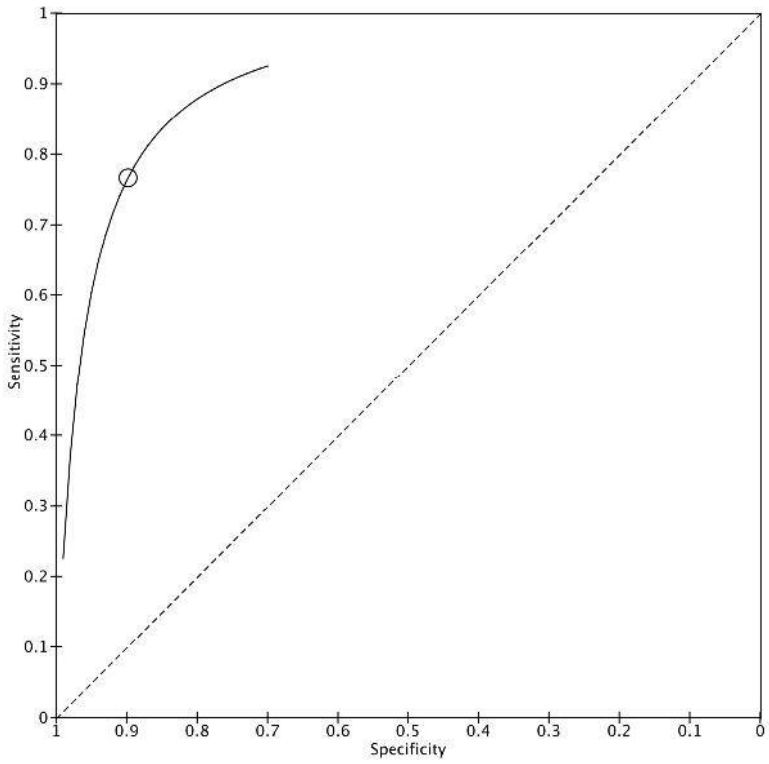
6.6. Index Test: DHT

6.6.1. Individual Study Data Table

INDEX TEST: DHT	**OUTCOME TYPE:** Continuous													
COMPARISON (if applicable): Non-PCOS														
Author, year	**Unit of outcome**	**Method of measurement**	**N**	**PCOS**	**non-PCOS**	**Threshold cut-off**	**True Pos**	**False Pos**	**True Neg**	**False Neg**	**Sensitivity (95% CI)**	**Specificity (95%CI)**	**AUC**	**Precision**
Kumar et al. 2022	pg/mL	ELISA	186	137	49	382 pg/mL	105	5	44	32	77	89	NR	NR

6.6.2. Forest Plot and SROC curve for DHT*:





**Due to the limited number of studies, a meta-analysis of diagnostic test accuracy studies was not performed*

6.7. Index Test: SHBG

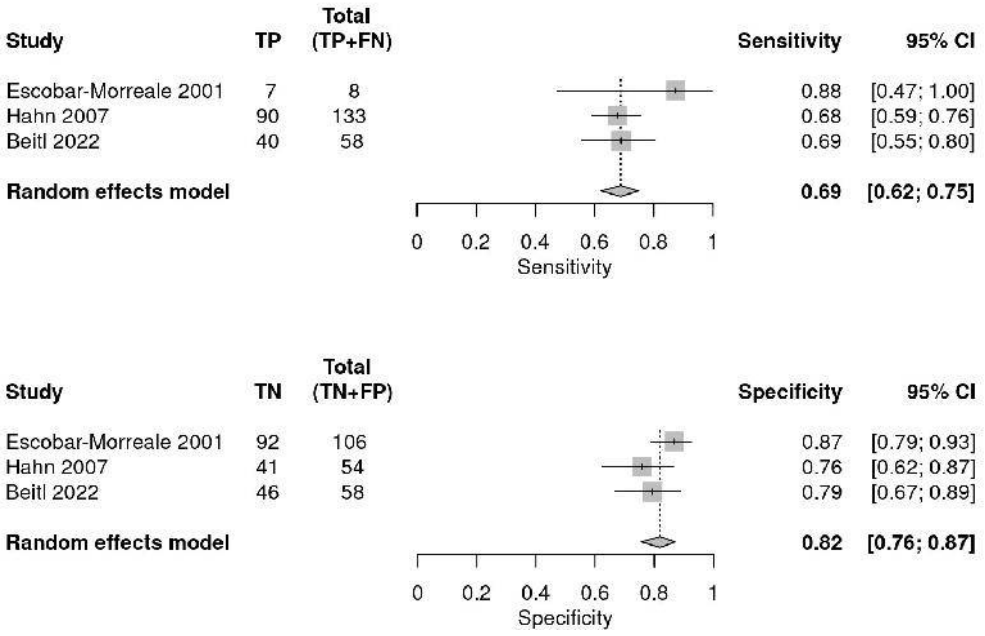
6.7.1. Individual Study Data Table

INDEX TEST: SHBG	OUTCOME TYPE: Continuous													
COMPARISON (if applicable): non-PCOS														
Author, year	Unit of outcome	Method of measurement	N	PCOS	non-PCOS	Threshold cut-off	True Pos	False Pos	True Neg	False Neg	Sensitivity (95% CI)	Specificity (95%CI)	AUC	Precision
Koskinen et al. 1996	microg/dL	Radioimmunoassay (RIA)	83	54	29	NR	NR	NR	NR	NR	NR	NR	0.540 ± 0.063	NR
Escobar-Morreale et al. 2001	nmol/l	Immunoassay (Siemens Immulite)	114	8	106	<37 nmol/l	7	14	92	1	0.875	0.868	0.875±0.045 (0.800±0.929)	NR
Hahn et al. 2007	nmol/L	Immunoassay (Siemens Immulite)	187	133	54	47.4 nmol/L	90	13	41	43	67.7	75.9	0.765 (0.697-0.824)	NR
Beitl et al. 2022	nmol/L	Immunoassay (Roche)	116	58	58	>61.4 nmol/L	40	12	46	18	68.97 (55.46, 80.46)	79.31 (66.65, 88.83)	0.761	p <0.001

6.7.2. Summary statistics for SHBG (univariate model*):

	SHBG
Sensitivity Estimate (95% CI)	**0.688 (0.621; 0.749)**
Specificity Estimate (95% CI)	**0.820 (0.755; 0.870)**
Studies (n)	**3**
PCOS (n)	**199**
non-PCOS (n)	**218**
Total (n)	**417**
Prevalence	**0.48**

6.7.3. Forest Plots* for SHBG:



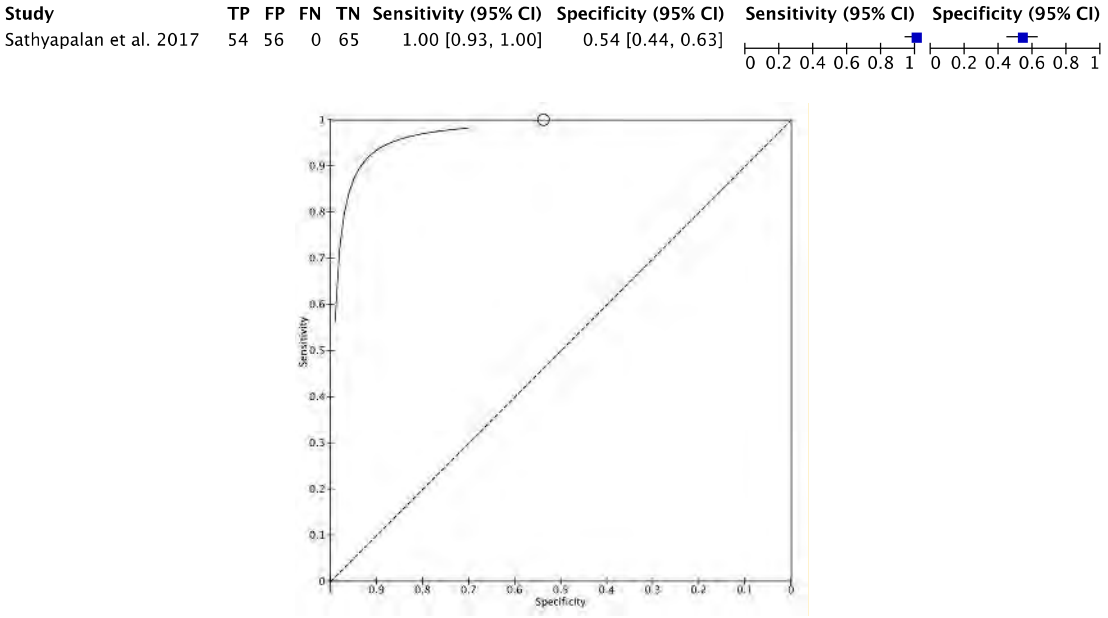
**Due to the limited number of studies, a bivariate model could not be generated*

6.8. Index Test: Salivary Testosterone

6.8.1. Individual Study Data Table Salivary Testosterone

INDEX TEST: Salivary Testosterone			OUTCOME TYPE: Continuous											
COMPARISON (if applicable): non-PCOS														
Author, year	Unit of outcome	Method of measurement	N	PCOS	Non-PCOS	Threshold cut-off	True Pos	False Pos	True Neg	False Neg	Sensitivity (95% CI)	Specificity (95%CI)	AUC	Precision
Sathyapalan et al. 2017	nmol/L	LC-MS/MS	175	110	65	19.9 pmol/L	54	0	65	56	1.00 (0.93, 1.00)	0.54 (0.44, 0.63)	0.757 (0.682, 0.832)	NR

6.8.2. Forest Plot and SROC curve for Salivary Testosterone*:



**Due to the limited number of studies, a meta-analysis of diagnostic test accuracy studies was not performed*

SUMMARY FOR GRADE (based on MAGIC suggestions for a cohort study and critical methodological factors for diagnostic studies)

Comparison: PCOS versus non-PCOS controls												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	PCOS	Non-PCOS	Outcome	Effect estimates (95% CI)	Certainty	Importance
Index test: Total testosterone												
11	observational	Very serious[1]	no serious inconsistency	Not serious	no serious imprecision	None	1026	589	Sensitivity Specificity	0.723 (0.602, 0.818) 0.871 (0,750; 0.939)	⊕◯◯◯ VERY LOW	CRITICAL
Index test: Androstenedione												
5	observational	Very serious[1]	no serious inconsistency	Not serious	no serious imprecision	None	641	197	Sensitivity Specificity	0.695 (0.491; 0.844) 0.744 (0.566; 0.866)	⊕◯◯◯ VERY LOW	CRITICAL
Index test: DHEA-S												
5	observational	Very serious[1]	Serious[2]	Not serious	no serious imprecision	None	480	320	Sensitivity Specificity	0.717 (0.508; 0.862) 0.780 (0.284; 0.953)	⊕◯◯◯ VERY LOW	CRITICAL
Index test: FAI												
9	observational	Very serious[1]	no serious inconsistency	Not serious	no serious imprecision	None	838	447	Sensitivity Specificity	0.802 (0.729; 0.860) 0.64 (0.767; 0.924)	⊕◯◯◯ VERY LOW	CRITICAL
Index test: Free testosterone												
6	observational	Very serious[1]	Serious[2]	Not serious	no serious imprecision	None	508	385	Sensitivity Specificity	0.803 (0.684; 0.885) 0.933 (0.799; 0.980)	⊕◯◯◯ VERY LOW	Critical
Index test: DHT												
1	observational	serious[1]	not applicable	Not serious	Very serious[3]	None	137	49	Sensitivity Specificity AUC	0.770 0.890 0.895 (0.843, 0.947)	⊕◯◯◯ VERY LOW	Critical
Index test: SHBG												
3	observational	serious[1]	no serious inconsistency	Not serious	no serious imprecision	None	199	218	Sensitivity Specificity	0.688 (0.621; 0.749) 0.820 (0.755; 0.870)	⊕◯◯◯ VERY LOW	Critical
Index test: Salivary testosterone												
1	observational	Very serious[1]	not applicable	Not serious	Very serious[3]	None	110	65	Sensitivity Specificity AUC	1.00 (0.93, 1.00) 0.54 (0.44, 0.63) 0.757 (0.682, 0.832)	⊕◯◯◯ VERY LOW	Critical

[1] Downgraded two levels as all studies are of moderate to high risk of bias
[2] Downgraded one level as results from some studies were inconsistent
[3] Downgraded two levels as only one study is available

APPENDIX. QUALITY APPRAISAL SUMMARY TABLE

Study ID	Inclusion and exclusion criteria reported?	Does the study have a clearly focused question?	Was the spectrum of patients representative of the patients who will receive the test in practice?	Was a consecutive or random sample of patients enrolled?	Was a case-control design avoided?	Did the study avoid inappropriate exclusions?	Were all participants assessed with both index test and reference standard?	Did all patients receive the same reference standard? (Q-2)	Is the reference standard likely to correctly classify the target condition? (Q-2)	Was the reference standard independent of the index test (ie. the index test did not form part of the reference standard)?	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	If a threshold was used, was it pre-specified?	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?	Were withdrawals from the study explained?	Were uninterruptable/ intermediate test results reported?	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Were there any conflicts of interest in the writing or funding of this study?	If statistical analysis was undertaken, was this appropriate?	Risk of Bias	Did the risk differ by outcome?
Bansal et al. 2020	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	No	NR	NR	Yes	Yes	NR	Yes	Yes	NR	NR	No	Partial	Mod	No
Beitl et al. 2022	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	NR	NR	Yes	Yes	NR	Yes	Yes	NR	NR	No	Partial	Mod	No
Chen et al. 2021	Yes	Yes	No	NR	No	No	Yes	Yes	Yes	No	NR	NR	Yes	Yes	NR	Yes	Yes	NR	NR	No	Partial	High	No
Diamandis et al. 2017	Yes	Yes	No	NR	No	No	Yes	Yes	Yes	No	NR	NR	Yes	Yes	NR	Yes	Yes	NR	NR	No	No	High	No
Grassi et al. 2021	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	No	NR	NR	Yes	Yes	Yes	Yes	Yes	NR	NR	No	Partial	Mod	No
Khashchenko et al. 2020	Yes	Yes	No	NR	No	No	Yes	Yes	Yes	No	NR	NR	Yes	Yes	NR	Yes	Yes	NR	NR	No	No	High	No
Kumar et al. 2022	Yes	Yes	No	NR	No	No	Yes	Yes	Yes	No	NR	NR	Yes	Yes	NR	Yes	Yes	NR	NR	No	Partial	High	No
Sathyapalan et al. 2017	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	No	NR	NR	Yes	Yes	NR	Yes	Yes	NR	NR	No	No	High	No
Imran et al. 2020	Yes	Yes	No	NR	No	No	Yes	Yes	Yes	No	NR	NR	Yes	Yes	NR	Yes	Yes	NR	NR	No	Partial	High	No

Bill 2014	Yes	Yes	No	NR	No	NR	NR	NR	Yes	No	NR	NR	NR	Yes	Yes	Yes	NR	NR	NR	Yes	Partial	High	No
Hahn 2007	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	NR	NR	Yes	Yes	NR	Yes	Yes	NR	Yes	NR	Yes	Mod	No
Escobar-Morreale 2001	Partial	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	No	NR	NR	Yes	Yes	NR	Yes	No	Yes	Yes	NR	Yes	Mod	No
Koskinen 1996	Partial	Yes	No	No	Yes	NR	Yes	Yes	Yes	No	NR	NR	Yes	Yes	NR	Yes	Yes	NR	Yes	NR	Partial	High	No
Rudnicka 2016	Yes	Yes	Partial	No	No	NR	NR	NR	Yes	No	NR	NR	NR	NR	Yes	Yes	Yes	NR	NR	NR	Partial	High	No
Villarroel 2015	Partial	Yes	No	NR	No	No	NR	NR	Yes	No	NR	NR	NR	NR	Yes	Yes	Yes	NR	NR	No	Partial	High	No
Stener-Victorin 2010	Partial	Yes	No	NR	Yes	No	Yes	Yes	Yes	No	NR	NR	Yes	Yes	NR	Yes	Yes	Yes	Yes	No	Yes	High	No

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 1

Question 1.2.

In women with suspected PCOS, what is the most effective measure to diagnose PCOS related hyperandrogenism (biochemical)?

BACKGROUND:
Hyperandrogenism is a well-established contributor to PCOS aetiology, detectable in around 60–100% of cases, depending on methods and criteria used, yet it is challenging to diagnose. It includes both biochemical hyperandrogenism and clinical signs of excess androgen activity (notably hirsutism, acne, and female pattern hair loss; see 1.3).

When determining biochemical hyperandrogenism, accurate diagnosis is hampered by a lack of ideal methods for measurement of the active androgen testosterone as most routine testosterone assays are designed for use in males, with accuracy and precision being much less for the lower androgen concentrations observed in women. The reference standard for the measurement of total testosterone is liquid chromatography-tandem mass spectrometry (1, 2). However, the widespread use of tandem mass spectrometry is currently still hampered by the technical demands and costs of the method as compared to immunoassays and, consequently, high variability in accessibility across different countries.

However, it is important to realise that most testosterone immunoassays, when used with a female matrix, have a concentration-dependent bias, getting results higher than the true value at low concentrations. Using immunoassays for the measurement of lower (=female) total testosterone concentrations results in decreased accuracy (= closeness to the true value, reflecting bias) and increased imprecision (= closeness of measurement results to each other, reflecting variability). In addition, immunoassays are subject to interference by structurally similar compounds, e.g. norethisterone contained in many oral contraceptives, which can significantly distort results.

Accuracy and precision of tandem mass spectrometry measurement of testosterone can be further enhanced by using testosterone standards labelled with carbon 13 rather than with deuterium 2 or 5 as the former have more consistent retention times and fewer matrix effects (3).

Free testosterone represents the proportion of testosterone molecules not bound to sex-hormone binding globulin (SHBG) and, therefore, able to bind and activate the androgen receptor and exert biological androgen action. The reference standard for the measurement of free testosterone is equilibrium dialysis, which is, however, a technically highly demanding method much less widely available than tandem mass spectrometry.
Alternatively, free, bioavailable testosterone concentrations can be estimated using the results of total testosterone measurement in conjunction with SHBG and albumin, employing various different formulas, most commonly the formula of Vermeulen et al. is used (Vermeulen, Verdonck et al. 1999). Similarly, the free androgen index (FAI = 100 x [total testosterone/SHBG]) is also a widely used measure of testosterone concentration and bioavailability. The accuracy of the calculated results for free testosterone and the free androgen index will depend on whether the total testosterone concentrations used for calculation was measured by tandem mass spectrometry or by immunoassay. However, beyond testosterone measurements, the accuracy of the FAI is severely hampered if SHBG concentrations are less than 30 nmol/L (4), which is often the case in women with PCOS, consequent to both androgen excess and insulin resistance. In that study, FAI and free testosterone calculated using total testosterone measured by reference standard LC-MS/MS were compared to free testosterone directly measured by reference standard equilibrium dialysis.

In the classic androgen biosynthesis pathway, the adrenal androgen precursor DHEA is converted to androstenedione, which in turn can be converted to testosterone, which binds and activates the androgen receptor and, therefore, exerts androgenic biological effects. Testosterone can be activated to the most potent androgen, 5□-dihydrotestosterone (DHT), which, however, circulates in even lower concentrations than testosterone and, therefore, can only be accurately quantified by LC-MS/MS. By contrast, the androgen precursors

androstenedione and DHEA are circulating in much higher nanomolar concentrations and the sulfate ester of DHEA, DHEAS, even in micromolar concentrations, which makes them much easier to quantify.

Previous studies have indicated that women with PCOS and serum testosterone concentrations within the female reference range often have increased serum androstenedione concentrations and hence biochemical evidence of androgen excess (5); detection of biochemical hyperandrogenism increases from 64 to 88% (14) and 80 to 89.5% (6), respectively, when adding androstenedione to testosterone for the assessment of androgen excess. Similarly, DHEA and DHEAS are increased in about 20-25% of women with PCOS (7). Furthermore, the advance of tandem mass spectrometry has led to the development of validated multi-steroid assays that cover all these androgenic steroids in one run (8, 9).

There is only a single study (10) that addresses the utility of serum DHEAS (measured by immunoassay) and androstenedione and testosterone (both measured by LC-MS/MS) in the differential diagnosis of PCOS. In this study, androgen profiling was requested based on clinical presentation in 1205 women, in 378 (303 premenopausal, 75 postmenopausal) at least one of the three steroids was increased above the reference range. The by far most prevalent underlying diagnosis was PCOS (270 premenopausal, 22 postmenopausal), other much rarer diagnoses included congenital adrenal hyperplasia (CAH), adrenocortical carcinomas (ACC) and adenomas, Cushing's disease, and, in postmenopausal women, also ovarian hyperthecosis (OHT) and ovarian tumours. Serum DHEAS >20 □mol/L was found in 17 women (4.5%; 8 PCOS, 9 ACC). Serum androstenedione >15 nmol/L was found in 21 women (5.6%; 3 PCOS, 10 CAH, 8 ACC). Serum testosterone >5 nmol/L was found in 24 women (6.4%; 6 PCOS, 6 CAH, 8 ACC, 4 OHT). In this study only 1.0-2.7% of women with PCOS had serum androgen concentrations in the concerning range. This limited evidence suggests that assessing all three androgens supports differential diagnosis but is specific enough to avoid unnecessary further evaluation in women with PCOS.

Another important consideration is the recently characterised 11-oxygenated androgen biosynthesis pathways. It is known for decades that androstenedione can be converted to 11-hydroxyandrostenedione (11OHA4) in the adrenal, which was considered a clinically irrelevant, dead-end metabolite. However, recent work has shown that 11OHA4 can be converted to the active androgen 11-ketotestosterone (11KT) (11, 12). Importantly, 11KT has been shown to bind and activate the androgen receptor with similar potency to testosterone (13, 14). In women, 11KT concentrations are similar if not higher than circulating testosterone and, importantly, while testosterone declines with age, 11KT concentrations remain unchanged (15-17), which makes 11KT the most significant androgen in women of postmenopausal age. 11-oxygenated androgens are more prevalent than classic androgens in women with PCOS (18). Therefore, they are likely to hold promise for diagnostic detection of biochemical hyperandrogenism in women with PCOS and multi-steroid profiling LC-MS/MS assays for their measurement have been developed (19, 20).
Given the above-described controversies, methodological challenges and variety of different options for the biochemical measurement of androgens and uncertainty in clinical practice, it is important to determine which measure is the most appropriate, which led to the prioritisation of this question for evidence synthesis.

It is important to state upfront that, in addition to multiple methodological shortcomings detailed below, none of the studies we included in the evidence summary has measured 11-oxygenated androgens and, therefore, an update of the evidence will be required sooner rather than later. Similarly, only the minority of included studies has used reference standard LC-MS/MS and none of the studies has validated a pre-specified cut-off for detection of

biochemical hyperandrogenism that was derived from a preceding proof-of-principle study in a general population.

Summary of evidence

Included studies

Eight studies were identified by our update search covering the period from August 2017 to July 2022. These were combined with the previously identified eight studies from the last guideline search.

Methodological quality/risk of bias

Due to the nature of the question of this review it is important that participants are entered into the study based on explicit selection criteria; from the same population and that entrance to the study is either random or consecutive. It is also important that studies are adequately powered to detect the specified outcome and that they include an independent, blinded comparison with a valid reference standard. These methodological issues are likely to have an impact on the direction of bias and reliability of the findings.

Findings of studies of moderate or high risk of bias should be interpreted with caution. Five of the 17 included studies were found to have a moderate risk of bias (6, 21-24); the eleven remaining studies were found to have a high risk of bias. Reasons include: selection criteria were not explicitly stated; it is unclear whether participants were entered into the study appropriately (random or consecutive); case-control design; and inadequacies around application of index and reference tests. In addition, most included studies had cohorts of limited size (median 93, range 8-165) and all were single centre studies, which increases the likelihood of bias further.

It is important to state that only three out of 16 studies did not study which measure could be used most effectively to detect biochemical hyperandrogenism in PCOS, but they assessed the effectiveness of androgen measurements in diagnosing PCOS, which is different to the precise question we asked. Therefore, the results of these studies are very likely to overestimate performance. The few studies addressing the precise question asked had various other methodological shortcomings and their low number prevented us from carrying out a sensitivity analysis. These studies include Imran et al. 2020 (25) and Kumar et al. 2022 (26) reporting on serum total testosterone and Sathyapalan et al. 2017 (27) reporting on salivary testosterone.

We also evaluated the quality of studies from a clinical biochemistry point of view (Table 5.3, Part 1 Q1.2), which raised further concerns, with even some of the mass spectrometry-based studies not providing enough methodological description to create confidence in the accuracy of quantifications.

Of further concern is that the overwhelming majority if not all studies included compared PCOS versus controls to differentiate the two groups but did not validate a previously defined cut-off from a preceding proof-of-principle study. This renders all evidence very preliminary.

Consistency of studies

Fourteen of the sixteen studies compared the diagnostic accuracy of different reproductive markers including the androgenic target analytes to detect PCOS while only two studies out

of 16 precisely addressed the question, as they looked at the diagnostic accuracy of the measurement of androgens in detecting biochemical hyperandrogenism in women with PCOS.

The included studies were very heterogenous and used a broad spectrum of biochemical assays to measure total testosterone (T), androstenedione (A4), DHEAS, and sex-hormone binding globulin (SHBG) and employed these measurements to calculate free androgen index (FAI) and free testosterone (Free T). However, none of the studies compared two different assays directly to each other and only very few studies looked at multiple androgen parameters and reported sensitivities and specificities for several of the measured parameters.

Generalisability

Where reported, the studies were consistent in terms of age and BMI and are generalisable to the target population for this evidence review. The tests that were addressed in the studies are routinely used and available in most settings.

Studies were single centre studies and conducted in outpatient clinics of secondary and tertiary care hospitals in Chile, China, Finland, Germany, Greece, India, Poland, Spain, Sweden, and the UK.

Findings

Data are presented in forest plots and summary ROC analyses wherever thresholds/cut off values were similar. Where thresholds/cut off values are different, only summary ROC analyses have been presented. Only studies with sensitivity and specificity data are able to be analysed and presented in these formats, using RevMan. It allows imputation to derive true positives (TP), false positives (FP), true negatives (TN) and false negatives (FN) to provide greater detail about the accuracy of the index test.

As the number of included studies has now risen from 8 to 16, we also conducted limited meta-analyses for pooled sensitivity and specificity estimates, which, however, should be interpreted with caution due to heterogeneity of the included studies.

We performed a subgroup analysis of studies using reference standard liquid chromatography - tandem mass spectrometry (LC-MS/MS) and studies using immunoassays, which generally have lower accuracy and higher imprecision than mass spectrometry-based assays; in addition, immunoassays are also subject to interference by other compounds. Thus, unsurprisingly, sub-group analyses indicated a slightly better performance of LC-MS/MS; however, not a single study directly compared immunoassay to LC-MS/MS.

In summary, there is insufficient evidence for the diagnostic accuracy of any of the index tests reported in the included studies. Certainty for all measured analytes was very low and the risk of bias was assessed as serious or very serious in all included studies (see Appendix – Quality Appraisal).

GRADE EVIDENCE CERTAINTY	
Comparison	GRADE for critical outcomes
o Serum total testosterone in women with PCOS versus non-PCOS Controls	⨁◯◯◯ VERY LOW
o Serum androstenedione in women with PCOS versus non-PCOS Controls	⨁◯◯◯ VERY LOW
o Serum DHEAS in women with PCOS versus non-PCOS Controls	⨁◯◯◯ VERY LOW
o Serum SHBG in women with PCOS versus non-PCOS Controls	⨁◯◯◯ VERY LOW
o Serum calculated free androgen index in women with PCOS versus non-PCOS Controls	⨁◯◯◯ VERY LOW
o Serum calculated free testosterone in women with PCOS versus non-PCOS Controls	⨁◯◯◯ VERY LOW
o Salivary testosterone in women with PCOS versus non-PCOS Controls	⨁◯◯◯ VERY LOW

Recommendations

EVIDENCE-BASED RECOMMENDATION
Healthcare professionals should use total and free testosterone to assess biochemical hyperandrogenism in the diagnosis of PCOS; free testosterone can be estimated by the calculated free androgen index.
EVIDENCE-BASED RECOMMENDATION
If testosterone or free testosterone is not elevated, health professionals could consider measuring androstenedione and dehydroepiandrosterone sulfate (DHEAS), noting their poorer specificity and the greater age associated decrease in DHEAS.
EVIDENCE-BASED RECOMMENDATION
Laboratories should use validated and highly accurate tandem mass spectrometry (LC-MS/MS) assays for measuring total testosterone, and if needed, for androstenedione, and DHEAS. Free testosterone should be assessed by calculation, equilibrium dialysis, or ammonium sulfate precipitation.
EVIDENCE-BASED RECOMMENDATION
Laboratories should only conditionally use direct immunoassays (e.g. radiometric, enzyme-linked, etc.) for assessing total or free testosterone as they have limited accuracy and demonstrate poor sensitivity and precision for diagnosing hyperandrogenism in PCOS.
PRACTICE POINT
For the detection of hyperandrogenism in PCOS, the assessment of biochemical hyperandrogenism is of greatest value in patients with minimal or no clinical signs of hyperandrogenism (i.e., hirsutism).
PRACTICE POINT
Biochemical hyperandrogenism assessment is unreliable in women on the combined oral contraceptive pill (COCP) as the pill increases sex hormone-binding globulin and reduces gonadotrophin-dependent androgen production. If already on the COCP, and assessment of biochemical androgens is imperative, the pill should be withdrawn for a minimum of three months and contraception managed otherwise during this time.
PRACTICE POINT
Repeated androgen measures for the ongoing assessment of PCOS in adults have a limited role.
PRACTICE POINT
In most adolescents, androgen levels reach adult ranges at the age of 12-15 years.
PRACTICE POINT
If androgen levels are markedly above laboratory reference ranges, causes of hyperandrogenemia other than PCOS, including ovarian and adrenal neoplastic growths, congenital adrenal hyperplasia, Cushing’s syndrome, ovarian hyperthecosis (in postmenopausal women), iatrogenic causes, and syndromes of severe insulin resistance, should be considered. However, some androgen-secreting neoplasms are associated with only mild to moderate increases in androgen levels. The clinical history of time of onset and/or rapid progression of symptoms is critical in assessing for an androgen-secreting tumour.
PRACTICE POINT

Reference ranges for different methods and laboratories vary widely, and are often based on an arbitrary percentile or variances of the mean from a population that has not been fully characterised and is highly likely to include women with PCOS. Normal values should be determined either by the range of values in a well characterised healthy control population or by cluster analysis of general population values.

PRACTICE POINT

Laboratories involved in androgen measurements in women should consider:

- Determining laboratory normal values by either the range of values in a well characterised healthy control population or by cluster analysis of the values of a large general population.
- Applying the most accurate methods where available
- Using extraction/chromatography immunoassays as an alternative to mass spectrometry only where adequate expertise is available.
- Future improvements may arise from measurement of 11-oxygenated androgens, and from establishing cut off levels or thresholds based on large-scale validation in populations of different ages and ethnicities.
-

Evidence to Recommendations Framework

COMPARISONS (option versus other option)

Women with PCOS versus Non-PCOS Controls

EVIDENCE-BASED RECOMMENDATION(S)

Healthcare professionals should use total and free testosterone to assess biochemical hyperandrogenism in the diagnosis of PCOS; free testosterone can be estimated by the calculated free androgen index

GRADE Direction and Strength of Recommendation:

☒ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

If testosterone or free testosterone is not elevated, health professionals could consider measuring androstenedione and dehydroepiandrosterone sulfate (DHEAS), noting their poorer specificity and the greater age associated decrease in DHEAS.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

Laboratories should use validated and highly accurate tandem mass spectrometry (LC-MS/MS) assays for measuring total testosterone, and if needed, for androstenedione, and DHEAS. Free testosterone should be assessed by calculation, equilibrium dialysis, or ammonium sulfate precipitation.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

Laboratories should only conditionally use direct immunoassays (e.g. radiometric, enzyme-linked, etc.) for assessing total or free testosterone as they have limited accuracy and demonstrate poor sensitivity and precision for diagnosing hyperandrogenism in PCOS.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

PRACTICE POINT(S)

For the detection of hyperandrogenism in PCOS, the assessment of biochemical hyperandrogenism is of greatest value in patients with minimal or no clinical signs of hyperandrogenism (i.e., hirsutism).

Biochemical hyperandrogenism assessment is unreliable in women on the combined oral contraceptive pill (COCP) as the pill increases sex hormone-binding globulin and reduces gonadotrophin-dependent androgen production. If already on the COCP, and assessment of biochemical androgens is imperative, the pill should be withdrawn for a minimum of three months and contraception managed otherwise during this time.

Repeated androgen measures for the ongoing assessment of PCOS in adults have a limited role.

In most adolescents, androgen levels reach adult ranges at the age of 12-15 years.

If androgen levels are markedly above laboratory reference ranges, causes of hyperandrogenemia other than PCOS, including ovarian and adrenal neoplastic growths, congenital adrenal hyperplasia, Cushing's syndrome, ovarian hyperthecosis (in postmenopausal women), iatrogenic causes, and syndromes of severe insulin resistance, should be considered. However, some androgen-secreting neoplasms are associated with only mild to moderate increases in androgen levels. The clinical history of time of onset and/or rapid progression of symptoms is critical in assessing for an androgen-secreting tumour.

Laboratories involved in androgen measurements in women should consider:

- Determining laboratory normal values by either the range of values in a well characterised healthy control population or by cluster analysis of the values of a large general population.
- Applying the most accurate methods where available
- Using extraction/chromatography immunoassays as an alternative to mass spectrometry only where adequate expertise is available.
- Future improvements may arise from measurement of 11-oxygenated androgens, and from establishing cut off levels or thresholds based on large-scale validation in populations of different ages and ethnicities.

GRADE CONSIDERATIONS

Justifications:

The update on the papers published since 2017 has increased the number of papers identified by the search from 8 to 16, but all are single centre studies of limited size and hampered by multiple methodological issues, with only a minority using tandem mass spectrometry, which based on evidence can be considered as the reference standard for quantifications of androgens in the female concentration range, with the exception of DHEAS, which due to its high circulating concentrations can usually be reliably quantified by immunoassays.

Subgroup considerations:

Subgroup considerations are important for measurement of androgens in adolescents and postmenopausal women.

Implementation considerations:

Important considerations are the accessibility of reference standard tandem mass spectrometry assays across a wide geographical spectrum, including considerations of assay costs, which are reduced when large numbers of samples are analysed.

Monitoring and evaluation considerations:

Monitoring may a feasible strategy when evaluating the impact of therapeutic interventions targeting androgen excess but in the current routine care context repeat measurement is not usually required..

Research priorities:

A major priority for further research is the execution of large-scale studies directly comparing DHEAS, A4 and Testosterone measured by reference standard tandem mass spectrometry using a robust design required for diagnostic test accuracy studies, including a predefined cut-off/threshold that is prospectively tested and validated in independent cohorts of women with well phenotyped PCOS and women without clinical evidence of PCOS.

Another major priority is to evaluate the diagnostic value of the active 11-oxygenated androgens (11-ketotestosterone, 11KT; 11-hydroxytestosterone, 11OHT) in detecting biochemical hyperandrogenism in PCOS, comparing it carefully to the diagnostic performance of the androgen precursors DHEAS and androstenedione and the active classic androgens T and DHT.

An important research priority is also the phenotyping of large cohorts of women with PCOS by multi-steroid profiling to comprehensively identify biochemically defined clusters of women and relate results to their clinical presentation.

Further research priorities include the evaluation of the diagnostic value of other biochemical parameters potentially indicative of biological androgen activity, e.g. prostate-specific antigen (PSA) as indicated by a small size, proof of principle study (28).

GRADE framework

GRADE DECIDE **Interactive Evidence to Decision Framework**

- DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

- UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

- CERTAINTY OF THE EVIDENCE

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☒ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

- VALUES

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☐ Important uncertainty or variability	☒ Possibly important uncertainty or variability	☐ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Research evidence:

No research evidence was identified

Panel discussion:

- BALANCE OF EFFECTS

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:

- COSTS

How large are the resource requirements (costs)?

Judgement:

☐ Don't know	☒ Varies	☐ Large costs	☐ Moderate costs	☐ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:

No research evidence was identified

Panel discussion:

- CERTAINTY OF COST EVIDENCE

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

No research evidence was identified

Panel discussion:

- COST-EFFECTIVENESS

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

No research evidence was identified

Panel discussion:

- EQUITY

What would be the impact on health equity?

Judgement:

☐ Don't know	☒ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☐ Probably increased	☐ Increased

Research evidence:

No research evidence was identified

Panel discussion:

- ACCEPTABILITY

Is the option acceptable to key stakeholders?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Key stakeholders likely to find the recommendation acceptable, given the relative importance they attach to the desirable and undesirable consequences of implementing the recommendation; the timing of the benefits, harms and costs; and their values and preferences.

- FEASIBILITY

Is the option feasible to implement?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

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PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by the Evidence Team: Jillian Tay, Aya Mousa
Other Members: Loyal Pattuwage, Yanan Hu, Joanne Enticott

GDG 1

Question 1.3.

In women with suspected PCOS, what is the most effective measure to clinically diagnose PCOS related hyperandrogenism ?

1. STUDY SELECTION

Table 1. PICO Criteria for Inclusion	
Question	**1.3 In women with suspected PCOS, what is the most effective measure to clinically diagnose PCOS related hyperandrogenism?**
Clinical leads (key contacts)	**Ricardo Azziz**
Allocation ranking	**Level 2 - systematic review update**

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(language, year)*
Inclusion	Females with PCOS (diagnosed by Rotterdam, NIH or AES) of any age, ethnicity and weight. Note preference and subgroup for untreated or must have stopped medication for minimum of 3 months.	Methods for assessment of androgens including: • modified Ferriman Gallway Score (mFGS) • Alopecia (See Lizneva 2016) • Acne (See Lizneva 2016) • Adapted/alternative score methods: • FGS • Self-rating • Clinician rating	**No intervention or comparison of the clinical methods or comparison with biochemical assessment of hyperandrogenism.**	**Diagnosed hyperandro genism in women with PCOS. Sensitivity and specificity data; and AUC data.**	**Evidence based guidelines, systematic reviews, RCTs and comparativ e, prospective cohort studies addressing the outcomes are sought.**	**English language. Human studies**
Exclusion	**Females without diagnosed PCOS.**	**No intervention or any intervention other intervention not listed above.**	**The assessment method used for the intervention.**	**None**	**Non- evidence based guidelines or any study lower than a comparativ e, prospective cohort study.**	**None**

2. SEARCH STRATEGY

Search details	
Search strategy source: 2018 PCOS Guideline Technical Report	
Evidence source	**Date of search**
Medline (Ovid)	1/1/2017 until 26/7/2022
PsychInfo (Ovid)	1/1/2017 until 26/7/2022
EMBASE	1/1/2017 until 26/7/2022
All EBM (Ovid)	1/1/2017 until 26/7/2022
CINAHL	1/1/2017 until 26/7/2022
Any subsequent updates - enter database and date: not applicable	

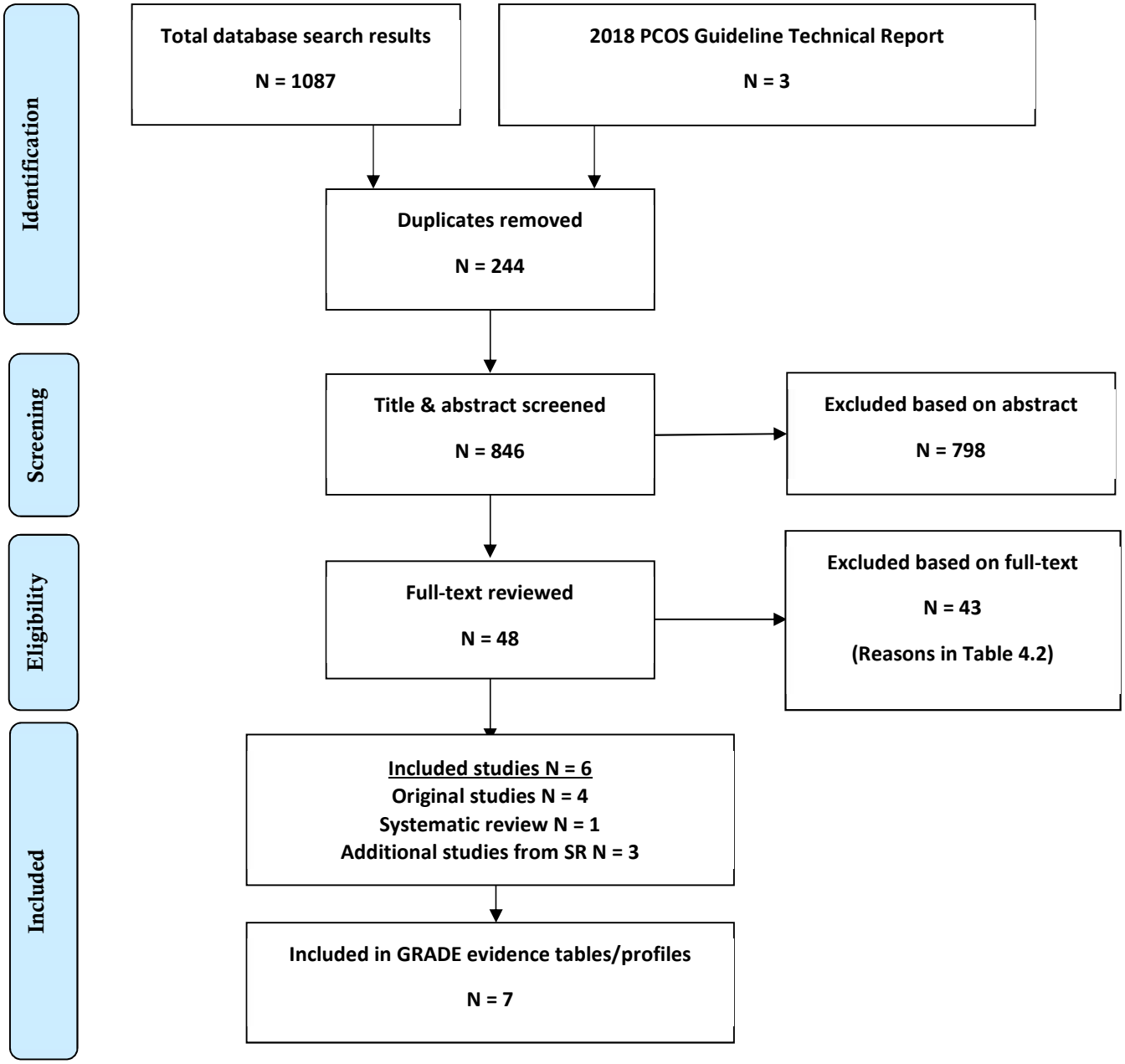
Questions addressed by this search:		
GDG	**Q#**	**Question**
1	1.3	In women with suspected PCOS, what is the most effective measure to clinically diagnose PCOS related hyperandrogenism?

OVID Medline	Embase Classis + Embase
1 exp polycystic ovary syndrome/ 2 polycystic ovar*.mp. 3 PCO*.mp. 4 poly-cystic ovar*.mp. 5 (stein-leventhal or leventhal).mp. 6 anovulation/ 7 anovulat*.mp. 8 oligo-ovulat*.mp. 9 oligoovulat*.mp. 10 (ovar* adj5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyperandrogen*)).mp. 11 or/1-1049819 12 exp Diagnosis/ 13 diagnos$.tw. 14 12 or 13 15 hyperandrogen$.tw. 16 hyper-androgen$.tw. 17 (androgen$ adj5 (excess$ or elevat$)).mp. 18 or/15-17 19 (sensitiv: or predictive value:).mp. or accurac:.tw. 20 11 and 14 and 18 and 19 21 limit 20 to (english language and humans and yr="2017 -Current") 22 10 and 14 and 18 23 limit 22 to (english language and humans and yr="2017 -Current")	1 exp polycystic ovary syndrome/ 2 polycystic ovar*.mp. 3 PCO*.mp. 4 poly-cystic ovar*.mp. 5 (stein-leventhal or leventhal).mp. 6 anovulation/ 7 anovulat*.mp. 8 oligo-ovulat*.mp. 9 oligoovulat*.mp. 10 (ovar* adj5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyperandrogen*)).mp. 11 or/1-10 12 exp Diagnosis/ 13 diagnos$.tw. 14 12 or 13 15 hyperandrogen$.tw. 16 hyper-androgen$.tw. 17 (androgen$ adj5 (excess$ or elevat$)).mp. 18 or/15-17 19 (sensitiv: or predictive value:).mp. or accurac:.tw. 20 11 and 14 and 18 and 19 21 limit 20 to (english language and humans and yr="2017 -Current")
APA PsychInfro	**CINAHL**
1 exp polycystic ovary syndrome/ 2 polycystic ovar*.mp. 3 PCO*.mp. 4 poly-cystic ovar*.mp. 5 (stein-leventhal or leventhal).mp.	S1 MH polycystic ovary syndrome S2 TX polycystic ovar* S3 TX poly-cystic ovar* S4 TX PCO* S5 TX (stein-leventhal or leventhal)

6 anovulation/ 7 anovulat*.mp. 8 oligo-ovulat*.mp. 9 oligoovulat*.mp. 10 (ovar* adj5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyperandrogen*)).mp. 11 or/1-10 12 exp Diagnosis/ 13 diagnos$.tw. 14 12 or 13 15 hyperandrogen$.tw. 16 hyper-androgen$.tw. 17 (androgen$ adj5 (excess$ or elevat$)).mp. 18 or/15-17 19 (sensitiv: or predictive value:).mp. or accurac:.tw. 20 11 and 14 and 18 and 19 21 limit 20 to (english language and humans and yr="2017 -Current") 22 from 21 keep 1-263	S6 MH anovulation S7 TX anovulat* S8 TX oligo-ovulat* S9 TX oligoovulat* S10 TX (ovar* N5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*)) S11 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 S12 MH diagnosis S13 TX diagnos* S14 S12 OR S13 S15 TX hyperandrogen* S16 TX hyper-androgen* S17 TX (androgen* N5 (excess* or elevat*)) S18 S15 OR S16 OR S17 S19 TX ((sensitiv* or predictive value)) OR TX accurac* S20 S11 AND S14 AND S18 AND S19 S21 S11 AND S14 AND S18 S22 S11 AND S14 AND S18 Limiters - Publication Year: 2017-2022; English Language; Human
EBM Reviews	
1 exp polycystic ovary syndrome/ 2 polycystic ovar*.mp. 3 PCO*.mp. 4 poly-cystic ovar*.mp. 5 (stein-leventhal or leventhal).mp. 6 anovulation/ 7 anovulat*.mp. 8 oligo-ovulat*.mp. 9 oligoovulat*.mp. 10 (ovar* adj5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyperandrogen*)).mp. 11 or/1-10 12 exp Diagnosis/ 13 diagnos$.tw. 14 12 or 13 15 hyperandrogen$.tw. 16 hyper-androgen$.tw. 17 (androgen$ adj5 (excess$ or elevat$)).mp. 18 or/15-17 19 (sensitiv: or predictive value:).mp. or accurac:.tw. 20 11 and 14 and 18 and 19 21 limit 20 to (english language and humans and yr="2017 -Current") 22 11 and 14 and 18 23 limit 22 to english language 24 limit 23 to yr="2017 -Current"	

Evidence processing: Studies were selected and appraised by 1 reviewers using study selection and appraisal criteria (PICO above) established a priori. The articles were reviewed by title and abstract by 2 reviewers. When a decision could not be made based on title and abstract alone, full text was retrieved. **A total of 7 studies met inclusion criteria for this review.**

3. SEARCH RESULTS - PRISMA flowchart



4. STUDY INCLUSION

4.1 Included studies

Systematic review

1. Amiri M, Ramezani Tehrani F, Nahidi F, Bidhendi Yarandi R, Behboudi-Gandevani S, Azizi F. Association between biochemical hyperandrogenism parameters and Ferriman-Gallwey score in patients with polycystic ovary syndrome: A systematic review and meta-regression analysis. Clin Endocrinol (Oxf). 2017 Sep;87(3):217-230. doi: 10.1111/cen.13389. Epub 2017 Jun 30. PMID: 28575537.

Original papers identified from systematic review

1. Amato MC, Galluzzo A, Merlino S, Mattina A, Richiusa P, Criscimanna A, Giordano C. Lower insulin sensitivity differentiates hirsute from non-hirsute Sicilian women with polycystic ovary syndrome. Eur J Endocrinol. 2006 Dec;155(6):859-65. doi: 10.1530/eje.1.02290. PMID: 17132756.
2. Panidis D, Tziomalos K, Papadakis E, Chatzis P, Kandaraki EA, Tsourdi EA, Vosnakis C, Katsikis I. The clinical significance and primary determinants of hirsutism in patients with polycystic ovary syndrome. Eur J Endocrinol. 2013 May 3;168(6):871-7. doi: 10.1530/EJE-13-0039. PMID: 23557988.
3. Quinn M, Shinkai K, Pasch L, Kuzmich L, Cedars M, Huddleston H. Prevalence of androgenic alopecia in patients with polycystic ovary syndrome and characterization of associated clinical and biochemical features. Fertil Steril. 2014 Apr;101(4):1129-34. doi: 10.1016/j.fertnstert.2014.01.003. Epub 2014 Feb 15. PMID: 24534277.

Original papers

1. Imran H. J, Dhaher S. A, Mansour M. A. A. Testosterone or Dehydroepiandrosterone Sulfate as A Biomarker for Hirsutism in Women with Polycystic Ovary Syndrome. Biomed Pharmacol J 2020;13(4).
2. Kumar, H., Halder, A., Sharma, M., Jain, M., & Kalsi, A. (2022). Dihydrotestosterone- A Potential Biomarker of Hyperandrogenaemia in Polycystic Ovary Syndrome: A Case-control Study from North India. *JOURNAL OF CLINICAL AND DIAGNOSTIC RESEARCH*. doi: 10.7860/jcdr/2022/51169.15962
3. Leerasiri, P., Wongwananuruk, T., Indhavivadhana, S., Techatraisak, K., Rattanachaiyanont, M., & Angsuwathana, S. (2016). Correlation of clinical and biochemical hyperandrogenism in Thai women with polycystic ovary syndrome. *Journal Of Obstetrics And Gynaecology Research*, *42*(6), 678-683. doi: 10.1111/jog.12945
4. Yang Y, Ouyang N, Ye Y, Hu Q, Du T, Di N, Xu W, Azziz R, Yang D, Zhao X. The predictive value of total testosterone alone for clinical hyperandrogenism in polycystic ovary syndrome. Reprod Biomed Online. 2020 Oct;41(4):734-742. doi: 10.1016/j.rbmo.2020.07.013. Epub 2020 Jul 21. PMID: 32912651.

4.2 Excluded studies (on full texts assessment)

#	Title	Author/ Year	Journal	Vol	Issue	Pages	Notes
1	Establishing the cut off values of androgen markers in the assessment of polycystic ovarian syndrome	Nadaraja 2018	Malaysian Journal of Pathology	40	1	33-39	Wrong intervention
2	Challenges in diagnosis of polycystic ovary syndrome in adolescence	Asanidze 2021	Gynecological Endocrinology	37	9	819-822	Wrong population
3	A prospective study of anti-mullerian hormone and other ovarian and adrenal hormones in adult female acne	Bansal 2020	Dermatologic Therapy	33	6	e13974	Wrong comparator
4	A prospective study examining isolated acne and acne with hyperandrogenic signs	Bansal 2021	Journal of Dermatological Treatment	32	7	752-755	Wrong population

	in adult females						
5	Screening for Androgen Excess in Women: Accuracy of Self-Reported Excess Body Hair Growth and Menstrual Dysfunction	Chan 2020	Journal of Clinical Endocrinology & Metabolism	105	10	1	Wrong outcome
6	Comparison of the efficacy of different androgens measured by LC-MS/MS in representing hyperandrogenemia and an evaluation of adrenal-origin androgens with a dexamethasone suppression test in patients with PCOS	Chen 2021	Journal of ovarian research	14	1	32	Wrong comparator
7	Metabolic and endocrine connections of 17-hydroxypregnenolone in polycystic ovary syndrome women	deMedeiros 2017	Endocrine Connections	6(7)		479-488	Wrong intervention
8	The role and importance of auxiliary tests in differential diagnosis in patients with mildly high basal 17-OH-progesterone levels in the evaluation of hirsutism	Demirci 2020	Turkish Journal of Medical Sciences	50	8	1976-1982	Wrong comparator
9	Hyperandrogenism by liquid chromatography tandem mass spectrometry in PCOS: Focus on testosterone and androstenedione	Grassi 2021	Journal of Clinical Medicine	10(1)		1-9	Wrong intervention
10	Comparison Of Free Androgen Index In Polycystic Ovary Syndrome And Non-Polycystic Ovary Syndrome Infertile Patients	Khattak 2021	Journal of Ayub Medical College, Abbottabad: JAMC	33	4	577-581	Wrong comparator
11	Certified testosterone immunoassays for hyperandrogenaemia	Luque-Ramirez 2018	European Journal of Clinical Investigation	48	12	e13029	Wrong comparator
12	Relationships Between Biochemical Markers of Hyperandrogenism and Metabolic Parameters in Women with Polycystic Ovary Syndrome: A Systematic Review and	Amiri 2019	Hormone & Metabolic Research	51	1	22-34	Wrong outcome

	Meta-Analysis						
13	No. 350-Hirsutism: Evaluation and Treatment	Liu 2017	Journal of Obstetrics & Gynaecology Canada: JOGC	39	11	1054-1068	Wrong intervention
14	New Criteria for the Clinical Diagnosis of Hyperandrogenism in Polycystic Ovarian Syndrome and the Risk of Overdiagnosis	Soares-Jr 2019	Revista Brasileira de Ginecologia e Obstetricia	41	6	361-362	Wrong study design
15	New Biomarkers to Evaluate Hyperandrogenemic Women and Hypogonadal Men	Karakas 2018	Advances in Clinical Chemistry	86		71-125	Wrong outcome
16	Metastatin as a Marker for Hyperandrogenemia in Iraqi Women with Polycystic Ovary Syndrome	Abdalqader 2020	Obstetrics and Gynecology International	2020 (no pagination)			Wrong study design
17	Menstrual patterns and self-reported hirsutism as assessed via the modified Ferriman-Gallwey scale: A cross-sectional study	Willis 2020	European Journal of Obstetrics, Gynecology, & Reproductive Biology	248		137-143	Wrong population
18	Menstrual dysfunction in polycystic ovary syndrome: association with dynamic state insulin resistance rather than hyperandrogenism	Ezeh 2021	Fertility and Sterility	115(6)		1557-1568	Wrong study design
19	MC4R variants rs12970134 and rs17782313 are associated with obese polycystic ovary syndrome patients in the Western region of Saudi Arabia	Batarfi 2019	BMC Medical Genetics	20	1	144	Wrong study design
20	Long Noncoding RNA HUPCOS Promotes Follicular Fluid Androgen Excess in PCOS Patients via Aromatase Inhibition	Che 2020	Journal of Clinical Endocrinology & Metabolism	105	4	1	Wrong outcome
21	Large-scale genome-wide meta-analysis of polycystic ovary syndrome suggests shared genetic architecture for different diagnosis criteria	Day 2018	PLoS Genetics	14	12	e1007813	Wrong outcome

22	Increased follicle recruitment and testosterone-related adiposity contribute to granulos a cell dysfunction in lean polycystic ovary syndrome (PCOS) women	Guedikian 2017	Fertility and Sterility	108 (3 Supp 1)		e245	Wrong study design
23	Increased chemerin serum levels in hyperandrogenic and normoandrogenic women from Argentina with polycystic ovary syndrome	Abruzzese 2020	Gynecological Endocrinology	36	12	1057-1061	Wrong outcome
24	Implications of the 2014 Androgen Excess and Polycystic Ovary Syndrome Society guidelines on polycystic ovarian morphology for polycystic ovary syndrome diagnosis	Christ 2017	Reproductive Biomedicine Online	35	4	480-483	Wrong study design
25	Impact of rs2414096 polymorphism of CYP19 gene on susceptibility of polycystic ovary syndrome and hyperandrogenism in Kashmiri women	Ashraf 2021	Scientific Reports	11	1	12942	Wrong study design
26	Hyperandrogenic Anovulation: Differential Diagnosis and Evaluation	Wierman 2021	Endocrinology & Metabolism Clinics of North America	50	1	1-10	Wrong study design
27	Hyperandrogenemia in women with polycystic ovary syndrome: prevalence, characteristics and association with body mass index	Alexiou 2017	Hormone Molecular Biology & Clinical Investigation	29	3	105-111	Wrong outcome
28	Free androgen index may be the most useful biochemical androgenic marker for the detection of PCOS	Kim 2018	International Journal of Gynecology and Obstetrics	143 (Supp3)		805	Wrong study design
29	Evaluating the association of TNF alpha promoter haplotype with its serum levels and the risk of PCOS: A case control study	Bhatnager 2019	Cytokine	114		86-91	Wrong study design

30	Establishing an Anti-Moullerian Hormone (Amh) Cut-Off to Determine Polycystic Ovarian Morphology (Pcom) Supporting Diagnosis of Polycystic Ovarian Syndrome (Pcos): The Aphrodite Study	DeLoos 2019	Fertility and Sterility	112 (3 SUPPL)		e391	Wrong study design
31	Establishing a new screening 17 hydroxyprogesterone cut-off value and evaluation of the reliability of the long intramuscular ACTH stimulation test in the diagnosis of nonclassical congenital adrenal hyperplasia	Cengiz 2021	European Review for Medical & Pharmacological Sciences	25	16	5235-5240	Wrong outcome
32	Elevated anti-Mullerian hormone in lean women may not indicate polycystic ovarian syndrome	Bradbury 2017	Australian & New Zealand Journal of Obstetrics & Gynaecology	57	5	552-557	Wrong outcome
33	Elevated circulating levels of secreted frizzled-related protein 4 in relation to insulin resistance and androgens in women with polycystic ovary syndrome	Bicer 2020	Journal of Endocrinological Investigation	43	3	305-313	Wrong study design
34	Effects of curcumin supplementation on blood glucose, insulin resistance and androgens in patients with polycystic ovary syndrome: A randomized double-blind placebo-controlled clinical trial	Heshmati 2021	Phytomedicine	80		153395	Wrong intervention
35	Distribution of Body Hair in Young Australian Women and Associations With Serum Androgen Concentrations	Skiba 2020	Journal of Clinical Endocrinology & Metabolism	105	4	1	Wrong study design
36	Dihydrotestosterone (DHT): A potential biomarker of hyperandrogenaemia in polycystic ovary	Halder 2018	Indian Journal of Endocrinology and Metabolism	22 (7 Supp 1)		S72	Abstract

	syndrome						
37	Diagnosis and management of polycystic ovary syndrome: Perspectives of clinicians in Singapore	Teoh 2022	Annals of the Academy of Medicine, Singapore	51	4	204-212	Wrong study design
38	Androgen excess and metabolic disorders in women with PCOS: beyond the body mass index	Condorelli 2018	Journal of Endocrinological Investigation	41	4	383-388	Wrong study design
39	ACOG Practice Bulletin No. 194: Polycystic Ovary Syndrome	American College of 2018	Obstetrics & Gynecology	131	6	e157-e171	Wrong outcome
40	The diagnosis and treatment of PCOS in adolescents: an update	Witchel 2019	Current Opinion in Pediatrics	31	4	562-569	Wrong study design
41	Androgen profile through life in women with polycystic ovary syndrome: a Nordic multicenter collaboration study	Pinola 2015	Journal of Clinical Endocrinology and Metabolism	100	9	3400-3407	Wrong outcome
42	Validation of a simplified method to assess hirsutism in the Iranian population	Tehrani 2014	European Journal of Obstetrics and Gynecology and Reproductive Biology	174		91-95	Wrong population
43	The modified Ferriman-Gallwey Score and hirsutism among Filipino Women	Ilagen 2019	Endocrinology and metabolism	34		374-381	No extractable outcome

5. STUDY CHARACTERISTICS TABLE FOR INCLUDED STUDIES

Author, year, country	Study design	Setting	Exclusion criteria	PCOS sample size (age, BMI)	HA measurement	Sensitivity	Specificity	AUC	Summary of findings	Pooled in MA?	RoB
Amato et al, 2006, Italy	Cross-sectional	Clinic	Amenorrhoic women (absence of vaginal bleeding O6 months); women treated with clomiphene citrate, oral contra- ceptives, anti-androgens, or drugs to control their appetite during the 6 months before the first visit were excluded from the study	Rotterdam 130 age = 24.56 (5.2) BMI = 31.13 (6.96)	Clinical HA measurement mFG > 8 Biochemical HA measurement ELISA: TT >2.08 nmol/l, FT>6.94 pmol/l, DHEAS >11.69 mmol/l androstenedione >6.98 nmol/l	Not reported	Not reported	Not reported	PCOS women with hirsutism (57.7% of participants) showed significant higher values of total testosterone levels (PZ0.016), free testosterone (PZ0.027), DHEA sulfate (PZ0.017), and androstenedione (PZ0.018).	No	Mod
Imran et al, 2020, Iraq	Case-control	clinic	Not reported	Rotterdam PCOS + hirsutism = 100 age = 24 (6) BMI = 32 (5.9) PCOS no	Clinical HA measurement mFG >= 8 Biochemical HA measurement: ECL assay: TT >46 ng/dL cFT > 0.56 ng/dL DHEAS >395 ug/dL for 18-19yo; >380 ug/dL for 20-29yo;	Not reported	Not reported	mFG >=8 against TT: AUC (SE) = 0.944 (0.013) mFG >=8 against FT: AUC (SE) = 1.000 (0.0001) mFG >=8 against DHEAS: AUC (SE) =	High TT, FT, DHEA-S, and overall androgens were seen in 69%, 76%, 37%, and 99% respectively of our PCOS women with hirsutism.	No	Mod

				hirsutism = 30 age = 26 (8) BMI = 27.4 (3.5)	>270 ug/dL for 30-40yo			0.839 (0.026)			
Kumar et al, 2022, India	Case-control	clinic	drug induced hyperandrogenism, androgen producing tumors (ovarian neoplasm, adrenal neoplasm, thecoma), hyperprolactinemia, congenital adrenal hyperplasia, Cushing syndrome, hypothyroidism, or premature ovarian failure and excluded from study. In some cases, chromosome analysis was also carried out to exclude rare secondary causes like disorder of sex development/ sex	Rotterdam 137 age = 23.7 (4.8) BMI = 25.23 (5.11)	Clinical HA measurement FG >= 9 Biochemical HA measurement CLIA: TT >=0.51 ng/mL FAI >= 2.55 DHEAS >=309 ug/dL Androstenedione >= 2.2 ng/mL DHT >=462 pg/mL	TT = 83.8% FAI = 71% DHEAS = 69% A = 48% DHT = 77%	TT = 71.4% FAI = 96.75% DHEAS = 71% A = 73% DHT = 89%	TT: AUC (95CI) = 0.817 (0..748-0.886) FAI: AUC (95CI) = 0.86 (0.803-0.917) DHEAS: AUC (95CI) = 0.895 (0.843-0.947) A: AUC (95CI) = 0.630 (0.538-0.722) DHT: AUC (95CI) = 0.721 (0.634-0.808)	FG score of ≥9 was observed in 75.9% PCOS cases. High (mean+2SD) levels of T (≥0.51 ng/mL), FAI (≥2.55), DHEAS (≥309 ug/dL), androstenedione (≥2.2 ng/mL) and DHT (≥462 pg/mL) were observed in 35.29%, 56.25%, 14.18%, 18.62% and 61.38% cases, respectively. Mean DHT value was 584.27 pg/mL in study group whereas in control was 257.15 pg/mL (p-value <0.00001) and area under ROC curve was 0.895. Similarly, area under ROC curve was 0.86, 0.817, 0.721 and 0.63 for FAI, testosterone, DHEAS and	No	Mod

			reversal.						androstenedione, respectively.		
Leerasiri et al, 2016, Thailand	Cross-sectional	Clinic	taking hormonal therapy within 3 months or steroid agents within 6 months before en- rollment; history of treatment for acne and hirsutism; previous surgery of the ovary; and history of severe medical diseases or endocrine disorders	Rotterdam 145 age = 25.5 (6.5) BMI = 26.2 (6.9)	Clinical HA measurement Hirsutism: mGF >=8 Alopecia: Ludwig scale Acne: American Academy of Dermatology 1990 criteria Biochemical HA measurement CLIA: TT>80ng/L, FT >6 pg/ml, DHEAS >350ug/dl	mFG and TT = 16.9% mFG and FT = 46.2% Acne and FT = 67.7%	mFG and TT = 90.0% mFG and FT = 99.1% Acne and FT = 52.5%	mFG >=8 against TT: AUC (SD) = 0.816 (0.056) mFG >=8 against FT: AUC (SD) = 0.839 (0.047)	The most common expression of clinical hyperandrogenism was acne (56.6%). Most of the participants (84.8%) had high serum-FT. There was a statistically significant correlation between clinical and biochemical hyperandrogenism in the following pairs: hirsutism and FT (r = 0.3, P < 0.001); hirsutism and TT (r = 0.26, P < 0.001); and acne and TT (r = 0.26, P = 0.002). The others had little or no correlations.	No	Mod
Panidis et al, 2013, Greece	Cross-sectional	Clinic	galactorrhea, endocrine or systemic disease that could affect reproductive physiology, use of previous semester any medication that could interfere with the normal function of the HPA axis. Rule	Rotterdam 1297 age = 24.3 (5.8) BMI = 26.8 (6.9)	Clinical HA measurement mFG >= 8 Biochemical HA measurement RIA: TT FAI DHEAS androstenedione	Not reported	Not reported	Not reported	Women with hirsutism were younger, had greater BMI, and had higher levels of circulating androgens than women without hirsutism; markers of IR did not differ between the two groups after adjustment for age and BMI. The	No	High

			out CAH, prolactinoma, Cushing's syndrome, androgen-secreating tumours						prevalence of hirsutism progressively declined with age, was lower in normal-weight women than in overweight and obese women, and was comparably prevalent in the hyperandrogenemic phenotypes of PCOS. In binary logistic regression analysis, independent predictors of the presence of hirsutism were younger age, larger waist circumference (W), and higher serum testosterone levels. In stepwise linear regression analysis, the Ferriman–Gallwey score independently correlated with age, W, free androgen index, and serum D4-androstenedione and DHEAS levels.		
Quinn et al, 2014	Cross-sectional	Clinic	discontinue oral contraceptives and/or antiandrogen	Rotterdam Total	Clinical HA measurement mFG >= 8 AGA was described	AGA vs TT = 18.56 AGA vs	AGA vs TT = 75.80 AGA vs	Not reported	Subjects with PCOS and AGA were more likely to have acne or hir- sutism than those	No	High

			medications for 1 month before clinical and lab-oratory evaluation. Excluded disorders include CAH, thyroid dysfunction, hypogonadotropic hypogonadism, premature ovarian insufficiency, hyperprlactinaemia	PCOS = 254 eith AGA = 56 age = 28.8 (5.67) BMI = 30.9 (8.45) without AGA = 198 age = 27.8 (6.10) BMI = 30.1 (8.17)	as present when mini- aturization of hair follicles was seen in a characteristic pattern with either diffuse (Ludwig classification) or frontal (Olsen clas-sification) accentuation Acne: Leeds Revised Acne Grading System and patient self assessment Biochemical HA measurement Assay methods not specified: TT FT DHEAS A4	FT = 23.46	FT = 78.61		without AGA (96.3% vs. 70.6%). Subjects with AGA were more likely to report concern with hair loss (70.4% vs. 37.7%); however, their BDI-FS scores were no different from subjects without AGA. There were no differences between subjects with and without AGA in biochemical hyperandrogenism or metabolic parameters.		
Yang et al, 2020	Cross section al	Clinic	used hormonal medications for at least 3 months prior to the study. Subjects with mimicking or other androgen excess disorders, such as androgen-secreting neoplasms and adrenal	Rotterdam 294 age = 27.36 (5.43) BMI = 23.24 (6.42)	Clinical HA measurement mFG >=5 sFG >=3 Biochemical HA measurement CLIA and LC-MS/MS TT >= 2.39 nmol/L FT >=26.00 pmolL DHEAS >=4.92 mmol/L	Not reported	Not reported	against TT (LC_MS/MS) mFG AUC (95CI) = 0.797 (0.745-0.849) sFG AUC (95CI) 0.894 (0.857-0.931) aginst FAI (LS-MS/MS) mFG AUC (95CI) = 0.725	The hirsute subjects presented higher LC-MS/MS-based total testosterone and FAI values than the non-hirsute subjects (all P < 0.001), including those defined based on mFG ≥5 or sFG ≥3. Total testosterone and FAI were both positively correlated with the	No	Mod

			hyperplasia, were excluded		FAI >= 6.1			(0.666-0.783) sFG AUC (95CI) = 0.817 (0.768-0.866) against TT (CLIA) mFG AUC (95CI) = 0.528 (0.461-0.595) sFG AUC (95CI) = 0.542 (0.477-0.608) aginst FAI (CLIA) mFG AUC (95CI) = 0.552 (0.486-0.618) sFG AUC (95CI) = 0.583 (0.518-0.648)	mFG (rank correlation coefficient [RCC] 0.598 and 0.443, P < 0.001) or sFG (RCC 0.747 and 0.568, P < 0.001) score, and a receiver operating characteristic curve analysis indicated that both parameters could significantly predict the presence of hirsutism determined by the mFG (area under the curve [AUC] 0.797 and 0.725, P <0.001) or sFG (AUC 0.894 and 0.817, P <0.001) score. However, similar results were not obtained with the CLIA platform.		

AGA: androgenic alopecia; BMI: body mass index; CLIA: chemiluminescent immunoassay; ECL: electrochemiluminescence assay; ELISA: enzyme-linked immunosorbent assay; LC-MS/MS: liquid chromatography and tandem mass spectrometry assay; RIA: radioimmunoassay; HA: hyperandrogenism; mFG: modified Ferriman-Gallwey Score; TT: total testosterone; FT: free testosterone; FAI free androgen index; DHEAS: dehydroepiandrosterone sulphate; A4: androstenedione; DHT: dihydrotestosterone

6. FINDINGS

Comparisons:

- **Comparison 1. mFG ≥8 vs total testosterone (3 studies)**
- **Comparison 2. mFG ≥8 vs free testosterone (3 studies)**
- **Comparison 3. mFG ≥8 vs DHEAS (2 studies)**
- **Comparison 4. mFG ≥8 vs Androstenedione (1 study)**
- **Comparison 5. FG ≥9 vs TT, FAI, DHT, DHEAS, androstenedione (1 study)**
- **Comparison 6. mFG ≥5 vs TT (LC_MS/MS and CLIA) (1 study)**
- **Comparison 7. mFG ≥5 vs FAI (LC-MS/MS and CLIA) (1 study)**
- **Comparison 8. sFG ≥3 vs TT (LC_MS/MS and CLIA) (1 study)**
- **Comparison 9. sFG ≥3 vs FAI (LC-MS/MS and CLIA) (1 study)**
- **Comparison 10. Alopecia vs total testosterone, free testosterone (1 study)**
- **Comparison 11. Acne vs free testosterone (1 study)**

▪ EVIDENCE SUMMARY

Three studies reported sensitivity and specificity of mFG ≥8 against total testosterone and free testosterone (Amato 2006, Imran 2020 and Leerasiri 2016). Meta-analysis was not possible due to significant heterogeneity. All three studies were judged as moderate risk of bias.

Two studies reported sensitivity and specificity of mFG ≥8 against DHEAS (Amato 2006 and Imran 2020). Meta-analysis was not possible due to significant heterogeneity. Both studies were judged as moderate risk of bias.
The rest of the comparisons were only reported by a single study and meta-analysis was not performed. Other than Panidis 2013 and Quinn 2014 which were judged as high risk of bias, the rest of the studies were judged as moderate risk of bias.

▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

Evidence for all outcomes was very low quality due primarily to imprecision (being derived from a single study or small sample sizes) and risk of bias as well as some inconsistency (heterogeneity or variations in confidence intervals).

Comparison	Studies	n	Sensitivity	Specificity	AUC (95% CI)	Certainty
mFG ≥8 vs total testosterone	3	505			-	⊕◯◯◯ VERY LOW
mFG ≥8 vs free testosterone	3	505			-	⊕◯◯◯ VERY LOW
mFG ≥8 vs DHEAS	2	260			-	⊕◯◯◯ VERY LOW
mFG ≥8 vs Androstenedione	1	130	58.82	42.48	-	⊕◯◯◯ VERY LOW
FG ≥9 vs TT	1	137	83.8	71.4	0.817 (0.748-0.886)	⊕◯◯◯ VERY LOW
FG ≥9 vs FAI	1	137	71	96.75	0.86 (0.803-0.917)	⊕◯◯◯ VERY LOW
FG ≥9 vs DHT	1	137	77	89	0.721 (0.634-0.808)	⊕◯◯◯ VERY LOW
FG ≥9 vs DHEAS	1	137	69	71	0.895 (0.843-0.947)	⊕◯◯◯ VERY LOW
FG ≥9 vs Androstenedione	1	137	48	73	0.630 (0.538-0.722)	⊕◯◯◯ VERY LOW
mFG ≥5 vs TT (LC_MS/MS)	1	294	-	-	0.797 (0.745-0.849)	⊕◯◯◯ VERY LOW
mFG ≥5 vs TT (CLIA)	1	294	-	-	0.528 (0.461-	⊕◯◯◯

					0.595)	VERY LOW
mFG ≥5 vs FAI (LC-MS/MS)	1	294	-	-	0.725 (0.666-0.783)	⊕◯◯◯ VERY LOW
mFG ≥5 vs FAI (CLIA)	1	294	-	-	0.552 (0.486-0.618)	⊕◯◯◯ VERY LOW
sFG ≥3 vs TT (LC_MS/MS)	1	294	-	-	0.894 (0.957-0.931)	⊕◯◯◯ VERY LOW
sFG ≥3 vs TT (CLIA)	1	294	-	-	0.542 (0.477-0.608)	⊕◯◯◯ VERY LOW
sFG ≥3 vs FAI (LC-MS/MS)	1	294	-	-	0.817 (0.768-0.866)	⊕◯◯◯ VERY LOW
sFG ≥3 vs FAI (CLIA)	1	294	-	-	0.583 (0.518-0.648)	⊕◯◯◯ VERY LOW
Alopecia vs total testosterone	1	254	18.56	75.80	-	⊕◯◯◯ VERY LOW
Alopecia vs free testosterone	1	254	23.46	78.61	-	⊕◯◯◯ VERY LOW
Acne vs free testosterone	1	145	67.7	52.5	-	⊕◯◯◯ VERY LOW

1.1 Individual Study Data Tables

Author, year	Method of biochemical measurement	Sample size of clinical HA	Sample size of biochemical HA	True +'ve	True –'ve	False +'ve	False – 've	Sensitivity	Specificity	PPV	NPV
mGF ≥8 vs total testosterone											
Amato 2006	ELISA: TT >2.08 nmol/l	75	57	35	33	40	22	61.40	45.21	46.67	60.00
Imran 2020	ECL: TT >46 ng/dL	100	72	69	27	31	3	95.83	46.55	95.83	90.00
Leerasiri 2016	CLIA: TT>80ng/L	41	65	NR	NR	NR	NR	16.9	90.0	68.3	67.4
mGF ≥8 vs free testosterone											
Amato 2006	ELISA: FT>6.94 pmol/l	75	80	52	27	23	28	65.00	54.00	69.33	49.09
Imran 2020	ECL: cFT > 0.56 ng/dL	100	86	76	20	24	10	88.37	45.45	88.37	66.67
Leerasiri 2016	CLIA: FT >6 pg/ml	41	123	NR	NR	NR	NR	46.2	99.1	95	19.2
mGF ≥8 vs DHEAS											
Amato 2006	ELISA: TT >2.08 nmol/l	75	17	10	48	65	7	58.82	42.48	13.33	87.27
Imran 2020	ECL: TT >46 ng/dL	100	37	37	30	63	0	100	32	100	100
mFG ≥8 vs Androstenedione											
Amato 2006	ELISA: androstenedione >6.98 nmol/l	75	80	48	23	27	32	60.00	46.00	64.00	41.82
FG ≥9 vs TT											
Kumar 2022	CLIA: TT >=0.51 ng/mL	101	48	NR	NR	NR	NR	83.8	71.4	NR	NR
FG ≥9 vs FAI											

Kumar 2022	CLIA: FAI >= 2.55	101	63	NR	NR	NR	NR	71	96.75	NR	NR
FG ≥9 vs DHT											
Kumar 2022	CLIA: DHT >=462 pg/mL	101	62	NR	NR	NR	NR	77	89	NR	NR
FG ≥9 vs DHEAS											
Kumar 2022	CLIA: DHEAS >=309 ug/dL	101	19	NR	NR	NR	NR	69	71	NR	NR
FG ≥9 vs Androstenedione											
Kumar 2022	CLIA: Androstenedione >= 2.2 ng/mL	101	19	NR	NR	NR	NR	48	73	NR	NR
mFG ≥5 vs TT (LC_MS/MS)											
Yang 2020	TT >= 2.39 nmol/L	161	NR	NR	NR	NR	NR	NR	NR	NR	NR
mFG ≥5 vs TT (CLIA)											
Yang 2020	TT >= 2.39 nmol/L	161	NR	NR	NR	NR	NR	NR	NR	NR	NR
mFG ≥5 vs FAI (LC-MS/MS)											
Yang 2020	FAI >= 6.1	161	NR	NR	NR	NR	NR	NR	NR	NR	NR
mFG ≥5 vs FAI (CLIA)											
Yang 2020	FAI >= 6.1	161	NR	NR	NR	NR	NR	NR	NR	NR	NR
sFG ≥3 vs TT (LC_MS/MS)											
Yang 2020	TT >= 2.39 nmol/L	141	NR	NR	NR	NR	NR	NR	NR	NR	NR
sFG ≥3 vs TT (CLIA)											
Yang 2020	TT >= 2.39 nmol/L	141	NR	NR	NR	NR	NR	NR	NR	NR	NR
sFG ≥3 vs FAI (LC-MS/MS)											
Yang 2020	FAI >= 6.1	141	NR	NR	NR	NR	NR	NR	NR	NR	NR
sFG ≥3 vs FAI (CLIA)											
Yang 2020	FAI >= 6.1	141	NR	NR	NR	NR	NR	NR	NR	NR	NR
Alopecia vs total testosterone											
Quinn 2014	Threshold unclear	56	97	18	119	38	79	18.56	75.80	18.56	60.10
Alopecia vs free testosterone											
Quinn 2014	Threshold unclear	56	81	19	136	37	62	23.46	78.61	23.46	68.69
Acne vs free testosterone											
Quinn 2014	Threshold unclear	156	81	NR	NR	NR	NR	67.7	52.5	53.7	66.7

7. GRADE ASSESSMENTS AND EVIDENCE PROFILE

	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Clinical HA	Bio-chemical HA	Outcome	Effect estimates: mean (95% CI)	Certainty	Importance
mFG ≥8 vs total testosterone												
3	observational	Serious[1]	Very serious[2]	Serious[3]	Serious[4]	None	75	57	Sensitivity Specificity	61.40% 45.21%	⨁◯◯◯ VERY LOW	Critical
							100	72	Sensitivity Specificity	95.83% 46.55%		
							41	65	Sensitivity Specificity	16.9% 90.0%		
mFG ≥8 vs free testosterone												
3	observational	Serious[1]	Very serious[2]	Serious[3]	Serious[4]	None	75	80	Sensitivity Specificity	65.00% 54.00%	⨁◯◯◯ VERY LOW	Critical
							100	86	Sensitivity Specificity	88.37% 45.45%		
							41	123	Sensitivity Specificity	46.2% 99.1%		
mFG ≥8 vs DHEAS												
2	observational	Serious[1]	Very serious[2]	Serious[3]	Serious[4]	None	75	17	Sensitivity Specificity	58.82% 42.48%	⨁◯◯◯ VERY LOW	Critical
							100	37	Sensitivity Specificity	100% 32%		
mFG ≥8 vs Androstenedione												
1	observational	Serious[1]	Not applicable	Not applicable	Very serious[5]	None	75	80	Sensitivity Specificity	58.82% 42.48%	⨁◯◯◯ VERY LOW	Critical
FG ≥9 vs TT												
1	observational	Serious[1]	Not applicable	Not applicable	Very serious[5]	None	101	48	Sensitivity Specificity AUC (95% CI)	83.8% 71.4% 0.817 (0.748-0.886)	⨁◯◯◯ VERY LOW	Critical
FG ≥9 vs FAI												
1	observational	Serious[1]	Not applicable	Not applicable	Very serious[5]	None	101	63	Sensitivity Specificity AUC (95% CI)	71% 96.75% 0.86 (0.803-0.917)	⨁◯◯◯ VERY LOW	Critical
FG ≥9 vs DHT												
1	observational	Serious[1]	Not applicable	Not applicable	Very serious[5]	None	101	62	Sensitivity Specificity AUC (95% CI)	77% 89% 0.721 (0.634-0.808)	⨁◯◯◯ VERY LOW	Critical
FG ≥9 vs DHEAS												
1	observation	Serious[1]	Not applicable	Not	Very	None	101	19	Sensitivity	69%	⨁◯◯◯	Critical

	al			applicable	serious[5]				Specificity AUC (95% CI)	71% 0.895 (0.843-0.947)	VERY LOW	
FG ≥9 vs Androstenedione												
1	observational	Serious[1]	Not applicable	Not applicable	Very serious[5]	None	101	19	Sensitivity Specificity AUC (95% CI)	48% 73% 0.630 (0.538-0.722)	⊕◯◯◯ VERY LOW	Critical
mFG ≥5 vs TT (LC_MS/MS)												
1	observational	Serious[1]	Not applicable	Not applicable	Very serious[5]	None	161	Not reported	AUC (95% CI)	0.797 (0.745-0.849)	⊕◯◯◯ VERY LOW	Critical
mFG ≥5 vs TT (CLIA)												
1	observational	Serious[1]	Not applicable	Not applicable	Very serious[5]	None	161	Not reported	AUC (95% CI)	0.528 (0.461-0.595)	⊕◯◯◯ VERY LOW	Critical
mFG ≥5 vs FAI (LC-MS/MS)												
1	observational	Serious[1]	Not applicable	Not applicable	Very serious[5]	None	161	Not reported	AUC (95% CI)	0.725 (0.666-0.783)	⊕◯◯◯ VERY LOW	Critical
mFG ≥5 vs FAI (CLIA)												
1	observational	Serious[1]	Not applicable	Not applicable	Very serious[5]	None	161	Not reported	AUC (95% CI)	0.552 (0.486-0.618)	⊕◯◯◯ VERY LOW	Critical
sFG ≥3 vs TT (LC_MS/MS)												
1	observational	Serious[1]	Not applicable	Not applicable	Very serious[5]	None	141	Not reported	AUC (95% CI)	0.894 (0.957-0.931)	⊕◯◯◯ VERY LOW	Critical
sFG ≥3 vs TT (CLIA)												
1	observational	Serious[1]	Not applicable	Not applicable	Very serious[5]	None	141	Not reported	AUC (95% CI)	0.542 (0.477-0.608)	⊕◯◯◯ VERY LOW	Critical
sFG ≥3 vs FAI (LC-MS/MS)												
1	observational	Serious[1]	Not applicable	Not applicable	Very serious[5]	None	141	Not reported	AUC (95% CI)	0.817 (0.768-0.866)	⊕◯◯◯ VERY LOW	Critical
sFG ≥3 vs FAI (CLIA)												
1	observational	Serious[1]	Not applicable	Not applicable	Very serious[5]	None	141	Not reported	AUC (95% CI)	0.583 (0.518-0.648)	⊕◯◯◯ VERY LOW	Critical
Alopecia vs total testosterone												
1	observational	Serious[1]	Not applicable	Not applicable	Very serious[5]	None	56	97	Sensitivity Specificity	18.56% 75.80%	⊕◯◯◯ VERY LOW	Critical
Alopecia vs free testosterone												
1	observational	Serious[1]	Not applicable	Not applicable	Very serious[5]	None	56	81	Sensitivity Specificity	23.46% 78.61%	⊕◯◯◯ VERY LOW	Critical
Acne vs free testosterone												
1	observational	Serious[1]	Not applicable	Not applicable	Very serious[5]	None	156	81	Sensitivity Specificity	67.7% 52.5%	⊕◯◯◯ VERY LOW	Critical

[1] Downgraded once because in majority of the studies were unclear if clinical hyperandrogenism was assessed in a standardised method
[2] Downgraded twice as point estimates vary widely and CIs not overlapping
[3] Downgraded once as the study populations are very different (studies are from Italy, Iraq, Thailand)
[4] Downgraded once as studies are of small populations
[5] Downgraded twice because only 1 study reported this comparison

APPENDIX. STUDY CHARACTERISTICS AND QUALITY APPRAISAL TEMPLATES

Study ID	*Amato 2006*		
Study Citation	*Amato MC, Galluzzo A, Merlino S, Mattina A, Richiusa P, Criscimanna A, Giordano C. Lower insulin sensitivity differentiates hirsute from non-hirsute Sicilian women with polycystic ovary syndrome. Eur J Endocrinol. 2006 Dec;155(6):859-65. doi: 10.1530/eje.1.02290. PMID: 17132756.*		
Study Country	*Italy*		
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/ participants	*130 women with PCOS according to the Rotterdam criteria.*		
PCOS diagnostic criteria	*Rotterdam*		
N per group	*Women with PCOS and hirsutism = 75.* *Women with PCOS without hirsutism = 55.*		
Setting	*Outpatient clinic*		
Index test	FG map scoring system, estimated from two observers, which has 11 domains depicting portions of the body. Hirsutism was defined as FG score >8.		
Reference Standard	total testosterone O2.08 nmol/l, free testosteroneO6.94 pmol/l, DHEAS O11.69 mmol/l, and androstenedione O6.98 nmol/l (calculated on the basis of the 95th percentile upper limits of basal serum androgen normality in a control group of 30 healthy eumenorrhoic women without hirsutism and family history of PCOS).		
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Our aim was to evaluate insulin sensitivity in PCOS women with or without hirsutism.*		
Inclusion and exclusion criteria reported?	Yes Partial No Not reported	*Yes*	
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*	
Summary Result/s	*PCOS women with hirsutism (57.7% of participants) showed significant higher values of total testosterone levels (PZ0.016), free testosterone (PZ0.027), DHEA sulfate (PZ0.017), and androstenedione (PZ0.018).*		
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
PATIENT SELECTION/SPECTRUM BIAS	Was the spectrum of patients representative of the patients who will receive the test in practice?	Yes Partial No Not reported	*Yes*
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes Partial No Not reported	*Not reported*

	Was a case-control design avoided? (Q-2)	Yes Partial No Not reported	*No* *Studies enrolling patients with known disease and a control group without the condition may exaggerate diagnostic accuracy.*
	Did the study avoid inappropriate exclusions? (Q-2)	Yes Partial No Not reported	*Yes*
CLASSIFICATION/ VERIFICATION/ INCORPORATION/ REVIEW BIAS	Were all participants assessed with both index test and reference standard?	Yes Partial No Not reported	*Yes*
	Did all patients receive the same reference standard? (Q-2)	Yes Partial No Not reported	*Yes*
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes Partial No Not reported	*Yes*
	Was the reference standard independent of the index test (ie. the index test did not form part of the reference standard)?	Yes Partial No Not reported	*Yes*
	Were the reference standard results interpreted without knowledge of the results of the index test?	Yes Partial No Not reported	*Not reported*
	Were the index test results interpreted without knowledge of the results of the reference standard test?	Yes Partial No Not reported	*Not reported*
	If a threshold was used, was it pre-specified?	Yes Partial No Not reported	*Yes*

DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	Were withdrawals from the study explained?	*X% treatment* *X% control/ comparison*	*Numbers described as enrolled are the same as those in results.*
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Yes Partial No Not reported	*Yes*
OTHER ISSUES – APPLICABILITY/ COMPARABILITY/ VARIATION	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes Partial No Not reported	*Yes*
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Yes Partial No Not reported	*Not reported*
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes Partial No Not reported	*Yes*
	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Partial*
COMMENTS		*The results used for this guideline evidence review are secondary aims.*	
What is the overall risk of bias?		*Moderate*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Imran 2020*		
Study Citation	*Imran H. J, Dhaher S. A, Mansour M. A. A. Testosterone or Dehydroepiandrosterone Sulfate as A Biomarker for Hirsutism in Women with Polycystic Ovary Syndrome. Biomed Pharmacol J 2020;13(4).*		
Study Country	*Iraq*		
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/ participants	*The first group (n=100) included women with PCOS and hirsutism, the second group (n=30) women with PCOS but no hirsutism.*		
PCOS diagnostic criteria	*Rotterdam*		
N per group	*PCOS with hirsutism = 100* *PCOS without hirsutism = 30* *Healthy contols = 70*		
Setting	*Clinic*		
Index test	*Ferriman-Gallwey Score ≥8*		
Reference Standard	*TT, FT, and DHEA-S*		
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Electrochemiluminescence (ECL) technology assay* *TT >46 ng/dL* *cFT > 0.56 ng/dL* *DHEAS >395 ug/dL for 18-19yo; >380 ug/dL for 20-29yo; >270 ug/dL for 30-40yo*		
Inclusion and exclusion criteria reported?	Yes Partial No Not reported	*Yes*	
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*	
Summary Result/s	*This study provides evidence that presence of hirsutism in women with PCOS was associated with a higher level of biochemical hyperandrogenism than seen in PCOS without hirsutism; however, there was no correlation between the studied androgens and mFG score.*		
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
PATIENT SELECTION/SPECTRUM BIAS	Was the spectrum of patients representative of the patients who will receive the test in practice?	Yes Partial No Not reported	*Yes*
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes Partial No Not reported	*Not reported*
	Was a case-control design avoided? (Q-2)	Yes Partial No Not	*No*

		reported	
	Did the study avoid inappropriate exclusions? (Q-2)	Yes Partial No Not reported	*Yes*
CLASSIFICATION/ VERIFICATION/ INCORPORATION/ REVIEW BIAS	Were all participants assessed with both index test and reference standard?	Yes Partial No Not reported	*Yes*
	Did all patients receive the same reference standard? (Q-2)	Yes Partial No Not reported	*Yes*
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes Partial No Not reported	*Yes*
	Was the reference standard independent of the index test (ie. the index test did not form part of the reference standard)?	Yes Partial No Not reported	*Yes*
	Were the reference standard results interpreted without knowledge of the results of the index test?	Yes Partial No Not reported	*Not reported*
	Were the index test results interpreted without knowledge of the results of the reference standard test?	Yes Partial No Not reported	*Not reported*
	If a threshold was used, was it pre-specified?	Yes Partial No Not reported	*Yes*
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?	Yes Partial No Not reported	*Not reported*

ATTRITION BIAS	Were withdrawals from the study explained?	*X% treatment X% control/ comparison*	*Numbers described as enrolled are the same as those in results.*
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Yes Partial No Not reported	*Yes*
OTHER ISSUES – APPLICABILITY/ COMPARABILITY/ VARIATION	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes Partial No Not reported	*Yes*
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Yes Partial No Not reported	*Not reported*
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes Partial No Not reported	*Not reported*
	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS			
What is the overall risk of bias?		*Moderate*	*Unsure if training to use Ferriman-Gallwey score occurred.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Kumar 2022*
Study Citation	*Kumar, H., Halder, A., Sharma, M., Jain, M., & Kalsi, A. (2022). Dihydrotestosterone- A Potential Biomarker of Hyperandrogenaemia in Polycystic Ovary Syndrome: A Case-control Study from North India. JOURNAL OF CLINICAL AND DIAGNOSTIC RESEARCH. doi: 10.7860/jcdr/2022/51169.15962*
Study Country	*India*

EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*137 women with PCOS evaluated with reproductive and menstrual history (oligomenorrhoea/ amenorrhoea), hirsutism (FG score) [14], testosterone level and ovarian ultrasonography (polycystic and/or enlarged).* *49 normal (having normal menstrual cycle and fertility) female in reproductive age as control for the comparison.*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	*137 women with PCOS.* *49 healthy controls*	
Setting	*Clinic*	
Index test	*Ferriman Gallway score ≥ 9*	
Reference Standard	*chemiluminescent microparticle immunoassay technology.* *TT >=0.51 ng/mL* *FAI >= 2.55* *DHEAS >=309 ug/dL* *Androstenedione >= 2.2 ng/mL* *DihydroT >=462 pg/mL*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*chemiluminescent microparticle immunoassay technology.* *TT >=0.51 ng/mL* *FAI >= 2.55* *DHEAS >=309 ug/dL* *Androstenedione >= 2.2 ng/mL* *DihydroT >=462 pg/mL*	
Inclusion and exclusion criteria reported?	Yes Partial No Not reported	*Yes*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Summary Result/s	*Dihydrotestosterone (DHT) is best available biomarker and can be considered as diagnostic biomarker of hyperandrogenemia in PCOS women from North India.*	

INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
PATIENT SELECTION/SPECTRUM BIAS	Was the spectrum of patients representative of the patients who will receive the test in practice?	Yes Partial No Not reported	*Yes*
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes Partial No Not reported	*Not reported*
	Was a case-control design avoided? (Q-2)	Yes Partial No Not reported	*No*

	Did the study avoid inappropriate exclusions? (Q-2)	Yes Partial No Not reported	*Yes*
CLASSIFICATION/ VERIFICATION/ INCORPORATION/ REVIEW BIAS	Were all participants assessed with both index test and reference standard?	Yes Partial No Not reported	*Yes*
	Did all patients receive the same reference standard? (Q-2)	Yes Partial No Not reported	*Yes*
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes Partial No Not reported	*Yes*
	Was the reference standard independent of the index test (ie. the index test did not form part of the reference standard)?	Yes Partial No Not reported	*Yes*
	Were the reference standard results interpreted without knowledge of the results of the index test?	Yes Partial No Not reported	*Not reported*
	Were the index test results interpreted without knowledge of the results of the reference standard test?	Yes Partial No Not reported	*Not reported*
	If a threshold was used, was it pre-specified?	Yes Partial No Not reported	*Yes*
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?	Yes Partial No Not reported	*Not reported*

ATTRITION BIAS	Were withdrawals from the study explained?	*X% treatment X% control/ comparison*	*Numbers described as enrolled are the same as those in results.*
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Yes Partial No Not reported	*Yes*
OTHER ISSUES – APPLICABILITY/ COMPARABILITY/ VARIATION	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes Partial No Not reported	*Yes*
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Yes Partial No Not reported	*Not reported*
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes Partial No Not reported	*Not reported*
	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS			
What is the overall risk of bias?		*Moderate*	*Unclear if clinical hyperandrogenism is assessed in a standardised method where assessors received training*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Leerasiri 2016*
Study Citation	*Leerasiri, P., Wongwananuruk, T., Indhavivadhana, S., Techatraisak, K., Rattanachaiyanont, M., & Angsuwathana, S. (2016). Correlation of clinical and biochemical hyperandrogenism in Thai women with polycystic ovary syndrome. Journal Of Obstetrics And Gynaecology Research, 42(6), 678-683. doi: 10.1111/jog.12945*
Study Country	*Thailand*

EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*145 women with PCOS.*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	*145 women with PCOS.*	
Setting	*Hospital clinic*	
Index test	*Hirsutism: mGF >=8* *Alopecia: Ludwig scale* *Acne:* *American Academy of Dermatology 1990 criteria*	
Reference Standard	*CLIA (chemiluminometric assay)* *TT>80ng/L,* *FT >6 pg/ml,* *DHEAS >350ug/dl*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*CLIA (chemiluminometric assay)* *TT>80ng/L,* *FT >6 pg/ml,* *DHEAS >350ug/dl*	
Inclusion and exclusion criteria reported?	Yes Partial No Not reported	*Yes*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Summary Result/s	*Clinical hyperandrogenism is not a good predictor for biochemical hyperandrogenism in Thai women with PCOS. A modified Ferriman–Gallwey score cut-off point of 8 has low sensitivity but high specificity for hyperandrogenemia; therefore, it is useful for the diagnosis but not useful for the exclusion of hyperandrogenemia in Thai women with PCOS.*	

INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
PATIENT SELECTION/SPECTRUM BIAS	Was the spectrum of patients representative of the patients who will receive the test in practice?	Yes Partial No Not reported	*Yes*
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes Partial No Not reported	*Not reported*
	Was a case-control design avoided? (Q-2)	Yes Partial No Not reported	*No*

	Did the study avoid inappropriate exclusions? (Q-2)	Yes Partial No Not reported	*Yes*
CLASSIFICATION/ VERIFICATION/ INCORPORATION/ REVIEW BIAS	Were all participants assessed with both index test and reference standard?	Yes Partial No Not reported	*Yes*
	Did all patients receive the same reference standard? (Q-2)	Yes Partial No Not reported	*Yes*
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes Partial No Not reported	*Yes*
	Was the reference standard independent of the index test (ie. the index test did not form part of the reference standard)?	Yes Partial No Not reported	*Yes*
	Were the reference standard results interpreted without knowledge of the results of the index test?	Yes Partial No Not reported	*Not reported*
	Were the index test results interpreted without knowledge of the results of the reference standard test?	Yes Partial No Not reported	*Not reported*
	If a threshold was used, was it pre-specified?	Yes Partial No Not reported	*Yes*
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?	Yes Partial No Not reported	*Not reported*

ATTRITION BIAS	Were withdrawals from the study explained?	*X% treatment X% control/ comparison*	*Numbers described as enrolled are the same as those in results.*
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Yes Partial No Not reported	*Yes*
OTHER ISSUES – APPLICABILITY/ COMPARABILITY/ VARIATION	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes Partial No Not reported	*Yes*
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Yes Partial No Not reported	*Not reported*
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes Partial No Not reported	*Not reported*
	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS			
What is the overall risk of bias?		*Moderate*	*No clear explanation if clinical hyperandrogenism was assessed by the same assessor or if training occurred for standardised assessment.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Panidis 2013*
Study Citation	*Panidis D, Tziomalos K, Papadakis E, Chatzis P, Kandaraki EA, Tsourdi EA, Vosnakis C, Katsikis I. The clinical significance and primary determinants of hirsutism in patients with polycystic ovary syndrome. Eur J Endocrinol. 2013 May 3;168(6):871-7. doi: 10.1530/EJE-13-0039. PMID: 23557988.*
Study Country	*Greece*

EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/ participants		*1297 women with PCOS*	
PCOS diagnostic criteria		*Rotterdam*	
N per group		*1297 women with PCOS*	
Setting		*All participants were outpatients at the Gynecological Endocrinology Infirmary of the Second Department of Obstetrics and Gynecology, Aristotle University of Thessaloniki, Greece*	
Index test		*mFG >= 8*	
Reference Standard		*RIA : TT, FAI, DHEAS, androstenedione*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)		*Via lab tests but normal ranges were not provided*	
Inclusion and exclusion criteria reported?		Yes Partial No Not reported	*Yes*
Does the study have a clearly focused question?		Yes Partial No Not reported	*Yes*
Summary Result/s		*Besides hyperandrogenemia, abdominal obesity, and young age are independently associated with the presence of hirsutism. In contrast, the relationship between IR and hirsutism appears to be mediated by the more severe obesity of insulin-resistant patients with PCOS.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
PATIENT SELECTION/SPECTRUM BIAS	Was the spectrum of patients representative of the patients who will receive the test in practice?	Yes Partial No Not reported	*Yes*
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes Partial No Not reported	*Not reported*
	Was a case-control design avoided? (Q-2)	Yes Partial No Not reported	*No*
	Did the study avoid inappropriate exclusions? (Q-2)	Yes Partial No Not reported	*Yes*
	Were all participants	Yes	*Yes*

CLASSIFICATION/ VERIFICATION/ INCORPORATION/ REVIEW BIAS	assessed with both index test and reference standard?	Partial No Not reported	
	Did all patients receive the same reference standard? (Q-2)	Yes Partial No Not reported	*Yes*
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes Partial No Not reported	*Yes*
	Was the reference standard independent of the index test (ie. the index test did not form part of the reference standard)?	Yes Partial No Not reported	*Yes*
	Were the reference standard results interpreted without knowledge of the results of the index test?	Yes Partial No Not reported	*Not reported*
	Were the index test results interpreted without knowledge of the results of the reference standard test?	Yes Partial No Not reported	*Not reported*
	If a threshold was used, was it pre-specified?	Yes Partial No Not reported	*Partial.* *Biochemical hyperandrogenism ranges were not provided*
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?	Yes Partial No Not reported	*Not reported*
ATTRITION BIAS	Were withdrawals from the study explained?	*X% treatment* *X% control/ comparison*	*Numbers described as enrolled are the same as those in results.*

REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Yes Partial No Not reported	*Yes*
OTHER ISSUES – APPLICABILITY/ COMPARABILITY/ VARIATION	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes Partial No Not reported	*Yes*
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Yes Partial No Not reported	*Not reported*
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes Partial No Not reported	*Not reported*
	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*No*
COMMENTS			
What is the overall risk of bias?		*High*	*No clear explanation if clinical hyperandrogenism was assessed by the same assessor or if training occurred for standardised assessment. Also normal ranges of biochemical hyperandrogenism were not provided.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No* *All outcomes high risk of bias*	

Study ID	*Quinn 2014*
Study Citation	*Quinn M, Shinkai K, Pasch L, Kuzmich L, Cedars M, Huddleston H. Prevalence of androgenic alopecia in patients with polycystic ovary syndrome and characterization of associated clinical and biochemical features. Fertil Steril. 2014 Apr;101(4):1129-34. doi: 10.1016/j.fertnstert.2014.01.003. Epub 2014 Feb 15. PMID: 24534277.*
Study Country	*US*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/	*Total participants with PCOS = 254*

participants			*Participants with PCOS and androgenic alopecia = 56* *Participants with PCOS without androgenic alopecia = 198* *Patients presenting for evaluation of symptoms suggestive of PCOS at a subspecialty multidisciplinary clinic at a tertiary referral center*
PCOS diagnostic criteria			*Rotterdam*
N per group			*Total participants with PCOS = 254* *Participants with PCOS and androgenic alopecia = 56* *Participants with PCOS without androgenic alopecia = 198*
Setting			*subspecialty multidisciplinary clinic at a tertiary referral center*
Index test			*mFG >= 8* *AGA was described as present when mini- aturization of hair follicles was seen in a characteristic pattern with either diffuse (Ludwig classification) or frontal (Olsen classification) accentuation* *Acne: Leeds Revised Acne Grading System and patient self assessment*
Reference Standard			*TT, FAI, DHEAS, androstenedione. Methods and normal ranges not provided.*
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)			*Biochemical hyperandrogenism frequency.*
Inclusion and exclusion criteria reported?		Yes Partial No Not reported	*Yes*
Does the study have a clearly focused question?		Yes Partial No Not reported	*Yes*
Summary Result/s			*AGA is prevalent in 22% of subjects meeting diagnostic criteria for PCOS. AGA is associated with other manifestations of clinical hyperandrogenism, but not with greater risk of biochemical hyperandrogenemia or metabolic dysfunction than with PCOS alone*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
PATIENT SELECTION/SPECTRUM BIAS	Was the spectrum of patients representative of the patients who will receive the test in practice?	Yes Partial No Not reported	*Yes*
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes Partial No Not reported	*Not reported*
	Was a case-control design avoided? (Q-2)	Yes Partial No Not reported	*No*
	Did the study avoid inappropriate	Yes Partial No	*Yes*

	exclusions? (Q-2)	Not reported	
CLASSIFICATION/ VERIFICATION/ INCORPORATION/ REVIEW BIAS	Were all participants assessed with both index test and reference standard?	Yes Partial No Not reported	*Not reported*
	Did all patients receive the same reference standard? (Q-2)	Yes Partial No Not reported	*Not reported*
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes Partial No Not reported	*Yes*
	Was the reference standard independent of the index test (ie. the index test did not form part of the reference standard)?	Yes Partial No Not reported	*Yes*
	Were the reference standard results interpreted without knowledge of the results of the index test?	Yes Partial No Not reported	*Not reported*
	Were the index test results interpreted without knowledge of the results of the reference standard test?	Yes Partial No Not reported	*Not reported*
	If a threshold was used, was it pre-specified?	Yes Partial No Not reported	*No*
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?	Yes Partial No Not reported	*Not reported*
ATTRITION BIAS	Were withdrawals from the study explained?	*X% treatment X% control/ comparison*	*Numbers described as enrolled are the same as those in results.*

REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Yes Partial No Not reported	*No*
OTHER ISSUES – APPLICABILITY/ COMPARABILITY/ VARIATION	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes Partial No Not reported	*Yes*
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Yes Partial No Not reported	*Not reported*
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes Partial No Not reported	*Not reported*
	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*No*
COMMENTS		*No clear explanation if clinical hyperandrogenism was assessed by the same assessor or if training occurred for standardised assessment.* *Methods and normal ranges of biochemical hyperandrogenism not reported.*	
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No* *All outcomes high risk of bias*	

Study ID	*Yang 2020*
Study Citation	*Yang Y, Ouyang N, Ye Y, Hu Q, Du T, Di N, Xu W, Azziz R, Yang D, Zhao X. The predictive value of total testosterone alone for clinical hyperandrogenism in polycystic ovary syndrome. Reprod Biomed Online. 2020 Oct;41(4):734-742. doi: 10.1016/j.rbmo.2020.07.013. Epub 2020 Jul 21. PMID: 32912651.*
Study Country	*China*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	

Patient/population/ participants	*A total of 294 consecutive women with PCOS aged 18 to 44 years were recruited at Sun Yat-Sen Memorial Hospital.*		
PCOS diagnostic criteria	*Rotterdam*		
N per group	*294 women with PCOS*		
Setting	*Hospital*		
Index test	*mFG >=5* *sFG >=3*		
Reference Standard	*CLIA and LC-MS/MS* *TT >= 2.39 nmol/L* *FT >=26.00 pmolL* *DHEAS >=4.92 mmol/L* *FAI >= 6.1*		
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Area under the curve to assess the ability* *to predict hirsutism based on the total testosterone level or its corresponding FAI*		
Inclusion and exclusion criteria reported?	Yes Partial No Not reported	*Yes*	
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*	
Summary Result/s	*In this East Asian population, total testosterone was found to be a strong predictor of the presence and degree of hyperandrogenism (i.e. assessed by the presence and degree of hirsutism), but this finding was obtained only if the total testosterone level was measured by LC-MS/MS and not by CLIA. These findings might have important implications for global epidemiologic, phenotypic and clinical studies of PCOS.*		
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
PATIENT SELECTION/SPECTRUM BIAS	Was the spectrum of patients representative of the patients who will receive the test in practice?	Yes Partial No Not reported	*Yes*
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes Partial No Not reported	*Not reported*
	Was a case-control design avoided? (Q-2)	Yes Partial No Not reported	*No*
	Did the study avoid inappropriate exclusions? (Q-2)	Yes Partial No Not reported	*Yes*

CLASSIFICATION/ VERIFICATION/ INCORPORATION/ REVIEW BIAS	Were all participants assessed with both index test and reference standard?	Yes Partial No Not reported	*Yes*
	Did all patients receive the same reference standard? (Q-2)	Yes Partial No Not reported	*Yes*
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes Partial No Not reported	*Yes*
	Was the reference standard independent of the index test (ie. the index test did not form part of the reference standard)?	Yes Partial No Not reported	*Yes*
	Were the reference standard results interpreted without knowledge of the results of the index test?	Yes Partial No Not reported	*Not reported*
	Were the index test results interpreted without knowledge of the results of the reference standard test?	Yes Partial No Not reported	*Not reported*
	If a threshold was used, was it pre-specified?	Yes Partial No Not reported	*Yes*
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?	Yes Partial No Not reported	*Not reported*
ATTRITION BIAS	Were withdrawals from the study explained?	*X% treatment* *X% control/ comparison*	*Numbers described as enrolled are the same as those in results.*

REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Yes Partial No Not reported	*Yes*
OTHER ISSUES – APPLICABILITY/ COMPARABILITY/ VARIATION	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes Partial No Not reported	*Yes*
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Yes Partial No Not reported	*Not reported*
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes Partial No Not reported	*Not reported*
	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS		*No clear explanation if clinical hyperandrogenism was assessed by the same assessor or if training occurred for standardised assessment.*	
What is the overall risk of bias?		*Moderate*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 1

Question 1.3.

In women with suspected PCOS, what is the most effective measure to clinically diagnose PCOS related hyperandrogenism?

BACKGROUND:

Prevalence and problem

Hyperandrogenism is one of three principal features of PCOS, and affects between 60% and 100% of patients, depending on diagnostic criteria used and PCOS phenotypes considered. Hyperandrogenism can be assessed biochemically (i.e., hyperandrogenemia) and/or clinically. Clinical features of hyperandrogenism are present in a significant majority of patients with PCOS, particularly in referral (clinical) population (1) and are relatively low cost to assess, solely requiring clinician vigilance, astuteness, and skill. Assessment is impacted by treatment (cosmetic and medical) of hirsutism.

Clinical practice gap and need for guidance

Signs and symptoms of severe degrees of androgen excess in women can result in virilization (e.g., male pattern balding, severe hirsutism, and clitoromegaly) and masculinization (e.g., deepening of the voice, breast atrophy, and android changes to skeletal muscles, bones and, in the case of fetus or young children, the external genitalia). In general, the presence of any of these signs (e.g., clitoromegaly, male-pattern balding, severe hirsutism, or evidence of masculinization) is highly predictive of androgen excess.

However, more common is clinical evidence of mild to moderate androgen excess, including hirsutism, acne, and female pattern hair loss (FPHL). Overall, the exact cut-off for defining what is ‘abnormal’ and the predictive value of these signs and symptoms remains unclear, may vary by ethnicity, and requires clinician training and vigilance.

Summary of key information

Responding to the question “In women with suspected PCOS, what is the most effective measure to clinically diagnose PCOS-related hyperandrogenism?” requires addressing two critical questions: a) What is the exact cut-off for defining what is ‘abnormal’ for the various signs and symptoms being considered; and b) What is the predictive value of ‘abnormal’ of these signs and symptoms? In this context, let us consider the three most common clinical signs of mild to moderate hyperandrogenism: hirsutism, acne, and alopecia.

Hirsutism: The most recognizable clinical sign of hyperandrogenism is the presence of terminal hairs in a male-like pattern in women, i.e., hirsutism. Elevated androgens are detected in the vast majority (>70%) of women with hirsutism and few women with hirsutism do not demonstrate other features of PCOS (<5%) (2,3). While various methods of visually assessing excess terminal hair growth in a male-like pattern in women have been reported, the one that is used in the vast majority of studies today is the modified Ferriman-Gallwey (m-FG) scoring method (4,5). The scale assesses the presence of terminal hairs (hairs that would grow >5 mm in length if left unmolested, are usually pigmented, and are medullated) in areas that are primarily masculine.

While Ferriman and Gallwey initially reported on hair growth in eleven body areas (4), they and others noted that hair growth on the lower legs and lower arms do not correlate well with hair growth in the remaining body areas (i.e., terminal hair growth can occur in the lower legs and lower arms in women, whether they are hyperandrogenic or not). Hence, the Ferriman-Gallwey visual score was ‘modified’ to include assessment of only nine body areas: upper lip, chin and neck, upper chest (excluding the nipples), upper abdomen (above the umbilicus), lower abdomen (below the umbilicus also known as male escutcheon), thighs (front and/or back), upper back, lower back, and upper arms (5,6). Each area is visually scored from zero (no terminal hair visible)

to four (terminal hair consistent with a well-developed male), and the score in each body area is summed to yield a total score. A photographic atlas for the modified Ferriman-Gallwey (mFG) scoring system has been published (5).

Defining what is 'abnormal' in hirsutism remains somewhat unclear. While many investigators define the cut-off value for an m-FG score by percentile (i.e., a score >6-8 is usually consistent with the 95th percentile of Black, White, or Asian populations of unselected (medically unbiased) women [4,6,7]) this may not actually represent the true 'abnormal' value. Studies using cluster analysis have suggested that a m-FG scores assessed by a health practitioner of >3 in White and Black women (8) and >5 in Asian (Han Chinese) women (9), represents true abnormality. In Han Chinese, the cut-off value determined by cluster analysis varied by age, with scores of 6, 5, and 4 for women aged 20–25, 26–30, and >30 years, respectively (9). In a study of non-health-care-seeking women of various races, aged 18 to 39 years, recruited from the eastern states of Australia the cut-off value for a self-reported mFG score that corresponded to their appearance when not using treatment for excess hair using cluster analysis was found to be 10 (10). These data suggest that women may overestimate the degree of hirsutism when self-reporting excess hair growth. An international multicenter study, the PCOS Phenotype in Unselected Populations (PPUP) Study, has been undertaken to assess the cut-off values of mFG determined by cluster analysis in different racial and ethnic groups (11).

Overall, pending the results of the PUPP Study (11), these limited data suggest that, while there may be differences in the degree and prevalence of hirsutism between ethnic groups (see below), there appears to be only small differences in the cut-off values for determining excess terminal facial and body hair as abnormal (i.e., defining 'hirsutism'), which may range from 3 to 5 using the mFG score when assessed by a healthcare provider. Greater than 50% of women with mFG scores in the range of 3-5 having evidence of hyperandrogenism and/or PCOS (12) and >70-90% of women with scores >5 demonstrating the same (5,7).

Ethnicity may impact body and facial hair growth (2,5,13-16). Alternatively, the prevalence and degree of hirsutism appears to be lower in Eastern Asian women, but higher in Southeastern Asian women (15,16). As referral bias may significantly skew results, we should note that in unselected women, there does not seem to be any significant difference between Black and White patients, at least in the United States (7,8).

When considering these data, it is important to keep in mind that there is important referral bias in patients seen clinically, who tend to be more hyperandrogenic than PCOS women identified in the general population in epidemiologic studies (1,17). Additionally, most women will cosmetically treat their excess hair growth, thus making it more difficult to detect the presence of hirsutism. Consequently, clinicians should be prepared to assess <u>any</u> patient that presents with complains of excess hair growth, regardless of whether there is obvious evidence of hirsutism or not (12,18).

<u>Acne:</u> Regarding cut-off value for defining acne, we note that there are none, at least not in the way cut-offs for hirsutism are being defined. Acne is simply defined by the presence of skin lesions, ranging from mild to severe. To date, there is no universally agreed upon grading system for acne (19). In general, there are four broad approaches to assessing acne severity: 1) lesion counting, 2) global acne severity grading, 3) subjective self-assessment, and 4) multimodal digital imaging (20).

A number of studies have found that acne is associated with biochemical evidence of hyperandrogenism (21,22). While acne not infrequently accompanies hirsutism, few studies have assessed the predictive value of

acne alone as a marker of hyperandrogenism, most of which have been retrospective in nature (2,22). In some studies, the timing of the emergence of acne (adolescent, persistent, or late-onset) has been related to the presence of hyperandrogenism, with persistent or late-onset more likely to be associated with androgen excess (19,21). Overall, while acne in women may be a clinical predictor of androgen excess, the predictive value of acne alone for hyperandrogenism remains unclear and is likely low.

Female Pattern Hair Loss (FPHL): As for acne, not attempt has been made to assess cut-off values to define FPHL, and instead note the extent of such hair loss. There are typically two patterns of hair loss in FPHL: centrifugal expansion in mid scalp with preservation of the frontal hair line (Ludwig pattern) (23) and a frontal accentuation or Christmas tree pattern (Olsen pattern) (24). There appears to be differences in the prevalence of FPHL by ethnicity (23). Most studies of women with FPHL, characterized by diffuse sagittal scalp alopecia, reveal a relatively low prevalence of hyperandrogenemia (2,25,26). Furthermore, most studies have not clearly separated women with FPHL alone vs. those with FPHL and hirsutism; thus the predictive value of FPHL alone for androgen excess remains unclear. A recent report from the multidisciplinary androgen excess and PCOS committee coordinated by the Androgen Excess and PCOS Society observed that isolated FPHL should not be considered a sign of hyperandrogenism when androgen levels are normal (26). Overall, FPHL alone, and not in the presence of hirsutism, is a modest clinical predictor of hyperandrogenism.

GRADE EVIDENCE CERTAINTY	
Comparison	**GRADE for critical outcomes**
○ **Comparison 1.** mFG ≥8 vs total testosterone (3 studies)	⨁◯◯◯ VERY LOW
○ **Comparison 2.** mFG ≥8 vs free testosterone (3 studies)	⨁◯◯◯ VERY LOW
○ **Comparison 3.** mFG ≥8 vs DHEAS (2 studies)	⨁◯◯◯ VERY LOW
○ **Comparison 4.** mFG ≥8 vs Androstenedione (1 study)	⨁◯◯◯ VERY LOW
○ **Comparison 5.** FG ≥9 vs TT, FAI, DHT, DHEAS, androstenedione (1 study)	⨁◯◯◯ VERY LOW
○ **Comparison 6.** mFG ≥5 vs TT (LC_MS/MS and CLIA) (1 study)	⨁◯◯◯ VERY LOW
○ **Comparison 7.** mFG ≥5 vs FAI (LC-MS/MS and CLIA) (1 study)	⨁◯◯◯ VERY LOW
○ **Comparison 8.** sFG ≥3 vs TT (LC_MS/MS and CLIA) (1 study)	⨁◯◯◯ VERY LOW
○ **Comparison 9.** sFG ≥3 vs FAI (LC-MS/MS and CLIA) (1 study)	⨁◯◯◯ VERY LOW
○ **Comparison 10.** Alopecia vs total testosterone, free testosterone (1 study)	⨁◯◯◯ VERY LOW
○ **Comparison 11.** Acne vs free testosterone (1 study)	⨁◯◯◯ VERY LOW

Evidence to Recommendations Framework

COMPARISONS (option versus other option)

The presence of clinical signs of hyperandrogenism (hirsutism, acne, and female pattern hair loss (FPHL) is comparable to the presence of biochemical hyperandrogenism (i.e., hyperandrogenemia).

EVIDENCE-BASED RECOMMENDATION(S)

EBR: The presence of hirsutism alone should be considered predictive of biochemical hyperandrogenism and PCOS in adults.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

EBR: Health professionals should recognize that female pattern hair loss and acne in isolation (without hirsutism), are relatively weak predictors of biochemical hyperandrogenism.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

CR: A comprehensive history and physical examination should be completed for symptoms and signs of clinical hyperandrogenism, including acne, female pattern hair loss and hirsutism in adults, and severe acne and hirsutism in adolescents.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

CR: Health professionals should be aware of the potential negative psychosocial impact of clinical hyperandrogenism and should consider the reporting of unwanted excess hair growth and/or female pattern hair loss as being important, regardless of apparent clinical severity.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

CR: A modified Ferriman Gallwey score (mFG) of 4 - 6 should be used to detect hirsutism, depending on ethnicity, acknowledging that self-treatment is common and can limit clinical assessment.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

CR: Healthcare professionals should consider that the severity of hirsutism may vary by ethnicity but the prevalence of hirsutism appears similar across ethnicities.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

PRACTICE POINT(S)

Health professionals should:

- Be aware that standardised visual scales are preferred when assessing hirsutism, such as the modified Ferriman-Gallwey scale in combination with a photographic atlas.
- Consider the Ludwig or Olsen visual scales for assessing female pattern hair loss.
- Note that there are no universally accepted visual instruments for assessing the presence of acne.
- Recognise that women commonly treat clinical hyperandrogenism cosmetically, diminishing apparent clinical severity.
- Appreciate that self-assessment of unwanted excess hair growth, and possibly acne and female pattern hair loss, has a high degree of validity and is important, even if overt clinical signs of hyperandrogenism are not readily evident on examination.
- Only terminal hairs should be considered in defining hirsutism, which can reach >5 mm if untreated, vary in shape and texture, and are generally pigmented.
- Note that new-onset severe or severely worsening hyperandrogenism, including hirsutism, requires further investigation to rule out androgen-secreting tumours or ovarian hyperthecosis.
- Monitor clinical signs of hyperandrogenism, including hirsutism, acne and female pattern hair loss, for improvement or treatment adjustment during therapy .

GRADE CONSIDERATIONS

Justifications:

- The additional studies identified since 2017 shed limited additional light on the question “In women with suspected PCOS, what is the most effective measure to clinically diagnose PCOS-related hyperandrogenism?”.
- While the studies compare clinical markers of hyperandrogenism (hirsutism, acne, and FPHL) to biochemical evidence of hyperandrogenism (hyperandrogenemia), the variability in androgens assessed, methodologies used, and normative values established for the measurement of hyperandrogenemia, accompanied by variances in the cut-offs values used for hirsutism, and the paucity of universally accepted scales for acne, make the results of this GRADE assessment weaker than desired.

Subgroup considerations:

- Ethnicity: Although current data indicates that the m-FG cut-off value for defining hirsutism does not appear to vary widely between ethnic groups, while the prevalence and degree of severity tends to vary by ethnicity, the data available is relatively limited. Furthermore, most of the data available exploring the impact of ethnicity is impacted by referral (clinical or medical) bias and lacks head-to-head comparisons of different ethnic groups in the same population.
- Age: Age impacts clinical markers of hyperandrogenism. For example, hirsutism is a progressive disorder, worsening with age, although it may begin to improve as patients approach menopause. In one study (9), the mFG cut-off scores, determined by cluster analysis. were of 6, 5, and 4 for women aged 20–25, 26–30, and >30 years, respectively. FPHL is a progressive disorder, which may worsen with age and menopause. Acne is most predominant among adolescents and less so among adults.
- Higher weight: This may impact the degree and presentation of clinical signs of hyperandrogenism, although unbiased data here is generally lacking.

Implementation considerations:

- There are no technical considerations to the implementation of these recommendations, excluding the need for greater education and awareness.
- Enhanced education of health practitioners is needed regarding the need to assess women for clinical signs of hyperandrogenism as part of the routine health assessment, whether the patient presents with these complaints or not, considering the high prevalence of these signs (e.g., > 10% of unselected women demonstrate hirsutism) and of PCOS (10-15%) in the general female population.
- Enhanced education of health practitioners is needed regarding the methods for assessing for clinical markers of hyperandrogenism and the significant negative psychosocial impact.
- Enhanced education of the general population is needed that unwanted excess male-like body hair growth, scalp hair loss, and persistent acne in women are more than a dermatologic nuisance and may be signs of an underlying endocrine-metabolic disorder and requires a medical evaluation.

Monitoring and evaluation considerations:

- Evaluation of the clinical implementation of the recommendation (e.g. reduce biochemical hyperandrogenism assessments)

Research priorities:

- In an unselected (i.e., medically unbiased) population, including adolescents, determine the predictive value of the following for biochemical hyperandrogenism and/or PCOS
    - acne alone, without hirsutism
    - Female pattern hair loss alone, without hirsutism
    - Hirsutism alone
- Determine the naturally occurring ‘abnormal’ cut-off value of the mFG score for defining hirsutism, by ethnicity, and BMI, in a large unselected (i.e., medically unbiased) population.
- Determine the prevalence of hirsute women in epidemiologic studies who have not explored medical attention for the disorder.
- Determining a simpler method of assessing hirsutism (including validity of self-reported hirsutism)
- Cost effectiveness of implementation of recommendation of clinical hyperandrogenism assessment.

GRADE framework

GRADE DECIDE Interactive Evidence to Decision Framework

● DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

- The current and past data indicates significant association between the presence of hirsutism and biochemical hyperandrogenism, although cut-off values for hirsutism varied widely, as did and the androgens assessed and the assay methods used.
- There is some data (1 study post 2017) suggesting an association of acne to biochemical hyperandrogenism, although it is less clear whether acne alone is a good predictor.
- There is some data (1 study post 2017) suggesting an association of FLHP to biochemical hyperandrogenism, although it is less clear whether FLHP alone is a good predictor.

● UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

Judgement:

☐ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☒ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Other options may be more costly.

● CERTAINTY OF THE EVIDENCE

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☒ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

- The overall certainty of the evidence of effects is very low.

● VALUES

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☐ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☒ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Research evidence:

No research evidence was identified

Panel discussion:

There is uncertainty regarding how much patients and health care practitioners appreciate the signs of hirsutism, acne and FHLP as markers of hyperandrogenism.

● BALANCE OF EFFECTS

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:

At a minimum, hirsutism appears to be associated with evidence of biochemical hyperandrogenism.

● COSTS

How large are the resource requirements (costs)?

Judgement:

☐ Don't know	☐ Varies	☐ Large costs	☐ Moderate costs	☒ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:

No research evidence was identified

Panel discussion:

Cost will vary depending on the extent of health practitioner and public education. Costs are minimal to implement recommendations if education is already in place.

Lower cost to health system and women.

● CERTAINTY OF COST EVIDENCE

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

No research evidence was identified

Panel discussion:

High certainty regarding the low costs of using visual scales for hirsutism, acne and FPHL. Unclear what the cost of widespread education regarding their use is.

● COST-EFFECTIVENESS

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

No research evidence was identified

Panel discussion:

The low cost of implementing visual scales for the assessment of hirsutism, acne and FPHL strongly suggests that the option of using signs of clinical hyperandrogenism instead of biochemical measures of hyperandrogenemia is cost-effective.

● EQUITY

What would be the impact on health equity?

Judgement:

☐ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☒ Probably increased	☐ Increased

Research evidence:

No research evidence was identified

Panel discussion:

The widespread use of low-cost visual scales for assessing clinical signs of hyperandrogenism (i.e., hirsutism, acne, and FPHL), instead of more costly biochemical measures of hyperandrogenemia, would have a positive effect on care for the underserved, under-resourced population.

● ACCEPTABILITY

Is the option acceptable to key stakeholders?

Judgement:

☐ Don't know	☒ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Women and many healthcare providers will likely find the recommendations acceptable, given the relative negative psychosocial impact of clinical signs of hyperandrogenism, the low cost and ease of implementing the use of these markers, and the value of these markers for predicting disease (including PCOS, metabolic dysfunction, etc.).

The limitation of frequent self-treatment of hirsutism will impact assessment.

● FEASIBILITY

Is the option feasible to implement?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

There are few significant barriers to the implementation of the recommendations, with the exception of the need for education.

Some healthcare providers may not find the recommendations easy to implement.

The limitation of frequent self-treatment of hirsutism will impact assessment.

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PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by ECR Lead: Marla Lujan

Other Members: Jeff Pea, Jahnay Bryan, Cynthia Wan, Alexis Oldfield

Supervised, edited and supported by the Evidence Team (Aya Mousa, Jillian Tay)

GDG 1

Question 1.4.

What is the most effective ultrasound criteria to diagnose PCOS? When is ultrasound indicated to diagnose PCOS?

1. SELECTION CRITERIA

Table 1. PICO Criteria for Inclusion – Not to be adapted
To be used by evidence team to decide which studies will be included when screening search results.

Question	1) What is the most effective ultrasound criteria to diagnose PCOS? 2) When is ultrasound indicated to diagnose PCOS?
Clinical leads (key contacts)	A/Prof Marla Lujan Division of Nutritional Sciences Cornell University, USA marla.lujan@cornell.edu Prof Sharon Oberfield Paediatric endocrinologist Columbia University Medical Centre, USA seo8@cumc.columbia.edu
Allocation ranking	Level 2- updated systematic review

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(language, year)*
Inclusion	Women of reproductive age of any ethnicity or across spectrum of adiposity. Includes both women with and without previous diagnosis of PCOS. PCOS diagnosed based on NIH (1990), Rotterdam (2003), AE-PCOS (2006) or International Guideline (2018) criteria.	Follicle number per ovary (FNPO or equivalent), follicle number per cross-section (FNPS, or equivalent), ovarian volume (OV), and/or stromal features used in the diagnosis of PCOS. Includes different machinery, different resolutions (MHz) and age-related criteria.	Not applicable. No comparison of different criteria / methods to assess polycystic ovarian morphology (PCOM).	Diagnosis of PCOS using a proposed diagnostic threshold from the study population. May contain sensitivity, specificity, and/or AUC data.	Observational (e.g., case control, cohort, cross-sectional), randomized and non-randomized control trials (baseline measures).	Studies in English language. Limited to studies published from 1990 to present.
Exclusion	Pregnant or menopausal-aged (>50yo) women. PCOS diagnosis does not comply with NIH, Rotterdam, AE-PCOS or International Guideline criteria.	Criteria that do not assess ovarian morphology associated with PCOM. Other imaging methods (e.g., MRI, CT)	None.	No diagnostic threshold is proposed or diagnostic accuracy measures determined from study population to diagnose PCOS.	Systematic reviews, evidence-based guidelines, non-peer reviewed studies (e.g., commentaries, letters, editorials), case series, and animal studies.	Studies not in the English language. Studies published prior to 1990.

2. SEARCH STRATEGY

Table 2.1. Search details	
Search strategy source: *[enter doi or 2018 technical report page number where search string was derived]*	
Evidence source	Date of search
Medline (Pubmed)	09/08/2022
Web of Science	09/08/2022
Scopus	09/08/2022
CENTRAL	09/08/2022
CINAHL	09/08/2022
Any subsequent updates - enter database and date:	

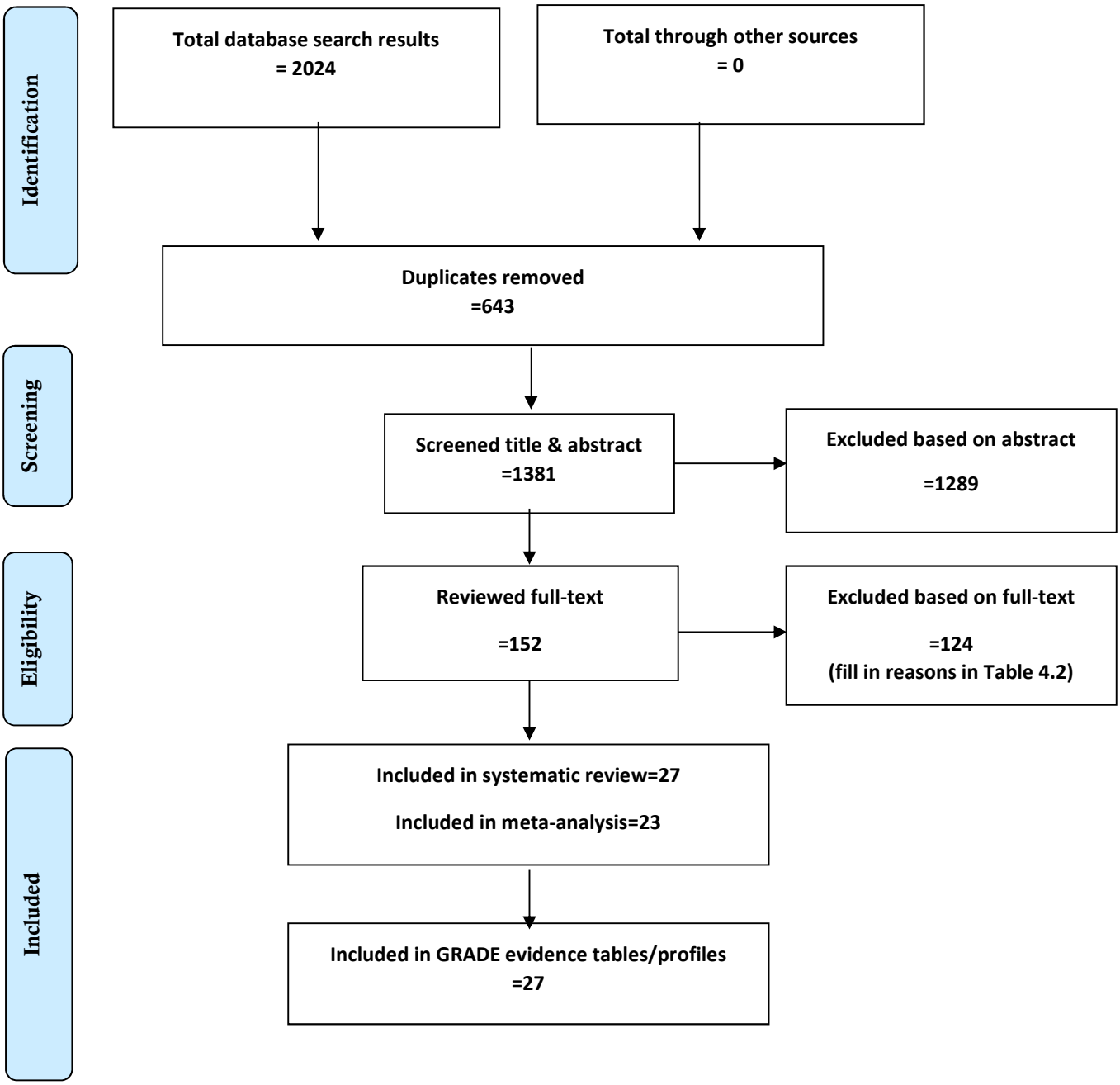
Table 2.2. Questions addressed by this search *(add more rows as needed)*:		
GDG	**Q#**	**Question**
1	1.4	What is the most effective ultrasound criteria to diagnose PCOS?

Table 2.3. Search strings used in OVID or other database/s – *please save a screenshot of search results to submit alongside this template*				
Medline (Pubmed)?	**Web of Science?**	**Similar Scopus?**	**CINAHL?**	**Same CENTRAL?**
1. polycystic ovary syndrome [mh] 2. polycystic ovar* [tiab] 3. poly-cystic ovar* [tiab] 4. PCOS or PCO* [tiab] 5. Stein-Leventhal or Leventhal [tiab] 6. anovulation [mh] 7. anovulat* [tiab] 8. oligo-ovulat* [tiab] 9. oligoovulat* [tiab] 10. sclerocystic ovary syndrome [tiab] 11. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 12. Diagnosis [mh] 13. diagnos* [tiab] 14. sensitivity [tiab] 15. specificity [tiab] 16. ROC curve [tiab] 17. AUC [tiab] 18. threshold [tiab] 19. accuracy [tiab] 20. diagnostic accuracy [tiab] 21. predictive value [tiab] 22. #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21	Similar terms appropriately translated	Similar terms appropriately translated	Similar terms appropriately translated	Similar terms appropriately translated

23. ultrasound [tiab] 24. ultrasonograph* [tiab] 25. sonograph* [tiab] 26. imag* [tiab] 27. #23 OR #24 OR #25 OR #26 28. Ovary [mh] 29. ovar* [tiab] 30. Cysts [mh] 31. cyst* [tiab] 32. follic* [tiab] 33. antral follicle* [tiab] 34. polycystic ovarian morphology [tiab] 35. PCOM [tiab] 36. #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 37. volume [tiab] 38. size [tiab] 39. diameter [tiab] 40. distribution [tiab] 41. population [tiab] 42. morphology [tiab] 43. #37 OR #38 OR #39 OR #40 OR #41 OR #42 44. #11 AND #22 AND #27 AND #36 AND #43 45. limit 44 to Humans 46. limit 45 to Journal Article 47. limit 46 to Female 48. limit 47 to English 49. limit 48 to yr “1990-2022”				

Evidence processing: Studies were selected and appraised by three reviewer/s in consultation with the evidence team/ key contact using study selection and appraisal criteria (PICO above) established a priori. The articles were reviewed by title and abstract by three reviewers. When a decision could not be made based on title and abstract alone, full text was retrieved. **A total of 27 studies met inclusion criteria for this review.**

3. SEARCH RESULTS - PRISMA flowchart



4. STUDY INCLUSION

Table 4.1. Included Studies (full citation with doi)
Ahmad AK, Quinn M, Kao CN, Greenwood E, Cedars MI, Huddleston HG. Improved diagnostic performance for the diagnosis of polycystic ovary syndrome using age-stratified criteria. *Fertil Steril* 2019;**111**:787–793. DOI: **10.1016/j.fertnstert.2018.11.044**
Allemand MC, Tummon IS, Phy JL, Foong SC, Dumesic DA, Session DR. Diagnosis of polycystic ovaries by three-dimensional transvaginal ultrasound. *Fertil Steril* 2006;**85**:214–219. DOI: **10.1016/j.fertnstert.2005.07.1279**
Alsamarai S, Adams JM, Murphy MK, Post MD, Hayden DL, Hall JE, Welt CK. Criteria for polycystic ovarian morphology in polycystic ovary syndrome as a function of age. *J Clin Endocrinol Metab* 2009;**94**:4961–4970. DOI: **10.1210/jc.2009-0839**
Bili AE, Dampala K, Iakovou I, Tsolakidis D, Giannakou A, Tarlatzis BC. The combination of ovarian volume and outline has better diagnostic accuracy than prostate-specific antigen (PSA) concentrations in women with polycystic ovarian syndrome (PCOs). *Eur J Obstet Gynecol Reprod Biol* 2014;**179**:32–35. DOI: **10.1016/j.ejogrb.2014.05.006**
Carmina E, Campagna AM, Fruzzetti F, Lobo RA. AMH measurement versus ovarian ultrasound in the diagnosis of polycystic ovary syndrome in different phenotypes. *Endocr Pract* 2016;**22**:287–293. DOI: **10.4158/EP15903.OR**
Chen Y, Li L, Chen X, Zhang Q, Wang W, Li Y, Yang D. Ovarian volume and follicle number in the diagnosis of polycystic ovary syndrome in Chinese women. *Ultrasound Obstet Gynecol* 2008;**32**:700–703. DOI: **10.1002/uog.5393**
Chen Y, Yang D, Li L, Chen X. The role of ovarian volume as a diagnostic criterion for Chinese adolescents with polycystic ovary syndrome. *J Pediatr Adolesc Gynecol* 2008; **21**:347-350. DOI: **https://doi.org/10.1016/j.jpag.2008.01.081**
Christ JP, Willis AD, Brooks ED, Brink H Vanden, Jarrett BY, Pierson RA, Chizen DR, Lujan ME. Follicle number, not assessments of the ovarian stroma, represents the best ultrasonographic marker of polycystic ovary syndrome. *Fertil Steril* 2014;**101**:280–287. DOI: **10.1016/j.fertnstert.2013.10.001**
Çiraci S, Tan S, Özcan AŞ, Aslan A, Keskin HL, Ateş ÖF, Akçay Y, Arslan H. Contribution of real-time elastography in diagnosis of polycystic ovary syndrome. *Diagnostic Interv Radiol* 2015;**21**:118–122. DOI: **10.5152/dir.2014.14094**
Dewailly D, Alebić M, Duhamel A, Stojanović N. Using cluster analysis to identify a homogeneous subpopulation of women with polycystic ovarian morphology in a population of non-hyperandrogenic women with regular menstrual cycles. *Hum Reprod* 2014;**29**:2536–2543. DOI: **10.1093/humrep/deu242**
Dewailly D, Gronier H, Poncelet E, Robin G, Leroy M, Pigny P, Duhamel A, Catteau-Jonard S. Diagnosis of polycystic ovary syndrome (PCOS): revisiting the threshold values of follicle count on ultrasound and of the serum AMH level for the definition of polycystic ovaries. *Hum Reprod* 2011;**26**:3123–3129. DOI: **10.1093/humrep/der297**
Diamanti-Kandarakis E, Livadas S, Katsikis I, Piperi C, Mantziou A, Papavassiliou AG, Panidis D. Serum concentrations of carboxylated osteocalcin are increased and associated with several components of the polycystic ovarian syndrome. *J Bone Miner Metab* 2011;**29**:201–206. DOI: **https://dx.doi.org/10.1007/s00774-010-0211-2**
Ersen E, Özgür DT, Özüm T. Is shear wave elastography relevant in the diagnosis of polycystic ovarian syndrome? *Med Ultrason* 2019;**21**:158-162. DOI: **10.11152/mu-1849**
Fulghesu AM, Ciampelli M, Belosi C, Apa R, Pavone V, Lanzone A. A new ultrasound criterion for the diagnosis of polycystic ovary syndrome: ovarian stroma/total area ratio. *Fertil Steril* 2001;**76**:326–331. DOI: **10.1016/s0015-0282(01)01919-7**
Jarrett BY, Brink H Vanden, Brooks ED, Hoeger KM, Spandorfer SD, Pierson RA, Chizen DR, Lujan ME. Impact of right–left differences in ovarian morphology on the ultrasound diagnosis of polycystic ovary syndrome. *Fertil Steril* 2019;**112**:939–946. DOI: **10.1016/j.fertnstert.2019.06.016**
Jonard S, Robert Y, Dewailly D. Revisiting the ovarian volume as a diagnostic criterion

for polycystic ovaries. *Hum Reprod* 2005;**20**:2893–2898. DOI: **10.1093/humrep/dei159**
Kar S, Swoyam S. 2D and 3D trans-vaginal sonography to determine cut-offs for ovarian volume and follicle number per ovary for diagnosis of polycystic ovary syndrome in Indian women. *J Reprod Infertil* 2018;**19**:146–151.
Khashchenko E, Uvarova E, Vysokikh M, Ivanets T, Krechetova L, Tarasova N, Sukhanova I, Mamedova F, Borovikov P, Balashov I, Sukhikh, G. The Relevant Hormonal Levels and Diagnostic Features of Polycystic Ovary Syndrome in Adolescents. *J of Clin Med* 2020;**9.** DOI: **10.3390/jcm9061831**
Kim HJ, Adams JM, Gudmundsson JA, Arason G, Pau CT, Welt CK. Polycystic ovary morphology: age-based ultrasound criteria. *Fertil Steril* 2017;**108**:548–553. DOI: **10.1016/j.fertnstert.2017.07.005**
Köninger A, Koch L, Edimiris P, Enekwe A, Nagarajah J, Kasimir-Bauer S, Kimmig R, Strowitzki T, Schmidt B. Anti-Mullerian Hormone: an indicator for the severity of polycystic ovarian syndrome. *Arch Gynecol Obstet* 2014;**290**:1023–1030. DOI: **10.1007/s00404-014-3317-2**
Kösüs N, Kösüs A, Turhan NÖ. Relationship of ovarian volume with mean platelet volume and lipid profile in patients with polycystic ovary syndrome. *Exp Ther Med* 2011;**2**:1141–1144. DOI: **10.3892/etm.2011.327**
Kösüs N, Kösüs A, Turhan NÖ, Kamalak Z. Do threshold values of ovarian volume and follicle number for diagnosing polycystic ovarian syndrome in Turkish women differ from western countries? *Eur J Obstet Gynecol Reprod Biol* 2011;**154**:177–181. DOI: **10.1016/j.ejogrb.2010.10.007**
Le NSV, Le MT, Nguyen ND, Tran NQT, Nguyen QHV, Cao TN. A cross-sectional study on potential ovarian volume and related factors in women with polycystic ovary syndrome from infertile couples. *Int J Womens Health* 2021;**13**:793–801. DOI: **10.2147/IJWH.S329082**
Lie Fong S, Laven JSE, Duhamel A, Dewailly D. Polycystic ovarian morphology and the diagnosis of polycystic ovary syndrome: redefining threshold levels for follicle count and serum anti-Müllerian hormone using cluster analysis. *Hum Reprod* 2017;**32**:1723–1731. DOI: **10.1093/humrep/dex226**
Lujan ME, Jarrett BY, Brooks ED, Reines JK, Peppin AK, Muhn N, Haider E, Pierson RA, Chizen DR. Updated ultrasound criteria for polycystic ovary syndrome: Reliable thresholds for elevated follicle population and ovarian volume. *Hum Reprod* 2013;**28**:1361–1368. DOI: **10.1093/humrep/det062**
Özay, OE, Özay AC, Gün, I. Comparison of stromal thickness and doppler findings in polycystic ovary syndrome and healthy women with ultrasonographic evidence of polycystic ovaries? A cross-sectional study. *J Obstet Gynaecol* 2022;**42:** 2367-2372. DOI: **10.1080/01443615.2022.2054684**
Villa P, Rossodivita A, Sagnella F, Moruzzi MC, Mariano N, Lassandro AP, Pontecorvi A, Scambia G, Lanzone A. Ovarian volume and gluco-insulinaemic markers in the diagnosis of PCOS during adolescence. *Clin Endocrinol* 2013;**78**:285-290. DOI: **10.1111/j.1365-2265.2012.04475.x**
Villaroel C, López P, Merino PM, Iñiguez G, Sir-Petermann T, Codner E. Hirsutism and oligomenorrhea are appropriate screening criteria for polycystic ovary syndrome in adolescents. *Gynecol Endocinol* 2015;**31**:625-629. DOI: **10.3109/09513590.2015.1025380**
Wongwananuruk T, Panichyawat N, Indhavivadhana S, Rattanachaiyanont M, Angsuwathana S, Techatraisak K, Pratumvinit B, Sa-nga-areekul N. Accuracy of anti-Müllerian hormone and total follicles count to diagnose polycystic ovary syndrome in reproductive women. *Taiwan J Obstet Gynecol* 2018;**57**:499–506. DOI: **10.1016/j.tjog.2018.06.004**

Table 4.2. Excluded Studies (on full text assessment)

Reference	Reason

Abarra et al. 2019	No comparisons between PCOS and control populations
Ahmed et al. 2020	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Ahmed et al. 2019	No comparisons between PCOS and control populations
Alebic et al. 2015	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Ali et al. 2016	Wrong PCOS diagnosis
Amer et al. 2002	Wrong PCOS diagnosis
Asanidze et al. 2021	No data on primary outcomes (e.g. no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Assens et al. 2020	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Atiomo et al. 2000	Wrong PCOS diagnosis
Avvad et al. 2001	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Azziz 2004	Wrong study design (e.g., review, commentary, opinion)
Battaglia et al. 1995	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Battaglia et al. 2012	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Battaglia et al. 2004	Wrong study design (e.g., review, commentary, opinion)
Bell et al. 2022	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Birdsall & Farquhar 1996	Wrong patient population (e.g., no PCOS or control group)
Botsis et al. 1995	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Buckett et al. 1999	Wrong PCOS diagnosis
Cao et al. 2019	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Carmina et al. 2005	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Carmina et al. 2012	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Carmina et al. 2016	Wrong study design (e.g., review, commentary, opinion)
Carmina et al. 2003	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Catteau-Jonard et al. 2012	Wrong study design (e.g., review, commentary, opinion)
Christ et al. 2017	No data for ultrasonographic measures available
Christ et al. 2018	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Christiansen et al. 2016	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Chu et al. 2005	Wrong PCOS diagnosis
Clayton et al. 1992	Wrong patient population (e.g., no PCOS or control group)
de Loos et al. 2021	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Dewailly et al. 2010	Wrong study design (e.g., review, commentary, opinion)
Dewailly et al. 1993	Wrong PCOS diagnosis
Dewailly et al. 2007	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Dewailly et al. 2014	Wrong study design (e.g., review, commentary, opinion)
Diamanti-Kandarakis &	No data on primary outcomes (e.g., no proposed thresholds /

Panidis 2007	diagnostic accuracy data for diagnosing PCOS)
Dolz et al. 1999	Wrong PCOS diagnosis
Eilertsen et al. 2012	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
El-Mazny & Abou-Salem 2013	Wrong patient population (e.g., no PCOS or control group)
Elting et al. 2003	Wrong patient population (e.g., no PCOS or control group)
Elting et al. 2001	Wrong PCOS diagnosis
Fiçicioğlu et al. 1995	Wrong PCOS diagnosis
Fiçicioğlu et al. 1996	Wrong PCOS diagnosis
Fox et al. 1999	Wrong PCOS diagnosis
Fox et al. 1993	Wrong study design (e.g., review, commentary, opinion)
Fraissinet et al. 2017	Wrong patient population (e.g., no PCOS or control group)
Fruzzetti et al. 2015	Wrong patient population (e.g., no PCOS or control group)
Fulghesu et al. 2006	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Fulghesu et al. 2007	Wrong patient population (e.g., no PCOS or control group)
Gabr & Marei 2019	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Guedikian et al. 2018	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Hajder et al. 2011	No full text available
Herter et al. 1996	Wrong patient population (e.g., no PCOS or control group)
Herter et al. 1993	No full text available
Homer et al. 2019	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Hudecova et al. 2019	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Indran et al. 2018	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Izhar et al. 2021	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Jacewicz-swiecka et al. 2021	Wrong patient population (e.g., no PCOS or control group)
Jiao et al. 2014	No full text available
Jonard et al. 2003	Wrong PCOS diagnosis
Karpagam et al. 2015	Wrong patient population (e.g., no PCOS or control group)
Kenigsberg et al. 2015	No comparisons between PCOS and control populations
Kiddy & Rae 1995	No full text available
Kilani et al. 2017	Wrong patient population (e.g., no PCOS or control group)
Kim et al. 2020	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Köninger et al. 2014	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Korsholm et al. 2017	Wrong patient population (e.g., no PCOS or control group)
Kristensen et al. 2010	No comparisons between PCOS and control populations
Kyei-Mensah et al. 1998	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Kyei-Mensah et al. 1996	Wrong study design (e.g., review, commentary, opinion)
Lam et al. 2009	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Lam et al. 2007	No data on primary outcomes (e.g., no proposed thresholds /

	diagnostic accuracy data for diagnosing PCOS)
Lauritsen et al. 2014	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Lebkowska et al. 2016	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Lee & Rausch 2012	Wrong study design (e.g., review, commentary, opinion)
Legro et al. 2005	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Lentscher et al. 2021	Wrong study design (e.g., review, commentary, opinion)
Leonhardt et al. 2014	No comparisons between PCOS and control populations
Low et al. 2005	Wrong patient population (e.g., no PCOS or control group)
Lujan et al. 2010	Wrong patient population (e.g., no PCOS or control group)
Maas et al. 2015	Wrong patient population (e.g., no PCOS or control group)
Matsuzaki et al. 2017	No data for ultrasonographic measures available
Murphy et al. 2006	Wrong patient population (e.g., no PCOS or control group)
Nardo et al. 2003	Wrong patient population (e.g., no PCOS or control group)
Ng et al. 2006	Wrong patient population (e.g., no PCOS or control group)
Norman et al. 1995	Wrong PCOS diagnosis
Pache et al. 1992	No full text available
Peigné et al. 2018	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Rashad et al. 2019	Wrong study design (e.g., review, commentary, opinion)
Razek & Abou 2021	Wrong patient population (e.g., no PCOS or control group)
Romualdi et al. 2016	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Rosenfield et al. 2012	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Sabahat et al. 2021	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Sahmay et al. 2013	No data for ultrasonographic measures available
Sahmay et al. 2014	No data for ultrasonographic measures available
Saxton et al. 1990	Wrong patient population (e.g., no PCOS or control group)
Shahrami et al. 2016	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Sipahi et al. 2019	Wrong patient population (e.g., no PCOS or control group)
Song et al. 2017	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Sumbul et al. 2022	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Sun & Fu 2007	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Svedsen et al. 2010	No data for ultrasonographic measures available
Svetlana et al. 2019	Wrong PCOS diagnosis
Takahashi et al. 1994	Wrong PCOS diagnosis
Takahashi et al. 1993	Wrong patient population (e.g., no PCOS or control group)
Takahashi et al. 1995	Wrong PCOS diagnosis
Takahashi et al. 1994	Wrong PCOS diagnosis
Takahashi et al. 1992	No full text available
Tena et al. 2011	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Tugrul et al. 2006	No full text available
Turhan et al. 1993	Wrong PCOS diagnosis
van der Westhuizen et al. 1996	Wrong patient population (e.g., no PCOS or control group)

van Santbrink et al. 1997	Wrong PCOS diagnosis
Venturella et al. 2015	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Vutyavanich et al. 2007	No comparisons between PCOS and control populations
Weerakiat et al. 2007	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Welt et al. 2006	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Wiser et al. 2013	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Wissing et al. 2019	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Wu et al. 1998	Wrong PCOS diagnosis
Younesi et al. 2019	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Yue et al. 2018	No comparisons between PCOS and control populations
Zhang et al. 2013	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)
Zhang et al. 2009	No data on primary outcomes (e.g., no proposed thresholds / diagnostic accuracy data for diagnosing PCOS)

5. STUDY CHARACTERISTICS TABLE

Author, year	Risk of Bias	Sample Size per group	Country	Age (yo)	BMI (kg/m^2)	Reference Standard	Index Test	Index Test Method	Transducer Frequency
Ahmad et al. 2019	Moderate	Control: 756 (FNPO, OV) PCOS: 245 (FNPO), 297 (OV)	United States	N/A	N/A	NIH	FNPO, OV	TVUS 2D Real-Time (FNPO)	4-8 MHz, 4-10 MHz
Allemand et al. 2006	Moderate	PCOS: 10 Control: 29	United States	Control: 30.5 ± 3.5y PCOS: 31.20 ± 3.90 p = 0.82	Control: 24.00 ± 5.50 PCOS: 32.20 ± 10.80 p = 0.004	NIH	FNPO, FNPS, OV	TVUS 3D Offline	4-8 MHz
Alsamarai et al. 2009	Moderate	PCOS: 483 (cross-sectional) and 11 (longitudinal) Control: 367 (cross-sectional) and 15 (longitudinal)	United States	Control: 28.1 ± 6.4yo (Younger), 48.1 ± 6.6yo (Older) PCOS: 27.8 ± 5.7yo (Younger), 46.3 ± 4.5yo (Older), p ≤ 0.05 (Control) p ≤ 0.05 (Older)	Control: 24.4 ± 5.1kg/m^2 (Younger), 26.7 ± 5.4kg/m^2 (Older) PCOS: 30.6 ± 8.7kg/m^2 (Younger), 31.3 ± 8.5kg/m^2 (Older) p = not significant	NIH	FNPS, OV	TVUS 2D Real-Time	5 MHz
Bili et al. 2014	High	PCOS: 43 Control: 40	Greece	Control: 30.8 ± 4.30 PCOS: 28.9 ± 5.0 p = 0.030	Control: 22.5 ± 3.7 PCOS: 24.9 ± 5.9 p = 0.029	Rotterdam	OV, OC	TVUS Machine Software	5-7 MHz
Carmina et al. 2016	High	PCOS: 113 Control: 47	Italy	Control: 23.1 ± 4.0 PCOS: 23 ± 4.3	Control: 27 ± 4 PCOS:	Rotterdam	FNPO, OV	TVUS 2D Real-	8-10 MHz

				p = not significant	27.9 ± 7.3 p = not significant			Time	
Chen et al. 2008a	High	PCOS: 432 Control: 153	China	Control: 27.15 ± 2.33 PCOS: 26.25 ± 2.01 p = 0.36	N/A	NIH	FNPO, OV	TVUS/TRUS 2D Real-Time	6 MHz
Chen et al. 2008b [adolescent]	Moderate	PCOS: 69 Control: 26	China	Control: 13.00 ± 1.23 PCOS: 12.57 ± 1.25 p = not significant	Control: 21.77 ± 4.60 PCOS: 20.12 ± 2.17 p = not significant	NIH	OV	TRUS 2D Real-Time	6 MHz
Christ et al. 2014	Moderate	PCOS: 82 Control: 60	United States / Canada	Control: 27 (24-31) PCOS: 28 (24-31) p = not significant	Control: 23.7 (21.9-27.2) PCOS: 31.2 (23.7-37.8) p < 0.0001	NIH	FNPO, FNPS, OV, OA, SA, S/A, SI, FDP	TVUS 2D Offline with Grid Overlay	5-9 MHz, 6-12 MHz
Çiraci et al. 2015	Moderate	PCOS: 48 Control: 48	Turkey	Control: 27.1 ± 5.2 PCOS: 25.7± 4.2 p = 0.092	N/A	Rotterdam	FNPO, OV, SSR	TVUS 2D Real-Time	6.5 MHz
Dewailly et al. 2011	Low	Control (Group 1A): 66 Control + PCOM (Group 1B): 39 HA or oligo-anovulation (Group 2): 72 PCOS (Group 3): 62	France	Control (Group 1A): 30.0 (21.9–34.6) PCOS (Group 3): 27.6 (20.1–34.0) p < 0.05	Control (Group 1A): 24.0 (18.7–37.6) PCOS (Group 3): 28.0 (18.7–41.7) p = not significant	NIH	FNPO, OV	TVUS 2D Real-Time (FNPO) Machine Software (OV)	5-9 MHz
Dewailly et al. 2014	Moderate	Control: 521 PCOS: 272	Croatia	Control: 32.5 (26.0–38.7)	Control: 23.0 (19.0–30.0)	Rotterdam	FNPO	TVUS 2D Real-	5-7 MHz

		- OA+HA (Full-blown): 95 - OA+PCOM: 110 - HA+PCOM: 67		OA + PCOM: 30.3 (24.3– 37.0) HA + PCOM: 30.6 (22.7– 37.5) Full-Blown PCOS: 29.8 (22.4 –36.5) p < 0.05	OA + PCOM: 23.0 (19.0 – 36.9) HA + PCOM: 25.0 (19.0– 34.6) Full-Blown PCOS: 27.0 (20.0-40.0) p < 0.05 (Control vs. HA + PCOM or Full-Blown PCOS)			Time	
Diamanti-Kandarakis et al. 2011	Moderate	Control: 47 PCOS: 50	Greece	Control: 27.15 ± 6.72yo, PCOS: 26.46 ± 5.86yo p = 0.748	Control: 26.27 ± 5.30yo, PCOS: 26.49 ± 5.00yo p = 0.833	NIH	FNPO	TVUS 2D Real-Time	5-7 MHz
Ertekin et al. 2019	Moderate	PCOS: 37 Control: 16	Turkey	Control: 23.0 ± 5.0 PCOS: 21.5 ± 3.7 p = 0.293	Control: 25.5 ± 3.8 PCOS: 24.5 ± 4.8 p = 0.698	Rotterdam	OV	TVUS 2D Real-Time	6 MHz
Fulghesu et al. 2001	Moderate	Control: 30 Multi-Follicular Ovaries (MFO): 27 PCOS: 53	Italy	N/A	Control: 23.15 ± 4.49 MFO: 22.54 ± 2.24 PCOS: 23.61 ± 3.88 p = not significant	Rotterdam	S/A		6.5 MHz
Jarrett et al. 2019	Moderate	Control: 67 PCOS: 87	United States / Canada	Control: 27 (23–31) PCOS: 27 (23–30) p = not significant	Control: 32.0 (23.7–38.2) PCOS: 23.6 (21.5–27.2) p < 0.05	NIH	OV	TVUS 2D Offline with Grid Overlay	5-9 MHz, 6-12 MHz

Jonard et al. 2005	Moderate	Control: 57 PCOS: 98	France	Control: 29.0 (24.5–35.0) PCOS: 27.2 (19.5–33.0) p = not significant	Control: 22.9 (19.0–31.5) PCOS: 27.9 (20.1–40.8) p < 0.002	NIH	FNPO, OV, OA	TVUS 2D Real-Time	7 MHz
Kar and Swoyam 2018	High	PCOS: 86 Control: 45	India	Control: 28.45yo ± 4.62 PCOS: 26.03yo ± 3.52 p = 0.003	Control: 23.02kg/m2 ± 3.58 PCOS: 25.71kg/m2 ± 4.87 p = 0.13	Rotterdam	FNPO, OV	TVUS 2D Real-Time 3D Real-Time	6-12 MHz
Khashchenko et al. 2020 [adolescent]	High	PCOS: 130 Control: 30	Russia	Control: 16.0 (15.0–17.0) PCOS: 16.0 (15.0–17.0)	Control: 20.2 (18.4–21.8) PCOS: 22.4 (19.9–27.2)	Rotterdam	OV, OUI	TAUS 2D Real-Time	1.8-6.0 MHz
Kim et al. 2017	High	Control: 666 (Boston) and 32 (Iceland) PCOS: 544 (Boston) and 105 (Iceland)	United States / Iceland	Control: 27.3 ± 6.2 (Boston) & 32.2 ± 5.5 (Iceland) PCOS: 28.4 ± 6.4 (Boston) & 30.2 ± 6.2 (Iceland) p = 0.002 (Boston) and p = 0.15 (Iceland)	Control: 24.3±4.8 (Boston) & 30.2±7.5 (Iceland) PCOS: 30.7±8.7 (Boston) & 31.5±7.7 (Iceland) p < 0.001 (Boston) and p = 0.3 (Iceland)	NIH	FNPS, OV	TVUS 2D Real-Time	4-8 MHz
Köninger et al. 2014	Moderate	Control: 48 PCOS: 80 - Severe PCOS: 59 - Mild PCOS (without HA): 21	Germany	Control: 34.0 ± 5.5 PCOS: 28.0 ± 5.9	N/A	Rotterdam	FNPO, OV	TVUS 2D Real-Time	3-9 MHz
Köşüş et al. 2011a	High	Control: 100 PCOS: 210	Turkey	Control: 26.7 ± 5.6 PCOS: 26.3 ± 5.4 p = not significant	Control: 20.8 ± 2.4 PCOS: 26.5 ± 5.3 p = not significant	Rotterdam	OV	TVUS 2D Real-Time	6.5 MHz

Köşüş et al. 2011b	High	Control: 65 PCOS: 251	Turkey	Control: 26.7 ± 5.6 PCOS: 24.9 ± 6.1 p = 0.143	Control: 20.8 ± 2.4 PCOS: 27.1 ± 6.2 p < 0.001	AE-PCOS	FNPO, OV	TVUS 2D Real-Time	6.5 MHz
Le et al. 2021	Moderate	Control: 273 PCOS: 119	Vietnam	Control: 33.99 ± 4.78 PCOS: 32.66 ± 4.10 p = 0.042	Control: 20.82 ± 2.56 PCOS: 21.31 ± 2.80 p < 0.001	Rotterdam	OV	TVUS 2D Real-Time	7 MHz
Lie Fong et al. 2017	High	Control: 297 - Young non-PCOM (Cluster 1): 118 - Young PCOM (Cluster 2): 28 - Old non-PCOM (Cluster 3): 100 - Old PCOM (Cluster 4): 51 PCOS: 700	Netherlands / United States	Control: 28.3 (18.4–39.8), PCOS: 27.3 (13.9–39.6) p < 0.001	Control: 22.6 (16.5–45.2), PCOS: 28.7 (17.3–50.6) p < 0.001	NIH	FNPO	N/A	N/A
Lujan et al. 2013	Moderate	Control: 70 PCOS: 98	United States / Canada	Control: 27 (23–35) PCOS: 28 (25–32) p = 0.204	Control: 23.9 (22.0–27.5) PCOS: 30.1 (23.7–37.3) p < 0.001	NIH	FNPO, FNPS, OV	TVUS 2D Offline with Grid Overlay	5-9 MHz 6-12 MHz
Özay et al. 2022	Moderate	PCOS: 106 PCOM: 68 Control: 46	Cyprus	Control: 22.00 (3.25) PCOM: 22.00 (4.00) PCOS: 21.00 (3.00) p = 0.443	Control: 21.01 (4.10) PCOM: 20.90 (5.09) PCOS: 23.05	Rotterdam	Left ST, Right ST	2D Real-Time	7-9 MHz

					(6.09) p = 0.005				
Villa et al. 2013 [adolescent]	High	PCOS: 86 Control: 48	Italy	Control: 15.3 ± 1.7 PCOS: 15.7 ± 1.4 p = not significant	Control: 23.9 ± 4.9 PCOS: 25.7 ± 5.4 p = not significant	NIH	OV	TAUS 2D Real-Time	3.5-5 MHz
Villarroel et al. 2015 [adolescent]	Moderate	PCOS: 26 Control: 63	Chile	Control: 16.6 ± 1.5 PCOS: 17.3 ± 1.9 p = not significant	N/A	NIH	FNPO, OV	TAUS 2D Real-Time	5 MHz
Wongwananuruk et al. 2018	Moderate	Control: 63 PCOS: 55	Thailand	Control: 29.7 ± 7.2 PCOS: 25.1 ± 5.3 p < 0.001	Control: 23.5 ± 5.1 PCOS: 25.3 ± 6.3 p = 0.085	NIH	FNPO, FNPS, OV	TVUS/TRUS 2D Real-Time	8 MHz

N/A: not available, FNPO: follicle number per ovary, FNPS: follicle number per cross-section, FDP: follicle distribution pattern, OV: ovarian volume, OA: ovarian area, OC: ovarian contour, OUI: ovarian to uterine index, SA: stromal area, S/A: stromal to ovarian area, SI: stromal index, SSR: stromal strain ratio, ST: stromal thickness, TAUS: transabdominal ultrasonography, TRUS: transrectal ultrasonography, TVUS: Transvaginal ultrasonography, MHz: megahertz

6. FINDINGS

- **EVIDENCE SUMMARY:**

Follicle excess

Fifteen studies were suitable for meta-analysis for diagnostic accuracy outcomes of follicle number per ovary (FNPO) in women with and without PCOS. Eleven of the studies provided an optimal diagnostic threshold for FNPO (Allemand 2006, Carmina 2016, Chen 2008a, Çiraci 2015, Dewailly 2011, Dewailly 2014, Diamanti-Kandarakis 2011, Jonard 2005, Köşuş 2011b, Lujan 2013, Wongwananuruk 2018), two proposed age-specific thresholds (Ahmad 2019, Lie Fong 2017), one proposed two- and three-dimensional thresholds (Kar and Swoyam 2018), and one proposed phenotype-specific thresholds (Köninger 2014). Most studies diagnosed PCOS using the NIH criteria (n = 9) with four using the Rotterdam criteria and one using the AE-PCOS criteria. Most studies were judged as moderate risk of bias (n = 10) and only one study was judged as low risk of bias, while the rest were high risk of bias (n = 6). One study had overlap in patient population with other included studies and was excluded from meta-analysis due to a smaller population size (Christ 2014).

Four studies were suitable for meta-analysis for diagnostic accuracy outcomes of follicle number per cross-sectional image (FNPS) in women with and without PCOS. Three studies provided an optimal diagnostic threshold for FNPS (Allemand 2006, Lujan 2013, Wongwananuruk 2018) and one proposed age-specific diagnostic thresholds (Kim 2017). All studies diagnosed PCOS using the NIH criteria. Two studies had overlap in patient populations with other included studies and were excluded from meta-analysis due to a smaller population size (Alsamarai 2009, Christ 2014).

Ovarian enlargement

Seventeen studies were suitable for meta-analysis for diagnostic accuracy outcomes of ovarian volume (OV) in adult women with and without PCOS. Thirteen of the studies proposed an optimal diagnostic threshold for OV (Allemand 2006, Bili 2014, Carmina 2016, Chen 2008a, Çiraci 2015, Dewailly 2011, Ertekin 2019, Jonard 2005, Köşuş 2011a, Köşuş 2011b, Le 2021, Lujan 2013, Wongwananuruk 2018), two proposed age-specific thresholds (Ahmad 2019, Kim 2017), one proposed two- and three-dimensional thresholds (Kar and Swoyam 2019), and one proposed phenotype-specific thresholds (Köninger 2014). Only one study was judged as low risk of bias, with the rest judged as moderate (n = 9) or high (n = 7) risk of bias. Three studies had overlap in patient populations with other included studies and were excluded from meta-analysis due to a smaller sample size (Alsamarai 2009, Christ 2014, Jarrett 2019).

Four studies were suitable for meta-analysis for diagnostic accuracy of OV in adolescent girls with and without PCOS (Chen 2008b, Khashchenko 2020, Villa 2013, Villarroel 2015). Three studies diagnosed PCOS using then NIH criteria whereas one study used the Rotterdam criteria. Majority of the studies used transabdominal ultrasonography (n = 3) whereas one study used transrectal ultrasonography. Studies were either judged as high (n = 2) or moderate (n = 2) risk of bias.

Additional ovarian morphology features

Seven studies proposed additional features of ovarian morphology not currently recommended by the International Guideline. This includes ovarian area (OA) (Christ 2014, Jonard 2005), ovarian contour (Bili 2014), stromal area (Christ 2014), stromal to total area ratio (Christ 2014, Fulghesu 2001), stromal thickness (Özay 2022), stromal index (Christ 2014), and stromal strain ratio (Çiraci 2015), peripheral follicle distribution (Christ 2014), and ovarian to uterine index (Khashchenko 2020). Due to the limited number of studies available, meta-analysis was not conducted on these markers. Most studies were judged as moderate risk of bias (n = 5) with two studies as high risk of bias.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

Pooled diagnostic accuracy measures (summary ROC curve, sensitivity, specificity) indicated that FNPO is the most accurate ultrasonographic marker to diagnose PCOS in adult women. The quality of evidence of these outcomes was low due to the observational design of included studies, lack of comparisons with previously proposed thresholds, and heterogeneity in patient characteristics and PCOS diagnosis. OV and FNPS offered inferior diagnostic accuracy compared FNPO but remained robust markers to detect PCOS (AUC >0.85).

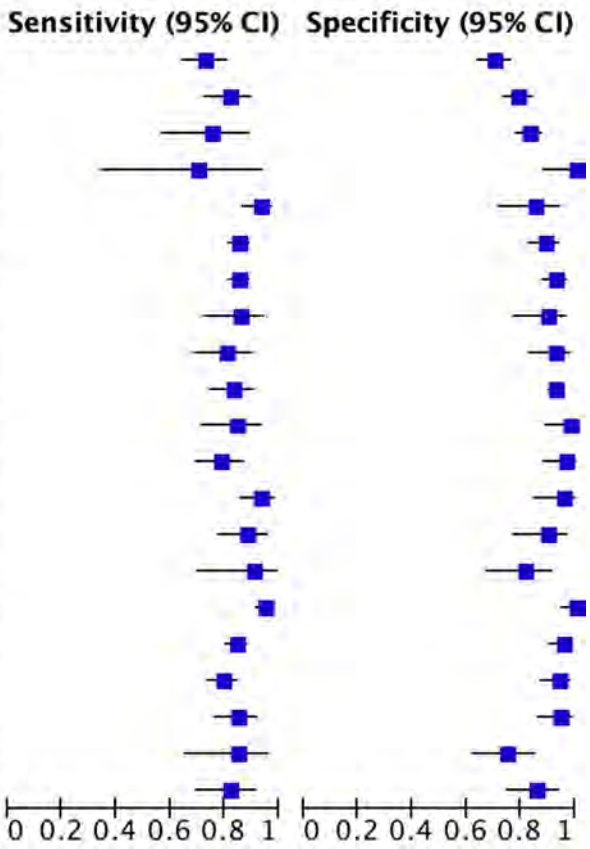
In subgroup analysis, OV exhibited robust accuracy to detect PCOS in adolescent girls. However, evidence remains limited as only two studies used the current recommendations of transabdominal ultrasonography and the NIH criteria in PCOS diagnosis. In addition, diagnostic performance of other ovarian ultrasound markers was largely unreported.

INDEX TEST: Follicle Number Per Ovary (FNPO)				OUTCOME TYPE: continuous								
COMPARISON (if applicable): N/A												
Author, year	**Unit of outcome**	**Method of measurement**	**N**	**Threshold cut-off**	**True Pos**	**False Pos**	**True Neg**	**False Neg**	**Sensitivity (95% CI)**	**Specificity (95%CI)**	**AUC**	**Precision**
Ahmad et al. 2019 (25 to <30yo)	Count	TVUS (2D Real-Time)	353	15 (Mean)	91	68	160	34	0.730	0.700	N/A	N/A
Ahmad et al. 2019 (30 to <35yo)	Count	TVUS (2D Real-Time)	336	14 (Mean)	72	52	196	16	0.820	0.790	N/A	N/A
Ahmad et al. 2019 (35 to <40yo)	Count	TVUS (2D Real-Time)	312	12 (Mean)	24	48	232	8	0.750	0.830	N/A	N/A
Allemand et al. 2006	Count	TVUS (3D-Offline)	39	20.1 (Mean)	7	0	29	3	0.700	1.00	0.987	N/A
Carmina et al. 2016	Count	TVUS (2D Real-Time)	160	22 (Mean)	105	7	40	8	0.930	0.850	N/A	N/A
Chen et al. 2008	Count	TVUS (2D Real-Time)	585	10 (Mean)	368	17	136	64	0.852	0.888	0.909	N/A
				12 (Max)	368	11	142	64	0.852	0.926	0.911	N/A
Christ et al. 2014	Count	TVUS (2D Offline with Grid Overlay)	142	28 (Mean)	70	1	59	12	0.850	0.980	0.971	0.948-0.993
Çiraci et al. 2015	Count	TVUS (2D Real-Time)	96	12 (Mean)	41	5	43	7	0.854	0.895	0.959	N/A
Dewailly et al. 2011	Count	TVUS (2D Real-Time)	128	19 (Mean)	50	5	61	12	0.810	0.920	0.950	0.915-0.982
Dewailly et al. 2014	Count	TVUS (2D Real-Time)	716	12 (Mean)	79	47	574	14	0.832	0.925	0.940	0.909-0.971
Diamanti-Kandarakis et al. 2011	Count	TVUS (2D Real-Time)	97	19.5 (Mean)	43	1	46	8	0.850	0.980	0.940	0.890-0.990

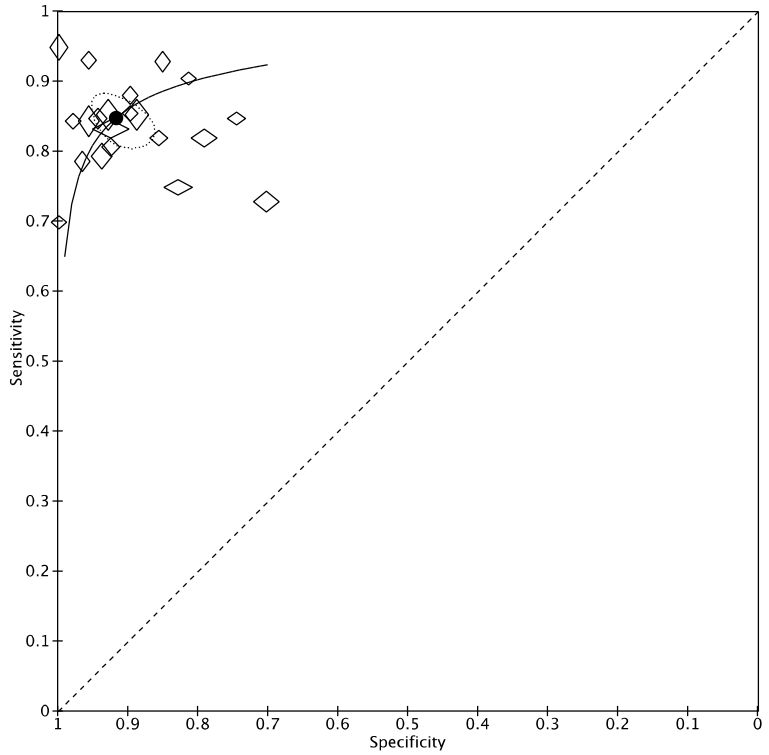
Jonard et al. 2005	Count	TVUS (2D Real-Time)	155	12 (Mean)	77	2	55	21	0.790	0.970	0.960	N/A
Kar and Swoyam 2018	Count	TVUS (2D Real-Time)	131	12 (Mean)	80	2	43	6	0.935	0.952	0.973	N/A
		TVUS (3D Real-Time)		10 (Max)	76	1	44	10	0.880	0.977	N/A	N/A
Köninger et al. 2014 (Severe PCOS)	Count	TVUS (2D Real-Time)	107	9.5 (Max)	52	5	43	7	0.881	0.896	0.940	0.880-0.980
Köninger et al. 2014 (Mild PCOS)	Count	TVUS (2D Real-Time)	69	8.5 (Max)	19	9	39	2	0.905	0.812	0.920	0.820-0.980
Köşüş et al 2011b	Count	TVUS (2D Real-Time)	316	8 (Mean)	238	0	65	13	0.950	1.00	0.998	0.992-1.004
Lie Fong et al. 2017 (Young)	Count	TVUS (2D Real-Time)	524	12.25 (Median)	346	5	108	65	0.842	0.956	0.915	0.891-0.940
Lie Fong et al. 2017 (Old)	Count	TVUS (2D Real-Time)	334	10.75 (Median)	188	6	91	49	0.795	0.935	0.874	0.836-0.912
Lujan et al. 2013	Count	TVUS (2D Offline with Grid Overlay)	168	26	83	4	66	15	0.850	0.940	0.969	0.948-0.990
Villaroel et al. 2015 (adolescent)	Count	TAUS	89	12 (Max)	22	16	47	4	0.846	0.746	0.877	P<0.0001
Wongwananuruk et al. 2018	Count	TVUS/TRUS (2D Real-Time)	118	15 (Max)	45	9	54	10	0.818	0.857	0.918	0.866-0.970

N/A: not available, TAUS: transabdominal ultrasonography, TRUS: transrectal ultrasonography, TVUS: transvaginal ultrasonography

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ahmad 2019a	91	68	34	160	0.73 [0.64, 0.80]	0.70 [0.64, 0.76]
Ahmad 2019b	72	52	16	196	0.82 [0.72, 0.89]	0.79 [0.73, 0.84]
Ahmad 2019c	24	48	8	232	0.75 [0.57, 0.89]	0.83 [0.78, 0.87]
Allemand 2006	7	0	3	29	0.70 [0.35, 0.93]	1.00 [0.88, 1.00]
Carmina 2016	105	7	8	40	0.93 [0.87, 0.97]	0.85 [0.72, 0.94]
Chen 2008a	368	17	64	136	0.85 [0.81, 0.88]	0.89 [0.83, 0.93]
Chen 2008b	368	11	64	142	0.85 [0.81, 0.88]	0.93 [0.88, 0.96]
Ciraci 2015	41	5	7	43	0.85 [0.72, 0.94]	0.90 [0.77, 0.97]
Dewailly 2011	50	5	12	61	0.81 [0.69, 0.90]	0.92 [0.83, 0.97]
Dewailly 2014	79	47	16	574	0.83 [0.74, 0.90]	0.92 [0.90, 0.94]
Diamanti-Kandarakis 2011	43	1	8	46	0.84 [0.71, 0.93]	0.98 [0.89, 1.00]
Jonard 2005	77	2	21	55	0.79 [0.69, 0.86]	0.96 [0.88, 1.00]
Kar 2018	80	2	6	43	0.93 [0.85, 0.97]	0.96 [0.85, 0.99]
Koninger 2014a	52	5	7	43	0.88 [0.77, 0.95]	0.90 [0.77, 0.97]
Koninger 2014b	19	9	2	39	0.90 [0.70, 0.99]	0.81 [0.67, 0.91]
Kosus 2011a	238	0	13	65	0.95 [0.91, 0.97]	1.00 [0.94, 1.00]
Lie Fong 2017a	346	5	65	108	0.84 [0.80, 0.88]	0.96 [0.90, 0.99]
Lie Fong 2017b	188	6	49	91	0.79 [0.74, 0.84]	0.94 [0.87, 0.98]
Lujan 2013	83	4	15	66	0.85 [0.76, 0.91]	0.94 [0.86, 0.98]
Villarroel 2015	22	16	4	47	0.85 [0.65, 0.96]	0.75 [0.62, 0.85]
Wongwananuruk 2018	45	9	10	54	0.82 [0.69, 0.91]	0.86 [0.75, 0.93]



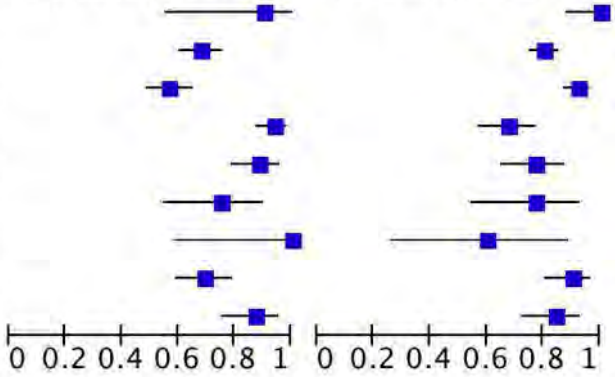
Summary ROC curve (omits one adolescent study – Villarroel 2015)



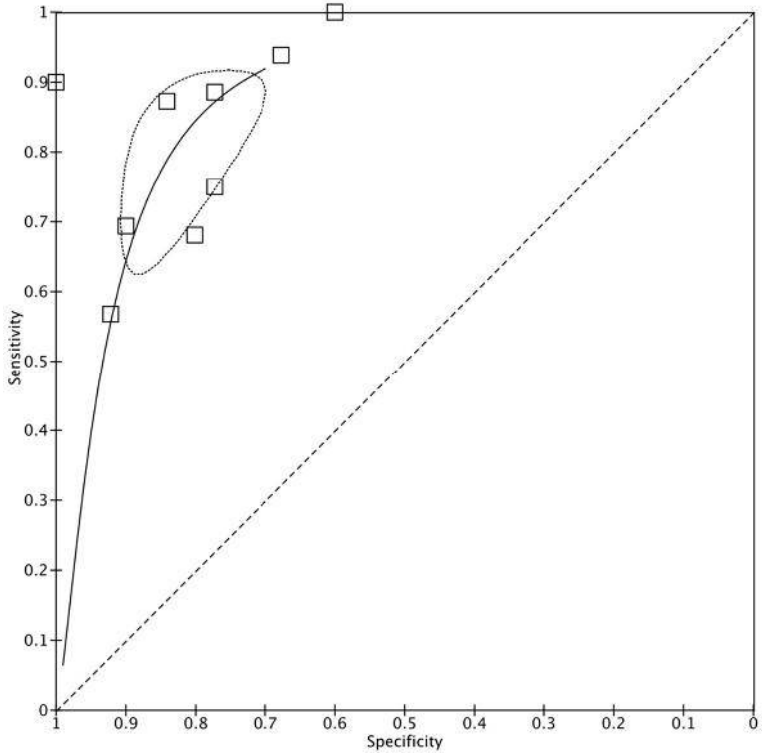
INDEX TEST: Follicle Number Per Cross-Section (FNPS)				**OUTCOME TYPE: continuous**								
COMPARISON (if applicable): N/A												
Author, year	Unit of outcome	Method of measurement	N	Threshold cut-off	True Pos	False Pos	True Neg	False Neg	Sensitivity (95% CI)	Specificity (95%CI)	AUC	Precision
Allemand et al. 2006	Count	TVUS (3D Offline)	39	10 (Mean)	9	0	29	1	0.900	1.000	0.990	N/A
Alsamarai et al. 2009	Count	TVUS (2D Real-Time)	850	12 (Max - Younger)	N/A	N/A	N/A	N/A	0.820	0.660	N/A	N/A
				12 (Max -Older)	N/A	N/A	N/A	N/A	0.210	1.000	N/A	N/A
Christ et al. 2014	Count	TVUS (2D Offline with Grid Overlay)	142	9 (Mean)	58	6	54	24	0.71	0.90	0.872	0.816-0.929
Kim et al. 2017 (18-24yo)	Count	TVUS (2D Real-Time)	445	13 (Max)	111	56	226	52	0.68	0.80	0.800	N/A
Kim et al. 2017 (25-29yo)	Count	TVUS (2D Real-Time)	341	14 (Max)	92	14	165	70	0.57	0.92	0.830	N/A
Kim et al. 2017 (30-34yo)	Count	TVUS (2D Real-Time)	210	10 (Max)	107	31	65	7	0.94	0.68	0.870	N/A
Kim et al. 2017 (35-39yo)	Count	TVUS (2D Real-Time)	136	10 (Max)	62	15	51	8	0.88	0.78	0.920	N/A
Kim et al. 2017 (40-45yo)	Count	TVUS (2D Real-Time)	50	9 (Max)	21	5	17	7	0.75	0.76	0.810	N/A
Kim et al. 2017 (>45yo)	Count	TVUS (2D Real-Time)	17	7 (Max)	7	4	6	0	1.00	0.60	0.800	N/A
Lujan et al. 2013	Count	TVUS (2D Offline with Grid Overlay)	168	9 (Mean)	68	7	63	30	0.69	0.90	0.88	0.830-0.930
Wongwananuruk et al. 2018	Count	TVUS/TRUS (2D Real-Time)	118	7 (Max)	48	10	53	7	0.873	0.841	0.904	0.844-0.963

N/A: not available, TRUS: transrectal ultrasonography, TVUS: transvaginal ultrasonography

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Allemand 2006	9	0	1	29	0.90 [0.55, 1.00]	1.00 [0.88, 1.00]
Kim 2017a	111	56	52	226	0.68 [0.60, 0.75]	0.80 [0.75, 0.85]
Kim 2017b	92	14	70	165	0.57 [0.49, 0.65]	0.92 [0.87, 0.96]
Kim 2017c	107	31	7	65	0.94 [0.88, 0.97]	0.68 [0.57, 0.77]
Kim 2017d	62	15	8	51	0.89 [0.79, 0.95]	0.77 [0.65, 0.87]
Kim 2017e	21	5	7	17	0.75 [0.55, 0.89]	0.77 [0.55, 0.92]
Kim 2017f	7	4	0	6	1.00 [0.59, 1.00]	0.60 [0.26, 0.88]
Lujan 2013	68	7	30	63	0.69 [0.59, 0.78]	0.90 [0.80, 0.96]
Wongwananuruk 2018	48	10	7	53	0.87 [0.76, 0.95]	0.84 [0.73, 0.92]



Summary ROC curve



INDEX TEST: Peripheral Follicle Distribution Pattern				**OUTCOME TYPE: categorical**								
COMPARISON (if applicable): N/A												
Author, year	Unit of outcome	Method of measurement	N	Threshold cut-off	True Pos	False Pos	True Neg	False Neg	Sensitivity (95% CI)	Specificity (95%CI)	AUC	Precision
Christ et al. 2014	Peripheral or Non-Peripheral	TVUS (2D Offline with Grid Overlay)	142	N/A	22	1	59	60	0.270	0.980	0.624	0.532-0.717

TVUS: transvaginal ultrasonography

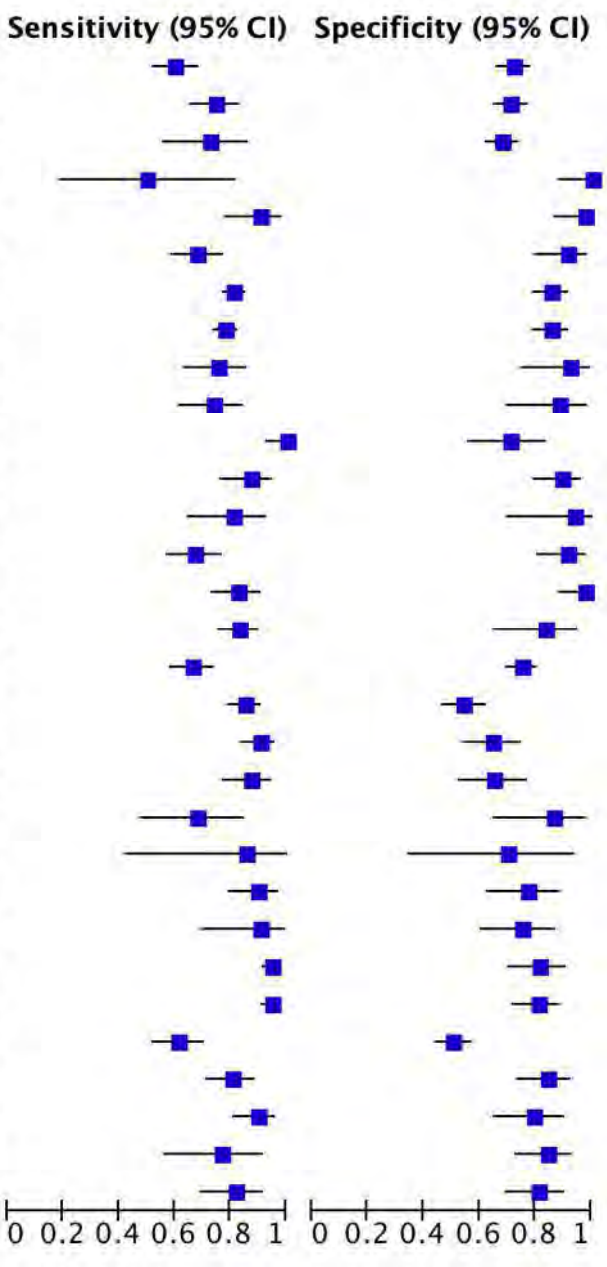
INDEX TEST: Ovarian Volume (OV)				**OUTCOME TYPE: continuous**								
COMPARISON (if applicable): N/A												
Author, year	Unit of outcome	Method of measurement	N	Threshold cut-off	True Pos	False Pos	True Neg	False Neg	Sensitivity (95% CI)	Specificity (95%CI)	AUC	Precision
Ahmad et al. 2019 (25 to <30yo)	cm^3	N/A	380	8.50 (Mean)	91	64	165	60	0.600	0.720	N/A	N/A
Ahmad et al. 2019 (25 to <30yo)	cm^3	N/A	352	7.00 (Mean)	80	71	175	27	0.750	0.710	N/A	N/A
Ahmad et al. 2019 (25 to <30yo)	cm^3	N/A	321	6.25 (Mean)	29	90	191	11	0.730	0.680	N/A	N/A
Allemand et al. 2006	cm^3	TVUS (2D Real-Time)	39	13.00 (Mean)	5	0	29	5	0.500	1.000	0.948	N/A
Alsamarai et al. 2009	ml	TVUS (2D Real-Time)	850 (total)	7.00 (Max - Younger)	N/A	N/A	N/A	N/A	0.820	0.610	N/A	N/A
				7.00 (Max - Older)	N/A	N/A	N/A	N/A	0.600	0.960	N/A	N/A
Bili et al. 2014	cm^3	Machine Software	83	9.64 (Mean)	39	1	39	4	0.907	0.975	0.940	0.870-1.000
Carmina et al. 2016	cc	TVUS (2D Real-Time)	160	8.00 (Mean)	77	4	43	36	0.680	0.910	N/A	N/A
Chen et al. 2008	cm^3	TVUS/TRUS (2D Real-Time)	585	6.40 (Mean)	350	22	131	82	0.810	0.856	0.898	N/A
				7.90 (Max)	337	22	131	95	0.780	0.856	0.882	N/A
Chen et al. 2008 (adolescent)	cm^3	TRUS (2D Real-Time)	95	6.74 (Mean)	52	2	24	17	0.754	0.923	0.863	0.790-0.940
				7.82 (Max)	51	3	23	18	0.739	0.885	0.832	0.750-0.920
Christ et al. 2014	cm^3	TVUS (2D Offline with Grid Overlay)	142	10.00 (Mean)	74	8	52	8	0.900	0.860	0.913	0.859-0.966
Çiraci et al. 2015	cm^3	TVUS (2D Real-Time)	96	10.00 (Mean)	48	14	34	0	1.000	0.708	0.962	N/A

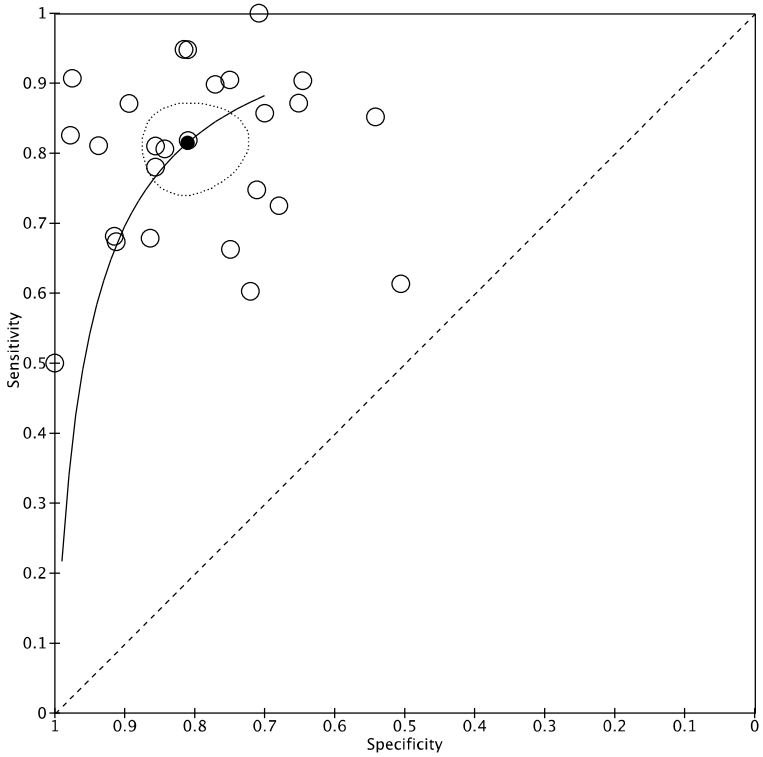
Dewailly et al. 2011	ml	Machine Software	128	7.00 (Mean)	54	7	59	8	0.870	0.890	0.923	0.874-0.973
Ertekin et al. 2019	ml	TAUS (2D Real-Time)	53	7.50 (Mean)	30	1	15	7	0.800	0.940	N/A	N/A
Jarrett et al. 2019	cm^3	TVUS (2D Offline with Grid Overlay)	154	10.00 (Left)	64	19	48	23	0.740	0.710	0.780	N/A
				9.00 (Right)	58	16	51	29	0.670	0.760	0.780	N/A
Jonard et al. 2005	cm^3	TVUS (2D Real-Time)	155	7.00 (Mean)	66	5	52	32	0.675	0.912	0.905	N/A
Kar and Swoyam 2018	cm^3	TVUS (2D Real-Time)	131	6.15 (Mean)	72	1	44	14	0.839	0.988	0.961	N/A
		TVUS (3D Real-Time)		7.00 (Mean)	72	3	42	14	0.840	0.930	N/A	N/A
Khashchenko et al. 2020 (adolescent)	cm^3	TAUS	160	10.70 (Mean)	108	5	25	22	0.830	0.830	0.848	$p < 0.05$
Kim et al. 2017 (18-24yo)	ml	TVUS (2D Real-Time)	445	12.00 (Max)	108	71	212	55	0.660	0.750	0.770	N/A
Kim et al. 2017 (25-29yo)	ml	TVUS (2D Real-Time)	341	10.00 (Max)	138	82	97	24	0.850	0.540	0.750	N/A
Kim et al. 2017 (30-34yo)	ml	TVUS (2D Real-Time)	210	9.00 (Max)	103	34	62	11	0.900	0.650	0.850	N/A
Kim et al. 2017 (35-39yo)	ml	TVUS (2D Real-Time)	136	8.00 (Max)	61	23	43	9	0.870	0.650	0.860	N/A
Kim et al. 2017 (40-45yo)	ml	TVUS (2D Real-Time)	50	10.00 (Max)	19	3	19	9	0.680	0.880	0.830	N/A
Kim et al. 2017 (>45yo)	ml	TVUS (2D Real-Time)	17	6.00 (Max)	6	3	7	1	0.860	0.670	0.760	N/A
Köninger et al. 2014 (Severe PCOS)	ml	TVUS (2D Real-Time)	107	10.50 (Max)	53	11	37	6	0.898	0.771	0.830	0.690-0.940
Köninger et al. 2014 (Mild PCOS)	ml	TVUS (2D Real-Time)	69	10.20 (Max)	19	12	36	2	0.905	0.750	0.770	0.630-0.910
Köşüş et al. 2011a	cm^3	TVUS (2D Real-Time)	310	6.43 (Mean)	200	19	81	11	0.950	0.812	N/A	N/A

Köşüş et al. 2011b	cm^3	TVUS (2D Real-Time)	316	6.43 (Mean)	238	12	53	13	0.950	0.812	0.938	0.874-1.001
Le et al. 2021	cm^3	TVUS (2D Real-Time)	392	6.00 (Mean)	73	135	138	46	0.613	0.505	0.613	0.557-0.670
Lujan et al. 2013	cm^3	TVUS (2D Offline with Grid Overlay)	168	10.00 (Mean)	79	11	59	19	0.810	0.840	0.873	0.817-0.930
Villa et al. 2013 (adolescent)	cm^3	TAUS	134	5.596 (Mean)	77	10	38	9	0.890	0.800	0.879	0.814-0.944
Villarroel et al. 2015 (adolescent)	ml	TAUS	89	10.00 (Max)	20	10	53	6	0.769	0.841	0.849	$p < 0.0001$
Wongwananuruk et al. 2018	ml	TVUS/TRUS (2D Real-Time)	118	6.50 (Max)	45	12	51	10	0.818	0.810	0.872	0.803-0.941

N/A: not available, TAUS: transabdominal ultrasonography, TRUS: transrectal ultrasonography, TVUS: transvaginal ultrasonography

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ahmad 2019a	91	64	60	165	0.60 [0.52, 0.68]	0.72 [0.66, 0.78]
Ahmad 2019b	80	71	27	175	0.75 [0.65, 0.83]	0.71 [0.65, 0.77]
Ahmad 2019c	29	90	11	191	0.72 [0.56, 0.85]	0.68 [0.62, 0.73]
Allemand 2006	5	0	5	29	0.50 [0.19, 0.81]	1.00 [0.88, 1.00]
Bili 2014	39	1	4	39	0.91 [0.78, 0.97]	0.97 [0.87, 1.00]
Carmina 2016	77	4	36	43	0.68 [0.59, 0.77]	0.91 [0.80, 0.98]
Chen 2008a	350	22	82	131	0.81 [0.77, 0.85]	0.86 [0.79, 0.91]
Chen 2008b	337	22	95	131	0.78 [0.74, 0.82]	0.86 [0.79, 0.91]
Chen 2008c	52	2	17	24	0.75 [0.64, 0.85]	0.92 [0.75, 0.99]
Chen 2008d	51	3	18	23	0.74 [0.62, 0.84]	0.88 [0.70, 0.98]
Ciraci 2015	48	14	0	34	1.00 [0.93, 1.00]	0.71 [0.56, 0.83]
Dewailly 2011	54	7	8	59	0.87 [0.76, 0.94]	0.89 [0.79, 0.96]
Ertekin 2019	30	1	7	15	0.81 [0.65, 0.92]	0.94 [0.70, 1.00]
Jonard 2005	66	5	32	52	0.67 [0.57, 0.76]	0.91 [0.81, 0.97]
Kar 2018	71	1	15	44	0.83 [0.73, 0.90]	0.98 [0.88, 1.00]
Khashchenko 2020	108	5	22	25	0.83 [0.76, 0.89]	0.83 [0.65, 0.94]
Kim 2017a	108	71	55	212	0.66 [0.58, 0.73]	0.75 [0.69, 0.80]
Kim 2017b	138	82	24	97	0.85 [0.79, 0.90]	0.54 [0.47, 0.62]
Kim 2017c	103	34	11	62	0.90 [0.83, 0.95]	0.65 [0.54, 0.74]
Kim 2017d	61	23	9	43	0.87 [0.77, 0.94]	0.65 [0.52, 0.76]
Kim 2017e	19	3	9	19	0.68 [0.48, 0.84]	0.86 [0.65, 0.97]
Kim 2017f	6	3	1	7	0.86 [0.42, 1.00]	0.70 [0.35, 0.93]
Koninger 2014a	53	11	6	37	0.90 [0.79, 0.96]	0.77 [0.63, 0.88]
Koninger 2014b	19	12	2	36	0.90 [0.70, 0.99]	0.75 [0.60, 0.86]
Kosus 2011a	238	12	13	53	0.95 [0.91, 0.97]	0.82 [0.70, 0.90]
Kosus 2011b	200	19	11	81	0.95 [0.91, 0.97]	0.81 [0.72, 0.88]
Le 2021	73	135	46	138	0.61 [0.52, 0.70]	0.51 [0.44, 0.57]
Lujan 2013	79	11	19	59	0.81 [0.71, 0.88]	0.84 [0.74, 0.92]
Villa 2013	77	10	9	38	0.90 [0.81, 0.95]	0.79 [0.65, 0.90]
Villarroel 2015	20	10	6	53	0.77 [0.56, 0.91]	0.84 [0.73, 0.92]
Wongwananuruk 2018	45	12	10	51	0.82 [0.69, 0.91]	0.81 [0.69, 0.90]




Sensitivity
Specificity
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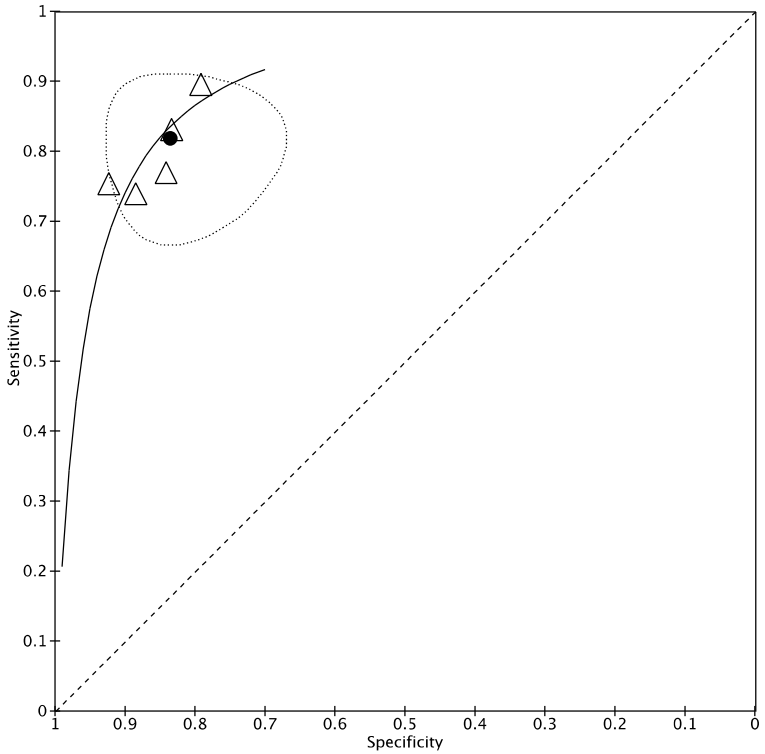
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0

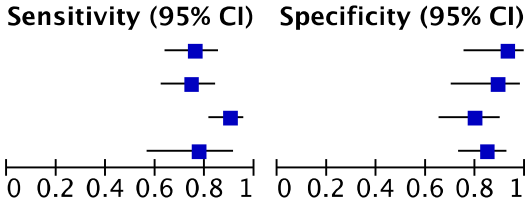
Summary ROC curve (adolescent)



Adolescent Study Subgroups

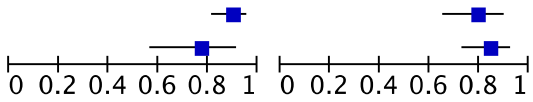
NIH PCOS Diagnosis only (3 studies)

Study	TP	FP	FN	TN	Diagnostic Criteria	Sensitivity (95% CI)	Specificity (95% CI)
Chen 2008c	52	2	17	24	NIH	0.75 [0.64, 0.85]	0.92 [0.75, 0.99]
Chen 2008d	51	3	18	23	NIH	0.74 [0.62, 0.84]	0.88 [0.70, 0.98]
Villa 2013	77	10	9	38	NIH	0.90 [0.81, 0.95]	0.79 [0.65, 0.90]
Villarroel 2015	20	10	6	53	NIH	0.77 [0.56, 0.91]	0.84 [0.73, 0.92]



NIH PCOS Diagnosis and TAUS only (2 studies)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Villa 2013	77	10	9	38	0.90 [0.81, 0.95]	0.79 [0.65, 0.90]
Villarroel 2015	20	10	6	53	0.77 [0.56, 0.91]	0.84 [0.73, 0.92]



INDEX TEST: Ovarian Area (OA)				**OUTCOME TYPE: continuous**								
COMPARISON (if applicable): N/A												
Author, year	Unit of outcome	Method of measurement	N	Threshold cut-off	True Pos	False Pos	True Neg	False Neg	Sensitivity (95% CI)	Specificity (95%CI)	AUC	Precision
Christ et al. 2014	cm^2	TVUS (2D Offline with Grid Overlay)	142	5.00 (Mean)	70	22	38	12	0.850	0.640	0.822	0.753-0.890
Jonard et al. 2005	cm^2	TVUS (2D Real-Time)	155	5.00 (Mean)	93	13	44	5	0.947	0.776	0.941	N/A

N/A: not available, TVUS: transvaginal ultrasonography

INDEX TEST: Ovarian Contour				**OUTCOME TYPE: continuous**								
COMPARISON (if applicable): N/A												
Author, year	Unit of outcome	Method of measurement	N	Threshold cut-off	True Pos	False Pos	True Neg	False Neg	Sensitivity (95% CI)	Specificity (95%CI)	AUC	Precision
Bili et al. 2014	cm	TVUS (2D Real-Time)	83	8.75 (Mean)	36	9	31	7	0.837	0.775	0.830	0.736-0.923

TVUS: transvaginal ultrasonography

INDEX TEST: Ovarian to Uterine Index (OUI)				**OUTCOME TYPE: continuous**								
COMPARISON (if applicable): N/A												
Author, year	Unit of outcome	Method of measurement	N	Threshold cut-off	True Pos	False Pos	True Neg	False Neg	Sensitivity (95% CI)	Specificity (95%CI)	AUC	Precision
Khashchenko et al. 2020	N/A	TAUS	160	3.95 (Median)	105	5	25	25	0.81	0.83	0.837	$p < 0.05$

TAUS: transabdominal ultrasonography

INDEX TEST: Stromal Area (SA)				**OUTCOME TYPE: continuous**								
COMPARISON (if applicable): N/A												
Author, year	Unit of outcome	Method of measurement	N	Threshold cut-off	True Pos	False Pos	True Neg	False Neg	Sensitivity (95% CI)	Specificity (95%CI)	AUC	Precision
Christ et al. 2014	cm^2	TVUS (2D Offline with Grid Overlay)	142	3.00 (Mean)	66	26	34	16	0.800	0.570	0.746	0.664-0.828

TVUS: transvaginal ultrasonography

INDEX TEST: Stromal to Total Area Ratio (S/A)				OUTCOME TYPE: continuous								
COMPARISON (if applicable): N/A												
Author, year	Unit of outcome	Method of measurement	N	Threshold cut-off	True Pos	False Pos	True Neg	False Neg	Sensitivity (95% CI)	Specificity (95%CI)	AUC	Precision
Christ et al.	N/A	TVUS	142	N/A	60	32	28	22	0.730	0.470	0.417	0.317-0.517

2014		(2D Offline with Grid Overlay)										
Fulghesu et al. 2001	N/A	TVUS (2D Real-Time)	83	0.34 (Mean)	53	0	30	0	1.000	1.000	N/A	N/A

'N/A: not available, TVUS: transvaginal ultrasonography

INDEX TEST: Stromal Thickness (ST)				**OUTCOME TYPE: continuous**								
COMPARISON (if applicable): N/A												
Author, year	Unit of outcome	Method of measurement	N	Threshold cut-off	True Pos	False Pos	True Neg	False Neg	Sensitivity (95% CI)	Specificity (95%CI)	AUC	Precision
Özay et al. 2022	NR	TVUS	152	N/A (Left)	78	28	43	3	0.736	0.939	0.874	0.827-0.922
				N/A (Right)	74	32	43	3	0.698	0.939	0.864	0.815-0.914

TVUS: transvaginal ultrasonography

INDEX TEST: Stromal Index (SI)				**OUTCOME TYPE: continuous**								
COMPARISON (if applicable): N/A												
Author, year	Unit of outcome	Method of measurement	N	Threshold cut-off	True Pos	False Pos	True Neg	False Neg	Sensitivity (95% CI)	Specificity (95%CI)	AUC	Precision
Christ et al. 2014	N/A	TVUS (2D Offline with Grid Overlay)	142	N/A	65	32	28	17	0.790	0.470	0.554	0.452-0.657

TVUS: transvaginal ultrasonography

INDEX TEST: Stromal Strain Ratio				**OUTCOME TYPE: continuous**								
COMPARISON (if applicable): N/A												
Author, year	Unit of outcome	Method of measurement	N	Threshold cut-off	True Pos	False Pos	True Neg	False Neg	Sensitivity (95% CI)	Specificity (95%CI)	AUC	Precision
Çiraci et al. 2015	N/A	TVUS (2D Elastography Real-Time)	96	3.80	43	8	40	5	0.895	0.833	0.939	N/A

N/A: not available, TVUS: transvaginal ultrasonography

8. GRADE ASSESSMENTS AND EVIDENCE PROFILE- ***add separate table for each comparison (if applicable) and row for each outcome***

OUTCOME: Diagnostic accuracy in detection of PCOS							
	Quality assessment						
No. studies	**Study Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Certainty**
Outcome: Follicle Number Per Ovary (FNPO)							
17	Cross-sectional, case-control, cohort	serious[1]	no serious inconsistency	serious indirectness[2]	serious imprecision[3]	none	⊕⊕◯◯ LOW (A, C, D)*
Outcome: Follicle Number Per Cross-Section (FNPS)							
4	Cross-sectional, case-control, cohort	serious[1]	serious inconsistency	serious indirectness[2]	very serious imprecision[3]	none	⊕⊕◯◯ VERY LOW (A, B, C, D2, E)*
Outcome: Peripheral Follicle Distribution Pattern (FDP)							
1	Cross-sectional	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	⊕⊕⊕◯ MODERATE (A)
Outcome: Ovarian Volume (OV)							
24	Cross-sectional, case-control, cohort	serious[1]	serious inconsistency	serious indirectness[2]	very serious imprecision[3]	serious[4]	⊕◯◯◯ VERY LOW (A ,B, C, D2, E)*
Outcome: Ovarian Area (OA)							
2	Cross-sectional, cohort	serious[1]	no serious inconsistency	serious indirectness[2]	serious imprecision[3]	none	⊕⊕◯◯ LOW (A, C, D)*
Outcome: Ovarian Contour							

[1] Downgraded once as the majority of evidence is at moderate or high risk of bias or downgraded twice as majority of evidence is at very high risk of bias
[2] Downgraded due to differences in age, body mass index, imaging modality, and diagnostic criteria for PCOS used
[3] Downgraded once due to imprecision as confidence intervals (CIs) were wide or precision is not provided for AUC or downgraded twice if both applicable
[4] Downgraded once due to funnel plot asymmetry (log diagnostic odds ratio vs. effective sample size)

1	Case-control	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	⊕⊕◯◯ LOW (A2)*
Outcome: Ovarian to Uterine Index (OUI)							
1	Case-control	very serious[1]	no serious inconsistency	no serious indirectness	very serious imprecision[3]	none	⊕◯◯◯ VERY LOW (A2, D2)*
Outcome: Stromal Area (SA)							
1	Cross-sectional	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	⊕⊕⊕◯ MODERATE (A)
Outcome: Stromal to Ovarian Area (S/A)							
2	Cross-sectional	serious[1]	very serious inconsistency	serious indirectness[2]	serious imprecision[3]	none	⊕◯◯◯ VERY LOW (A, B2, C, D)*
Outcome: Stromal Thickness (ST)							
1	Cohort	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	⊕⊕⊕◯ MODERATE (A)
Outcome: Stromal Index (SI)							
1	Cross-sectional	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	⊕⊕⊕◯ MODERATE (A)
Outcome: Stromal Strain Ratio (SSR)							
1	Case-control	serious[1]	no serious inconsistency	no serious indirectness	very serious imprecision[3]	none	⊕◯◯◯ VERY LOW (A, D2)*

[1] Downgraded once as the majority of evidence is at moderate or high risk of bias or downgraded twice as majority of evidence is at very high risk of bias
[2] Downgraded due to differences in age, body mass index, imaging modality, and diagnostic criteria for PCOS used
[3] Downgraded once due to imprecision as confidence intervals (CIs) were wide
[4] Downgraded once due to funnel plot asymmetry (log diagnostic odds ratio vs. effective sample size)

* Legend for GRADE certainty: A: serious risk of bias, A2: very serious risk of bias, B: serious inconsistency, B2: very serious inconsistency, C: serious indirectness, D: serious imprecision, D2: very serious imprecision, E, serious risk of publication bias

APPENDIX. Quality Appraisal for DIAGNOSTIC / ACCURACY STUDIES

Study ID	Ahmad 2019	
Study Citation	Ahmad, A. K. et al. (2019). "Improved diagnostic performance for the diagnosis of polycystic ovary syndrome using age-stratified criteria." Fertility and Sterility 111(4): 787-793.	
Study Country	USA	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	Control: Community controls enrolled in a prospective longitudinal study of healthy women with regular menstrual cycles. PCOS: Subjects aged 25-40 years old were enrolled in a cross-sectional PCOS cohort study and were diagnosed originally using 2003 Rotterdam criteria. To exclude ovarian morphology as one of the required diagnostic components, only those subjects that met NIH criteria were included in this study. Age and BMI: Not available	
PCOS diagnostic criteria	NIH	
N per group	Control: 756 (FNPO, OV) PCOS: 245 (FNPO), 297 (OV)	
Setting	Multidisciplinary polycystic ovary syndrome (PCOS) clinic at a tertiary academic center. Controls were recruited from 2006 to 2011 PCOS were recruited from 2006 to 2015	
Index test	Ovarian Volume (OV – mean) Follicle Number Per Ovary (FNPO – mean)	
Reference Standard	NIH criteria (oligo-anovulation and biochemical and/or clinical hyperandrogenism)	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Accuracy to diagnose PCOS Sensitivity and specificity Proposed Threshold Youden's index (maximum)	
Inclusion and exclusion criteria reported?	Yes	Inclusion criteria: Control: healthy women with regular menstrual cycles (22-35 day intervals) and intact ovaries PCOS: women aged 25-40 years old and were diagnosed originally using 2003 Rotterdam criteria Exclusion Criteria: Control: Chronic medical illness, oligo- or anovulation, surgically diagnosed endometriosis, premature ovarian insufficiency or failure, history of uterine or ovarian surgery or ovarian cysts. PCOS: Women with other identified causes of amenorrhea and/or hyperandrogenism including hyperprolactinemia, thyroid dysfunction, functional hypothalamic amenorrhea, androgen-secreting tumors, and congenital adrenal hyperplasia were excluded.
Does the study have a clearly focused question?	Partial	What are the optimal criteria for polycystic ovary morphology?
Summary Result/s	Receiver operating characteristic curves were created for both FNPO and OV and analyzed across age group categories (25 to <30, 30 to <35, and 35 to <40 years). Youden's and minimum distance (d) were used to compare efficacies of FNPO and OV thresholds. The optimal threshold for distinguishing PCOS from OVA controls was FNPO > 13. There was a decreasing	

		trend in FNPO threshold with increasing age group (>15, >14, and >12, respectively). The overall threshold was OV > 6.75 cm^3, with a trend toward decreasing OV with increase in age group (>8.5, >7, and >6.25 cm^3, respectively). Our findings reflect that age-stratified thresholds demonstrate superior diagnostic performance, with an improved balance of sensitivity and specificity compared with a single threshold.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
PATIENT SELECTION/SPECTRUM BIAS	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	Studies that recruit a group of healthy controls and a group known to have the target disorder will be coded as "No" in most scenarios. Studies enrolling patients with known disease and control group without the condition may exaggerate diagnostic accuracy. Controls may not be routinely assessed for ovarian volume using ultrasound. The PCOS group is representative of those who will be assessed with these criteria in practice.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Not reported	No random element was described in the selection of participants into the study. Study is described as cross-sectional and uses previously collected data from a cross-sectional cohort study (PCOS) and a prospective longitudinal study (controls).
	Was a case-control design avoided? (Q-2)	No	Both the control group (regular cycling women) and group with known disease (PCOS) were identified and diagnosed prior to study enrollment. Study design involves retrospective enrollment.
	Did the study avoid inappropriate exclusions? (Q-2)	Yes	Exclusion criteria for both PCOS and control group are appropriate. In citing previous studies that use the same study population (Johnstone et al. [2012], Lamb et al. [2011]), exclusion criteria for the PCOS were as follows: "Women with other identified causes of amenorrhea and/or hyperandrogenism including hyperprolactinemia, thyroid dysfunction, functional hypothalamic amenorrhea, androgen-secreting tumors, and congenital adrenal hyperplasia were excluded. For women on hormonal contraceptives at the time of evaluation, the diagnosis of PCOS was deferred." For the control group, "women were excluded from this study if they had any of the following: chronic medical illness, oligo- or anovulation, surgically diagnosed endometriosis, premature ovarian insufficiency or failure, history of uterine or ovarian surgery, or ovarian cysts."
CLASSIFICATION/ VERIFICATION/ INCORPORATION/ REVIEW BIAS	Were all participants assessed with both index test and reference standard?	No	All participants were assessed with the NIH criteria as the reference standard for PCOS. In the PCOS group, 245 participants were assessed with the FNPO index test and 297 participants were assessed with the OV index test. In the control group, 756 participants were assessed with both the FNPO and OV index tests.
	Did all patients receive the same reference standard? (Q-2)	Yes	All participants in the study received the same reference standard, which was the NIH diagnostic criteria for PCOS. For the Control group, the study mentions that "None of these subjects met NIH criteria for a PCOS diagnosis".
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	PCOS diagnosis was determined by the NIH (1990) criteria, "which was defined as oligo-ovulation (defined as eight or fewer menstrual cycles per year) or anovulation, as well as either biochemical hyperandrogenemia (free T, total T, and/or DHEAS above normal range for the reporting clinical laboratory) and/or clinical hyperandrogenism (defined as a modified Ferriman-Gallwey score >7)."
	Was the reference standard independent of the index test (ie. the index test did not form part of	Yes	To exclude ovarian morphology as one of the required diagnostic components, only those subjects that met NIH criteria were included in this study.

	the reference standard)?		
	Were the reference standard results interpreted without knowledge of the results of the index test?	No	Although the women with PCOS were included if they met the NIH criteria, they were initially diagnosed using the Rotterdam criteria which includes PCOM.
	Were the index test results interpreted without knowledge of the results of the reference standard test?	No	Although the women with PCOS were included if they met the NIH criteria, they were initially diagnosed using the Rotterdam criteria which includes PCOM.
	If a threshold was used, was it pre-specified?	No	Authors describe that "Optimal thresholds were determined as the threshold that maximized Youden's J statistic (sensitivity + specificity – 1). In cases in which more than one threshold value achieved the same Youden's J statistic, the threshold that achieved the smaller d (distance from upper-left-hand corner of the ROC plot, defined as sensitivity and specificity = 100%) was chosen". However, the study also compared optimal thresholds with previously proposed thresholds (Rotterdam and AE-PCOS) though not specified a priori.
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?	Not reported	Authors describe the interval between index test and reference standard as: "All control subjects were scanned during cycle 2–4 of their menstrual cycle, or in the early follicular phase. Subjects with PCOS were scanned in the early follicular phase if ovulatory, and if anovulatory, were scanned when patient schedule allowed". However, it is unclear when the reference standard was determined in both the control and PCOS group.
ATTRITION BIAS	Were withdrawals from the study explained?	No 83% treatment 100% control/ comparison	In the PCOS group, 245 participants were assessed with the FNPO index test and 297 participants were assessed with the OV index test. In the control group, 756 participants were assessed with both the FNPO and OV index tests. Authors do not describe the difference in numbers evaluated by each index test.
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Yes	There are no uninterruptable/intermediate test results and all results are reported.
	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	Authors provided the following description of the ultrasound examination: "For both cohorts, ultrasound was performed to measure the FNPO (measuring 2–9 mm) and OV in each ovary. If one ovary could not be evaluated because of poor visualization, presence of cyst or follicle >10 mm, or absence of ovary, that subject was excluded from this study. The same examiners (H.G.H., M.I.C., and Mitchell Rosen, MD) and same ultrasound machines (Shimadzu SDU-450XL ultrasound with variable transducer frequency of 4–8 MHz and General Electric Volusun s8E8C-RS ultrasound with variable transducer frequency of 4–10 MHz) were used for all control and PCOS subjects. All control subjects were scanned during cycle 2–4 of their menstrual cycle, or in the early follicular phase. Subjects with PCOS were scanned in the early follicular phase if ovulatory, and if anovulatory, were scanned when patient schedule allowed. To minimize interobserver variation, only three individuals performed

OTHER ISSUES – APPLICABILITY/ COMPARABILITY/ VARIATION			all scans, and strict quality control was set in place. In addition, two of the examiners (H.G.H., M.R.) were trained in performing measurements by the third examiner (M.I.C.)."
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Yes	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
	Were there any conflicts of interest in the writing or funding of this study?	No	Authors did not any conflicts of interest to disclose.
	If statistical analysis was undertaken, was this appropriate?	Partial	Study describes statistical analyses conducted as follows: Receiver operating characteristic (ROC) curves were used to investigate the effectiveness of PCO thresholds (FNPO and OV) for PCOS diagnosis as a single factor. A ROC was generated for the overall population and subsequently stratified by age category: 25 to <30, 30 to <35, and 35 to <40 years. Optimal thresholds were determined as the threshold that maximized Youden's *J* statistic (sensitivity + specificity − 1). In cases in which more than one threshold value achieved the same Youden statistic, the threshold that achieved the smaller d (distance from upper-left-hand corner of the ROC plot, defined as sensitivity and specificity = 100%) was chosen. However, unclear if an adequate sample size calculation was undertaken. A 4x4 table of test performance was not presented. Sensitivity, specificity, and Youden's J were provided but not AUC.
COMMENTS			
What is the overall risk of bias?		Moderate	Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No. All outcomes had the same risk of bias.	

Study ID	Allemand 2006	
Study Citation	Allemand, M. C. et al. (2006). "Diagnosis of polycystic ovaries by three-dimensional transvaginal ultrasound." Fertility and Sterility 85(1):214-219.	
Study Country	USA	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	Control: Normo-androgenic, regular cycling women with a history of male factor or tubal factor infertility. All women had ovulatory menstrual cycles of 21–35 days with luteal serum progesterone >3.0 ng/mL, normal physical examination confirming lack of hirsutism with a modified Ferriman-Gallwey score ≤7, no active thyroid disease, galactorrhea, 21-hydroxylase deficiency, or diabetes mellitus (2-hour postprandial glucose <200 mg/dL). PCOS: The PCOS patients with a history of anovulatory infertility and undergoing preparations for IVF. All PCOS patients had chronic anovulation and hirsutism or biochemical hyperandrogenism, excluding specific ovarian, adrenal, and pituitary disorders. No PCOS patient had a history of ovarian surgery or had any taken any medications known to affect ovarian function over the preceding two months. Age: Control: 30.5 ± 3.5yo, PCOS: 31.20 ± 3.90yo p = 0.82 BMI: Control: 24.00 ± 5.50kg/m2, PCOS: 32.20 ± 10.80kg/m2 p = 0.004	
PCOS diagnostic criteria	NIH	
N per group	PCOS: 10 Control: 29	
Setting	Academic Hospital Controls were recruited between July 2001 and May 2002 PCOS group were recruited from May 2002 to February 2004	
Index test	Ovarian Volume (OV - mean) Follicle Number Per Ovary (FNPO – mean) Follicles in a Single Sonographic Plane (FSSP/FNPS – mean)	
Reference Standard	NIH criteria (chronic anovulation and hirsutism or biochemical hyperandrogenism)	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Accuracy to diagnose PCOS Sensitivity and specificity Area under the ROC curve Proposed threshold	
Inclusion and exclusion criteria reported?	Yes	Inclusion criteria: Control: Normoandrogenic ovulatory women with a history of male factor or tubal factor infertility. All women had ovulatory menstrual cycles of 21–35 days with luteal serum progesterone >3.0 ng/mL, normal physical examination confirming lack of hirsutism with a modified Ferriman-Gallwey score ≤7. PCOS: All PCOS patients had chronic anovulation and hirsutism or biochemical hyperandrogenism. Exclusion criteria: Control: Active thyroid disease, galactorrhea, 21-hydroxylase deficiency, or diabetes mellitus (2-hour postprandial glucose 200 mg/dL).

		PCOS: Ovarian surgery or any medications known to affect ovarian function over the preceding two months. Excludes specific ovarian, adrenal, and pituitary disorders.
Does the study have a clearly focused question?	Partial	What are diagnostic thresholds for PCO and what is the accuracy of these thresholds?
Summary Result/s	Diagnostic thresholds for PCO with 100% specificity as determined by receiver operator characteristic (ROC) curves were ≥20 for mean FNPO, ≥10 for maximum FSSP, and ≥13 cm^3 for ovarian volume. Both 2D and 3D transvaginal ultrasound were highly accurate in the diagnosis of PCO as determined by areas under the curve (AUC) that were >90% for all three measures. Mean FNPO and maximum FSSP by 3D transvaginal ultrasound have comparable high accuracy for diagnosis of PCO. The diagnostic threshold with 100% specificity for mean FNPO is ≥20, which is greater than suggested by the Rotterdam Consensus Workshop in 2003. Use of the consensus standard, consequently, may result in overdiagnosis of PCO. A threshold of ≥20 mean FNPO using 3D transvaginal ultrasound may be appropriate to minimize false-positive diagnoses of PCO.	

INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
PATIENT SELECTION/SPECTRUM BIAS	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	Studies that recruit a group of healthy controls and a group known to have the target disorder will be coded as "No" in most scenarios. Studies enrolling patients with known disease and control group without the condition may exaggerate diagnostic accuracy. Controls may not be routinely assessed for ovarian volume using ultrasound. The PCOS group is representative of those who will be assessed with these criteria in practice.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Not reported	No random element was described in the selection of participants into the study. Study is described a retrospective cohort study.
	Was a case-control design avoided? (Q-2)	No	Both the control group (regular cycling, normo-androgenic women) and group with known disease (PCOS) were identified and diagnosed during study enrolment as part of a retrospective cohort study.
	Did the study avoid inappropriate exclusions? (Q-2)	Yes	Exclusion criteria for the control and PCOS group were considered appropriate. Exclusion criteria for controls included active thyroid disease, galactorrhea, 21-hydroxylase deficiency, or diabetes mellitus (2-hour postprandial glucose 200 mg/dL). Exclusion criteria for PCOS included ovarian surgery, any medications known to affect ovarian function over the preceding two months, and specific ovarian, adrenal, and pituitary disorders.
CLASSIFICATION/	Were all participants assessed with both index test and reference standard?	Yes	All PCOS patients were assessed with the NIH criteria as the reference standard for PCOS and the mean ovarian volume, mean follicle number per ovary and mean follicles in a single sonographic plane for the index tests.
	Did all patients receive the same reference standard? (Q-2)	Yes	All participants in the study received the same reference standard, which was the NIH diagnostic criteria for PCOS. For the Control group, the study mentions that "All women had ovulatory menstrual cycles of 21–35 days with luteal serum progesterone >3.0 ng/mL, normal physical examination confirming lack of hirsutism with a modified Ferriman-Gallwey score ≤7".
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	PCOS diagnosis was determined by the NIH criteria, which is described as a combination of "chronic anovulation and hirsutism or biochemical hyperandrogenism... chronic anovulation was defined as amenorrhea of 3 months' duration or oligomenorrhea (i.e., intermenstrual intervals greater than 35 days) with adequately timed serum progesterone levels <3.0 ng/mL.

			Hirsutism was defined as a modified Ferriman-Gallwey score >7. Biochemical hyperandrogenism was defined as serum testosterone, non-sex hormone-binding globulin- bound testosterone, or dihydrotestosterone greater than two SD above the mean for non-hirsute, ovulatory women."
	Was the reference standard independent of the index test (ie. the index test did not form part of the reference standard)?	Yes	NIH criteria for the diagnosis of PCOS only includes the presence oligo-anovulation/anovulation and hyperandrogenism (clinical and/or biochemical). Sonographic markers of ovarian morphology are not part of the reference standard.
	Were the reference standard results interpreted without knowledge of the results of the index test?	Not reported	Method description does not describe the timing of the reference standard in relation to the index test results.
	Were the index test results interpreted without knowledge of the results of the reference standard test?	Not reported	Method description does not describe the timing of the reference standard in relation to the index test results.
	If a threshold was used, was it pre-specified?	No	Authors describe that "Receiver operator characteristic (ROC) curves… were used to examine whether mean FNPO, maximum FSSP, and ovarian volume were related to the dependent variable, with PCO considered as a binary outcome".
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?	Partial	Study methods describe that "two-dimensional transvaginal ultrasound was performed in normoandrogenic and PCOS patients on cycle day 5 of the follicular phase of the menstrual cycle and during a period of amenorrhea, respectively… following 2D transvaginal ultrasound, three-dimensional (3D) transvaginal ultrasound was performed with the same ultrasound machine… On the day after transvaginal ultrasound, serum glucose, dehydroepiandrosterone sulfate (DHEAS), and total testosterone were measured after a 12-hour fast as previously described". Therefore, those who were diagnosed with PCOS using biochemical hyperandrogenism were in a short enough time frame from the index tests. However, it is unclear when diagnosis of PCOS without using biochemical hyperandrogenism occurred.
ATTRITION BIAS	Were withdrawals from the study explained?	Yes 100% treatment 100% control/ comparison	Numbers described as enrolled are the same as those in results.
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Yes	There are no uninterruptable/intermediate test results and all results are reported.
	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	Ovarian volume (OV) – 2D – Prolapsed Ellipsoid Formula Follicle Number Per Ovary – FNPO – 3D-Offline Number of Follicles in a Single Sonographic Plane (FSSP) [equivalent to FNPS] – 3D-Offline

OTHER ISSUES – APPLICABILITY/ COMPARABILITY/ VARIATION			A 4–8 MHz vaginal probe (C8-4v, Advanced Technology Laboratories Ultrasound, Inc.) was used to determine follicle size and ovarian volume using the formula for a prolate ellipsoid (0.5237 x D1 x D2 x D3, with D1, D2, and D3 representing the maximum longitudinal, anteroposterior, and transverse diameters). Following 2D transvaginal ultrasound, three-dimensional (3D) transvaginal ultrasound was performed with the same ultrasound machine (Advanced Technology Laboratories Ultrasound, Inc.) and stored on CD-ROM to determine the mean FNPO of both ovaries as well as the maximum FSSP of either ovary. Note: FSSP=FNPS.
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Yes	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Not reported	Study does not describe what clinical data was available during test result interpretation.
	Were there any conflicts of interest in the writing or funding of this study?	Yes	Authors were funded by a grant from Serono Pharmaceuticals.
	If statistical analysis was undertaken, was this appropriate?	Partial	Authors describe statistical methods as "Receiver operator characteristic (ROC) curves (Medcalc 7.2; Mariakerke, Belgium) were used to examine whether mean FNPO, maximum FSSP, and ovarian volume were related to the dependent variable, with PCO considered as a binary outcome". However, unclear if an adequate sample size calculation was undertaken. A 4x4 table of test performance was not presented.
COMMENTS			
What is the overall risk of bias?		Moderate	Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No. All outcomes had the same risk of bias.	

Study ID	Alsamarai 2009
Study Citation	Alsamarai, S. et al. (2009). "Criteria for polycystic ovarian morphology in polycystic ovary syndrome as a function of age." The Journal of Clinical Endocrinology & Metabolism 94(12): 4961-4970.
Study Country	USA
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	Control: Control subjects had menstrual cycle lengths of 25–35 days and no hyperandrogenism.

	PCOS: Diagnosed by age 40 year as chronic oligomenorrhea (fewer than nine menstrual periods/year) and clinical and/or biochemical hyperandrogenism in the absence of other disorders causing the same phenotype. Age: PCOS: 27.8 ± 5.7yo (Younger), 46.3 ± 4.5yo (Older), Control: 28.1 ± 6.4yo (Younger), 48.1 ± 6.6yo (Older) p ≤ 0.05 (Control), p ≤ 0.05 (Older) BMI: PCOS: 30.6 ± 8.7kg/m^2 (Younger), 31.3 ± 8.5kg/m^2 (Older), Control: 24.4 ± 5.1kg/m^2 (Younger), 26.7 ± 5.4kg/m^2 (Older) p = not significant	
PCOS diagnostic criteria	NIH	
N per group	PCOS: 483 (cross-sectional) and 11 (longitudinal) Control: 367 (cross-sectional) and 15 (longitudinal)	
Setting	Cross-sectional study subjects were diagnosed at Massachusetts General Hospital Reproductive Endocrine Unit between 2003 and 2008 and longitudinal study patients over age 40 were recruited between 2007 and 2008 from previous studies (7–15 y earlier).	
Index test	Ovarian volume (OV – maximum) Follicle Number in a Single Plane (FNPS – maximum)	
Reference Standard	NIH criteria (chronic oligomenorrhea and clinical and/or biochemical hyperandrogenism)	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Accuracy to diagnose PCOS Sensitivity and specificity Proposed threshold	
Inclusion and exclusion criteria reported?	Yes	Inclusion criteria: Controls: control subjects had menstrual cycle lengths of 25–35 days and no hyperandrogenism. PCOS: Diagnosed by age 40 year as chronic oligomenorrhea (fewer than nine menstrual periods/year) and clinical and/or biochemical hyperandrogenism in the absence of other disorders causing the same phenotype. Exclusion Criteria: all subjects had normal thyroid function and prolactin levels. Subjects were on no hormone medication.
Does the study have a clearly focused question?	Yes	Since ovarian volume and follicle number decrease with age in women with polycystic ovary syndrome (PCOS), should there be age-dependent criteria for PCOM?
Summary Result/s	Ovarian volume (15.2 ± 7.4 vs. 7.1 ± 3.7 ml; P < 0.01) and follicle number (12.8 ± 3.2 vs. 8.1 ± 3.9; P < 0.05) decreased longitudinally in PCOS and control women (volume 11.6 ± 4.4 vs .5.4 ± 2.2 ml and follicle number 8.3 ± 1.9 vs. 6.3 ± 1.8; both P < 0.005). Using cross-sectional data, log ovarian volume and follicle number decreased in both groups, but the decrease in log ovarian volume was less pronounced in women with PCOS than in controls (P < 0.01). A combination of age, log ovarian volume, follicle number, and testosterone distinguished PCOS subjects from controls with a receiver operator characteristic curve area of 0.90. Ovarian volume and follicle number decrease with age in women with PCOS and controls necessitating age-based criteria to define polycystic ovarian morphology. It is possible to use these criteria to distinguish PCOS in women over age 40 yr.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

PATIENT SELECTION/SPECTRUM BIAS	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	Studies that recruit a group of healthy controls and a group known to have the target disorder will be coded as "No" in most scenarios. Studies enrolling patients with known disease and control group without the condition may exaggerate diagnostic accuracy. Controls may not be routinely assessed for ovarian volume using ultrasound. The PCOS group is representative of those who will be assessed with these criteria in practice.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Not reported	No random element was described in the selection of participants into the study. Study is described as combining data from both cross-sectional and longitudinal study designs.
	Was a case-control design avoided? (Q-2)	No	Both the control group (regular cycling, normo-androgenic women) and group with known disease (PCOS) were identified and diagnosed prior to study enrollment.
	Did the study avoid inappropriate exclusions? (Q-2)	Yes	Exclusion criteria for both PCOS and Control group are appropriate. For both groups, the study describes the exclusion criteria as: "all subjects had normal thyroid function and prolactin levels. Subjects were on no hormone medication."
CLASSIFICATION/ VERIFICATION/ INCORPORATION/ REVIEW BIAS	Were all participants assessed with both index test and reference standard?	Not reported	The study provides the total number of participants for the PCOS (n = 483) and Control (n = 367) groups. However, no additional information is provided on the number of participants for each index test and their subsequent diagnostic accuracy measures. In addition, numbers for the "Young" and "Old" groups within the PCOS and Control populations are not provided.
	Did all patients receive the same reference standard? (Q-2)	Yes	All participants in the study received the same reference standard, which was the NIH diagnostic criteria for PCOS. For the Control group, the study mentions that "Control subjects had menstrual cycle lengths of 25–35 d and no hyperandrogenism".
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	PCOS diagnosis was determined by the NIH (1990) criteria, which is described as a "chronic oligomenorrhea (fewer than nine menstrual periods/year) and clinical and/or biochemical hyperandrogenism in the absence of other disorders causing the same phenotype. Clinical hyperandrogenism was defined by an elevated Ferriman-Gallwey score >9. Biochemical hyperandrogenism was defined as an androgen level greater than the 95% confidence limits in ovulatory control subjects: testosterone >63 ng/ml (2.8 nmol/liter) or androstenedione levels >3.8 ng/ml (13.3 nmol/liter)."
	Was the reference standard independent of the index test (ie. the index test did not form part of the reference standard)?	Yes	NIH criteria for the diagnosis of PCOS only includes the presence oligo-anovulation/anovulation and hyperandrogenism (clinical and/or biochemical). Sonographic markers of ovarian morphology are not part of the reference standard.
	Were the reference standard results interpreted without knowledge of the results of the index test?	Not reported	Even though some study participants were diagnosed with PCOS or categorized as a control prior to index test conducted, method description does not describe the timing of the reference standard in relation to the index test results for all participants.
	Were the index test results interpreted without knowledge of the results	No	Study methods describe that "Women with PCOS who were over the age of 40 yr had been diagnosed at the Massachusetts General Hospital Reproductive Endocrine Unit between the ages of 23 and 40 yr… Subjects over age 40 yr were recruited (2007–2008) from

	of the reference standard test?		previous studies (7–15 yr earlier) of women with PCOS". Therefore, for some of the participants PCOS diagnosis was known before interpretation of index test.
	If a threshold was used, was it pre-specified?	Yes	Authors used "previously defined criteria to predict PCOS in women under 36 yr old" for FNPS (Jonard et al., 2003) and OV (Jonard et al., 2005) for evaluating their diagnostic accuracy in the "Young" and "Old" comparison groups.
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?	Not reported	Study methods mention that "All cross-sectional and longitudinal subjects with PCOS were studied ond6orlater in the follicular phase with the exception of one subject who presented in the luteal phase, and her gonadotropins and sex steroids were not included. Control subjects were studied on d1– 8 of the follicular phase. Menopausal subjects were studied at random. Subjects arrived after a 12-h fast and underwent a menstrual history, physical exam and blood sampling, with additional samples at 10 and 20 min to obtain average gonadotropin concentrations." However, it is unclear the timing of the ultrasound scan relative to the visit for the reference standard.
ATTRITION BIAS	Were withdrawals from the study explained?	No ? treatment ? control/ comparison	The study provides the total number of participants for the PCOS (n = 483) and Control (n = 367) groups. However, no additional information is provided on the number of participants for each index test and their subsequent diagnostic accuracy measures. In addition, numbers for the "Young" and "Old" groups within the PCOS and Control populations are not provided.
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Yes	There are no uninterruptable/intermediate test results and all results are reported.
OTHER ISSUES – APPLICABILITY/ COMPARABILITY/ VARIATION	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	The second ultrasound for the longitudinal study and all ultrasounds for the cross-sectional study were performed on an ATL HDI 1500, 5-MHz convex array transducer, and multiple images of the ovary were recorded. Ovarian volume was calculated at the time of the ultrasound procedure using length x width x height in centimeters multiplied by 0.5233. Follicles were counted on a fixed image in a plane in which the maximum number of follicles was visualized. PCOM was defined as at least one ovary with 12 or more follicles of 2–10 mm in a single plane or an ovarian volume greater than 10 ml in the absence of a dominant follicle bigger than 10 mm in diameter, a corpus luteum, or a cyst. A consensus was reached on the reading of all ultrasounds by the reviewers (J.M.A., M.K.M., and C.K.W). The maximum ovarian volume and follicle number in both ovaries was used for analysis, excluding the volume of an ovary with a dominant follicle (>10 mm) or a corpus luteum.
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Yes	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Not reported	Study does not describe what clinical data was available during test result interpretation.
	Were there any conflicts of interest in the writing	No	Authors stated that there were no conflicts of interest to disclose.

	or funding of this study?		
	If statistical analysis was undertaken, was this appropriate?	Partial	For the primary outcome, diagnostic accuracy, the study describes the statistical analysis as: "A receiver operator characteristic curve was constructed to evaluate the logistic regression model for predicting PCOS". However, unclear if an adequate sample size calculation was undertaken. A 4x4 table of test performance was not presented. For OV and FNPS, sensitivity and specificity data were provided but not AUC.
COMMENTS			
What is the overall risk of bias?		Moderate	Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No. All outcomes had the same risk of bias.	

Study ID	Bili 2014
Study Citation	Bili, E. et al. (2014). "The combination of ovarian volume and outline has better diagnostic accuracy than prostate-specific antigen (PSA) concentrations in women with polycystic ovarian syndrome (PCOs)." European Journal of Obstetrics & Gynecology and Reproductive Biology 179: 32-35.
Study Country	Greece
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	Control: Women aged 18 to 35 with normal ovulatory cycles, absence of clinical or biochemical hyperandrogenemia and absence of polycystic morphology on ultrasound examination PCOS: Women aged 18 to 35. For the homogeneity of the PCOS group, women with regular cycles but with signs of hyperandrogenism and polycystic ultrasound morphology were excluded. Age: Control: 30.8 ± 4.30yo, PCOS: 28.9 ± 5.0yo p = 0.030 BMI: Control: 22.5 ± 3.7kg/m^2, PCOS: 24.9 ± 5.9kg/m^2 p = 0.029
PCOS diagnostic criteria	Rotterdam
N per group	PCOS: 43 Control: 40
Setting	Tertiary care, academic hospital from January 2009 until May 2012 as part of a prospective, observational, case-controlled study
Index test	Ovarian volume (OV – mean) Ovarian contour (mean)
Reference Standard	Rotterdam criteria (irregular cycles, hyperandrogenism, PCOM) Women with regular cycles but with signs of hyperandrogenism and polycystic ultrasound morphology were excluded.

Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)		Accuracy to diagnose PCOS Sensitivity and specificity Area under the ROC curve Proposed threshold	
Inclusion and exclusion criteria reported?		Yes	Inclusion criteria: Control: Ages of 18 to 35 years with normal ovulatory cycles, absence of clinical or biochemical hyperandrogenemia and absence of polycystic morphology on ultrasound examination PCOS: Ages of 18 to 35 years old attending the outpatient clinic for investigation of irregular menses and/or signs of androgen excess. PCOS diagnosis was made according to the Rotterdam ESHRE/ASRM criteria Exclusion Criteria: Control: any other cause of hyperandrogenemia or/and anovulation, history of cardiovascular disease, chronic disease under medication and history of drug or alcohol abuse. PCOS: For the homogeneity of the PCOS group, women with regular cycles but with signs of hyperandrogenism and polycystic ultrasound morphology were excluded. Additional exclusion criteria were Cushing syndrome, thyroid dysfunction, congenital adrenal hyperplasia hyperprolactinemia, ovarian or adrenal tumors, recent pregnancy or use of oral contraceptives, ovulatory agents, antidiabetic medications and glucocorticoids, within three months prior to enrolment. Women seeking fertility were also excluded, as they often receive hormonal therapies, which may interfere with study results.
Does the study have a clearly focused question?		Partial	How do prostate specific antigen (PSA) and ultrasound parameters, such as ovarian volume and outline, perform in the diagnosis of polycystic ovary syndrome (PCOS)?
Summary Result/s		The tPSA and tPSA:fPSA ratio resulted in AUC of 0.74 and 0.70, respectively, with moderate specificity/sensitivity and insufficient LR+/- values. In the multivariate logistic regression model, the combination of ovarian volume and outline had a sensitivity of 97.7% and a specificity of 97.5% in the diagnosis of PCOS, with +LR and -LR values of 39.1 and 0.02, respectively. In women with PCOS, tPSA and tPSA:fPSA ratio have similar diagnostic performance.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
PATIENT SELECTION/SPECTRUM BIAS	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	Studies that recruit a group of healthy controls and a group known to have the target disorder will be coded as “No” in most scenarios. Studies enrolling patients with known disease and control group without the condition may exaggerate diagnostic accuracy. Controls may not be routinely assessed for ovarian volume using ultrasound. The PCOS group is representative of those who will be assessed with these criteria in practice.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Not reported	No random element was described in the selection of participants into the study. Study is described as a prospective case-controlled study but does not mention methods for allocation.
	Was a case-control design avoided? (Q-2)	No	Both the control group (regular cycling, normo-androgenic, non-PCOM women) and group with known disease (PCOS) were identified and diagnosed prior or during study enrollment.
	Did the study avoid inappropriate exclusions? (Q-2)	Yes	For the PCOS group, the exclusions include: “Cushing syndrome, thyroid dysfunction, congenital adrenal hyperplasia hyperprolactinemia, ovarian or adrenal tumors, recent pregnancy or use of oral contraceptives, ovulatory agents, antidiabetic medications and glucocorticoids, within three months prior

			to enrolment. Women seeking fertility were also excluded, as they often receive hormonal therapies, which may interfere with study results." In addition, the study mentions that "For the homogeneity of the PCOS group, women with regular cycles but with signs of hyperandrogenism and polycystic ultrasound morphology were excluded". While this choice excludes one PCOS phenotype from Rotterdam criteria (Normo-ovulatory PCOS), it removes a PCOS phenotype that uses the index test as part of the reference standard. Therefore, this exclusion is considered appropriate. For the Control Group, the study describes the exclusion criteria as "any other cause of hyperandrogenemia or/and anovulation, history of cardiovascular disease, chronic disease under medication and history of drug or alcohol abuse" and is considered appropriate as they likely do not alter diagnostic accuracy for PCOS.
CLASSIFICATION/ VERIFICATION/ INCORPORATION/ REVIEW BIAS	Were all participants assessed with both index test and reference standard?	Yes	All participants in the Control group (n = 43) and PCOS group (n = 40) received the relevant index test (OV).
	Did all patients receive the same reference standard? (Q-2)	Yes	All participants in the study received the same reference standard, which was the Rotterdam diagnostic criteria for PCOS. For the Control group, the study mentions that "Inclusion criteria for the control were normal ovulatory cycles, absence of clinical or biochemical hyperandrogenemia and absence of polycystic morphology on ultrasound examination".
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	PCOS diagnosis was done "according to the Rotterdam ESHRE/ASRM criteria", which is described as a combination of at least two of the following: oligo-anovulation/anovulation, hyperandrogenism (clinical and/or biochemical), and polycystic ovarian morphology.
	Was the reference standard independent of the index test (ie. the index test did not form part of the reference standard)?	No	PCOS diagnosis of the Rotterdam criteria includes the evaluation of ovarian ultrasounds to measure either follicle number per ovary (FNPO) or ovarian volume (OV). Thus, the index test is part of the reference standard.
	Were the reference standard results interpreted without knowledge of the results of the index test?	No	PCOS diagnosis of the Rotterdam criteria includes the evaluation of ovarian ultrasounds to measure either follicle number per ovary (FNPO) or ovarian volume (OV). Thus, the reference standard is interpreted with knowledge of the index test.
	Were the index test results interpreted without knowledge of the results of the reference standard test?	No	Study methods describe that "Women with PCOS were attending the outpatient clinic for investigation of irregular menses and/or signs of androgen excess". Therefore, knowledge of PCOS features prior would impact index test interpretation and reference standard classification (since Rotterdam criteria is used).
	If a threshold was used, was it pre-specified?	No	The study mentions that "diagnostic performance was assessed by means of receiver operating characteristics (ROC) curves… Using ROC curves, the optimal threshold for ovarian volume in this study was 9.64 cm^3".

DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?	Not reported	Study methods describe that "in all women, fasting blood serum samples were collected in the early follicular phase (between days 3 and 5 of the menstrual cycle) or after a progesterone-induced withdrawal bleeding progesterone (10 mg of oral medroxyprogesterone acetate daily for 5 days)… Ovarian ultrasound was performed on the same day as blood sample collection". However, it is unclear the timing of clinical evaluations relative to the ultrasound scan and blood draw (given that normo-ovulatory PCOS phenotype was excluded).
ATTRITION BIAS	Were withdrawals from the study explained?	Yes 100% treatment 100% control/ comparison	Numbers described as enrolled are the same as those in results.
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Yes	There are no uninterruptable/intermediate test results and all results are reported.
OTHER ISSUES – APPLICABILITY/ COMPARABILITY/ VARIATION	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Partial	The following description of the ultrasound examination was provided: "Ovarian ultrasound was performed on the same day as blood sample collection, using a transvaginal ultrasound transducer (Voluson 730 Expert vaginal probe, GE Healthcare, St. Giles, England) at 5–7 MHz. All scans were performed by a single physician (K.D.), in order to prevent inter-observer error. Measurements were taken in real time, with the highest possible magnification. The ovaries were scanned in both the anteroposterior and transverse cross-section dimensions, from the inner to the outer margins. Ovarian volumes (cm^3) and outlines (cm) were calculated by the machine software." However, further details about machine software used for measuring OV is not provided.
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Yes	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Not reported	Study does not describe what clinical data was available during test result interpretation.
	Were there any conflicts of interest in the writing or funding of this study?	Yes	Authors are funded by grants from Merck Serono, Merck Sharp & Dohme, and IBSA & Ferring
	If statistical analysis was undertaken, was this appropriate?	Partial	Diagnostic performance was assessed by means of receiver operating characteristics (ROC) curves. The estimation and 95% confidence interval (CI) of the area under curve (AUC) of each diagnostic variable was calculated. DeLong's test was used to compare AUC of different diagnostic variables. However, unclear if an adequate sample size calculation was undertaken. A 4x4 table of test performance was not presented.
COMMENTS			

What is the overall risk of bias?	High	Few criteria fulfilled and the conclusions of the study are likely to be affected.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?	No. All outcomes had the same risk of bias.	

Study ID	Carmina 2016	
Study Citation	Carmina, E. et al. (2016). "AMH measurement versus ovarian ultrasound in the diagnosis of polycystic ovary syndrome in different phenotypes." Endocrine Practice 22(3): 287-293.	
Study Country	Italy	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	Control: Family members of hospital workers were selected as controls and had regular menses, no symptoms of hyperandrogenism (acne or hirsutism), and normal androgen levels. No control had any serious diseases. Normal menses were defined as cycles lasting 25 to 34 days. Control group were age- and BMI-matched to the PCOS group. PCOS: Women aged 19 to 35 years old diagnosed with PCOS according to conventional Rotterdam criteria. None of patients or controls was taking medications for at least 3 months before entering the study. Age: Control: 23.1 ± 4.0yo, PCOS: 23 ± 4.3yo p = not significant BMI: Control: 27 ± 4kg/m^2, PCOS: 27.9 ± 7.3 kg/m^2 p = not significant	
PCOS diagnostic criteria	Rotterdam	
N per group	PCOS: 113 Control: 47	
Setting	Endocrine Unit of the University of Palermo and the department of Obstetrics and Gynecology of the University of Pisa, Italy between 2013 and 2014	
Index test	Follicle Number Per Ovary (FNPO – Mean) Ovarian Volume (OV – Mean)	
Reference Standard	Rotterdam Criteria (oligo-anovulation, hyperandrogenism, PCOM)	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Accuracy to diagnose PCOS Sensitivity and specificity Proposed threshold	
Inclusion and exclusion criteria reported?	Yes	Inclusion Criteria: Controls: The controls were family members of hospital workers and had to have regular menses, no symptoms of hyperandrogenism (acne or hirsutism), and normal androgen levels. Normal menses were defined as cycles lasting 25 to 34 days. PCOS: The diagnosis of PCOS was made according to conventional Rotterdam criteria, including the original ultrasound criteria. Some patients had been treated previously with various therapies for menstrual irregularity (oligomenorrhea or amenorrhea, defined by absence of menses for 6 or more months) and/or hyperandrogenism (acne or hirsutism). Menstrual cycles were recorded for ≥3 months, and oligomenorrhea was defined as irregular menstrual cycles at intervals of ≥35 days. The subjects with oligomenorrhea or amenorrhea were

			considered anovulatory. In patients reporting normal menses, at least 2 consecutive menstrual cycles were evaluated, and the finding of low levels of serum progesterone (<3 ng/mL, <9.54 nmol/L) in both cycles suggested the presence of chronic anovulation despite fairly regular withdrawal bleeding. In those with regular cycles and elevated serum progesterone, the diagnosis of ovulatory function was confirmed. Therefore, the study population included both anovulatory (n = 93) and ovulatory (n = 20) patients. Exclusion Criteria: For both groups: Treatment for at least 3 months before evaluation in this study, serious diseases, those with pelvic pathology, hyperprolactinemia, and congenital adrenal hyperplasia
Does the study have a clearly focused question?		Partial	What is the value of serum anti-Müllerian hormone (AMH) in the diagnosis of polycystic ovary syndrome (PCOS) in various phenotypes and to assess ovarian ultrasound parameters?
Summary Result/s		In the entire cohort, AMH had a low sensitivity of 79%; while FNPO and OV were 93% and 68%, respectively. Specificities ranged from 85 to 96%. In classic anovulatory PCOS, AMH exhibited a sensitivity of 91%, and for FNPO and OV the corresponding sensitivities were 92% and 72%. In the ovulatory phenotype, AMH sensitivity was only 50%, while FNPO and OV were 95% and 50%, respectively. In the nonhyperandrogenic phenotype, the sensitivity of AMH was 53% while those for FNPO and OV were 93% and 67%.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
PATIENT SELECTION/SPECTRUM BIAS	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	
	Was a consecutive or random sample of patients enrolled? (Q-2)	Not reported	Study is described as a retrospective matched control study. For Control group selection, study describes selection process as “family members of hospital workers”. This indicates convenience sampling that may not be representative of study population as a whole. Study does not describe enrollments process for PCOS group.
	Was a case-control design avoided? (Q-2)	No	Both the control group (regular cycling, normo-androgenic women) and group with known disease (PCOS) were identified and diagnosed prior to study enrollment. Study design involves retrospective enrollment.
	Did the study avoid inappropriate exclusions? (Q-2)	Yes	Exclusion criteria for both PCOS and control group are appropriate. The study describes exclusion criteria for both groups as: “Exclusion criteria includes those with pelvic pathology, hyperprolactinemia, and congenital adrenal hyperplasia. No controls had any serious diseases. None of patients or controls was taking medications for at least 3 months before entering the study.”
CLASSIFICATION	Were all participants assessed with both index test and reference standard?	Yes	All participants in the Control group (n = 47) and PCOS group (n = 113) received all three index tests (OV, FNPO).
	Did all patients receive the same reference standard? (Q-2)	Not reported	For the Control group, the study mentions that they had “regular menses, no symptoms of hyperandrogenism (acne or hirsutism), and normal androgen levels.” However, it is unclear if PCOM was evaluated.
	Is the reference standard likely to	Yes	PCOS diagnosis was determined “according to conventional Rotterdam criteria, including the original ultrasound criteria” which specifically includes “menstrual cycles were recorded for ≥3 months, and oligomenorrhea was

	correctly classify the target condition? (Q-2)		defined as irregular menstrual cycles at intervals of ≥35 days. In patients reporting normal menses, at least 2 consecutive menstrual cycles were evaluated, and the finding of low levels of serum progesterone (<3 ng/mL, <9.54 nmol/L) in both cycles suggested the presence of chronic anovulation despite fairly regular withdrawal bleeding. In those with regular cycles and elevated serum progesterone, the diagnosis of ovulatory function was confirmed. Biochemical hyperandrogenism was defined as serum T >60 ng/dL (≥2.08 nmol/L) and/or serum DHEAS ≥3 mg/mL (>7.8 mmol/L). These values for hyperandrogenism have been validated with the use of the previously described assays."
	Was the reference standard independent of the index test (ie. the index test did not form part of the reference standard)?	No	PCOS diagnosis of the Rotterdam criteria includes the evaluation of ovarian ultrasounds to measure either follicle number per ovary (FNPO)or ovarian volume (OV). Thus, the index test is part of the reference standard.
	Were the reference standard results interpreted without knowledge of the results of the index test?	No	PCOS diagnosis of the Rotterdam criteria includes the evaluation of ovarian ultrasounds to measure either follicle number per ovary (FNPO) or ovarian volume (OV). Thus, the reference standard is interpreted with knowledge of the index test.
	Were the index test results interpreted without knowledge of the results of the reference standard test?	No	Study describes that "some patients had been treated previously with various therapies for menstrual irregularity (oligomenorrhea or amenorrhea, defined by absence of menses for 6 or more months) and/or hyperandrogenism (acne or hirsutism) but had not received any treatment for at least 3 months before evaluation in this study." Therefore, some patients were identified for symptoms of PCOS prior to index tests.
	If a threshold was used, was it pre-specified?	No	Authors describe that "Cutoff values for elevations compared to the control population were determined with receiver operating characteristic (ROC) curve analyses".
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?	Not reported	Method description does not describe the timing of the reference standard in relation to the index test results.
ATTRITION BIAS	Were withdrawals from the study explained?	Yes 100% treatment 100% control/ comparison	Numbers described as enrolled are the same as those in results.
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Yes	There are no uninterruptable/intermediate test results and all results are reported.
	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	The following description of the ultrasound examination was provided: "In all patients and control subjects, on days 3 to 6 of withdrawal bleeding, ovarian morphology was assessed by transvaginal ultrasound using a transducer frequency of 8- to 10- MHz (MyLab 50 Xvision; Esaote, Genoa, Italy) Ovarian volume (OV) was determined as was the presence, size, and total number of

OTHER ISSUES – APPLICABILITY/ COMPARABILITY/ VARIATION			ovarian follicles that were 2 to 10 mm (FNPO). OV was calculated by the formula p/6 (D1 × D2 × D3) where the dimensions (D) of length, width, and thickness were used. The sizes of both ovaries were assessed, and mean OV was calculated."
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Yes	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Not reported	Study does not describe what clinical data was available during test result interpretation
	Were there any conflicts of interest in the writing or funding of this study?	No	Authors stated that there were no conflicts of interest to disclose.
	If statistical analysis was undertaken, was this appropriate?	Partial	Study describes statistical analysis as follows: "Cutoff values for elevations compared to the control population were determined with receiver operating characteristic (ROC) curve analyses. Here a plot of sensitivity against 1-specificity provides the curve analysis. The area under the curve of this plot provides information about sensitivity and specificity for various threshold values." However, unclear if an adequate sample size calculation was undertaken. A 4x4 table of test performance was not presented. AUC data not provided for any index tests.
COMMENTS			
What is the overall risk of bias?		High	Few criteria fulfilled and the conclusions of the study are likely to be affected.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No. All outcomes had the same risk of bias.	

Study ID	Chen 2008
Study Citation	Chen, Y. et al. (2008). "Ovarian volume and follicle number in the diagnosis of polycystic ovary syndrome in Chinese women." Ultrasound in Obstetrics and Gynecology 32(5): 700-703.
Study Country	China
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	Control: Women who attended the hospital and volunteered as age-matched controls. Regular menses; normal serum level of androgen; no history of menstrual disorders or endocrine disease; and no sign of hirsutism or acne. PCOS: Women diagnosed with PCOS was based on NIH criteria: association of oligo-anovulation (mostly manifested as oligomenorrhea) and clinical and/or biochemical signs of hyperandrogenisms with exclusions of other etiologies (congenital adrenal hyperplasia, Cushing's syndrome or androgen-secreting tumor).

	Age: Control: 27.15 ± 2.33yo, PCOS: 26.25 ± 2.01yo p = 0.36 BMI: Not available	
PCOS diagnostic criteria	NIH	
N per group	PCOS: 432 Control: 153	
Setting	The Second Affiliated Hospital of Sun Yat-Sen University of Guangzhou, China between 2004 and 2007	
Index test	Follicle Number Per Ovary (FNPO – Mean and Max) Ovarian Volume (OV – Mean and Max)	
Reference Standard	NIH criteria (oligoanovulation [mostly manifested as oligoamenorrhea] and clinical and/or biochemical signs of hyperandrogenism)	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Accuracy to diagnose PCOS Sensitivity and specificity Area under the ROC curve Proposed threshold	
Inclusion and exclusion criteria reported?	Yes	Inclusion Criteria: Control: regular menses; normal serum level of androgen; no history of menstrual disorders or endocrine disease; and no sign of hirsutism or acne. PCOS: Diagnosis of PCOS was based on NIH criteria: association of oligo-anovulation (mostly manifested as oligomenorrhea) and clinical and/or biochemical signs of hyperandrogenisms Exclusion Criteria: Control: a history of ovarian surgery; hormonal treatment in the previous 3 months or for PCOS-related treatment before this research; and ovarian mass or cyst (more than 10 mm in diameter) detected by ultrasound examination in this study. PCOS: congenital adrenal hyperplasia, Cushing's syndrome or androgen-secreting tumor… a history of ovarian surgery; hormonal treatment in the previous 3 months or for PCOS-related treatment before this research; and ovarian mass or cyst (more than 10 mm in diameter) detected by ultrasound examination in this study.
Does the study have a clearly focused question?	Yes	What is the value of ovarian volume and follicle number in the diagnosis of polycystic ovary syndrome (PCOS) in a Chinese population?
Summary Result/s	The 10th and 90th centiles of ovarian volume in PCOS patients were 4.89 and 15.79 cm^3, respectively, and the median was 9.21 cm^3; the 10th and 90th centiles of follicle number were 8 and 19, respectively, and the median was 12. The 10th and 90th centiles of ovarian volume in controls were 2.43 and 7.75 cm^3, respectively, and the median was 4.46 cm^3; the 10th and 90th centiles of follicle number were 3 and 10, respectively, and the median was 6. The differences in ovarian volume and follicle number between patients and controls were statistically significant. The areas under the ROC curves for mean ovarian volume (MOV), maximum ovarian volume (MaxOV), mean follicle number (MFN) and maximum follicle number (MaxFN) to diagnose PCOS were 0.898, 0.882, 0.909 and 0.911, respectively. Setting the threshold for MOV at 6.4 cm^3 (sensitivity 81%, specificity 85.6%), the threshold for MaxOV at 7.9 cm^3 (sensitivity 78%, specificity 85.6%), the threshold for MFN at 10 (sensitivity 85.2%, specificity 88.8%) and the threshold for MaxFN at 12 (sensitivity 85.2%, specificity 92.6%) obtained the best compromise between sensitivity and specificity, based on the Youden index. We conclude that ovarian	

		volume and follicle number have satisfactory power for use in the diagnosis of PCOS. Cut-offs of 6.4 cm^3, 7.9 cm^3, 10 and 12, for MOV, MaxOV, MFN and MaxFN, respectively, obtained the best compromise between sensitivity and specificity for the diagnosis of PCOS in Chinese women.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
PATIENT SELECTION/SPECTRUM BIAS	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	Studies that recruit a group of healthy controls and a group known to have the target disorder will be coded as "No" in most scenarios. Studies enrolling patients with known disease and control group without the condition may exaggerate diagnostic accuracy. Controls may not be routinely assessed for ovarian volume using ultrasound. The PCOS group is representative of those who will be assessed with these criteria in practice.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Not reported	No random element was described in the selection of participants into the study. Study is described as cross-sectional and uses previously collected data.
	Was a case-control design avoided? (Q-2)	No	Both the control group (regular cycling, normo-androgenic women) and group with known disease (PCOS) were identified and diagnosed prior to study enrollment.
	Did the study avoid inappropriate exclusions? (Q-2)	Yes	Exclusion criteria for both PCOS and Control group are appropriate. For both groups, the study describes the exclusion criteria as: "a history of ovarian surgery; hormonal treatment in the previous 3 months or for PCOS-related treatment before this research; and ovarian mass or cyst (more than 10 mm in diameter) detected by ultrasound examination in this study". For the PCOS group, the additional exclusions include: "congenital adrenal hyperplasia, Cushing's syndrome or androgen-secreting tumor."
CLASSIFICATION/ VERIFICATION/ INCORPORATION/ REVIEW BIAS	Were all participants assessed with both index test and reference standard?	Yes	All participants in the Control group (n = 153) and PCOS group (n = 432) received both index tests (OV, FNPO).
	Did all patients receive the same reference standard? (Q-2)	Yes	All participants in the study received the same reference standard, which was the NIH diagnostic criteria for PCOS. For the Control group, the study mentions that they must have "regular menses; normal serum level of androgen; no history of menstrual disorders or endocrine disease; and no sign of hirsutism or acne".
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	PCOS diagnosis was determined by the NIH (1990) criteria, which is the "association of oligo-anovulation (mostly manifested as oligomenorrhea) and clinical and/or biochemical signs of hyperandrogenisms with exclusions of other etiologies (congenital adrenal hyperplasia, Cushing's syndrome or androgen-secreting tumor). Biochemical hyperandrogenemia was defined as an elevated serum concentration of at least one of the androgens mentioned above, i.e. total testosterone >2.60 nmol/L, free testosterone >6.6 pg/mL, androstenedione >2.57 ng/mL or dehydroepiandrosterone sulfate >5871 ng/mL (this value was determined as the upper threshold according to our hospital laboratory, measured by enzyme-linked immunosorbent assay). Hirsutism and acne were evaluated by modified Ferriman–Gallwey score and acne score by the method proposed by Rosenfield. A Ferriman–Gallwey score ≥6 and/or acne score ≥2 were defined as clinical signs of hyperandrogenism".
	Was the reference standard independent of the index test (ie. the index	Yes	NIH criteria for the diagnosis of PCOS only includes the presence oligo-anovulation/anovulation and hyperandrogenism (clinical and/or biochemical). Sonographic markers of ovarian morphology are not part of the reference standard.

	test did not form part of the reference standard)?		
	Were the reference standard results interpreted without knowledge of the results of the index test?	Yes	Study methods describe that “each subject was given a serum androgen test and physical examination to evaluate the severity of clinical hyperandrogenism (hirsutism and acne) before inclusion”, with “Regularly menstruating women were scanned in the early follicular phase (cycle days 3–5)” and “Oligomenorrheic or amenorrheic women were scanned either at random or between days 3 and 5 after a progestin-induced withdrawal bleed”. This confirms that the reference standard (PCOS diagnosis) was interpreted prior to results of index tests.
	Were the index test results interpreted without knowledge of the results of the reference standard test?	No	Study methods describe that “each subject was given a serum androgen test and physical examination to evaluate the severity of clinical hyperandrogenism (hirsutism and acne) before inclusion”, with “Regularly menstruating women were scanned in the early follicular phase (cycle days 3–5)” and “Oligomenorrheic or amenorrheic women were scanned either at random or between days 3 and 5 after a progestin-induced withdrawal bleed”. This confirms that the index tests were conducted with prior knowledge of reference standard (PCOS diagnosis).
	If a threshold was used, was it pre-specified?	No	Study methods describe that “the Youden index (sensitivity + specificity − 1) was calculated to determine the best compromise between sensitivity and specificity”.
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?	Not reported	Although study methods describe that “each subject was given a serum androgen test and physical examination to evaluate the severity of clinical hyperandrogenism (hirsutism and acne) before inclusion”, it is unclear whether these were conducted at an appropriate interval with the ultrasound scan, which was mentioned to occur during cycle days 3-5 for regularly menstruating women or either at random or between days 3 and 5 after a progestin-induced withdraw bleed for oligomenorrheic or amenorrheic women.
ATTRITION BIAS	Were withdrawals from the study explained?	Yes 100% treatment 100% control/ comparison	Numbers described as enrolled are the same as those in results.
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Yes	There are no uninterruptable/intermediate test results and all results are reported.
	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	The following description of the ultrasound examination was provided: “Transvaginal or transrectal ultrasound examination was performed to evaluate the ovaries, using a Toshiba Sonolayer SSA-220A (Toshiba, Tokyo, Japan) with a mechanical 6-MHz transvaginal probe. Regularly menstruating women were scanned in the early follicular phase (cycle days 3–5). Oligomenorrheic or amenorrheic women were scanned either at random or between days 3 and 5 after a progestin-induced withdrawal bleed. Ultrasound measurements were taken in real time, according to a standard protocol. The highest possible magnification was used to examine the ovaries. After the longest medial axis of the ovary had been determined, the length and height were measured and then the probe was turned to determine the width. Ovarian volume was estimated using a simplified formula for the volume of a prolate ellipsoid: V = 0.5 × length × height × width, and follicle number was established by scanning each ovary from the inner margin to the outer margin in longitudinal cross-

OTHER ISSUES – APPLICABILITY/ COMPARABILITY/ VARIATION			section and obtaining the number of all countable follicles. Follicles were measured in two planes of the ovary and the diameter of the follicles was taken as the mean of two diameters (longitudinal and anteroposterior)."
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Yes	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Not reported	Study does not describe what clinical data was available during test result interpretation.
	Were there any conflicts of interest in the writing or funding of this study?	No	Authors stated that there were no conflicts of interest to disclose.
	If statistical analysis was undertaken, was this appropriate?	Partial	Study describes that "ROC analysis was performed to examine their diagnostic test performance, i.e. the ability to discriminate between controls and PCOS patients. Sensitivity against (1 − specificity) was plotted at each level, and the area under the curve (AUC) – which reflects the probability of correctly identifying controls and PCOS patients – was calculated. The Youden index (sensitivity + specificity − 1) was calculated to determine the best compromise between sensitivity and specificity; the closer the value is to 1, the greater the diagnostic power." However, unclear if an adequate sample size calculation was undertaken. A 4x4 table of test performance was not presented.
COMMENT			
What is the overall risk of bias?		Moderate	Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No. All outcomes had the same risk of bias.	

Study ID	Chen 2008
Study Citation	Chen, Y. et al. (2008). "The role of ovarian volume as a diagnostic criterion for Chinese adolescents with polycystic ovary syndrome." Journal of Pediatric and Adolescent Gynecology 21(6):347-350.
Study Country	China
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	Control: Age-matched volunteers with regular menses and without the sign of hirsutism and/or acne or a history of operation on ovary. PCOS: Pubertal patients with suspected PCOS were selected by using the NIH criteria to be free from any inclusion bias. i.e. association of an oligo-anovulation and clinical and/or biochemical

	signs of hyperandrogenism with exclusion of other etiologies (congenital adrenal hyperplasia, thyroid dysfunction, Cushing's syndrome or androgen-secreting tumor). Age: Control: 13.00 ± 1.23yo, PCOS: 12.57 ± 1.25yo p = not significant BMI: Control: 21.77 ± 4.60kg/m^2, PCOS: 20.12 ± 2.17kg/m^2 p = not significant	
PCOS diagnostic criteria	NIH	
N per group	PCOS: 69 Control: 26	
Setting	Reproductive endocrinology clinic in The Second Affiliated Hospital of Sun Yat-Sen University of Guangzhou, Guangdong, China.	
Index test	Ovarian Volume (OV – Mean and Maximum)	
Reference Standard	NIH criteria (association of an oligo-anovulation and clinical and/or biochemical signs of hyperandrogenism)	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Accuracy to diagnose PCOS Sensitivity and specificity Area under the ROC curve Proposed threshold	
Inclusion and exclusion criteria reported?	Yes	Inclusion Criteria: Control: regular menses and without the sign of hirsutism and/or acne or a history of operation on ovary. PCOS: association of an oligo-anovulation and clinical and/or biochemical signs of hyperandrogenism Exclusion Criteria: Control: Those who had even one of the following situations were excluded from this study: (1) a history of ovarian surgery; (2) hormonal treatment in the previous 3 mouths or for PCOS patients any other related treatment before this research; (3) ovarian mass or cyst (more than 10mm in diameter) detected by ultrasound scanning in this study. PCOS: Other etiologies (congenital adrenal hyperplasia, thyroid dysfunction, Cushing's syndrome or androgen-secreting tumor).
Does the study have a clearly focused question?	Yes	What is the accuracy of ovarian volume (OV) as one of the diagnostic criteria for Chinese adolescents with polycystic ovary syndrome (PCOS)?
Summary Result/s	OV yields good diagnostic accuracy to distinguish normal ovaries from polycystic ovaries in Chinese adolescents, but for Chinese PCOS adolescents, the best compromise between sensitivity and specificity was obtained with a threshold set at 6.74 cm^3 for mean ovarian volume and at 7.82 cm^3 for maximum ovarian volume instead of the 10 cm^3 threshold proposed by the Rotterdam consensus conference based on general PCOS patients.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

PATIENT SELECTION/SPECTRUM BIAS	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	Studies that recruit a group of healthy controls and a group known to have the target disorder will be coded as "No" in most scenarios. Studies enrolling patients with known disease and control group without the condition may exaggerate diagnostic accuracy. Controls may not be routinely assessed for ovarian volume using ultrasound. The PCOS group is representative of those who will be assessed with these criteria in practice.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Not reported	No random element was described in the selection of participants into the study.
	Was a case-control design avoided? (Q-2)	No	No random element was described in the selection of participants into the study.
	Did the study avoid inappropriate exclusions? (Q-2)	Yes	The exclusion criteria for Controls are as follows: (1) a history of ovarian surgery; (2) hormonal treatment in the previous 3 months or for PCOS patients any other related treatment before this research; (3) ovarian mass or cyst (more than 10mm in diameter) detected by ultrasound scanning in this study". The exclusion criteria for PCOS includes "other etiologies (congenital adrenal hyperplasia, thyroid dysfunction, Cushing's syndrome or androgen-secreting tumor)."
CLASSIFICATION/ VERIFICATION/ INCORPORATION/ REVIEW BIAS	Were all participants assessed with both index test and reference standard?	Yes	All participants in the Control group (n = 26) and PCOS group (n = 69) received the relevant index test (OV).
	Did all patients receive the same reference standard? (Q-2)	Yes	All participants in the study received the same reference standard, which was the NIH diagnostic criteria for PCOS. For the Control group, the study mentions that they had "regular menses and without the sign of hirsutism and/or acne or a history of operation on ovary."
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	The study describes the diagnosis of PCOS as follows: "the oligo- and/or anovulation was manifested by the menstrual disturbance (i.e. oligomenorrhea or amenorrhea or cycle >25days or <35 days and/or ovulatory disturbances as assessed by basal body temperature chart and/or serum progesterone level >3 ng/ml in luteal phase). The clinical and/or biochemical signs of hyperandrogenism was defined as a modified Ferriman and Gallwey score of >8 and/or acne and/or an elevated serum concentration of total testosterone values above 2 SD from the mean in the control subjects."
	Was the reference standard independent of the index test (ie. the index test did not form part of the reference standard)?	Yes	NIH criteria for the diagnosis of PCOS only includes the presence oligo-anovulation/anovulation and hyperandrogenism (clinical and/or biochemical). Sonographic markers of ovarian morphology are not part of the reference standard.
	Were the reference standard results interpreted without knowledge of the results of the index test?	Not reported	Method description does not describe the timing of the reference standard in relation to the index test results for all participants.
	Were the index test results	Not reported	Method description does not describe the timing of the reference standard in relation to the index test results for all participants.

	interpreted without knowledge of the results of the reference standard test?		
	If a threshold was used, was it pre-specified?	No	Authors describe that the "best compromise between sensitivity and specificity was determined by Youden index (sensitivity + specificity-1)".
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?	Not reported	Study procedure does not indicate when the diagnosis for PCOS was made relative to when the ultrasound was done. However, since the ultrasounds were not completed for all patients at the same time, it may be reasonable to infer that the time period is inconsistent and depends on the specific patient.
ATTRITION BIAS	Were withdrawals from the study explained?	Yes 100% treatment 100% control/ comparison	Numbers described as enrolled are the same as those in results.
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Yes	There are no uninterruptable/intermediate test results and all results are reported.
OTHER ISSUES – APPLICABILITY/ COMPARABILITY/ VARIATION	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	Authors provided the following description of the ultrasound examination: "Transrectal ultrasound was performed to evaluated the uterus and ovaries, used a Toshiba Sonolayer SSA-220A (Toshiba, Tokyo, Japan) real-time sonography fitted with a 6-MHz transvaginal transducer. Regularly menstruating women were scanned between cycle 3 and 5, oligomenorrheic or amenorrheic women were scanned either at random or between days 3-5 after a progestin-induced withdrawal bleeding. Ultrasound measurements were taken in real time, according to a standardized protocol. If the ultrasound scanning revealed a ovarian mass or dominant follicle (more than 10mm in diameter), the participant was excluded from this study. The highest possible magnification was used to examine the ovaries. After the longest medial axis of the ovary had been determined, the length and thickness were measured and ovarian volume was calculated using a manual simplified formula: 0.5 x length x width x thickness as described previously."
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Yes	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Not reported	Study does not describe what clinical data was available during test result interpretation.
	Were there any conflicts of interest in the writing	Not reported	No conflicts of interest were reported.

	or funding of this study?		
	If statistical analysis was undertaken, was this appropriate?	Partial	Study describes statistical analysis as follows: "Receiver Operating Characteristic (ROC) curves were constructed to examine the diagnostic test performance of ovarian volume, i.e. the ability to discriminate between controls and adolescents with PCOS. The data used for this statistical analysis was (1) the mean value of bilateral ovaries (mean OV); (2) the larger value of bilateral ovaries (maximum OV). Sensitivity against (1 - specificity) was plotted at each level, and the area under the curve (AUC) was computed by SPSS13.0 for Windows statistical package. The AUC represents the probability of correctly identifying controls and patients with PCOS. The best compromise between sensitivity and specificity was determined by Youden index (sensitivity + specificity -1). A value closer to 1 indicates a greater diagnostic significance. Statistical significance was defined as two-tailed P<0.05." However, unclear if an adequate sample size calculation was undertaken. A 4x4 table of test performance was not presented.
COMMENTS			
What is the overall risk of bias?		Moderate	Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No. All outcomes had the same risk of bias.	

Study ID	Christ 2014
Study Citation	Christ, J. P. et al. (2014). "Follicle number, not assessments of the ovarian stroma, represents the best ultrasonographic marker of polycystic ovary syndrome." Fertility and Sterility 101(1): 280-287.
Study Country	USA/Canada
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	Control: Women from the general population with no hyperandrogenism and regular menstrual cycles served as controls. Participants were recruited from the general population using ads seeking healthy women of reproductive age or women with concerns of out- ward features of PCOS such as irregular periods, obesity, excess hair growth, and/or infertility. Volunteers ranged in age from 18–38 years. PCOS: Diagnosed with PCOS by the NIH criteria as having oligo-amenorrhea and hyperandrogenism were recruited to the study. Age (yo): Control: 27 (24-31), PCOS: 28 (24-31) p = not significant BMI (kg/m^2): Control: 23.7 (21.9-27.2), PCOS: 31.2 (23.7-37.8) p < 0.0001
PCOS diagnostic criteria	NIH
N per group	PCOS: 82 Control: 60
Setting	Royal University Hospital within the Department of Obstetrics, Gynecology and Reproductive Sciences, University of Saskatchewan (Saskatoon, Saskatchewan, Canada) from 2006–2008,

	and in the Division of Nutritional Sciences' Human Metabolic Research Unit, Cornell University (Ithaca, New York, USA) from 2009–2011.		
Index test	Follicle Number Per Ovary (FNPO – Mean) Ovarian Volume (OV – Mean) Follicle Number Per Cross-Section (FNPS – Mean) Stromal Area (SA – Mean) Stromal-to-Ovarian Area (S/A) Stromal Index (SI) Follicle Distribution Pattern (FDP)		
Reference Standard	NIH criteria (oligomenorrhea and hyperandrogenism)		
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Accuracy to diagnose PCOS Sensitivity and specificity Area under the ROC curve Proposed threshold		
Inclusion and exclusion criteria reported?	Yes	Inclusion Criteria: Control: women from the general population with no hyperandrogenism and regular menstrual cycles served as controls. Participants were recruited from the general population using ads seeking healthy women of reproductive age or women with concerns of outward features of PCOS such as irregular periods, obesity, excess hair growth, and/or infertility. PCOS: women diagnosed with PCOS by the NIH criteria as having oligo-amenorrhea and hyperandrogenism were recruited to the study. Exclusion Criteria: Both groups: those who could not have used hormonal contraception, fertility medications, or insulin sensitizers in the 3 months before enrollment. Subjects were ineligible if they had a previous history of ovarian surgery or current abnormalities in cortisol (F), PRL, thyroid hormone, DHEAS, or 17-hydroxyprogesterone (17-OHP) secretion	
Does the study have a clearly focused question?	Partial	What is the diagnostic potential of ultrasonographic markers of ovarian morphology, used alone or in combination, to predict polycystic ovary syndrome (PCOS)?	
Summary Result/s	Follicle number per ovary best predicted PCOS (R^2=67%) with 85% sensitivity and 98% specificity, followed by OV (R^2=44%), and FNPS (R^2=36%). Neither S:A nor SI had predictive power for PCOS. In combination, FNPO+S:A and FNPO+SI most significantly predicted PCOS (R^2= 74% vs. 73%, respectively). The diagnostic potentials of OV and FNPS were substantially improved when used in combination (OV+FNPO, R^2=55%). As a single metric, FNPO best predicted PCOS. Although the addition of S:A or SI improved the predictive power of FNPO, gains were marginal, suggesting limited use in clinical practice. When image quality precludes a reliable estimation of FNPO, measurements of OV+FNPS provide the next closest level of diagnostic potential.		
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
PATIENT SELECTION/SPECTRU	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	Studies that recruit a group of healthy controls and a group known to have the target disorder will be coded as “No” in most scenarios. Studies enrolling patients with known disease and control group without the condition may exaggerate diagnostic accuracy. Controls may not be routinely assessed for ovarian volume using ultrasound. The PCOS group is representative of those who will be assessed with these criteria in practice.

	Was a consecutive or random sample of patients enrolled? (Q-2)	Not reported	No random element was described in the selection of participants into the study. Study is described as a cross-sectional study and uses previously collected data.
	Was a case-control design avoided? (Q-2)	No	Both the control group (regular cycling, normo-androgenic women) and group with known disease (PCOS) were identified and diagnosed prior to study enrollment. Study design involves retrospective enrollment.
	Did the study avoid inappropriate exclusions? (Q-2)	Yes	Exclusion criteria for both PCOS and control group are appropriate. The exclusion criteria for both groups included: those who "could not have used hormonal contraception, fertility medications, or insulin sensitizers in the 3 months before enrollment. Subjects were ineligible if they had a previous history of ovarian surgery or current abnormalities in cortisol (F), PRL, thyroid hormone, DHEAS, or 17-hydroxyprogesterone (17-OHP) secretion."
CLASSIFICATION/ VERIFICATION/ INCORPORATION/ REVIEW BIAS	Were all participants assessed with both index test and reference standard?	Yes	All participants in the Control group (n = 60) and PCOS group (n = 82) received all three index tests (FNPS, Stroma, OV, FNPO).
	Did all patients receive the same reference standard? (Q-2)	Yes	All participants in the study received the same reference standard, which was the NIH diagnostic criteria for PCOS. For the Control group, the participants were "from the general population with no hyperandrogenism and regular menstrual cycles...".
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	PCOS diagnosis was determined by the NIH (1990) criteria: "Oligo-amenorrhea was defined as a history of unpredictable menstrual cycles shorter than 21 days or longer than 36 days. Hyperandrogenism was defined as a modified hirsutism score ≥7 (internally validated value having 83% sensitivity and 96% specificity to distinguish between PCOS and controls) and/or an elevated total T concentration ≥114.12 ng/dL (internally validated value having 87% sensitivity and 100% specificity to distinguish between PCOS and controls)".
	Was the reference standard independent of the index test (ie. the index test did not form part of the reference standard)?	Yes	NIH criteria for the diagnosis of PCOS only includes the presence oligo-anovulation/anovulation and hyperandrogenism (clinical and/or biochemical). Sonographic markers of ovarian morphology are not part of the reference standard.
	Were the reference standard results interpreted without knowledge of the results of the index test?	Not reported	Method description does not describe the timing of the reference standard in relation to the index test results.
	Were the index test results interpreted without knowledge of the results of the reference standard test?	Not reported	Method description does not describe the timing of the index test in relation to the reference standard.
	If a threshold was used, was it pre-specified?	No	Authors describe that "Diagnostic thresholds for sonographic features were based on Youden's index, which balanced maximum test sensitivity and test specificity".

DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?	Not reported	Although study methods describe that "control subjects were scanned on days 2–5 of the menstrual cycle and women with PCOS were scanned at an unspecified time", it is unclear whether the blood draw or physical examination were conducted at an appropriate interval with the ultrasound scan.
ATTRITION BIAS	Were withdrawals from the study explained?	Yes 100% treatment 100% control/ compariso nu	Numbers described as enrolled are the same as those in results.
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Yes	There are no uninterruptable/intermediate test results and all results are reported.
OTHER ISSUES – APPLICABILITY/	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	Follicle Number Per Cross-Section (FNPS) – 2D-Offline Stromal Area (SA) – 2D-Offline – Peripheral Stromal Profile Stromal Area / Ovarian Area (S:A) – 2D-Offline Stromal Index (SI) – 2D-Offline – Mean Stromal Echogenicity / Ovarian Echogenicity Follicle Distribution Pattern (FDP) – Peripheral Distribution (Y/N) Ovarian Area (OA) – 2D-Offline Ovarian Volume (OV) – 2D-Offline – Prolapsed Ellipsoid Formula Follicle Number Per Ovary (FNPO) – 2D-Offline Grid "The stromal area was measured by outlining the peripheral profile of the stroma, avoiding antral follicles represented by anechoic structures in the ovary. The outline was extended to the periphery of the ovary when no follicles were present around that peripheral portion of the ovary. Mean Follicle distribution pattern was determined in ovaries if a follicle >10 mm in size was not present. Participants were considered to have peripherally distributed follicles if the largest cross-sectional plane of both ovaries contained >9 follicles in a clear aggregation around the periphery with no more than 1 central follicle. Mean echogenicity was defined as the sum of the product of each intensity level and the number of pixels for that intensity concentration, divided by the total number of pixels in the measured area. The SI was calculated by dividing the mean stromal echogenicity by the echogenicity of the entire ovary. The ultrasound scans were also evaluated for the number of antral follicles (2–10 mm) per ovary (FNPO), follicle number in the largest cross-sectional plane (FNPS), and OV. Reliable follicle counts were achieved for each ovary by imposing a programmable grid onto the viewing window as previously described. The OV was estimated using the equation: p/6 (Transverse diameter) x (Anteroposterior diameter) x (Longitudinal diameter). When all follicles in the left and right ovary were <10 mm in size, a value for OV was designated as the mean recorded values of both ovaries."
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	No	
	Were the same clinical data available when test results were interpreted	Not reported	Study does not describe what clinical data was available during test result interpretation.

	as would be available when the test is used in practice?		
	Were there any conflicts of interest in the writing or funding of this study?	No	Authors stated that there were no conflicts of interest to disclose.
	If statistical analysis was undertaken, was this appropriate?	Partial	Authors describe the statistical analysis as follows: "Receiver operating characteristic curve analysis was used to evaluate the accuracy of sonographic end points in the diagnosis of PCOS. Diagnostic thresholds for sonographic features were based on Youden's index, which balanced maximum test sensitivity and test specificity." However, unclear if an adequate sample size calculation was undertaken. A 4x4 table of test performance was not presented.
COMMENTS			
What is the overall risk of bias?		Moderate	Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No. All outcomes had the same risk of bias.	

Study ID	Çiraci 2015
Study Citation	Çiraci, S. et al. (2015). "Contribution of real-time elastography in diagnosis of polycystic ovary syndrome." Diagnostic and Interventional Radiology 21(2): 118.
Study Country	Turkey
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	Control: Healthy women from consecutive patients who were referred to the Gynecology Department for routine control were included in the study. Did not have patients with polycystic ovary appearance in the control group. PCOS: PCOS diagnoses were made according to the Rotterdam (ESHRE/ASRM) criteria. The patients who had a diagnosis of Cushing syndrome, congenital adrenal hyperplasia, hyperprolactinemia, thyroid dysfunction, virilizing tumors, type 2 diabetes mellitus, or patients on medication such as oral contraceptives, glucocorticoids, antiandrogens, insulin sensitizers, or drugs that may cause hirsutism were excluded from the study. Age: Control: 27.1±5.2 yo PCOS: 25.7± 4.2yo p = 0.092 BMI: Not available
PCOS diagnostic criteria	Rotterdam
N per group	PCOS: 48 Control: 48
Setting	Gynecology Department of the Ankara Training and Research Hospital of Ankara, Turkey
Index test	Follicle Number Per Ovary (FNPO – Mean) Ovarian Volume (OV – Mean) Stromal Strain Ratio
Reference Standard	Rotterdam criteria (oligo-anovulation, hyperandrogenism, PCOM)

Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)		Accuracy to diagnose PCOS Sensitivity and specificity Area under the ROC curve Proposed threshold	
Inclusion and exclusion criteria reported?		Yes	Inclusion criteria Controls: healthy women who were referred to the Gynecology Department for routine control PCOS: PCOS diagnoses were made according to the Rotterdam (ESHRE/ASRM) criteria Exclusion Criteria: Controls: Patients with polycystic ovary appearance, patients who had follicles larger than 9 mm or corpus luteum cysts because these features could potentially alter the results PCOS: Patients who had a diagnosis of Cushing syndrome, congenital adrenal hyperplasia, hyperprolactinemia, thyroid dysfunction, virilizing tumors, type 2 diabetes mellitus, or patients on medication such as oral contraceptives, glucocorticoids, antiandrogens, insulin sensitizers, or drugs that may cause hirsutism were excluded from the study. Patients who had follicles larger than 9 mm or corpus luteum cysts were also excluded because these features could potentially alter the results.
Does the study have a clearly focused question?		Partial	What is feasibility and reproducibility of real-time elastography (RTE) for displaying the effects of morphological changes in the ovary in polycystic ovary syndrome (PCOS)?
Summary Result/s		Both radiologists determined the elasticity pattern as mostly type 1 in the PCOS group and type 3 in the control group ($P < 0.01$). The mean strain ratios obtained by the first and second radiologist were 6.1±1.8 (2.7–10.1) and 6.0±1.5 (3.0–9.0) in PCOS and 3.3±1.2 (1.7–7.2) and 3.2±0.9 (1.7– 6.8) in the control group, respectively ($P < 0.001$). Interobserver agreement was moderate for the elasticity pattern (κ=0.48) and good for the strain ratio (intraclass correlation coefficient, 0.77). A strain ratio of 3.8 was determined as the optimized cutoff point by receiver operating curve analysis. Strain ratio was correlated with the ovarian volume and the number of detected follicles ($P < 0.001$). Elasticity pattern and strain ratio can help identify morphological changes that make PCOS ovaries stiffer than normal ovaries.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
PATIENT SELECTION/SPECTRUM BIAS	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	Studies that recruit a group of healthy controls and a group known to have the target disorder will be coded as “No” in most scenarios. Studies enrolling patients with known disease and control group without the condition may exaggerate diagnostic accuracy. Controls may not be routinely assessed for ovarian volume using ultrasound. The PCOS group is representative of those who will be assessed with these criteria in practice.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Partial	Although selection the Control group was described as “healthy women from consecutive patients who were referred to the Gynecology Department for routine control”, selection of the PCOS participants is not described.
	Was a case-control design avoided? (Q-2)	No	Both the control group and group with known disease (PCOS) were identified and diagnosed prior or during study enrollment.
	Did the study avoid inappropriate exclusions? (Q-2)	Yes	The exclusion criteria for both the Control group and PCOS group were appropriate. For both groups, the study excludes “patients who had follicles larger than 9 mm or corpus luteum cysts were also excluded because these features could potentially alter the results”. For the PCOS group, exclusions

			also included those “who had a diagnosis of Cushing syndrome, congenital adrenal hyperplasia, hyperprolactinemia, thyroid dysfunction, virilizing tumors, type 2 diabetes mellitus, or patients on medication such as oral contraceptives, glucocorticoids, antiandrogens, insulin sensitizers, or drugs that may cause hirsutism”.
CLASSIFICATION/ VERIFICATION/ INCORPORATION/ REVIEW BIAS	Were all participants assessed with both index test and reference standard?	Yes	All participants in the Control group (n = 48) and PCOS group (n = 48) received all three index tests (Stroma, OV, FNPO).
	Did all patients receive the same reference standard? (Q-2)	Not reported	Study methods do not describe details of the participants in the Control group, only mentioning that they were “healthy women from consecutive patients who were referred to the Gynecology Department for routine control were included in the study”.
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Not reported	PCOS diagnosis was determined “according to the Rotterdam (ESHRE/ASRM) criteria”, which is the presence of at least two of the following: (1) oligo- or anovulation, (2) clinical and/or biochemical signs of hyperandrogenism, 3) polycystic ovaries and exclusion of other etiologies (congenital adrenal hyperplasia, androgen-secreting tumors, Cushing’s syndrome). However, no details are provided on the definitions used to classify each cardinal feature for PCOS diagnosis.
	Was the reference standard independent of the index test (ie. the index test did not form part of the reference standard)?	No	PCOS diagnosis of the Rotterdam criteria includes the evaluation of ovarian ultrasounds to measure either follicle number per ovary (FNPO) or ovarian volume (OV). Thus, the index test (except Stroma) is part of the reference standard.
	Were the reference standard results interpreted without knowledge of the results of the index test?	No	PCOS diagnosis of the Rotterdam criteria includes the evaluation of ovarian ultrasounds to measure either follicle number per ovary (FNPO) or ovarian volume (OV). Thus, the reference standard is interpreted with knowledge of the index test.
	Were the index test results interpreted without knowledge of the results of the reference standard test?	Yes	Study methods describe that “The gray-scale US and RTE studies were done using a 6.5 MHz vaginal probe… by one of two radiologists having 3–5 years of experience with sonography and one year of experience in elastography, who were blinded to the patients’ diagnosis, clinical features, or complaints”.
	If a threshold was used, was it pre-specified?	No	Study methods describe that “Youden’s index (J) was used to determine the optimal cutoff points for the presence of PCOS, giving the same weight to sensitivity and specificity”.
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?	Not reported	Method description does not describe the timing of the reference standard in relation to the index test results.

ATTRITION BIAS	Were withdrawals from the study explained?	Yes 100% treatment 100% control/ comparison u	Numbers described as enrolled are the same as those in results.
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Yes	There are no uninterruptable/intermediate test results and all results are reported.
OTHER ISSUES – APPLICABILITY/ COMPARABILITY/ VARIATION	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	The following description for the ultrasound examination was provided: "The gray-scale US and RTE studies were done using a 6.5 MHz vaginal probe (Logiq E9, GE Healthcare, Milwaukee, Wisconsin, USA) on the 3rd day of the menstrual cycle by one of two radiologists having 3–5 years of experience with sonography and one year of experience in elastography, who were blinded to the patients' diagnosis, clinical features, or complaints. All transvaginal US studies were performed in a gynecologic position, when the bladder was empty. The ovaries were examined by grayscale US and maximum diameters in three planes (longitudinal, antero-posterior and transverse) were measured to calculate the ovarian volume by the prolate ellipsoid formula (V = D1×D2×D3×0.523 cm^3). The number and maximum diameter of detected follicles were noted. Scanning of ovaries was completed when each ovary was scanned from medial to lateral aspects. RTE was performed with the same probe used in gray-scale US evaluation. Manual light compression and decompression of the ovaries by the transducer was performed attentively to achieve an optimal and consistent color coding. The quality factor of compression applied to the ovary, represented on a bar scale of 1–7, was used to select the optimal image, and images having an adequate compression (bar scale of 5–7) were evaluated. The scanning protocol was completed after the ovarian stroma was imaged adequately. RTE and B-mode US images were simultaneously displayed as a two-panel image. The elastographic box contained the ovary, the fallopian tube, and the surrounding tissue for all patients. The elastogram was visualized on a color scale with type 1 appearing as blue or blue-green (hardest tissue, no strain), type 2 as green or green-yellow (intermediate tissue, average strain), and type 3 as red or orange-red (softest tissue, greatest strain) over the B-mode US image (Fig. 1). Cine RTE images (at least five seconds per ovary) were recorded by the sonography device digitally for later evaluation."
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Yes	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
	Were there any conflicts of interest in the writing or funding of this study?	No	Authors stated that there were no conflicts of interest to disclose.

	If statistical analysis was undertaken, was this appropriate?	Partial	Statistical analyses included "Receiver operating characteristic (ROC) curve analysis was performed to evaluate strain ratio values in patients with and without PCOS, and Youden's index (J) was used to determine the optimal cutoff points for the presence of PCOS, giving the same weight to sensitivity and specificity". However, unclear if an adequate sample size calculation was undertaken. A 4x4 table of test performance was not presented.
COMMENTS			
What is the overall risk of bias?		Moderate	Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No. All outcomes had the same risk of bias.	

Study ID	Dewailly 2011
Study Citation	Dewailly, D. et al. (2011). "Diagnosis of polycystic ovary syndrome (PCOS): revisiting the threshold values of follicle count on ultrasound and of the serum AMH level for the definition of polycystic ovaries." Human Reproduction 26(11): 3123-3129.
Study Country	France
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	PCOS and Control: Data were obtained from database of referred patients, including clinical, hormonal, and US features, that were consecutively recorded between 2008 and 2010. Patients were referred for exploration of HA, menstrual disorders and/or infertility due to male factor and/or tubal abnormality. Age: Control (Group 1A): 30.0yo (21.9–34.6), PCOS (Group 3): 27.6yo (20.1–34.0) $p < 0.05$ BMI: Control (Group 1A): 24.0kg/m^2 (18.7–37.6), PCOS (Group 3): 28.0kg/m^2 (18.7–41.7) P = not significant
PCOS diagnostic criteria	NIH
N per group	Control (Group 1A): 66 Control + PCOM (Group 1B): 39 HA or oligo-anovulation (Group 2): 72 PCOS (Group 3): 62
Setting	Service de Gynécologie Endocrinienne et de Médecine de la Reproduction of Hôpital Jeanne de Flandre of Lille, France between 2008 and 2010
Index test	Follicle Number (FN / FNPO – Median) Ovarian Volume (OV – Median)
Reference Standard	NIH criteria (oligo-anovulation, hyperandrogenism)
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Accuracy to diagnose PCOS Sensitivity and specificity Area under the ROC curve Proposed threshold

Inclusion and exclusion criteria reported?		Yes	Inclusion criteria: patients were referred for exploration of HA, menstrual disorders and/or infertility due to male factor and/or tubal abnormality Exclusion criteria: women with unexplained infertility or endometriosis, aged 18 or more than 35 years, suspicion of low ovarian reserve (FSH >12 IU/l), hyperprolactinemia (serum prolactin >20 ng/ml on two subsequent determinations) or non-classic 21-hydroxylase deficiency [basal 17-hydroxyprogesterone (17-OHP) >5 ng/ml and/or post-adrenocorticotrophic hormone-stimulated value >12 ng/ml]. Ovarian or adrenal tumours were excluded on the basis of serum total testosterone (TT) or dehydroepiandrosterone sulphate (DHEA-S) levels lower than 1.5 ng/ml or 15 mmol/l, respectively. Any patient with criteria for hypothalamic amenorrhea was also excluded. Furthermore, any patient with at least one follicle with a diameter >9mm at U/S or a serum estradiol (E2) level above 80 pg/ml was excluded from the study… Patients excluded from analysis included those whom transvaginal ultrasonography was not possible (due to virginity or patient refusal) and those with a history of ovarian surgery".
Does the study have a clearly focused question?		Partial	What are the thresholds for FN and for the serum Anti-Müllerian hormone (AMH) level (a possible surrogate for FN) for the definition of PCOM?
Summary Result/s		Receiver operating characteristic curve analysis was applied to distinguish the non-PCOM non-PCO members of group 1 and to group 3. For FN and serum AMH respectively, the areas under the curve were 0.949 and 0.973 and the best compromise between sensitivity (81 and 92%) and specificity (92 and 97%) was obtained with threshold values of 19 follicles and 35 pmol/l (5 ng/ml).	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
PATIENT SELECTION/SPECTRUM BIAS	Was the spectrum of patients representative of the patients who will receive the test in practice?	Yes	Patients that were recruited were part of a database of referred patients, including clinical, hormonal, and US features.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	Study is described as a being "consecutively recorded between 2007 and 2010 from patients referred to our department".
	Was a case-control design avoided? (Q-2)	Yes	Study methods describe that "patients were referred for exploration of HA, menstrual disorders and/or infertility due to male factor and/or tubal abnormality" and that "cluster analysis is a statistical multivariate classification procedure used to classify patients in different groups or clusters according to different profiles… these clusters are not defined a priori and are such that individuals in a given cluster are close to each other in the sense of a similar measure and individuals in different clusters tend to be dissimilar".
	Did the study avoid inappropriate exclusions? (Q-2)	Yes	Exclusion criteria for the study was considered appropriate and included the following: "women with unexplained infertility or endometriosis, aged 18 or more than 35 years, suspicion of low ovarian reserve (FSH >12 IU/l), hyperprolactinemia (serum prolactin >20 ng/ml on two subsequent determinations) or non-classic 21-hydroxylase deficiency [basal 17-hydroxyprogesterone (17-OHP) >5 ng/ml and/or post-adrenocorticotrophic hormone-stimulated value >12 ng/ml]. Ovarian or adrenal tumours were excluded on the basis of serum total testosterone (TT) or dehydroepiandrosterone sulphate (DHEA-S) levels lower than 1.5 ng/ml or 15 mmol/l, respectively. Any patient with criteria for hypothalamic amenorrhea was also excluded. Furthermore, any patient with at least one follicle with a diameter >9mm at U/S or a serum estradiol (E2) level above 80 pg/ml was excluded from the study… Patients excluded from analysis included those

			whom transvaginal ultrasonography was not possible (due to virginity or patient refusal) and those with a history of ovarian surgery".
CLASSIFICATION/ VERIFICATION/ INCORPORATION/ REVIEW BIAS	Were all participants assessed with both index test and reference standard?	Yes	All participants had clinical, hormonal, and US features to allow for clustering into groups through cluster analysis.
	Did all patients receive the same reference standard? (Q-2)	Yes	All participants in the study received the same reference standard. For the Control group, the study mentions that "Group 1 (n = 105) including women without HA (clinical or biological) and with regular menses (non-PCOS group)" and that the Control subgroup for testing diagnostic accuracy of index tests, Group 1A, was specifically classified as "non-PCOM non-PCOS controls".
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	Study methods describe that Group 3 were "women with HA and oligo-anovulation, i.e., patients with genuine PCOS as defined by the current classifications (The Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group, 2004; Azziz et al., 2006)."
	Was the reference standard independent of the index test (ie. the index test did not form part of the reference standard)?	Yes	Study methods describe that Group 3 were "patients with genuine PCOS as defined by the current classifications (The Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group, 2004; Azziz et al., 2006)." Although the Rotterdam criteria thresholds were used, authors write that "U/S data were not used in this classification."
	Were the reference standard results interpreted without knowledge of the results of the index test?	Not reported	Method description does not describe whether the reference standard was interpreted without knowledge of index test results. It should be noted that authors write that "U/S data were not used" in the classification of PCOS.
	Were the index test results interpreted without knowledge of the results of the reference standard test?	Yes	Study methods describe that "cluster analysis is a statistical multivariate classification procedure used to classify patients in different groups or clusters according to different profiles… these clusters are not defined a priori and are such that individuals in a given cluster are close to each other in the sense of a similar measure and individuals in different clusters tend to be dissimilar". These clusters were used to classify patients into the Control group and PCOS group. Therefore, index test results were interpreted prior to the reference standard.
	If a threshold was used, was it pre-specified?	No	Study method describes that "ROC curves were constructed to examine the diagnostic test performance, i.e. the ability to discriminate between groups… Se (y-axis) against [1-Spe (x-axis)] was plotted at each threshold level, and the area under the curve (AUC) was computed by the non- parametric Wilcoxon test". In the results, authors mention that "the best compromise between Se and Spe was obtained with threshold values of FN at 19, of OV at 7 ml…".
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?	Not reported	Study methods describe that "Clinical, hormonal and U/S examinations were performed in the early follicular phase, between Day 2 and 5 of the menstrual cycle. In patients with menstrual disorders, the last menstrual period was either spontaneous or induced by the administration of dydrogesterone (10 mg/day for 7 days)." However, it was not clear of the timing between reference standard and index tests.

ATTRITION BIAS	Were withdrawals from the study explained?	Yes 100% treatment 100% control/ comparison u	Numbers described as enrolled are the same as those in results. As part of the cluster analysis, the study also identified Group 1B (n = 39), which was classified as "asymptomatic women with PCOM" and Group 2 (n = 73), which was classified as "women with only HA or only oligo-anovulation (presumption of PCOS)". Group 1B and Group 2 were part of the selected patients but were not analyzed for diagnostic accuracy in the study.
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Yes	There are no uninterruptable/intermediate test results and all results are reported.
OTHER ISSUES – APPLICABILITY/ COMPARABILITY/ VARIATION	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	The following description for the ultrasound examination was provided: "For every patient, U/S examination was performed with a Voluson E8 Expert (General Electric Systems, VELIZY, France) with a 5 – 9 MHz transvaginal transducer. U/S measurements were taken in real-time, according to as standardized protocol. The highest possible magnification was used to examine the ovaries. After determination of the longest medial axis of the ovary, the length and thickness were measured and the ovarian volume (OV) was calculated as described previously (Jonard et al., 2003). For each ovary, the total number of all visible follicles smaller than 10 mm in diameter was counted by slow and continuous scanning of the entire ovary, from one margin to the other in longitudinal crosssection. Every operator was asked to count any follicle that can now be detected with the new equipment (Fig. 1) without using any lower cut-off value. For the OV and the FN, the data used for statistical analysis were the mean of recorded values for the left and right ovaries. We excluded from the analysis patients in whom transvaginal ultrasonography was not possible (due to virginity or patient refusal) and those with a history of ovarian surgery."
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Yes	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
	Were there any conflicts of interest in the writing or funding of this study?	Not reported	Authors do not state whether there were conflicts of interest.
	If statistical analysis was undertaken, was this appropriate?	Partial	Study describes the statistical analyses as follows: "ROC curves were constructed to examine the diagnostic test performance, i.e. the ability to discriminate between groups. Se (y-axis) against [1-Spe (x-axis)] was plotted at each threshold level, and the area under the curve (AUC) was computed by the nonparametric Wilcoxon test. The AUC represents the probability of correctly identifying controls and patients with PCOS. A value of 0.5 means that the result is no better than chance." However, unclear if an adequate sample size calculation was undertaken. A 4x4 table of test performancewas not presented.

COMMENTS		
What is the overall risk of bias?	Low	Most criteria fulfilled and the conclusions of the study are unlikely to be affected.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?	No. All outcomes had the same risk of bias.	

Study ID	Dewailly 2014	
Study Citation	Dewailly, D. et al. (2014). "Using cluster analysis to identify a homogeneous subpopulation of women with polycystic ovarian morphology in a population of non-hyperandrogenic women with regular menstrual cycles." Human Reproduction 29(11): 2536-2543.	
Study Country	Croatia	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	Control: The control group included women from infertile couples with regular menstrual cycles and no signs of HA. PCOS: Women with PCOS were classified into two groups: full-blown PCOS (women who were diagnosed as having PCOS based on the presence of both HA and oligo/amenorrhea [OA]) and mild PCOS (PCOM at U/S according to the FNPO threshold of 12 or more as defined by the Rotterdam consensus and either OA [PCOM + OA] or HA [PCOM + HA]. Age (yo): Control: 32.5 (26.0–38.7), OA + PCOM: 30.3 (24.3– 37.0), HA + PCOM: 30.6 (22.7–37.5), Full-Blown PCOS: 29.8 (22.4 –36.5) $p < 0.05$ BMI (kg/m^2): Control: 23.0 (19.0–30.0), OA + PCOM: 23.0 (19.0 –36.9), HA + PCOM: 25.0 (19.0– 34.6), Full-Blown PCOS: 27.0 (20.0 –40.0) $p < 0.05$ (Control vs. HA + PCOM or Full-Blown PCOS)	
PCOS diagnostic criteria	Rotterdam	
N per group	Control: 521 PCOS: 272 • OA + HA (Full-blown): 95 • OA + PCOM: 110 • HA + PCOM: 67	
Setting	Department of Human Reproduction of Merkur University Hospital of Zagreb, Croatia between March 2011 and May 2013	
Index test	Follicle Number Per Ovary (FNPO – mean)	
Reference Standard	Rotterdam criteria (oligo/amenorrhea, hyperandrogenism, PCOM)	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Accuracy to diagnose PCOS Sensitivity and specificity Area under the ROC curve Proposed threshold	
Inclusion and exclusion criteria reported?	Yes	Inclusion criteria: Control: Women from infertile couples with regular menstrual cycles and no signs of HA. PCOS: Women with PCOS were classified into two groups: full-blown PCOS (women who were diagnosed as having PCOS based on the presence of both HA and oligo/amenorrhea [OA]) and mild PCOS (PCOM at U/S according to the

			FNPO threshold of 12 or more as defined by the Rotterdam consensus and either OA [PCOM + OA] or HA [PCOM + HA]. Exclusion criteria: Women aged ≥40 years, basal serum FSH concentration >12 IU/l, non-classic congenital adrenal hyperplasia, pelvic surgery, hyperprolactinemia, diabetes, thyroid dysfunction, endometriosis, abnormal U/S scan defined as the presence of an ovarian mass or at least one follicle with diameter >9 mm and use of medications that might have an influence on endocrine profile. Other etiologies of HA and/or OA were carefully ruled out in both PCOS groups.
Does the study have a clearly focused question?		Yes	Can cluster analysis can be used to identify a homogeneous subpopulation of women with polycystic ovarian morphology (PCOM) within a very large population of control women in a non-subjective way?
Summary Result/s		After exclusion of women with PCOM from the controls, the AMH threshold of 28 pmol/l with specificity 97.5% and sensitivity 84.2% [area under the curve (AUC) 0.948 (95% confidence interval (CI) 0.915 –0.982)] and FNPO threshold of 12 with specificity 92.5% and sensitivity 83.2% [AUC 0.940 (95% CI 0.909 –0.971)] for identifying PCOS were derived from the receiver operating characteristic curve analysis. The AMH threshold of 28 pmol/l had the same specificity for discriminating the mild and the full-blown PCOS phenotypes from controls.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
PATIENT SELECTION/SPECTRUM BIAS	Was the spectrum of patients representative of the patients who will receive the test in practice?	Yes	Patients that were recruited were part of a computerized database of patients referred for routine infertility evaluation and treatment.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Not reported	No random element was described in the selection of participants into the study. Study is described as a prospective case-controlled study but does not mention methods for allocation.
	Was a case-control design avoided? (Q-2)	No	Both the control group (regular cycling, normo-androgenic women) and group with known disease (Full-blown and Milder phenotypes of PCOS) were identified and diagnosed prior or during study enrollment.
	Did the study avoid inappropriate exclusions? (Q-2)	Yes	Exclusion criteria was considered appropriate and includes the following: "women aged ≥40 years, basal serum FSH concentration >12 IU/l, non-classic congenital adrenal hyperplasia, pelvic surgery, hyperprolactinemia, diabetes, thyroid dysfunction, endometriosis, abnormal U/S scan defined as the presence of an ovarian mass or at least one follicle with diameter >9 mm and use of medications that might have an influence on endocrine profile".
	Were all participants assessed with both index test and reference standard?	Yes	All participants in the Control group (n = 521) and PCOS group (n = 272) received the index tests. However, two groups (OA + PCOM [n= 110] and HA + PCOM [n = 67]) were enrolled but not included in analysis for diagnostic accuracy.
	Did all patients receive the same reference standard? (Q-2)	Not reported	The study methods describe ""The study population was divided into groups according to their symptoms: (i) the control group… included women from infertile couples with regular menstrual cycles and no signs of HA, (ii) the full-blown PCOS group… consisted of women who were diagnosed as having PCOS based on the presence of both HA and oligo/amenorrhoea (OA), i.e. women who all met the different classifications for PCOS without having to use U/S criteria and (iii) the mild PCOS group included women with only two items of the Rotterdam classification, i.e. PCOM at U/S according to the FNPO threshold of 12 or more as defined by the Rotterdam consensus and either OA… or HA… (Balen et al., 2003; The Rotterdam ESHRE/ASRM-sponsored

CLASSIFICATION/ VERIFICATION/ INCORPORATION/ REVIEW BIAS			PCOS consensus workshop group, 2004)." However, it is unclear if the control group was also evaluated for PCOM.
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	Study methods describe that "PCOM at U/S according to the FNPO threshold of 12 or more as defined by the Rotterdam consensus (Balen et al., 2003; The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group, 2004)… HA was defined as serum total testosterone concentration >2.7 nmol/l and/or clinically by hirsutism defined as a modified Ferriman –Gallwey (mFG) score >7 (Hatch et al., 1981). OA was defined as a mean menstrual cycle length (MCL) >35 days in the preceding year."
	Was the reference standard independent of the index test (ie. the index test did not form part of the reference standard)?	Not reported	Although study method describes that "physical examination and U/S assessment of ovarian morphology were performed the same day as blood drawing for the laboratory analysis", it is unclear whether the reference standard was interpreted without knowledge of index test results.
	Were the reference standard results interpreted without knowledge of the results of the index test?	No	PCOS diagnosis of the Rotterdam criteria includes the evaluation of ovarian ultrasounds to measure either follicle number per ovary (FNPO) or ovarian volume (OV). Thus, the reference standard is interpreted with knowledge of the index test.
	Were the index test results interpreted without knowledge of the results of the reference standard test?	Not reported	Although study methods mention that "physical examination and U/S assessment of ovarian morphology were performed the same day as blood drawing for the laboratory analysis", method description does not describe the timing of the index test in relation to the reference standard.
	If a threshold was used, was it pre-specified?	No	Study method describes that "Receiver operating characteristic (ROC) curves were constructed to examine the diagnostic test performance, i.e. the ability to discriminate between groups... Sensitivity (y-axis) against [1 - specificity (x-axis)] was plotted at each threshold level, and the area under the ROC curve (AUC) was computed by the non-parametric Wilcoxon test".
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?	Yes	Study methods describe that "Blood samples for the hormone and glucose measurements were taken during the early follicular phase of the menstrual cycle (i.e. between Day 3 and 5 after a spontaneous menstrual cycle or a withdrawal bleeding induced by 100 mg of micronized progesterone vaginally tid for 10 days) between 8:00 and 10:00 h after an overnight fast… Physical examination and U/S assessment of ovarian morphology were performed the same day as blood drawing for the laboratory analysis".
ATTRITION BIAS	Were withdrawals from the study explained?	Yes 100% treatment 100% control/ comparison	Numbers described as enrolled are the same as those in results.
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Yes	There are no uninterruptable/intermediate test results and all results are reported.
	Was the execution of all tests described in sufficient detail to	Yes	The following description for the ultrasound examination was provided: "The number of follicles in each ovary was assessed by a single investigator (M.Š.A.) using a two-dimensional transvaginal probe 5–7 MHz (Toshiba,

OTHER ISSUES – APPLICABILITY/ COMPARABILITY/ VARIATION	permit replication of the tests?		Nemio, Japan). Ultrasonographic examinations were performed in real-time and all follicles between 2 and 9 mm in diameter were counted by scanning from one margin of ovary to the other in longitudinal cross-sections. Follicular size was measured using the internal diameter of the sonolucent area, and the follicular diameters were calculated as a mean of two perpendicular measurements."
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Yes	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Not reported	Study does not describe what clinical data was available during test result interpretation.
	Were there any conflicts of interest in the writing or funding of this study?	No	Authors stated that there were no conflicts of interest to disclose.
	If statistical analysis was undertaken, was this appropriate?	Partial	Study describes statistical analyses as follows: "Receiver operating characteristic (ROC) curves were constructed to examine the diagnostic test performance, i.e. the ability to discriminate between groups (Zweig and Campbell, 1993). Sensitivity (y-axis) against [1 - specificity (x-axis)] was plotted at each threshold level, and the area under the ROC curve (AUC) was computed by the non-parametric Wilcoxon test. The AUC represents the probability of correctly identifying controls and patients with PCOS. A value of 0.5 means that the result is no better than chance." However, unclear if an adequate sample size calculation was undertaken. A 4x4 table of test performancewas not presented.
COMMENTS			
What is the overall risk of bias?		Moderate	Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No. All outcomes had the same risk of bias.	

Study ID	Diamanti-Kandarakis 2011
Study Citation	Diamanti-Kandarakis, E. et al. (2011). "Serum concentrations of carboxylated osteocalcin are increased and associated with several components of the polycystic ovarian syndrome." Journal of Bone and Mineral Metabolism 29(2): 201-206.
Study Country	Greece
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	Control: Women who visited our endocrine center with a possible diagnosis of goiter or were healthy wives of infertile couples with male infertility factor. Women in the control group had regular periods

	and no hyperandrogenemia, hirsutism, or acne. Tall control subjects were studied during the follicular phase (progesterone <5 ng/ml) and were euthyroid, normoandrogenemic, and normoprolactinemic, and none had 17-OHP > 1.0 ng/ml. PCOS: The PCOS group consisted of women who were presented to the PCOS endocrine clinic because of menstrual irregularities and were referred from their physicians to our center for evaluation with a running diagnosis of PCOS. The diagnosis of PCOS was based on National Institutes of Health (NIH) consensus criteria. Age: Control: 27.15 ± 6.72yo, PCOS: 26.46 ± 5.86yo p = 0.748 BMI: Control: 26.27 ± 5.30yo, PCOS: 26.49 ± 5.00yo p = 0.833	
PCOS diagnostic criteria	NIH	
N per group	Control: 47 PCOS: 50	
Setting	PCOS endocrine clinic of Laiko General Hospital	
Index test	Follicle Number Per Ovary (FNPO – Mean)	
Reference Standard	NIH criteria (anovulation and hyperandrogenism)	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Accuracy to diagnose PCOS Sensitivity and specificity Area under the ROC curve Proposed threshold	
Inclusion and exclusion criteria reported?	Yes	Inclusion criteria: Control: Women who visited our endocrine center with a possible diagnosis of goiter or were healthy wives of infertile couples with male infertility factor. Women in the control group had regular periods and no hyperandrogenemia, hirsutism, or acne. Tall control subjects were studied during the follicular phase (progesterone <5 ng/ml) and were euthyroid, normoandrogenemic, and normoprolactinemic, and none had 17-OHP > 1.0 ng/ml. PCOS: Women who were presented to the PCOS endocrine clinic because of menstrual irregularities and were referred from their physicians to our center for evaluation with a running diagnosis of PCOS. The diagnosis of PCOS was based on National Institutes of Health (NIH) consensus criteria. Exclusion Criteria: Both groups: Age over 40 years, known cardiovascular disease, neoplasms, current smoking, diabetes mellitus, renal impairment (serum creatinine >120 umol/l), or hypertension (blood pressure >140/ 85 mmHg). Oral contraceptives, steroid use, or other drugs or vitamins involved in bone and carbohydrate metabolism, if administered, were discontinued for at least 3 months before the study. None of the study subjects had a history of fracture the past 6 months and none was taking any drug known to affect vitamin K status (warfarin, ketoconazole, etc.). Subjects with an ovarian cyst >10 mm were excluded from the study.
Does the study have a clearly focused question?	Partial	What are the possible associations between the serum levels of osteocalcin and Gla osteocalcin, and the metabolic, hormonal, and ultrasonographic components of PCOS?
Summary Result/s	Receiver operating curve analysis revealed that Gla osteocalcin [AUC, 0.975 (95% CI, 0.93– 1.00)] as well as AGEs are significant prognostic factors of PCOS [AUC, 0.986 (95% CI, 0.97–1.00)]. Lower osteocalcin and elevated serum levels of its carboxylated form are displayed in PCOS	

		subjects and are associated with several PCOS components. These findings suggest a potential interaction between bone-derived markers and the metabolic/hormonal abnormalities observed in PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
PATIENT SELECTION/SPECTRUM BIAS	Was the spectrum of patients representative of the patients who will receive the test in practice?	Not reported	Studies that recruit a group of healthy controls and a group known to have the target disorder will be coded as "No" in most scenarios. Studies enrolling patients with known disease and control group without the condition may exaggerate diagnostic accuracy. Controls may not be routinely assessed for ovarian volume using ultrasound. The PCOS group is representative of those who will be assessed with these criteria in practice.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Not reported	No random element was described in the selection of participants into the study.
	Was a case-control design avoided? (Q-2)	No	Both the control group (regular cycling, normo-androgenic women) and group with known disease (PCOS) were identified and diagnosed prior or during study enrollment.
	Did the study avoid inappropriate exclusions? (Q-2)	Yes	The exclusion criteria for the study are appropriate. Study methods describe that exclusions include "Age over 40 years, known cardiovascular disease, neoplasms, current smoking, diabetes mellitus, renal impairment (serum creatinine >120 umol/l), or hypertension (blood pressure >140/ 85 mmHg). Oral contraceptives, steroid use, or other drugs or vitamins involved in bone and carbohydrate metabolism, if administered, were discontinued for at least 3 months before the study. None of the study subjects had a history of fracture the past 6 months and none was taking any drug known to affect vitamin K status (warfarin, ketoconazole, etc.). Subjects with an ovarian cyst >10 mm were excluded from the study." Although there are additional exclusions related to the study's primary research question relating to bone metabolism, they are not known to impact the index tests and their subsequent estimation of diagnostic accuracy.
CLASSIFICATION/ VERIFICATION/ INCORPORATION/ REVIEW BIAS	Were all participants assessed with both index test and reference standard?	Yes	All participants in the Control group (n = 47) and PCOS group (n = 50) received the index tests.
	Did all patients receive the same reference standard? (Q-2)	Yes	All participants in the study received the same reference standard, which was the NIH diagnostic criteria for PCOS. For the Control group, the study mentions that "All control subjects were euthyroid, normoandrogenemic, and normoprolactinemic, and none had 17-OHP >1.0 ng/ml".
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	PCOS diagnosis was determined by the NIH (1990) criteria, which is described as a combination of chronic anovulation and biochemical hyperandrogenism. "Chronic anovulation was assessed as fewer than eight cycles per year, and serum progesterone levels were below 3 ng/ml during the study period. Hyperandrogenemia was assessed as total testosterone levels above the 95th percentile of the levels detected in the group of normal menstruating women".
	Was the reference standard independent of the index test (ie. the index test did not form part of the reference standard)?	Yes	NIH criteria for the diagnosis of PCOS only includes the presence oligo-anovulation/anovulation and hyperandrogenism (clinical and/or biochemical). Sonographic markers of ovarian morphology are not part of the reference standard.

	Were the reference standard results interpreted without knowledge of the results of the index test?	Not reported	Method description does not describe the timing of the reference standard in relation to the index test results.
	Were the index test results interpreted without knowledge of the results of the reference standard test?	Not reported	Method description does not describe the timing of the index test in relation to the reference standard.
	If a threshold was used, was it pre-specified?	No	Study method describes that "A receiver operating curve (ROC) analysis was conducted to obtain cutoff levels of biochemical markers for the classification of patients as PCOS patients or controls by calculating the respective areas under the curve (AUC). The areas under the ROC curves (AUC) with their standard error and 95% confidence interval (CI) were calculated using the maximum likelihood estimation method. Furthermore, the sensitivity and specificity of different cutoff points of biochemical markers were estimated using the PCOS status as the gold standard".
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?	Not reported	Study method describes that "Blood samples were collected from all patients and healthy controls between 8:00 and 10:00, after an overnight fast. All samples were obtained during the early follicular phase (day 2–4 from the first day of a spontaneous bleeding episode) or at any time in anovulatory subjects with progesterone levels <3 ng/ml. Transvaginal ultrasound scans of the ovaries were performed during the follicular phase for ovulatory subjects and during the study period for the anovulatory subjects confirmed with progesterone levels <3 ng/ml as previously described". However, it is unclear of the timing between reference standard and index test.
ATTRITION BIAS	Were withdrawals from the study explained?	Yes 100% treatment 100% control/ compariso nu	Numbers described as enrolled are the same as those in results.
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Yes	There are no uninterruptable/intermediate test results and all results are reported.
	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	The following description for the ultrasound examination was provided: "Ovarian morphology and ovarian size, in three dimensions, were determined and registered in films in all subjects (in each case by the same operator at each centre and all sonographic records were reviewed and scored by a third sonographer for the statistical analysis assessment) according to Rotterdam criteria by transvaginal ultrasound... Transvaginal ultrasound scans of the ovaries were performed by experienced sonographers in all the subjects who participated in the study (PCOS women and controls). The presence of polycystic ovaries was diagnosed by the presence of 12 or more follicles in each ovary measuring 2–9 mm in diameter, and/or increased ovarian volume (> 10 cm^3). Ovarian volume was calculated by the formula: $V = (\pi/6) \times (D_{length} \times D_{width} \times D_{thickness})$ where, D: dimension. Adding the volume of each ovary and dividing by 2 calculated the mean ovarian volume for each participant.

OTHER ISSUES – APPLICABILITY/ COMPARABILITY/ VARIATION			Only one ovary fitting this definition was sufficient to define PCO. Subjects with a developing follicle (defined as largest follicle with mean diameter > 10 mm) or an ovarian cyst were excluded from the study."
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Yes	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Not reported	Study does not describe what clinical data was available during test result interpretation.
	Were there any conflicts of interest in the writing or funding of this study?	No	Authors stated that there were no conflicts of interest to disclose.
	If statistical analysis was undertaken, was this appropriate?	Partial	Statistical analyses included: "A receiver operating curve (ROC) analysis was conducted to obtain cutoff levels of biochemical markers for the classification of patients as PCOS patients or controls by calculating the respective areas under the curve (AUC). The areas under the ROC curves (AUC) with their standard error and 95% confidence interval (CI) were calculated using the maximum likelihood estimation method. Furthermore, the sensitivity and specificity of different cutoff points of biochemical markers were estimated using the PCOS status as the gold standard". However, unclear if an adequate sample size calculation was undertaken. A 4x4 table of test performancewas not presented.
COMMENTS			
What is the overall risk of bias?		Moderate	Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No. All outcomes had the same risk of bias.	

Study ID	Ertekin 2019
Study Citation	Ertekin, E. et al. (2019). "Is shear wave elastography relevant in the diagnosis of polycystic ovarian syndrome?" Medical Ultrasonography 21(2): 158-162.
Study Country	Turkey
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	Control: Sixteen volunteer patients with no hormonal imbalance and normal menstrual cycles were evaluated as control group.

	PCOS: One hundred and fifty-six female patients admitted to the infertility outpatient department between January 2017 and January 2018 were evaluated according to the Rotterdam criteria for PCOS diagnosis. Thirty-seven patients who matched these criteria were included in the study. Age: Control: 23.0±5.0yo, PCOS: 21.5±3.7yo, p = 0.293 BMI: Control: 25.5±3.8kg/m^2, PCOS: 24.5±4.8kg/m^2 p = 0.698		
PCOS diagnostic criteria	Rotterdam		
N per group	PCOS: 37 Control: 16		
Setting	Infertility outpatient department between January 2017 and January 2018		
Index test	Ovarian Volume (OV – Mean)		
Reference Standard	Rotterdam criteria (oligo-anovulation, hyperandrogenism, PCOM)		
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Accuracy to diagnose PCOS Sensitivity and specificity Proposed threshold		
Inclusion and exclusion criteria reported?	Partial	Inclusion Criteria: Control: no hormonal imbalance and normal menstrual cycles. PCOS: Rotterdam criteria was used for PCOS diagnosis. The criteria for PCOM were based on the presence of at least 12 cysts <10 mm per ovary and/or >10 ml of ovarian volume. Exclusion Criteria: lack of information regarding exclusions were provided by the authors.	
Does the study have a clearly focused question?	Partial	Is shear wave elastography relevant in the diagnosis of polycystic ovarian syndrome?	
Summary Result/s	The ovarian morphology is still the most reliable imaging finding in the diagnosis of PCOS, although it is controversial especially among adolescents. Although the diagnostic efficacy of SWE is demonstrated in a variety of soft tissue lesions, we did not find any significant contribution of SWE to the diagnosis PCOS. Therefore, the promising value of elastography is yet to be defined for the diagnosis of PCOS.		
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
PATIENT SELECTION/SPECTRUM BIAS	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	Studies that recruit a group of healthy controls and a group known to have the target disorder will be coded as "No" in most scenarios. Studies enrolling patients with known disease and control group without the condition may exaggerate diagnostic accuracy. Controls may not be routinely assessed for ovarian volume using ultrasound. The PCOS group is representative of those who will be assessed with these criteria in practice.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Not reported	Patients were included based on the date of admission, specifically between January 2017 and January 2018. Authors describe that "thirty-seven patients who matched these criteria were included in the study".

	Was a case-control design avoided? (Q-2)	No	PCOS patients were selected for the PCOS group due to their diagnosis using the Rotterdam criteria. The controls were selected as they had no hormonal imbalance and normal menstrual cycles.
	Did the study avoid inappropriate exclusions? (Q-2)	Not reported	Lack of information regarding exclusions were provided by the authors.
CLASSIFICATION/ VERIFICATION/ INCORPORATION/ REVIEW BIAS	Were all participants assessed with both index test and reference standard?	Yes	All participants in the Control group (n =16) and PCOS group (n = 37) received the index test (OV).
	Did all patients receive the same reference standard? (Q-2)	Not reported	For the Control group, patients had “hormonal imbalance and normal menstrual cycles”. However, it is unclear whether PCOM was evaluated in the Control group as well.
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Not reported	Rotterdam criteria was used to diagnose the PCOS patients. However, only the definition of PCOM was provided and does not provide information regarding how other cardinal features were evaluated.
	Was the reference standard independent of the index test (ie. the index test did not form part of the reference standard)?	No	PCOS diagnosis of the Rotterdam criteria includes the evaluation of ovarian ultrasounds to measure either follicle number per ovary (FNPO) or ovarian volume (OV). Thus, the index test is part of the reference standard.
	Were the reference standard results interpreted without knowledge of the results of the index test?	No	PCOS diagnosis of the Rotterdam criteria includes the evaluation of ovarian ultrasounds to measure either follicle number per ovary (FNPO) or ovarian volume (OV). Thus, the reference standard is interpreted with knowledge of the index test.
	Were the index test results interpreted without knowledge of the results of the reference standard test?	Not reported	Method description does not describe the timing of the reference standard in relation to the index test results.
	If a threshold was used, was it pre-specified?	No	Authors describe that “ROC (receiver operating characteristic) analysis was performed in order to determine the threshold value for the ovarian volumes which has significant correlation with the diagnosis of PCOS”.
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?	Not reported	Although authors describe that the index test was done on the third day of the menstrual cycle, it is unclear however when PCOS diagnosis occurred as it is not described.

ATTRITION BIAS	Were withdrawals from the study explained?	Yes 100% treatment 100% control/ comparison	Numbers described as enrolled are the same as those in results.
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Yes	There are no uninterruptable/intermediate test results and all results are reported.
OTHER ISSUES – APPLICABILITY/ COMPARABILITY/ VARIATION	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	Authors provided the following description of the ultrasound examination: "For all patients, gray scale US (ovarian size, presence, number and size of cysts), SWE measurements and laboratory tests (FSH, LH, Progesterone, DHEA) were performed on the 3rd day of the menstrual cycle. Gray scale US and SWE measurements were performed by a single radiologist who was blinded to the clinical and laboratory results. In gray scale US, ovaries were evaluated in terms of PCOM. The criteria for PCOM were based on the presence of at least 12 cysts <10 mm per ovary and/or >10 ml of ovarian volume. The cases interpreted as suspicious for PCOM were re-evaluated with the participation of a second radiologist and the final decisions were made by consensus. All US and SWE measurements were performed transabdominally on a Samsung RS80 US device using a 6 MHz convex probe by a radiologist with 6 years of experience in USE. First, the number of cysts was evaluated and the ovarian volumes were measured by gray scale US. Then, in SWE evaluation, cysts were excluded from the measurement area and all SWE measurements were performed from the ovarian stroma, at least 10 consecutive measurements for each ovary. For the optimization of the SWE measurements, the quality factor (RMI), which the device automatically provides, was considered to be between 0.4-1.0. The RMI values below 0.4 were excluded. The average of 10 measurements with the appropriate quality factor was recorded as the elasticity of that ovary. The unit of SWE measurement was determined as kilopascal (kPa)."
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Yes	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Not reported	
	Were there any conflicts of interest in the writing or funding of this study?	No	Authors stated that there were no conflicts of interest to disclose.
	If statistical analysis was undertaken, was this appropriate?	Partial	Statistical analyses includes: "ROC (receiver operating characteristic) analysis was performed in order to determine the threshold value for the ovarian volumes which has significant correlation with the diagnosis of PCOS". However, unclear if an adequate sample size calculation was undertaken. A 4x4 table of test performance was not presented. AUC data not provided for any index tests.

COMMENTS		
What is the overall risk of bias?	High	Few criteria fulfilled and the conclusions of the study are likely to be affected.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?	No. All outcomes have the same risk of bias.	

Study ID	Fulghesu 2001	
Study Citation	Fulghesu, A. M. et al. (2001). "A new ultrasound criterion for the diagnosis of polycystic ovary syndrome: the ovarian stroma/total area ratio." Fertility and Sterility 76(2): 326-331.	
Study Country	Italy	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	Control: Normal ovulatory women served as controls; the mean (+/- SD) length of the menstrual cycle in these patients was 28.5 +/- 2.6 days. Ovulatory cycles were previously confirmed by midluteal plasma progesterone (P) values of ≥ 25.4 nmol/L for three consecutive cycles. PCOS: Consecutive, amenorrheic or oligomenorrheic patients aged 18 to 38 years who had been referred to our department between June 1998 and May 1999 with a diagnosis of supposed PCOS. The diagnostic criteria for PCOS were: (1) Clinical findings of amenorrhea or oligomenorrhea and hirsutism, and presence of chronic anovulation. (2) Plasma androgen values at the upper limit of or above the normal range (androstenedione level of 2.0 to 5.5 nmol/L, and testosterone level of 0.6 to 2.0 nmol/L). (3) Presence of bilaterally normal or enlarged ovaries with > 10 cortical follicles (<6 mm in diameter) at the time of ultrasonography. Age: Not available. BMI: Control: 23.15±4.49kg/m^2, MFO: 22.54±2.24kg/m^2, PCOS: 23.61±3.88kg/m^2 p = not significant	
PCOS diagnostic criteria	Rotterdam	
N per group	Control: 30 Multi-Follicular Ovaries (MFO): 27 PCOS: 53 Twenty-seven of these 80 amenorrheic or oligomenorrheic women showed a multifollicular pattern—both ovaries were of normal size or slightly enlarged; and seven to nine anechoic follicles, 4 to 10 mm in diameter, were spread throughout the ovary—with normal androgen levels. These patients were defined as multifollicular (MFO), according to the criteria described by Adams et al. (1985).	
Setting	Department of Obstetrics and Gynecology of Università Cattolica del Sacro Cuore of Rome, Italy between June 1998 and May 1999	
Index test	Stromal Area / Ovarian Area (S/A – Mean)	
Reference Standard	Rotterdam criteria (Frank PCOS – oligo-anovulation, hyperandrogenism, PCOM)	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Accuracy to diagnose PCOS Sensitivity and specificity Proposed threshold	
Inclusion and exclusion criteria reported?	Yes	Inclusion Criteria: Control: normal ovulatory women served as controls; the mean (+/- SD) length of the menstrual cycle in these patients was 28.5 +/- 2.6 days. Ovulatory cycles

		were previously confirmed by midluteal plasma progesterone (P) values of ≥ 25.4 nmol/L for three consecutive cycles. PCOS: amenorrheic or oligomenorrheic patients aged 18 to 38 years who had been referred to our department with a diagnosis of supposed PCOS. The diagnostic criteria for PCOS were: (1) Clinical findings of amenorrhea or oligomenorrhea and hirsutism, and presence of chronic anovulation. (2) Plasma androgen values at the upper limit of or above the normal range (androstenedione level of 2.0 to 5.5 nmol/L, and testosterone level of 0.6 to 2.0 nmol/L). (3) Presence of bilaterally normal or enlarged ovaries with > 10 cortical follicles (<6 mm in diameter) at the time of ultrasonography. Exclusion criteria: We verified that all women were euthyroid, and that for at least 3 months before the study none had taken medications known to affect plasma sex steroids. To exclude the presence of a late-onset adrenal enzyme defect in the 80 patients referred to us for evaluation of supposed PCOS, we performed an ACTH test (250 ug IV; Synacthen, Ciba-Geigy, Basel, Switzerland) according to the criteria described by New et al. (1983).
Does the study have a clearly focused question?	Yes	Can some ultrasound parameters of ovarian morphology discriminate between control women and patients with polycystic ovary syndrome (PCOS)?
Summary Result/s	Patients with PCOS showed significantly higher ovarian volume, area, stroma, and mean S/A ratio when compared to multifollicular and control groups. Cut-off values have been defined for ovarian volume (13.21 mL), area (7.00 cm^2), stroma (1.95 cm^2), and S/A ratio (0.34). The sensitivity for PCOS diagnosis was 21%, 4%, 62%, and 100%, respectively. The S/A ratio showed the most significant correlation with the androgen levels. Conclusion(s): The evaluation of the S/A ratio can differentiate between PCOS and control or multifollicular women with both a sensitivity and a specificity of 100%. Furthermore, this ultrasound parameter is strictly related to hormonal milieu and to anthropometric characteristics.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
PATIENT SELECTION/SPECTRUM BIAS	Was the spectrum of patients representative of the patients who will receive the test in practice?	Not reported	Studies that recruit a group of healthy controls and a group known to have the target disorder will be coded as "No" in most scenarios. Studies enrolling patients with known disease and control group without the condition may exaggerate diagnostic accuracy. Controls may not be routinely assessed for ovarian volume using ultrasound. The PCOS group is representative of those who will be assessed with these criteria in practice.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Not reported	Study is described enrollment of participants in the PCOS group as "consecutive, amenorrheic or oligomenorrheic patients aged 18 to 38 years who had been referred to our department between June 1998 and May 1999 with a diagnosis of supposed PCOS", however consecutive enrollment was not described for the Control group.
	Was a case-control design avoided? (Q-2)	No	Both the control group (regular cycling women) and group with known disease (PCOS) were identified and diagnosed prior or during study enrollment.
	Did the study avoid inappropriate exclusions? (Q-2)	Yes	The exclusion criteria for the study are appropriate. Study methods describe that "to exclude the presence of a late-onset adrenal enzyme defect in the 80 patients referred to us for evaluation of supposed PCOS, we performed an ACTH test (250 ug IV; Synacthen, Ciba-Geigy, Basel, Switzerland) according to the criteria described by New et al… We verified that all women were euthyroid, and that for at least 3 months before the study none had taken medications known to affect plasma sex steroids".
	Were all participants assessed with both	Yes	All participants in the Control group (n = 30) and PCOS group (n = 53) received both index tests (S/A).

CLASSIFICATION/ VERIFICATION/ INCORPORATION/ REVIEW BIAS	index test and reference standard?		
	Did all patients receive the same reference standard? (Q-2)	Not reported	It is unclear if the Control group received the same reference standard, as it is only described as consisting of "normal ovulatory women". It is unclear whether hyperandrogenism and polycystic ovarian morphology was also evaluated during patient selection of the control population.
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	Diagnostic criteria for PCOS were determined by the presence of all cardinal features of PCOS, including "oligo-anovulation, clinical hyperandrogenism, and polycystic ovaries". Specifically, "Clinical findings of amenorrhea or oligomenorrhea and hirsutism, and presence of chronic anovulation. Plasma androgen values at the upper limit of or above the normal range (androstenedione level of 2.0 to 5.5 nmol/L, and testosterone level of 0.6 to 2.0 nmol/L). Presence of bilaterally normal or enlarged ovaries with >10 cortical follicles (>6 mm in diameter) at the time of ultrasonography".
	Was the reference standard independent of the index test (ie. the index test did not form part of the reference standard)?	No	PCOS diagnosis criteria used in the study includes the evaluation of ovarian ultrasounds to measure follicle number per ovary (FNPO) and ovarian volume (OV). Thus, the index test is part of the reference standard.
	Were the reference standard results interpreted without knowledge of the results of the index test?	Not reported	Method description does not describe the timing of the reference standard in relation to the index test results.
	Were the index test results interpreted without knowledge of the results of the reference standard test?	Yes	Study methods describe that "all of the ultrasound examinations were performed by one of two well-trained observers (A.M.F. and M.C.), who were not aware of the patients' endocrine profile".
	If a threshold was used, was it pre-specified?	No	Study methods describe that "the upper normal limit for the ultrasound parameters of ovarian morphology was computed according to mean + 2 SD".
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?	Not reported	Study methods describe that "the ultrasound examination was performed on the same day as the blood samples were obtained". However, it is unclear the timing of when clinical evaluations for PCOS were evaluated.
ATTRITION BIAS	Were withdrawals from the study explained?	Yes 100% treatment 100% control/ comparison u	Numbers described as enrolled are the same as those in results.
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Yes	There are no uninterruptable/intermediate test results and all results are reported.

OTHER ISSUES – APPLICABILITY/ COMPARABILITY/ VARIATION	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	The following description for the ultrasound examination was provided: "A transvaginal pelvic ultrasound was performed on each patient using a 6.5-MHz endovaginal probe (Logiq 500, GE Medical Systems, WI). All of the ultrasound examinations were performed by one of two well-trained observers (A.M.F. and M.C.), who were not aware of the patients' endocrine profiles. The ultrasound examination was performed on the same day as the blood samples were obtained. The examinations of 30 patients were performed by both observers to assess the interobserver coefficient of variation (evaluated as the difference between the two measurements expressed as a percentage with respect to the higher measurement). The following parameters were evaluated echographically: 1. Ovarian volume, estimated according to the formula 1/2 (A x B x C), where A is the longitudinal diameter, B the anteroposterior diameter, and C the transverse diameter of the ovary (10). 2. Ovarian area, evaluated by outlining with the caliper the external limits of the ovary in the maximum plane section. 3. Ovarian stromal area, evaluated by outlining with the caliper the peripheral profile of the stroma, identified by a central area slightly hyperechoic with respect to the other ovarian area. 4. The stromal/total area ratio (S/A). The mean ovarian volume, area, stroma, and S/A ratio for each individual patient were calculated by adding the sizes of each ovary and then dividing by two."
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Yes	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Not reported	Study does not describe what clinical data was available during test result interpretation.
	Were there any conflicts of interest in the writing or funding of this study?	Not reported	Authors did not state whether there were conflicts of interest to disclose.
	If statistical analysis was undertaken, was this appropriate?	Partial	Statistical analyses included: "the upper normal limit for the ultrasound parameters of ovarian morphology was computed according to mean + 2 SD". However, unclear if an adequate sample size calculation was undertaken. A 4x4 table of test performance was not presented. Sensitivity, specificity, and Youden's J were provided but not AUC.
COMMENTS			
What is the overall risk of bias?		Moderate	Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No. The risk of bias is the same across all outcomes.	

Study ID	Jarrett 2019

Study Citation	Jarrett, B. Y. et al. (2019). "Impact of right–left differences in ovarian morphology on the ultrasound diagnosis of polycystic ovary syndrome." Fertility and Sterility 112(5): 939-946.	
Study Country	United States/Canada	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	Control: Women of reproductive age (18–38years) recruited from the general population. Women with regular cycles and no evidence of hyperandrogenism were included as controls. PCOS: Women of reproductive age (18–38years) were recruited from the general population. Women with PCOS were identified by the combined presence of oligomenorrhea and hyperandrogenism. Age (yo): Control: 27 (23–31), PCOS: 27 (23–30) p = not significant BMI (kg/m^2): Control: 32.0 (23.7–38.2), PCOS: 23.6 (21.5–27.2) p < 0.05	
PCOS diagnostic criteria	NIH	
N per group	Control: 67 PCOS: 87	
Setting	Studies were conducted at four clinical research centers in North America from 2006 to 2018. Cornell University of Ithaca, USA University of Rochester of Rochester, USA Weill Cornell Medicine of New York City, USA University of Saskatchewan of Saskatoon, Canada	
Index test	Ovarian Volume (OV – Right Mean) Ovarian Volume (OV – Left Mean)	
Reference Standard	NIH criteria (oligo-anovulation, hyperandrogenism)	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Accuracy to diagnose PCOS Sensitivity and specificity Area under the ROC curve Proposed threshold	
Inclusion and exclusion criteria reported?	Yes	Inclusion Criteria: Control: women of reproductive age (18–38 years) were recruited from the general population. Women with regular cycles and no evidence of hyperandrogenism were included as controls. PCOS: women of reproductive age (18–38 years) were recruited from the general population. Women with PCOS were identified by the combined presence of oligomenorrhea and hyperandrogenism. Exclusion criteria: women who were pregnant, lactating, or taking hormonal contraceptives or insulin sensitizers were not eligible to participate in any of the protocols. Those with thyroid abnormalities, hyperprolactinemia, history of oophorectomy, or limited visualization of the ovaries on ultrasound were excluded from the present study.
Does the study have a clearly focused question?	Partial	What are the right–left differences in ultrasonographic markers of ovarian morphology and what is the impact on the diagnosis of polycystic ovarian morphology (PCOM)?

Summary Result/s			Overall, mean right–left differences were two follicles for FNPO, one follicle for FNPS, and 2 mL for OV. FNPO showed the strongest correlation between ovaries. Its assessment in a single ovary did not impact the diagnosis of PCOM in women with PCOS. However, there were differences in the probability of unilateral versus bilateral PCOM based on FNPS and OV in both groups. FNPO is the most reliable unilateral marker of PCOM in light of right–left differences in ovarian morphology. Use of FNPS or OV to define PCOM is discouraged when only one ovary is visualized.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
PATIENT SELECTION/SPECTRUM BIAS	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	Studies that recruit a group of healthy controls and a group known to have the target disorder will be coded as "No" in most scenarios. Studies enrolling patients with known disease and control group without the condition may exaggerate diagnostic accuracy. Controls may not be routinely assessed for ovarian volume using ultrasound. The PCOS group is representative of those who will be assessed with these criteria in practice.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Not reported	No random element was described in the selection of participants into the study. Study is described as a cross-sectional study.
	Was a case-control design avoided? (Q-2)	No	Both the control group (regular cycling, normo-androgenic women) and group with known disease (PCOS) were identified and diagnosed prior or during study enrollment.
	Did the study avoid inappropriate exclusions? (Q-2)	Yes	The exclusion criteria for the study are appropriate. Study methods describe that "Women who were pregnant, lactating, or taking hormonal contraceptives or insulin sensitizers were not eligible to participate in any of the protocols. Those with thyroid abnormalities, hyperprolactinemia, history of oophorectomy, or limited visualization of the ovaries on ultrasound were excluded from the present study".
CLASSIFICATION/ VERIFICATION/ INCORPORATION/ REVIEW BIAS	Were all participants assessed with both index test and reference standard?	Yes	All participants in the Control group (n = 67) and PCOS group (n = 87) received all three index tests (FNPS, OV, FNPO).
	Did all patients receive the same reference standard? (Q-2)	Yes	All participants in the study received the same reference standard, which was the equivalent of the NIH diagnostic criteria for PCOS. For the Control group, the study mentions that it consisted of "women with regular cycles and no evidence of hyperandrogenism".
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	PCOS diagnosis was conducted using the 1990 NIH criteria, which includes the combined presence of oligomenorrhea and hyperandrogenism. Specifically, "hyperandrogenism was defined as a modified hirsutism score ≥7 or serum total T concentration ≥61.5 or ≥127.1 ng/dL (depending on the protocol and hormone assay used). Thresholds reflected the 95th percentiles of modified hirsutism score and serum total T concentration in a reference cohort".
	Was the reference standard independent of the index test (ie. the index test did not form part of the reference standard)?	Yes	NIH criteria for the diagnosis of PCOS only includes the presence oligo-anovulation/anovulation and hyperandrogenism (clinical and/or biochemical). Sonographic markers of ovarian morphology are not part of the reference standard.

	Were the reference standard results interpreted without knowledge of the results of the index test?	Not reported	Method description does not describe the timing of the reference standard in relation to the index test results.
	Were the index test results interpreted without knowledge of the results of the reference standard test?	Not reported	Method description does not describe the timing of the index test in relation to the reference standard.
	If a threshold was used, was it pre-specified?	No	Study method describes that “Post-hoc analyses of our data revealed that right OV (area un- and left OV (area under the receiver operating characteristic der the receiver operating characteristic curve = 0.78; P<.05) for PCOS. However, a higher threshold for OV was required curve = 0.78; P<.05) offered similar diagnostic potential in the right ovary (threshold: 10 mL; sensitivity: 74%; specificity: 71%) versus the left ovary (threshold: 9 mL; sensitivity: 67%; specificity: 76%) to distinguish women with PCOS from controls”.
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?	Not reported	Method description does not describe the timing of the reference standard in relation to the index test results.
ATTRITION BIAS	Were withdrawals from the study explained?	Yes 100% treatment 100% control/ comparison u	Numbers described as enrolled are the same as those in results.
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Yes	There are no uninterruptable/intermediate test results and all results are reported.
	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	The following description for the ultrasound examination was provided: “Participants were evaluated with high-resolution transvaginal ultrasonography. Ultrasonographic data were obtained using UltraSonix RP (version 2.3.5; UltraSonix Medical Corporation) and GE Voluson ultrasound machines (E8, S6, or S10 Series; GE Healthcare) with 5–9 or 6–12 MHz multifrequency transducers. Ultrasound examinations were conducted in the early follicular phase of the menstrual cycle (controls) or when no dominant follicles or active corpora lutea (CLs) were present (PCOS). Whole ovaries were scanned from their inner to outer margins in the longitudinal plane. Two-dimensional cineloops were archived for offline analysis using customized imaging software (Sante DICOM Editor, Santesoft LTD). Images were reviewed by one of three investigators. Each investigator demonstrated strong inter-rater agreement in FNPO as part of an internal reliability assessment. End points of interest included FNPO, FNPS, and OV. FNPO was assessed throughout each ovary by imposing a programmable grid onto the viewing window and making focused follicle counts in each grid section. FNPS and OV were obtained in the largest cross-section of each ovary. OV was calculated using the simplified formula for a prolate ellipsoid. If a cystic structure was detected (e.g., hemorrhagic anovulatory follicle, CL, or unspecified cyst), then OV was

OTHER ISSUES – APPLICABILITY/ COMPARABILITY/ VARIATION			excluded for both ovaries (n = 5). FNPO, FNPS, and OV were tabulated for each ovary. Mean values between ovaries were calculated and rounded to the nearest whole numbers. Sided and mean values were ascribed a morphological diagnosis based on recent international consensus guidelines or proposed thresholds for PCOM. PCOM was defined by an FNPO ≥20 (3), FNPO ≥25 (7), FNPS ≥9 , or OV ≥10 mL."
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	No	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Not reported	Study does not describe what clinical data was available during test result interpretation.
	Were there any conflicts of interest in the writing or funding of this study?	Yes	The following conflicts of interest were disclosed: "B.Y.J. has nothing to disclose. H.V.B. has nothing to disclose. E.D.B. has nothing to disclose. K.M.H. has nothing to disclose. S.D.S. has nothing to disclose. R.A.P. is President and CSO of Synergyne Imaging Technology, Inc. Saskatoon, Saskatchewan Canada. D.R.C. has nothing to disclose. M.E.L. has nothing to disclose."
	If statistical analysis was undertaken, was this appropriate?	Partial	Study describes relevant statistical analyses as using ROC curve analysis to identify diagnostic accuracy of left vs. right OV. However, there is no information regarding sample size calculation and a 4x4 table of test performance is not presented.
COMMENTS			
What is the overall risk of bias?		Moderate	Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No. All outcomes had the same risk of bias.	

Study ID	Jonard 2005
Study Citation	Jonard, S. et al. (2005). "Revisiting the ovarian volume as a diagnostic criterion for polycystic ovaries." Human Reproduction 20(10): 2893-2898.
Study Country	France
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	

Patient/population/ participants	Control: Women with normal ovarian function (regular menstrual cycles, no signs of clinical and biochemical hyperandrogenism) were referred for IVF because of tubal and/or male infertility. PCOS: women were consecutively recruited and were defined as having PCOS according to the NIH criteria (oligo-anovulation, clinical and/or biochemical signs of hyperandrogenism). Age: Control: 29.0yo (24.5–35.0), PCOS: 27.2yo (19.5–33.0) p = not significant BMI: Control: 22.9kg/m^2 (19.0–31.5), PCOS: 27.9kg/m^2 (20.1–40.8) p < 0.002	
PCOS diagnostic criteria	NIH	
N per group	Control: 57 PCOS: 98	
Setting	Hôpital Jeanne de Flandre of Lille, France	
Index test	Follicle Number Per ovary (FNPO – Median) Ovarian Volume (OV - Median) Ovarian Area (OA – Median)	
Reference Standard	NIH criteria (oligo-anovulation, hyperandrogenism)	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Accuracy to diagnose PCOS Sensitivity and specificity Area under the ROC curve Proposed threshold	
Inclusion and exclusion criteria reported?	Yes	Inclusion criteria: Controls: Women were consecutively recruited and were defined as having PCOS according to the NIH criteria (oligo-anovulation, clinical and/or biochemical signs of hyperandrogenism). PCOS: Women were consecutively recruited and were defined as having PCOS according to the NIH criteria (oligo-anovulation, clinical and/or biochemical signs of hyperandrogenism). Exclusion criteria Both groups: Patients in whom transvaginal ultrasonography was inappropriate (virgins or patients who refused) were excluded from the analysis, as well as those in whom no follicle was seen in either the right or the left ovary and/or in whom the ovarian area was below the lower normal limit, i.e. 2.5 cm^2. Patients with at least one follicle >9 mm in diameter at ultrasonography, or a serum estradiol level >80 pg/ml, were also excluded from the study so as not to confound the data with the presence of a dominant follicle or a corpus luteum. Controls: a history of menstrual disturbances (i.e. cycle length either <25 days or >35 days), hirsutism [as assessed by the modified Ferriman and Gallway (F–G) score >6], serum level of prolactin >20 mg/ml, serum testosterone higher than our previously reported upper normal threshold, i.e. 0.5 ng/ml and hormonal treatment during the 3 months prior to the study. PCOS: other aetiologies (congenital adrenal hyperplasia, androgen-secreting tumour or Cushing's syndrome.

Does the study have a clearly focused question?	Partial	Is 10 cm^3 the best threshold for OV in the diagnosis of PCOS? How does the diagnostic potency of OV compare to that of FN and of ovarian area?
Summary Result/s	Mean OV, ovarian area (OA) and follicle number (FN) values were significantly higher in the PCOS group than in controls. The area under the ROC curve (AUC) was >0.9 for all three criteria, indicating a satisfactory diagnostic potency for each. Concerning the OV, setting the threshold at 7 cm^3 offered the best compromise between specificity (91.2%) and sensitivity (67.5%). In comparison, specificity and sensitivity were 98.2 and 45%, respectively, with a threshold at 10 cm^3. Nevertheless, the highest AUC was obtained for FN (0.956) and then for OA (0.941). OV is a good diagnostic criterion for PCO but, on the basis of the present data, we propose to lower its threshold to 7 cm^3. The FN >12 still appears as the best diagnostic criterion. The OA could be used as a surrogate for OV in difficult situations.	

INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
PATIENT SELECTION/SPECTRUM BIAS	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	Studies that recruit a group of healthy controls and a group known to have the target disorder will be coded as "No" in most scenarios. Studies enrolling patients with known disease and control group without the condition may exaggerate diagnostic accuracy. Controls may not be routinely assessed for ovarian volume using ultrasound. The PCOS group is representative of those who will be assessed with these criteria in practice.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Not reported	Although the study methods describe that the PCOS group were consecutively recruited, selection of Control participants into the study is not described.
	Was a case-control design avoided? (Q-2)	No	Both the control group (regular cycling, normo-androgenic women) and group with known disease (PCOS) were identified and diagnosed prior or during study enrollment.
	Did the study avoid inappropriate exclusions? (Q-2)	Yes	Exclusion criteria was considered appropriate. For both groups, study details mention that "Patients in whom transvaginal ultrasonography was inappropriate (virgins or patients who refused) were excluded from the analysis, as well as those in whom no follicle was seen in either the right or the left ovary and/or in whom the ovarian area was below the lower normal limit, i.e. 2.5 cm^2. Patients with at least one follicle >9 mm in diameter at ultrasonography, or a serum estradiol level >80 pg/ml, were also excluded from the study so as not to confound the data with the presence of a dominant follicle or a corpus luteum". For the Control group, "exclusion criteria included a history of menstrual disturbances (i.e. cycle length either <25 days or >35 days), hirsutism [as assessed by the modified Ferriman and Gallway (F–G) score >6], serum level of prolactin >20 mg/ml, serum testosterone higher than our previously reported upper normal threshold, i.e. 0.5 ng/ml and hormonal treatment during the 3 months prior to the study". The exclusion criteria for the PCOS group include "other aetiologies (congenital adrenal hyperplasia, androgen-secreting tumour or Cushing's syndrome)".

CLASSIFICATION/ VERIFICATION/ INCORPORATION/ REVIEW BIAS	Were all participants assessed with both index test and reference standard?	Yes	All participants in the Control group (n = 57) and PCOS group (n = 98) received all three index tests (OV, FNPO).
	Did all patients receive the same reference standard? (Q-2)	Yes	All participants in the study received the same reference standard, which was the equivalent of the NIH diagnostic criteria for PCOS. For the Control group, the study mentions that it consisted of women were included with “normal ovarian function” and were excluded based on “history of menstrual disturbances (i.e. cycle length either <25 days or >35 days), hirsutism [as assessed by the modified Ferriman and Gallway (F–G) score >6], serum level of prolactin >20 mg/ml, serum testosterone higher than our previously reported upper normal threshold, i.e. 0.5 ng/ml, and hormonal treatment during the 3 months prior to the study”.
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Partial	PCOS diagnosis was conducted using the 1990 NIH criteria, specifically “definition of oligo-anovulation is defined as oligomenorrhoea or amenorrhoea or cycle length either <25 days or >35 days and/or ovulatory disturbances as assessed by basal body temperature chart and/or serum progesterone level <3 ng/ml in the luteal phase at day 24 in the cycle, and clinical and/or biochemical signs of hyperandrogenism (F–G score >6 and/or testosterone level >0.5 ng/ml)”. It should be noted that definition of oligo-anovulation differs slightly from the NIH definition.
	Was the reference standard independent of the index test (ie. the index test did not form part of the reference standard)?	Yes	NIH criteria for the diagnosis of PCOS only includes the presence oligo-anovulation/anovulation and hyperandrogenism (clinical and/or biochemical). Sonographic markers of ovarian morphology are not part of the reference standard.
	Were the reference standard results interpreted without knowledge of the results of the index test?	Not reported	Study methods describe that they used “this former definition of PCOS in order not to use the OV, OA or FN as selection criteria, since our goal was to study their diagnostic potency, free from any inclusion bias”, however the method description does not describe the timing of the reference standard in relation to the index test.
	Were the index test results interpreted without knowledge of the results of the reference standard test?	Not reported	Study methods describe that they used “this former definition of PCOS in order not to use the OV, OA or FN as selection criteria, since our goal was to study their diagnostic potency, free from any inclusion bias”, however the method description does not describe the timing of the index test in relation to the reference standard.

	If a threshold was used, was it pre-specified?	No	Study method describes that "ROC curves were constructed to examine the diagnostic test performance, i.e. the ability to discriminate between controls and patients with PCOS. Sensitivity against (1 - specificity) was plotted at each level, and the area under the curve (AUC) was computed by the non-parametric Wilcoxon statistical test".
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?	Not reported	Study methods describe that "Blood sampling was performed during the early follicular phase (i.e. between days 2 and 7 after the last menstrual period) in both PCOS patients and control women, as described previously. In PCOS patients, the last menstrual period was either spontaneous or induced by the administration of didrogesterone (10 mg/day during 7 days)… Ultrasound examination was performed between cycle days 2 and 7". However, it is unclear when the reference standard was evaluated relative to the ultrasound scan.
ATTRITION BIAS	Were withdrawals from the study explained?	Yes 100% treatment 100% control/ comparison u	Numbers described as enrolled are the same as those in results.
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Yes	There are no uninterruptable/intermediate test results and all results are reported.
	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	The following description was provided for the ultrasound examination: "Ultrasound examination was performed between cycle days 2 and 7 with a 7 MHz transvaginal transducer (Logic 400 General Electric, Milwaukee, USA). Ultrasound measurements were taken in real time, according to a standardized protocol. The highest possible magnification was used to examine the ovaries. After the longest medial axis of the ovary was determined, the length and thickness were measured and the OA was calculated using a manual or automatic ellipse to outline the ovary as described previously (Dewailly et al., 2002). The OV was estimated after the measurement of the length, width and the thickness and use of the classical formula for a prolate ellipsoid: L × W × T × 0.523 (Sample et al., 1977; Adams et al., 1985; Orsini et al., 1985). The FN was established as described previously (Jonard et al., 2003) by scanning each ovary from the inner margin to the outer margin in longitudinal cross-section. All follicles of 2 mm were counted. Follicle diameter was the mean of two recorded diameters in the longitudinal and antero-posterior planes. Patients in whom transvaginal ultrasonography was inappropriate (virgins or patients who refused) were excluded from the analysis, as well as those in whom no follicle was seen in either the right or the left ovary and/or in whom the ovarian area was below the lower normal limit, i.e. 2.5 cm^2. Patients with at least one follicle >9 mm in diameter at ultrasonography, or a serum estradiol level >80 pg/ml, were also excluded from the study so as not to confound the data with the presence of a dominant follicle or a corpus luteum."

OTHER ISSUES – APPLICABILITY/ COMPARABILITY/ VARIATION	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Yes	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Not reported	Study does not describe what clinical data was available during test result interpretation.
	Were there any conflicts of interest in the writing or funding of this study?	Not reported	Authors did not state whether there were any conflicts of interest to disclose.
	If statistical analysis was undertaken, was this appropriate?	Partial	Statistical analyses included: "ROC curves were constructed to examine the diagnostic test performance, i.e. the ability to discriminate between controls and patients with PCOS. Sensitivity against (1 - specificity) was plotted at each level, and the area under the curve (AUC) was computed by the non-parametric Wilcoxon statistical test". However, unclear if an adequate sample size calculation was undertaken. A 4x4 table of test performance was not presented.
COMMENTS			
What is the overall risk of bias?		Moderate	Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No. All outcomes had the same risk of bias.	

Study ID	Kar and Swoyam 2018	
Study Citation	Kar S. & Swoyam S. (2018). "2D and 3D trans-vaginal sonography to determine cut-offs for ovarian volume and follicle number per ovary for diagnosis of polycystic ovary syndrome in Indian women." Journal of Reproduction & Infertility 19(3):146.	
Study Country	India	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	Control: Women between the ages of 18-45 years in all BMI groups. Controls were women who were requested to volunteer for the study. Most were hospital staff and relatives, married and fertile, with no medical or gynecological complaints, regular menstrual cycles (21-35 days) and no features of hyperandrogenemia (Acne, hirsutism based on modified FG score ≤8). PCOS: Women between the ages of 18-45 years in all BMI. All PCOS patients were diagnosed using the following 2003 Rotterdam criteria (2 out of 3); 1. Oligo- anovulation (menstrual cycle >35 days) 2. Clinical and/or biochemical (Signs of hyperandrogenism); and 3. PCOM as identified by ultrasonography. PCOM on ultrasound was defined as follows: the presence of ≥12 follicles (FNPO) in each ovary measuring 2-9 mm in diameter and/or increased OV (>10 cm^3). Age: Controls: 28.45yo ± 4.62, PCOS: 26.03yo ± 3.52 p = 0.003 BMI: Controls: 23.02kg/m2 ± 3.58, PCOS: 25.71kg/m2 ± 4.87 p = 0.13	
PCOS diagnostic criteria	Rotterdam	
N per group	PCOS: 86 Control: 45	
Setting	Gynecology outpatient department of Kar Clinic and Hospital of Bhubaneswar, India between June 2015 to December 2016	
Index test	Follicle Number Per Ovary (FNPO – 3D & 2D – Mean) Ovarian Volume (OV – 3D & 2D – Mean) Stromal Volume (3D & 2D – Mean)	
Reference Standard	Rotterdam criteria (oligo-anovulation, hyperandrogenism, PCOM)	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Accuracy (comparison with the reference standard test) Sensitivity and specificity Area under the ROC curve Proposed threshold	
Inclusion and exclusion criteria reported?	Yes	Inclusion criteria: Control: Women between the ages of 18-45 year across all BMI groups. Controls were women who were requested to volunteer for the study. Most were hospital staff and relatives, married and fertile, with no medical or gynecological complaints, regular menstrual cycles (21-35 days) and no features of hyperandrogenemia (Acne, hirsutism based on modified FG score ≤8). PCOS group: Women between the ages of 18-45 years across all BMI. All PCOS patients were diagnosed using the following 2003 Rotterdam criteria (2 out of 3); 1. Oligo- anovulation (menstrual cycle >35 days) 2. Clinical and/or biochemical (Signs of hyperandrogenism); and 3. PCOM as identified by ultrasonography. PCOM on ultrasound was defined as follows: the presence of ≥12 follicles (FNPO) in each ovary measuring 2-9 mm in diameter and/or increased OV (>10 cm^3).

			Exclusion criteria: women with endometriosis, previous ovarian or tubal surgery, any hormonal treatment over the last three months, and any abnormal ovarian cyst >10 mm detected during the present scan were excluded from the study.
Does the study have a clearly focused question?		Yes	What are the cut-off values for ovarian volume (OV) and follicle number per ovary (FNPO) in Indian women with polycystic ovary syndrome (PCOS)?
Summary Result/s		Mean ovarian volume was 13.7±5.89 and 5.06±2.44 (p<0.0001), FNPO was 19.18±6.89 and 7.13±3.51 (p<0.0001) in PCOS and controls, respectively. The cut-offs for the diagnosis of PCOS were 2D OV=6.15 cm³, 2D FNPO=12. By 3D scan, OV=7 cm³, FNPO=10, stromal volume=6 cm³, VI=4.546, VFI=2.925 and FI= 19.266. Youden's Index (To select optimal predicted probability cut-off) was the highest for 2D FNPO (0.88786). 2D FNPO showed the highest specificity and sensitivity (AUC), 0.95238 and 0.93548, for the diagnostic accuracy of PCOS. 2D and 3D trans-vaginal scans are equally accurate for assessment of ovarian morphology. FNPO has better diagnostic accuracy for PCOS compared to ovarian volume. Cut-off for FNPO and OV in Indian PCOS women is 12 and 6.15 cm³ by 2D, 10 and 7 cm³ by 3D trans-vaginal scan.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
PATIENT SELECTION/SPECTRUM BIAS	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	Studies that recruit a group of healthy controls and a group known to have the target disorder will be coded as "No" in most scenarios. Studies enrolling patients with known disease and control group without the condition may exaggerate diagnostic accuracy. Controls may not be routinely assessed for ovarian volume using ultrasound. The PCOS group is representative of those who will be assessed with these criteria in practice.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Not reported	No random element was described in the selection of participants into the study.
	Was a case-control design avoided? (Q-2)	No	Both the control group (healthy) and group with the disease (PCOS) were identified and diagnosed prior to study enrollment.
	Did the study avoid inappropriate exclusions? (Q-2)	Yes	Exclusion criteria for both PCOS and control group are appropriate, which is described as: "women with endometriosis, previous ovarian or tubal surgery, any hormonal treatment over the last three months, and any abnormal ovarian cyst >10 mm detected during the present scan were excluded from the study".
CLASSIFICATION/	Were all participants assessed with both index test and reference standard?	Yes	All participants in the Control group (n = 45) and PCOS group (n = 86) received all three index tests (Stroma, OV, FNPO).
	Did all patients receive the same reference standard? (Q-2)	Not reported	Study methods describe the use of the reference standard for the Control group. Specifically, it only mentions that "Most were hospital staff and relatives, married and fertile, with no medical or gynecological complaints, regular menstrual cycles (21-35 days) and no features of hyperandrogenemia (Acne, hirsutism based on modified FG score ≤8)". However, it is unclear whether PCOM was also evaluated as part of the Rotterdam criteria.
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	PCOS diagnosis was determined by the Rotterdam criteria. Specifically, "all PCOS patients were diagnosed using the following 2003 Rotterdam criteria (2 out of 3); 1. Oligo- anovulation (menstrual cycle >35 days) 2. Clinical and/or biochemical (Signs of hyperandrogenism); and 3. PCOM as identified by ultrasonography. PCOM on ultrasound was defined as follows: the presence of

			≥12 follicles (FNPO) in each ovary measuring 2-9 mm in diameter and/or increased OV (>10 cm³)".
	Was the reference standard independent of the index test (ie. the index test did not form part of the reference standard)?	No	PCOS diagnosis of the Rotterdam criteria includes the evaluation of ovarian ultrasounds to measure either follicle number per ovary (FNPO) or ovarian volume (OV). Thus, the index test is part of the reference standard.
	Were the reference standard results interpreted without knowledge of the results of the index test?	No	PCOS diagnosis of the Rotterdam criteria includes the evaluation of ovarian ultrasounds to measure either follicle number per ovary (FNPO) or ovarian volume (OV). Thus, the reference standard is interpreted with knowledge of the index test.
	Were the index test results interpreted without knowledge of the results of the reference standard test?	Not reported	Method description does not describe the timing of the index test in relation to the reference standard.
	If a threshold was used, was it pre-specified?	No	Authors describe that "Logistic analysis using PROC LOGISTIC function of SAS® was used to calculate best cut-offs for the diagnosis of PCOS".
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?	Not reported	Although study methods describe that "both controls and PCOS subjects were scanned immediately after menstruation, day 2-day 6 of menses. In case of amenorrhea, PCOS women went through progesterone withdrawal, after urine beta HCG test", it is unclear when the clinical procedures and blood draw occurred relative to the ultrasound scan.
ATTRITION BIAS	Were withdrawals from the study explained?	Yes 100% treatment 100% control/ comparison u	Numbers described as enrolled are the same as those in results.
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Yes	There are no uninterruptable/intermediate test results and all results are reported.
	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	The following description for the ultrasound examination was provided: "All participants went through a detailed trans-vaginal ultrasound exam by a single physician. Both controls and PCOS subjects were scanned immediately after menstruation, day 2-day 6 of menses. In case of amenorrhea, PCOS women went through progesterone withdrawal, after urine beta HCG test. An exhaustive 2D and 3D imaging of bilateral ovaries was done using a 6-12 MHz transvaginal volume transducer (RIC6-12-D) on a GE Voluson E8 system. Highest possible magnification was used to scan the ovaries. Real time 2D scans in long axis of the ovary from inner to outer margin were taken to determine the largest plane and its transverse section. The total number of visible follicles (FNPO) measuring 2-3 mm in diameter was counted manually by continuous scanning of the entire ovary. The ovarian volume (OV) was

OTHER ISSUES – APPLICABILITY/ COMPARABILITY/ VARIATION			calculated using the simplified formula for prolate ellipsoid (0.5 x length x width x thickness) (4). For the 3D imaging, the 3D power Doppler image data was acquired. Vocal and sono AVC software was used to generate the data related to ovarian stromal volume, blood flow and follicle counts."
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Yes	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Not reported	Study does not describe what clinical data was available during test result interpretation.
	Were there any conflicts of interest in the writing or funding of this study?	No	Authors stated that there were no conflicts of interest to disclose.
	If statistical analysis was undertaken, was this appropriate?	Partial	Study describes that "Logistic analysis using PROC LOGISTIC function of SAS® was used to calculate best cut-offs for the diagnosis of PCOS". However, unclear if an adequate sample size calculation was undertaken. A 4x4 table of test performance was not presented.
COMMENTS			
What is the overall risk of bias?		High	Few criteria have been fulfilled and the conclusions of the study are likely to be affected.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No. All outcomes have the same risk of bias.	

Study ID	Khashchenko 2020
Study Citation	Khashchenko, E., et al. (2020). "The relevant hormonal levels and diagnostic features of polycystic ovary syndrome in adolescents." Journal of Clinical Medicine 9(6): 1831.
Study Country	Russia
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	Control: Healthy adolescent girls of the same age with regular menstruations and without gynecological and endocrine pathology. The girls in the control group had normative weight and BMI values. All girls had regular menstrual cycles. The duration of menstrual bleeding ranged from 4 to 8 days. The majority of girls had moderate menstrual bleeding. PCOS: Girls aged 15 to 17 years, presenting complete Rotterdam PCOS diagnostic criteria (oligo-/amenorrhea; clinical and/or biochemical signs of HA; polycystic ovaries detected by ultrasound). The additional inclusion criteria were: the onset of menarche at least 2 years prior; the absence of other endocrine diseases; absence of drug administration over 3 months preceding the study, including oral combined contraceptives; informed consent of the patient and her legal representative for participation in the research study.

	Age (yo): Control: 16.0 (15.0–17.0), PCOS: 16.0 (15.0–17.0) BMI (kg/m^2): Control: 20.2 (18.4–21.8), PCOS: 22.4 (19.9–27.2)		
PCOS diagnostic criteria	Rotterdam		
N per group	PCOS: 130 Control: 30		
Setting	Unclear		
Index test	Ovarian Volume (OV – Mean) Ovarian to Uterine Index (OUI - Median		
Reference Standard	Rotterdam criteria (oligo-/amenorrhea; clinical and/or biochemical signs of HA; polycystic ovaries detected by ultrasound)		
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Accuracy to diagnose PCOS Sensitivity and specificity Area under the ROC curve Proposed threshold		
Inclusion and exclusion criteria reported?	Partial	Inclusion criteria: Control: Regular menstruations, without gynecological and endocrine pathology, normative weight and BMI values and regular menstrual cycles. The duration of menstrual bleeding ranged from 4 to 8 days. The majority of girls had moderate menstrual bleeding. PCOS: Aged 15 to 17 years, presenting complete Rotterdam PCOS diagnostic criteria (oligo-/amenorrhea; clinical and/or biochemical signs of HA; polycystic ovaries detected by ultrasound). The onset of menarche at least 2 years prior; the absence of other endocrine diseases; absence of drug administration over 3 months preceding the study, including oral combined contraceptives; informed consent of the patient and her legal representative for participation in the research study. Exclusion criteria: Controls: not reported PCOS group: an aggravation of chronic or acute somatic and/or infectious disease; mental illnesses; inherited syndromes and congenital malformations; hyperprolactinemia; congenital dysfunction of the adrenal cortex; thyroid disorders; Cushing syndrome and disease; tumors of the pelvic organs.
Does the study have a clearly focused question?	Partial	What are the pivotal clinical and hormonal features of PCOS in adolescents? What are the age-specific thresholds of the most essential hormonal parameters?
Summary Result/s	The results of the study estimate the threshold for AMH, FAI, androstenedione, testosterone, LH/FSH, and ovarian volume, which could be suggested for use in the PCOS diagnostics in adolescents with a high sensitivity and specificity. Moreover, the combination of either four determined indexes improved the diagnostic accuracy for the PCOS detection in adolescents.		
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
PATIENT SELECTION/SPECTRU	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	Studies that recruit a group of healthy controls and a group known to have the target disorder will be coded as “No” in most scenarios. Studies enrolling patients with known disease and control group without the condition may exaggerate diagnostic accuracy. Controls may not be routinely assessed for ovarian volume using ultrasound. The PCOS group is representative of those who will be assessed with these criteria in practice.

	Was a consecutive or random sample of patients enrolled? (Q-2)	No	No random or consecutive element was described in the selection of participants into the study.
	Was a case-control design avoided? (Q-2)	No	Both the control group (regular cycling girls with no gynecological or endocrinological pathologies) and group with known disease (PCOS) were identified and diagnosed prior to study enrolment
	Did the study avoid inappropriate exclusions? (Q-2)	No	Authors describe exclusions as "an aggravation of chronic or acute somatic and/or infectious disease; mental illnesses; inherited syndromes and congenital malformations; hyperprolactinemia; congenital dysfunction of the adrenal cortex; thyroid disorders; Cushing syndrome and disease; tumors of the pelvic organs". Acute somatic and/or infectious disease; mental illnesses; inherited syndromes and congenital malformations are typically not considered conventional exclusions for PCOS and therefore may modify study population's characteristics.
CLASSIFICATION/ VERIFICATION/ INCORPORATION/ REVIEW BIAS	Were all participants assessed with both index test and reference standard?	Yes	All control patients (N=30) and PCOS patients (N=130) were assessed by the reference standard and index test.
	Did all patients receive the same reference standard? (Q-2)	Not reported	Study describes the control population as "regular menstruations and without gynecological and endocrine pathology". However, it does not specify whether this aligns with absence of hyperandrogenism or PCOM in accordance with Rotterdam criteria.
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Not reported	Rotterdam criteria was used to diagnose the PCOS patients, however no details are provided as to the definitions for classifying each feature.
	Was the reference standard independent of the index test (ie. the index test did not form part of the reference standard)?	No	PCOS diagnosis of the Rotterdam criteria includes the evaluation of ovarian ultrasounds to measure either follicle number per ovary (FNPO)or ovarian volume (OV). Thus, the index test is part of the reference standard.
	Were the reference standard results interpreted without knowledge of the results of the index test?	No	PCOS diagnosis of the Rotterdam criteria includes the evaluation of ovarian ultrasounds to measure either follicle number per ovary (FNPO) or ovarian volume (OV). Thus, the reference standard is interpreted with knowledge of the index test.
	Were the index test results interpreted without knowledge of the results of the reference standard test?	Not reported	Method description does not describe the timing of the reference standard in relation to the index test results.
	If a threshold was used, was it pre-specified?	No	Authors describe that "the diagnostic accuracy and cutoff values were assessed by multivariate analysis with the logistic regression models using receiver operator characteristic (ROC) curves and calculating the area under the curve (AUC)". No pre-specified thresholds were mentioned.

DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?	Not reported	Although it is mentioned that the index test was done on days 3-5 of the menstrual cycle, it is unclear however when PCOS diagnosis occurred as it is not described.
ATTRITION BIAS	Were withdrawals from the study explained?	Yes 100% treatment 100% control/ comparison	Numbers described as enrolled are the same as those in results.
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Yes	There are no uninterruptable/intermediate test results and all results are reported.
OTHER ISSUES – APPLICABILITY/ COMPARABILITY/ VARIATION	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	Authors provided the following description of the ultrasound examination: "All girls underwent ultrasound examination of pelvic organs as well as mammary and thyroid glands on days 3–5 of a spontaneous or gestagen-induced menstrual cycle. The study was performed on a Vivid-q ultrasonic device of GE HEALTHCARE company using a linear and convex probe with a frequency of 1.8–6.0 MHz. The study was conducted with a full filled bladder by the transabdominal approach. The sonographic features including length, width, and thickness (L, W, T, consequently) of left and right ovaries and uterine (U) measurements (L, W, T) were described, and the ovarian volume (OV) was calculated. The ovarian to uterine index (OUI) was established according to the formula: OUI = (OVleft + OVright) ÷ (2 × UT), where OV is measured in cm^3, and UT (thickness of the uterus) is in cm."
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Yes	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Not reported	Study does not describe what clinical data was available during test result interpretation.
	Were there any conflicts of interest in the writing or funding of this study?	No	Authors stated that there were no conflicts of interest to disclose.
	If statistical analysis was undertaken, was this appropriate?	Partial	Study describes that "the diagnostic accuracy and cutoff values were assessed by multivariate analysis with the logistic regression models using receiver operator characteristic (ROC) curves and calculating the area under the curve (AUC)". However, unclear if an adequate sample size calculation was undertaken. A 4x4 table of test performance was not presented.

COMMENTS		
What is the overall risk of bias?	High	Few criteria have been fulfilled and the conclusions of the study are likely to be affected.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?	No. All outcomes had the same risk of bias.	

Study ID	Kim 2017	
Study Citation	Kim, H. J. et al. (2017). "Polycystic ovary morphology: age-based ultrasound criteria." Fertility and Sterility 108(3): 548-553.	
Study Country	USA	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	Control: Control subjects, aged 18 to 51 years, had regular menstrual cycles, 21 to 35 days, and no physical exam or biochemical evidence of hyperandrogenism in Boston (n=666) and Iceland (n=32). PCOS: PCOS subjects recruited at Massachusetts General Hospital in Boston from 2003 to 2013 were between the ages of 18 and 56 years (n = 544). PCOS subjects recruited in Iceland from 2003 to 2006 were between the ages of 18 and 40 years (n=105). All subjects had oligomenorrhea (< 9 menstrual periods/yr) and clinical and/or biochemical evidence of hyperandrogenism, fulfilling the NIH criteria. Age (yo): Control: 27.3±6.2 (Boston) & 32.2±5.5 (Iceland), PCOS: 28.4±6.4 (Boston) & 30.2±6.2 (Iceland) p = 0.002 (Boston) and p = 0.15 (Iceland) BMI (kg/m^2): Control: 24.3±4.8 (Boston) & 30.2±7.5 (Iceland), PCOS: 30.7±8.7 (Boston) & 31.5±7.7 (Iceland) p < 0.001 (Boston) and p = 0.3 (Iceland)	
PCOS diagnostic criteria	NIH	
N per group	Control: 666 (Boston) and 32 (Iceland) PCOS: 544 (Boston) and 105 (Iceland)	
Setting	Massachusetts General Hospital of Boston, USA between 2003 and 2013 and Landspitali University Hospital in Iceland between 2003 and 2006 (PCOS only)	
Index test	Ovarian Volume (OV – maximum) Follicle Number Per Cross-Section (FNPS – Maximum)	
Reference Standard	NIH criteria (oligomenorrhea & hyperandrogenism)	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Accuracy to diagnose PCOS Sensitivity and specificity Area under the ROC curve Proposed threshold	
Inclusion and exclusion criteria reported?	Yes	Inclusion criteria: Control: Aged 18 to 51 years, had regular menstrual cycles, 21 to 35 days, and no physical exam or biochemical evidence of hyperandrogenism

		PCOS: Aged of 18 and 56 years (Boston) or aged 18 and 40 years (Iceland). All subjects had oligomenorrhea (< 9 menstrual periods/yr) and clinical and/or biochemical evidence of hyperandrogenism, fulfilling the NIH criteria. Exclusion criteria: personal history or biochemical evidence of late onset congenital adrenal hyperplasia. All subjects had normal thyroid function and prolactin levels and a follicular phase FSH level in the premenopausal range. Subjects were on no hormonal medication for at least 3 months, except for stable thyroid hormone replacement and were not taking metformin.
Does the study have a clearly focused question?	Partial	What are the best age-based criteria for polycystic ovary morphology?
Summary Result/s	The best sensitivity and specificity were obtained using a threshold volume of 12 mL and 13 follicles for ages >24 years, 10 mL and 14 follicles for ages 25–29 years, 9 mL and 10 follicles for ages 30–34 years, 8 mL and 10 follicles for ages 35–39 years, 10 mL and 9 follicles for ages 40–44 years, and 6 mL and 7 follicles for ages >44 years. Data from a second cohort confirmed the need to decrease volume and follicle number with increasing age to diagnose PCOS. Polycystic ovary morphology was most accurate at predicting the PCOS diagnosis for women ages 30–39 years. The ovarian volume and follicle number threshold to define polycystic ovary morphology should be lowered starting at age 30.	

INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
PATIENT SELECTION/SPECTRUM BIAS	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	Studies that recruit a group of healthy controls and a group known to have the target disorder will be coded as “No” in most scenarios. Studies enrolling patients with known disease and control group without the condition may exaggerate diagnostic accuracy. Controls may not be routinely assessed for ovarian volume using ultrasound. The PCOS group is representative of those who will be assessed with these criteria in practice.
	Was a consecutive or random sample of patients enrolled? (Q-2)	No	No random element was described in the selection of participants into the study. Study is described as a cross-sectional study, with data from the second visit of a longitudinal study used for certain participants (control or PCOS) at the Boston site to provide a “broader age range for assessment”.
	Was a case-control design avoided? (Q-2)	No	Both the control group (regular cycling, normo-androgenic women) and group with known disease (PCOS) were identified and diagnosed prior or during study enrollment.
	Did the study avoid inappropriate exclusions? (Q-2)	Yes	The exclusion criteria for the study are appropriate. Study methods describe that participants cannot have “personal history or biochemical evidence of late onset congenital adrenal hyperplasia. All subjects had normal thyroid function and prolactin levels and a follicular phase FSH level in the premenopausal range. Subjects were on no hormonal medication for at least 3 months, except for stable thyroid hormone replacement and were not taking metformin”.
	Were all participants assessed with both index test and reference standard?	No	The study had a total of 666 subjects included as Controls for both index tests. However, 655 Control subjects were used when generating diagnostic thresholds.
	Did all patients receive the same reference standard? (Q-2)	Yes	All participants in the study received the same reference standard, which was the equivalent of the NIH diagnostic criteria for PCOS. For the Control group, the study mentions that it consisted of women “aged 18 to 51 years, had regular menstrual cycles, 21 to 35 days, and no physical exam or biochemical evidence of hyperandrogenism”.

CLASSIFICATION/ VERIFICATION/ INCORPORATION/ REVIEW BIAS	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	PCOS diagnosis was conducted using the 1990 NIH criteria, which includes the presence of "oligomenorrhea (< 9 menstrual periods/yr) and clinical and/or biochemical evidence of hyperandrogenism…". Specifically, "clinical hyperandrogenism was defined by: 1) an elevated Ferriman Gallwey score > 9; or 2) acne on the face or back. Biochemical hyperandrogenism was defined as testosterone >63 ng/dL (2.8 nmol/L), DHEAS >430 µg/dL (1.16 µmoL/L) or androstenedione levels >3.8 ng/mL (13.3 nmol/L)".
	Was the reference standard independent of the index test (ie. the index test did not form part of the reference standard)?	Yes	NIH criteria for the diagnosis of PCOS only includes the presence oligo-anovulation/anovulation and hyperandrogenism (clinical and/or biochemical). Sonographic markers of ovarian morphology are not part of the reference standard.
	Were the reference standard results interpreted without knowledge of the results of the index test?	Not reported	Even though some study participants were diagnosed with PCOS or categorized as a control prior to index test conducted during the second study visit (longitudinal study), method description does not describe the timing of the reference standard in relation to the index test results for all participants.
	Were the index test results interpreted without knowledge of the results of the reference standard test?	No	Study methods describe that "in Boston, all women were diagnosed with PCOS or confirmed as controls before the age of 40 years but some came back at a later age for a longitudinal study. They were only included in the data at their second visit, providing a broader age range for assessment". Therefore, for some of the participants PCOS diagnosis was known before interpretation of index test.
	If a threshold was used, was it pre-specified?	No	Study method describes that "using data from the Boston cohort, a receiver operating characteristic (ROC) curve was constructed for each (approximately) 5 year age group (18–24, >24–29, >29–34, >34–39, >39–44 and >44 years) for both ovarian volume and follicle number. Youden's index (sensitivity + specificity − 1) was used to choose the value that maximized the sensitivity and specificity across all possible results, rather than optimize one or the other criteria to avoid bias".
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?	Not reported	Study methods describe that "women with PCOS were studied 10 days after their last menstrual period to avoid the time period in which LH is suppressed after a progesterone rise and after a 12 hour fast. Control subjects were studied in the follicular phase. All subjects underwent a physical exam, blood draw for hormonal assessment and oral glucose tolerance test at baseline". However, since some participants returned at a later age for a longitudinal study and were only included in the data at their second visit to provide a broader age range for assessment, it is unclear if PCOS diagnosis was reassessed at the second visit.
ATTRITION BIAS	Were withdrawals from the study explained?	No 100% treatment 98.3% control/ comparison u	The study had a total of 666 subjects included as Controls for both index tests. However, 655 Control subjects were used when generating diagnostic thresholds. The withdrawals were not explained.
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Yes	There are no uninterruptable/intermediate test results and all results are reported.

OTHER ISSUES – APPLICABILITY/ COMPARABILITY/ VARIATION	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	The following description was provided for the ultrasound examination: "Ultrasounds were performed by one operator in Boston (J.M.A.), using the ATL HDI 1500 Ultrasound with a 4- to 8-mHZ convex array probe from 2003 to 2006. Ultrasounds were also performed by one operator in Iceland (trained by J.M.A.) using the ATL Envisor Ultrasound with a 4- to 8-mHZ convex array probe, which was well matched to the Boston device, from 2003 to 2006. In April 2006, the Boston group changed the ultrasound machine to a Phillips HD11 XE with a 4- to 8-mHZ endovaginal curved array transducer. In all cases, multiple images of the ovary were recorded. Ovarian volume was calculated using length width height in centimeters multiplied by 0.5233. All follicles were counted on a fixed image in a plane in which the maximum number of follicles was visualized. The maximum ovarian volume and maximum follicle number in the ovary with the maximum number of follicles was used for analysis, excluding the volume of an ovary with a dominant follicle (>10 mm) or a corpus luteum. Initial measurements were recorded in Boston and in Iceland and were over read by two observers (J.M.A, H.J.K, C.T.P., and/or C.K.W.). If readings were not in agreement, a consensus reading was agreed upon after review by all parties."
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Yes	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Not reported	Study does not describe what clinical data was available during test result interpretation.
	Were there any conflicts of interest in the writing or funding of this study?	No	C.K.W. has received consulting fees from Novartis and royalties from UptoDate unrelated to the current topic.
	If statistical analysis was undertaken, was this appropriate?	Partial	Statistical analyses included "receiver operating characteristic (ROC) curve was constructed for each (approximately) 5 year age group (18–24, >24–29, >29–34, >34–39, >39–44 and >44 years) for both ovarian volume and follicle number. Youden's index (sensitivity + specificity − 1) was used to choose the value that maximized the sensitivity and specificity across all possible results, rather than optimize one or the other criteria to avoid bias". However, unclear if an adequate sample size calculation was undertaken. A 4x4 table of test performance was not presented.
COMMENTS			
What is the overall risk of bias?		High	Few criteria have been fulfilled and the conclusions of the study are likely to be affected.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No. All outcomes had the same risk of bias.	

Study ID	Köninger 2014

Study Citation	Köninger, A. et al. (2014). "Anti-Mullerian Hormone: an indicator for the severity of polycystic ovarian syndrome." Archives of Gynecology and Obstetrics 290(5): 1023-1030.	
Study Country	Germany	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	Control: Women with tubal or male sterility or recurrent miscarriages without any kind of endocrine disorders were consecutively included as they were presented in the clinic. All controls presented with regular menstrual cycle, normal ovarian morphology in the vaginal scan and no clinical or serological signs of hyperandrogenism. PCOS: Women with PCOS by the 2003 Rotterdam Criteria were consecutively included as they were presented in the clinic. Oligomenorrhoea was defined as cycles lasting longer than 35 days, amenorrhoea was defined as cycles lasting longer than 3 months. Age (yo): Control: 34.0 ± 5.5, PCOS: 28.0 ± 5.9 BMI (kg/m^2): Not available	
PCOS diagnostic criteria	Rotterdam	
N per group	Control: 48 PCOS: 80 • Severe PCOS = 59 • Mild PCOS (without hyperandrogenism) = 21	
Setting	Department of Gynecology and Obstetrics of the University Hospital of Essen, Germany between 2011 and 2013	
Index test	Follicle Number Per Ovary (FNPO – Maximum) Ovarian Volume (OV – Maximum)	
Reference Standard	Rotterdam criteria (oligo-anovulation, hyperandrogenism, PCOM)	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Accuracy to diagnose PCOS Sensitivity and specificity Area under the ROC curve Proposed threshold	
Inclusion and exclusion criteria reported?	Yes	Inclusion criteria: Control: Women with tubal or male sterility or recurrent miscarriages without any kind of endocrine disorders were consecutively included as they were presented in the clinic. All controls presented with regular menstrual cycle, normal ovarian morphology in the vaginal scan and no clinical or serological signs of hyperandrogenism. PCOS: Women with PCOS by the 2003 Rotterdam Criteria were consecutively included as they were presented in the clinic. Oligomenorrhoea was defined as cycles lasting longer than 35 days, amenorrhoea was defined as cycles lasting longer than 3 months. Exclusion criteria: Both groups: Patients with other pituitary, adrenal, adrenogenital syndrome or ovarian diseases were also excluded. None of the participants had taken hormonal contraceptives at least three months before participating in the study".
Does the study have a clearly focused question?	Partial	What is the diagnostic potency of the features of polycystic ovarian syndrome (PCOS) including sonographic aspects, androgens, LH and LH/FSH ratio as well as Anti-Mullerian Hormone (AMH), in detecting different degrees of PCOS severity?

Summary Result/s			The strongest group difference between controls and severe PCOS patients was observed for AMH showing an age-adjusted odds ratio of 2.56 [95 % confidence interval (CI) 2.00–3.27; p < 0.0001]. Age-adjusted receiver operating characteristic analysis showed that the area under the curve (AUC) of 0.88 (95 % CI: 0.80–0.95) for AMH and 0.94 (95 % CI 0.88–0.98) for antral follicle count did not differ significantly in their ability to discriminate between severe PCOS patients and controls. AMH showed higher AUC estimates than androgens, ovarian volume, LH and LH/FSH ratio and an AUC of 0.80 (95 % CI: 0.65– 0.91) for detecting mild PCOS.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
PATIENT SELECTION/SPECTRUM BIAS	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	Studies that recruit a group of healthy controls and a group known to have the target disorder will be coded as "No" in most scenarios. Studies enrolling patients with known disease and control group without the condition may exaggerate diagnostic accuracy. Controls may not be routinely assessed for ovarian volume using ultrasound. The PCOS group is representative of those who will be assessed with these criteria in practice.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	Study methods describe that "patients were consecutively included as they presented in our clinic".
	Was a case-control design avoided? (Q-2)	No	Both the control group (regular cycling, normo-androgenic women with normal ovarian morphology) and group with known disease (PCOS) were identified and diagnosed prior or during study enrollment.
	Did the study avoid inappropriate exclusions? (Q-2)	Yes	The exclusion criteria for the study are appropriate. Study methods describe that "patients with other pituitary, adrenal, adrenogenital syndrome or ovarian diseases were also excluded. None of the participants had taken hormonal contraceptives at least three months before participating in the study".
CLASSIFICATION/ VERIFICATION/ INCORPORATION/ REVIEW BIAS	Were all participants assessed with both index test and reference standard?	Yes	All participants in the Control group (n = 48) and PCOS group (n = 80) received both index tests (OV, FNPO).
	Did all patients receive the same reference standard? (Q-2)	Yes	All participants in the study received the same reference standard, which was the equivalent of the NIH diagnostic criteria for PCOS. For the Control group, the study mentions that it consisted of "all controls presented with regular menstrual cycle, normal ovarian morphology in the vaginal scan and no clinical or serological signs of hyperandrogenism".
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	PCOS diagnosis was conducted using the 2003 Rotterdam criteria, which is defined by the presence of two of the three following diagnostic criteria: oligo-/amenorrhoea, polycystic ovaries with ≥12 sonographically measured small follicles between 2 and 9 mm and/or an ovarian volume greater than 10 ml and hyperandrogenemia. Specifically, "oligomenorrhoea was defined as cycles lasting longer than 35 days, amenorrhoea was defined as cycles lasting longer than 3 months. Hyperandrogenism was diagnosed with an elevated total testosterone (normal range 0.5– 2.6 nmol/l) and/or DHEAS (normal range 6–123 µg/dl) and/ or androstenedione (normal range 0.3–3.3 ng/ml)".
	Was the reference standard independent of the index test (ie. the index test did not form part of the reference standard)?	No	PCOS diagnosis of the Rotterdam criteria includes the evaluation of ovarian ultrasounds to measure either follicle number per ovary (FNPO) or ovarian volume (OV). Thus, the index test is part of the reference standard.

	Were the reference standard results interpreted without knowledge of the results of the index test?	Not reported	Method description does not describe the timing of the reference standard in relation to the index test results.
	Were the index test results interpreted without knowledge of the results of the reference standard test?	Not reported	Method description does not describe the timing of the index test in relation to the reference standard.
	If a threshold was used, was it pre-specified?	No	Study method describes that "the optimal cut-off, i.e., the threshold that maximizes the sum of (sensitivity + specificity) according to Youden, was calculated for each parameter".
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?	Not reported	Study methods describe that "Endocrine variables, i.e., AMH, LH, FSH, LH/FSH ratio (ratio), androstenedione, total testosterone and sonographic parameters, i.e., antral follicle count (AFC) and ovarian volume, were assessed between the second and fifth day of menstrual cycle or after artificial bleeding induction in cases of amenorrhoea". However, it is unclear when clinical evaluations of reproductive health were evaluated.
ATTRITION BIAS	Were withdrawals from the study explained?	Yes 100% treatment 100% control/ comparison u	Numbers described as enrolled are the same as those in results.
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Yes	There are no uninterruptable/intermediate test results and all results are reported.
	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	The following description was provided for the ultrasound examination: "All women were scanned transvaginally between the second and fifth day of menstrual cycle or after artificial bleeding induction in cases of amenorrhoea. For real-time ultrasound measurements, we used the following transducers: Voluson E8, General Electric Systems, RIC 5-i-C 4D Endocavity probe, 4–9 MHz and IU22, Philips Healthcare, probe 3D9–3v, 3–9 MHz and Sonoline Elegra, Siemens Ultrasound Division, 6.5 MHz-probe. All women were scanned by the same experienced physician to avoid interobserver differences in outcome measurements. Ovarian volume was obtained by measuring the greatest diameter in every plane. The formula for a prolate ellipsoid V = x × y × z × 0.5236/1,000 was used in accordance with Balen et al. [19]. We calculated small follicles between 2 and 9 mm diameter in the longitudinal, transverse and anterior– posterior cross-sections of each ovary using the most available magnification factor available for the determination of the AFC. Patients with any kind of ovarian masses or follicles greater than 10 mm were excluded. For statistical analysis, the ovary showing the maximum AFC value and maximum ovarian volume per participant was used, respectively."
OTHER ISSUES –	Were the clinicians undertaking the tests representative of the clinicians who will	Yes	

	be undertaking the tests in the clinical setting?		
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Not reported	Study does not describe what clinical data was available during test result interpretation.
	Were there any conflicts of interest in the writing or funding of this study?	No	Authors stated that there were no conflicts of interest to disclose.
	If statistical analysis was undertaken, was this appropriate?	Partial	Statistical analysis includes: "the optimal cut-off, i.e., the threshold that maximizes the sum of (sensitivity + specificity) according to Youden, was calculated for each parameter". However, unclear if an adequate sample size calculation was undertaken. A 4x4 table of test performance was not presented.
COMMENTS			
What is the overall risk of bias?		Moderate	Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No. All outcomes had the same risk of bias.	

Study ID	Köşüş, 2011a
Study Citation	Köşüş, N. et al. (2011). "Relationship of ovarian volume with mean platelet volume and lipid profile in patients with polycystic ovary syndrome." Experimental and Therapeutic Medicine 2(6): 1141-1144.
Study Country	Turkey
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	Control: Regularly menstruating healthy non-hirsute, normo-ovulatory women. PCOS: Women newly diagnosed with PCOS with the Rotterdam criteria. Age (yo): Control: 26.7±5.6, PCOS: 26.3±5.4 p = not significant BMI (kg/m^2): Control: 20.8±2.4, PCOS: 26.5±5.3 p = not significant
PCOS diagnostic criteria	Rotterdam
N per group	Control: 100 PCOS: 210
Setting	Department of Obstetrics and Gynecology of Fatih University of Istanbul, Turkey between January 2008 and August 2010
Index test	Ovarian Volume (OV – Mean)

Reference Standard		Rotterdam criteria (oligo-anovulation, hyperandrogenism, PCOM)	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)		Accuracy to diagnose PCOS Sensitivity and specificity Area under the ROC curve Proposed threshold	
Inclusion and exclusion criteria reported?		Yes	Inclusion Criteria: Control: Regularly menstruating healthy non-hirsute, normo-ovulatory women were enrolled into the study between January 2008 and August 2010 PCOS: Women newly diagnosed with PCOS with the Rotterdam criteria were enrolled into the study between January 2008 and August 2010 Exclusion Criteria: Both groups: any patient known to have hypertension, diabetes, using anti-coagulant therapy or having a propensity to thrombotic or bleeding disorders was excluded from the study group. Cases with a history of ovarian surgery, having received hormonal treatment in the previous 3 months or for PCOS-related treatment before this research were excluded from the study.
Does the study have a clearly focused question?		Yes	What is the relationship between ovarian volume (OV) and mean platelet volume (MPV) in women with polycystic ovary syndrome (PCOS)?
Summary Result/s		It was found that MPV increased gradually as OV increased. This implies a higher risk of hypercoagulability and therefore an increased risk of future cardiovascular disease.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
PATIENT SELECTION/SPECTRUM BIAS	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	Studies that recruit a group of healthy controls and a group known to have the target disorder will be coded as “No” in most scenarios. Studies enrolling patients with known disease and control group without the condition may exaggerate diagnostic accuracy. Controls may not be routinely assessed for ovarian volume using ultrasound. The PCOS group is representative of those who will be assessed with these criteria in practice.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Not reported	No random element was described in the selection of participants into the study. Study is described as a prospective study.
	Was a case-control design avoided? (Q-2)	No	Both the control group (regular cycling, normo-androgenic women) and group with known disease (PCOS) were identified and diagnosed during study enrollment.
	Did the study avoid inappropriate exclusions? (Q-2)	Yes	The exclusion criteria for the study are appropriate. Study methods describe that “any patient known to have hypertension, diabetes, using anti-coagulant therapy or having a propensity to thrombotic or bleeding disorders was excluded from the study group. Cases with a history of ovarian surgery, having received hormonal treatment in the previous 3 months or for PCOS-related treatment before this research were excluded from the study”.
	Were all participants assessed with both index test and reference standard?	Yes	All participants in the Control group (n = 100) and PCOS group (n = 210) received the index test.

CLASSIFICATION/ VERIFICATION/ INCORPORATION/ REVIEW BIAS	Did all patients receive the same reference standard? (Q-2)	Not reported	For the Control group, the study mentions that it consisted of “regularly menstruating healthy non-hirsute, normo-ovulatory women”. However, it is unclear whether PCOM was evaluated.
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Not reported	PCOS diagnosis was conducted using the 2003 Rotterdam criteria, specifically “the presence of two of three of the following criteria were used for the diagnosis of PCOS: i) oligo and/or anovulation, ii) clinical and/or biochemical signs of hyperandrogenism, and iii) echographic PCO, after the exclusion of other pathologies with a similar clinical presentation”. However, the study does not define the evaluations of each cardinal feature.
	Was the reference standard independent of the index test (ie. the index test did not form part of the reference standard)?	No	PCOS diagnosis of the Rotterdam criteria includes the evaluation of ovarian ultrasounds to measure either follicle number per ovary (FNPO) or ovarian volume (OV). Thus, the index test is part of the reference standard.
	Were the reference standard results interpreted without knowledge of the results of the index test?	Not reported	Method description does not describe the timing of the reference standard in relation to the index test results.
	Were the index test results interpreted without knowledge of the results of the reference standard test?	Not reported	Method description does not describe the timing of the index test in relation to the reference standard.
	If a threshold was used, was it pre-specified?	No	Study method describes that “cutoff values for OV were determined by receiver operating characteristics (ROC) curve analysis. Sensitivity against (1 - specificity) was plotted at each level, and the area under the curve (AUC), which reflects the probability of correctly identifying controls and PCOS patients, was calculated”.
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?	Not reported	Method description does not describe the timing of the reference standard in relation to the index test results.
ATTRITION BIAS	Were withdrawals from the study explained?	Yes 100% treatment 100% control/ comparison	Numbers described as enrolled are the same as those in results.
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Yes	There are no uninterruptable/intermediate test results and all results are reported.
	Was the execution of all tests described in sufficient detail to	Yes	The following description was provided for the ultrasound examination: “Transvaginal ultrasound examination was performed to evaluate the ovaries using a Logic 200 Pro (GE Healthcare, UK) with a 6.5-MHz transvaginal probe. Regularly menstruating women were scanned in the

OTHER ISSUES – APPLICABILITY/ COMPARABILITY/ VARIATION	permit replication of the tests?		early follicular phase (cycle days 3-5). Oligomenorrheic or amenorrheic women were scanned between days 3 and 5 after a progestin-induced withdrawal bleeding. Three diameters of ovaries were measured. OV was estimated using a simplified formula for the volume of a prolate ellipsoid: V = 0.523 x length x height x width. The mean volume of bilateral ovaries was recorded for study."
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Yes	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Not reported	
	Were there any conflicts of interest in the writing or funding of this study?	Not reported	Authors did not state whether there were conflicts of interest to disclose.
	If statistical analysis was undertaken, was this appropriate?	Partial	Statistical analyses describe ""cutoff values for OV were determined by receiver operating characteristics (ROC) curve analysis. Sensitivity against (1 - specificity) was plotted at each level, and the area under the curve (AUC), which reflects the probability of correctly identifying controls and PCOS patients, was calculated". However, unclear if an adequate sample size calculation was undertaken. A 4x4 table of test performancewas not presented.
COMMENTS			
What is the overall risk of bias?		High	Few criteria have been fulfilled and the conclusions of the study are likely to be affected.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No. All outcomes had the same risk of bias.	

Study ID	Köşüş, 2011b
Study Citation	Köşüş, N. et al. (2011). "Do threshold values of ovarian volume and follicle number for diagnosing polycystic ovarian syndrome in Turkish women differ from western countries?". European Journal of Obstetrics & Gynecology and Reproductive Biology 154(2): 177-181.
Study Country	Turkey
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	Control: Regularly menstruating healthy, non-hirsute, normo-ovulatory volunteers.. A normal menstrual cycle was defined as cyclic uterine bleeding with a duration of 4–6 days and a frequency of 25–35 days/month. Ovulation was confirmed by serum progesterone

	measurements during the luteal phase 7 days before anticipated menses in two consecutive cycles and ultrasound (whenever possible) in the control group. PCOS: Women diagnosed with PCOS using the AE-PCOS criteria. PCOS was diagnosed using the presence of the following: (i) clinical and/or biochemical hyperandrogenism, (ii) ovarian dysfunction, including ovulation dysfunction and/or polycystic ovaries, and (iii) exclusion of other causes of androgen excess. Age (yo): Control: 26.7±5.6, PCOS: 24.9±6.1 p = 0.143 BMI (kg/m^2): Control: 20.8±2.4, PCOS: 27.1±6.2 p < 0.001	
PCOS diagnostic criteria	AE-PCOS	
N per group	Control: 65 PCOS: 251	
Setting	Fatih University Hospital of Istanbul, Turkey between January 2007 and August 2009	
Index test	Follicle Number Per Ovary (FNPO – Mean) Ovarian Volume (OV – Mean)	
Reference Standard	AE-PCOS criteria (hyperandrogenism and ovarian dysfuction [ovulatory dysfunction and/or PCOM])	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Accuracy to diagnose PCOS Sensitivity and specificity Area under the ROC curve Proposed threshold	
Inclusion and exclusion criteria reported?	Yes	Inclusion Criteria: Controls: Regularly menstruating healthy, non-hirsute, normo-ovulatory volunteers. A normal menstrual cycle was defined as cyclic uterine bleeding with a duration of 4–6 days and a frequency of 25–35 days/month. Ovulation was confirmed by serum progesterone measurements during the luteal phase 7 days before anticipated menses in two consecutive cycles and ultrasound (whenever possible) in the control group. PCOS: Women diagnosed with PCOS using the AE-PCOS criteria. PCOS was diagnosed using the presence of the following: (i) clinical and/or biochemical hyperandrogenism, (ii) ovarian dysfunction, including ovulation dysfunction and/or polycystic ovaries, and (iii) exclusion of other causes of androgen excess. Exclusion Criteria: Control: All subjects [that] were age less than 16 or more than 40 years, pregnancy or presence of other androgen excess disorders. For the exclusion of other causes of androgen excess, hormonal evaluations were performed before PCOS diagnosis… Any patient known to have hypertension, diabetes, or cases with a history of ovarian surgery, having hormonal treatment in the previous 3 months or for PCOS-related treatment before this research, and ovarian mass or cyst (more than 10 mm in diameter) detected by ultrasound examination were also excluded from the study. PCOS: Exclusion of other causes of androgen excess, all subjects [that] were age less than 16 or more than 40 years, pregnancy or presence of other androgen excess disorders. For the exclusion of other causes of androgen excess, hormonal evaluations were performed before PCOS diagnosis… Any patient known to have hypertension, diabetes, or cases with a history of ovarian surgery, having hormonal treatment in the previous 3 months or for PCOS-related

		treatment before this research, and ovarian mass or cyst (more than 10 mm in diameter) detected by ultrasound examination were also excluded from the study.
Does the study have a clearly focused question?	Yes	What are the diagnostic values and thresholds of ovarian volume and follicle number for Turkish patients with polycystic ovarian syndrome (PCOS)?
Summary Result/s	Mean and median OV were 12.5 ± 8.1 and 10.1 cm^3 in PCOS cases. Mean and median FN in the PCOS group were 9.8 ± 2.8 and 10, respectively. In the control group, the mean and median OV were 5.4 ± 1.8 and 5.5 cm^3. Mean and median FN of controls was 5 ± 1.5 and 5, respectively. There were statistically significant differences in both OV and FN between PCOS patients and controls (all $p < 0.001$). Cut off values for ovarian volume in PCOS cases for the Turkish population were determined by receiver-operating characteristics (ROC) analysis. The areas under the curve (AUCs) for mean OV and mean FN were 0.938 and 0.998, respectively, indicating a good diagnostic power of the tested variables. Combining sensitivity and specificity using the Youden index, setting the cut off value for threshold OV and FN at 6.43 cm^3 and 8, respectively, yielded the best compromise between sensitivity and specificity. There may be some differences in ultrasound characteristics of PCOS, resulting in differing diagnostic power and cut off points for different populations. OV and FN have powerful diagnostic value in determination of PCOS with different threshold values for different ethnicities.	

INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
PATIENT SELECTION/SPECTRUM BIAS	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	Studies that recruit a group of healthy controls and a group known to have the target disorder will be coded as "No" in most scenarios. Studies enrolling patients with known disease and control group without the condition may exaggerate diagnostic accuracy. Controls may not be routinely assessed for ovarian volume using ultrasound. The PCOS group is representative of those who will be assessed with these criteria in practice.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Not reported	No random element was described in the selection of participants into the study. Study is described as a prospective study.
	Was a case-control design avoided? (Q-2)	No	Both the control group (regular cycling, non-hirsute women) and group with known disease (PCOS) were identified and diagnosed during study enrollment.
	Did the study avoid inappropriate exclusions? (Q-2)	Yes	The exclusion criteria for the study are appropriate. Study methods describes the exclusion criteria as "all subjects [that] were age less than 16 or more than 40 years, pregnancy or presence of other androgen excess disorders. For the exclusion of other causes of androgen excess, hormonal evaluations were performed before PCOS diagnosis… Any patient known to have hypertension, diabetes, or cases with a history of ovarian surgery, having hormonal treatment in the previous 3 months or for PCOS-related treatment before this research, and ovarian mass or cyst (more than 10 mm in diameter) detected by ultrasound examination were also excluded from the study". The study also mentions "exclusion of other causes of androgen excess" in the PCOS group.
CLASSIFIC	Were all participants assessed with both index test and reference standard?	Yes	All participants in the Control group (n = 251) and PCOS group (n = 65) received the index test.
	Did all patients receive the same reference standard? (Q-2)	Not reported	For the Control group, the study mentions that it consisted of "non-hirsute, normoovulatory women". However, it is unclear if PCOM was also evaluated.
	Is the reference standard likely to	Partial	PCOS diagnosis was conducted using the AE-PCOS criteria, specifically "diagnosis of PCOS was established when three of the following criteria were

	correctly classify the target condition? (Q-2)		present: (i) clinical and/or biochemical hyperandrogenism, (ii) ovarian dysfunction, including ovulation dysfunction and/or polycystic ovaries, and (iii) exclusion of other causes of androgen excess… Clinical hyperandrogenism was defined by a Ferriman–Gallwey score ≥6, and/or the presence of obvious acne on the face or back. Biochemical hyperandrogenism was defined as increased serum testosterone or dehydroepiandrosterone sulfate (DHEAS) levels higher than two standard deviations above the mean level of the controls (>61.1 ng/dl for total testesterone and >282.3 mg/dl for DHEAS). Ovarian and/or ovulatory dysfunction were defined as menstrual disturbances in the form of oligoamenorrhea for more than 6 months and/or presence of anovulation detected by serum progesterone measurements during the luteal phase 7 days before anticipated menses in two consecutive cycles." It is unclear what definition of PCOM was as part of the AE-PCOS criteria, however it is not required to satisfy PCOS diagnostic criteria.
	Was the reference standard independent of the index test (ie. the index test did not form part of the reference standard)?	No	PCOS diagnosis of the AE-PCOS criteria includes the evaluation of ovarian ultrasounds to measure either follicle number per ovary (FNPO) or ovarian volume (OV). Thus, the index test is part of the reference standard.
	Were the reference standard results interpreted without knowledge of the results of the index test?	Not reported	Method description does not describe the timing of the reference standard in relation to the index test results.
	Were the index test results interpreted without knowledge of the results of the reference standard test?	Not reported	Method description does not describe the timing of the index test in relation to the reference standard.
	If a threshold was used, was it pre-specified?	No	Study method describes that "the Youden index (sensitivity + specificity - 1) was calculated to determine the best compromise between sensitivity and specificity; the closer the value is to 1, the greater the diagnostic power".
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?	Partial	Study methods describe that "Hormonal measurement was done in all cases by taking fasting blood samples between day 2 and day 4 of the cycle. Regularly menstruating women were scanned in the early follicular phase (cycle days 3–5). Progestin was administered to the PCOS cases with oligomenorrhea or amenorrhea. Amenorrhea was defined as lack of periods for at least 3 months and oligomenorrhea as menstrual periods occurring at intervals of greater than 35 days. These women were scanned between days 3 and 5 after a progestin-induced withdrawal bleed and those who did not respond to progestin were examined at random". However, study does not describe when other features of the reference standard, including oligo-amenorrhea and clinical hyperandrogenism, were evaluated.
ATTRITION BIAS	Were withdrawals from the study explained?	Yes 100% treatment 100% control/ comparison	Numbers described as enrolled are the same as those in results.

REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Yes	There are no uninterruptable/intermediate test results and all results are reported.
OTHER ISSUES – APPLICABILITY/ COMPARABILITY/ VARIATION	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	The following description was provided for the ultrasound examination: "Evaluation of the ovaries and measurement of ovarian volumes of all cases were performed by transvaginal ultrasound using a Logic 200 Pro (GE Healthcare, United Kingdom) 6.5 MHz transvaginal probe. Regularly menstruating women were scanned in the early follicular phase (cycle days 3–5). Progestin was administered to the PCOS cases with oligomenorrhea or amenorrhea. Amenorrhea was defined as lack of periods for at least 3 months and oligomenorrhea as menstrual periods occurring at intervals of greater than 35 days. These women were scanned between days 3 and 5 after a progestin-induced withdrawal bleed and those who did not respond to progestin were examined at random. Three diameters of ovaries were measured by the same clinician. Ultrasound measurements were taken in real time, according to a standard protocol [21–24]. The highest possible magnification was used to examine the ovaries. After the longest medial axis of the ovary had been determined, the length and height were measured and then the probe was turned to determine the width. Follicle number was established by scanning each ovary from the inner margin to the outer margin in longitudinal crosssection and obtaining the number of all countable follicles. A large number of different ultrasound formulae are used for calculation of ovarian volume. In this study ovarian volume was estimated using a simplified formula for the volume of a prolate ellipsoid: V = 0.523 x length x height x width, which is more widely accepted and easier to use. Correlation between the simplified formula and other formulas was calculated."
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Yes	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Not reported	Study does not describe what clinical data was available during test result interpretation.
	Were there any conflicts of interest in the writing or funding of this study?	Not reported	Authors did not state whether there were conflicts of interest to disclose.
	If statistical analysis was undertaken, was this appropriate?	Partial	Statistical analyses described include: ""the Youden index (sensitivity + specificity - 1) was calculated to determine the best compromise between sensitivity and specificity; the closer the value is to 1, the greater the diagnostic power". However, unclear if an adequate sample size calculation was undertaken. A 4x4 table of test performancewas not presented.
COMMENTS			
What is the overall risk of bias?		High	Few criteria have been fulfilled and the conclusions of the study are likely to be affected.

Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?	No. All outcomes had the same risk of bias.

Study ID	Le 2021	
Study Citation	Le, N. S. V. et al. (2021). "A Cross-Sectional Study on Potential Ovarian Volume and Related Factors in Women with Polycystic Ovary Syndrome from Infertile Couples." International Journal of Women's Health 13: 793.	
Study Country	Vietnam	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	Control: Infertile women who were remaining without PCOS diagnosis using the Rotterdam criteria. PCOS: Infertile women diagnosed with PCOS by the Rotterdam criteria. Age (yo): Control: 33.99 ± 4.78, PCOS: 32.66 ± 4.10 p = 0.042 BMI (kg/m^2): Control: 20.82 ± 2.56 , PCOS: 21.31 ± 2.80 p < 0.001	
PCOS diagnostic criteria	Rotterdam	
N per group	Control: 273 PCOS: 119	
Setting	Hue Center for Reproductive Endocrinology and Infertility of Hue City, Vietnam between January 2019 and December 2020	
Index test	Ovarian Volume (OV – Mean)	
Reference Standard	Rotterdam criteria (oligo-anovulation, hyperandrogenism, PCOM)	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Accuracy to diagnose PCOS Sensitivity and specificity Area under the ROC curve Proposed threshold	
Inclusion and exclusion criteria reported?	Yes	Inclusion Criteria: Control: infertile women who were not diagnosed with PCOS using the Rotterdam criteria PCOS: infertile women diagnosed with PCOS by the Rotterdam criteria. Exclusion Criteria: Both groups: presence of ovarian diseases (ovarian cyst/tumor or endometrioma), history of adnexal surgery, ovarian failure, history of hormonal contraception use, or any hormonal treatment within three months prior to enrollment
Does the study have a clearly focused question?	Yes	What is the value of ovarian volume (OV) measured by transvaginal ultrasound and what is its relationship with anthropometry and serum hormonal levels in a polycystic ovary syndrome (PCOS) population?
Summary Result/s	The mean age of the participants was 32.66±4.10 years compared to 33.99±4.78 years in 273 cases (69.6%) without PCOS. The mean OV was statistically larger in the PCOS group than in	

		the non-PCOS group (7.65±3.23 mL vs 6.08±3.67 mL, p < 0.001) and positively correlated with serum anti-Mullerian (AMH) and luteinizing hormone (LH) levels (r=0.30; p < 0.001 and r=0.23; p < 0.001, respectively), and weakly and inversely correlated with age (−0.182, p < 0.001). The area under the receiver operating characteristic (ROC) curve of OV in the diagnosis of PCOS was 0.613 (0.557–0.670, 95% CI). The enlarged OV is remarkable in women with PCOS and is related to AMH and LH concentrations.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
PATIENT SELECTION/SPECTRUM BIAS	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	Studies that recruit a group of healthy controls and a group known to have the target disorder will be coded as "No" in most scenarios. Studies enrolling patients with known disease and control group without the condition may exaggerate diagnostic accuracy. Controls may not be routinely assessed for ovarian volume using ultrasound. The PCOS group is representative of those who will be assessed with these criteria in practice.
	Was a consecutive or random sample of patients enrolled? (Q-2)	No	No random element was described in the selection of participants into the study. Study is described as a cross-sectional study.
	Was a case-control design avoided? (Q-2)	No	Both the control group (regular cycling, normo-androgenic women) and group with known disease (PCOS) were identified and diagnosed prior or during study enrollment.
	Did the study avoid inappropriate exclusions? (Q-2)	Yes	The exclusion criteria for the study are appropriate. Study methods describe that "exclusions include presence of ovarian diseases (ovarian cyst/tumor or endometrioma), history of adnexal surgery, ovarian failure, history of hormonal contraception use, or any hormonal treatment within three months prior to enrollment".
CLASSIFICATION/ VERIFICATION/ INCORPORATION/ REVIEW BIAS	Were all participants assessed with both index test and reference standard?	Yes	All participants in the Control group (n = 273) and PCOS group (n = 119) received all index tests (OV, FNPO).
	Did all patients receive the same reference standard? (Q-2)	Not reported	Study mentions that all infertile patients who were not diagnosed with PCOS by the Rotterdam criteria were included in the control group. However, it is unclear whether the control group exhibited one or none of the cardinal features.
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	PCOS diagnosis was conducted using the equivalent of the Rotterdam criteria, which is "at least two of the following three features (study group): (i) oligo- and/or anovulation, (ii) clinical and/or biochemical signs of hyperandrogenism, and/or (iii) polycystic ovaries by transvaginal ultrasound scan (more than 12 follicles in the 2–9 mm range in each ovary and/or OV > 10 mL). Oligomenorrhea was defined as having fewer than 8 menstrual cycles per year, the absence of 3–6 consecutive menstrual cycles per year or the length of menstrual cycle greater than 35 days. Hirsutism was visually graded using a modification of the Ferriman and Gallwey scoring system (mFG). We defined clinical hirsutism as mFG ≥5 using the mFG cut-off criterion for the Asian PCOS population".
	Was the reference standard independent of the index test (ie. the index test did not form part of the reference standard)?	No	PCOS diagnosis of the Rotterdam criteria includes the evaluation of ovarian ultrasounds to measure either follicle number per ovary (FNPO) or ovarian volume (OV). Thus, the index test is part of the reference standard.

	Were the reference standard results interpreted without knowledge of the results of the index test?	Not reported	Method description does not describe the timing of the reference standard in relation to the index test results.
	Were the index test results interpreted without knowledge of the results of the reference standard test?	Yes	Method description does not describe whether index test results were interpreted without knowledge of the results of the reference standard.
	If a threshold was used, was it pre-specified?	No	Study method describes that "the Youden index was used to identify the best threshold values for AMH levels and OV. ROC curves were con- structed to assess the diagnostic ability of AMH and OV. Sensitivity against 1- specificity was plotted at each threshold level, and the area under the curve (AUC) was calculated. AUC represents the probability of correctly identifying controls and patients with PCOS ".
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?	Not reported	Method description does not describe the timing of the reference standard in relation to the index test results.
ATTRITION BIAS	Were withdrawals from the study explained?	Yes 100% treatment 100% control/ comparison	Numbers described as enrolled are the same as those in results.
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Yes	There are no uninterruptable/intermediate test results and all results are reported.
OTHER ISSUES – APPLICABILITY/	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	The following description was provided for the ultrasound examination: "On day 2–4 of natural cycle or on day 2–4 of progesterone withdrawal in case of oligo or amenorrhea condition, transvaginal ultrasound examination was performed by the same experienced physician by ultrasonography (ALOKA ProSound SSD-3500, Hitachi, Japan) using a vaginal probe of 7 MHz to evaluate each participant's antral follicle number and OV. Ovaries were scanned from the inner to the outer margin ovaries in both the transverse and sagittal planes. Three dimensions of each ovary were measured, and the total number of antral follicles that were 2–9 mm in diameter were counted. The OV was for each ovary using the π/6 × (D1 × D2 × D3) formula. D presented the longest diameter of each ovary dimension (long, anterior-posterior, and transverse sections)."
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Yes	

	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Not reported	Study does not describe what clinical data was available during test result interpretation.
	Were there any conflicts of interest in the writing or funding of this study?	No	Authors stated that there were no conflicts of interest to disclose.
	If statistical analysis was undertaken, was this appropriate?	Partial	Study method describes that "the Youden index was used to identify the best threshold values for AMH levels and OV. ROC curves were con- structed to assess the diagnostic ability of AMH and OV. Sensitivity against 1- specificity was plotted at each threshold level, and the area under the curve (AUC) was calculated. AUC represents the probability of correctly identifying controls and patients with PCOS ". However, unclear if an adequate sample size calculation was undertaken. A 4x4 table of test performance was not presented. Sensitivity, specificity, and Youden's J were provided but not AUC.
COMMENTS			
What is the overall risk of bias?		Moderate	Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No. All outcomes had the same risk of bias.	

Study ID	Lie Fong 2017
Study Citation	Lie Fong, S., Laven, J. S. E., Duhamel, A., & Dewailly, D. (2017). Polycystic ovarian morphology and the diagnosis of polycystic ovary syndrome: redefining threshold levels for follicle count and serum anti-Müllerian hormone using cluster analysis. Human Reproduction, 32(8), 1723-1731.
Study Country	Netherlands / United States
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	Control: This large cohort comprised women that had been recruited for different purposes and these women had been included in four different original studies (two in the Netherlands and two in North America). Common inclusion criteria were healthy, regularly cycling and non-hirsute women. In addition, these women were not using sex-steroids for at least 3 months prior to inclusion and never had ovarian surgery in the past. In some cases, they had been pregnant spontaneously and had given live birth to a healthy child. In the current study, women aged between 18 and 40 years with regular menstrual cycles and no clinical signs of HA and/or elevated testosterone levels were included. PCOS: Women with PCOS were prospectively recruited at the out-patient clinic in a tertiary care university hospital, as described earlier, and therefore all had anovulatory cycles. Only women with both HA and oligo-anovulation were included in this study in order to avoid using pre-fixed thresholds for the item 'PCOM' since the aim of this study was to re-visit those threshold values. Age (yo): Control: 28.3 (18.4–39.8), PCOS: 27.3 (13.9–39.6) $p < 0.001$

	BMI (kg/m^2): Control: 22.6 (16.5–45.2), PCOS: 28.7 (17.3–50.6) p < 0.001	
PCOS diagnostic criteria	NIH	
N per group	Control: 297 • Young non-PCOM (Cluster 1): 118 • Young PCOM (Cluster 2): 28 • Old non-PCOM (Cluster 3): 100 • Old PCOM (Cluster 4): 51 PCOS: 700	
Setting	Erasmus University Medical School of Rotterdam, Netherlands and Massachusetts General Hospital of Boston, USA	
Index test	Follicle Number Per Ovary (FNPO – Median)	
Reference Standard	NIH criteria (oligo-anovulation, hyperandrogenism)	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Accuracy to diagnose PCOS Sensitivity and specificity Area under the ROC curve Proposed threshold	
Inclusion and exclusion criteria reported?	Partial	Inclusion Criteria: Control: Healthy, regularly cycling and non-hirsute women. In some cases, they had been pregnant spontaneously and had given live birth to a healthy child. In the current study, women aged between 18 and 40 years with regular menstrual cycles and no clinical signs of HA and/or elevated testosterone levels were included. PCOS: All had anovulatory cycles. Only women with both HA and oligo-anovulation were included in this study in order to avoid using pre-fixed thresholds for the item 'PCOM' since the aim of this study was to re-visit those threshold values. Exclusion Criteria: Control: Women were not using sex-steroids for at least 3 months prior to inclusion and never had ovarian surgery in the past PCOS: No details were reported for the exclusion criteria for the PCOS group
Does the study have a clearly focused question?	Yes	Can cluster analysis be used to differentiate between normo-ovulatory women with normal ovaries and normoovulatory women with polycystic ovarian morphology (PCOM) in a non-subjective manner?
Summary Result/s	The optimal number of clusters was four; age was the most important classifying variable, followed by the FNPO and serum AMH. Two distinct clusters of normo-ovulatory women with PCOM were isolated and differed solely by age, i.e. 'young' and 'old'. Both 'PCOM' clusters had their similarly aged counterpart of 'non-PCOM' clusters. Likewise, two clusters comprised women younger than 30 years, with (n = 28, 'PCOM regularly cycling women') or without (n = 118, 'normal regularly cycling women') features of PCOM (increased FNPO and/or serum AMH). The two other clusters in older women could be labelled 'normal regularly cycling women' or 'PCOM regularly cycling women' (n = 100 and 51, respectively). The prevalence of PCOM was significantly greater in old than in young regularly cycling women controls. In the young population, after exclusion of the 'PCOM regularly cycling women', the diagnostic performance of AMH, expressed by area under the curve (AUC) (AUC = 0.903; CI (0.876–0.930)) to differentiate PCOS women from normal regularly cycling women was similar to that using the FNPO (AUC = 0.915, CI (0.891–0.940)) (P = 0.25), confirming results from earlier studies. In the old population, the diagnostic performance of AMH was greater than that of FNPO (AUCs = 0.948 (0.927–	

		0.970) vs 0.874 (0.836–0.912), respectively, P = 0.00035). Cut-off levels of AMH and antral follicle count distinguishing regularly cycling non-PCOM women from PCOS women were higher in young women than in older women.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
PATIENT SELECTION/SPECTRUM BIAS	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	Studies that recruit a group of healthy controls and a group known to have the target disorder will be coded as "No" in most scenarios. Studies enrolling patients with known disease and control group without the condition may exaggerate diagnostic accuracy. Controls may not be routinely assessed for ovarian volume using ultrasound. The PCOS group is representative of those who will be assessed with these criteria in practice.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Not reported	No random element was described in the selection of participants into the study. The study methods describe that the Control group population was part of a large cohort of healthy females from four different original studies and the PCOS group population was prospectively recruited.
	Was a case-control design avoided? (Q-2)	No	Both the control group (regular cycling, normo-androgenic women) and group with known disease (PCOS) were identified and diagnosed prior or during study enrollment.
	Did the study avoid inappropriate exclusions? (Q-2)	Partial	Study methods describe that exclusions for the Control group are as follows: "these women were not using sex-steroids for at least 3 months prior to inclusion and never had ovarian surgery in the past." However, there are no details reported for the exclusion criteria for the PCOS group.
CLASSIFICATION/ VERIFICATION/ INCORPORATION/ REVIEW BIAS	Were all participants assessed with both index test and reference standard?	Yes	All participants in the Control group (n = 297) and PCOS group (n = 700) received the index test (FNPO) and PCOS patients were assessed using the NIH criteria.
	Did all patients receive the same reference standard? (Q-2)	Yes	All participants in the study received the same reference standard, which was the NIH diagnostic criteria for PCOS. For the Control group, the study mentions that it consisted of "women aged between 18 and 40 years with regular menstrual cycles and no clinical signs of HA and/or elevated testosterone levels…".
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Not reported	"HA was defined as serum testosterone levels higher than 3.0 nmol/l and/ or free androgen index (100 × serum testosterone [nmol/l]/sex hormone-binding globulin [nmol/l]) exceeding 4.5". However, it is unclear what definitions for oligo-anovulation was used for PCOS diagnosis (NIH criteria).
	Was the reference standard independent of the index test (ie. the index test did not form part of the reference standard)?	Yes	NIH criteria for the diagnosis of PCOS only includes the presence oligo-anovulation/anovulation and hyperandrogenism (clinical and/or biochemical). Sonographic markers of ovarian morphology are not part of the reference standard.
	Were the reference standard results interpreted without knowledge of the results of the index test?	No	Although only PCOS patients who met the NIH criteria were included in this study, diagnosis of all PCOS patients was conducted using the Rotterdam criteria. Therefore, reference standard would have been interpreted with knowledge of index test results during the recruitment process.
	Were the index test results	No	Although only PCOS patients who met the NIH criteria were included in this study, diagnosis of all PCOS patients was conducted using the Rotterdam

	interpreted without knowledge of the results of the reference standard test?		criteria. Therefore, index test would have been interpreted with knowledge of reference standard results during the recruitment process.
	If a threshold was used, was it pre-specified?	No	Study method describes that "Receiver operating characteristics curves (ROC) were constructed to examine the diagnostic performance of follicle count and serum AMH in discriminating PCOS patients from 'normal regularly cycling non-PCOM women'… Sensitivity (y-axis) against [1 − specificity (x-axis)] was plotted at each cut-off level and the area under the ROC curve (AUC) was computed by a non-parametric Wilcoxon test".
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?	Not reported	Although study methods describe that "serum samples were drawn during the follicular phase for assessment of FSH, AMH, oestradiol and testosterone" for the Control group, it is unclear whether the blood draw or physical examination were conducted at an appropriate interval with the ultrasound scan for both groups.
ATTRITION BIAS	Were withdrawals from the study explained?	Yes 100% treatment 100% control/ comparison u	Numbers described as enrolled are the same as those in results.
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Yes	There are no uninterruptable/intermediate test results and all results are reported.
OTHER ISSUES – APPLICABILITY/ COMPARABILITY/ VARIATION	Was the execution of all tests described in sufficient detail to permit replication of the tests?	No	The following description for the ultrasound examination in the control group was provided: "In all 297 women, weight and height were assessed and pelvic ultrasound was performed to assess the FNPO using a 5–7.5 mHz transvaginal probe." No description was provided for the ultrasound examination in the PCOS group.
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Yes	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Not reported	Study does not describe what clinical data was available during test result interpretation.
	Were there any conflicts of interest in the writing or funding of this study?	Yes	J.S.E.L. has received grants and support from Ferring, MSD, Organon, Merck-Serono, Schering Plough and Serono during recruitment and analysis of data for this study. S.L.F., A.D. and D. D. do not have any conflict of interest to disclose.
	If statistical analysis was undertaken, was this appropriate?	Partial	Study describes statistical analyses as: "Receiver operating characteristics curves (ROC) were constructed to examine the diagnostic performance of follicle count and serum AMH in discriminating PCOS patients from 'normal

			regularly cycling non-PCOM women'… Sensitivity (y-axis) against [1 − specificity (x-axis)] was plotted at each cut-off level and the area under the ROC curve (AUC) was computed by a non-parametric Wilcoxon test". However, unclear if an adequate sample size calculation was undertaken. A 4x4 table of test performance was not presented. For OV and FNPS, sensitivity and specificity data were provided but not AUC.
COMMENTS			
What is the overall risk of bias?		High	Few criteria have been fulfilled and the conclusions of the study are likely to be affected.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No. All outcomes had the same risk of bias.	

Study ID	Lujan 2013
Study Citation	Lujan, M. E. et al. (2013). "Updated ultrasound criteria for polycystic ovary syndrome: reliable thresholds for elevated follicle population and ovarian volume." Human Reproduction 28(5): 1361-1368.
Study Country	USA/Canada
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	Control: Study participants were recruited from the general population using ads seeking healthy women of reproductive age or women with concerns over outward features of PCOS such as irregular periods, excess hair growth, obesity and/or infertility. Women from the general population aged 18-35 with regular menstrual cycles and no hyperandrogenism were included for the Control Group. PCOS: Study participants were recruited from the general population using ads seeking healthy women of reproductive age or women with concerns over outward features of PCOS such as irregular periods, excess hair growth, obesity and/or infertility. Women aged 18-35 diagnosed with PCOS by the National Institutes of Health criteria as having both oligo-amenorrhea and hyperandrogenism were recruited to the study. Age (yo): Control: 27 (23–35), PCOS: 28 (25 –32) p = 0.204 BMI (kg/m^2): Control: 23.9 (22.0–27.5), PCOS: 30.1 (23.7 –37.3) p < 0.001
PCOS diagnostic criteria	NIH
N per group	Control: 70 PCOS: 98
Setting	Human Metabolic Research Unit at Cornell University of Ithaca, USA between 2009 and 2011 Royal University Hospital at University of Saskatchewan of Saskatoon, Canada between 2006 and 2008
Index test	Follicle Number Per Ovary (FNPO – Mean) Ovarian Volume (OV – Mean) Follicle Number Per Cross-Section (FNPS – Mean)
Reference Standard	NIH criteria (oligo-anovulation, hyperandrogenism)

Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)		Accuracy to diagnose PCOS Sensitivity and specificity Area under the ROC curve Proposed threshold	
Inclusion and exclusion criteria reported?		Yes	Inclusion Criteria: Control: Study participants were recruited from the general population using ads seeking healthy women of reproductive age or women with concerns over outward features of PCOS such as irregular periods, excess hair growth, obesity and/or infertility. Women from the general population aged 18-35 with regular menstrual cycles and no hyperandrogenism were included for the Control Group. PCOS: Study participants were recruited from the general population using ads seeking healthy women of reproductive age or women with concerns over outward features of PCOS such as irregular periods, excess hair growth, obesity and/or infertility. W omen aged 18-35 diagnosed with PCOS by the National Institutes of Health criteria as having both oligo-amenorrhea and hyperandrogenism were recruited to the study. Exclusion criteria: Both groups could not have used hormonal contraception, fertility medications or insulin sensitizers in the 3 months prior to enrollment. Participants were ineligible if they had a previous history of ovarian surgery or current abnormalities in cortisol, prolactin, thyroid hormone, dehydroepiandrosterone sulfate or 17-hydroxyprogesterone secretion.
Does the study have a clearly focused question?		Partial	Do the ultrasonographic criteria for polycystic ovaries supported by the 2003 Rotterdam consensus adequately discriminate between the normal and polycystic ovary syndrome (PCOS) condition in light of recent advancements in imaging technology and reliable methods for estimating follicle populations in PCOS?
Summary Result/s		Diagnostic potential for PCOS was highest for FNPO (0.969), followed by FNPS (0.880) and OV (0.873) as judged by the area under the ROC curve. An FNPO threshold of 26 follicles had the best compromise between sensitivity (85%) and specificity (94%) when discriminating between controls and PCOS. Similarly, an FNPS threshold of nine follicles had a 69% sensitivity and 90% specificity, and an OV of 10 cm3 had a 81% sensitivity and 84% specificity. Levels of intra-observer reliability were 0.81, 0.80 and 0.86 when assessing FNPO, FNPS and OV, respectively. Inter-observer reliability was 0.71, 0.72 and 0.82, respectively.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
PATIENT SELECTION/SPECTRUM BIAS	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	Studies that recruit a group of healthy controls and a group known to have the target disorder will be coded as “No” in most scenarios. Studies enrolling patients with known disease and control group without the condition may exaggerate diagnostic accuracy. Controls may not be routinely assessed for ovarian volume using ultrasound. The PCOS group is representative of those who will be assessed with these criteria in practice.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Not reported	No random element was described in the selection of participants into the study. Study is described as a cross-sectional study.
	Was a case-control design avoided? (Q-2)	No	Both the control group (regular cycling, normo-androgenic women) and group with known disease (PCOS) were identified and diagnosed prior or during study enrollment.
	Did the study avoid inappropriate exclusions? (Q-2)	Yes	The exclusion criteria for the study are appropriate. Study methods describe that participants “could not have used hormonal contraception, fertility medications or insulin sensitizers in the 3 months prior to enrollment. Participants were ineligible

			if they had a previous history of ovarian surgery or current abnormalities in cortisol, prolactin, thyroid hormone, dehydroepiandrosterone sulfate or 17-hydroxyprogesterone secretion".
CLASSIFICATION/ VERIFICATION/ INCORPORATION/ REVIEW BIAS	Were all participants assessed with both index test and reference standard?	Yes	All participants in the Control group (n = 70) and PCOS group (n = 98) received all three index tests (FNPS, OV, FNPO).
	Did all patients receive the same reference standard? (Q-2)	Yes	All participants in the study received the same reference standard, which was the equivalent of the NIH diagnostic criteria for PCOS. For the Control group, the study mentions that it consisted of "women from the general population [aged 18-35] with regular menstrual cycles and no hyperandrogenism".
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	PCOS diagnosis was conducted using the 1990 NIH criteria, which includes the presence of "both oligo-amenorrhea and hyperandrogenism…". Specifically, "oligo-amenorrhea was defined as a history of unpredictable menstrual cycles shorter than 21 days or longer than 36 days. Hyperandrogenism was defined as a modified hirsutism score ≥7 (internally validated value having a 83% sensitivity and 96% specificity to distinguish between PCOS and controls) and/or an elevated total testosterone value ≥3.96 nmol/l (internally validated value having a 87% sensitivity and 100% specificity to distinguish between PCOS and controls)".
	Was the reference standard independent of the index test (ie. the index test did not form part of the reference standard)?	Yes	NIH criteria for the diagnosis of PCOS only includes the presence oligo-anovulation/anovulation and hyperandrogenism (clinical and/or biochemical). Sonographic markers of ovarian morphology are not part of the reference standard.
	Were the reference standard results interpreted without knowledge of the results of the index test?	Not reported	Method description does not describe the timing of the reference standard in relation to the index test results.
	Were the index test results interpreted without knowledge of the results of the reference standard test?	Not reported	Method description does not describe the timing of the index test in relation to the reference standard.
	If a threshold was used, was it pre-specified?	No	Study method describes that "accuracy of FNPO, FNPS and OV to discriminate between PCOS and controls was evaluated using a receiver operating characteristic (ROC) curve analysis… Diagnostic thresholds for FNPO, FNPS and OV were proposed based on Youden's index, which balanced maximum test sensitivity and test specificity".
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?	Not reported	Method description does not describe the timing of the reference standard in relation to the index test results.

ATTRITION BIAS	Were withdrawals from the study explained?	Yes 100% treatment 100% control/ comparison u	Numbers described as enrolled are the same as those in results.
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Yes	There are no uninterruptable/intermediate test results and all results are reported.
OTHER ISSUES – APPLICABILITY/ COMPARABILITY/ VARIATION	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	The following description was provided for the ultrasound examination: "Participants were evaluated by transvaginal ultrasonography by two experienced ultrasonographers. Control subjects were scanned on Days 2 – 5 of the menstrual cycle and women with PCOS were scanned at an unspecified time. Images were included for analysis if there was an absence of a dominant follicle (≥10 mm) and corpus luteum. Ovaries were scanned from their inner to outer margins in the longitudinal plane using a 5 – 9-MHz transducer on an Ultrasonix RP System (Version 2.3.5, Vancouver, BC, Canada) or a 6 – 12-MHz transducer on a GE Voluson E8 System (GE Healthcare, Milwaukee, WI, USA). Digital cineloops throughout each ovary (DICOM file format) and static images of the largest cross-sectional view of each ovary (JPEG file format) were digitally archived for off-line analysis. Ultrasound images of each ovary were analyzed using Santesoft DICOM Editor software (Emmanouil Kanellopoulus, Athens, Greece) for the following parameters: (i) FNPO, (ii) FNPS and (iii) OV. Reliable follicle counts were achieved for each ovary by imposing a programmable grid system onto the viewing window (Fig. 1) as previously described (Lujan et al., 2010a). Based on an intra-class correlation coefficient analysis, the level of inter-observer agreement for FNPO and FNPS by three observers was 0.84 and 0.94, respectively. OV was estimated using the equation: p/6 (transverse diameter) × (anteroposterior diameter) × (longitudinal diameter). The level of inter-observer agreement for OV by three observers was 0.96. A value for FNPO, FNPS and OV for each participant was designated as the mean recorded values."
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	No	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Not reported	
	Were there any conflicts of interest in the writing or funding of this study?	No	Authors stated that there were no conflicts of interest to disclose.
	If statistical analysis was undertaken, was this appropriate?	Partial	Study method describes that "accuracy of FNPO, FNPS and OV to discriminate between PCOS and controls was evaluated using a receiver operating characteristic (ROC) curve analysis… Diagnostic thresholds for FNPO, FNPS and OV were proposed based on Youden's index, which balanced maximum test sensitivity and test specificity".

			However, unclear if an adequate sample size calculation was undertaken. A 4x4 table of test performance was not presented. Sensitivity, specificity, and Youden's J were provided but not AUC.
COMMENTS			
What is the overall risk of bias?		Moderate	Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No. All outcomes had the same risk of bias.	

Study ID	Özay 2022
Study Citation	Özay, Ö.E. et al. (2022). "Comparison of stromal thickness and doppler findings in polycystic ovary syndrome and healthy women with ultrasonographic evidence of polycystic ovaries? A cross-sectional study." Journal of Obstetrics and Gynaecology 1-6.
Study Country	Cyprus
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	Control: NOM group consisted from healthy women with regular cycles and normal initial baseline transvaginal ultrasound imaging without any gynecological symptoms and fertility problems. PCOS: Participants were selected among patients who met the inclusion criteria, applied to the gynaecology clinic for any gynecological reason and had gone under transvaginal ultrasonography. A detailed medical and gynecological history was obtained for all the women in the study. The diagnosis of PCOS was made in accordance with criteria from Rotterdam Consensus. The polycystic ovarian morphology was defined according to the Rotterdam criteria. Hirsutism was defined as Ferriman-Gallwey score (FGS) ≥8. Age (yo): Control: 22.00 (3.25), PCOM: 22.00 (4.00), PCOS: 21.00 (3.00) p = 0.443 BMI (kg/m^2): Control: 21.01 (4.10), PCOM: 20.90 (5.09), PCOS: 23.05 (6.09) p = 0.005
PCOS diagnostic criteria	Rotterdam
N per group	PCOS: 106 PCOM: 68 Control: 46
Setting	Department of Obstetrics and Gynaecology at Near East University Hospital, Faculty of Medicine, Nicosia, Cyprus between March 2018 and May 2019.
Index test	Stromal Thickness (Median – Left) Stromal Thickness (Median – Right)
Reference Standard	Rotterdam (oligo-anovulation, hyperandrogenism, PCOM)
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Accuracy to diagnose PCOS Sensitivity and specificity Area under the ROC curve

Inclusion and exclusion criteria reported?		Yes	Inclusion Criteria: Control: All healthy women in NOM group have regular cycles and normal initial baseline transvaginal ultrasound imaging without any gynecological symptoms and fertility problems. PCOS: The diagnosis of PCOS was made in accordance with criteria from Rotterdam Consensus. The polycystic ovarian morphology was defined according to the Rotterdam criteria. Hirsutism was defined as Ferriman-Gallwey score (FGS) ≥8. Exclusion Criteria: All groups: Age over 35 years, current pregnancy, hyperprolactinaemia, thyroid disease, congenital adrenal hyperplasia, a history of ovarian surgery, any other systemic disease or drugs that could influence hypothalamic pituitary ovarian axis, androgen production, insulin and or/glycemic metabolism, patients who received any hormone therapy including contraceptives up to 6 months before study. The presence of any ovarian lesion, ovarian cyst or follicle greater than 10 mm were also considered as exclusion criteria.
Does the study have a clearly focused question?		Yes	How does the ovarian stromal blood flow and stromal thickness (ST) of polycystic ovary syndrome (PCOS) patients compare with healthy women with polycystic ovarian morphology (PCOM) and normal ovarian morphology (NOM)?
Summary Result/s		There is no statistically significant difference between PCOM women and healthy women in ovarian stromal thickness, doppler findings, clinical and hormonal status. Ovarian stromal blood flow and ovarian stromal thickness increased statistically significantly in PCOS patients compared to healthy women. Based on the ROC analysis and statistical results, it can be recommended that ovarian ST and/or S/A ratio may be an ultrasonograpic indicator of FAI, and may be used in PCOS diagnostic criterias in the future.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
PATIENT SELECTION/SPECTRUM BIAS	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	Studies that recruit a group of healthy controls and a group known to have the target disorder will be coded as “No” in most scenarios. Studies enrolling patients with known disease and control group without the condition may exaggerate diagnostic accuracy. Controls may not be routinely assessed for ovarian volume using ultrasound. The PCOS group is representative of those who will be assessed with these criteria in practice.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Not reported	No random element was described in the selection of participants into the study. Authors describe that “participants were selected among patients who met the inclusion criteria, applied to the gynaecology clinic for any gynecological reason and had gone under transvaginal ultrasonography”.
	Was a case-control design avoided? (Q-2)	No	Patients were categorized as PCOS, PCOM and controls upon enrollment. PCOS patients were selected for the PCOS group due to their diagnosis using the Rotterdam criteria. The controls were selected as they had regular cycles and normal initial baseline transvaginal ultrasound imaging without any gynecological symptoms and fertility problems.
	Did the study avoid inappropriate exclusions? (Q-2)	Yes	The exclusion criteria were considered appropriate. The criteria included: “age over 35 years, current pregnancy, hyperprolactinaemia, thyroid disease, congenital adrenal hyperplasia, a history of ovarian surgery, any other systemic disease or drugs that could influence hypothalamic pituitary ovarian axis, androgen production, insulin and or/glycemic metabolism, patients who received any hormone therapy including contraceptives up to 6 months before study. The presence of any ovarian lesion, ovarian cyst or follicle greater than 10 mm were also considered as exclusion criteria.”

CLASSIFICATION/ VERIFICATION/ INCORPORATION/ REVIEW BIAS	Were all participants assessed with both index test and reference standard?	Yes	All participants in the Control group (n=46) and PCOS group (n=106) received the index test (stromal thickness).
	Did all patients receive the same reference standard? (Q-2)	Yes	For the Control group, patients had "all healthy women in NOM group have regular cycles and normal initial baseline transvaginal ultrasound imaging without any gynecological symptoms and fertility problems".
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Not reported	Study describes diagnosis of PCOS via Rotterdam criteria as follows: "The diagnosis of PCOS was made in accordance with criteria from Rotterdam Consensus (ESHRE/ASRM 2004). The polycystic ovarian morphology was defined according to the Rotterdam criteria (ESHRE/ASRM 2004)… Hirsutism was defined as Ferriman-Gallwey score (FGS) ≥ 8". However, it is unclear how authors define oligo-anovulation and biochemical hyperandrogenism.
	Was the reference standard independent of the index test (ie. the index test did not form part of the reference standard)?	Yes	Rotterdam criteria was used, however, stromal thickness is not part of the reference standard (PCOM).
	Were the reference standard results interpreted without knowledge of the results of the index test?	Not reported	Study method describes that "the examiner was blinded to clinical data and hormonal status of all the women" when evaluating the index test. However, it is unclear when the reference standard was determined relative to the index test.
	Were the index test results interpreted without knowledge of the results of the reference standard test?	Yes	Rotterdam criteria was used for PCOS diagnosis. However, it was noted that the "the examiner was blinded to clinical data and hormonal status of all the women" and therefore the index test was evaluated without knowledge of their phenotype.
	If a threshold was used, was it pre-specified?	No	Stromal thickness is not part of Rotterdam criteria, and therefore there were no pre-specified thresholds available. Study describes statistical analyses as follows: "in the diagnosis of PCOS, receiver operating characteristic (ROC) analysis was performed for laboratory and ultrasonographic findings that were statistically significant ($p < .001$) between PCOS vs. PCOM and NOM".
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?	Not reported	Ultrasound was completed between certain hours of the day, not by menstrual cycle. Although it is mentioned that "all peripheral blood samples were taken after an overnight fasting within first 5 days of the menstrual cycle", it is unclear if the index test was conducted at a reasonable time compared to the reference standard.
ATTRITION BIAS	Were withdrawals from the study explained?	Yes 100% treatment 100% control/ comparison	Numbers described as enrolled are the same as those in results.

REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Yes	There are no uninterruptable/intermediate test results and all results are reported.
OTHER ISSUES – APPLICABILITY/ COMPARABILITY/ VARIATION	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	Authors provided the following description of the ultrasound examination: "All doppler ultrasound examinations were performed between 8.00 am and 11.00 am to exclude the effects of the circadian rhythmicity on ovarian blood flows by the same gynaecologist (A.C.O) using Voluson 730 Expert ultrasound machine equipped with a 7–9 MHz transvaginal transducer. The examiner was blinded to clinical data and hormonal status of all the women. Patients rested in a waiting room for at least 15 min before being scanned and completely emptied their bladders, in order to minimize the external effects on blood flow. Maximum ST of both ovaries were measured perpendicularly at the thickest region of ovarian stroma."
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Yes	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Not reported	Study does not describe what clinical data was available during test result interpretation.
	Were there any conflicts of interest in the writing or funding of this study?	No	Authors stated that there were no conflicts of interest to disclose.
	If statistical analysis was undertaken, was this appropriate?	Partial	Statistical analyses were described as follows: "in the diagnosis of PCOS, receiver operating characteristic (ROC) analysis was performed for laboratory and ultrasonographic findings that were statistically significant ($p < .001$) between PCOS vs. PCOM and NOM". However, unclear if an adequate sample size calculation was undertaken. A 4x4 table of test performance was not presented.
COMMENTS			
What is the overall risk of bias?		Moderate	Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No. All outcomes had the same risk of bias.	

Study ID	Villa 2013
Study Citation	Villa, P. et al. (2013). "Ovarian volume and gluco-insulinaemic markers in the diagnosis of PCOS during adolescence." Clinical Endocrinology 78(2): 285-290.
Study Country	Italy

EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	All subjects had a spontaneous onset of puberty and normal sexual development. They were euthyroid and none had had any medications that might affect plasma sex steroids for at least 3 months before the study. Control: Healthy normo-ovulatory adolescent girls, attending our service for Human Papilloma Virus (HPV) vaccination, were studied as a control group; the length of cycle in these subjects was 26.8 ± 2.5 days. PCOS: Aged 13–18 years with more than 2 years of gynaecological age. PCOS was ascertained by the presence of clinical or biochemical evidence of hyperandrogenism and chronic anovulation, with the exclusion of other known disorders, following the National Institute of Health (NIH) criteria (where ovarian volume and morphology was not a diagnostic criterion). The presence of acne and hirsutism was assessed. The Ferriman-Gallwey (FG) score was used to determine the grade of hirsutism. On the base of this method, four hirsutism levels were identified: score <8, no hirsutism; score of 8–16, low hirsutism; score of 17–25, moderate hirsutism; score >25, severe hirsutism. Nonclassical 21-hydroxylase deficiency, hyperprolactinaemia, and androgen secreting tumours were excluded by appropriate tests before the diagnosis of PCOS was made. The menstrual patterns were defined according to Van Hooff et al.: regular cycles: length of cycle between 21 and 42 days; irregular cycles-oligomenorrhoea: length of cycle between 42 and 180 days; polymenorrhoea: length of cycle 21 days or less; amenorrhoea: absence of menstruation for 180 days or more. Age (yo): Control: 15.3 ± 1.7, PCOS: 15.7 ± 1.4 p = not significant BMI (kg/m^2): Control: 23.9 ± 4.9, PCOS: 25.7 ± 5.4 p = not significant	
PCOS diagnostic criteria	NIH	
N per group	PCOS: 86 Control: 48	
Setting	Outpatient Paediatric and Gynecology Department of Catholic University of Sacred Heart starting July 2009	
Index test	Ovarian Volume (OV)	
Reference Standard	NIH criteria (oligo-anovulation, hyperandrogenism)	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Accuracy to diagnose PCOS Sensitivity and specificity Area under the ROC curve Proposed threshold	
Inclusion and exclusion criteria reported?	Partial	Inclusion Criteria: Both groups: All subjects had a spontaneous onset of puberty and normal sexual development. They were euthyroid and none had had any medications that might affect plasma sex steroids for at least 3 months before the study. Control: Healthy normo-ovulatory adolescent girls, attending our service for Human Papilloma Virus (HPV) vaccination. PCOS: Aged 13–18 years with more than 2 years of gynaecological age. PCOS was ascertained by the presence of clinical or biochemical evidence of hyperandrogenism and chronic anovulation, with the exclusion of other known disorders, following the National Institute of Health (NIH) criteria (where ovarian volume and morphology was not a diagnostic criterion). The presence of acne and hirsutism was assessed. The Ferriman-Gallwey (FG) score was used to determine the grade of hirsutism. On the base of this method, four hirsutism levels were identified: score <8, no hirsutism; score of 8–16, low hirsutism; score of 17–25, moderate hirsutism; score >25, severe

			hirsutism. The menstrual patterns were defined according to Van Hooff et al.: regular cycles: length of cycle between 21 and 42 days; irregular cycles-oligomenorrhoea: length of cycle between 42 and 180 days; polymenorrhoea: length of cycle 21 days or less; amenorrhoea: absence of menstruation for 180 days or more. Exclusion Criteria: Control: Not available PCOS: Nonclassical 21-hydroxylase deficiency, hyperprolactinaemia, and androgen secreting tumours were excluded by appropriate tests before the diagnosis of PCOS was made.
Does the study have a clearly focused question?		Yes	What is the role of mean ovarian volume (MOV) in the diagnosis of polycystic ovary syndrome (PCOS) during adolescence?
Summary Result/s		Androgens, free androgen index (FAI), LH and insulin resistance indexes were higher in the PCOS group. MOV was significantly different between the two groups: control group 4.6 ± 1.9 cm^3, adolescent PCOS group 9.6 ± 4.4 cm^3. The MOV threshold of 5.596 cm^3 offered the best compromise between sensitivity and specificity based on the characteristics of the operating receiver curve analysis. Therefore, an ovarian volume higher than 5.6 increased the risk of PCOS by about 15 times (OR 16.25 IC 95% 6.3–41.3). In adolescent PCOS girls, the ovarian volume was significantly associated with circulating testosterone and insulin, and indices of insulin resistance.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
PATIENT SELECTION/SPECTRUM BIAS	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	
	Was a consecutive or random sample of patients enrolled? (Q-2)	Not reported	No random element was described in the selection of participants into the study. Patients were enrolled based on location and date of admission. Study was described as an observational study.
	Was a case-control design avoided? (Q-2)	No	Both the control group (regular cycling women) and group with known disease (PCOS) were identified and diagnosed prior or during study enrollment.
	Did the study avoid inappropriate exclusions? (Q-2)	Not reported	The exclusion criteria for PCOS were “nonclassical 21-hydroxylase deficiency, hyperprolactinaemia, and androgen secreting tumours.” However, the exclusion criteria for the Control group were not described.
CLASSIFICATION/ VERIFICATION/	Were all participants assessed with both index test and reference standard?	Yes	All participants in the Control group (n=48) and PCOS group (n=86) received the index tests.
	Did all patients receive the same reference standard? (Q-2)	Not reported	The control population was included were described as “normo-ovulatory”. However, it is unclear whether hyperandrogenism was also evaluated in line with NIH criteria.
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Partial	Study describes diagnosis of PCOS as “the presence of clinical or biochemical evidence of hyperandrogenism and chronic anovulation, with the exclusion of other known disorders, following the National Institute of Health (NIH) criteria… The presence of acne and hirsutism was assessed. The Ferriman-Gallwey (FG) score was used to determine the grade of hirsutism. On the base of this method, four hirsutism levels were identified: score <8, no hirsutism; score of 8–16, low hirsutism; score of 17–25, moderate hirsutism; score >25, severe hirsutism… The menstrual patterns were defined according to Van Hooff et al.11: regular cycles: length of cycle between 21 and 42 days; irregular cycles-oligomenorrhoea: length of cycle between 42 and 180 days; polymenorrhoea: length of cycle 21 days or less; amenorrhoea: absence of menstruation for 180 days or more.”

			It should be noted that no definitions for biochemical hyperandrogenism was described but not necessary to satisfy PCOS diagnostic criteria.
	Was the reference standard independent of the index test (ie. the index test did not form part of the reference standard)?	Yes	NIH criteria for the diagnosis of PCOS only includes the presence oligo-anovulation/anovulation and hyperandrogenism (clinical and/or biochemical). Sonographic markers of ovarian morphology are not part of the reference standard.
	Were the reference standard results interpreted without knowledge of the results of the index test?	Not reported	Method description does not describe the timing of the reference standard in relation to the index test results.
	Were the index test results interpreted without knowledge of the results of the reference standard test?	Not reported	Method description does not describe the timing of the index test in relation to the reference standard.
	If a threshold was used, was it pre-specified?	No	Authors describe that "In young women, in order to evaluate the ability of the MOV to predict PCOS, the cut-off value coming from ROC curves was analysed by means of the Chi-Squared test and the Odds Ratio was computed."
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?	Not reported	Study describes that "Studies were conducted during the early follicular phase, at day 3–5 of a spontaneous or induced menstrual cycle. Furthermore, in order to ascertain that ovulation had not occurred recently, the progesterone plasma level was measured on the day of the study. Patients attending the day hospital underwent a gynaecological and medical examination. The hormonal study included a baseline plasma determination of LH, FSH, E2, Androstenedione (A), Testosterone (T), 17-hydroxy-progesterone (17-OHP) and sex-hormone-binding globulin (SHBG)… Ultrasound examinations were performed on the same day as the baseline hormonal determination." However, it remains uncertain the timing of the reference standard to the index test.
ATTRITION BIAS	Were withdrawals from the study explained?	Yes 100% treatment 100% control/ comparison	Numbers described as enrolled are the same as those in results.
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Yes	There are no uninterruptable/intermediate test results and all results are reported.
	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	Authors provided the following description of the ultrasound examination: "Ultrasound examinations were performed on the same day as the baseline hormonal determination. The trans abdominal ultrasound (TAUS) was performed on each adolescent patient using a 35–5 MHz convex probe (MyLab25Gold; Esaote, Milan, Italy). Ovarian volume was calculated for each ovary in cubic centimetres, using the ellipse formula: 0.5 9 (D1 9 D2 9 D3), where D represented the maximum diameter in transverse, antero-posterior and long section. Two different operators performed the US examinations. We verified that the inter-observer variation did not exceed 3% in

OTHER ISSUES – APPLICABILITY/ COMPARABILITY/ VARIATION			all measurements. The MOV determination was the average of the observed values of both the left and right ovary volume = (left ovarian volume + right ovarian volume)/2. If on ultrasound examination there was a follicle in excess of 10 mm in diameter, the ultrasound scan had to be repeated."
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Yes	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Not reported	Study does not describe what clinical data was available during test result interpretation.
	Were there any conflicts of interest in the writing or funding of this study?	No	Authors stated that there were no conflicts of interest to disclose.
	If statistical analysis was undertaken, was this appropriate?	Partial	Study describes that "The ROC (receiver operator characteristic) curves were constructed to examine the diagnostic test performance not only for MOV but also for insulin and glucose metabolic indexes. In a ROC curve, the true-positive rate (sensitivity) is plotted as a function of the false-positive rate (specificity) for different cutoff points. Each point in the ROC plot represents a sensitivity/ specificity pair corresponding to a particular threshold. A test with perfect discrimination has a ROC plot that passes through the upper left corner (100% sensitivity and specificity); the closer the ROC plot is to the upper left corner the greater is the overall accuracy of the test... In young women, in order to evaluate the ability of the MOV to predict PCOS, the cut-off value coming from ROC curves was analysed by means of the Chi-Squared test and the Odds Ratio was computed." However, unclear if an adequate sample size calculation was undertaken. A 4x4 table of test performance was not presented.
COMMENTS			
What is the overall risk of bias?		High	Few criteria fulfilled and the conclusions of the study are likely to be affected.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No. All outcomes had the same risk of bias.	

Study ID	Villaroel 2015
Study Citation	Villarroel, C. et al. (2015). "Hirsutism and oligomenorrhea are appropriate screening criteria for polycystic ovary syndrome in adolescents." Gynecological Endocrinology 31(8): 625-629.
Study Country	Chile
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	Control: Non-hirsute girls (FG score ≤6) with regular menses (cycle length between 21 and 45 days) were recruited as Control Group (C) from nearby schools. All the C girls who were 6 years past menarche had menstrual cycles less than 35 days.

	PCOS: Girls who were at least 1 year past menarche and 20 years of age. Girls exhibited oligomenorrhea and hirsutism (Hirs/Oligo). Hirsutism (Ferriman– Gallwey [FG] scores ≥8). Oligomenorrhea: persistent menstrual cycle lengths equal ≥45 days. The Hirs/Oligo girls were recruited in the gynecological and pediatric endocrinology clinics of San Borja Arriaran Hospital. Twenty-two girls of the Hirs/Oligo girls were naïve for treatment. Four girls ceased medication at least two months prior to recruitment. Age (yo): Control: 16.6 ± 1.5, PCOS: 17.3 ± 1.9 p = not significant BMI-SDS: Control: 0.4 ± 0.8, PCOS: 1.0 ± 1.0 p = not significant	
PCOS diagnostic criteria	NIH	
N per group	PCOS: 26 Control: 63	
Setting	Gynecological and pediatric endocrinology clinics of San Borja Arriaran Hospital of Santiago, Chile	
Index test	Follicle Number Per Ovary (FNPO – Maximum) Ovarian Volume (OV – Maximum)	
Reference Standard	NIH criteria (oligo-anovulation, hyperandrogenism)	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Accuracy to diagnose PCOS Sensitivity and specificity Area under the ROC curve Proposed threshold	
Inclusion and exclusion criteria reported?	Yes	Inclusion Criteria: Control: Non-hirsute girls (FG score ≤6) with regular menses (cycle length between 21 and 45 days) were recruited as Control Group (C) from nearby schools. All the C girls who were 6 years past menarche had menstrual cycles less than 35 days. PCOS: Girls who were at least 1 year past menarche, 20 years of age and exhibited oligomenorrhea and hirsutism (Hirs/Oligo). Hirsutism (Ferriman–Gallwey [FG] scores ≥8). Oligomenorrhea: persistent menstrual cycle lengths equal ≥45 days. Exclusion Criteria: Control: Girls with severe acne, obesity, premature pubarche or intrauterine growth retardation. Pregnancy during the previous 6 months, sex steroid usage, abnormal thyroid function or prolactin levels, or chronic conditions such as genetic syndromes, celiac disease, renal, liver, or cardiac disease, or undernourishment. PCOS: Pregnancy during the previous 6 months, sex steroid usage, abnormal thyroid function or prolactin levels, or chronic conditions such as genetic syndromes, celiac disease, renal, liver, or cardiac disease, or undernourishment.
Does the study have a clearly focused question?	Yes	What is the association of hirsutism and oligomenorrhea (persistent menstrual cycles >45 days) as screening criteria for the detection of biochemical hyperandrogenism (BH) and polycystic ovaries (PCOM) during adolescence?
Summary Result/s	BH and PCOM prevalence were higher in the Hirs/Oligo girls than in the C girls (76.9% versus 25.5%; 92.3% versus 33.3%, respectively; p<0.0001). The parameters with the best diagnostic performance were free androgen index ≥6.1, testosterone ≥2.4 nmol/L, follicle number ≥12 and ovarian volume ≥10 ml anti-Mullerian hormone (AMH) exhibited a low diagnostic accuracy.	

		Hirsutism and persistent menstrual cycle over 45 days are highly associated with BH and PCOM suggesting that the presences of both criteria are necessary for the diagnosis of PCOS during adolescence.	
INTERNAL VALIDITY – HAS THIS STUDY B EEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
PATIENT SELECTION/SPECTRUM BIAS	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	Studies that recruit a group of healthy controls and a group known to have the target disorder will be coded as "No" in most scenarios. Studies enrolling patients with known disease and control group without the condition may exaggerate diagnostic accuracy. Controls may not be routinely assessed for ovarian volume using ultrasound. The PCOS group is representative of those who will be assessed with these criteria in practice.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Not reported	No random element was described in the selection of participants into the study. Participants were enrolled based on location (hospital and nearby schools).
	Was a case-control design avoided? (Q-2)	No	Both the control group (regular cycling, non-hirsute women) and group with known disease (PCOS) were identified and diagnosed prior or during study enrollment. They also originated from different locations and were allocated to specific groups accordingly.
	Did the study avoid inappropriate exclusions? (Q-2)	Yes	The exclusion criteria were considered appropriate. The exclusion criteria included: pregnancy during the previous 6 months, sex steroid usage, abnormal thyroid function or prolactin levels, or chronic conditions such as genetic syndromes, celiac disease, renal, liver, or cardiac disease, undernourishment, severe acne, obesity, premature pubarche or intrauterine growth retardation.
CLASSIFICATION/ VERIFICATION/ INCORPORATION/ REVIEW BIAS	Were all participants assessed with both index test and reference standard?	Yes	All participants in the Control group (n = 63) and PCOS group (n = 26) received the index tests (OV, FNPO).
	Did all patients receive the same reference standard? (Q-2)	Yes	All participants in the study received the same reference standard, which was the NIH diagnostic criteria for PCOS. For the Control group, the study mentions that non-hirsute girls with regular menses.
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	PCOS diagnosis was determined using the NIH criteria. Specifically, "Hirsutism (Ferriman Gallwey [FG] scores ≥8). Oligomenorrhea: persistent menstrual cycle lengths equal ≥45 days."
	Was the reference standard independent of the index test (ie. the index test did not form part of the reference standard)?	Yes	NIH criteria for the diagnosis of PCOS only includes the presence oligo-anovulation/anovulation and hyperandrogenism (clinical and/or biochemical). Sonographic markers of ovarian morphology are not part of the reference standard.
	Were the reference standard results interpreted without knowledge of the results of the index test?	Not reported	Method description does not describe the timing of the reference standard in relation to the index test results.

	Were the index test results interpreted without knowledge of the results of the reference standard test?	Not reported	Method description does not describe the timing of the index test in relation to the reference standard.
	If a threshold was used, was it pre-specified?	No	Study describes that "Receiver operating characteristic (ROC) analysis was used to determine the ability of hormonal markers and cut-off values to diagnose PCOS. Differences between ROCs were analyzed according to the method described by Hanley and McNeil".
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?	Not reported	Authors describe that "clinical evaluations, blood sampling and ultrasonographic examinations were performed during early follicular phase". However, details of the timing between the reference standard and index test are unclear.
ATTRITION BIAS	Were withdrawals from the study explained?	Yes 100% treatment 100% control/ comparison	Numbers described as enrolled are the same as those in results.
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Yes	There are no uninterruptable/intermediate test results and all results are reported.
OTHER ISSUES – APPLICABILITY/	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	Authors provided the following description of the ultrasound examination: "TA-US was performed during the follicular phase (days 1–7 of the cycle) by a single observer on the same day that the blood sample was obtained. The exam was performed with a 5-MHz transabdominal probe using a Medison SonoAce 6000C. Measurements were performed in real time, using the highest possible magnification to view the ovaries. The longest medial axis (length) and its corresponding thickness and width were measured to calculate OV. OV was estimated according to the formula for a prolate ellipsoid: OV = π/6 × length × width × thickness. The FN was established by scanning each ovary from the inner to the outer margins in a longitudinal cross-section. Follicle diameter was obtained from the mean of the maximum and its corresponding perpendicular diameter. All follicles between 2.0 and 9.0 mm were counted. Then, the numbers of follicles measuring between 2–5 mm and 6–9 mm were determined. The intra-observer variation coefficients of the ultrasonographic study were 3.2 and 4.1% for OV and FN, respectively. In cases where a dominant cyst/follicle larger than 10 mm was observed, the ultrasonographic exam was repeated in the following menstrual cycle. The ovary with the larger OV and the number of follicles of the ovary with the larger FN was reported."
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Yes	
	Were the same clinical data available when test results were interpreted	Not reported	Study does not describe what clinical data was available during test result interpretation.

	as would be available when the test is used in practice?		
	Were there any conflicts of interest in the writing or funding of this study?	No	Authors stated that there were no conflicts of interest to disclose.
	If statistical analysis was undertaken, was this appropriate?	Partial	Study describes that "Receiver operating characteristic (ROC) analysis was used to determine the ability of hormonal markers and cut-off values to diagnose PCOS. Differences between ROCs were analyzed according to the method described by Hanley and McNeil". However, unclear if an adequate sample size calculation was undertaken. A 4x4 table of test performance was not presented.
COMMENTS			
What is the overall risk of bias?		Moderate	Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No. All outcomes had the same risk of bias.	

Study ID	Wongwananuruk 2018
Study Citation	Wongwananuruk, T. et al. (2018). "Accuracy of anti-Müllerian hormone and total follicles count to diagnose polycystic ovary syndrome in reproductive women." Taiwanese Journal of Obstetrics and Gynecology 57(4): 499-506.
Study Country	Thailand
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	Control: Normal ovulatory, non-hyperandrogenic women aged 18-45 years old. They had to have regular menstrual cycle with interval of 21-35 days and no clinical and biochemical hyperandrogenism. PCOS: Women 18-45 years of age, who diagnosed with PCOS by the Revised Rotterdam Criteria 2003 as having both 1) oligo-anovulation and 2) clinical and/or biochemical signs of hyperandrogenism, were enrolled in the study between April 2016 and March 2017. Other etiologies, such as congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome, thyroid disease or hyperprolactinemia were assessed before diagnosis of PCOS. Age: Control: 29.7 ± 7.2, PCOS: 25.1 ± 5.3 $p < 0.001$ BMI (kg/m^2): Control: 23.5 ± 5.1, PCOS: 25.3 ± 6.3 $p = 0.085$
PCOS diagnostic criteria	NIH
N per group	Control: 63 PCOS: 55
Setting	Gynecologic Endocrinology Unit, Department of Obstetrics and Gynecology, Faculty of Medicine of Siriraj Hospital of Mahidol University of Bangkok, Thailand between April 2016 and March 2017.

Index test	Follicle Number Per Ovary (FNPO – Maximum) Ovarian Volume (OV – Maximum) Follicle Number Per Cross-Section (FNPS – Maximum)		
Reference Standard	NIH criteria (oligo-anovulation, hyperandrogenism)		
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Accuracy to diagnose PCOS Sensitivity and specificity Area under the ROC curve Proposed threshold		
Inclusion and exclusion criteria reported?	Yes	Inclusion Criteria: Control: Normal ovulatory, non-hyperandrogenic women aged 18-45 years old. They had to have regular menstrual cycle with interval of 21-35 days and no clinical and biochemical hyperandrogenism. PCOS: Women 18-45 years of age, who diagnosed with PCOS by the Revised Rotterdam Criteria 2003 as having both 1) oligo-anovulation and 2) clinical and/or biochemical signs of hyperandrogenism. Other etiologies, such as congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome, thyroid disease or hyperprolactinemia were assessed before diagnosis of PCOS. Exclusion Criteria: Both groups: Steroid drug or hormone during the 3 months prior to enrollment and had previous history of ovarian surgery. The participant was excluded if there was a dominant follicle (>=10mm), corpus luteum or other abnormal ovarian mass. In case of suspicious evidence of ovulation at the time of ultrasound performing, the participant was also excluded from the study. PCOS: Other etiologies, such as congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome, thyroid disease or hyperprolactinemia
Does the study have a clearly focused question?	Partial	What is the accuracy of serum AMH and the new ultrasonographic criteria, follicle number per ovary (FNPO) threshold ≥ 25 follicles and ovarian volume (OV) > 10 mL, for diagnosis of PCOS?
Summary Result/s	The mean age of the participants was 25.1 ± 5.3 years old in PCOS group and 29.7 ± 7.2 years old in control group. Mean AMH, FNPO and OV in PCOS women were significantly higher than those in non-PCOS women. The area under the receiver-operating characteristic (ROC) curve of AMH was 0.903. The threshold of AMH at 4.7 ng/mL offered the best compromise between 80% sensitivity and 77.8% specificity. The appropriated threshold values for FNPO, follicle number per cross-section (FNPS) and OV were 15 follicles, 7 follicles and 6.5 mL, respectively. Serum AMH level was significantly positively correlated with FNPO, FNPS and OV in both PCOS and control groups. In PCOS women, serum AMH showed strongly correlation with FNPO ($r = 0.53$, $p < 0.001$) and weakly correlation with total testosterone ($r = 0.283$, $p = 0.036$). Serum AMH had a good diagnostic performance for diagnosis of PCOS presenting with oligo/ anovulation and hyperandrogenism. AMH threshold at 4.7 ng/mL was the best compromise level for diagnosis of PCOS. FNPO ≥15, FNPS ≥7 and OV ≥ 6.5 mL were reliable threshold for detecting polycystic ovaries in women with frank manifestation of PCOS.		
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
PATIENT SELECTION/SPECTRUM	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	
	Was a consecutive or random sample of patients enrolled? (Q-2)	Not reported	No random element was described in the selection of participants into the study. Study is described as a cross-sectional study.

	Was a case-control design avoided? (Q-2)	No	Both the control group (regular cycling, normo-androgenic women) and group with known disease (PCOS) were identified and diagnosed prior or during study enrollment.
	Did the study avoid inappropriate exclusions? (Q-2)	Yes	The exclusion criteria for the study are appropriate. Study methods describe that "both PCOS and control groups were ineligible if they had used steroid drug or hormone during the 3 months prior to enrollment and had previous history of ovarian surgery… In case of suspicious evidence of ovulation at the time of ultrasound performing, the participant was also excluded from the study". In addition, the study methods describe the exclusion criteria for the PCOS group as "Other etiologies, such as congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome, thyroid disease or hyperprolactinemia…".
CLASSIFICATION/ VERIFICATION/ INCORPORATION/ REVIEW BIAS	Were all participants assessed with both index test and reference standard?	Yes	All participants in the Control group (n = 63) and PCOS group (n = 55) received all three index tests (FNPS, OV, FNPO).
	Did all patients receive the same reference standard? (Q-2)	Yes	All participants in the study received the same reference standard, which was the equivalent of the NIH diagnostic criteria for PCOS. For the Control group, the study mentions that it consisted of "healthy women aged 18-45 years old. They had to have regular menstrual cycle with interval of 21-35 days and no clinical and biochemical hyperandrogenism".
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	PCOS diagnosis was conducted using the equivalent of the 1990 NIH criteria. Method description describes diagnosis of PCOS patients using "the Revised Rotterdam Criteria 2003 as having both 1) oligo-anovulation and 2) clinical and/or biochemical signs of hyperandrogenism…. Oligo-anovulation was defined as menstrual interval longer than 35 days. Clinical hyperandrogenism was defined as presence of acne, hirsutism or androgenic alopecia. Acne was assessed by using the recommended criteria from Dermatological Society of Thailand in 2011. Severity of acne was graded as three levels. Mild acne was defined as presence of comedone and/or <10 papules or pustules. Moderate acne was presented as > 10 papules or pustules and/or <5 nodules. Severe acne was shown as numerous of papules or pustules or nodules. Hirsutism was evaluated by using the modified Ferriman-Gallwey scoring system (mFG), cut-off score >= 5 indicated hirsutism. This cut-off score was used because mFG score of 5-6 was appropriated to define hirsutism in the studies including East Asian population. Androgenic alopecia was evaluated using Ludwig scale. Biochemical hyperandrogenemia was defined as serum total testosterone level greater than 0.8 ng/mL."
	Was the reference standard independent of the index test (ie. the index test did not form part of the reference standard)?	Yes	Study describes the use of an NIH-equivalent criteria for the diagnosis of PCOS, which only includes the presence oligo-anovulation/anovulation and hyperandrogenism (clinical and/or biochemical). Sonographic markers of ovarian morphology are not part of the reference standard.
	Were the reference standard results interpreted without knowledge of the results of the index test?	Not reported	Method description does not describe the timing of the reference standard in relation to the index test results.
	Were the index test results interpreted without knowledge of the results	Not reported	Method description does not describe whether index test results were interpreted without knowledge of the results of the reference standard.

	of the reference standard test?		
	If a threshold was used, was it pre-specified?	No	Study method describes that "The receiver-operating characteristic (ROC) curves were constructed to evaluate the diagnostic test performance such as sensitivity, specificity of AMH and ultrasonographic ovarian parameters for diagnosis of PCOS. Sensitivity against 1-specificity was plotted at each threshold level. The area under the ROC curve (AUC) was computed to represent the probability of correctly identifying controls and patients with PCOS".
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?	Yes	Study methods describe that "All participants were asked about general gynecologic history and their menstruation. They were received physical examination and evaluated signs of hyperandrogenism. Then all participants were scanned pelvic ultrasonography and taken venous blood puncture."
ATTRITION BIAS	Were withdrawals from the study explained?	Yes 100% treatment 100% control/ comparison	Numbers described as enrolled are the same as those in results.
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Yes	There are no uninterruptable/intermediate test results and all results are reported.
OTHER ISSUES – APPLICABILITY/	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	The following description was provided for the ultrasound examination: "Transvaginal or transrectal ultrasonography (TVS or TRS) was performed by one of two examiners to evaluate follicle number and ovarian volume. Control subjects were evaluated in the early follicular phase between days 2nd-5th of menstrual period. Women with PCOS were evaluated at anovulatory or follicular phase. Ultrasonography measurements followed the protocol as mention in literature [10,19], using an Aloga Alpha 6 with 8 MHz transvaginal transducer. Ultrasonography measurements were taken in real-time. Both ovaries were scanned from inner to outer margin in the longitudinal plane. The participant was excluded if there was a dominant follicle (≥10 mm), corpus luteum or other abnormal ovarian mass. In case of suspicious evidence of ovulation at the time of ultrasound performing, the participant was also excluded from the study. After determination of the longest axis of the ovary, the length and thickness were measured and the OV was calculated by using the formula for a prolate ellipsoid (0.5 x length x width x thickness). Follicle size was expressed as the mean of two perpendicular measurements and follicles between 2 and 9 mm were counted. For each ovary, follicle number per cross-section (FNPS) were counted in the plane of the ovary that contained maximum follicles and FNPO were counted by slow and continuous scanning of the entire ovary, from one margin to the other. The ovarian parameters were recorded from both ovaries in each participant and greater values of FNPO, FNPS, OV in each participant were used for analysis."
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Yes	
	Were the same clinical data available when test results were interpreted	Not reported	Study does not describe what clinical data was available during test result interpretation.

	as would be available when the test is used in practice?		
	Were there any conflicts of interest in the writing or funding of this study?	No	Authors stated that there were no conflicts of interest to disclose.
	If statistical analysis was undertaken, was this appropriate?	Partial	Study method describes that “The receiver-operating characteristic (ROC) curves were constructed to evaluate the diagnostic test performance such as sensitivity, specificity of AMH and ultrasonographic ovarian parameters for diagnosis of PCOS. Sensitivity against 1-specificity was plotted at each threshold level. The area under the ROC curve (AUC) was computed to represent the probability of correctly identifying controls and patients with PCOS”. However, unclear if an adequatesample size calculation was undertaken. A 4x4 table of test performance was not presented.
COMMENTS			
What is the overall risk of bias?		Moderate	Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No. All outcomes had the same risk of bias.	

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 1

Question 1.4.

What is the most effective ultrasound criteria to diagnose PCOS? When is ultrasound indicated to diagnose PCOS?

BACKGROUND:

Polycystic ovarian morphology (PCOM) on ultrasonography was incorporated into the diagnosis of polycystic ovary syndrome (PCOS) in 2003 as part of the Rotterdam criteria as it was felt that PCOM was a consistent feature in women with clinical and endocrine features of PCOS (1). The recommended criteria to define PCOM was 12 or more follicles measuring between 2-9mm throughout the entire ovary (FNPO) and/or an ovarian volume (OV) of 10mL or more – consistent with follicle excess and ovarian enlargement being the key features of PCOM (1). Other ovarian features, such as stromal hypertrophy, increased stromal echogenicity, and peripheral follicle distribution pattern were judged to be too subjective based on current technology and excluded as markers of PCOM (1). The Rotterdam criteria for PCOM were criticized for overlapping with ovarian features in healthy women with regular menstrual cycles (2-5), and in up to 70% of adolescent females (6). In 2014, the Androgen Excess and PCOS Society proposed updated criteria to define PCOM which accounted for advances in imaging technology (7). Namely, a new FNPO threshold of 25 or more follicles was proposed, and the threshold for OV (10mL or more) upheld based on a review of available data on the upper limits of normal (P95) for ovarian measures in healthy women with regular menstrual cycles and normal androgens – as well as consideration of the ultrasound diagnostic test studies available at the time (7). In 2018, the International Evidence Based Guideline for the Assessment and Management of PCOS proposed thresholds of FNPO ≥ 20 and/or OV ≥10 mL on either ovary as part of a Clinical Consensus Recommendation (CCR) (8). At present, there is a need for clarification on the most accurate ultrasound marker for PCOM, and the appropriate threshold(s) to define PCOM on ultrasonography.

All criteria for PCOM proposed to date are limited by their lack of consideration of age or life-stage, use of hospital-based populations and challenges in standardizing ultrasound measurements and their reporting. First, there are no large studies across the lifespan to validate normal ovarian development on ultrasonography but data based on various imaging modalities indicate an increase in ovarian size and follicle count after age 6, and an increased in ovarian size throughout puberty correlating with age, height, weight and pubertal status (9-11). Ovarian size increases from age 9 – 11 peri-pubertally and is greatest after age 12 consistent with pubertal progress (10). Normative models suggest maximum ovarian volume is reached at age 20 (12). Analogous data are not available for antral follicle counts, or other ovarian features. The correlation between menstrual function and ovarian morphology is not entirely straightforward in adolescence or early adulthood as in a study of Danish women aged 19 – 21y, 68% were shown to have PCOM based on adult Rotterdam criteria but without clinical features of PCOS.6 There are few longitudinal studies of ovarian morphology during adolescence, but a small study in healthy adolescents examined with ultrasound over 2 – 4 years post-menarche suggests PCOM, as defined by adult criteria, is common and not associated with reproductive dysfunction in this age group (13). Based on the likelihood of peak ovarian size and follicle presence in adolescence and early adulthood, adult criteria for PCOM are not appropriate for use in adolescents (14). Diagnostic test studies of ovarian morphology in adolescents are few and restricted to assessments of OV in mostly older teens using transabdominal or transrectal ultrasonography (15-18). However, studies are of insufficient power to support increased OV in older teens meeting an endocrine-based definition of PCOS compared to age-matched controls. Second, data on ovarian morphology in adults and adolescents with PCOS are largely limited to hospital-based populations which represent the severest manifestations of PCOS. Studies involving community-based populations are few and primarily, cross-sectional in nature. To our knowledge, a comprehensive longitudinal assessment of ovarian morphology in unselected PCOS populations has not been conducted across the lifespan. Likewise, racial, ethnic and geographical differences in ovarian morphology cannot be defined at this time – despite evidence to suggest differences in other PCOS symptomology and health risks across diverse populations. Last, it should be acknowledged that medical sonographers receive limited training in assessments of antral follicle counts and there is no accepted standard for the measurement and reporting of ovarian features. In the case of follicle counts, follicle distribution pattern and stromal features, there is a significant problem of inter-rater variability, particularly in polycystic ovaries (19-22). A reproducible technique to reliably estimate antral follicle count in PCOM, which is feasible in a busy clinical workflow, is critical if FNPO is to be used as the main marker to diagnose PCOS on ultrasonography. Of importance, thresholds to define PCOM garnered across transvaginal, transabdominal and transrectal ultrasonography may be method-specific, and their degree of interchangeability is uncertain at this time. Other factors impacting the use of consensus thresholds for PCOM could include

variability in the caliber of ultrasound equipment available across settings, patient habitus can affect image quality, and different techniques for measuring ovarian endpoints (i.e. real-time vs. off-line, 2D vs. 3D). As ultrasound technology improves and machine learning applications become available (23-26), there will be a continued need to reassess the quantitative definition of PCOM.

GRADE EVIDENCE CERTAINTY	
Comparison	
Comparison 1. PCOS versus Controls	⨁⨁◯◯ LOW

Evidence to Recommendations Framework

COMPARISONS (option versus other option)

Follicle excess (option) versus other sonographic markers (e.g. ovarian enlargement, stromal features, follicle pattern, etc.)*
*Based on qualitative comparisons of summary ROC curves and pooled estimates of Se and Sp where available.

EVIDENCE-BASED RECOMMENDATION(S)

EBR: Follicle number per ovary (FNPO) should be considered the most effective ultrasound marker in diagnosing polycystic ovarian morphology (PCOM) in adults.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

EBR: Follicle number per ovary (FNPO), follicle number per cross-section (FNPS) and ovarian volume (OV) should be considered accurate ultrasound markers for PCOM in adults.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

CR: PCOM criteria should be based on follicle excess (FNPO, FNPS) and/or ovarian enlargement (OV).

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

CR: Follicle number per ovary (FNPO) ≥ 20 in at least one ovary should be considered the threshold for PCOM in adults.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

CR: Ovarian volume (OV) ≥ 10ml or follicle number per section (FNPS) ≥ 10 in at least one ovary in adults should be considered the threshold for PCOM if using older technology or image quality is insufficient to allow for an accurate assessment of follicle counts throughout the entire ovary.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

PRACTICE POINT(S)

1. There are no definitive criteria to define PCOM on ultrasound in adolescents, hence it is not recommended in adolescents.
2. When an ultrasound is indicated, if acceptable to the individual, the transvaginal approach is the most accurate for detection of PCOM.
3. Transabdominal ultrasound should primarily report ovarian volume (OV) with a threshold of ≥ 10ml, or follicle number per section (FNPS) ≥ 10 in either ovary in adults given the difficulty of assessing follicle counts throughout the entire ovary with this approach.
4. In patients with irregular menstrual cycles and hyperandrogenism, an ovarian ultrasound is not necessary for PCOS diagnosis.
5. Thresholds for PCOM should be revised regularly with advancing ultrasound technology, and age-specific cut off values for PCOM should be defined.
6. There is a need for training in careful and meticulous follicle counting per ovary and clear standardized protocols are recommended for PCOM reporting on ultrasound including at a minimum:
    - Last menstrual period (or stage of cycle)
    - Transducer bandwidth frequency
    - Approach/route assessed

- Total number of 2 – 9 mm follicle per ovary
- Other ovarian features and/or pathology including ovarian cysts, corpus lutea, dominant follicles (≥10 mm) (which should not be included in ovarian volume calculations)
- Where a dominant follicle, corpus luteum or large cyst is present, reliance on the contralateral ovary for the detection of PCOM is sufficient.
- For uterine features and/or pathology including endometrial thickness and pattern.

GRADE CONSIDERATIONS

Justifications:
See Part 1- Evidence Summary and GRADE document.

Subgroup considerations:
These recommendations are only for adults.

Implementation considerations:
Recommendations for adults are limited to transvaginal ultrasonography wherein the modality for assessment must be acceptable to women with suspected PCOS.
This will limit overdiagnosis in adolescents.
Strategies are required to improve reporting adherence.
Ultrasound evaluation of PCOS is in broad use across certain specialities.
However, availability of high-quality ultrasound and/or trained sonographers may be limited in some settings.

Monitoring and evaluation considerations:
Quality of reporting should be monitored.

Research priorities:
Further methodologically rigorous trials are important to address:
1) Natural history of ovarian morphology in community-based populations across the lifespan and across the globe.
2) An understanding of how ovarian morphology tracks with PCOS-related health outcomes.
3) Establishment of rigor and reproducibility in measuring and reporting of ovarian ultrasonographic markers in a clinical workflow.
4) Impact of COCP on PCOM.

GRADE framework

GRADE DECIDE Interactive Evidence to Decision Framework

● DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

Judgement:

☒ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Improve accuracy and better reporting and diagnosis.

● UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

No research evidence was identified.

Panel discussion:

Adoption of recommendation may be associated with misclassification of PCOM in healthy adults.

● CERTAINTY OF THE EVIDENCE

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☐ Very low	☒ Low	☐ Moderate	☐ High

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Diagnostic test studies have serious to very serious risk of bias and inconsistency. Imprecision for certain metrics is also an issue.

● VALUES

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☐ Important uncertainty or variability	☒ Possibly important uncertainty or variability	☐ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Research evidence:

No research evidence was identified.

Panel discussion:

There is controversy over the value of PCOM to the diagnosis of PCOS. However, PCOM is required to elaborate the full phenotype consistent with the Rotterdam criteria for PCOS.

● BALANCE OF EFFECTS

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:

Despite the possibility of misclassification, the recommendation allows for application of the most robust ultrasound marker of PCOS.

● COSTS

How large are the resource requirements (costs)?

Judgement:

☒ Don't know	☐ Varies	☐ Large costs	☐ Moderate costs	☐ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:

No research evidence was identified

Panel discussion:

No cost analysis performed.

● CERTAINTY OF COST EVIDENCE

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

No research evidence was identified

Panel discussion:

No cost analysis performed.

● COST-EFFECTIVENESS

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

No research evidence was identified

Panel discussion:

No cost analysis performed.

● EQUITY

What would be the impact on health equity?

Judgement:

☐ Don't know	☒ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☐ Probably increased	☐ Increased

Research evidence:

No research evidence was identified

Panel discussion:

Uncertain.

Availability of high-quality ultrasound and/or trained sonographers may be limited in some settings.

● ACCEPTABILITY

Is the option acceptable to key stakeholders?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

There is likely a willingness to define PCOM for adults in order to elaborate the full PCOS features and/or provide additional confidence to an endocrine diagnosis.

● FEASIBILITY

Is the option feasible to implement?

Judgement:

☐ Don't know	☒ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

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PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by Yvonne Louwers & Kim van der Ham
Supervised, edited and supported by the Evidence Team

GDG 1

Question 1.5.

Is AMH effective for diagnosis of PCOS? Is AMH effective to diagnosis of PCOM?

1. SELECTION CRITERIA

Table 1. PICO Criteria for Inclusion – Not to be adapted To be used by evidence team to decide which studies will be included when screening search results.	
Question	1.5.1) Is AMH effective for diagnosis of PCOS? 1.5.2) Is AMH effective to diagnosis of PCOM?
Clinical leads (key contacts)	Prof Joop Laven Reproductive endocrinologist Erasmus MC Rotterdam j.laven@erasmusmc.nl Prof Helena Teede Endocrinologist Monash University, Australia Helena.teede@monash.edu
Allocation ranking	Level 2- updated systematic review

Q 1.5.1 Is AMH effective to diagnosis of PCOS?

	Participants (P)	**Intervention (I)**	**Comparison (C)**	**Outcomes (O)**	**Study type**	**Limits**
Inclusion criteria	Females of any age, ethnicity, weight or phenotype of PCOS (diagnosed by Rotterdam, NIH or AES); and women without PCOS, as controls. Both with an AMH measurement.	AMH measurement by any method.	Don't need a comparison measurement as long as there is a PCOS and non-PCOS group. Can compare to different criteria/methods to diagnose PCOS.	Diagnosed PCOS. Sensitivity and specificity data; and AUC data or ROC curves.	Evidence based guidelines, systematic reviews, health technology assessments, randomised controlled trials, prospective and retrospective cohort studies, cross-sectional and case-control studies.	English language. Any date. New search - same search as above.
Exclusion criteria	Those who do not have an AMH measurement. MM added:Those undergoing ovulation induction or prediction of response to intervention.		Single characteristics of PCOS.		Non-evidence based guidelines, non-systematic reviews, case series, editorials, letters, commentaries.	

Q 1.5.2 Is AMH effective to diagnosis of PCOM?

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type	Limits
Inclusion criteria	Females of any age, ethnicity, weight or phenotype of PCOS (diagnosed by Rotterdam, NIH or AES); and women without PCOS, as controls. Both with an AMH measurement.	AMH measurement by any method.	Ultrasound assessment of antral follicle count and/or volume in both ovaries. Can have no comparison measurement as long as there is a PCOS and non-PCOS group.	Diagnosed PCOM. Sensitivity and specificity data; and AUC data or ROC curves.	Evidence based guidelines, systematic reviews, health technology assessments, randomised controlled trials, prospective and retrospective cohort studies, cross-sectional and case-control studies.	English language. Any date. New search - same search as above.
Exclusion criteria	MM added:Those undergoing ovulation induction or prediction of response to intervention.				Non-evidence based guidelines, non-systematic reviews, case series, editorials, letters, commentaries.	

2. SEARCH STRATEGY

Table 2.1. Search details

Search strategy source: *[enter doi or 2018 technical report page number where search string was derived]*	
Evidence source	**Date of search**
Medline (Ovid)	August 3rd 2022
PsychInfo (Ovid)	August 3rd 2022
EMBASE (Ovid)	August 3rd 2022
Web of Science	August 3rd 2022
CINAHL	August 3rd 2022
Cochrane Central	August 3rd 2022

Table 2.2. Questions addressed by this search *(add more rows as needed)*:

GDG	Q#	Question
1	1.5.1	Is AMH effective for diagnosis of PCOS?
1	1.5.2	Is AMH effective to diagnosis of PCOM?

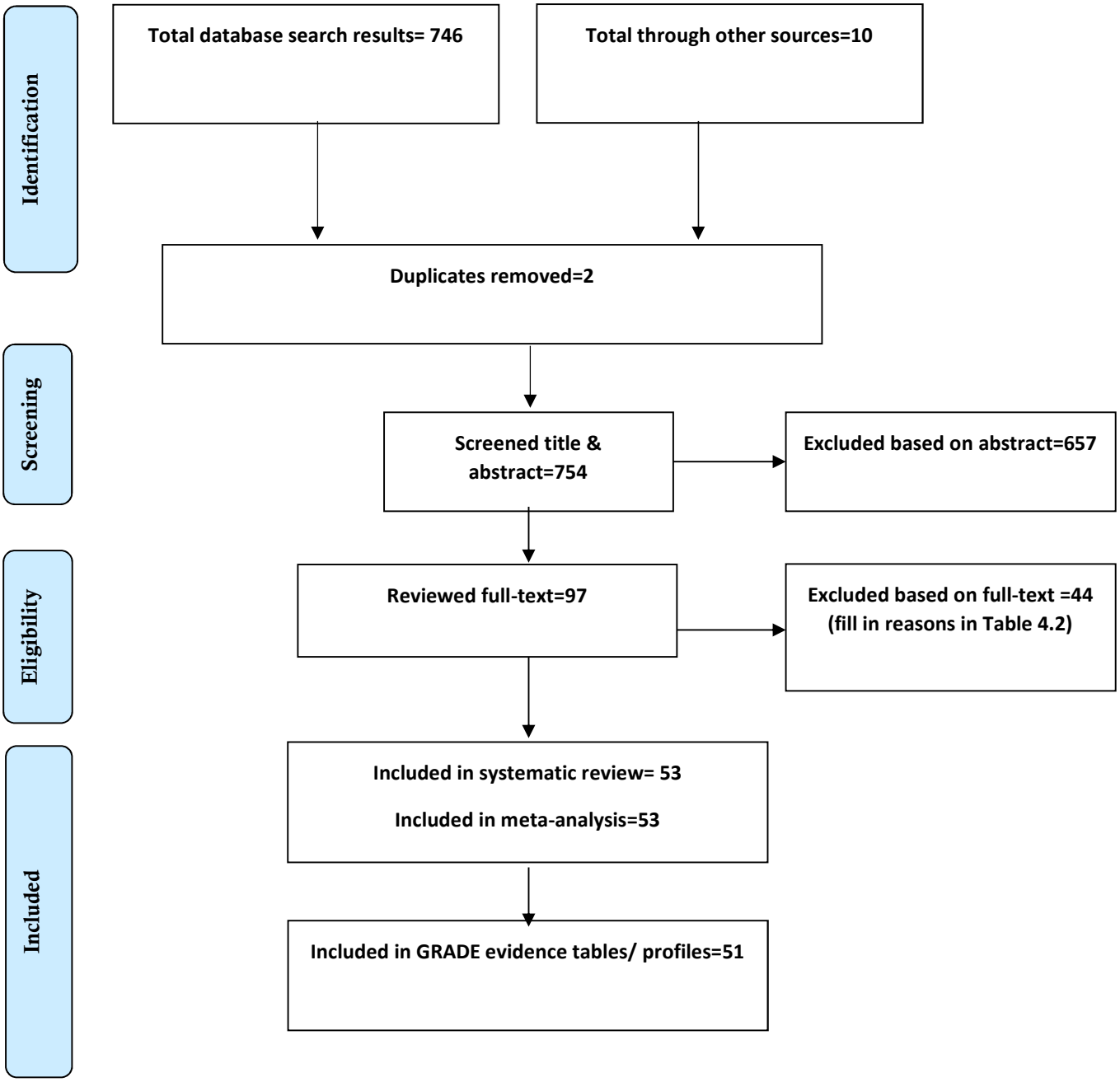
Table 2.3. Search strings used in OVID or other database/s – please save a screenshot of search results to submit alongside this template

Embase.com
('ovary polycystic disease'/exp OR 'anovulation'/exp OR (polycystic-ovar* OR poly-cystic-ovar* OR PCO* OR Leventhal OR anovulat* OR oligo-ovulat* OR oligoovulat* OR (ovar* NEAR/5 (sclerocystic OR polycystic OR poly-cystic OR degenerate* OR hyperandrogen* OR hyper-androgen*))):ab,ti,kw) AND ('Muellerian inhibiting factor'/exp OR (antimullerian-hormone* OR antimuellerian-hormone* OR anti-mullerian-hormone* OR anti-muellerian-hormone* OR AMH OR muellerian-inhibi* OR mullerian-inhibi*):ab,ti,kw) AND ('diagnosis'/exp OR 'diagnosis':lnk OR (diagn*):ab,ti,kw) AND [2017-2030]/py AND [English]/lim NOT ((animal/exp OR animal*:de OR nonhuman/de) NOT ('human'/exp)) NOT [conference abstract]/lim
Medline Ovid
(exp polycystic ovary syndrome/ OR anovulation/ OR (polycystic-ovar* OR poly-cystic-ovar* OR PCO* OR Leventhal OR anovulat* OR oligo-ovulat* OR oligoovulat* OR (ovar* ADJ5 (sclerocystic OR polycystic OR poly-cystic OR degenerate* OR hyperandrogen* OR hyper-androgen*))).ab,ti,kf.) AND (Anti-Mullerian Hormone/ OR (antimullerian-hormone* OR antimuellerian-hormone* OR anti-mullerian-hormone* OR anti-muellerian-hormone* OR AMH OR muellerian-inhibi* OR mullerian-inhibi*).ab,ti,kf.) AND (exp Diagnosis/ OR diagnosis.fx. OR (diagn*).ab,ti,kf.) AND 2017:2030.(sa_year) AND english.lg. NOT (exp animals/ NOT humans/) NOT (news OR congres* OR abstract* OR book* OR chapter* OR dissertation abstract*).pt.
Web of Science
TS=(((polycystic-ovar* OR poly-cystic-ovar* OR PCO* OR Leventhal OR anovulat* OR oligo-ovulat* OR oligoovulat* OR (ovar* NEAR/5 (sclerocystic OR polycystic OR poly-cystic OR degenerate* OR hyperandrogen* OR hyper-androgen*)))) AND ((antimullerian-hormone* OR antimuellerian-hormone* OR anti-mullerian-hormone* OR anti-muellerian-hormone* OR AMH OR

muellerian-inhibi* OR mullerian-inhibi*)) AND ((diagn*)) NOT ((animal* OR rat OR rats OR mouse OR mice OR murine OR dog OR dogs OR canine OR cat OR cats OR feline OR rabbit OR cow OR cows OR bovine OR rodent* OR sheep OR ovine OR pig OR swine OR porcine OR veterinar* OR chick* OR zebrafish* OR baboon* OR nonhuman* OR primate* OR cattle* OR goose OR geese OR duck OR macaque* OR avian* OR bird* OR fish*) NOT (human* OR patient* OR women OR woman OR men OR man))) AND DT=(Article OR Review OR Letter OR Early Access) AND LA=(English) AND PY=(2017-2030)
Cochrane Central
((polycystic-ovar* OR poly-cystic-ovar* OR PCO* OR Leventhal OR anovulat* OR oligo-ovulat* OR oligoovulat* OR (ovar* NEAR/5 (sclerocystic OR polycystic OR poly-cystic OR degenerate* OR hyperandrogen* OR hyper-androgen*))):ab,ti,kw) AND ((antimullerian-hormone* OR antimuellerian-hormone* OR anti-mullerian-hormone* OR anti-muellerian-hormone* OR AMH OR muellerian-inhibi* OR mullerian-inhibi*):ab,ti,kw) AND ((diagn*):ab,ti,kw) NOT "conference abstract":pt
Filtered in database: 01/01/2017 to 31/12/2022
Cinahl
(MH Polycystic Ovary Syndrome OR MH Anovulation OR TI(polycystic-ovar* OR poly-cystic-ovar* OR PCO* OR Leventhal OR anovulat* OR oligo-ovulat* OR oligoovulat* OR (ovar* N5 (sclerocystic OR polycystic OR poly-cystic or degenerate* OR hyperandrogen* OR hyper-androgen*))) OR AB(polycystic-ovar* OR poly-cystic-ovar* OR PCO* OR Leventhal OR anovulat* OR oligo-ovulat* OR oligoovulat* OR (ovar* N5 (sclerocystic OR polycystic OR poly-cystic OR degenerate* OR hyperandrogen* OR hyper-androgen*)))) AND (TI(antimullerian-hormone* OR antimuellerian-hormone* OR anti-mullerian-hormone* OR anti-muellerian-hormone* OR AMH OR muellerian-inhibi* OR mullerian-inhibi*) OR AB(antimullerian-hormone* OR antimuellerian-hormone* OR anti-mullerian-hormone* OR anti-muellerian-hormone* OR AMH OR muellerian-inhibi* OR mullerian-inhibi*)) AND (MH Diagnosis+ OR TI(diagn*) OR AB(diagn*)) NOT (MH animals+ NOT human+)
Limits
Language: English
Publication date: 2017-2030
Source types: Academic journals
PsycINFO Ovid
((polycystic-ovar* OR poly-cystic-ovar* OR PCO* OR Leventhal OR anovulat* OR oligo-ovulat* OR oligoovulat* OR (ovar* ADJ5 (sclerocystic OR polycystic OR poly-cystic or degenerate* OR hyperandrogen* OR hyper-androgen*))).ab,ti.) AND ((antimullerian-hormone* OR antimuellerian-hormone* OR anti-mullerian-hormone* OR anti-muellerian-hormone* OR AMH OR muellerian-inhibi* OR mullerian-inhibi*).ab,ti.) AND (exp Diagnosis/ OR (diagn*).ab,ti.) AND 2017:2030.(sa_year) AND english.lg. NOT ((animal.po. OR exp animals/) NOT human.po.) NOT (news OR congres* OR abstract* OR book* OR chapter* OR dissertation abstract*).pt.

Evidence processing: Studies were selected and appraised by two reviewer/s in consultation with the evidence team/ key contact using study selection and appraisal criteria (PICO above) established a priori. The articles were reviewed by title and abstract by two reviewers. When a decision could not be made based on title and abstract alone, full text was retrieved. **A total of 49 studies met inclusion criteria for this review.**

3. SEARCH RESULTS - PRISMA flowchart



4. STUDY INCLUSION

Table 4.1. Included Studies (full citation with doi)- *add more rows as needed*
Agrawal, N.; Sharma, R. Correlation of anti-müllerian hormone with clinical, hormonal and ultrasonographic parameters in pcos and normo-ovulatory women: An experience of single tertiary care center. Ital J Gynaecol Obstet 2018;30(4):37-43.
Ahmed N, Batarfi AA, Bajouh OS, Bakhashab S. Serum Anti-Müllerian Hormone in the Diagnosis of Polycystic Ovary Syndrome in Association with Clinical Symptoms. Diagnostics (Basel). 2019 Oct 1;9(4):136. doi: 10.3390/diagnostics9040136. PMID: 31581541; PMCID: PMC6963945.
Al-Jefout M, Alnawaiseh C, Saleh M, Warwar K. Anti-Müllerianhormone (AMH) new cutoff as a possible tool for thediagnosis of polycystic ovary syndrome (PCOS). J Biomed Sci Res. 2021;3(2):139. Doi: 10.36266/JBSR/139.
Al-Naffakh AS, Risan FA. Assessment of anti-Mullerian hormone and anti ovarian antibody in the sera of patients with polycystic ovarian syndrome in AL-Najaf Al-Ashraf Province. Medico-Legal Update 2020;20(1):600–8. Doi: 0.37506/v20/i1/2020/mlu/194384.
Aydoğmuş H, Kelekçi S, Elmalı F, Aydoğmuş S. Can we use serum Anti-Mullerian hormone to differentiate the diagnosis between polycystic ovary syndrome patients and healthy women with polycystic ovarian morphology and regular menstrual cycles. Saudi Med J. 2018 Oct;39(10):1011-1016. doi: 10.15537/smj.2018.10.23413. PMID: 30284584; PMCID: PMC6201027.
Bakeer E, Radwan R, El Mandoury A, El Rahman AA, Gad M, El Maksoud SA. Anti-Müllerian Hormone as a Diagnostic Marker in Egyptian Infertile Polycystic Ovary Syndrome Females: Correlations with Vitamin D, Total Testosterone, Dyslipidemia and Anthropometric Parameters. J Med Biochem. 2018 Dec 1;37(4):448-455. doi: 10.1515/jomb-2017-0068. PMID: 30584404; PMCID: PMC6298483.
Bansal P, Sardana K, Arora P, Khurana A, Garga UC, Sharma L. A prospective study of anti-mullerian hormone and other ovarian and adrenal hormones in adult female acne. Dermatol Ther. 2020 Nov;33(6):e13974. doi: 10.1111/dth.13974. Epub 2020 Jul 27. PMID: 33185003.
Bell RJ, Islam RM, Skiba MA, Herbert D, Martinez Garcia A, Davis SR. Substituting serum anti-Müllerian hormone for polycystic ovary morphology increases the number of women diagnosed with polycystic ovary syndrome: a community-based cross-sectional study. Hum Reprod. 2021 Dec 27;37(1):109-118. doi: 10.1093/humrep/deab232. PMID: 34741176.
Bozdag G, Mumusoglu S, Coskun ZY, Yarali H, Yildiz BO. Anti-Müllerian hormone as a diagnostic tool for PCOS under different diagnostic criteria in an unselected population. Reprod Biomed Online. 2019 Sep;39(3):522-529. doi: 10.1016/j.rbmo.2019.04.002. Epub 2019 Apr 10. PMID: 31182353.
Calzada M, López N, Noguera JA, Mendiola J, Hernández AI, Corbalán S, Sanchez M, Torres AM. AMH in combination with SHBG for the diagnosis of polycystic ovary syndrome. J Obstet Gynaecol. 2019 Nov;39(8):1130-1136. doi: 10.1080/01443615.2019.1587604. Epub 2019 Jun 17. PMID: 31208261.
Casadei L, Fanisio F, Sorge RP, Collamarini M, Piccolo E, Piccione E. The diagnosis of PCOS in young infertile women according to different diagnostic criteria: the role of serum anti-Müllerian hormone. Arch Gynecol Obstet. 2018 Jul;298(1):207-215. doi: 10.1007/s00404-018-4803-8. Epub 2018 May 25. PMID: 29802450.
Cengiz H, Ekin M, Dagdeviren H, Yildiz Ş, Kaya C, Kanawati A. Comparison of serum anti-Müllerian hormone levels in normal weight and overweight-obese adolescent patients with polycystic ovary syndrome. Eur J Obstet Gynecol Reprod Biol. 2014 Sep;180:46-50. doi: 10.1016/j.ejogrb.2014.06.018. Epub 2014 Jun 28. PMID: 25036408.
Deveer M, Deveer R, Basaran O, Turkcu UO, Akbaba E, Cullu N, Turhan N, Kucuk M, Kasap B. Serum Copeptin, Pentraxin 3, Anti-Mullerian Hormone Levels With Echocardiography and Carotid Artery Intima-Media Thickness in Adolescents With Polycystic Ovary Syndrome. J Clin Med Res. 2015 Dec;7(12):989-94. doi: 10.14740/jocmr2375w. Epub 2015 Oct 23. PMID: 26566413; PMCID: PMC4625820.
Dietz de Loos A, Hund M, Buck K, Meun C, Sillman J, Laven JSE. Antimüllerian hormone to determine polycystic ovarian morphology. Fertil Steril. 2021 Oct;116(4):1149-1157. doi: 10.1016/j.fertnstert.2021.05.094. PMID: 34579824.
Evliyaoglu O, Imöhl M, Weiskirchen R, van Helden J. Age-specific reference values improve the diagnostic performance of AMH in polycystic ovary syndrome. Clin Chem Lab Med. 2020 Jul 28;58(8):1291-1301. doi: 10.1515/cclm-2019-1059. PMID: 32069226.
Farooq S, Baloch S, Awan S, Fakharunissa. Relationship of Anti-Mullerian Hormone in Polycystic Ovary Syndrome Patients with Different Subgroups. Pak J Med Health Sci 2022;16(5):612-615. No doi
Fu H, Lin Y, Deng X, Wu L. Correlation between anti-Mullerian hormone levels and antral follicle counts in polycystic ovary and metabolic syndromes. Syst Biol Reprod Med. 2021 Apr;67(2):112-120. doi: 10.1080/19396368.2020.1860155. Epub 2021 Jan 7. PMID: 33406916.
Gabr H, Marei ES, The Relation between Anti-Mullerian Hormone with Antral Follicle Count and Ovarian Volume in Polycystic Ovary Syndrome. Arab Journal of Nuclear Sciences and Applications 2019;52(2):84-93.

Indran IR, Huang Z, Khin LW, Chan JKY, Viardot-Foucault V, Yong EL. Simplified 4-item criteria for polycystic ovary syndrome: A bridge too far? Clin Endocrinol (Oxf). 2018 Aug;89(2):202-211. doi: 10.1111/cen.13755. Epub 2018 Jun 19. PMID: 29851127.
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Jamil AS, Alalaf SK, Al-Tawil NG, Al-Shawaf T. Comparison of clinical and hormonal characteristics among four phenotypes of polycystic ovary syndrome based on the Rotterdam criteria. Arch Gynecol Obstet. 2016 Feb;293(2):447-56. doi: 10.1007/s00404-015-3889-5. Epub 2015 Sep 25. PMID: 26408006.
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Yue CY, Lu LK, Li M, Zhang QL, Ying CM. Threshold value of anti-Mullerian hormone for the diagnosis of polycystic ovary syndrome in Chinese women. PLoS One. 2018 Aug 28;13(8):e0203129.

Table 4.2. Excluded Studies (on full text assessment)- *add more rows as needed*

Reference	Reason
Abbara A, Eng PC, Phylactou M, Clarke SA, Hunjan T, Roberts R, Vimalesvaran S, Christopoulos G, Islam R, Purugganan K, Comninos AN, Trew GH, Salim R, Hramyka A, Owens L, Kelsey T, Dhillo WS. Anti-Müllerian hormone (AMH) in the Diagnosis of Menstrual Disturbance Due to Polycystic Ovarian Syndrome. Front Endocrinol (Lausanne). 2019 Sep 26;10:656. doi: 10.3389/fendo.2019.00656. PMID: 31616381; PMCID: PMC6775233.	Wrong patient population
Alebic MŠ, Stojanovic N, Dewailly D. Discordance between serum anti-Müllerian hormone concentrations and antral follicle counts: not only technical issues. Hum Reprod. 2018 Jun 1;33(6):1141-1148. doi: 10.1093/humrep/dey098. PMID: 29688494.	Wrong outcomes
Anand S, Kumar A, Prasad A, Trivedi K. Updated meta-analysis on the diagnostic accuracy of serum anti-Mullerian hormone in poly cystic ovary syndrome involving 13 509 subjects. J Obstet	Meta-analysis/ systematic review

Gynaecol Res. 2022 Aug;48(8):2162-2174. doi: 10.1111/jog.15233. Epub 2022 Apr 8. PMID: 35394100.	
Asanidze E, Kristesashvili J, Pkhaladze L, Khomasuridze A. The value of anti-Mullerian hormone in the management of polycystic ovary syndrome in adolescents. Gynecol Endocrinol. 2019 Nov;35(11):974-977. doi: 10.1080/09513590.2019.1616689. Epub 2019 May 22. PMID: 31116610.	Wrong outcomes
Asanidze E, Kristesashvili J, Parunashvili N, Karelishvili N, Etsadashvili N. Challenges in diagnosis of polycystic ovary syndrome in adolescence. Gynecol Endocrinol. 2021 Sep;37(9):819-822. doi: 10.1080/09513590.2021.1943344. Epub 2021 Jun 29. PMID: 34184963.	Wrong outcomes
Bhide P, Kulkarni A, Dilgil M, Dhir P, Shah A, Gudi A, Homburg R. Phenotypic variation in anti-Mullerian hormone (AMH) production per follicle in women with polycystic ovary syndrome (PCOS) and isolated polycystic ovarian morphology (PCOM): an observational cross-sectional study. Gynecol Endocrinol. 2017 Oct;33(10):801-806. doi: 10.1080/09513590.2017.1320377. Epub 2017 Apr 28. PMID: 28454499.	Wrong outcomes
Butt MS, Saleem J, Aiman S, Zakar R, Sadique I, Fischer F. Serum anti-Müllerian hormone as a predictor of polycystic ovarian syndrome among women of reproductive age. BMC Womens Health. 2022 May 28;22(1):199. doi: 10.1186/s12905-022-01782-2. PMID: 35643521; PMCID: PMC9148456.	Wrong outcomes
Bradbury RA, Lee P, Smith HC. Elevated anti-Mullerian hormone in lean women may not indicate polycystic ovarian syndrome. Aust N Z J Obstet Gynaecol. 2017 Oct;57(5):552-557. doi: 10.1111/ajo.12647. Epub 2017 Jun 9. PMID: 28597496.	Wrong outcomes
Caanen MR, Peters HE, van de Ven PM, Jüttner AMFM, Laven JSE, van Hooff MHA, Lambalk CB. Anti-Müllerian Hormone Levels in Adolescence in Relation to Long-term Follow-up for Presence of Polycystic Ovary Syndrome. J Clin Endocrinol Metab. 2021 Mar 8;106(3):e1084-e1095. doi: 10.1210/clinem/dgaa949. PMID: 33351079; PMCID: PMC7947839.	Wrong patient population
Capuzzo M, Donno V, LA Marca A. Polycystic ovary syndrome, amenorrhea and the diagnostic role of anti-Müllerian hormone. Minerva Endocrinol. 2020 Dec;45(4):376-380. doi: 10.23736/S0391-1977.20.03390-8. PMID: 33478206.	Wrong study design (review)
Capuzzo M, La Marca A. Use of AMH in the Differential Diagnosis of Anovulatory Disorders Including PCOS. Front Endocrinol (Lausanne). 2021 Feb 3;11:616766. doi: 10.3389/fendo.2020.616766. PMID: 33633686; PMCID: PMC7901963.	Wrong study design
Chu MC, Carmina E, Wang J, Lobo RA. Müllerian-inhibiting substance reflects ovarian findings in women with polycystic ovary syndrome better than does inhibin B. Fertil Steril. 2005 Dec;84(6):1685-8. doi: 10.1016/j.fertnstert.2005.06.026. PMID: 16359965.	Wrong outcomes
Cortes, C. I., Armstrong, J. C., Hawkins, K. C., & Younis, A. (2021). Anti-mullerian hormone (AMH) levels is effective in detection and diagnosis of various polycystic ovarian syndrome (PCOS) phenotypes. In Fertility and Sterility (Vol. 116, Issue 3, p. e120). Elsevier BV. https://doi.org/10.1016/j.fertnstert.2021.07.337	No full text available
Dewailly D. Toward a universal serum antimüllerian hormone threshold as a surrogate for polycystic ovarian morphology on ultrasound: the story is not over…. Fertil Steril. 2021 Oct;116(4):1158-1159. doi: 10.1016/j.fertnstert.2021.08.005. Epub 2021 Sep 2. PMID: 34481641.	Commentary/letter/editorial
Dewailly D. Age-stratified thresholds of anti-Müllerian hormone improve prediction of polycystic ovary syndrome over a population-based threshold. Clin Endocrinol (Oxf). 2017 Dec;87(6):649-650. doi: 10.1111/cen.13479. Epub 2017 Oct 12. PMID: 28949024.	Commentary/letter/editorial
Dumont A, Robin G, Dewailly D. Anti-müllerian hormone in the pathophysiology and diagnosis of polycystic ovarian syndrome. Curr Opin Endocrinol Diabetes Obes. 2018 Dec;25(6):377-384. doi: 10.1097/MED.0000000000000445. PMID: 30299432.	Wrong study design
Farooq, B.; Jahan, S.; Ara, J.; Ghani, U.; Malik, A.; Abbasi, S. Is antimullerian hormone a true ovarian marker for fibroid, polycystic ovary syndrome and hypogonadotropic hypogonadism in infertile women? Rawal Med J 2019;44(4):713-716 No doi	Wrong outcomes
Fraissinet A, Robin G, Pigny P, Lefebvre T, Catteau-Jonard S, Dewailly D. Use of the serum anti-Müllerian hormone assay as a surrogate for polycystic ovarian morphology: impact on diagnosis and phenotypic classification of polycystic ovary syndrome. Hum Reprod. 2017 Aug 1;32(8):1716-1722. doi: 10.1093/humrep/dex239. PMID: 28854589.	No control group
Hanedan N, Ersoy B, Hanedan C, Ozyurt BC, Taneli F. Effect of the presence of polycystic ovary syndrome-related features on anti-Mullerian hormone and androstenedione levels in adolescents with or without menstrual irregularity. Arch Gynecol Obstet. 2022 Aug;306(2):523-531. doi: 10.1007/s00404-022-06505-4. Epub 2022 Mar 30. PMID: 35355114.	Wrong patient population

Hariton, Eduardo; Morris, Jerrine R.; Kao, Chia-Ning; Jaswa, Eleni Greenwood; Quinn, Molly M.; Cedars, Marcelle I.; Huddleston, Heather G. An AMH-based screening tool is both sensitive and specific for predicting a diagnosis of PCOS by Rotterdam criteria. Fertility & Sterility 2020;114():e42-e42. doi: 10.1016/j.fertnstert.2020.08.137	No full text available
Kim, J. Y.; Tfayli, H. M.; Michaliszyn, S. F.; Lee, S.; Nasr, A.; Arslanian, S. A. Anti-mullerian hormone (AMH) in obese adolescent girls with polycystic ovary syndrome (PCOS): cross-sectional and treatment-associated longitudinal changes. Endocrine reviews 2016;37(2): DOI: 10.1210/endo-meetings.2016.RE.12.OR21-3	Wrong study design
Kocaay P, Siklar Z, Buyukfirat S, Berberoglu M. The Diagnostic Value of Anti-Müllerian Hormone in Early Post Menarche Adolescent Girls with Polycystic Ovarian Syndrome. J Pediatr Adolesc Gynecol. 2018 Aug;31(4):362-366. doi: 10.1016/j.jpag.2018.02.126. Epub 2018 Feb 17. PMID: 29462707.	Wrong outcomes
Li M, Ruan X, Ju R, Min M, Xu Z, Luo S, Wang H, Mueck AO. Is anti-Mullerian hormone a useful biomarker in the diagnosis of polycystic ovary syndrome in Chinese adolescents? Gynecol Endocrinol. 2022 Feb;38(2):148-152. doi: 10.1080/09513590.2021.2016694. Epub 2022 Jan 7. PMID: 34994668.	Wrong patient population
Lim, J. W., Brill, S., Shanazarian, M., & Samonte, K. (2019). 90. Anti-Mullerian Hormone As A Diagnostic Tool For Polycystic Ovarian Syndrome In Adolescent Population. In Journal of Adolescent Health (Vol. 64, Issue 2, pp. S48–S49). Elsevier BV. https://doi.org/10.1016/j.jadohealth.2018.10.106	No full text available
Mahboobifard, F., Rahmati, M., & Ramezani Tehrani, F. (2022). A single cut-off value of anti-Müllerian hormone should not be used for the diagnosis of PCOS in all reproductive-aged women. In Human Reproduction (Vol. 37, Issue 3, pp. 621–622). Oxford University Press (OUP). https://doi.org/10.1093/humrep/deac012	commentary/letter/editorial
Merino PM, Villarroel C, Jesam C, López P, Codner E. New Diagnostic Criteria of Polycystic Ovarian Morphology for Adolescents: Impact on Prevalence and Hormonal Profile. Horm Res Paediatr. 2017;88(6):401-407. doi: 10.1159/000481532. Epub 2017 Oct 19. PMID: 29049986.	Wrong patient population
Moolhuijsen LME, Louwers YV, Laven JSE, Visser JA. Comparison of 3 Different AMH Assays With AMH Levels and Follicle Count in Women With Polycystic Ovary Syndrome. J Clin Endocrinol Metab. 2022 Aug 18;107(9):e3714-e3722. doi: 10.1210/clinem/dgac370. PMID: 35737957; PMCID: PMC9387710.	No control group
Nylander M, Frøssing S, Bjerre AH, Chabanova E, Clausen HV, Faber J, Skouby SO. Ovarian morphology in polycystic ovary syndrome: estimates from 2D and 3D ultrasound and magnetic resonance imaging and their correlation to anti-Müllerian hormone. Acta Radiol. 2017 Aug;58(8):997-1004. doi: 10.1177/0284185116676656. Epub 2016 Nov 13. PMID: 28273731.	No control group
Palomaki GE, Kalra B, Kumar T, Patel AS, Savjani G, Torchen LC, Dunaif A, Morrison A, Lambert-Messerlian GM, Kumar A. Adjusting antimüllerian hormone levels for age and body mass index improves detection of polycystic ovary syndrome. Fertil Steril. 2020 Apr;113(4):876-884.e2. doi: 10.1016/j.fertnstert.2019.12.012. Epub 2020 Mar 5. PMID: 32147175; PMCID: PMC7583345.	Wrong outcomes
Ran Y, Yi Q, Li C. The Relationship of Anti-Mullerian Hormone in Polycystic Ovary Syndrome Patients with Different Subgroups. Diabetes Metab Syndr Obes. 2021 Mar 25;14:1419-1424. doi: 10.2147/DMSO.S299558. PMID: 33790608; PMCID: PMC8006968.	Wrong outcomes
Rudnicka E, Kunicki M, Calik-Ksepka A, Suchta K, Duszewska A, Smolarczyk K, Smolarczyk R. Anti-Müllerian Hormone in Pathogenesis, Diagnostic and Treatment of PCOS. Int J Mol Sci. 2021 Nov 19;22(22):12507. doi: 10.3390/ijms222212507. PMID: 34830389; PMCID: PMC8619458.	Wrong study design
Sadiq, I.; Qamar, M.; Janjua, Q.M. Anti-mullerian hormone (AMH) levels in women with and without polycystic ovary syndrome (PCOS). Pak J Med Health Sci 2018;12(2):564-566 No DOI	Wrong outcomes
Sathyapalan T, Al-Qaissi A, Kilpatrick ES, Dargham SR, Keevil B, Atkin SL. Salivary and serum androgens with anti-Müllerian hormone measurement for the diagnosis of polycystic ovary syndrome. Sci Rep. 2018 Feb 28;8(1):3795. doi: 10.1038/s41598-018-22176-1. PMID: 29491484; PMCID: PMC5830572.	Wrong outcomes
Shin, Y. J.; Lee, S.; Lee, J. E.; Won, S.; Kim, M. J. Clinical presentation, hormonal profiles in nulliparous Korean women with polycystic ovarian morphology. (2020). In Clinical and Experimental Obstetrics & Gynecology (Vol. 47, Issue 3, p. 359). IMR Press. https://doi.org/10.31083/j.ceog.2020.03.5287	No control group
Simpson S, Seifer DB, Shabanova V, Lynn AY, Howe C, Rowe E, Caprio S, Vash-Margita A. The association between anti-Müllerian hormone and vitamin 25(OH)D serum levels and	Wrong outcomes

polycystic ovarian syndrome in adolescent females. Reprod Biol Endocrinol. 2020 Nov 21;18(1):118. doi: 10.1186/s12958-020-00676-y. PMID: 33218348; PMCID: PMC7679991.	
Singh, K.; Kumari, S.; Shashi, K.; Tiwary, B.; Nishat, H. A Study of the Status of Ovarian Reserve in Infertile Women Attending Tertiary Care Centre. Intl J Pharm Clin Res 2021;13(5):239-249 No DOI	Wrong patient population
Strowitzki T. Advanced diagnosis of polycystic ovary syndrome-new prediction models with standard parameters. Fertil Steril. 2021 Jan;115(1):92-93. doi: 10.1016/j.fertnstert.2020.09.031. Epub 2020 Sep 25. PMID: 32988616.	Commentary/letter/editorial
Svetlana E, Natalia A, Anzhelika B. Indicators of an ovarian reserve in women of early reproductive age with PCOS depending on the phenotype. Horm Mol Biol Clin Investig. 2019 Jun 20;39(3):/j/hmbci.2019.39.issue-3/hmbci-2018-0081/hmbci-2018-0081.xml. doi: 10.1515/hmbci-2018-0081. PMID: 31219793.	Wrong outcomes
Tang, L.-L., Zhang, L.-S., Zhu, X.-Y., & Shi, Y.-L. (2020). Potential Application of Anti-Müllerian Hormone in Polycystic Ovary Syndrome According to Chinese Classification Criteria: A Retrospective Analysis. In Reproductive and Developmental Medicine (Vol. 4, Issue 4, pp. 228–232). Ovid Technologies (Wolters Kluwer Health). https://doi.org/10.4103/2096-2924.305927	Wrong patient population
Teede H, Misso M, Tassone EC, Dewailly D, Ng EH, Azziz R, Norman RJ, Andersen M, Franks S, Hoeger K, Hutchison S, Oberfield S, Shah D, Hohmann F, Ottey S, Dabadghao P, Laven JSE. Anti-Müllerian Hormone in PCOS: A Review Informing International Guidelines. Trends Endocrinol Metab. 2019 Jul;30(7):467-478. doi: 10.1016/j.tem.2019.04.006. Epub 2019 May 31. PMID: 31160167.	Meta-analysis/ systematic review
Tsukui Y, Kitahara Y, Hasegawa Y, Kobayashi M, Osuka S, Iwase A. Anti-Müllerian hormone levels in the diagnosis of adolescent polycystic ovarian syndrome: a systematic review and meta-analysis. Endocr J. 2022 Aug 29;69(8):897-906. doi: 10.1507/endocrj.EJ22-0081. Epub 2022 Jun 8. PMID: 35675999.	Meta-analysis/ systematic review
Weedin, Elizabeth A.; Burks, Heather R.; Yu, Xichun; Li, Hong Liang; Aston, Christopher E.; Kem, David C.; Craig, LaTasha B. A novel diagnostic approach for polycystic ovary syndrome diagnosis using gonadotropin releasing hormone receptor autoantibody activity and antimullerian hormone. Fertility & Sterility 2020;114():e41-e41. DOI: 10.1016/j.fertnstert.2020.08.134.	No full text available
Xu H, Feng G, Alpadi K, Han Y, Yang R, Chen L, Li R, Qiao J. A Model for Predicting Polycystic Ovary Syndrome Using Serum AMH, Menstrual Cycle Length, Body Mass Index and Serum Androstenedione in Chinese Reproductive Aged Population: A Retrospective Cohort Study. Front Endocrinol (Lausanne). 2022 Mar 17;13:821368. doi: 10.3389/fendo.2022.821368. PMID: 35370993; PMCID: PMC8970043.	Wrong outcomes
Zhao Y, Zhao Y, Wang C, Liang Z, Liu X. Diagnostic value of anti-müllerian hormone as a biomarker for polycystic ovary syndrome: a meta-analysis update. Endocr Pract. 2019 Oct;25(10):1056-1066. doi: 10.4158/EP-2019-0098. Epub 2019 Aug 15. PMID: 31414908.	Meta-analysis/ systematic review

1. STUDY CHARACTERISTICS AND DATA EXTRACTION TABLE

INDEX TEST: AMH					OUTCOME TYPE: PCOS								
COMPARISON: case control (PCOS versus Controls)													
Author, year	**Unit of outcome**	**Method of measurement**	**N**		**Threshold cut-off**	**True Pos**	**False Pos**	**False Neg**	**True Neg**	**Sensitivity (95% CI)**	**Specificity (95%CI)**	**AUC**	**Precision**
Al-Naffakh 2020	ng/ml	Elfa MINIVIDAS	Rotterdam P: 80, C: 40		1.19	46	6	31	34	0.61 (0.50-0.72)	0.85 (0.70-0.94)	0.575	0.471-0.679
Al-Jefout 2021	pmol/l	Roche COBAS 8000	Rotterdam P: 85, C: 20		23.97	65	3	20	17	0.76 (0.66-0.85)	0.85 (0.62-0.97)	0.844	0.756-0.932
Agrawal 2018	ng/mL	ELISA	Rotterdam P: 32 C: 32		3.6	25	4	7	28	0.78 (0.60-0.91)	0.88 (0.71-0.96)	0.907	0.808-0.965
Ahmed 2019	ng/mL	Ultrasensitive ELISA AnshLabs	Rotterdam P: 79 C: 69		3.19	57	21	22	48	0.72 (0.61-0.82)	0.70 (0.57-0.80)	0.785	0.713-0.858
Aydogmus 2018	ng/mL	ELISA Beckman Coulter	Rotterdam P: 70 C: 70 (PCOM)		3.51	51	17	19	53	0.73 (0.61-0.83)	0.76 (0.64-0.85)	0.781	not reported
Bakeer 2018	pmol/l	Gen II ELISA (Beckman Coulter, Inc.)	Rotterdam P: 53 C: 17		42.63	38	3	15	14	0.72 (0.58-0.83)	0.82 (0.57-0.96)	0.634	0.5-0.798
Bansal 2020	ng/mL	random access fully automated immunoassay system (DXI-600, Beckman Coulter, USA	Rotterdam P: 31 C: 89		5.1	22	16	9	73	0.71 (0.52-0.86)	0.82 (0.72-0.89)	0.814	not reported
Bozdag 2019	ng/mL	Elecsys AMH Roche	C: 190 P : PCOM≥12	Rotterdam: 78	4.17	31	15	47	175	0.40	0.922	0.74	0.67-0.81
				NIH: 24	5.00					0.50	0.932	0.83	0.75-0.91
				AE: 60	4.38					0.333	0.91	0.8	0.74-0.85
			C:233 P: PCOM≥20	Rotterdam: 40	4.68					0.40	0.922	0.83	0.77-0.88
				AE: 35	4.86					0.40	0.926	0.82	0.76-0.88
Calsadei 2018	ng/mL	till 2013 AMH-EIA (reference A11893, Immunotech, Beckman Coulter; from 2013 AMH Gen II ELISA kit (Beckman Coulter).	NIH: P 38 suspected P 36 C 56		5.20					0.79	0.80	0.86	not reported
			Rotterdam: P: 56 C: 84		4.57	44	16	12	68	0.79	0.81	0.85	NR
			AEPCOS P 41		4.85					0.80	0.78	0.85	NR

			C: 99									
Calzada 2019	ng/mL	CobasE170, Roche, Mannheim, Germany	Rotterdam P: 77 C: 106	5.17	48	17	29	89	0.62 (0.51-0.73)	0.84 (0.76-0.90)		
Carmina 2016	pmol/l	Gen II ELISA Beckman	Rotterdam P: 113 ; C: 47	33.57	89	2	24	45	0.79 (0.70-0.86)	0.96 (0.85-0.99)	0.952	SD=0.014
			A+B phenotype P: 78 ; C: 47	33.57					0.91	0.96	0.985	SD=0.002
			C phenotype P: 20	33.57					0.50	0.96	NR	NR
			D phenotype P:15	33.57					0.53	0.96	NR	NR
Casadei 2013	pmol/L	Gen II ELISA Beckman	NIH P: 22; C: 22	33	21	1	1	21	0.77 (0.55-0.92)	0.95 (0.77-1.00)	0.970	0.02-0.92
Cassar 2014	pmol/l	Automated Beckman	Rotterdam P: 43; C: 35	30	35	7	8	28	0.81 (0.67-0.92)	0.80 (0.63-0.92)	0.829	0.736-0.923
Chao 2012	ng/ml	Active MIS/AMH ELISA USA	Rotterdam P: 31; C24	25	23	5	8	19	0.74 (0.55-0.88)	0.79 (0.58-0.93)	NR	NR
Cengiz 2014 (adolescents)	ng/ml	Eastbiopharm Hangzou	Rotterdam (OA+HA+PCOM) P: 58; C: 28	NR	NR	NR	NR	NR	NR	NR	0.592	0.460-0.725
Deveer 2015	ng/ml	Gen II Beckman	Rotterdam (OA+HA+PCOM) P 50; C 25	6.66	31	6	19	19	0.62(0.47-0.75)	0.76 (0.55-0.91)	0.82	NR
Dewailly 2011	pmol/l	Automated Beckman	Rotterdam P: 62; C: 66	35	57	2	5	64	0.92 (0.82-0.97)	0.97 (0.89-1.00)	0.973	0.947-0.998
Dewailly 2014	pmol/l	Gen II ELISA Beckman	Rotterdam P: 95; C: 521	28	80	13	15	508	0.84 (0.75-0.91)	0.98 (0.96-0.99)	0.948	0.915-0.982
			HA+PCOM P: 67; C: 521	28					0.612	0.975	0.894	0.852-0.936
			OA+ PCOM P: 110; C: 521	28					0.818	0.975	0.938	0.908-0.969
Eilertsen 2012	pmol/l	ELISA DSL	Rotterdam P: 56; C: 206	10	55	11	1	195	0.98 (0.90-1.00)	0.95 (0.91-0.97)	0.992	0.986-0.999
			AES P: 44; C218	20							0.994	0.987-1.00
Evliyaoglu 2020	ng/mL	Roche AMH-Elecsys Assay	Rottedam P: 1132; C: 3055	5.33	1007	122	125	2933	0.89 (0.87-0.91)	0.96 (0.95-0.97)	0.98	0.94-1.00
Farooq 2022 (adolescents)	ng/mL	ELISA Immunoconcept	Rotterdam P: 50; C: 50	14	24	12	26	38	0.48 (0.34-0.63)	0.76 (0.62-0.87)	0.678	NR
Fu 2021	ng/ml	ELISA kit (MBS 702,605, MyBioSource Company, USA	Rotterdam P: 30; C: 30	5.8	30	0	0	30	1.00 (0.88-1.00)	1.00 (0.88-1.00)	0.882	NR
Gabr 2019	ng/mL	AMH was analyzed using an ELISA kit (MBS 702605, My	Rotterdam P: 30; C15	5.8	30	0	0	15	1.00 (0.88-1.00)	1.00 (0.78-1.00)	1.00	NR

		Biosource Company, USA)									
Hart 2010 (adolescents)	pmol/l	Gen II ELISA Beckman	Rotterdam P: 64; C 149	30	34	45	30	104	0.53 (0.40-0.66)	0.70 (0.62-0.77)	0.64	0.55-0.72
			NIH P: 36; C: 177	30							0.61	0.49-0.72
Homburg 2013	ng/ml	Gen II LISA Beckman	Rotterdam P: 90; C 90	48	54	2	36	88	0.60 (0.49-0.70)	0.98 (0.92-1.00)	0.805	NR
Jacob 2017	pmol/l	Beckman Coulter Gen II ELISA kit	Rotterdam P: 102 C: 151	29	90	41	12	110	0.88(0.80-0.94)	0.73 (0.64-0.81)	0.84	NR
Jamil 2016	ng/ml	Gen II Beckman	Rotterdam P: 26; C: 263	3.375	227	68	36	195	0.86(0.82-0.90)	0.74 (0.68-0.79)	0.866	0.836-0.896
Kakkad 2021	ng/ml	Beckman Coulter Immunotech - Unicel Dx1800	Rotterdam, all ages P: 200; C:488	3.75	162	148	38	340	0.81 (0.75-0.86)	0.70 (0.65-0.74)	0.837	0.80-0.87
			age 20-09 years P: 98; C:184	5.46					0.671	0.812	0.801	
			age 30-40 years P:102; C: 304	3.46					0.852	0.726	0.851	
Khashchenko 2020 (adolescents)	ng/ml	immune DYNEX DSC system analyzers	Rotterdam (OA+HA+PCOM) P: 130; C: 30	7.20	99	3	31	27	0.76	0.89	0.869	NR
Kim 2017 & 2016 (adolescents)	pmol/l	Ultrasens ELISA Ansh	NIH P: 46; C:43	44.71	31	8	15	35	0.67 (0.52-0.80)	0.81 (0.67-0.92)	0.788	0.687-0.868
Koninger 2014	pmol/ml	Gen II Elisa Beckman	Rotterdam severe P: 59; C: 48	25	50	5	9	43	0.71 (0.58-0.82)	0.90 (0.77-0.97)	0.88	0.80-0.95
			Rotterdam mild P: 21; C:48	25					71.4	0.896	0.80	0.65-0.91
Kumari 2018	ng/mL	AMH-EIA Beckman Coulter	Rotterdam P: 80; C: 80	5	73	4	7	76	0.91 (0.83-0.96)	0.95 (0.88-0.99)	0.99	NR
Lauritsen 2014	pmol/l	Automated Beckman	Rotterdam P: 74; C: 373	18	68	7	6	366	0.92 (0.83-0.97)	0.98 (0.96-0.99)	0.994	0.990-0.999
Le 2019	pmol/l	Elecsys Roche (ECLIA technology)	Rotterdam P: 441; C:422	32.79	346	102	95	320	0.78 (0.74-0.82)	0.76 (0.71-0.80)	0.852	0.826-0.875
Li 2010	pmol/l	ELISA DSL	Rotterdam P: 47; C: 40	14	29	12	18	28	0.62 (0.46-0.75)	0.70 (0.53-0.83)	0.664	0.551-0.778
Li 2012	pmol/l	ELISA DSL	Rotterdam P: 131; C:61	3.92	85	23	46	38	0.65 (0.56-0.73)	0.62 (0.49-0.74)	0.68	0.60-0.76
			HA+ P: 62; C: 61	4.23					0.82	0.64	0.82	0.72-0.92
			HA- P: 69; C61	3.76					0.64	0.62	0.66	0.56-0.75
Li 2020	MoM	Beckman-Coulter	Rotterdam C: 473; C: 278	1.32	378	78	95	200	0.80 (0.76-0.83)	0.72 (0.66-0.77)	0.852	0.825-0.877
Lie Fong 2017	ng/ml	ELISA Gen II Beckman Coulter	Rotterdam (OA+HA) Young: P: 411; C 113	5.5	337	21	74	92	0.82 (0.78-0.86)	0.81 (0.73-0.88)	0.903	0.876-0.930

			Rotterdam (OA+HA) Old" P: 237 , C 97	5.0	195	6	42	91	0.824	0.935	0.948	0.927-0.970
Lin 2011	ng/ml	ELISA Diagnostic systems	Rotterdam P 126, C 164	7.3	88	39	38	125	0.70(0.61-0.78)	0.76 (0.69-0.83)	0.774	0.720-0.829
Mahajan 2019	ng/ml	Elecsys Roche	Rotterdam P: 133 ; C: 165	5.03	94	33	39	132	0.71 (0.62-0.78)	0.80 (0.73-0.86)	0.826	NR
Matsuzaki 2017	ng/ml	Elecsys Roche	Rotterdam P: 114 C; 95	7.33	51	22	63	73	0.45 (0.35-0.54)	0.77 (0.67-0.85)	NR	NR
Okcu 2018	ng/ml	ELISA	Rotterdam P: 50, C: 50	4.1	42	10	8	40	0.84 (0.71-0.93)	0.80 (0.66-0.90)	0.88	NR
Oueslati 2022	ng/ml	ELISA	Rotterdam P: 20, C: 30	1.14	17	13	3	17	0.85 (0.62-0.97)	0.57 (0.37-0.75)	0.714	0.535-0.865
Pankhurst 2017	ng/ml	GenII Beckman	Rotterdam P: 45, C: 23	NR	34	3	11	20	0.76 (0.60-0.87)	0.87 (0.66-0.97)	0.86	0.73-0.94
Pigny 2006	pmol/l	Automated Beckman	Rotterdam P: 73, C: 96	60	49	8	24	88	0.67 (0.55-0.78)	0.92 (0.84-0.96)	0.851	0.796-0.905
Pigny 2016	pmol/l	Gen II ELISA Beckman	Rotterdam equiv P: 47, C 48	57.28	35	4	12	44	0.74 (0.60-0.86)	0.92 (0.80-0.98)	0.944	0.901-0.987
Prieto-Sanchez 2022	ng/ml	Elecsys, Roche.	Rotterdam P: 126, C: 159	3.68	103	46	23	113	0.82 (0.74-0.88)	0.71 (0.63-0.78)	0.84	0.79-0.88
Quinn 2017	pmol/l	ELISA Ansh	Rotterdam (total group) P: 391, C: 245	55.36	321	54	70	191	0.82 (0.78-0.86)	0.78 (0.72-0.83)	NR	NR
			age : 25-29 years n= 269	73.21					0.76	0.84		
			age 30-34 years n= 244	62.50					0.75	0.84		
			age 35-39 years n= 123	37.50					0.84	0.77		
Ramezani Tehrani 2021	ng/ml	Gen II Beckman	Rotterdam P: 303, C: 500	NR	NR	NR	NR	NR	NR	NR	NR	Bayesian method
Sahmay 2013	pmol/l	ELISA	Rotterdam P: 419, C 151	28.14	335	15	84	136	0.80 (0.76-0.84)	0.90 (0.84-0.94)	0.916	0.897-0.935
Sahmay 2014	pmol/l	ELISA	Rotterdam P: 228, C: 378	27.14	186	56	42	322	0.82 (0.76-0.86)	0.85 (0.81-0.89)	0.89	0.87-0.92
			AES P: 195. C: 411	27.14					0.80	0.802	0.87	0.84-0.90
			NIH P: 164, C: 442	27.14					0.807	0.747	0.86	0.82-0.89
Saikumar 2013	pmol/l	ELISA Beckman	Rotterdam P: 60, C: 60	23.86	59	4	1	56	0.98 (0.91-1.00)	0.93 (0.84-0.98)	0.956	NR
Sathyapalan 2018	pmol/l	Automated Beckman	Rotterdam (OA+HA+PCOM) P: 105, C: 65	35 (literature)	58	15	47	50	0.55(0.45-0.64)	0.77 (0.65-0.86)		

				46 (95th percentile AMH controls					0.41	0.86	0.76	SE= 0.04
Savas-Erdeve 2016 (adolescents)	ng/ml	Ultra sens ELISA Ansh	Rotterdam P: 21 C: 30	7.25	17	12	4	18	0.833	0.585	0.7	0.591-0.808, P=0.001
Saxena 2018	ng/l	ELISA Immunoconcept	Rotterdam P: 45, C: 45	3.44	35	14	10	31	0.78 (0.63-0.89)	0.69 (0.53-0.82)	0.778	0.678-0.859
Sharma 2019	ng/mL	Ultrasensitive AMH, Ansh	Rotterdam P: 45, C: 45	3.98	37	3	8	42	0.82 (0.68-0.92)	0.93 (0.82-0.99)	0.987	NR
Shi 2019	ng/mL	Elecsys Roche	Rotterdam P: 56, C: 52	6.09	49	6	7	46	0.88 (0.76-0.95)	0.88 (0.77-0.96)	0.952	0.92-0.99
Singh 2020	ng/ml	ELISA Newconcept Biodetect	Rotterdam P: 50, C: 50	4.22	46	0	4	50	0.92 (0.81-0.98)	1.00(0.93-1.00)	0.98	0.929-0.998
Song 2017	ng/ml	ELISA Beckman	Rotterdam P: 207, C: 220	10	146	17	61	204	0.71 (0.64-0.77)	0.92 (0.88-0.95)	0.876	0.838-0.914
Song 2021	ng/ml	Elecsys Roche	Rotterdam 12-20 years P: 87, C: 42	4.12	67	14	20	28	0.77 (0.67-0.85)	0.67 (0.50-0.80)	0.741	0.641-0.840
			Rotterdam 21-34 years P: 308, C: 161	5.67	213	37	95	124	0.69 (0.64-0.74)	0.77 (0.70-0.83)	0.785	0.740-0.830
			Rotterdam 35-46 years P45 C: 126	1.90	35	34	10	92	0.78 (0.63-0.89)	0.73 (0.64-0.81)	0.789	0.704-0.874
Sopher 2014 (adolescents)	pmol/l	Gen II ELISA Beckman	NIH P: 15, C:16	24.29	6	1	9	15	0.40 (0.16-0.68)	0.94 (0.70-1.00)	NR	NR
Sova 2019	pmol/l	VIDAS (bioMérieux)	Rotterdam P: 319, C 96	41.2	214	16	105	80	0.67 (0.62-0.72)	0.83 (0.74-0.90)	NR	NR
Tokmak 2015 (adolescents)	ng/ml	Immunoassay Eastbiopharm Co	Rotterdam P: 43, C 47	14	21	11	22	36	0.49 (0.33-0.65)	0.77 (0.62-0.88)	0.579	0.453-0.705
Tola 2018	ng/ml	ELISA (Beckman)	Rotterdam P: 230, C: 100	3.1	212	4	18	96	0.92 (0.88-0.95)	0.96 (0.90-0.99)	0.98	NR
Tremellen 2015	pmol/l	Elecsys AMH Beckman	Rotterdam P: 43, C: 113	36	36	20	7	93	0.84 (0.69-0.93)	0.82 (0.74-0.89)	0.917	NR
Tunc 2021 (adolescents)	ng/ml	ELISA	Rotterdam P: 55, C: 25	5.8	39	4	17	22	0.70 (0.56-0.81)	0.85 (0.65-0.96)	NR	NR
Vagios 2021	ng/ml	Ansh, pico	Rotterdam P: 228, C 689	6.25	165	101	63	588	0.72 (0.66-0.78)	0.85 (0.82-0.88)	0.86	0.83-0.90
Villarroel 2015 (adolescents)	Pmol/l	Automated Beckman	Hirsutism + oligomenorrhea P: 26; C: 42	61.5	17	11	9	32	0.667	0.75	0.74	NR
Wissing 2019	-	Anshlabs ELISAs AL-124 (also other assays)	Rotterdam P: 88, C 24	-	-	-	-	-	NR	NR	0.899	0.827-0.972
Wiweko 2014	pmol/l	Gen II ELISA Beckman	Rotterdam P: 71, C: 71	31.79	54	18	17	53	0.76 (0.64-0.85)	0.75 (0.63-0.84)	0.870	0.81-0.92
Wongwananuruk 2018	ng/ml	Elecsys Roche	Rotterdam P: 55, C: 63	6.3	34	2	21	61	0.62 (0.48-0.75)	0.97 (0.89-1.00)	0.903	0.851-0.956

Woo 2012	pmol/l	Automated AMH Beckman	Rotterdam P: 87, C: 53	55.86	66	7	21	46	0.76 (0.65-0.84)	0.87 (0.75-0.95)	0.868	0.801-0.919
Yetim 2016 (adolescents)	pmol/l	Automated Beckman	Rotterdam P: 53, C: 26	43.57	43	2	10	24	0.81 (0.68-0.91)	0.92 (0.75-0.99)	0.88	0.80-0.96
Yue 2018	ng/ml	Union immunoanalyzer	Rotterdam (all ages) P: 653, C: 118	7.69	485	22	168	96	0.74 (0.71-0.78)	0.81 (0.73-0.88)	0.854	0.826-872
			20-29 years	8.16					0.78	0.809	0.846	
			30-49 years	5.89					0.826	0.798	0.865	
Zadehmodarres 2015	pmol/l	ELISA Beckman	Rotterdam P: 60, C: 57	22.5	42	13	18	44	0.70 (0.57-0.81)	0.77 (0.64-0.87)	NR	NR

6. FINDINGS

- **EVIDENCE SUMMARY:**

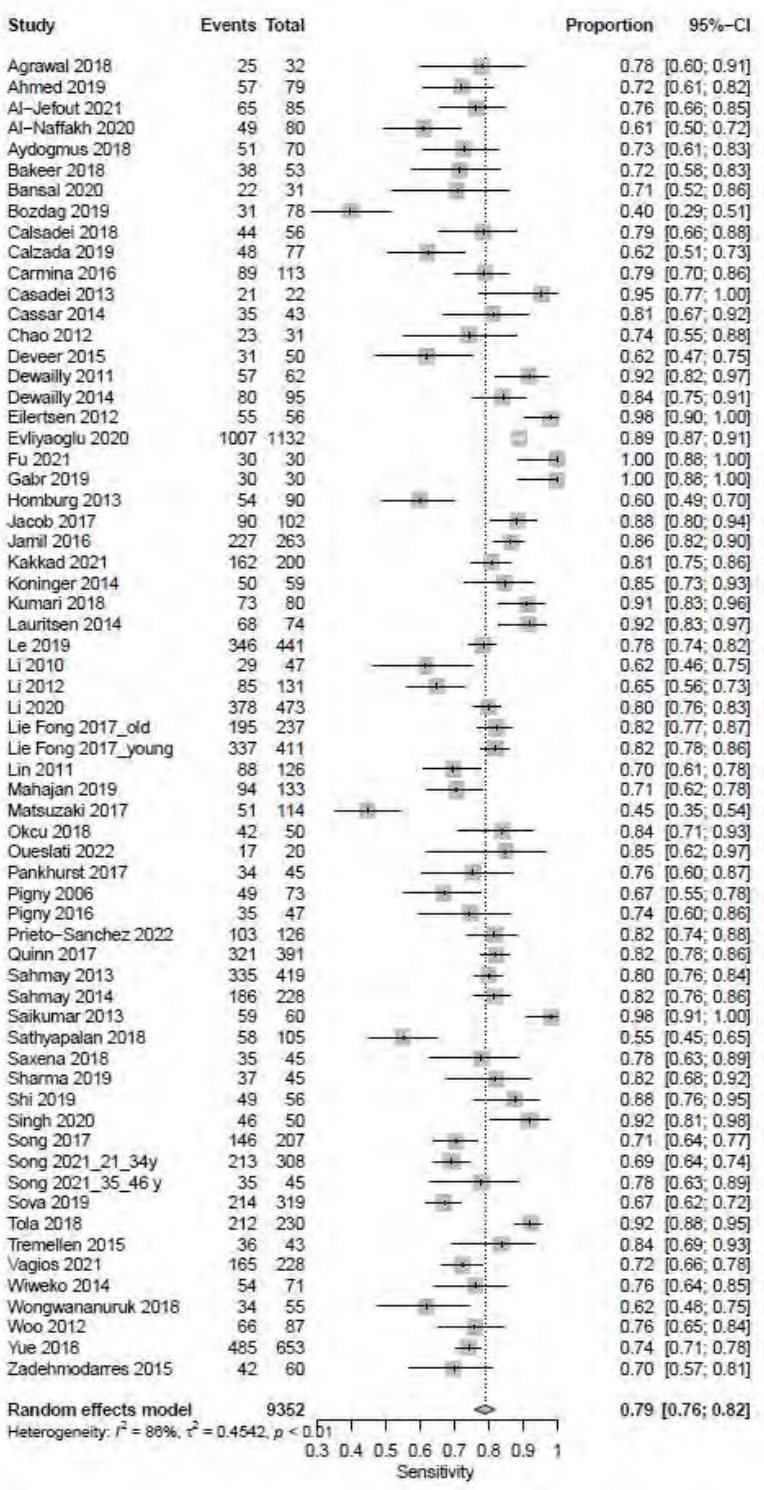
A total of 53 new studies were included in the systematic review in addition to the 28 studies included in the previous search for the guideline in 2018. In total 62 studies were included in meta-analysis in adults and 11 studies for adolescents for AMH as a substitute for PCOS. Six studies addressing AMH as a substitute for PCOM in adults were included. Two recent published meta-analyses on this topic (Anand et al and Zhao et al) were also included in the systematic review.

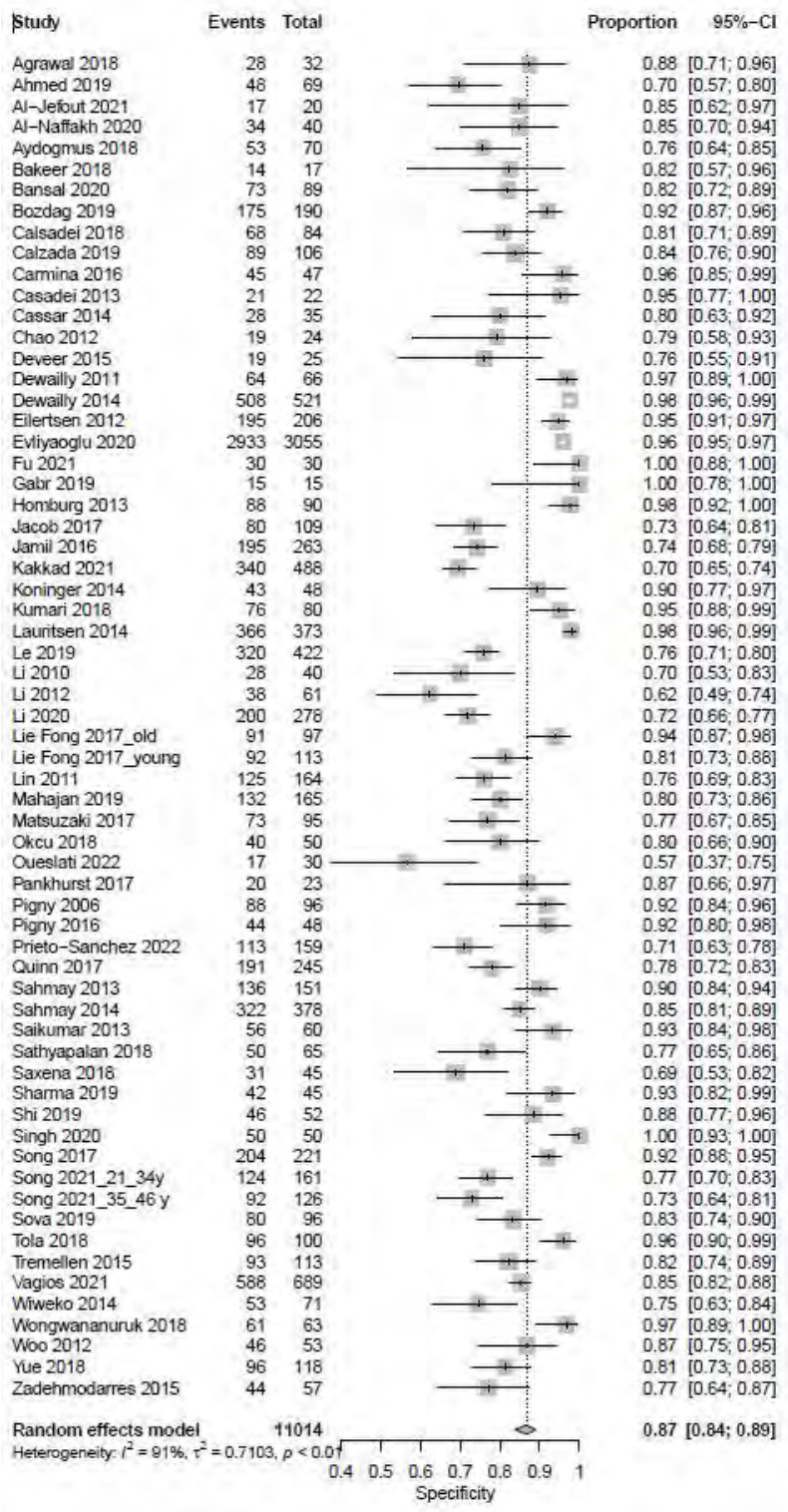
- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

Included studies determined the diagnostic test accuracy of AMH for PCOS or AMH for PCOM. Hierarchical random effects models combine the estimates of sensitivity and specificity. The bivariate model was used, which focusses on estimation of a summary point. Pooled analysis showed a sensitivity and specificity of 0.66 (0.58-0.73) and 0.78 (0.71-0.83) respectively in adolescents (n=11 studies) for the use of AMH as a substitute for PCOS diagnosis. In adults, pooled sensitivity was 0.79 (0.76-0.82) and pooled specificity was 0.87 (0.84-0.89) for AMH as a substitute for PCOS diagnosis. Excluding studies with high risk of bias, did not change the results. Also, the pooled sensitivity and specificity didn't change between studies where PCOM was excluded from the control group and studies where PCOM was not excluded. Pooled sensitivity and specificity were significantly different between automated immunoassay (n=13), Elecsys immunoassay (n=10) and ELISA assay except high sensitivity assay (n=34), with pooled sensitivity ranging from 0.74 to 0.82 and pooled specificity ranging from 0.85 to 0.88. Only 6 studies investigated the diagnostic accuracy of AMH as a substitute for PCOM in adults. A large heterogeneity exists between the studies (I2 = 93% for sensitivity and I2 = 76% for specificity). Random effects model revealed a pooled sensitivity of 0.80 (0.72-0.86) and pooled specificity of 0.84 (0.79-0.88).

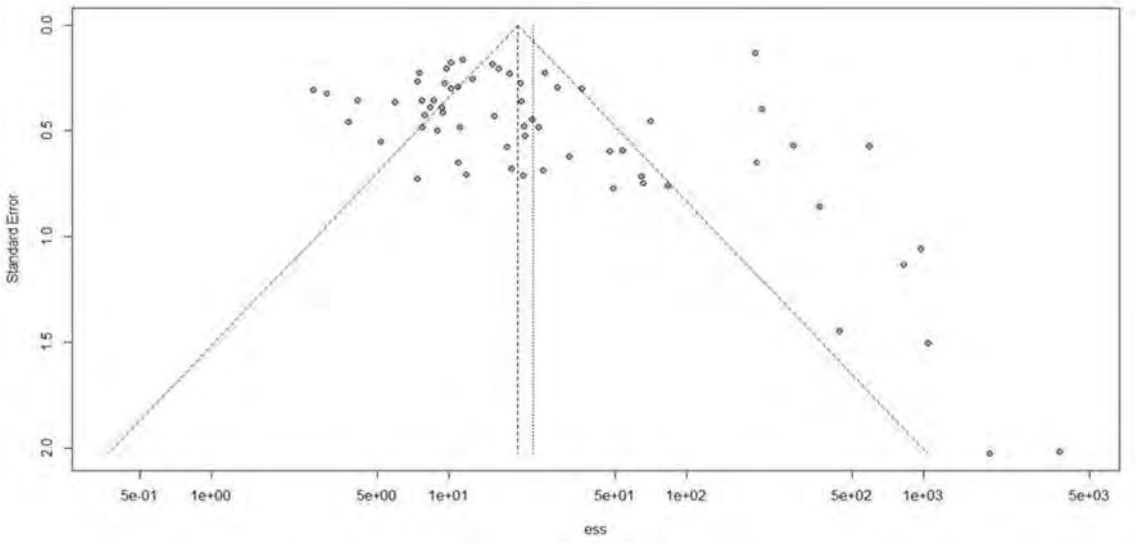
AMH assays have improved over time, however there is no international reference standard for AMH assay. The included studies identified different AMH thresholds from their ROC curves. Factors influencing these thresholds include the use of different AMH assays, differences in age or BMI and whether PCOS or PCOM was excluded in the control population.

5.1. Forest plot. AMH as diagnostic marker for PCOS in adults. Sensitivity and specificity of all studies in adults. No covariates included. Additional analyses in subgroups are possible.

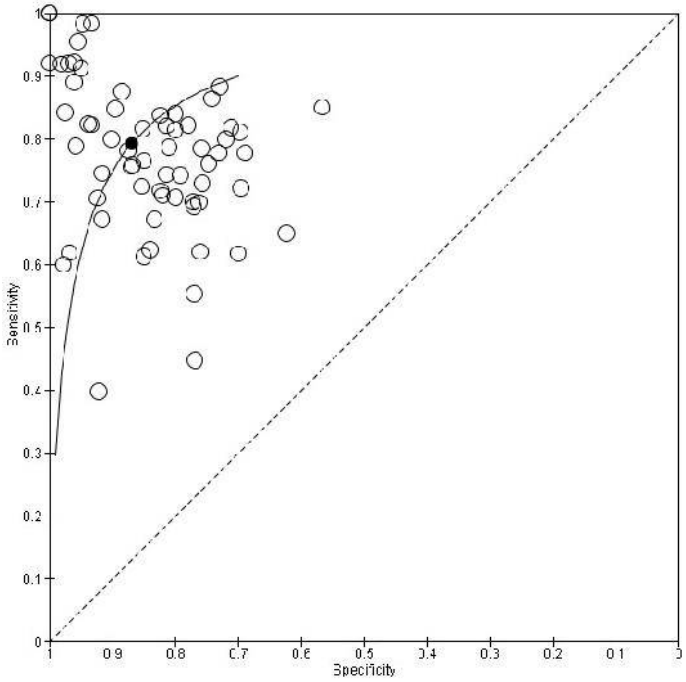



Study Events Total Proportion 95%−CI
Agrawal 2018 28 32 0.88 [0.71; 0.96]
Ahmed 2019 48 69 0.70 [0.57; 0.80]
Al−Jefout 2021 17 20 0.85 [0.62; 0.97]
Al−Naffakh 2020 34 40 0.85 [0.70; 0.94]
Aydogmus 2018 53 70 0.76 [0.64; 0.85]
Bakeer 2018 14 17 0.82 [0.57; 0.96]
Bansal 2020 73 89 0.82 [0.72; 0.89]
Bozdag 2019 175 190 0.92 [0.87; 0.96]
Calsadei 2018 68 84 0.81 [0.71; 0.89]
Calzada 2019 89 106 0.84 [0.76; 0.90]
Carmina 2016 45 47 0.96 [0.85; 0.99]
Casadei 2013 21 22 0.95 [0.77; 1.00]
Cassar 2014 28 35 0.80 [0.63; 0.92]
Chao 2012 19 24 0.79 [0.58; 0.93]
Deveer 2015 19 25 0.76 [0.55; 0.91]
Dewailly 2011 64 66 0.97 [0.89; 1.00]
Dewailly 2014 508 521 0.98 [0.96; 0.99]
Eilertsen 2012 195 206 0.95 [0.91; 0.97]
Evliyaoglu 2020 2933 3055 0.96 [0.95; 0.97]
Fu 2021 30 30 1.00 [0.88; 1.00]
Gabr 2019 15 15 1.00 [0.78; 1.00]
Homburg 2013 88 90 0.98 [0.92; 1.00]
Jacob 2017 80 109 0.73 [0.64; 0.81]
Jamil 2016 195 263 0.74 [0.68; 0.79]
Kakkad 2021 340 488 0.70 [0.65; 0.74]
Koninger 2014 43 48 0.90 [0.77; 0.97]
Kumari 2018 76 80 0.95 [0.88; 0.99]
Lauritsen 2014 366 373 0.98 [0.96; 0.99]
Le 2019 320 422 0.76 [0.71; 0.80]
Li 2010 28 40 0.70 [0.53; 0.83]
Li 2012 38 61 0.62 [0.49; 0.74]
Li 2020 200 278 0.72 [0.66; 0.77]
Lie Fong 2017_old 91 97 0.94 [0.87; 0.98]
Lie Fong 2017_young 92 113 0.81 [0.73; 0.88]
Lin 2011 125 164 0.76 [0.69; 0.83]
Mahajan 2019 132 165 0.80 [0.73; 0.86]
Matsuzaki 2017 73 95 0.77 [0.67; 0.85]
Okcu 2018 40 50 0.80 [0.66; 0.90]
Oueslati 2022 17 30 0.57 [0.37; 0.75]
Pankhurst 2017 20 23 0.87 [0.66; 0.97]
Pigny 2006 88 96 0.92 [0.84; 0.96]
Pigny 2016 44 48 0.92 [0.80; 0.98]
Prieto−Sanchez 2022 113 159 0.71 [0.63; 0.78]
Quinn 2017 191 245 0.78 [0.72; 0.83]
Sahmay 2013 136 151 0.90 [0.84; 0.94]
Sahmay 2014 322 378 0.85 [0.81; 0.89]
Saikumar 2013 56 60 0.93 [0.84; 0.98]
Sathyapalan 2018 50 65 0.77 [0.65; 0.86]
Saxena 2018 31 45 0.69 [0.53; 0.82]
Sharma 2019 42 45 0.93 [0.82; 0.99]
Shi 2019 46 52 0.88 [0.77; 0.96]
Singh 2020 50 50 1.00 [0.93; 1.00]
Song 2017 204 221 0.92 [0.88; 0.95]
Song 2021_21_34y 124 161 0.77 [0.70; 0.83]
Song 2021_35_46 y 92 126 0.73 [0.64; 0.81]
Sova 2019 80 96 0.83 [0.74; 0.90]
Tola 2018 96 100 0.96 [0.90; 0.99]
Tremellen 2015 93 113 0.82 [0.74; 0.89]
Vagios 2021 588 689 0.85 [0.82; 0.88]
Wiweko 2014 53 71 0.75 [0.63; 0.84]
Wongwananuruk 2018 61 63 0.97 [0.89; 1.00]
Woo 2012 46 53 0.87 [0.75; 0.95]
Yue 2018 96 118 0.81 [0.73; 0.88]
Zadehmodarres 2015 44 57 0.77 [0.64; 0.87]
Random effects model 11014 0.87 [0.84; 0.89]
Heterogeneity: I^2 = 91%, τ^2 = 0.7103, p < 0.01
0.4 0.5 0.6 0.7 0.8 0.9 1
Specificity

Funnel plot – Diagnostic marker AMH for PCOS in adults

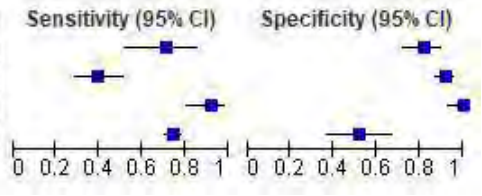


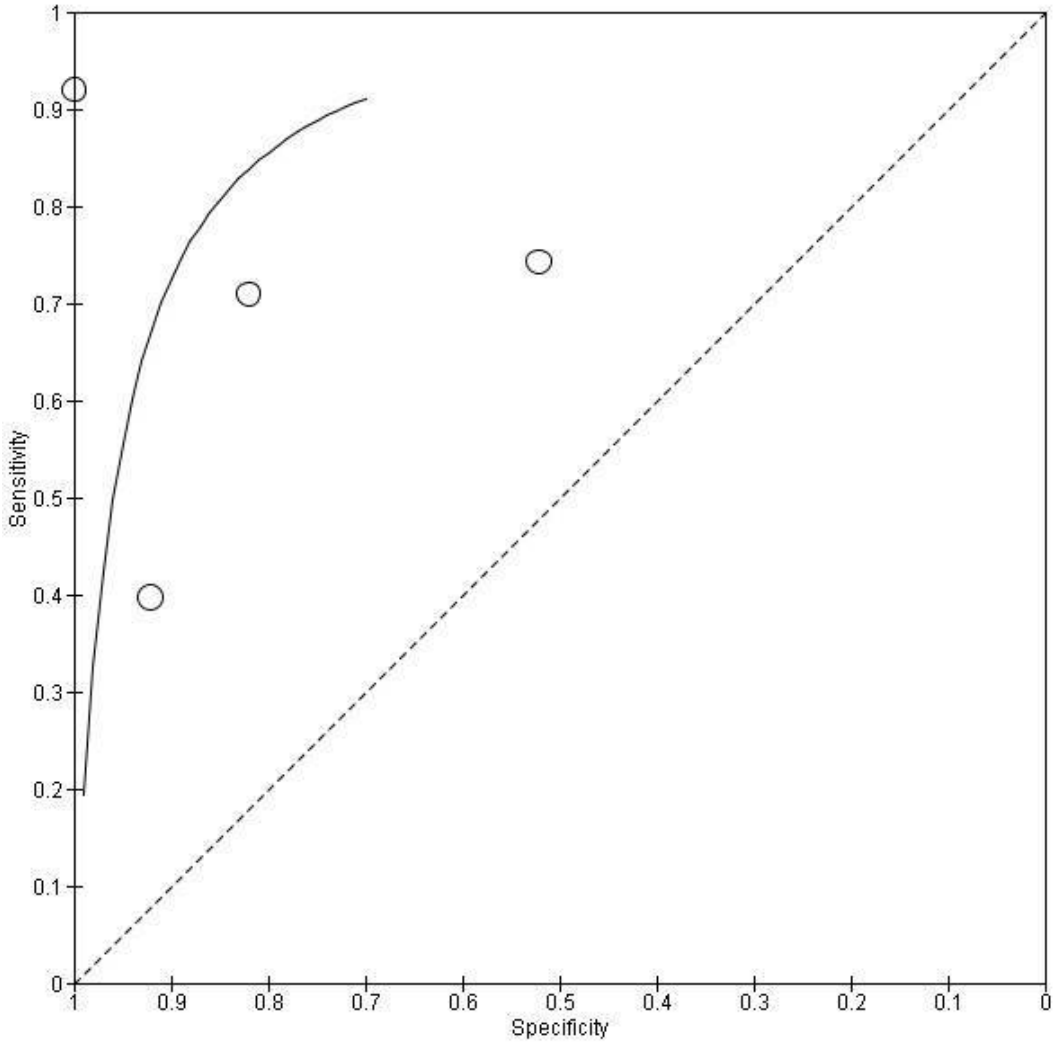
Summary ROC curve with summary point in black (bivariate model) AMH for PCOS in adults



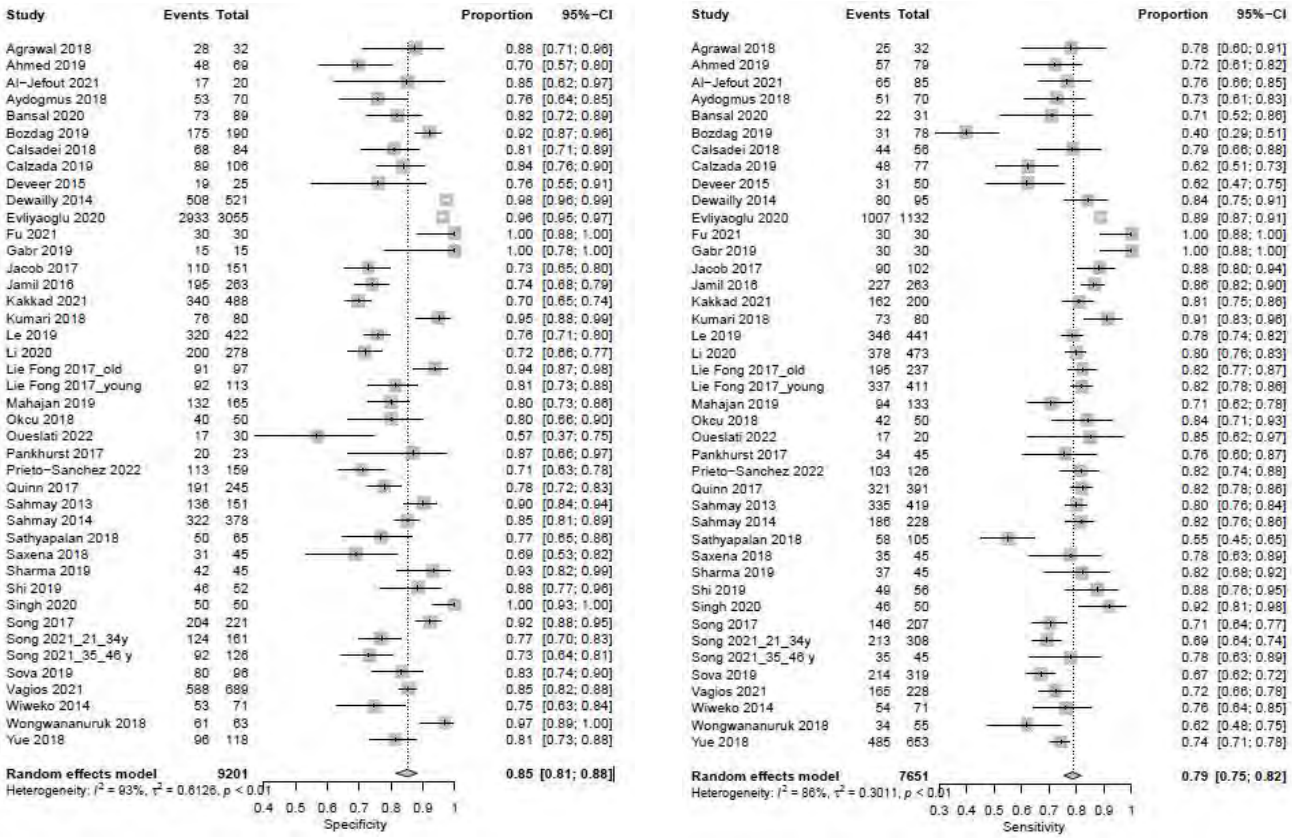
5.2. Forest plot. AMH as diagnostic marker for PCOS in adults

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bansal 2020	22	16	9	73	0.71 [0.52, 0.86]	0.82 [0.72, 0.89]
Bozdag 2019	31	15	47	175	0.40 [0.29, 0.51]	0.92 [0.87, 0.96]
Singh 2020	46	0	4	50	0.92 [0.81, 0.98]	1.00 [0.93, 1.00]
Yue 2018	485	22	168	24	0.74 [0.71, 0.78]	0.52 [0.37, 0.67]

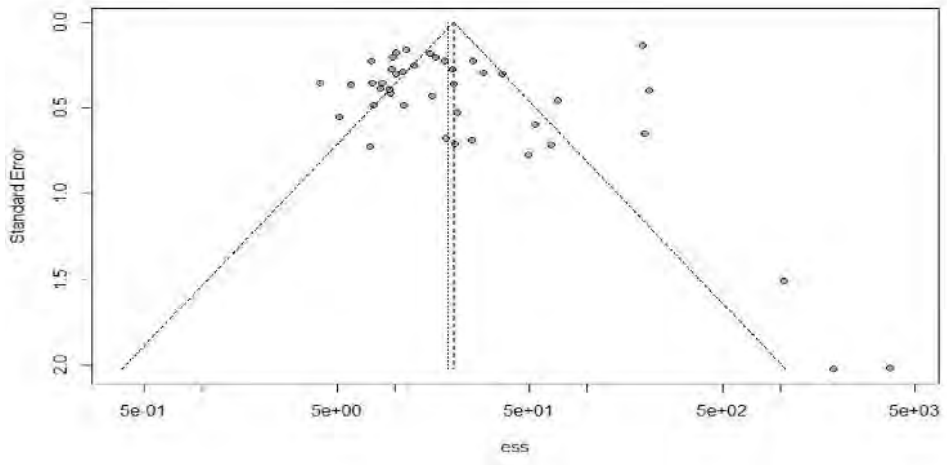




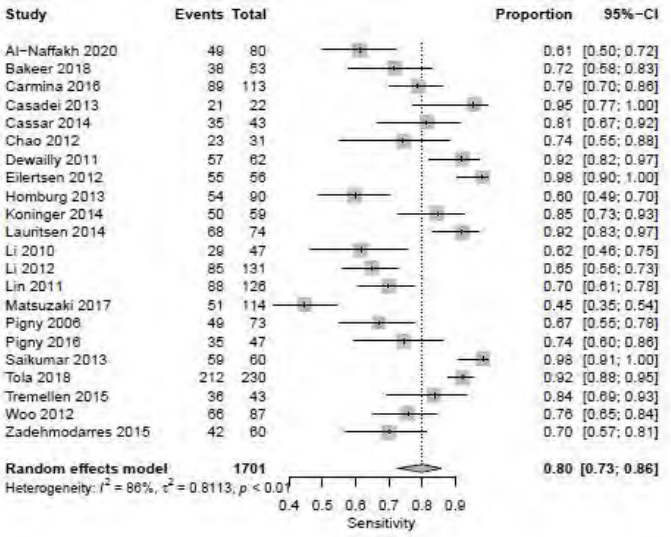
Forest plots of studies classified as low and moderate risk of bias

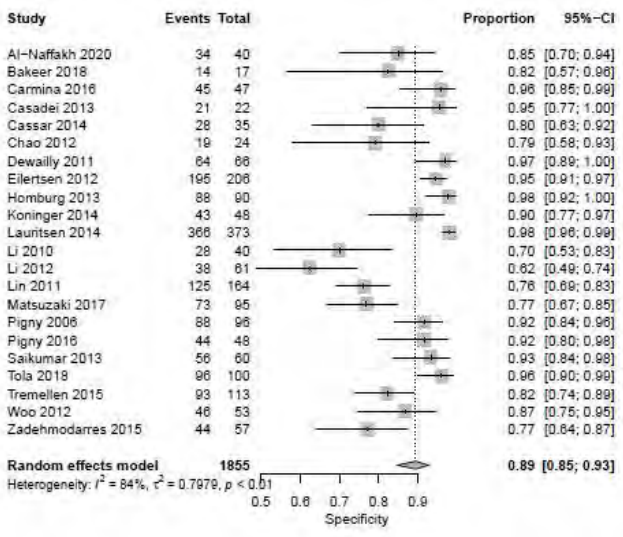


Funnel plot of studies classified as low and moderate risk of bias

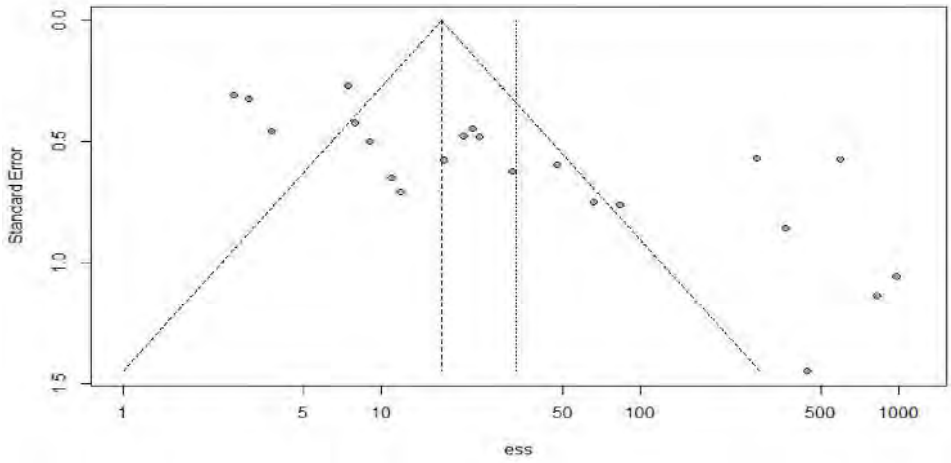


Forest plots of studies classified as high risk of bias





Funnel plot of studies classified as high risk of bias



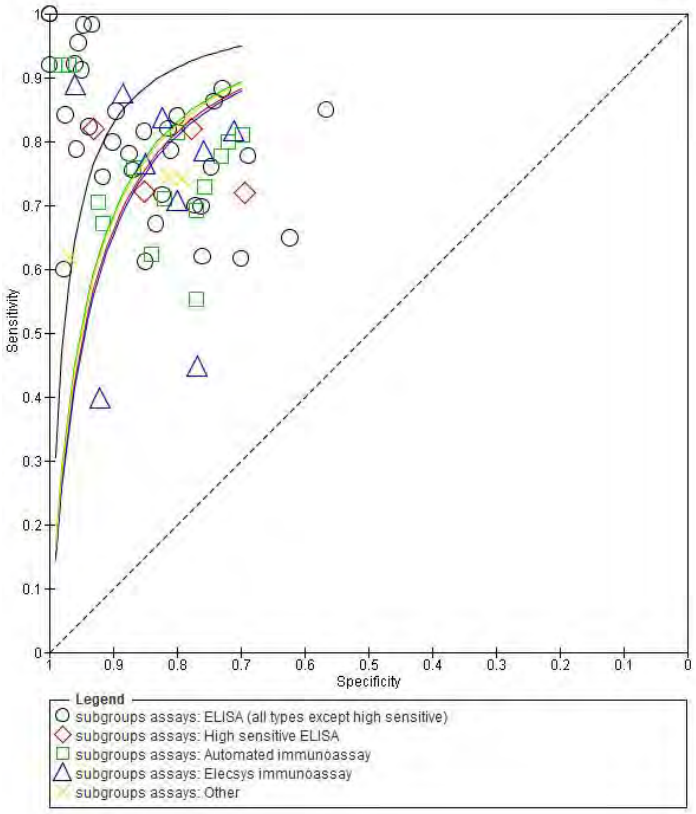
Meta-analysis of studies with adults and three different assays as covariates

N=13 Automated immunoassay

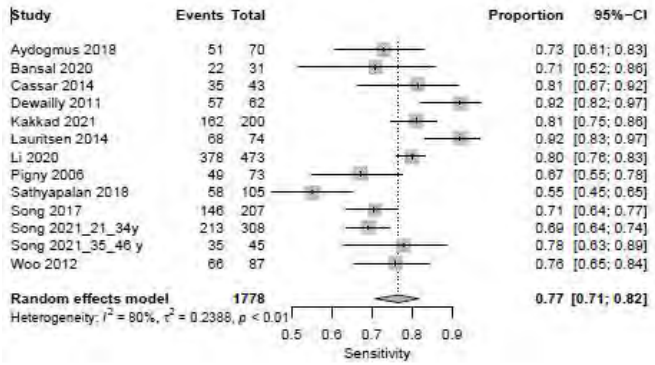
N= 10 Elecsys immunoassay

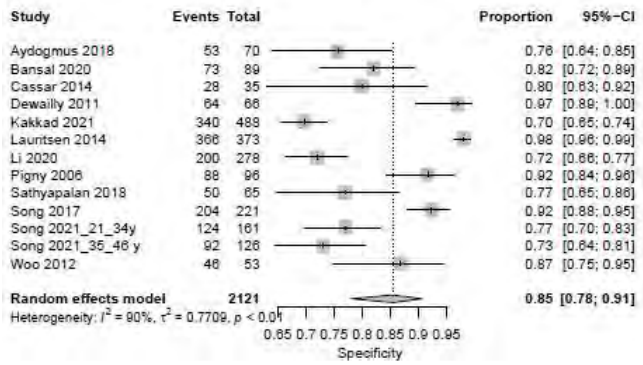
N= 34 ELISA, except high sensitivity

Summary ROC curve AMH for PCOS in adults, subgroups based on assay used

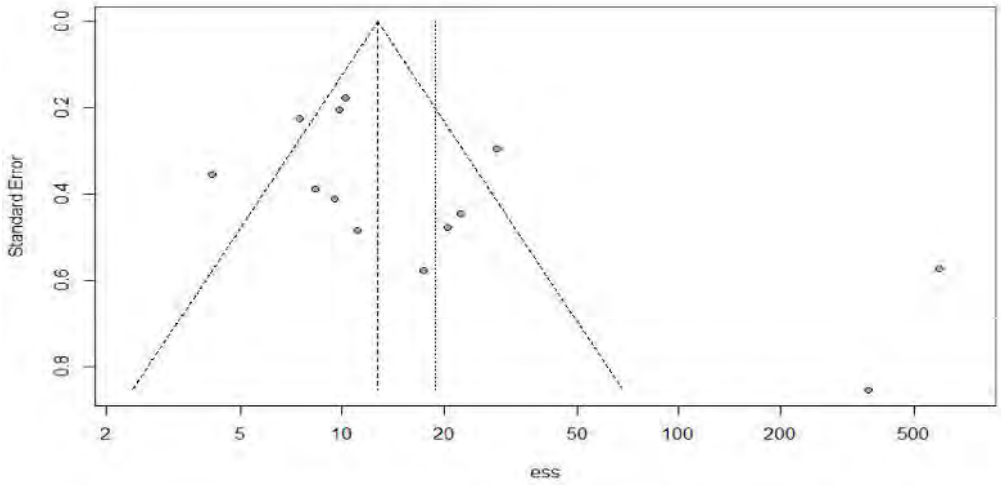


Forest plots of studies that used automated immunoassay

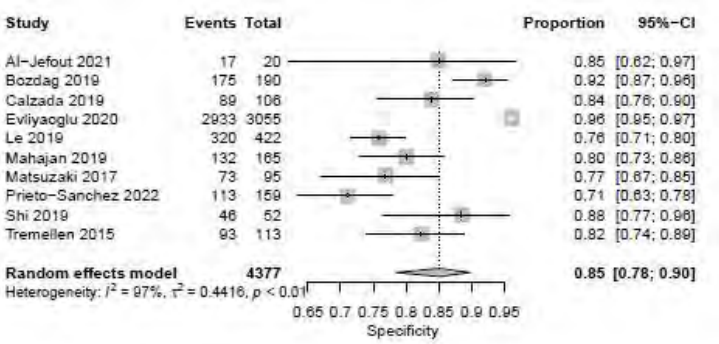


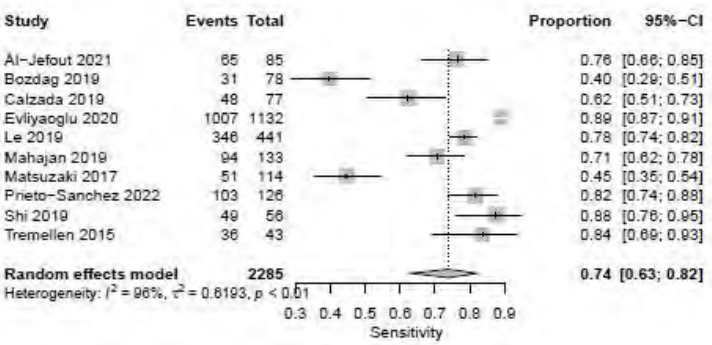


Funnel plot of studies that used the automated immunoassay

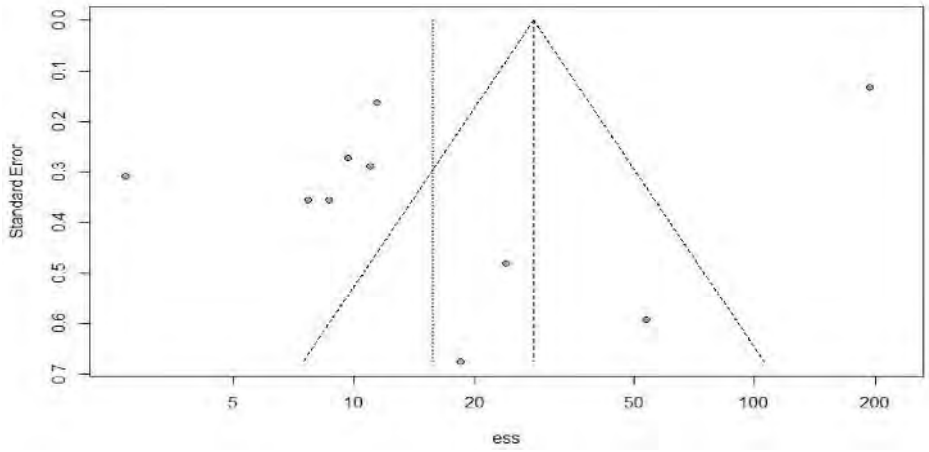


Forest plots of studies that used Elecsys immunoassay

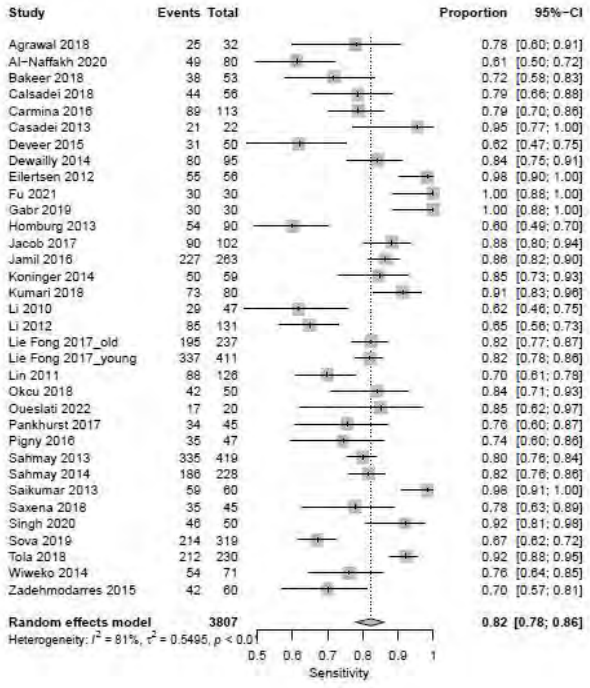


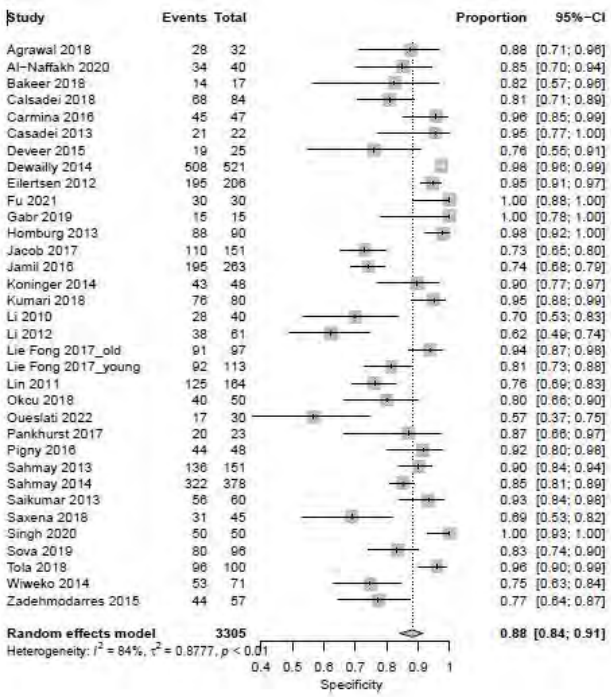


Funnel plot of studies that used the Elecsys immunoassay



Forest plots of studies that used ELISA assay





Funnel plot of studies that used the ELISA assay

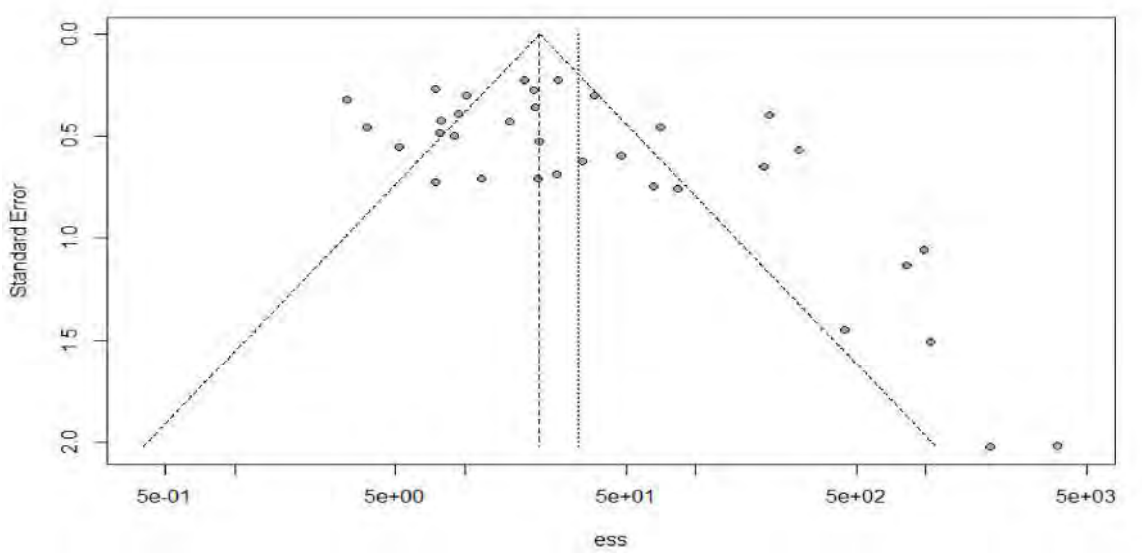
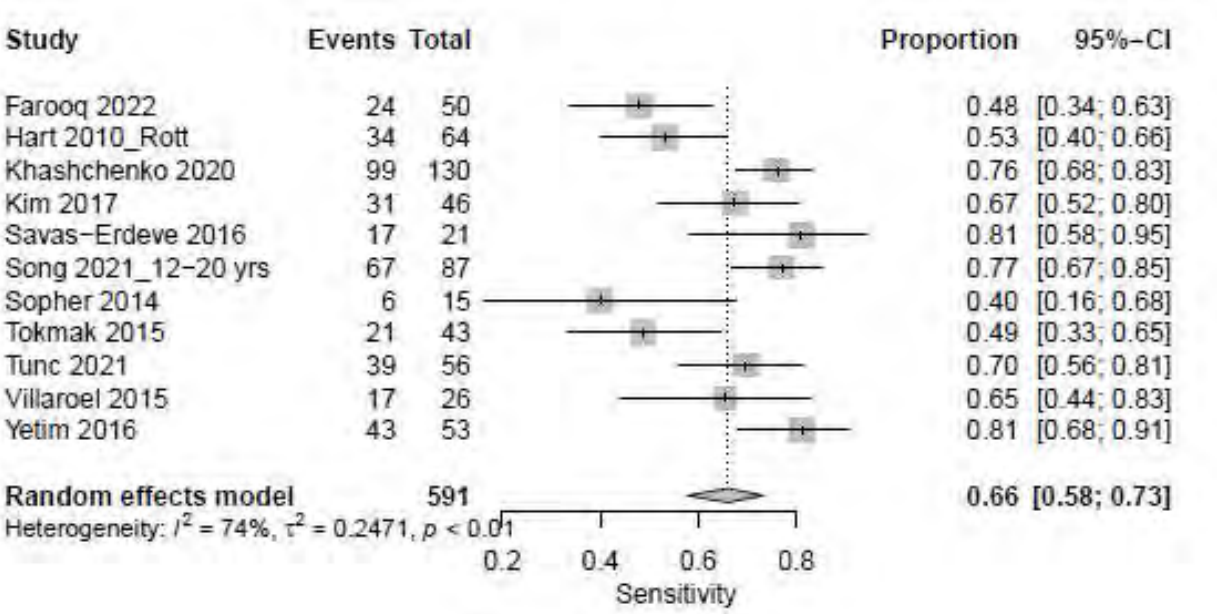


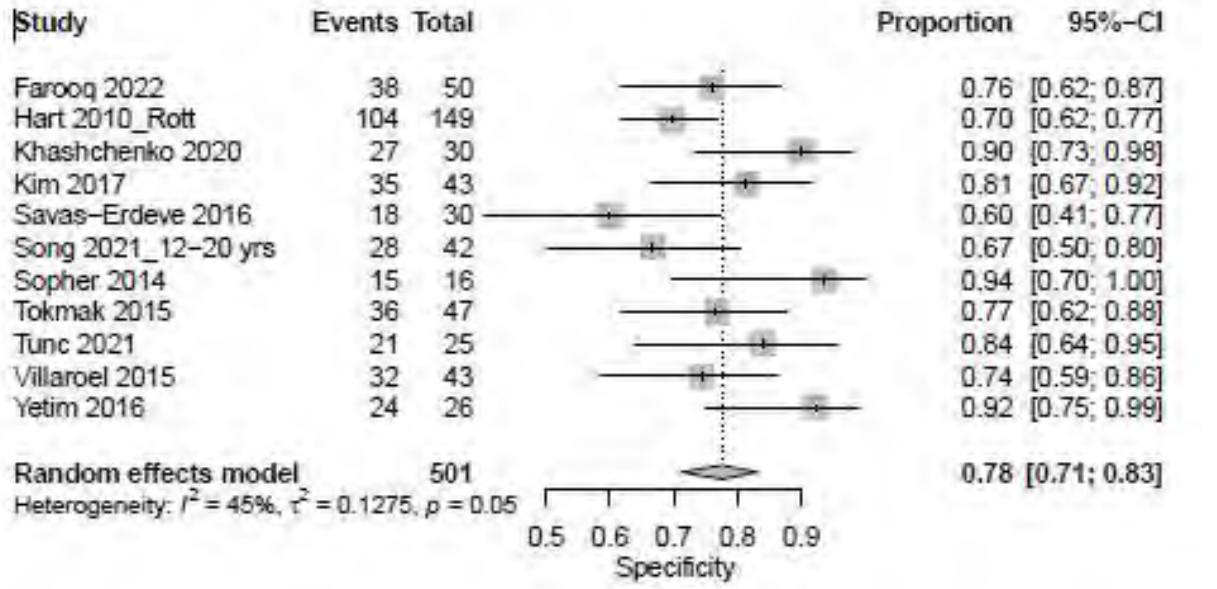
Table with the three main used assays and the p-values.

	Automated	Elecsys	ELISA	P-value[1]	P-value[2]	P-value[3]
Sensitivity (pooled)	0.77 [0.71; 0.82]	0.74 [0.63; 0.82]	0.82 [0.78; 0.86]	$3.75e^{-16}$	$1.07e^{-08}$	$8.01e^{-10}$
Specificity (pooled)	0.85 [0.78; 0.91]	0.85 [0.78; 0.90]	0.88 [0.84; 0.91]	$2.08e^{-15}$	$7.75e^{-05}$	$3.84e^{-07}$

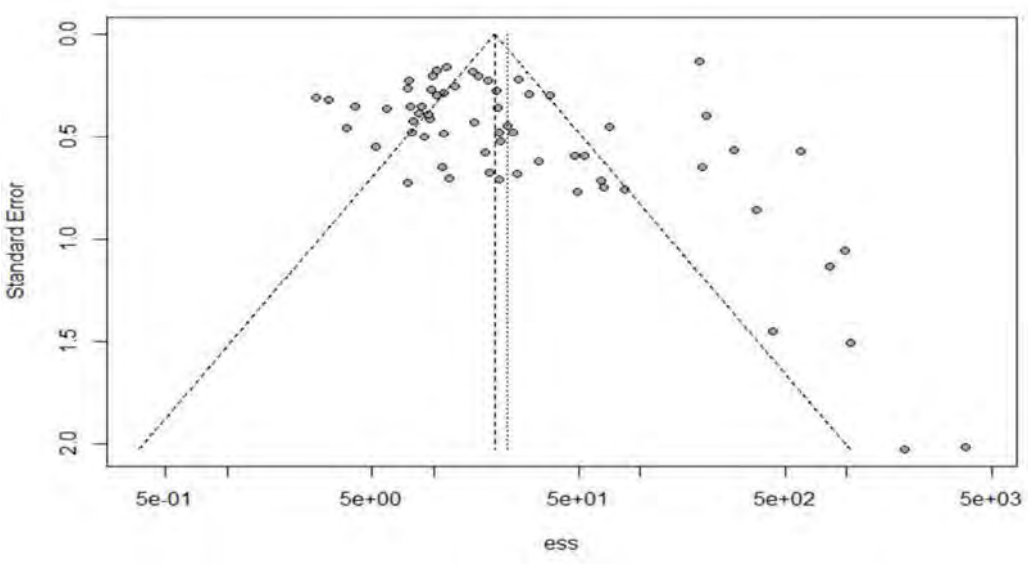
[1]Difference between automated immunoassay and Elecsys assay. [2]Difference between automated and ELISA assay. [3]Difference between Elecsys and ELISA.

Forest plot. AMH as diagnostic marker for PCOS in adolescents. Sensitivity and specificity of all studies in adolescents. No covariates included. Additional analyses in subgroups are possible.

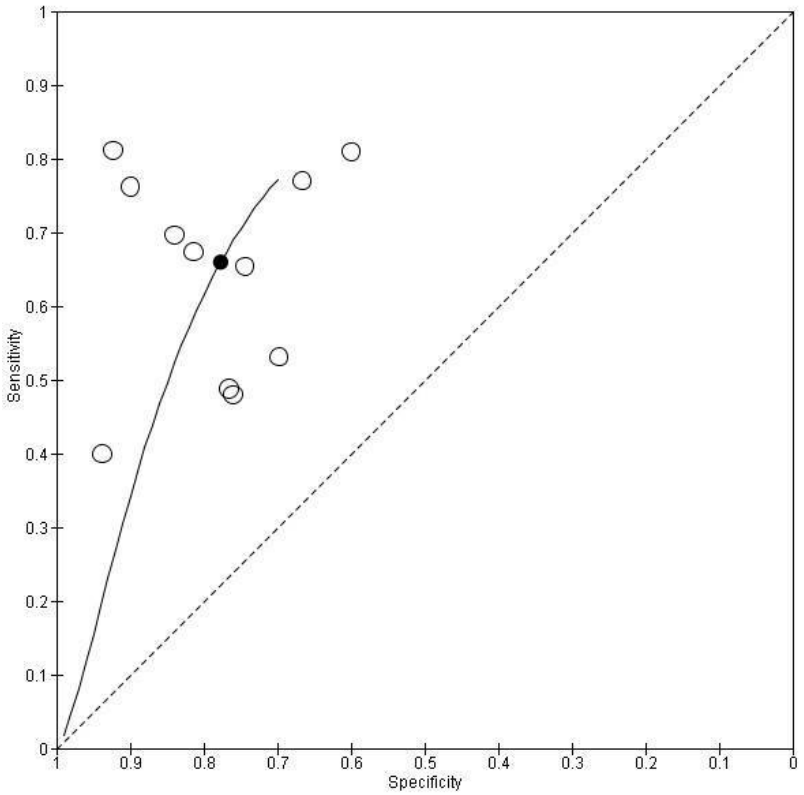




Funnel plot. AMH as diagnostic marker for PCOS in adolescents



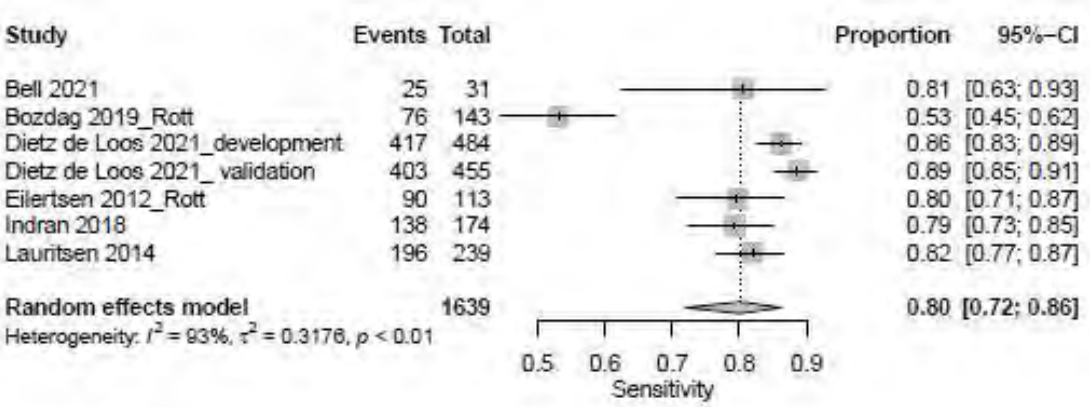
Summary ROC curve with summary point in black (bivariate model) AMH for PCOS in adolescents

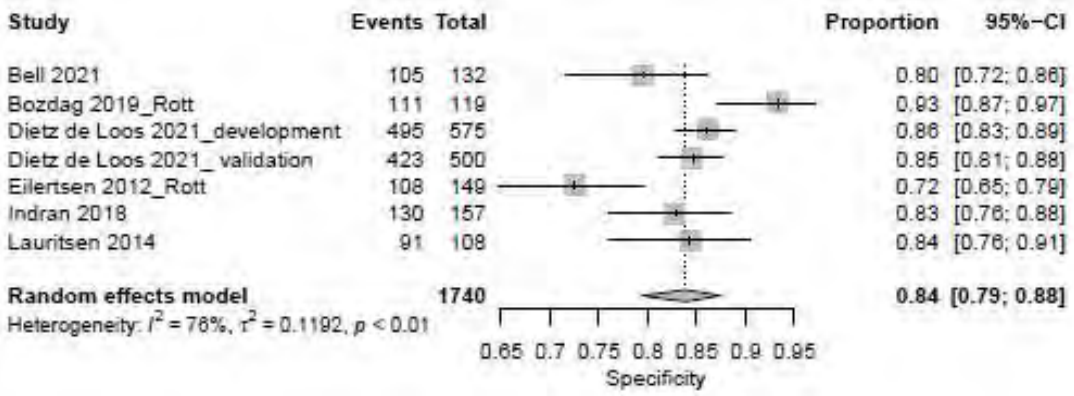


1.5.2 Is AMH effective to diagnose PCOM?

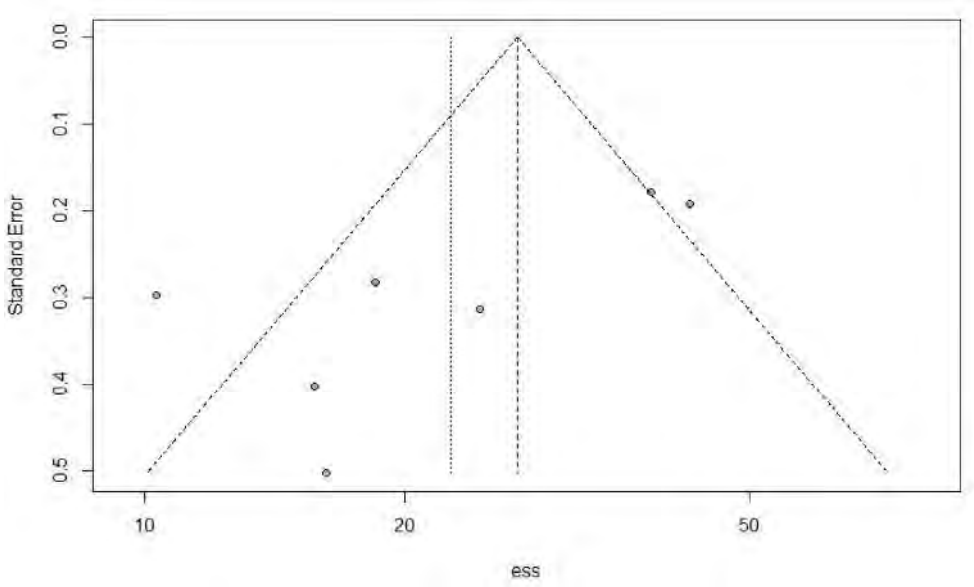
Adults (n=7)

Forest plots of AMH for PCOM





Funnel plot AMH for PCOM



INDEX TEST: AMH			OUTCOME TYPE: PCOM									
COMPARISON (if applicable):												
Author, year	Unit of outcome	Method of measurement	N	Threshold cut-off	True Pos	False Pos	True Neg	False Neg	Sensitivity (95% CI)	Specificity (95%CI)	AUC	Precision
Bell 2021	pmol/l	Ansh pico AMH	PCOM 31 non PCOM 132	44.0					0.806	0.848	0.92	0.849-0.954
	pmol/l	Beckman Coulter	PCOM 31 non PCOM 132	33.2	25	27	105	6	0.806	0.795	0.878	0.817-0.939
Dietz de Loos 2021	ng/mL	Elecsys AMH Plus immunoassay (Roche Diagnostics International Ltd, Rotkreuz, Switzerland)	Development cohort PCOS: 484 (OA+HA+PCOM) Non PCOM : 575	3.2	417	80	495	67	0.862	0.861	0.936	0.922-0.950
			Validation cohort: PCOS: 455 (OA+HA+PCOM) Non PCOM : 500	3.2	403	77	423	52	0.886	0.846	0.936	0.922-0.951
Indran 2018	pmol/l	Beckman Coulter Inc.	P: 174 C: 157	37	138	27	130	36	0.792	0.826	0.809	0.73-0.887
Bozdag 2019	ng/ml	Elecsys AMH; Roche Diagnostic International, IN, USA	n= 392 unselected population PCOM = 143 controls 119	3.31	76	8	111	67	0.531	0.932	0.87	0.83-0.90
Lauritsen 2014	pmol/l	AMH/MIS kit (Immunotech, BeckmanCoulter, Marseilles,France	total PCOS n=447, PCOM=239 Non PCOM=108	20	196	17	91	43	0.820	0.846	0.906	0.878-0.933
Eilertsen 2012	pmol/l	ACTIVEw MIS/AMH enzyme-linked immunosorbent assay (ELISA) , DSL Webster Texas USA	PCOM 113 Non PCOM 149	20 (more cut offs)	90	41	108	23	0.796	0.725	0.896	0.855-0.937

8. GRADE ASSESSMENTS AND EVIDENCE PROFILE

Quality assessment							No. participants				
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**PCOS**	**Controls**	**Effect Estimate**	**Certainty**	**Importance**
Outcome: AMH as diagnostic marker for PCOS											
64 (adults)	Case control and cohort	serious[2]	serious inconsistency	no serious indirectness	serious imprecision	none	9203	11205	Sensitivity: 0.79 (0.76, 0.82) Specificity: 0.87 (0.84, 0.89)	⨁⨁⨁◯ MODERATE	CRITICAL
11 (adoles cents)	Case control and cohort	serious[3]	serious inconsistency	no serious indirectness	serious imprecision	none	550	542	Sensitivity: 0.66 (0.58, 0.73) Specificity: 0.78 (0.71, 0.83)		
Outcome: AMH as diagnostic marker for PCOM											
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**PCOM**	**No PCOM**	**Effect Estimate**	**Certainty**	**Importance**
7	Case control and cohort	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1639	1740	Sensitivity: 0.80 (0.72, 0.86) Specificity: 0.84 (0.79, 0.88)	⨁⨁⨁◯ MODERATE	CRITICAL

[2] Downgraded once as the majority of evidence is at moderate or high risk of bias or downgraded twice as majority of evidence is at very high risk of bias

[3] Downgraded once as the majority of evidence is at moderate or high risk of bias or downgraded twice as majority of evidence is at very high risk of bias

APPENDIX. Quality Appraisal for DIAGNOSTIC / ACCURACY STUDIES

Study ID		Kakkad 2021	
Study citation		Kakkad V, Reddy NS, Nihlani H, Gundewar T. Age-related diagnostic threshold of anti-Müllerian hormone for polycystic ovarian syndrome. Int J Gynecol Obstet. 2021;153:443–448. https://doi.org/10.1002/ijgo.13515	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/participants		Healthcare seeking population. PCOS: aged 20-40 years, excluding thyroid disorders, hyperprolactinemia, 21OH deficiency, ovarian and adrenal tumor, and WHO I. Women who were referred because of subfertility. Exclusion criteria: same as the PCOS patients.	
N		PCOS: 200 Controls: 488	
Setting		Department of Reproductive Medicine and Surgery, January 2017-November 2019, India.	
Index test		AMH measurement, measured between day 2 -5 of the menstrual cycle (together with ultrasound).	
Reference standard		PCOS diagnosis	
Outcomes		- Difference of AMH levels between cases and controls. - ROC analysis of AMH for the diagnosis of PCOS and stratified in two age groups.	
Inclusion criteria		Yes	
Exclusion criteria		Yes	Thyroid disorders, hyperprolactinemia, 21OH deficiency, ovarian and adrenal tumor, and WHO I.
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Yes, but missing some important exclusion criteria, i.e.: women with POI or IOF. Furthermore, they don't report anything about medication or oral contraceptive use.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	Yes	All infertile couples
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	
	Was a case-control design avoided? (Q-2)	No	
	Did the study avoid Inappropriate exclusions? (Q-2)	Partial	Missing some important exclusion criteria, i.e.: women with POI or IOF. Furthermore, they don't report anything about medication or oral contraceptive use.
	Are the cohorts comparable on the basis of design or analysis?	Yes	Mean BMI was similar in both groups. Mean age was a little bit different between both groups, but not statistically different and they stratified into two age groups.
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Yes	
	Did all patients receive the same reference standard? (Q-2)	Yes	
	Is the reference standard likely to correctly classify the	Partial	They used a cut-off value for mFGs of 6 or above.

	target condition? (Q-2)		
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	No	Diagnosis of PCOS was already known during ROC analysis of AMH for the diagnosis PCOS.
	If a threshold was used, was it prespecified?	No	Two approached were used to determine the best cut-off value of AMH: Youden index and the shortest distance on the ROC curve.
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Not reported	
ATTRIT _ ON	Were withdrawals from the study explained?	Not reported	
REPO RT BIAS	Were uninterruptable/ intermediate test results reported?	No	
	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Not reported	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
	Were there any conflicts of interest in the writing or funding of this study?	No	
OTHER ISSUES	If statistical analysis was undertaken, was this appropriate?	No	Power analysis not reported
Comments			
What is the overall risk of bias?		Moderate	Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.

Study ID		Sathyapalan 2018	
Study citation		Sathyapalan T, Al-Qaissi A, Kilpatrick ES, Dargham SR, Atkin SL. Anti-Müllerian hormone measurement for the diagnosis of polycystic ovary syndrome. Clin Endocrinol (Oxf). 2018 Feb;88(2):258-262. doi: 10.1111/cen.13517. Epub 2017 Dec 7. PMID: 29144548.	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/participants		PCOS patients who met all three criteria, phenotype A. Not planning to conceive. Controls: Women with regular periods, no clinical or biochemical hyperandrogenaemia. For both groups: No use of medication or oral contraceptive pills. Not planning to conceive. Both groups presented sequentially to the Department of Endocrinology.	
N		PCOS: 105 Controls: 65	
Setting		Department of Endocrinology, in the UK.	
Index test		AMH measurement.	
Reference standard		PCOS diagnosis, using Rotterdam critiera, phenotype A (all 3 criteria).	
Outcomes		- Baseline characteristics, including differences in AMH levels between cases and controls - AUC, sens en spec for 2 AMH cut-off values - Correlations between AMH and different parameters	
Inclusion criteria		Yes	
Exclusion criteria		Yes	
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Yes, For both groups: No use of medication or oral contraceptive pills. Not planning to conceive. Both groups presented sequentially to the Department of Endocrinology.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	Partial	In practice also women with other phenotypes of PCOS will receive the test.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	
	Was a case-control design avoided? (Q-2)		
	Did the study avoid Inappropriate exclusions? (Q-2)	Partial	To exclude phenotype B, C and D, you only include the most extreme PCOS phenotype.
	Are the cohorts comparable on the basis of design or analysis?	Partial	Age and BMI differed significantly between cases and controls. Cases and controls presented sequentially to the department of endocrinology.
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Yes	
	Did all patients receive the same reference standard? (Q-2)	Yes	
	Is the reference standard likely to correctly classify the	Partial	Only phenotype A, according to Rotterdam criteria. FGs >8 and FAI >4. Definition of PCOM and oligo-amenorrhea was not specified.

	target condition? (Q-2)		
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	No	Diagnosis of PCOS was already known before AMH as analyzed.
	If a threshold was used, was it prespecified?	Partial	Predefined AMH threshold: an AMH categorical value of greater than 46 (based on the 95thpercentile sensitivity of the ROC) and secondly based on AMH with a categorical value of greater than 35 according to the literature.
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRITION	Were withdrawals from the study explained?	Yes	4/65 controls and 3/105 PCOS subjects did not have a FAI level available.
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Not reported	
OTHER ISSUES	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Not reported	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	No	Most of the clinical data it is, but not all women underwent a glucose tolerance test, to exclude impaired glucose tolerance.
	Were there any conflicts of interest in the writing or funding of this study?	No	
	If statistical analysis was undertaken, was this appropriate?	Partial	No power analysis reported.
Comments			
What is the overall risk of bias?		Moderate	

Study ID		Ramezani Tehrani 2021	
Study citation		Ramezani Tehrani F, Rahmati M, Mahboobifard F, Firouzi F, Hashemi N, Azizi F. Age-specific cut-off levels of anti-Müllerian hormone can be used as diagnostic markers for polycystic ovary syndrome. Reprod Biol Endocrinol. 2021 May 22;19(1):76. doi: 10.1186/s12958-021-00755-8. PMID: 34022904; PMCID: PMC8140506.	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/participants		Patients: PCOS aged 20-40 years, according to Rotterdam criteria. Controls: Eumenorrheic non-hirsute women, aged 20-40 years, from the Glucose cohort Study. Not one of the PCOS criteria.	
N		PCOS: 303 (18 excl) Controls: 500 (18 excl)	
Setting		PCOS patients who were refereed to Reproductive Endocrinology Research Center, Tehran, Iran. Controls were selected controls who participated in Tehran Lipid and Glucose Cohort Study.	
Index test		AMH measurement, second or third day of their spontaneous or progesterone-induced menstrual cycle.	
Reference standard		PCOS diagnosis, according to Rotterdam criteria. PCOM >=12 follicles, mFGs>= 8.	
Outcomes		- Differences of AMH levels between cases and controls. - Correlation of AMH with age and BMI - AUC, NPV, PPV of AMH and PCOS diagnosis, with two different methods: Bayesian method and PSI method.	
Inclusion criteria		Yes	
Exclusion criteria		Yes	
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		For controls: excluded if one of the PCOS criteria was present, irregular menstrual cycle, subclinical anovulation. Furthermore: menopause, history of hysterectomy, oophorectomy, ovarian surgeries, history of endocrine disorders or use of medications that could affect function of HPG axis, lack of available information on reproductive history, having outlier AMH value.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	Yes	
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	
	Was a case-control design avoided? (Q-2)	No	
	Did the study avoid Inappropriate exclusions? (Q-2)	Yes	
	Are the cohorts comparable on the basis of design or analysis?	Partial	Cases were referred to the Reproductive Endocrinology Research Center. The control group was selected among women, aged 20–40 years, who participated in 'Tehran Lipid and Glucose' cohort Study (TLGS). BMI similar, age was different but the authors stratified for that.
CLASSIFICATION/VERIFICATION/INCORPORAT	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Yes	
	Did all patients	Yes	

	receive the same reference standard? (Q-2)		
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Partial	PCOS adequately assessed according to Rotterdam criteria, only cut-off for hirsutism was mFGS >=8. PCOM >= 12 follicles.
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	No	
	If a threshold was used, was it prespecified?	No	
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRITION BIAS	Were withdrawals from the study explained?	Yes	In the method section they reported how many patients they excluded because of the exclusion criteria. In the result section they reported how many participants with outlier AMH levels were detected and excluded.
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Partial	A boxplot method was used to exclude participants with outlier AMH levels.
	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Not reported	They only reported that the mFGs was asses by a general practitioner under the supervision of a gynecologist. Not reported who made the ultrasounds i.e..
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
OTHER ISSUES	Were there any conflicts of interest in the writing or funding of this study?	No	

	If statistical analysis was undertaken, was this appropriate?	Yes	Optimal cut-off point for various age categories based on generalized additive models (GAMs). No report of power calculation.
Comments			
What is the overall risk of bias?		Low	

Study ID		Quinn 2017	
Study citation		Quinn MM, Kao CN, Ahmad AK, Haisenleder DJ, Santoro N, Eisenberg E, Legro RS, Cedars MI, Huddleston HG; NIH/NICHD Reproductive Medicine Network. Age-stratified thresholds of anti-Müllerian hormone improve prediction of polycystic ovary syndrome over a population-based threshold. Clin Endocrinol (Oxf). 2017 Dec;87(6):733-740. doi: 10.1111/cen.13415. Epub 2017 Aug 4. PMID: 28681949.	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/participants		PCOS patients, 25-40 years of age, with stored serum from index visits between 2010 and 2015. Additionally, PCOS patients from PPCOS II trial (enrolled between 2009 and 2012) were also included. Controls: Healthy multi-ethnic ovulatory women, aged 25-40 years, not seeking treatment for fertility, who had AMH tested as part of the ovarian ageing (OVA) study.	
N		PCOS: 391 Controls: 245	
Setting		University of California-San Francisco (UCSF) Multidisciplinary PCOS Clinic.	
Index test		AMH measurement, ELISA, Ansh.	
Reference standard		PCOS, Rotterdam criteria. PCOM >=12 follicles. How hirsutism is defined is not reported. In the second PCOS group all women had anovulatory infertility plus either hyperandrogenism or PCOM.	
Outcomes		- AMH per age category and the differences between PCOS and controls. - AUC of AMH and PCOS diagnosis age-stratified. - Odds ratios for PCOS diagnosis - Age-stratified threshold of AMH for prediction PCOS, comparison to population reference threshold.	
Inclusion criteria		Yes	
Exclusion criteria		Yes	
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Inclusion yes. Exclusion no.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	Partial	PCOS group is representative, but the control group not (not seeking treatment for fertility).
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	
	Was a case-control design avoided? (Q-2)	No	
	Did the study avoid Inappropriate exclusions? (Q-2)	Yes	

	Are the cohorts comparable on the basis of design or analysis?	No	The cases were from another population and study than the controls. And the PCOS group were from two different PCOS populations. Age and BMI were significantly different between groups, but stratified for age.
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Yes	
	Did all patients receive the same reference standard? (Q-2)	No	PCOS diagnosis in the UCSF population was made according to the Rotterdam criteria, while in the PPCOSII population all women had anovulatory infertility plus either clinical/biochemical hyperandrogenism or PCOM.
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Partial	In two groups two different PCOS diagnosis and hirsutism not defined.
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	No	
	If a threshold was used, was it prespecified?	No	
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)		
ATTRITION BIAS	Were withdrawals from the study explained?	Not reported	
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	No	
OTHER ISSUES	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the	Not reported	

	clinical setting?		
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
	Were there any conflicts of interest in the writing or funding of this study?	No	
	If statistical analysis was undertaken, was this appropriate?	Partial	Youden statistics, optimal age specific AMH thresholds were validated. No report of power calculation
Comments			
What is the overall risk of bias?		Moderate	

Study ID		Prieto-Sánchez 2022	
Study citation		Prieto-Sánchez MT, Hernández-Peñalver AI, Sánchez-Ferrer ML, Mendiola J, Torres-Cantero AM. Anogenital distance and anti-Müllerian hormone combined improves the diagnosis of polycystic ovary syndrome. Hum Fertil (Camb). 2022 Apr;25(2):274-282. doi: 10.1080/14647273.2020.1795574. Epub 2020 Jul 27. PMID: 32713212.	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/participants		Cases: Women with PCOS, aged 18-40 years, attending the hospital. Controls: Women without PCOS, or other major gynaecological condition, such as endometriosis, attending the clinic for routine gynaecological examinations.	
N		PCOS: 126 Controls: 159	
Setting		Department of Obstetrics and Gynaecology of the University Clinical Hospital 'Virgen de la Arrixaca' in Murcia (Spain), between September 2014 and May 2016.	
Index test		AMH measurement during second and fifth day of menstrual cycle, using Elecsys Roche.	
Reference standard		PCOS diagnosis, Rotterdam criteria. Not further specified.	
Outcomes		- OR with an AMH cut-off value (based on literature) - OR for PCOS using AMH and AGD - ROC curves for AGD and AMH for diagnosis PCOS	
Inclusion criteria		Yes	Rotterdam criteria were not further specified, i.e. cut-off value for PCOM, mFGs, FAI.
Exclusion criteria		Yes	Cases: pregnancy, breastfeeding, genitourinary prolapse, endocrine disorders, oncological treatment or hormonal medication during three months prior to the study. Controls: major gynaecological conditions, such as endometriosis
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Yes	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	Yes	

	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	
	Was a case-control design avoided? (Q-2)	No	
	Did the study avoid Inappropriate exclusions? (Q-2)	Yes	
	Are the cohorts comparable on the basis of design or analysis?	Partial	Cases and controls both attended the Gynaecological outpatient clinic. However, PCOS patients were younger and had a higher BMI.
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Yes	
	Did all patients receive the same reference standard? (Q-2)	Yes	
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Not reported	Rotterdam criteria, but not specified the cut-off values.
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	No	PCOS diagnosis already known when analyzing the AMH data.
	If a threshold was used, was it prespecified?	Partial	Cut-off value for serum AMH level was set at >3.8 ng/ml as described previously in a large cross-sectional study of PCOS women, to calculate the OR. To assess the sensitivity and specificity they determined their own cut-off value.
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRITION BIAS	Were withdrawals from the study explained?	No	

REPORT BIAS	Were uninterruptable/ intermediate test results reported?	No	
OTHER ISSUES	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Yes	By gynaecologists.
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	Except for anogenital distance, but this data not used for the systematic review.
	Were there any conflicts of interest in the writing or funding of this study?	No	
	If statistical analysis was undertaken, was this appropriate?	Partial	No power calculation reported.
Comments			
What is the overall risk of bias?		Moderate	

Study ID	Oueslati 2022	
Study citation	Oueslati I, Hammami MB, Boukriba S, Ben Hadj Hassen H, Yazidi M, Chaker F, Mizouni H, Feki M, Chihaoui M. Anti Mullerian hormone as a diagnostic tool for polycystic ovary syndrome in women of reproductive age with morbid obesity. Horm Mol Biol Clin Investig. 2022 May 5. doi: 10.1515/hmbci-2021-0078. Epub ahead of print. PMID: 35506902.	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/participants	Patients: PCOS patients aged 18-45 years with morbid obesity (BMI ≥40). Controls: All other patients without PCOS, aged 18-45 years, with a BMI >= 40. (See also exclusion criteria)	
N	PCOS: 20 Controls: 30	
Setting	Cross-sectional descriptive study in the Endocrinology outpatient department of the University Hospital la Rabta (Tunisia), between October 2017-March 2018.	
Index test	AMH measurement, between third and fifth day of menstrual cycle (spontaneously or progesterone induced), using ELISA sandwich.	
Reference standard	Rotterdam criteria, sus-pubic ultrasound. PCOM>12, cut-off value for mFGs not reported.	
Outcomes	- Differences in AMH level between PCOS and controls. - Correlations between AMH and other parameters - ROC curve analysis for AMH and diagnosis of PCOS, stratified in 2 age groups.	
Inclusion criteria	Yes	

Exclusion criteria		Yes	Hyperprolactinemia, thyroid dysfunction, Cushing syndrome, pregnant, menopaused or the use of hormonal contraception, metformin, cyproterone acetate and/or corticosteroids.
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Yes, controls: hyperprolactinemia, thyroid dysfunction, Cushing syndrome, pregnant, menopaused or the use of hormonal contraception, metformin, cyproterone acetate and/or corticosteroids.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	A BMI >40 kg/m2 is not common.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	
	Was a case-control design avoided? (Q-2)	No	
	Did the study avoid Inappropriate exclusions? (Q-2)	Yes	
	Are the cohorts comparable on the basis of design or analysis?	Yes	The authors performed an extra analysis stratified for age, all individuals had BMI> 40.
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Yes	
	Did all patients receive the same reference standard? (Q-2)	Yes	
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Partial	Rotterdam criteria, but sus-pub ultrasound instead of transvaginal. mFGs and FAI cut-off values not reported.
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	No	PCOS diagnosis was known during analyses of AMH.
	If a threshold was used, was it prespecified?	No	

DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRITION BIAS	Were withdrawals from the study explained?	No	
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	No	Not assessed.
OTHER ISSUES	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Partial	No cut-off values for mFGs and FAI were reported.
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	No	Radiologists made the ultrasound. But in most clinics the gynaecologists will do that and diagnose the patients.
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
	Were there any conflicts of interest in the writing or funding of this study?	No	
	If statistical analysis was undertaken, was this appropriate?	Partial	No report of power calculation.
Comments			
What is the overall risk of bias?		moderate	

Study ID	Pankhurst 2017
Study citation	Pankhurst MW, Shorakae S, Rodgers RJ, Teede HJ, Moran LJ. Efficacy of predictive models for polycystic ovary syndrome using serum levels of two antimüllerian hormone isoforms (proAMH and AMHN,C). Fertil Steril. 2017 Nov;108(5):851-857.e2. doi: 10.1016/j.fertnstert.2017.08.012. PMID: 29079276.
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/participants	PCOS: aged 18-45 years, recruited through community advertisement asking for women with irregular periods and above average weight. Controls: aged 18-45 years, recruited through community advertisement asking for women above average weight and with normal periods.
N	PCOS: 45

		Controls: 23	
Setting		Participants recruited between July 2008 and January 2010. Not reported where measurements took place.	
Index test		AMH measurements on day 0-14 for the controls (regular cycling), but unspecified when it is measured in the PCOS patients. Gen II ELISA Beckman.	
Reference standard		PCOS diagnosis, using NIH criteria and Rotterdam criteria.	
Outcomes		- pro AMH, AMHnc and total AMH levels in PCOS patients and controls. - ROC analysis for proAMH, AMHnc and total AMH for prediction of PCOS.	
Inclusion criteria		Yes	First inclusion criteria was NIH criteria, but at the end they also included Rotterdam criteria only.
Exclusion criteria		Yes	Pregnant, smoking, DMII, uncontrolled hypertension, nonstable use of antihypertensives, taking lipid-lowering medication, fish oil medication, using hormonal or insulin-sensitizing medication 3 months prior to the study.
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Yes	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	Yes	
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	
	Was a case-control design avoided? (Q-2)	No	
	Did the study avoid Inappropriate exclusions? (Q-2)	Yes	
	Are the cohorts comparable on the basis of design or analysis?	Partial	Previously published investigation, participants were recruited through community advertisement. Controls were older than PCOS patients and had a lower BMI.
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Partial	Ultrasound was only requested for diagnostic purposes in women with only one other PCOS diagnostic feature. Not reported when AMH was measured in PCOS group (probably random cycle day).
	Did all patients receive the same reference standard? (Q-2)	No	21 qualifying for NIH criteria and 24 by Rotterdam criteria only.
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	

	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	No	
	If a threshold was used, was it prespecified?	No	
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRITION BIAS	Were withdrawals from the study explained?	No	
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	No	
OTHER ISSUES	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Not reported	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
	Were there any conflicts of interest in the writing or funding of this study?	No	Consider: - if any of the authors are/were employed, sponsored etc by pharmaceutical companies, or have other financial/other ties - if any commercial companies were involved in funding, writing, editing, data analysis or manuscript approval
	If statistical analysis was undertaken, was this appropriate?	Partial	The analyses were fine, but not age stratified and some data are not reported.
Comments			
What is the overall risk of bias?		Moderate	

Study ID		Okcu 2018	
Study citation		Okcu NT, Nazik H, Akduman AT, Uncu G. The relation between the serum anti-Mullerian hormone levels and follicle count in polycystic ovary syndrome. The European Research Journal. P -2149-3189;4;N1 doi: 10.18621/eurj.332118	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/participants		PCOS patients, based on Rotterdam criteria, aged 18-35 years. Controls: normo-ovulatory cases, aged 18-35 years.	
N		PCOS: 50 Controls: 50	
Setting		Participants were recruited from the Obstetrics and Gynecology polyclinics of University Medical School between November 2012 - May 2013. Country or city is not reported.	
Index test		AMH on day three of menstrual bleeding. Measured using ELISA (Sunred Biological Technology (China)).	
Reference standard		PCOS diagnosis,2 groups: 2 or 3 criteria according to Rotterdam criteria. In virgin patients transabdominal transducer. Cut-off for PCOM was not reported.	
Outcomes		- AMH levels between PCOS patients and controls - AMH levels between mild PCOS group (2 criteria: PCOM and OD) and sever PCOS (3 criteria) - ROC analysis of AMH for PCOS diagnosis.	
Inclusion criteria		Yes	
Exclusion criteria		Yes	Ovarian surgery.
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		No, only the exclusion of ovarian surgery.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	Yes	
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	
	Was a case-control design avoided? (Q-2)	No	
	Did the study avoid Inappropriate exclusions? (Q-2)	Yes	
	Are the cohorts comparable on the basis of design or analysis?	Partial	Recruited from the same polyclinics (Obstetrics and Gynecology), but not specified how they were derived. Age and BMI was significantly different between both groups.
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Yes	
	Did all patients receive the same reference standard? (Q-2)	Yes	

	Is the reference standard likely to correctly classify the target condition? (Q-2)	Partial	Rotterdam criteria. But cut-off of mFGs >8. Cut-off for PCOM not reported.
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	No	
	If a threshold was used, was it prespecified?	No	
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRITION BIAS	Were withdrawals from the study explained?	No	
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	No	
	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Not reported	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
OTHER ISSUES	Were there any conflicts of interest in the writing or funding of this study?	No	

	If statistical analysis was undertaken, was this appropriate?	Yes	Yes. Power calculation was performed, based on mean AMH levels in 60 patients in a pilot study. Youden index was used to determine the cutoff values.
Comments			
What is the overall risk of bias?		Moderate	Some of the criteria have been fulfilled and those

Study ID		Matsuzaki 2017	
Study citation		Matsuzaki T, Munkhzaya M, Iwasa T, Tungalagsuvd A, Yano K, Mayila Y, Yanagihara R, Tokui T, Kato T, Kuwahara A, Matsui S, Irahara M. Relationship between serum anti-Mullerian hormone and clinical parameters in polycystic ovary syndrome. Endocr J. 2017 May 30;64(5):531-541. doi: 10.1507/endocrj.EJ16-0501. Epub 2017 Apr 1. PMID: 28381699.	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/participants		PCOS: Women with PCOS, Rotterdam criteria. Controls: Women with normal menstrual cycles	
N		PCOS: 114 Controls: 95	
Setting		Missing	
Index test		AMH on day 6-8 of the menstrual cycle in control group. Sampling PCOS group was not timed.	
Reference standard		Rotterdam criteria, but used cutoff values were not reported.	
Outcomes		- Differences in AMH levels in cases and controls. - Correlation of AMH levels with age and BMI - Differences in AMH levels between controls and cases BMI stratified. - ROC analysis of AMH in the diagnosis PCOS, with sensitivity and specificity at different cutoff values.	
Inclusion criteria		Not reported	
Exclusion criteria		Not reported	
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Not reported	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT CLASSIFIC	Was the spectrum of patients representative of the patients who will receive the test in practice?	Not reported	Inclusion and exclusion criteria are not reported. Women with PCOS according to Rotterdam criteria and women with an ovulatory cycle are representative of patients who will receive an AMH test in practice, but important information about participants and the setting is missing.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Not reported	
	Was a case-control design avoided? (Q-2)	No	
	Did the study avoid Inappropriate exclusions? (Q-2)	Not reported	No information about exclusion criteria.
	Are the cohorts comparable on the basis of design or analysis?	No	Not reported how the participants were recruited. The PCOS group was older and had a higher BMI.
	Were all participants assessed with both	Yes	

	index test and reference standard? (Also in Q-2)		
	Did all patients receive the same reference standard? (Q-2)	No	No ultrasound in the control group.
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Not reported	Missing information about cutoff values for the diagnosis PCOS.
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	No	
	If a threshold was used, was it prespecified?	No	
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRITION BIAS	Were withdrawals from the study explained?	Not reported	
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	No	
OTHER ISSUES	Was the execution of all tests described in sufficient detail to permit replication of the tests?	No	It is not described which cutoff values they used for PCOM or mFGs for example.
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Not reported	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	

	Were there any conflicts of interest in the writing or funding of this study?	No	Research was supported by research grant of Roche. AMH levels were measured and provided by Roche, but Roche had no role in the design and conduct of the study; analysis and interpretation of the data.
	If statistical analysis was undertaken, was this appropriate?	Partial	No power calculation, different age in case and control group, no description of how the cutoff was set (Youden index?).
Comments			
What is the overall risk of bias?		High	

Study ID		Mahajan 2019	
Study citation		Mahajan N, Kaur J. Establishing an Anti-Müllerian Hormone Cutoff for Diagnosis of Polycystic Ovarian Syndrome in Women of Reproductive Age-Bearing Indian Ethnicity Using the Automated Anti-Müllerian Hormone Assay. J Hum Reprod Sci. 2019 Apr-Jun;12(2):104-113. doi: 10.4103/jhrs.JHRS_149_18. PMID: 31293324; PMCID: PMC6594116.	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/participants		PCOS: Women who underwent treatment at fertility center and were diagnosed with PCOS, according to Rotterdam criteria. Controls: - Patients with normal ovaries on ultrasound - Patients with isolated polycystic ovaries.	
N		PCOS: 133 Controls: 165 PCOM only: 69	
Setting		Women who underwent treatment at the Department of Reproductive Medicine, Mother and Child Hospital (Delhi, India), between February 2017 - August 2017.	
Index test		AMH measurement, cycle day 2-5, using Elecsys Roche.	
Reference standard		PCOS according to Rotterdam criteria. Cutoff value PCOM > 25 follicles.	
Outcomes		- AMH concentrations in Controls, PCOS and women with PCOM only. - AMH in various PCOS phenotypes. - Correlation of age and AMH in the three groups. - ROC analysis of AMH for diagnosis PCOS.	
Inclusion criteria		Yes	
Exclusion criteria		Yes	Non Indian origin, OCP use in the last 4 weeks, and oophorectomy.
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Yes	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	Yes	
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	
	Was a case-control design avoided? (Q-2)	No	
	Did the study avoid	Yes	They also included non PCOS women with PCOM.

	Inappropriate exclusions? (Q-2)		
	Are the cohorts comparable on the basis of design or analysis?	Partial	Recruited from the same infertile population. PCOS group was younger than control groups and had a higher BMI.
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Yes	
	Did all patients receive the same reference standard? (Q-2)	Yes	
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Partial	Cutoff value for PCOM >25 follicles. Cutoff value for mFGs or FAI is not reported.
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	No	
	If a threshold was used, was it prespecified?	No	
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRITION BIAS	Were withdrawals from the study explained?	Yes	43/410 were excluded, because of exclusion criteria.
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	No	
OTHER ISSUES	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Not reported	
	Were the same	Yes	

	clinical data available when test results were interpreted as would be available when the test is used in practice?		
	Were there any conflicts of interest in the writing or funding of this study?	No	
	If statistical analysis was undertaken, was this appropriate?	Partial	Power analysis not reported.
Comments			
What is the overall risk of bias?		Moderate	

Study ID	Li 2020	
Study citation	Li H, He YL, Li R, Wong C, Sy B, Lam CW, Lam K, Peng HM, Mu S, Schooling M, Yeung W, Ho PC, Ng E. Age-specific reference ranges of serum anti-müllerian hormone in healthy women and its application in diagnosis of polycystic ovary syndrome: a population study. BJOG. 2020 May;127(6):720-728. doi: 10.1111/1471-0528.16147. Epub 2020 Feb 25. PMID: 32009280.	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/participants	PCOS: Women once diagnosed with PCOS (according to Rotterdam criteria) from whose serum samples were stored. Controls: Adult Chinese women who attended one of the institutions (see 'setting').	
N	For comparing PCOS patients with controls: PCOS: 473 Controls: 278 (They used more controls for making reference ranges. But also used more controls with the age-stratified analyses and AUC. Not clear what kind of controls.)	
Setting	Queen Mary Hospital (Hong Kong), School of Public Health (Hong Kong), The Family Planning Association (Hong Kong), The University of Hong Kong-Shenzhen Hospital and Peking University Third Hospital (Bejing).	
Index test	AMH, collected on a random day of the cycle. Beckman-Coulter.	
Reference standard	PCOS diagnosis, Rotterdam criteria, not further specified.	
Outcomes	- Age specific reference ranges - MoM AMH of each subject in validation cohort - MoM AMH difference between PCOS women and controls - ROC analysis for discriminating women with PCOS from ovulatory controls by MoM AMH	
Inclusion criteria	Yes	Controls: - Ethnically Chinese - Aged between 20 and 44 years - Not having a known history of irregular menstrual cycles (shorter than 21 days or longer than 35 days for subjects aged below 40 years, but not mandatory for subjects aged ≥40 years considering the possibility of ovarian ageing). - Not having hormonal treatment in the past 3 months - No history of infertility, radiotherapy, chemotherapy, ovarian surgery, hysterectomy or any endocrine disease which affect ovarian function.

Exclusion criteria		Partial	For the control group it is reported, but for the PCOS group not.
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Yes	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	Yes	
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	
	Was a case-control design avoided? (Q-2)	No	
	Did the study avoid Inappropriate exclusions? (Q-2)	Yes	
	Are the cohorts comparable on the basis of design or analysis?	No	No baseline characteristics available about the PCOS group. Controls were recruited when they were attending the following institutions for health check-ups, family planning services or participation in other research projects, archived serum samples from a separate cohort of 751 women, including 473 women diagnosed with PCOS according to the Rotterdam criteria and 278 ovulatory women without polycystic ovary morphology. For the ROC analysis it is not clear which controls they used.
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	No	Only a subset of women underwent an ultrasound.
	Did all patients receive the same reference standard? (Q-2)	No	Only a subset of women underwent an ultrasound. Women were included in the control group if they had a regular menstrual cycle. It was not assessed if they had PCOM or hyperandrogenism.
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Partial	Rotterdam criteria was used, but not further specified (cutoff values for mFGs, FAI and PCOM).
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	No	
	If a threshold was used, was it prespecified?	No	

DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	The samples of the PCOS group were stored.
ATTRITION BIAS	Were withdrawals from the study explained?	Not reported	
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	No	
OTHER ISSUES	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Not reported	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
	Were there any conflicts of interest in the writing or funding of this study?	No	Consider: - if any of the authors are/were employed, sponsored etc by pharmaceutical companies, or have other financial/other ties - if any commercial companies were involved in funding, writing, editing, data analysis or manuscript approval
	If statistical analysis was undertaken, was this appropriate?	Yes	Age specific MoM is used.
Comments			
What is the overall risk of bias?		Moderate	

Study ID	Lie Fong 2017
Study citation	Lie Fong S, Laven JSE, Duhamel A, Dewailly D. Polycystic ovarian morphology and the diagnosis of polycystic ovary syndrome: redefining threshold levels for follicle count and serum anti-Müllerian hormone using cluster analysis. Hum Reprod. 2017 Aug 1;32(8):1723-1731. doi: 10.1093/humrep/dex226. PMID: 28854584.
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/participants	PCOS: according to Rotterdam criteria. Controls: Women aged up to 18 years from different original studies: - Healthy ovulatory women recruited between 1997-1999. - Healthy ovulatory women between 1993 and 1999.

		- Healthy ovulatory women recruited 2006-2010.	
N		Used for ROC analysis Young group: PCOS: 411 Controls: 113 Old group: PCOS: 237 Controls: 97	
Setting		Tertiary hospital: Erasmus Medical Center Rotterdam and Sophia Children's hospital.	
Index test		AMH, measured by Gen II Beckman Coulter.	
Reference standard		PCOS diagnosis, according to Rotterdam criteria, but only women included with both oligo-anovulation and hyperandrogenism. FAI > 3.0nmol/L, FAI>4.5, PCOM >= 12 follicles.	
Outcomes		- Differences AMH between controls and PCOS - Cluster analysis of the controls, based on AMH, FNPO (follicle number per ovary), serum FSH and testosterone, resulting in 4 clusters (1. young, normal AMH and FNPO), 2. young high AMH and FNPO, 3. old and normal AMH and FNPO, 4. old and high AMH and FNPO) - ROC analyses of AMH and FNPO of cluster 1 controls and PCOS women with similarly age - ROC analyses of AMH and FNPO of cluster 3 and similarly aged women with PCOS.	
Inclusion criteria		Yes	Controls: no hirsutism, no use of sex-steroids at least 3 months prior to study, no ovarian surgery in the past.
Exclusion criteria		Yes	Only for PCOS not specified,
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Partial, no exclusion criteria for PCOS group.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	Partial	The PCOS was group is representative, but the control group not, because they are healthy ovulatory participants.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	
	Was a case-control design avoided? (Q-2)	No	
	Did the study avoid Inappropriate exclusions? (Q-2)	No	Women with only hyperandrogenism and PCOM were excluded. Normally these patients are within the PCOS population.
	Are the cohorts comparable on the basis of design or analysis?	Partial	Both derived from different studies. BMI levels were different between cases and controls. Age was also different, they adjust for that by stratifying into two age groups before comparing.
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Yes	
	Did all patients receive the same reference standard? (Q-2)	Yes	

	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	No	
	If a threshold was used, was it prespecified?	No	
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRITION BIAS	Were withdrawals from the study explained?	Not reported	
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	No	
	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Not reported	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
	Were there any conflicts of interest in the writing or funding of this study?	No	
OTHER ISSUES	If statistical analysis was undertaken,	Partial	ROC stratified for age, no power calculation.

	was this appropriate?		
Comments			
What is the overall risk of bias?		Moderate	

Study ID		Le 2019	
Study citation		Le MT, Le VNS, Le DD, Nguyen VQH, Chen C, Cao NT. Exploration of the role of anti-Mullerian hormone and LH/FSH ratio in diagnosis of polycystic ovary syndrome. Clin Endocrinol (Oxf). 2019 Apr;90(4):579-585. doi: 10.1111/cen.13934. Epub 2019 Feb 10. PMID: 30636332.	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/participants		PCOS: Aged 18-45 years and infertility for at least 1 year with PCOS. Controls: Aged 18-45 years and infertility for at least 1 year without PCOS, and having regular menstrual cycle every 26-35 days, collected at the same time of PCOS recruitments, with exclusion of any existing ovarian surgery, and ovarian failure.	
N		PCOS: 441 Controls: 422	
Setting		Three medical centers: - Hue University Hospital - Hue Central Hospital - Danang Hospital for Women and Children From June 2017 to June 2017.	
Index test		AMH measurement,	
Reference standard		PCOS diagnosis, according to Rotterdam criteria. PCOM> 12 follicles, mFGs >=6, T > 2.8 nmol/L.	
Outcomes		- Difference in AMH levels between women with PCOS and controls. - ROC analyses with optimum cut-off level of AMH and the sensitivity and specificity. - Association of AMH levels and increased risk of PCOS - Differences in AMH and LH/FSH ratio in PCOS diagnosis.	
Inclusion criteria		yes	
Exclusion criteria		Yes	Nothing reported about medication or hormone use.
Does the study have a clearly focused question? (yes/no/partial)		Partial, they said nothing about AMH and predicting PCOS. Only about exploring the role of AMH and LH/FSH ratio.	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Yes	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	Yes	
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	
	Was a case-control design avoided? (Q-2)	No	
	Did the study avoid Inappropriate exclusions? (Q-2)	Yes	
	Are the cohorts comparable on the basis of design or analysis?	Partial	All infertile women, but the control group was older and consisted of a higher prevalence of secondary infertility type and a lower prevalence of primary infertility type.
CLASSIFIC	Were all participants assessed with both	Yes	

	index test and reference standard? (Also in Q-2)		
	Did all patients receive the same reference standard? (Q-2)	Yes	
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	No	
	If a threshold was used, was it prespecified?	No	
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRITION BIAS	Were withdrawals from the study explained?	No	Not reported
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	No	Not reported
	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Not reported	
OTHER ISSUES	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	

	Were there any conflicts of interest in the writing or funding of this study?	No	
	If statistical analysis was undertaken, was this appropriate?	Partial	Power analysis not reported.
Comments			
What is the overall risk of bias?		Moderate	

Study ID		Kumari 2018	
Study citation		Kumari A, Tiwari HC, Srivastav R. Comparative Evaluation of Diagnostic Efficacy of Serum Anti-Müllerian Hormone and Ultrasound in Polycystic Ovarian Syndrome. J South Asian Feder Obs Gynae 2018; 10 (2):98-103	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/participants		Women with PCOS (according to Rotterdam criteria), aged 18-35 years, who visited the outpatient department and had both ovaries present, no current hormone therapy, adequate visualization of ovaries, and no preexisting illness. Women without PCOS with the same in- and exclusion criteria as the PCOS group.	
N		PCOS: 80 Controls: 80	
Setting		Gynecological Outpatient Department of B.R.D, Medical College, Gorakhpur, India (tertiary academic hospital), recruitment from January 2015-December 2016.	
Index test		AMH measurement, cycle day 2 or 3, using Beckman.	
Reference standard		PCOS diagnosis, Rotterdam criteria, FGs >8, cutoff value for PCOM not specified.	
Outcomes		- Distribution of cases and controls according to serum AMH levels. - ROC analysis of AMH in diagnosing PCOS (sens, spec, PPV, NPV) - ROC analysis of PCOM and diagnosing PCOS (also compared to AMH). - Correlation of AMH and studied variables.	
Inclusion criteria		Yes	Both ovaries present, no current hormone therapy, adequate visualization of ovaries, and no preexisting illness.
Exclusion criteria		Yes	PCOS: endocrinological abnormalities. Controls: hormonal medication, known infertility, endocrinological or dermatologic problems.
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Yes	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	Partial	Controls were healthy women without fertility problems
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	

	Was a case-control design avoided? (Q-2)	No	
	Did the study avoid Inappropriate exclusions? (Q-2)	Yes	
	Are the cohorts comparable on the basis of design or analysis?	Partial	The age seems to be different between both groups. However, the mean age is not compared in the total population, they compared it after stratification. But the ROC analysis was not stratified by age. BMI and ethnicity were also different.
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Yes	
	Did all patients receive the same reference standard? (Q-2)	Yes	
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Partial	Rotterdam criteria, FGs >8, cutoff value for PCOM not specified.
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	No	Cochrane suggests that diagnostic review bias may occur when interpretation of the results of the reference standard is influenced by knowledge of the results of the index test. This is similar to the issue of blinded outcome assessment in intervention studies.
	If a threshold was used, was it prespecified?	Yes	5.0 ng/mL.
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRITION BIAS	Were withdrawals from the study explained?	No	
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	No	

OTHER ISSUES	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Not reported	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
	Were there any conflicts of interest in the writing or funding of this study?	No	
	If statistical analysis was undertaken, was this appropriate?	Partial	Case and control group were different in BMI. no power calculation was performed. Different ethnicity. Probably age also different in the total population.
Comments			
What is the overall risk of bias?		Moderate	

Study ID	Wissing 2019	
Study citation	Wissing ML, Mikkelsen AL, Kumar A, Kalra B, Pors SE, Flachs EM, Andersen CY. Associations of different molecular forms of antimüllerian hormone and biomarkers of polycystic ovary syndrome and normal women. Fertil Steril. 2019 Jul;112(1):149-155.e1.	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/participants	PCOS: women referred to one of the four Danish hospitals because of gynecology or infertility symptoms and having PCOS with or without metformin treatment, aged 18-40 years. Controls: women referred to one of the four Danish hospitals because of gynecology or infertility symptoms, aged 18-40 years, without known disease and having regular menstrual cycles. In PICOLO study is noted: male or tubal factor.	
N	PCOS: 62 PCOS with metformin: 26 Controls: 24	
Setting	April 2010 - February 2013, women referred to four Danish University hospitals because of infertility or gynecological symptoms.	
Index test	AMH, measured by three different assays: Anshlabs ELISAs AL-124, AL-132 and AL-145, on cycle day 3-5 or random in anovulatory women.	
Reference standard	PCOS diagnosis, Rotterdam criteria. Cutoff for PCOM, FAI and mFGs were not specified.	
Outcomes	AUC's of three different AMH assays. Association of AMH isoform with metabolic parameters. AUC's of AMH with the use of BMI, androgen level and TFC.	
Inclusion criteria	Yes	
Exclusion criteria	Yes	Diabetes type 1 or 2, impaired thyroid, renal, or hepatic function, congenital adrenal hyperplasia, endometriosis, poor ovarian reserve, POI, hypothalamic amenorrhea, or age > 36 years.

Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Yes	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	Yes	Also in practice women with PCOS can use metformin, only a smaller percentage. Controls women with regular cycle, but with gynecology or infertility symptoms.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	It is best if the patients are randomly selected or consecutive admissions so that selection bias is minimized.
	Was a case-control design avoided? (Q-2)	No	
	Did the study avoid Inappropriate exclusions? (Q-2)	Yes	
	Are the cohorts comparable on the basis of design or analysis?	Yes	Age and BMI not different.
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Yes	
	Did all patients receive the same reference standard? (Q-2)	Yes	
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Not reported	They only mentioned that they used the Rotterdam criteria, but did not specify the cutoff values (FAI, mFGs and PCOM)
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	No	
	If a threshold was used, was it prespecified?	No	No threshold prespecified, but also not calculated.
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	

ATTRITION BIAS	Were withdrawals from the study explained?	No	
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	No	
OTHER ISSUES	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Not reported	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
	Were there any conflicts of interest in the writing or funding of this study?	No	Supported by MRC project grant.
	If statistical analysis was undertaken, was this appropriate?	Partial	No power calculation.
Comments			
What is the overall risk of bias?		Low	

Study ID	Yue 2018
Study citation	Yue CY, Lu LK, Li M, Zhang QL, Ying CM. Threshold value of anti-Mullerian hormone for the diagnosis of polycystic ovary syndrome in Chinese women. PLoS One. 2018 Aug 28;13(8):e0203129.
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/participants	PCOS: women who consulted the endocrinology clinic between Jan 2016 and Oct 2016 and were diagnosed with PCOS, aged 20-40 years. Controls: Women who consulted the endocrinology clinic between Jan 2016 and Oct 2016 after exclusion of other endocrine and gynecological diseases.
N	PCOS: 653 Controls: 118
Setting	Endocrinology clinical at Obstetrics and Gynecology Hospital of Fudan University.
Index test	AMH measurement, by UNION immune analyzers (ShenZhen, China), at cycle day 2-5. Not reported when or how they measured it in anovulatory women (progesterone induced?).
Reference standard	PCOS diagnosis, ESHRE/ASRM criteria. PCOM >= 12 follicles. Biochemical HA total testosterone levels above the 95th percentile. mFGs >= 8.

Outcomes		-Difference in hormone levels between PCOS phenotypes. -Difference in AMH levels (between phenotypes, all PCOS and all controls). -AUC, sensitivity and specificity of AMH in different age groups.	
Inclusion criteria		Yes	20-40 years of age.
Exclusion criteria		Yes	Cushing, dysfunctional uterine bleeding, primary amenorrhea, hypothalamic or pituitary amenorrhea, uterine amenorrhea, hyperprolactinemia, POI, ovarian functional tumors, theca cell proliferation, adrenal cortical hyperplasia or tumor, thyroid dysfunction, auto-immune disease, malignancy, central nervous system disease, current or previous use of OAC within 6 months prior to study, use of medication affecting the HPO axis, steroid drugs, absence of complete records of hormone testing or ultrasound.
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Yes	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	Yes	
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	
	Was a case-control design avoided? (Q-2)	No	
	Did the study avoid Inappropriate exclusions? (Q-2)	Yes	
	Are the cohorts comparable on the basis of design or analysis?	Yes	BMI was similar and they made age categories.
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Yes	
	Did all patients receive the same reference standard? (Q-2)	Yes	
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	They only used mFGs >= 8.
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the	No	

	reference standard test? (Q-2)		
	If a threshold was used, was it prespecified?	No	
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)		Yes
ATTRITION BIAS	Were withdrawals from the study explained?		
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	No	
OTHER ISSUES	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Not reported	Senior doctors made the ultrasound, but not specified what kind of doctors (e.g. endocrinologists, radiologists, gynecologists).
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
	Were there any conflicts of interest in the writing or funding of this study?	No	
	If statistical analysis was undertaken, was this appropriate?	Partial	No power calculation reported. But there was stratification for age. They used Youden index to calculate the optimal cutoff for AMH.
Comments			
What is the overall risk of bias?		Low	Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.

Study ID		Wongwananuruk 2018	
Study citation		Wongwananuruk T, Panichyawat N, Indhavivadhana S, Rattanachaiyanont M, Angsuwathana S, Techatraisak K, Pratumvinit B, Sa-Nga-Areekul N. Accuracy of anti-Müllerian hormone and total follicles count to diagnose polycystic ovary syndrome in reproductive women. Taiwan J Obstet Gynecol. 2018 Aug;57(4):499-506.	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/participants		PCOS: women with PCOS, 18-45 years of age. Controls: healthy women, 18-45 years of age with regular menstrual cycles and no clinical and biochemical hyperandrogenism.	
N		PCOS: 55 Controls: 63	
Setting		April 2016 - March 2017 Gynecologic Endocrinology Unit, Siriraj Hospital, Mahidol University.	
Index test		AMH measurement, using Elecsys on Cobas e602 from Roche, for controls at cycle day 2-5, for women with PCOS at anovulatory or follicular phase.	
Reference standard		Revised Rotterdam Criteria 2003 as having both 1) oligo-anovulation and 2) clinical and/or biochemical sign of hyperandrogenism. mFGs >= 5.	
Outcomes		- Differences between AMH and ultrasonographical findings between cases and controls. - Sensitivity, specificity and AUC with a threshold for AMH, follicle numbers per ovary, follicle number per cross-section and ovarian volume.	
Inclusion criteria		Yes	18-45 years of age and controls with regular menstrual cycles and no clinical and biochemical hyperandrogenism.
Exclusion criteria		Yes	Use of steroid drugs, hormones 3 months prior to study.
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Yes	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	In the control groups women with irregular menstrual cycles and hyperandrogenism were excluded.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	
	Was a case-control design avoided? (Q-2)	No	
	Did the study avoid Inappropriate exclusions? (Q-2)	Yes	
	Are the cohorts comparable on the basis of design or analysis?	Partial	Age was significantly different between both groups. Not clear how women were included.
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Yes	
	Did all patients receive the same reference standard?	Yes	

	(Q-2)		
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	When using NIH criteria.
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	No	
	If a threshold was used, was it prespecified?	No	
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRITION BIAS	Were withdrawals from the study explained?	Not reported	
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	No	
	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Not reported	It is reported that the ultrasonography was performed by two examiners, but not specified what they are (i.e. doctors, PhD students). Not reported who assessed the acne and hirsutism.
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
OTHER ISSUES	Were there any conflicts of interest in the writing or funding of this study?	No	

	If statistical analysis was undertaken, was this appropriate?	Partial	The sample size was not large, but they performed a power calculation based on a published meta-analysis. No age adjustment and it is not reported how they measured the best cutoff value for AMH (i.e. Youden Index).
Comments			
What is the overall risk of bias?		Moderate	

Study ID		Vagios 2021	
Study citation		Vagios S, James KE, Sacha CR, Hsu JY, Dimitriadis I, Bormann CL, Souter I. A patient-specific model combining antimüllerian hormone and body mass index as a predictor of polycystic ovary syndrome and other oligo-anovulation disorders. Fertil Steril. 2021 Jan;115(1):229-237. doi: 10.1016/j.fertnstert.2020.07.023.	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/participants		Patients who underwent intrauterine insemination or ovulation induction, divided in three groups: - PCOS patients - Ovulatory dysfunction (OVDYS) - Other causes of infertility (controls)	
N		PCOS: 228 OVDYS: 93 Controls: 689	
Setting		Retrospective study of patients who underwent intrauterine insemination or ovulation induction at the Massachusetts General Hospital Fertility Center, between May 2011 and March 2019.	
Index test		AMH measurement, by Ansh ELISA, not reported on which cycle day. FSH was measured at cycle day 3.	
Reference standard		PCOS diagnosis, Rotterdam criteria. Cutoff values not reported (i.e. mFGs, FAI, PCOM).	
Outcomes		- Differences in AMH levels between groups, stratified by percentile. - OR of PCOS diagnosis and OVDYS using AMH. - ROC analysis with AMH threshold for PCOS diagnosis.	
Inclusion criteria		Yes	
Exclusion criteria		Yes	Diminished ovarian reserve.
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Yes	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	Partial/Yes	They included PCOS patients and compared it with ovulatory dysfunction patients and other infertility problems. By not excluding ovulatory dysfunction patients the control group is more representative in practice.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	
	Was a case-control design avoided? (Q-2)	No	
	Did the study avoid Inappropriate exclusions? (Q-2)	Yes	

	Are the cohorts comparable on the basis of design or analysis?	Partial	Age and BMI were different between groups. For ROC analysis they did a stratification for BMI, but not for age.
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Yes	
	Did all patients receive the same reference standard? (Q-2)	Yes	
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Partial	Rotterdam criteria can be used, however cutoff values were not reported.
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	No	
	If a threshold was used, was it prespecified?	No	
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRITION BIAS	Were withdrawals from the study explained?	No	
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	No	
OTHER ISSUES	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?		
	Were the same	Yes	

	clinical data available when test results were interpreted as would be available when the test is used in practice?		
	Were there any conflicts of interest in the writing or funding of this study?	No	
	If statistical analysis was undertaken, was this appropriate?	Partial	Power calculation not reported. However, a validation as well as a replications et was u sed. Not reported how they assessed the best cutoff value of the AUC curve.
Comments			
What is the overall risk of bias?		Moderate	

Study ID		Tunç 2021	
Study citation		Tunç S, and Ozkan B. Analysis of New Biomarkers for the Diagnosis of Polycystic Ovary Syndrome in Adolescents Ergenlerde Polikistik Over Sendromu Tanisi icin Yeni Biyobelirteclerin Analizi. The Journal of Current Pediatrics, vol. 19, no. 3, Dec. 2021, pp. 311+. Gale OneFile: Health and Medicine.	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/participants		PCOS: Adolescents, aged 15-20 years, with hirsutism and/or menstrual irregularity, with the PCOS diagnosis. Controls: Adolescents with a regular menstrual cycle for at least two years.	
N		P: 55 C: 25	
Setting		Patients and controls who presented at the pediatric endocrinology outpatient clinic, Diyarbakir children Hospital, between 2017-2020.	
Index test		AMH measurement, by ELISA (not further specified).	
Reference standard		PCOS diagnosis, Rotterdam criteria. Pelvic ultrasound. PCOM >= 12 follicles.	
Outcomes		- Difference in AMH levels between cases and controls - ROC curve with a cut-off value, sensitivity and specificity of AMH for diagnosis PCOS.	
Inclusion criteria			
Exclusion criteria		Yes	Endocrine disorders, chronic disease, tumor, genetic syndrome, using drug that may affect laboratory findings.
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		partial	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	Controls were healthy adolescents with a regular menstrual cycle.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	

	Was a case-control design avoided? (Q-2)	No	
	Did the study avoid Inappropriate exclusions? (Q-2)	Yes	
	Are the cohorts comparable on the basis of design or analysis?	Partial	Not clear if the cases and controls were taken from comparable populations: not clear how controls were recruited. However, there were no differences in BMI and age.
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	No	Controls did not underwent a pelvic ultrasonography.
	Did all patients receive the same reference standard? (Q-2)	Yes	
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Partial	Rotterdam criteria. But a pelvic ultrasound was used. Cutoff value for FAI of mFGs was not reported.
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	No	
	If a threshold was used, was it prespecified?	No	
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	of the condition.
ATTRITION BIAS	Were withdrawals from the study explained?	No	Not reported.
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	No	

OTHER ISSUES	Was the execution of all tests described in sufficient detail to permit replication of the tests?	No	They only mentioned that AMH was measured by ELSIA, but not from which brand or laboratory.
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Not reported	Only reported that pelvic ultrasound was performed by a pediatric radiologist.
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
	Were there any conflicts of interest in the writing or funding of this study?	No	
	If statistical analysis was undertaken, was this appropriate?	No	No power calculation was reported and AUC was missing. Also the method to calculate the best cutoff value was not reported.
Comments			
What is the overall risk of bias?		High	

Study ID	Tola 2018	
Study citation	Tola H, Abbas M, Alhassan EA, Shrif NE, Rida M. Assessment of the Role of the Anti-Mullerian Hormone, Luteinizing Hormone/Follicle Stimulating Hormone Ratio in the Diagnosis of Polycystic Ovary Syndrome in Sudanese Women. Open Access Maced J Med Sci. 2018;6(7):1244-1247. Published 2018 Jul 17.	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/participants	Sudanese women with or without PCOS.	
N	P: 230 C: 100	
Setting	Dr Elsir Abu Alhassan Fertility Center, Khartoum, Sudan. When the inclusion started and ended is not reported.	
Index test	AMH measurement, by Beckman, on cycle day2-5 in both cases and controls.	
Reference standard	PCOS diagnosis, Rotterdam criteria.	
Outcomes	- Differences in AMH levels between cases and controls. - AUC, sensitivity, specificity, PPV, NPV of AMH in de diagnosis of PCOS	
Inclusion criteria	No	Information about controls is missing.
Exclusion criteria	Partial	Hypothyroidism, congenital adrenal hyperplasia, Cushing's syndrome, hyperprolactinemia, hirsutism. But not clear of these exclusion criteria were applicable for the control group or for the patients group as well.
Does the study have a clearly focused question? (yes/no/partial)	Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)	Partial, information about controls is missing, except for some exclusion criteria.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)		

PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	Specific PCOS patients and controls without PCOS were included.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Not reported	
	Was a case-control design avoided? (Q-2)	No	
	Did the study avoid Inappropriate exclusions? (Q-2)	Not reported	Only reported PCOS diagnosis according to Rotterdam criteria, but not further specified about the cutoff values for hyperandrogenism and PCOM.
	Are the cohorts comparable on the basis of design or analysis?	Partial	Unclear how patients were included and nothing reported about characteristics of the control population. Cases and controls were age and BMI matched.
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Yes	
	Did all patients receive the same reference standard? (Q-2)	Not reported	Not reported if controls also underwent an ultrasound. AMH measurement in both groups determined between cycle day 2 and 5.
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Partial	The Rotterdam criteria. But not specified the specific cutoff values.
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	No	
	If a threshold was used, was it prespecified?	No	
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRITION	Were withdrawals from the study explained?	Not reported	
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Not reported	

OTHER ISSUES	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Not reported	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
	Were there any conflicts of interest in the writing or funding of this study?	No	
	If statistical analysis was undertaken, was this appropriate?	Partial	No power calculation reported. The authors describe 'the best compromise between sensitivity and specificity'.
Comments			
What is the overall risk of bias?		High	

Study ID	Sova 2019	
Study citation	Sova H, Unkila-Kallio L, Tiitinen A, Hippeläinen M, Perheentupa A, Tinkanen H, Puukka K, Bloigu R, Piltonen T, Tapanainen JS, Morin-Papunen L. Hormone profiling, including anti-Müllerian hormone (AMH), for the diagnosis of polycystic ovary syndrome (PCOS) and characterization of PCOS phenotypes. Gynecol Endocrinol. 2019 Jul;35(7):595-600.	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/participants	PCOS patients originally recruited to a randomized controlled study investigating the efficacy of metformin, aged 18-39 years, BMI >19 kg/m2. Healthy Caucasian women, aged 18-39 years, BMI 19-35 kg/m2, non-smokers, no hormonal contraception use, regular menstrual cycles, no hirsutism/hyperandrogenemia, no use of medication.	
N	P: 319 C: 96	
Setting	Multicenter study conducted in all university hospitals of Finland (five sites). During the study period (January 2003 to December 2009), the women with PCOS referred to the clinics because of anovulatory infertility were asked for inclusion.	
Index test	AMH measurement, using VIDAS (bioMérieux), but also with Gen II (Beckman). Not reported on which cycle day.	
Reference standard	PCOS diagnosis, Rotterdam criteria. Cutoff for hisutism: mFGs >6. Testosterone levels >= +2SD was defined as biochemical hyperandrogenism. Cutoff value for PCOM not reported.	
Outcomes	- Difference of AMH levels in cases versus controls - AUC, sensitivity and specificity using AMH for PCOS diagnosis. - Difference in AMH levels between methods - AMH concentration according to PCOS phenotypes - Correlation between AMH and other parameters	
Inclusion criteria	Yes	

Exclusion criteria		Yes	
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Yes	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	Healthy controls, with regular menstrual cycles, n or hirsutism/hyperandrogenemia.
	Was a consecutive or random sample of patients enrolled? (Q-2)		It is best if the patients are randomly selected or consecutive admissions so that selection bias is minimized.
	Was a case-control design avoided? (Q-2)	No	
	Did the study avoid Inappropriate exclusions? (Q-2)	Yes	
	Are the cohorts comparable on the basis of design or analysis?	No	PCOS cases from a previous RCT investigating the efficiency of metformin use; healthy controls were recruited via newspapers and advertisements. BMI and age were significantly different. The controls consist of 96% Caucasian women, this is not reported about the PCOS women. f
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Yes	
	Did all patients receive the same reference standard? (Q-2)	Yes	
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Partial	Rotterdam criteria. Cutoff for hisutism: mFGs >6. Testosterone levels >= +2SD was defined as biochemical hyperandrogenism. Cutoff value for PCOM not reported.
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	No	
	If a threshold was used, was it prespecified?	No	

DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRIT I ON	Were withdrawals from the study explained?	No	Not reported
REPO RT BIAS	Were uninterruptable/ intermediate test results reported?	No	Not reported
OTHER ISSUES	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Not reported	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
	Were there any conflicts of interest in the writing or funding of this study?	No	
	If statistical analysis was undertaken, was this appropriate?	Partial	No power calculation was reported. BMI was different in the groups. No Youden index. Intraclass correlation was calculated between AMH values measured by two assays.
Comments			
What is the overall risk of bias?		Moderate	Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.

Study ID		Song 2021	
Study citation		Song J, Park Y, Cho HW, Lee SG, Kim S, Lim JB. Age-group-specific reference intervals for anti-Müllerian hormone and its diagnostic performance for polycystic ovary syndrome in a Korean population. J Clin Lab Anal. 2021 Jul;35(7):e23861. doi: 10.1002/jcla.23861. Epub 2021 Jun 7. PMID: 34097316; PMCID: PMC8274997.	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/participants		PCOS: from medical records in a Korean population. Controls: - Healthy group - Benign diseases group All based on patient records in a Korean population.	
N		PCOS: 440 Healthy: 347 Benign gyn disease: 753	
Setting		Retrospective study, serum AMH, FSH and E2 were requested for females, aged 12-52 years at Severance Hospital in South Korea, between May 2017 and January 2019.	
Index test		AMH measurement, by Elecsys Roche, unspecified day of menstrual cycle.	
Reference standard		PCOS diagnosis, according to Rotterdam criteria. Specified in other article: mFGs >= 6, PCOM > 12 follicles, T >2.8 nmol/L.	
Outcomes		- Differences in AMH levels between groups. - AUC's for the PCOS diagnosis in different age groups.	
Inclusion criteria		Yes	12-52 years of age.
Exclusion criteria		Yes	Any kind of cancers, POI and pregnancy or wre pregnant recently.
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Yes	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	Healthy population and a benign gynecologic disease group as two control groups.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	
	Was a case-control design avoided? (Q-2)	No	
	Did the study avoid Inappropriate exclusions? (Q-2)	Yes	
	Are the cohorts comparable on the basis of design or analysis?	Partial	Benign gynecologic disease group, not quite clear why this a separate group. Exclusion POI, pregnancy, age above 50 years. Cases were younger and had a higher BMI. But age specific reference interval.
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Not reported	Diagnosis was assessed from medical records. So it is not clear whether healthy controls also underwent ultrasound and other PCOS related assessments.
	Did all patients receive the same reference standard? (Q-2)	Yes	
	Is the reference	Yes	mFGs >= 6, PCOM > 12 follicles, T >2.8 nmol/L.

	standard likely to correctly classify the target condition? (Q-2)		
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	No	
	If a threshold was used, was it prespecified?	No	
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Partial	Subjects' medical records between 180 days before and 90 days after the AMH measurement were requested.
ATTRITION	Were withdrawals from the study explained?	Not reported	
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	No	Not reported
OTHER ISSUES	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Not reported	Data from medical records, thus diagnosis was made by different doctors and specialists.
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
	Were there any conflicts of interest in the writing or funding of this study?	No	
	If statistical analysis was undertaken, was this appropriate?	Partial	No power calculation was reported. Youden's index was used and age specific reference interval. However, there were differences in BMI.
Comments			
What is the overall risk of bias?		Moderate	

Study ID		Song 2017	
Study citation		Song DK, Oh JY, Lee H, Sung YA. Differentiation between polycystic ovary syndrome and polycystic ovarian morphology by means of an anti-Müllerian hormone cutoff value. Korean J Intern Med. 2017 Jul;32(4):690-698. doi: 10.3904/kjim.2016.038. Epub 2016 Nov 30.	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/participants		PCOS: women with PCOS with and without PCOM, under the age of 40 years. Controls: regular cycling women with normoandrogenemia, under the age of 40.	
N		P: 207 C: 220	
Setting		Between 2008 and 2010 a survey about menstrual health was performed of young women under the age of 40 years, living in Seoul, Korea. Participant were divided in PCOS and controls. These two groups were also both divided in PCOM and no PCOM.	
Index test		AMH measurement, y Beckman, cycle day 3 or in women with amenorrhea random.	
Reference standard		PCOS diagnosis, Rotterdam criteria. Hyperandrogenemia: testosterone above 95th percentile. mFGw >= 3. PCOM >= 12 follicles, by transvaginal ultrasonography or transrectal ultrasound for virginal women (not specified in how many women this is performed).	
Outcomes		- Differences in parameters, including AMH, between the two and the four groups. - AUC, sensitivity and specificity of AMH for diagnosis of PCOS.	
Inclusion criteria		Yes	
Exclusion criteria		Yes	Congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome, 21-hydroxylase0deficient, medication (e.g., steroids, oral contraceptives, metformin, thiazide diuretics) within 3 months of the evaluation.
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Yes	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	In control groups criteria for PCOS were excluded (irregular cycle and hyperandrogenemia).
	Was a consecutive or random sample of patients enrolled? (Q-2)	Partial	Because they were recruited via newspaper and online advertisements there will be a bias in included patients.
	Was a case-control design avoided? (Q-2)	No	
	Did the study avoid Inappropriate exclusions? (Q-2)	Yes	
	Are the cohorts comparable on the basis of design or analysis?	Partial	Newspaper and online advertisements. Stratified for age, significant differences in BMI.
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Yes	
	Did all patients receive the same reference standard?	Yes	

	(Q-2)		
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	No	
	If a threshold was used, was it prespecified?	No	
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)		
ATTRITION	Were withdrawals from the study explained?	Not reported	
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	No	Not reported
OTHER ISSUES	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Not reported	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
	Were there any conflicts of interest in the writing or funding of this study?	No	
	If statistical analysis was undertaken, was this appropriate?	Partial	No power calculation was reported. Differences in BMI.
Comments			
What is the overall risk of bias?		Moderate	

Study ID		Saxena 2018	
Study citation		Saxena, U., Ramani, M. & Singh, P. Role of AMH as Diagnostic Tool for Polycystic Ovarian Syndrome. J Obstet Gynecol India 68, 117–122 (2018). https://doi.org/10.1007/s13224-017-1066-4	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/participants		PCOS: Rotterdam criteria, 18-35 years attending outpatient department of Gynaecology. Controls: regular menstrual cycle, no PCOM, no endocrine abnormalities, BMI and age matched.	
N		PCOS: 45 Controls: 45	
Setting		Outpatient department of Obstetrics and Gynaecology, PGIMER & Dr. RML hospital, New Delhi, India. From November 2015 until March 2017	
Index test		AMH measurement, by ELISA (Immunoconcept), on cycle day 2-3, or after withdrawal bleeding.	
Reference standard		PCOS, Rotterdam criteria, mFGs >8, PCOM > 12 follicles, testosterone >2.67 nmol/L.	
Outcomes		- Difference of AMH levels between cases and controls. - AUC, sensitivity, specificity of AMH for PCOS diagnosis.	
Inclusion criteria		Yes	
Exclusion criteria		Yes	History of ovarian surgery and intake of COC in past 3 months.
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Yes	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	In control groups women with irregular menstrual cycle or PCOM were excluded.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	
	Was a case-control design avoided? (Q-2)	No	
	Did the study avoid Inappropriate exclusions? (Q-2)	Yes	
	Are the cohorts comparable on the basis of design or analysis?	Yes	Patients who attended the Department of Obstetrics and Gynaecology. Age and BMI similar in both groups.
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Yes	
	Did all patients receive the same reference standard? (Q-2)	Yes	
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	
	Were the reference standard results interpreted without	Yes	

	knowledge of the results of the index test? (Q-2)		
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	No	
	If a threshold was used, was it prespecified?	No	
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRITION	Were withdrawals from the study explained?	No	Not reported
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	No	
OTHER ISSUES	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Not reported	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
	Were there any conflicts of interest in the writing or funding of this study?	No	
	If statistical analysis was undertaken, was this appropriate?	Partial	No power calculation.
Comments			
What is the overall risk of bias?		Moderate	

Study ID		Kim 2017	
Study citation		Kim JY, Tfayli H, Michaliszyn SF, Lee S, Nasr A, Arslanian S. Anti-Müllerian Hormone in Obese Adolescent Girls With Polycystic Ovary Syndrome. J Adolesc Health. 2017 Mar;60(3):333-339. doi: 10.1016/j.jadohealth.2016.10.015. Epub 2016 Dec 18. PMID: 27998701; PMCID: PMC5326592.	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/participants		Adolescents with overweight or obesity with PCOS.	
N		PCOS: 46 Controls: 43	
Setting		PCOS Center at Children's Hospital of Pittsburgh.	
Index test		AMH measurement, by Ansh ultra-sensitive AMH ELISA. Not reported on which cycle day.	
Reference standard		PCOS diagnosis, NIH criteria. Cutoff values not further specified.	
Outcomes		- Difference in AMH levels between PCOS girls and controls. - The relationship of AMH to age and other parameters. - ROC curve analyses of AMH and other parameters.	
Inclusion criteria		Yes	Age 10-20 years and post menarche, BMI ≥85th percentile for age and sex.
Exclusion criteria		Yes	Systemic or psychiatric disease and taking any medications that impact carbohydrate or lipid metabolism (oral contraceptive pills [OCPs], metformin, anti-epileptics, anti-psychotics, statins and fish oil).
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Yes	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	Controls did not had PCOS. All had overweight or obesity, with a very high prevalence of obesity.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	
	Was a case-control design avoided? (Q-2)	No	
	Did the study avoid Inappropriate exclusions? (Q-2)	Yes	
	Are the cohorts comparable on the basis of design or analysis?	No	Cases were health seeking, controls were derived from a different study. Age was the same, but BMI was higher in PCOS patients. Also the prevalence of the different ethnicities was different between the two groups.
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Yes	
	Did all patients receive the same reference standard? (Q-2)	Yes	
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Partial	The diagnosis was made based on the presence of clinical signs and symptoms of hyperandrogenism and/or biochemical hyperandrogenemia.
	Were the reference standard results	Yes	

	interpreted without knowledge of the results of the index test? (Q-2)		
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	No	
	If a threshold was used, was it prespecified?	No	
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRITI	Were withdrawals from the study explained?	No	Not reported
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Not reported	
OTHER ISSUES	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Not reported	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
	Were there any conflicts of interest in the writing or funding of this study?	No	
	If statistical analysis was undertaken, was this appropriate?	Partial	No power calculation, no adjustment for the differences in BMI.
Comments			
What is the overall risk of bias?		Moderate	

Study ID	Sharma 2019
Study citation	Sharma P, Chawla R, Ahuja R, et al. Anti-Müllerian Hormone as a Surrogate Marker for Hormonal Dysfunction and Sonographic Pattern in Polycystic Ovarian Syndrome. J South Asian Feder Obst Gynae 2019;11(3):175–180.
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/participants	PCOS: who attended the gynecology OPD and fulfilled the Rotterdam criteria. Controls: age-matched controls, normo-ovulatory women who attended the gynecology OPD.
N	PCOS: 45 Controls: 45
Setting	Cross-sectional study, at the ESIC Medical College and Hospital, Faridabad, Haryana (India), from March 2017 to September 2017.

Index test		AMH measurement, using ultrasensitive AMH/MIS ELISA Ansh, between day 2-5 of natural or progesterone-induced menstrual cycle.	
Reference standard		PCOS diagnosis, Rotterdam criteria, PCOM >12 follicles, mFGs >8, testosterone >2.5nmol/L. Anovulation: absence of menses for 3 months, oligo-ovulation was defined as fewer than 9 menstrual cycles per year.	
Outcomes		- Differences in AMH and AMH/AFC between PCOS and controls. - Correlation of AMH with various biochemical and sonographic characteristics - ROC curve analysis of AMH for diagnosis PCOS	
Inclusion criteria		Yes	
Exclusion criteria		Yes	Hepatic, renal and autoimmune disease, abnormal serum albumin, overt hyper/hypothyroidism, adrenal disorders, history of use of hormones, ovulation-induction drugs, and insulin-sensitizing drugs in the past 3 months, and past history of ovarian drilling.
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Yes	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	Partial	Controls were normo-ovulatory women. Not much information about the controls is reported. Only that they were normo-ovulatory. Not described if PCOS was excluded, for example no differences in FG.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	
	Was a case-control design avoided? (Q-2)	No	
	Did the study avoid Inappropriate exclusions? (Q-2)	Yes	
	Are the cohorts comparable on the basis of design or analysis?	Yes	Both were attending the OBGYN department, they were age matched, BMI was not different between the two groups.
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Yes	
	Did all patients receive the same reference standard? (Q-2)	Yes	
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	Only mFGs >8 was used.
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge	No	

	of the results of the reference standard test? (Q-2)		
	If a threshold was used, was it prespecified?	No	
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRITION	Were withdrawals from the study explained?	Not reported	
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Not reported	
OTHER ISSUES	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Not reported	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
	Were there any conflicts of interest in the writing or funding of this study?	No	
	If statistical analysis was undertaken, was this appropriate?	Partial	No power calculation reported, the authors describe 'with acceptable sensitivity and specificity'.
Comments			
What is the overall risk of bias?		Moderate	No power calculation, but relatively small sample sizes.

Study ID	Jacob 2017
Study citation	Jacob SL, Field HP, Calder N, Picton HM, Balen AH, Barth JH. Anti-Müllerian hormone reflects the severity of polycystic ovary syndrome. Clin Endocrinol (Oxf). 2017 Mar;86(3):395-400. doi: 10.1111/cen.13269. Epub 2016 Dec 1. PMID: 27805276.
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/participants	Patients who attended the tertiary infertility clinic.
N	P: 102 PCOM: 42 Controls: 109
Setting	Tertiary infertility clinic

Index test		AMH measurement, by Beckman, not reported on what cycle day (only reported for FSH, LH, estradiol and testosterone).	
Reference standard		PCOS diagnosis, Rotterdam criteria, further categorized in the four phenotypes.	
Outcomes		- Differences in AMH levels between controls, PCOM and PCOS patients. - ROC curve analysis of AMH for PCOS diagnosis	
Inclusion criteria		Yes	
Exclusion criteria		Yes	Active hormonal treatment.
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Partial, only exclusion criteria was active hormonal treatment. PCOS diagnosis was clearly reported.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	Partial	The controls had no features of PCOS and normal ovaries. However, for ROC analysis they included controls with PCOM (an isolated PCOS feature).
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	
	Was a case-control design avoided? (Q-2)	No	
	Did the study avoid Inappropriate exclusions? (Q-2)	Yes	
	Are the cohorts comparable on the basis of design or analysis?	Partial	Age was significantly different between normal group and PCOS group, but similar between PCOM and PCOS group. The latter have been used for ROC analyses. All patients from infertility clinic.
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Yes	
	Did all patients receive the same reference standard? (Q-2)	Yes	
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	No	
	If a threshold was used, was it prespecified?	No	

DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRITION	Were withdrawals from the study explained?	No	Not reported
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	No	
OTHER ISSUES	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Not reported	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
	Were there any conflicts of interest in the writing or funding of this study?	No	
	If statistical analysis was undertaken, was this appropriate?	Partial	No power calculation. Youden's index.
Comments			
What is the overall risk of bias?		Moderate	Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.

Study ID	Indran 2018
Study citation	Indran IR, Huang Z, Khin LW, Chan JKY, Viardot-Foucault V, Yong EL. Simplified 4-item criteria for polycystic ovary syndrome: A bridge too far? Clin Endocrinol (Oxf). 2018 Aug;89(2):202-211. doi: 10.1111/cen.13755. Epub 2018 Jun 19. PMID: 29851127.
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/participants	Referred for suspected PCOS. Controls recruited at an annual hospital health screen for staff and volunteers from the university community.
N	P: 174 C: 157

Setting		Healthy cohort (annual health screen offered to all employees of National University Hospital (NUH), Singapore and from the National University of Singapore community) and patient cohort (the gynecological clinics of NUH and KK Women's and Children's Hospital (KKH). NUH and KKH are the two largest tertiary referral gynecological clinics in Singapore).	
Index test		AMH measurement, by Beckman, cycle days 2-6.	
Reference standard		PCOS diagnosis, Rotterdam criteria. mFGs >= 5, AFC and/or OV above threshold in either ovary.	
Outcomes		Questionnaires, physical examination, blood sampling.	
Inclusion criteria		Yes	Age 21-45 years.
Exclusion criteria		Yes	Cases: previous PCOS diagnosis For cases and controls: conditions that might affect reproductive function such as pregnancy conditions, hormonal medications and adrenal disease.
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Yes	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	Controls were healthy women, PCOS was excluded.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	
	Was a case-control design avoided? (Q-2)	No	
	Did the study avoid Inappropriate exclusions? (Q-2)	Yes	
	Are the cohorts comparable on the basis of design or analysis?	Partial	Same age, but different BMI.
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Yes	
	Did all patients receive the same reference standard? (Q-2)	Yes	
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	No	
	If a threshold was	No	

	used, was it prespecified?		
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRITION BIAS	Were withdrawals from the study explained?	Yes	Controls: a total of 943 subjects were approached and 206 met inclusion /exclusion criteria and agreed to participate in the study. A further 49 women were then excluded as they were previously diagnosed as PCOS (n=15), unable to tolerate transvaginal vaginal scans (iv), had persistent cysts >10mm in either ovary on repeated Days 2-6 transvaginal ultrasound scans, had hyperprolactinemia (4), had estradiol below detection limit (4), or raised FSH (1). PCOS: Four referral subjects were excluded due to persistent cysts.
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	No	
OTHER ISSUES	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Not reported	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
	Were there any conflicts of interest in the writing or funding of this study?	No	
	If statistical analysis was undertaken, was this appropriate?	Partial	No power calculation.
Comments			
What is the overall risk of bias?		Low	

Study ID	Al-Naffakh 2020
Study citation	Al-Naffakh AS, Risan FA. Assessment of anti-Mullerian hormone and anti ovarian antibody in the sera of patients with polycystic ovarian syndrome in AL-Najaf Al-Ashraf Province. Medico-Legal Update 2020;20(1):600–8. Doi: 10.37506/v20/i1/2020/mlu/194384
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	

Patient/population/participants		PCOS patients and controls who attended the Al-Furat teaching hospital and fertility center.	
N		P: 80 C: 40	
Setting			
Index test		AMH measurement, ELFS technique, Biomerieux, cycle day 2-7.	
Reference standard		PCOS diagnosis, international diagnostic criteria (not specified).	
Outcomes		- Differences AMH levels between cases and controls - Roc analysis of AMH for diagnosis PCOS - ROC analysis of anti-ovarian antibodies for diagnosis PCOS	
Inclusion criteria		Yes	15-40 years of age. PCOS: diagnosed for not than one year ago.
Exclusion criteria		Yes	PCOS: under current medication Controls: with a previous history of PCOS and recovered. Patients with unexplained causes of infertility, with other chronic disease.
Does the study have a clearly focused question? (yes/no/partial)		No, not in the introduction. In the abstract a study aim is reported.	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Yes	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	No detailed information about the PCOS criteria that are used. Also very limited information about controls. No baseline characteristics.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	
	Was a case-control design avoided? (Q-2)	No	
	Did the study avoid Inappropriate exclusions? (Q-2)	Not reported	Specific PCOS criteria not reported.
	Are the cohorts comparable on the basis of design or analysis?	Not reported	
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Yes	
	Did all patients receive the same reference standard? (Q-2)	Yes	
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Not reported	Specific PCOS criteria not reported.
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the	No	

	reference standard test? (Q-2)		
	If a threshold was used, was it prespecified?	No	QUADAS suggests that selecting the test threshold to optimize sensitivity and/or specificity may lead to overoptimistic estimates of test performance, which is likely to be poorer in an independent sample of patients in whom the same threshold is used.
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRITION	Were withdrawals from the study explained?	No	Not reported
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	No	
OTHER ISSUES	Was the execution of all tests described in sufficient detail to permit replication of the tests?	No	No information about specific PCOS criteria, no method section about statistical analyses.
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Not reported	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
	Were there any conflicts of interest in the writing or funding of this study?	No	
	If statistical analysis was undertaken, was this appropriate?	Not reported	No power calculation reported. No method section about statistical analyses. Not reported how the optimal cutoff value was determined.
Comments			
What is the overall risk of bias?		High	

Study ID		Lin 2011	
Study citation		Lin YH, Chiu WC, Wu CH, Tzeng CR, Hsu CS, Hsu MI. Antimüllerian hormone and polycystic ovary syndrome. Fertil Steril. 2011 Jul;96(1):230-5. doi: 10.1016/j.fertnstert.2011.04.003. Epub 2011 May 5. PMID: 21549367.	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/participants		Patients and healthy volunteers. Patients who complained of infertility, menstrual irregularity and hyperandrogenism were recruited from the gynecologic outpatient clinic.	
N		P: 126 C: 164	
Setting		Reproductive Endocrinology Clinic, Taiwan, June 2009 to September 2010.	
Index test		AMH measurement, ELISA (Diagnostic Systems Laboratories)	
Reference standard		PCOS diagnosis, Rotterdam criteria, HA: T >= 2.98 mmol/L, mFGs >= 6, PCOM >= 12 follicles.	
Outcomes		- Differences in AMH levels between normal controls, HA, ANOV, PCOM, HA+ANOV, HA+PCOM, ANOV+PCOM, and HA+ANOV+PCOM. - Differences in clinical characteristics between three groups stratified in AMH levels (cases and controls together) - ROC curve analysis of AMH for diagnosis PCOS	
Inclusion criteria		Yes	
Exclusion criteria		Yes	Women who had been diagnosed with other etiologies that should be excluded when diagnosis PCOS, menarche <3 years before study, using hormones or drugs for major medical diseases, women with ovarian cysts or tumors, >45 years of age.
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Yes	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	Partial	Controls were also healthy volunteers. However, PCOS symptoms were not excluded in the control population.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	
	Was a case-control design avoided? (Q-2)	No	
	Did the study avoid Inappropriate exclusions? (Q-2)	Yes	
	Are the cohorts comparable on the basis of design or analysis?	Not reported	Cases and controls were from different populations: health seeking versus volunteers. Baseline characteristics were not compared between total case population and total control population.
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Yes	
	Did all patients receive the same reference standard? (Q-2)	Yes	

	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	No	
	If a threshold was used, was it prespecified?	No	
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRITION	Were withdrawals from the study explained?	No	Not reported
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	No	
	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Not reported	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
	Were there any conflicts of interest in the writing or funding of this study?	Not reported	
OTHER ISSUES	If statistical analysis was undertaken, was this appropriate?	Partial	No power calculation. Optimal AMH threshold by Youden's index.
Comments			
What is the overall risk of bias?		High	

Study ID		Singh 2020	
Study citation		Singh S, Firdaus A, Choudhary R, Dhama V. Role of antimullerian hormone as a diagnostic tool for polycystic ovary syndrome. Int J Reprod Contracept Obstet Gynecol. 2020;9(9):3730. DOI: 10.18203/2320-1770.ijrcog20203847	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/participants		Patients visiting the obstetrics and gynecology outpatient department.	
N		P: 50 C: 50	
Setting		Obstetrics and gynecology outpatient department of LLRM Medical College, Meerut, from May 2018 to June 2019.	
Index test		AMH measurement, ELISA immune concept bio-detect, cycle day 2-3.	
Reference standard		PCOS diagnosis, Rotterdam criteria, mFGs >8, PCOM >= 12 follicles	
Outcomes		- Mean AMH in different PCOS phenotypes - AMH between PCOS and controls - ROC curve analysis of AMH for PCOS diagnosis	
Inclusion criteria		Yes	Controls: regular menstrual cycles, morphologically normal ovaries on ultrasound. Overall: age 18-39 years.
Exclusion criteria		Yes	Control: endometriosis, cysts, other ovarian gynecological disorders, endocrine abnormalities. All: hormonal therapy within 3 months prior to study.
Does the study have a clearly focused question? (yes/no/partial)		No	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Yes	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	Controls had regular menstrual cycles, and normal ovaries (no PCOM).
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	
	Was a case-control design avoided? (Q-2)	No	
	Did the study avoid Inappropriate exclusions? (Q-2)	Yes	
	Are the cohorts comparable on the basis of design or analysis?	Yes	Age and BMI were not significant different between both groups.
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Yes	
	Did all patients receive the same reference standard? (Q-2)	Yes	
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	Only remarkable: mFGs >8.
	Were the reference standard results interpreted without knowledge of the	Yes	

	results of the index test? (Q-2)		
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	No	
	If a threshold was used, was it prespecified?	No	
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRITION	Were withdrawals from the study explained?	No	Not reported
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	No	
OTHER ISSUES	Was the execution of all tests described in sufficient detail to permit replication of the tests?	No	Not reported what kind of AMH assay is used, only: ELISA immune concept bio-detect.
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Not reported	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
	Were there any conflicts of interest in the writing or funding of this study?	No	
	If statistical analysis was undertaken, was this appropriate?	Partial	No power analysis. Not reported how the optimal cutoff value was calculated for AMH.
Comments			
What is the overall risk of bias?		Low	

Study ID		Jamil 2016	
Study citation		Jamil AS, Alalaf SK, Al-Tawil NG, Al-Shawaf T. Comparison of clinical and hormonal characteristics among four phenotypes of polycystic ovary syndrome based on the Rotterdam criteria. Arch Gynecol Obstet. 2016 Feb;293(2):447-56. doi: 10.1007/s00404-015-3889-5. Epub 2015 Sep 25. PMID: 26408006.	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/participants		Infertile women, attending gynecology and fertility clinics. Controls: male tubal factor, unexplained infertility or other non-endocrine related conditions.	
N			
Setting		Maternity Teaching Hospital gynecology and fertility clinics, Iraq, April 2012 – June 2013.	
Index test		AMH measurement, cycle day 2-3 or random in case of amenorrhea. Measured by ELISA Gen II Beckman.	
Reference standard		PCOS diagnosis, Rotterdam criteria, HA total testosterone >95th percentile, PCOM >= 12 follicles, mFGs >=8.	
Outcomes			
Inclusion criteria		Yes	C: 18-39 years, regular menstrual cycles, no evidence of hirsutism or PCOM.
Exclusion criteria		Yes	FSH >12.5 mIU/mL, 17-OHP > 1.5 ng/ml, and those on hormonal medication for =< 6 months prior to study. Endocrinological abnormalities: hyperprolactinemia, thyroid dysfunction, Cushing's syndrome, congenital adrenal hyperplasia, androgen producing neoplasm.
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Yes	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	Criteria for PCOS diagnosis were excluded in the control population.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	
	Was a case-control design avoided? (Q-2)	No	
	Did the study avoid Inappropriate exclusions? (Q-2)	Yes	All phenotypes were included.
	Are the cohorts comparable on the basis of design or analysis?	No	Age and BMI were significantly different between both groups.
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Yes	
	Did all patients receive the same reference standard? (Q-2)	Yes	
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	mFGs >= 8.
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	

	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	No	
	If a threshold was used, was it prespecified?	No	
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRITION	Were withdrawals from the study explained?	No	Not reported
REPORT	Were uninterruptable/ intermediate test results reported?	No	
OTHER ISSUES	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Not reported	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
	Were there any conflicts of interest in the writing or funding of this study?	No	
	If statistical analysis was undertaken, was this appropriate?	Partial	No power analysis reported. No adjustment for the differences in age and BMI.
Comments			
What is the overall risk of bias?		Moderate	

Study ID	Al-Jefout 2021	
Study citation	Al-Jefout M, Alnawaiseh C, Saleh M, Warwar K. Anti-Müllerian hormone (AMH) new cutoff as a possible tool for the diagnosis of polycystic ovary syndrome (PCOS). J Biomed Sci Res. 2021;3(2):139. Doi: 10.36266/JBSR/139	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/participants	Women who had a new diagnosis of PCOS, aged 14-50 years. Control women without PCOS, attending for other gynecological conditions.	
N		
Setting	Women who were seen in the ObGyn department in Tawam Hospital, from January 2017 – December 2020.	
Index test	AMH measurement, cycle days 2-6 (natural or progesterone withdrawal). Measured by Roche platform: Cobas 8000)	
Reference standard	PCOS diagnosis, Rotterdam criteria. PCOM > 12 follicle in each ovary, mFGs >6.	
Outcomes		
Inclusion criteria	Partial	Only PCOS Rotterdam criteria and controls without PCOS.
Exclusion criteria	No	
Does the study have a clearly focused question? (yes/no/partial)	Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)	No	

INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	Yes	Patients with and without PCOS, without excluding one PCOS symptom in the control group.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	
	Was a case-control design avoided? (Q-2)	No	
	Did the study avoid Inappropriate exclusions? (Q-2)	Not reported	No exclusion criteria reported.
	Are the cohorts comparable on the basis of design or analysis?	Yes	Age and BMI were similar is reported, however data not presented.
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Yes	
	Did all patients receive the same reference standard? (Q-2)	Yes	
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	Only mFGs >6.
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	No	
	If a threshold was used, was it prespecified?	No	
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRITION	Were withdrawals from the study explained?	Not reported	
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	No	Not reported
OTHER ISSUES	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians	Not reported	

	undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?		
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
	Were there any conflicts of interest in the writing or funding of this study?	No	
	If statistical analysis was undertaken, was this appropriate?	Partial	No power analysis reported.
Comments			
What is the overall risk of bias?		Moderate	

Study ID		Deveer 2015	
Study citation		Deveer M, Deveer R, Basaran O, Turkcu UO, Akbaba E, Cullu N, Turhan N, Kucuk M, Kasap B. Serum Copeptin, Pentraxin 3, Anti-Mullerian Hormone Levels With Echocardiography and Carotid Artery Intima-Media Thickness in Adolescents With Polycystic Ovary Syndrome. J Clin Med Res. 2015 Dec;7(12):989-94. doi: 10.14740/jocmr2375w. Epub 2015 Oct 23. PMID: 26566413; PMCID: PMC4625820.	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/participants		PCOS patients who were complaining of menstrual irregularity, hirsutism or infertility. Healthy volunteers with regular menses.	
N		PCOS: 50 Controls: 25	
Setting		ObGyn department, May 2013 – Jun 2014.	
Index test		AMH measurement, Gen II Beckman, cycle days 3-5 (spontaneous or progestin-induced).	
Reference standard		PCOS diagnosis, Rotterdam criteria, but with all three features. Cutoff values not reported (e.g. mFGs, FAI, PCOM).	
Outcomes		- Metabolic profile of adolescent PCOS, adults PCOS and controls - ROC analysis of AMH for diagnosis PCOS (adults and adolescents together)	
Inclusion criteria		Yes	Controls: Regular menses. All: menstruating for at least 2 years.
Exclusion criteria		Yes	Controls: hirsutism, hyperandrogenism, systemic or endocrine disease.
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Yes	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	Features of PCOS excluded in the control group.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	
	Was a case-control design avoided? (Q-2)	No	
	Did the study avoid Inappropriate exclusions? (Q-2)	No	Rotterdam criteria, but only with all three features present.

	Are the cohorts comparable on the basis of design or analysis?	No	Age is different between cases and controls.
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Yes	
	Did all patients receive the same reference standard? (Q-2)	Yes	
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Partial	Rotterdam criteria is likely to classify the target condition correctly, however cutoff values were not reported for hyperandrogenism and PCOM.
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	No	
	If a threshold was used, was it prespecified?	No	
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRIT_ON	Were withdrawals from the study explained?	No	Not reported
REPO RT BIAS	Were uninterruptable/ intermediate test results reported?	Not reported	
OTHER ISSUES	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Not reported	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	

	Were there any conflicts of interest in the writing or funding of this study?	No	
	If statistical analysis was undertaken, was this appropriate?	Partial	No power calculation, no adjustments or stratification for age in the ROC analysis.
Comments		Sample size of control group is small.	
What is the overall risk of bias?		Moderate	

Study ID		Agrawal 2018	
Study citation		Namita Agrawal, Rajrani Sharma. 2018 Correlation of Anti-Müllerian hormone with clinical, hormonal and ultrasonographic parameters in PCOS and normo-ovulatory women:an experience of single tertiary care center. Italian Journal of Gynaecology and Obstetrics. Dec 2018. Vol 30.	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/participants		- Health seeking, subfertile population, diagnosed with PCOS according to Rotterdam criteria. However PCOM was defined as minimum of 9 follicles - Controls were normoovulatory-matched investigated for male, tubal or unexplained infertility with regular menstrual cycle (25-35 days), PCOS excluded. Control women were matched with PCOS women for mean age (±5 years) and mean body mass index, BMI (±3kg/m2) - The inclusion criteria were: age between 21-35 year, both ovary present, no previous history of ovarian surgery, adequate visualization of ovary by transvaginal ultrasound and no regular & continuous hormonal therapy since six months	
N		PCOS 32 Control 32	
Setting		Rabindra Nath Tagore Medical College and attached hospital, pannadhay mahila chikitsalaya, Udaipur, Rajasthan, INDIA between September 2013 to March 2015.	
Index test		The serum levels of AMH were determined by enzyme –linked immunosorbent assay (ELISA) test kit.	
Reference standard		Rotterdam criteria	
Outcomes		Accuracy (for detecting PCOS) Sensitivity and specificity and AUC	
Inclusion criteria		Yes	
Exclusion criteria		Yes	
Does the study have a clearly focused question? (yes/no/partial)		Partial	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Yes	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	PCOS was excluded in control group, which will exaggerate the diagnostic accuracy
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	
	Was a case-control design avoided? (Q-2)	Yes	Women were divided into PCOS and control group based on their symptoms after enrolment, it doesn't state that they had to either have PCOS or be a healthy control before inclusion.
	Did the study avoid Inappropriate exclusions? (Q-2)	Yes	
CLA	Were all participants	Yes	

	assessed with both index test and reference standard? (Also in Q-2)		
	Did all patients receive the same reference standard? (Q-2)	Yes	
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Partial	PCOM was diagnosed as ≥ 9 follicles and/or ovarian volume > 10 ml, which is not the definition for PCOM according to the Rotterdam criteria
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	No	
	If a threshold was used, was it prespecified?	No	Shortest distance on the ROC curve was used to determine the best cut-off value of AMH
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRITION	Were withdrawals from the study explained?	NA	No report of withdrawals
REPORT	Were uninterruptable/ intermediate test results reported?	Not reported	
OTHER ISSUES	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Yes	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
	Were there any conflicts of interest in the writing or funding of this study?	No	
	If statistical analysis was undertaken, was this appropriate?	Partial	Power calculation not reported
Comments			
What is the overall risk of bias?		Moderate	Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.

Study ID	Ahmed 2019
Study citation	Nada Ahmed , Asma A Batarfi, Osama S Bajouh, Sherin Bakhashab Serum Anti-Müllerian Hormone in the Diagnosis of Polycystic Ovary Syndrome in Association with Clinical Symptoms. Diagnostics (Basel) 2019 Oct 1;9(4):136. doi: 10.3390/diagnostics9040136.
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/participants	- PCOS was diagnosed according to Rotterdam criteria - control group had a normal ovulation

		- Previously published randomized case control study - Using Raosoft (www.raosoft.com), the appropriate sample size was calculated to be 196 women of reproductive age between 18 and 38 years old - BMI was different in the case/control group	
N		PCOS; 98 Controls 98	
Setting		Obstetrics and Gynecology Clinics, King Abdulaziz University Hospital, Jeddah, Saudi Arabia and Center of Innovation in Personalized Medicine (CIPM), KAU, Jeddah, Saudi Arabia	
Index test		Serum AMH levels were determined by an enzyme-linked immunosorbent assay using an Ultra-Sensitive Anti-Müllerian hormone/Müllerian inhibiting substance Kit (AnshLabs, Webster, TX, USA) according to the manufacturer's instructions.	
Reference standard		Rotterdam criteria	
Outcomes		Accuracy Sensitivity and specificity, AUC	
Inclusion criteria		Yes	
Exclusion criteria		Yes	Medication use
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Yes	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	Partial	The control group was selected on having a regular cycle, but PCOM/HA was nog determined on forehand
	Was a consecutive or random sample of patients enrolled? (Q-2)	Not reported	Data from an existing case control study population was used.
	Was a case-control design avoided? (Q-2)	No	It was a predefined case control group
	Did the study avoid Inappropriate exclusions? (Q-2)	No	
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Yes	
	Did all patients receive the same reference standard? (Q-2)	Yes	
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	No	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	No	

	If a threshold was used, was it prespecified?	Partial	They first determined the AMH threshold in the studied population and then, after the selection of the AMH threshold value at 3.19 ng/mL, the PCOS group was re-evaluated twice.
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRITION BIAS	Were withdrawals from the study explained?	Yes	Poor quality samples were excluded from the statistical analyses, resulting in 79 cases and 69 controls.
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	No	
OTHER ISSUES	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Not reported	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
	Were there any conflicts of interest in the writing or funding of this study?	No	
	If statistical analysis was undertaken, was this appropriate?	Yes	
Comments			
What is the overall risk of bias?		Moderate	Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.

Study ID	Aydoğmuş 2018
Study citation	Aydoğmuş H, Kelekçi S, Elmalı F, Aydoğmuş S. Can we use serum Anti-Mullerian hormone to differentiate the diagnosis between polycystic ovary syndrome patients and healthy women with polycystic ovarian morphology and regular menstrual cycles. Saudi Med J. 2018 Oct;39(10):1011-1016. doi: 10.15537/smj.2018.10.23413. PMID: 30284584; PMCID: PMC6201027.
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/participants	- Cases were 15 and 45 years old and diagnosed as PCOS according to Rotterdam criteria - controls were otherwise healthy, non-hirsute women in the same age group who had normal menstrual cycles and PCOM on ultrasonography.
N	PCOS 70 Control 70
Setting	Department of Obstetrics & Gynecology, İzmir Katip Çelebi University Atatürk Training and Research Hospital, Izmir, Turkey.
Index test	Serum AMH levels were measured by ELISA using an appropriate commercial kit (Beckman Coulter, Chaska, MN, USA), mean inter- and

		intra-assay Coefficient of Variability (CVS) of 4.5% and 3.6%, respectively.	
Reference standard		Rotterdam criteria	
Outcomes		Receiver operating characteristic (ROC) analyses was used to determine cutoff, sensitivity, specificity, positive and negative predictive values.	
Inclusion criteria		Yes	
Exclusion criteria		Yes	diabetes, thyroid dysfunction, ovarian surgery, endometriosis, using drugs altering endocrine function. Subjects with serum AMH <1 ng/mL and serum FSH >12 mU / mL were excluded from the study.
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Yes	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	Studies which recruit a group of healthy controls and a group known to have the target disorder will be coded as "no" on this item in nearly all circumstances. Studies enrolling patients with known disease and a control group without the condition may exaggerate diagnostic accuracy. All controls had PCOM
	Was a consecutive or random sample of patients enrolled? (Q-2)	Not reported	
	Was a case-control design avoided? (Q-2)	Not reported	
	Did the study avoid inappropriate exclusions? (Q-2)	Yes	
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Yes	
	Did all patients receive the same reference standard? (Q-2)	Yes	
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Partial	Cut off of FG is not specified
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	Not reported	
	If a threshold was used, was it prespecified?	No	
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRITION	Were withdrawals from the study explained?	Not reported	

REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Not reported	
	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Not reported	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	Cochrane suggests that where tests report an objective measurement (such as a biochemical assay) which is unaltered by external information, an unbiased estimate of test accuracy may be obtained by interpreting it in isolation from other clinical information.
	Were there any conflicts of interest in the writing or funding of this study?	No	
OTHER ISSUES	If statistical analysis was undertaken, was this appropriate?	Partial	Power of the study was calculated using G-Power software (version 3.1). In order to determine the difference between the AMH values between 2 groups by using the mean effect size d = 0.05 suggested by Cohen (1988), with type 1 error = 0.05, and statistical power = 0.80, the sample size was determined at 64 patients. Age was significantly different in case and controls, this could influence AMH levels
Comments			
What is the overall risk of bias?		Moderate	Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.

Study ID	Bakeer 2018
Study citation	Engy Bakeer, Rasha Radwan, Ahmed El Mandoury, Abdullah Abd El Rahman, Mohamed Gad, Sahar Abd El Maksoud. Anti-Müllerian Hormone as a Diagnostic Marker in Egyptian Infertile Polycystic Ovary Syndrome Females: Correlations with Vitamin D, Total Testosterone, Dyslipidemia and Anthropometric Parameters. J Med Biochem. 2018 Dec 1;37(4):448-455. doi: 10.1515/jomb-2017-0068. eCollection 2018 Dec.
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/participants	- PCOS females aged from 17 to 39 with primary or secondary infertility. - The control group comprised 17 apparently healthy females aged from 19 to 35. All control females had regular cycles ranging from 25 to 35 days and had no ovarian gynecological disorders or endocrine abnormalities. Presence/absence of other PCOS characteristic were not reported.
N	PCOS : 53 Controls 17
Setting	Patients and control subjects were recruited from the outpatient clinics of different hospitals all over the governorates of Egypt.
Index test	Serum AMH was measured using AMH Gen II ELISA (Beckman Coulter, Inc.,USA)
Reference standard	Rotterdam criteria
Outcomes	Accuracy

		Sensitivity, specificity, AUC	
Inclusion criteria		Yes	
Exclusion criteria		Yes	
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Yes	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	Partial	Not described how controls were recruited. All controls had a regular menstrual cycle, presence/absence of other PCOS characteristic were not reported.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Not reported	It is best if the patients are randomly selected or consecutive admissions so that selection bias is minimized.
	Was a case-control design avoided? (Q-2)	Partial	All controls had a regular menstrual cycle, presence/absence of other PCOS characteristic were not reported.
	Did the study avoid Inappropriate exclusions? (Q-2)	Yes	
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Partial	All participants were assessed with the index tests but not clear whether all participants were assessed with the reference test.
	Did all patients receive the same reference standard? (Q-2)	Yes	
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	No	
	If a threshold was used, was it prespecified?	No	
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRITION BIAS	Were withdrawals from the study explained?	Not reported	
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Not reported	
OTHER ISSUES	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the	Not reported	

	clinical setting?		
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
	Were there any conflicts of interest in the writing or funding of this study?	No	
	If statistical analysis was undertaken, was this appropriate?	Partial	Power calculation not reported. Youden's index was used. No differences in age between the groups
Comments			
What is the overall risk of bias?		High	

Study ID		Bansal 2020	
Study citation		Bansal P, Sardana K, Arora P, Khurana A, Garga UC, Sharma L. A prospective study of anti-mullerian hormone and other ovarian and adrenal hormones in adult female acne. Dermatol Ther. 2020 Nov;33(6):e13974. doi: 10.1111/dth.13974. Epub 2020 Jul 27. PMID: 33185003.	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/participants		This prospective study included females aged≥25 years who presented with acne to the dermatology outpatient department (OPD)	
N		PCOS 31 Controls 89	
Setting		Tertiary care hospital in Delhi from November 2017 to March 2019	
Index test		AMH was quantified on random access fully automated immunoassay system (DXI-600, Beckman Coulter, USA).The analytical range of the AMH assay was 0.02 to 24 ng/mL (0.14-171 pmol/L)	
Reference standard		Rotterdam criteria	
Outcomes		Accuracy Sensitivity and specificity, AUC	
Inclusion criteria			
Exclusion criteria			Pregnant patients and those on hormonal therapy in the past 3 months were excluded.
Does the study have a clearly focused question? (yes/no/partial)			
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)			
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	Partial	The case and control group were recruited from a group of women with acne
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	It is best if the patients are randomly selected or consecutive admissions so that selection bias is minimized.
	Was a case-control design avoided? (Q-2)	Yes	
	Did the study avoid Inappropriate exclusions? (Q-2)	Yes	
CLASSIFICATION/VERIFICATI	Were all participants assessed with both index test and reference standard?	Yes	

	(Also in Q-2)		
	Did all patients receive the same reference standard? (Q-2)	Yes	
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	No	
	If a threshold was used, was it prespecified?	No	
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRITION	Were withdrawals from the study explained?	Not reported	
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Not reported	
	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Not reported	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	BMI is not reported
OTHER ISSUES	Were there any conflicts of interest in the writing or funding of this study?	No	
	If statistical analysis was undertaken, was this appropriate?	Yes	No adjustment for difference in age, however the majority was < 30 years of age
Comments			
What is the overall risk of bias?		Low	

Study ID		Bell 2021	
Study citation		Bell RJ, Islam RM, Skiba MA, Herbert D, Martinez Garcia A, Davis SR. Substituting serum anti-Müllerian hormone for polycystic ovary morphology increases the number of women diagnosed with polycystic ovary syndrome: a community-based cross-sectional study. Hum Reprod. 2021 Dec 27;37(1):109-118. doi: 10.1093/humrep/deab232. PMID: 34741176.	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/participants		- Non healthcare seeking women, recruited via online database, who agreed to be re-contacted for future studies were asked to participate in a study 'to understand what normal ovaries looked like' - Participation involved medical history review, having a pelvic ultrasound examination and providing a blood sample	
N		163	
Setting		Non health care seeking women, aged 18–39years, living in the Australian states of Queensland, Victoria and New South Wales	
Index test		Aliquots of serum samples collected in gel-based serum separator tubes were kept at 4ºC until analysis within 24hr by the Beckman Access 2, 2-site immunometric assay (BA2 assay, Beckman Coulter Australia, Queensland, Australia). Intra-assay coefficients of variation(CVs) ranged from 1.5% to 1.7% and inter-assay CVs ranged from3.5% to 3.6% over the range of 7.4–108.9 pmol/l. The assay limit of detection (LOD) was 0.11pmol/l (15.4 pg/ml). For AMH measurement by the MenoCheckVR pico AMH enzyme-linked immunosorbent assay (ELISA) assay, serum aliquots stored at -80C were thawed fortesting (Ansh assay; Ansh Labs, Webster, TX, USA). The intra-assayand inter-assay CVs range from 2.07% to 3.69% and 3.15% to 5.84%,respectively, with an LOD of 0.0086 pmol/l (1.2 pg/ml). Findings for both AMH assays are reported as we have previously demonstrated that although serum AMH values measured by the two assays are highly correlated, the assays were performed in a discordant manner at high and low concentrations	
Reference standard		In line with the AE-PCOS Society's 2014 recommendations, PCOM was defined as an FNPO of ≥25 follicles in at least one ovary	
Outcomes		AMH as predictor for PCOM, Sensitivity specificity AUC	
Inclusion criteria		Yes	Both ovaries visible with ultrasound, euthyroid, normoprolactinemic.
Exclusion criteria		Yes	Using hormonal contraception, currently or recently pregnant or breast feeding and post-menopausal.
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Yes	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	Yes	Obviously some bias occurred because not all women agreed to be re contacted, however this is likely to be minimal.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	
	Was a case-control design avoided? (Q-2)	Yes	
	Did the study avoid Inappropriate exclusions? (Q-2)	Yes	
CLASSIFIC	Were all participants assessed with both	Yes	

	index test and reference standard? (Also in Q-2)		
	Did all patients receive the same reference standard? (Q-2)	Yes	
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	Not reported	
	If a threshold was used, was it prespecified?	No	
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRITION	Were withdrawals from the study explained?	Yes	
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Not reported	
	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Yes	Ultrasound were performed by gynecologists
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
OTHER ISSUES	Were there any conflicts of interest in the writing or funding of this	No	

	study?		
	If statistical analysis was undertaken, was this appropriate?	Partial	Power was determined by proportion of women who agreed to be recontacted, no power calculation was reported
Comments			
What is the overall risk of bias?		Low	Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.

Study ID		Bozdag 2019	
Study citation		Gurkan Bozdag, Sezcan Mumusoglu, Zuhal Yapici Coskun, Hakan Yarali, Bulent Okan Yildiz. Anti-Müllerian hormone as a diagnostic tool for PCOS under different diagnostic criteria in an unselected population Reprod Biomed Online. 2019 Sep;39(3):522-529. doi: 10.1016/j.rbmo.2019.04.002. Epub 2019 Apr 10.	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/participants		- Unselected group of women: female staff within a single structure among 21 institutes in Ankara, Turkey - PCOS diagnosis according to Rotterdam criteria/NIH/AE. Controls were healthy, non-hirsute, eumenorrheic women without PCOM; - Pregnant or post-menopausal women and women with a history of hysterectomy or bilateral oophorectomy were excluded.	
N		total group 392 PCOS (PCOM≥12) NIH : 24 AE: 60 Rotterdam: 78 Patiënts (PCOM≥20) AE: 35 Rotterdam: 40 Controls: 190 (PCOM≥12); 233 (PCOM≥20)	
Setting		Ankara, Turkey	
Index test		To detect AMH levels, frozen serum aliquots from 392 women were used in which a prevalence study was conducted after following the manufacturer's protocol for a single freeze–thaw procedure (Elecsys AMH; Roche Diagnostic International, IN, USA). The minimum detectable concentration was 0.01 ng/ml, the upper level of quantification was 23.0 ng/ml and the inter- and intra-assay coefficients of variation were 2.1% and 2.9%, respectively. The conversion factor for pmol/l was 7.14	
Reference standard		PCOS diagnosis according to Rotterdam criteria/NIH/AE	
Outcomes		Accuracy, adjusted for BMI and age Sensitivity, specificity, AUC	
Inclusion criteria		Yes	
Exclusion criteria		Yes	Pregnant or post-menopausal women and women with a history of hysterectomy or bilateral oophorectomy were excluded;
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Yes	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	Yes	
	Was a consecutive	Yes	

	or random sample of patients enrolled? (Q-2)		
	Was a case-control design avoided? (Q-2)	Yes	
	Did the study avoid Inappropriate exclusions? (Q-2)	Yes	
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Yes	
	Did all patients receive the same reference standard? (Q-2)	Yes	
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	The authors compared different PCOS criteria.
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	Not reported	
	If a threshold was used, was it prespecified?	No	
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRIT _ ON	Were withdrawals from the study explained?	Not reported	
REPO RT BIAS	Were uninterruptable/ intermediate test results reported?	Not reported	
OTHER ISSUES	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Not reported	
	Were the same	Yes	

	clinical data available when test results were interpreted as would be available when the test is used in practice?		
	Were there any conflicts of interest in the writing or funding of this study?	No	
	If statistical analysis was undertaken, was this appropriate?	Yes	Power calculation was showed. The initial sample size estimation was based on documentation of the prevalence of the syndrome. When the prevalence of PCOS according to NIH was set to 8% with a precision of 2.2% and a 95% CI, the sample size required for a prevalence survey was found to be 400 subjects, and hence it was possible to recruit 392 women to the initial study (Yildiz et al., 2012). It should also be noted that, for a given threshold of AMH (>3.24 ng/ml) to detect PCOM (n = 96) among the whole population (n = 392), the calculated power is 80.4%
Comments			
What is the overall risk of bias?		Low	Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.

Study ID	Calzada 2019	
Study citation	Calzada M, López N, Noguera JA, Mendiola J, Hernández AI, Corbalán S, Sanchez M, Torres AM.AMH in combination with SHBG for the diagnosis of polycystic ovary syndrome. J Obstet Gynaecol. 2019 Nov;39(8):1130-1136.	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/participants	- Participants visited the Gynaecology Service outpatient clinics at the Clinic University Virgen - 77 women diagnosed with PCOS - Control group were 106 subjects, healthy volunteers with normal menstrual cycles and who had no clinical or biochemical features of HA Mean age was similar in both groups	
N	PCOS 77 Controls 106	
Setting	the Gynaecology Service outpatient clinics at the Clinic University Virgen de la Arrixaca Hospital,Murcia (Spain)	
Index test	AMH was measured with a chemiluminescent enzymatically two-site immunoas-says on a multiparameter system (CobasE170VR, Roche, Mannheim, Germany).	
Reference standard	Rotterdam	
Outcomes	Accuracy AUC, sensitivity, specificity. ROC	
Inclusion criteria	Yes	
Exclusion criteria	Yes	<18 years, above 40 years, previous ovarian surgery, presence of endocrinology pathology (hyperprolactinemia, Cushing's, congenital adrenal hyperplasia of thyroid disorders), no hormone use 3 months before the study
Does the study have a clearly focused question? (yes/no/partial)	Yes	
Does the study have specified	Yes	

inclusion/exclusion criteria? (yes/no/partial)			
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	Partial	PCOS was excluded in the control group
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	
	Was a case-control design avoided? (Q-2)	No	It was set up as a case control study
	Did the study avoid inappropriate exclusions? (Q-2)	Yes	
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Partial	All participants were assessed with the index tests but not clear whether all participants were assessed with the reference test. Diagnostic criteria for PCOS (Rotterdam) also included an ultrasound, no ultrasound is described in controls
	Did all patients receive the same reference standard? (Q-2)	Yes	
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	Not reported	
	If a threshold was used, was it prespecified?	No	
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	.
ATTRITION	Were withdrawals from the study explained?	Not reported	
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Not reported	
OTHER ISSUES	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Not reported	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	

	Were there any conflicts of interest in the writing or funding of this study?	No	
	If statistical analysis was undertaken, was this appropriate?	Partial	Power analysis not reported. Mean age was similar in both groups
Comments			
What is the overall risk of bias?		Moderate	Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.

Study ID		Casadei 2018	
Study citation		Casadei L, Fanisio F, Sorge RP, Collamarini M, Piccolo E, Piccione E. The diagnosis of PCOS in young infertile women according to different diagnostic criteria: the role of serum anti-Müllerian hormone. Arch Gynecol Obstet. 2018 Jul;298(1):207-215. doi: 10.1007/s00404-018-4803-8. Epub 2018 May 25. PMID: 29802450.	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/participants		140 patients were selected out of a database of 1349 infertile women referred to the Infertility Center of Tor Vergata University Hospital, Section of Gynecology and Obstetrics between October 2007 and December 2014. Age was not significant. PCOS was excluded in controls	
N		total group 140 NIH: P 38 suspected P 36; C 56 Rotterdam: P: 56, C: 84 AEPCOS: P 41, C: 99	
Setting		Infertility Center of Tor Vergata University Hospital, Section of Gynecology and Obstetrics	
Index test		AMH blood levels were measured using the enzyme immunoassay AMH-EIA (reference A11893, Immunotech, Beckman Coulter company from Marseille, France) while from 2013 onwards AMH Gen II ELISA kit was applied (reference A79765 Beckman Coulter).	
Reference standard		All PCOS criteria, Rotterdam NIH	
Outcomes		Accuracy. Sensitivity, specificity, AUC	
Inclusion criteria		Yes	The inclusion criteria were the presence of both ovaries and their adequate visualization on transvaginal ultrasonography.
Exclusion criteria		Yes	congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome, galactorrhea, hyperprolactinemia, thyroid dysfunctions and other endocrinological disorders, autoimmune diseases, hypothalamic amenorrhea, premature ovarian failure, age<18 or >35 years, serum FSH levels >12 mIU/ml, use of hormonal contraceptive, pregnancy, puerperium, ovarian cysts or ovarian tumors, endometriosis, previous ovarian and uterine surgery or chemotherapy
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Yes	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	PCOS was excluded in the control group

	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	It is best if the patients are randomly selected or consecutive admissions so that selection bias is minimized.
	Was a case-control design avoided? (Q-2)	Yes	Patient and controls were form a similar health seeking population
	Did the study avoid Inappropriate exclusions? (Q-2)	Yes	
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Yes	
	Did all patients receive the same reference standard? (Q-2)	Yes	Those who received the reference standard all received the same standard, i.e. Rotterdam and NIH and AEPCOS.
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Not reported	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	Not reported	
	If a threshold was used, was it prespecified?	No	
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRITION	Were withdrawals from the study explained?	Not reported	
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Not reported	
OTHER ISSUES	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Not reported	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
	Were there any conflicts of interest in the writing or funding of this study?	No	
	If statistical analysis was undertaken, was this appropriate?	Partial	No power calculation. Age was similar between the groups
Comments			

What is the overall risk of bias?	Moderate	Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.

Study ID		Dietz de Loos	
Study citation		Dietz de Loos A, Hund M, Buck K, Meun C, Sillman J, Laven JSE. Antimüllerian hormone to determine polycystic ovarian morphology. Fertil Steril. 2021 Oct;116(4):1149-1157. doi: 10.1016/j.fertnstert.2021.05.094.	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/participants		Cases were derived from a local database, PCOS Controls were used from a previous study by Roche: aged25–45 years with a regular menstrual cycle (average 25–35days) no major uterine or ovarian abnormalities detected using TVUS, no previous in vitro fertilization cycles, and an AFC of 20 per ovary (per current international guidelines; VUS frequency bandwidth includes 8 MHz or higher). Cases were from a tertiary hospital in Rotterdam, The Netherlands. Controls were from another population from Germany. However, part from the control group is also recruited in an Infertility clinic. The mean age of women with PCOS was lower than the controls. However, they investigated the effect of age on AMH cutoff and made two age groups.	
N		Development cohort cases n= 484 ; controls = 575 validation cohort: cases n= 455 and controls n=500	
Setting		Cases were from a tertiary hospital in Rotterdam, The Netherlands. Controls were from another population from Germany.	
Index test		The serum AMH levels were measured on the cobas e 411 analyzer (Roche Diagnostics InternationalLtd, Rotkreuz, Switzerland) using the Elecsys AMH Plus for the cases and Elecsys AMH assay for the controls (measuring range, 0.01–23 ng/mL)	
Reference standard		Rotterdam criteria	
Outcomes		Accuracy, AUC, sensitivity, specificity	
Inclusion criteria		Yes	
Exclusion criteria		Yes	
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Yes	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	PCOS was excluded in controls
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	
	Was a case-control design avoided? (Q-2)	Partial	It was set up a case control study, but a validation cohort was included
	Did the study avoid Inappropriate exclusions? (Q-2)	Yes	
CLASSIFICATION/VERIFICATION/INCORPORATION/REVI	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Yes	Diagnostic criteria for PCOS (reference standard) were the exclusion criteria for control participants.
	Did all patients receive the same reference standard?	Yes	

	(Q-2)		
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	Not reported	
	If a threshold was used, was it prespecified?	Yes	The identified threshold was validated in an independent cohort
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRIT_ON	Were withdrawals from the study explained?	Not reported	
REPO RT BIAS	Were uninterruptable/ intermediate test results reported?	Not reported	
	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Yes	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
	Were there any conflicts of interest in the writing or funding of this study?	Yes	Manuscript is written together with employees of a pharmaceutical company. The corresponding author had full access to all the data in the study and had the final responsibility of the decision to submit for publication.
OTHER ISSUES	If statistical analysis was undertaken, was this appropriate?	Partial	Power analysis not reported. A validation cohort was included. The serum samples collected from patients with PCOS were of various ages at the time of AMH measurement (range 1–18years). Therefore, a statistical model was used to assess the effect of sample age on AMH concentration. The model showed no significant difference in the AMH concentrations over time
Comments			
What is the overall risk of bias?		Low	Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.

Study ID		Evliyaoglu 2020	
Study citation		Evliyaoglu O, Imöhl M, Weiskirchen R, van Helden J.Age-specific reference values improve the diagnostic performance of AMH in polycystic ovary syndrome.Clin Chem Lab Med. 2020 Jul 28;58(8):1291-1301. doi: 10.1515/cclm-2019-1059.	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/participants		Patients ranging from 14 to 50 years with no history of gynecological surgery, normal thyroid function and normoprolactinemia. PCOS diagnose was based on information on the order form and confirmed with some blood test, no information about ultrasound data.	
N		PCOS: 1132 Controls 3055	
Setting		single reference laboratory in North Rhine-Westfalia, Germany	
Index test		Elecsys® AMH assay, Roche. In the case of AMH, a comparison was made with the Gen II ELISA and the automated AMH Access Assay of Beckman Coulter (Krefeld, Germany) according to the method of Passing and Bablok	
Reference standard		Rotterdam	
Outcomes		Accuracy, sensitivity, specificity For different age groups	
Inclusion criteria		Yes	Inclusion criteria were: (i) patients having no history of gynecological surgery, (ii) normal thyroid function and (iii) normoprolactinemia.
Exclusion criteria		No	
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Partial	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	Partial	Studies which recruit a group of healthy controls and a group known to have the target disorder will be coded as "no" on this item in nearly all circumstances. Studies enrolling patients with known disease and a control group without the condition may exaggerate diagnostic accuracy. Controls would not be routinely assessed for ovarian volume using ultrasound. The PCOS group is representative of those who will be assessed with these criteria in practice, however, the method of ultrasound may not be routine practice in the patient group relevant to this question.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	
	Was a case-control design avoided? (Q-2)	Yes	Random selected group of participants
	Did the study avoid Inappropriate exclusions? (Q-2)	Yes	
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Not reported	Unclear whether all participants underwent an ultrasound to determine PCOS
	Did all patients receive the same reference standard?	Not reported	Just stated, according to the Rotterdam criteria, not further specified

	(Q-2)		
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Not reported	
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	Yes	
	If a threshold was used, was it prespecified?	No	
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRITION	Were withdrawals from the study explained?	Not reported	
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Not reported	
OTHER ISSUES	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Not reported	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
	Were there any conflicts of interest in the writing or funding of this study?	No	
	If statistical analysis was undertaken, was this appropriate?	Partial	Power analysis not reported. PCOS group was younger than the reference group. For the reference values they stratified in age groups, however for the ROC analysis they did not.
Comments			
What is the overall risk of bias?		Moderate	Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.

Study ID		Farooq 2022	
Study citation			
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/participants		Patients who visited the Department of Obstetrics and Gynecology at Indus Medical College Tando Muhammad Khan.	
N		PCOS 50 Controls 50	
Setting		Chinese cohort of patients, adolescent outpatient clinic	
Index test		ELISA kits from immunological concept bio-detect were used to measure Anti-Mullerian hormone levels in 96-well plates with six reference standards included. Using an Anti-Mullerian hormone-HRP conjugate on an Anti-Mullerian hormone coated plate, the researchers performed the analysis using a competitive enzyme immunoassay approach. The kit has a 0.025 ng/ml detection limit.	
Reference standard		Rotterdam	
Outcomes		Accuracy, sensitivity and specificity	
Inclusion criteria		Yes	
Exclusion criteria		Yes	
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Yes	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	PCOS was excluded in the controls
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	consecutive admissions
	Was a case-control design avoided? (Q-2)	Partial	
	Did the study avoid Inappropriate exclusions? (Q-2)	Yes	
CLASSIFICATION/VERIFICATION/ INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Yes	All participants were assessed with the index tests and diagnostic criteria for PCOS (reference standard) were the exclusion criteria for control participants.
	Did all patients receive the same reference standard? (Q-2)	Yes	
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	Not reported	
	If a threshold was	No	

	used, was it prespecified?		
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRITION	Were withdrawals from the study explained?	Not reported	
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Not reported	
OTHER ISSUES	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Yes	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
	Were there any conflicts of interest in the writing or funding of this study?	No	
	If statistical analysis was undertaken, was this appropriate?	Partial	Power calculation not reported
Comments			
What is the overall risk of bias?		Low	

Study ID	Fu 2021
Study citation	Fu H, Lin Y, Deng X, Wu L.Correlation between anti-Mullerian hormone levels and antral follicle counts in polycystic ovary and metabolic syndromes. Syst Biol Reprod Med. 2021 Apr;67(2):112-120. doi: 10.1080/19396368.2020.1860155. Epub 2021 Jan 7.
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/participants	Health care seeking population PCOS was defined according to the Rotterdam criteria Controls regular menstrual cycle, normal findings on ultrasound. No difference in age between the groups
N	PCOS 30 Controls 30
Setting	Beijing Maternal and Child Health Care Hospital
Index test	AMH serum concentrations were estimated using an ELISA kit (MBS 702,605, MyBioSource Company, USA).
Reference standard	Rotterdam criteria
Outcomes	Accuracy , AUC, sensitivity, specificity
Inclusion criteria	Yes

Exclusion criteria		Yes	
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Yes	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	Studies enrolling patients with known disease and a control group without the condition may exaggerate diagnostic accuracy.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	
	Was a case-control design avoided? (Q-2)	No	The set-up of the case control design
	Did the study avoid Inappropriate exclusions? (Q-2)	Yes	
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Yes	
	Did all patients receive the same reference standard? (Q-2)	Yes	Those who received the reference standard all received the same standard
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	Not reported	
	If a threshold was used, was it prespecified?	No	
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	.
ATTRITION	Were withdrawals from the study explained?	Not reported	
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Not reported	
OTHER ISSUES	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Yes	
	Were the same	Yes	

	clinical data available when test results were interpreted as would be available when the test is used in practice?		
	Were there any conflicts of interest in the writing or funding of this study?	No	
	If statistical analysis was undertaken, was this appropriate?	Partial	Power calculation not reported
Comments			
What is the overall risk of bias?		Moderate	Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.

Study ID		Gabr 2019	
Study citation		Hanan Mohamed Gabr and Elham Sayed Mare. The Relation between Anti-Müllerian Hormone with Antral Follicle Count and Ovarian Volume in Polycystic Ovary Syndrome. Arab J. Nucl. Sci. Appl., Vol.52, 2, 84-93(2019)	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/participants		Healthcare seeking women were included, PCOS was defined according to Rotterdam criteria (Fullblown PCOS) PCOS was excluded in controls. No difference in age between the groups. BMI was significantly different	
N		PCOS 30 Controls 15	
Setting		Ain Shams Maternity Hospital	
Index test		AMH was analyzed using an ELISA kit (MBS 702605, My Biosource Company, USA) in a single batch from frozen serum	
Reference standard		Rotterdam criteria	
Outcomes		AUC, sensitivity, specificity	
Inclusion criteria		Yes	Complete history taking to clarify irregularity of menstrual cycles. Clinical examination was conducted for all participants to detect the relevant data as the degree of hirsutism, weight and height. Ultrasonography
Exclusion criteria		Yes	
Does the study have a clearly focused question? (yes/no/partial)		Partial	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Yes	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	PCOS was excluded in control group. Studies enrolling patients with known disease and a control group without the condition may exaggerate diagnostic accuracy. Women with full blown phenotype was included
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	
	Was a case-control design avoided? (Q-2)	No	Set up was a case control design
	Did the study avoid	Yes	

	Inappropriate exclusions? (Q-2)		
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Yes	
	Did all patients receive the same reference standard? (Q-2)	Yes	
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	Not reported	
	If a threshold was used, was it prespecified?	No	
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRITION	Were withdrawals from the study explained?	Not reported	
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Not reported	
OTHER ISSUES	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Yes	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
	Were there any conflicts of interest in the writing or funding of this study?	No	
	If statistical analysis was undertaken, was this appropriate?	Partial	Power calculation was not reported. No Youden index
Comments			
What is the overall risk of bias?		Moderate	Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.

Study ID		Shi 2019	
Study citation		Xinyan Shi, MS, Duo Peng, BS, Yanfei Liu, MS, Xiaofen Miao, BS, Hui Ye, MS, Jun Zhang, PhD, Advantages of Serum Anti-Müllerian Hormone as a Marker for Polycystic Ovarian Syndrome, Laboratory Medicine, Volume 50, Issue 3, August 2019, Pages 236–242, ttps://doi.org/10.1093/labmed/lmy068	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/participants		PCOS: Hangzhou Women's Hospital Outpatient Clinic, between January 2016 and July 2016. Age 19-42 years Control group: 52 reproductive-age individuals (aged 19–39 years) with normal menstrual cycles (26–35 days) who were age-matched to the PCOS group. They underwent transvaginal ultrasound to exclude the diagnosis of PCOM, and none of them had hirsutism, acne, high androgen levels, or clinical manifestations of PCOS	
N		PCOS 56 Controls 52	
Setting		Hangzhou Women's Hospital Outpatient Clinic	
Index test		anti-Müllerian hormone (AMH) concentration was determined using an automated electrochemiluminescence immunoassay (Elecsys Corporation) and the Roche Cobas e411 (F. Hoffman-La Roche, Ltd). S	
Reference standard		Rotterdam	
Outcomes		Accuracy ROC Sensitivity and specificity, AUC	
Inclusion criteria		Partial	Cutoff for PCOM not described
Exclusion criteria		Yes	Exclusion criteria: pituitary tumor, reproductive endocrine diseases, hormonal drugs within past 3 months
Does the study have a clearly focused question? (yes/no/partial)		No, there is no question or aim mentioned in the introduction	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Partial	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	Studies which recruit a group of healthy controls and a group known to have the target disorder will be coded as "no" on this item in nearly all circumstances. PCOS was excluded in controls
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	
	Was a case-control design avoided? (Q-2)	No	It was set up as case control study
	Did the study avoid Inappropriate exclusions? (Q-2)	Yes	
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference \ standard? (Also in Q-2)	Yes	
	Did all patients receive the same reference standard? (Q-2)	Yes	
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes	
	Were the reference standard results interpreted without knowledge of the	Not reported	

	results of the index test? (Q-2)		
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	Not reported	
	If a threshold was used, was it prespecified?	No	
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRITION	Were withdrawals from the study explained?	Not reported	
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Not reported	
OTHER ISSUES	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Not reported	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
	Were there any conflicts of interest in the writing or funding of this study?	No	
	If statistical analysis was undertaken, was this appropriate?	Partial	Youden index was used. Age matched. No power calculation
Comments			
What is the overall risk of bias?		Moderate	Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.

Study ID	Cengiz 2014
Study citation	Cengiz H, Ekin M, Dagdeviren H, Yildiz Ş, Kaya C, Kanawati A. Comparison of serum anti-Müllerian hormone levels in normal weight and overweight-obese adolescent patients with polycystic ovary syndrome. Eur J Obstet Gynecol Reprod Biol. 2014 Sep;180:46-50. doi: 10.1016/j.ejogrb.2014.06.018. Epub 2014 Jun 28. PMID: 25036408.
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/participants	Consecutive patients with PCOS and healthy volunteers, age matched.
N	PCOS: 58 (29 normal weight, 29 overweight/obese) Controls: 28
Setting	Between April and September 2013.

Index test		AMH measurement, cycle days 1-7, by AMH ELISA Eastbiopharm Hangzou.	
Reference standard		PCOS, Rotterdam criteria, diagnosed 2 years after menarche. PCOM >= 12 follicles. mFGs or biochemical hyperandrogenism not specified.	
Outcomes		- Differences in AMH between PCOS adolescents and controls (age matched, PCOS group stratified in normal weight and overweight/obese). - Correlations between AMH and clinical, hormonal, and metabolic parameters. - ROC analysis of AMH for diagnosing PCOS.	
Inclusion criteria			Control group: regular cycle.
Exclusion criteria			PCOS group: hyperprolactinemia, thyroid dysfunction, Cushing's syndrome, congenital adrenal hyperplasia, adrenal tumor, ovarian tumor, current or previous pregnancy within 1 year of enrolment, auto-immune disease, malignancy, central nervous system disease, current or previous use of oral contraceptives within 6 months of enrolment, use of medication affecting HPO axis. Patients without ultrasound appearance of polycystic ovaries were also excluded. Controls: hirsutism, abnormal serum prolactin or androgens, polycystic ovaries on ultrasound, hormonal treatment during 3 months preceding the study.
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Yes	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	PCOS was excluded in control group. All PCOS patients had polycystic ovaries on ultrasound (see exclusion criteria).
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	
	Was a case-control design avoided? (Q-2)	No	
	Did the study avoid Inappropriate exclusions? (Q-2)	No	They excluded PCOS patients without polycystic ovaries.
	Are the cohorts comparable on the basis of design or analysis?	Yes	They divided the PCOS group in a normal weight and an overweight/obese group. However, BMI of both PCOS groups were similar compared to the control group.
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Yes	
	Did all patients receive the same reference standard? (Q-2)	Yes	
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Partial	Normally when using the Rotterdam criteria there are also patients with PCOS without polycystic ovaries on ultrasound.
	Were the reference standard results	Yes	

	interpreted without knowledge of the results of the index test? (Q-2)		
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	No	
	If a threshold was used, was it prespecified?	No	
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRITION	Were withdrawals from the study explained?	No	Not reported
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	No	
	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Not reported	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
	Were there any conflicts of interest in the writing or funding of this study?	No	
OTHER ISSUES	If statistical analysis was undertaken, was this appropriate?	Partial	No power calculation reported. Failed to reveal cut off points for AMH.
Comments			
What is the overall risk of bias?		Moderate	

Study ID		Khashchenko 2020	
Study citation		Khashchenko E, Uvarova E, Vysokikh M, Ivanets T, Krechetova L, Tarasova N, Sukhanova I, Mamedova F, Borovikov P, Balashov I, Sukhikh G. The Relevant Hormonal Levels and Diagnostic Features of Polycystic Ovary Syndrome in Adolescents. J Clin Med. 2020 Jun 11;9(6):1831. doi: 10.3390/jcm9061831. PMID: 32545404; PMCID: PMC7355484.	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/participants		Girls with PCOS and healthy girls (with regular menstrual cycles) aged 15 to 17 years.	
N		P: 130 C: 30	
Setting		It is not reported how cases and controls were recruited.	
Index test		AMH measurement, on cycle days 2-4 (spontaneous or gestagen-induced) measured by DYNEX DSX System Analyzers.	
Reference standard		Complete Rotterdam criteria (three criteria). No cutoff values reported. Ultrasound on menstrual cycle days 3-5 (spontaneous or gestagen-induced).	
Outcomes		- Differences in AMH levels between adolescents with PCOS compared to controls. - Multivariate analysis to determine cutoffs for hormonal levels, including AMH. - ROC analysis of AMH for diagnosing PCOS	
Inclusion criteria		Yes	The onset of menarche at least 2 years prior; the absence of other endocrine diseases; absence of drug administration over 3 months preceding the study, including oral combined contraceptives; informed consent of the patient and her legal representative for participation in the research study.
Exclusion criteria		Yes	An aggravation of chronic or acute somatic and/or infectious disease; mental illnesses; inherited syndromes and congenital malformations; hyperprolactinemia; congenital dysfunction of the adrenal cortex; thyroid disorders; Cushing syndrome and disease; tumors of the pelvic organs.
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Yes	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	Complete Rotterdam criteria was used. Normally also two out of three will be diagnosed with PCOS. Controls were healthy controls with regular menstrual cycle.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Not reported	
	Was a case-control design avoided? (Q-2)	No	
	Did the study avoid Inappropriate exclusions? (Q-2)	Partial	Exclusion of women with two out of three PCOS criteria.
	Are the cohorts comparable on the basis of design or analysis?	No	Not reported how cases and controls were recruited. PCOS group had a higher BMI.
CLASSIFICATION VERIFI	Were all participants assessed with both index test and reference standard?	Yes	

	(Also in Q-2)		
	Did all patients receive the same reference standard? (Q-2)	Yes	
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Partial	Rotterdam criteria, but cutoff values were not reported (e.g. mFGs, FAI, PCOM). They performed transabdominal ultrasound.
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	No	
	If a threshold was used, was it prespecified?	No	
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Not reported	
ATTRITION	Were withdrawals from the study explained?	No	Not reported
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	No	
	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Not reported	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Partial	Normally no ultrasound of the mammary and thyroid gland will be performed by default.
OTHER ISSUES	Were there any conflicts of interest in the writing or funding of this study?	No	

	If statistical analysis was undertaken, was this appropriate?	Partial	No power analysis. Multivariate analysis to determine the cutoff value for AMH. No 95% CI for the AUC is reported.
Comments			
What is the overall risk of bias?		High	

Study ID		Savas-Erdeve 2016	
Study citation		Savas-Erdeve S, Keskin M, Sagsak E, Cenesiz F, Cetinkaya S, Aycan Z. Do the Anti-Müllerian Hormone Levels of Adolescents with Polycystic Ovary Syndrome, Those Who Are at Risk for Developing Polycystic Ovary Syndrome, and Those Who Exhibit Isolated Oligomenorrhea Differ from Those of Adolescents with Normal Menstrual Cycles? Horm Res Paediatr. 2016;85(6):406-11. doi: 10.1159/000446111. Epub 2016 May 13. PMID: 27173790.	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/participants		Girls with PCOS: Met all three criteria. PCOS risk: two of the three criteria. OM group: only isolated OM. Controls: regular menstrual cycle.	
N		PCOS: 21 Risk PCOS: 20 OM: 21 Control: 30	
Setting		Pediatric Endocrinology Outpatient Unit.	
Index test		AMH, early-to-midfollicular phase in controls, in other groups random. Measured by Ansh labs.	
Reference standard		PCOS diagnosis, Rotterdam criteria. mFGs >= 8, PCOM (transabdominal ultrasound) >= 12 follicles. OM or amenorrhea persisting for 2 years after menarche.	
Outcomes		- Differences in AMH levels between four groups. - ROC analysis of AMH for diagnosis PCOS.	
Inclusion criteria		Yes	PCOS with all three Rotterdam criteria or two out of three. Controls had a regular menstrual cycle or isolated oligomenorrhea.
Exclusion criteria		Yes	- Medications that modulate or modify the menstrual cycle - Chronic systemic illness - 21-OH deficiency - Hormonal, adrenal or gonadal disorder
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Yes	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	Yes	Women with two and three out of the three criteria were included. They included a control group with women with regular cycles, but also a control group with isolated oligomenorrhea.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Not reported	
	Was a case-control design avoided? (Q-2)	No	
	Did the study avoid	Yes	

	Inappropriate exclusions? (Q-2)		
	Are the cohorts comparable on the basis of design or analysis?	Yes	All recruited from the Pediatric Endocrinology unit. Age and BMI were similar between the groups.
CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Yes	
	Did all patients receive the same reference standard? (Q-2)	Yes	
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Partial	Transabdominal pelvic ultrasound, instead of transvaginal ultrasound. mFGs >= 8.
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	No	
	If a threshold was used, was it prespecified?	No	
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRITION	Were withdrawals from the study explained?	No	
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	No	
OTHER ISSUES	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Not reported	
	Were the same clinical data available when test results were interpreted as would	Yes	

	be available when the test is used in practice?		
	Were there any conflicts of interest in the writing or funding of this study?	Not reported	
	If statistical analysis was undertaken, was this appropriate?	Partial	No power calculation. Not clear if they included the OM group as control group in the ROC analysis.
Comments			
What is the overall risk of bias?		Moderate	

Study ID		Villarroel 2015	
Study citation		Villarroel C, López P, Merino PM, Iñiguez G, Sir-Petermann T, Codner E. Hirsutism and oligomenorrhea are appropriate screening criteria for polycystic ovary syndrome in adolescents. Gynecol Endocrinol. 2015;31(8):625-9. doi: 10.3109/09513590.2015.1025380. Epub 2015 Jul 20. PMID: 26190534.	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/participants		Girls who were at least 1 year past menarche and =< 20 years of age.	
N		P: 26 C; 63	
Setting		Cases: pediatric endocrinology clinics. Controls were recruited from nearby schools.	
Index test		AMH measurement.	
Reference standard		Young patients with hirsutism and oligomenorrhea.	
Outcomes		- Differences in PCOM and AMH levels between hirsutism+oligo girls and controls.	
Inclusion criteria		Yes	1 year past menarche. Controls had regular menses.
Exclusion criteria		Yes	Controls: severe acne, obesity, premature pubarche, intrauterine growth retardation. All: Were pregnant during the previous 6 months, used sex steroids, had abnormal thyroid function or prolactin levels, or presented chronic conditions such as genetic syndromes, celiac disease, renal, liver, or cardiac disease, or undernourishment.
Does the study have a clearly focused question? (yes/no/partial)		Yes	
Does the study have specified inclusion/exclusion criteria? (yes/no/partial)		Yes	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS? (INCLUDING ITEMS FROM THE QUADAS-2 TOOL)			
PATIENT	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	Controls had regular menstrual cycles.
	Was a consecutive or random sample of patients enrolled? (Q-2)	Yes	
	Was a case-control design avoided? (Q-2)	No	
	Did the study avoid Inappropriate exclusions? (Q-2)	Yes	
	Are the cohorts comparable on the basis of design or analysis?	No	Cases were recruited from a hospital. Controls were recruited from nearby schools. BMI was significantly higher in case group.

CLASSIFICATION/VERIFICATION/INCORPORATION/REVIEW BIAS	Were all participants assessed with both index test and reference standard? (Also in Q-2)	Yes	
	Did all patients receive the same reference standard? (Q-2)	Yes	
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Partial	They included girls with hirsutism and oligomenorrhea in the case group. But they did not diagnose PCOS according to Rotterdam criteria using two out of three criteria. They performed a transabdominal ultrasound.
	Were the reference standard results interpreted without knowledge of the results of the index test? (Q-2)	Yes	
	Were the index test results interpreted without knowledge of the results of the reference standard test? (Q-2)	No	
	If a threshold was used, was it prespecified?	No	
DETECTION BIAS	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests? (Also in Q-2)	Yes	
ATTRITION	Were withdrawals from the study explained?	No	
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	No	Not reported
OTHER ISSUES	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes	
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Not reported	
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	
	Were there any conflicts of interest	No	Supported by the Fondo Nacional de Desarrollo Científico y Tecnológico (FONDECYT) Grant No. 1100123 (to E.C).

	in the writing or funding of this study?		We are grateful to Prof. Robert L. Rosenfield, M.D., University of Chicago Medical Center, for his careful review of and insightful comments on this article. The authors do not have any relevant disclosures or conflicts of interest to report regarding this article. The authors do not have any conflicts of interest to disclose.
	If statistical analysis was undertaken, was this appropriate?	Partial	No power analysis performed. Not reported whether ROC analysis was adjusted for BMI. Not reported how optimal cutoff value was determined.
Comments			
What is the overall risk of bias?		Moderate	

Data analyses

The systematic review to answer the question 'Is AMH effective for diagnosis PCOS' includes diagnostic accuracy studies. Therefore we used 'Chapter 9: Understanding meta-analysis' of Cochrane handbook (9-understanding-meta-analysis (cochrane.org)).

As stated in this handbook heterogeneity is to be expected in results of test accuracy studies, and therefore hierarchical random-effects models are required. The bivariate model focusses on the estimation of a summary point. These analyses have to be performed with other software than Revman. We used R (Version 4.2.2) for these analyses. Parameters estimates that were calculated with R, can be entered in RevMan to generate a SROC plot.

Meta-analyses in R

A binomial likelihood should be used to model within-study variability. Therefore packages such as *mada* and *mvmeta* that use a normal approximation (as described by Reitsma 2005) are not recommended.

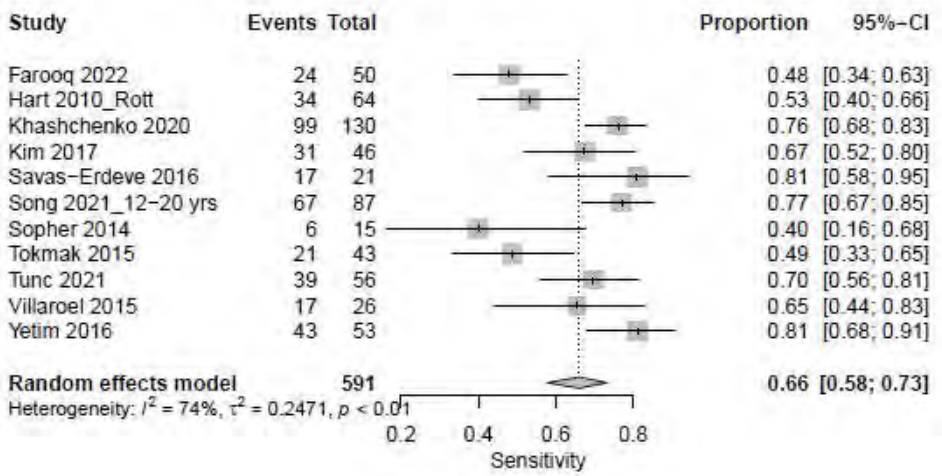
The *glmer* function in *lme4* fits a bivariate model using a generalized linear mixed model (GLMM) approach (chapter 10.2.3 '10 Undertaking meta-analysis Cochrane handbook). In a GLMM the linear predictor contains random effects in addition to the usual fixed effects. To perform these GLMM analyses we used the script that is reported in Appendix 12 in 'Supplementary material 1 to Chapter 10: Code for undertaking meta-analysis' in the Cochrane Handbook (10s1-supplementary-material-code-undertaking-meta-analysis (cochrane.org)).

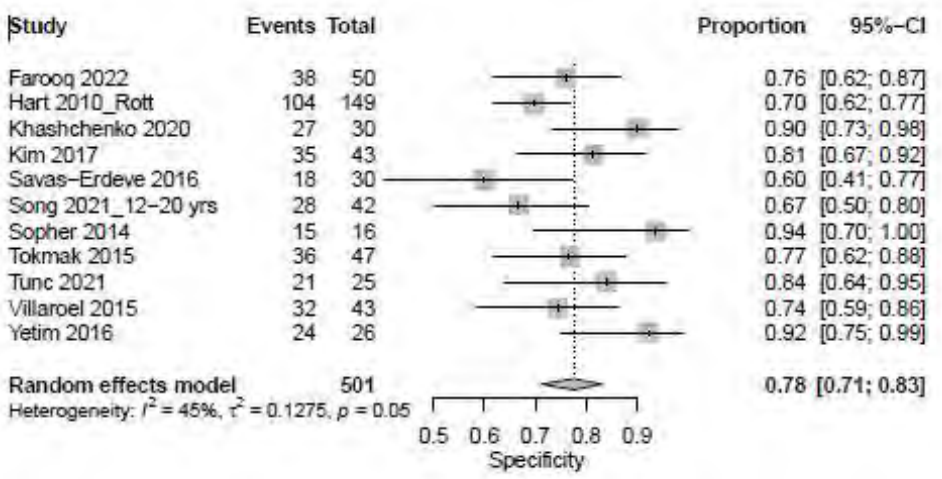
Meta-analysis 'Is AMH effective for diagnosis PCOS?'

Adolescents

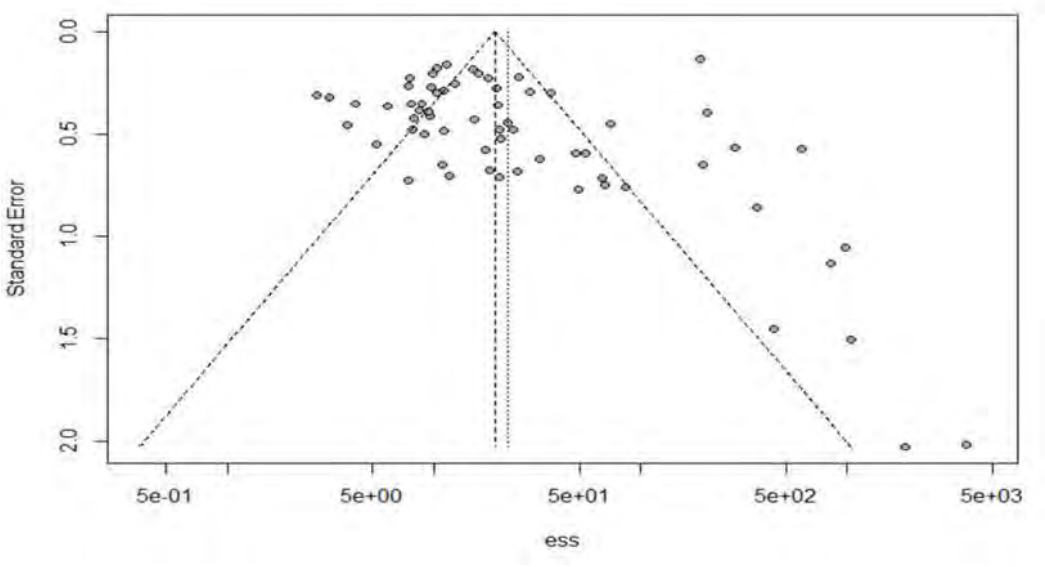
N=11

Forest plots

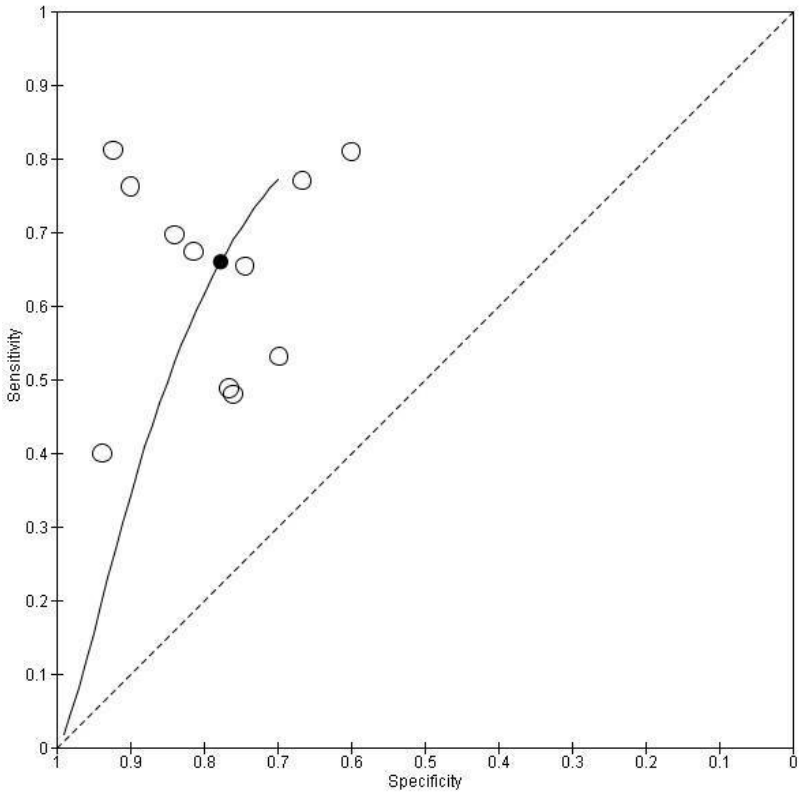




Funnel plot

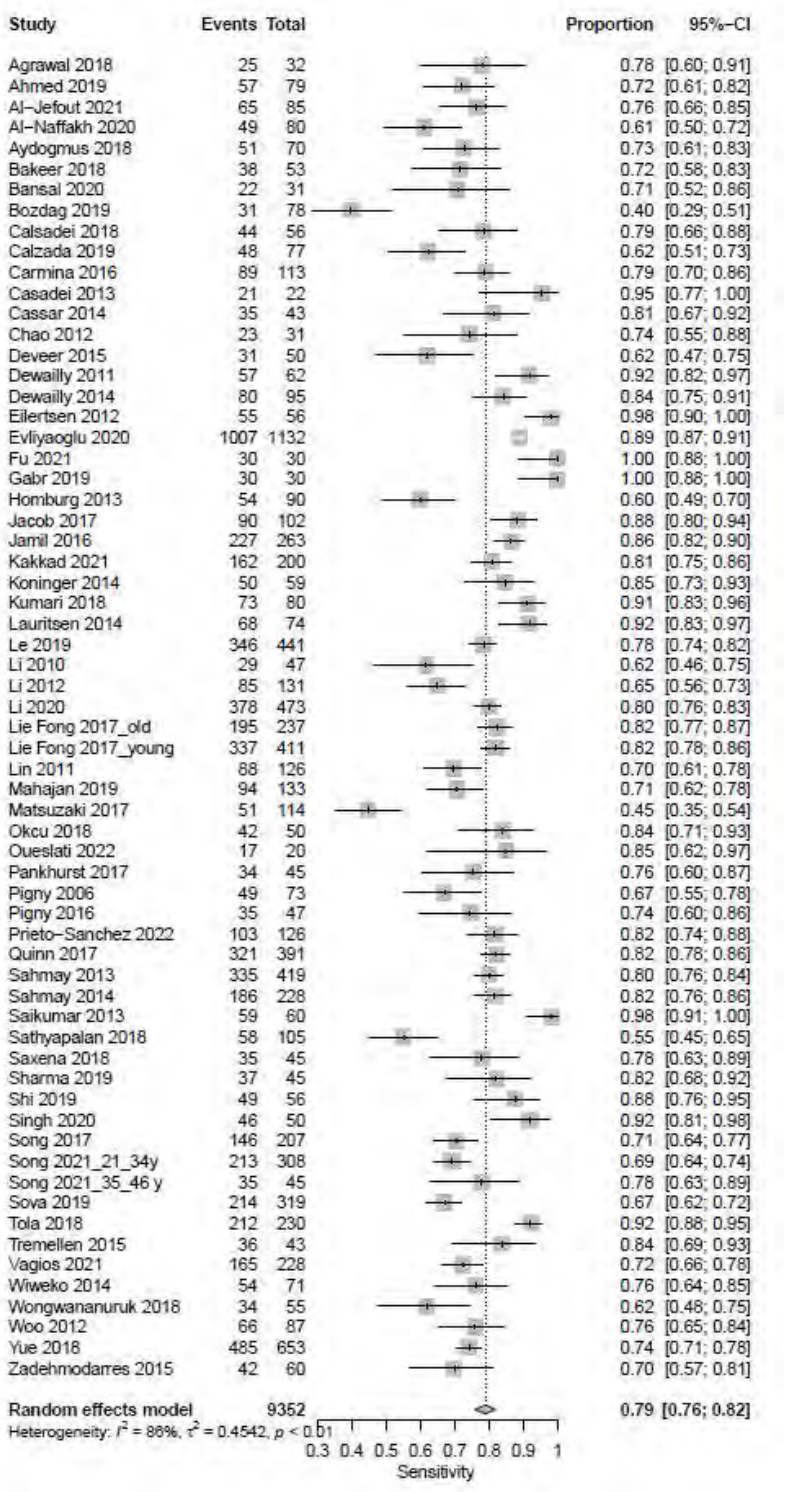


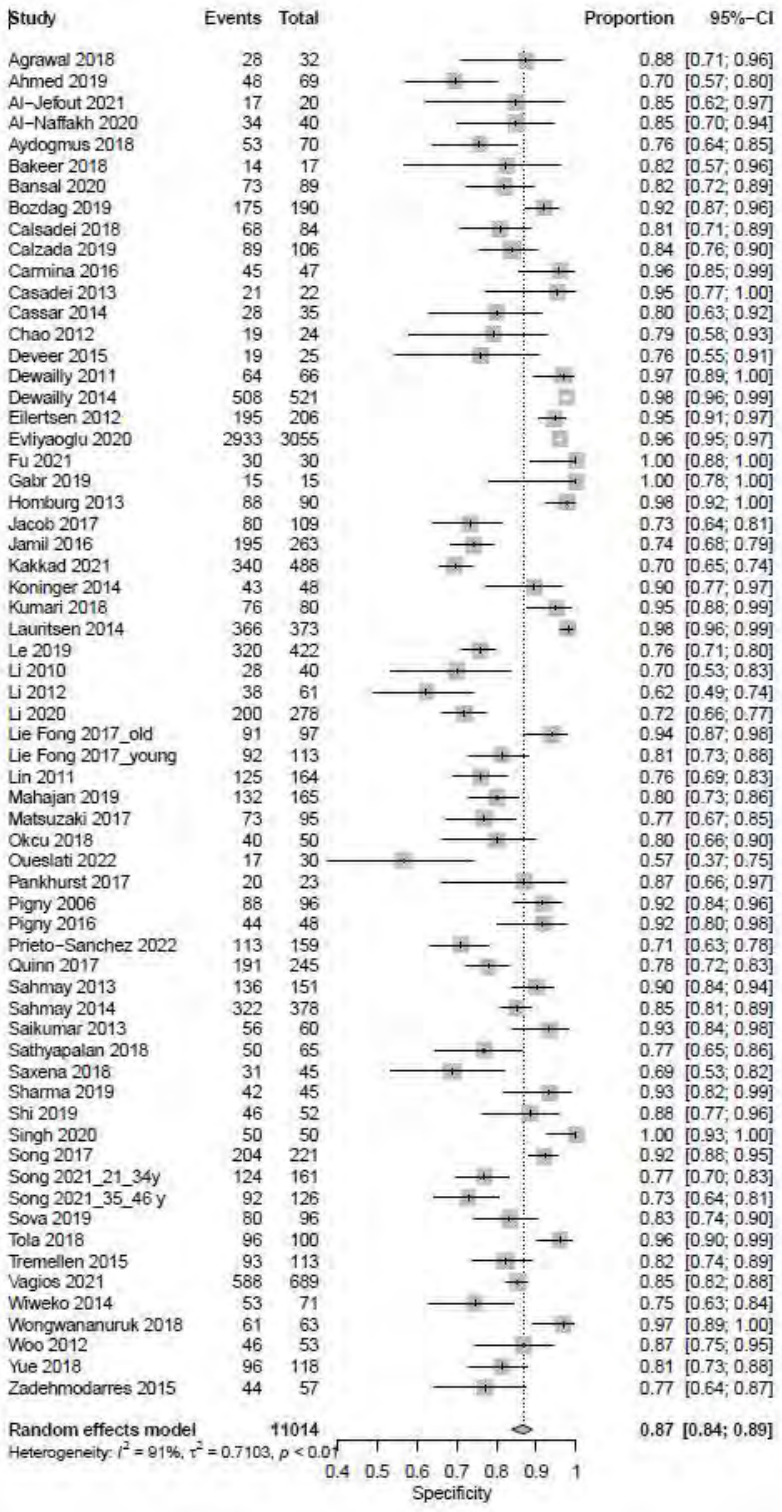
Summary ROC curve with summary point in black (bivariate model) AMH for PCOS in adolescents



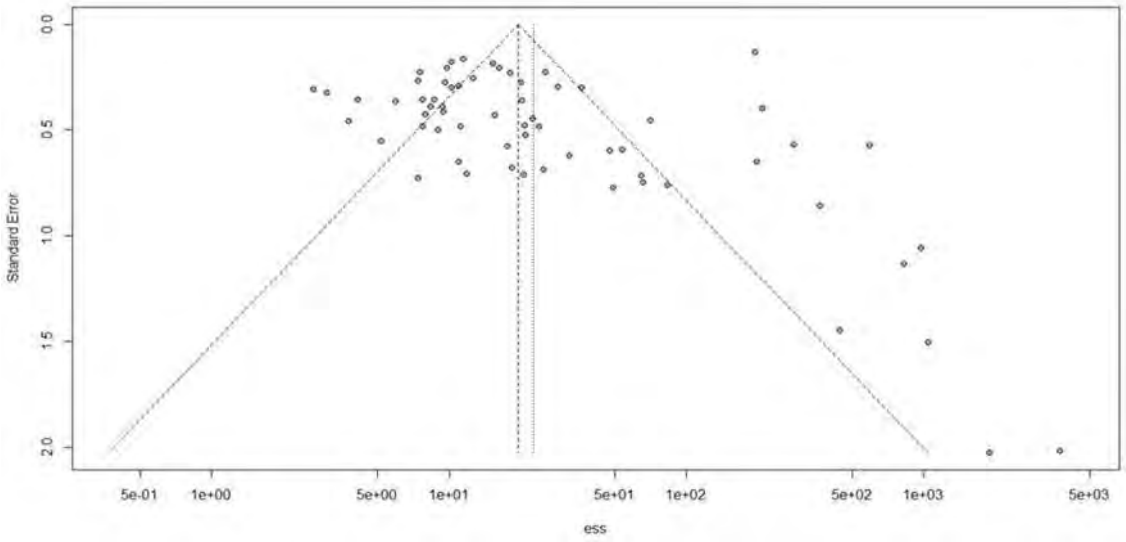
Adults (n=64)

Forest plots

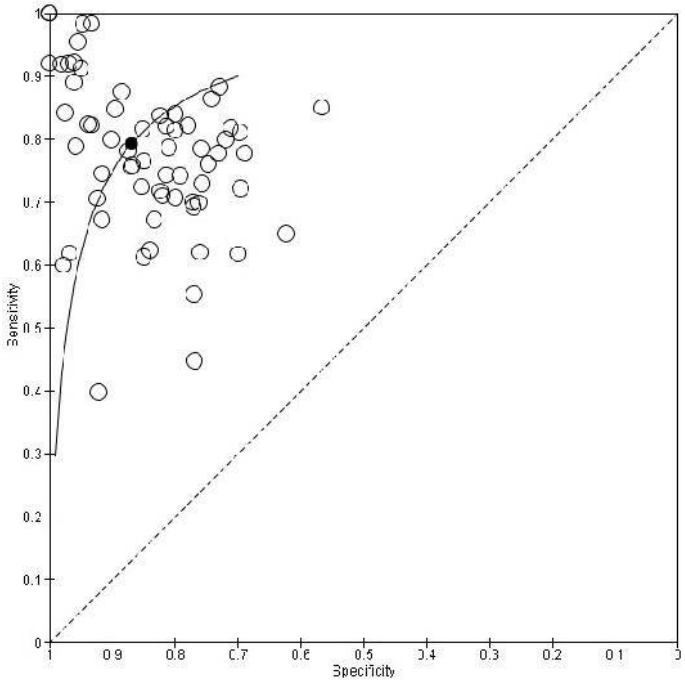



Study Events Total Proportion 95%−CI
Agrawal 2018 28 32 0.88 [0.71; 0.96]
Ahmed 2019 48 69 0.70 [0.57; 0.80]
Al−Jefout 2021 17 20 0.85 [0.62; 0.97]
Al−Naffakh 2020 34 40 0.85 [0.70; 0.94]
Aydogmus 2018 53 70 0.76 [0.64; 0.85]
Bakeer 2018 14 17 0.82 [0.57; 0.96]
Bansal 2020 73 89 0.82 [0.72; 0.89]
Bozdag 2019 175 190 0.92 [0.87; 0.96]
Calsadei 2018 68 84 0.81 [0.71; 0.89]
Calzada 2019 89 106 0.84 [0.76; 0.90]
Carmina 2016 45 47 0.96 [0.85; 0.99]
Casadei 2013 21 22 0.95 [0.77; 1.00]
Cassar 2014 28 35 0.80 [0.63; 0.92]
Chao 2012 19 24 0.79 [0.58; 0.93]
Deveer 2015 19 25 0.76 [0.55; 0.91]
Dewailly 2011 64 66 0.97 [0.89; 1.00]
Dewailly 2014 508 521 0.98 [0.96; 0.99]
Eilertsen 2012 195 206 0.95 [0.91; 0.97]
Evliyaoglu 2020 2933 3055 0.96 [0.95; 0.97]
Fu 2021 30 30 1.00 [0.88; 1.00]
Gabr 2019 15 15 1.00 [0.78; 1.00]
Homburg 2013 88 90 0.98 [0.92; 1.00]
Jacob 2017 80 109 0.73 [0.64; 0.81]
Jamil 2016 195 263 0.74 [0.68; 0.79]
Kakkad 2021 340 488 0.70 [0.65; 0.74]
Koninger 2014 43 48 0.90 [0.77; 0.97]
Kumari 2018 76 80 0.95 [0.88; 0.99]
Lauritsen 2014 366 373 0.98 [0.96; 0.99]
Le 2019 320 422 0.76 [0.71; 0.80]
Li 2010 28 40 0.70 [0.53; 0.83]
Li 2012 38 61 0.62 [0.49; 0.74]
Li 2020 200 278 0.72 [0.66; 0.77]
Lie Fong 2017_old 91 97 0.94 [0.87; 0.98]
Lie Fong 2017_young 92 113 0.81 [0.73; 0.88]
Lin 2011 125 164 0.76 [0.69; 0.83]
Mahajan 2019 132 165 0.80 [0.73; 0.86]
Matsuzaki 2017 73 95 0.77 [0.67; 0.85]
Okcu 2018 40 50 0.80 [0.66; 0.90]
Oueslati 2022 17 30 0.57 [0.37; 0.75]
Pankhurst 2017 20 23 0.87 [0.66; 0.97]
Pigny 2006 88 96 0.92 [0.84; 0.96]
Pigny 2016 44 48 0.92 [0.80; 0.98]
Prieto−Sanchez 2022 113 159 0.71 [0.63; 0.78]
Quinn 2017 191 245 0.78 [0.72; 0.83]
Sahmay 2013 136 151 0.90 [0.84; 0.94]
Sahmay 2014 322 378 0.85 [0.81; 0.89]
Saikumar 2013 56 60 0.93 [0.84; 0.98]
Sathyapalan 2018 50 65 0.77 [0.65; 0.86]
Saxena 2018 31 45 0.69 [0.53; 0.82]
Sharma 2019 42 45 0.93 [0.82; 0.99]
Shi 2019 46 52 0.88 [0.77; 0.96]
Singh 2020 50 50 1.00 [0.93; 1.00]
Song 2017 204 221 0.92 [0.88; 0.95]
Song 2021_21_34y 124 161 0.77 [0.70; 0.83]
Song 2021_35_46 y 92 126 0.73 [0.64; 0.81]
Sova 2019 80 96 0.83 [0.74; 0.90]
Tola 2018 96 100 0.96 [0.90; 0.99]
Tremellen 2015 93 113 0.82 [0.74; 0.89]
Vagios 2021 588 689 0.85 [0.82; 0.88]
Wiweko 2014 53 71 0.75 [0.63; 0.84]
Wongwananuruk 2018 61 63 0.97 [0.89; 1.00]
Woo 2012 46 53 0.87 [0.75; 0.95]
Yue 2018 96 118 0.81 [0.73; 0.88]
Zadehmodarres 2015 44 57 0.77 [0.64; 0.87]
Random effects model 11014 0.87 [0.84; 0.89]
Heterogeneity: I^2 = 91%, τ^2 = 0.7103, p < 0.01
0.4 0.5 0.6 0.7 0.8 0.9 1
Specificity

Funnel plot

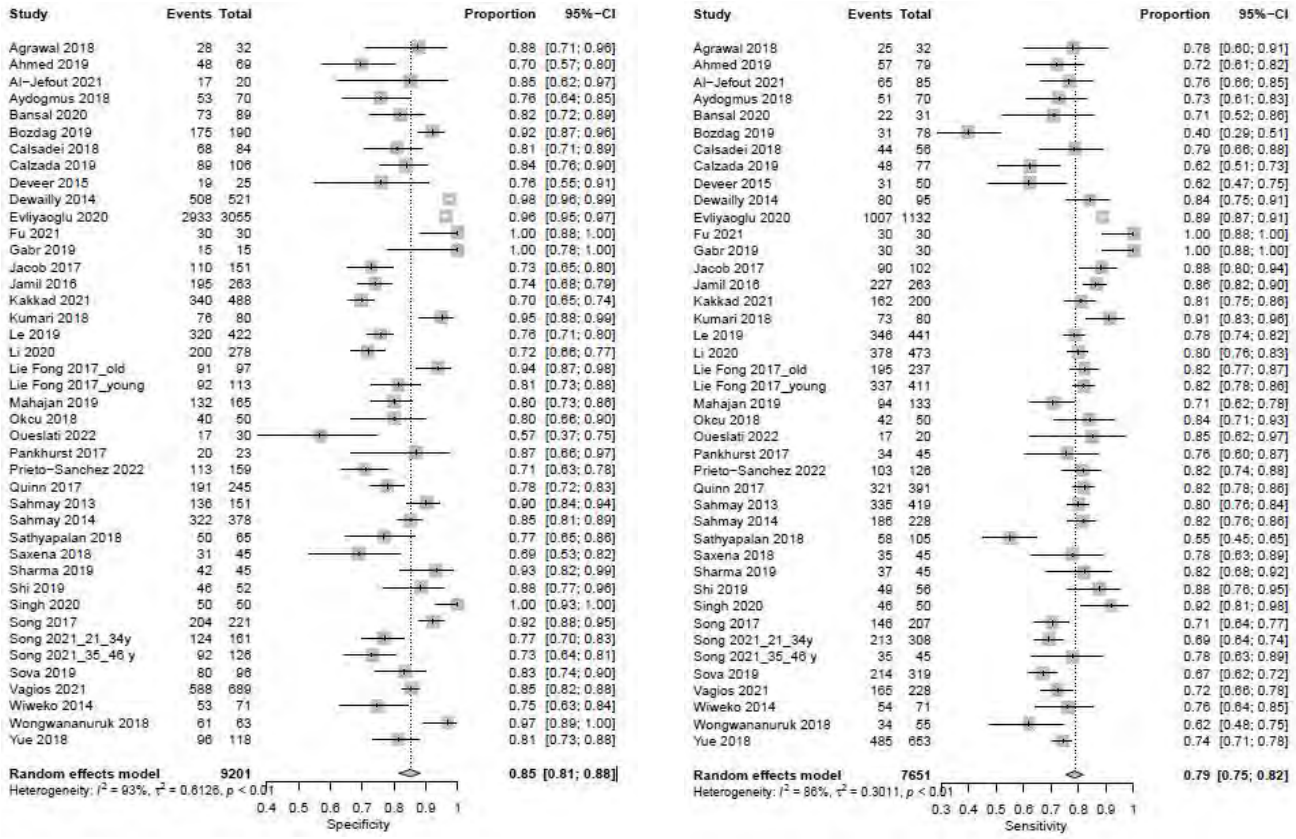


Summary ROC curve with summary point in black (bivariate model) AMH for PCOS in adults

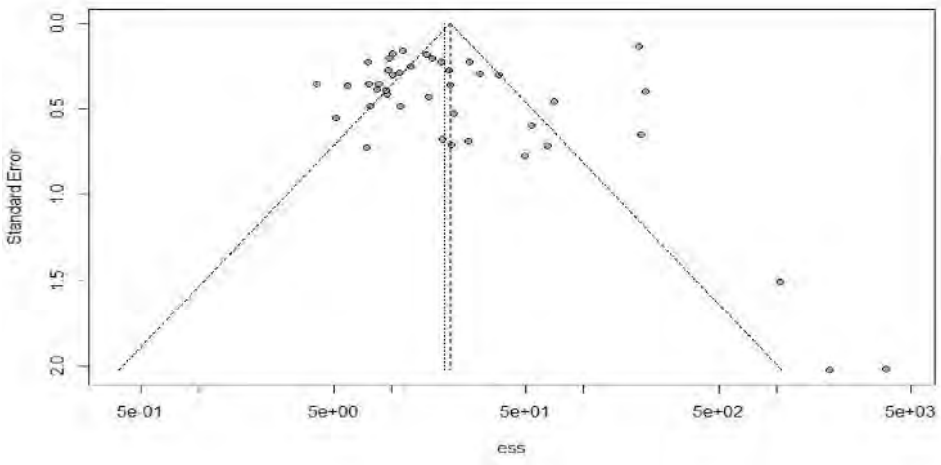


Adults with risk of bias as covariate

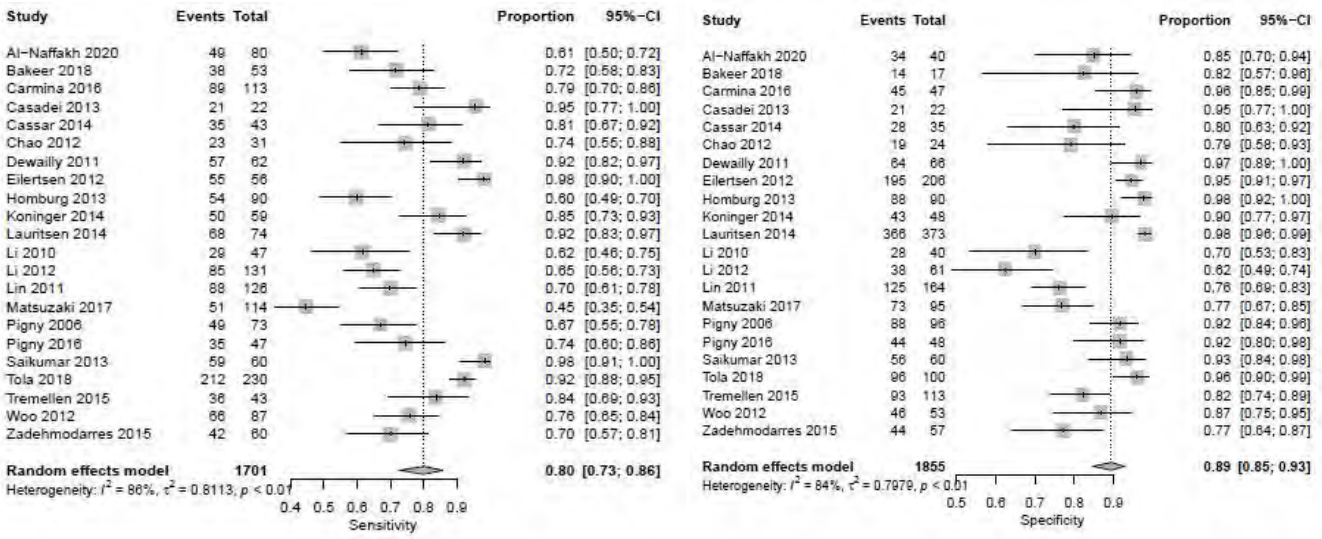
Forest plots of studies classified as low and moderate risk of bias



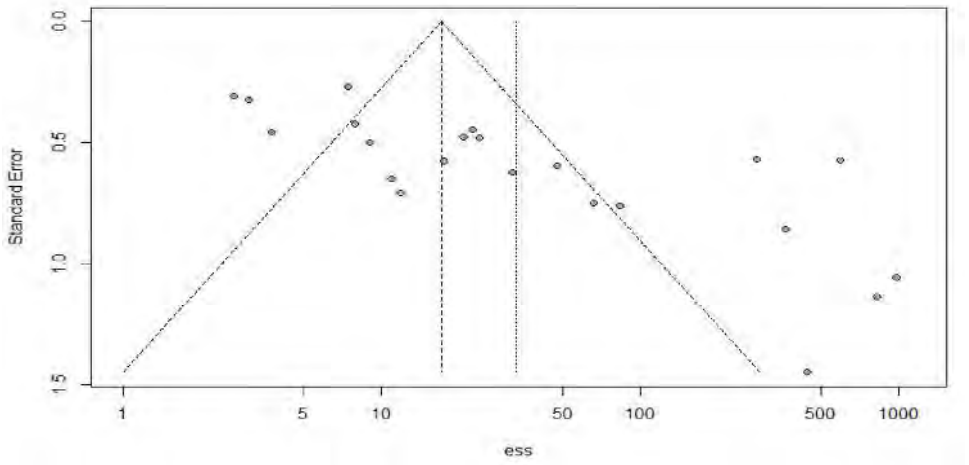
Funnel plot of studies classified as low and moderate risk of bias



Forest plots of studies classified as high risk of bias



Funnel plot of studies classified as high risk of bias



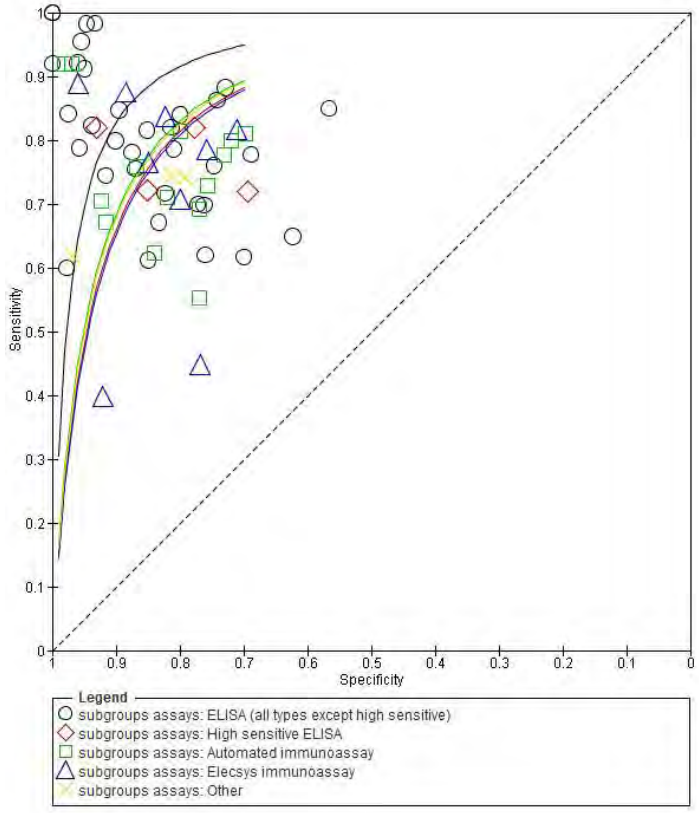
Adults with different assays as covariate

N=13 Automated immunoassay

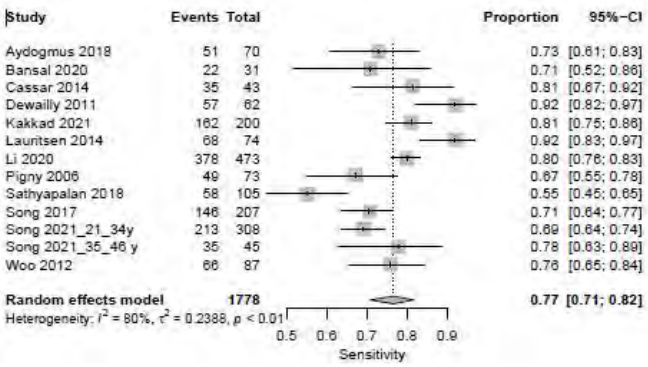
N= 10 Elecsys immunoassay

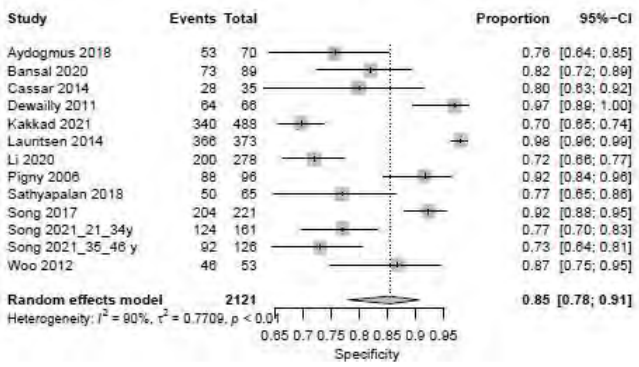
N= 34 ELISA, except high sensitivity

Summary ROC curve AMH for PCOS in adults, subgroups based on assay used

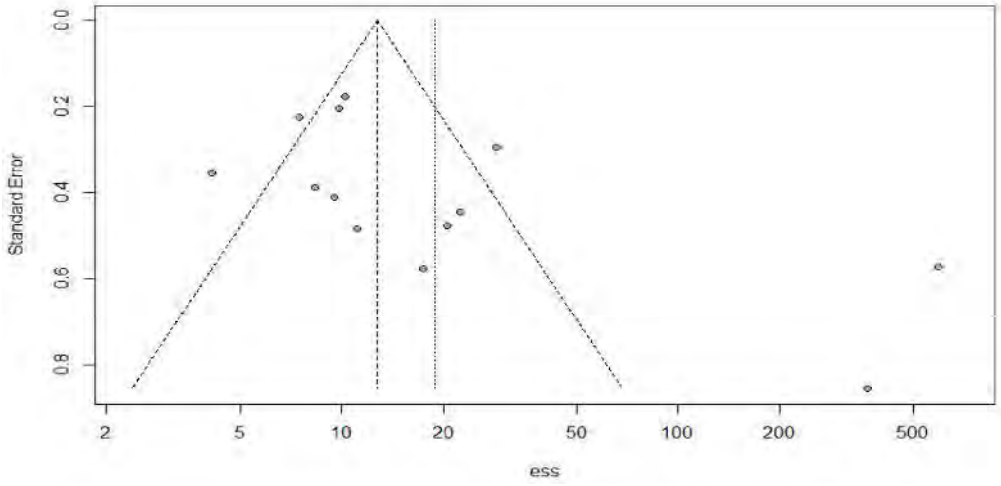


Forest plots of studies that used automated immunoassay

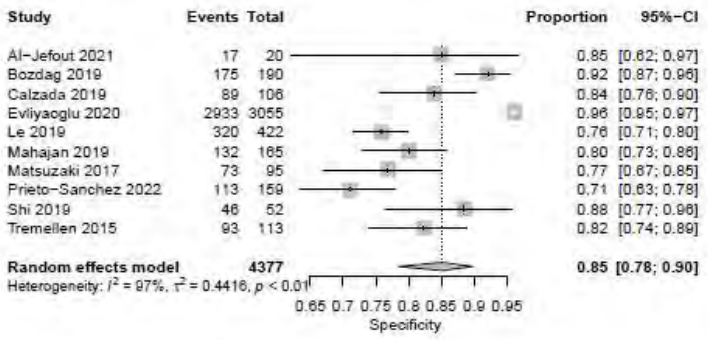


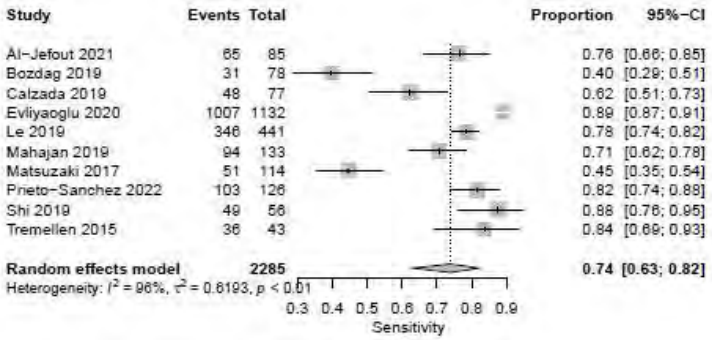


Funnel plot of studies that used the automated immunoassay

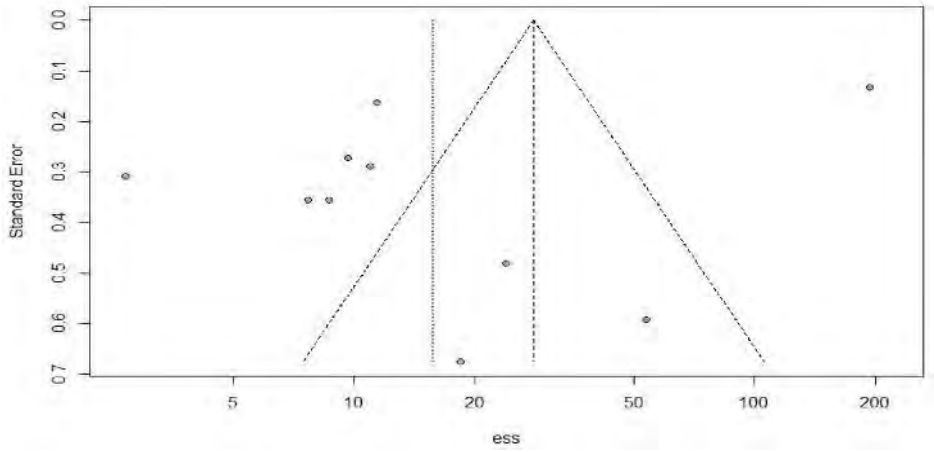


Forest plots of studies that used Elecsys immunoassay

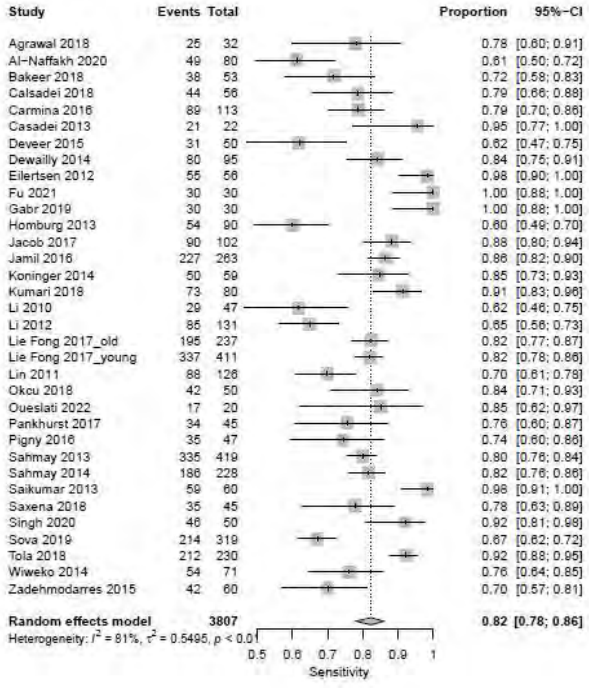


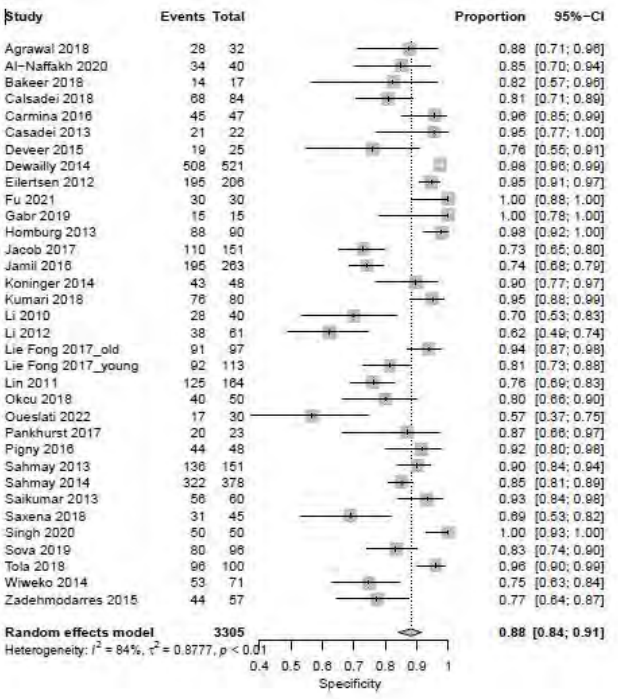


Funnel plot of studies that used the Elecsys immunoassay

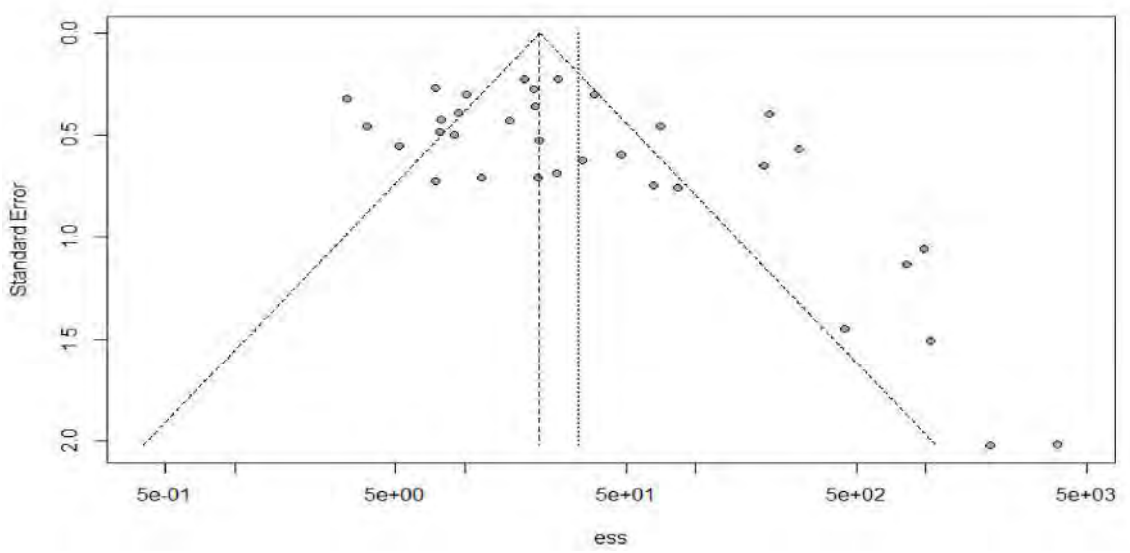


Forest plots of studies that used ELISA assay





Funnel plot of studies that used the ELISA assay

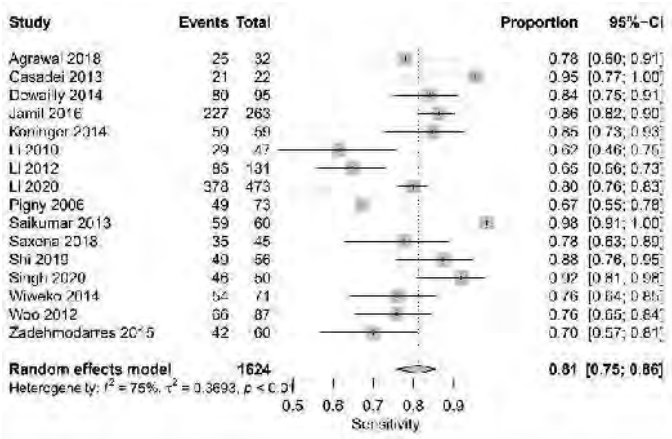


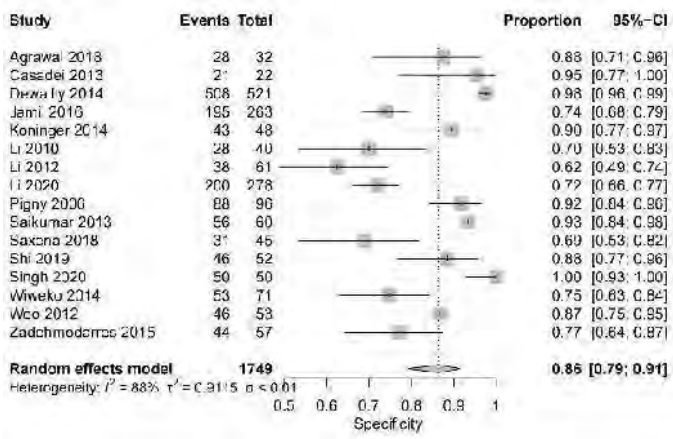
	Automated	Elecsys	ELISA	P-value[1]	P-value[2]	P-value[3]
Sensitivity (pooled)	**0.77 [0.71; 0.82)**	**0.74 [0.63; 0.82]**	**0.82 [0.78; 0.86]**	**$3.75e^{-16}$**	**$1.07e^{-08}$**	**$8.01e^{-10}$**
Specificity (pooled)	**0.85 [0.78; 0.91]**	**0.85 [0.78; 0.90]**	**0.88 [0.84; 0.91]**	**$2.08e^{-15}$**	**$7.75e^{-05}$**	**$3.84e^{-07}$**

[1]Difference between automated immunoassay and Elecsys assay. [2]Difference between automated and ELISA assay. [3]Difference between Elecsys and ELISA.

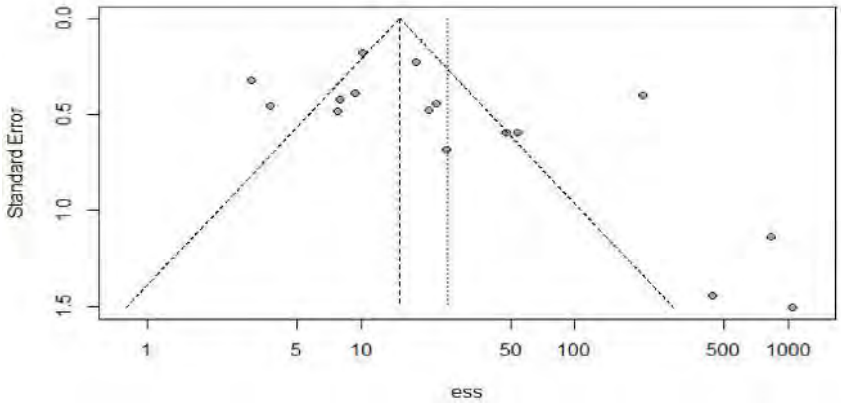
Adults with covariate 'PCOM excluded versus included in the control group'

Forrest plots of studies that excluded PCOM in the control group

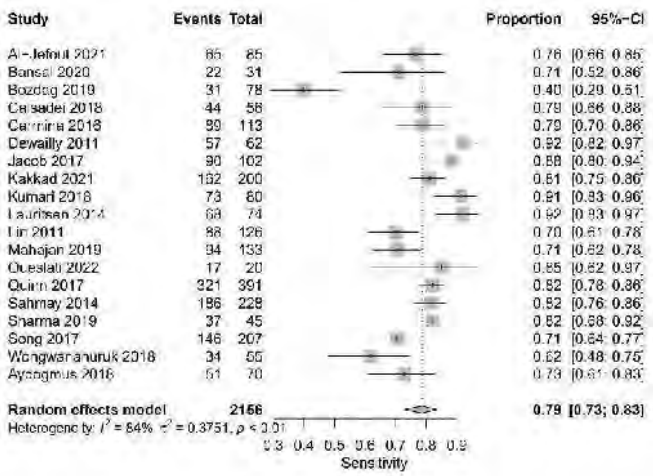


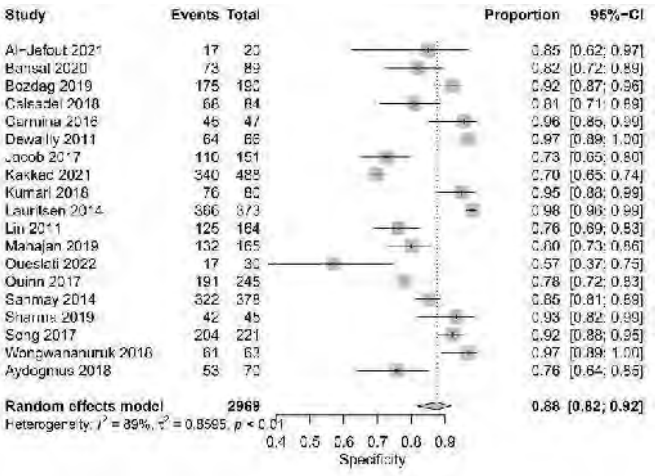


Funnel plot of studies that excluded PCOM in the control group

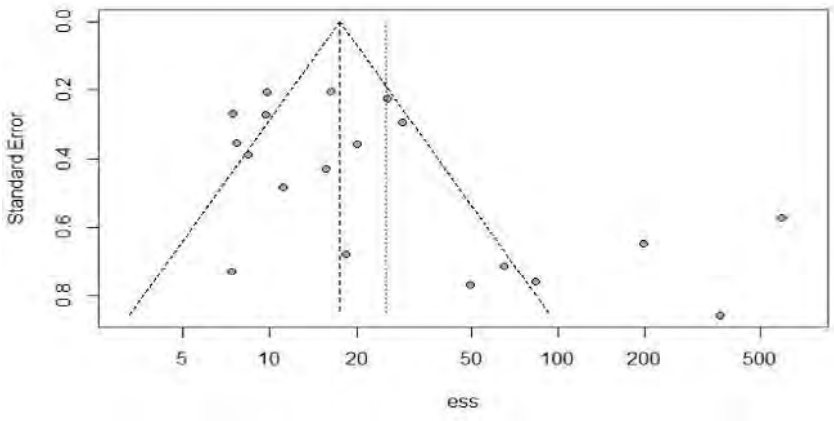


Forrest plots of studies that did not exclude PCOM in the control group





Funnel plot of studies that did not exclude PCOM in the control group

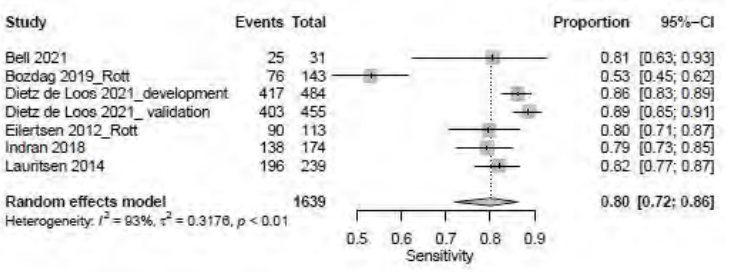


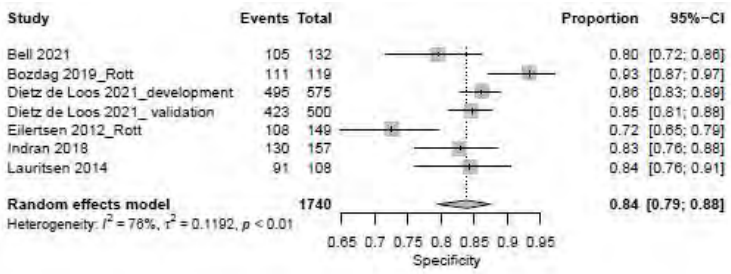
	PCOM excluded in controls	PCOM not excluded in controls	Chisq	P value
Sensitivity (pooled)	**0.81 [0.75; 0.86]**	**0.79 [0.73; 0.83]**	**0.5952**	**0.4404**
Specificity (pooled)	**0.86 [0.79; 0.91]**	**0.88 [0.82; 0.92]**	**0.0595**	**0.8072**

Meta-analysis 'Is AMH effective to diagnose PCOM?'

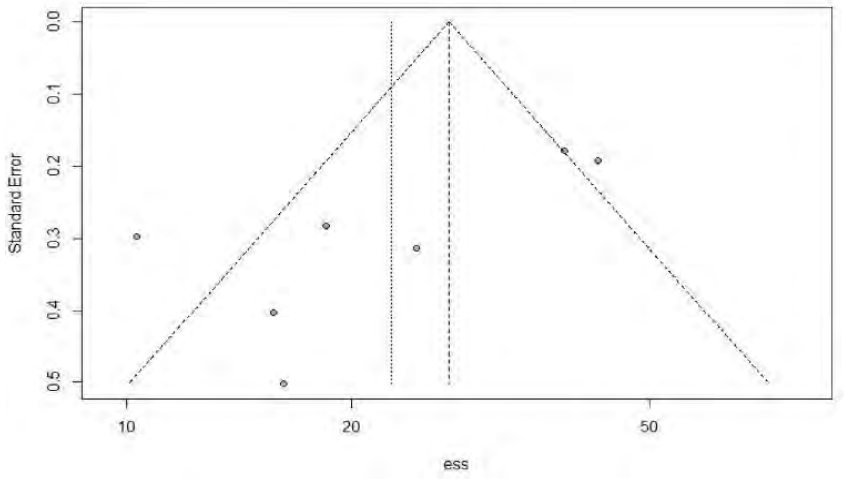
Adults (n=7)

Forest plots of studies that assessed the accuracy of AMH to diagnose PCOM





Funnel plot



PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 1

Question 1.5.

Is AMH effective for diagnosis of PCOS? Is AMH effective to diagnosis of PCOM?

BACKGROUND:

Polycystic ovary morphology is defined by transvaginal ultrasound scan showing at least 20 follicles between 2 to 9 mm in diameter or an ovarian volume of more than 10 ml in either ovary (1). It has since become the most widely adopted diagnostic criteria contributing essentially to the standardization for research and clinical practice purposes. Counting of antral follicles is both operator- and equipment-dependent, which limits its use in some clinical settings and its comparability among centers.

AMH is a polypeptide of the TGF® family solely secreted by granulosa cells of the preantral and small antral ovarian follicles. AMH serum levels generally increase in newborns until early adulthood and start decreasing around an age of 20-25 years of age (2). Indeed, it has been reported that the amount of active AMH is lower during puberty due to suppression of the conversion of the precursor of AMH into the active form of AMH (3) . Serum AMH levels may be affected in the short term after drug application. Specifically, the combined oral contraceptive pills suppress serum AMH levels significantly typically within 3 months. Similarly, Metformin and Clomiphene citrate lead to decreased serum AMH concentrations. Dehydroepiandrosterone (DHEA) and vitamin-D may give rise to increased serum AMH levels (4) Moreover, BMI seems to modify serum AMH levels as well since obese women have lower levels of inactive pro-AMH compared to women that have a normal weight (3, 5) . Ethnic differences seem to influence AMH serum levels as well. Indian women do have lower levels of AMH compared to women from Western European countries (6). The same holds true for women form China presenting with lower AMH serum levels amongst all age classes from age 25 years onwards (7) . A recent review however, showed that the relationship between AMH and BMI in reproductive-aged women remains inconclusive, with studies in women with and without PCOS producing mixed results. Research in this area is currently limited by failure to analyse the full spectrum of obesity, hindering generalization to a global population increasingly affected by the condition. Some authors pointed to evidence of race/ethnicity as a confounding factor of the relationship, but results between studies are contradictory. Limited evidence on weight loss suggests it may decrease AMH levels despite improving fertility outcomes(8).

A significantly higher serum level of AMH has been demonstrated in women with PCOS compared with normal ovulatory women (9, 10). It leads to the postulation that AMH could be a valuable surrogate marker in place of AFC by ultrasound in diagnosis of PCOS. Indeed, high levels of AMH are positively correlated to the number of small antral follicles on ultrasound. In women with PCOS the number of small antral follicles is increased compared to controls. However, this so called polycystic ovarian morphology (PCOM) is also commonly encountered amongst adolescents without any other feature of PCOS. This has led to disagreement as to whether women with PCOM should be excluded from the control population when establishing FNPO and AMH diagnostic thresholds for the definition of PCOS. A large cluster analysis showed that identification and exclusion of the cluster corresponding to healthy women with PCOM from controls improved the diagnostic power of serum AMH level and follicle number per ovary (FNPO) in discriminating between women with or without PCOS (11).

Given its strong involvement in the pathophysiology of PCOS, serum AMH is a subject of special interest for clinicians involved in this field. There is considerable interest in whether it might become part of the diagnostic criteria for the condition. It may also shed light on different subtypes of this diverse condition leading to greater understanding of the disordered follicle growth.

Certainly, the serum AMH concentration appears to be greatly increased in most patients with PCOS. Many authors have reported a strong correlation between plasma levels of AMH and antral follicle count (AFC) on ultrasound in PCOS patients. This has led several authors to compare the performance of one against the other for the diagnosis of PCOS. However, the results in the current literature are not homogeneous between studies, for many reasons. Most studies are case control or cohort studies most of them suffering from serious risk of bias. Moreover, a lot of them suffer from serious indirectness and imprecision as far as the diagnosis of PCOS is concerned.

The diagnostic value of serum AMH concentrations has also been studied in adolescents since ultrasound is often unreliable in detecting PCOM in this population.

As the AFC suffers from great controversy in the current literature, there was a great expectation that AMH assay may replace (or be an alternative for) AFC in the Rotterdam classification, and the number of studies assessing this relationship has considerably increased from 2018 onwards.

Two recent meta-analyses have combined these results, these and other studies are included in our systematic review. These meta-analyses concluded that serum AMH seems to be a promising biomarker for the diagnosis of PCOS, however, substantial heterogeneity among studies needs individual patient data analysis in order to identify an optimal cut-off value and homogenous findings (12, 13). This is exactly what we tried to do in the current analysis.

GRADE EVIDENCE CERTAINTY

Comparison	GRADE for critical outcomes
o AMH as diagnostic marker for PCOS	⊕⊕⊕◯ MODERATE
o AMH as diagnostic marker for PCOM	⊕⊕⊕◯ MODERATE

Evidence to Recommendations Framework

COMPARISONS (option versus other option)

AMH as a diagnostic marker for PCOS in adult women with PCOS vs adult controls
AMH as a diagnostic marker for PCOS in adolescent girls with PCOS vs adolescent control girls
AMH as a diagnostic marker for PCOM in adult women with PCOS vs adult controls

EVIDENCE-BASED RECOMMENDATION(S)

EBR: Serum AMH could be used for defining PCOM in adults.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

EBR: Serum AMH should only be used in accordance with the diagnostic algorithm.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

EBR: We recommend that serum AMH should not be used as a single test for the diagnosis of PCOS.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

EBR: Serum AMH should not yet be used in adolescents.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

Justification:
Specificity and sensitivity indexes are generally very good for AMH as a marker for antral follicle excess in adults, but not in adolescents.
The diagnostic accuracy is very good and areas under the curve are between 0.81 and 0.94, and have a pooled sensitivity of 0.80 and a pooled specificity of 0.84.
Specificity and sensitivity indexes are generally similar for AMH as a single marker for PCOS in adults and adolescents (pooled sensitivity of 0.79 and specificity of 0.87).

PRACTICE POINT(S)

Either serum AMH or ultrasound may be used to define PCOM; however, both tests should not be performed together (as it may contribute to overdiagnosis).

Laboratories and healthcare professionals need to be aware of factors that could influence AMH in the general population, including:

- Age: Serum AMH generally peaks between the ages of 20-25 years in the general population
- Body mass index (BMI): Serum AMH is lower in those with higher BMI in the general population by ethnicity in the general population
- Hormonal contraception and ovarian surgery: Serum AMH may be suppressed by current or recent COCP use
- Menstrual cycle day: Serum AMH may vary across the menstrual cycle

Laboratories involved in AMH measurements in females should use population and assay specific cut-offs.

GRADE CONSIDERATIONS

Justifications:

In adults, there are 62 relevant studies (2 studies are included twice in the meta-analysis) showing a pooled sensitivity of 0.79 [CI 0.76; 0.82) and a pooled specificity of 0.87 [CI 0.84; 0.89] of AMH for diagnosis of PCOS. The threshold ranges from 8.5-57 pmol/L.

In adolescents, there are 11 relevant studies showing area under ROC of AMH for diagnosis PCOS with a pooled sensitivity of 0.66 [CI 0.58; 0.73] and a pooled specficity of 0.78 [0.71; 0.83]. The threshold ranges from 24 to 100 pmol/L.

Although serum AMH levels in adolescent and adult PCOS women are significantly higher than those of non-PCOS counterparts in all studies, there are overlaps between them. The variations among studies may be partially related to the AMH assays used, the population and the phenotype definitions applied.

There are 7 relevant studies concerning the role of a single serum AMH measurement to diagnose follicle excess in adults, showing a pooled sensitivity of 0.80 [CI 0.72; 0.86] and a pooled specificity of 0.84 [0.70;0.88]. The threshold ranges from 22.8 - 44 pmol/L.

Although serum AMH levels in adolescent and adult follicle excess women are significantly higher than those of non-follicle excess counterparts in all studies, there are overlaps between them. The threshold of AMH making a diagnosis of follicle excess has a wide range for practical use. Moreover, there seems to be an age effect in that in women above age 30 the diagnosis of follicle excess based on one serum AMH measurement seems to only restricted to women with PCOS.

The results from the current literature are not homogeneous. Part of this heterogeneity is due to the lack of well-defined populations. In particular, some authors have used the PCOS definition established in 2003 at the Rotterdam conference**,** using 12 follicles of 2-9mm diameter per ovary for the polycystic ovaries morphology (PCOM) whereas others use 20 follicles of 2-9mm diameter as the criterion to define PCOM. This cut off is highly dependent on ultrasound equipment and operator skills. Therefore, with the latest ultrasound generation, the threshold has evolved and is now up to 20**.** This threshold will probably continue to increase as newer ultrasound technologies and equipment are developed.

Additionally, there are critical issues regarding what populations are included or excluded in the normative population. In particular, the inclusion of controls with follicle excess is questioning. These women are not defined as having PCOS according to the Rotterdam classification, but when it comes to defining a threshold for follicle excess, they cannot be used as controls. This leads to an overlap of the AFC and AMH values between the control and the PCOS groups, which undermines the quality of the ROC analysis and forces placement of the threshold relatively high, to minimize this overlap.

Subgroup considerations:

A single serum AMH measurement is most reliably predicting follicle excess in adult women with PCOS.

AMH levels vary widely between adolescents and generally are increasing up to an age of 20 - 25 years AMH measurements are less reliable in this group.

Subgroup analyses showed that stratification in risk of bias still showed high heterogeneity and did not change the outcome in sensitivity and specificity. The pooled sensitivity of AMH for diagnosis PCOS in adults, including only studies classified as low and moderate risk of bias, was 0.79 [0.75; 0.82] and the pooled specificity 0.85 [CI 0.81; 0.88]. The meta-analysis that included only studies with high risk of bias showed a pooled sensitivity of 0.80 [0.73; 0.86] and a pooled specificity of 0.89 [0.85; 0.93]. The likelihood ratio test showed no statistically difference between groups (p= 0.92).
The subgroup analyses in which we stratified the three main assays (automated immunoassay, Elecsys immunoassay and ELISA), did show differences in summary points of sensitivity and specificity, p-value ranging from 7.8e-5 to 3.8e-16. The meta-analysis including studies that used the automated immunoassay showed a pooled sensitivity of 0.77 and specificity of 0.85, studies that used Elecsys showed a pooled sensitivity of 0.74 and specificity of 0.85, and studies that used ELISA showed a pooled sensitivity of 0.82 and specificity of 0.88.
Subgroup analyses restricting to studies that only included controls without PCOM revealed similar results.

Implementation considerations:
A single serum AMH measurement is most reliably predicting follicle excess in adult women with PCOS.
If an ovarian ultrasound is performed according to a fixed protocol (see elsewhere in this document),, which includes the assessment of follicle count per ovary and/or ovarian volume, serum AMH is not necessary.

Monitoring and evaluation considerations:
The acceptability to women and healthcare professionals
The cost of using AMH vs ultrasound.

Research priorities:
- The role of AMH in adolescents.
- Normative data and cut-offs per age class, especially in adolescents are lacking
- Longitudinal data in AMH
- Cost effectiveness studies comparing US and AMH measurements
- Long lasting effects of COCP use on AMH serum levels
- Impact of BMI, ethnicity and androgens on serum AMH
- The predictive value of AMH in epidemiologic studies
- Comparing predictive value of AMH and/or ultrasound

GRADE framework

GRADE DECIDE Interactive Evidence to Decision Framework

● DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Women will have the option

AMH measurements may be of lower cost and more convenient than ultrasound assessments

● UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Women will have the option to choose serum AMH or ultrasound

● CERTAINTY OF THE EVIDENCE

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☐ Very low	☐ Low	☒ Moderate	☐ High

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

PCOS in adults is Moderate

Follicle excess in adults is High

● VALUES

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☐ Important uncertainty or variability	☒ Possibly important uncertainty or variability	☐ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Research evidence:

No research evidence was identified

Panel discussion:

There are subgroups and inter-related factors that could impact serum AMH

● BALANCE OF EFFECTS

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:

High ROC curve for AMH and follicle excess in adults.

● COSTS

How large are the resource requirements (costs)?

Judgement:

☐ Don't know	☒ Varies	☐ Large costs	☐ Moderate costs	☐ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:

No research evidence was identified

Panel discussion:

AMH may be lower cost to ultrasound assessment.

If guideline recommendations result in change in reimbursement, this may reduce patients' cost.

● CERTAINTY OF COST EVIDENCE

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

No research evidence was identified

Panel discussion:

Cost effectiveness studies are needed

● COST-EFFECTIVENESS

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

No research evidence was identified

Panel discussion:

No data available yet

● EQUITY

What would be the impact on health equity?

Judgement:

☐ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☒ Probably increased	☐ Increased

Research evidence:

No research evidence was identified

Panel discussion:

More women gain access to health care due to a correct and timely diagnosis of PCOS

● ACCEPTABILITY

Is the option acceptable to key stakeholders?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Serum AMH may be more acceptable than transvaginal ultrasound.

● FEASIBILITY

Is the option feasible to implement?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

- Availability of AMH assays

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PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by ECR Lead: Adriana Catharina Helena Neven
Other Members: Jacqueline A Boyle, Helena J Teede, Loyal Pattuwage, Maria Forslund, Pauline Shun Lin

Supervised, edited and supported by the Evidence Team

GDG 1

Question 1.6.

In women with PCOS, is there evidence of ethnic variations in the prevalence?

PLEASE NOTE THIS EVIDENCE SUMMARY IS BEING UPDATED AFTER REVIEW AND PUBLIC CONSULTATION, HENCE SOME RESULTS MAY HAVE CHANGED. PLEASE REFER TO T.HE PUBLICATION OR FINAL GUIDELINE FOR UPDATES OR ADDITIONAL ANALYSES.

1. SELECTION CRITERIA

Table 1. PICO Criteria for Inclusion	
Question	**1.6 In women with PCOS is there evidence of ethnic variations in prevalence and presentation?**
Clinical leads (key contacts)	**Dr Malika Patel** **Gynaecologist** **The University of Cape Town, South Africa** **m.patel@uct.ac.za** **Prof Fahimeh Ramezani Tehrani** **Obstetric and Gynaecologist** **Shahid Beheshti University of Medical Sciences, Iran** **fah.tehrani@gmail.com**
Allocation ranking	**Level 1 - New systematic review**

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(language, year)*
Inclusion	If on PCOS prevalence: Adolescent and adult women with PCOS (self-reported or diagnosed by Rotterdam, NIH or AE-PCOS Society). There will be no restrictions on participants' location. If on PCOS presentation and complications: adolescent and adult women with suspected PCOS (diagnosed by Rotterdam, NIH or AE-PCOS Society) of any ethnicity, and weight. Note preference and subgroup for untreated or must have stopped medication for a minimum of 3 months.	None	Various ethnicity, race	If on PCOS prevalence: Prevalence of PCOS (diagnosed by Rotterdam, NIH or AE-PCOS Society or self-reported) of any age, ethnicity, race and weight. If on PCOS presentation/ complications: PCOS Characteristics such as oligomenorrhea, Amenorrhea, Hyperandrogenism, (Clinical and/or biochemical), polycystic ovarian morphology (PCOM), Insulin resistance, Type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), Metabolic Syndrome (Met S), Obesity and Overweight, Depression, Anxiety and self-esteem, eating disorders, disordered eating, fatty liver, sexual dysfunction, infertility, cancer, sleep apnoea)	Evidence based guidelines, systematic reviews, health technology assessments, randomised controlled trials, prospective and retrospective cohort studies, cross- sectional and case-control studies;	English language only, 1990-current
Exclusion	Selected populations, eg. women presenting with hirsutism, infertility, oligomenorrhea, hyperandrogenism, diabetes.	N/A	N/A	Outcomes not described according to ethnicity/race	Qualitative studies, commentaries, abstracts, protocols, editorials, narrative reviews	

2. SEARCH STRATEGY

Table 2.1. Search details	
Search strategy source: *N/A*	
Evidence source	**Date of search**
Medline (Ovid)	26/08/2022
PsychInfo (Ovid)	26/08/2022
EMBASE (Ovid)	26/08/2022
All EBM (Ovid)	26/08/2022
CINAHL	26/08/2022

Table 2.2. Questions addressed by this search		
GDG	Q#	Question
1	6	In women with suspected PCOS is there evidence of ethnic and geographic variations in the prevalence and presentation?

Table 2.3. Search strings used in OVID or other database/s – *please save a screenshot of search results to submit alongside this template*		
OVID Medline, All EBM, PsychInfo, EMBASE (results= 13174)	CINAHL (results = 1062)	Other
OVID MEDLINE 1. 1 Polycystic ovary syndrome/ 16992 2 Polycystic ovar*.mp. 22548 3 Poly-cystic ovar*.mp. 52 4 PCO*.mp. 36307 5 (stein-leventhal or Leventhal).mp. 915 6 Anovulation/ 2267 7 Anovulat*.mp. 6774 8 Oligo-ovulat*.mp. 108 9 Oligoovulat*.mp. 61 10 (ovar* adj5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*)).mp. 23536 11 or/1-1049903 12 exp Population Groups/ 319199 13 "Ethnic and Racial Minorities"/ 383 14 Minority Groups/ 16884 15 Arabs/ 5294 16 Indigenous Peoples/ 1019 17 Vulnerable Populations/ 12553 18 Roma/ 1026 19 (aborigin* or native* or inuit* or eskimo* or kalaallit* or amerind* or romany or romani* or gypsies or gipsies or maori* or metis* or First Nation* or Torres Strait island*).tw. 277028 20 ((afro or African or asian or latin* or Indian) adj1 American*).tw. 80311 21 (Africa* or "mixed ancestry*" or Afro* or ((Asian or Bangladeshi or		N/A

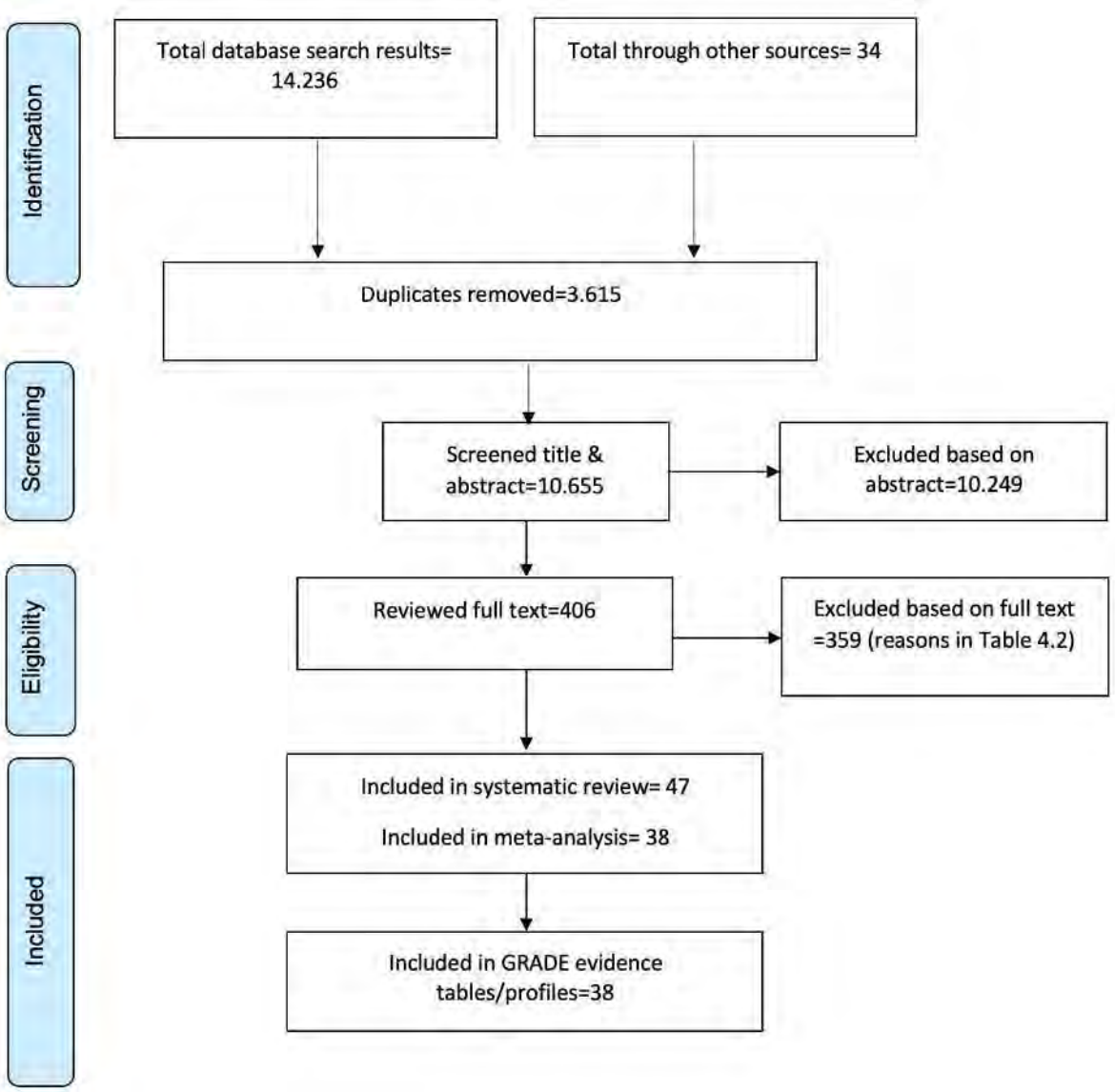
Caribbean or Chinese or Hispanic or Indian or Pakistani or "South Asian" or Black) adj2 (women or people or person$1 or heritage or ancestry or population$1 or adolescen$2 or female$1 or girl$1 or individual$1 or patient$1)) or Ethnic* or Minorit* or Race or Racial).tw. 668366 22 or/12-21 1096626 23 11 and 22 2049 24 exp Polycystic Ovary Syndrome/cl, di, ep, pc, sn [Classification, Diagnosis, Epidemiology, Prevention & Control, Statistics & Numerical Data] 3428 25 11 and (22 or 24) 5172 26 limit 25 to (english language and humans and yr="1990 -Current") 4013 *Embase Classic+Embase <1947 to 2022 August 24>* 1 "Polycystic ovary syndrome"/ 17270 2 "Polycystic ovar*".mp. 28959 3 "Poly-cystic ovar*".mp. 205 4 PCO*.mp. 53876 5 (stein-leventhal or Leventhal).mp. 1502 6 Anovulation/ 6709 7 Anovulat*.mp. 11183 8 Oligo-ovulat*.mp. 155 9 Oligoovulat*.mp. 123 10 (ovar* adj5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*)).mp. 38448 11 or/1-10 78839 12 exp "Population Groups"/ 1149091 13 "Ethnic and Racial Minorities".tw. 288 14 "Minority Groups"/ 16123 15 Arabs/ 8112 16 Indigenous Peoples/ 8027 17 "Vulnerable Populations"/ 21158 18 Roma/ 622 19 (aborigin* or native* or inuit* or eskimo* or kalaallit* or amerind* or romany or romani* or gypsies or gipsies or maori* or metis* or First Nation* or Torres Strait island*).tw. 333785 20 ((afro or African or asian or latin* or Indian) adj1 American*).tw. 123655 21 (Africa* or "mixed ancestry*" or Afro* or ((Asian or Bangladeshi or Caribbean or Chinese or Hispanic or Indian or Pakistani or "South Asian" or Black) adj2 (women or people or person$1 or heritage or ancestry or population$1 or adolescen$2 or female$1 or girl$1 or individual$1 or patient$1)) or Ethnic* or Minorit* or Race or Racial).tw. 915082 22 or/12-21 2036015 23 11 and 22 5366 24 exp ovary polycystic disease/di, ep [Diagnosis, Epidemiology] 3921 25 11 and (22 or 24) 8956 26 limit 25 to (human and english language and yr="1990 -Current") 7663 *ALL EBM* 1 Polycystic ovary syndrome/ 1712 2 Polycystic ovar*.mp. 4675		

3 Poly-cystic ovar*.mp. 136 4 PCO*.mp. 6256 5 (stein-leventhal or Leventhal).mp. 99 6 Anovulation/ 154 7 Anovulat*.mp. 1193 8 Oligo-ovulat*.mp. 55 9 Oligoovulat*.mp. 32 10 (ovar* adj5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*)).mp. 4868 11 or/1-10 8226 12 (Population groups or Racial groups or Black or African Americans or American Native Continental Ancestry Group or Asians or Asian Americans or Whites or "Native Hawaiian or Other Pacific Islander" or Ethnicity).tw. 21961 13 "Ethnic and Racial Minorities".tw. 43 14 Minority Groups.tw. 497 15 Arabs.tw. 41 16 Indigenous Peoples.tw. 39 17 Vulnerable Populations.tw. 646 18 Roma.tw. 180 19 (aborigin* or native* or inuit* or eskimo* or kalaallit* or amerind* or romany or romani* or gypsies or gipsies or maori* or metis* or First Nation* or Torres Strait island*).tw. 6837 20 ((afro or African or asian or latin* or Indian) adj1 American*).tw. 10767 21 (Africa* or "mixed ancestry*" or Afro* or ((Asian or Bangladeshi or Caribbean or Chinese or Hispanic or Indian or Pakistani or "South Asian" or Black) adj2 (women or people or person$1 or heritage or ancestry or population$1 or adolescen$2 or female$1 or girl$1 or individual$1 or patient$1)) or Ethnic* or Minorit* or Race or Racial).tw. 57000 22 or/12-21 70994 23 11 and 22 385 24 (prevalen* or inciden* or epidemiolog*).tw. 215613 25 11 and (22 or 24) 1311 26 limit 25 to english language 1263 27 limit 26 to yr="1990 -Current" 1177 28 limit 27 to humans 1174 *APA PsycInfo* 1 Polycystic Ovary Syndrome.mp. 425 2 Polycystic ovar*.mp. 524 3 Poly-cystic ovar*.mp. 1 4 PCO*.mp. 1119 5 (stein-leventhal or Leventhal).mp. 319 6 Anovulation.mp. 78 7 Anovulat*.mp. 161 8 Oligo-ovulat*.mp. 0 9 Oligoovulat*.mp. 0 10 (ovar* adj5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*)).mp. 543 11 or/1-10 1772 12 (Population groups or Racial groups or Black or African Americans or American Native Continental Ancestry Group or Asians or Asian Americans or Whites or "Native Hawaiian or Other Pacific Islander" or Ethnicity).tw.		

137223 13 "Ethnic and Racial Minorities".tw. 223 14 Minority Groups.tw. 6775 15 Arabs.tw. 1398 16 Indigenous Peoples.tw. 1484 17 Vulnerable Populations.tw. 3183 18 Roma.tw. 728 19 (aborigin* or native* or inuit* or eskimo* or kalaallit* or amerind* or romany or romani* or gypsies or gipsies or maori* or metis* or First Nation* or Torres Strait island*).tw. 43122 20 ((afro or African or asian or latin* or Indian) adj1 American*).tw. 66904 21 (Africa* or "mixed ancestry*" or Afro* or ((Asian or Bangladeshi or Caribbean or Chinese or Hispanic or Indian or Pakistani or "South Asian" or Black) adj2 (women or people or person$1 or heritage or ancestry or population$1 or adolescen$2 or female$1 or girl$1 or individual$1 or patient$1)) or Ethnic* or Minorit* or Race or Racial).tw. 294496 22 or/12-21 368829 23 exp epidemiology/ 94795 24 (prevalen* or inciden* or epidemiolog*).tw. 285980 25 23 or 24 322039 26 11 and 25 248 27 11 and (22 or 25) 366 28 27 366 29 limit 28 to (human and english language and yr="1990 -Current") 324		

Note: The search for prevalence and characteristics were done together. For feasibility reasons only studies reporting on prevalence were included for the guideline.

3. SEARCH RESULTS- PRISMA Flowchart



4. STUDY INCLUSION

Table 4.1. Included Studies
Region of the Americas
Asfari MM, Sarmini MT, Baidoun F, et al. Association of non-alcoholic fatty liver disease and polycystic ovarian syndrome. *BMJ Open Gastroenterology.* 2020;7(1):08. doi: 10.1136/bmjgast-2019-000352
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Evidence processing: The literature search and screening were performed in Covidence. Studies were selected by one reviewer in consultation with the evidence team/ key contacts using study selection and appraisal criteria (PICOs) established a priori. The articles were screened by title and abstract by one reviewer. When a decision could not be made based on title and abstract alone, full text was retrieved. Study appraisal was conducted by one reviewer with discussion with the evidence team to resolve any queries. **In total, we included 47 papers reporting on 45 studies. In two cases, results of a single study were reported in two papers**. We nominated the study as the unit of interest, the earliest publication as the primary source, and retained the secondary papers.

Table 4.2. Excluded Studies (on full text assessment)	
Reference	**Reason**
Aarestrup et al. 2021	Outcomes not reported according to race/ethnicity
Actkins et al. 2021	Conference abstract
Agrawal et al. 2004	Outcomes not reported according to race/ethnicity
Akarsu et al. 2019	Outcomes not reported according to race/ethnicity
Akgul et al. 2018	Outcomes not reported according to race/ethnicity
Al Khaduri et al. 2014	PCOS prevalence in related selected population
Al-Ruhaily et al. 2008	PCOS prevalence in related selected population
Alemyar et al. 2020	Outcomes not reported according to race/ethnicity
Alur-Gupta et al. 2021	PCOS prevalence in related selected population
Alvarez-Blasco et al. 2006	Outcomes not reported according to race/ethnicity
Amini et al. 2008	PCOS prevalence in related selected population
Anderson et al. 1997	Outcomes not reported according to race/ethnicity
Ansarin et al. 2007	PCOS prevalence in related selected population
Asgharnia et al. 2011	Outcomes not reported according to race/ethnicity
Attlee et al. 2014	Outcomes not reported according to race/ethnicity
Avvad et al. 2001	Outcomes not reported according to race/ethnicity
Awang et al. 2014	PCOS prevalence in unrelated selected population
Ayonrinde et al. 2016	Outcomes not reported according to race/ethnicity
Azargoon et al. 2020	Outcomes not reported according to race/ethnicity
Aziz et al. 2013	Conference abstract
Azziz et al. 2005	Narrative review/editorial/protocol
Baba et al. 2011	PCOS prevalence in unrelated selected population
Bachani et al. 2016	PCOS prevalence in related selected population
Balaji et al. 2015	PCOS prevalence in related selected population
Balen et al. 1993	PCOS prevalence in unrelated selected population
Balen et al. 2009	Narrative review/editorial/protocol
Bansal et al. 2020	Outcomes not reported according to race/ethnicity
Barday-Karbanee et al. 2006	Narrative review/editorial/protocol
Bayona et al. 2022	PCOS prevalence in related selected population
Bayona et al. 2021	Conference abstract
Beavis et al. 2021	Conference abstract
Becerra-Fernandez et al. 2014	Outcomes not reported according to race/ethnicity
Bell et al. 2018	PCOS prevalence in related selected population
Bell et al. 2021	No data on prevalence of PCOS
Betti et al. 1990	Outcomes not reported according to race/ethnicity
BhaleraoGandhi et al. 2015	PCOS prevalence in related selected population
Bhide et al. 2015	PCOS prevalence in related selected population
Bhuvanashree et al. 2013	Outcomes not reported according to race/ethnicity
Bigambo et al. 2022	PCOS prevalence in related selected population
Bin Mahmoud et al. 2014	Outcomes not reported according to race/ethnicity
Birdsall et al. 1997	Outcomes not reported according to race/ethnicity
Blumenfeld et al. 2019	Narrative review/editorial/protocol
Bodis et al. 1993	Narrative review/editorial/protocol
Bond et al. 2017	Outcomes not reported according to race/ethnicity
Bouzas et al. 2014	Outcomes not reported according to race/ethnicity
Bozdag et al. 2016	Systematic review
Brouzeng et al. 2019	PCOS prevalence in related selected population
Busiah et al. 2017	Outcomes not reported according to race/ethnicity
Carmina et al. 2007	Outcomes not reported according to race/ethnicity
Carmina et al. 1999	Outcomes not reported according to race/ethnicity
Carmina et al. 2006	Outcomes not reported according to race/ethnicity
Casadei et al. 2018	PCOS prevalence in related selected population
Casals et al. 2021	Outcomes not reported according to race/ethnicity
Castro et al. 2015	No data on prevalence of PCOS
Celik et al. 2013	Conference abstract
Chan et al. 2020	PCOS prevalence in related selected population

Chandrasekera et al. 2007	PCOS prevalence in related selected population
Chang et al. 2011	Outcomes not reported according to race/ethnicity
Chang et al. 2021	No data on prevalence of PCOS
Chanyachailert et al. 2021	PCOS prevalence in related selected population
Chen et al. 2020	PCOS prevalence in unrelated selected population
Chen et al. 2020	Conference abstract
Chen et al. 2020	No data on prevalence of PCOS
Cioana et al. 2021	PCOS prevalence in related selected population
Cipriani et al. 2015	Conference abstract
Ciresi et al. 2016	PCOS prevalence in related selected population
Clark et al. 2014	PCOS prevalence in related selected population
Clayton et al. 1992	Outcomes not reported according to race/ethnicity
Cocksedge et al. 2009	Outcomes not reported according to race/ethnicity
Codner et al. 2007	PCOS prevalence in related selected population
Codner et al. 2006	PCOS prevalence in related selected population
Cohen et al. 2012	PCOS prevalence in unrelated selected population
Cohn et al. 2014	Conference abstract
Conn et al. 2000	Outcomes not reported according to race/ethnicity
Cresswell et al. 1997	PCOS prevalence in related selected population
D'Amelio et al. 2001	PCOS prevalence in unrelated selected population
Dabadghao et al. 2013	Conference abstract
Dabadghao et al. 2012	Conference abstract
Dadgostar et al. 2009	PCOS prevalence in related selected population
Dargham et al. 2017	Conference abstract
Davies et al. 2012	Outcomes not reported according to race/ethnicity
Dayo et al. 2020	Conference abstract
De Faria et al. 1992	Outcomes not reported according to race/ethnicity
DeSutter et al. 2008	PCOS prevalence in unrelated selected population
Desai et al. 2018	Outcomes not reported according to race/ethnicity
Desai et al. 2019	Narrative review/editorial/protocol
Deshmukh et al. 2022	No data on prevalence of PCOS
Deswal et al. 2019	Systematic review
Deswal et al. 2020	Outcomes not reported according to race/ethnicity
Dewailly et al. 2011	Outcomes not reported according to race/ethnicity
Dhandapani et al. 2021	PCOS prevalence in related selected population
DiFede et al. 2010	Outcomes not reported according to race/ethnicity
Dilek et al. 2022	Outcomes not reported according to race/ethnicity
Dimitriadis et al. 2017	PCOS prevalence in related selected population
Ding et al. 2016	Outcomes not reported according to race/ethnicity
Ding et al. 2016	Outcomes not reported according to race/ethnicity
Ding et al. 2018	Outcomes not reported according to race/ethnicity
Ding et al. 2017	Systematic review
Dodson et al. 1994	Outcomes not reported according to race/ethnicity
Douglas et al. 2022	Outcomes not reported according to race/ethnicity
Dubey et al. 2021	No data on prevalence of PCOS
Edison et al. 2016	Outcomes not reported according to race/ethnicity
Eilertsen et al. 2012	PCOS prevalence in unrelated selected population
Eilertsen et al. 2012	Outcomes not reported according to race/ethnicity
Elfassy et al. 2021	Narrative review/editorial/protocol
Escobar-Morreale et al. 2001	Outcomes not reported according to race/ethnicity
Escobar-Morreale et al. 2012	Outcomes not reported according to race/ethnicity
Escobar-Morreale et al. 2000	PCOS prevalence in related selected population
Escobar-Morreale et al. 2016	PCOS prevalence in related selected population
Faria et al. 2013	Outcomes not reported according to race/ethnicity
Farnaghi et al. 2002	PCOS prevalence in related selected population
Farquhar et al. 1994	Outcomes not reported according to race/ethnicity
Feichtinger et al. 2015	PCOS prevalence in related selected population
Fernandez et al. 2021	Outcomes not reported according to race/ethnicity

Fiander et al. 1990	No data on prevalence of PCOS
Flannery et al. 2013	PCOS prevalence in related selected population
Flannery et al. 2010	Conference abstract
Fornes et al. 2022	Outcomes not reported according to race/ethnicity
Franceschi et al. 2010	PCOS prevalence in unrelated selected population
Gabrielli et al. 2015	PCOS criteria used not correct
Gadir et al. 1992	No data on prevalence of PCOS
Ganie et al. 2010	PCOS prevalence in unrelated selected population
Ganie et al. 2020	Outcomes not reported according to race/ethnicity
Garg et al. 2019	Outcomes not reported according to race/ethnicity
Gaskins et al. 2016	Conference abstract
Ghasemi et al. 2010	Outcomes not reported according to race/ethnicity
Ghiasi et al. 2019	Systematic Review
Ghidei et al. 2022	Outcomes not reported according to race/ethnicity
Gilbert et al. 2021	Systematic review
Gill et al. 2013	Outcomes not reported according to race/ethnicity
Glintborg et al. 2004	PCOS prevalence in related selected population
Glintborg et al. 2012	No data on prevalence of PCOS
Glintborg et al. 2011	No data on prevalence of PCOS
Goodarzi et al. 2005	PCOS prevalence in related selected population
Glueck et al. 2005	PCOS prevalence in unrelated selected population
Glueck et al. 2003	PCOS prevalence in unrelated selected population
Glueck et al. 2015	Outcomes not reported according to race/ethnicity
Goswami et al. 2022	PCOS prevalence in related selected population
Gottschau et al. 2015	No data on prevalence of PCOS
Gupta et al. 2017	Outcomes not reported according to race/ethnicity
Gupta et al. 2018	Outcomes not reported according to race/ethnicity
Guzick et al. 2008	Narrative review/editorial/protocol
Hammarstrand et al. 2021	Outcomes not reported according to race/ethnicity
Hashemipour et al. 2004	Outcomes not reported according to race/ethnicity
He et al. 2020	No data on prevalence of PCOS
Hickey et al. 2011	Outcomes not reported according to race/ethnicity
Ho et al. 2020	Outcomes not reported according to race/ethnicity
Holte et al. 1998	Outcomes not reported according to race/ethnicity
Holton et al. 2018	Outcomes not reported according to race/ethnicity
Hopkins et al. 2019	PCOS prevalence in unrelated selected population
Hornberger et al. 2019	Conference abstract
Horri et al. 2006	PCOS prevalence in related selected population
Hsu et al. 2007	No data on prevalence of PCOS
Hu et al. 2011	Outcomes not reported according to race/ethnicity
Huddleston et al. 2022	Narrative review/editorial/protocol
Jabeen et al. 2022	Outcomes not reported according to race/ethnicity
Jahanfar et al. 1993	Outcomes not reported according to race/ethnicity
Jahanfar et al. 2004	Outcomes not reported according to race/ethnicity
Jayaraman et al. 2009	Narrative review/editorial/protocol
Jena et al. 2021	PCOS prevalence in related selected population
Joham et al. 2021	PCOS prevalence in related selected population
Joham et al. 2016	Outcomes not reported according to race/ethnicity
Joham et al. 2014	Outcomes not reported according to race/ethnicity
Joham et al. 2015	Outcomes not reported according to race/ethnicity
Johnston et al. 2014	Conference abstract
Josepth et al. 2016	Outcomes not reported according to race/ethnicity
Joseph et al. 2022	Outcomes not reported according to race/ethnicity
Joshi et al. 2014	Outcomes not reported according to race/ethnicity
Joy et al. 2008	Outcomes not reported according to race/ethnicity
Kakkad et al. 2021	PCOS prevalence in related selected population
Kaltsas et al. 2000	Outcomes not reported according to race/ethnicity
KantaGoswami et al. 2016	PCOS prevalence in related selected population

Kao et al. 2015	Conference abstract
Karakas et al. 2018	Conference abstract
Karavani et al. 2021	Outcomes not reported according to race/ethnicity
Karjula et al. 2022	Outcomes not reported according to race/ethnicity
Karmarkar et al. 2015	PCOS prevalence in unrelated selected population
Kakoly et al. 2017	Outcomes not reported according to race/ethnicity
Kataoka et al. 2019	Outcomes not reported according to race/ethnicity
Kc et al. 2020	Outcomes not reported according to race/ethnicity
Khademi et al. 2010	Outcomes not reported according to race/ethnicity
Kiconco et al. 2020	Outcomes not reported according to race/ethnicity
Kim et al. 2020	Conference abstract
Kim et al. 2016	PCOS prevalence in unrelated selected population
Kirthika et al. 2019	Outcomes not reported according to race/ethnicity
Koivunen et al. 1999	No data on prevalence of PCOS
Koric et al. 2021	PCOS prevalence in related selected population
Kostroun et al. 2020	PCOS prevalence in related selected population
Kristensen et al. 2010	Outcomes not reported according to race/ethnicity
Kudesia et al. 2017	PCOS prevalence in related selected population
Kudesia et al. 2013	No full text available
Kuijper et al. 2009	Outcomes not reported according to race/ethnicity
Kukreja et al. 2013	Conference abstract
Kusum et al. 2020	No data on prevalence of PCOS
Laddad et al. 2019	Outcomes not reported according to race/ethnicity
Lakshmi et al. 2015	PCOS prevalence in related selected population
Lambert-Messerlian et al. 2011	No data on prevalence of PCOS
Lauritsen et al. 2014	Outcomes not reported according to race/ethnicity
Lee et al. 2021	PCOS prevalence in related selected population
Lee et al. 2019	Conference abstract
Lee et al. 2018	PCOS prevalence in related selected population
Liang et al. 2017	PCOS prevalence in related selected population
Liang et al. 2010	Narrative review/editorial/protocol
Liao et al. 2019	No data on prevalence of PCOS
Lidegaard et al. 2016	Conference abstract
LieFong et al. 2017	No data on prevalence of PCOS
Lin et al. 2019	Outcomes not reported according to race/ethnicity
Lindholm et al. 2008	Outcomes not reported according to race/ethnicity
Liu et al. 2021	Outcomes not reported according to race/ethnicity
Lo et al. 2006	Outcomes not reported according to race/ethnicity
Lowe et al. 2005	Outcomes not reported according to race/ethnicity
Ma et al. 2010	Outcomes not reported according to race/ethnicity
Mahajan et al. 2021	PCOS prevalence in related selected population
Mahalingaiah et al. 2021	Outcomes not reported according to race/ethnicity
Mahdi et al. 2015	PCOS prevalence in related selected population
Malone et al. 2011	Conference abstract
Mandeville et al. 2021	PCOS prevalence in related selected population
Mani et al. 2015	No data on prevalence of PCOS
March et al. 2010	Outcomes not reported according to race/ethnicity
Margolin et al. 2005	Outcomes not reported according to race/ethnicity
Maya et al. 2022	PCOS prevalence in related selected population
Mayrhofer et al. 2020	Outcomes not reported according to race/ethnicity
McAvey et al. 2013	Conference abstract
Meifong et al. 2014	No data on prevalence of PCOS
Melo et al. 2010	Outcomes not reported according to race/ethnicity
Memon et al. 2020	PCOS prevalence in related selected population
Merlino et al. 2003	Outcomes not reported according to race/ethnicity
Merz et al. 2016	Outcomes not reported according to race/ethnicity
Meun et al. 2015	Outcomes not reported according to race/ethnicity
Miazgowski et al. 2021	Outcomes not reported according to race/ethnicity

Michelmore et al. 1999	Outcomes not reported according to race/ethnicity
Milczarek et al. 2019	Outcomes not reported according to race/ethnicity
Mirzaei et al. 2008	PCOS prevalence in related selected population
Miyoshi et al. 2013	PCOS prevalence in related selected population
Morgan et al. 2008	Outcomes not reported according to race/ethnicity
Moro et al. 2013	PCOS prevalence in unrelated selected population
Morrell et al. 2005	PCOS prevalence in unrelated selected population
Motlagh Asghari et al. 2022	Outcomes not reported according to race/ethnicity
Mu et al. 2019	PCOS prevalence in related selected population
Mueller et al. 2008	Outcomes not reported according to race/ethnicity
Mumusoglu et al. 2020	Narrative review/editorial/protocol
Natsuki et al. 2021	Conference abstract
Nayak et al. 2020	Outcomes not reported according to race/ethnicity
Neubronner et al. 2021	PCOS prevalence in related selected population
Nohr et al. 2022	Outcomes not reported according to race/ethnicity
Noorbala et al. 2010	PCOS prevalence in related selected population
O'Donovan et al. 2002	PCOS prevalence in unrelated selected population
O'Driscoll et al. 1994	Outcomes not reported according to race/ethnicity
Ogueh et al. 2014	PCOS prevalence in related selected population
Okoroh et al. 2012	Outcomes not reported according to race/ethnicity
Orio et al. 2016	Narrative review/editorial/protocol
Ortega et al. 2017	Conference abstract
Pache et al. 1993	Outcomes not reported according to race/ethnicity
Palomba et al. 2016	Narrative review/editorial/protocol
Pan et al. 2022	Outcomes not reported according to race/ethnicity
Pan et al. 2020	Outcomes not reported according to race/ethnicity
Parlak et al. 2016	PCOS prevalence in related selected population
Patel et al. 2022	PCOS prevalence in related selected population
Paviani et al. 2022	Outcomes not reported according to race/ethnicity
Pinola et al. 2014	Single population - no ethnicity details
Polotsky et al. 2011	Conference abstract
Purohit et al. 2015	Conference abstract
Rafferty et al. 2021	Conference abstract
Rahmanpour et al. 2009	Article not in English
Rajkumari et al. 2016	Outcomes not reported according to race/ethnicity
Ranasinghe et al. 2016	Conference abstract
Rashidi et al. 2014	Outcomes not reported according to race/ethnicity
Rasool et al. 2019	No full text available
Reinauer et al. 2017	PCOS prevalence in related selected population
Riestenberg et al. 2022	Outcomes not reported according to race/ethnicity
Rifkin et al. 2014	Conference abstract
Ring et al. 2021	Conference abstract
Rios et al. 2021	PCOS prevalence in unrelated selected population
Robinson et al. 2020	PCOS prevalence in related selected population
Robinson et al. 2021	Conference abstract
Rodin et al. 1998	No data on prevalence of PCOS
Roe et al. 2013	PCOS prevalence in related selected population
Roepke et al. 2010	Outcomes not reported according to race/ethnicity
Roos et al. 2011	Outcomes not reported according to race/ethnicity
Rudick et al. 2011	Conference abstract
Saei Ghare Naz et al. 2019	Outcomes not reported according to race/ethnicity
Safier et al. 2016	Outcomes not reported according to race/ethnicity
Safiri et al. 2022	Outcomes not reported according to race/ethnicity
Sahmay et al. 2014	Outcomes not reported according to race/ethnicity
Sahota et al. 2008	PCOS prevalence in unrelated selected population
Sahu et al. 2018	No full text available
Sanad et al. 2014	PCOS prevalence in related selected population
Sanchon et al. 2012	Outcomes not reported according to race/ethnicity

Sarkar et al. 2020	PCOS prevalence in related selected population
Sayehmiri et al. 2014	Systematic Review
Schildkraut et al. 1996	PCOS prevalence in unrelated selected population
Schoenaker et al. 2018	Outcomes not reported according to race/ethnicity
Seshadri et al. 1994	PCOS prevalence in related selected population
Sharif et al. 2013	Conference abstract
Sharma et al. 2021	Systematic review
Sharma et al. 2008	PCOS prevalence in related selected population
Shin et al. 2020	PCOS prevalence in related selected population
Siam et al. 2014	PCOS prevalence in related selected population
Singh et al. 2018	Outcomes not reported according to race/ethnicity
Sirdah et al. 2013	PCOS prevalence in related selected population
Sirmans et al. 2014	Outcomes not reported according to race/ethnicity
Sivayoganathan et al. 2011	Outcomes not reported according to race/ethnicity
Skiba et al. 2021	Outcomes not reported according to race/ethnicity
Skiba et al. 2018	Systematic review
Smith et al. 2011	Outcomes not reported according to race/ethnicity
Smith et al. 2010	PCOS prevalence in unrelated selected population
Sokumbi et al. 2022	Outcomes not reported according to race/ethnicity
Stachenfeld et al. 2009	Narrative review/editorial/protocol
Stahlman et al. 2017	PCOS prevalence in unrelated selected population
Sumida et al. 2022	Conference abstract
Suresh et al. 2020	Outcomes not reported according to race/ethnicity
Szydlarska et al. 2012	No data on prevalence of PCOS
Takahashi et al. 1991	PCOS prevalence in related selected population
Tamilselvi et al. 2019	Outcomes not reported according to race/ethnicity
Tannus et al. 2018	Outcomes not reported according to race/ethnicity
Taponen et al. 2004	Outcomes not reported according to race/ethnicity
Tay et al. 2020	Outcomes not reported according to race/ethnicity
Teede et al. 2013	Outcomes not reported according to race/ethnicity
Tehrani et al. 2011	Outcomes not reported according to race/ethnicity
Thong et al. 2020	Outcomes not reported according to race/ethnicity
Timpatanapong et al. 1997	PCOS prevalence in related selected population
Tok et al. 2004	PCOS prevalence in related selected population
Torres et al. 2016	Conference abstract
Tyrmi et al. 2022	Outcomes not reported according to race/ethnicity
Ugwu et al. 2013	PCOS prevalence in related selected population
Valkenburg et al. 2011	PCOS prevalence in related selected population
van Drunick et al. 2022	Outcomes not reported according to race/ethnicity
Varanasi et al. 2018	Outcomes not reported according to race/ethnicity
Vassilatou et al. 2015	PCOS prevalence in related selected population
Vijayan et al. 2013	No full text available
Villarroel et al. 2015	Outcomes not reported according to race/ethnicity
Vural Solak et al. 2022	PCOS prevalence in related selected population
Vutyavanich et al. 2007	PCOS prevalence in related selected population
Wang et al. 2010	Conference abstract
Wang et al. 2019	PCOS prevalence in related selected population
Wang et al. 2018	Outcomes not reported according to race/ethnicity
Wen et al. 2021	No data on prevalence of PCOS
West et al. 2014	Outcomes not reported according to race/ethnicity
West et al. 2015	Systematic Review
West et al. 2014	Conference abstract
Wijeyaratne et al. 2007	PCOS prevalence in related selected population
Wijeyaratne et al. 2002	Narrative review/editorial/protocol
Willenberg et al. 2008	PCOS prevalence in related selected population
Williamson et al. 2001	PCOS prevalence in related selected population
Willis et al. 2020	Outcomes not reported according to race/ethnicity
Wolf et al. 2018	Narrative review/editorial/protocol

Wu et al. 2021	Systematic Review
Xu et al. 2022	PCOS prevalence in related selected population
Yang et al. 2010	PCOS prevalence in related selected population
Ybarra et al. 2018	Outcomes not reported according to race/ethnicity
Ye et al. 2019	Conference abstract
Yildiz et al. 2008	Outcomes not reported according to race/ethnicity
Yin et al. 2019	No data on prevalence of PCOS
Zahid et al. 2022	PCOS prevalence in related selected population
Zandi et al. 2010	PCOS prevalence in related selected population
Zhao et al. 2011	No data on prevalence of PCOS
Zhao et al. 2010	No data on prevalence of PCOS
Zreik et al. 2014	PCOS prevalence in related selected population

5. STUDY CHARACTERISTICS TABLE FOR INCLUDED STUDIES

Author, year, country	Population/ Setting	Sample size (age range)	Study Design	N per group	PCO diagnostic criteria	MD/Oligo-anovulation/ID	Hyperandrogenism	Hyperandrogenemia	PCO	Ethnicity definition	Management of hormonal use	Summary of findings	RoB
Region of the Americas													
Asfari 2020, USA	50 785 354 female hospital stays, adult women with PCOS (≥18 years old) identified using the International Classification of Diseases Ninth Version (ICD-9)	50785 354 (≥18 years old)	Cross-sectional	Total: 50785354 White:34185 819 Black:73720 82 Hispanic:605 0192 Asian or Pacific islander:132 2045 Native American: 305176 Other: 1525882	International Classification of Diseases Ninth Version (ICD-9), using the code 256.4	NA	NA	NA	NA	White, Black, Hispanic, Asian or Pacific Islander, Native American, Other Not clear how this was measured	Included in the study but not the analysis	- Our nationwide cohort evaluated a total of 50785354 female hospital stays, of whom 77415 (0.15%) had PCOS - Using multivariate logistic regression, patients with PCOS had significantly higher rate of NAFLD (OR 4.30, 95%CI 4.11 to 4.50, p<0.001).	Moderate
Azziz, 2004	50 785 354 female hospital stays, adult women with PCOS (≥18 years old) identified	347 (18–45)	Cross-sectional	Total: 347 White: 166 Black: 223	NIH	≤8 Menstrual cycles/yr or cycle <26 or >35 d or a d 22–24 (midluteal) P4 level of less than 4 ng/ml	Hirsutism (mF–G ≥ 6), acne	T, A4 and/or DHEAS > 95th percentile of 98 healthy women	NA	Black White Not reported how this was measured	Included in the study but not the analysis	- the estimated prevalence of PCOS was 6.6%. - Eighteen (8.0%) of the 223 Black women studied	Moderate

	using the International Classification of Diseases Ninth Version (ICD-9)					in subjects with cycles 26–35d						and eight (4.8%) of the 166 White women studied were classified as having PCOS, a difference that was not statistically significant (2 1.61; P 0.05)	
Christensen, 2013	Subset (adolescent girls aged 15 through to 19 years) of the population-based cohort study Kaiser Permanente Southern California (KPSC) Children's Health Study from 2007-2009. Total of 144,426 women identified.	137,502 (15-19)	Cross-sectional	Non-Hispanic White: 36,089 Black: 11,435 Hispanic white: 62,126 Asian/Pacific Islander: 7,800 Other/Multiple races: 2,601 Unknown: 17,451	NIH	Chronic oligoanovulation identified by ICD-9 codes for amenorrhoea (ICD-9 code 626.0), oligomenorrhoea (ICD-9 code 626.1), irregular menstrual cycles (ICD-9 code 626.4)	Diagnosis of hirustism (ICD-9 code 704.1), other ovarian hyperfunction (ICD-9 code 256.1), or laboratory evidence of elevated testosterone	Diagnosis of hirustism (ICD-9 code 704.1), other ovarian hyperfunction (ICD-9 code 256.1), or laboratory evidence of elevated T	NA	Based on the health plan administrative records and birth certificate information,	Included in the study but not the analysis	- Prevalence of a confirmed diagnosis of PCOS was 0.56%, which increased to 1.14% when undiagnosed cases with documented symptoms qualifying for PCOS according to NIH criteria were included.	Moderate
Gabrielli, 2012	859 women of 18–45 years of age screened for cervical	859 (18-45)	Cross-sectional	Total: 859 Black: 760 Other: 99	NIH/Rotterdam	History of oligoamenorrhoea (≥35 days); AUB (bleeding >10	Hirsutism (F–G ≥ 6) or acne or alopecia	Total T > 95th percentile of normal women evaluated in the	>12 Follicles measuring 2–9mm in diameter	Black/other. Ethnicity according to the ethnic	Excluded	The present results showed a prevalence of PCOS of 8.5% (95%CI: 6.80 - 10.56) in	Low

	cancer in the primary healthcare network of the city of Salvador, Brazil					at intervals <25 days)		study.	and/or follicles with a volume >10 cm3	classifications of the Brazilian Institute of Geography and Statistics		accordance with the Rotterdam criteria in users of the primary public healthcare service in the city of Salvador. When this finding was compared with the prevalence obtained using the NIH criteria (8.03%; 95%CI: 6.39 - 10.05), no statistically significant difference was found, as shown by the overlapping confidence intervals.	
Greenwood, 2019	1127 black and white women participating in Coronary Artery Risk Development in Young Adults study.	1127 (20-32)	Cohort study	Total: 1127 Black: 597 White: 530	NIH	Self report on questionnaire: Women indicating regular or irregular cycles ≥32 to 45 days apart	Hirsutism, as indicated by self-report (Women reporting unwanted body hair growth in androgen-sensitive regions) were considered to meet evidence	baseline serum androgens > 75th percentile, corresponding to total T >53 ng/dL and/or FT >0.38 ng/dL	NA	Black/white Not reported	Included with no adjustment	Eighty-three of 1127 (7.4%) met NIH criteria for PCOS. Of these women, 33 women (40%) were black and 50 women (60%) were white.	Low

							for clinical hyperandrogenism)						
Guo, 2021	19,258 Chinese, 23,213 Filipina, and 19,108 South Asian women aged 21–44 years who had ≥1 clinical encounter in 2016 with measured (nongestational) weight and height data for calculation of BMI.	19,258 Chinese, 23,213 Filipina, and 19,108 South Asian (21–44)	Cross-sectional	19,258 Chinese 23,213 Filipina 19,108 South Asian	having ≥2 ambulatory diagnoses of PCOS (ICD-9 256.4, ICD-10 E28.2)	NA	NA	NA	NA	Chinese, Filipina, South Asian Self-identified race/ethnicity was derived from electronic health record and survey data, including primary language in a subset, and assignment by ethnic surname was used for Asian women without specified ethnicity	Included with no adjustment	These findings indicate that risk profiles for PCOS and diabetes differ among younger Chinese, Filipina, and South Asian women. In our clinical population, the risk of PCOS was higher for South Asian than Chinese (and Filipina) women.	Moderate
He, 2020	1247 female participants who participated in the Bogalusa	1247 (26-57)	Prospective cohort study	1247 white: 730 black: 517	Women were defined as having PCOS if they self-reported that they had ever been told by a doctor or they reported two	menstrual cycle of ≥35 days, <25 days, or totally variable	Hirsutism, as indicated as determined by a series questions asking about	NA	NA	Race (white/black) was recorded at the	Included	The prevalence of PCOS was 7.4% in CDAH (the average of CDAH-1 and CDAH-2) and	Moderate

	Heart Study when they were aged 26–40 years, and had height and weight reported between ages 26 and 40 years to align with their report of their menstrual cycle characteristics prior to age 40 years				symptoms of PCOS. The symptoms were menstrual cycle ≥35 days or totally variable and hirsutism.		the tendency to grow dark, coarse hair on eight body sites including upper lip, chin, breast, chest between the breasts, back, belly, upper arms and upper thighs. Those who indicated three or more sites were considered as having clinical hirsutism.			initial BHS visit		8.0% (white: 10.7%; black: 4.3%) in BBS. Overall, in both cohorts, childhood obesity but not abdominal obesity was associated with greater risks of menstrual irregularity. A significant racial difference was observed in the associations of childhood obesity and abdominal obesity with PCOS, with significant associations found in white participants, but not in black participants.	
Khil, 2022	244,642 adolescent females (ages 13-17) with well-child visits during 2012-2018 in a Northern California	244,642 (13-17)	Retrospective cohort study	Total 244,642 Non-Hispanic White: 86,620 Black: 24,143	International Classification of Diseases, 9th/10th Revision, ICD-9 256.4 or ICD-10 E28.2	amenorrhea (ICD-9 626.0, ICD-10 N91.0-N91.2), or oligomenorrhea (ICD-9 626.1, ICD-10 N91.3-N91.5	ICD-9 704.1, ICD-10 L68.0	NA	NA	Race/ethnicity was classified using self-reported data from health record or administrat	Not reported	The overall prevalence of PCOS was 0.7% and increased substantially with weight. Among those with obesity, PCOS	High

	healthcare system			Hisplanic/Latina: 73,281 Asian/Pacific Islander: 45,631 Other/unknown: 14,967						ive databases		prevalence was 4.2, 2.9, 2.4, 2.1% in Asian/Pacific Islander (PI), Hispanic/Latina, Non-Hispanic White, Black adolescents and 7.8, 6.7, 5.7, 3.4% in South Asian, Chinese, Filipina, Native Hawaiian/PI adolescents, respectively. Compared to White adolescents, Asian/PIs had two-fold higher risk of PCOS, and Hispanic/Latinas had 1.3-fold higher risk. Compared to Chinese adolescents, South Asians had 1.7-fold higher risk, while Native Ha- waiian/PIs had half the risk.	

Knochenhauer, 1998	Prospective university female employees attending pre-employment physical exam, regardless of hormonal therapy.	277 (18–45)	Cross-sectional	Total: 277 White: 129 Black: 148	NIH	≤8 Menstrual cycles/yr	Hirsutism (mF–G ≥ 6) or acne	T, A4 and/or DHEAS > 95th percentile of the women studied	NA	White and Black. (Measurement not reported)	Included in the study but not in the analysis (prevalence imputed)	Of the 277 women consenting to a history and hormonal evaluation, 4.0% had PCOS as defined, 4.7% (6 of 129) of Whites and 3.4% (5 of 148) of Blacks.	Moderate
Meyer, 2018	1427 women age 24 to 44 years from the Hispanic CommunityHealth Study/Study of Latinos	1427 (24-44)	Cross-sectional	Hispanic/Latina: 1427 716 Mexica 183 Central American 151 Puerto Rican 132 Dominican 107 Cuban 73 South American 65 other/mixed)	Self-reported (Interviewer-administered questionnaires asking about prior self-reported PCOS diagnosis)	NA	NA	NA	NA	Hispanic/Latina Self-identified	Included with no adjustment	Overall, 18.2% women had menstrual cycles greater than 35 days or irregular, 14% reported OC use toregulate periods or acne, 6% self-reported PCOS, and 30% had any PCOS sign.	Moderate
Moran, 2018	150 female Mexican volunteers, 20–45 years of age, whose parents and grandparents were of Mexican origin. All of	150 (20-45)	Cross-sectional	Mexican: 150	NIH	Cycles >35 days or <26 days, or if there was amenorrhoea	Hirsutism (mF–G ≥ 8) with or without acne	Androgen levels > + 1.96 SD in participants without PCOS	12 Or more follicles in each ovary measuring <10 mm	Mexican: whose parents and grandparents were of Mexican origin	Included in the study but not in the analysis	The present study prospectively assesses the prevalence of PCOS in Mexican women according to the currently available criteria. It	Moderate

	them were employees of an Obstetrics and Gynecology Hospital of the IMSS											shows a prevalence of nine PCOS cases among 150 Mexican women, representing 6.0% (95% CI: 1.9–10.1), according to NIH criteria. However, by ESHRE/ASRM (Rotterdam) criteria, taking into account ovarian morphology, the prevalence is 10 of 150 women, approximately 6.6% (95% CI: 2.3–10.9%).	
Morrison, 2011	370 women of the prospective cohort study, the National Heart, Lung, and Blood Institute Growth and Health Study (NGHS), which recruited schoolgirls starting at	370 (19-25)	Prospective cohort study	Total 370 White: 150 Black: 174 46 ethnicity not specified	Rotterdam (oligomenorrhoea + biochemical hyperandrogenism)	Cycle length ≥42 days	NA	DHEAS > 280 µg/ dL, race-specific bottom decile sex hormone binding globulin (SHBG) (≤6 nmol/L for black, ≤7 nmol/L for white), or race-specific top decile FT (≥2.13 pg/mL	NA	White and Black Self-declared as black or white and lived in racially concordant households	Not reported	this is the first prospective study to report an independent association of adolescent oligomenorrhea with young adult IFG + T2DM and with insulin and glucose levels and IR. In the current study, IFG + T2DM	Moderate

	age 9 or 10. This study was a 15 year follow up.							for black and white)				during ages 19 to 24 were most common (38%) in girls having at least 3 oligomenorrhea reports during ages 14 to 19 and were also higher in girls having 2 (11%) or 1 (6%) oligomenorrhea reports than in those without oligomenorrhea (3%).	
Wang, 2011	1,127 white women and black women in the Coronary Artery Risk Development In young Adults (CARDIA) cohort.	1127 (20-32)	Prospective cohort (CARDIA study)	African American: 596 White: 531	NIH	Self report on questionnaire: regular or irregular menstrual cycles 34 days or more	Hirsutism: Women who reported unwanted hair growth, excluding the lower leg and underarm	76 ng/dL or more of total T or 0.69 ng/dL or more of fT based on the 95th percentile for the non oligomenorrheic, nonhirsute women	NA	African American and white Self-reported:	Excluded	Of 1,127 women, 53 (4.7%) met criteria for PCOS at ages 20–32 years. Polycystic ovary syndrome was associated with a twofold higher odds of incident diabetes (23.1% compared with 13.1%, adjusted odds ratio [AOR] 2.4, confidence interval [CI] 1.2–4.9) and	Moderate

												dyslipidemia (41.9% compared with 27.7%, AOR 1.9, CI 1.0 – 3.6) over the course of 18 years; the association with incident hyperten- sion was not significant (26.9% compared with 26.3%, AOR 1.7, CI 0.8 – 3.3).	
South-East Asian Region													
Deswal, 2014	325 women (18-24 years of age) from multiple localities of Rohtak district.	325 (18-24)	Cross-sectional	North Indian: 325	Rotterdam	<8 cycles annually or no ycle for more than 6 months	Hirsutism, measurement tool not specified	Laboratory assessment, not specified	10 or more 2–9 mm follicles in at least one ovary	Indian (definition or measurement not reported)	Unclear	The prevalence of PCOS was found to be 6.8%	High
Kaewnin, 2018	548 universitye female participants aged 17-19 years from Mahidol University in Bankok	548 (17-19)	Cross-sectional	Thai: 548	Rotterdam	absence of menstruation for 45 days or more and/or ≤8 cycles per year.	FG score >6 , moderate-to-severe acne based on the Global Acne Grading System (GAGS), or androgenic alopecia.	testosterone >63 ng/dL (2.8 nmol/L)	presence of >12 cysts measuring 2–9mm in diameter and/or ovarian volume >10 cm3	Thai (definition or measurement not reported)	Included with no adjustment	The prevalence of PCOS in the present study was 5.29% (29 out of 548 participants). phenotype A – OA, HA, and PCOM (12 participants; 41.38%), phenotype B – OA and HA	High

												(one participant; 3.44%), phenotype C – HA and PCOM (eight participants; 27.59%), and phenotype D – OA and PCOM (eight participants; 27.59%).	
Kumarapeli, 2008	A community-based cross-sectional study among women aged 15–39 years who were permanent residents of the district of Gampaha, Sri Lanka. Four of 13 divisional secretariat areas were randomly selected.	2 915 (15–39	Cross-sectional	Sri Lankan: 2915	Rotterdam	Absence of menstruation for ≥35 days	Hirsutism (F–G ≥ 8) with or without acne and/or alopecia	T 2 SD above the mean of normal women	Ovarian volume >10 cm3 and/or 12 or more 2–9 mm follicles	Sri Lankan (definition or measurement not reported)	Excluded	Thus, the community prevalence of PCOS was 6.3 percent (95 percent confidence interval: 5.9, 6.8).	Low
Nidhi, 2011	adolescent girls between 15 to 18 years from a College in Anantapur,	460 (15-18)	Cross-sectional	Indian: 460	Rotterdam	absence of menstruation for 45 days or more and/or ≤8 menses per year.	Hirsutism (mF–G ≥ 6) with or without acne and/or alopecia	T > 82 ng/dl in the absence of other causes of hyperandrogenism.	10 or more 2-8 mm follicles, and/or ovarian volume	Indian (definition or measurement not reported)	Included with no adjustment	In summary, out of the 460 girls screened, 42 girls satisfied Rotterdam criteria of	Moderate

	Andhra Pradesh, India.								>10 cm3, and an echo-densestroma in pelvic ultrasound scan.			PCOS. Thus, the prevalence of PCOS was 9.13% in this population.	
Vidya Barathi, 2017	502 young women (between 18 and 24 years) from Chennai and collectively 566 girls from Thiruvallur and Dindugal districts	1068 (18-24)	Cross-sectional	Indian: 1068	Rotterdam (self-administered questionnaire)	Unclear	Unclear	Unclear	NA	Indian (definition or measurement not reported)	Not reported	In our study, we have established the prevalence rate of PCOS in India to be around 6% (Z test score – 5.92, 95% Confidence Interval (95%CI); p < 0.05)	High
European Region													
Assens, 2020	Girls part of the Copenhagen Mother-Child Cohort, a population-based longitudinal birth cohort of healthy Danish children born between 1997 and 2002	317 (12-18)	population-based longitudinal birth cohort	Danish: 317	Rotterdam	electronic questionnaire reported cycle >35 days/21 to 35 days/"too irregular to tell" in combination with 1 to 3 bleedings in the pats 6 months.	Not systematically assessed	girls with the 10% highest concentrations of either testosterone, free testosterone, SHBG, or androstenedione in the study population.	at least 1 ovary with 12 or more follicles of 2 to 7.9 mm.	both parents and grandparents of the unborn child were born and raised in Denmark	Included with no adjustment	Twenty girls (6.3%) had oligomenorrhea and differed significantly in serum androgens and AMH, age at and time since menarche from girls with regular cycles. Twenty-seven girls were classified with PCOS (8.5%) and had	High

												significantly higher 17-OH-progesterone, estradiol, AMH, LH, and age at menarche than the reference group	
Asuncion, 2000	Caucasian female blood donors reporting to the Department of Hematology of the Hospital Ramo´n y Cajal	154 (18–45)	Cross-sectional	Caucasian: 154	NIH	>6 Cycles/yr with a length of more than 35 days and/or no bleeding for 3 consecutive months	Hirsutism (mF–G ≥ 8) and/or Acne and/or Androgenic alopecia	T, DHEAS and/or FAI > 95th percentile for the women studied	NA	Caucasian Definition or measurement not reported	Included with no adjustment	Using strict NIH/NICHHD criteria, we found a 6.5% prevalence of PCOS in Caucasian women from Madrid, Spain.	Moderate
Diamanti-Kandarakis, 1999	192 women of reproductive age who lived on the Greek island of Lesbos and accepted our invitation of free medical examination, no reference was made to the specific disorders being studied.	192 (17–45)	Cross-sectional	Greek: 192	NIH	<8 Cycles/yr	Hirsutism (mF–G ≥ 8) , Acne	FT > 95th percentile in the women without PCOS in the study	NA	Greek Definition: women who lived on the Greek island of Lesbos.	No participants with hormonal use	the prevalence of PCOS in the population under study was 6.77% (13 of 192)	Moderate

Gambineri, 2013	Italian females aged 16-19 years	394 (16-19)	Cross-sectional	Italian: 394	NIH	> 6 cycles with a length of > 35 days per year or the lack of menstrual bleeding for 3 consecutive months, respectively	Hirsutism (mF–G ≥ 8) or androgenic alopecia	a circulating total T level > 97.5th centile of t he reference interval	NA	Italian (definition or measurement not reported)	Excluded	we found that the prevalence rates were approximately 10% for isolated menstrual irregularity; 17% for isolated clinical hyperandrogenism (mainly represented by hirsutism); 7% for hyperandrogenemia, isolated, or combined with clinical hyperandrogenism; and 4% for PCOS.	High
Mumm, 2013	523,757 female children born of Danish mothers in Denmark between 1973 and 1991 were included	523,757	Register study	Danish: 523757	ICD codes	NA	NA	NA	NA	Born in Denmark by Danish mothers	Included with no adjustment	In the present study we found a significantly increased risk of PCOS in adult life in women with birth weights R4,500 g, which represented the 98.5th percentile of birth weights during the study period. Increased birth	Moderate

												weight as a risk factor for PCOS is supported by two previous studies. A total of 3,204 PCOS events occurred during follow-up	
Valgeirsdottir, 2019	All singleton, live-born girls between 1 January 1982 and 31 December 1995 who reached at least 15 years of age were included in the study population."	681123 (15-28)	National registry-based cohort study	Total: 681123 Nordic: 62.6661 Non-Nordic: 50.334 Missing: 4128	ICD codes	NA	NA	NA	NA	Nordic and Non-Nordic (based on maternal country of birth)	Included with no adjustment	In the final cohort of 681 123 girls, 3738 (0.54%) had been diagnosed with PCOS.	Moderate
Yildiz, 2012	Turkish female staff in a government-based institute, between the ages of 18-45 years	392 (18-45)	Cross-sectional	Turkish: 392	NIH/Rotterdam/AE-PCOS	Menstrual cycles ≥35 or ≤ 23 days	Hirsutism (mF–G ≥ 6)	Any androgen exceeding 95th percentile of healthy women	Antral follicle count of ≥12 in 2–9mm diameter and/or ovarian volume of ≥10 cm3 in a single ovary	Turkish (definition or measurement not reported)	Included with no adjustment	We report here the prevalence of PCOS according to NIH, Rotterdam and AE-PCOS Society criteria as 6.1, 19.9 and 15.3%, respectively, among a relatively large Caucasian population.	Low

Eastern Mediterranean Region													
Dargham, 2017&2018	3,017 Qatari subjects volunteered to be phenotyped and genotyped for the Qatar Biobank from which all women between the ages of 18±40 years were identified (750).	750 (18-40)	Cross-sectional	Qatari: 720	NIH	Oligomenorrhea or amenorrhea - not defined	NA	FAI >4.5 or T > 2.7nmol/l	NA	Qatari nationals and long-term residents (>15 years residence) (Measurement not reported)	Not reported	97 of 720 women fulfilled the NIH guidelines (12.1%) for PCOS specifically using a free androgen index greater than 4.5 ((testosterone/ SHBG) x 100), or an elevated isolated total testosterone greater than 2.7nmol/l and menstrual irregularity.	Moderate
Esmaeilzadeh, 2014	1549 girl high school students aged 16–20 years who were in the 10th–12th grades of high school in the urban area of Babol City, Iran.	1549 (16-20)	Cross-sectional	Iranian: 1549	Rotterdam (with the presence of all three criteria)	Menstrual cycles ≥35 or <8 Cycles/yr	Hirsutism (mF–G ≥ 8), acne (standardized criteria)	Elevated FT	peripheral follicles and volume < 10 mL	Irani Definition or measurement not specified"	Not reported	The overall prevalence of PCOS among adolescence was 8.3%, which was determined by the presence of all three criteria.	Moderate
Farhadi-Azar, 2022	a total of 1,960 eligible women, aged (18–45 years) were	1960 (18-45)	Cross-sectional	Iranian: 1960	NIH/Rotterdam/AE-PCOS	cycles ≥34 days or <8 Cycles/yr	Hirsutism (mF–G ≥ 8), acne (standardized criteria) or	Any androgen exceeding 95th percentile of healthy women in study population	Antral follicle count of ≥12 in 2–9mm diameter	Iranian Definition or measurement not specified"	Hormonal assessment not performed among women	The prevalence of PCOS according to the diagnostic criteria	Low

	recruited from the Tehran-Lipid and Glucose-Study participants						androgenic alopecia.		and/or ovarian volume of ≥10 cm3 in a single ovary		with hormonal use	of NIH, Rotterdam and AE-PCOS Society were 13.6% (267/ 1,960), 19.4% (380/1,960), and 17.8 (349/1,960), respectively.	
Mehrabian , 2011	Females aged 17-34 referred to the mandatory pre-marriage screening clinic affiliated to Isfahan University of Medical Sciences.	820 (17-34)	Cross-sectional	Iranian: 820	NIH/Rotterdam/AE-PCOS	chronic amenorrhea or menstrual cycles ≤ 21 or ≥35 days, or more than four days variation between cycles.	self-reported degree of hirsutism using mF-G. Clinical hirsutism was defined by an mF-G score ≥ 8, unclear if assessed by clinican.	A testosterone level higher than 0.75 ng/dl considered to be high	Antral follicle count of ≥12 in 2–9mm diameter and/or ovarian volume of ≥10 cm3 in a single ovary	Iranian Definition or measurement not specified"	Included with no adjustment	The estimated prevalence of PCOS was 7% based on the NIH criteria, 15.2% under the Rotterdam criteria, and 7.92% according to the AES criteria.	High
Musmar, 2013	137 female students (18-24 years) attending An-Najah National University in Nablus city in the north of West Bank/Palestine, Recruited using advertisement by posters	137 (18-24)	Cross-sectional	Palestinian: 137	NIH	<8 Cycles/yr and/or absence of menses for 6 months or more	Hirsutism (mF–G ≥ 8)	Elevated FT	NA	Palestinian Definition or measurement not specified	Excluded	The prevalence of PCOS at An-Najah National University in age groups 18–24 years was found to be 7.3%.	Moderate

	and student electronic boards targeting all female university students.												
Pramodh, 2020	493 Female Emirati students taking undergraduate and graduate courses at Zayed University, Dubai campus in the age group of 18–25 years	493 (18-25)	Cross-sectional	Emirati: 493	Self report	Students who answered the question, "Have you been diagnosed with PCOS by a Physician?" in affirmative	NA	NA	NA	Emirati (defined as local Emirati women, not reported how this was measured)	Not reported	Of the students, 13% self-reported being diagnosed with PCOS, with 3.5% also taking medication for the same, 6% reported having high androgen levels, 30.7% reported polymenorrhea, and 3.5% reported oligomenorrhea for frequency of menstrual cycle. Also, 12.4% students experienced abnormal bleeding (heavy/none) during menstruation and 24% reported excessive body hair.	Moderate

Salehpour, 2010	15-18 years old girls from a number of high schools in Tehran	1430 (15-18)	Cross-sectional	Iranian: 1430	Rotterdam	Menstrual irregularity, not further specified	Hirsutism (mF–G ≥ 8)	Elevated FT	Antral follicle count of ≥12 in 2–9mm diameter and/or ovarian volume of ≥10 cm3 in a single ovary	Irani Definition or measurement not specified	Excluded	Thus, the frequency of the syndrome in this age group was 3.42%.	Moderate
Sharif, 2017	120 female Qatari students between the ages of 18 and 30 years	120 (18-30)	Cross-sectional	Qatari: 120	NIH.	≤8 Menstrual cycles/yr, or>35 days in length and/or the presence of chronic amenorrhea.	hirsutism, alopecia, acne, and/or [mFG] ≥17 as published among women of the same ethnic background in Arab Gulf States	FT above the normal level of .0.663 nmol/L,	NA	Qatari Definition or measurement not specified	Excluded	The frequency of PCOS in this study was 18.33% according to the NIH criteria.	High
Tehrani, 2011	A total of 1126 women, aged 18-45 years, were recruited from among reproductive aged women living in urban areas of four randomly selected provinces of	929 (18–45)	Cross-sectional	Iranian: 929	NIH/Rotterdam/AE-PCOS	≤8 Menstrual cycles/yr, or >35 days in length and/or the presence of chronic amenorrhea.	Hirsutism (mF–G ≥ 8) or acne or androgenic alopecia	FAI, DHEAS or A4 >95th percentile of 362 women in the study without PCOS	>12 Follicles in each ovary, 2–9 mm in diameter and/or increased ovarian volume (10 cm3)	Iranian Definition or measurement not specified	Included in the study but not the analysis	The prevalence of PCOS was 7.1% (95% CI: 5.4 -8.8%) using the NIH definition, 11.7% (95% CI: 9.5- 13.7%) by AES criteria and 14.6% (95% CI: 12.3-16.9%) using the Rott. criteria in our sample	Low

	different geographic regions i.e. Ghazvin (Central), Kermanshah (East), Golestan (North) and Hormozgan (South).											of an Iranian population.	
Western Pacific Region													
Boyle, 2012	Indigenous women, aged 15–44 years, living in a defined area in and around Darwin, Northern Territory, Australia,	248 (15-44)	Cross-sectional	Australian Indigenous: 248	NIH	≤8 Menstrual cycles/yr, or menstrual cycle <26 days or >35 days in length	Not used as a diagnostic criterion because it was only assessed by self-report (questionnaire)	FTI > 95th percentile for a group of women known to be free of PCOS whose samples were assessed on the same machine with the same assay	NA	Australian Indigenous Not reported how this was defined or assessed	Excluded	Using the NIH 1990 criteria for diagnosis, PCOS was present in around one in six (15.3%) urban Indigenous women volunteering for our study in Darwin.	Moderate
Chen, 2008	915 Han Chinese women of reproductive age, who lived in Guangzhou in Southern-China. All participants were undergoing their annual routine	915 (20-45)	Cross-sectional	Chinese: 915 (20-45)	Rotterdam/AE-PCOS	≤8 Menstrual cycles/yr, or menstrual cycle <26 days or >35 days in length	Hirsutism (mF–G ≥ 6) or acne or alopecia	T, A4 and DHEAS > 95th percentile of the women studied	US performed – no criteria provided	Han Chinese Not reported how this was defined or measured	Incuded with no adjustment	In this study of an unselected sample of 915 women of reproductive age, the estimated prevalence of PCOS was 2.2% (20/915) based on AES 2006 criteria for PCOS. If we identify the	Moderate

	physical examination and were not presenting for a medical reason or complaint.											potential phenotype of women solely with oligo-ovulation and polycystic ovaries, and not those with hyperandrogenemia or hirsutism, the prevalence of PCOS was 2.4% (22/915) based on Rotterdam 2003 criteria.	
Dashti, 2019	675 females of reproductive age working at University Putra Malaysia, Selangor, Malaysia	675 (18-49)	Cross-sectional	Malaysian (675)	Rotterdam	lack of menstruation for at least 35 days or 3-6 consecutive menstrual cycles, or ≤ 4 menstrual periods per year	mF-G score of ≥ 6 with or without acne, and/or androgenic alopecia	hyperandrogenism including serum androstenedione of 10.8 nmol/l or total testosterone of 2.81 nmol/l.	>12 Follicles in each ovary, 2–9 mm in diameter and/or increased ovarian volume (10 cm3)	Malaysian (definition or measurement not reported)	Excluded	A total of 675 females with the mean age of 26.01±7.14 years participated in this study. The prevalence rate of PCOS was obtained as 12.6%. All PCOS subjects were detected with hyperandrogenism and polycystic ovary, while anovulation was present in only one	Moderate

												participant (1.2%).	
Davis, 2002	38 Indigenous Australian women	38 (>18)	Cross-sectional	Australian Indigenous: 38	NIH	irregular cycles with cycle length > 35 days	Hirsutism: limited to facial scoring derived from the F–G scoring system	Elevated FAI	NA	Indigenous Australian (not reported how this was assessed)	Not reported	Taken together with the physical characteristics, these findings are suggestive of possible PCOS in at least ten of the 38 premenopausal women evaluated (26%).	High
Li, 2013	15 924 Han Chinese women, aged 19-45 recruited from the top 10 provinces and municipalities in China (multi layered, stratified sample)	15 924 (19-45)	Cross-sectional	Han Chinese: 15924	Rotterdam	<8 Cycles/yr or cycle >35 days. Absence of 3–6 consecutive cycles	Hirsutism (mF–G > 6) with or without acne and/or alopecia	>95th percentile was calculated for the hormonal values in the population to determine the upper-normal limits.	≥12 Follicles in either ovary, measuring 2–9 mm and/or ovarian volume of each ovary >10 ml	Han Chinese Not clear how this was measured or defined.	Not reported	In this large epidemiological study, the incidence of women with PCOS in the Chinese Han population is 5.6% (894/15 924), according to the Rotterdam PCOS criteria.	Low
Jiao, 2014	Han women of reproductive age in Liaoning Province in Northeastern China	1600 (19-45)	Cross-sectional	Han Chinese: 1600	Rotterdam	Cycles last >35 days.	Hirsutism (F–G ≥ 6), acne, seborrhoeic, alopecia	Not reported	The number of 2–9 mm follicles were recorded	Han Chinese Not clear how this was measured or defined.	Excluded	The prevalence of PCOS in this study population was 8.25%, with an infertility rate of 27.8%.	Moderate

Kim, 2022	544619 Korean women in the population-based National Health Information Databases from 2010 to 2019	54461 9 (15-49)	Cross-sectional	Korean: 544619	Korean Informative Classification of Disease, 10th revision (KICD-10)	NA	NA	NA	NA	Korean citizens, not clear how this was defined or measured	Included with no adjustme nt	In summary, this is the first study to investigate the prevalence of PCOS in a nationwide population of reproductive-aged Korean women. The age-adjusted incidence and prevalence of PCOS in Korean women aged 19–49 years were 2.8% and 4.3%, respectively	Moder ate
Min, 2022	328 female university students from July 25 to August 30, 2020. Data collected using an oline survey.	328 (18-25)	Cross-sectional	Korean: 328	Self report: Online survey, asking if had been diagnosed with PCOS by a doctor	NA	NA	NA	NA	South Korean, not clear how this was defined or measured	Not reported	The average age of participants was 21.67 years, 7.3% of whom had been diagnosed with PCOS. Perceived disability (b=0.30, P<0.001) and perceived benefit (b=0.26, P<0.001) of health behavior were associated with	High

												preventive behavior intentions. However, knowledge was not a significant factor.	
Maredia, 2018	Samoan women 25–39 years of age (n=470) from a larger population-based genome-wide association study (GWAS) of adiposity and cardiometabolic disease	470 (25-39)	Cross-sectional	Samoan: 470	NIH	Amenorrhea: no cycle in the last 12 months. Oligomenorrhea: menstrual period "3–6 months ago," "6–9 months ago," or "9–12 months ago"	NA	FAI > 95th percentile of the lowest BMI tertile, FAI > 8.5	AMH levels > 5.6 ng/mL as a surrogate marker for ultrasound	Samoan women	excluding women using contraceptive injections	PCOS was estimated to be 6.8% (95% CI: 4.5, 9.1), with PCO + HA being the most common sub-group, but the OM/AM + HA and OM/AM + HA + PCO sub-groups had the greatest degree of metabolic abnormality.	Moderate
Park, 2021	462 undergraduate and graduate students at K University	462 (18-29)	Cross-sectional	Korean: 462	NIH	< 10 cycles per year	NA	Elevated T or FAI	NA	Korean women Not clear how this was defined or measured	Excluded	24 women of 88 participants had T ≥ 0.520 ng/mL or FAI ≥ 5.36. Generalizing this result to the entire population (462), the prevalence of PCOS was estimated to be 5.2% based on the PCOS	Moderate

												criteria for this study.	
Yang, 2022, China	12,815 married women aged 20-49 years from 15 provinces from mainland China were selected as part of the China Fertility Survey of Married Women (CFSMW) 2020 survey The results were compared to results of a similar study done in 2010 involving 15,924 Han Chinese women aged 19-45 years from 10 provinces and municipalities in China.	12815 (20-49)	Cross-sectional	Chinese: 12,815	Rotterdam	Oligo/amenorrhoea defined as irregular cycles of duration ≥35 days	mF-G score >4 [or ≥2 in the lower abdomen, thighs, and upper lip] with/without acne and/or androgenic alopecia	Total testosterone level >2.91 nmol/L or an androstenedione level of >10.8 nmol/L	12 or more follicles measuring 2-9mm in diameter	Chinese women Not clear how this was defined or measured	Not reported	- 826 participants could be diagnosed as having PCOS, with a weight prevalence of 7.8% (95% CI: 7.0%, 9.0%) among women aged 20-49 years, leading to an estimate of 24.0 million women of reproductive age affected by this condition in China as a whole.	Low
Zhuang, 2014, China	- Female residents of Chengdu,	1645 (12-44)	Cross-sectional	Chinese: 1,645	NIH/Rotterdam/AES(Androgen Excess Society)-2006	Cycles ≥35 days and no	Ferriman-Gallway hirsutism	FT 2 SD above the mean level	≥12 Follicles 2–9mm	Chinese women	Excluded	- The prevalence of PCOS in	Low

	China aged 12-44 - Residents of two buildings, students of two units of a women's dormitory in two local universities, and all the female students in one class of each grade (from junior one to senior three) in three middle schools were recruited					cycle for 3 months	score ≥ 6, with or without acne	in normal controls	diameter and/or ovarian volume ≥10 ml one or both ovaries	Not clear how this was defined or measured		women aged 12-44 was 7.1, 11.2 and 7.4% respectively, according to the three different criteria (NIH, Rotterdam, Androgen Excess). - After the onset of puberty, the prevalence of PCOS increased rapidly from 12-14 years of age, peaked between 15 and 24 and decreased gradually thereafter and reached its lowest point before menopause	
Author, year, country	Population/ Setting	Sample size (age range)	Study Design	N per group	PCO diagnostic criteria	MD/Oligo-anovulation/ID	Hyperandrogenism	Hyperandrogenemia	PCO	Ethnicity definition	Management of hormonal use	Summary of findings	RoB

4. FINDINGS

Outcomes Included:

- **Outcome 1: Prevalence of PCOS among adult women from different ethnicities using NIH, Rotterdam, AE-PCOS and Self report diagnostic criteria**
- **Outcome 2: Prevalence of PCOS among adult women from different ethnicities using NIH criteria**
- **Outcome 3: Prevalence of PCOS among adult women from different ethnicities using Rotterdam criteria.**
- **Outcome 4: Prevalence of PCOS among adolescent women from different ethnicities using NIH and Rotterdam criteria**

OUTCOME 1. Prevalence of PCOS among adult women from different ethnicities using NIH, Rotterdam, AE-PCOS and Self report diagnostic criteria

- **EVIDENCE SUMMARY:**

In total, 38 cross-sectional and cohort studies studied the prevalence of PCOS among adult women from different ethnicities. Ethnicities included Black or African American and American (Wang, 2011, Azziz, 2004, Knochenhauer, 1998, Morrison, 2011, He, 2020), European (Asuncion, 2000 Diamanti-Kandarakis, 1999), South/North East Asian (Park, 2021; Li, 2013; Chen, 2008; Jiao, 2014; Dashti, 2019; Yang, 2022; Zhuang, 2014; Min, 2022), Australian Indigenous (Boyle, 2012; Davis, 2002), Polynesian (Maredia, 2018), North African and Middle Eastern (Sharif, 2017, Dargham, 2017&2018; Tehrani, 2011; Mehrabian, 2011; Farhadi-Azar, 2022; Yildiz, 2012; Pramodh, 2020; Musmar, 2013), Southern and Central Asian (Kumarapeli, 2008; Deswal, 2014; Vidya Barathi, 2017), South American (Gabrielli, 2012), Central American (Moran, 2010) and Hispanic North American (Meyer, 2018).

Studies using ICD codes to diagnose PCOS (Asfari, 2020; Mumm, 2013; Valgeirsdottir, 2019) and studies reporting on cumulative incidence or age adjusted prevalence rates (Valgeirsdottir, 2019; Kim, 2022) were excluded from the meta-analysis

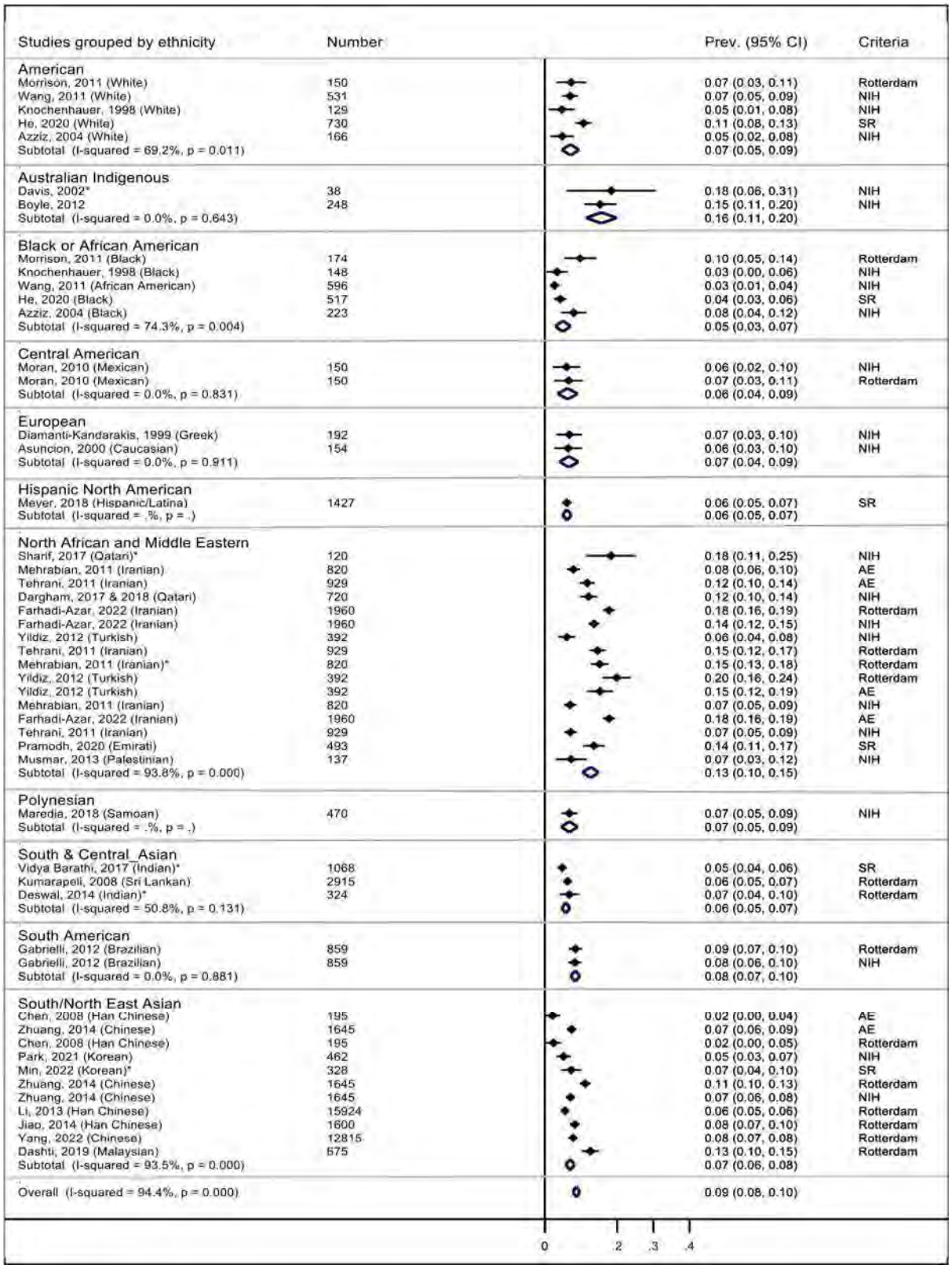
- **META-ANALYSIS/DESCRIPTIVE ANALYSIS SUMMARY**

Pooled prevalence among all adult women (95% CI) was 0.09 (0.08, 0.10) (n=38 studies).When studies reported their prevalence according to several criteria (Chen, 2008; Zhuang, 2014; Yildiz, 2012; Farhadi-Azar, 2022; Mehrabian, 2011; Tehrani, 2011; Gabrielli, 2012; Moran, 2010), each of their result were included in the analysis.

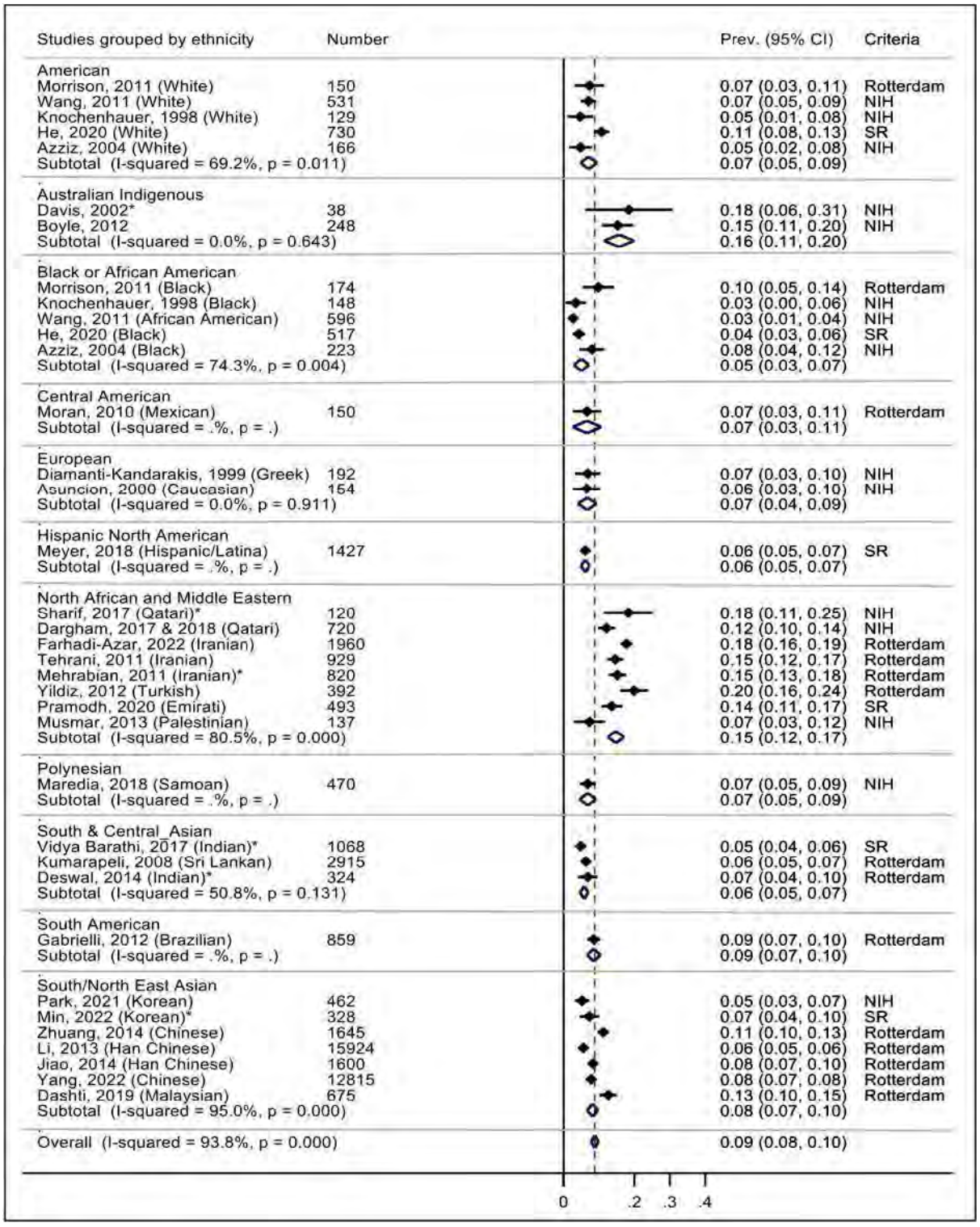
A sensitivity analysis was generated by estimating the prevalence in the presence of only one criteria (e.g. when a result was reported according to NIH, Rotterdam, AE-PCOS, only Rotterdam was selected). If we exclude these results, the prevalence stays the same.

Outcome per subgroup	Studies	N	Effect Estimate; % (95% CI), Random	Certainty
PCOS prevalence – American	5	1706	0.07 (0.05, 0.9)	⊕⊕◯◯ LOW
PCOS prevalence – Australian Indigenous	2	286	0.16 (0.11, 0.20)	⊕⊕◯◯ LOW
PCOS prevalence – Black or African American	5	1658	0.05 (0.03, 0.07)	⊕⊕◯◯ LOW
PCOS prevalence – Central American	1	150	0.06 (0.04, 0.09)	⊕⊕◯◯ LOW
PCOS prevalence - European	2	346	0.07 (0.04, 0.09)	⊕⊕⊕◯ MODERATE
PCOS prevalence – Hispanic North American	1	1427	0.06 (0.05, 0.09)	⊕⊕◯◯ LOW
PCOS prevalence – North African and Middle Eastern	8	5571	0.13 (0.10, 0.15)	⊕◯◯◯ VERY LOW
PCOS prevalence - Polynesian	1	470	0.07 (0.05, 0.09)	⊕⊕◯◯ LOW
PCOS prevalence – Southern & Central Asian	3	4307	0.06 (0.05, 0.07)	⊕⊕◯◯ LOW
PCOS prevalence – South American	1	859	0.08 (0.07, 0.10)	⊕⊕◯◯ LOW
PCOS prevalence – South/North East Asian	8	33644	0.07 (0.06, 0.08)	⊕◯◯◯ VERY LOW

Prevalence grouped by ethnicity



Prevalence grouped by ethnicity (sensitivity analysis)



OUTCOME 1.1. Prevalence among American women

1.1.1. Forest plot of all included studies regarding prevalence among American women

Pooled prevalence among American adult women (95% CI) was 0.07 (0.05, 0.09) (N=6 studies).

1.1.2 Individual Study Data Table

OUTCOME: PCOS prevalence American women			**OUTCOME TYPE: Dichotomous**						
COMPARISON (if applicable): N/A									
Author, year	**Unit of outcome**	**Adjusted or crude?**	**If adjusted, what variables included in the model?**	**N events**	**N total**	**Prevalence NIH**	**Prevalence Rotterdam**	**Prevalence AE-PCOS**	**Prevalence Self report**
Azziz, 2004	Prevalence (%)	Crude	N/A	White: 8	White: 166	White: 8/166 (4.8%)	-	-	-
He, 2020	Prevalence (%)	Crude	N/A	White: 78	white: 730	-	-	-	White: 78/730 (10.7%)
Knochenhauer, 1998	Prevalence (%)	Crude	N/A	White: 6	White: 129	White: 6/129 (4.7%)	-	-	-
Morrison, 2011	Prevalence (%)	Crude	N/A	White: 11	White: 150	-	White: 11/150 (7.3%)	-	-
Wang, 2011	Prevalence (%)	Crude	N/A	White: 37	White: 531	White: 37/531 (7.0%)	--		--

OUTCOME 1.2. Prevalence among Australian Indigenous women

Pooled prevalence among Australian Indigenous adult women (95% CI) was 0.16 (0.11, 0.20) (n=2 studies)

1.2.1. Forest plot of all included studies regarding prevalence among Australian Indigenous women women

1.2.2 Individual Study Data Table

OUTCOME: PCOS prevalence Australian Indigenous women			OUTCOME TYPE: Dichotomous						
COMPARISON (if applicable): N/A									
Author, year	**Unit of outcome**	**Adjusted or crude?**	**If adjusted, what variables included in the model?**	**N events**	**N total**	**Prevalence NIH**	**Prevalence Rotterdam**	**Prevalence AE-PCOS**	**Prevalence Self report**
Davis, 2002	Prevalence (%)	Crude	N/A	7	38	7/38 (18.4%)	-	-	-
Boyle, 2012	Prevalence (%)	Crude	N/A	38	248	Australian Indigenous: 38/248 (15.3%)		-	-

OUTCOME 1.3. Prevalence among Black or African American women

Pooled prevalence among Black or African American adult women (95% CI) was 0.05 (0.03, 0.07). (N=5 studies)

1.3.1. Forest plot of all included studies regarding prevalence among Black or African American women

1.3.2 Individual Study Data Table

OUTCOME: PCOS prevalence American women			OUTCOME TYPE: Dichotomous						
COMPARISON (if applicable): N/A									
Author, year	**Unit of outcome**	**Adjusted or crude?**	**If adjusted, what variables included in the model?**	**N events**	**N total**	**Prevalence NIH**	**Prevalence Rotterdam**	**Prevalence AE-PCOS**	**Prevalence Self report**
Azziz, 2004	Prevalence (%)	Crude	N/A	Black: 18	Black: 223	Black: 18/223 (8.0%	-	-	-

He, 2020	Prevalence (%)	Crude	N/A	Black: 22	Black: 517	-	-	-	Black: 22/517 (4.3%)
Knochenhauer, 1998	Prevalence (%)	Crude	N/A	Black: 5	Black: 148	Black: 5/148 (3.4%)	-	-	-
Morrison, 2011	Prevalence (%)	Crude	N/A	Black: 17	Black: 174	-	Black: 17/174 (9.8%)	-	-
Wang, 2011	Prevalence (%)	Crude	N/A	African American: 16	African American: 596	African American: 16/596 (2.7%)	--	-	-

OUTCOME 1.4. Prevalence among Central American Women

Prevalence among Central American adult women (95% CI) was 0.06 (0.04, 0.09) (N=1 study)

1.4.1. Forest plot of all included studies regarding prevalence among Central American women

1.4.2 Individual Study Data Table

OUTCOME: PCOS prevalence Central American women			**OUTCOME TYPE: Dichotomous**						
COMPARISON (if applicable): N/A									
Author, year	**Unit of outcome**	**Adjusted or crude?**	**If adjusted, what variables included in the model?**	**N events**	**N total**	**Prevalence NIH**	**Prevalence Rotterdam**	**Prevalence AE-PCOS**	**Prevalence Self report**
Moran, 2010	Prevalence (%)	Crude	N/A	Mexican: 9 (NIH), 10 (Rotterdam	Mexican: 150	Mexican: 9/150 (6.0%),	Mexican: 10/150 (6.6%)	-	-

OUTCOME 1.5. Prevalence among European women

Prevalence among European adult women (95% CI) was 0.07 (0.04, 0.09) (N= 2 studies)

1.5.1. Forest plot of all included studies regarding prevalence among European women

1.5.2 Individual Study Data Table

OUTCOME: PCOS prevalence European women			OUTCOME TYPE: Dichotomous						
COMPARISON (if applicable): N/A									
Author, year	**Unit of outcome**	**Adjusted or crude?**	**If adjusted, what variables included in the model?**	**N events**	**N total**	**Prevalence NIH**	**Prevalence Rotterdam**	**Prevalence AE-PCOS**	**Prevalence Self report**
Diamanti-Kandarakis, 1999	Prevalence (%)	Crude	N/A	13	192	Greek: 13/192 (6.77%)	-	-	-
Asuncion, 2000	Prevalence (%)	Crude	N/A	10	154	Caucasian: 10/154 (6.49%)	-	-	-

Outcome 1.6. Prevalence among Hispanic North American women

Prevalence among Hispanic North American women (95% CI) was 0.06 (0.05, 0.07) (N=1 study)

1.6.1. Forest plot of all included studies regarding prevalence among Hispanic North American women

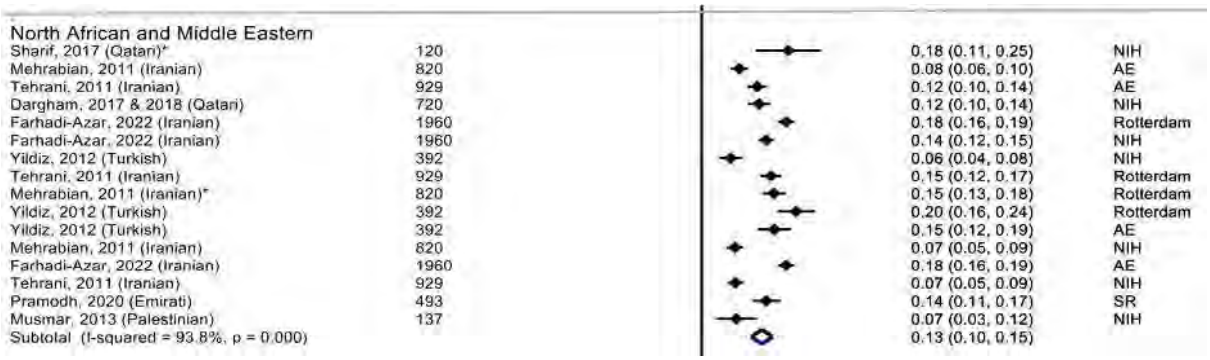
1.6.2 Individual Study Data Table

OUTCOME: PCOS prevalence Hispanic North American women			OUTCOME TYPE: Dichotomous						
COMPARISON (if applicable): N/A									
Author, year	**Unit of outcome**	**Adjusted or crude?**	**If adjusted, what variables included in the model?**	**N events**	**N total**	**Prevalence NIH**	**Prevalence Rotterdam**	**Prevalence AE-PCOS**	**Prevalence Self report**
Meyer, 2018	Prevalence (%)	Crude	N/A	Hispanic/Latina: 87	Hispanic/Latina: 1427	-		-	Hispanic/Latina: 87/1427 (6.1%)

Outcome 1.7. Prevalence among North African and Middle Eastern women

Prevalence among North African and Middle Eastern women 95% (CI) was 0.13 (0.10, 0.15) (n=8 studies)

1.7.1. Forest plot of all included studies regarding prevalence among North African and Middle Eastern women



1.7.2 Individual Study Data Table

OUTCOME: PCOS prevalence North African and Middle Eastern women			**OUTCOME TYPE: Dichotomous**						
COMPARISON (if applicable): N/A									
Author, year	**Unit of outcome**	**Adjusted or crude?**	**If adjusted, what variables included in the model?**	**N events**	**N total**	**Prevalence NIH**	**Prevalence Rotterdam**	**Prevalence AE-PCOS**	**Prevalence Self report**
Sharif, 2017	Prevalence (%)	Crude	N/A	Qatari: 22	Qatari: 120	Qatari: 22/120 (18.33%)	-	-	-
Mehrabian, 2011	Prevalence (%)	Crude	N/A	Iranian: 57.77 (NIH), 124.67 (Rotterdam), 67.70 (AE-PCOS)	Iranian: 820	Iranian: 57.77/820 (7%)	Iranian: 124.67/820 (15.2%)	Iranian: 67.70/820 (7.92%)	-
Tehrani, 2011	Prevalence (%)	Crude	N/A	Iranian: 66 (NIH), 136 (Rotterdam), 109 (AE-PCOS)	Iranian: 929	Iranian: 66/929 (7.1%)	Iranian: 136/929 (14.6%)	Iranian: 109/929 (11.7%)	-
Dargham, 2017 & 2018	Prevalence (%)	Crude	N/A	Qatari: 97	Qatari: 720	Qatari: 97/720 (12.1%)	-	-	-

Farhadi-Azar, 2022	Prevalence (%)	Crude	N/A	Iranian: 267 (NIH), 380 (Rotterdam), 349 (AE-PCOS)	Iranian: 1960	Iranian: 267/1960 (13.6%)	Iranian: 380/1960 (19.4%)	Iranian: 349/1960 (17.8%)	-
Yildiz, 2012	Prevalence (%)	Crude	N/A	Turkish: 24 (NIH), 78 (Rotterdam), 60 (AE-PCOS)	Turkish: 292	Turkish: 24/392 (6.1%)	Turkish: 78/392 (19.9%)	Turkish: 78/392 (19.9%)	-
Musmar, 2013	Prevalence (%)	Crude	N/A	Palestinian: 10	Palestinian: 137	Palestinian: 10/137 (7.3%)	-	-	-
Pramodh, 2020	Prevalence (%)	Crude	N/A	Emirati: 67	Emirati: 493	-	-	-	Emirati: 67/493 (13.6%)

Outcome 1.8. Prevalence among Polynesian women

Prevalence among Polynesian women (95% CI) was 0.07 (0.05, 0.09) (N=1 study)

1.8.1. Forest plot of all included studies regarding prevalence among Polynesian women

1.8.2 Individual Study Data Table

OUTCOME: PCOS prevalence Polynesian women			**OUTCOME TYPE: Dichotomous**						
COMPARISON (if applicable): N/A									
Author, year	**Unit of outcome**	**Adjusted or crude?**	**If adjusted, what variables included in the model?**	**N events**	**N total**	**Prevalence NIH**	**Prevalence Rotterdam**	**Prevalence AE-PCOS**	**Prevalence Self report**
Maredia, 2018	Prevalence (%)	Crude	N/A	Samoan: 32	Samoan: 470	Samoan: 32/470 (6.8%)	-	-	-

Outcome 1.9. Prevalence among Southern & Central Asian women

Prevalence among Southern and Central Asian women (95% CI) was 0.06 (0.05, 0.07) (N=3 studies)

1.9.1. Forest plot of all included studies regarding prevalence among Southern & Central Asian women

1.9.2 Individual Study Data Table

OUTCOME: PCOS prevalence Southern & Central Asian women			OUTCOME TYPE: Dichotomous						
COMPARISON (if applicable): N/A									
Author, year	**Unit of outcome**	**Adjusted or crude?**	**If adjusted, what variables were in the model?**	**N events**	**N total**	**Prevalence NIH**	**Prevalence Rotterdam**	**Prevalence AE-PCOS**	**Prevalence Self report**
Vidya Barathi, 2017	Prevalence (%)	Crude	N/A	Indian: 51	Indian: 1068	-	-	-	Indian: 51/1068 (4.8%)
Kumarapeli, 2008	Prevalence (%)	Crude	N/A	Sri Lankan: 183	Sri Lankan: 2915	-	Sri Lankan: 183/2915 (6.3%)	-	-
Deswal, 2014	Prevalence (%)	Crude	N/A	Indian: 22	Indian: 324	-	Indian: 22/324 (6.8%)	-	-

Outcome 1.10. Prevalence among South American women

Prevalence among South American women (95% CI) was 0.07 (0.06, 0.10) (N=1 study)

1.10.1. Forest plot of all included studies regarding prevalence among South American women

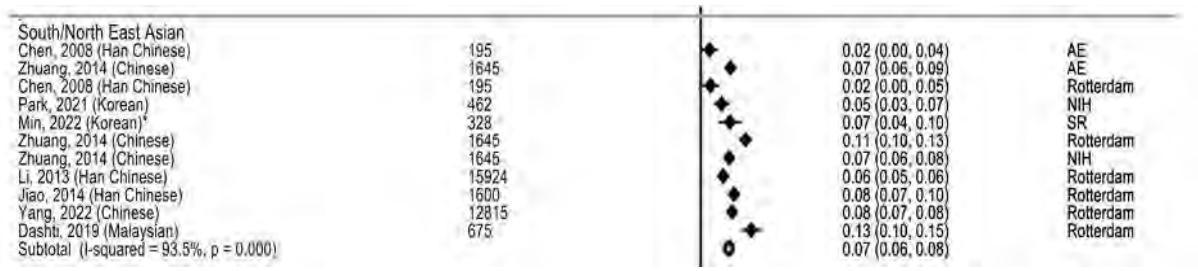
1.10.2 Individual Study Data Table

OUTCOME: PCOS prevalence South American women			OUTCOME TYPE: Dichotomous						
COMPARISON (if applicable): N/A									
Author, year	**Unit of outcome**	**Adjusted or crude?**	**If adjusted, what variables included in the model?**	**N events**	**N total**	**Prevalence NIH**	**Prevalence Rotterdam**	**Prevalence AE-PCOS**	**Prevalence Self report**
Gabrielli, 2012	Prevalence (%)	Crude	N/A	69 (NIH), 73 (Rotterdam	859	69/859 (8.03%)	73/859 (8.5%)	-	-

Outcome 1.11. Prevalence among South/North East Asian women

Prevalence among South/North East Asian women (95% CI) was 0.07 (0.06, 0.08) (N=8 studies)

1.12.1. Forest plot of all included studies regarding prevalence among American women



1.11.2 Individual Study Data Table

OUTCOME: PCOS prevalence South/North East Asian			**OUTCOME TYPE: Dichotomous**						
COMPARISON (if applicable): N/A									
Author, year	**Unit of outcome**	**Adjusted or crude ?**	**If adjusted, what variables were in the model?**	**N events**	**N total**	**Prevalence NIH**	**Prevalence Rotterdam**	**Prevalence AE-PCOS**	**Prevalence Self report**
Chen, 2008	Prevalence (%)	Crude	N/A	Han Chinese: 22 (Rotterdam), 20 (AE-PCOS)	Han Chinese: 915	-	Han Chinese: 22/195 (2.4%)	Han Chinese: 20/195 (2.2%)	-
Zhuang, 2014	Prevalence (%)	Crude	N/A	Chinese: 116 (NIH), 184(Rotterdam), 122(AE-PCOS)	Chinese: 1,645	Chinese: 116/1,645 (7.1%)	Chinese: 184/1,645 (11.2%)	Chinese: 122/1,645 (7.4%)	-
Park, 2021	Prevalence (%)	Crude	N/A	Korean: 24	Korean: 462	Korean: 24/462 (5.2%)	-	-	-
Min, 2022	Prevalence (%)	Crude	N/A	Korean: 24	Korean: 328	-	-	-	Korean: 24/328 (7.3%)
Li, 2013	Prevalence (%)	Crude	N/A	Han Chinese: 894	Han Chinese: 15 924	-	Han Chinese: 894/15 924 (5.6%)	-	-
Jiao, 2014	Prevalence (%)	Crude	N/A	Han Chinese: 132	Han Chinese: 1600	-	Han chinese: 132/1600 (8.25%)	-	-

Yang, 2022	Prevalence (%)	Crude	N/A	Chinese: 826	Chinese: 12,815	-	Chinese: 826/12,815 (7.8%)	-	-
Dashti, 2019	Prevalence (%)	Crude	N/A	Malaysian:85	Malaysian: 675	-	Malaysian: 85/675 (12.6%)	-	-

OUTCOME 2. Prevalence of PCOS among adult women from different ethnicities using NIH diagnostic criteria

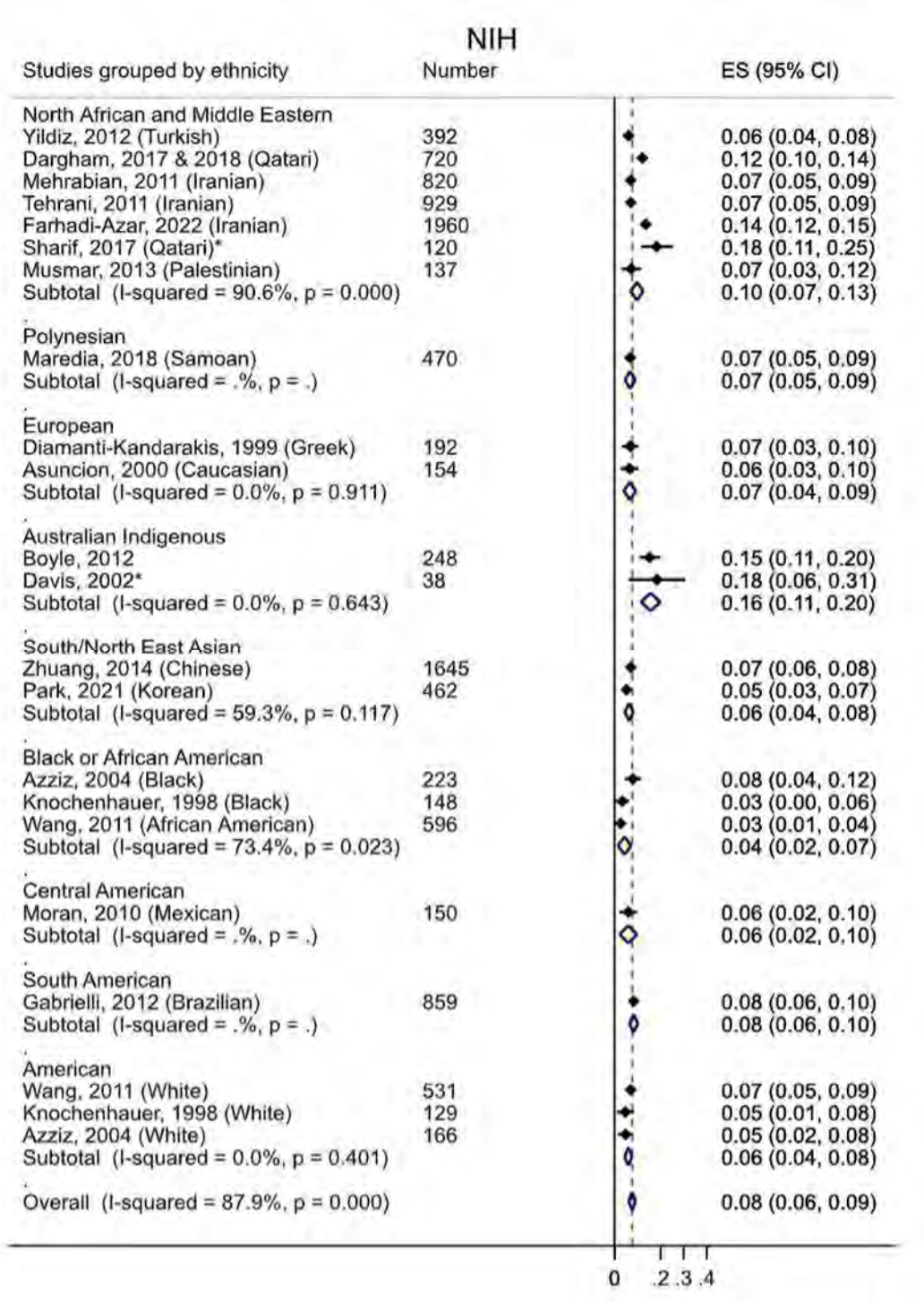
- **EVIDENCE SUMMARY:**

We identified 19 cross-sectional and cohort studies which studied prevalence of PCOS among adult women from different ethnicities using NIH criteria. Ethnicities included Black or African American and American (Wang, 2011, Azziz, 2004, Knochenhauer, 1998, He, 2020), European (Asuncion, 2000 Diamanti-Kandarakis, 1999), South/North East Asian (Park, 2021; Zhuang, 2014), Australian Indigenous (Boyle, 2012; Davis, 2002), Polynesian (Maredia, 2018), North African and Middle Eastern (Sharif, 2017, Dargham, 2017&2018; Tehrani, 2011; Mehrabian, 2011; Farhadi-Azar, 2022; Yildiz, 2012; Musmar, 2013), South American (Gabrielli, 2012) and Central American (Moran, 2010).

- **META-ANALYSIS/DESCRIPTIVE ANALYSIS SUMMARY**

Pooled prevalence among all adult women using NIH criteria (95% CI) was 0.08 (0.06, 0.09) (n=19 studies).

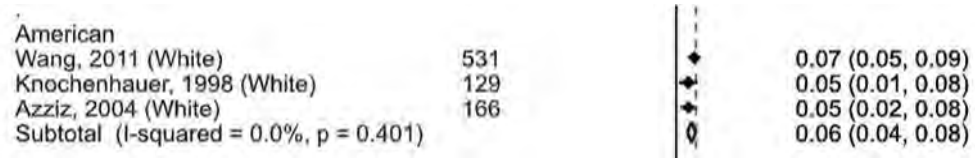
Outcome per subgroup	Studies	N	Effect Estimate; % (95% CI), Random	Certainty
PCOS prevalence – American	3	826	0.06 (0.04, 0.08)	⊕⊕◯◯ LOW
PCOS prevalence – Australian Indigenous	2	286	0.16 (0.11, 0.20)	⊕⊕◯◯ LOW
PCOS prevalence – Black or African American	3	967	0.05 (0.02, 0.07)	⊕◯◯◯ VERY LOW
PCOS prevalence – Central American	1	150	0.06 (0.04, 0.09)	⊕⊕◯◯ LOW
PCOS prevalence - European	2	346	0.05 (0.04, 0.07)	⊕⊕⊕◯ MODERATE
PCOS prevalence – North African and Middle Eastern	7	5078	0.10 (0.07, 0.13)	⊕◯◯◯ VERY LOW
PCOS prevalence – South American	1	859	0.07 (0.05, 0.09)	⊕⊕⊕◯ MODERATE
PCOS prevalence - Polynesian	1	470	0.08 (0.07, 0.10)	⊕⊕⊕◯ MODERATE
PCOS prevalence – South/North East Asian	2	2107	0.06 (0.04, 0.08)	⊕⊕⊕◯ MODERATE



Outcome 2.1. Prevalence among American women using NIH criteria

Prevalence among American adult women using NIH criteria (95% CI) was 0.06 (0.04, 0.08) (=3 studies)

2.1.1. Forest plot of all included studies regarding prevalence among American women



2.1.2 Individual Study Data Table

OUTCOME: PCOS prevalence American women using NIH criteria			**OUTCOME TYPE: Dichotomous**			
COMPARISON (if applicable): N/A						
Author, year	**Unit of outcome**	**Adjusted or crude?**	**If adjusted, what variables included in the model?**	**N events**	**N total**	**Prevalence NIH**
Azziz, 2004	Prevalence (%)	Crude	N/A	White: 8	White: 166	White: 8/166 (4.8%)
Knochenhauer, 1998	Prevalence (%)	Crude	N/A	White: 6	White: 129	White: 6/129 (4.7%)
Wang, 2011	Prevalence (%)	Crude	N/A	White: 37	White: 531	White: 37/531 (7.0%)

OUTCOME 2.2. Prevalence among Australian Indigenous women using NIH criteria

Prevalence among Australian Indigenous adult women using NIH criteria (95% CI) was 0.16 (0.11, 0.20). (N=2 studies)

2.2.1. Forest plot of all included studies regarding prevalence among Australian Indigenous women

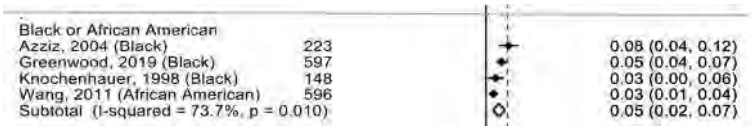
2.2.2 Individual Study Data Table

OUTCOME: PCOS prevalence Australian Indigenous women using NIH criteria			**OUTCOME TYPE: Dichotomous**			
COMPARISON (if applicable): N/A						
Author, year	**Unit of outcome**	**Adjusted or crude?**	**If adjusted, what variables included in the model?**	**N events**	**N total**	**Prevalence NIH**
Davis, 2002	Prevalence (%)	Crude	N/A	7	38	7/38 (18.4%)
Boyle, 2012	Prevalence (%)	Crude	N/A	38	248	Australian Indigenous: 38/248 (15.3%)

OUTCOME 2.3. Prevalence among Black or African American women using NIH criteria

Prevalence among Black or African American adult women using NIH criteria (95% CI) was 0.05 (0.02, 0.07). (N=3 studies)

2.3.1. Forest plot of all included studies regarding prevalence among Black or African American women



2.3.2 Individual Study Data Table

OUTCOME: PCOS prevalence American women using NIH criteria			**OUTCOME TYPE: Dichotomous**			
COMPARISON (if applicable): N/A						
Author, year	**Unit of outcome**	**Adjusted or crude?**	**If adjusted, what variables included in the model?**	**N events**	**N total**	**Prevalence NIH**
Azziz, 2004	Prevalence (%)	Crude	N/A	Black: 18	Black: 223	Black: 18/223 (8.0%
Knochenhauer, 1998	Prevalence (%)	Crude	N/A	Black: 5	Black: 148	Black: 5/148 (3.4%)
Wang, 2011	Prevalence (%)	Crude	N/A	African American: 16	African American: 596	African American: 16/596 (2.7%)

OUTCOME 2.4. Prevalence among Central American Women using NIH criteria

Prevalence among Central American adult women using NIH criteria (95% CI) was 0.06 (0.04, 0.09) (N= 1 study)

2.1.1. Forest plot of all included studies regarding prevalence among Central American women

2.4.2 Individual Study Data Table

OUTCOME: PCOS prevalence Central American women using NIH criteria	**OUTCOME TYPE: Dichotomous**	
COMPARISON (if applicable): N/A		

Author, year	Unit of outcome	Adjusted or crude?	If adjusted, what variables included in the model?	N events	N total	Prevalence NIH
Moran, 2010	Prevalence (%)	Crude	N/A	Mexican: 9	Mexican: 150	Mexican: 9/150 (6.0%)

OUTCOME 2.5. Prevalence among European women using NIH criteria

Prevalence among European adult women using NIH criteria (95% CI) was 0.05 (0.04, 0.07) (N= 2 studies)

2.5.1. Forest plot of all included studies regarding prevalence among European women

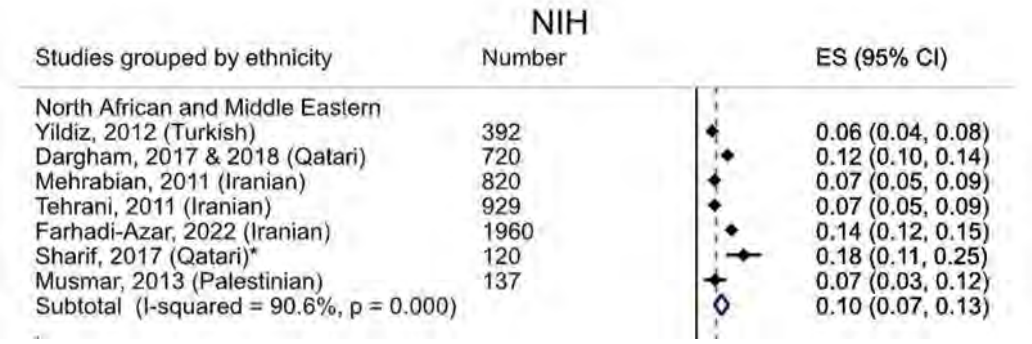
2.5.2 Individual Study Data Table

OUTCOME: PCOS prevalence European women using NIH criteria			OUTCOME TYPE: Dichotomous			
COMPARISON (if applicable): N/A						
Author, year	**Unit of outcome**	**Adjusted or crude?**	**If adjusted, what variables included in the model?**	**N events**	**N total**	**Prevalence NIH**
Asuncion, 2000	Prevalence (%)	Crude	N/A	10	154	Caucasian: 10/154 (6.49%)
Diamanti-Kandarakis, 1999	Prevalence (%)	Crude	N/A	13	192	Greek: 13/192 (6.77%)

Outcome 2.6. Prevalence among North African and Middle Eastern women using NIH criteria

Prevalence among North African and Middle Eastern women using NIH criteria 95% (CI) was 0.10 (0.07, 0.13) (N=7 studies)

2.6.1. Forest plot of all included studies regarding prevalence among North African and Middle Eastern women



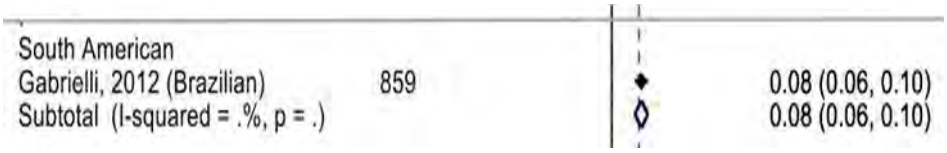
2.6.2 Individual Study Data Table

OUTCOME: PCOS prevalence North African and Middle Eastern women using NIH criteria			**OUTCOME TYPE: Dichotomous**			
COMPARISON (if applicable): N/A						
Author, year	**Unit of outcome**	**Adjusted or crude?**	**If adjusted, what variables included in the model?**	**N events**	**N total**	**Prevalence NIH**
Yildiz, 2012	Prevalence (%)	Crude	N/A	Turkish: 24	Turkish: 292	Turkish: 24/392 (6.1%)
Dargham, 2017 & 2018	Prevalence (%)	Crude	N/A	Qatari: 97	Qatari: 720	Qatari: 97/720 (12.1%)
Farhadi-Azar, 2022	Prevalence (%)	Crude	N/A	Iranian: 267	Iranian: 1960	Iranian: 267/1960 (13.6%)
Mehrabian, 2011	Prevalence (%)	Crude	N/A	Iranian: 57.77	Iranian: 820	Iranian: 57.77/820 (7%)
Sharif, 2017	Prevalence (%)	Crude	N/A	Qatari: 22	Qatari: 120	Qatari: 22/120 (18.33%)
Musmar, 2013	Prevalence (%)	Crude	N/A	Palestinian: 10	Palestinian: 137	Palestinian: 10/137 (7.3%)
Tehrani, 2011	Prevalence (%)	Crude	N/A	Iranian: 66	Iranian: 929	Iranian: 66/929 (7.1%)

Outcome 2.7. Prevalence among South American women using NIH criteria

Prevalence among South American women using NIH criteria (95% CI) was 0.07 (0.05, 0.09) (N=1 study)

2.7.1. Forest plot of all included studies regarding prevalence among South American women



2.7.2 Individual Study Data Table

OUTCOME: PCOS prevalence South American women using NIH criteria			OUTCOME TYPE: Dichotomous			
COMPARISON (if applicable): N/A						
Author, year	**Unit of outcome**	**Adjusted or crude?**	**If adjusted, what variables included in the model?**	**N events**	**N total**	**Prevalence NIH**
Gabrielli, 2012	Prevalence (%)	Crude	N/A	69	859	69/859 (8.03%)

Outcome 2.8. Prevalence among Polynesian women using NIH criteria

Prevalence among Polynesian women using NIH criteria (95% CI) was 0.08 (0.07, 0.10) (N=1 study)

2.8.1. Forest plot of all included studies regarding prevalence among Polynesian women

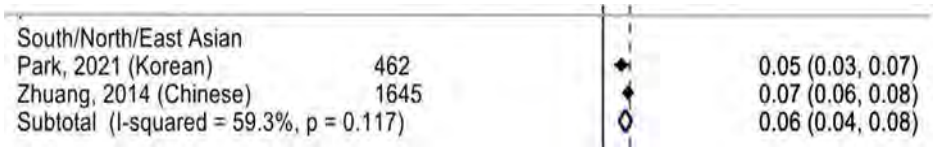
2.8.2 Individual Study Data Table

OUTCOME: PCOS prevalence Polynesian women using NIH criteria			OUTCOME TYPE: Dichotomous			
COMPARISON (if applicable): N/A						
Author, year	**Unit of outcome**	**Adjusted or crude?**	**If adjusted, what variables included in the model?**	**N events**	**N total**	**Prevalence NIH**
Maredia, 2018	Prevalence (%)	Crude	N/A	Samoan: 32	Samoan: 470	Samoan: 32/470 (6.8%)

Outcome 2.9. Prevalence among South/North East Asian women using NIH criteria

Prevalence among South/North East Asian women using NIH criteria (95% CI) was 0.06 (0.04, 0.08) (N=2 studies)

2.9.1. Forest plot of all included studies regarding prevalence among South/Nort East Asian women



2.9.2 Individual Study Data Table

OUTCOME: PCOS prevalence South/North East Asian using NIH criteria			**OUTCOME TYPE: Dichotomous**			
COMPARISON (if applicable): N/A						
Author, year	**Unit of outcome**	**Adjusted or crude?**	**If adjusted, what variables included in the model?**	**N events**	**N total**	**Prevalence NIH**
Park, 2021	Prevalence (%)	Crude	N/A	Korean: 24	Korean: 462	Korean: 24/462 (5.2%)
Zhuang, 2014	Prevalence (%)	Crude	N/A	Chinese: 116	Chinese: 1,645	Chinese: 116/1,645 (7.1%)

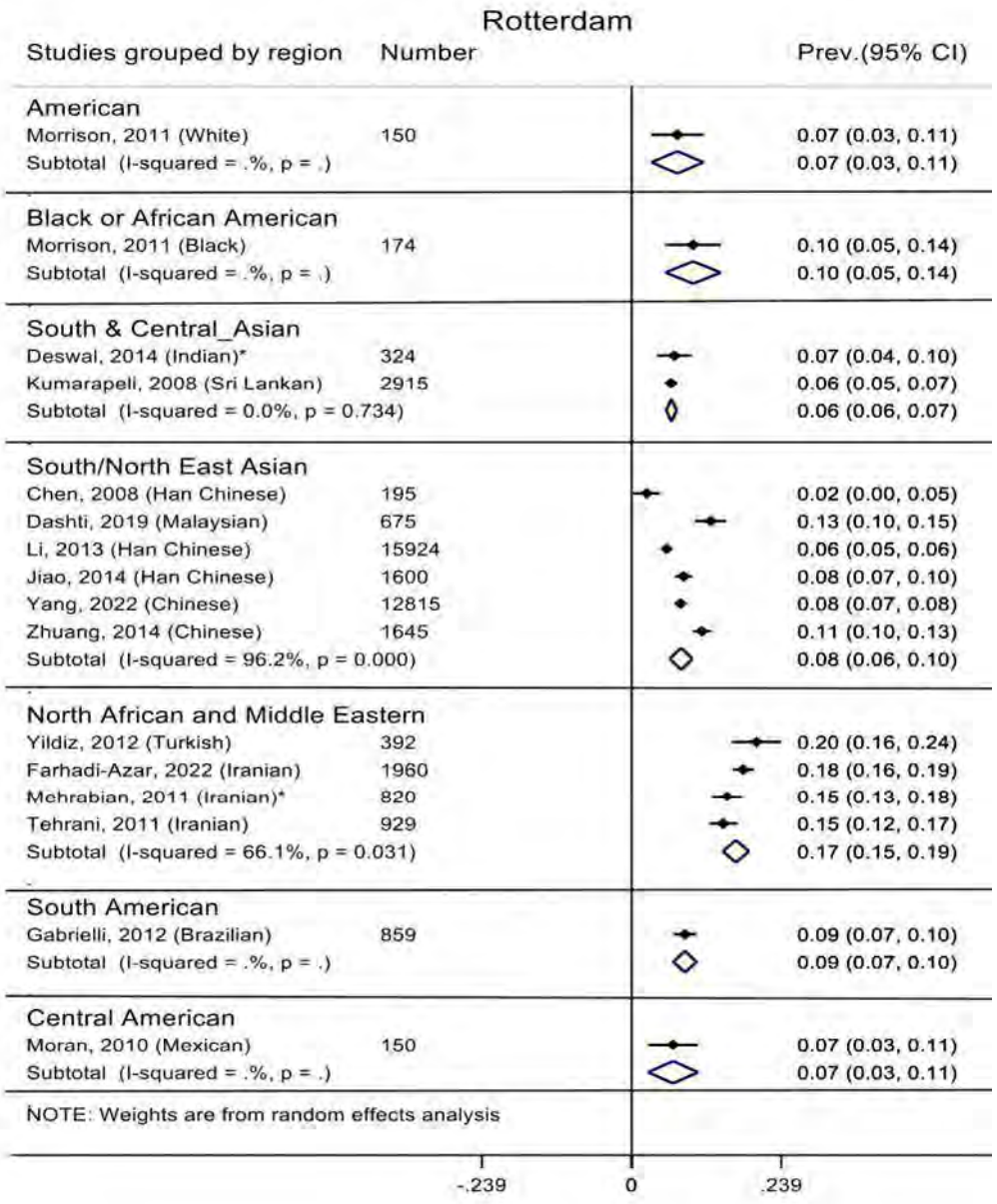
OUTCOME 3. Prevalence of PCOS among adult women from different ethnicities using Rotterdam criteria

- **EVIDENCE SUMMARY:**

A total of 15 cross-sectional and cohort studies studied the prevalence of PCOS among adult women from different ethnicities using Rotterdam criteria. Ethnicities included Black or African American and American (Morrison, 2011), South/North East Asian (Chen, 2008; Dashti, 2019; Li, 2013; Jiao, 2014; Yang, 2022; Zhuang, 2014), North African and Middle Eastern (Tehrani, 2011; Mehrabian, 2011; Farhadi-Azar, 2022; Yildiz, 2012), South American (Gabrielli, 2012) and Central American (Moran, 2010).

- **META-ANALYSIS/DESCRIPTIVE ANALYSIS SUMMARY**

Pooled prevalence among all adult women using Rotterdam criteria (95% CI) was 0.10 (0.08, 0.12) (n=15 studies)



OUTCOME 3.1. Prevalence among American women using Rotterdam criteria

Prevalence among American adult women using Rotterdam criteria (95% CI) was 0.07 (0.03, 0.11). (N=1 study)

3.1.1. Forest plot of all included studies regarding prevalence among American women

3.1.2 Individual Study Data Table

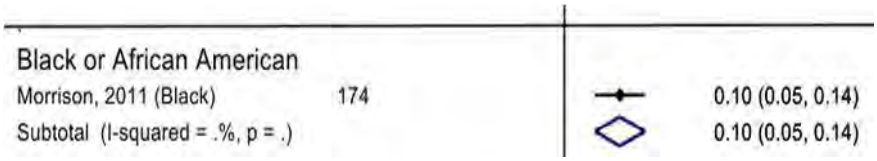
OUTCOME: PCOS prevalence American women using Rotterdam criteria	**OUTCOME TYPE: Dichotomous**	

COMPARISON (if applicable): N/A						
Author, year	**Unit of outcome**	**Adjusted or crude?**	**If adjusted, what variables included in the model?**	**N events**	**N total**	**Prevalence Rotterdam**
Morrison, 2011	Prevalence (%)	Crude	N/A	White: 11	White: 150	White: 11/150 (7.3%)

OUTCOME 3.2. Prevalence among Black or African American women using Rotterdam criteria

Prevalence among Black or African American adult women using Rotterdam criteria (95% CI) was 0.10 (0.05, 0.14). (N=1 study)

3.2.1. Forest plot of all included studies regarding prevalence among Black or African American women



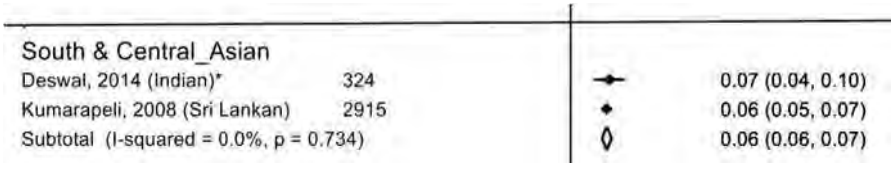
3.2.2 Individual Study Data Table

OUTCOME: PCOS prevalence American women using Rotterdam criteria			OUTCOME TYPE: Dichotomous			
COMPARISON (if applicable): N/A						
Author, year	**Unit of outcome**	**Adjusted or crude?**	**If adjusted, what variables included in the model?**	**N events**	**N total**	**Prevalence Rotterdam**
Morrison, 2011	Prevalence (%)	Crude	N/A	Black: 17	Black: 174	Black: 17/174 (9.8%)

Outcome 3.3. Prevalence among South & Central Asian women using Rotterdam criteria

Prevalence among Southern and Central Asian women using Rotterdam criteria (95% CI) was 0.06 (0.06, 0.07). (N=2 studies)

3.3.1. Forest plot of all included studies regarding prevalence among Southern and Central Asian women



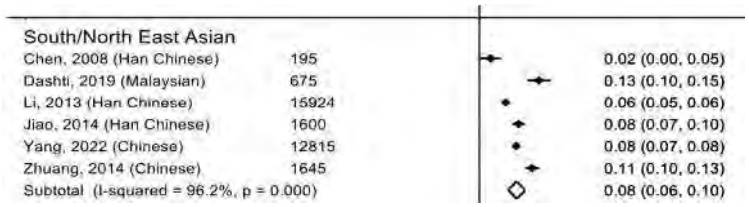
3.3.2 Individual Study Data Table

OUTCOME: PCOS prevalence Southern & Central Asian women using Rotterdam criteria			OUTCOME TYPE: Dichotomous			
COMPARISON (if applicable): N/A						
Author, year	**Unit of outcome**	**Adjusted or crude?**	**If adjusted, what variables included in the model?**	**N events**	**N total**	**Prevalence Rotterdam**
Deswal, 2014	Prevalence (%)	Crude	N/A	Indian: 22	Indian: 324	Indian: 22/324 (6.8%)
Kumarapeli, 2008	Prevalence (%)	Crude	N/A	Sri Lankan: 183	Sri Lankan: 2915	Sri Lankan: 183/2915 (6.3%)

Outcome 3.4. Prevalence among South/North East Asian women using Rotterdam criteria

Prevalence among South/North East Asian women using Rotterdam criteria (95% CI) was 0.08 (0.06, 0.10). (N=6 studies)

3.4.1. Forest plot of all included studies regarding prevalence among South/North East Asian women



3.4.2 Individual Study Data Table

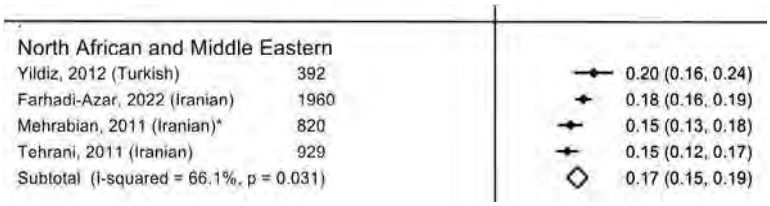
OUTCOME: PCOS prevalence South/North East Asian using Rotterdam criteria			OUTCOME TYPE: Dichotomous			
COMPARISON (if applicable): N/A						
Author, year	**Unit of outcome**	**Adjusted or crude?**	**If adjusted, what variables included in the model?**	**N events**	**N total**	**Prevalence Rotterdam**
Chen, 2008	Prevalence (%)	Crude	N/A	Han Chinese: 22	Han Chinese: 915	Han Chinese: 22/195 (2.4%)
Dashti, 2019	Prevalence (%)	Crude	N/A	Malaysian:85	Malaysian: 675	Malaysian: 85/675 (12.6%)
Li, 2013	Prevalence (%)	Crude	N/A	Han Chinese: 894	Han Chinese: 15 924	Han Chinese: 894/15 924 (5.6%)
Jiao, 2014	Prevalence (%)	Crude	N/A	Han Chinese: 132	Han Chinese: 1600	Han chinese: 132/1600 (8.25%)

Yang, 2022	Prevalence (%)	Crude	N/A	Chinese: 826	Chinese: 12,815	Chinese: 826/12,815 (7.8%)
Zhuang, 2014	Prevalence (%)	Crude	N/A	Chinese: 184	Chinese: 1,645	Chinese: 184/1,645 (11.2%)

Outcome 3.5. Prevalence among North African and Middle Eastern women using Rotterdam criteria

Prevalence among North African and Middle Eastern women using Rotterdam Criteria 95% (CI) was 0.17 (0.15, 0.19). (N=4 studies)

3.5.1. Forest plot of all included studies regarding prevalence among North African and Middle Eastern women



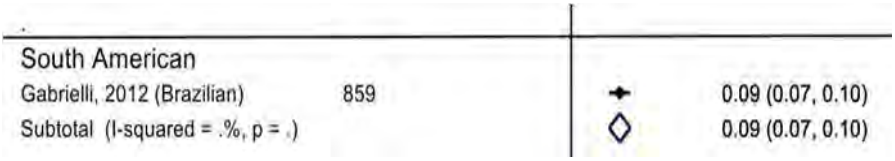
3.5.2 Individual Study Data Table

OUTCOME: PCOS prevalence North African and Middle Eastern women using Rotterdam criteria			**OUTCOME TYPE: Dichotomous**			
COMPARISON (if applicable): N/A						
Author, year	**Unit of outcome**	**Adjusted or crude?**	**If adjusted, what variables included in the model?**	**N events**	**N total**	**Prevalence Rotterdam**
Yildiz, 2012	Prevalence (%)	Crude	N/A	Turkish: 78	Turkish: 292	Turkish: 78/392 (19.9%)
Farhadi-Azar, 2022	Prevalence (%)	Crude	N/A	Iranian: 380	Iranian: 1960	Iranian: 380/1960 (19.4%)
Mehrabian, 2011	Prevalence (%)	Crude	N/A	Iranian: 124.67	Iranian: 820	Iranian: 124.67/820 (15.2%)
Tehrani, 2011	Prevalence (%)	Crude	N/A	Iranian: 136	Iranian: 929	Iranian: 136/929 (14.6%)

Outcome 3.6. Prevalence among South American women using Rotterdam criteria

Prevalence among South American women using Rotterdam criteria (95% CI) was 0.09 (0.07, 0.10). (N=1 study)

3.6.1. Forest plot of all included studies regarding prevalence among South American women



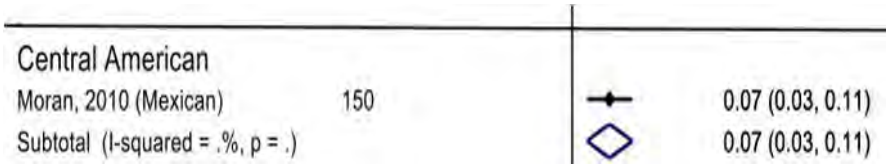
3.6.2 Individual Study Data Table

OUTCOME: PCOS prevalence South American women using Rotterdam criteria			**OUTCOME TYPE: Dichotomous**			
COMPARISON (if applicable): N/A						
Author, year	**Unit of outcome**	**Adjusted or crude?**	**If adjusted, what variables included in the model?**	**N events**	**N total**	**Prevalence Rotterdam**
Gabrielli, 2012	Prevalence (%)	Crude	N/A	73	859	73/859 (8.5%)

OUTCOME 3.7. Prevalence among Central American Women using Rotterdam criteria

Prevalence among Central American adult women using Rotterdam criteria (95% CI) was 0.07 (0.03, 0.11). (N= 1 study)

3.7.1. Forest plot of all included studies regarding prevalence among American women



3.7.2 Individual Study Data Table

OUTCOME: PCOS prevalence Central American women using Rotterdam criteria			**OUTCOME TYPE: Dichotomous**			
COMPARISON (if applicable): N/A						
Author, year	**Unit of outcome**	**Adjusted or crude?**	**If adjusted, what variables included in the model?**	**N events**	**N total**	**Prevalence Rotterdam**
Moran, 2010	Prevalence (%)	Crude	N/A	Mexican: 10	Mexican: 150	Mexican: 10/150 (6.6%)

Outcome 4. Prevalence of PCOS among adolescent women from different ethnicities

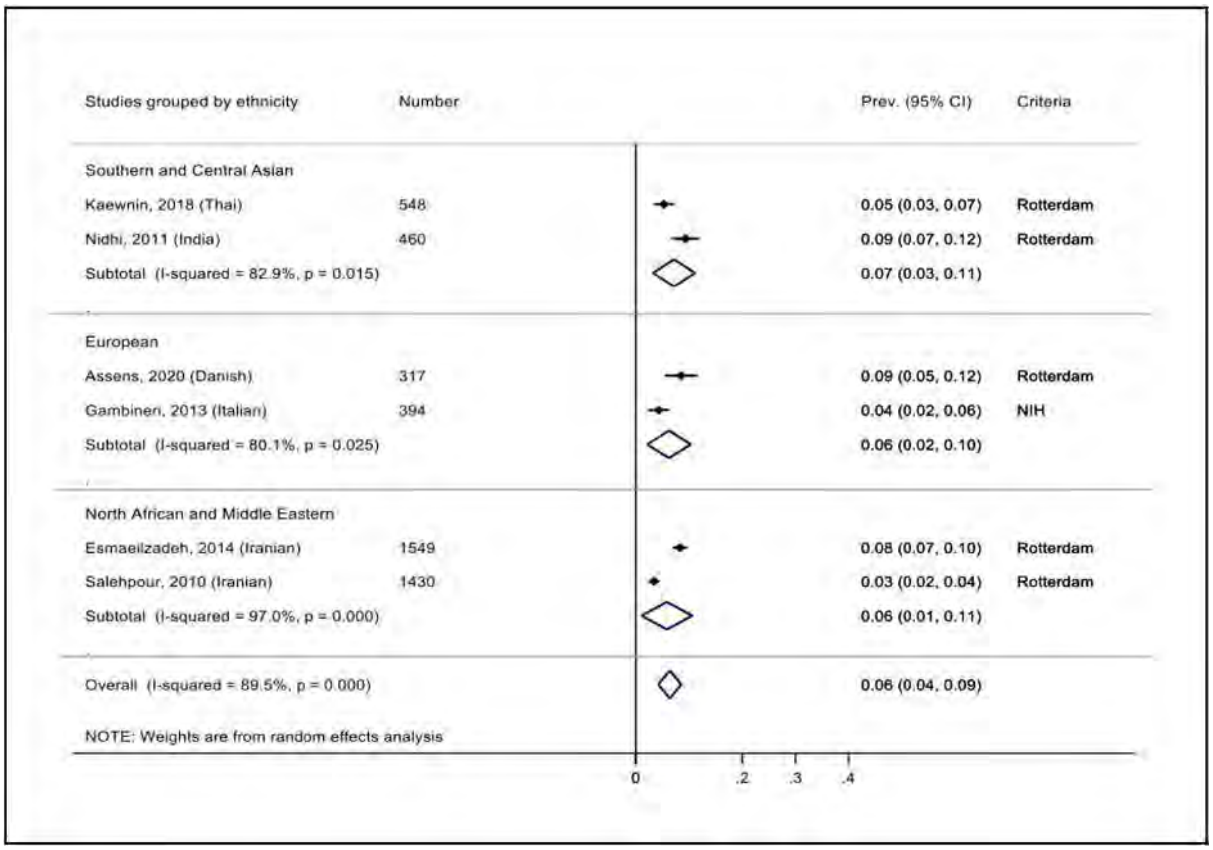
- **EVIDENCE SUMMARY:**

Six cross-sectional studies studied the prevalence of PCOS among adolescent women from different ethnicities using Rotterdam and NIH criteria. Ethnicities included Southern and Central Asian (Kaewnin, 2018; Nidhi,2011), European (Assens, 2020; Gambineri, 2013) and North African and Middle Eastern (Esmaeilzadeh, 2014; Salehpour, 2010).

- **META-ANALYSIS/DESCRIPTIVE ANALYSIS SUMMARY**

Pooled prevalence among all adolescent women (95% CI) was 0.06 (0.04, 0.09) (n=6 studies)

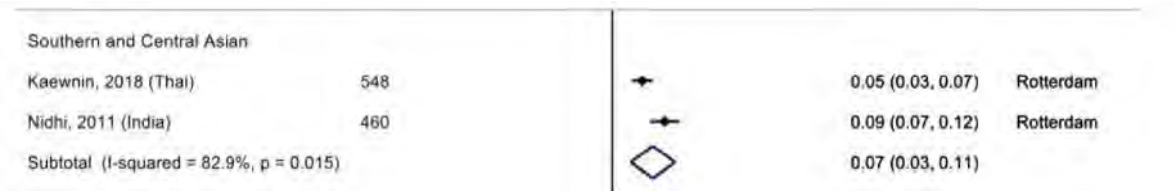
Outcome per subgroup	Studies	N	Effect Estimate; % (95% CI), Random	Certainty
PCOS prevalence – Southern and Central Asian	2	1008	0.07 (0.03, 0.11)	◯◯◯◯ VERY LOW
PCOS prevalence – European	2	711	0.06 (0.02, 0.10)	⊕◯◯◯ VERY LOW
PCOS prevalence – North African and Middle Eastern	2	2979	0.06 (0.01, 0.11)	◯◯◯◯ VERY LOW



4.1. Prevalence among Southern and Central Asian adolescent women

Prevalence among Southern and Central Asian adolescent women (95% CI) was 0.07 (0.03, 0.11). (N=2 studies)

4.1.1. Forest plot of all included studies regarding prevalence among Southern and Central Asian women



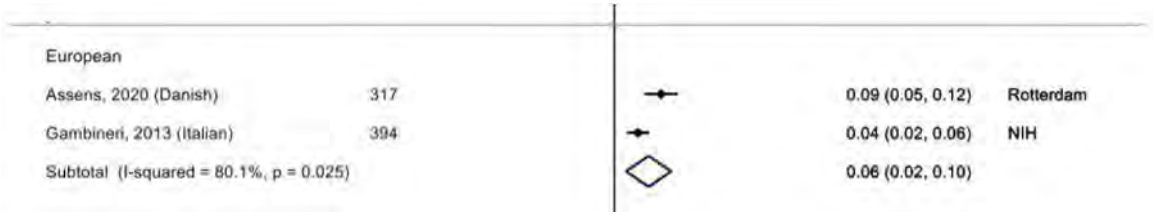
4.1.2 Individual Study Data Table

OUTCOME: PCOS prevalence Southern and Central Asian adolescent women			**OUTCOME TYPE: Dichotomous**				
COMPARISON (if applicable): N/A							
Author, year	**Unit of outcome**	**Adjusted or crude?**	**If adjusted, what variables included in the model?**	**N events**	**N total**	**Prevalence NIH**	**Prevalence Rotterdam**
Kaewnin, 2018	Prevalence (%)	Crude	N/A	Thai: 29	Thai: 548	-	Thai: 29/548 (5.29%)
Nidhi, 2011	Prevalence (%)	Crude	N/A	Indian: 42	Indian: 460	-	Indian: 42/460 (9.3%)

4.2. Prevalence among European adolescent women

Prevalence among European adolescent women (95% CI) was 0.06 (0.02, 0.10). (N=2 studies)

4.2.1. Forest plot of all included studies regarding prevalence among European women



4.2.2 Individual Study Data Table

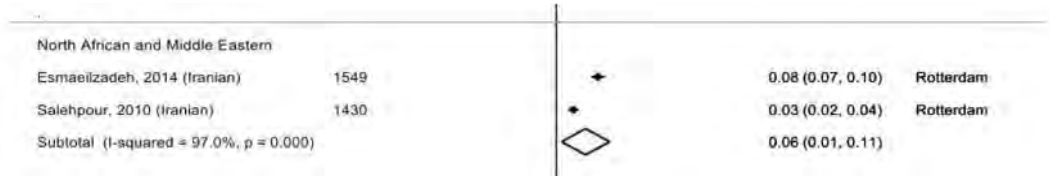
OUTCOME: PCOS prevalence European adolescent women			**OUTCOME TYPE: Dichotomous**				
COMPARISON (if applicable): N/A							
Author, year	**Unit of outcome**	**Adjusted or crude?**	**If adjusted, what variables included in the model?**	**N events**	**N total**	**Prevalence NIH**	**Prevalence Rotterdam**

Assens, 2020	Prevalence (%)	Crude	N/A	Danish: 27	Danish: 317	-	Danish: 27/317 (8.5%)
Gambineri, 2013	Prevalence (%)	Crude	N/A	Italian: 27	Italian: 394	Italian: 27/394 (4.3%)	-

4.3. Prevalence among North African and Middle Eastern adolescent women

Prevalence among North African and Middle Eastern adolescent women (95% CI) was 0.06 (0.01, 0.11). (N=2 studies)

4.3.1. Forest plot of all included studies regarding prevalence among North African and Middle Eastern women



4.3.2 Individual Study Data Table

OUTCOME: PCOS prevalence North African and Middle Eastern adolescent women			**OUTCOME TYPE: Dichotomous**				
COMPARISON (if applicable): N/A							
Author, year	**Unit of outcome**	**Adjusted or crude?**	**If adjusted, what variables included in the model?**	**N events**	**N total**	**Prevalence NIH**	**Prevalence Rotterdam**
Esmaeilzadeh, 2014	Prevalence (%)	Crude	N/A	Iranian: 129	Iranian: 1549	-	Iranian: 129/1549
Salehpour,2010	Prevalence (%)	Crude	N/A	Iranian: 49	Iranian: 1430	-	Iranian: 49/1430 (3.42%)

6. GRADE ASSESSMENTS AND EVIDENCE PROFILE

OUTCOME: PCOS prevalence among adult women from different ethnicities using NIH, Rotterdam, AE-PCOS and Self report diagnostic criteria											
	Quality assessment										
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**No. participants**	**Effect, fixed [95% CI]**	**Favours**	**Certainty**	**Importance**
Outcome: Pooled Prevalence among all adults											
32	Cross-sectional or Cohort	Serious risk of bias[1]	Very serious inconsistency[2]	No serious indirectness	No serious imprecision	None	50.424	0.09 (0.08, 0.10)	N/A	⊕◯◯◯ VERY LOW	Critical
Outcome: PCOS prevalence among American adults											
5	Cross-sectional or Cohort	Serious risk of bias[4]	Serious inconsistency[5]	No serious indirectness	No serious imprecision	None	1706	0.07 (0.05, 0.9)	N/A	⊕⊕◯◯ LOW	Critical
Outcome: PCOS prevalence among Australian Indigenous adults											
2	Cross-sectional	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Serious imprecision[6]	None	286	0.16 (0.11, 0.20)	N/A	⊕⊕◯◯ LOW	Critical
Outcome: PCOS prevalence among Black or African American adults											
5	Cross-sectional or Cohort	Serious risk of bias[1]	Serious inconsistency[2]	No serious indirectness	No serious imprecision	None	1658	0.05 (0.03, 0.07)	N/A	⊕⊕◯◯ LOW	Critical
Outcome: PCOS prevalence among Central American adults											
1	**Cross-sectional**	Serious risk of bias[1]	N/A	Serious indirectness[4]	No serious imprecision	None	150	0.06 (0.04, 0.09)	N/A	⊕⊕◯◯ LOW	Critical
Outcome: PCOS prevalence among European adults											
2	Cross-sectional	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	346	0.07 (0.04, 0.09)	N/A	⊕⊕⊕◯ MODERATE	Critical
Outcome: PCOS prevalence among Hispanic North American adults											

[4] Downgraded once as the majority of the evidence was at moderate risk of bias or downgraded twice as majority of evidence is at high risk of bias
[5] Downgraded once as I square >50% or downgraded twice as I square >50% and Confidence Intervals were not overlapping
[6] Downgraded based on width of Confidence Intervals of the pooled estimate
[4] Downgraded once due to only one study

1	Cross-sectional	Serious risk of bias[1]	N/A	Serious indirectness[4]	No serious imprecision	None	1427	0.06 (0.05, 0.09)	N/A	⊕⊕◯◯ LOW	Critical
Outcome: PCOS prevalence among North African and Middle Eastern adults											
8	Cross-sectional	Serious risk of bias[1]	Very serious inconsistency[2]	No serious indirectness	No serious imprecision	None	5571	0.13 (0.10, 0.15)	N/A	⊕◯◯◯ VERY LOW	Critical
Outcome: PCOS prevalence among Polynesian adults											
1	Cross-sectional	Serious risk of bias[1]	N/A	Serious indirectness[4]	No serious imprecision	None	470	0.07 (0.05, 0.09)	N/A	⊕⊕◯◯ LOW	Critical
Outcome: PCOS prevalence among South and Central Asian adults											
3	Cross-sectional	Serious risk of bias[1]	Serious inconsistency[2]	No serious indirectness	No serious imprecision	None	4307	0.06 (0.05, 0.07)	N/A	⊕⊕◯◯ LOW	Critical
Outcome: PCOS prevalence among South American adults											
1	Cross-sectional	No serious risk of bias	N/A	Serious indirectness[4]	No serious imprecision	None	859	0.08 (0.07, 0.10)	N/A	⊕⊕◯◯ LOW	Critical
Outcome: PCOS prevalence among South/North East Asian adults											
8	Cross-sectional	Serious risk of bias	Very serious inconsistency	No serious indirectness	No serious imprecision	None	33.644	0.07 (0.06, 0.08)	N/A	⊕◯◯◯ VERY LOW	Critical

COMPARISON:Prevalence of PCOS among adult women from different ethnicities using NIH criteria											
	Quality assessment										
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**No. participants**	**Effect, fixed [95% CI]**	**Favours**	**Certainty**	**Importance**
Outcome: Pooled Prevalence among all adults											
23	Cross-sectional or cohort	Serious risk of bias[1]	Very serious inconsistency[2]	No serious indirectness	No serious imprecision	None	11089	0.08 (0.06, 0.09)	N/A	⊕◯ ◯◯ LOW	Critical
Outcome: PCOS prevalence among American adults											
3	Cross-sectional or cohort	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	826	0.06 (0.04, 0.08)	N/A	⊕⊕⊕◯ MODERATE	Critical
Outcome: PCOS prevalence among Australian Indigenous adults											
2	Cross-sectional or cohort	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	Serious imprecision[3]	None	286	0.16 (0.11, 0.20)	N/A	⊕⊕◯◯ LOW	Critical

Outcome: PCOS prevalence among Black or African American adults											
3	Cross-sectional or cohort	Serious risk of bias[1]	Very serious inconsistency[2]	No serious indirectness	No serious imprecision	None	967	0.05 (0.02, 0.07)	N/A	⊕◯◯◯ VERY LOW	Critical
Outcome: PCOS prevalence among Central American adults											
1	Cross-sectional or cohort	Serious risk of bias[1]	N/A	No serious indirectness	No serious imprecision	None	150	0.06 (0.04, 0.09)	N/A	⊕⊕◯◯ LOW	Critical
Outcome: PCOS prevalence among European adults											
2	Cross-sectional or cohort	Serious risk of bias[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	346	0.05 (0.04, 0.07)	N/A	⊕⊕⊕◯ MODERATE	Critical
Outcome: PCOS prevalence among North African and Middle Eastern adults											
7	Cross-sectional or cohort	Serious risk of bias[1]	Very serious inconsistency[2]	No serious indirectness	No serious imprecision	None	5078	0.10 (0.07, 0.13)	N/A	⊕◯◯◯ VERY LOW	Critical
Outcome: PCOS prevalence among Polynesian adults											
1	Cross-sectional or cohort	Serious risk of bias[1]	N/A	Seriousindindirectness[4]	No serious imprecision	None	470	0.07 (0.05, 0.09)	N/A	⊕⊕◯◯ LOW	Critical
Outcome: PCOS prevalence among South American adults											
1	Cross-sectional or cohort	No serious risk of bias	N/A	Serious indirectness [4]	No serious imprecision	None	859	0.08 (0.07, 0.10)	N/A	⊕⊕⊕◯ MODERATE	Critical
Outcome: PCOS prevalence among South/North East Asian adults											
2	Cross-sectional or cohort	No serious risk of bias	Serious inconsistency[2]	No serious indirectness	No serious imprecision	None	2107	0.06 (0.04, 0.08)	N/A	⊕⊕⊕◯ MODERATE	Critical

COMPARISON:PCOS prevalence in different ethnicities using Rotterdam criteria

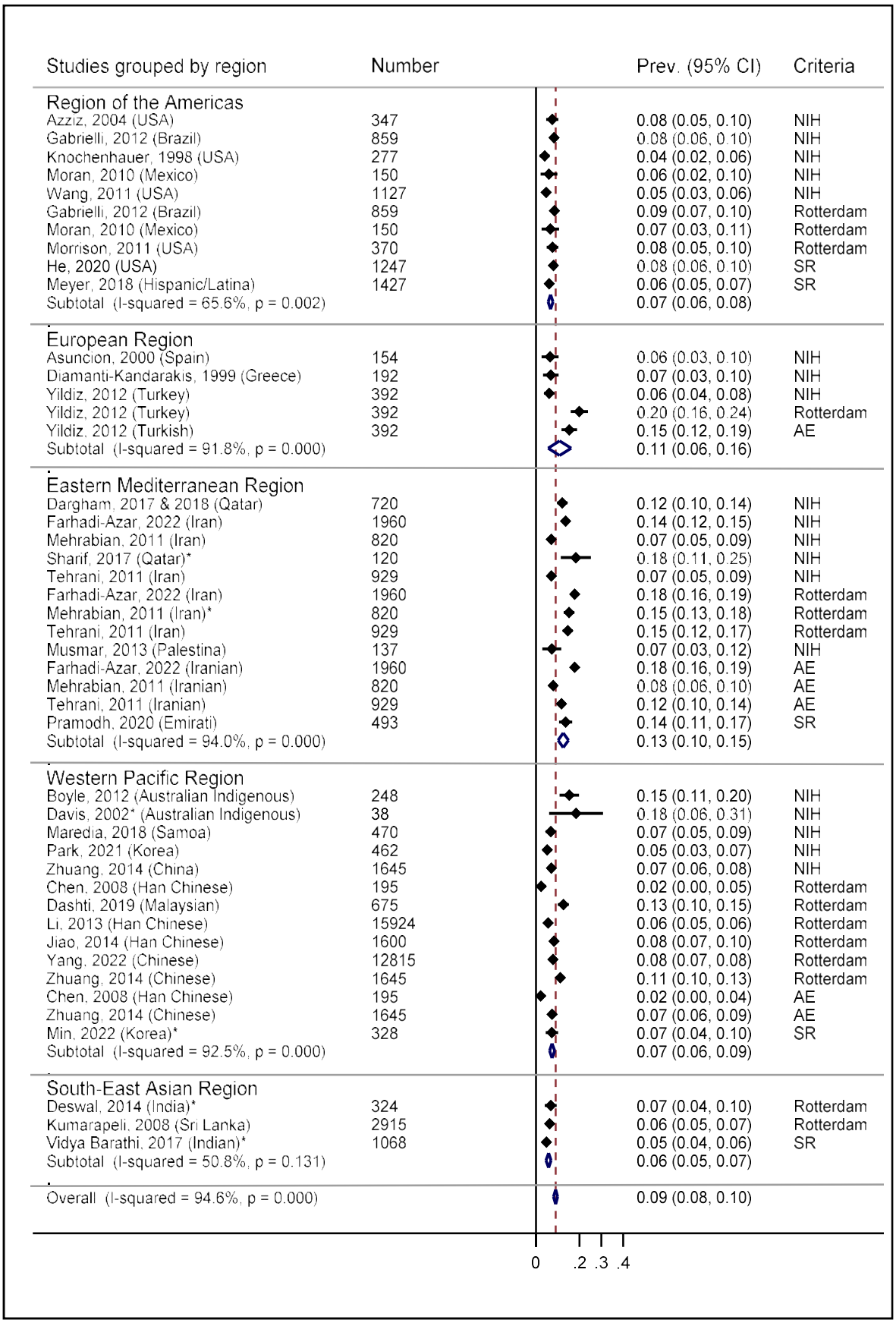
	Quality assessment										
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**No. participants**	**Effect, fixed [95% CI]**	**Favours**	**Certainty**	**Importance**
Outcome: Pooled Prevalence among all adults											
15	Cross-sectional or cohort	No serious risk of bias	Very serious inconsistency[2]	No serious indirectness	No serious imprecision	None	38.288	0.10 (0.08, 0.12)	N/A	⊕⊕◯◯ LOW	Critical
Outcome: PCOS prevalence among American adults											
1	Cohort	Serious risk of bias[1]	N/A	Serious indirectness[4]	No serious imprecision	None	150	00.07 (0.03, 0.11)	N/A	⊕⊕◯◯ LOW	Critical
Outcome: PCOS prevalence among Black or African American adults											
1	Cohort	Serious risk of bias[1]	N/A	Serious indirectness[4]	No serious imprecision	None	174	0.10 (0.05, 0.14)	N/A	⊕⊕◯◯ LOW	Critical
Outcome: PCOS prevalence among Central American adults											

1	Cross-sectional	Serious risk of bias[1]	N/A	No serious indirectness	No serious imprecision	None	150	0.07 (0.03, 0.11)	N/A	⊕⊕◯◯ LOW	Critical
Outcome: PCOS prevalence among North African and Middle Eastern adults											
4	Cross-sectional	No serious risk of bias	Serious inconsistency[2]	No serious indirectness	No serious imprecision	None	4101	0.17 (0.15, 0.19)	N/A	⊕⊕⊕◯ MODERATE	Critical
Outcome: PCOS prevalence among South American adults											
1	Cross-sectional	No serious risk of bias	N/A	Serious indirectness[4]	No serious imprecision	None	859	0.09 (0.07, 0.10)	N/A	⊕⊕⊕◯ MODERATE	Critical
Outcome: PCOS prevalence among South/North East Asian adults											
6	Cross-sectional	No serious risk of bias	Very serious inconsistency[2]	No serious indirectness	No serious imprecision	None	32.854	0.08 (0.06, 0.10)	N/A	⊕⊕◯◯ LOW	Critical

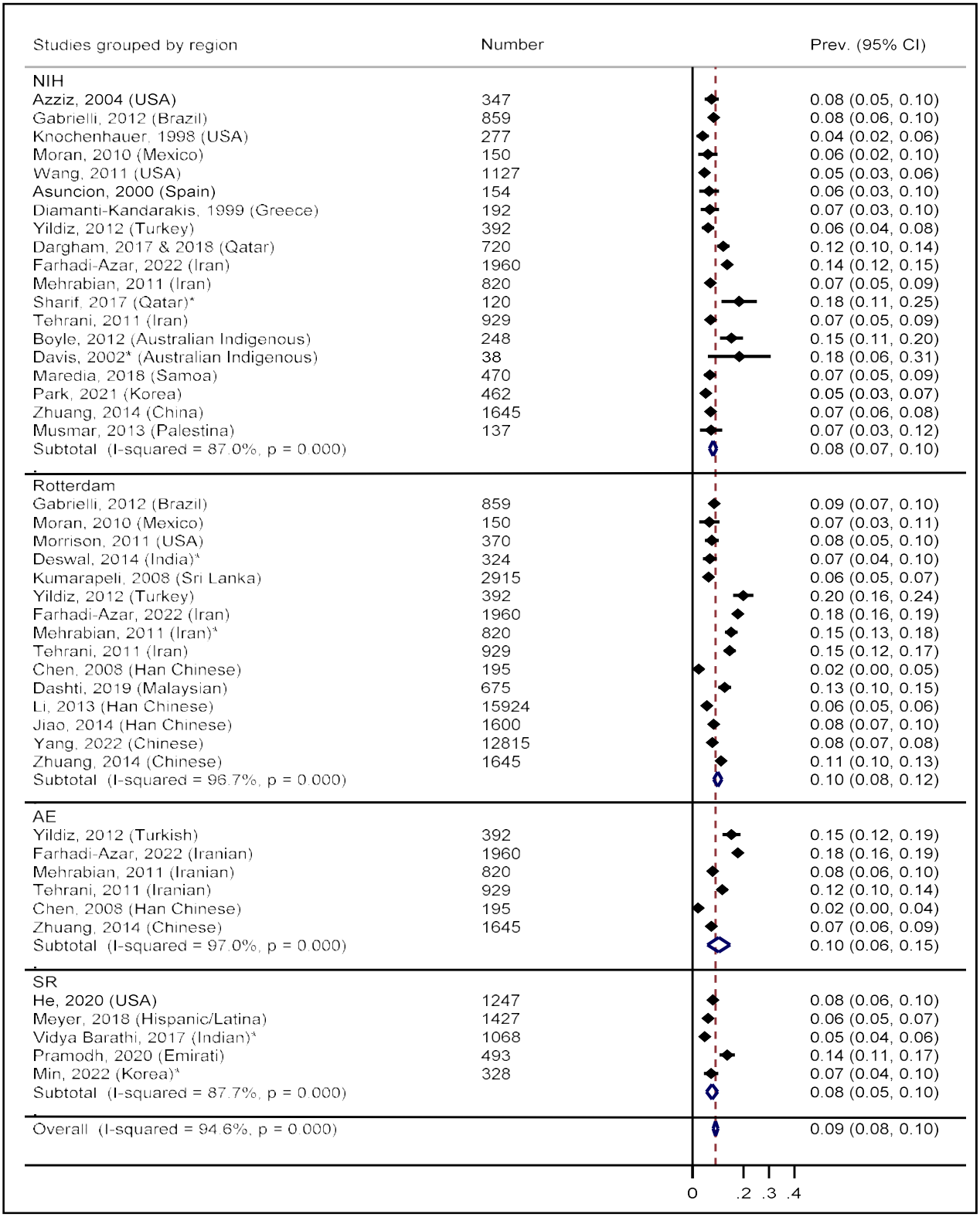
COMPARISON:PCOS prevalence in among adolescents using different criteria

	Quality assessment										
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**No. participants**	**Effect, fixed [95% CI]**	**Favours**	**Certainty**	**Importance**
Outcome: Pooled Prevalence among all adolescents											
6	Cross-sectional or cohort	Very serious risk of bias[1]	Very serious inconsistency[2]	No serious indirectness	No serious imprecision	None	4698	0.06 (0.04, 0.09)	N/A	◯◯◯◯ VERY LOW	Critical
Outcome: PCOS prevalence among Southern and Central Asian adolescents											
2	Cross-sectional	Very serious risk of bias[1]	Very serious inconsistency[2]	No serious indirectness	No serious imprecision	None	1008	0.07 (0.03, 0.11)	N/A	◯◯◯◯ VERY LOW	Critical
Outcome: PCOS prevalence among European adolescents											
2	Cross-sectional or cohort	Very serious risk of bias[1]	Serious inconsistency[2]	No serious indirectness	No serious imprecision	None	711	0.06 (0.02, 0.10)	N/A	⊕◯◯◯ VERY LOW	Critical
Outcome: PCOS prevalence among North African and Middle Eastern adults											
2	Cross-sectional	Serious risk of bias[1]	Very serious inconsistency[2]	No serious indirectness	Serious imprecision[3]	None	2979	0.06 (0.01, 0.11)	N/A	◯◯◯◯ VERY LOW	Critical

Appendix S1. Meta-analysis according to region



Sensitivity analysis



6. STUDY CHARACTERISTICS AND QUALITY APPRAISAL

Please select the appropriate template from those available below depending on your study design:

TEMPLATE	Page No
Risk of Bias for Prevalence studies based on Hoy et al. (2012) and the JBI Critical Appraisal tool for Prevalence studies (see explanation below)	

The risk-of-bias of the included studies was assessed based on

- a tool designed for prevalence studies (Hoy et al., 2012)[1]. This risk-of-bias tool evaluates external validity (items 1–4) and internal validity (items 5–10). The tool comprises 10 items: (1) national representativeness, (2) target population representativeness, (3) random selection or census undertaken, (4) minimal non-response bias, (5) data collected from subjects, (6) acceptable case definition used, (7) valid and reliable study instrument used, (8) same mode of data collection for all subjects, (9) length of the shortest prevalence period and (10) appropriateness of numerator(s) and denominator(s) for the parameter, respectively. Item 9 was not relevant to the studies in this review therefore this item was not included.

- JBI Critical appraisal checklist for prevalence studies.[2] This tool has been developed by the JBI and collaborators and approved by the JBI Scientific Committee following extensive peer reivew. The tool evaluates: (1) target population representativeness, (2) random selection or census undertaken, (3) Adequate sample size, (4) Adequate and detailed description of study subjects, (5) minimal coverage bias, (6) adequate identification of the condition, (7) condition measured in standard, reliable way for all participants, (8) Appropriate statistical analysis, (9) adequate response rate.

Since most questions were similar between those protocols, we kept the versions as in the original tool from Hoy et al. However, questions 5 and 6 were not defined in Hoy et al. and for these items the questions from the JBI Critical appraisal checklist for prevalence studies was used.

External validity

1. **Was the study's target population a close representation of the national population in relation to relevant variables, e.g. age, sex, occupation? (Q1 Hoy et al. 2012)**

   The target population refers to the group of people or entities to which the results of the study will be generalised. Examples:

- The study was a national health survey of people 15 years and over and the sample was drawn from a list that included all individuals in the population aged 15 years and over. The answer is: Yes (LOW RISK).
- The study was conducted in one province only, and it is not clear if this was representative of the national population. The answer is: No (HIGH RISK).
- The study was undertaken in one village only and it is clear this. was not representative of the national population. The answer is: No (HIGH RISK).

2. **Was the sampling frame a true or close representation of the target population (Q2 Hoy et al. 2012 & Q1 JBI Checklist for Prevalence studies)**

   The sampling frame is a list of the sampling units in the target population and the study sample is drawn from this list. Examples:

- The sampling frame was a list of almost every individual within the target population (i.e. a census or complete registry data). The answer is: Yes (LOW RISK).
- The cluster sampling method was used and the sample of clusters/villages was drawn from a list of all villages in the target population. The answer is: Yes (LOW RISK).
- The sampling frame was a list of just one particular group within the overall target population, which comprised many groups (e.g. those working for one organisation, or one profession). The answer is: No (HIGH RISK).

3. **Was some form of random selection used to select the sample, OR was a census undertaken? (Q3 Hoy et al. 2012 & Q2 JBI Checklist for Prevalence studies)**

   A census collects information from every unit in the sampling frame. In this case random sampling is not needed. In a survey, only part of the sampling frame is sampled. In these instances, random selection of the sample helps minimise study bias. Examples:

- The sample was selected using simple random sampling. The answer is: Yes (LOW RISK).
- The target population was the village and every person in the village was sampled. The answer is: Yes (LOW RISK).

- The nearest villages to the capital city were selected in order to save on the cost of fuel. The answer is: No (HIGH RISK).

4. Was the likelihood of non-response bias minimal? (Q4Hoy et al. 2012 & Q5&9 JBI Checklist for Prevalence studies)

The authors should report the number of dropouts or refusals and their reasons. A high proportion of dropouts and refusals might call into question the validity of the findings of a given study. By documenting the reasons for dropouts and comparing their characteristics with other participants, readers can decide whether the reported prevalence rate is reliable or misestimated. Obviously, reasons unrelated to the study outcome and similarity between the characteristics of dropouts and respondents can justify those findings. By contrast, if the type of assessment/measurement is the leading aetiology for dropouts, then the results cannot be valid. Examples:

- The response rate was >75% OR The response rate was <75%; however the researchers did an analysis and found no significant difference between responders and non-responders in terms of relevant demographic characteristics. (LOW RISK)
- The response rate was <75% and the researchers did NOT carry out an analysis to compare relevant demographic characteristics.
- The response rate was <75% and the analysis comparing responders and non-responders showed a significant difference in relevant demographic characteristics between responders and non-responders.

5. Was the sample size adequate? (Q3 JBI Checklist for Prevalence studies)

Not only the sampling method but also the 'sample size' is critical for deciding whether the study group is representative of the target population. Although sample size calculation has been generally employed in interventional studies, it is also valid in prevalence studies. The mathematical method and attributed ratios that the authors use should be mentioned in their prevalence studies. However, large and national survey studies might be excepted from the requirement of sample size calculation.

$$n = Z^2P(1 - P)/d^2,$$

where, n = sample size; Z = Z statistic for a level of confidence; P = expected prevalence or proportion (in proportion of one; if 20%, P = 0.2); d = precision (in proportion of one; if 5%, d = 0.05).

According to the above-mentioned formula, Bozdag et al. (2016)[3] calculated the optimal sample size for PCOS prevalence studies. The calculated sample size of expected PCOS prevalence was accepted as 5.6% for the subset criteria of NIH and 10.0% for the subset criteria of Rotterdam. Detection precision was considered as 2.0% for NIH criteria and 3.0% for Rotterdam criteria. As a result, they found that the required minimal sample size for NIH criteria and Rotterdam criteria are 408 and 384

patients, respectively. Therefore, we considered sample size to be adequate if the study population consists of more than 408 patients.

6. **Were the study subjects and setting described in detail? (Q4 JBI Checklist for Prevalence studies)**

   Study sample should be described in sufficient detail (e.g. inclusion/exclusion criteria, ethnicity of participants) so that other researchers can determine if it is comparable to the population of interest to them.

Internal validity

7. **Were data collected directly from the subjects (as opposed to a proxy) (Q5 Hoy et al. 2012)**

   A proxy is a representative of the subject. Examples relevant to PCOS prevalence:

- All eligible subjects were examined separately. The answer is: Yes (LOW RISK).
- A representative of the household was interviewed and questioned about the presence of PCOS or data were collected from hospital records. The answer is: No (HIGH RISK).

8. **Was an acceptable case definition used in the study? (Q6 Hoy et al. 2012, Q6 JBI Checklist for Prevalence studies)**

   What criteria were used to define PCOS?

- NIH/Rotterdam/AE-PCOS criteria were used (appropriately) – LOW RISK
- PCOS diagnosis based on self-report/ICD codes/hospital records – HIGH risk
- There was no description of what criteria were used for PCOS (e.g. self-report but unclear what questions were asked to participants) – HIGH risk

9. **Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity. (Q7 from Hoy et al. 2012, Q7 JBI Checklist for Prevalence studies)**

   Hirsutism scoring and definition performed with standard and objective criteria?

   The amount of terminal hair growth should be assessed using the modified Ferriman–Gallwey (mF–G) method in which the upper lip, chin, chest, upper and lower abdomen, thighs, upper and lower back and upper arms are scored. The cut-off level of hirsutism was defined as exceeding an mF–G score of 6 or 8.

   Reliable hyperandrogenaemia measurement methods used?

   Biochemical hyperandrogenism (hyperandrogenaemia) involves any androgen—including total testosterone (TT), androstenedione (A), dehydroepiandrosterone

sulphate (DHEAS) and/or the free androgen index (FAI) level—exceeding the respective 95th percentile of healthy, non-hirsute, eumenorrhoeic women without PCO.

Was oligo-anovulation defined according to correct terminology, not merely the patients' own reports?

Menstrual cycles ≥35 or ≤21 days were defined as oligoanovulation. In patients with hirsutism or PCO appearance who had apparently regular menstrual bleeding, luteal phase (Days 21–24) progesterone levels should be determined. The threshold for the presence of ovulation was taken as >4 ng/ml.

Was the ultrasonography performed on the whole target population by measuring both antral follicle count (AFC) and ovarian volume to identify PCO?

An AFC of ≥12 within a 2–9 mm diameter and/or ovarian volume of ≥10 cm3 in at least a single ovary was defined as PCO. If there was more than one data collector, were they similar in terms of level of education, clinical or research experience, or level of responsibility in the piece of research being appraised? When there was more than one observer or collector, was there comparison of results from across the observers?

10. Was the same mode of data collection used for all subjects? (Q8 Hoy et al. 2012, Q7 JBI Checklist for Prevalence studies)

The mode of data collection is the method used for collecting information from the subjects. Face-to-face or telephone interviews and self-administered questionnaires are some options that might be encountered in prevalence studies. Considerable judgment is required to determine the presence of some health outcomes (e.g. establishing hirsutism). Having established the validity of the outcome measurement instrument (see item 9), it is important to establish how the measurement was conducted. Were those involved in collecting data trained or educated in the use of the instrument/s? If there was more than one data collector, were they similar in terms of level of education, clinical or research experience, or level of responsibility in the piece of research being appraised? When there was more than one observer or collector, was there comparison of results from across the observers? Was the condition measured in the same way for all participants?

Examples:

- All eligible subjects had a face-to-face interview. The answer is: Yes (LOW RISK).
- Some subjects were interviewed over the telephone and some filled in postal questionnaires. The answer is: No (HIGH RISK).

11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? (Q10 from Hoy et al. 2012, Q8 JBI Checklist for Prevalence studies)

Importantly, the numerator and denominator should be clearly reported, and percentages should be given with confidence intervals. The methods section should be detailed enough for reviewers to identify the analytical technique used and how specific variables were measured. Additionally, it is also important to assess the appropriateness of the analytical strategy in terms of the assumptions associated with the approach as differing methods of analysis are based on differing assumptions about the data and how it will respond**.**

References

1. Hoy D, Brooks P, Woolf A, Blyth F, March L, Bain C, Baker P, Smith E, Buchbinder R. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J Clin Epidemiol. 2012 Sep;65(9):934-9. doi: 10.1016/j.jclinepi.2011.11.014. Epub 2012 Jun 27. PMID: 22742910.

2. Munn Z, Moola S, Lisy K, Riitano D, Tufanaru C. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and incidence data. Int J Evid Based Healthc. 2015;13(3):147–153.

3. Gurkan Bozdag, Sezcan Mumusoglu, Dila Zengin, Erdem Karabulut, Bulent Okan Yildiz, The prevalence and phenotypic features of polycystic ovary syndrome: a systematic review and meta-analysis, *Human Reproduction*, Volume 31, Issue 12, 1 December 2016, Pages 2841–**2855, https://doi.org/10.1093/humrep/dew218**

APPENDIX S2. STUDY CHARACTERISTICS AND QUALITY APPRAISAL

Study ID	*Asfari 2020*	
Study Citation	*Asfari MM, Sarmini MT, Baidoun F, et al. Association of non-alcoholic fatty liver disease and polycystic ovarian syndrome. BMJ Open Gastroenterology. 2020;7(1):08. doi: 10.1136/bmjgast-2019-000352*	
Study Country	*USA*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*50 785 354 female hospital stays, adult women with PCOS (≥18 years old) identified using the International Classification of Diseases Ninth Version (ICD-9)*	
PCOS diagnostic criteria	*Rotterdam 2003*	
N per group	*Total: 50785354* *White:34185819* *Black:7372082* *Hispanic:6050192* *Asian or Pacific islander:1322045* *Native American: 305176* *Other: 1525882*	
Setting	*National Inpatient Sample (NIS) containing inpatient hospitalisations*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcomes:* *- Non-alcoholic fatty liver disease (NAFLD) (ICD-9 code 571.8)* *- Polycystic ovarian syndrome (ICD-9 code 256.4* *Other outcomes:* *- Race* *- Obesity* *- Hypertension* *- Dyslipidaemia* *- Diabetes Mellitus* *- Hypothyroidism*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* *- All adult female patients (≥18 years old)*
Exclusion criteria	Yes Partial No Not reported	*No exclusion criteria*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No	*Yes*

	Not reported	
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes, cross-sectional*
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	Yes Partial No Not reported	*Yes* *National Inpatient Sample (NIS) data was used. The NIS is the largest all-payer inpatient database in the USA and contains a sample of over eight million inpatient hospitalisations each year, which represents approximately 20% of all discharges from all community hospitals*
2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*Yes.* *The sampling frame was a list of almost every individual within the target population*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*Yes*
4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*Yes*
5. Was the sample size adequate?	Yes Partial No Not reported	*Yes* *Study large enough whereby sample size calculation not required.*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*
Summary Result/s	*- Our nationwide cohort evaluated a total of 50785354 female hospital stays, of whom 77415 (0.15%) had PCOS* *- Using multivariate logistic regression, patients with PCOS had significantly higher rate of NAFLD (OR 4.30, 95%CI 4.11 to 4.50, p<0.001).*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*No*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*No* *ICD codes*
9. Was the study instrument that measured the	Yes Partial	*No*

parameter of interest (PCOS diagnosis) shown to have reliability and validity -	No Not reported	*PCOS identified by ICD codes. No measurement of PCO/menstrual irregularity/hyperandrogenism/hypernadrogenemia*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*Yes* *Same method used for all participants and details of ICD codes are given.* *Using the International Classification of Diseases Ninth Version (ICD-9) code, we identified all records with PCOS and NAFLD using the following codes: 256.4 and 571.8, respectively.*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*No* *Number of women with a PCOS ICD code out of total women in the study population, but no Confidence Intervals.*
Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Not reported* *No protocol or PROSPERO*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*Not reported*
COMMENTS		
What is the overall risk of bias?	Low Moderate High Insufficient information	*7/11* *Moderate* External validity risk of bias low Internal risk of bias medium due to use of suboptimal reliable measurement tool for PCOS (ICD codes).
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*N/A*	

Study ID	*Azziz, 2004*
Study Citation	*Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. Journal of Clinical Endocrinology & Metabolism. 2004;89(6):2745-2749. doi: 10.1210/jc.2003-032046*
Study Country	*USA*
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	

Patient/population/ participants	*Prospective university premenopausal female employees attending pre-employment physical exam, regardless of hormonal therapy)*	
PCOS diagnostic criteria	*NIH*	
N per group	*Total: 347 White: 166 Black: 223*	
Setting	*University (all female employees)*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcomes:* *- Prevalence of PCOS in a well-defined population of unselected reproductive-aged women in the US* *- Phenotyping of the women involved* *Secondary outcomes:* *- the impact of race (Black vs. White) on the prevalence* *Other outcomes:* *- Prevalence of menstrual dysfunction only* *- Prevalence of hirsutism only*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes,* *Prospective university premenopausal female employees attending pre-employment physical exam* *all women regardless of hormonal therapy, including oral contraceptive pills or continuous progestin, glucocorticoid, or insulin sensitizer therapy. This is particularly important because PCOS may predispose patients to the use of hormonal therapy."*
Exclusion criteria	Yes Partial No Not reported	*Yes* *Women younger than 18 yr of age or older than 45 yr of age* *Menopausal women* *Women who have undergone a previous hysterectomy or bilateral oophorectomy* *Women who were pregnant at the time of the evaluation*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	Yes Partial No Not reported	*No* *Study is not representative of national population: university staff*

2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*Yes* *All female university staff attending pre-employment exam, so sampling frame was a true or close representation of the target population.*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*No* *Only those employees that underwent pre-employment exam between july 1 1998 and october 31 1999*
4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*No* *The 208 women who were excluded due to pregnancy or menopause or refusal to participate did not differ from the 400 women agreeing to enter the study in racial composition or body mass index although they did slightly differ in mean age.*
5. Was the sample size adequate?	Yes Partial No Not reported	*No* *Sample size calculation not reported.*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*
Summary Result/s	*- the estimated prevalence of PCOS was 6.6%.* *- Eighteen (8.0%) of the 223 Black women studied and eight (4.8%) of the 166 White women studied were classified as having PCOS)*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*Yes*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*Yes*
9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*Yes* *Measurements of PCO/menstrual irregularity/hyperandrogenism/hypernadrogenemia were valid/reliable*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*Yes*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical	Yes Partial No Not reported	*No* *No confidence intervals.*

analysis was undertaken, was this appropriate?		
Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Not reported.*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*Not reported.*
COMMENTS	*Unclear whether women with acne only or alopecia only were classified as hyperandrogenemic or if women required hirsutism as a minimum.* *Subjects determined to have no hirsutism or menstrual dysfunction by the history and physical examination were not further evaluated and were deemed to not have PCOS. it may be argued that it is possible that they underestimated the prevalence of PCOS when they assumed that those women presenting with regular menstrual function and without hirsutism did not have PCOS*	
What is the overall risk of bias?	Low Moderate High Insufficient information	*6/11* *6/11* *Medium risk of bias* *External validity of the study high risk of bias. Concerns regarding national representativeness, random selection and non-response bias.* *Internal validity medium risk of bias based on unclear how ethnicity was identified or defined. Subjects without hirsutism or menstrual dysfunction not further evaluated. No sample size calculation.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		

Study ID	*Christensen, 2013*
Study Citation	*Christensen SB, Black MH, Smith N, et al. Prevalence of polycystic ovary syndrome in adolescents. Fertility & Sterility. 2013;100(2):470-477. doi: 10.1016/j.fertnstert.2013.04.001*
Study Country	*USA*
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Subset (adolescent girls aged 15 through to 19 years) of the population-based cohort study Kaiser Permanente Southern California (KPSC) Children's Health Study from 2007-2009. Total of 144,426 women identified.*
PCOS diagnostic criteria	*NIH*
N per group	*Non-Hispanic White: 36,089*

	Black: 11,435 *Hispanic white: 62,126* *Asian/Pacific Islander: 7,800* *Other/Multiple races: 2,601* *Unknown: 17,451*	
Setting	*Population (subset of population-based cohort study)*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcome:* *Prevalence of PCOS in adolescents* *Secondary outcome:* *Evaluate the association between BMI for age and PCOS*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes:* *Adolescent girls aged 15 through to 19 years of the population-based cohort study Kaiser Permanente Southern California (KPSC) Children's Health Study from 2007-2009*
Exclusion criteria	Yes Partial No Not reported	*Yes:* *Women who were pregnant* *Women with congenital adrenal hyperplasia or Cushing's syndrome* *Adrenal, ovarian or pituitary cancer* *Prolactinoma or hyperprolactinaemia (defined as at least one prolactin >60ng/dL)*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	Yes Partial No Not reported	*No* *Study is not representative of national population: enrolled in cohort study KPSC*
2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*Yes*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*Yes*

4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*Yes*
5. Was the sample size adequate?	Yes Partial No Not reported	*Yes* *Study large enough whereby sample size calculation is not required.*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*
Summary Result/s	*- Prevalence of a confirmed diagnosis of PCOS was 0.56%, which increased to 1.14% when undiagnosed cases with documented symptoms qualifying for PCOS according to NIH criteria were included.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*No*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*No* *ICD codes*
9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*No* *PCOS identified by ICD codes. No measurement of PCO/menstrual irregularity/ hyperandrogenism/ hyperandrogenemia*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*Yes*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes* *Number of women with a PCOS diagnosis in each ethnic group. Confidence intervals for the total group.*
Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*Not reported*

COMMENTS		
What is the overall risk of bias?	Low Moderate High Insufficient information	*7/11* *Medium risk of bias* *External validity risk of bias low based on national representativeness* *Internal validity risk of bias is medium due to using ICD-9 codes for PCOS diagnosis and symptoms (suboptimal reliable measurement tool).*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*N/A*	

Study ID	*Gabrielli, 2012*	
Study Citation	*Gabrielli L, Aquino EM. Polycystic ovary syndrome in Salvador, Brazil: a prevalence study in primary healthcare. Reproductive Biology & Endocrinology. 2012;10:96. doi:10.1186/1477-7827-10-96*	
Study Country	*Brazil*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*859 women of 18–45 years of age screened for cervical cancer in the primary healthcare network of the city of Salvador, Brazil*	
PCOS diagnostic criteria	*NIH/Rotterdam*	
N per group	*Total: 859* *Black: 760* *Other: 99*	
Setting	*Community (women attending for cervical cancer screening in all the sanitary districts of the city.)*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcome:* *to estimate the prevalence of PCOS in Salvador, Brazil.*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* *women of 18–45 years of age attending primary healthcare units for cervical cancer screening in all the sanitary districts of the city.*
Exclusion criteria	Yes	*Yes*

	Partial No Not reported	*All participants with FSH levels > 25 mIU/ml* *those taking any exogenous sex steroid hormones as contraception or hormone therapy.* *Pregnant or nursing women* *those with cognitive and/or physical limitations that prevented them from answering the questionnaire*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	Yes Partial No Not reported	*No* *The study was conducted in one city only: city of Salvador, Brazil. It is not clear if this was representative of the national population.*
2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*Yes* *Stratified sampling was adopted according to the sanitary district, making a total of 12 strata,*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*Yes* *with one randomly selected unit* *in each district. The work shifts during which the subjects would be approached were also chosen at random by elaborating a schedule of pre established dates on which to conduct the study at each center.*
4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*Yes* *response rate of 96.1%.*
5. Was the sample size adequate?	Yes Partial No Not reported	*Yes*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*
Summary Result/s	*The present results showed a prevalence of PCOS of 8.5% (95%CI: 6.80 - 10.56) in accordance with the Rotterdam criteria in users of the primary public healthcare service in the city of Salvador. When this finding was compared with the prevalence obtained using the NIH criteria (8.03%; 95%CI: 6.39 - 10.05), no statistically significant difference was found, as shown by the overlapping confidence intervals.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*Yes*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*Yes*
9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*Yes*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*Yes*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes* *% of women with a certain ethnicity with PCOS and confidence intervals for total group.*
Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Not reported*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
COMMENTS		
What is the overall risk of bias?	Low Moderate High Insufficient information	*10/11* *10/11* *Low risk of bias* *External validity of the study low risk of bias. Only concern regarding national representativeness.* *Internal validity risk of bias low*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*N/A*	

Study ID	*Greenwood, 2019*	
Study Citation	*Greenwood EA, Yaffe K, Wellons MF, Cedars MI, Huddleston HG. Depression Over the Lifespan in a Population-Based Cohort of Women With Polycystic Ovary Syndrome: Longitudinal Analysis. Journal of Clinical Endocrinology & Metabolism. 2019;104(7):2809-2819. doi: 10.1210/jc.2019-00234*	
Study Country	*USA*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*1127 black and white women participating in Coronary Artery Risk Development in Young Adults* *study.*	
PCOS diagnostic criteria	*NIH*	
N per group	*Total: 1127* *Black: 597* *White: 530*	
Setting	*Population based*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcomes:* *characterize depressive symptoms in a population-based sample of women with and without PCOS across the lifespan and* *compare trajectories of depression symptoms in women with and without PCOS.*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* *Black and white women* *Participation in the year-15 examination of the CARDIA study*
Exclusion criteria	Yes Partial No Not reported	*Yes* *Pregnant women and those lacking ovaries were*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
1. Was the study's target population a close representation of the national population in relation to relevant	Yes Partial No Not reported	*Yes*

variables, e.g. occupation, socio-economic status)		
2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*Yes*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*Yes* *Census: all participants in visit*
4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*Yes* *response rate of 86%*
5. Was the sample size adequate?	Yes Partial No Not reported	*Yes*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes* *Although it was not clear how race was measured*
Summary Result/s	*Eighty-three of 1127 (7.4%) met NIH criteria for PCOS. Of these women, 33 women (40%) were black and 50 women (60%) were white.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*Yes*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*Yes* *NIH*
9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*No* *Hirsutism: mFG method not used* *Hyperandrogenemia: 75th percentile used* *Oligo-anovulation: based on patients own reports*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*No* *Hirsutism and oligo-anovulation on self-report, so although same mode of data collection for all subjects, not a standard and reliable way*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*No* *Numerator and denominators reported for the whole population, but not clearly for black/white (only % of black/white among women with/without PCOS). No confidence intervals.*

Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
COMMENTS	*Same cohort as in Wang, 2011, but different cut off levels used for hyperandrogenemia*	
What is the overall risk of bias?	Low Moderate High Insufficient information	*8/11* *Low risk of bias* *External validity of the study low risk of bias.* *Internal validity risk of bias medium. Concern regarding measurement of PCOS.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*N/A*	

Study ID	*Guo, 2021*
Study Citation	*Guo L, Gordon NP, Chandra M, Dayo O, Lo JC. The Risks of Polycystic Ovary Syndrome and Diabetes Vary by Ethnic Subgroup Among Young Asian Women. Diabetes Care. 2021;44(6):e129-e130. doi: 10.2337/dc21-0373*
Study Country	*USA*
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*1127 black and white women participating in Coronary Artery Risk Development in Young Adults* *study.*
PCOS diagnostic criteria	*NIH*
N per group	*Total: 1127* *Black: 597* *White: 530*
Setting	*Population based*
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcomes:* *characterize depressive symptoms in a population-based sample of women with and without PCOS across the lifespan and* *compare trajectories of depression symptoms in women with and without PCOS.*

Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* *Chinese, Filipina, and South Asian women aged 21–44 years who had more than 1 clinical encounter in 2016 with measured (non gestational) weight and height data for calculation of BMI.*
Exclusion criteria	Yes Partial No Not reported	*No*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Partial* *Inclusion criteria appropriate* *No exclusion criteria listed*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	Yes Partial No Not reported	*No* *The study was conducted in one state of the USA. It is not clear if this was representative of the national population.*
2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*Yes* *The sampling frame was a list of almost every individual within the target population*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*Yes*
4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*Yes*
5. Was the sample size adequate?	Yes Partial No Not reported	*Yes*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*
Summary Result/s		

INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*No* *ICD*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*No* *ICD codes*
9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*No* *suboptimal reliable measurement tool for PCOS (ICD codes)*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*Yes* *Same for all participants and details on ICD codes used.*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*No* *No details of numbers of subjects with PCOS, only percentages. No confidence intervals*
Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Not reported*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*Yes* *One author has a family member who has received research funding from Novartis, Pfiser and Bristol-Myers Squibb unrelated to the current study.*
COMMENTS		
What is the overall risk of bias?	Low Moderate High Insufficient information	*6/11* *Medium risk of bias* *External validity of the study low risk of bias.* *Internal validity of the study high risk of bias. Concern regarding measurement of PCOS.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*N/A*	

Study ID	*He, 2020*	
Study Citation	*He Y, Tian J, Blizzard L, et al. Associations of childhood adiposity with menstrual irregularity and polycystic ovary syndrome in adulthood: the Childhood Determinants of Adult Health Study and the Bogalusa Heart Study. Human Reproduction. 2020;35(5):1185-1198. doi:10.1093/humrep/deaa069*	
Study Country	*USA*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*1247 female participants who participated in the Bogalusa Heart Study when they were aged 26–40 years, and had height and weight reported between ages 26 and 40 years to align with their report of their menstrual cycle characteristics prior to age 40 years*	
PCOS diagnostic criteria	*Women were defined as having PCOS if they self-reported that they had ever been told by a doctor or they reported two symptoms of PCOS. The symptoms were menstrual cycle ≥35 days or totally variable and hirsutism.*	
N per group	*1247* *white: 730* *black: 517*	
Setting	*Population based*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcome:* *to investigate the associations of obesity (including abdominal obesity) in childhood with menstrual irregularity and PCOS in adulthood* *Secondary outcome:* *to determine whether these associations differed by country (Australia and USA) and race (white and black).*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* *female participants who participated in the Bogalusa Heart Study when they were aged 26–40 years, and had height and weight reported between ages 26 and 40 years to align with their report of their menstrual cycle characteristics prior to age 40 years*
Exclusion criteria	Yes Partial No Not reported	*Yes* *Women aged 41-57*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*No. A prospective cohort study was used.*

1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	Yes Partial No Not reported	*No* *The study was conducted in one specific region*
2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*Yes*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*No* *Women with at least one BHS visit (n = 5914) were eligible to participate.They included a select group of women out of these eligible participants.*
4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*Yes* *1601 women out of 1694 women completed questions on menstruation and PCOS (95%)*
5. Was the sample size adequate?	Yes Partial No Not reported	*Yes* *No sample size calculation but sample size big enough.*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*
Summary Result/s	*The prevalence of PCOS was 7.4% in CDAH (the average of CDAH-1 and CDAH-2) and 8.0% (white: 10.7%; black: 4.3%) in BBS.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*Yes*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*No* *Self-reported or based on presence of both menstrual irregularity and hirsutism.*
9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*No* *Hirsutism: no (no mFG score)* *Hyperandrogenemia:* *Oligo-anovulation: Yes (questionnaire administered by interviewer)* *PCO: NA*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*Yes*

11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*No* *Numerator and denominator presented for the whole group, but not for black/white. Only percentages for black/white. No confidence intervals.*
Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
COMMENTS	*Study uses two cohorts, but only one cohort was used for this study as in the other cohort ethnicity details were not provided*	
What is the overall risk of bias?	Low Moderate High Insufficient information	*6/11* *Medium risk of bias.* *External validity of the study medium risk of bias. Concerns regarding national representativeness, and random sampling.* *Internal validity of the study medium risk of bias. Main concern regarding measurement of PCOS (self-report).*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*N/A*	

Study ID	*Khil, 2022*
Study Citation	*Khil J, Darbinian J A, Guo L,; Greenspan LC, Ramalingam ND, Lo JC. Ethnic diversity and burden of polycystic ovary syndrome among US adolescent females. Journal of Pediatric Endocrinology & Metabolism. 2022;35(6):821-825. https://doi.org/10.1515/jpem-2022-0160*
Study Country	*USA*
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*244,642 adolescent females (ages 13-17) with well-child visits during 2012-2018 in a Northern California healthcare system*
PCOS diagnostic criteria	*International Classification of Diseases, 9th/10th Revision, ICD-9 256.4 or ICD-10 E28.2*
N per group	*Total 244,642* *Non-Hispanic White: 86,620* *Black: 24,143* *Hisplanic/Latina: 73,281*

	Asian/Pacific Islander: 45,631 *Other/unknown: 14,967*	
Setting	*Population based*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcome:* *to examine the prevalence and risk of PCOS in a large Northern California cohort of adolescent females by weight status, race/ethnicity, and Asian ethnicity*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* *adolescent females who were age 13–17 years at a well-child visit in 2012–2018 in Kaiser Permanente Northern California (KPNC)*
Exclusion criteria	Yes Partial No Not reported	*No*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Partial* *Inclusion criteria appropriate* *No exclusion criteria listed*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*No.* *A retrospective cohort study was used.*
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	Yes Partial No Not reported	*No* *Study only conducted on participants at a well-child visit in KPNC (only Northern California)*
2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*No* *Sampling frame not reported*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*No* *Not reported*
4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*No* *Response rate not reported*
5. Was the sample size adequate?	Yes Partial No	*Yes* *No sample size calculation but sample size big enough.*

	Not reported	
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*
Summary Result/s		
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*No* *ICD*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*No* *ICD codes*
9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*No* *suboptimal reliable measurement tool for PCOS (ICD codes)*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*Yes*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*No* *Only %PCOS cases for each ethnicity given, numerator of number of PCOS cases for each ethnicity was own calculation and also prevalence of PCOS for each ethnicity*
Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Not reported*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
COMMENTS		
What is the overall risk of bias?	Low Moderate High Insufficient information	*3/11* *High risk of bias* *External validity high risk of bias. Concerns regarding national representativeness, and random sampling.* *Internal validity high risk of bias. Concern regarding measurement of PCOS.*

Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*N/A*

Study ID	*Knochenhauer, 1998*	
Study Citation	*Knochenhauer ES, Key TJ, Kahsar-Miller M, Waggoner W, Boots LR, Azziz R. Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study. Journal of Clinical Endocrinology & Metabolism. 1998;83(9):3078-3082. doi: 10.1210/jcem.83.9.5090*	
Study Country	*USA*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Prospective university female employees attending pre-employment physical exam, regardless of hormonal therapy.*	
PCOS diagnostic criteria	*NIH*	
N per group	*Total: 277* *White: 129* *Black: 148*	
Setting	*University (all female employees)*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcomes:* *Prevalence of PCOS in Black and White women* *Secondary outcomes:* *The extent of hirsutism*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes,* *Prospective university premenopausal female employees attending pre-employment physical exam* *all women regardless of hormonal therapy, including oral contraceptive pills or continuous progestin, glucocorticoid, or insulin sensitizer therapy. This is particularly important because PCOS may predispose patients to the use of hormonal therapy.*
Exclusion criteria	Yes Partial No Not reported	*Not reported*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Partial* *Yes for inclusion criteria* *Exclusion criteria not reported*

Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	Yes Partial No Not reported	*No* *Study is not representative of national population: university staff*
2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*Yes* *All female university staff attending pre-employment exam, so sampling frame was a true or close representation of the target population.*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*No*
4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*No* *The 92 women who refused to participate did not differ in racial composition or mean BMI from those agreeing to enter the study, although they did differ in mean age and mean initial F-G score from those 277 women consenting to the full study.*
5. Was the sample size adequate?	Yes Partial No Not reported	*Yes* *With a sample size of 150 in each racial group, the size of a two-sided 95% confidence interval ranged from 1.6–8.4%, assuming a prevalence of 5%, and from 5.2–14.8% for a prevalence of 10%. P , 0.05 was considered significant.*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*
Summary Result/s	*Of the 277 women consenting to a history and hormonal evaluation, 4.0% had PCOS as defined, 4.7% (6 of 129) of Whites and 3.4% (5 of 148) of Blacks.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*Yes*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*Yes* *NIH*
9. Was the study instrument that measured the	Yes Partial	*Yes*

parameter of interest (PCOS diagnosis) shown to have reliability and validity -	No Not reported	
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*Yes*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*No* *Number of women with a PCOS diagnosis in each ethnic group, but no confidence intervals.*
Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Not reported*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*Not reported*
COMMENTS		
What is the overall risk of bias?	Low Moderate High Insufficient information	*7/11* *Medium risk of bias* *External validity medium risk of bias based on inadequate sampling, non-response bias.* *Internal validity risk of bias low.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*N/A*	

Study ID	*Meyer, 2018*
Study Citation	*Meyer ML, Sotres-Alvarez D, Steiner A, et al. Associations of self-reported polycystic ovary syndrome (PCOS), irregular menstrual cycles, and the metabolic syndrome in premenopausal hispanic/latina women in the hispanic community health study/study of latinos (HCHS/SOL). Journal of Women's Health. 2018;27(11):1425. doi: 10.1210/clinem/dgaa012*
Study Country	*USA*
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*1427 women age 24 to 44 years from the Hispanic CommunityHealth Study/Study of Latinos*

PCOS diagnostic criteria	*Self-reported (Interviewer-administered questionnaires asking about prior self-reported PCOS diagnosis)*	
N per group	*Hispanic/Latina: 1427* *716 Mexican* *183 Central American* *151 Puerto Rican* *132 Dominican* *107 Cuban* *73 South American* *65 other/mixed*	
Setting	*Community*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcomes:* *to examine the association of PCOS signs, an indication of androgen excess, with the prevalence of MetS in premenopausal Hispanic/Latina women*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* *women of reproductive age (24-44 years) who participated in visit 2 of the HCHS/SOL study which was when PCOS symptoms were assessed.*
Exclusion criteria	Yes Partial No Not reported	*Yes* *women who self-reported as postmenopausal* *women who had had a hysterectomy* *had had ovaries removed* *had had breast or cervical cancer* *who were missing outcomes or covariates of interest*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	Yes Partial No Not reported	*No* *The study was conducted among women recruited through four field centers in Miami, San Diego, Chicago and the Bronx area of New york. It was not clear if this was representative of the national population.*
2. Was the sampling frame a true or close	Yes Partial No	*No* *the sampling frame was a list of women from four different areas*

representation of the target population?	Not reported	
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*Yes* *Households were chosen using a stratified 2-stage area probability sample design. Census block groups were randomly selected in specified geographic areas of each study site, and households were randomly selected in each sample block group*
4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*Yes*
5. Was the sample size adequate?	Yes Partial No Not reported	*Yes*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*
Summary Result/s	*Overall, 18.2% women had menstrual cycles greater than 35 days or irregular, 14% reported OC use toregulate periods or acne, 6% self-reported PCOS, and 30% had any PCOS sign*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*Yes*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*No* *No established criteria used. Self-report.*
9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*No* *Individual criteria of PCOS not assessed. Prevalence based on Self-report of PCOS (interviewer-administered questionnaire: "Has a health care provider ever told you that you have polycystic ovary syndrome or PCOS?*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*Yes* *Interviewer administered*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*No* *No confidence intervals*

Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes (study protocol)*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
COMMENTS		
What is the overall risk of bias?	Low Moderate High Insufficient information	*6/11* *Medium risk of bias* *External validity medium risk of bias based on national representativeness and sample frame.* *Internal validity medium risk of bias based on self report of PCOS.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*N/A*	

Study ID	*Moran, 2010*	
Study Citation	*Moran C, Tena G, Moran S, Ruiz P, Reyna R, Duque X. Prevalence of polycystic ovary syndrome and related disorders in mexican women. Gynecologic & Obstetric Investigation. 2010;69(4):274-280. doi: 10.1159/000277640*	
Study Country	*Mexico*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*150 female Mexican volunteers, 20–45 years of age, whose parents and grandparents were of Mexican origin. All of them were employees of an Obstetrics and Gynecology Hospital of the IMSS*	
PCOS diagnostic criteria	*NIH*	
N per group	*Mexican: 150*	
Setting	*Hospital (female employees)*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcomes:* *to determine the prevalence of PCOS in a group of Mexican women living in Mexico City, based upon NIH and Rotterdam criteria.*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*

Inclusion criteria	Yes Partial No Not reported	*Yes* *Female mexican Volunteers, 20-45 years of age, whose parents and grandparents were of Mexican origin.* *Employees of an Obstetrics and Gynaecology Hospital of the IMSS* *All patients regardless of hormonal therapy or previous hysterectomy/oophorectomy.*
Exclusion criteria	Yes Partial No Not reported	*Pregnant women*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	Yes Partial No Not reported	*No* *The study was conducted among employees of one hospital only and it is not clear if this was representative of the national population.*
2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*No* *Sampling frame not reported*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*No* *Not reported*
4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*No* *Response rate not reported*
5. Was the sample size adequate?	Yes Partial No Not reported	*No* *No sample size calculation*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*
Summary Result/s	*The present study prospectively assesses the prevalence of PCOS in Mexican women according to the currently available criteria. It shows a prevalence of nine PCOS cases among 150 Mexican women, representing 6.0% (95% CI: 1.9–10.1), according to NIH criteria. However, by ESHRE/ASRM (Rotterdam) criteria, taking into account ovarian morphology, the prevalence is 10 of 150 women, approximately 6.6% (95% CI: 2.3–10.9%).*	

INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*Yes*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*Yes* *NIH/Rotterdam*
9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*Yes*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*Yes*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Not reported*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*Not reported*
COMMENTS		
What is the overall risk of bias?	Low Moderate High Insufficient information	*6/11* *Medium risk of bias* *External validity high risk of bias. Concerns regarding national representativeness, sampling frame, sample selection and non-response bias.* *Internal validity low risk of bias.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*N/A*	

Study ID	*Morrison, 2011*	
Study Citation	*Morrison JA, Glueck CJ, Daniels S, Wang P, Stroop D. Adolescent oligomenorrhea in a biracial schoolgirl cohort: a simple clinical parameter predicting impaired fasting glucose plus type 2 diabetes mellitus, insulin, glucose, insulin resistance, and centripetal obesity from age 19 to 25 years. Metabolism: Clinical & Experimental. 2011;60(9):1285-1293. doi: 10.1016/j.metabol.2011.01.012*	
Study Country	*USA*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*370 women of the prospective cohort study, the National Heart, Lung, and Blood Institute Growth and Health Study (NGHS), which recruited schoolgirls starting at age 9 or 10. This study was a 15 year follow up.*	
PCOS diagnostic criteria	*Rotterdam (oligomenorrhoea + biochemical hyperandrogenism)*	
N per group	*Total 370* *White: 150* *Black: 174* *46 ethnicity not specified*	
Setting	*Population based*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcome:* *investigate if adolescent oligomenorrhoea predict impaired fasting glucose plus T2DM, homeostatic model assessment (HOMA) of insulin resistance (IR) from ages 19 to 24, and insulin levels from ages 19 to 25.*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* *Part of prospective cohort study the National Heart, Lung, and Blood Institute Growth and Health Study (NGHS), which recruited schoolgirls starting at age 9 or 10.* *they declared themselves as being either Black or White* *they were within 2 weeks of age 9 or 10 at the time of the first clinical visit* *they had parents or guardians who identified themselves as the same race as the child* *their parents or guardians completed a household demographic information form and gave consent*
Exclusion criteria	Yes Partial No Not reported	*Yes* *eligibility was restricted to girls living in racially concordant households and excluded Hispanics of either race and other ethnic groups.*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*

Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*No.* *A prospective cohort study was used.*
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	Yes Partial No Not reported	*No* *Study is not representative of national population: enrolled in NGHS*
2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*Yes*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*Yes*
4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*Yes* *54/424 (12.7%) did not have at least 5 annual reports on menstrual status over a 6-year period (ages 14-19)* *46 participants not included in ethnicity data, unclear why not included* *Overall response rate 324/424 (76.4%)*
5. Was the sample size adequate?	Yes Partial No Not reported	*No* *No sample size calculation*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*
Summary Result/s	*this is the first prospective study to report an independent association of adolescent oligomenorrhea with young adult IFG + T2DM and with insulin and glucose levels and IR. In the current study, IFG + T2DM during ages 19 to 24 were most common (38%) in girls having at least 3 oligomenorrhea reports during ages 14 to 19 and were also higher in girls having 2 (11%) or 1 (6%) oligomenorrhea reports than in those without oligomenorrhea (3%).*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*Yes*
8. Was an acceptable case definition used in the study?	Yes Partial	*No*

	No Not reported	*Based on Rotterdam Consensus criteria but clinical hyperandrogenism not included/measured*
9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*No* *Oligo/anovulation: no* *Hyperandrogenemia: no*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*Yes* *Menstrual regularity assessed by trained staff*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*No* *PCOS prevalence % for each ethnicity not included* *No confidence intervals, but does have χ2 and P values*
Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Not reported*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*Not reported*
COMMENTS		
What is the overall risk of bias?	Low Moderate High Insufficient information	*6/11* *Medium risk of bias* *External validity medium risk of bias. Concerns regrading national representativeness and sample size* *Internal validity medium risk of bias. Concern regarding definition and measurement of PCOS. Prevalence of PCOS in each ethnicity not clearly reported*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*N/A*	

Study ID	*Wang, 2011*
Study Citation	*Wang ET, Calderon-Margalit R, Cedars MI, et al. Polycystic ovary syndrome and risk for long-term diabetes and dyslipidemia. Obstetrics & Gynecology. 2011;117(1):6-13. doi:10.1097/AOG.0b013e31820209bb*
Study Country	*USA*

CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*1,127 white women and black women in the Coronary Artery Risk Development In young Adults (CARDIA) cohort.*	
PCOS diagnostic criteria	*NIH*	
N per group	*African American: 596* *White: 531*	
Setting	*Population based*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcomes:* *the association of PCOS and the subsequent development of cardiovascular risk factors*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* *participation in CARDIA (Coronary Artery Risk Development in Young Adults) study* *The study enrolled women aged 18–30 years at baseline in 1985–1986, who were recruited from four cities (Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California)* *women had to have attended the year 15 examination* *have at least one ovary*
Exclusion criteria	Yes Partial No Not reported	*Yes* *pregnant*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*No. A prospective cohort study (CARDIA study) was used.*
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	Yes Partial No Not reported	*No* *Study is not representative of national population: enrolled in CARDIA*
2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*Yes*

3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*Yes*
4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*No* *Participants underwent a baseline examination and follow-up examinations at years 2, 5, 7, 10, 15, and 20, with retention rates of 91%, 88%, 81%, 79%, 74%, and 72%, respectively*
5. Was the sample size adequate?	Yes Partial No Not reported	*Yes*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*
Summary Result/s	*Of 1,127 women, 53 (4.7%) met criteria for PCOS at ages 20–32 years. Polycystic ovary syndrome was associated with a twofold higher odds of incident diabetes (23.1% compared with 13.1%, adjusted odds ratio [AOR] 2.4, confidence interval [CI] 1.2–4.9) and dyslipidemia (41.9% compared with 27.7%, AOR 1.9, CI 1.0 –3.6) over the course of 18 years; the association with incident hyperten- sion was not significant (26.9% compared with 26.3%, AOR 1.7, CI 0.8 –3.3).*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*Yes*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*Yes*
9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*No* *Hirsutism: mFG method not used* *Hyperandrogenemia: no* *Oligo-anovulation: based on patients own reports*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*No* *Hirsutism and oligo-anovulation on self-report, so although same mode of data collection for all subjects, not a standard and reliable way*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*No* *No confidence intervals*

Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*No reported*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
COMMENTS		
What is the overall risk of bias?	Low Moderate High Insufficient information	*6/11* *Medium risk of bias* *External validity medium risk of bias. Concerns regarding national representativeness (participatns recruited from four cities in USA) and rentention rates.* *Internal validity medium risk of bias. Concern regarding measurement of PCOS.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*N/A*	

South-East Asian Region

Study ID	*Deswal, 2014*	
Study Citation	*Deswal R, Dang AS, Nanda S. Prevalence of Poly Cystic Ovary Syndrome (PCOS) in North Indian women. Indian Journal of Health and Wellbeing. 2014;5(6):742-744.*	
Study Country	*India*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*325 women (18-24 years of age) from multiple localities of Rohtak district*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	*325*	
Setting	*Community*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcome:* *- To find out PCOS prevalence in North Indian women*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No	*Yes*

	Not reported	
Inclusion criteria	Yes Partial No Not reported	*Yes* *Women ages 18-24 years of age recruited from multiple localities of Rohtak district*
Exclusion criteria	Yes Partial No Not reported	*Yes* *- Pregnant women* *- Women with congenital adrenal hyperplasia, androgen secreting tumors, Cushing syndrome, hyper-prolactinemia and thyroid abnormalities*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	Yes Partial No Not reported	*No* *The study was undertaken in one district only and it is clear this was not representative of the national population.*
2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*No* *The sampling frame was multiple localities of Rohtak district. Unclear if cluster sampling was used.*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*No*
4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*No* *No data on response rate*
5. Was the sample size adequate?	Yes Partial No Not reported	*No*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*
Summary Result/s	*The prevalence of PCOS was found to be 6.8%*	

INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*Yes*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*Yes* *Rotterdam*
9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*No* *Oligo/anovulation: no* *Hirsutism: no - not defined* *Hyperandrogenemia: not defined* *PCO: no, no ovarian volume*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*No* *Menstrual cycles, hirsutism on self report. Hyperandrogenemia no cut off values or type of assays used.*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*No* *Numerator and denominator appropriate, but no Confidence intervals.*
Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Not reported*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*Not reported*
COMMENTS		
What is the overall risk of bias?	Low Moderate High Insufficient information	*3/11* *High risk of bias* *External risk of bias high based on national representativeness, sample frame, sampling and non-response.* *Internal validity risk of bias high based on measurement of PCOS and reliability/validity of the measurements.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*N/A*	

Study ID	*Kaewnin, 2018*	
Study Citation	*Kaewnin J, Vallibhakara O, Arj-Ong Vallibhakara S, et al. Prevalence of polycystic ovary syndrome in Thai University adolescents. Gynecological Endocrinology. 2018;34(6):476-480. doi: 10.1080/09513590.2017.1409716*	
Study Country	*Thailand*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*548 university female participants aged 17-19 years from Mahidol University in Bangkok*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	*Thai: 548*	
Setting	*University*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcome:* *to estimate the prevalence of PCOS in Thai adolescents based on Rotterdam criteria* *Secondary outcome:* *to investigate factors associated with PCOS in adolescents.*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* *Thai University adolescents between the ages of 17 and 19 recruited from the medical and nursing schools at Ramathibodi Hospital and the* *Faculty of Science at Mahidol University.*
Exclusion criteria	Yes Partial No Not reported	*Not reported*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Partial* *Inclusion: yes, Exclusion: not reported*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	Yes Partial No Not reported	*No* *study was undertaken at one university. This is not likely to be representative of the national population.*

2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*No* *The studied population were Thai University adolescents recruited from medical and nursing schools. Not clear if all students were sampled.*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*No* *No random sampling or census.*
4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*Yes* *Response rate 91%*
5. Was the sample size adequate?	Yes Partial No Not reported	*Yes*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*
Summary Result/s	*The prevalence of PCOS in the present study was 5.29% (29 out of 548 participants).*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*Yes*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*Yes* *Rotterdam*
9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*No* *Oligomenorrhea: no - menstrual cycles of 45 or more (not 35 or more), determined by own report on questionnaire* *Hirsutism: yes FG score on physical examination* *Hyperandrogenemia:no >95th percentile not used* *PCO: yes*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*No* *Not clear who administered the questionnaire or who performed the physical examination.*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*No* *Numerator and denominator appropriate, but no confidence intervals.*

Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
COMMENTS	*A 'probable case'* *was defined as an adolescent with any symptom suggestive of PCOS including OA, and/or phenotypes of HA, including acne, seborrhea, androgenic alopecia, or a history of acne treatment.* *Two hundred and seventy nine (50.91%) 'probable cases' were invited to continue with the study, of which, 248 (88.88%) agreed to a complete history, physical examination, and trans-abdominal ultrasound to diagnose PCOS* *potentially underestimating PCOS prevalence by missing biochemical hyperandrogenism only + polycystic ovaries?* *USS not reliable in adolescence*	
What is the overall risk of bias?	Low Moderate High Insufficient information	*5/11* *High risk of bias.* *External validity medium risk of bias: main concern regarding national representativeness, sample frame and random sampling.* *Internal validity high risk of bias: main concern regarding measurement of PCOS and reliable data collection.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*N/A*	

Study ID	*Kumarapeli, 2008*
Study Citation	*Kumarapeli V, Seneviratne RDA, Wijeyaratne CN, Yapa RMSC, Dodampahala SH. A simple screening approach for assessing community prevalence and phenotype of polycystic ovary syndrome in a semiurban population in Sri Lanka. American Journal of Epidemiology. 2008;168(3):321-328. doi: 10.1093/aje/kwn137*
Study Country	*Sri Lanka*
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*A community-based cross-sectional study among women aged 15–39 years who were permanent residents of the district of Gampaha, Sri Lanka. Four of 13 divisional secretariat areas were randomly selected.*
PCOS diagnostic criteria	*Rotterdam*

N per group	*Sri Lankan: 2915*	
Setting	*Community*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcomes:* *the prevalence and phenotype of PCOS among young women in Sri Lanka, using recommended diagnostic criteria.*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* *- Women aged 15-39 years, permanent residents of Gampaha*
Exclusion criteria	Yes Partial No Not reported	*a 2.5-year limit after menarche was taken subject to a minimum of 15 years.* *The upper age limit was 39 years, because approximately 5 percent of Sri Lankan women aged 40–44 years have premenopausal menstrual irregularity, which could lead to misclassification bias (16).* *Women who were pregnant or within 1.5 years of childbirth* *current use of oral contraceptives for family planning* *use of hormone replacement therapy during the previous year* *use of progesterone injections or implants during the preceding 1.5 years.*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	Yes Partial No Not reported	*No* *target population not representative of the national population because study was carried out in one specific district.*
2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*Yes*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*Yes*

4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*Yes*
5. Was the sample size adequate?	Yes Partial No Not reported	*Yes* *Sample size calculation was carried out*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*
Summary Result/s	*The community prevalence of PCOS was 6.3 percent (95 percent confidence interval: 5.9, 6.8).*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*Yes*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*Yes* *Rotterdam*
9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*No* *No >95th percentile for hyperandrogenemia used.*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*Yes*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes* *Number of women with a PCOS diagnosis in Sri Lankan women. Confidence interval given.*
Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Not reported*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
COMMENTS		

What is the overall risk of bias?	Low Moderate High Insufficient information	*9/11* *Low risk of bias* *external validity risk of bias low based on adequate sampling, low response rate (however dropout rate high)* *internal validity risk of bias low.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*N/A*	

Study ID	*Nidhi, 2011*	
Study Citation	*Nidhi R, Padmalatha V, Nagarathna R, Amritanshu R. Prevalence of polycystic ovarian syndrome in Indian adolescents. Journal of Pediatric & Adolescent Gynecology. 2011;24(4):223-227. doi:10.1016/j.jpag.2011.03.002*	
Study Country	*India*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Adolescent girls between 15 to 18 years from a College in Anantapur, Andhra Pradesh, India.*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	*Indian: 460*	
Setting	*College (students)*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcomes:* *- to estimate the prevalence of PCOS among adolescent girls in South India using Rotterdam's criteria.*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* *- adolescent girls between 15 to 18 years from a College in Anantapur, Andhra Pradesh, India.*
Exclusion criteria	Yes Partial No Not reported	*Partial* *2 girls were excluded because they had* *- Hypothyroidism* *- Hyperthyroidism* *However, exclusion criteria were not pre-specified.*

If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Partial* *Exclusion criteria not pre-specified*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	Yes Partial No Not reported	*No* *This study was conducted among girls at one college in India. It is not clear if this was representative of the national population.*
2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*No* *The sampling frame was not a true or close representation of the target population.*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*No*
4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*Yes* *Response rate was 89%*
5. Was the sample size adequate?	Yes Partial No Not reported	*Yes* *Sample size calculation not carried out however seems not necessary with current sample size (460)*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*
Summary Result/s	*Out of the 460 girls screened, 42 girls satisfied Rotterdam criteria of PCOS. Thus, the prevalence of PCOS was 9.13% in this population.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*Yes*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*Yes* *Rotterdam*
9. Was the study instrument that measured the parameter of interest	Yes Partial No	*No* *Oligo/anovulation: No*

(PCOS diagnosis) shown to have reliability and validity -	Not reported	*Hirsutism: Yes* *Hyperandrogenemia: No >95th percentile used.* *PCO: no, presence of >10 cysts*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*Yes* *Menstrual cyclicity on interview. HIrsutism on physical examination. Assays used are reported"*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes* *Number of women with a PCOS diagnosis in Indian women*
Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Not reported*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*Not reported*
COMMENTS		
What is the overall risk of bias?	Low Moderate High Insufficient information	*6/11* *Medium risk of bias* *External validity risk of bias high based on national representativeness, sample frame and sampling.* *Internal validity risk of bias low. Only relevant concern was measurement of PCOS.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*N/A*	

Study ID	*Vidya Barathi, 2017*
Study Citation	*Vidya Bharathi R, Swetha S, Neerajaa J, et al. An epidemiological survey: Effect of predisposing factors for PCOS in Indian urban and rural population. Middle East Fertility Society Journal. 2017;22(4):313-316. doi: 10.1016/j.mefs.2017.05.007*
Study Country	*India*
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*502 young women (between 18 and 24 years) from* *Chennai and collectively 566 girls from Thiruvallur and Dindugal districts*

PCOS diagnostic criteria	*Rotterdam (self-administered questionnaire)*	
N per group	*Indian: 1068*	
Setting	*Community (Urban and rural)*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcomes:* *to identify and compare the prevalence of PCOS in urban and rural population in young south Indian females aged between 18 to 24 years* *Secondary outcomes:* *to analyse the influence of lifestyle factors like BMI, Diet, Physical Activity, Stress and Family History with PCOS manifestation.*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* *young south Indian females aged between 18 to 24 years in urban and rural populations*
Exclusion criteria	Yes Partial No Not reported	*Yes* *forms with incomplete data*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	Yes Partial No Not reported	*No* *This study was conducted among women in two areas in India. it was not clear if this was representative of the national population.*
2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*No* *The sample of areas was not randomly drawn from a list of all areas in the target population.*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*No* *Authors write that subjects were randomly recruited from the two areas but no description of random sampling and only the total women that were willing to participate was reported, not the total number women that were sampled.*

4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*No* *Response rate was not reported*
5. Was the sample size adequate?	Yes Partial No Not reported	*Yes*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*No* *No table with characteristics or description of demographics.*
Summary Result/s	*In our study, we have established the prevalence rate of PCOS in India to be around 6% (Z test score – 5.92, 95% Confidence Interval (95%CI); p < 0.05)*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*Yes*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*No* *Authors claim subjects are diagnosed using Rotterdam criteria but diagnosis is based on self-report on self-administered questionnaire*
9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*No* *Self-administered questionnaire and not clear what the questions were.* *"A self-administered survey questionnaire was prepared based on the available literature on predisposing factors for PCOS. The subjects were classified as affected, if they were ever diagnosed with the syndrome and underwent any treatment in the last 12 months."*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*No* *Same mode of data collection for all the women but not clear if data was collected in a standard and reliable way.*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*No* *Numerator and denominator derived from a table, the text only gives a percentage. Also, when calculating the percentage, prevalence seems lower than reported by the authors?*
Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*

Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
COMMENTS		
What is the overall risk of bias?	Low Moderate High Insufficient information	*2/11* *High risk of bias* *External validity high risk of bias based oon national representativeness, sample frame, random sampling, response rate, description of subjects.* *Internal validity high risk of bias based on concerns regarding diagnosistic critieria, measurements used to diagnose PCOS, data collection and data analysis.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*N/A*	

European Region

Study ID	*Assens, 2020*
Study Citation	*Assens M, Dyre L, Henriksen LS, et al. Menstrual Pattern, Reproductive Hormones, and Transabdominal 3D Ultrasound in 317 Adolescent Girls. Journal of Clinical Endocrinology and Metabolism. 2020;105(9):E3257-E3266. doi:10.1210/clinem/dgaa355*
Study Country	*Denmark*
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Girls part of the Copenhagen Mother-Child Cohort, a population-based longitudinal birth cohort of healthy Danish children born between 1997 and 2002*
PCOS diagnostic criteria	*Rotterdam*
N per group	*Danish: 317*
Setting	*Mother-Child Cohort (Population based)*
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcomes:* *to describe the normal variation of uterine and ovarian development, bleeding patterns as well as serum reproductive hormone concentrations in healthy, postmenarchal girls.* *Secondary outcomes:* *- to describe the frequency of oligomenorrhea, PCOS, and use of hormonal contraception in an unselected study population.* *- to describe the uterine/ovarian volume and number of ovarian follicles measured by 3D TAUS in relation to reproductive hormone concentrations and menstrual cyclicity.*

Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* *Girls part of the Copenhagen Mother-Child Cohort, a population-based longitudinal birth cohort of healthy Danish children born between 1997 and 2002* *Girls with available contact information* *Girls examined at or any time after their 3-month visit*
Exclusion criteria	Yes Partial No Not reported	*Yes* *Turner syndrome (N=1)* *Thyroid disease (N=2)* *Girls seen at time of ovulation (based on hormone concentrations) (N=2)*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*No. Population-based longitudinal birth cohort was used.*
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	Yes Partial No Not reported	*No* *This study was conducted among girls in the Copenhagen area. It was not clear if this was representative of the national population.*
2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*Yes* *All girls active in the Copenhagen Mother Child Cohort*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*No* *Girls that were active in the Mother-Child Cohort were selected. No random selection or census*
4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*No* *38.4% of eligible girls consented. No analysis done for difference between responders and non-responders in terms of relevant demographic characteristics.*
5. Was the sample size adequate?	Yes Partial No Not reported	*No.* *No sample size calculation*

6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*
Summary Result/s	*Twenty girls (6.3%) had oligomenorrhea and differed significantly in serum androgens and AMH, age at and time since menarche from girls with regular cycles. Twenty-seven girls were classified with PCOS (8.5%) and had significantly higher 17-OH-progesterone, estradiol, AMH, LH, and age at menarche than the reference group*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*Yes*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*Yes* *Rotterdam criteria*
9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*No* *Oligo-anovulation: no - self administered questionnaire* *Hirsutism: not assessed* *Hyperandrogenemia: no - no 95th percentile used* *PCO: The criterion of ovarian volume above 10 mL was not included*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*No* *Oligo-anovulation: self report not reliable* *Hirsutism: not assessed* *Hyperandrogenemia: yes* *PCO: yes, All scans were performed by a single trained examiner (M.A.) with the Voluson E8 Ultrasound System (GE Healthcare Medical Systems, Zipf, Austria) with a multifrequency transabdominal probe (RM6C, 3-8 MHz).*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*No* *27 girls were classified with PCOS out of 317 (8.5%)* *But no Confidence Intervals*
Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
COMMENTS		
What is the overall risk of bias?	Low Moderate	*4/11*

	High Insufficient information	*High risk of bias* *External validity medium risk of bias based on national representativeness, random sampling, response rate, sample size.* *Internal validity high risk of bias based on concerns regarding measurements used to diagnose PCOS and data analysis.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*N/A*	

Study ID	*Asuncion, 2000*	
Study Citation	*Asuncion M, Calvo RM, San Millan JL, Sancho J, Avila S, Escobar-Morreale HF. A prospective study of the prevalence of the polycystic ovary syndrome in unselected Caucasian women from Spain. Journal of Clinical Endocrinology & Metabolism. 2000;85(7):2434-2438. doi: 10.1210/jcem.85.7.6682*	
Study Country	*Spain*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Caucasian female blood donors reporting to the Department of Hematology of the Hospital Ramo´n y Cajal*	
PCOS diagnostic criteria	*NIH*	
N per group	*Caucasian: 154*	
Setting	*Hospital (volunteer blood donors)*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcomes:* *- the prevalence of PCOS and hirsutism*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* *Female blood donors above 18 years old (minimum legal age for blood donation in Spain)*
Exclusion criteria	Yes Partial No Not reported	*Yes* *Women with physiological menopause*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No	*Yes*

	Not reported	
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	Yes Partial No Not reported	*No* *The study was not representative of the national population (blood donors).*
2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*Yes*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*Yes*
4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*No* *Non response not reported*
5. Was the sample size adequate?	Yes Partial No Not reported	*Yes* *The authors state: considering hat all of the women who entered our present study were Caucasian, the size of the sample we studied was similar to the number of White women included in the study from Knochenhauer et al. (11) and was adequate to estimate the prevalence of PCOS as previously discussed (11).*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*
Summary Result/s	*Using strict NIH/NICHD criteria, we found a 6.5% prevalence of PCOS in Caucasian women from Madrid, Spain.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*Yes*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*Yes* *NIH*
9. Was the study instrument that measured the parameter of interest	Yes Partial No	*Yes*

(PCOS diagnosis) shown to have reliability and validity -	Not reported	
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*No* *History form was completed for menstrual cycle and hirsutism. Not clear if this was clinician administered. No evidence of physical examination.*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*No* *Numerator and denominator appropriate but no confidence intervals.*
Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Not reported*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*Not reported*
COMMENTS		
What is the overall risk of bias?	Low Moderate High Insufficient information	*7/11* *Medium risk of bias* *External risk of bias low based on national representativeness and non-response bias.* *Internal validity medium risk of bias. Only concern was that it was not clear if PCOS was measured in a reliable, valid way, prevalence not reported with confidence intervals.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*N/A*	
Study ID	*Diamanti-Kandarakis, 1999*	
Study Citation	*Diamanti-Kandarakis E, Kouli CR, Bergiele AT, et al. A survey of the polycystic ovary syndrome in the Greek island of Lesbos: hormonal and metabolic profile. Journal of Clinical Endocrinology & Metabolism. 1999;84(11):4006-4011. doi: 10.1210/jcem.84.11.6148*	
Study Country	*Greece*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*192 women of reproductive age who lived on the Greek island of Lesbos and accepted our invitation of free medical examination, no reference was made to the specific disorders being studied.*	
PCOS diagnostic criteria	*NIH*	

N per group	*Greek: 192*	
Setting	*Community (Greek island not otherwise specified)*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcomes:* *- prevalence of PCOS in a sample of the population of a Greek island* *Secondary outcomes:* *- hormonal and metabolic parameters of women with PCOS and, in particular, among women with clinical signs of hyperandrogenemia* *- associations of the above-mentioned clinical manifestations with family history of diabetes mellitus, menstrual disorders, cardiovascular disease, hirsutism, and premature baldness in male relatives.*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* *Women of reproductive age who lived on the Greek island of Lesbos*
Exclusion criteria	Yes Partial No Not reported	*Partial* *Postpmenopausal women* *All women were clinically healthy, none of them suffered from chronic or acute disease, and all were euthyroid according to the clinical evaluation. (not clear why this is, on exclusion?)*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	Yes Partial No Not reported	*No* *This study was conducted among women who accepted invitation of free medical examination and on one specific Greek island. This might not be representative of the national population.*
2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*Yes*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*No* *A census was not undertaken and some form of random selection was not used to select the sample.*

4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*No* *Non-response was not reported*
5. Was the sample size adequate?	Yes Partial No Not reported	*Not reported* *No sample size calculation.*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*
Summary Result/s	*The prevalence of PCOS in the population under study was 6.77% (13 of 192)*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*Yes*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*Yes*
9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*Yes*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*Yes* *During physical examination and personal medical history was obtained.*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*No* *Numerator and denominator appropriate but no confidence intervals.*
Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes* *The protocol was approved by the institutional review committee of Bostanion General Hospital in Lesbos*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*Not reported*
COMMENTS	*Unclear whether women with acne only or alopecia only were classified as hyperandrogenemia or if women required hirsutism as a minimum.*	

What is the overall risk of bias?	Low Moderate High Insufficient information	*6/11* *Medium risk of bias* *external risk of bias medium based on sub-optimal sampling and recruitment and sample size.* *Internal validity low risk of bias. Only concern was lack of confidence intervals.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*N/A*	

Study ID	*Gambineri, 2013*	
Study Citation	*Gambineri A, Fanelli F, Prontera O, et al. Prevalence of hyperandrogenic states in late adolescent and young women: epidemiological survey on italian high-school students. J Clin Endocrinol Metab. 2013;98(4):1641-1650. doi: 10.1210/jc.2012-3537*	
Study Country	*Italy*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Italian females aged 16-19 years*	
PCOS diagnostic criteria	*NIH*	
N per group	*Italian: 394*	
Setting	*Convenience (university)*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcomes: To provide an estimate of the prevalence of hyperandrogenic states in adolescence and youth* *Secondary outcomes: to evaluate potential independent predictors*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* *High school female students aged 16-19 recruited from 2 provinces (Bologna and Forli-Cesena) of the Emilia-Romagna region of Italy.*
Exclusion criteria	Yes Partial No Not reported	*Yes* *Active treatment with oral contraceptives* *Thyroid dysfunction* *Hyperprolactinemia*

If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	Yes Partial No Not reported	*No* *The study was conducted among high school students in 2 provinces of Italy. It was not clear if this was representative of the national population.*
2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*No* *Unclear if all high school students were sampled*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*No* *No census, no random selection*
4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*No* *The response rate was <75% and the researchers did NOT carry out an analysis to compare relevant demographic characteristics.*
5. Was the sample size adequate?	Yes Partial No Not reported	*No* *No sample size calculation, total number of girls included in analysis of PCOS only 394*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*
Summary Result/s	*the prevalence rates were approximately 10% for isolated menstrual irregularity; 17% for isolated clinical hyperandrogenism (mainly represented by hirsutism); 7% for hyperandrogenemia, isolated, or combined with clinical hyperandrogenism; and 4% for PCOS.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*Yes*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*Yes* *NIH criteria*

9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*No* *Oligo/anovulation: Yes* *Hirsutism: Yes* *Hyperandrogenemia: No, exceeding 97th percentile of reference interval*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*Yes* *Oligo-anovulation: assessed during a structured interview by a trained medical doctors* *Hirsutism: by a trained medical doctor* *Hyperandrogenemia: Central Lab PCO: NA*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*No* *The text reported a prevalence of PCOS of 4.3%, but no numerator or denominator. Table 3 shows n=17 for PCOS, and number of women that were normal/isolated menstrual irregularity/isolated hyperandrogenemia/isolated clinical hyperandrogenism. It says a total of n=394 however the numbers in the table add up to 384. 17/394 would be 4.3* *No Confidence intervals*
Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*Not reported*
COMMENTS		
What is the overall risk of bias?	Low Moderate High Insufficient information	*4/11* *High risk of bias* *External validity high risk of bias based on national representativeness, sample frame, random sampling, response rate, sample size.* *Internal validity medium risk of bias based on concers regarding measurements used to diagnose PCOS and data analysis.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*N/A*	

Study ID	*Mumm, 2013*

Study Citation	*Mumm H, Kamper-Jorgensen M, Nybo Andersen AM, Glintborg D, Andersen M. Birth weight and polycystic ovary syndrome in adult life: a register-based study on 523,757 Danish women born 1973-1991. Fertility & Sterility. 2013;99(3):777-782. doi: 10.1016/j.fertnstert.2012.11.004*	
Study Country	*Denmark*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*523,757 female children born of Danish mothers in Denmark between 1973 and 1991 were included*	
PCOS diagnostic criteria	*ICD codes* *In NPR we identified PCOS defined as the diagnosis codes for hirsutism or PCOS according to ICD-8 (256,9) and ICD-10 (L68 and E28.2)* *exclusion* *ICD-8 codes: 226.20 (pituitary adenoma), 253 (hypofunction or hyperfunction of the pituitary gland), 258 (Cushing disease), 255 (hypofunction or hyperfunction of the adrenal glands), 183 (ovarian tumor), and 759.5 (Turner syndrome) and ICD-10 codes: D352 (pituitary adenoma), E22 (pituitary hypersecretion), E24 (Cushing disease), E25 (adrenogenital syndrome), N64.3 (galactorrhea), C56 (ovarian tumor), C74 (suprarenal tumor), and Q96 (Turner syndrome).*	
N per group	*Danish: 523757*	
Setting	*Population (National registry)*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcome:* *- To study the association between birth weight and polycystic ovary syndrome (PCOS) in adult life in Danish women born 1973–1991.* *Secondary outcome:* *- the possible influence of maternal diabetes on the association between birth weight and PCOS.* *- the association between accrued calendar period and PCOS.*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* *all female singleton children with a plausible registration of birth weight born in Denmark by Danish mothers between 1973 and 1991*
Exclusion criteria	Yes Partial No Not reported	*Yes*

		37,504 women were excluded because of stillbirth, emigration, death before 15th birthday, or missing or implausible birth weight.
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*No. Register study was used.*
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	Yes Partial No Not reported	*Yes* *The study contains all female singleton children with a plausible registration of birth weight born in Denmark by Danish mothers between 1973 and 1991*
2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*Yes* *The sample frame was a list of almost all girls in the target population*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*Yes* *A census was undertaken*
4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*Yes*
5. Was the sample size adequate?	Yes Partial No Not reported	*Yes*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*
Summary Result/s	*In the present study we found a significantly increased risk of PCOS in adult life in women with birth weights R4,500 g, which represented the 98.5th percentile of birth weights during the study period. Increased birth weight as a risk factor for PCOS is supported by two previous studies.* *A total of 3,204 PCOS events occurred during follow-up.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*No* *ICD codes*

8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*No*
9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*No* *ICD codes have not been shown to have reliability and validity*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*Yes* *Same for all participants and clearly described what ICD codes were used.*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*No* *Numerator and denominator appropriate but no confidence intervals.*
Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
COMMENTS		
What is the overall risk of bias?	Low Moderate High Insufficient information	*7/11* *Medium risk of bias* *External validity low risk of bias.* *Internal validity high risk of bias based on concerns regarding measurement of PCOS.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*N/A*	

Study ID	*Valgeirsdottir, 2019*
Study Citation	*Valgeirsdottir H, Vanky E, Sundstrom-Poromaa I, et al. Prenatal exposures and birth indices, and subsequent risk of polycystic ovary syndrome: a national registry-based cohort study. BJOG: An International Journal of Obstetrics & Gynaecology. 2019;126(2):244-251. doi: 10.1111/1471-0528.15236*

Study Country	*Sweden*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*All singleton, live-born girls between 1 January 1982 and 31 December 1995 who reached at least 15 years of age were included in the study population.*	
PCOS diagnostic criteria	*ICD codes* *PCOS diagnosis was defined as ICD-7 code 275.20, ICD-8 code 256.90, ICD-9 code 256E, and ICD-10 code E28.2. In the Swedish version of ICD 7 and ICD 8 the codes correspond to the formerly known Stein–Leventhals syndrome. For versions ICD 9 and ICD 10 the code is specified as PCOS and Stein–Leventhals syndrome.*	
N per group	*Total: 681123* *Nordic: 62.6661* *Non-Nordic: 50.334* *Missing: 4128*	
Setting	*Population (National registry)*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcome:* *to investigate whether prenatal exposures were associated with the risk of developing PCOS in women.*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* *All singleton, live-born girls between 1 January 1982 and 31 December 1995 who reached at least 15 years of age were included in the study population.*
Exclusion criteria	Yes Partial No Not reported	*Yes* *- Stillborn* *- incorrect or missing personal identification number* *- Death before 15 years of age Emigration before 15 years of age*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*No. National registry-based cohort study design was used.*
1. Was the study's target population a close representation of the	Yes Partial No	*Yes*

national population in relation to relevant variables, e.g. occupation, socio-economic status)	Not reported	*The study contains All singleton, live-born girls between 1 January 1982 and 31 December 1995 who reached at least 15 years of age*
2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*Yes* *The sample frame was a list of almost all girls in the target population*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*Yes* *A census was undertaken*
4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*Yes*
5. Was the sample size adequate?	Yes Partial No Not reported	*Yes*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*
Summary Result/s	*In the final cohort of 681 123 girls, 3738 (0.54%) had been diagnosed with PCOS.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*No* *ICD codes*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*No*
9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*No* *ICD codes have not been shown to have reliability and validity*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*Yes* *Same for all participants and clearly described what ICD codes were used.*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical	Yes Partial No Not reported	*No* *Numerator and denominator appropriate but no confidence intervals.*

analysis was undertaken, was this appropriate?		
Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
COMMENTS		
What is the overall risk of bias?	Low Moderate High Insufficient information	*7/11* *Medium risk of bias.* *External validity low risk of bias.* *Internal validity high risk of bias based on concerns regarding measurement of PCOS.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*N/A*	

Study ID	*Yildiz, 2012*	
Study Citation	*Yildiz BO, Bozdag G, Yapici Z, Esinler I, Yarali H. Prevalence, phenotype and cardiometabolic risk of polycystic ovary syndrome under different diagnostic criteria. Human Reproduction. 2012;27(10):3067-3073. doi:10.1093/humrep/des232*	
Study Country	*Turkey*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Turkish female staff in a government-based institute, between the ages of 18-45 years*	
PCOS diagnostic criteria	*NIH/Rotterdam/AE-PCOS*	
N per group	*Turkish: 392*	
Setting	*Convenience sample (government based institute)*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcomes:* *to determine the prevalence of PCOS according to NIH, Rotterdam, and the AE-PCOS Society sets of diagnostic criteria* *and associated metabolic syndrome among the same population.*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No	*Yes*

	Not reported	
Inclusion criteria	Yes Partial No Not reported	*Yes* *female staff in a government-based institute, between the ages of 18-45 years*
Exclusion criteria	Yes Partial No Not reported	*Yes* *- Women older than 45 or younger than 18 years,* *- post-menopausal women* *- women with a history of hysterectomy or bilateral oophorectomy* *- pregnant women*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	Yes Partial No Not reported	*No* *This study was conducted among female staff in a government-based institute. it is not clear if this was representative of the national population.*
2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*Yes* *The sample frame was a list of almost every female within the target population.*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*No*
4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*Yes* *Response rate 93.3%*
5. Was the sample size adequate?	Yes Partial No Not reported	*Yes* *When the prevalence of PCOS according to NIH was set to 8% with a precision of 2.2% and confidence interval of 95%, the sample size required for a prevalence survey was found to be 400 subjects*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*

Summary Result/s	*We report here the prevalence of PCOS according to NIH, Rotterdam and AE-PCOS Society criteria as 6.1, 19.9 and 15.3%, respectively, among a relatively large Caucasian population.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*Yes*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*Yes* *NIH/Rotterdam/AE-PCOS*
9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*Yes*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*Yes* *Interview-based medical form used to obtain menstrual regularity. Hirsutism scored by a single physician. Description of blood sample analysis.*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*No* *Numerator and denominator appropriate but no confidence intervals.*
Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
COMMENTS		
What is the overall risk of bias?	Low Moderate High Insufficient information	*8/11* *Low risk of bias* *External validity of the study low risk of bias. Only concern regarding national representativeness and random sampling.* *Internal validity of the study low risk of bias. Only concern was lack of confidence intervals.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*N/A*	

Eastern Mediterranean Region

Study ID	*Dargham, 2017&2018*	
Study Citation	*Dargham SR, Ahmed L, Kilpatrick ES, Atkin SL. The prevalence and metabolic characteristics of polycystic ovary syndrome in the Qatari population. PLoS ONE [Electronic Resource]. 2017;12(7):e0181467. doi: 10.1371/journal.pone.0181467* *Dargham SR, Shewehy AE, Dakroury Y, Kilpatrick ES, Atkin SL. Prediabetes and diabetes in a cohort of Qatari women screened for polycystic ovary syndrome. Scientific Reports. 2018;8(1):3619. doi: 10.1038/s41598-018-21987-6*	
Study Country	*Qatar*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*3,017 Qatari subjects volunteered to be phenotyped and genotyped for the Qatar Biobank from which all women between the ages of 18±40 years were identified (750).*	
PCOS diagnostic criteria	*NIH*	
N per group	*Qatari: 720*	
Setting	*Convenience (Biobank)*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcome: to estimate the prevalence and metabolic features of PCOS among Qatari women.*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* *Qatari subjects who volunteered to be phenotyped and genotyped for the Qatar Biobank* *from which all women between the ages of 18±40 years were identified*
Exclusion criteria	Yes Partial No Not reported	*No*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Partial* *No exclusion critieria. Inclusion criteiria appropriate.*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
1. Was the study's target population a close	Yes Partial	*No*

representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	No Not reported	*This study was conducted among women from the qatar biobank and it is not clear if this was representative of the national population*
2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*Yes*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*Yes* *All women in the sampling frame are included*
4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*Yes* *720 out of 750 women had complete information and were included (96%)*
5. Was the sample size adequate?	Yes Partial No Not reported	*Yes*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*
Summary Result/s	*97 of 720 women fulfilled the NIH guidelines (12.1%) for PCOS specifically using a free androgen index greater than 4.5 ((testosterone/SHBG) x 100), or an elevated isolated total testosterone greater than 2.7nmol/l and menstrual irregularity.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*Yes* *NIH*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*Yes*
9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*No* *- HIrsutism no - not assessed* *- Oligo-anovulation no - not defined* *- Biochemical hyperandrogenemia no 95th centile used* *- PCO not assessed*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*No* *Seems a questionnaire was used but not clear who administered this and what the questions were*

11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*No* *Numerator and denominator appropriate, but no confidence intervals.*
Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*No* *No evidence of ethics approval*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*Not reported*
COMMENTS		
What is the overall risk of bias?	Low Moderate High Insufficient information	*7/11* *Medium risk of bias* *External validity of the study low risk of bias. Concerns regarding national representativeness* *Internal validity high risk of bias. Main concern regarding PCOS definition (criteria used were not true NIH), PCOS not being measured in a standard and reliable way.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*N/A*	

Study ID	*Esmaeilzadeh, 2014*
Study Citation	*Esmaeilzadeh S, Delavar MA, Amiri M, Khafri S, Pasha NG. Polycystic ovary syndrome in Iranian adolescents. International Journal of Adolescent Medicine & Health. 2014;26(4):559-565. doi: 10.1515/ijamh-2013-03*
Study Country	*Iran*
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*1549 girl high school students aged 16–20 years who were in the 10th–12th grades of high school in the urban area of Babol City, Iran.*
PCOS diagnostic criteria	*Rotterdam (with the presence of all three criteria, including irregular menses, polycystic ovaries on pelvic ultrasonography and hyperandrogenemia or hyperandrogenism)*
N per group	*Iranian: 1549*
Setting	*Community (high schools)*

Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcome:* *- to determine the prevalence of adolescent PCOS and the characteristics associated with PCOS in adolescence* *Secondary outcome:* *- the prevalence of metabolic syndrome and associated risk factors*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* *girls 16–20 years of age who have undergone menarche at least 2 years prior to the study.*
Exclusion criteria	Yes Partial No Not reported	*Yes* *girls thyroid or adrenal disorders as well as hyperprolactinemia*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	Yes Partial No Not reported	*No* *The study was conducted in one province/city only and it was not clear if this was representative of the national population*
2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*Yes* *The cluster sampling method was used and the sample of clusters was drawn from a list of all high schools in the city.*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*Yes* *The sample size of each high school was proportionality allocated according to the number of girl students in each school and required sample was selected randomly within each high school and each grade.*
4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*Yes* *Complete data were obtained for the remaining 1549 participants (95.3%).*
5. Was the sample size adequate?	Yes Partial	*Yes*

	No Not reported	*Power calculation was conducted*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*
Summary Result/s	*The overall prevalence of PCOS among adolescence was 8.3%, which was determined by the presence of all three criteria.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*Yes*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*No?* *The Rotterdam criteria were used to determine PCOS with the presence of all three criteria, including irregular menses, polycystic ovaries on pelvic ultrasonography and hyperandrogenemia or hyperandrogenism* *They did not report the number of women that met 2 out of 3 criteria.*
9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*No* *- Hirsutism yes* *- Oligo-anovulation yes* *- PCO unclear - cut offs for follicle number or volume not listed* *- Biochemical hyperandrogenemia cut offs not listed*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*No* *Hirsutism - no - assessed by two observers, no report of comparison of their results or their level of education.* *Menstrual irregulrity: yes, assessed during interview.*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*No* *No confidence intervals.*
Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Not reported*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*Not reported*
COMMENTS	*Only students who reported menstrual irregularity and/ or had hirsutism (a modified Ferriman and Gallwey score ≥ 8) were*	

	evaluated for PCOS during the early follicular phase	
What is the overall risk of bias?	Low Moderate High Insufficient information	*6/11* *Medium risk of bias* *External validity of the study low risk of bias. Only concerns was regarding national representativeness.* *Internal validity of the study high risk of bias. Concern regarding measurement of PCOS, only women meeting all three Rotterdam criteria were diagnosed with PCOS. No confidence intervals.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*N/A*	

Study ID	*Farhadi-Azar, 2022*	
Study Citation	*Farhadi-Azar M, Behboudi-Gandevani S, Rahmati M, et al. The Prevalence of Polycystic Ovary Syndrome, Its Phenotypes and Cardio-Metabolic Features in a Community Sample of Iranian Population: Tehran Lipid and Glucose Study. Frontiers in Endocrinology. 2022;13:825528. doi: 10.3389/fendo.2022.825528*	
Study Country	*Iran*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*a total of 1,960 eligible women, aged (18–45 years) were recruited from the Tehran-Lipid and Glucose-Study participants*	
PCOS diagnostic criteria	*NIH/Rotterdam/AE-PCOS*	
N per group	*Iranian: 1960*	
Setting	*Community*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcome:* *- to investigate the prevalence of PCOS, and its phenotypical Cardio-metabolic features compared to healthy eumenorrheic, non-hirsute women without polycystic ovaries* *Secondary outcome:* *- to assess the cardio-metabolic characteristics of women who suffered from one criteria of PCOS compared to those healthy eumenorrheic, non-hirsute women without polycystic ovaries in those populations.*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial	*Yes*

	No Not reported	*- women recruited from the third follow-up visit of the Tehran Lipid Glucose Study (2005–2008)* *- all women aged 18–45 years, regardless of using medications, namely, those taking glucocorticoid, an insulin sensitizer, anti-androgen therapy, oral contraceptive pills or continuous progestin prevalence.*
Exclusion criteria	Yes Partial No Not reported	*Yes* *- Pregnant women* *- Menopausal women* *- those with a history of endocrine disorders, namely, thyroid disease, congenital adrenal hyperplasia, hyperprolactinemia, Cushing's syndrome, and androgen-secreting neoplasm*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	Yes Partial No Not reported	*No* *Women were recruited from the TLGS containing individuals selected from cohorts of three medical health centers. It is not clear if this was representative of the national population.*
2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*Yes*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*Yes* *The target population was women in the third follow-up visit of the TLGS and every individua in this visit was sampled.*
4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*Yes* *All eligible participants were included*
5. Was the sample size adequate?	Yes Partial No Not reported	*Yes*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*
Summary Result/s	*The prevalence of PCOS according to the diagnostic criteria*	

	of NIH, Rotterdam and AE-PCOS Society were 13.6% (267/ 1,960), 19.4% (380/1,960), and 17.8 (349/1,960), respectively. Among those who met the Rotterdam criteria for PCOS, the proportion of PCOS phenotype was 23.9% (91/380) for phenotype A (namely, OA, HA, PCOM), 46.3% (176/380) for phenotype B (namely, OA, HA), 21.6% (82/380) for phenotype C (namely, HA, PCOM), and 8.2 (31/380) for phenotype D (namely, OA, PCOM), respectively.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*Yes*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*Yes*
9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*Yes* *- Hirsutism yes* *- Oligo-anovulation yes - interview by trained physician* *- PCO yes* *- Biochemical hyperandrogenemia yes*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*No* *Unclear if hirsutism was diagnosed by questionnaire of physical exam*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*No* *Numerator and denominator appropriate but no confidence intervals.*
Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
COMMENTS		
What is the overall risk of bias?	Low Moderate High Insufficient information	*8/11* *Low risk of bias* *External validity of the study medium risk of bias. Concern regarding national representativeness.*

		Internal validity of the study low risk of bias. Only concern regarding measurement of hirsutism (by questionnaire, or clinical diagnosis?) and lack of confidence intervals.
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		

Study ID	*Mehrabian, 2011*	
Study Citation	*Mehrabian F, Khani B, Kelishadi R, Ghanbari E. The prevalence of polycystic ovary syndrome in Iranian women based on different diagnostic criteria. Endokrynologia Polska. 2011;62(3):238-242.*	
Study Country	*Iran*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Females aged 17-34 referred to the mandatory pre-marriage screening clinic affiliated to Isfahan University of Medical Sciences.*	
PCOS diagnostic criteria	*NIH/Rotterdam/AE-PCOS*	
N per group	*Iranian: 820*	
Setting	*Hospital (pre-marriage clinic)*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcome:* *- to estimate the prevalence of PCOS in a representative sample of Iranian females, and to compare it according to different sets of criteria.*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Females aged 17-34 referred to the mandatory pre-marriage screening clinic affiliated to Isfahan University of Medical Sciences.*
Exclusion criteria	Yes Partial No Not reported	*Partial* *2 subjects were excluded due to thyroid hormone replacement therapy but this was not pre-specified as an exclusion criteria.*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*

1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	Yes Partial No Not reported	*No* *The study was conducted among women at one clinic and it is not clear if this was representative of the national population.*
2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*Yes* *the sample frame was a close representation of women presenting to the pre-mariage clinic*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*No*
4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*No* *Non-response was 30.5%.* *The researchers did an analysis and found no significant difference between responders and non-responders in terms of age and BMI, but other relevant factors such as socio-economic status or occupation were not considered.*
5. Was the sample size adequate?	Yes Partial No Not reported	*Yes* *No power calculation but sample size high enough*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*
Summary Result/s	*The estimated prevalence of PCOS was 7% based on the NIH criteria, 15.2% under the Rotterdam criteria, and 7.92% according to the AES criteria.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*Yes*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*Yes*
9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*No* *No 95th percentile cut off used for hyperandrogenemia*

10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*No* *Hirsutism was self-reported*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*No* *See comment*
Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Not reported*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
COMMENTS	*Those participants who reported menstrual irregularity and/or had an mF-G score of 8 were invited for a clinical examination. Those who did not have these criteria were not further evaluated and were deemed not to have PCOS.* *Only reported prevalence percentages and didn't provide full details on the number of cases.*	
What is the overall risk of bias?	Low Moderate High Insufficient information	*5/11* *High risk of bias* *External validity of the study medium risk of bias. Concerns regarding national representativeness, random sampling and non-response bias.* *Internal validity of the study high risk of bias due to measurement of PCOS, No full details on number of cases.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*N/A*	

Study ID	*Musmar, 2013*
Study Citation	*Musmar S, Afaneh A, Mo'alla H. Epidemiology of polycystic ovary syndrome: a cross sectional study of university students at An-Najah national university-Palestine. Reproductive Biology & Endocrinology. 2013;11:47. doi: 10.1186/1477-7827-11-47*
Study Country	*Israel*
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	

Patient/population/ participants	*137 female students (18-24 years) attending An-Najah National University in Nablus city in the north of West Bank/Palestine,* *Recruited using advertisement by posters and student electronic boards targeting all female university students.*	
PCOS diagnostic criteria	*NIH*	
N per group	*Palestinian: 137*	
Setting	*Convenience sample (university students)*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcome:* *- to establish prevalence of PCOS among female university students at An-Najah National University-Palestine* *Secondary outcome:* *- to explore its possible risk factors.*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* *women, aged 18-24*
Exclusion criteria	Yes Partial No Not reported	*Yes* *- hyperprolactinemia* *- taking oral contraceptives* *- being pregnant* *- using insulin sensitizers* *- having clinical Cushing disease* *- having diabetes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	Yes Partial No Not reported	*No* *The study was conducted at one university, in one province only, and it is not clear if this was representative of the national population.*
2. Was the sampling frame a true or close	Yes Partial No	*Yes*

representation of the target population?	Not reported	*the sample frame waws a close representation of female university students*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*No* *Some form of random sampling was not undertaken*
4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*No* *Non-response was not reported*
5. Was the sample size adequate?	Yes Partial No Not reported	*Yes* *A convenient study sample of 136 participant was calculated using Finite Population Correction formula*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*
Summary Result/s	*The prevalence of PCOS at An-Najah National University in age groups 18–24 years was found to be 7.3%.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*Yes*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*Yes*
9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*No* *No cut off levels for hyperandrogenemia*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*Yes*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes* *Numerator and denominator appropriate and confidence intervals given.*
Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Not reported*

Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
COMMENTS		
What is the overall risk of bias?	Low Moderate High Insufficient information	*7/11* *Medium risk of bias* *External validity of the study medium risk of bias. Concern regarding national representativeness, random selection and non-reponse bias.* *Internal validity of the study low risk of bias.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		

Study ID	*Pramodh, 2020*	
Study Citation	*Pramodh S. Exploration of lifestyle choices, reproductive health knowledge, and polycystic ovary syndrome (Pcos) awareness among female emirati university students. International Journal of Women's Health. 2020;12:927-938. doi: 10.2147/IJWH.S272867*	
Study Country	*Emirates*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*493 Female Emirati students taking undergraduate and graduate courses at Zayed University, Dubai campus in the age group of 18–25 years*	
PCOS diagnostic criteria	*Self report*	
N per group	*Emirati: 493*	
Setting	*Convenience (University students)*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcome:* *- to assess if young Emirati female university students were consciously making life-style choices related to fast food, smoking, physical exercise, and their awareness of basic terms pertaining to their reproductive health.* *Secondary outcome:* *- their awareness of PCOS and its symptoms were also evaluated.*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*

Inclusion criteria	Yes Partial No Not reported	*Yes* *Female Emirati students taking undergraduate and graduate courses at Zayed University, Dubai campus in the age group of 18–25 years*
Exclusion criteria	Yes Partial No Not reported	*Yes* *Incomplete questionnaires Non-Emirati women*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	Yes Partial No Not reported	*No* *The study was conducted at one university, it is not clear if this was representative of the national population.*
2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*No* *The sample frame was a list of just one particular group within the overall target population.*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*No* *No random sampling or census was undertaken.*
4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*"No* *Non-response was not reported*
5. Was the sample size adequate?	Yes Partial No Not reported	*Yes*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*
Summary Result/s	*Of the students, 13% self-reported being diagnosed with PCOS, with 3.5% also taking medication for the same, 6% reported having high androgen levels, 30.7% reported polymenorrhea, and 3.5% reported oligomenorrhea for frequency of menstrual cycle. Also,12.4% students experienced abnormal bleeding (heavy/none) during menstruation and 24% reported excessive body hair.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*Yes*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*No* *Students who answered the question, "Have you been diagnosed with PCOS by a Physician?" in affirmative were considered to be categorized as having PCOS.*
9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*No* *See question 8.*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*Yes* *Key terms in the survey were translated into Arabic and rechecked by a native Arabic speaker* *The survey was initially piloted in a small group of 15 students and their recommendations were considered. Instructors from different colleges in the University were contacted by e-mail and requested for participation in the survey. Eighteen instructors obliged and provided 30 minutes of their class time for administering hard copies of the survey instrument.*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*No* *Only percentage was given, no numerator, no confidence intervals.*
Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
COMMENTS		
What is the overall risk of bias?	Low Moderate High Insufficient information	*5/11* *Medium risk of bias* *External validity of the study high risk of bias. Concern regarding national representativeness, sample frame, random sampling and non-response.* *Internal validity of the study medium risk of bias. Concern regarding measurement of PCOS and data analysis.*

Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*N/A*

Study ID	*Salehpour, 2020*	
Study Citation	*Salehpour S, Shirvani HE, Entezari A. Evaluation of the prevalence of polycystic ovarian syndrome among adolescent (15-18 years old) girls in Tehran during 2005-2006. International Journal of Fertility and Sterility. 2010;4(3):122-127.*	
Study Country	*Iran*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*15-18 years old girls from a number of high schools in Tehran*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	*Iranian: 1430*	
Setting	*Community (High schools)*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*"Primary outcome:* *- to achieve an accurate estimation of the prevalence of PCOS as well as the predominant clinical features among adolescents in order to facilitate future studies on both the control and treatment of PCOS in its early stages.*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* *15-18 years old girls from a number of high schools in Tehran*
Exclusion criteria	Yes Partial No Not reported	*Yes* *- Adolescents who had not experienced puberty* *- those with a history of an endocrine disorder diagnosed by an endocrinologist (Cushing's syndrome, congenital adrenal hyperplasia, adrenal neoplasia, ovarian neoplasia, and h ypophysis or hypothalamus dysfunctions)*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the	Yes Partial No	*Yes*

appropriate design to answer this question?	Not reported	
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	Yes Partial No Not reported	*No* *The study was conducted in one province/city only and it was not clear if this was representative of the national population*
2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*"No* *The cluster sampling method was used but it was not clear if the sample of highschools was drawn from a list of all highschools in Tehran*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*Yes* *Some form of random sampling was undertaken*
4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*Yes* *All included participants completed the study*
5. Was the sample size adequate?	Yes Partial No Not reported	*Yes* *Sample size calculation was conducted*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*
Summary Result/s	*The frequency of the syndrome in this age group was 3.42%.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*Yes*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*Yes* *Rotterdam*
9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*No* *- Oligo-anovulation no - not defined* *- Hirsutism - yes, defined and examined by a group of physicians and trained midwives* *- Biochemical hyperandrogenaemia no - no cut offs.* *- PCO - yes and collected by one gynaecologist and rechecked.*

10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*Yes*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*No* *PCOS diagnosis based on Rotterdam criteria. However, no details on number of girls meeting certain criteria, only prevalence of PCOS* *Numerator and denominator appropriate but no confidence intervals.*
Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Not reported*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
COMMENTS	*Only girls with at least one clinical feature that included menstrual irregularity, hirsutism and obesity underwent blood testing and sonographic examination.*	
What is the overall risk of bias?	Low Moderate High Insufficient information	*7/11* *Medium risk of bias* *External validity of the study medium risk of bias. Concern regarding national representativeness and sample frame.* *Internal validity of the study medium risk of bias. Concern regarding measurement of PCOS (oligo-anovulation not defined, no cut-offs for hyperandrogenaemia), not all girls underwent blood testing and ultrasonography. No confidence intervals.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		

Study ID	*Sharif, 2017*
Study Citation	*Sharif E, Rahman S, Zia Y, Rizk NM. The frequency of polycystic ovary syndrome in young reproductive females in Qatar. Int J Womens Health. 2017;9:1-10. doi: 10.2147/IJWH.S120027*
Study Country	*Qatar*
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*120 female Qatari students between the ages of 18 and 30 years*

PCOS diagnostic criteria	*NIH.*	
N per group	*Qatari: 120*	
Setting	*Convenience (University)*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcome: to determine the frequency of PCOS defined by the NIH criterias.* *Secondary outcome: To determine PCOS features*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* *- age 18–30 years* *- menarche from 10 to 15 years* *- no history of anatomical deformity* *- no use of tablets or hair-removal methods* *- normal prolactin and thyroid-stimulating hormone (TSH) levels* *- a history of MI, such as oligomenorrhea and amenorrhea.*
Exclusion criteria	Yes Partial No Not reported	*Yes* *- Diagnosis of idiopathic hirsutism (IH) in which ovulatory dysfunction, HA, and other defined androgen excess disorders are ruled out.*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*No. Prospective cross-sectional study design was used.*
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	Yes Partial No Not reported	*No* *the study was conducted at one university only and it was not clear if this was representative of the national population.*
2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*No*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*No* *No form of random sampling was undertaken.*

4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*No* *Participants were recruited through a campaign (flyers, posters, social media) so non-response was not reported.*
5. Was the sample size adequate?	Yes Partial No Not reported	*No*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*
Summary Result/s	*The frequency of PCOS in this study was 18.33% according to the NIH criteria.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*Yes*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*Yes* *NIH*
9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*No* *- Oligo-anovulation - yes* *- Hirsutism - no - cut off of >17 was used on self report.* *- Biochemical hyperandrogenemia - no* *- PCO not performed*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*No* *All girls underwent same examinations. Oligo/anovulation assessed using a questionnaire, not sure if this was carried out by a clinician. Hirsutism on self report.*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*No* *Numerator and denominator appropriate but no confidence intervals.*
Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Not reported*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*

COMMENTS	*Women were recruited by a campaign called "PCOS study in Qatar University". This could have encouraged some students experiencing PCOS-like symptoms to come forward for this study.*	
What is the overall risk of bias?	Low Moderate High Insufficient information	*3/11* *High risk of bias* *External validity of the study high risk of bias. Concern regarding national representativeness, sample frame, random sampling and non-response.* *Internal validity of the study medium risk of bias. Concern regarding measurement of PCOS and reliable data collection.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		

Study ID	*Tehrani, 2011*	
Study Citation	*Tehrani FR, Simbar M, Tohidi M, Hosseinpanah F, Azizi F. The prevalence of polycystic ovary syndrome in a community sample of Iranian population: Iranian PCOS prevalence study. Reproductive Biology & Endocrinology. 2011;9:39. doi: 10.1186/1477-7827-9-144*	
Study Country	*Iran*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*A total of 1126 women, aged 18-45 years, were recruited from among reproductive aged women living in urban areas of four randomly selected provinces of different geographic regions i.e. Ghazvin (Central), Kermanshah (East), Golestan (North) and Hormozgan (South).*	
PCOS diagnostic criteria	*NIH/Rotterdam/AE-PCOS*	
N per group	*Iranian: 929*	
Setting	*Community*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcome:* *to determine the prevalence of PCOS under the NIH, Rott. and the AES criteria, in a well-defined, non-selected population of Iranian reproductive aged women, using universal assessment of ultrasonographic parameters, hormonal profiles and clinical histories.*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* *women, aged 18-45 years, were*

		recruited from among reproductive aged women living in urban areas of four randomly selected provinces
Exclusion criteria	Yes Partial No Not reported	*Yes* *Postmenopausal women* *Those who had undergone hysterectomy or bilateral oophorectomy* *Pregnant women*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	Yes Partial No Not reported	*No* *The study was conducted in urban populations only. ALthough the authors state that the age and sex distribution of the population of these provinces is representative of national general population based on 2006 national population and housing census of Iran, it is not clear if this was representative in terms of other demographic characteristics.*
2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*Yes* *The cluster sampling method was used and the sample of clusters was drawn from a list of all provinces in the target population*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*Yes* *Random sampling was used*
4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*Yes* *Of 1036 women who met our inclusion criteria, 929 ones completed the study procedure. (90% response rate)*
5. Was the sample size adequate?	Yes Partial No Not reported	*Yes* *Sample size calculation was carried out*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*
Summary Result/s	*The prevalence of PCOS was 7.1% (95% CI: 5.4 -8.8%) using the NIH definition, 11.7% (95% CI: 9.5- 13.7%) by AES criteria and 14.6% (95% CI: 12.3- 16.9%) using the Rott. criteria in our sample of an Iranian population.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*Yes*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*Yes*
9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*Yes*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*Yes*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Not reported*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
COMMENTS		
What is the overall risk of bias?	Low Moderate High Insufficient information	*10/11* *Low risk of bias* *External validity of the study low risk of bias. National representativeness was the only concern but was not deemed o affect the overal results of the study.* *Internal validity low risk of bias.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*N/A*	

Western Pacific Region

Study ID	*Boyle, 2012*

Study Citation	*Boyle JA, Cunningham J, O'Dea K, Dunbar T, Norman RJ. Prevalence of polycystic ovary syndrome in a sample of Indigenous women in Darwin, Australia. Medical Journal of Australia. 2012;196(1):62-66. doi: 10.5694/mja11.10553*	
Study Country	*Australia*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Indigenous women, aged 15–44 years, living in a defined area in and around Darwin, Northern Territory, Australia,*	
PCOS diagnostic criteria	*NIH*	
N per group	*248*	
Setting	*Community*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcome:* *the prevalence of PCOS* *the characteristics of women with and without PCOS, in a group of urban Indigenous women in Darwin, Northern Territory, Australia.*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes.* *Indigenous women, aged 15–44 years, living in a defined area in and around Darwin, Northern Territory, Australia,*
Exclusion criteria	Yes Partial No Not reported	*Yes* *Women who were pregnant or breastfeeding* *Those who did not consent to complete a reproductive health questionnaire* *Those without androgen level assessment* *those who reported to be menopausal* *using hormonal contraception* *those who had a hysterectomy or oophorectomy* *those with missing information about cycle regularity*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
1. Was the study's target population a close representation of the national population in	Yes Partial No Not reported	*No* *The study was conducted in one specific area.*

relation to relevant variables, e.g. occupation, socio-economic status)		
2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*No*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*No*
4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*Yes* *248 women assessed out of 293 eligible women (85%)*
5. Was the sample size adequate?	Yes Partial No Not reported	*No* *No sample size calculation and unclear if sample size of 248 is high enough*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*
Summary Result/s	*Using the NIH 1990 criteria for diagnosis, PCOS was present in around one in six (15.3%) urban Indigenous women volunteering for our study in Darwin.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*Yes*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*No* *NIH, but hirsutism not assessed*
9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*Yes* *the criteria that were used for diagnosis were valid measurements*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*Yes*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*No* *Numerator and denominator appropriate, but no confidence interval.*

Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes* *Participants of DRUID study, earlier described*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
COMMENTS	*Hirsutism not used in diagnosis.*	
What is the overall risk of bias?	Low Moderate High Insufficient information	*5/11* *Medium risk of bias.* *External validity of the study high risk of bias based on national representativeness, sample frame and sampling, sample size.* *Internal validity medium risk of bias: PCOS diagnoses based on biochemical hyperandrogenism and menstrual irregularity only, hirsutism not part of diagnostic criteria, no confidence intervals.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*N/A*	

Study ID	*Chen, 2008*
Study Citation	*Chen X, Yang D, Mo Y, Li L, Chen Y, Huang Y. Prevalence of polycystic ovary syndrome in unselected women from southern China. European Journal of Obstetrics, Gynecology, & Reproductive Biology. 2008;139(1):59-64. doi: 10.1016/j.ejogrb.2007.12.018*
Study Country	*China*
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*915 Han Chinese women of reproductive age, who lived in Guangzhou in Southern-China. All participants were undergoing their annual routine physical examination and were not presenting for a medical reason or complaint.*
PCOS diagnostic criteria	*Rotterdam/AE-PCOS*
N per group	*Chinese: 915 (20-45)*
Setting	*Community*
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcome: determine the prevalence of the PCOS in a sample of the population of southern China.* *Secondary outcome: identify hormonal and metabolic parameters of women with PCOS and, in particular, among women with clinical signs of hyperandrogenemia.*

Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* *Han chinese women of reproductive age undergoing annual routine physical examination and not presenting for a medical reason or complaint.*
Exclusion criteria	Yes Partial No Not reported	*Yes* *menopausal (including natural and surgical menopause) women women who were pregnant at the time of the evaluation.*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	Yes Partial No Not reported	*No* *The study was conducted in Guangzhou in Southern-China. It is not clear if this was representative of the national population.*
2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*Yes* *Sampling frame was a list of almost every individual within the target population.*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*No* *Unclear*
4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*Yes* *Only 2.3% refused to participate*
5. Was the sample size adequate?	Yes Partial No Not reported	*Yes* *No sample size calculation but size seems large enough that it is not necessary.*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*

Summary Result/s	*In this study of an unselected sample of 915 women of reproductive age, the estimated prevalence of PCOS was 2.2% (20/915) based on AES 2006 criteria for PCOS. If we identify the potential phenotype of women solely with oligo-ovulation and polycystic ovaries, and not those with hyperandrogenemia or hirsutism, the prevalence of PCOS was 2.4% (22/915) based on Rotterdam 2003 criteria.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*Yes*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*Yes*
9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*No* *PCO: no criteria reported*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*Yes*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*No* *Numerator and denominator appropriate, but no confidence interval.*
Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Not reported*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*Not reported*
COMMENTS		
What is the overall risk of bias?	Low Moderate High Insufficient information	*6/11* *Medium risk of bias* *External validity of the study low risk of bias. Only concern regarding national representativeness and random sampling.* *Internal validity medium risk of bias. Concern regarding measurement of PCOS (criteria for PCO not reported) and lack of confidence intervals.*

Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*N/A*

Study ID	*Dhashti, 2019*	
Study Citation	*Dashti S, Latiffah Abdul L, Habibah Abdul H, et al. Prevalence of Polycystic Ovary Syndrome among Malaysian Female University Staff. Journal of Midwifery & Reproductive Health. 2019;7(1):1560-1568. doi: 10.22038/jmrh.2018.30370.1329*	
Study Country	*Malaysia*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*675 females of reproductive age working at University Putra Malaysia, Selangor, Malaysia*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	*Malaysian (675)*	
Setting	*Convenience (university)*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcome:* *to assess the prevalence of PCOS and its risk factors among the university staff working at a large governmental university of Malaysia.*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* *Female university staff of childbearing age (18-49 years) and those willing to participate*
Exclusion criteria	Yes Partial No Not reported	*"Yes* *- consumption of oral contraceptives for more than 4 weeks* *- use of hormonal treatment or insulin-sensitizing agents for more than 2 weeks* *- abnormal thyroid findings* *- nonclassical adrenal hyperplasia* *- diagnosis with such conditions as hyperprolactinemia, hypogonadotropic hypogonadism, premature ovarian failure, ovarian cysts or tumors, congenital adrenal hyperplasia, androgen-secreting tumor, Cushing's syndrome, uterine* *- disorders, and chromosomal anomalies* *- Pregnancy* *- Menopause*

If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	Yes Partial No Not reported	*No* *The study was conducted at one specific university, it was not clear if this was representative of the national population.*
2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*Yes* *Target population was Malaysian university staff. Sample frame was a complete list of staff members.*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*Yes* *Random sampling was used to select participants from the sampling frame.*
4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*No* *47.4% participated in the study.*
5. Was the sample size adequate?	Yes Partial No Not reported	*Yes*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*
Summary Result/s	*A total of 675 females with the mean age of 26.01±7.14 years participated in this study. The prevalence rate of PCOS was obtained as 12.6%. All PCOS subjects were detected with hyperandrogenism and polycystic ovary, while anovulation was present in only one participant (1.2%).*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*Yes*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*Yes* *Rotterdam*

9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*No* *Oligo/anovulation: no, definition is fine but assessed on questionnaire* *Hirsutism: Yes* *Hyperandrogenemia: no, no 95th percentile cut off used.*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*No* *Three interviewers (i.e., one postgraduate student studying at the university under investigation and two research assistants) were fully instructed to use the standardized questionnaire and perform the required physical examinations. There was no evidence of comparison of results from across the observers.*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*No* *Numerator and denominator appropriate, but no confidence interval.*
Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
COMMENTS		
What is the overall risk of bias?	Low Moderate High Insufficient information	*6/11* *Medium risk of bias* *External validity of the study medium risk of bias. Main concern regarding national represenattiveness and non-response.* *Internal validity of the study medium risk of bias. Maiin concern regarding measurement of PCOS.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*N/A*	

Study ID	*Davis, 2002*
Study Citation	*Davis SR, Knight S, White V, Claridge C, Davis BJ, Bell R. Preliminary indication of a high prevalence of polycystic ovary syndrome in indigenous Australian women. Gynecological Endocrinology. 2002;16(6):443-446. doi: 10.1080/gye.16.6.443.446*
Study Country	*Australia*

CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*38 Indigenous Australian women*	
PCOS diagnostic criteria	*NIH*	
N per group	*Australian Indigenous: 38*	
Setting	*Community*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcome:* *to estimate the likely prevalence of polycystic ovary syndrome (PCOS) in indigenous Australian women in a cross-sectional survey based on structured interviews.*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* *Indigenous women from the Kimberley region of Western Australia and the south-western region of victoria* *Aged 18 or more* *Able to give written informed consent*
Exclusion criteria	Yes Partial No Not reported	*Yes* *Women that were not currently pregnant* *(< 12 months' amenorrhea and no climacteric symptoms*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	Yes Partial No Not reported	*No* *The study was conducted in one specific region*
2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*No* *Recruitment was a selective process determined exclusively by the women from these highly mobile populations who were in the communities at the time of our visit and the wishes of the women involved.*

3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*No*
4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*No* *Non-response not reported*
5. Was the sample size adequate?	Yes Partial No Not reported	*No*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*
Summary Result/s	*Taken together with the physical characteristics, these findings are suggestive of possible PCOS in at least ten of the 38 premenopausal women evaluated (26%).*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*Yes*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*Yes* *NIH*
9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*No* *Hirsutism: no - only facial* *Hyperandrogenemia: Total T and FAI, normal ranges are given* *Oligo-anovulation: Yes*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*Yes* *Hirsutism: yes, by all women were assessed the same* *Hyperandrogenemia: all women assessed the same* *Oligo-anovulation: Yes, all women assessed by psychologist/nurse who took questionnaire*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*No* *Numerator and denominator are clear, but no confidence intervals.*
Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*

Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*Not reported*
COMMENTS	*Reported prevalence was 10/38 (26,3%) however we changed to 7/38 (18.4%) because women with hirsutism & elevated FAI only were classified as PCOS.*	
What is the overall risk of bias?	Low Moderate High Insufficient information	*4/11* *High risk of bias* *External validity of the study high risk of bias. Concerns regarding national representativeness, sample frame, random sampling, non-response bias, sample size.* *Internal validity of the study medium risk of bias. Main concern regarding measurement of PCOS (e.g. hirsutism scoring only facial), Fasting samples of blood for biochemical analysis were obtained from only 13 women)*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*N/A*	

Study ID	*Jiao, 2014*	
Study Citation	*Jiao J, Fang Y, Wang T, Wang Z, Zhou M, Wang X. Epidemiologic investigation of polycystic ovarian syndrome (PCOS) in Han ethnic women of reproductive age in Liaoning Province, China. Clinical & Experimental Obstetrics & Gynecology. 2014;41(3):304-309. doi: 10.12891/ceog16282014*	
Study Country	*China*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Han women of reproductive age in Liaoning Province in Northeastern China*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	*Han Chinese: 1600*	
Setting	*Community*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcome:* *To determine the incidence of polycystic ovary syndrome (PCOS) among Han women of reproductive age in Liaoning Province in Northeastern China, based on the Revised Rotterdam 2003 criteria*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes	*Yes*

	Partial No Not reported	*Han ethnic women aged 19 years to 45 years who were permanent residents in four different areas in Liaoning Province, Northern China, including the two cities Shenyang and Yingkou, and the two towns Benxi and Zhangwu.*
Exclusion criteria	Yes Partial No Not reported	*Yes* *- Pregnant women* *- Those suspected of pregnancy* *- Lactating women* *- those with endocrien diseases* *- Those on long-term oral contraceptives or subcutaneously injected contraceptive*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	Yes Partial No Not reported	*No* *The study was conducted in one province only, and it is not clear if this was representative of the national population*
2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*Yes.* *All the Han ethnic women aged 19 years to 45 years were investigated, and finally, 1,600 women participated the study.*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*No*
4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*No* *Response rate not reported*
5. Was the sample size adequate?	Yes Partial No Not reported	*Yes*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*
Summary Result/s	*The prevalence of PCOS in this study population was 8.25%, with an infertility rate of 27.8%.*	

INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*Yes*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*Yes*
9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*No*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*No* *Menstrual cyclicity on self report.*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*No* *Numerator and denominator clear, but no confidence intervals.*
Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Not reported*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*Not reported*
COMMENTS	*Unclear whether women with acne only or alopecia only were classified as hyperandrogenemia or if women required hirsutism as a minimum.* *fasting bloods that were only done in suspected PCOS cases.*	
What is the overall risk of bias?	Low Moderate High Insufficient information	*5/11* *Medium risk of bias* *External validity of the study medium risk of bias. Concerns regarding national representativeness, random selection and non-response bias.* *Internal validity of the study has a high risk of bias. Main concern regarding measurement of PCOS and lack of reliable data collection.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*N/A*	

Study ID	*Kim, 2022*	
Study Citation	*Kim JH, Jung MH, Hong SH, Moon N, Kang DR. Age-Adjusted Prevalence and Characteristics of Women with Polycystic Ovarian Syndrome in Korea: A Nationwide Population-Based Study (2010-2019). Yonsei Medical Journal. 2022;63(8):794-798. doi: 10.3349/ymj.2022.63.8.794*	
Study Country	*Korea*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*544619 Korean women in the population- based National Health Information Databases from 2010 to 2019*	
PCOS diagnostic criteria	*Diagnoses were coded using the Korean Informative Classification of Disease, 10th revision (KICD-10).*	
N per group	*Korean: 544619*	
Setting	*Nationwide population-based*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcome:* *To evaluate the prevalence and characteristics of women with PCOS over the past 10 years in Korea.*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* *women in the population- based National Health Information Databases from 2010 to 2019*
Exclusion criteria	Yes Partial No Not reported	*Yes* *women with missing residences (n=9)* *missing insurance information (n=823* *overlapping cases (n=12385).*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*No* *Not clear why missing insurance information would be relevant*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
1. Was the study's target population a close representation of the national population in	Yes Partial No Not reported	*Yes*

relation to relevant variables, e.g. occupation, socio-economic status)		
2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*Yes*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*Yes*
4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*Yes*
5. Was the sample size adequate?	Yes Partial No Not reported	*Yes*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*
Summary Result/s	*In summary, this is the first study to investigate the prevalence of PCOS in a nationwide population of reproductive-aged Korean women. The age-adjusted incidence and prevalence of PCOS in Korean women aged 19–49 years were 2.8% and 4.3%, respectively*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*No* *ICD codes were used*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*No* *at least one claim per year, under the KICD-10 codes E28.0–E28.9,.*
9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*No* *at least one claim per year, under the KICD-10 codes E28.0–E28.9, were included in this study.* *Unclear what these codes mean. ICD codes not a reliable tool to measure PCOS.*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*Yes*
11. Were the numerator(s) and denominator(s) for the	Yes Partial	*No*

parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	No Not reported	*Denumerator not reported* *The age-adjusted annual prevalence rates of PCOS from 2010 to 2019 were calculate by dividing the number of women with PCOS by the number of Korean women from the 2010 Population and Housing Census. The age-adjusted incidence rate was calculated by dividing the number of new cases of PCOS annually by the number* *of women at risk.*
Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Not reported*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*Not reported*
COMMENTS	*Age adjusted prevalence rates*	
What is the overall risk of bias?	Low Moderate High Insufficient information	*7/11* *Medium risk of bias* *External validity of the study low risk of bias.* *Internal validity of the study high risk of bias. Concern regarding measurement of PCOS (ICD codes), denumerator not reported.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*N/A*	

Study ID	*Li, 2013*
Study Citation	*Li R, Zhang Q, Yang D, et al. Prevalence of polycystic ovary syndrome in women in China: a large community-based study. Human Reproduction. 2013;28(9):2562-2569. doi:10.1093/humrep/det262*
Study Country	*China*
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*15 924 Han Chinese women, aged 19-45 recruited from the top 10 provinces and municipalities in China (multi layered, stratified sample*
PCOS diagnostic criteria	*Rotterdam*
N per group	*Han Chinese: 15 924*
Setting	*cross-community population-based*

Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcome:* *to determine the prevalence of polycystic ovary syndrome (PCOS) in Han Chinese women from different communities* *Secondary outcomes:* *- PCOS subtypes* *- Characteristics of Chinese women with and without PCOS* *- The complications in women with different subtypes of PCOS* *- Complication rates in women with PCOS according to age* *- The complications between obese and non-obse women with PCOS*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* *women of Han Chinese ethnicity, of reproductive age (19–45 years) from the top 10 provinces and municipalities in China*
Exclusion criteria	Yes Partial No Not reported	*Yes* *Women experiencing menopause or an ongoing pregnancy at the time of the investigation were excluded.*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	Yes Partial No Not reported	*Yes* *Study was conducted in 10 provinces, representative of the national population*
2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*Yes* *A multi-layer, stratified sampling method was performed from each province or municipality by city or district, town/township and village/street order and ultimately selected communities.*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*Yes* *In the selected villages, participants aged 19–45 years were identified and 80–120 residential women per community were recruited.*

4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*Yes* *the overall response rate was 94.3%*
5. Was the sample size adequate?	Yes Partial No Not reported	*Yes*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*
Summary Result/s	*In this large epidemiological study, the incidence of women with PCOS in the Chinese Han population is 5.6% (894/15 924), according to the Rotterdam PCOS criteria.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*Yes*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*Yes*
9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*Yes*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*Yes* *Twenty interviewers (one senior and one junior gynecologist or postgraduate student from each participating university hospital) were well trained to manage the standardized questionnaire and physical examination. All investigators were fully trained in their respective regions, including pilot interviews in non-sampled communities that were monitored by the principal investigators and on-site supervisors.*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*No* *Numerator and denominator are clear, but no confidence intervals.*
Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Not reported*

Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
COMMENTS		
What is the overall risk of bias?	Low Moderate High Insufficient information	*10/11* *Low risk of bias* *External validity of the study low risk of bias.* *Internal validity of the study low risk of bias. Only concern was lack of confidence intervals.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*N/A*	

Study ID	*Min, 2022*	
Study Citation	*Min D, Jang IS, Park S. Preventive Behavior Intentions for Polycystic Ovary Syndrome in Young Students. Metabolic Syndrome & Related Disorders. 2022;20(5):273-279. doi: 10.1089/met.2021.0123*	
Study Country	*Korea*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*328 female university students from July 25 to August 30, 2020. Data collected using an oline survey.*	
PCOS diagnostic criteria	*Self-report*	
N per group	*Korean: 328*	
Setting	*Convenience (university)*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcome:* *this study aimed to explore the health beliefs and knowledge of PCOS of South Korean female college students and their preventive behavior intentions*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* *- Female university students from across South Korea*

Exclusion criteria	Yes Partial No Not reported	*No*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Partial* *No exclusion critieria. Inclusion criteiria appropriate.*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	Yes Partial No Not reported	*No* *Only university students*
2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*No* *Only those who responded to online survey link*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*No*
4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*No* *Response rate not reported*
5. Was the sample size adequate?	Yes Partial No Not reported	*No* *No sample size calculation*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*
Summary Result/s	*The average age of participants was 21.67 years, 7.3% of whom had been diagnosed with PCOS. Perceived disability (b=0.30, P<0.001) and perceived benefit (b=0.26, P<0.001) of health behavior were associated with preventive behavior intentions. However, knowledge was not a significant factor.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*Yes*
8. Was an acceptable case definition used in the study?	Yes Partial	*No*

	No Not reported	*Self report by survey was diagnosed with PCOS by a doctor*
9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*No*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*Yes*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*No* *Numerator and denominator clear, but no confidence intervals.*
Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Not reported*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
COMMENTS		
What is the overall risk of bias?	Low Moderate High Insufficient information	*3/11* *High risk of bias* *External validity of the study high risk of bias. Concerns regarding national representativeness, sample frame, random sampling, non-response bias, sample size.* *Internal validity of the study high risk of bias. Concern regarding measurement of PCOS (self-report) and no confidence intervals.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*N/A*	

Study ID	*Maredia, 2018*
Study Citation	*Maredia H, Hawley NL, Lambert-Messerlian G, et al. Reproductive health, obesity, and cardiometabolic risk factors among Samoan women. American Journal of Human Biology. 2018;30(3):e23106. doi:10.1002/ajhb.23106*
Study Country	*Samoa*

CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Samoan women 25–39 years of age (n=470) from a larger population-based genome-wide association study (GWAS) of adiposity and cardiometabolic disease*	
PCOS diagnostic criteria	*NIH*	
N per group	*Samoan: 470*	
Setting	*Population based*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcome:* *to update and improve upon current estimates of the prevalence of menstrual irregularity and PCOS among reproductive-aged Samoan women* *Secondary outcome:* *to examine their associations with adiposity and cardiometabolic risk factors*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* *- Samoan women from all four census regions of Samoa* *- women <40 years of age, i.e., 25–39 years*
Exclusion criteria	Yes Partial No Not reported	*Yes* *- pregnancy/lactation (n = 17)* *- hysterectomy or oophorectomy (n = 14)* *- cancer treatment (n = 1)* *- who did not report their menstrual cycle data (n = 10)* *- who lacked anthropometric measurements (n = 1) or fasting serum samples (n = 49)* *- women who indicated ever using contraceptive injections (n = 173).* *- ambiguity of the response regarding menstrual cycle (n=24).*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	Yes Partial No Not reported	*Yes* *The study was a national health survey of people 24.5 to <65 years and the sample was drawn from a list that included all census regions of Samoa.*

2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*Yes*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*No* *No random sampling*
4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*No* *Non response was not reported*
5. Was the sample size adequate?	Yes Partial No Not reported	*Yes*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*
Summary Result/s		
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*Yes*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*Yes* *To categorize any participant as having PCOS, we required two of the following three conditions: menstrual irregularity, biochemical hyperandrogenism, and/or high serum AMH levels as a marker of polycystic ovary morphology (NIH 2012)*
9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*No* *Oligo/anovulation: No - self report on questionnaire.* *Hyperandrogenism: NA* *Hyperandrogenemia: Yes* *PCO: AMH levels*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*Yes* *Ethnity:* *Samoan origin, which was determined by having four Samoan grandparents (based on self-report)*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes* *Numerator and denominator appropriate, prevalence with Confidence Interval.*

Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
COMMENTS	*Clinical hyperandrogenism not assessed*	
What is the overall risk of bias?	Low Moderate High Insufficient information	*7/11* *Medium risk of bias* *External validity of the study medium risk of bias. Concern regarding random sampling and non-response.* *Internal validity low risk of bias. Only concern was measurement of PCOS*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*N/A*	

Study ID	*Park, 2021*
Study Citation	*Park YJ, Shin H, Jeon S, Cho I, Kim YJ. Menstrual Cycle Patterns and the Prevalence of Premenstrual Syndrome and Polycystic Ovary Syndrome in Korean Young Adult Women. Healthcare (Basel). 2021 Jan 7;9(1):56. doi: 10.3390/healthcare9010056. PMID: 33430265; PMCID: PMC7825721.*
Study Country	*Korea*
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*462 undergraduate and graduate students at K University*
PCOS diagnostic criteria	*NIH*
N per group	*Korean: 462*
Setting	*Convenience (university)*
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcome:* *to investigate menstrual cycle;* *Secondary outcomes:* *- to identify the symptoms and prevalence of clinically significant PMS;* *- to estimate the prevalence of PCOS;*

	- to identify the relationship between health-related behaviors (smoking, drinking, eating habits and nutrients intake), body composition and blood indexes (total testosterone (T), sex hormone binding globulin (sHBG), fasting blood sugar (FBS) and insulin) according to menstrual cycle regularity and the presence or absence of PCOS.	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* *462 undergraduate and graduate students at K University*
Exclusion criteria	Yes Partial No Not reported	*Yes* *Estrogen and progesterone-containing hormone drugs*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	Yes Partial No Not reported	*No* *Only women from a certain university*
2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*Yes*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*No* *No random sampling*
4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*No* *Recruitment through advertisement so non-response not reported*
5. Was the sample size adequate?	Yes Partial No Not reported	*Yes*

6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*
Summary Result/s	*In the second phase, 88 women with irregular menstruation in phase one had blood tests taken and body composition measured.* *In the second phase, 24 women of 88 participants had T ≥ 0.520 ng/mL or FAI ≥ 5.36. Generalizing this result to the entire population (462), the prevalence of PCOS was estimated to be 5.2% based on the PCOS criteria for this study.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*Yes*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*Yes*
9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*No* *Oligo/anovulation: No - self report on questionnaire* *Hyperandrogenism: Not assessed* *Hyperandrogenism was defined as the biochemical expression of T ≥ 0.520 ng/mL or FAI* *≥ 5.36* *PCO: not assessed*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*No* *Oligo/anovulation: self report not standard, reliable* *Hyperandrogenism: NA* *Hyperandrogenemia: yes* *PCO: not assessed*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*No* *Numerator and denominator appropriate, prevalence without Confidence Interval.*
Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
COMMENTS		

What is the overall risk of bias?	Low Moderate High Insufficient information	*5/11* *Medium risk of bias* *External validity of the study medium risk of bias. Concern regarding national representativeness, random sampling and non-response.* *Internal validity of the study medium risk of bias. Concern regarding measurement of PCOS, data analysis.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*N/A*	

Study ID	*Yang, 2022*	
Study Citation	*Yang R, Li Q, Zhou Z, et al. Changes in the prevalence of polycystic ovary syndrome in China over the past decade. Lancet Reg Health West Pac. 2022;25:100494. doi: 10.1016/j.lanwpc.2022.100494*	
Study Country	*China*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*12,815 married women aged 20-49 years from 15 provinces from mainland China were selected as part of the China Fertility Survey of Married Women (CFSMW) 2020 survey* *The results were compared to results of a similar study done in 2010 involving 15,924 Han Chinese women aged 19-45 years from 10 provinces and municipalities in China.*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	*Chinese: 12815*	
Setting	*Community*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcome:* *- Investigate the prevalence of PCOS in Chinese women of reproductive age* *Secondary outcome:* *- examine the long-term trends in the prevalence of PCOS over the past decade, with specific emphasis on changes in subtypes and complications*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes:*

		- Married women of ethan Han Chinese lineage, aged 20-49 years and had lived in the selected village/residential area for 6 months or longer *- Selected from 15 provinces from mainland China, geographically distrubuted in southeast, southwest, central, and northest regions*
Exclusion criteria	Yes Partial No Not reported	*Yes:* *- Women who are <20 and >49 years of age at the time of visit (n=408)* *- Excluded women for whom data on their fertility condition was lacking (n=285)*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Partial* *Unclear why only women who were married were selected*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	Yes Partial No Not reported	*No* *Only married women selected to represent women of reproductive age*
2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*Yes* *- Multistage stratified sampling scheme* *- Selected 15 provinces from mainland China, geographically distrubuted in soueast, southwest, central and northest regions* *- Then selected 3 townships or districts from each province according to their degree of urbanization an dpopulation size*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*Yes* *- Random sampling method used to select 2-4 villages/residental areas from each township or district*
4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*Yes* *285 out of 13,100 (2.2%) women excluded due to data on their fertility condition was lacking*
5. Was the sample size adequate?	Yes Partial No Not reported	*Yes*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*

Summary Result/s	*- 826 participants could be diagnosed as having PCOS, with a weight prevalence of 7.8% (95% CI: 7.0%, 9.0%) among women aged 20-49 years, leading to an estimate of 24.0 million women of reproductive age affected by this condition in China as a whole.* *- The estimated prevalence in 2020 was higher than tha tof a decade ago, suggesting a two-thirds increase over the study period. Women with PCOS in 2020 also appeared to have a more severe phenotype overall than those of a decade ago, possibility reflecting a significantly higher prevalnce of obsetiy, hyeprandrogenism, and infertility.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*Yes*
8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*Yes*
9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*No* *Oligo:anovulation: yes* *Hyperandrogenism: yes* *Hyperandrogenemia: no* *PCO: No - We did not count cases with increased ovarian volume (>10 cm) as ovarian volume is affected by the menstrual cycle and it is difficult to examine at a particular time of the menstrual cycle in a field survey.*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*Yes*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
COMMENTS		
What is the overall risk of bias?	Low Moderate High Insufficient information	*8/11* *Low risk of bias* *External validity low risk of bias. Only concern regarding national representativeness.*

		Internal validity low risk of bias
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*N/A*	

Study ID	*Zhuang, 2014*	
Study Citation	*Zhuang J, Liu Y, Xu L, et al. Prevalence of the polycystic ovary syndrome in female residents of Chengdu, China. Gynecologic & Obstetric Investigation. 2014;77(4):217-223. doi: 10.1159/000358485*	
Study Country	*China*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*- Female residents of Chengdu, China aged 12-44* *- Residents of two buildings, students of two units of a women's domitory in two local universities, and all the female students in one class of each grade (from junior one to senior three) in three middle schools were recruited*	
PCOS diagnostic criteria	*NIH/Rotterdam/AES(Androgen Excess Society)-2006*	
N per group	*Chinese: 1,645*	
Setting	*Chinese: 1,645*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcome:* *- Investigate the prevalence of PCOS in a Chinese population* *Secondary outcome:* *- Investigate the changes in prevalence of PCOS with age*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes:* *- Female residents in Chengdu aged between 12 and 44* *- Adolescent girl's menarche happened at least 2 years ago*
Exclusion criteria	Yes Partial No Not reported	*Yes:* *- Not resident in Chengdu* *- In the previous 3 months took gonadal hormone or drugs which could apparently affect ovarian function*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*

Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g. occupation, socio-economic status)	Yes Partial No Not reported	*No* *The study was conducted in one city/province in China. It is not clear if this was representative of the national population.*
2. Was the sampling frame a true or close representation of the target population?	Yes Partial No Not reported	*Yes* *- Cluster sampling used* *- Residents of two buildings, students of two units of a women's domitory in two local universities, and all the female students in one class of each grade (from junior one to senior three) in three middle schools were recruited*
3. Was some random selection used to select the sample, OR, was a census undertaken?	Yes Partial No Not reported	*Yes* *- Cluster-randomised sampling used* *- Used constituent ratio of women at different age levels obtained in the population census in the 2004 Yearbook of Sichuan Province to calculate the exact number of participants needed to included at each age* *- Respondents were recruited by the order of house number or student number,*
4. Was the likelihood of non-response bias minimal?	Yes Partial No Not reported	*Yes* *- Overall, 405/2,050 (19.7%) participants recruited did not complete the study* *- Response rate for questionnaires was 83.1% (1,703/2,050)* *- 58 participants were excluded: 32 suffered from acute disease, 26 were unwilling to complete the blood collection*
5. Was the sample size adequate?	Yes Partial No Not reported	*Yes*
6. Were the study subjects and setting described in detail?	Yes Partial No Not reported	*Yes*
Summary Result/s	*- The prevalence of PCOS in women aged 12-44 was 7.1, 11.2 and 7.4% respectively, according to the three different criteria (NIH, Rotterdam, Androgen Excess).* *- After the osnet of puberty, the prevalence of PCOS increased rapidly from 12-14 years of age, peaked between 15 and 24 and decreased gradually thereafter and reached its lowest point before menopause*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
7. Were data collected directly from the subjects (as opposed to a proxy)	Yes Partial No Not reported	*Yes*

8. Was an acceptable case definition used in the study?	Yes Partial No Not reported	*Yes*
9. Was the study instrument that measured the parameter of interest (PCOS diagnosis) shown to have reliability and validity -	Yes Partial No Not reported	*No* *No >95th percentile used for hyperandrogenemia*
10. Was the same mode of data collection used for all subjects and in a standard, reliable way?	Yes Partial No Not reported	*Yes*
11. Were the numerator(s) and denominator(s) for the parameter of interest appropriate? If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Not reported*
Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
COMMENTS		
What is the overall risk of bias?	Low Moderate High Insufficient information	*9/11* *Low risk of bias* *External validity of the study low risk of bias. Only concern regarding national representativeness.* *Internal validity low risk of bias*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*N/A*	

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 1

Question 1.6.

In women with PCOS is there evidence of ethnic variations in the prevalence?

BACKGROUND:

Polycystic ovary syndrome (PCOS) is a reproductive and metabolic disorder with prevalence increasing all over the world (1, 2). The prevalence of this heterogeneous disorder, may be affected by geographical regions and race/ethnicity (3). Furthermore, there are different diagnostic criteria for PCOS including the National Institutes of Health (1990), Rotterdam (2003), and Androgen Excess & PCOS society (2006) (4). It has been shown that diagnosing according to Rotterdam criteria - endorsed by the 2018 International Guideline for PCOS. leads to a 1.5 times prevalence over NIH criteria (5).

According to a recent meta-analysis, there is variation in prevalence of PCOS among different races. This study reported that the lowest prevalence was observed in Chinese women using 2003 Rotterdam criterion (5.6%), and then in an ascending order for Caucasians using 1990 NIH criterion was (5.5%), in Middle Eastern the prevalence according to the 1990 NIH was 6.1%; based on the 2003 Rotterdam was 16.0% and using 2006 AES was 12.6%, and among Black women according to the 1990 NIH was 6.1% (6).

Genetic and environmental factors are major drivers of PCOS (7). Although the aetiological risk factors leading to development or progression of PCOS are well recognized, there are still areas of uncertainty. A number of lifestyle risk factors which are known to be an important factor in developing PCOS include low physical inactivity, physical and emotional stress, and improper diet (8, 9). Adherence to the treatment modalities of PCOS including lifestyle, complementary and alternative medicine, and hormonal medication is varied by ethnicity (9).

There have been very few descriptions of differences in PCOS presentation and prevalence between different ethnic groups except in the same country. These are often flawed based on a failure to take into consideration modifying factors. For instance, several descriptions from the United States, comparing people of Caucasian origin with those of African American and immigrant Asian background do not take into consideration differences in diet, lifestyle and occupation.

Clinical practice gap: need for guidance

Health personnel see patients of different ethnic backgrounds and apply the same principles to the diagnosis of PCOS. It is important to provide guidance on potential differences between groups.

Prevalence: Based on the available evidence in this guideline meta-analysis, the prevalence of PCOS in adult women appears to be similar across various populations and ethnic groups when grouped by either by ethnicities or regions around the world. When grouped by ethnicities the prevalence ranges between 5-7% specifically in American, Black or African American, Hispanic North American, Central American, South American, European, South & Central Asian, South & North east Asian and Polynesian women. The prevalence was found to be 13% and 16% in North African & Middle Eastern and Australian Indigenous populations. These were similar irrespective of criteria used for the diagnosis of PCOS.

The prevalence of PCOS in adolescent women from different ethnicities was 6% - specifically 7% and 6% for Southern and central Asian and European adolescent women respectively.

All populations came from 5 broad regions, namely the America's, European, Eastern Mediterranean, Western Pacific, and South East Asian regions. The prevalence by region was 7%, 11%, 13%, 7% and 6% respectively.

Using the diagnostic criteria for sub-analysis showed a prevalence of 8% using NIH criteria, 10% using Rotterdam criteria, 10% using AE-PCOS and 9% for self-reported diagnosis.

Summary of key diagnostic features between ethnic and geographic origins:

1. Ovulation - There is little evidence that this varies across different groups.

2. Testosterone measurements – Most studies from Asia, Europe and North America show similar levels of testosterone in the blood of subjects with PCOS.

3. Ultrasound features – Data on this aspect are compromised by the differences of ultrasound probes used, diagnostic features and skill and consistency of the operator. However, there is little evidence to suggest a difference in ultrasound features between ethnic groups.

4. Skin manifestations – As part of the hyperandrogenism definition, hirsutism is taken into consideration and there are clear differences between ethnic groups, with women from Middle Eastern and South Asian origin having far greater hirsutism that for example, those of Eastern Asian origin. In the latter group acne seems to be more common.

5. Metabolic features – There are clear differences in body mass index between different ethnic groups but this is probably not genetic and is more dependent on lifestyle and environmental factors. Body mass index (BMI) in parts of North America are enormous compared to some parts of Europe and East Asia. There is therefore a concomitant increase in insulin resistance, diabetes mellitus and lipid profiles but much of this is probably dependent on BMI rather than ethnic factors.

6. Prevalence – The highest prevalence has been reported among Australian indigenous women and North African & Middle Eastern women

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GRADE EVIDENCE CERTAINTY	
Comparison	**GRADE for critical outcomes**
o **Comparison 1**. PCOS prevalence among adult women from different ethnicities using NIH, Rotterdam, AE-PCOS and Self report diagnostic criteria	⨁◯◯◯ VERY LOW
o **Comparison 2.** Prevalence of PCOS among adult women from different ethnicities using NIH criteria	⨁◯◯◯ VERY LOW
o **Comparison 3.** PCOS prevalence in different ethnicities using Rotterdam criteria	⨁⨁◯◯ LOW
o **Comparison 4.** PCOS prevalence in among adolescents using different criteria	⨁◯◯◯ VERY LOW

Evidence to Recommendations Framework

COMPARISONS (option versus other option)

Comparison 1. PCOS prevalence among adult women from different ethnicities using NIH, Rotterdam, AE-PCOS and Self report diagnostic criteria
Comparison 2. Prevalence of PCOS among adult women from different ethnicities using NIH criteria
Comparison 3. PCOS prevalence in different ethnicities using Rotterdam criteria
Comparison 4. PCOS prevalence in among adolescents using different criteria

EVIDENCE-BASED RECOMMENDATION(S)

EBR: Healthcare professionals should be aware of the high prevalence of PCOS across different ethnicities and word regions, ranging from 10-13% globally using the Rotterdam criteria.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

EBR: Healthcare professionals should be aware that PCOS prevalence is similar across world regions and ethnicities.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

PRACTICE POINT

Health professionals should be aware that the presentation of PCOS may vary across ethnic groups.

GRADE CONSIDERATIONS

Justifications:
The meta-analysis only included unselected populations with well-defined ethnicity and held up in sensitivity analysis of high-quality studies.

Subgroup considerations:
The prevalence of PCOS is similar in adolescent women from different ethnicities.

Implementation considerations:
Not applicable

Monitoring and evaluation considerations:
Not applicable

Research priorities:
There may be a higher prevalence of PCOS in women from the North African, Middle Eastern region and Indigenous Australian people with more research needed.
Need to capture more diverse populations, particularly from the African and South American continents.
Need more research on ethnic variation, including prevalence, phenotype and manifestations in adults and adolescents.
Need research on PCOS in people of diverse ethnic backgrounds.
Need more research on the impact of migration and environment on PCOS prevalence.
All research in PCOS should report on ethnicities.

GRADE framework

GRADE DECIDE **Interactive Evidence to Decision Framework**

• DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

individualised care

awareness of the condition

● UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

Judgement:

☐ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☒ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

No undesirable effects

● CERTAINTY OF THE EVIDENCE

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☐ Very low	☒ Low	☐ Moderate	☐ High

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

The evidence applies only to the populations who were studied

Overall quality of evidence is ranked low based on the use of observational studies. However this topic can only be investigated using observational design.

Rotterdam is the endorsed diagnostic criteria dn for this the evidence was low certainty

● VALUES

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☐ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☒ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Research evidence:

No research evidence was identified

Panel discussion:

Different ethnicity shows similar prevalences.

● BALANCE OF EFFECTS

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:

● COSTS

How large are the resource requirements (costs)?

Judgement:

☐ Don't know	☐ Varies	☐ Large costs	☐ Moderate costs	☒ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:

No research evidence was identified

Panel discussion:

● CERTAINTY OF COST EVIDENCE

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

No research evidence was identified

Panel discussion:

● COST-EFFECTIVENESS

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

No research evidence was identified

Panel discussion:

● EQUITY

What would be the impact on health equity?

Judgement:

☐ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☒ Probably increased	☐ Increased

Research evidence:

No research evidence was identified

Panel discussion:

● ACCEPTABILITY

Is the option acceptable to key stakeholders?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☐ Probably Yes	☒ Yes

Research evidence:

No research evidence was identified

Panel discussion:

● FEASIBILITY

Is the option feasible to implement?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☐ Probably Yes	☒ Yes

Research evidence:

No research evidence was identified

Panel discussion:

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PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by the Evidence Team

GDG 1

Question 1.7.

What is the post-menopausal phenotype of PCOS and how elevated should androgens be to indicate PCOS?

1. STUDY SELECTION

Table 1. PICO Criteria for Inclusion	
Question	What is the post-menopausal phenotype of PCOS and how elevated should androgens be to indicate PCOS?
Clinical leads (key contacts)	Carolyn Ee; Wiebke Arlt
Allocation ranking	Level 4 Narrative Review

Selection criteria: No PICO defined for narrative review.

2. SEARCH STRATEGY

Evidence processing: This question was allocated as a narrative review. Hence, no search or screening was undertaken and recommendations will be consensus based. Below is a narrative review in response to the clinical question.

3. FINDINGS

See Part 2 for this question.

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 1

Question 1.7.

What is the post-menopausal phenotype of PCOS and how elevated should androgens be to indicate PCOS?

BACKGROUND:

The diagnosis of PCOS by the 2003 Rotterdam Criteria with two out of three criteria of oligo- and/or anovulation, clinical or biochemical hyperandrogenism and polycystic ovaries by ultrasound is well - established in PCOS.

Clinical practice gap: need for guidance

However, these three criteria for diagnosis are altered with aging hence the aging and postmenopausal phenotypes of PCOS are poorly defined. Additionally, it is not possible to rely on menstrual regularity as a diagnostic criterion after menopause as menses cease. Diagnostic criteria for PCOS after menopause is important for individual patient management as well as to guide research investigating long-term outcomes in PCOS.

Summary of key information

There is little data on changes to PCOS diagnostic criteria during the menopausal transition and post-menopause. There is some indirect evidence on the impact of aging in premenopausal women on PCOS diagnostic criteria.

Menstrual cycles

There is inconsistent evidence on the impact of ageing on menstrual regularity in PCOS. Menstrual cycles have been reported to become more regular with aging in women with PCOS (1-3). However, a cross-sectional study of pre-menopausal women with PCOS in Brazil (up to age 39) reported that the proportion of women with infrequent menstruation or amenorrhoea increased with age (4).

Ovarian morphology

Ovarian volume has been demonstrated to decrease with age in the general population (5). In a large cross-sectional study of women attending for annual TVU as part of a cancer screening program, mean ovarian volume in premenopausal women was 4.9 + 0.03cm^3 and in postmenopausal women was 2.2 + 0.01cm^3.

Follicle count

Ovarian volume and follicle number decrease longitudinally women with PCOS and women without. Using cross-sectional data, ovarian volume and follicle number decrease in both groups, but the decrease in ovarian volume is less pronounced in women with PCOS than in controls. Age-based criteria to define polycystic ovarian morphology have been proposed using a combination of age, log ovarian volume, follicle number, and testosterone to distinguish women with PCOS from those without PCOS (6). Aging women with PCOS and regular cycles have a lower follicle count than those with irregular cycles (7).

There have been conflicting results for postmenopausal PCOM. A study using a definition of PCO as defined by eight or more follicles of 2–8mm and an increase in ovarian stroma suggested PCO are present in postmenopausal women (8). However, pathology demonstrates absence of secondary follicles in postmenopausal ovaries (9). In PCOS, a small study using direct comparison between ultrasound and pathology found that hypoechoic structures on ultrasound in postmenopausal women with PCOS corresponded to inclusion cysts and vascular structures rather than follicles 6. More recently a small cohort study of premenopausal women with PCOS reported that prevalence of PCOM decreased by half over ten years of follow-up (10).

Hyperandrogenism – clinical

Postmenopausal women with PCOS report more hirsutism than controls (13, 20). One long-term cohort study reported that the frequency of hirsutism (mFG$\geq$5) was higher in women with PCOS compared to age matched controls at age 80 (after 32 years of follow-up), despite no corresponding difference in biochemical HA (13).

Little is known about alopecia in postmenopausal women with PCOS.

In premenopausal women, longitudinal studies report no change in CHA with time in women with PCOS. Three studies with follow-up of 2-10 years did not find a change over time for mFG (10, 11). Cross-sectional studies comparing rates of CHA between different age brackets have reported higher prevalence of reporting of CHA in younger women compared to older (4,14) including a lower prevalence of reporting acne in older (35-39yo) women (4).

Hyperandrogenism – biochemical

There is evidence that DHEAS declines over time in women with PCOS, and this decline is greater compared to non-PCOS controls (11). Most, but not all, longitudinal studies have also reported declines in total testosterone in women with PCOS over time, including a greater decline compared to non-PCOS controls (11) while one study has reported a significant decline in free T over time in women with PCOS but not in age-matched controls (12). However, androgen levels have previously been noted to increase after age 50 in women with PCOS (13) although one long-term study reported that testosterone and FAI decreased continuously over 32 years of followup in cases (14). There is inconsistent evidence for changes in FAI, SHBG and androstenedione over time and for any differences in changes over time for these outcomes between women with PCOS and controls (4,11,14,15).

Recent work has demonstrated that while classic androgens including testosterone decline with age, the adrenal-derived 11-oxygenated androgens including the active androgens 11-ketotestosterone and 11-hydroxytestosterone do not (16, 17). 11-oxygenated androgens have been shown to be increased in women with polycystic ovary syndrome (18) and girls with premature adrenarche (19), and their circulating concentrations increase with body mass index (20). In healthy premenopausal women, active 11-oxygenated androgens circulate in at least equal concentrations to testosterone, which makes them the dominant androgens during the post-menopause. At present, there is no information available on circulating concentrations of 11-oxygenated androgens in postmenopausal women with PCOS.

Age of menopause

A two-year delay in the age of menopause has been estimated using AMH levels in PCOS compared to non-PCOS women (21). Women with PCOS have a later menopause compared to women with no history of PCOS (HR 0.44, 95% CI 0.28-0.71) (22). Data from two case-control studies report mean ages of natural menopause (ANM) in women with PCOS of 51.4 (23) and 53.3 (24) years while ANM in non-PCOS controls was 49.7 (23) and 49.3 years (24).

Post-menopausal women with PCOS have been shown to have persistence of abnormal glucose metabolism (25) and higher triglycerides than controls (26). Other methods to identify PCOS in postmenopausal women have been proposed. For PCOS diagnosis in menopause some studies have relied on a previous history of oligoovulation, the presence of PCO and current features of hyperandrogenism: hyperandrogenemia or hirsutism (27), the top quartile of androgens to define hyperandrogenaemia (28) or inclusion of insulin resistance (29).

In the absence of diagnostic criteria for PCOS in women going through the menopausal transition and in the postmenopause, a presumptive diagnosis of PCOS can be based upon a well-documented long-term history of oligomenorrhea and hyperandrogenism during the reproductive years. Hirsutism may persist post-menopause, however limited evidence does not suggest this is associated with persistent biochemical hyperandrogenism. Presence of PCOM is unreliable to diagnose PCOS in the postmenopause.

Recommendations Framework

CONSENSUS RECOMMENDATION(S)

CR: A diagnosis of PCOS could be considered as enduring / lifelong.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

CR: Healthcare professionals could consider that both clinical and biochemical hyperandrogenism persist in the post-menopause for women with PCOS.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

CR: PCOS diagnosis could be considered postmenopause, if there is a past diagnosis, or a long-term history of oligo-amenorrhoea with hyperandrogenism and/or PCOM, during the earlier reproductive years (age 20-40 years).

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

CR: Further investigations should be considered to rule out androgen-secreting tumours and ovarian hyperthecosis in postmenopausal women presenting with new-onset, severe or worsening hyperandrogenism including hirsutism, require further investigation.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

CONSIDERATIONS

Justifications:
Postmenopausal women with PCOS report more hirsutism than women without PCOS. Evidence for differences in biochemical hyperandrogenism between women with and without PCOS in the postmenopause is inconsistent due to limited data.

Subgroup considerations:
Ethnicity, BMI subgroups, PCOS features

Implementation considerations: This recommendation is pragmatic and is likely to be acceptable to patients and clinicians.
Monitoring and evaluation considerations: Monitor the implementation of the recommendation.
Research priorities: ● How does the postmenopausal features of PCOS vary with ethnicity and BMI subgroups. ● Long term cohort studies need to follow up into the postmenopause on various health outcomes including androgen levels, cardio-metabolic disease, bone health, psychosexual function (accounting for treatment).
Equity: None.
Acceptability: This recommendation is a pragmatic one which is likely to be acceptable to patients and clinicians.
FEASIBILITY No major issues are foreseen.

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PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by the Evidence Team (Aya Mousa, Jillian Tay)
Other Members: Loyal Pattuwage, Darren Rajit, Aadhya Vyas, Yanan Hu

GDG 1

Question 1.8.

Are women with PCOS at increased risk for cardiovascular disease (CVD)?

PLEASE NOTE THIS EVIDENCE SUMMARY IS BEING UPDATED AFTER REVIEW AND PUBLIC CONSULTATION, HENCE SOME RESULTS MAY HAVE CHANGED. PLEASE REFER TO THE PUBLICATION OR FINAL GUIDELINE FOR UPDATES OR ADDITIONAL ANALYSES.

1. STUDY SELECTION

Table 1. PICO Criteria for Inclusion	
Question	**1.8 Are women with PCOS at increased risk for cardiovascular disease (CVD)?** **CLINICAL PRACTICE POINT:** **What tools/methods can be used to assess risk of cardiovascular disease (CVD) in women with PCOS?**
Clinical leads (key contacts)	**Fatimeh Tehrani, Helena Teede**
Allocation ranking	**Level 2 - systematic review update**

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(language, year)*
Inclusion	Females of any age, ethnicity, weight or phenotype of PCOS (diagnosed by Rotterdam, NIH or AES). Make note of those with CVD history. Subgroups: Adolescents Ethnicity Phenotype	None	Females without PCOS	Observed onset of CVD – defined as a CVD event including: • angina (heart pain), heart attack, stroke, peripheral vascular disease, CVD-related death. If allowed, note down secondary outcomes: Surrogate markers of CVD (change to risk factors of CVD) • Waist circumference • Waist-to-hip ratio (WHR) • BMI • lipid profile (triglycerides, cholesterols) • blood pressure • Framingham risk score • Vascular function: Flow mediated dilatation • Other vascular surrogate markers (CIM, CAC, CRP)	Evidence based guidelines, systematic reviews, health technology assessments, randomised controlled trials and comparative cohort studies. JL guideline and update underway (can include cross sectional or case control if it compares CVD events in PCOS and non-PCOS)	English language. Human studies
Exclusion	None	None	None	None	Non-evidence based guidelines, non-systematic reviews, non- comparative cohort studies, case series, editorials, letters, commentaries.	None

2. SEARCH STRATEGY

Search details	
Search strategy source: 2018 PCOS Guideline Technical Report	
Evidence source	Date of search (day/month/year)
Medline (Ovid)	1/1/2017 until 25/7/2022
PsychInfo (Ovid)	1/1/2017 until 25/7/2022
EMBASE	1/1/2017 until 25/7/2022
All EBM (Ovid)	1/1/2017 until 25/7/2022
CINAHL	1/1/2017 until 25/7/2022
Any subsequent updates - enter database and date: not applicable	

Questions addressed by this search:		
GDG	**Q#**	**Question**
1	1.8	Are women with PCOS at increased risk for cardiovascular disease (CVD)? CLINICAL PRACTICE POINT: What tools/methods can be used to assess risk of cardiovascular disease (CVD) in women with PCOS?

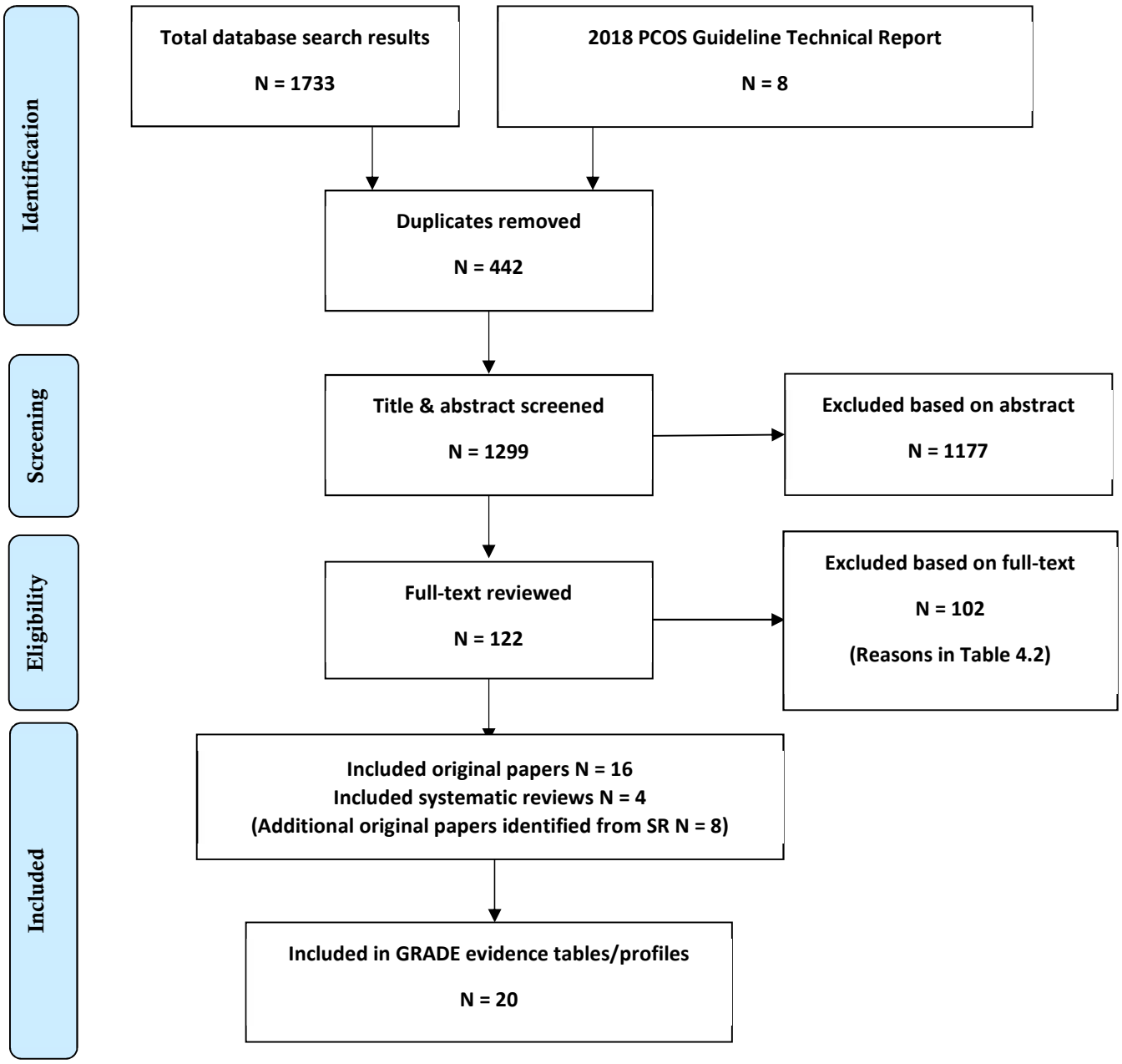
OVID Medline, All EBM, EMBASE, PsychInfo		CINAHL
1	exp Polycystic Ovary Syndrome/	S1 (MM "Polycystic Ovary Syndrome")
2	polycystic ovar$.mp.	S2 TX polycystic ovar*
3	poly-cystic ovar$.mp.	S3 TX poly-cystic ovar*
4	PCO$.mp.	S4 TX PCO*
5	(stein-leventhal or leventhal).mp.	S5 TX (stein-leventhal or leventhal)
6	anovulation/	S6 (MM "Anovulation")
7	anovulat$.mp.	S7 TX anovulati*
8	oligo-ovulat$.mp.	S8 TX oligoovulat*
9	oligoovulat$.mp.	S9 TX oligo-ovulat*
10	(ovar$ adj5 (scelerocystic or polycystic or poly-cystic or degenerat$ or hyperandrogen$ or hyper-androgen$)).mp.	S10 TX (ovar* N5 (scelerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*)).
11	or/1-10	S11 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10
12	(decision aid$ or decision tool).tw.	S12 TI ((decision aid* or decision tool)) OR AB ((decision aid* or decision tool))
13	tool$.tw.	S13 TI tool* OR AB tool*
14	rule$.tw.	S14 TI rule* OR AB rule*
15	measure$.tw.	S15 TI measure* OR AB measure*
16	model.tw.	S16 TI model OR AB model
17	assess$.tw.	S17 TI assess* OR AB assess*
18	calculat$.tw.	S18 TI calculat* OR AB calculat*
19	class$.tw.	S19 TI class* OR AB class*
20	(estimate$ or estimation$).tw.	S20 TI ((estimate* or estimation*)) OR AB ((estimate* or estimation*))
21	equation$.tw.	S21 TI equation* OR AB equation*
22	(score$ or scoring).tw.	S22 TI ((score* or scoring)) OR AB ((score* or scoring))
23	algorithm$.tw.	S23 TI algorithm* OR AB algorithm*
24	chart$.tw.	S24 TI chart* OR AB chart*
25	table$.tw.	S25 TI table* OR AB table*
26	tabulat$.tw.	S26 TI tabulat* OR AB tabulat*
27	test$.tw.	S27 TI test* OR AB test*
28	screen$.tw.	S28 TI screen* OR AB screen*
29	checklist.tw.	S29 TI checklist OR AB checklist
30	check-list.tw.	S30 TI check-list OR AB check-list
31	checksheet.tw.	S31 TI checksheet OR AB checksheet
32	check-sheet.tw.	S32 TI check-sheet OR AB check-sheet
33	ticklist.tw.	S33 TI ticklist OR AB ticklist
34	tick-list.tw.	
35	instrument.tw.	
36	or/12-35	

37 exp risk assessment/	S34 TI instrument OR AB instrument
38 exp risk/	S35 TI tick-list OR AB tick-list
39 risk$.tw.	S36 S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35
40 chance$.tw.	S37 (MM "Risk Assessment")
41 likelihood.tw.	S38 TI risk* OR AB risk*
42 potential.tw.	S39 TI chance* OR AB chance*
43 probabilit$.tw.	S40 TI chance* OR AB chance*
44 possib$.tw.	S41 TI likelihood* OR AB likelihood*
45 prognosis.tw.	S42 TI potential OR AB potential
46 inciden$.tw.	S43 TI probabilit* OR AB probabilit*
47 or/37-46	S44 TI possib* OR AB possib*
48 exp Coronary Disease/	S45 TI prognosis OR AB prognosis
49 exp cerebrovascular disorders/	S46 TI inciden* OR AB inciden*
50 cardiovascular disorders.mp.	S47 S37 OR S38 OR S39 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46
51 exp atherosclerosis/	S48 (MM "Coronary Disease+")
52 heart attack$.tw.	S49 (MM "Cerebrovascular Disorders+")
53 stroke$.tw.	S50 (MM "Cardiovascular Diseases+")
54 myocardial infarction.tw.	S51 (MM "Atherosclerosis")
55 cerebral vascular accident.mp.	S52 TI heart attack* OR AB heart attack*
56 coronary vascular accident.mp.	S53 TI stroke* OR AB stroke*
57 (coronary adj (event$ or disease or heart disease or mortality)).mp.	S54 TI myocardial infarction OR AB myocardial infarction
58 coronary thrombosis.mp.	S55 TI cerebral vascular accident* OR AB cerebral vascular accident*
59 coronary atherosclerosis.mp.	S56 TI coronary vascular accident OR AB coronary vascular accident
60 (cardiovascular adj (event$ or mortality)).mp.	S57 TI ((coronary N1 (event* or disease or heart disease or mortality))) OR AB ((coronary N1 (event* or disease or heart disease or mortality)))
61 CAD.mp.	S58 TI coronary thrombosis OR AB coronary thrombosis
62 CVD.mp.	S59 TI coronary atherosclerosis OR AB coronary atherosclerosis
63 diabetes mellitus/	S60 TI ((cardiovascular N1 (event$ or mortality))) OR AB ((cardiovascular N1 (event$ or mortality)))
64 iabet$.tw.	S61 TX CAD
65 IDDM.tw.	S62 TX CVD
66 NIDDM.tw.	S63 (MM "Diabetes Mellitus+")
67 MODY.tw.	S64 TI diabet* OR AB diabet*
68 (late onset adj diabet$).tw.	S65 TI IDDM OR AB IDDM
69 (maturity onset adj diabet$).tw.	S66 TI NIDDM OR AB NIDDM
70 (non insulin$ depend$ or non-insulin$ depend$ or noninsulin$ depend$ or non insulin?depend$ or noninsulin?depend$).tw.	S67 TI MODY OR AB MODY
71 (insulin$ depend$ or insulin-depend$ or insulin?depend$).tw.	S68 TI (late onset N1 diabet*) OR AB (late onset N1 diabet*)
72 (typ$ 2 adj6 diabet$).tw.	S69 TI (maturity onset N1 diabet*) OR AB (maturity onset N1 diabet*)
73 (typ$ II adj6 diabet$).tw.	S70 TI ((non insulin* depend* or non-insulin* depend* or noninsulin* depend* or non insulin#depend* or noninsulin#depend*)) OR AB ((non insulin* depend* or non-insulin* depend* or noninsulin* depend* or non insulin#depend* or noninsulin#depend*))
74 T2DM.tw.	S71 TI ((insulin* depend* or insulin-depend* or insulin#depend*)) OR AB ((insulin* depend* or insulin-depend* or insulin#depend*))
75 DM2.tw.	S72 TI (typ* 2 N6 diabet*) OR AB (typ* 2 N6 diabet*)
76 or/48-75	S73 TI (typ* II N6 diabet*) OR AB (typ* II N6 diabet*)
77 (sensitiv: or predictive value:).mp. or accurac:.tw. or specificit$.tw.	S74 TI T2DM OR AB T2DM
78 11 and 36 and 47 and 76 and 77	S75 TI DM2 OR AB DM2
79 limit 78 to (english language and humans and yr="2017 -Current")	S76 S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62
80 11 and 47 and 76	
81 limit 80 to (english language and female and humans and yr="2017 -Current")	
82 limit 80 to (english language and humans and yr="2017 -Current")	
83 82 not 81	
84 or/1-10	
85 or/48-62	
86 or/37-46	
87 84 and 85 and 86	
88 limit 87 to (english language and humans and yr="2017 -Current")	

89 11 and 36 and 85 90 limit 89 to (English language and humans and yr="2017-Current") 91 90 NOT	OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75 S77 TX (sensitiv* OR predictive value OR accurac* OR specificit*) S78 S11 AND S36 AND S47 AND S76 AND S77 S79 S11 AND S36 AND S47 AND S76 AND S77 S80 S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 S81 S11 AND S47 AND S80 S82 S11 AND S47 AND S80 Limiters - Publication Year: 2017-2022; English Language; Human S83 S11 AND S36 AND S80 S84 S11 AND S36 AND S80 Limiters - Publication Year: 2017-2022; English Language; Human S85 S84 NOT S82

Evidence processing: Studies were selected and appraised by 1 reviewers using study selection and appraisal criteria (PICO above) established a priori. The articles were reviewed by title and abstract by 1 reviewers. When a decision could not be made based on title and abstract alone, full text was retrieved. **A total of 25 studies met inclusion criteria for this review.**

3. SEARCH RESULTS - PRISMA flowchart



4. STUDY INCLUSION

4.1 Included studies
Original studies included: Berni TR, Morgan CL, Rees DA. Women With Polycystic Ovary Syndrome Have an Increased Risk of Major Cardiovascular Events: a Population Study. J Clin Endocrinol Metab. 2021 Aug 18;106(9):e3369-e3380. doi: 10.1210/clinem/dgab392. PMID: 34061968; PMCID: PMC8372630. Calderon-Margalit R, Siscovick D, Merkin SS, Wang E, Daviglus ML, Schreiner PJ, Sternfeld B, Williams OD, Lewis CE, Azziz R, Schwartz SM, Wellons MF. Prospective association of polycystic ovary syndrome with coronary artery calcification and carotid-intima-media thickness: the Coronary Artery Risk Development in Young Adults Women's study. Arterioscler Thromb Vasc Biol. 2014 Dec;34(12):2688-94. doi: 10.1161/ATVBAHA.114.304136. Epub 2014 Oct 30. PMID: 25359859. Cibula D, Cífková R, Fanta M, Poledne R, Zivny J, Skibová J. Increased risk of non-insulin dependent diabetes mellitus, arterial hypertension and coronary artery disease in perimenopausal women with a history of the polycystic ovary syndrome. Hum Reprod. 2000 Apr;15(4):785-9. doi: 10.1093/humrep/15.4.785. PMID: 10739820. Ding DC, Tsai IJ, Wang JH, Lin SZ, Sung FC. Coronary artery disease risk in young women with polycystic ovary syndrome. Oncotarget. 2018 Jan 4;9(9):8756-8764. doi: 10.18632/oncotarget.23985. PMID: 29492235; PMCID: PMC5823557. Forslund M, Schmidt J, Brännström M, Landin-Wilhelmsen K, Dahlgren E. Morbidity and mortality in PCOS: A prospective follow-up up to a mean age above 80 years. Eur J Obstet Gynecol Reprod Biol. 2022 Apr;271:195-203. doi: 10.1016/j.ejogrb.2022.02.020. Epub 2022 Feb 23. PMID: 35220175. Glintborg D, Rubin KH, Nybo M, Abrahamsen B, Andersen M. Cardiovascular disease in a nationwide population of Danish women with polycystic ovary syndrome. Cardiovasc Diabetol. 2018 Mar 8;17(1):37. doi: 10.1186/s12933-018-0680-5. PMID: 29519249; PMCID: PMC5844097. Iftikhar S, Collazo-Clavell ML, Roger VL, St Sauver J, Brown RD Jr, Cha S, Rhodes DJ. Risk of cardiovascular events in patients with polycystic ovary syndrome. Neth J Med. 2012 Mar;70(2):74-80. PMID: 22418753; PMCID: PMC3582228. Lunde O, Tanbo T. Polycystic ovary syndrome: a follow-up study on diabetes mellitus, cardiovascular disease and malignancy 15-25 years after ovarian wedge resection. Gynecol Endocrinol. 2007 Dec;23(12):704-9. doi: 10.1080/09513590701705189. PMID: 18075845. Mahboobifard F, Rahmati M, Niknam A, Rojhani E, Momenan AA, Azizi F, Ramezani Tehrani F. Impact of Polycystic Ovary Syndrome on Silent Coronary Artery Disease and Cardiovascular Events; A Long-term Population-based Cohort Study. Arch Med Res. 2022 Apr;53(3):312-322. doi: 10.1016/j.arcmed.2021.11.001. Epub 2021 Nov 22. PMID: 34823887. Mani H, Levy MJ, Davies MJ, Morris DH, Gray LJ, Bankart J, Blackledge H, Khunti K, Howlett TA. Diabetes and cardiovascular events in women with polycystic ovary syndrome: a 20-year retrospective cohort study. Clin Endocrinol (Oxf). 2013 Jun;78(6):926-34. doi: 10.1111/cen.12068. Epub 2013 Apr 6. PMID: 23046078. Meun C, Franco OH, Dhana K, Jaspers L, Muka T, Louwers Y, Ikram MA, Fauser BCJM, Kavousi M, Laven JSE. High Androgens in Postmenopausal Women and the Risk for Atherosclerosis and Cardiovascular Disease: The Rotterdam Study. J Clin Endocrinol Metab. 2018 Apr 1;103(4):1622-1630. doi: 10.1210/jc.2017-02421. PMID: 29408955. Morgan CL, Jenkins-Jones S, Currie CJ, Rees DA. Evaluation of adverse outcome in young women with polycystic ovary syndrome versus matched, reference controls: a retrospective, observational study. J Clin Endocrinol Metab. 2012 Sep;97(9):3251-60. doi: 10.1210/jc.2012-1690. Epub 2012 Jul 5. PMID: 22767635. Ollila ME, Kaikkonen K, Järvelin MR, Huikuri HV, Tapanainen JS, Franks S, Piltonen TT, Morin-Papunen L. Self-Reported Polycystic Ovary Syndrome Is Associated With Hypertension: A Northern Finland Birth Cohort 1966 Study. J Clin Endocrinol Metab. 2019 Apr 1;104(4):1221-1231. doi: 10.1210/jc.2018-00570. PMID: 30445634; PMCID: PMC7296204. Schmidt J, Landin-Wilhelmsen K, Brännström M, Dahlgren E. Cardiovascular disease and risk factors in PCOS women of postmenopausal age: a 21-year controlled follow-up study. J Clin Endocrinol Metab. 2011 Dec;96(12):3794-803. doi: 10.1210/jc.2011-1677. Epub 2011 Sep 28. PMID: 21956415. Wild S, Pierpoint T, McKeigue P, Jacobs H. Cardiovascular disease in women with polycystic ovary syndrome at long-term follow-up: a retrospective cohort study. Clin Endocrinol (Oxf). 2000 May;52(5):595-600. doi: 10.1046/j.1365-2265.2000.01000.x. PMID: 10792339. Systematic reviews included: Bolijn R, Onland-Moret NC, Asselbergs FW, van der Schouw YT. Reproductive factors in relation to heart failure in women: A systematic review. Maturitas. 2017 Dec;106:57-72. doi: 10.1016/j.maturitas.2017.09.004. Epub 2017 Sep 9. PMID: 29150167. Helvaci N, Yildiz BO. Cardiovascular health and menopause in aging women with polycystic ovary syndrome. Expert Rev Endocrinol Metab. 2020 Jan;15(1):29-39. doi: 10.1080/17446651.2020.1719067. Epub 2020 Jan 28. PMID: 31990594.

Ramezani Tehrani F, Amiri M, Behboudi-Gandevani S, Bidhendi-Yarandi R, Carmina E. Cardiovascular events among reproductive and menopausal age women with polycystic ovary syndrome: a systematic review and meta-analysis. Gynecol Endocrinol. 2020 Jan;36(1):12-23. doi: 10.1080/09513590.2019.1650337. Epub 2019 Aug 6. PMID: 31385729.
Wekker V, van Dammen L, Koning A, Heida KY, Painter RC, Limpens J, Laven JSE, Roeters van Lennep JE, Roseboom TJ, Hoek A. Long-term cardiometabolic disease risk in women with PCOS: a systematic review and meta-analysis. Hum Reprod Update. 2020 Nov 1;26(6):942-960. doi: 10.1093/humupd/dmaa029. PMID: 32995872; PMCID: PMC7600286.

Additional original studies identified from systematic reviews:
Glintborg D, Hass Rubin K, Nybo M, Abrahamsen B, Andersen M. Morbidity and medicine prescriptions in a nationwide Danish population of patients diagnosed with polycystic ovary syndrome. Eur J Endocrinol. 2015 May;172(5):627-38. doi: 10.1530/EJE-14-1108. Epub 2015 Feb 5. PMID: 25656495.
Haakova L, Cibula D, Rezabek K, Hill M, Fanta M, Zivny J. Pregnancy outcome in women with PCOS and in controls matched by age and weight. Hum Reprod. 2003 Jul;18(7):1438-41. doi: 10.1093/humrep/deg289. PMID: 12832369.
Hart R, Doherty DA. The potential implications of a PCOS diagnosis on a woman's long-term health using data linkage. J Clin Endocrinol Metab. 2015 Mar;100(3):911-9. doi: 10.1210/jc.2014-3886. Epub 2014 Dec 22. Erratum in: J Clin Endocrinol Metab. 2015 Jun;100(6):2502. PMID: 25532045.
Lo JC, Feigenbaum SL, Yang J, Pressman AR, Selby JV, Go AS. Epidemiology and adverse cardiovascular risk profile of diagnosed polycystic ovary syndrome. J Clin Endocrinol Metab. 2006 Apr;91(4):1357-63. doi: 10.1210/jc.2005-2430. Epub 2006 Jan 24. PMID: 16434451.
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4.2.Excluded Studies with Reasons

#	Title	Study	Journal	Vol	Issue	Pages	Notes
1	Risk of Cardiovascular Disease after Menopause among Women with Polycystic Ovary Syndrome (Pcos)	Christ 2020	Fertility and Sterility	114 (3 SUPPL)		e15	Wrong study design
2	Women with Polycystic Ovary Syndrome and Risk of Cardiovascular Disease	Blagojevic 2017	Journal of Medical Biochemistry	36(3)		259-269	Wrong outcome
3	Cardiometabolic Risk in Polycystic Ovary Syndrome: Current Guidelines	Cooney 2021	Endocrinology & Metabolism Clinics of North America	50	1	83-95	Wrong study design
4	Are women with polycystic ovary syndrome at increased cardiovascular disease risk later in life?	Gunning 2017	Climacteric	20(3)		222-227	Wrong study design
5	Comprehensive Evaluation of Type 2 Diabetes and Cardiovascular Disease Risk Profiles in Reproductive-Age Women with Polycystic Ovary Syndrome: A Large Canadian Cohort	Kazemi 2019	Journal of Obstetrics & Gynaecology Canada: JOGC	41	10	1453-1460	Wrong outcome
6	Risk Factors in Young Female Patient with Polycystic Ovary Syndrome presenting with Acute Myocardial Infarction	Manade 2020	Indian Journal of Cardiovascular Disease in Women - WINCARS	5(4)		327-330	Wrong study design
7	The cardiometabolic risk profile of middle-aged women with polycystic ovary syndrome (PCOS)	Meun 2019	Human Reproduction	34 (SUPPL 1)		i454	Wrong study design
8	Polycystic ovarian syndrome and its metabolic consequences: A mini review	Nair 2019	International Journal of Pharmaceutical Sciences and Research	10(7)		3210-3218	Wrong study design
9	Polycystic ovary syndrome as a novel risk factor for atrial fibrillation: Results from a national Danish registry cohort study	Oliver-Williams 2021	European Journal of Preventive Cardiology	28(12)		E20-E22	Wrong outcome
10	A Systematic Review and Meta-Analysis of the Association Between Polycystic Ovary Syndrome and Coronary Artery Calcification	Osibogun 2022	Journal of Women's Health	31	6	762-771	Wrong outcome
11	Is cardiovascular risk in women with PCOS a real risk? Current insights	Papadakis 2017	Minerva Endocrinologica	42	4	340-355	Wrong study design
12	Causal relationship between polycystic ovary syndrome and coronary artery disease: A Mendelian randomisation study	Simons 2022	Clinical Endocrinology	96	4	599-604	Wrong study design
13	Cardiometabolic risk in polycystic ovary syndrome	Studen 2018	Endocrine Connections	7(7)		R238-R251	Wrong study design

14	Cardiometabolic Risk in PCOS: More than a Reproductive Disorder	Torchen 2017	Current Diabetes Reports	17	12	137	Wrong study design
15	Polycystic ovary syndrome and risk of type 2 diabetes, coronary heart disease, and stroke	Zhu 2021	Diabetes	70(2)		627-637	Wrong study design
16	Impact of air pollution on subclinical atherosclerosis risk in middle aged women with and without polycystic ovary syndrome	Zhu 2020	Circulation. Conference: American Heart Association's Epidemiology and Prevention/Lifestyle and Cardiometabolic Health	141	SUPPL 1		Wrong study design
17	PCOS and its biochemical correlation	Pal 2021	Indian Journal of Clinical Biochemistry	36 (SUPPL 1)		S36	Wrong study design
18	Androgens, estrogens, and cardiovascular disease: considerations for women with polycystic ovary syndrome	Kim 2019	Fertility and Sterility	112(3)		478-479	Wrong study design
19	Polycystic ovary syndrome, epicardial fat thickness, and cardiovascular diseases	Cerit 2017	Clinical Nutrition	36(3)		906	Wrong study design
20	Non-dipping nocturnal blood pressure an early CV risk marker in adolescent PCOS	Galla 2018	Endocrine Reviews. Conference: 100th Annual Meeting of the Endocrine Society, ENDO	39	2 Supp 1		Wrong outcome
21	Should we go for prevention of long term health consequences?	Tapanainen 2019	Human Reproduction	34 (SUPPL 1)		i123	Wrong study design
22	Prevalence of cardiovascular disorders in greek women with polycystic ovary syndrome. A retrospective study	Kyrkou 2018	Review of Clinical Pharmacology and Pharmacokinetics, International Edition	32(3)		109-113	Wrong study design
23	The interrelationship between metabolic syndrome and polycystic ovary syndrome in greek women. A retrospective study	Kyrkou 2019	Review of Clinical Pharmacology and Pharmacokinetics, International Edition	33(1)		13-18	Wrong study design
24	Are women with polycystic ovary syndrome more vulnerable to covid-19 infection?	Dilbaz 2021	Turkish Journal of Obstetrics and Gynecology	18(3)		221-223	Wrong study design
25	Association of polycystic ovary syndrome and risk or cardiovascular disease, coronary heart disease and stroke	Charlotte Onland-Moret 2019	European Journal of Preventive Cardiology	26 (Supp 1)		S172	Wrong study design
26	Cardiometabolic risks in polycystic ovary syndrome: long-term population-based follow-up study	Behboudi-Gandevani 2018	Fertility & Sterility	110	7	1377-1386	Wrong outcome
27	Polycystic ovary syndrome: a reproductive and metabolic web of risk, comorbidities, and disease	Bates 2019	Fertility and Sterility	111(3)		471-472	Wrong study design
28	Cardiovascular Risk in Postmenopausal Women with Polycystic Ovary Syndrome	Armeni 2019	Current Vascular Pharmacology	17	6	579-590	Wrong study design

29	A biochemical and molecular study of tumor necrosis factor-a in female with polycystic ovarian syndrome	Al-Assadi 2018	Biochemical and Cellular Archives	18(1)		677-682	Wrong outcome
30	Association between polycystic ovary syndrome and the risk of subclinical vascular disease in normal-weight women with type 1 diabetes	Lebkowska 2017	Polish Archives Of Internal Medicine	127	11	741-748	Wrong patient population
31	Serum sclerostin level and its relation to subclinical atherosclerosis in the polycystic ovary syndrome phenotypes: A prospective controlled study	Cintesun 2021	Turkish Journal of Obstetrics and Gynecology	18(3)		167-174	Wrong outcome
32	Cardiovascular Risk Factors and Subclinical Atherosclerosis in Greek Adolescents with Polycystic Ovary Syndrome: Its Relationship with Body Mass Index	Garoufi 2022	Children	9	1	4-4	Wrong outcome
33	Role of IL-6 signalling in Polycystic Ovarian Syndrome associated inflammation	Borthakur 2020	Journal of Reproductive Immunology	141		103155	Wrong intervention
34	The predictive effect of inflammatory markers and lipid accumulation product index on clinical symptoms associated with polycystic ovary syndrome in nonobese adolescents and younger aged women	Tola 2017	European Journal of Obstetrics, Gynecology, & Reproductive Biology	214		168-172	Wrong outcome
35	Impaired Cardiovagal Baroreflex in Black Women with AE-PCOS	Chiles 2021	FASEB Journal. Conference: Experimental Biology, EB	35	SUPPL 1		abstract
36	Comprehensive Meta-Analysis of Functional and Structural Markers of Subclinical Atherosclerosis in Women with Polycystic Ovary Syndrome	Sun 2022	Angiology	73	7	622-634	Wrong outcome
37	Biomediators in polycystic ovary syndrome and cardiovascular risk	Pandurevic 2021	Biomolecules	11(9)			Wrong outcome
38	Risk of Cardiovascular Events in Tunisian Polycystic Ovary Syndrome Patients	Chaabouni 2022	Journal of Hypertension	40 (Supp 1)		e137-e138	Wrong outcome
39	Cardio-vascular profile of greek adolescents with polycystic ovary syndrome	Geronikolo 2017	European Journal of Pediatrics	176(11)		1469	Wrong outcome
40	Cardiometabolic health in offspring of women with PCOS compared to healthy controls: a systematic review and individual participant data meta-analysis	Gunning 2020	Human Reproduction Update	26	1	103-117	Wrong patient population
41	Cardiovascular disease risk in the siblings of women with polycystic ovary syndrome	Karthik 2019	Human Reproduction	34	8	1559-1566	Wrong patient population
42	Potential later-life health implications of polycystic ovary syndrome are underserved and understudied	Fauser 2021	Fertility and Sterility	116(3)		682-683	Wrong study design

43	Prevalence of Dyslipidaemia and Pre-Diabetes Among Women with Polycystic Ovary Syndrome (PCOS): Do We Overestimate Cardiovascular Risk?	Lewandowski 2019	Hormone & Metabolic Research	51	8	539-545	Wrong outcome
44	Role of Non-Alcoholic Fatty Liver Disease in Cardiovascular Morbidity in Polycystic Ovarian Syndrome	Nath 2022	Journal of the Association of Physicians of India	70	4	11-12	Wrong patient population
45	Reproductive endocrinology and infertility: Clinical expert series polycystic ovary syndrome	Azziz 2018	Obstetrics and Gynecology	132(2)		321-336	Wrong outcome
46	Saturated fat ingestion stimulates proatherogenic inflammation in polycystic ovary syndrome	Gonzalez 2021	American Journal of Physiology - Endocrinology & Metabolism	321	5	E689-E701	abstract
47	Serum visfatin as predictive marker of cardiometabolic risk in women with polycystic ovary syndrome	Rashad 2018	Middle East Fertility Society Journal	23(4)		335-341	Wrong outcome
48	Use of transient elastography (FIBROSCAN) for Assessment of NAFLD in young women with PCOS	Chakraborty 2017	Endocrine Reviews. Conference: 99th Annual Meeting of the Endocrine Society, ENDO	38	3 Supp 1		abstract
49	Arterial stiffness measured by cardio-ankle vascular index in Korean women with polycystic ovary syndrome	Kim 2019	Journal of Obstetrics and Gynaecology	39(5)		681-686	Wrong outcome
50	Women with Polycystic Ovary Syndrome have different levels of abdominal fat distribution, insulin resistance, and cardiovascular risk profiles	Acharya 2022	European Journal of Molecular and Clinical Medicine	9(3)		3199-3203	Wrong outcome
51	Identification of the metabolic fingerprints in women with polycystic ovary syndrome using the multiplatform metabolomics technique	Buszewska-Forajta 2019	Journal of Steroid Biochemistry & Molecular Biology	186		176-184	Wrong outcome
52	Health Care-Related Economic Burden of Polycystic Ovary Syndrome in the United States: Pregnancy-Related and Long-Term Health Consequences	Riestenberg 2022	Journal of Clinical Endocrinology and Metabolism	107(2)		575-585	Wrong study design
53	Detecting Early Markers of Cardiovascular Disease in High-Risk Women With and Without PCOS	Uren 2021	Canadian Journal of Diabetes	45 (7 Supp)		S40	Wrong outcome
54	Polycystic ovary syndrome as an independent risk factor for gestational diabetes and hypertensive disorders of pregnancy: a population-based study on 9.1 million pregnancies	Mills 2020	Human Reproduction	35	7	1666-1674	Wrong study design

55	Reduced cardiovascular risks in women with endometriosis or polycystic ovary syndrome carrying a common functional IGF1R variant	Powell 2022	Human Reproduction	37	5	1083-1094	Wrong study design
56	ACC/AHA 2017 definition of high blood pressure: implications for women with polycystic ovary syndrome	Marchesan 2019	Fertility & Sterility	111	3	579-579	Exclusion reason: Wrong outcomes;
57	Oxidative Marker and Insulin Resistance in Women with PCOS	Zainab 2022	Pakistan Journal of Medical and Health Sciences	16(2)		707-709	Exclusion reason: Wrong intervention;
58	Normoandrogenic Versus Hyperandrogenic Women with Polycystic Ovary Syndrome and Their Metabolic and Cardiovascular Profile Later in Life	VanDerHam 2021	Fertility and Sterility	116 (3 SUPPL)		e83	Wrong outcome
59	Metabolic disturbances in non-obese women with polycystic ovary syndrome: a systematic review and meta-analysis	Zhu 2019	Fertility & Sterility	111	1	168-177	Wrong outcome
60	Obese adolescents with polycystic ovarian syndrome have elevated cardiovascular disease risk markers	Patel 2017	Vascular Medicine	22	2	85-95	Wrong outcome
61	Does cardiovascular risk vary according to the criteria for the diagnosis of PCOS?	Yoldemir 2017	Maturitas	100		174-175	Wrong outcome
62	The cardiovascular risk profile of middle-aged women with polycystic ovary syndrome	Meun 2020	Clinical Endocrinology	92	2	150-158	Exclusion reason: Wrong intervention;
63	Impaired ApoB-Lipoprotein and Triglyceride Metabolism in Obese Adolescents With Polycystic Ovary Syndrome	Vine 2017	Journal of Clinical Endocrinology & Metabolism	102	3	970-982	Exclusion reason: Wrong comparator;
64	Lipid accumulation product as a marker of cardiovascular disease risk among women with polycystic ovarian syndrome- a hospital based case-control study	Babu 2021	Journal of Clinical and Diagnostic Research	15(3)		BC11-BC15	Wrong outcome
65	Relationship of Polycystic Ovarian Syndrome with Cardiovascular Risk Factors	Bilal 2018	Diabetes & Metabolic Syndrome	12	3	375-380	Wrong outcome
66	The association between anthropometric parameters and cardiovascular risk indicators in women with polycystic ovarian syndrome	Mirdamadi 2020	ARYA Atherosclerosis	16(1)		39-43	Wrong outcome
67	The Relationship of Objective Physical Activity with Traditional and Nontraditional Cardiovascular Disease Risk Factors in Women	Gorczyca 2018	Current Cardiovascular Risk Reports	12(8)			Exclusion reason: Wrong patient population;
68	Prevalence and associated factors of non-alcoholic fatty liver disease in South Asian women with polycystic ovary syndrome:	Shengir 2020	Canadian Liver Journal	3(1)		153-154	Wrong outcome

	A prospective study using transient elastography						
69	Polycystic ovary syndrome, adipose tissue and metabolic syndrome	Delitala 2017	Archives of Gynecology & Obstetrics	296	3	405-419	Wrong outcome
70	The polycystic ovary syndrome increases levels of augmentation index similar than women with systemic diseases as psoriasis and rheumatoid arthritis	Paterno Marchioli 2017	Journal of Hypertension	35 (Supp 2)		e314-e315	Wrong outcome
71	Metabolic syndrome: A short review	Vaishali 2019	Indian Journal of Public Health Research and Development	10(11)		1574-1579	Exclusion reason: Wrong setting;
72	Metabolic features of adult and adolescent first-degree relatives of women with polycystic ovary syndrome: A systematic review and meta-analysis	Chae 2017	Fertility and Sterility	108 (3 Supp 1)		e248-e249	Exclusion reason: Wrong patient population;
73	A Canary in the Coal Mine: Reproductive Health and Cardiovascular Disease in Women	Quinn 2017	Seminars in Reproductive Medicine	35(3)		250-255	Wrong outcome
74	Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility	Morley 2018	Cochrane Database of Systematic Reviews		2		Exclusion reason: Wrong setting;
75	Metabolic Syndrome in Polycystic Ovary Syndrome	Pasquali 2018	Frontiers of Hormone Research	49		114-130	Exclusion reason: Wrong comparator;
76	Visceral adiposity index and lipid accumulation product as diagnostic markers of metabolic syndrome in South Indians with polycystic ovary syndrome	Naghshband 2021	Journal of Human Reproductive Sciences	14(3)		234-243	Wrong outcome
77	Assessment of early markers of cardiovascular risk in polycystic ovary syndrome	Alexandraki 2021	European Endocrinology	1(1)		37-53	Wrong outcome
78	The Impact of a Pharmaceutical Care Model on Improving Polycystic Ovary Syndrome						Wrong intervention
79	Elevated Prevalence of Polycystic Ovary Syndrome and Cardiometabolic Disease in South Asian Infertility Patients	Kudesia 2017	Journal of Immigrant & Minority Health	19	6	1338-1342	Wrong patient population
80	The effect of PCOS status on atherosclerosis markers and cardiovascular disease risk factors in young women with vitamin D deficiency	Atasayan 2021	Gynecological Endocrinology	37	3	225-229	Wrong outcome
81	Dyslipidemia in polycystic ovary syndrome	Boshku 2018	Atherosclerosis Supplements	32		46	Wrong outcome
82	ApoB48-lipoproteins are associated with cardiometabolic risk in adolescents with and without polycystic ovary syndrome	Vine 2020	Journal of the Endocrine Society	4(8)			Wrong outcome

83	Intercellular adhesion molecule-1 expression and serum levels as markers of pre-clinical atherosclerosis in polycystic ovary syndrome	Rashad 2019	Journal of ovarian research	12	1	97	Wrong outcome
84	Metabolic Syndrome and Myocardial Infarction in Women	Macut 2021	Current Pharmaceutical Design	27	36	3786-3794	Wrong population
85	Progression of glucose intolerance and cardiometabolic risk factors over a decade in Chinese women with polycystic ovary syndrome: A case-control study	Ng 2019	PLoS Medicine	16	10	1-20	Wrong outcome
86	A Comparison of a Pulse-Based Diet and the Therapeutic Lifestyle Changes Diet in Combination with Exercise and Health Counselling on the Cardio-Metabolic Risk Profile in Women with Polycystic Ovary Syndrome: A Randomized Controlled Trial	Kazemi 2018	Nutrients	10	10	1387	Wrong outcome
87	Hypertension Risk in Young Women With Polycystic Ovary Syndrome: A Nationwide Population-Based Cohort Study	Wu 2020	Frontiers in Medicine	7			Wrong outcome
88	Association of coronary heart disease risk & lipid profile in Indian women with poly cystic ovarian syndrome	Sur 2017	Endocrine Practice	23(1)		15A-16A	Wrong outcome
89	Association between polycystic ovary syndrome and the risk of stroke and all-cause mortality: insights from a meta-analysis	Zhou 2017	Gynecological Endocrinology	33	12	904-910	Wrong outcome
90	A comparative study of LDL-C levels in polycystic ovary syndrome women with different cardiovascular risks according to american heart association criteria	Tingthanatikul 2017	Journal of the Medical Association of Thailand	100(9)		927-934	Wrong outcome
91	Causes and Consequences of Polycystic Ovary Syndrome: Insights From Mendelian Randomization	Zhu 2022	Journal of Clinical Endocrinology & Metabolism	107	3	e899-e911	Wrong outcome
92	Comprehensive evaluation of disparities in cardiometabolic and reproductive risk between Hispanic and White women with polycystic ovary syndrome in the United States: a systematic review and meta-analysis	Kazemi 2022	American Journal of Obstetrics & Gynecology	226	2	187-204.e15	Wrong outcome
93	Disparities in cardio metabolic risk between Black and White women with polycystic ovary syndrome: a systematic review and meta-analysis	Kazemi 2021	American Journal of Obstetrics & Gynecology	224	5	428-444.e8	Wrong outcome

94	Coronary microvascular dysfunction is not associated with a history of reproductive risk factors in women with angina pectoris-An iPOWER substudy	Suhrs 2018	Maturitas	107		110-115	Wrong patient population
95	Polycystic ovary syndrome, androgen excess, and the risk of nonalcoholic fatty liver disease in women: A longitudinal study based on a United Kingdom primary care database	Kumarendran 2018	PLoS Medicine / Public Library of Science	15	3	e1002542	Wrong outcome
96	Activation of systemic inflammation and oxidative stress in adolescent girls with polycystic ovary syndrome in combination with metabolic disorders and excessive body weight	Khashchenko 2020	Journal of Clinical Medicine	9(5)			Wrong outcome
97	The combination of cardiovascular risk factors in PCOS and the risk for cardiovascular disease events	Papadakis 2019	Archives of Hellenic Medicine	36 (Supp 2)		35	Wrong outcome
98	Cardiovascular evaluation and serum paraoxonase-1 levels in adolescents with polycystic ovary syndrome	Çetin 2020	Journal of Obstetrics & Gynaecology	40	1	90-95	Wrong outcome
99	Hypertension Predisposition and Thermoregulation Delays in Adolescents with Polycystic Ovary Syndrome: A Pilot Study	Geronikolou 2022	Children	9	3	316	Wrong outcome
100	Assessment of Inflammatory Markers in Women with PCOS and their Correlation with Insulin Resistance	Khichar 2021	Clinical Laboratory	67	11	1	Wrong outcome
101	Lipid Accumulation Product (LAP) and Visceral Adiposity Index (VAI) as Markers of Insulin Resistance and Metabolic Associated Disturbances in Young Argentine Women with Polycystic Ovary Syndrome	Abruzzese 2017	Hormone & Metabolic Research	49	1	23-29	Wrong outcome
102	Mitochondrial Dysfunction in Polycystic Ovary Syndrome	Zeng 2020	DNA & Cell Biology	39	8	1401-1409	Wrong study design

5. STUDY CHARACTERISTICS TABLE FOR INCLUDED STUDIES

Author, year, country	Study design	Setting	PCOS criteria	PCOS sample size	Control sample size	Outcomes	Methods of measurement	Follow up Duration	Summary of findings	Pooled in MA?	RoB
Berni et al, 2021, UK	Cohort	Clinical Practice Research Datalink Aurum database, population-based	ICD-10	N=174660 Age=29 (median)	N=174660 Age=29 (median) matched to controls (1:1) by age, body mass index (BMI) category, and primary care practice	Incidence: Composite CVD (stoke, MI, angina, revascularization, CV mortality), Stroke, MI, Angina, Revascularization, Cardiovascular mortality	ICD-10	Median=3.83 years for PCOS Median=3.00 years for Controls	The risk of incident MI, angina, and revascularization is increased in young women with PCOS. Weight andT2DM are potentially modifiable risk factors amenable to intervention.	Yes	Mod
Caldernon-Margalit et al, 2014, USA	Cohort	CARDIA Women's Study (CWS), population based	NIH	N=55 Age=45.4 (3.44) BMI=29.3 (6.50)	N=668 Age=45.4 (3.57) BMI=29.9 (7.47)	Prevalence: Ischemic heart disease (history of acute myocardial infarction or angina)	Self-report	20 years	Women with PCOS comprise a unique group at risk for the development of cardiovascular disease; the effect of PCOS is beyond the effects of either hyperandrogenism or oligomenorrhea.	No, outlier	High
Cibula et al, 2020, Czech Republic	Case-control	University hospital,	NIH	N=28 Age=51.9 (4.64) BMI=28.0 (4.21) Perimenopausal women with a history of polycystic ovary syndrome (PCOS) treatment, undergone wedge ovarian	N=752 Age=51.0 (4.21) BMI=28.2 (5.42) Women aged 45–59 years and were selected from 3209 women representing a random population sample	Prevalence: Coronary artery disease (angina, MI, angioplasty, CABG)	Clinical investigations: chest pain evaluated as definite or possible angina, history of definite or possible MI, history of coronary angioplasty or coronary	N/A	Patients with markedly expressed clinical symptoms of PCOS made up a subgroup in the general population at high risk for developing NIDDM and coronary artery disease.	Yes	Mod

				resection, all Caucasian.			artery bypass grafting				
Ding et al, 2018, Taiwan	Cohort	Community-based	ICD code	N=8048 Age=28.11 (6.89)	N=32192 Age=28.11 (6.90) matched by age and diagnosis date	Incidence: Coronary artery disease (MI, angina, IHD)	Taiwan National Health Insurance claim record, ICD-9-CM diagnoses	Mean=5.9 years	Women with PCOS are at an elevated risk of coronary artery disease, the incidence of coronary artery disease increased further in those with cardiometabolic comorbidities. Among women with PCOS, those with comorbid diabetes had an incidence of 35.2 per 1000 person-years, 20-fold greater than those without cardiometabolic comorbidities.	Yes	Mod
Forslund et al, 2022, Sweden	Cohort	University hospital	Rotterdam	N=21 Age=80.8 (5.3) BMI=25.5 (3.6)	N=55 Age=80.6 (4.8) BMI=26.1 (5.5) Age-matched at 4:1 reference group	Incidence and prevalence: MI, angina, stroke, TIA. Composite CVD (MI, angina, stroke, TIA)	For deceased women register data was used, for women alive interviews were done, and medical records studied	32 years	No evidence of increased all-cause mortality or CVD was found in women with PCOS. The elevated testosterone levels and CVD risk profile in PCOS present during perimenopause do not seem to be associated with increased CVD morbidity/mortality risk later in life.	Yes	Mod
Glintborg et al, 2015, Denmark	Cohort	Hospital and community	Rotterdam And ICD codes	PCOS Denmark N=19199 Age=30.6 (9.6) PCOS OUH N=1217 Age=29.3 (8.5)	N=57483 Age=30.6 (9.6) BMI=not reported three control women born in the same year as the patient were randomly drawn from	Prevalence: Cardiovascular disease (angina, heart failure), MI, TIA, stoke, thrombosis, lung embolism	Diagnosis codes	n/a	PCOS was associated with a two times increased risk of stroke and thrombosis, whereas the risk of other cardiovascular diseases was not increased.	Yes	Mod

				BMI (median (quartiles))=27.3 (23.0-32.7)	the civil population register.						
Glintborg et al, 2018, Denmark	Cohort	Hospital and community	Rotterdam And ICD codes	PCOS Denmark N=17995 Age=29 (median); 12-60 (range) BMI=not reported PCOS OUH N=1159 Age=29 (median); 12-54 (range) BMI=27.0 (median)	N=52329 Age=29 (median); 12-60 (range) BMI=not reported	Incidence and prevalence: Stroke, VTE lung, VTE extremities, extremities, IHD (angina, MI, IHD)	ICD codes, National Patient Register (NPR), the National Prescription Registry and the National Cause of Death Register	Median (quartiles)=11.1 (6.9-16.0) years	The event rate of CVD including hypertension and dyslipidemia was higher in PCOS compared to controls. The risk of developing CVD must be considered even in young women with PCOS.	Yes	Mod
Haakova et al, 2003, Czech Republic	Case-control	Hospital	NIH	N=66 Age=29 (2.97) BMI=23.7 (4.27) Pregnant women	N=66 Age=29.8 (4.94) BMI=23.2 (3.89) Healthy age- and weight-matched pregnant women	Prevalence: Ischemic heart disease (MI, angina)	Self-report	N/A	PCOS is not associated with a higher risk of pregnancy complications.	No, outlier	Mod
Hart et al, 2014, Australia	Cohort	Hospital	ICD	N=2566 Age=27.9 (23.6, 32.0)	N=25660 Age=range 15-47 Randomly selected age-matched women without a PCOS diagnosis derived from the electoral roll	Incidence and prevalence: Cerebrovascular disease, Ischemic heart disease	ICD-10	From 15 years of age until a median age of 35.8 years	PCOS was associated with more ischemic heart disease (0.8 vs 0.2%), cerebrovascular disease (0.6 vs 0.2%).	Yes	Mod
Iftikhar et al, 2012, USA	Cohort	Community	Rotterdam	N=309 Age=25.0 (5.3) BMI=29.4 (7.77)	N=343 Age=range 18-40 BMI=28.3 (7.47) Age and calendar year during their clinic visit plus three	Incidence and prevalence: MI, angina, stoke, CABG, composite CVD (MI, angina, stroke, CABG), CVD deaths	Self-report or Death certificates record	Mean (SD)=23.7 (13.7) years	Although women with PCOS weighed more than controls, there was no increased prevalence of other CV risk factors. Furthermore, we found no increase in CV events. While	Yes	Mod

					years were matching factors				prospective studies are needed to confirm these findings, women with PCOS do not appear to have adverse CV outcomes in midlife.		
Lo et al; 2006, USA	Cross-sectional	Community	ICD	N=11035 Age=30.7 (7.2) BMI=not reported	N=55175 Age=30.8 (7.5) BMI=not reported 1:5 case to control ratio to match on the 5-yr age distribution of the PCOS women	Prevalences: Cerebrovascular disease, CAD, PVD	Diagnoses and relevant procedures in ambulatory visit, hospital discharge, and billing claims database	N/A	Within a large, community-based population receiving health care, diagnosed PCOS was highly prevalent and associated with a much higher frequency of cardiovascular risk factors that varied by race/ethnicity. Among women with PCOS, compared with whites, Blacks and Hispanics were more likely and Asians less likely to be obese; Asians and Hispanics were more likely to have diabetes; and Blacks were more likely and Hispanics less likely to have hypertension.	Yes	Mod
Lunde et al, 2007, Norway	Cohort	Hospital	Laproscopic PCOS	N=131 Age=24.7 Women previously treated with ovarian wedge resection	N=723 Age=not reported Age-adjusted group of women from the Norwegian Health Survey 1995	Prevalence: MI, Stroke	Self-report and confirmed by reports from the hospitals	15-25 years after ovarian wedge resection	The relative risk of cardiovascular disease was not affected.	Yes	High
Mahboobifard et al, 2022, Iran	Cohort	Community	Rotterdam	N=356 Age=29.7 (6.8) BMI=26.0 (4.8)	N=1235 Age=31.1 (7.6) BMI=25.7 (4.6)	Prevalence and incidence: CVD (Stroke, MI, angina,	Self-report cross-checked by medical	Median=15.4 years	Whereas silent CAD, regardless of PCOS, accelerated CVD, PCOS preserved it, most likely	Yes	Mod

						angiographic evidence), silent CVD (possible and probable ECG changes)	interview and records		due to a combination of protective factors, including the endocrine pattern in the late reproductive period, environmental/social elements, and recruiting additional counseling and lifestyle modifications		
Mani et al, 2013, UK	Cohort	Community	AES	N=2301 Age=36.3 (10.0) BMI=30.1 (7.6)	Comparison with National and local population data	Only prevalence was compared with national /local data: Cerebrovascular accident, MI, Angina, Heart failure, CV Death, Composite CVD Outcome (any of MI, Angina, HF, cerebrovascular accident, or CV death)	Hospital records	Mean (SD) observation period per person-years=5.2 (5.1)	We have shown a high incidence and age-group- specific prevalence of T2DM, MI and angina in the women with PCOS, with over a quarter having had MI or angina in those >65 years. These findings should be considered in the treatment strategies and long-term planning for women with PCOS.	Yes	Mod
Merz et al, 2016, USA	Cohort	Community	NIH	N=25 Age=62.6 (11.6) BM =28.7 (5.9)	N=270 Age=64.8 (9.6) BMI=30.0 (6.7)	Prevalence: CAD >50% stenosis Composite CVD (MI, stroke, CV death), CVD death ((sudden cardiac deaths, CHF, MI, PAD, stroke) Incidence: CVD death ((sudden cardiac deaths, CHF, MI, PAD, stroke)	CAD via angiogram with >50% stenosis. CVD deaths: When available, death certificates were used to discern cause of death, otherwise narratives from relatives	10 years	From this longer-term follow up of a relatively small cohort of postmenopausal women with suspected ischemia, the prevalence of PCOS is similar to the general population, and clinical features of PCOS are not associated with CAD or mortality.	Yes	Mod

							and hospital records				
Meun et al, 2018, Netherlands	Cohort	Community	NIH	N=106 Age=69.57 (8.72) BMI=27.92 (4.53)	N=171 Age=69.20 (8.60) BMI=26.84 (3.83)	Incidence: Coronary heart disease (MI or CV deaths), Stroke, composite CVD (coronary heart disease, MI, CV death or stroke)	Letters by medical specialists and discharge reports in case of hospitalization	Median=11.36 years	No association between high androgen levels and incident stroke, CHD, or CVD.	Yes	Mod
Morgan et al, 2012, UK	Cohort	General Practice Research Database	Medical records	N=21734 Age=27.1 (7.1) BMI=28.7 (8.2)	N=86936 Age=27.1 (7.1) BMI=25.5 (5.8) Group 1: matched according to primary-care practice and age Group 2: also matched on body mass index	Incidence and prevalence: Large-vessel disease (LVD): first record of myocardial infarction, stroke, angina, or central or peripheral revascularization	Medical records	Median=4.7 years for PCOS Median=5.8 years for Controls	During this follow-up period, women with PCOS were not at increased risk of LVD, cancer, or death, but they had increased risk of type 2 diabetes.	Yes	Mod
Okoroh et al, 2015, USA	Cross-sectional	Community	ICD codes	N=125268 Age=33.4	N=250536 Age=33.4 Each woman with PCOS was exactly matched with two non-PCOS controls based on age at first PCOS diagnosis for the cases and age at first enrollment for the controls.	Prevalence: VTE (PE or DVT), composite CVD (stroke, MI, PAD), stroke, MI, PAD	Health insurance claims data	N/A	Overall, women with PCOS were more likely to have aCVD, with stroke being the most prevalent manifestation. Although VTE often occurred before any aCVD, it appeared to have an inverse association with the development of ISCH, AMI, and PAD among women with PCOS, suggesting that aggressively treating VTE or aCVD early may limit the chances of developing the other thrombogenic condition	Yes	Mod

									among women with PCOS.		
Ollila et al, 2018, Finland	Cross-sectional	Community	Self-reported	N=279 Age=46	N=1577 Age=46	Prevalence: Angina pectoris, MI, Heart failure, Atherosclerosis, Transitory cerebral ischemia , Intracranial haemorrhage, Stroke, composite CVD events (angina pectoris, myocardial infarction, heart failure, atherosclerosis, transitory cerebral ischemia, intracranial hemorrhage, stroke, other disturbance in intracranial blood flow (I65–I68) and sequelae of cerebrovascular disease)	ICD from hospital discharge, hospital outpatient clinic, and basic health care registers	N/A	Women with srPCOS displayed higher BP compared with controls already at early age and srPCOS was associated with hypertension independently of overweight/obesity. srPCOS was associated with increased cardiovascular morbidity in premenopausal women, suggesting that cardiovascular disease risk factors should be screened and efficiently managed early enough in women with PCOS.	Yes	Mod
Pierpoint et al, 1998, UK	Cohort	Hospital	Laproscopic criteria and hospital records	N = 786 Age=26.4	National mortality rates were used to calculate expected deaths by underlying cause from the number of woman-years at risk in each five-year age group and five-year calendar period.	Standardised mortality ratio: Death due to ischemic heart disease, Death due to other circulatory, Circulatory deaths	Death certificates record, ICD	Mean=30 years	We conclude that women with polycystic ovary syndrome do not have markedly higher than average mortality from circulatory disease, even though the condition is strongly associated with diabetes, lipid abnormalities, and other	No	Mod

									cardiovascular risk factors. The characteristic endocrine profile of women with polycystic ovary syndrome may protect against circulatory disease in this condition.		
Polotsky et al, 2013, USA	Cohort	Community (SWAN study)	NIH	N=66 Age=46.5 (45.7, 47.2) BMI=27.1 (25.4, 28.8) Women age 42-52 years, with high androgens and a history of menstrual irregularity	Normoandrogenemia: Oligomenorrhea N=149 Age=45.9 (45.5, 46.3) BMI=25.5 (24.6, 26.6) Eumenorrhea N=1186 Age=46.2 (46.0, 46.3) BMI=25.1 (24.8, 25.4)	Stroke, MI	Self report	13 years	There was no significant difference in incidence of self-reported stroke or MI by HA/Oligo status. Longitudinal evidence suggests that a history of androgen excess and menstrual irregularity is not associated with worsening of metabolic health after menopause.	No extractable outcome of interest	Mod
Schmidt et al, 2011, Sweden	Cohort	University hospital	Rotterdam	N=25 Age=70.4 (5.0) BMI=27.1 (5.0)	N=68 Age=70.7 (5.6) BMI=26.4 (4.8)	Prevalence: Stroke, MI, CVD (MI+Stroke), Death due to MI	ICD	21 years	The well-described cardiovascular/metabolic risk profile in pre- and perimenopausal PCOS women does not entail an evident increase in cardiovascular events during the postmeno- pausal period.	Yes	Mod
Sirmans et al, 2014, USA	Cross-sectional	Community	ICD	N=1689 Age=25.24	N=5067 Age=25.23 Age- and race-matched controls	Prevalence: AMI, heart failure, CABG, coronary heart disease, Ischemic stroke, PTCA, PAD or PVD, TIA, angina	ICD	N/A	diagnosed PCOS and its defining char- acteristics are associated with an increased risk for cardiovas- cular risk factors independent of age and race. However, PCOS was not associated with an increase of cardiovascular events in	Yes	Mod

									this relatively young population of women.		
Wild et al, 2000, UK	Cohort	Community	Laproscopic criteria	N=319 Age=56.7 (range 38-98) BMI=26.6	N=1060 Age=56.7 (range 38-98) BMI=25.9 Age-matched control women	Prevalence: Composite CVD (MI, angina, coronary revascularization, positive treadmill test), cerebrovascular disease (stroke/TIA)	ICD, self-report	Mean=31 (range 15-47) years since diagnosis of PCOS	A history of coronary heart disease (CHD) was not significantly more common in women with PCOS. At long-term follow-up, a history of nonfatal cerebrovascular disease and cardiovascular risk factors including diabetes are more prevalent among women with polycystic ovary syndrome. Morbidity and mortality from of coronary heart disease among women with polycystic ovary syndrome is not as high as previously predicted.	Yes	Mod

6. QUALITY APPRAISAL OF INCLUDED STUDIES

		Selection bias			Performance bias	Detection bias				Attrition bias		Report Bias	Confounding	Other bias			
Study ID	Design	Comparable cases & controls	Established case definition	Established control definition	Groups treated the same	Standard measurements for exposure	Assessors blinded to case/control status	Standard measurements for outcomes	Outcomes assessed objectively and independently	% lost to follow up	% included in analysis	Free of selective outcome reporting	Groups similar at baseline	Funding/COI reported	Sufficient power	Adequate statistical analysis	Overall risk
Berni, 2021	Cohort	Partial	Partial	Partial	Yes	Yes	NR	Yes	Yes	NR	100%	NA	Partial	Yes	Yes	Yes	Mod
Calderon-Margalit, 2014	Cross sectional	NR	Yes	Yes	Yes	Partial	Partial	Partial	Yes	NA	NR	NA	NR	No	NR	Yes	High
Cibula, 2000	Cross sectional	NR	Yes	Yes	Yes	Yes	NR	Yes	Yes	NA	NR	NA	Yes	No	No	Yes	Mod
Ding, 2018	Cohort	Partial	Yes	Yes	Yes	Yes	NR	NR	Yes	NR	NR	NA	Partial	Yes	NR	Yes	Mod
Forslund, 2022	Cross sectional	Partial	Yes	Yes	Yes	Yes	NR	Yes	Yes	NA	NR	NA	Yes	Yes	NR	Yes	Mod
Glintborg, 2015	Cross sectional	Partial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	NR	NA	No	Yes	NR	Yes	Mod
Glintborg, 2018	Cross sectional	Partial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	NR	NA	No	Yes	NR	Yes	Mod
Haakova, 2003	Cohort	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	NR	NR	NA	Yes	No	NR	Yes	Mod
Hart, 2015	Cross sectional	Partial	Partial	Partial	Yes	Yes	NR	Yes	Yes	NA	88.57%	NA	NR	Yes	NR	Yes	Mod
Iftikhar, 2012	case control	Partial	Yes	Yes	Yes	Yes	NR	Yes	Yes	0.25% (1/400)	87.80%	NA	Partial	No	Yes	Yes	Mod
Lo, 2006	Cross sectional	partial	Yes	Yes	Yes	Yes	NR	Yes	Yes	NA	85.40%	NA	Partial	No	NR	Yes	Mod
Lunde, 2007	Cross sectional	NR	Yes	NR	NR	Yes	NR	Yes	Yes	NA	NR	NA	NR	No	No	Yes	High
Mahboobifard, 2022	Cross sectional	NR	Yes	Yes	Yes	Yes	NR	Yes	Yes	NA	NR	NA	Partial	Yes	Yes	Yes	Mod
Mani, 2013	Cohort	NA	Yes	NA	NA	Yes	NA	Yes	Yes	NR	NR	NA	NA	Yes	NR	Yes	Mod
Merz, 2016	Cohort	NR	Yes	No	NR	Yes	Yes	Yes	Yes	NR	NR	NA	Partial	yes	NR	Yes	Mod
Meun, 2018	Cross sectional	NR	Yes	Yes	NR	Yes	NR	Yes	Yes	NR	NR	NA	NR	Yes	NR	Yes	Mod
Morgan, 2012	Cohort	Yes	Partial	Partial	Yes	Yes	NR	Yes	Yes	NR	NR	NA	Partial	Yes	Yes	Yes	Mod
Okoroh, 2015	Cross sectional	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	NA	NR	NA	Partial	Yes	NR	Yes	Mod
Ollila, 2018	Cross sectional	NR	Yes	Yes	Yes	Yes	NR	Yes	Yes	NA	NR	NA	No	Yes	NR	Yes	Mod

Pierpoint, 1998	Cross sectional	NA	Yes	NA	NA	Yes	NR	Yes	Yes	NA	NR	NA	NA	NR	Yes	Yes	Mod
Polotsky,2013	Cohort	NA	Yes	NA	NA	Yes	NR	Yes	Yes	NR	NR	NA	NA	Yes	NR	Yes	Mod
Schmidt, 2011	Cross sectional	Partial	Yes	Yes	Yes	Yes	NR	Yes	Yes	NA	NR	NA	Yes	yes	No	Yes	Mod
Sirmans, 2014	case control	yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	NR	4.71%	NA	Partial	No	NR	Yes	Mod
Wild, 2000	Cohort	Partial	Yes	Yes	Yes	Yes	NR	Yes	Yes	NR	NR	NA	NR	No	Yes	partial	Mod

7. FINDINGS

Comparisons included:
- **PCOS versus controls**

Outcomes included:
- **Outcome 1. Composite cardiovascular disease (CVD) odds ratio**
- **Outcome 2. Composite ischaemic heart disease (IHD) odds ratio**
- **Outcome 3. Myocardial infarction (MI) odds ratio**
- **Outcome 4. Stroke odds ratio**
- **Outcome 5. Composite CVD incident rate ratio**
- **Outcome 6. MI hazard incident rate ratio**
- **Outcome 7. Stroke incident rate ratio**
- **Outcome 8. Cardiovascular mortality incident rate ratio**
- **Outcome 9. Composite CVD hazard ratio**
- **Outcome 10. MI hazard ratio**
- **Outcome 11. Stroke hazard ratio**
- **Outcome 12. Cardiovascular mortality hazard ratio**

Definitions
Composite CVD: Including angina, MI, coronary artery angioplasty, revascularisation, peripheral vascular disease (PVD), stroke, transient ischaemic accident (TIA), CVD related deaths
Composite IHD: Including angina, MI, coronary artery angioplasty, revascularisation
Stroke: Including ischemic and haemorrhagic cerebrovascular accidents
Cardiovascular mortality: death due to MI, angina, sudden cardiac death, congestive heart failure, peripheral arterial disease, stroke, TIA

▪ EVIDENCE SUMMARY:

Composite cardiovascular disease (CVD)
Ten studies report prevalence or odds ratio of composite CVD in women with and without PCOS (Forslund 2022, Iftikhar 2012, Mahboobifard 2022, Mani 2013, Merz 2016, Morgan 2012, Okoroh 2015, Ollila 2018, Schmidt 2011 and Wild 2000) were included in the meta-analysis. All ten studies were judged as moderate risk of bias.

Nine studies reported longitudinal outcomes of composite CVD in women with and without PCOS which were all judged as moderate risk of bais. Eight studies were included in the meta-analysis for incidence rate ratios (Berni 2021, Ding 2018, Forslund 2022, Glintborg 2018, Hart 2015, Iftikhar 2012, Mahboobifard 2022, Morgan 2012) while five studies were included in the meta-analysis for hazard ratio (Ding 2018, Forslund 2022, Iftikhar 2012, Mahboobifard 2022, Morgan 2012).

Composite ischemic heart disease (IHD) odds ratio
Eleven studies report prevalence or odds ratio of composite IHD in women with and without PCOS (Calderon-Margalit 2014, Cibula 2000, Glintborg 2015, Glintborg 2018, Haakova 2003, Hart 2015, Lo 2006, Mahboobifard 2022, Merz 2016, Sirmans 2017 and Wild 2000). Three studies were excluded from the meta-analysis: Glintborg 2015 uses an overlapping study population as Glintborg 2018; Calderon-Margalit 2014 and Haakova 2003 reported no composite IHD event in women with PCOS and were considered as outliers. The remaining eight studies were included in the meta-analysis. The study by Calderon-Margalit 2014 was judged as high risk of bias, the rest of the studies were judged as moderate risk of bias.

Myocardial infarction (MI)
Nine studies report prevalence or odds ratio of MI in women with and without PCOS and all were included in the meta-analysis (Forslund 2022, Glintborg 2015, Iftikhar 2012, Lunde 2007, Mani

2013, Okoroh 2015, Ollila 2018, Schmidt 2011, Sirmans 2013). Except for the study by Lunde 2007 which was judged as high risk of bias, the rest of the studies were judged as moderate risk of bias.
Only three studies reported longitudinal myocardial infarction outcomes in women with and without PCOS and they were of moderate risk of bias. Forslund 2022 and Iftikhar 2012 were included in meta-analysis for incidence rate ratio and hazard ratio but Berni 2021 was only included in meta-analysis for incidence rate ratio.

Stroke
Twelve studies report prevalence or odds ratio of stroke in women with and without PCOS (Forslund 2022, Glintborg 2015, Glintborg 2018, Hart 2015, Iftikhar 2012, Lo 2006, Lunde 2007, Okoroh 2015, Ollila 2018, Schmidt 2011, Sirmans 2013, Wild 2000). Two studies were excluded in the meta-analysis: Glintborg 2015 uses an overlapping study population as Glintborg 2018; and Lunde 2007 reported no stroke event in women with PCOS and was considered an outlier. The remaining ten studies were included in the meta-analysis. Except for the study by Lunde 2007 which was judged as high risk of bias, the rest of the studies were judged as moderate risk of bias.

Five studies reported longitudinal stroke outcome in women with and without PCOS (Berni 2021, Forslund 2022, Glintborg 2018, Hart 2015, Iftikhar 2012) and all were judged as moderate risk of bias. All five studies were included in meta-analysis for incidence rate ratio while only Forslund 2022 and Iftikhar 2012 were included in meta-analsis for hazard ratio.

Cardiovascular mortality
Only four cohort studies reported cardiovascular mortality outcomes in women with and without PCOS (Berni 2021, Forslund 2022, Iftikhar 2012, Merz 2016) and they were judged moderate risk of bias. Berni 2021 was only included in meta-analysis for incidence rate ratio but the rest of the four studies were included in meta-analysis for both incidence rate ratio and hazard ratio.

▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

Compared to general women, women with PCOS had higher odds ratio and/or incidence rate ratio for composite cardiovascular disease, composite ischemic heart disease, myocardial infarction, stroke and cardiovascular mortality. The level of evidence for these outcomes are of very low to low quality as all the evidence were generated from observational studies.

Outcome	Studies	n	Effect Estimate; OR/HR/IRR [95% CI], M-H, random	P	Favours	Certainty
Composite cardiovascular disease (CVD)						
Cross-sectional study – Overall	10	489071	OR 1.68 (1.26 – 2.23)	<0.001	Higher in PCOS	⊕○○○ Very low
Cross-sectional study – Defined PCOS	6	2614	OR 1.64 (1.01 – 2.67)	0.001	Higher in PCOS	⊕⊕○○ Low
Cross-sectional study - ≥10-year follow up	6	2446	OR 1.16 (0.78 – 1.73)	0.162	No difference	⊕⊕○○ Low
Cohort study – incidence rate ratio	8	595593	IRR 1.14 (1.08 – 1.21)	<0.001	Higher in PCOS	⊕⊕○○ Low
Cohort study – hazard ratio	5	151229	HR 1.01 (0.66 – 1.53)	<0.001	No difference	⊕⊕○○ Low
Composite ischaemic heart disease (IHD)						
Cross-sectional study – Overall	8	175341	OR 1.48 (1.07 – 2.05)	<0.001	Higher in PCOS	⊕○○○ Very low
Cross-sectional study – Defined PCOS	5	74149	OR 1.28 (0.94 – 1.74)	0.016	Higher in PCOS	⊕⊕○○ Low

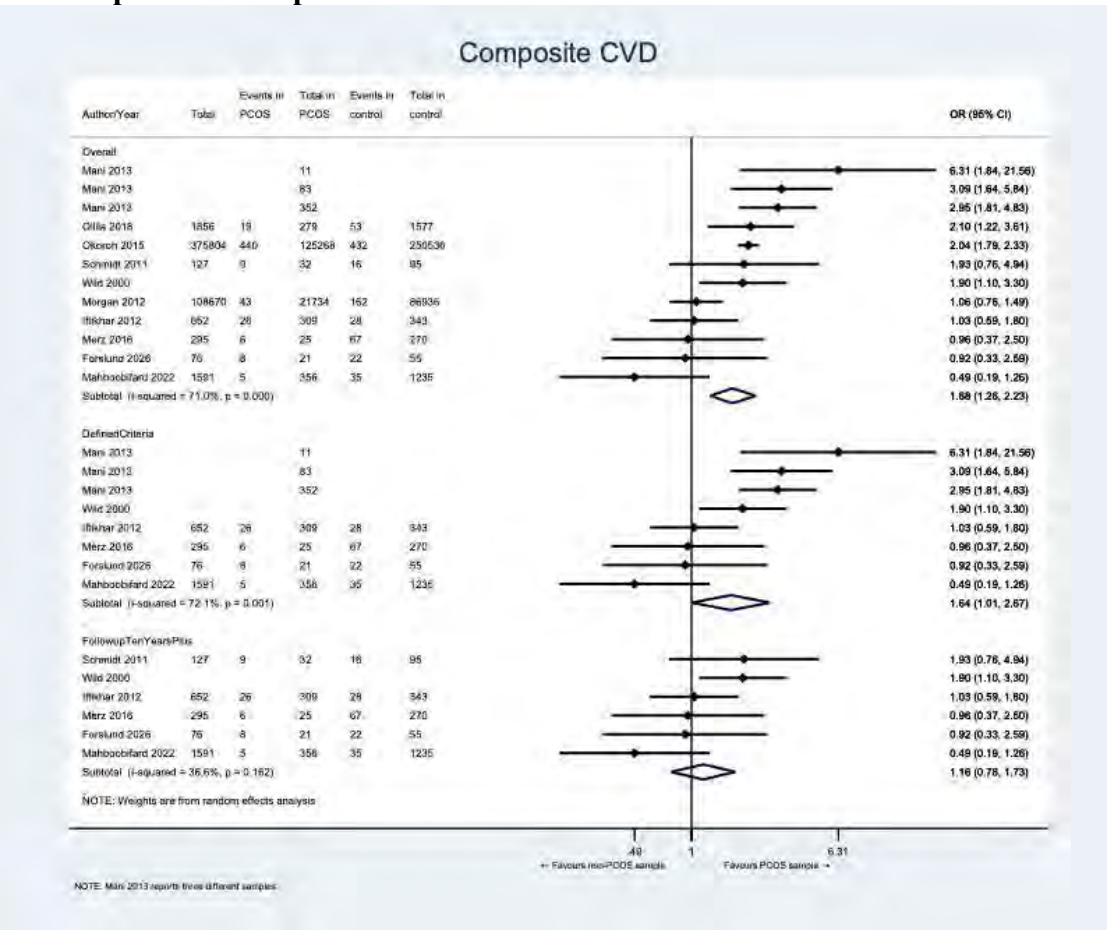
Cross-sectional study - ≥10-year follow up	5	101595	OR 1.45 (0.97 – 2.18)	<0.001	Higher in PCOS	⊕⊕○○ Low
Myocardial infarction (MI)						
Cross-sectional study – Overall	9	464024	OR 2.50 (1.43 – 4.38)	<0.001	Higher in PCOS	⊕○○○ Very low
Cross-sectional study – Defined PCOS	5	79481	OR 3.08 (1.14 – 8.34)	<0.001	Higher in PCOS	⊕○○○ Very low
Cross-sectional study - ≥10-year follow up	4	1709	OR 1.15 (0.65 – 2.03)	0.697	No difference	⊕○○○ Very low
Cohort study – incidence rate ratio	3	346542	IRR 1.32 (1.17 – 1.48)	0.012	Higher in PCOS	⊕⊕○○ Low
Cohort study – hazard ratio	2	728	HR 0.91 (0.52 – 1.82)	0.383	No difference	⊕○○○ Very low
Stroke						
Cross-sectional study – Overall	10	485365	OR 1.71 (2.20 – 2.44)	<0.001	Higher in PCOS	⊕○○○ Very low
Cross-sectional study – Defined PCOS	4	72211	OR 1.24 (0.76 – 2.01)	0.193	No difference	⊕○○○ Very low
Cross-sectional study - ≥10-year follow up	6	100564	OR 1.59 (0.95 – 2.64)	0.013	Higher in PCOS	⊕○○○ Very low
Cohort study – incidence rate ratio	5	446251	IRR 1.02 (0.94 – 1.12)	0.069	No difference	⊕⊕○○ Low
Cohort study – hazard ratio	2	728	HR 0.89 (0.45 – 1.75)	0.696	No difference	⊕⊕○○ Low
Cardiovascular mortality						
Cohort study – incidence rate ratio	4	346837	IRR 1.26 (1.19 – 1.34)	<0.001	Higher in PCOS	⊕⊕○○ Low
Cohort study – hazard ratio	3	1023	HR 1.14 (0.65 – 2.02)	0.498	No difference	⊕⊕○○ Low

OUTCOME 1. Composite Cardiovascular Disease (CVD) Odds Ratio (OR)

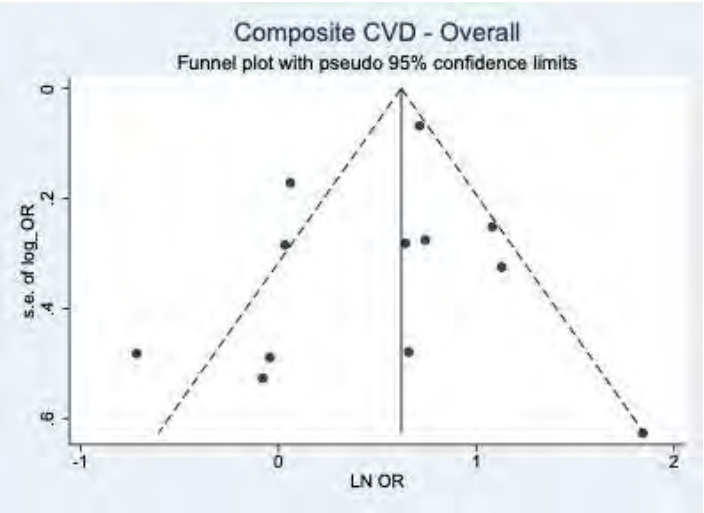
1.1. Individual Study Data Table

OUTCOME: Composite CVD			**OUTCOME TYPE: Dichotomous**					
COMPARISON (if applicable): PCOS and control								
Author, year	**PCOS criteria**	**Follow up duration (mean or median)**	**N events in PCOS**	**N total in PCOS**	**N events in control**	**N total in control**	**Crude OR (95% CI)**	**Pooled in MA?**
Forslund 2022	Rotterdam	32 years	8	21	22	55	NR	Yes
Iftikhar 2012	Rotterdam	23.7 years	26	309	28	343	NR	Yes
Mahboobifard 2022	Rotterdam	15.4 years	5	356	35	1235	NR	Yes
Mani 2013 (45-54yo)	AES	5.2 person years	NR	352	NR	NR	2.95 (1.81-4.83)	Yes
Mani 2013 (55-64yo)	AES	5.2 person years	NR	83	NR	NR	3.09 (1.64-5.84)	Yes
Mani 2013 (≥65yo)	AES	5.2 person years	NR	11	NR	NR	6.31 (1.84-21.56)	Yes
Merz 2016	AES	10 years	6	25	67	270	NR	Yes
Morgan 2012	Medical records	4.7 years	43	21734	162	86936	NR	Yes
Okoroh 2015	ICD	N/A	440	125268	432	250536	NR	Yes
Ollila 2018	Self-report	N/A	19	279	53	1577	NR	Yes
Schmidt 2011	ICD	21 years	9	32	16	95	NR	Yes
Wild 2000	Laparoscopic PCOS	31 years	NR	NR	NR	NR	1.9 (1.1-3.3)	Yes

1.2. Forest plots for composite CVD OR



1.3. Funnel plots for composite CVD OR

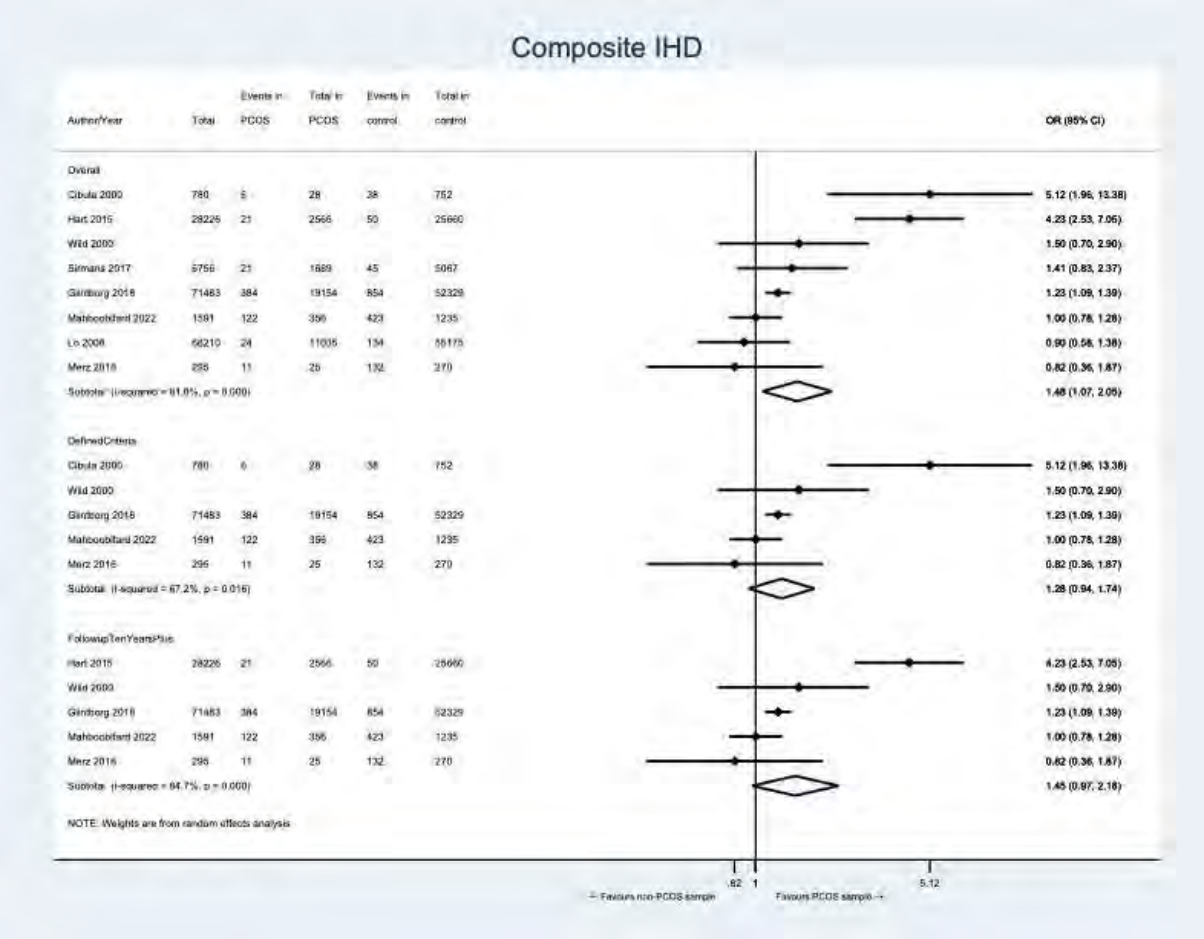


OUTCOME 2. Composite Ischaemic Heart Disease (IHD) Odds Ratio

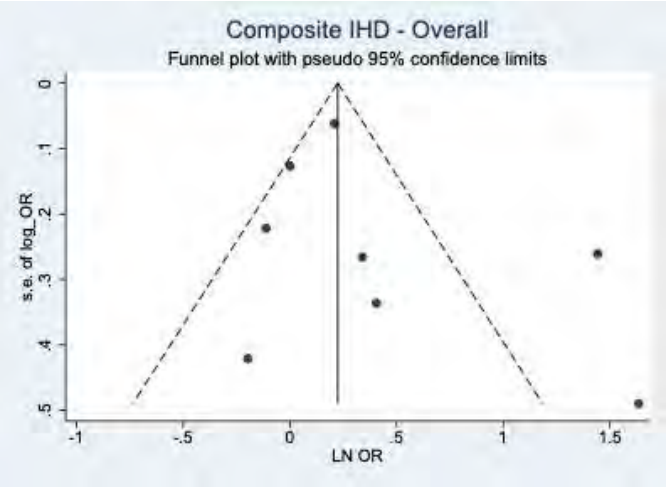
2.1. Individual Study Data Table

OUTCOME: Composite IHD				OUTCOME TYPE: Dichotomous				
COMPARISON (if applicable): PCOS and control								
Author, year	**PCOS criteria**	**Follow up duration (mean or median)**	**N events in PCOS**	**N total in PCOS**	**N events in control**	**N total in control**	**Crude OR (95% CI)**	**Pooled in MA?**
Calderon-Margalit 2014	NIH	N/A	0	55	7	668	NR	No
Cibula 2000	NIH	N/A	6	28	38	752	NR	Yes
Glintborg 2015	Rotterdam and ICD	N/A	74	20416	177	57483	NR	No
Glintborg 2018	Rotterdam and ICD	11.1 years	384	19154	854	52329	NR	Yes
Haakova 2003	NIH	N/A	0	66	0	66	NR	No
Hart 2015	ICD	15yo until median 35.8yo	21	2566	50	25660	NR	Yes
Lo 2006	ICD	N/A	24	11035	134	55175	NR	Yes
Mahboobifard 2022	Rotterdam	15.4 years	122	356	423	1235	NR	Yes
Merz 2016	AES	10 years	11	25	132	270	NR	Yes
Sirmans 2017	ICD	N/A	21	1689	45	5067	NR	Yes
Wild 2000	Laproscopic PCOS	31 years	NR	NR	NR	NR	1 5 (0.7-2.9)	Yes

2.2. Forest plots for composite IHD OR



2.3. Funnel plots for composite IHD OR

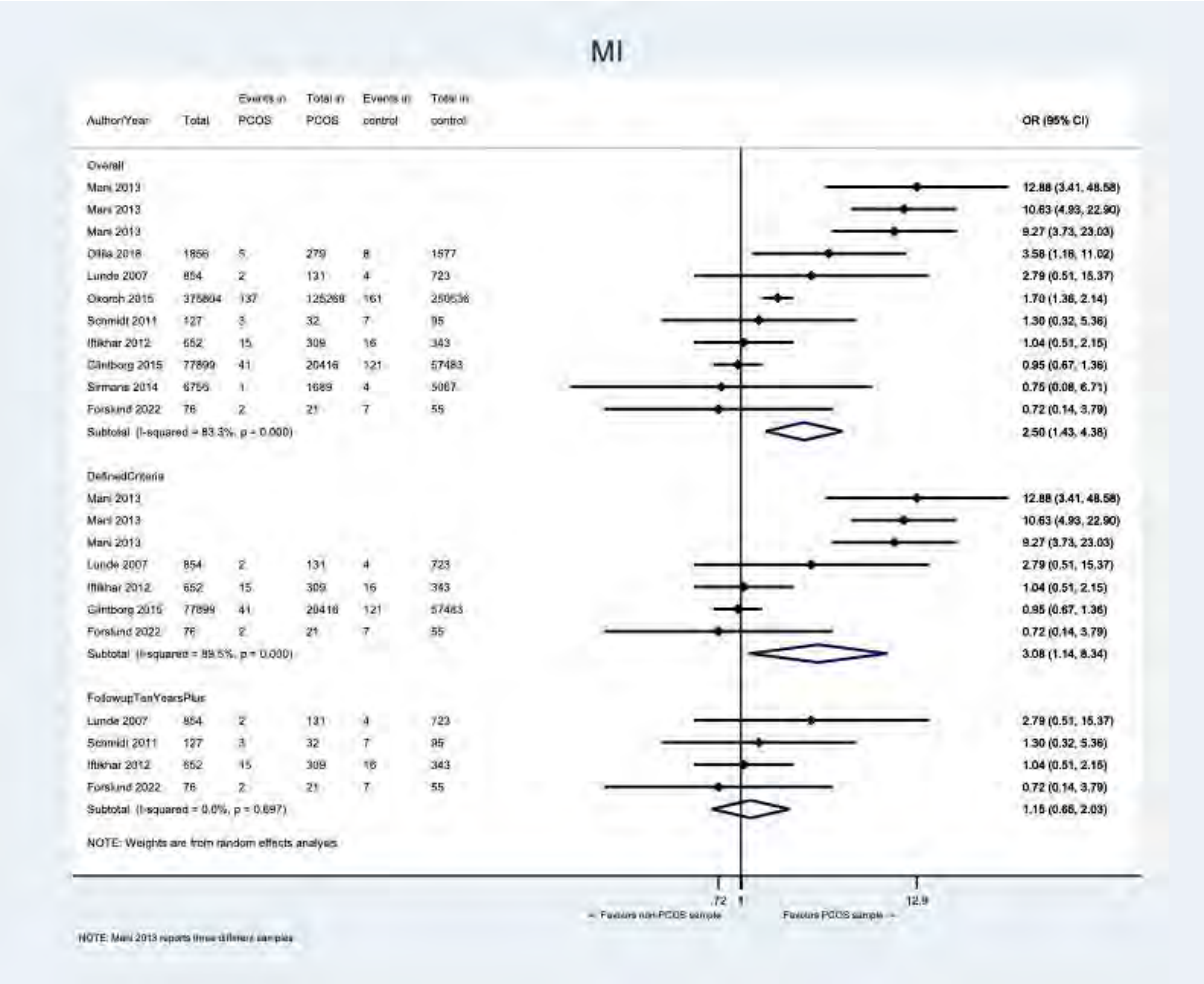


OUTCOME 3. Myocardial Infarction (MI) Odds Ratio (OR)

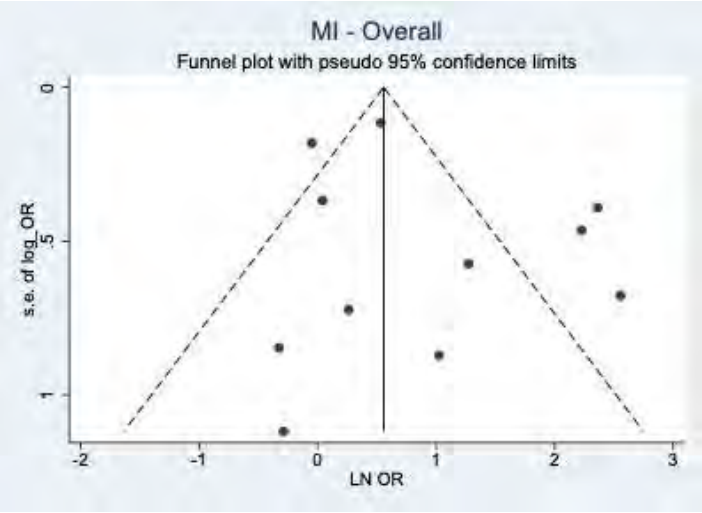
3.1 Individual Study Data Table

OUTCOME: MI				OUTCOME TYPE: Dichotomous				
COMPARISON (if applicable): PCOS and control								
Author, year	**PCOS criteria**	**Follow up duration (mean or median)**	**N events in PCOS**	**N total in PCOS**	**N events in control**	**N total in control**	**Crude OR (95% CI)**	**Pooled in MA?**
Forslund 2022	Rotterdam	32 years	2	21	7	55	NR	Yes
Glintborg 2015	Rotterdam and ICD	N/A	41	20416	121	57483	NR	Yes
Iftikhar 2012	Rotterdam	23.7 years	15	309	16	343	NR	Yes
Lunde 2007	Laproscopic PCOS	11.1 years	2	131	4	723	NR	Yes
Mani 2013 (45-54yo)	AES	5.2 person years	NR	NR	NR	NR	10.63 (4.93-22.9)	Yes
Mani 2013 (55-64yo)	AES	5.2 person years	NR	NR	NR	NR	9.27 (3.73-23.03)	Yes
Mani 2013 (≥65yo)	AES	5.2 person years	NR	NR	NR	NR	12.88 (3.41-48.58)	Yes
Okoroh 2015	ICD	15.4 years	137	125268	161	250536	NR	Yes
Ollila 2018	Self-report	10 years	5	279	8	1577	NR	Yes
Schmidt 2011	ICD	21 years	3	32	7	95	NR	
Sirmans 2014	ICD	N/A	1	1689	4	5067	NR	Yes

3.2. Forest plots for MI OR



3.3. Funnel plots for MI OR

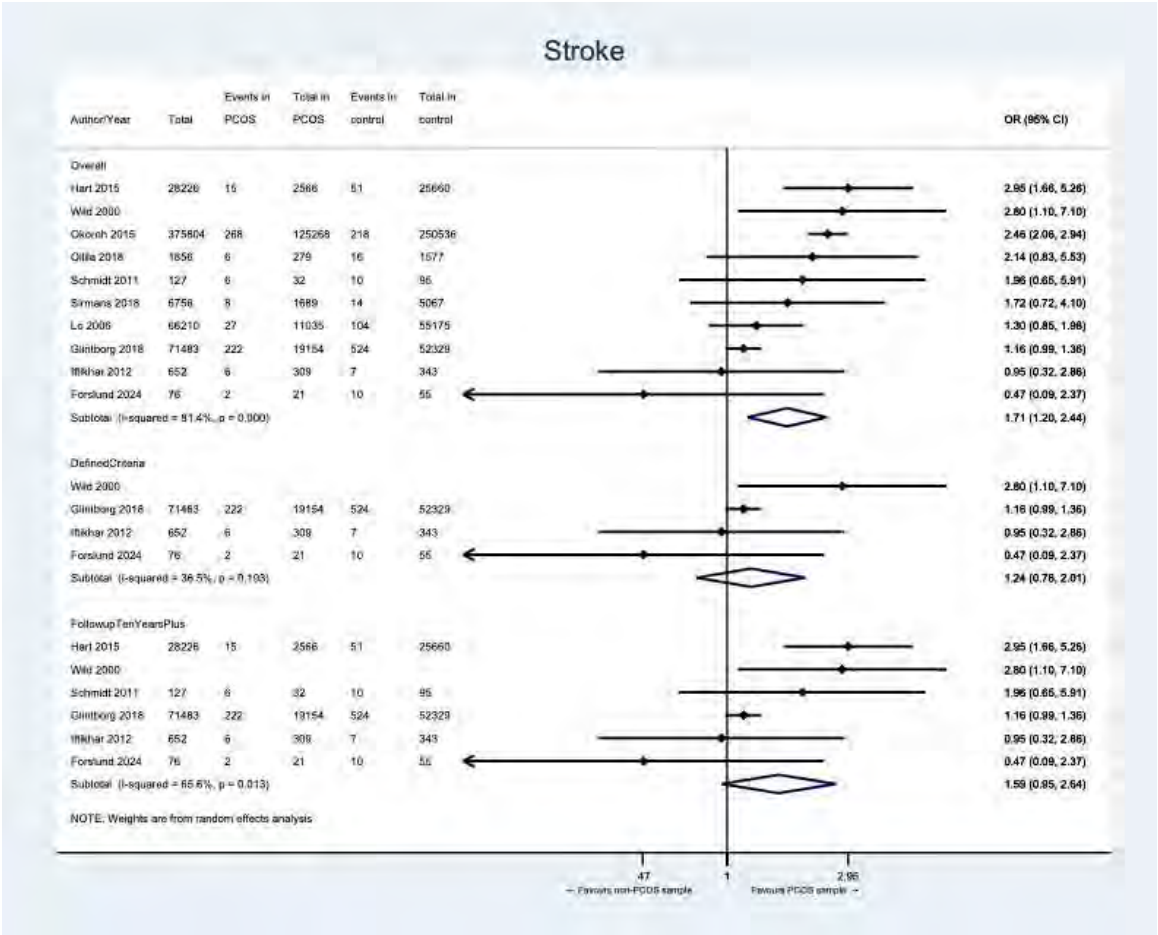


OUTCOME 4. Stroke Odds Ratio (OR)

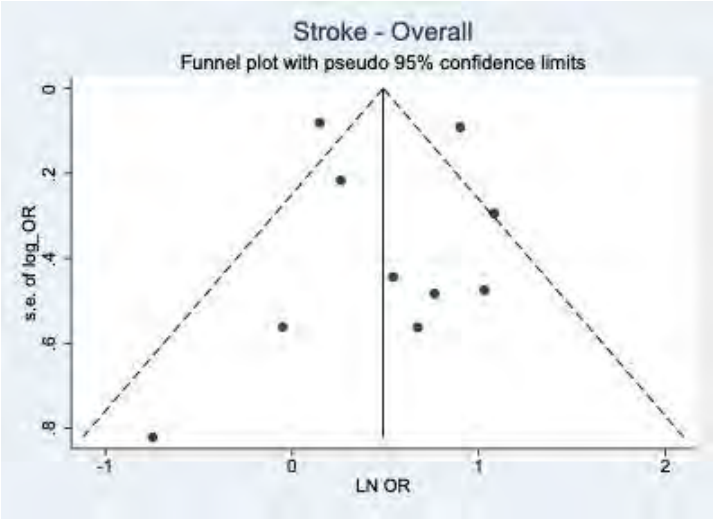
1.1 Individual Study Data Table

OUTCOME: Stroke			OUTCOME TYPE: Dichotomous					
COMPARISON (if applicable): PCOS and control								
Author, year	**PCOS criteria**	**Follow up duration (mean or median)**	**N events in PCOS**	**N total in PCOS**	**N events in control**	**N total in control**	**Crude OR (95% CI)**	**Pooled in MA?**
Forslund 2024	Rotterdam	32 years	2	21	10	55	NR	Yes
Glintborg 2015	Rotterdam and ICD	N/A	51	20416	82	57483	NR	No
Glintborg 2018	Rotterdam and ICD	11.1 years	222	19154	524	52329	NR	Yes
Hart 2015	ICD	15yo until median 35.8yo	15	2566	51	25660	NR	Yes
Iftikhar 2012	Rotterdam	23.7 years	6	309	7	343	NR	Yes
Lo 2006	ICD	N/A	27	11035	104	55175	NR	Yes
Lunde 2007	Laproscopic PCOS	15-25 years	0	131	8	723	NR	No
Okoroh 2015	ICD	N/A	268	125268	218	250536	NR	Yes
Ollila 2018	Self-report	N/A	6	279	16	1577	NR	Yes
Schmidt 2011	ICD	21 years	6	32	10	95	NR	Yes
Sirmans 2018	ICD	N/A	8	1689	14	5067	NR	Yes
Wild 2000	Laproscopic PCOS	31 years	NR	NR	NR	NR	(1.1-7.1)	Yes

1.2 Forest plots for stroke OR



4.3 Funnel plots for stroke OR

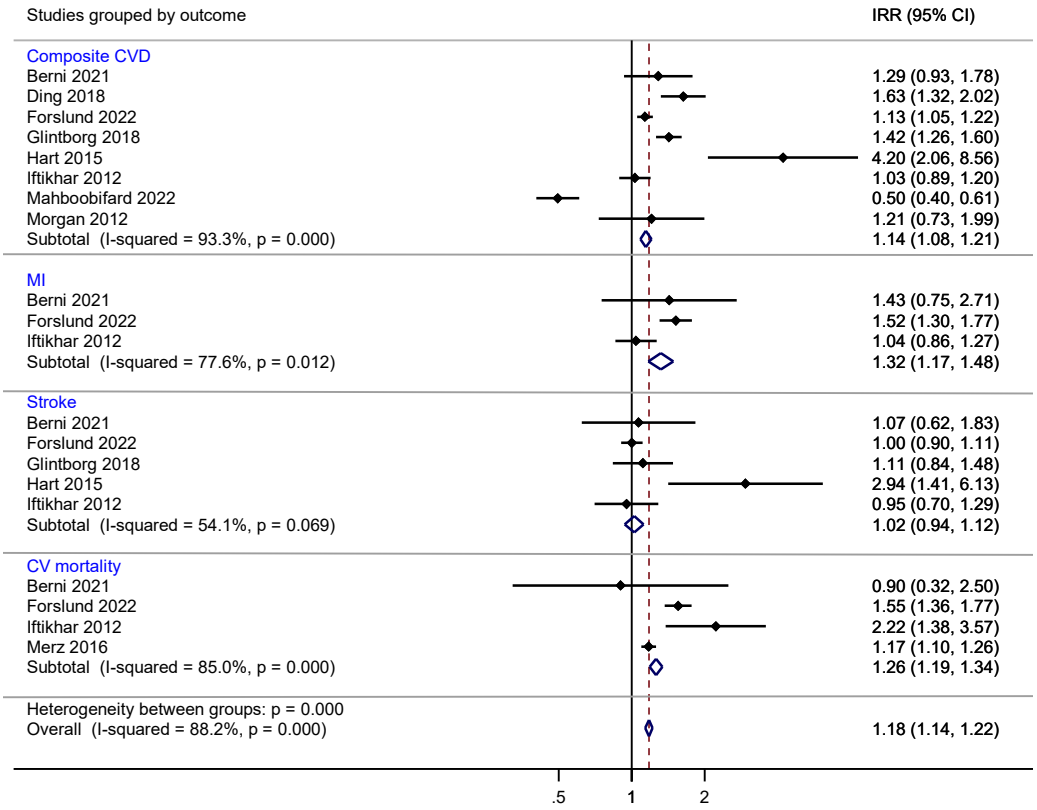


OUTCOME 5 – 8. Composite CVD, MI, Stroke and CV Mortality Incident Rate Ratios

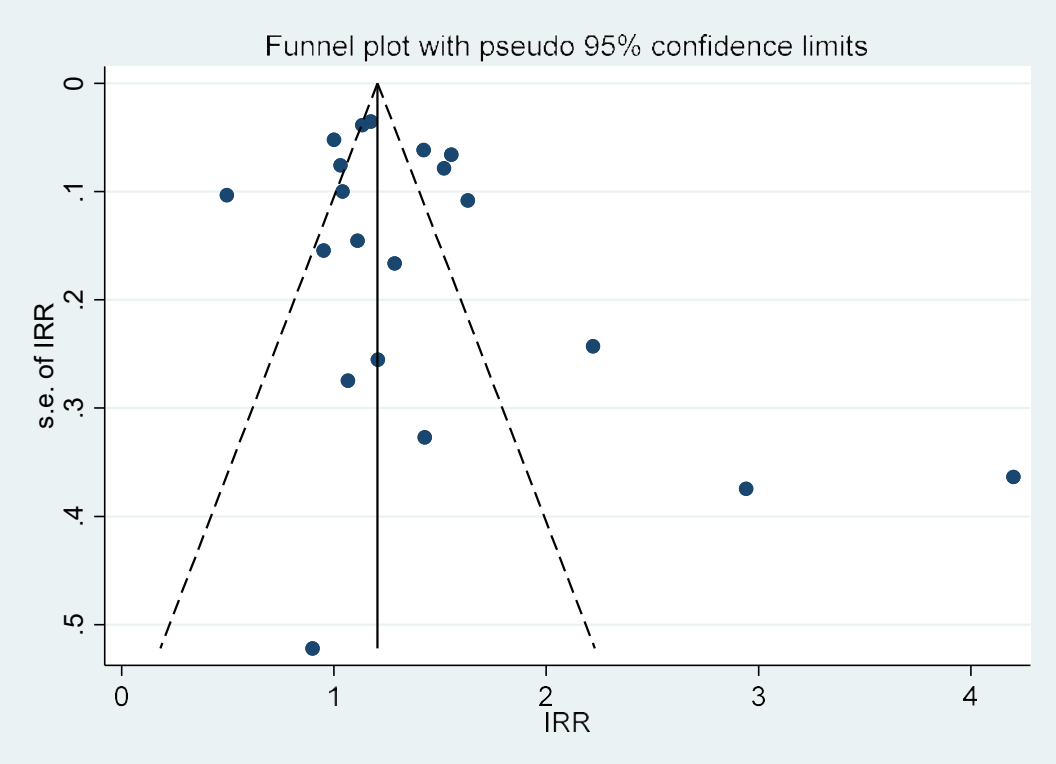
5.1. - 8.1. Individual Study Data Table

COMPARISON (if applicable): PCOS and control									
Author, year	PCOS criteria	Follow up duration (mean or median)	N events in PCOS	N total in PCOS	N events in control	N total in control	PCOS IR per 100kpy	Control IR per 100kpy	Pooled in MA?
Composite CVD									
Berni 2021	ICD	PCOS = 3.83y Control = 3y	804	172907	522	172907	82.7	64.3	Yes
Ding 2018	ICD	5.9y	107	8048	259	32192	225	138	Yes
Forslund 2022	Rotterdam	32y		21		55	1440	1270	Yes
Glintborg 2018	Rotterdam and ICD	11.1y	1290	17995	2678	52329	640	450	Yes
Hart 2015	ICD	20.8y	21	2566	50	25660	39.3	9.4	Yes
Iftikhar 2012	Rotterdam	23.7y	26	309	28	343	355.0	344.4	Yes
Mahboobifard 2022	Rotterdam	10y	5	356	35	1235	140.4	283.4	Yes
Morgan 2012	Medical records	PCOS = 4.7y Control = 5.8y	43	21734	162	86936	28	34	Yes
Myocardial infarction									
Berni 2021	ICD	PCOS = 3.83y Control = 3y	221	172907	129	172907	22.7	15.9	Yes
Forslund 2022	Rotterdam	32y		21		55	410	270	Yes
Iftikhar 2012	Rotterdam	23.7y	15	309	16	343	204.8	196.8	Yes
Stroke									
Berni 2021	ICD	PCOS = 3.83y Control = 3y	267	172907	209	172907	27.4	25.7	Yes
Forslund 2022	Rotterdam	32y		21		55	740	740	Yes
Glintborg 2018	Rotterdam and ICD	11.1y	222	19154	524	52329	100	90	Yes
Hart 2015	ICD	20.8y	15	2566	51	25660	28.1	9.6	Yes
Iftikhar 2012	Rotterdam	23.7y	6	309	7	343	81.9	86.1	Yes
CV mortality									
Berni 2021	ICD	PCOS = 3.83y Control = 3y	68	172907	63	172907	172907	3.83	Yes
Forslund 2022	Rotterdam	32y		21		55	55	32	Yes
Iftikhar 2012	Rotterdam	23.7y	4	309	2	343	343	23.7	Yes
Merz 2016	NIH	11.36y	5	25	46	270	270	11.36	Yes

5.1.- 8.1.Forest plots for Composite CVD, MI, Stroke and CV Mortality Incidence Rate Ratios



5-8.1 Funnel plots for Composite CVD, MI, Stroke and CV Mortality Hazard Ratios

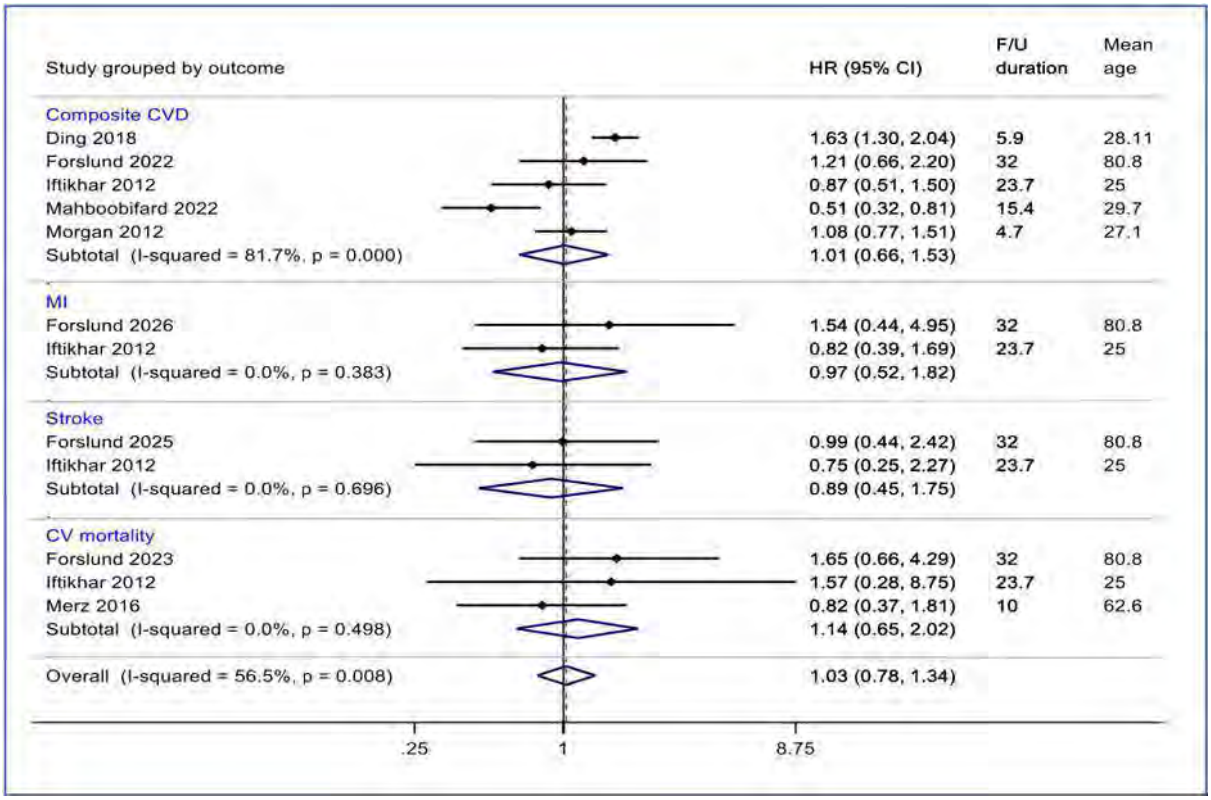


OUTCOME 9-12. Co Composite CVD, MI, Stroke and CV Mortality Hazard Ratios

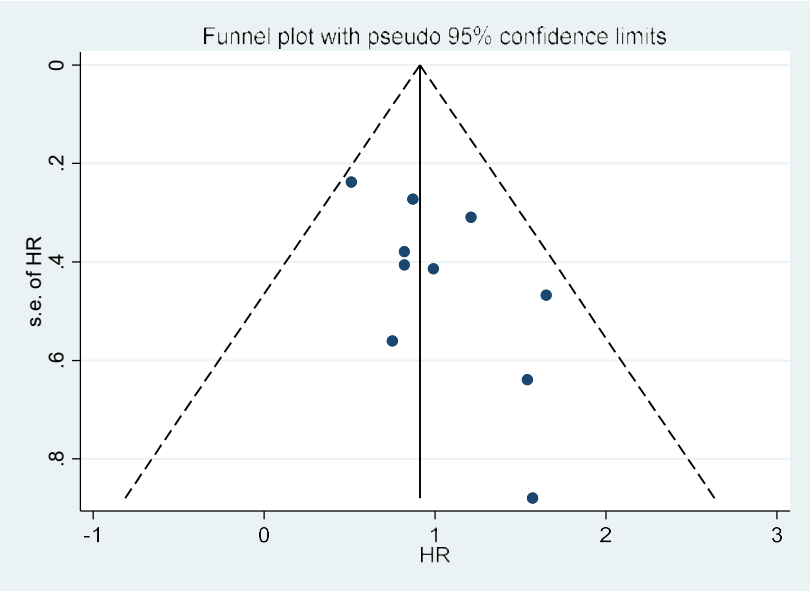
9.1. – 12.1. Individual Study Data Table

COMPARISON (if applicable): PCOS and control									
Author, year	**PCOS criteria**	**Follow up duration (mean or median)**	**N events in PCOS**	**N total in PCOS**	**N events in control**	**N total in control**	**HR**	**95% CI**	**Pooled in MA?**
Composite CVD									
Ding 2018	ICD	5.9y	107	8048	259	32192	1.63	1.2 – 2.04	Yes
Forslund 2022	Rotterdam	32y		21		55	1.21	0.66 – 2.2	Yes
Iftikhar 2012	Rotterdam	23.7y	26	309	28	343	0.87	0.51 – 1.5	Yes
Mahboobifard 2022	Rotterdam	10y	5	356	35	1235	0.51	0.32-0.81	Yes
Morgan 2012	Medical records	PCOS = 4.7y Controls = 5.8y	43	21734	162	86936	1.08	0.767 – 1.512	Yes
Myocardial infarction									
Forslund 2022	Rotterdam	32y		21		55	1.54	0.44 – 4.95	Yes
Iftikhar 2012	Rotterdam	23.7y	15	309	16	343	0.82	0.39 – 1.69	Yes
Stroke									
Forslund 2022	Rotterdam	32y		21		55	0.99	0.44 – 2.42	Yes
Iftikhar 2012	Rotterdam	23.7y	6	309	7	343	0.75	0.25 – 2.27	Yes
CV mortality									
Forslund 2022	Rotterdam	32y		21		55	1.65	0.66 – 4.29	Yes
Iftikhar 2012	Rotterdam	23.7y	4	309	2	343	1.57	0.28 – 8.75	Yes
Merz 2016	NIH	11.36y	5	25	46	270	0.82	0.37 – 1.81	Yes

9.2.- 12.2. Forrest plots for composite CVD



9.3.- 12.3. Funnel plots for composite CVD



8. GRADE ASSESSMENTS AND EVIDENCE PROFILE

COMPARISON 1: PCOS vs control													
	Quality assessment						No. participants						
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Subgroup	PCOS	Controls	Effect estimate OR/HR/IRR (95% CI)	Favours	Certainty	Importance
Outcome: Composite cardiovascular disease													
10	Observational	Not serious	Serious[1]	Not serious	Not serious	Serious[3]	Overall	148470	341047	OR 1.68 (1.26 – 2.23)	Higher in PCOS	⊕○○○ Very low	Critical
6	Observational	Not serious	Serious[1]	Not serious	Not serious	Not serious	Defined PCOS	1157	1903	OR 1.64 (1.01 – 2.67)	Higher in PCOS	⊕⊕○○ Low	Critical
6	Observational	Not serious	Not serious	Not serious	Not serious	Serious[3]	≥10y f/u	743	1998	OR 1.16 (0.78 – 1.73)	No difference	⊕⊕○○ Low	Critical
8	Cohort	Not serious	Serious[1]	Not serious	Not serious	Not serious	Overall	223936	371657	IRR 1.14 (1.08 – 1.21)	Higher in PCOS	⊕⊕○○ Low	Critical
5	Cohort	Not serious	Serious[1]	Not serious	Not serious	Not serious	Overall	30468	120761	HR 1.01 (0.66 – 1.53)	No difference	⊕⊕○○ Low	Critical
Outcome: Composite ischaemic heart disease													
8	Observational	Not serious	Serious[1]	Not serious	Not serious	Serious[3]	Overall	34853	139736	OR 1.48 (1.07 – 2.05)	Higher in PCOS	⊕○○○ Very low	Critical
5	Observational	Not serious	Not serious	Not serious	Not serious	Serious[3]	Defined PCOS	19563	53834	OR 1.28 (0.94 – 1.74)	Higher in PCOS	⊕⊕○○ Low	Critical
5	Observational	Not serious	Not serious	Not serious	Not serious	Serious[3]	≥10y f/u	22101	53834	OR 1.45 (0.97 – 2.18)	Higher in PCOS	⊕⊕○○ Low	Critical
Outcome: Myocardial infarction													
9	Observational	Not serious	Serious[1]	Not serious	Serious[2]	Serious[3]	Overall	148145	314302	OR 2.50 (1.43 – 4.38)	Higher in PCOS	⊕○○○ Very low	Critical
5	Observational	Not serious	Not serious	Not serious	Serious[2]	Serious[3]	Defined PCOS	461	1121	OR 3.08 (1.14 – 8.34)	Higher in PCOS	⊕○○○ Very low	Critical
4	Observational	Not serious	Not serious	Not serious	Serious[2]	Serious[3]	≥10y f/u	493	1216	OR 1.15 (0.65 – 2.03)	No difference	⊕○○○ Very low	Critical
3	Cohort	Not serious	Serious[1]	Not serious	Not serious	Not serious	Overall	173237	173305	IRR 1.32 (1.17 – 1.48)	Higher in PCOS	⊕⊕○○ Low	Critical
2	Cohort	Not serious	Not serious	Not serious	Serious[2]	Not serious	Overall	330	398	HR 0.91 (0.52 – 1.82)	No difference	⊕⊕○○ Low	Critical

Outcome: Stroke													
10	Observational	Not serious	Serious[1]	Not serious	Not serious	Serious[3]	Overall	160353	365077	OR 1.71 (2.20 – 2.44)	Higher in PCOS	⊕◯◯◯ Very low	Critical
4	Observational	Not serious	Serious[1]	Not serious	Not serious	Serious[3]	Defined PCOS	19484	52727	OR 1.24 (0.76 – 2.01)	No difference	⊕◯◯◯ Very low	Critical
6	Observational	Not serious	Serious[1]	Not serious	Not serious	Serious[3]	≥10y f/u	22082	78482	OR 1.59 (0.95 – 2.64)	Higher in PCOS	⊕◯◯◯ Very low	Critical
5	Cohort	Not serious	Serious[1]	Not serious	Not serious	Not serious	Overall	194957	251294	IRR 1.02 (0.94 – 1.12)	No difference	⊕⊕◯◯ Low	Critical
2	Cohort	Not serious	Not serious	Not serious	Serious[2]	Not serious	Overall	330	398	HR 0.89 (0.45 – 1.75)	No difference	⊕⊕◯◯ Low	Critical
Outcome: Cardiovascular mortality													
4	Cohort	Not serious	Serious[1]	Not serious	Not serious	Not serious	Overall	173262	173575	IRR 1.26 (1.19 – 1.34)	Higher in PCOS	⊕⊕◯◯ Low	Critical
3	Cohort	Not serious	Not serious	Not serious	Serious[2]	Not serious	Overall	355	668	HR 1.14 (0.65 – 2.02)	No difference	⊕⊕◯◯ Low	Critical

[1] Downgraded once as direction of effect not consistent or significant heterogeneity
[2] Downgraded once as number of events are small or small population
[3] Downgraded once as some studies did not report funding or conflict of interest information

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 1

Question 1.8.

Are women with PCOS at increased risk for cardiovascular disease (CVD)?

BACKGROUND:

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in women [1]. Early identification of high risk populations with subsequent prevention and treatment of risk factors will reduce CVD incidence [2] that hopefully result in a reduction of the global burden of CVD in women by 2030 [1]. Polycystic ovary syndrome (PCOS) traditionally is considered as a CVD risk factor. Increased cardio-metabolic risk factors, which are independent of, but exacerbated by higher weight and are seen in women with polycystic ovary syndrome (PCOS) [3, 4].Several studies revealed β cell dysfunction (independent of higher weight)[5] , atherogenic lipid profile and enhanced plasminogen activator inhibitor type 1(PAI-I) production in women with PCOS [6]; as a result surrogate markers of CVD including carotid intima media thickness [7], endothelial dysfunction [8], coronary artery calcification and arterial stiffness are increased in women with PCOS. While a previous study showed that both hyperandrogenemia and low SHBG are linked to increase in CVD risk in both pre and post-menopausal women [9], the Rotterdam Study among 2578 women aged >55 years reported that postmenopausal high androgen levels were not associated with an elevated risk for CVD [10].

It remains unclear if PCOS is an independent risk factor for hypertension (HTN), as higher weight has been reported to be the main determinant of hypertension in women with PCOS [11]. A meta-analysis reported that the pooled relative risk (RR) of HTN patients was increased only in reproductive age PCOS (1.70-fold, 95% CI: 1.43-2.07) but not in menopausal/aging patients who had PCOS during their reproductive years [12].

Despite the indisputable presence of multiple cardiovascular risk factors at a young age in women with PCOS, uncertainty also remains regarding the increased incidence of CVD later in life [13-21]. This assumed paradox of early high prevalence of cardio metabolic risk factors and no increase in CVD may partly be explained by reproductive characteristics of PCOS women including late menarche [22], late menopause [23, 24], fewer children, later pregnancy [25], and the re-establishment of the negative feedback loops in the hypothalamic-pituitary-gonadal (HPG) axis that giving them a longer exposure to endogenous estrogen and the reproductive phase of HPG axis [26]. Additionally, HTN is one of the main cardiovascular risks and normalization of the prevalence of HTN by ageing in women with PCOS plays a role for lack of increasing in CVD, later in life [12]. Decreasing in androgen levels during late reproductive age may result in a progressive decrease in cardiovascular risk factors in women with PCOS and occurrence of ovulatory cycles by aging may modifies their trajectory of CVD risk factors [27]. Furthermore, women with PCOS may adopt a healthier lifestyle and receive additional counselling and medications to prevent cardio-metabolic disturbances. Recently a well-developed animal model of PCOS demonstrated that cardiac function and tolerance to ischemia/perfusion injury in elderly female rats who had PCOS at younger ages were not worse than age-matched control rats [28, 29].

Studies to date regarding the impact of PCOS on the risk of developing CVD are conflicting. The majority of available studies have methodological limitations due to study design, enrolling women beyond menopause without sufficient evidence of PCOS during the reproductive period, using retrospective cohort design, including more sever phenotypes of PCOS and lack of adjustment for main potential confounders. Therefore, the results of the meta-analysis on this topic should be interpreted with cautious, since they have a high degree of heterogeneity in terms of design and quality of included studies.

In the last five years 4 meta-analyses were conducted on CVD risk factors or events. A meta-analysis based on 23 cohort studies, demonstrated that women with PCOS had increased risks of HT, T2D, a higher serum concentration of TC, a lower serum concentration of HDL-C and increased risks of non-fatal cerebrovascular disease events, however no differences were reported for LDL-C, TG or coronary disease events [30]. A meta-analysis of ten cohort studies revealed a pooled risk of CVD events of 1.7 in PCOS compared to non-PCOS women. Moreover they reported an increase in the risk of myocardial infarction (OR: 2.57), ischemic heart disease (OR: 2.77), and stroke (OR: 1.96), but no significant difference in the overall mortality and CVD-related death [31]. In another meta-analysis with sixteen studies including 12 population-based ones showed that the pooled HRs of CVD events in PCOS patients of reproductive age and in menopausal/aging women in comparison to healthy controls were 1.38 and 1.53, respectively; however by excluding non-population based studies the increased risk of CVD disappeared in menopausal/aging PCOS patients (HR:1.03-fold, 95% CI: 0.41, 2.59); although the number of studies conducted in older populations was low [32]. A recent meta-analysis

on cardiovascular risk according to BMI among reproductive aged women was published [4], however had fundamental criticisms [33]. The 32-year follow-up of the Gothenburg PCOS cohort has showed that neither total mortality nor CVD-mortality increased in elderly women (age range 72–91 years) with PCOS [18].

CVD is the most common cause of mortality among women and is mainly preventable [34]. Despite the lack of solid evidences in terms of the impact of PCOS on CVD, especially among late reproductive age and menopausal women [21, 32, 35], the public health impact of early identification of CVD and prevention in reproductive age women is likely to be very significant and remained critical [1, 36-40]. However, the best method for CVD risk assessment, its interval and preventive approaches, especially in reproductive aged women remains unclear. Nevertheless, lifestyle interventions and weight management are the main preventive approaches.

GRADE EVIDENCE CERTAINTY	
Comparison	**GRADE for critical outcomes**
Comparison 1. Composite cardiovascular disease (CVD) in women with and without PCOS	⨁⨁◯◯ LOW
Comparison 2. Composite ischemic heart disease (IHD) in women with and without PCOS	⨁⨁◯◯ LOW
Comparison 3. Myocardial infarction (MI) in women with and without PCOS	⨁◯◯◯ VERY LOW
Comparison 4. Stroke in women with and without PCOS	⨁◯◯◯ VERY LOW
Comparison 5 Cardiovascular mortality in women with and without PCOS	⨁◯◯◯ VERY LOW

Evidence to Recommendations Framework

COMPARISONS (option versus other option)

Comparison 1. Composite cardiovascular disease (CVD) in women with and without PCOS
Comparison 2. Composite ischaemic heart disease (IHD) in women with and without PCOS
Comparison 3. Myocardial infarction (MI) in women with and without PCOS
Comparison 4. Stroke in women with and without PCOS
Comparison 5 Cardiovascular mortality in women with and without PCOS

EVIDENCE-BASED RECOMMENDATION(S)

EBR: Women with PCOS should be considered at increased risk of cardiovascular disease and potentially of cardiovascular mortality, acknowledging that the overall risk of cardiovascular disease in pre-manopausal women is low.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

EBR: All women with polycystic ovary syndrome should be assessed for cardiovascular disease risk factors.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

CR: All women with PCOS regardless of age and BMI, should have a lipid profile (cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol and triglyceride level) at diagnosis. Thereafter, frequency of measurement should be based on the presence of hyperlipidemia and additional risk factors or global cardiovascular risk.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

CR: All women with PCOS, regardless of age and BMI, should have blood pressure measured annually and when planning pregnancy or seeking fertility treatment, given the high risk of hypertensive disorders in pregnancy and the associated comorbidities.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

CR: Funding bodies should recognise that PCOS is highly prevalent and has multisystem effects, including cardiometabolic disease, and should diversify and increase research support accordingly.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

CR: Cardiovascular general population guidelines could consider the inclusion of PCOS as a cardiovascular risk factor.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

CR: Health professionals, women with PCOS and other stakeholders should all prioritise preventative strategies to reduce cardiovascular risk.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

PRACTICE POINT

Consideration should be given to the differences in cardiovascular risk factors, and cardiovascular disease, across ethnicities (see 1.6.1) and age, when determining frequency of risk assessment.

GRADE CONSIDERATIONS

Justifications:

High prevalence of cardiometabolic risk factors such as higher weight, impaired glucose tolerance, diabetes, dyslipidemia, metabolic syndrome in women with PCOS which have been estimated by several studies (4, 32, 41-43) highlights needs for regular screening of individual markers, including weight with permission from women (see section 3), waist circumference, fasting glucose, lipid profiles, and systolic and diastolic blood pressure in these patients (42). Despite lots of efforts to identify CVD risk factors in the PCOS population, there is not a specific and valid instrument for CVD risk prediction in this population. Among risk prediction instruments, Framingham Risk Score (FRS) and Pooled Cohort Equations (PCE) are frequently used to predict CVD risk in general populations, which calculates CVD risk based on the traditional risk factors (44, 45). Although CVD risk prediction by using instruments like the pooled cohort equations (PCE) might help to identify CVD risk and manage all high-risk groups, it should be considered that these instruments have not been validated for PCOS patients. On the other hand, PCE and other similar risk estimation equations are race- and sex-specific and might be associated with a misestimation of CVD risk (45, 46).

Beyond these traditional tools, more advanced screening tools have been used to predict CVD risk in women with PCOS, which assess for subclinical CVD by taking endothelial dysfunction and subclinical atherosclerosis into consideration. These markers include coronary artery calcium (CAC), ultrasound flow-mediated dilation (FMD), intima-media thickness (IMT), and pulse wave velocity (PWV), electron-beam computed tomography (EBCT), magnetic resonance imaging (MRI), and echocardiographic methods like coronary flow reserve (CFR) (8, 47-50). Moreover, various biochemical markers have been introduced that indicate elevated levels of systemic inflammation, including c-reactive protein (CRP), plasminogen-activated inhibitor 1 (PAI-1), homocysteine and endothelin-1 (ET-1) (49-53). Despite a role for these biomarkers to identify women at risk for CVD, using these tools should not be routinely recommended since they are not only more expensive but also more importantly are not affordable for all women. On the other hand, use of these instruments might be associated with stress and anxiety in these patients, leading to adverse effects on their quality of life (54).

Recent studies suggested that all age groups of women with PCOS do not have the same CVD risk profiles (32, 55). Despite the presence of plenty of cardiovascular risk factors in PCOS patients during their reproductive years (41-43) , this may not be translated to a higher rate of CVD or CVD mortality in elderly (31, 32). Therefore, CVD risk assessment needs to be stratified by age group, while reproductive-age women have to be considered as a high-risk group, postmenopausal PCOS women may have similar risk for CVD as general populations in this age group. Moreover, additional CVD risk factors in women with PCOS such as using hormonal medications should be considered (47, 48, 57) and their lipid profile should be assessed both before and intermittently during hormonal therapy (56).

Subgroup considerations:

Risk assessments need to be stratified according to the age (adolescent/reproductive/menopause), and thresholds for some items need to be specified according to various ethnicity.

Implementation considerations:

This recommendation is likely to be controversial but is based on a wealth of evidence on cardiovascular risk factors and meta-analysis on cardiovascular disease risk.

Leaders in cardiovascular health need to recognise that PCOS is a risk factor for cardiovascular disease and this requires implementation in general population screening and prevention guidelines.

Monitoring and evaluation considerations:
Monitor the implementation of the recommendation in general population cardiovascular guidelines and clinical practice.

Research priorities:
Long term, large, comprehensive longitudinal studies for assessment of CVD events are a priority. CVD risk prediction models need to be validated in women with PCOS, considering ethnicity variation. The implementation of screening and interventions need to be evaluated.

Consider the treatment paradox in assessing cardiovascular outcomes.

Cost effectiveness in screening and prevention programs for cardiovascular disease in women with PCOS.

GRADE framework

GRADE DECIDE Interactive Evidence to Decision Framework

● DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

Judgement:

☒ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See evidence report

Panel discussion:

There is solid evidence in terms of the impact of PCOS on CV risk factors and on CVD.

● UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

Judgement:

☐ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☒ Probably favours other options	☐ Favours other options

Research evidence:

See above

Panel discussion:

Over screening without having convincing evidence may result in high costs, low yields, and potential harm due to over diagnosis. This needs to be investigated and have a focus on prevention.

Additionally, PCOS patients already suffer from a lower quality of life due to their condition, therefore, excessive screening could be more detrimental in this group compared to others.

● CERTAINTY OF THE EVIDENCE

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☐ Very low	☒ Low	☐ Moderate	☐ High

Research evidence:

See evidence report.

Panel discussion:

Observational studies are considered low certainty. However, this question can only be answered through observational evidence.

● VALUES

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☐ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☒ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Research evidence:

No research evidence was identified.

Panel discussion:

It is important for both health professionals and women with PCOS to understand cardiovascular risk and understand PCOS extends beyond ovarian and fertility.

● BALANCE OF EFFECTS

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:

On balance favours this option.

● COSTS

How large are the resource requirements (costs)?

Judgement:

☐ Don't know	☒ Varies	☐ Large costs	☐ Moderate costs	☐ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:

No research evidence was identified

Panel discussion:

Possible increase in cost for screening but likely offset by reduced incidence of cardiovascular events.

● CERTAINTY OF COST EVIDENCE

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

No research evidence was identified

Panel discussion:

● COST-EFFECTIVENESS

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

No evidence was identified to address this criterion

Panel discussion:

● EQUITY

What would be the impact on health equity?

Judgement:

☐ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☒ Probably increased	☐ Increased

Research evidence:

No research evidence was identified;

Panel discussion:

Since CVD risk factors especially obesity are more prevalent in women in the lower strata of socio-economic class; this probably has positive impact on health equity.

Increased screening will increase equity, however differential patterns in screening may result in inequity.

● ACCEPTABILITY

Is the option acceptable to key stakeholders?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

● FEASIBILITY

Is the option feasible to implement?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Education, guideline and system change.

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PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by ECR Lead: Negar Naderpoor

Other Members: Noel Ng, Mahnaz Bahri-Khomami, Loyal Pattuwage

Supervised, edited and supported by the Evidence Team

GDG 1

Question 1.9.1

Q.1.9.1. Are women with PCOS at increased risk for impaired glucose tolerance and type 2 diabetes?

1. STUDY SELECTION

Table 1. PICO Criteria for Inclusion	
Question	1.9.2 Are women with PCOS at increased risk for impaired glucose tolerance and type 2 diabetes mellitus? CLINICAL PRACTICE POINTS: - Do women with PCOS need more frequent risk assessment and screening for impaired glucose tolerance and type 2 diabetes compared to general population? - In women with PCOS, what tools/methods can be used to assess dysglycaemia?
Clinical leads (key contacts)	Prof Ronald Ma
Allocation ranking	Level 2 - systematic review update

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(language, year)*
Inclusion	• Females of any age, ethnicity, weight or phenotype of PCOS • PCOS diagnosed by Rotterdam criteria/ National Institutes of Health/ Androgen Excess and PCOS society criteria	None.	Females without PCOS	Prevalence and incidence of 1) Type 2 diabetes, 2) Impaired fasting glucose, 3) Impaired glucose tolerance defined based on ADA criteria or WHO criteria, current diabetes treatment or medical history of type 2 DM (including ICD9, ICD10)	Any original study. E.g. case-control, cross-sectional	English language. Human studies, published after June 2016 (to update SR)
Exclusion	Studies where PCOS was diagnosed by self-report, hospital records without criteria noted, ICD-9 or ICD-10.	None	None	Diabetes or IGT based on self-report.	Case reports, case series, editorials. Non-evidence based guidelines, non-systematic reviews, non-comparative cohort studies, case series, editorials, letters, commentaries	Full text not available Abstracts Posters PhD theses

2. SEARCH STRATEGY

Search details	
Search strategy source: update from Kakoly, N. S. et al. Ethnicity, obesity and the prevalence of impaired glucose tolerance and type 2 diabetes in PCOS: a systematic review and meta-regression. Human Reproduction Update 24, 455-467, doi:10.1093/humupd/dmy007 (2018).	
Evidence source	**Date of search**
Medline (Ovid)	28/07/2022
EMBASE	28/07/2022
All EBMs (Ovid)	27/07/2022
CINAHL Plus	03/08/2022
Clinical trials.gov	03/08/2022
Any subsequent updates - enter database and date: not applicable	

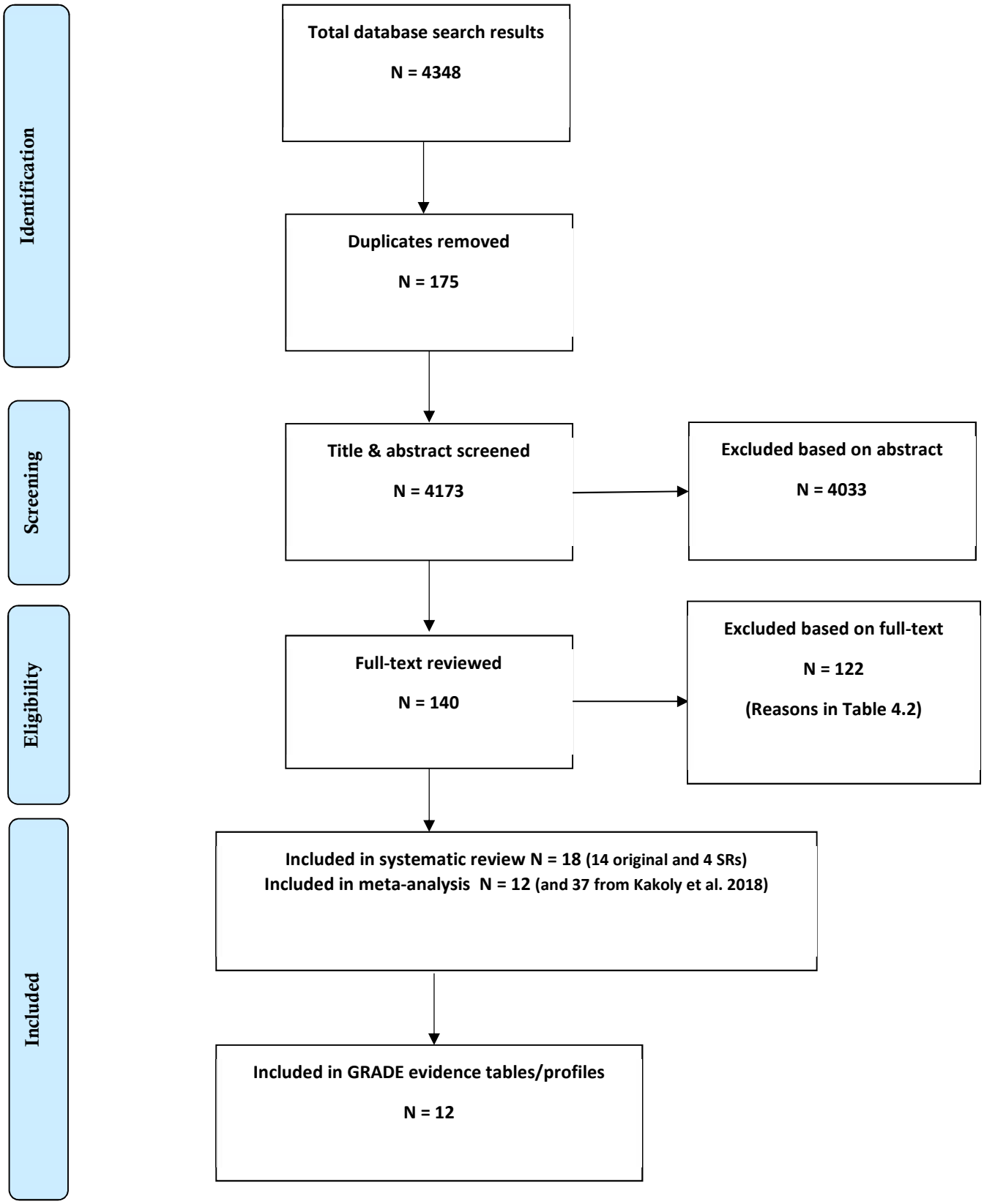
Questions addressed by this search:		
GDG	**Q#**	**Question**
1	1.9.2	Are women with PCOS at increased risk for impaired glucose tolerance and type 2 diabetes mellitus?
		CLINICAL PRACTICE POINTS: - Do women with PCOS need more frequent risk assessment and screening for impaired glucose tolerance and type 2 diabetes compared to general population? - In women with PCOS, what tools/methods can be used to assess dysglycaemia?

Search strategy	
OVID Medline, All EBMs (including Cochrane dataset for SRs), EMBASE	CINAHL Plus
exp Polycystic Ovary Syndrome/ Polycystic Ovar*.tw. (pco or pcos).tw. (sclerocystic adj3 ovar*).tw. stein leventhal.tw. or/1-5 animals/ not (animals/ and humans/) 6 not 7 diabet*.tw. NIDDM.tw. exp Diabetes Mellitus, Type 2/ exp glucose intolerance/ glucose intoleran*.tw. impaired glucose toleran*.tw. (obes* adj diabet*).tw. dm2.tw. (non insulin* depend* or noninsulin* depend* or noninsulindepend* or non insulin?depend*).tw. ((typ* 2 or typ*II or typ* ii) adj diabet*).tw. ((keto?resist* or non?keto*) adj diabet*).tw. ((adult* or matur* or late or slow or stabl*) adj diabet*).tw. (insulin* defic* adj relativ*).tw. (exp obesity/ or obes*.mp.) and (exp diabetes mellitus/ or Diabet*.mp.) or/9-22 exp Diabetes Insipidus/	S31 S7 AND S29 S30 S7 AND S29 S29 S23 OR S28 S28 S24 OR S25 OR S26 OR S27 S27 syndrome* x S26 pluri metabolic* syndrom* or plurimetabolic* syndrom* S25 metabolic* syndrom* OR (MH "metabolic syndrome X") S24 insulin* resistan* N3 syndrome* S23 S19 NOT S22 S22 S20 OR S21 S21 diabet* insipidus S20 (MH "diabetes insipidus") S19 S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 S18 Diabet* AND obes* S17 (insulin* defic* relativ*) S16 TI ((adult* or matur* or late or slow or stabl*) diabet*)) OR AB ((adult* or matur* or late or slow or stabl*) diabet*)) S15 "(keto?resist* or non? keto*) diabet*" S14 "typ* 2 or typ*II or typ* ii diabet*" S13 non insulin?depend* S12 non insulin* depend* or noninsulin* depend* or noninsulindepend* S11 (MH "glucose intolerance")

diabet* insipidus.tw. 24 or 25 23 not 26 (insulin* resistan* adj3 syndrome*).tw. metabolic* syndrom*.tw. or exp metabolic syndrome X/ (pluri metabolic* syndrom* or plurimetabolic* syndrom*).tw. (syndrome* adj x).tw. or/28-31 8 and (27 or 32) limit 33 to english language limit 34 to yr="2016 -Current"	S10 (MH "diabetes mellitus, type 2") S9 TX (diabet* OR NIDDM OR glucose intoleran* OR impaired glucose toleran* OR dm2) S8 TX "obes* diabet*" S7 S1 OR S6 S6 S2 OR S3 OR S4 OR S5 S5 stein leventhal S4 PCO* S3 Polycystic Ovar* S2 sclerocystic N3 ovar*

Evidence processing: Studies were selected and appraised by 1 reviewer using study selection and appraisal criteria (PICO above) established a priori. The articles were reviewed by title and abstract by 1 reviewer. When a decision could not be made based on title and abstract alone, full text was retrieved. A total of **18 studies met inclusion criteria for this review** (including 14 original studies and 4 systematic reviews/ meta-analyses).

3. SEARCH RESULTS - PRISMA flowchart



4. STUDY INCLUSION

4.1. Included studies

Original studies from 2022 search:

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2 Begum, N., Arayousuf, N., Farooq, M. S., Chowdhury, M. A. K. & Ferdous, M. Association of Impaired Glucose Tolerance and Insulin Resistance in Women with Polycystic Ovary Syndrome. Bangladesh Journal of Obstetrics and Gynecology 34(2), 93-98, doi:https://dx.doi.org/10.3329/BJOG.V34I2.58273 (2019).

3 Carmina, E., Nasrallah, M. P., Guastella, E. & Lobo, R. A. Characterization of metabolic changes in the phenotypes of women with polycystic ovary syndrome in a large Mediterranean population from Sicily. Clin Endocrinol (Oxf) 91, 553-560, doi:https://dx.doi.org/10.1111/cen.14063 (2019).

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9 Kazemi, M. et al. Comprehensive Evaluation of Type 2 Diabetes and Cardiovascular Disease Risk Profiles in Reproductive-Age Women with Polycystic Ovary Syndrome: A Large Canadian Cohort. J Obstet Gynaecol Can 41, 1453-1460, doi:10.1016/j.jogc.2018.11.026 (2019).

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12 Meun, C. et al. The cardiovascular risk profile of middle-aged women with polycystic ovary syndrome. Clin Endocrinol (Oxf) 92, 150-158, doi:10.1111/cen.14117 (2020).

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4.2. Number of excluded studies in recent SR (on full text assessment)

N	Reason
50	Wrong outcomes
21	No comparison with non-pcos group
13	Wrong study design
13	Wrong study type
8	Wrong patient population
6	Wrong PCOS diagnostic criteria/tool
4	Did not find full text
4	Wrong comparator
1	Corrigendum for already excluded study
1	Wrong setting

4.3. Excluded Studies (on full text assessment)

No.	Reference	Reason
1	https://clinicaltrials.gov/ct2/show/NCT05126199 (study protocol)	No comparison with non-pcos group
2	Saadati et al. 2021, Heliyon	
3	Reyes-Munoz 2016, BMJ Open	
4	Abdulkadhm 2020, European Journal of Molecular and clinical medicine	
5	Tao 2018, Human Reproduction	
6	Agrawal 2019, Indian Journal of Endocrinology and Metabolism	
7	Anastasiou 2017, Archives of Gynecology & Obstetrics	
8	Andrisse 2021, Journal of the Endocrine Society	
9	Ashraf 2022, Pakistan Journal of Medical and Health Sciences	
10	Ata 2016, Journal of the Turkish-German Gynecological Association	
11	Basaranoglu 2016, Hepatology International	
12	Chantrapanichkul 2020, Archives of Gynecology & Obstetrics	
13	Choi 2021,Clinical Endocrinology	
14	Coles 2016, Journal of Pediatric & Adolescent Gynecology	
15	Hudnut-Beumler 2021, Pediatric Diabetes	
16	Jacewicz-swiecka 2020, Journal of Clinical Medicine	
17	Javed 2022, Pakistan Journal of Medical and Health Sciences	
18	Lee 2020, Fertility & Sterility	
19	Lee 2022, Journal of Clinical Endocrinology & Metabolism	
20	Leelaphiwat 2019, Journal of the Medical Association of Thailand	
21	Pilgrim 2018, Reproductive Sciences	
22	Meissner 2020, Clinical Advisor	
23	Abomandour 2020, European Heart Journal	
24	Akbarzadeh 2019, Journal of Research in Medical Sciences	

25	Anikllhan 2018, Fertility and Sterility	Wrong outcomes
26	Yao 2017, Experimental and Therapeutic Medicine	
27	Anwar 2017, Diabetes & Metabolic Syndrome	
28	Baro 2017,Indian Journal of Endocrinology and Metabolism	
29	Bayona 2022, Human Reproduction	
30	Behboudi-Gandevani 2016, European Journal of Obstetrics & Gynecology & Reproductive Biology	
31	Behboudi-Gandevani 2018, Fertility & Sterility	
32	Behboudi-Gandevani 2018, Clinical Endocrinology	
33	Belenkaia 2019,Minerva Ginecologica	
34	Benharrat 2021, Romanian Journal of Diabetes	
35	Borzan 2021, Journal of Clinical Medicine	
36	Boshku 2018, Atherosclerosis Supplements	
37	Boshku 2016,Gynecological Endocrinology	
38	Bouzas 2019,Diabetology and Metabolic Syndrome	
39	Chen 2017,Diabetes/Metabolism Research and Reviews	
40	DincgezCakmak 2019, Gynecological Endocrinology	
41	Ding 2021, Metabolic Syndrome & Related Disorders	
42	Echiburu 2016, Metabolism: Clinical & Experimental	
43	Errayya 2022, European Journal of Molecular and Clinical Medicine	
44	Farhadi-Azar 2022, Frontiers in Endocrinology	
45	Fazleen 2018, Diabetes & Metabolic Syndrome	
46	Forslund 2022, European Journal of Obstetrics & Gynecology & Reproductive Biology	
47	Fu 2020, Hormones	
48	Gunn 2018, Hormone research in paediatrics	
49	Gunn 2019, Archives of Disease in Childhood	
50	Hong 2017,Clinical Endocrinology	
51	Hussain 2018, Pakistan Journal of Medical and Health Sciences	
52	Jacewicz-Święcka 2018, Diabetes/Metabolism Research & Reviews	
53	Lee 2021, American Journal of Obstetrics & Gynecology	
54	Liu 2022, Endocrine Journal	
55	Maldonado 2022,Gastroenterology	
56	Maldonado 2022,Hepatology Communications	
57	Mario 2017, Experimental & Clinical Endocrinology & Diabetes	
58	Marques 2016, Clinical & Experimental Obstetrics & Gynecology	
59	Obaid 2021, Biochemical and Cellular Archives	
60	Ollila 2016,Human Reproduction	
61	Otaghi 2019, Diabetes & Metabolic Syndrome	
62	Pinola 2017, Fertility & Sterility	
63	Renuka 2018, Asian Journal of Pharmaceutical and Clinical Research	
64	Yin 2021, International Journal of Endocrinology	
65	Rezaee 2016, Journal of Pediatric & Adolescent Gynecology	
66	Rimmer 2020, Gynecological Endocrinology	
67	Satyaraddi 2019, Journal of Human Reproductive Sciences	
68	Stuppy 2019, Journal of Investigative Medicine	
69	Yheulon 2019, American Surgeon	
70	Udesen 2019, Human Reproduction	
71	Wu 2020, Frontiers in Medicine	
72	ACOG Practice Bulletin Summary, 2018, Obs & Gyn	Wrong study design
73	Adeniji 2016, Journal of Women's Health	
74	Ahmed 2022,Surgeon(Elsevier Science)	
75	Akgul 2019, Journal of Adolescent Health	
76	Gilbert 2018, Clinical Endocrinology	
77	Gunning 2017,Climacteric	
78	Joshi 2018, International Journal of Diabetes in Developing Countries	
79	Ollila 2017, Human Reproduction	
80	Paalanne 2021, European Journal of Endocrinology	
81	Pani 2020, International Journal of Endocrinology	

82	Satyaraddi 2017, Indian Journal of Endocrinology and Metabolism	
83	SatykoKogure 2016, Medicine & Science in Sports & Exercise	
84	Zhu 2021, Diabetes	
85	Ali 2022, Reproductive Sciences	Wrong patient population
86	Andreeva 2020, Obesity Reviews Conference: European and International Congress on Obesity	
87	Begum 2020, Bangladesh Medical Research Council Bulletin	
88	Belva 2020, Human Reproduction Open	
89	Kiconco 2022, Clinical Endocrinology	
90	Patel 2021, Hepatology	
91	SreeLalitha 2018, International Journal of Gynecology and Obstetrics	
92	Yilmaz 2018, Fertility & Sterility	
93	Andersen 2018, European Journal of Endocrinology	Wrong comparator
94	Azargoon 2020,Acta Medica Iranica	
95	Bond 2017, Diabetic Medicine	
96	Guo 2021, Arlington, Virginia American Diabetes Association	
97	Andreeva 2016, Gynecological Endocrinology	Wrong setting
98	Ollila 2017, Human Reproduction	Corrigendum for excluded study
99	Asfari 2020, BMJ Open Gastroenterology	Wrong PCOS diagnostic criteria/tool
100	Berni 2021, Journal of Clinical Endocrinology & Metabolism	
101	Ding 2018, Oncotarget 2018	
102	Kakoly 2019, Diabetes Care	
103	Kumarendran 2021, Diabetes Care	
104	Persson 2021, Fertility & Sterility	
105	Atkin 2017,Diabetes	Did not find full text
106	Ngan 2016, Human Reproduction	
107	Saritha 2021, International Journal of Pharmaceutical and Clinical Research	
108	Srivastava 2016, Endocrine Reviews	
109	Azziz 2016, Nature Reviews	Wrong study type
110	Azziz 2018,Obstetrics & Gynecology	
111	Bell 2018, Human Reproduction	
112	Belzarena 2016, Gynecological Endocrinology	
113	Bender 2020, American Journal of Obstetrics and Gynecology	
114	Delitala 2017, Archives of Gynecology & Obstetrics	
115	Glintborg 2018, Journal of Clinical Endocrinology & Metabolism	
116	Pirotta 2020, Seminars in Reproductive Medicine	
118	Rodgers 2019, Endocrine Connections	
119	Silva 2022, Journal of Endocrinological Investigation	
120	Uludag 2022, Diabetes Research and Clinical Practice	
121	Verma 2021, Indian Journal of Clinical Biochemistry	
122	Yau 2017, Hong Kong Medical Journal	

5. STUDY CHARACTERISTICS TABLE FOR INCLUDED STUDIES

Author (year)	Study design	age range	BMI-matched	Age-matched	Country	PCOS Dx	ROB	N_PCOS	N_ control	Summary of findings
Begum et al. (2019)	cross sectional	N/A, mean 27.6(6.2), 27.3 (5.9)	0	1	Bangladesh	oligomenorrhoea, HA, infertility, PCOM, obesity	High	50	50	The prevalence of insulin resistance, IFG, IGT after 75 gm of glucose were higher among PCOS group compared to control group.
Carmina et al. (2019)	retrospective	18-40, PCOS 24 (5), controls 24(3)	NR	1	Italy	Rotterdam criteria (4 phenotypes)	Low	1215	108	In Mediterranean women with PCOS from Sicily with a lower prevalence of obesity, the prevalence of diabetes, altered glucose metabolism and metabolic syndrome were much lower than reported in US studies
Fuad et al. (2018)	cross sectional	PCOs 20-37, control?, mean PCOS 26.95 (4.77), control 23.9 (2.71)	0	0	Iraq	NIH	High	42	42	BMI is positively correlated with HbA1c and associated with glycemic control in PCOS.
Kazemi Jaliseh et al. (2017)	Prospective	18-49, mean pcos 26.4 (8.5), control 28.9 (8.6)	1	0	Iran	NIH	Low	178	1524	The incidence rates of diabetes were 12.9 and 4.9 per 1,000 person-years for PCOS and controls, respectively. This incidence rate in women younger than 40 with and without PCOS was 13.4 and 4.2, respectively. There were no statistically significant differences between the PCOS and groups studied after age 40.
Forslund et al. (2020)	longitudinal and cross sectional	follow up of PCOS from age 30 to 50, age difference NS between PCOS and control at follow up, 52.4 both PCOS and controls	0	1	Sweden	NIH (also fulfilled Rotterdam)	Mod	27	94	Obesity and abdominal fat distribution, but not hyperandrogenism per se, in women with PCOS in the mid-fertile years were the major risk factors for T2DM development 24 years later when peri/postmenopausal. Lifestyle factors were similar to controls at that time.
Kazemi et al. (2019)	cross sectional	18-36	0	1	Canada	AEPCOS 2006	Low	237	42	The prevalence of MetS was 29.5% in the PCOS group, which was approximately six-fold higher than age-matched controls (P < 0.001).
Liao et al. (2022)	retrospective cohort	over age 18, 10 yrs follow up, 58% 18-24Y, 22.9% 25-29Y, 18.3% >age 30, mean PCOS 25.1 (5.81), control 25.2 (5.91)	0	1	Taiwan	?Rotterdam (PCOM + oligomenorrhoea or HA)	Mod	2545	2545	During a 10-year follow-up period, the overall incidence of T2DM was 6.25 per 1000 person-years in the PCOS group compared with 1.49 in the control group. The risk of developing T2DM subsequent to PCOS decreased with increasing diagnosis age
Meun et al. (2019)	cross sectional	>45y, mean pcos 50.5, controls 51 (5.2)	0	1	Netherland	Rotterdam	Mod	200	200	Middle-aged women with PCOS exhibit only a moderately unfavourable cardiometabolic profile compared to age-matched controls, even though they present with an increased BMI and waist

										circumference. Furthermore, we found no evidence for increased (10-year) CVD risk or more severe atherosclerosis compared with controls from the general population
Ng et al. (2019)	prospective	mean pcos 41.2 (6.4), control 54.1 (6.7)	0	0	Hong Kong	Rotterdam	Low	199	242	We found that the age-standardised incidence rate of T2DM among women with PCOS was around 2.5-fold higher compared with the local female population incidence rate.
Ryu et al. (2021)	longtudinal case-control	15-44Y (follow up about 4yrs)	0	1	South Korea	NIH	Mod	1136	5675	PCOS is independently associated with an increased incidence of T2DM in both obese and nonobese women.
Rubin et al. (2017)	register-based cohort-Danish National health registers	12-60 yrs old. 6.9 to 16 yrs follow up (11.1), mean pcos 31 (36-37), controls 35 (27-44)	NR	1	Denmark	diagnosed through a hospital contact with PCOS (E282) and/or hirsutism (L680) – used Rotterdam	Mod			The event rate of T2D was higher in PCOS compared with controls, and T2D was diagnosed at a younger age.
Vuguin et al. (2016)	cross sectional	all 16Yrs	1	1	USA	NIH	High	74	82	A significant interaction between BMI and PCOS and indices of post-glucose load was observed.
Dos Reis et al. (1995)	Cross-sectional				Brazil	NIH	0	29	19	There was also a high prevalence of insulin resistance in patients with PCO regardless of obesity, and hyperandrogenism-aggravated insulin resistance.
Rajkhowa et al. (1996)	Cross-sectional	17 to 39	0	0	U.K.	ESHRE/ASRM	1	90	62	The Xbal polymorphism of the glycogen synthetase gene was not over represented in PCOS group and didn't related to the indices of insulin sensitivity or glucose Intolerance.
Ciampelli et al. (1998)	Cross-sectional	21-36			Italy	NIH	0	35	11	A highly significant relationship was found between the insulin response to OGTT and to glucagon administration in the PCOS population which was maintained also after controlling for obesity.
Cibula et al. (2000)	Cross-sectional	controls 45-59 (mean PCOS 51.9 (4.64, control 51 (4.21)	1	1	Czech Republic	NIH	0	28	752	The prevalence of T2DM and CAD was significantly higher in PCOS women.
Dunaif et al. (2001)	Cross-sectional	19-41 yrs, mean pcos 29 (1), control 30 (2)	1	1	America	NIH	1	14	12	There was no significant difference in the abundance of IR, IRS-1, or the p85 regulatory subunit of PI 3K in PCOS compared with control muscle. The abundance of IRS-2 was significantly increased in PCOS skeletal muscle, suggesting a compensatory change. There is a physiologically relevant defect in insulin receptor

										signalling in PCOS that is independent of obesity and type 2 diabetes mellitus.
Yarali et al. (2001)	Cross-sectional	no range, mean pcos 27.9 (6.1), control 31.4 (6.5)	1	0	Turkey	NIH	1	30	30	The mean serum homocysteine and uric acid concentrations were significantly higher in the PCOS group. Patients with PCOS had significant hyperinsulinemia.
Faloia et al. (2004)	Cross-sectional	matched for age and bmi according to text, no range, mean pcos 22 (5), control 26 (4)	1	1	Italy	NIH	0	50	20	No significant metabolic alterations in lean PCOS women indicating that obesity might underpin metabolic alterations exhibited by overweight obese PCOS patients.
Phy et al. (2004)	Cross-sectional	no range, mean pcos 31.1 (2.6), control (30.9 (4.5))	1	1	America	NIH	0	7	18	Total IR mRNA expression, but not intrafollicular insulin levels, was elevated in PCOS patients, whereas intrafollicular insulin levels were increased in women with IGT.
Sir-Petermann et al. (2004)	Cross-sectional	median range pcos 22 (14-38), control 24 (15-36),	0	0	Chile	NIH	0	146	97	In controls with healthy weight Gly972Arg polymorphism appears to be associated with a decrease in insulin secretion; In PCOS women, this polymorphism interacts with obesity to influence insulin resistance, thus contributing to the pathogenesis of the metabolic component of PCOS.
Apridonidze et al. (2005)	Cross-sectional				America	NIH	0	106	0	
Diamanti-Kandarakis et al. (2005)	Cross-sectional	no age range, mean 25.79 PCOS, 28.12 in controls	1	1	Greece	NIH	1	29	22	PCOS women without overt hyperglycaemia have increased AGE levels and elevated RAGE expression when compared with controls.
Legro et al. (2005)	Cohort	no range, mean pcos 27.4 and 29.56 vs control 36.17 (5.46)	0	0	America	NIH	0	71	23	Women with PCOS and baseline IGT had a low conversion risk of 6% to T2DM over approx 3 yr, or 2% per year. The effect of PCOS, given normal glucose tolerance at baseline, is more pronounced with 16% conversion to IGT per year.
Sawathiparnich et al. (2005)	Cross-sectional	adolescents	1	1	Thailand	NIH	0	6	6	
Alvarez-Blasco et al. (2006)	Cross-sectional	all <50 yrs, no menopausal symptoms	1	0	Spanish	NIH	1	32	72	28.3% prevalence of PCOS in overweight and obese women from Spain, compared with the 5.5% prevalence in lean women of our country.
Boudreaux et al. (2006)	Cohort	mean pcos 38 (5.9), 40 (5.2)	0	0	America	NIH	0	97	95	The 8-year incidence rate among cases and controls was 13.4% and 5.8%, respectively (relative risk = 2.3). Obese cases had a fivefold risk of T2DM developing (P < 0.01) compared with age-adjusted obese

										controls, indicating significant interaction between PCOS and obesity to effect T2DM risk.
Leibel et al. (2006)	Cross-sectional	adolescent 12-19 yrs, mean 16		1	America	ESHRE/ASRM	0	36	21	Familial factors related to paternal MetS seem to be fundamental to the pathogenesis of PCOS.
Attaoua et al. (2008)	Cross-sectional	no range, mean control 34.1 (1.1), pcos lean 23.1 (0.5), pcos obese 26.3 (0.6)	0	0	Romania	ESHRE	1	207	100	The FTO (Fat mass and obesity associated) homozygous C/C genotype showed increased prevalence in PCOS patients either obese or with metabolic syndrome compared to lean PCOS patients or controls
Echiburu et al. (2004)	Cross-sectional	15-36, mean pcos 24.3 (5.8), control 24.6 (5.9)	0	1	Chile	NIH	1	159	93	the frequency of the CYP17A2 allele is similar between PCOS and control; however, the presence of this gene defect in PCOS patients seems to be associated with increase in body weight, abdominal adiposity, and metabolic components.
Marquez et al. (2008)	Cross-sectional	16-43y pcos, 20-45 controls, mean pcos 28.8 (8.2), control 28.6 (8.6)	0	1	Chile	NIH	1	50	70	The presence of uncommon allele (A) for the UCSNP-43 was associated with increased risk of PCOS.
Bhattacharya (2009)	Cross-sectional	16 to 39 yrs, mean pcos 22.6, 25.3 (5.4), no mean age for controls	NR	NR	India	NIH	0	264	116	While abnormal glucose tolerance (AGT) was not associated with PCOS, the women with both PCOS & AGT were significantly more obese, hyperandrogenic, and insulin resistant than those with PCOS and normal glucose tolerance.
Moini & Eslami (2009)	Cross sectional	mean pcos 27.94 (4.16), control 31.1 (5.77)	1	0	Iran	Rotterdam	1	273	276	women and their relatives with PCOS had an increased prevalence of diabetes and it was more common in mother's side of the family.
Nur et al. (2009)	Cross-sectional				USA	ESHRE/ASRM	1	101	40	
Fulghesu et al. (2010)	Cross-sectional	adolescent (13-18), mean pcos 18.61 (0.4), 18.10 (0.38)	1	1	Italy	Rotterdam	1	71	94	In the adolescent population studied, no differences were revealed in lipid profile between PCOS and controls.
Huang et al. (2010)	Cross-sectional	adolescents, median 19 (17-19)controls, 18 (17-19) pcos, some<18Y, no age range	1	1	China	Rotterdam	1	128	40	
Zhao et al. (2010)	Cross-sectional	pcos 18-41 yr, control 20-45, mean pcos 25.7 (5.3), control 30.5 (4.3)	NR	NR	China	Rotterdam 2003	1	818	717	Hyperandrogenemia is associated with T2DM & obesity in Chinese women with PCOS and should be considered at first-line management of hyperandrogenism and infertility due to PCOS.
Angioni et al. (2011)	Cross-sectional	adolescent, mean pcos 16.37 (3.79), control 16.87 (4.55)	1	1	Italy	Rotterdam	1	79	50	In young normal weight patients with PCOS the prevalence of early alterations of insulin metabolism are not detectable by QUICKI studies.

Hossain et al. (2011)	Cohort	mean pcos 38.62 (9.96), control 38.38 (9.91)	1	1	USA	NIH/Rotterdam	0	34	32	Despite similar clinical and laboratory profiles to the matched controls, PCOS patients seem to have more histologic NASH.
Hudecova et al. (2011)	Cohort	pcos 15 to 39Y baseline (follow up 13.9), at follow up pcos 43 (5.8), control 43.7 (6.2)	0	1	Sweden	Rotterdam	1	84	87	IGT and T2DM occurred more often in PCOS patients. Independent on PCOS phenotype at index assessment and persistence of PCOS symptoms at the follow-up investigation, women with PCOS had lower insulin sensitivity but a well-preserved beta cell function in comparison with control subjects.
Lerchbaum et al. (2011)	Cross-sectional	mean pcos 27.94 (4.16), control 31.1 (5.77)	1	0	Austria	NIH	1	611	139	High FLI (fatty liver index) levels are a common finding in obese PCOS women and are closely linked to MetS.
Li et al. (2012)	Cross-sectional	adolescent, 15-19, mean pcos 17.59 (1.36), control 17.38 (0.75)	0	1	China	Rotterdam	1	56	26	Chinese adolescents with PCOS manifest clinical and metabolic features similar to those of adult Chinese women with PCOS except for the increased prevalence of hyperandrogenism and insulin resistance.
Liang et al. (2012)	Cross-sectional	mean age pcos 26.9 (5.8), control 28.3 (4.4)	0	1	Taiwan	Rotterdam 2003	1	220	70	Body weight status was the major factor determining the risk of impaired glucose tolerance and metabolic syndrome in women with PCOS.
Okoroh et al. (2012)	Cohort	18-45Y, mean age pcos 31.44 (7.19), control 32.2 (8.4)		0	USA	Rotterdam/NIH	0	192936	12000000	The prevalence of PCOS was 1585.1 per 100,000; Women with PCOS were more likely than those without PCOS to be 25-34 years old, be from the South, be infertile, have metabolic syndrome, have been seen by an endocrinologist, and have taken oral contraceptives.
Celik et al. (2014)	Cohort	mean age at follow up pcos 27.7 (6.6) control 30.1 (5.8)	0	0	Turkey	Rotterdam	0	84	45	Conversion rates from NGT to IGT or T2DM were accelerated in women with PCOS compared with healthy subjects
Boyle et al. (2015)	Cross-sectional	15-44Y, median pcos 32 (21-37), control 33 (23,39)	0	1	Australia	NIH	1	35	74	While MetS was more common in Indigenous women with PCOS, PCOS was not an independent predictor of MetS.
Ozegowska & Pawelczyk (2015)	Cross-sectional	18-43, median pcos 27 (24-30), control 28.5 (26-31)	0	0	Poland	Rotterdam	0	168	110	The PCOS group had significantly higher BMI), waist circumference, and waist-to-hip ratio. MetS was only defined among PCOS patients (8.9%).
Valderhaug et al. (2015)	Cross-sectional	<50Y, pcos 34 (1), control 39(2)	NR	0	Norway	NIH	1	312	1588	Morbidly obese women with hyperandrogenism had an approximately 1.5-fold increased odds of having MetS even

										in the absence of PCOS.
Glintborg et al. (2015)	Cohort	mean age 30.6 (12-60y)premenopuasal	NR	1	Denmark	Rotterdam	0	1217	57483	Cardiometabolic (including T2DM) and psychiatric morbidity were significantly increased in PCOS group.

RoB (risk of bias): 0= high risk, 1= moderate or low risk

6. FINDINGS

Comparisons included:

- Comparison 1: Women with PCOS versus controls

Outcomes included:

1. **T2DM odds ratio**
   Subgroups:
   - T2DM odds ratio in BMI matched/similar studies
   - T2DM odds ratio in age matched/similar studies
   - T2DM odds ratio in adolescents
   - T2DM odds ratio in premenopausal adults
   - T2DM odds ratio in combined pre and post-menopausal women
   - T2DM odds ratio among moderate to high quality studies

2. **IFG odds ratio**
   Subgroups:
   - IFG odds ratio in BMI matched/similar studies
   - IFG odds ratio in age matched/similar studies
   - IFG odds ratio in adolescents
   - IFG odds ratio in premenopausal adults
   - IFG odds ratio among moderate to high quality studies

3. **IGT odds ratio**
   Subgroups:
   - IGT odds ratio in BMI matched/similar studies
   - IGT odds ratio in age matched/similar studies
   - IGT odds ratio in adolescents
   - IGT odds ratio in premenopausal adults
   - IGT odds ratio among moderate to high quality studies

4. **Pre-diabetes odds ratio**
   Subgroups:
   - Pre-diabetes odds ratio in BMI matched/similar studies
   - Pre-diabetes odds ratio in age matched/similar studies
   - Pre-diabetes odds ratio in adolescents
   - Pre-diabetes odds ratio in premenopausal adults
   - Pre-diabetes odds ratio among moderate to high quality studies

Definitions

Pre-diabetes: IFG +/-IGT+/- High HbA1c [5.7 to 6.4%]

For studies with outcomes of IFG and IGT that didn't report the number of individuals with both IFG and IGT, we included the number of IGTs for pre-diabetes outcome to avoid duplication of individuals with both conditions.

IFG: Impaired fasting glucose, IGT: Impaired glucose tolerance, T2DM: type 2 diabetes

COMPARISON 1: Women with PCOS versus Controls

- **EVIDENCE SUMMARY:**

Total of 54 studies were included in the systematic review and 48 studies were included in meta-analysis. Nineteen had high risk of bias and remaining 29 had moderate to low risk of bias. Ten studies reported zero T2DM in both PCOS and control groups and were excluded from the meta-analysis. These mainly included adolescents and younger adults (<30 years old). Six studies from recent systematic review and seven from 2018 systematic review (Kakoly et al.) were cohort studies with significantly variable follow up durations from 2 to 24 years. Their reported prevalence of diabetes, IFG or IGT at follow up was included for the meta-analyses.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

Pooled analysis showed a higher risk of T2DM, IFG, IGT and pre-diabetes among women with PCOS compared with controls. These results remained unchanged after excluding studies with high risk of bias. Among age-matched studies combined with those with no significant difference in age between PCOS and control groups, women with PCOS remained to show higher risk of T2DM, IFG, IGT and pre-diabetes compared with controls. Among studies with no significant difference in BMI between PCOs and control groups, women with PCOS had a similar risk of IFG but higher risk of T2DM, IGT and pre-diabetes.

In subgroup analysis, the risk of T2DM, IFG and pre-diabetes in adolescents with PCOS was similar to controls. Adolescents were still at a higher risk of IGT.

Studies that included both pre and post-menopausal adult women, demonstrated a higher risk of T2DM in PCOS compared with control groups. There were no studies investigating the risk of IFG, IGT and pre-diabetes in this older population.

Outcome	Studies	Effect size [95% CI]	P	Favours	I^2	Certainty
T2DM	41	OR 2.87 [1.37, 6.01]	0.005	Higher in PCOS	97.8%	⊕⊕⊕◯ Moderate
BMI matched/similar	15	OR 3.04 [2.06, 4.49]	<0.001	Higher in PCOS	0.0%	⊕⊕⊕◯ Moderate
Age matched/similar	24	OR 4.18 [3.30, 5.29]	<0.001	Higher in PCOS	43.7%	⊕⊕⊕◯ Moderate
Adolescent	6	OR 5.73 [0.93, 35.31]	0.060	No difference	0.0%	⊕◯◯◯ Very low
Pre-menopausal adults	29	OR 2.49 [1.03, 6.03]	0.042	Higher in PCOS	98.3%	⊕⊕⊕◯ Moderate
Including post-menopausal adults	4	OR 3.20 [1.41, 7.24]	0.005	Higher in PCOS	74.3%	⊕⊕◯◯ Low
Moderate to High quality	27	OR 2.75 [1.85, 4.10]	<0.001	Higher in PCOS	75.4%	⊕⊕⊕◯ Moderate
IFG	12	OR 3.18 [2.22, 4.56]	<0.001	Higher in PCOS	0.0%	⊕⊕◯◯ Low
BMI matched/similar	4	OR 1.05 [0.32, 3.46]	0.930	No difference	0.0%	⊕◯◯◯ Very low
Age matched/similar	7	OR 3.65 [1.59, 8.36]	0.002	Higher in PCOS	0.0%	⊕⊕⊕◯ Moderate
Adolescent	4	OR 1.52 [0.35, 6.60]	0.572	No difference	0.0%	⊕◯◯◯ Very low
Pre-menopausal adults	7	OR 3.33 [2.28, 4.87]	<0.001	Higher in PCOS	0.8%	⊕⊕⊕◯ Moderate
Including post-	-	-	-	-	-	-

menopausal women						
Moderate to High quality	8	OR 2.98 [1.99, 4.46]	<0.001	Higher in PCOS	0.0%	⊕⊕⊕◯ Moderate
IGT	19	OR 3.90 [2.44, 6.22]	<0.001	Higher in PCOS	40.4%	⊕⊕⊕◯ Moderate
BMI matched/similar	9	OR 2.53 [1.27, 5.04]	0.009	Higher in PCOS	16.4%	⊕⊕⊕◯ Moderate
Age matched/similar	14	OR 5.51 [3.44, 8.80]	<0.001	Higher in PCOS	0.0%	⊕⊕⊕◯ Moderate
Adolescent	5	OR 4.87 [1.68, 14.06]	0.003	Higher in PCOS	0.0%	⊕◯◯◯ Very low
Pre-menopausal adults	14	OR 3.75 [2.22, 6.36]	<0.001	Higher in PCOS	48.2%	⊕⊕⊕◯ Moderate
Including post-menopausal women	-	-	-	-	-	-
Moderate to High quality	13	OR 3.48 [2.18, 5.56]	<0.001	Higher in PCOS	17.3%	⊕⊕⊕◯ Moderate
Pre-Diabetes	27	OR 2.71 [1.90, 3.86]	<0.001	Higher in PCOS	41.6%	⊕⊕◯◯ Low
BMI matched/similar	12	OR 1.81 [1.02, 3.20]	0.042	Higher in PCOS	39.5%	⊕⊕⊕◯ Moderate
Age matched/similar	16	OR 4.18 [2.68, 6.51]	<0.001	Higher in PCOS	0.0%	⊕⊕⊕◯ Moderate
Adolescent	6	OR 3.88 [0.88, 17.12]	0.073	No difference	43.5%	⊕◯◯◯ Very low
Premenopausal adults	19	OR 2.44 [1.70, 3.50]	<0.001	Higher in PCOS	42.3%	⊕⊕⊕◯ Moderate
Including post-menopausal women	-	-	-	-	-	-
Moderate to High quality	18	OR 2.72 [1.79, 4.12]	0.001	Higher in PCOS	45.5%	⊕⊕⊕◯ Moderate

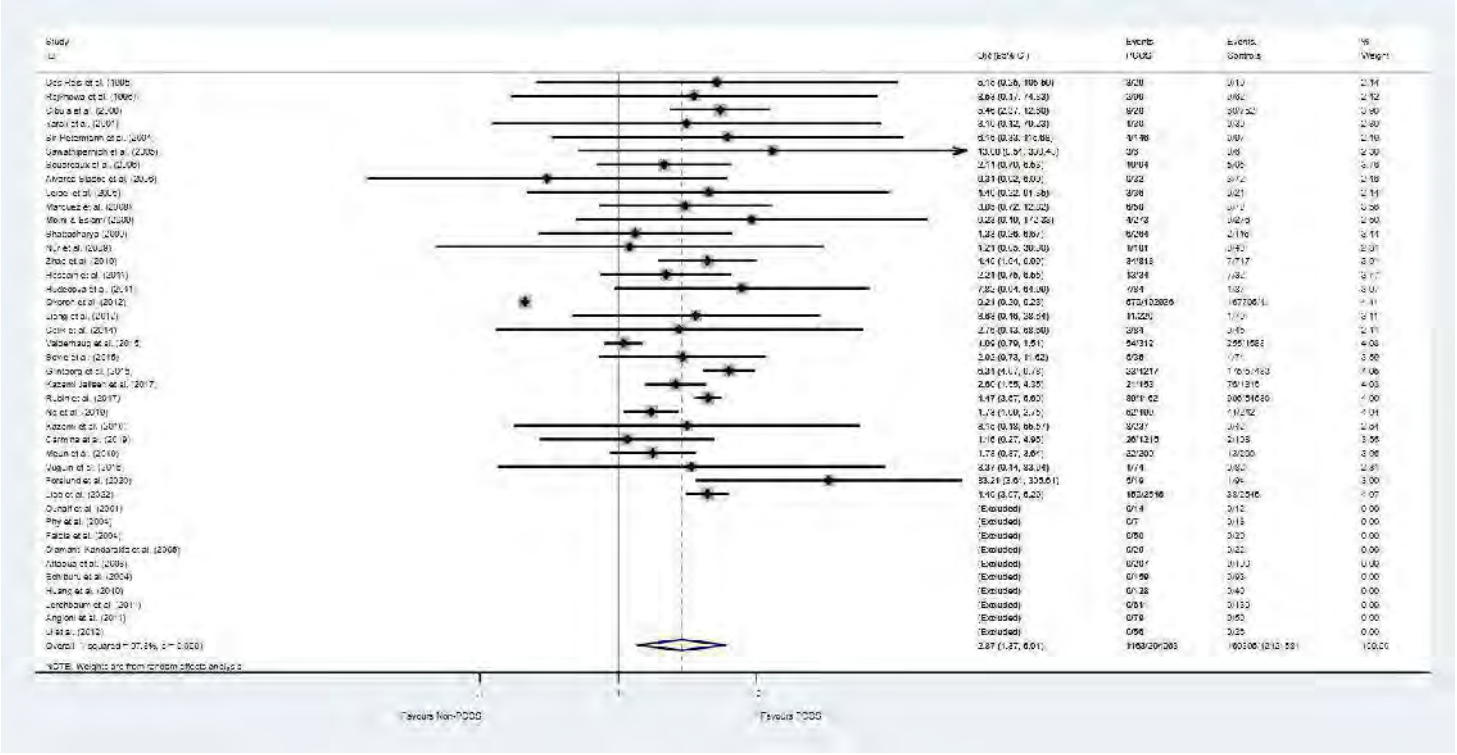
*based on statistically significant difference in scores when PCOS was compared with controls within each individual study (since all studies used the same control groups, this effect was not pooled to avoid duplication of the control group in the same analysis

OUTCOME 1. Type 2 DM

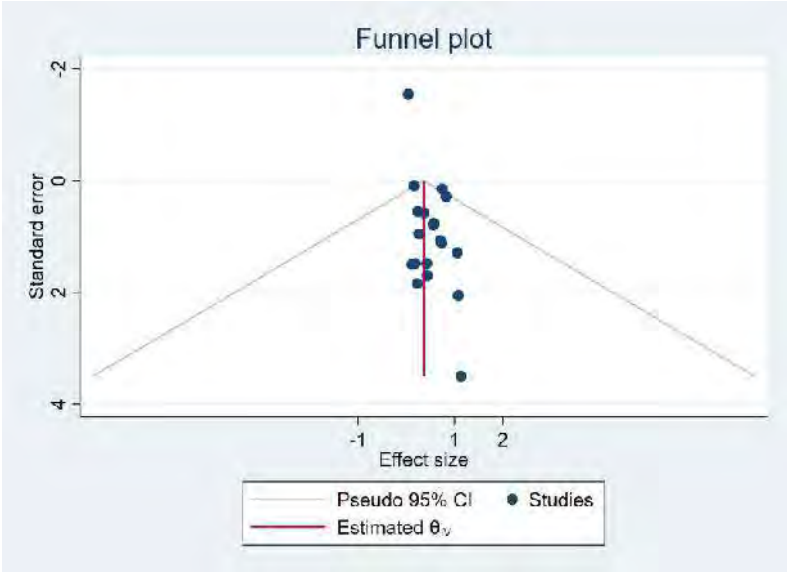
1.1. Individual Study Data Tables

OUTCOME: T2DM				Outcome type: Dichotomous				
Comparison: PCOS and control								
Author, year	**PCOS criteria**	**N events in PCOS**	**N total in PCOS**	**N events in control**	**N total in control**	**Crude OR**	**95% CI**	**Pooled in MA?**
Dos Reis et al. (1995)	NIH	3	29	0	19	5.15	0.25-105.59	Yes
Rajkhowa et al. (1996)	ESHRE/ASRM	2	90	0	62	3.53	0.17-74.83	Yes
Cibula et al. (2000)	NIH	9	28	60	752	5.46	2.37-12.60	Yes
Yarali et al. (2001)	NIH	1	30	0	30	3.10	0.12-79.23	Yes
Sir-Petermann et al. (2004)	NIH	4	146	0	97	6.16	0.33-115.68	Yes
Sawathipamich et al. (2005)	NIH	3	6	0	6	13	0.51-330.48	Yes
Bourdeaux et al (2006)	NIH	10	94	5	95	2.14	0.70-6.53	Yes
Alvarez-Blasco et al. (2006)	NIH	0	32	3	72	0.31	0.02-6.09	Yes
Leibel et al. (2006)	ESHRE/ASRM	3	36	0	21	4.49	0.22-91.35	Yes
Marquez et al. (2008)	NIH	6	50	3	70	3.05	0.72-12.82	Yes
Moini & Eslami (2009)	Rotterdam	4	273	0	276	9.23	0.49-172.33	Yes
Bhattacharya (2009)	NIH	6	264	2	116	1.33	0.26-6.67	Yes
Nur et al. (2009)	ESHRE/ASRM	1	101	0	40	1.21	0.05-30.30	Yes
Zhao et al. (2010)	Rotterdam	34	818	7	717	4.40	1.94-9.99	Yes
Hossain et al. (2011)	NIH/Rotterdam	13	34	7	32	2.21	0.75=6.55	Yes
Hudecova et al. (2011)	Rotterdam	7	84	1	87	7.82	0.94-64.99	Yes
Okoroh et al (2012)	Rotterdam	579	192936	167705	11978894	0.21	0.20-0.23	Yes
Liang et al. (2012)	Rotterdam	11	220	1	70	3.63	0.46-28.64	Yes
Celik et al. (2014)	Rotterdam	2	84	0	45	2.76	0.13-58.69	Yes
Valderhaung et al. (2015)	NIH	54	312	255	1588	1.09	0.79-1.51	Yes
Boyle et al. (2015)	NIH	5	35	4	74	2.92	0.73-11.62	Yes
Glintborg et al. (2015)	Rotterdam	23	1217	175	57483	6.31	4.07-9.78	Yes
Kazemi Jaliseh et al. (2017)	NIH	21	153	76	1316	2.60	1.55-4.35	Yes
Rubin et al. (2017)	Rotterdam (or clinical and/or biochemical hyperandrogenism)	89	1162	996	54680	4.47	3.57-5.60	Yes
Ng et al. (2019)	Rotterdam	52	199	41	242	1.73	1.09-2.75	Yes
Kazemi et al. (2019)	NIH	8	237	0	42	3.15	0.18-55.57	Yes
Carmina et al. (2019)	Rotterdam	26	1215	2	108	1.16	0.27-4.95	Yes
Meun et al. (2019)	Rotterdam	22	200	13	200	1.78	0.87-3.64	Yes
Vuguin et al. (2016)	NIH	1	74	0	82	3.37	0.14-83.94	Yes
Forslund et al. (2020)	NIH/Rotterdam	5	19	1	94	33.21	3.61-305.61	Yes
Liao et al. (2022)	? Rotterdam (PCOM + oligomenorrhoea or HA)	159	2545	38	2545	4.40	3.07-6.29	Yes

1.2. Forest plot for T2DM in women with PCOS compared with controls

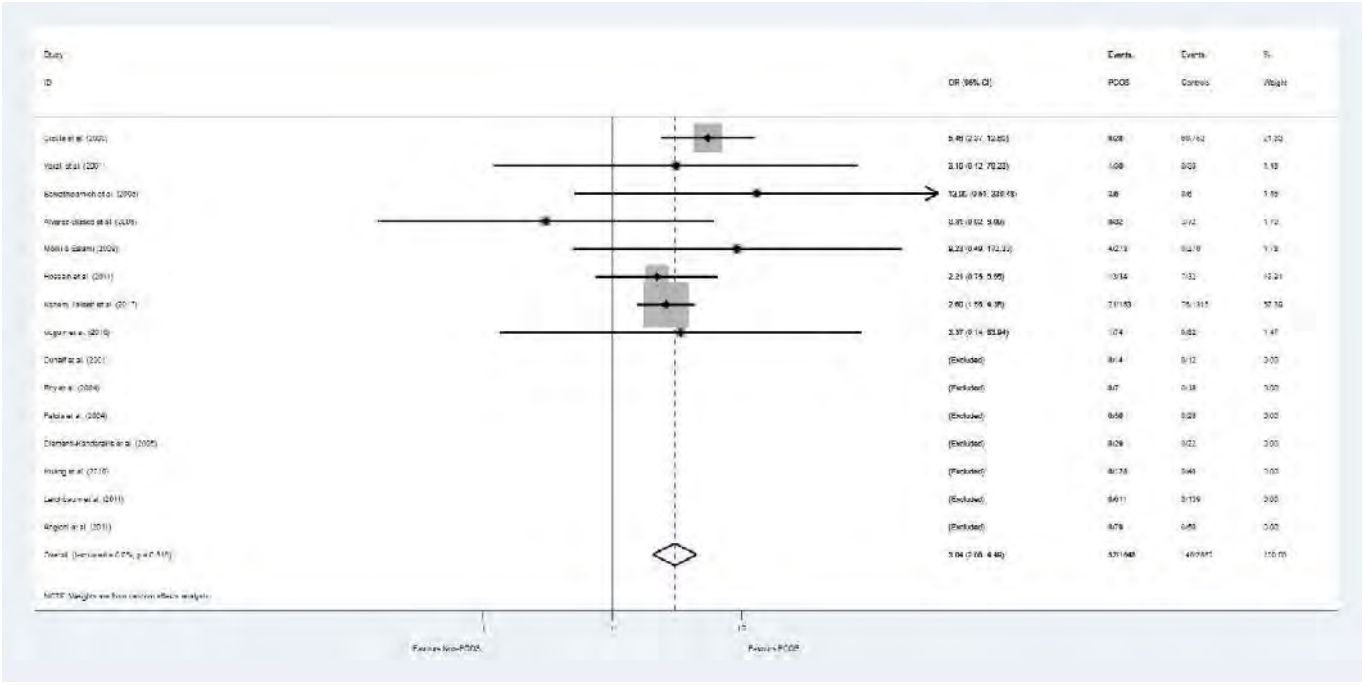


1.3. Funnel plot for T2DM

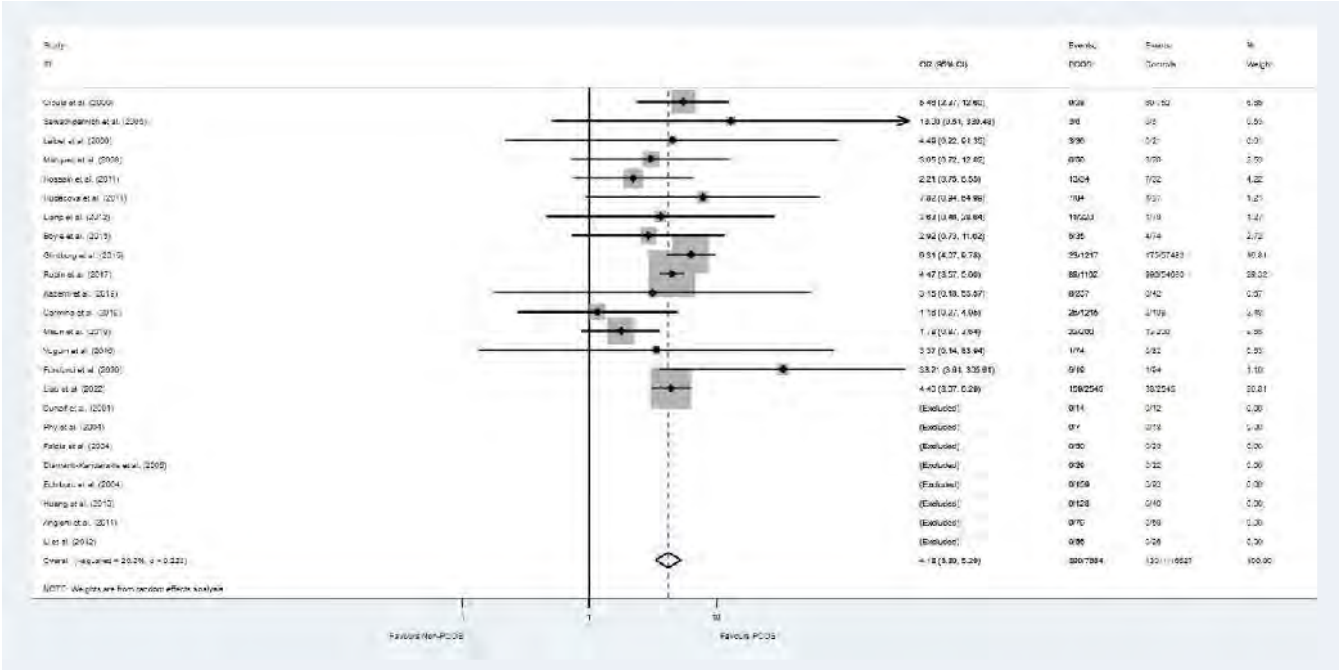


1.4. Subgroup analyses

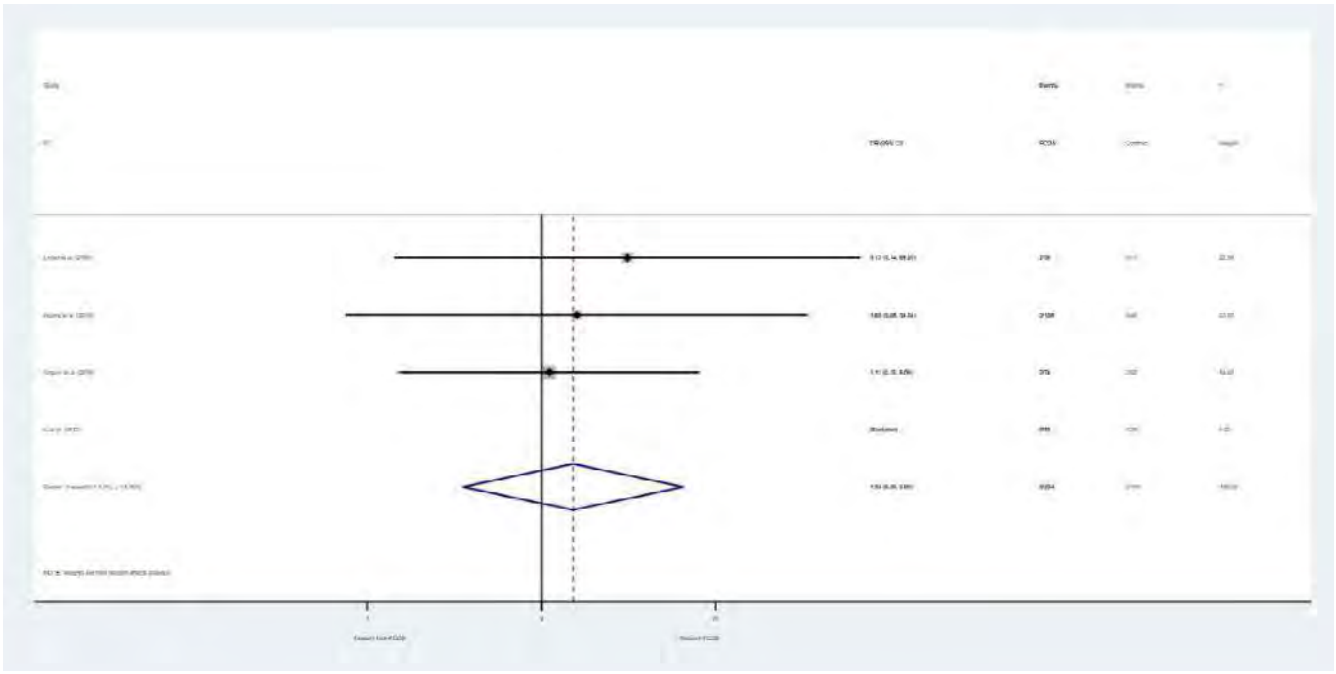
1.4.1. T2DM in BMI-matched/similar groups



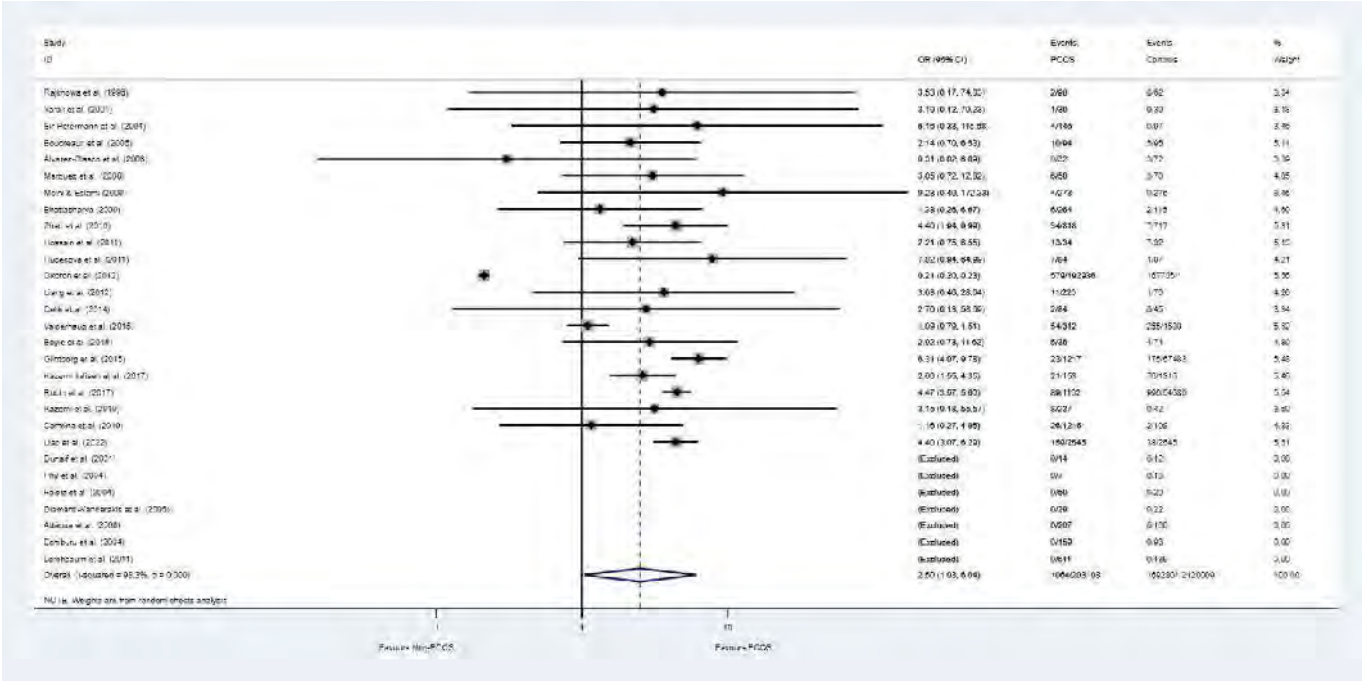
1.4.2. T2DM in aged-matched/similar groups



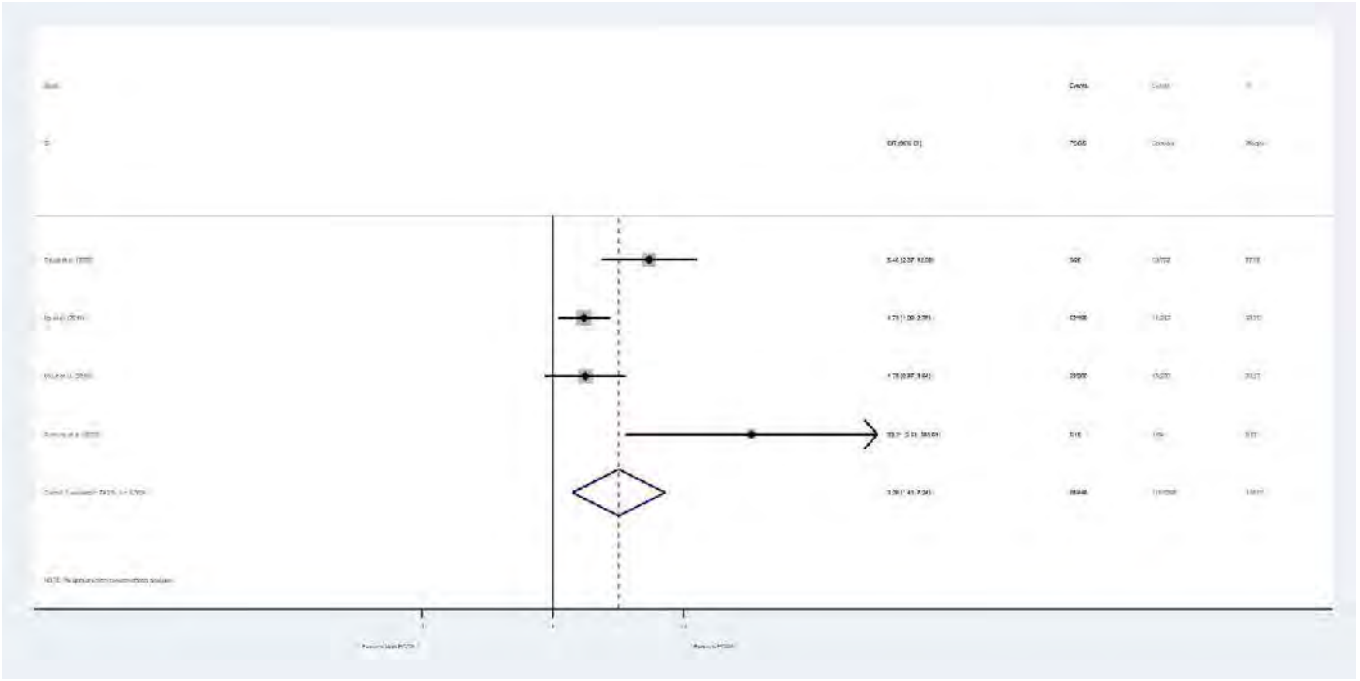
1.4.3. T2DM in adolescents



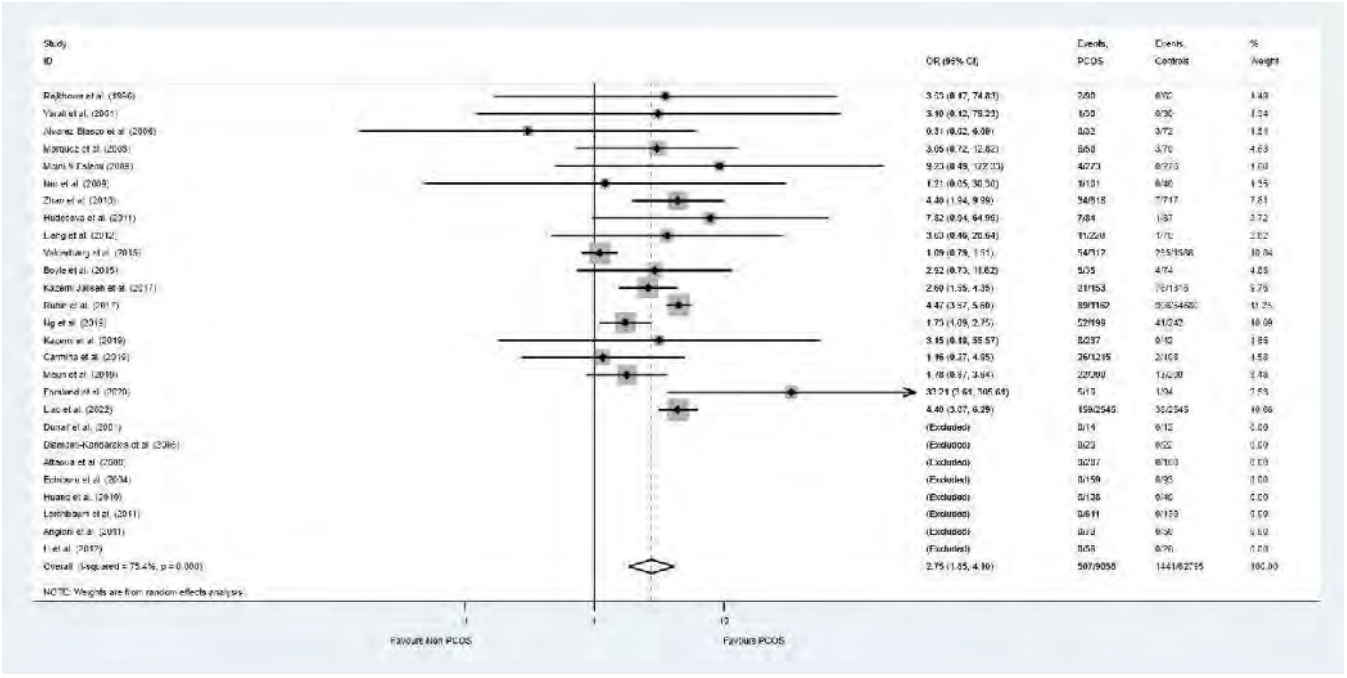
1.4.4. T2DM in premenopausal adults



1.4.5. T2DM in combined pre and post-menopausal women



1.4.6. T2DM odds ratio among moderate to high quality studies

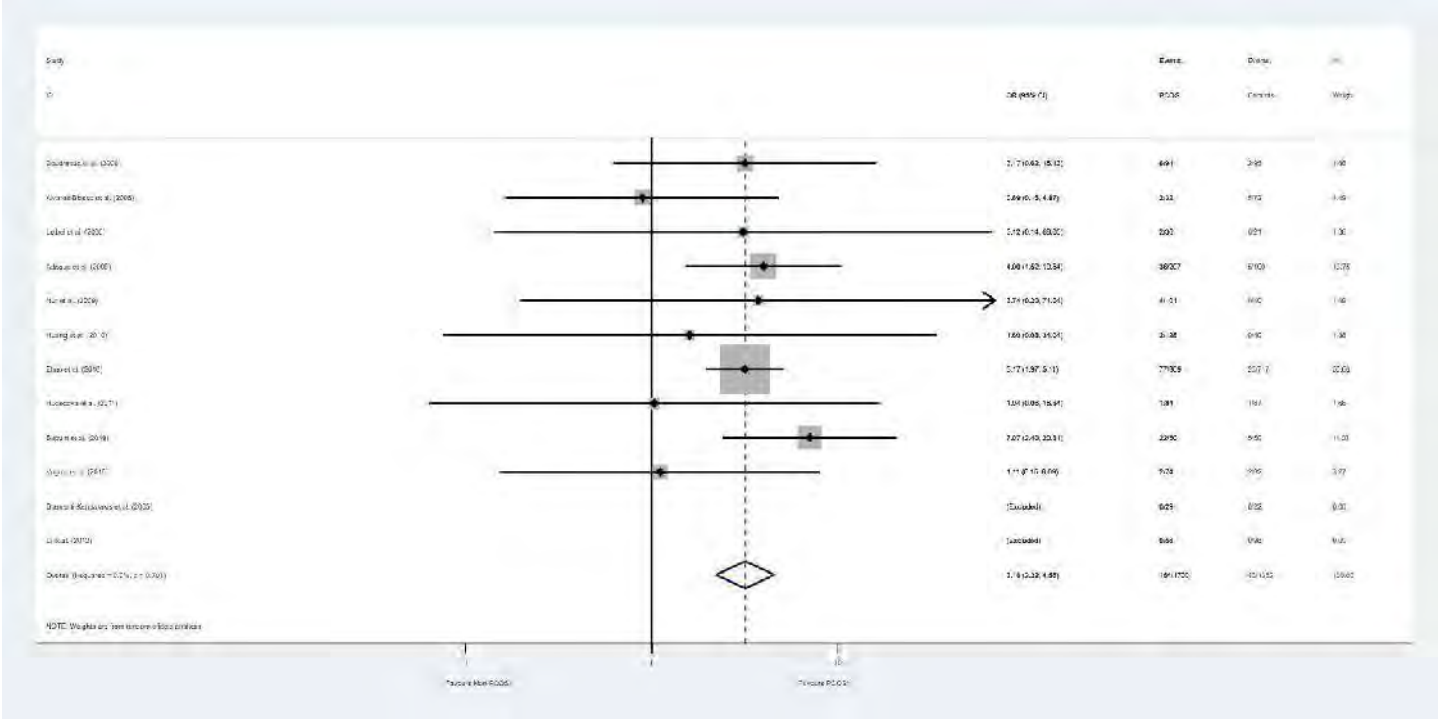


OUTCOME 2. Impaired fasting glucose

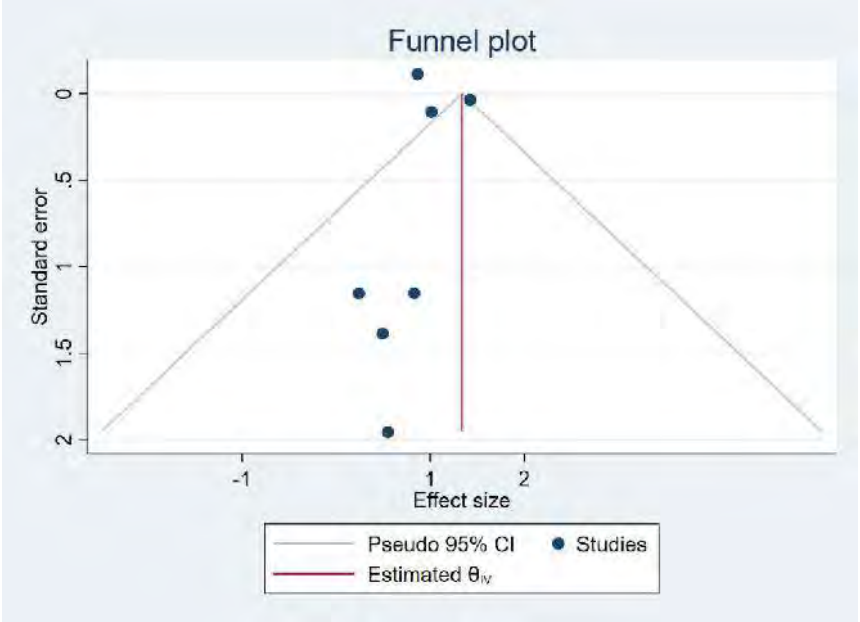
2.1. Individual Study Data Tables

OUTCOME: IFG							OUTCOME TYPE: Dichotomous	
COMPARISON: PCOS and control								
Author, year	PCOS criteria	N events in PCOS	N total in PCOS	N events in control	N total in control	Crude OR	95% CI	Pooled in MA?
Bourdeaux et al (2006)	NIH	6	94	2	95	3.17	0.62-16.13	Yes
Alvarez-Blasco et al. (2006)	NIH	2	32	5	72	0.89	0.16-4.87	Yes
Leibel et al. (2006)	ESHRE/ASRM	2	36	0	21	3.12	0.14-68.05	Yes
Attaoua et al.	ESHRE/ASRM	36	207	5	100	4.00	1.52-10.54	Yes
Nur et al. (2009)	ESHRE/ASRM	4	101	0	40	3.74	0.20-71.04	Yes
Huang et al. (2010)	Rotterdam	2	128	0	40	1.60	0.08-34.04	Yes
Zhao et al. (2010)	Rotterdam	77	809	23	717	3.17	1.97-5.11	Yes
Hudecova et al. (2011)	Rotterdam	1	84	1	87	1.04	0.06-16.84	Yes
Begum et al. (2019)	Rotterdam	22	50	5	50	7.07	2.40-20.81	Yes
Diamanti-Kandarakis et al. (2005)	NIH	2	74	2	82	1.11	0.15-8.09	Yes

2.2 Forest plot for IFG

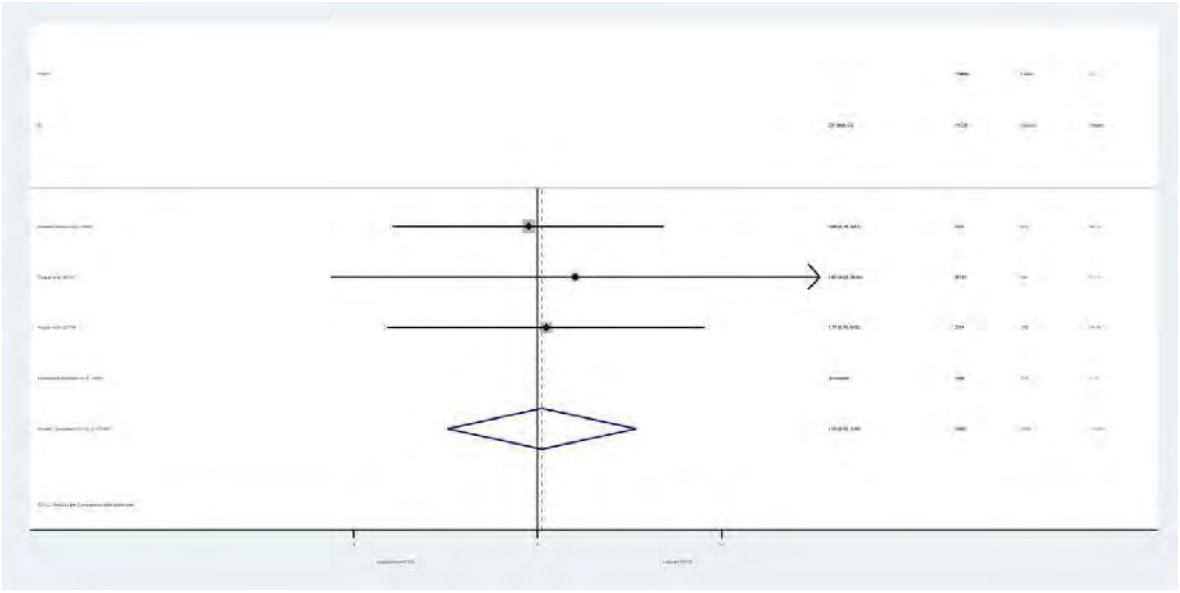


2.3 Funnel plot for IFG

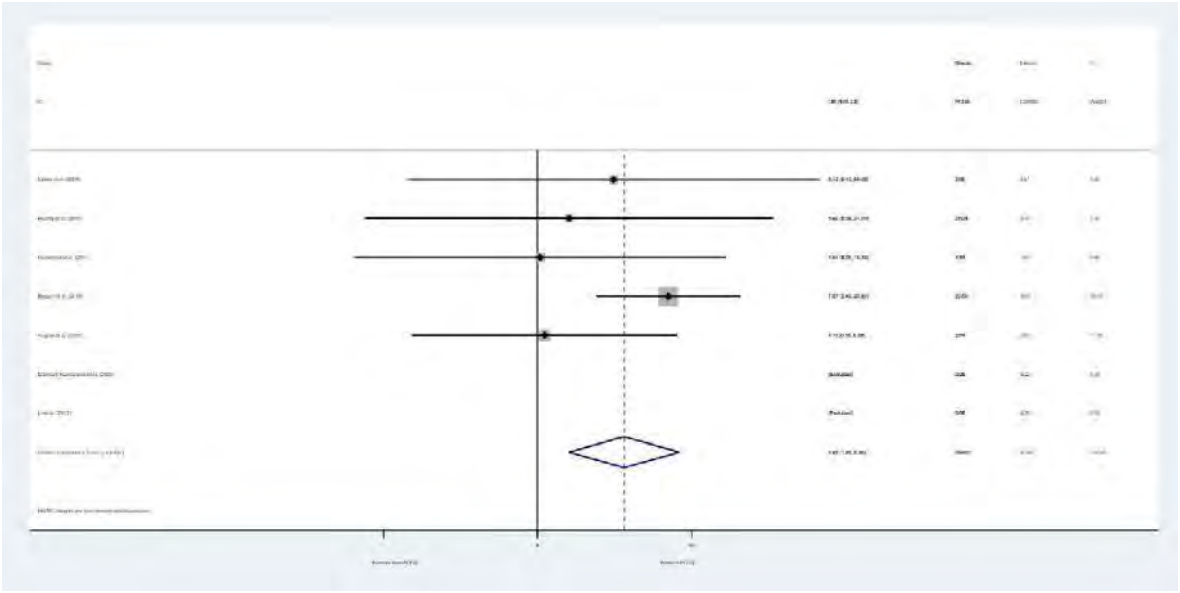


2.4. Subgroup analyses

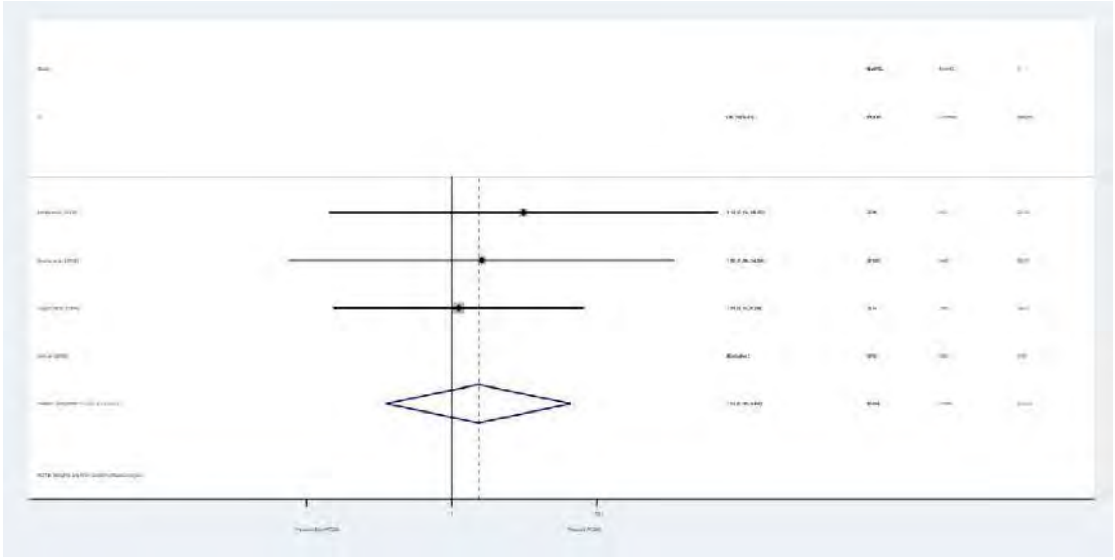
2.4.1. IFG in BMI matched/similar studies



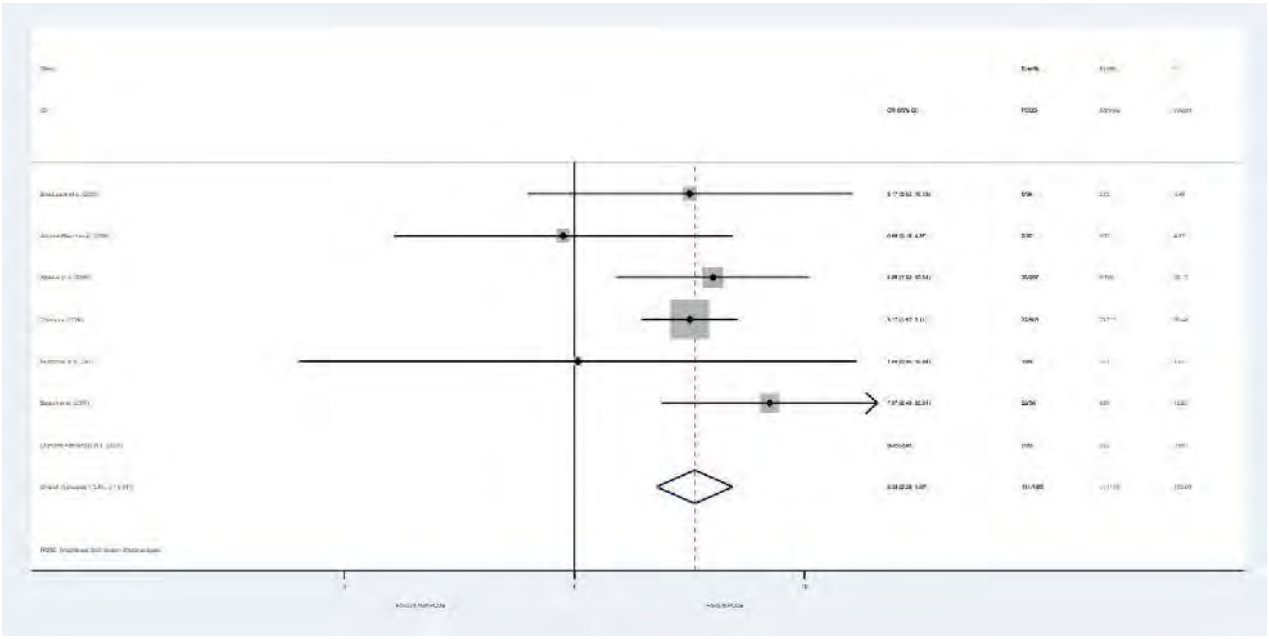
2.4.2. IFG in age matched/similar studies



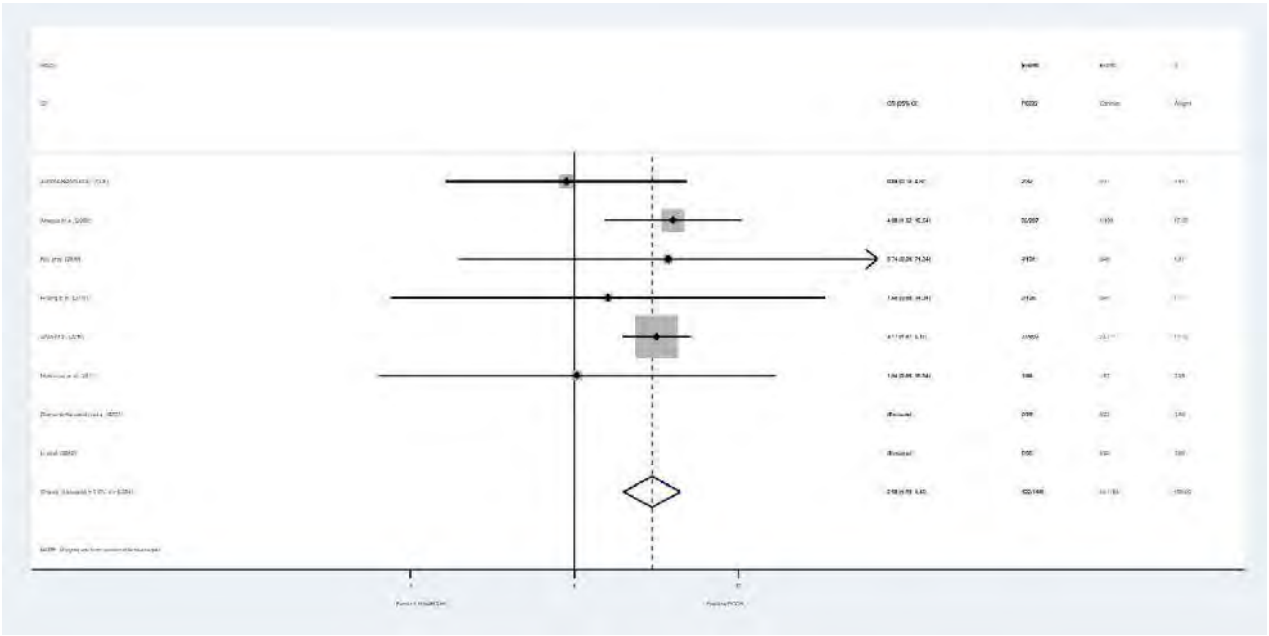
2.4.3. IFG in adolescents



2.4.4. IFG in premenopausal adults



2.4.5. IFG among moderate to high quality studies

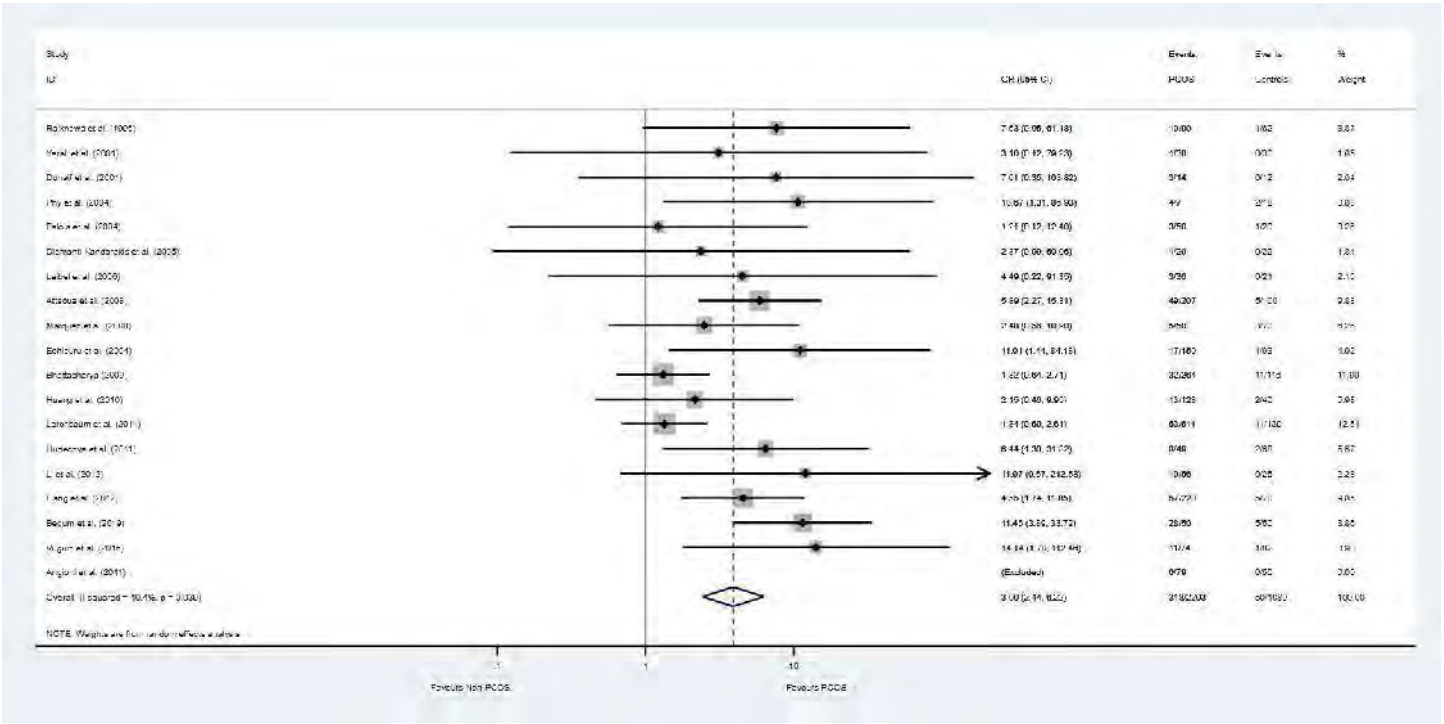


OUTCOME 3. IGT

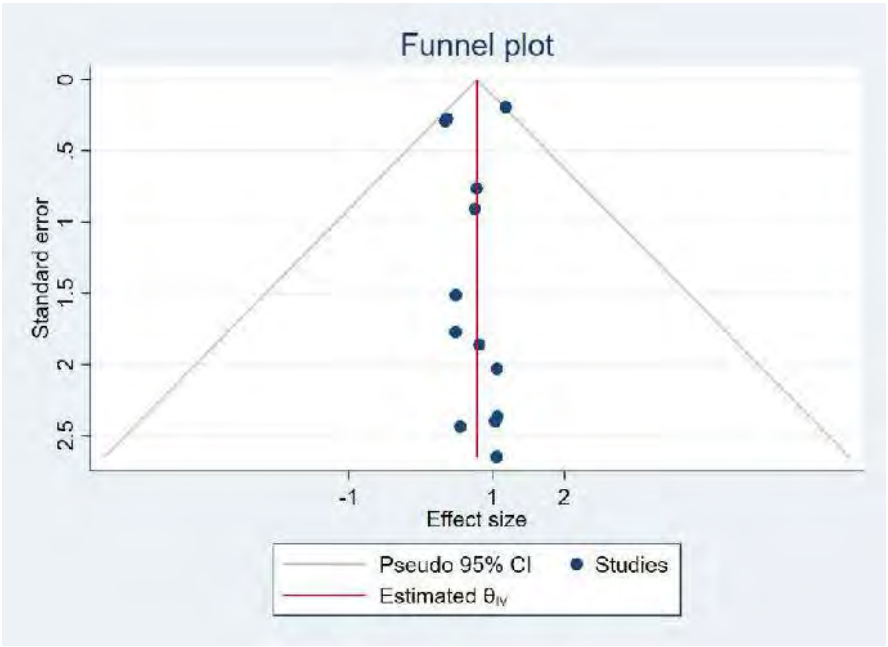
3.1. Individual Study Data Tables

OUTCOME: IGT							OUTCOME TYPE: Dichotomous	
COMPARISON: PCOS and control								
Author, year	PCOS criteria	N events in PCOS	N total in PCOS	N events in control	N total in control	Crude OR	95% CI	Pooled in MA?
Rajkhowa et al. (1996)	ESHRE/ASRM	10	90	1	62	7.63	0.95-61.18	Yes
Yarali et al. (2001)	NIH	1	30	0	30	3.10	0.12-79.23	Yes
Dunaif et al. (2001)	NIH	3	14	0	12	7.61	0.35-163.82	Yes
Phy et al. (2004)	NIH	4	7	2	18	10.67	1.31-88.93	Yes
Faloia et al. (2004)	NIH	3	50	1	20	1.21	0.12-12.40	Yes
Diamanti-Kandarakis et al. (2005)	NIH	1	29	0	22	2.37	0.09-60.96	Yes
Leibel et al. (2006)	ESHRE/ASRM	3	36	0	21	4.49	0.22-91.35	Yes
Attaoua et al. (2008)	ESHRE/ASRM	49	207	5	100	5.89	2.27-15.31	Yes
Marquez et al. (2008)	NIH	5	50	3	70	2.48	0.58-10.90	Yes
Echiburu et al. (2004)	NIH	17	159	1	93	11.01	1.44-84.18	Yes
Bhattacharya (2009)	NIH	32	264	11	116	1.32	0.64-2.71	Yes
Huang et al. (2010)	Rotterdam	13	128	2	40	2.15	0.48-9.95	Yes
Lerchbaum et al. (2011)	NIH	63	611	11	139	1.34	0.69-2.61	Yes
Hudecova et al. (2011)	Rotterdam	8	49	2	68	6.44	1.30-31.82	Yes
Li et al. (2012)	Rotterdam	10	56	0	26	11.97	0.67-212.53	Yes
Liang et al. (2012)	Rotterdam	57	220	5	70	4.55	1.74-11.85	Yes
Begum et al. (2019)	oligomenorrhoea, HA, infertility, PCOM, obesity	28	50	5	50	11.45	3.89-33.72	Yes
Vuguin et al. (2019)	NIH	11	74	1	82	14.14	1.78-112.46	Yes

3.2. Forest plot for IGT

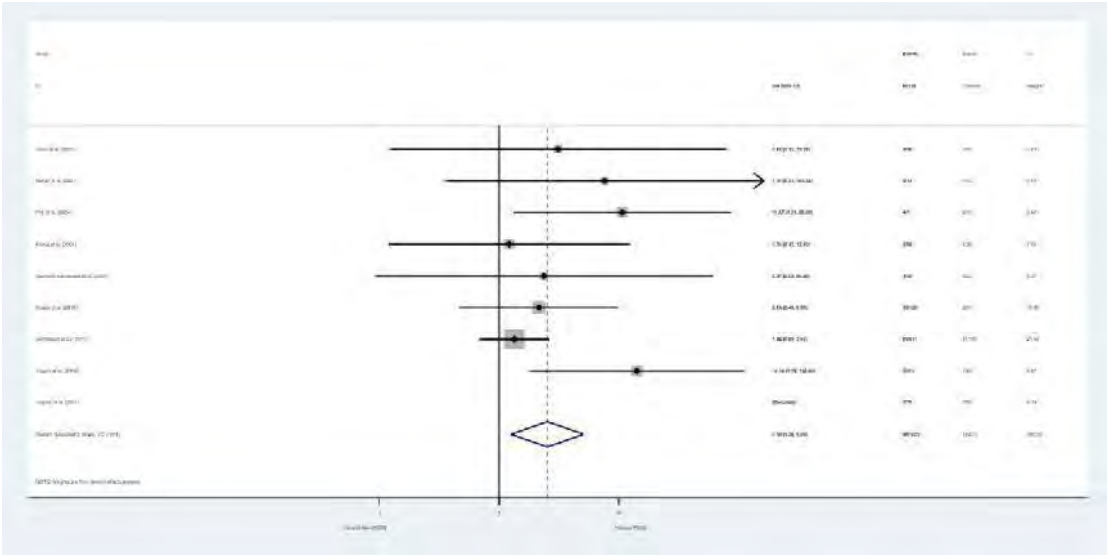


3.3. Funnel plot for IGT

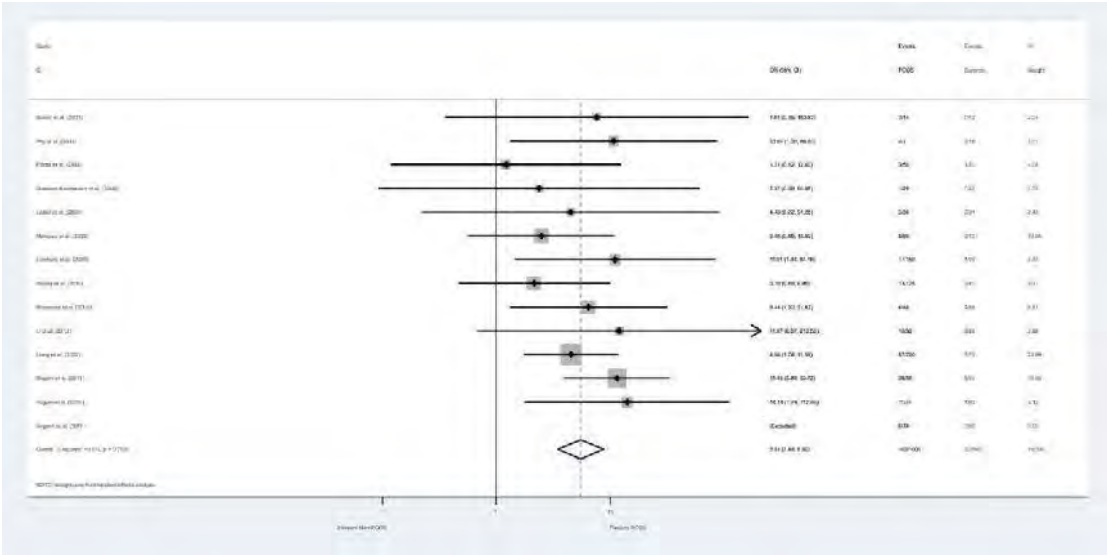


3.4. Subgroup analyses

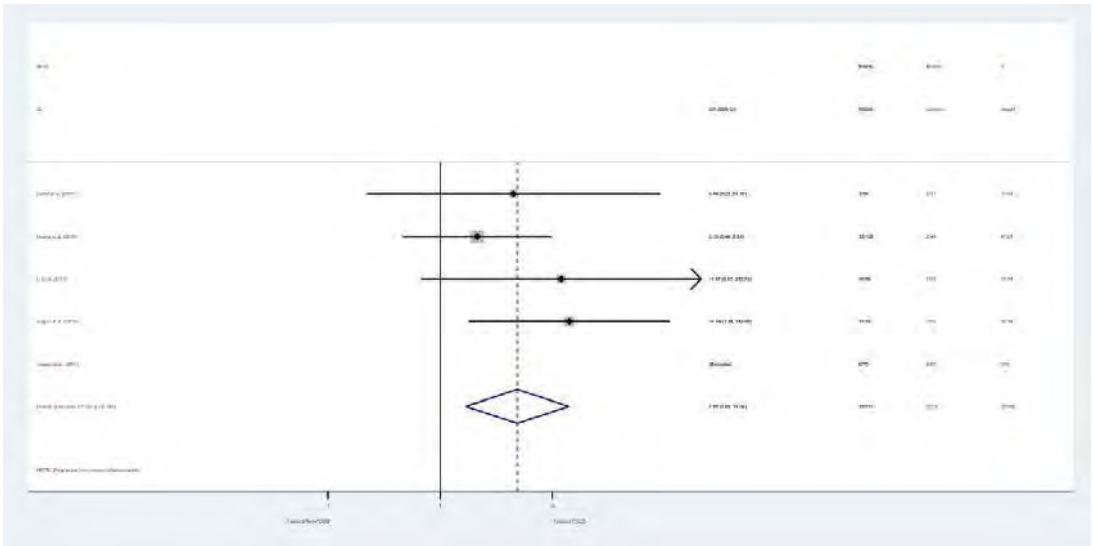
3.4.1. IGT in BMI matched/similar studies



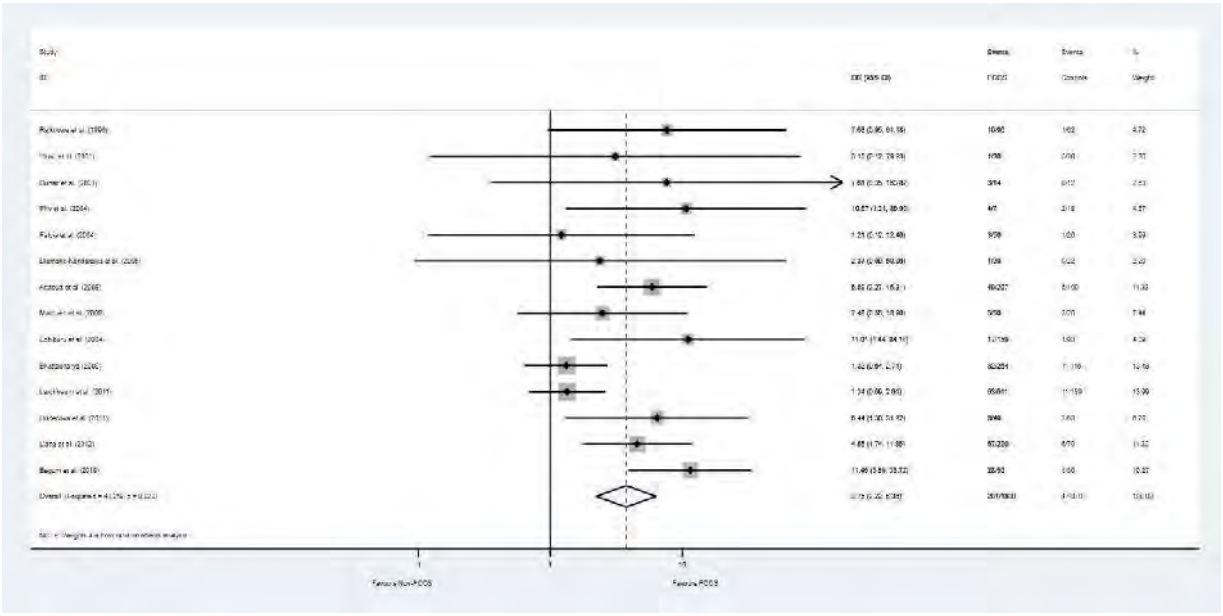
3.4.2. IGT odds ratio in age matched/similar studies



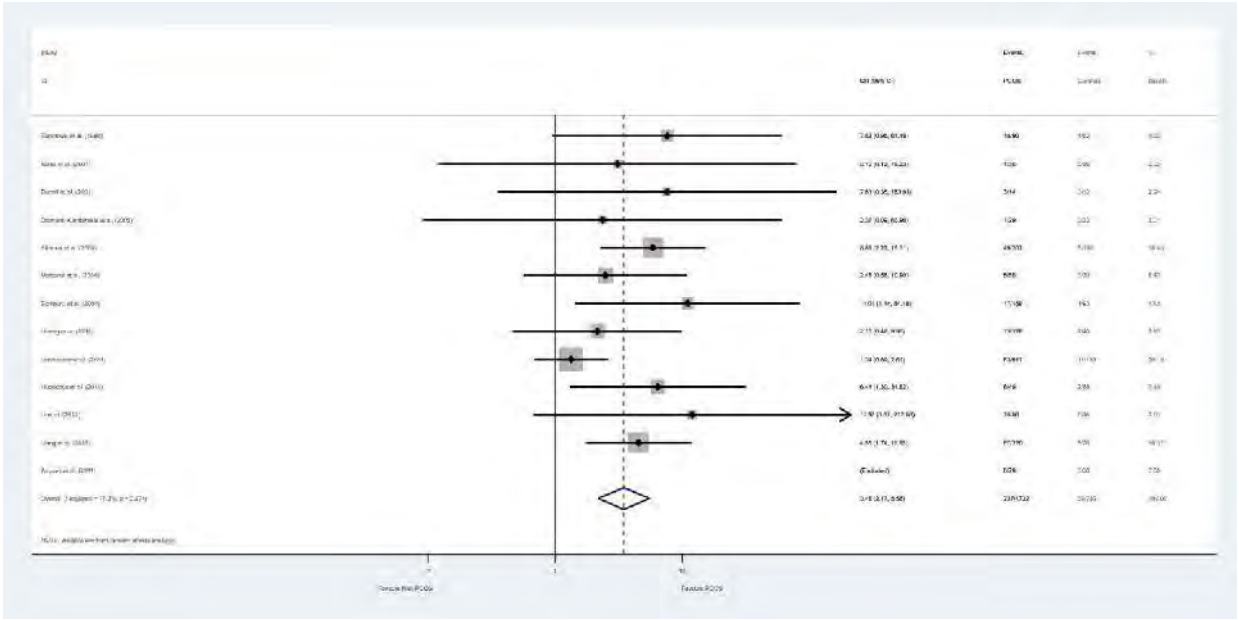
3.4.3. IGT in adolescents



3.4.4. IGT in premenopausal adults



3.4.5. IGT among moderate to high quality studies

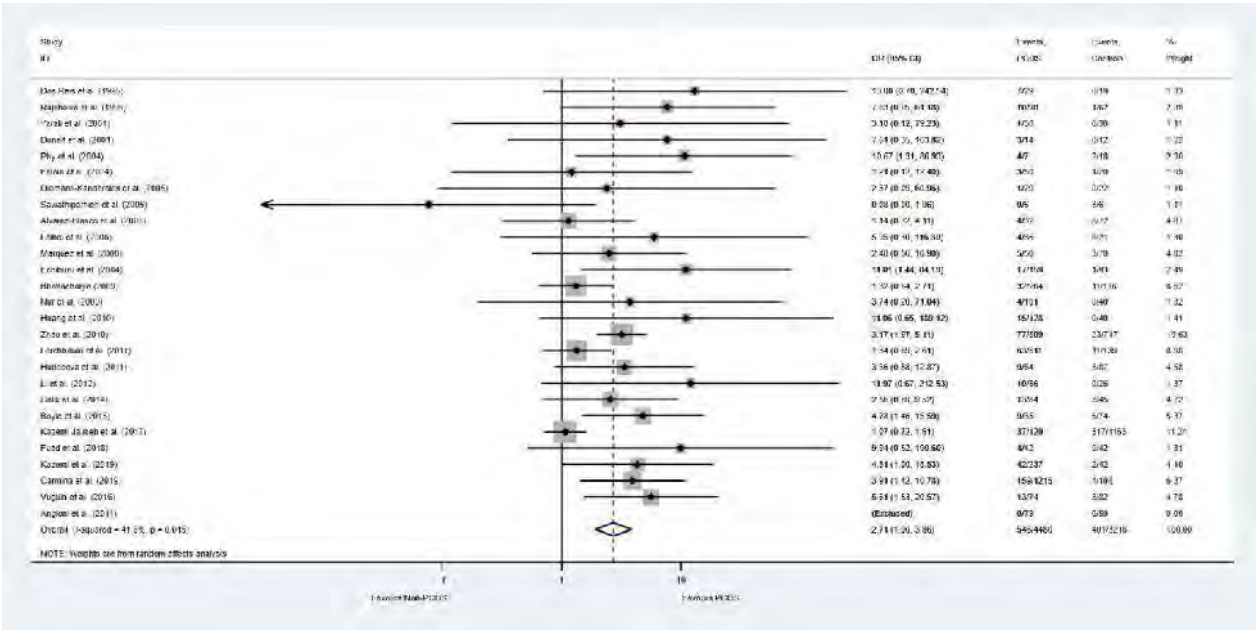


OUTCOME 4. Pre-diabetes

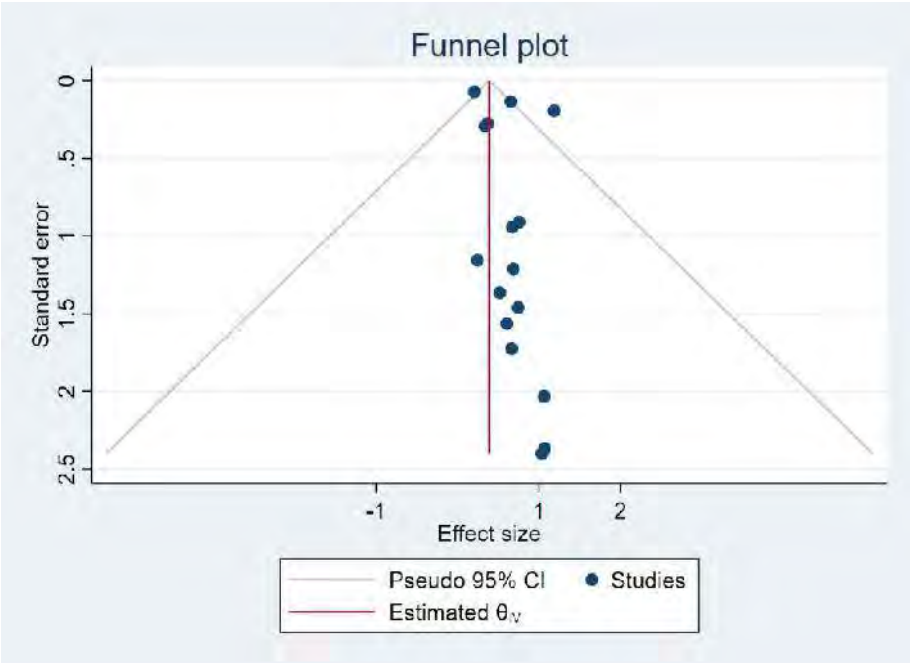
4.1. Individual Study Data Tables

OUTCOME: pre-diabetes						OUTCOME TYPE: Dichotomous		
		COMPARISON: PCOS and control						
Author, year	PCOS criteria	N events in PCOS	N total in PCOS	N events in control	N total in control	Crude OR	95% CI	Pooled in MA?
Dos Reis et al. (199	NIH	7	29	0	19	**13.0**	0.70-242.54	Yes
Rajkhowa et al. (1996)	ESHRE/ASRM	10	90	1	62	7.36	0.95-61.18	Yes
Dunaif et al. (2001)	NIH	1	30	0	30	3.10	0.12-79.23	Yes
Yarali et al. (2001)	NIH	3	14	0	12	7.61	0.35-163.82	Yes
Faloia et al. (2004)	NIH	4	7	2	18	10.67	1.31-86.93	Yes
Phy et al. (2004)	NIH	3	50	1	20	1.21	0.12-12.40	Yes
Diamanti-Kandarakis	NIH	1	29	0	22	2.37	0.09-60.96	Yes
Sawathiparnich et al	NIH	0	6	3	6	0.08	000-1.96	Yes
Alvarez-Blasco et al	NIH	4	32	8	72	1.14	0.32-4.11	Yes
Leibel et al. (2006)	ESHRE/ASRM	4	36	0	21	5.95	0.30-116.30	Yes
Echiburu et al. (2004)	NIH	5	50	3	70	2.48	0.56-10.90	Yes
Marquez et al. (2008)	NIH	17	159	1	93	11.01	1.44-84.18	Yes
Bhattacharya (2009)	NIH	32	264	11	116	1.32	0.64-2.71	Yes
Nur et al. (2009)	ESHRE/ASRM	4	101	0	40	3.74	0.20-71.04	Yes
Huang et al. (2010)	Rotterdam	15	128	0	40	11.06	0.65-189.12	Yes
Zhao et al. (2010)	Rotterdam	77	809	23	717	3.17	1.97-5.11	Yes
Hudecova et al. (201	Rotterdam	63	611	11	139	1.34	0.69-2.61	Yes
Lerchbaum et al. (20	NIH	9	84	3	87	3.36	0.88-12.87	Yes
Li et al. (2012)	Rotterdam	10	56	0	26	11.97	0.67-212.53	Yes
Celik et al. (2014)	Rotterdam	13	84	3	45	2.56	0.69-9.52	Yes
Boyle et al. (2015)	NIH	9	35	5	74	4.78	1.46-15.59	Yes
Kazemi Jaliseh et al	NIH	37	129	317	1163	1.07	0.72-1.61	Yes
Fuad et al. (2018)		4	42	0	42	9.94	0.52-190.60	Yes
Carmina et al. (2019)	Rotterdam	42	237	2	42	4.31	1.00-18.53	Yes
Kazemi et al. (2019)	NIH	159	1215	4	108	3.91	1.42-10.78	Yes
Vuguin et al. (2016)	NIH	13	74	3	82	5.61	1.53-20.57	Yes
Angioni et al. (2011)								No

4.2. Forest plot for pre-diabetes

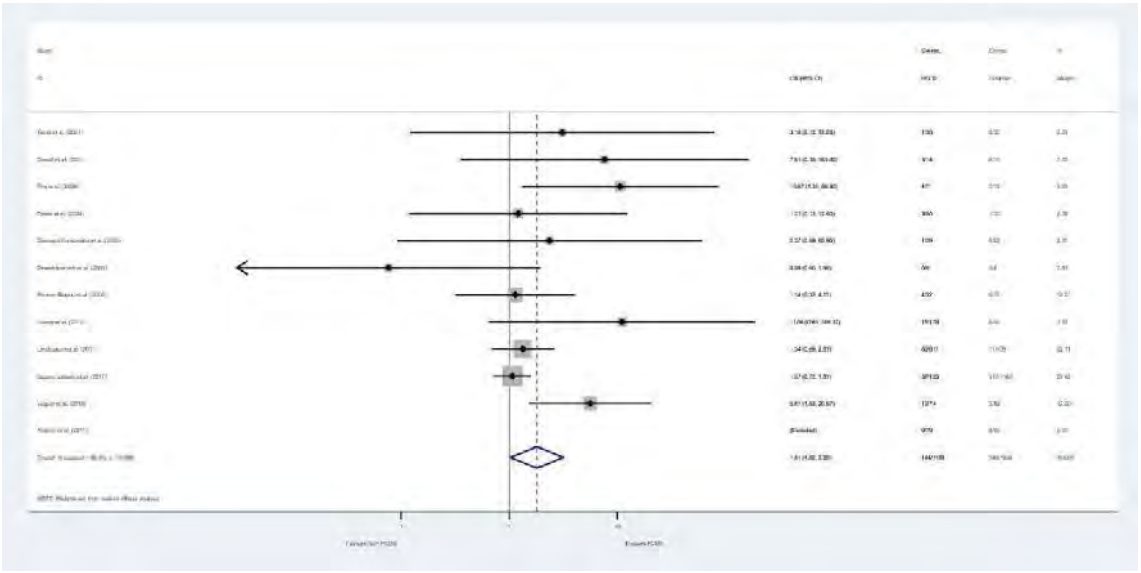


4.3 Funnel plot for pre-diabetes

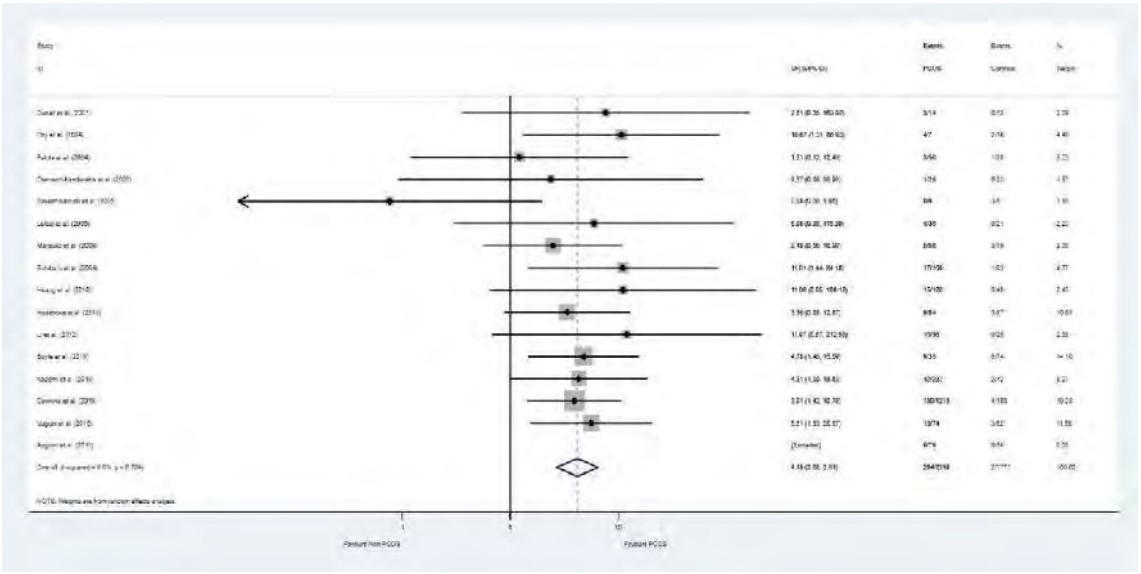


4.4. Subgroup analyses

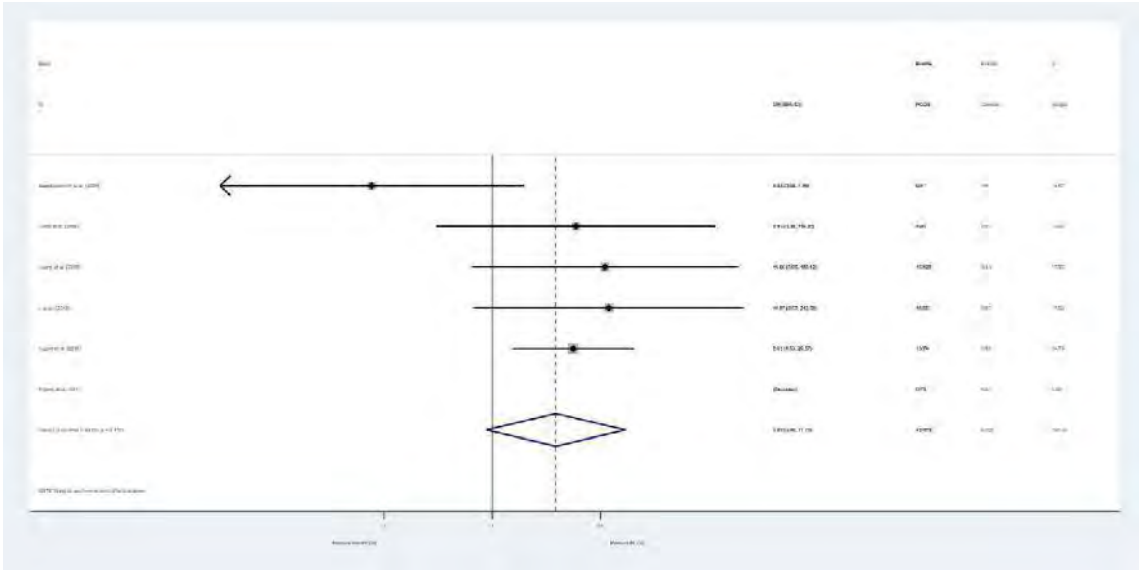
4.4.1. Pre-diabetes in BMI matched/similar studies



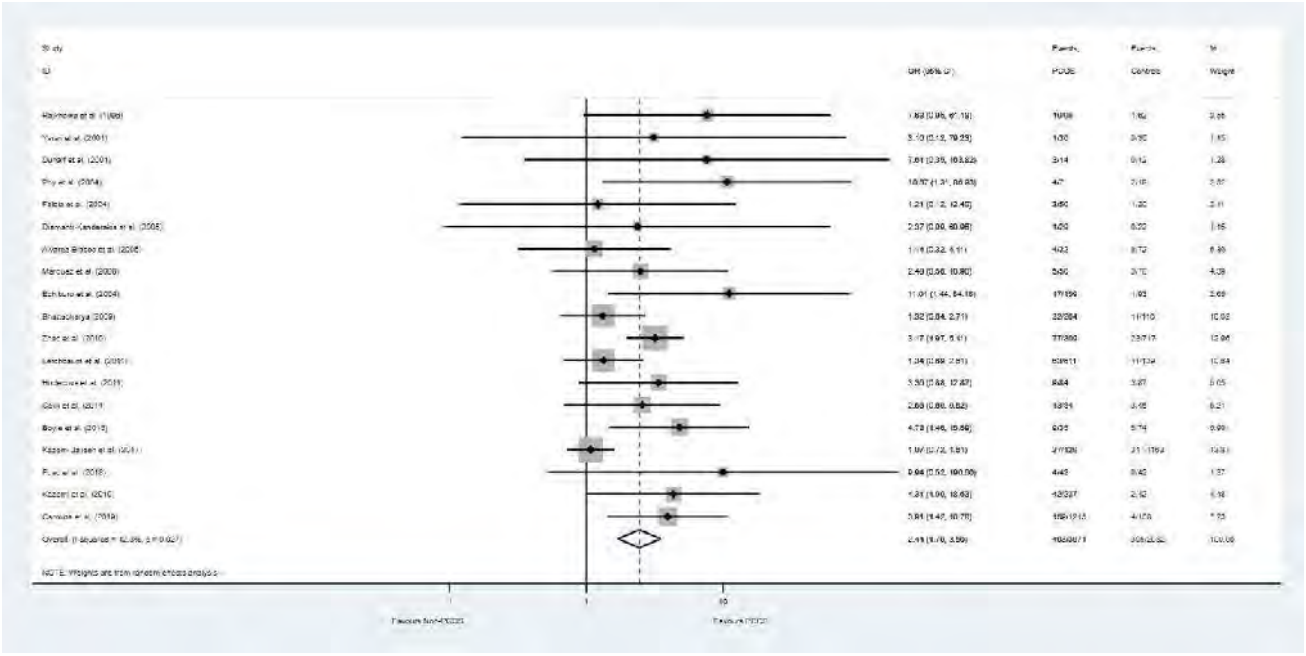
4.4.2. Pre-diabetes in age matched/similar studies



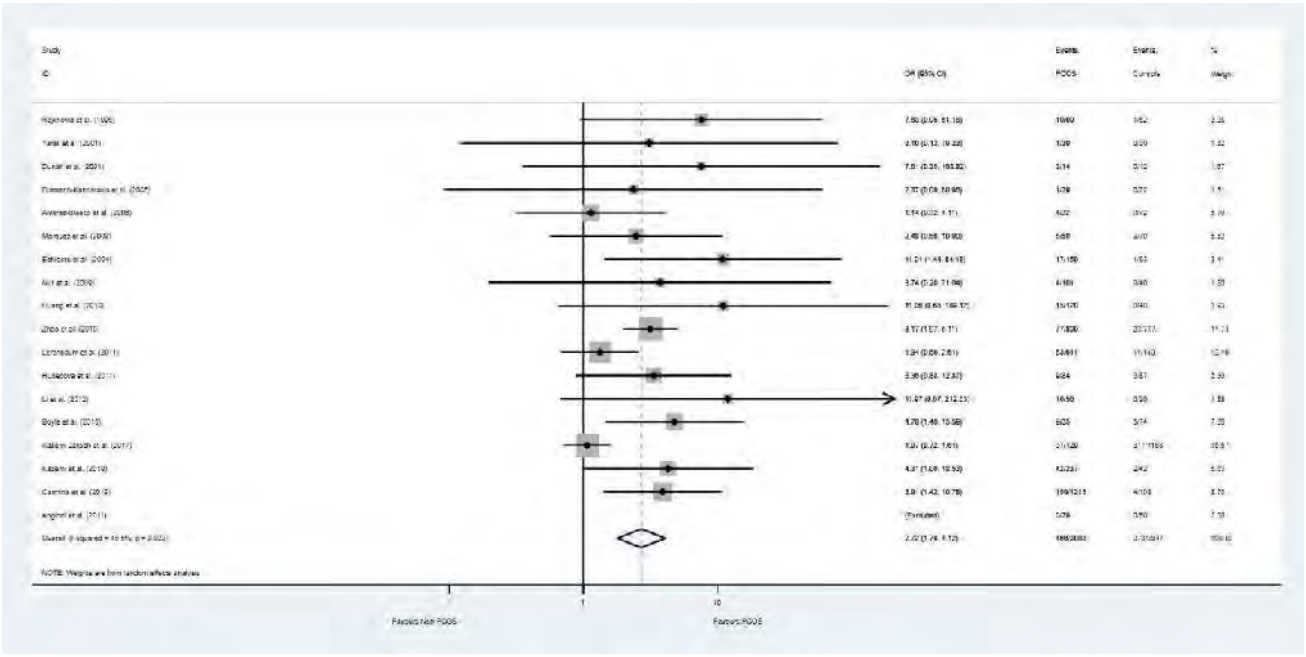
4.4.3. Pre-diabetes in adolescents



4.4.4. Pre-diabetes in premenopausal adults



4.4.5. Pre-diabetes among moderate to high quality studies



8. GRADE ASSESSMENTS AND EVIDENCE PROFILE

COMPARISON 1: Women with PCOS versus controls													
Quality assessment								No. participants					
	No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other (including publication bias)	PCOS	Control	Effect Estimate: MD (95% CI)	Favours	Certainty	Importance
Outcome: T2DM													
Total	41 (*10 excluded)	Cross-sectional Cohort	Not serious	Not serious[1,4]	Not serious	Not serious	Strong association	204063	12121581	2.87 [1.37, 6.01]	Higher in PCOS	⊕⊕⊕◯ Moderate	CRITICAL
BMI-matched	15 (7 excluded)	Cross-sectional Cohort	Not serious	Not serious	Not serious	Not serious	Strong association	1548	2867	3.04 [2.06, 4.49]	Higher in PCOS	⊕⊕⊕◯ Moderate	CRITICAL
Age-matched	24 (8 excluded)	Cross-sectional Cohort	Not serious	Not serious	Not serious	Not serious	Strong association	7684	116627	4.18 [3.30, 5.29]	Higher in PCOS	⊕⊕⊕◯ Moderate	CRITICAL
Adolescent	6 (3 excluded)	Cross-sectional	Serious	Not serious	Not serious	[4]Serious	undetected	379	225	5.73 [0.93, 35.31]	Not different	⊕◯◯◯ Very low	CRITICAL
Pre-menopausal adults	29 (7 excluded)	Cross-sectional Cohort	Not serious	Not serious[1,4]	Not serious	Not serious	Strong association	203108	121200009	2.49 [1.03, 6.03]	Higher in PCOS	⊕⊕⊕◯ Moderate	CRITICAL
Including post-menopausal women	4	Cross-sectional Cohort	Not serious	Serious[1]	Not serious	Not serious	Strong association	446	1288	3.20 [1.41, 7.24]	Higher in PCOS	⊕⊕◯◯ Low	CRITICAL
Low & mod RoB	27 (8 excluded)	Cross-sectional Cohort	Not serious	Not serious[1,4]	Not serious	Not serious	Strong association	9058	62795	2.75 [1.85, 4.10]	Higher in PCOS	⊕⊕⊕◯ Moderate	CRITICAL
Outcome: IFG													
Total	12 (2 excluded)	Cross-sectional Cohort	Not serious	Not serious	Not serious	Not serious	[2]Suspected publication bias Strong association	1700	1352	3.18 [2.22, 4.56]	Higher in PCOS	⊕⊕◯◯ Low	CRITICAL
BMI-matched	4 (1 excluded)	Cross-sectional	Serious	Not serious	Not serious	Serious	Undetected	283	216	1.05 [0.32, 3.46]	Not different	⊕◯◯◯ Very low	CRITICAL
Age-matched	7 (2 excluded)	Cross-sectional Cohort	Not serious	Not serious	Not serious	Not serious	Strong association	457	328	3.65 [1.59, 8.36]	Higher in PCOS	⊕⊕⊕◯ Moderate	CRITICAL
Adolescent	4 (1 excluded)	Cross-sectional	Serious	Not serious	Not serious	Serious	Undetected	294	169	1.52 [0.35, 6.60]	Not different	⊕◯◯◯ Very low	IMPORTANT

Pre-menopausal adults	7 (1 excluded)	Cross-sectional Cohort	Not serious	Not serious	Not serious	Not serious	Strong association	1305	1143	3.33 [2.28, 4.87]	Higher in PCOS	⊕⊕⊕◯ Moderate	IMPORTANT
Low & mod RoB	8 (2 excluded)	Cross-sectional Cohort	Not serious	Not serious	Not serious	Not serious	Strong association	1446	1104	2.98 [1.99, 4.46]	Higher in PCOS	⊕⊕⊕◯ Moderate	CRITICAL
Outcome: IGT													
Total	19 (1 excluded)	Cross-sectional Cohort	Not serious	Not serious[1,4]	Not serious	Not serious	Strong association	2203	1089	3.90 [2.44, 6.22]	Higher in PCOS	⊕⊕⊕◯ Moderate	CRITICAL
BMI-matched	9 (1 excluded)	Cross-sectional	Not serious	Not serious	Not serious	Not serious	Strong association	1022	413	2.53 [1.27, 5.04]	Higher in PCOS	⊕⊕⊕◯ Moderate	CRITICAL
Age-matched	14 (1 excluded)	Cross-sectional Cohort	Not serious	Not serious	Not serious	Not serious	Strong association	1001	642	5.51 [3.44, 8.80]	Higher in PCOS	⊕⊕⊕◯ Moderate	CRITICAL
Adolescent	5 (1 excluded)	Cross-sectional	Serious	Not serious	Not serious	Serious	Strong association	373	219	4.87 [1.68, 14.06]	Higher in PCOS	⊕◯◯◯ Very low	IMPORTANT
Pre-menopausal adults	14	Cross-sectional Cohort	Not serious	Not serious[1,4]	Not serious	Not serious	Strong association	1830	870	3.75 [2.22, 6.36]	Higher in PCOS	⊕⊕⊕◯ Moderate	IMPORTANT
Low & mod RoB	13 (1 excluded)	Cross-sectional Cohort	Not serious	Not serious	Not serious	Not serious	Strong association	1722	782	3.48 [2.18, 5.56]	Higher in PCOS	⊕⊕⊕◯ Moderate	CRITICAL
Outcome: Pre-diabetes													
Total	27 (1 excluded)	Cross-sectional Cohort	Not serious	Not serious[1,4]	Not serious	Not serious	[2]Suspected publication bias, strong association	4480	3216	2.71 [1.90, 3.86]	Higher in PCOS	⊕⊕◯◯ Low	CRITICAL
BMI-matched	12 (1 excluded)	Cross-sectional	Not serious	Not serious	Not serious	Not serious	Strong association	1189	1654	1.81 [1.02, 3.20]	Higher in PCOS	⊕⊕⊕◯ Moderate	CRITICAL
Age-matched	16 (1 excluded)	Cross-sectional Cohort	Not serious	Not serious	Not serious	Not serious	Strong association	2259	771	4.18 [2.68, 6.51]	Higher in PCOS	⊕⊕⊕◯ Moderate	CRITICAL
Adolescent	6 (1 excluded)	Cross-sectional	Not serious	Not serious	Not serious	Serious	Undetected	379	225	3.88 [0.88, 17.12]	Not different	⊕◯◯◯ Very low	IMPORTANT
Pre-menopausal adults	19	Cross-sectional Cohort	Not serious	Not serious[1,4]	Not serious	Not serious	Strong association	3971	2932	2.44 [1.70, 3.50]	Higher in PCOS	⊕⊕⊕◯ Moderate	IMPORTANT
Low & mod RoB	18 (1 excluded)	Cross-sectional Cohort	Not serious	Not serious[1,4]	Not serious	Not serious	Strong association	3888	2847	2.72 [1.79, 4.12]	Higher in PCOS	⊕⊕⊕◯ Moderate	CRITICAL

[1] Downgraded once due to high statistical heterogeneity
[2] Downgraded once due to asymmetric funnel plots on visual inspection
[3] Downgraded once due to CI including OR of 1.0
[4] Upgraded once because subgroup analyses persistently confirmed similar OR (We evaluated heterogeneity by assessing subgroups. Heterogeneity was reduced in BMI and Age-matched subgroups).

*The studies were excluded in STATA meta-analyses when the number of events were zero in both PCOS and control groups.

APPENDIX. QUALITY APPRAISAL OF INCLUDED STUDIES

		Selection bias			Performance bias	Detection bias				Attrition bias		Report Bias	Confounding	Other bias			
Study ID	Design	Comparable cases & controls	Established case definition	Established control definition	Groups treated the same	Standard measurements for exposure	Assessors blinded to case/control status	Standard measurements for outcomes	Outcomes assessed objectively and independently	% lost to follow up	% included in analysis	Free of selective outcome reporting	Groups similar at baseline	Funding/ COI reported	Sufficient power	Adequate statistical analysis	Overall risk
Begum et al. (2019)	Cross sectional	Yes	Partial	Yes	Yes	Yes	NR	Yes	Yes	NR	100%	Yes	Partial	No	NR	Yes	High
Carmina et al. (2019)	Cross sectional	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	NR	Yes	Partial	Yes	NR	Yes	Low
Fuad et al. (2018)	Cross sectional	Yes	Yes	Yes	Partial	Partial	No	Partial	Yes	NA	NR	Yes	No	No	NR	Partial	High
Kazemi Jaliseh et al. (2017)	Cohort	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	9.26%	91%	Yes	Partial	Yes	NR	Yes	Low
Forslund et al. (2020)	Cohort	Yes	Yes	Yes	Yes	Partial	No	Partial	Yes	18.18%	82%	Yes	Partial	Yes	Yes	Yes	Mod
Kazemi et al. (2019)	Cross sectional	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	NR	Yes	Partial	Yes	NR	Yes	Low
Liao et al. (2022)	Cohort	Yes	Yes	Yes	Yes	Partial	No	Partial	Yes	NA	NR	Yes	Partial	Yes	NR	Yes	Mod
Meun et al. (2019)	Cross sectional	Yes	Yes	Yes	Yes	Partial	No	Partial	Yes	NR	NR	Yes	Partial	Yes	NR	Yes	Mod
Ng et al. (2019)	Cohort	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	32.50%	90.5%	Yes	Partial	Yes	NR	Yes	Low
Ryu et al. (2021)	Cohort	Yes	Yes	Yes	Yes	Partial	No	Partial	Yes	NR	NA	Yes	Partial	Yes	NR	Yes	Mod
Rubin et al. (2017)	Cohort	Yes	Yes	Yes	Yes	Partial	No	Partial	Yes	NA	85.40%	Yes	Partial	Yes	NR	Yes	Mod
Vuguin et al. (2016)	Cross sectional	Yes	Yes	Yes	Yes	Partial	No	Partial	Yes	NA	NR	Yes	Yes	Yes	NR	Partial	High

PART 2

RECOMMENDATIONS

GDG 1

Question 1.9.1

Q.1.9.1. Are women with PCOS at increased risk for impaired glucose tolerance and type 2 diabetes?

BACKGROUND:

Prevalence and problem

Diabetes is a common metabolic disorder characterized by hyperglycaemia, and can be associated with significantly increased co-morbidities and mortality. The great majority of people with diabetes have type 2 diabetes (T2D), which accounts for around 95% of the number of people with diabetes. Other types of diabetes include type 1 diabetes (T1D), and diabetes arising due to specific causes, such as endocrine disorders, diseases of the exocrine pancreas, or monogenic forms of diabetes (1). Importantly, the pathophysiology and natural history of T2D has been extensively studied, and T2D is preceded by an intermediate state of hyperglycaemia, often broadly termed pre-diabetes, which may be detected based on elevated fasting glucose (impaired fasting glucose), elevated postprandial glucose during OGTT (impaired glucose tolerance), or elevated HbA1c (2). There is marked geographical variation in the prevalence and incidence of T2D, partly driven by differences in risks related to ethnicity, genetic factors, lifestyle and dietary pattern, as well as environmental factors, among others. Multiple studies have demonstrated that lifestyle intervention (3), and some pharmacological agents, may delay the progression from pre-diabetes to T2D (4). Recent studies have also highlighted that early T2D may be reversed through intensive lifestyle intervention (5). Multiple pathophysiology defects have been identified to be associated with T2D, including higher weight and related insulin resistance, impaired beta-cell function, altered incretin effects etc. (6). There has been a marked increase in the prevalence of T2D over recent decades, partly due to the global increase in rates of higher weight (7). With increasing higher weight in childhood, there is also an increasing burden of young-onset diabetes, with an increasing proportion of young adults diagnosed with diabetes. Alarmingly, an increasing proportion of pregnancies are complicated by hyperglycaemia in pregnancy (HIP) and gestational diabetes mellitus (8) (9), which are associated with adverse pregnancy outcomes.

PCOS is closely linked with insulin resistance, with insulin resistance present in 75% of lean PCOS, and as high as 95% of women with PCOS with a BMI >30(10). It has been proposed that women with PCOS are at increased risk of metabolic syndrome (11) and type 2 diabetes (T2D) (12). PCOS is also associated with other manifestations of insulin resistance including dyslipidaemia, hypertension, non-alcoholic fatty liver disease and cardiovascular disease (13).

In a longitudinal study from a Danish registry, it was reported that women with PCOS have approximately 4 times the risk of T2D compared to controls (14). Factors that may affect the risk of T2D in PCOS include ethnicity, age, higher weight, positive family history of diabetes and presence of other risk factors for T2D (12, 14, 15).

It is worth noting that the converse has also been observed, that women with type 1 diabetes (T1D) or T2D have been reported to have a higher prevalence of PCOS. A systematic review reported that approximately 1 in 4 women with T1D have PCOS and related hyperandrogenic traits (16). A systematic review reported that the prevalence of PCOS in women with T2D was approximately 21% (17). These studies highlight that PCOS is a common condition among women with T1D or T2D.

Clinical practice gap: need for guidance

Previous systematic reviews and meta-analyses have highlighted the increased risk of diabetes and dysglycaemia in PCOS. Previous studies have also examined the risk of diabetes according to

subgroups including ethnicity and presence/absence of higher weight. The relative risk of T2D and impaired glucose tolerance need to be defined in PCOS. It is also important to understand how the risk varies according to different age groups. It would also be useful to address which tests of glycaemia should be undertaken to assess diabetes, and how often they need to be repeated.

Summary of key information

Additional studies on the risk of T2D or IGT in PCOS have been published since the last version of the International PCOS Guidelines. A systematic review and meta-analysis was therefore undertaken. It is worth noting that the current systematic review on risk of T2D in PCOS included fewer studies compared to an earlier systematic review (12). This is due to differences in the inclusion criteria, in particular in relation to the diagnostic criteria for PCOS. In the current evidence synthesis, the diagnosis of PCOS by ICD codes alone have been excluded for the majority of outcomes. In the current evidence synthesis, the diagnosis of PCOS by ICD codes alone have been excluded.

In general, more recent studies have confirmed the relative risk of T2D in PCOS to be around 3-fold.

The current analysis did not examine risk in relation to ethnicity, but included subgroups according to different age groups, as well as in studies matched for age or BMI, and subgroup analysis restricting to studies with less bias. Findings from the subgroup analyses are in general consistent with those in the overall study population, though limited by the smaller sample sizes.

GRADE EVIDENCE CERTAINTY	
Comparison	**GRADE for critical outcomes**
o PCOS versus non-PCOS Controls – T2DM	⨁⨁⨁◯ Moderate
o Impaired fasting glucose	⨁⨁◯◯ Low
o Impaired glucose tolerance	⨁⨁⨁◯ Moderate

Evidence to Recommendations Framework

COMPARISONS (option versus other option)

Risk of T2D, IFG, IGT and prediabetes in PCOS vs non-PCOS controls

EVIDENCE-BASED RECOMMENDATION(S)

EBR: Healthcare professionals and women with PCOS should be aware that, regardless of age and BMI, women with PCOS have an increased risk of impaired fasting glucose, impaired glucose tolerance and type 2 diabetes.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

EBR: Glycaemic status should be assessed at baseline in all adults and adolescents with PCOS.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

CR: Glycaemic status should be reassessed every one to three years, based on additional individual risk factors for diabetes.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

CR: Health professionals, women with PCOS and other stakeholders should prioritise preventative strategies to reduce type 2 diabetes risk.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

CR: Funding bodies should recognise that PCOS is highly prevalent, has significant high risk for diabetes and should be supported accordingly.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

CR: Diabetes guidelines in the general population should consider the inclusion of PCOS as an independent risk factor for diabetes.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

PRACTICE POINT(S)

Health professionals, adults and adolescents with PCOS and their first-degree relatives should be aware of the increased risk of diabetes and the need for regular glycaemic assessment.

Women with type 1 and type 2 diabetes have an increased risk of PCOS and screening should be considered in individuals with diabetes.

GRADE CONSIDERATIONS

Justifications:
PCOS, when compared to non-PCOS women, was associated with significantly increased risk of diabetes in the overall group. There was strong association, quality of evidence moderate. However, the overall quality graded by the Evidence team as “Very low”, probably due to low grading of some of the subgroup analyses included (see adolescent and pre- and postmenopausal). If restricted to the overall effect for diabetes, this should be a strong recommendation with moderate quality of evidence.
For the other critical outcomes (IFG, IGT and pre-diabetes), the number of studies available were limited and quality of evidence low to moderate. The findings are consistent and supported by the age-matched or BMI-matched analyses which had less heterogeneity.

Subgroup considerations:
Subgroups considered included T2D/IFG/IGT/pre-diabetes as separate outcomes, and also subgroups according to BMI matched, age matched, adolescents, pre-menopausal, combined pre and post-menopausal age groups, and among moderate to high quality studies.

Among studies with no significant difference in BMI between PCOS and control groups, women with PCOS had a similar risk of IFG but higher risk of T2DM, IGT and pre-diabetes. In subgroup analysis, the risk of T2DM, IFG and pre-diabetes in adolescents with PCOS was similar to controls, though the quality of evidence was very low in this subgroup. Adolescents were still at a higher risk of IGT.

Results from the studies including both pre- and postmenopausal women, or results of subgroup analyses restricting to studies with low or moderate risk of bias, in general echo findings from the overall group.

Ethnicity diversity and postmenopausal age group were not covered in these analyses.

Implementation considerations:
Whilst OGTT may be the preferred mode of glycaemic evaluation, there are logistic difficulties which may limit its implementation. Other tests of glycaemia, such as FPG and HbA1c, were not found to have adequate performance in the direct comparisons (see 1.9.2), but these tend to use OGTT as the gold standard for comparison.
Women with PCOS need to be aware of the risk of diabetes in PCOS, and the need for regular evaluation for diabetes. It would also be helpful for them to be aware of the other risk factors for diabetes.

Monitoring and evaluation considerations:
Some monitoring of the proportion of adults and adolescents with PCOS who have undergone OGTT or other glycaemic measurements at baseline would be helpful.
Compliance to subsequent glucose evaluation (through regular OGTT and/or other glycaemic parameters), and frequency of monitoring, would also be useful.

Research priorities:
The extent of increased risk of T2D and IGT that persist into later adult life.
Evaluation of the relative risk of diabetes at different age groups, including postmenopausal.
Risk of type 2 diabetes in different subgroups including ethnicities variation and hyperandrogenic population.
The impact of insulin treatment in diabetes on reproductive outcomes and PCOS features.
The rate of progression of prediabetes into diabetes in women with and without PCOS.

GRADE framework

GRADE DECIDE Interactive Evidence to Decision Framework

● DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

Judgement:

☒ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

The effects/benefits are probably quite substantial in high risk population. Recommendations to undergo OGTT in all women with PCOS seems warranted, with periodic screening thereafter.

● UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

Judgement:

☐ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☒ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:
Undesirable effects is probably limited. Potential anxiety related to regular screening. Testing in otherwise healthy women may have negative effects.

● CERTAINTY OF THE EVIDENCE

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☐ Very low	☐ Low	☒ Moderate	☐ High

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

The nature of the questions relies on observational research which inherently reduces the quality of the evidence.

● VALUES

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☐ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☐ Probably no important uncertainty or variability	☒ No important uncertainty or variability

Research evidence:

No research evidence was identified

Panel discussion:

Assessing risk of diabetes likely to be valued as a main outcome

● BALANCE OF EFFECTS

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☒ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:

Given the benefits of earlier detection of dysglycaemia and early initiation of education and treatment, the balance likely favours the option rather than the comparison.

● COSTS

How large are the resource requirements (costs)?

Judgement:

☐ Don't know	☒ Varies	☐ Large costs	☐ Moderate costs	☐ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:

No research evidence was identified

Panel discussion:

Resource requirements not examined but would differ in different healthcare settings, and not insignificant.

There will be cost for implementing screening of diabetes but this may be offset by prevention of complications.

● CERTAINTY OF COST EVIDENCE

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

No research evidence was identified

Panel discussion:

Not evaluated

● COST-EFFECTIVENESS

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

No research evidence was identified

Panel discussion:

This needs to be formally evaluated with cost-effectiveness analysis.

There will be costs for implementing screening of diabetes but this may be offset by prevention of complications.

● EQUITY

What would be the impact on health equity?

Judgement:

☐ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☒ Probably increased	☐ Increased

Research evidence:

No research evidence was identified

Panel discussion:

[key contact to draft discussion points and justification for above judgement]

Undertaking OGTT regularly may be difficult in low- and middle-income settings and more likely to be performed in settings with better healthcare resources. So, access may be restricted in some at risk subjects. May be associated with reduction of health equity.

However, increasing screening will overall improve equity in women with PCOS.

● ACCEPTABILITY

Is the option acceptable to key stakeholders?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Probably, given the high risk and long-term implication.

● FEASIBILITY

Is the option feasible to implement?

Judgement:

☐ Don't know	☒ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Probable yes but depending on resource available and healthcare settings, with some barrier in low income groups and countries

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PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by ECR Lead: Yitayeh Mengitsu

Other Members: Rafiatu Azumah

Supervised, edited and supported by the Evidence Team

GDG 1

Question 1.9.2

Q.1.9.2. In women with PCOS, what is the most effective tool/method to assess risk of type 2 diabetes mellitus?

Background

Polycystic Ovary Syndrome (PCOS) is a common endocrinologic disorder in women of reproductive age, with prevalence varying from 2-26% in different population groups (1–3). Irregular menstrual cycle, hirsutism, polycystic ovaries, dyslipidemia, infertility, and insulin resistance are common PCOS symptoms with different genetic and environmental risk factors. Currently, PCOS is commonly diagnosed by the Rotterdam criteria which requires two of the following: oligomenorrhea/anovulation, clinical/biochemical hyperandrogenism, and polycystic ovaries (≥12 follicles in each ovary measuring 2–9 mm)(4). Varying by body mass index, 50% to 95% of women with PCOS have insulin resistance, which is the major risk factor for the development of type 2 diabetes mellitus (T2DM) (5,6). A recent ten-year retrospective study showed that the incidence of T2DM was about 6.25/1000-person years in women with PCOS as compared to 1.49 in control groups (7).

However, there is no consensus on which tool/method and whether to use selective or universal screening for T2DM in women with PCOS. Although the prevalence of T2DM varies depending on different risk factors (8), the Australian PCOS diagnosis and management guideline, Endocrine Society and Androgen Excess, and Polycystic Ovary Syndrome Society recommend universal screening (9–11). However, others recommend T2DM screening in those women with PCOS having at least one risk factor, such as a family history of T2DM/GDM, age >40 years, and/or obesity (12,13). In addition, there is no agreement among experts on whether fasting plasma glucose (FPG), oral glucose tolerance test (OGTT), or glycated haemoglobin (HbA1c) is the best laboratory method to use for the diagnosis of T2DM (14,15). Although OGTT is still considered the gold standard to diagnose T2DM; it is complex, time-consuming and expensive (16,17).

Key findings of the review

A systematic review was conducted by searching four databases (OVID Medline, Ovid Embase classic, ALL EMB and APA PsycInfo. The systematic review retrieved 6 eligible publications. Standard study characteristics and quality appraisal templates were used to assess the risk of bias and applicability of the studies.

This systematic review indicates that all retrieved articles recommend OGTT for the diagnosis of glucose abnormalities including T2DM for women with PCOS rather than FPG and HbA1c. A cross-sectional study conducted by Altemimi 2021 in premenopausal women with PCOS in Iraq recommends that glycaemic disorders including T2DM should be screened by 2-h OGTT regardless of risk factors like BMI or family history of diabetes mellitus (18). The pros of OGTT in the diagnosis of T2DM were also supported by the remaining five studies (15,19–22). However, our review also found that none of the studies support the recommendation that FPG or HbA1c can be used for the screening of prediabetes or diabetes in women with PCOS, since haemoglobin A1c is found to be a relatively poor diagnostic marker (15,18,20) and FPG is less accurate in predicting IGT and diabetes in these women (19,20). However, their combination was thought to reduce the misdiagnosis to some degree (22).

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1. SELECTION CRITERIA

Table 1. PICO Criteria for Inclusion – Not to be adapted To be used by evidence team to decide which studies will be included when screening search results.	
Question	1.9.1) In women with PCOS, what is the most effective test/method to diagnose type 2 diabetes?
Clinical leads (key contacts)	Prof Ronald Ma Endocrinologist Chinese University of Hong Kong rcwma@cuhk.edu.hk
Allocation ranking	Level 2 - updated systematic review

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(language, year)*
Inclusion	Females of any age, ethnicity, weight or phenotype of PCOS (diagnosed by Rotterdam,NIH or AES). Note studies that include women taking metformin and prefermin of 3 months without metformin.	Observed onset of type 2 diabetes (diagnosis method must be reported) using relevant risk assessment methods, including: FBG/FPG and OGTT (2 hour), HOMA-IR, HbA1c, Fasting Insulin, Glucose stimulated insulin, Waist circumference, WHR, BMI, Framingham risk score, Obesity, Family history, Previous GDM, Ethnicity, Rotterdam phenotype	Placebo usual care or comparison of different relevant risk assessment methods.	Observed onset of type two diabetes-defined as a type 2 diabetes defined by NHMRC type 2 diabetes case detection and diagnosis. Sensitivity and specificity data, and AUC data will be collected.	Evidence based guidelines, systematic reviews,health technology assessments, RCTs, and comparative cohort studies. (can include cross sectional or case control if it compares onset if type 2 diabetes in PCOS and non-PCOS)	
Exclusion	Females without diagnosed PCOS, Females with history of type 2 diabetes	Placebo, Usual care	The assessment method used for the intervention	None	Non-evidence-based guidelines, non-systematic reviews, non-comparative cohort studies, case control studies, case series, editorials, letters, commentaries	

2. SEARCH STRATEGY

Table 2.1. Search details

Search strategy source: *[enter doi or 2018 technical report page number where search string was derived]*

Evidence source	Date of search
Medline (Ovid)	July 1, 2022
PsychInfo (Ovid)	July 1, 2022
EMBASE (Ovid)	July 1, 2022
All EBM (Ovid)	July 1, 2022
CINAHL	July 1, 2022
Any subsequent updates - enter database and date:	

Table 2.2. Questions addressed by this search *(add more rows as needed)*:

GDG	Q#	Question
1	1.9.2	In women with PCOS, what is the most effective test/method to diagnose type 2 diabetes?

Table 2.3. Search strings used in OVID or other database/s

OVID Medline, All EBM, PsychInfo, EMBASE	CINAHL	Other
OVID Medline: 73 Ovid Embase classic: 271 ALLEMB Results: 62 APA PsycInfo: 3	*CINHAL Plus: 357*	Manual searching: 4

Database:
Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to June 30, 2022>

#	Query	Results from 2 Jul 2022
1	exp Polycystic Ovary Syndrome/	16,820
2	polycystic ovar$.mp.	22,317
3	poly-cystic ovar$.mp.	52
4	PCO$.mp.	35,945
5	(stein-leventhal or leventhal).mp.	914
6	exp Anovulation/	2,265
7	anovulat$.mp.	6,748
8	oligo-ovulat$.mp.	108
9	oligoovulat$.mp.	61
10	(ovar$ adj5 (scelerocystic or polycystic or poly-cystic or degenerat$ or hyperandrogen$ or hyper-androgen$)).mp.	23,261
11	or/1-10	49,448
12	(decision aid$ or decision tool).tw.	4,545
13	tool$.tw.	887,689
14	rule$.tw.	182,193
15	measure$.tw.	3,718,362
16	model.tw.	2,463,204
17	assess$.tw.	3,493,311

18	calculat$.tw.	1,019,554
19	class$.tw.	1,573,846
20	(estimate$ or estimation$).tw.	1,204,042
21	equation$.tw.	208,674
22	(score$ or scoring).tw.	1,179,101
23	algorithm$.tw.	315,833
24	chart$.tw.	120,918
25	table$.tw.	145,866
26	tabulat$.tw.	16,607
27	test$.tw.	3,631,867
28	screen$.tw.	885,947
29	checklist.tw.	44,423
30	check-list.tw.	3,038
31	checksheet.tw.	9
32	check-sheet.tw.	62
33	ticklist.tw.	1
34	tick-list.tw.	13
35	instrument.tw.	133,535
36	or/12-35	12,881,850
37	exp Risk Assessment/	304,435
38	exp Risk/	1,345,719
39	risk$.tw.	2,653,508
40	chance$.tw.	95,214
41	likelihood.tw.	168,746
42	potential.tw.	2,655,972
43	probabilit$.tw.	239,841
44	possib$.tw.	2,082,841
45	prognosis.tw.	461,643
46	inciden$.tw.	1,007,169
47	or/37-46	8,032,525
48	exp Coronary Disease/	231,023
49	exp Cerebrovascular Disorders/	410,602
50	exp Cardiovascular Diseases/	2,629,855
51	exp Atherosclerosis/	52,415
52	heart attack$.tw.	6,108
53	stroke$.tw.	288,529
54	myocardial infarction.tw.	196,733
55	cerebral vascular accident.mp.	638
56	coronary vascular accident.mp.	0
57	(coronary adj (event$ or disease or heart disease or mortality)).mp.	146,264
58	coronary thrombosis.mp.	9,459
59	coronary atherosclerosis.mp.	8,534
60	(cardiovascular adj (event$ or mortality)).mp.	58,293
61	CAD.mp.	47,152
62	CVD.mp.	45,083
63	exp Diabetes Mellitus/	482,623
64	diabet$.tw.	718,718
65	IDDM.tw.	6,879
66	NIDDM.tw.	6,953
67	MODY.tw.	1,442
68	(late onset adj diabet$).tw.	125
69	(maturity onset adj diabet$).tw.	2,207
70	(non insulin$ depend$ or non-insulin$ depend$ or noninsulin$ depend$ or non insulin?depend$ or noninsulin?depend$).tw.	12,396
71	(insulin$ depend$ or insulin-depend$ or insulin?depend$).tw.	29,959
72	(typ$ 2 adj6 diabet$).tw.	161,945
73	(typ$ II adj6 diabet$).tw.	12,095

74	T2DM.tw.	27,712
75	DM2.tw.	2,403
76	or/48-75	3,371,570
77	(sensitiv: or predictive value:).mp. or accurac:.tw. or specificit$.tw.	2,668,074
78	11 and 36 and 47 and 76 and 77	445
79	limit 78 to (human and english language and yr="2017 -Current")	89
80	limit 78 to (english language and humans and yr="2017 - 2022")	89
81	or/63-75	785,762
82	11 and 36 and 47 and 81 and 77	267
83	limit 82 to (english language and yr="2017 - 2022")	73

Database:
Embase Classic+Embase <1947 to 2022 June 30>

#	Query	Results from 2 Jul 2022
1	exp Polycystic Ovary Syndrome/	33,351
2	polycystic ovar$.mp.	28,651
3	poly-cystic ovar$.mp.	208
4	PCO$.mp.	53,392
5	(stein-leventhal or leventhal).mp.	1,520
6	exp Anovulation/	6,675
7	anovulat$.mp.	11,123
8	oligo-ovulat$.mp.	153
9	oligoovulat$.mp.	120
10	(ovar$ adj5 (scelerocystic or polycystic or poly-cystic or degenerat$ or hyperandrogen$ or hyper-androgen$)).mp.	37,989
11	or/1-10	78,148
12	(decision aid$ or decision tool).tw.	6,428
13	tool$.tw.	1,184,569
14	rule$.tw.	254,750
15	measure$.tw.	4,932,907
16	model.tw.	3,121,707
17	assess$.tw.	4,993,336
18	calculat$.tw.	1,389,962
19	class$.tw.	2,142,833
20	(estimate$ or estimation$).tw.	1,628,418
21	equation$.tw.	247,494
22	(score$ or scoring).tw.	1,836,840
23	algorithm$.tw.	401,453
24	chart$.tw.	223,816
25	table$.tw.	594,751
26	tabulat$.tw.	28,939
27	test$.tw.	5,158,339
28	screen$.tw.	1,252,962
29	checklist.tw.	59,387
30	check-list.tw.	4,759
31	checksheet.tw.	13
32	check-sheet.tw.	95
33	ticklist.tw.	3
34	tick-list.tw.	24
35	instrument.tw.	179,591
36	or/12-35	17,241,999
37	exp Risk Assessment/	672,090
38	exp Risk/	2,866,864
39	risk$.tw.	3,850,523
40	chance$.tw.	148,741
41	likelihood.tw.	223,539

42	potential.tw.	3,325,654
43	probabilit$.tw.	316,244
44	possib$.tw.	2,851,899
45	prognosis.tw.	716,652
46	inciden$.tw.	1,517,320
47	or/37-46	11,062,649
48	exp Coronary Disease/	384,232
49	exp Cerebrovascular Disorders/	771,305
50	exp Cardiovascular Diseases/	4,989,083
51	exp Atherosclerosis/	253,710
52	heart attack$.tw.	9,145
53	stroke$.tw.	464,970
54	myocardial infarction.tw.	305,567
55	cerebral vascular accident.mp.	1,214
56	coronary vascular accident.mp.	3
57	(coronary adj (event$ or disease or heart disease or mortality)).mp.	40,864
58	coronary thrombosis.mp.	3,354
59	coronary atherosclerosis.mp.	13,316
60	(cardiovascular adj (event$ or mortality)).mp.	134,330
61	CAD.mp.	80,866
62	CVD.mp.	70,157
63	exp Diabetes Mellitus/	1,161,973
64	diabet$.tw.	1,118,697
65	IDDM.tw.	7,943
66	NIDDM.tw.	8,072
67	MODY.tw.	2,512
68	(late onset adj diabet$).tw.	182
69	(maturity onset adj diabet$).tw.	3,348
70	(non insulin$ depend$ or non-insulin$ depend$ or noninsulin$ depend$ or non insulin?depend$ or noninsulin?depend$).tw.	14,613
71	(insulin$ depend$ or insulin-depend$ or insulin?depend$).tw.	36,531
72	(typ$ 2 adj6 diabet$).tw.	248,459
73	(typ$ II adj6 diabet$).tw.	19,652
74	T2DM.tw.	47,372
75	DM2.tw.	4,705
76	or/48-75	5,947,599
77	(sensitiv: or predictive value:).mp. or accurac:.tw. or specificit$.tw.	3,334,913
78	11 and 36 and 47 and 76 and 77	1,064
79	limit 78 to (human and english language and yr="2017 -Current")	390
80	limit 78 to (english language and humans and yr="2017 - 2022")	390
81	or/63-75	1,368,424
82	11 and 36 and 47 and 81 and 77	674
83	limit 82 to (english language and yr="2017 - 2022")	271

Database:
EBM Reviews - Cochrane Database of Systematic Reviews <2005 to June 29, 2022>
EBM Reviews - ACP Journal Club <1991 to June 2022>
EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016>
EBM Reviews - Cochrane Clinical Answers <June 2022>
EBM Reviews - Cochrane Central Register of Controlled Trials <May 2022>
EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012>
EBM Reviews - Health Technology Assessment <4th Quarter 2016>
EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>

#	Query	Results from 2 Jul 2022
1	exp Polycystic Ovary Syndrome/	1,697

2	polycystic ovar$.mp.	4,598
3	poly-cystic ovar$.mp.	132
4	PCO$.mp.	6,171
5	(stein-leventhal or leventhal).mp.	98
6	exp Anovulation/	154
7	anovulat$.mp.	1,175
8	oligo-ovulat$.mp.	55
9	oligoovulat$.mp.	31
10	(ovar$ adj5 (scelerocystic or polycystic or poly-cystic or degenerat$ or hyperandrogen$ or hyper-androgen$)).mp.	4,791
11	or/1-10	8,115
12	(decision aid$ or decision tool).tw.	1,919
13	tool$.tw.	52,170
14	rule$.tw.	14,962
15	measure$.tw.	520,519
16	model.tw.	113,223
17	assess$.tw.	595,770
18	calculat$.tw.	102,538
19	class$.tw.	127,387
20	(estimate$ or estimation$).tw.	117,524
21	equation$.tw.	9,696
22	(score$ or scoring).tw.	317,651
23	algorithm$.tw.	16,076
24	chart$.tw.	12,842
25	table$.tw.	107,543
26	tabulat$.tw.	3,648
27	test$.tw.	420,757
28	screen$.tw.	100,506
29	checklist.tw.	10,711
30	check-list.tw.	1,182
31	checksheet.tw.	2
32	check-sheet.tw.	19
33	ticklist.tw.	0
34	tick-list.tw.	7
35	instrument.tw.	14,712
36	or/12-35	1,256,988
37	exp Risk Assessment/	10,244
38	exp Risk/	42,256
39	risk$.tw.	291,774
40	chance$.tw.	16,168
41	likelihood.tw.	17,640
42	potential.tw.	142,814
43	probabilit$.tw.	24,547
44	possib$.tw.	114,117
45	prognosis.tw.	25,317
46	inciden$.tw.	151,452
47	or/37-46	592,208
48	exp Coronary Disease/	15,347
49	exp Cerebrovascular Disorders/	17,516
50	exp Cardiovascular Diseases/	121,194
51	exp Atherosclerosis/	2,722
52	heart attack$.tw.	1,992
53	stroke$.tw.	65,882
54	myocardial infarction.tw.	36,114
55	cerebral vascular accident.mp.	126
56	coronary vascular accident.mp.	0
57	(coronary adj (event$ or disease or heart disease or mortality)).mp.	12,059

58	coronary thrombosis.mp.	676
59	coronary atherosclerosis.mp.	907
60	(cardiovascular adj (event$ or mortality)).mp.	16,910
61	CAD.mp.	6,375
62	CVD.mp.	6,991
63	exp Diabetes Mellitus/	36,270
64	diabet$.tw.	110,178
65	IDDM.tw.	653
66	NIDDM.tw.	1,196
67	MODY.tw.	91
68	(late onset adj diabet$).tw.	6
69	(maturity onset adj diabet$).tw.	131
70	(non insulin$ depend$ or non-insulin$ depend$ or noninsulin$ depend$ or non insulin?depend$ or noninsulin?depend$).tw.	2,499
71	(insulin$ depend$ or insulin-depend$ or insulin?depend$).tw.	4,018
72	(typ$ 2 adj6 diabet$).tw.	43,224
73	(typ$ II adj6 diabet$).tw.	3,127
74	T2DM.tw.	7,528
75	DM2.tw.	424
76	or/48-75	288,007
77	(sensitiv: or predictive value:).mp. or accurac:.tw. or specificit$.tw.	147,035
78	11 and 36 and 47 and 76 and 77	220
79	limit 78 to (human and english language and yr="2017 -Current") [Limit not valid in CDSR,ACP Journal Club,DARE,CCA,CCTR,CLCMR; records were retained]	78
80	limit 78 to (english language and humans and yr="2017 - 2022") [Limit not valid in CDSR,ACP Journal Club,DARE,CCA,CCTR,CLCMR; records were retained]	78
81	or/63-75	113,084
82	11 and 36 and 47 and 81 and 77	178
83	limit 82 to (english language and yr="2017 - 2022") [Limit not valid in CDSR,ACP Journal Club,DARE,CCA,CLCMR; records were retained]	62

Database:
APA PsycInfo <1806 to June Week 3 2022>

#	Query	Results from 2 Jul 2022
1	exp Polycystic Ovary Syndrome/	0
2	polycystic ovar$.mp.	519
3	poly-cystic ovar$.mp.	1
4	PCO$.mp.	1,113
5	(stein-leventhal or leventhal).mp.	317
6	exp Anovulation/	0
7	anovulat$.mp.	161
8	oligo-ovulat$.mp.	0
9	oligoovulat$.mp.	0
10	(ovar$ adj5 (scelerocystic or polycystic or poly-cystic or degenerat$ or hyperandrogen$ or hyper-androgen$)).mp.	538
11	or/1-10	1,763
12	(decision aid$ or decision tool).tw.	1,701
13	tool$.tw.	178,539
14	rule$.tw.	67,515
15	measure$.tw.	838,837
16	model.tw.	574,771
17	assess$.tw.	856,935
18	calculat$.tw.	67,751
19	class$.tw.	418,371
20	(estimate$ or estimation$).tw.	170,369

21	equation$.tw.	59,007
22	(score$ or scoring).tw.	386,774
23	algorithm$.tw.	37,823
24	chart$.tw.	22,939
25	table$.tw.	37,356
26	tabulat$.tw.	3,792
27	test$.tw.	895,060
28	screen$.tw.	113,025
29	checklist.tw.	29,785
30	check-list.tw.	4,174
31	checksheet.tw.	9
32	check-sheet.tw.	26
33	ticklist.tw.	0
34	tick-list.tw.	2
35	instrument.tw.	74,224
36	or/12-35	2,769,408
37	exp Risk Assessment/	14,907
38	exp Risk/	0
39	risk$.tw.	448,831
40	chance$.tw.	32,656
41	likelihood.tw.	59,091
42	potential.tw.	367,942
43	probabilit$.tw.	60,565
44	possib$.tw.	385,800
45	prognosis.tw.	21,088
46	inciden$.tw.	89,558
47	or/37-46	1,240,325
48	exp Coronary Disease/	0
49	exp Cerebrovascular Disorders/	30,844
50	exp Cardiovascular Diseases/	0
51	exp Atherosclerosis/	1,153
52	heart attack$.tw.	1,123
53	stroke$.tw.	38,670
54	myocardial infarction.tw.	4,502
55	cerebral vascular accident.mp.	169
56	coronary vascular accident.mp.	0
57	(coronary adj (event$ or disease or heart disease or mortality)).mp.	3,032
58	coronary thrombosis.mp.	39
59	coronary atherosclerosis.mp.	111
60	(cardiovascular adj (event$ or mortality)).mp.	1,533
61	CAD.mp.	1,389
62	CVD.mp.	3,270
63	exp Diabetes Mellitus/	9,634
64	diabet$.tw.	35,229
65	IDDM.tw.	251
66	NIDDM.tw.	100
67	MODY.tw.	36
68	(late onset adj diabet$).tw.	5
69	(maturity onset adj diabet$).tw.	12
70	(non insulin$ depend$ or non-insulin$ depend$ or noninsulin$ depend$ or non insulin?depend$ or noninsulin?depend$).tw.	291
71	(insulin$ depend$ or insulin-depend$ or insulin?depend$).tw.	1,099
72	(typ$ 2 adj6 diabet$).tw.	8,516
73	(typ$ II adj6 diabet$).tw.	864
74	T2DM.tw.	1,264
75	DM2.tw.	159
76	or/48-75	89,965

77	(sensitiv: or predictive value:).mp. or accurac:.tw. or specificit$.tw.	314,565
78	11 and 36 and 47 and 76 and 77	11
79	limit 78 to (human and english language and yr="2017 -Current")	3
80	limit 78 to (english language and humans and yr="2017 - 2022") [Limit not valid in APA PsycInfo; records were retained]	3
81	or/63-75	35,894
82	11 and 36 and 47 and 81 and 77	8
83	limit 82 to (english language and yr="2017 - 2022")	3

CINHAL CINAHL Plus

Search Terms	Actions	
S90	S28 and S47 and S57 and S89	(357)
S89	S76 or S88	(940,899)
S88	S77 or S78 or S79 or S80 or S81 or S82 or S83 or S84 or S85 or S86 or S87	(277,628)
S87	DM2	(521)
S86	T2DM	(8,007)
S85	type II diabet*	(2,628)
S84	type 2 diabet*	(89,057)
S83	maturity onset diab*	(506)
S82	late onset diab*	(111)
S81	MODY	(1,193)
S80	NIDDM	(1,323)
S79	IDDM	(1,193)
S78	diabet*	(275,364)
S77	(MH "Diabetes Mellitus+") or (MH "Diabetes Mellitus, Gestational") or (MH "Diabetes Mellitus, Insulin-Dependent") or (MH "Diabetes Mellitus, Non-Insulin- Dependent")	(187,581)
S76	S58 or S59 or S60 or S61 or S62 or S63 or S64 or S65 or S66 or S67 or S68 or S69 or S70 or S71 or S72 or S73 or S74 or S75	(741,986)
S75	cvd	(15,537)
S74	cad	(11,424)
S73	cardiovascular mortality	(20,483)
S72	cardiovascular event*	(17,834)
S71	coronary atherosclerosis	(2,720)
S70	coronary thrombosis	(2,491)
S69	coronary mortality	(8,999)
S68	heart disease	(67,478)
S67	coronary event*	(5,112)
S66	coronary vascular accident	(4)
S65	cerebral vascular accident	(317)
S64	myocardial infarction	(71,620)
S63	stroke*	(140,219)
S62	heart attack*	(4,720)
S61	(MH "Atherosclerosis")	(10,760)
S60	(MH "Cardiovascular Abnormalities+") or (MH "Cardiovascular Diseases+")	(669,662)

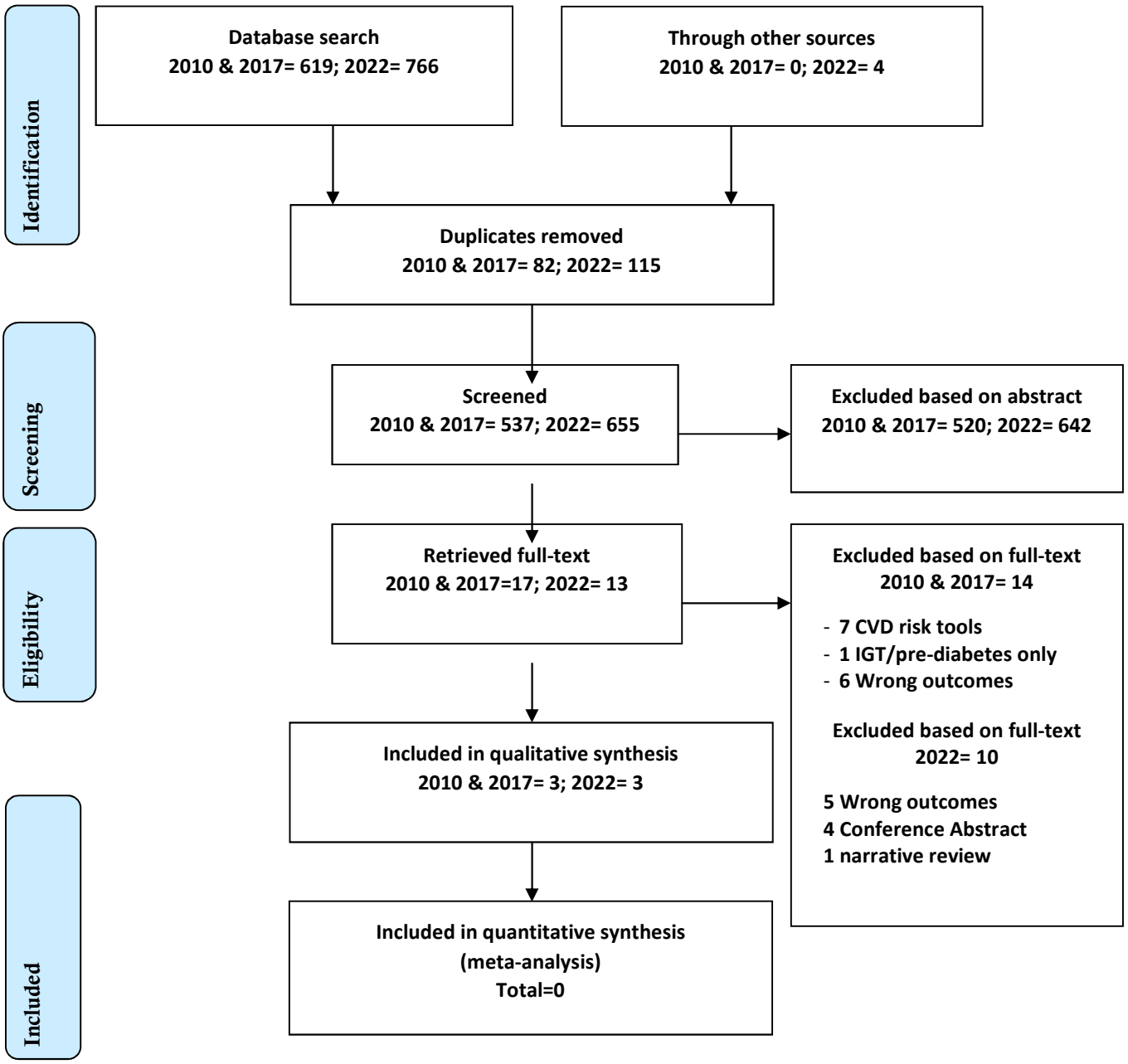
S59	(MH "Coronary Disease+") or (MH"Myocardial Infarction+") or (MH "Coronary Arteriosclerosis+")	(101,181)
S58	(MH "Cerebrovascular Disorders+")	(124,534)
S57	S48 or S49 or S50 or S51 or S52 or S53 or S54 or S55 or S56	(1,943,399)
S56	inciden*	(277,510)
S55	prognosis	(181,582)
S54	possib*	(288,911)
S53	probabilit*	(74,015)
S52	potential	(440,565)
S51	likelihood	(55,891)
S50	chance*	(27,789)
S49	risk*	(1,129,587)
S48	("risk assessment") or (MH "Risk Assessment")	(145,098)
S47	S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46	(11,562)
S46	ovar* N5 sclerocystic or ovar* N5 polycystic or ovar* N5 poly-cystic or ovar* N5 degenerat* or ovar* N5 hyperandrogen* or ovar* N5 hyperandrogen*	(6,086)
S45	oligoovulat*	(15)
S44	oligo-ovulat*	(10)
S43	SU anovulation	(367)
S42	SU ovarian cysts	(1,066)
S41	stein-leventhal or leventhal	(1,306)
S40	PCO*	(6,094)
S39	poly-cystic ovar*	(28)
S38	polycystic ovar*	(5,999)
S37	SU polycystic ovary syndrome	(4,696)
S36	S29 or S30 or S31 or S32 or S33 or S34 or S35	(280,196)
S35	likelihood ratio*	(6,611)
S34	predictive value*	(78,742)
S33	post-test probability	(300)
S32	(pre-test or pretest) and probability	(1,529)
S31	specificity	(131,827)
S30	sensitivity	(215,340)
S29	(MH "Sensitivity and Specificity")	(91,891)
S28	S19 or S27	(3,347,222)
S27	S20 or S21 or S24 or S25 or S26	(222,402)
S26	check sheet	(49)
S25	check sheet	(49)
S24	tick-list	(12)
S23	ticklist	(0)
S22	ticklist	(0)
S21	checklist	(49,875)
S20	instrument*	(177,688)

S19	(S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18)	(3,319,730)
S18	("checklist") or (MH "Checklists")	(48,347)
S17	screen*	(253,790)
S16	test*	(1,236,798)
S15	tabulat*	(4,927)
S14	table*	(48,800)
S13	chart*	(52,892)
S12	algorithm*	(70,357)
S11	score* or scoring	(419,572)
S10	equation*	(40,339)
S9	estimate* or estimation*	(248,150)
S8	("calculat*") or (MH "Algorithms")	(221,907)
S7	assess*	(1,345,353)
S6	"measure*"	(960,796)
S5	"class*"	(419,009)
S4	"model"	(444,648)
S3	"rule"	(20,475)
S2	("tool") or (MH "Clinical Assessment Tools+")	(409,482)
S1	(("decision") or (MH "Decision Making, Clinical")) or decision tool or decision aid	(217,720)

Evidence processing: Studies were selected and appraised by two reviewer/s in consultation with the evidence team/ key contact using study selection and appraisal criteria (PICO above) established a priori. The articles were reviewed by title and abstract by two reviewers. When a decision could not be made based on title and abstract alone, full text was retrieved. **Six studies met inclusion criteria for this review.**

3. SEARCH RESULTS - PRISMA flowchart

PRISMA flowchart



4. STUDY INCLUSION

Table 4.1. Included Studies (full citation with doi)

1. Altemimi MT, Musa AK, Mansour AA. The Performance of Glycated Hemoglobin vs. Oral Glucose Tolerance Test in the Diagnosis of Glycemic Disorders among Women with Polycystic Ovary Syndrome in Southern Iraq. The Indonesian Biomedical Journal. 2021 Jun 14;13(2):178-85.
2. Ortiz-Flores AE, Luque-Ramírez M, Fernández-Durán E, Alvarez-Blasco F, Escobar-Morreale HF. Diagnosis of disorders of glucose tolerance in women with polycystic ovary syndrome (PCOS) at a tertiary care center: fasting plasma glucose or oral glucose tolerance test? Metabolism. 2019 Apr;93:86-92. doi: 10.1016/j.metabol.2019.01.015. Epub 2019 Jan 30. PMID: 30710572.
3. Lerchbaum E, Schwetz V, Giuliani A, Obermayer-Pietsch B. Assessment of glucose metabolism in polycystic ovary syndrome: HbA1c or fasting glucose compared with the oral glucose tolerance test as a screening method. Human Reproduction. 2013 Sep 1;28(9):2537-44.
4. Li HW, Lam KS, Tam S, Lee VC, Yeung TW, Cheung PT, Yeung WS, Ho PC, Ng EH Screening for dysglycaemia by oral glucose tolerance test should be recommended in all women with polycystic ovary syndrome. Human Reproduction. 2015 Sep 1;30(9):2178-83.
5. Magnussen LV, Mumm H, Andersen M, Glintborg D. Hemoglobin A1c as a tool for the diagnosis of type 2 diabetes in 208 premenopausal women with polycystic ovary syndrome. Fertility and sterility. 2011 Nov 1;96(5):1275-80.
6. Zhen Y, Yang P, Dong R, Wu Y, Sang Y, Du X, Wang Y, Song Q, Yu L, Rao X. Effect of HbA1C detection on the diagnostic screening for glucose metabolic disorders in polycystic ovary syndrome. Clinical and Experimental Obstetrics & Gynecology. 2014 Feb 10;41(1):58-61.

Table 4.2. Excluded Studies (on full text assessment)

Reference	Reason
Sagili et al. 2020	Wrong outcomes
Zhao et al. 2021	Wrong outcomes
Kravitz et al. 2021	Conference Abstract
Cree-Green et al. 2018	Wrong outcomes
de Mola et al. 2020	Conference Abstract
Essah et al. 2006	Wrong outcomes
Crespo et al. 2018	Conference Abstract
Liu et al. 2021	Wrong outcomes
Cree-Green et al. 2017	Conference Abstract
Andersen 2018	Narrative review

5. STUDY CHARACTERISTICS TABLE

Author, year, country	Population/ Setting	Study Design	Sample Size per group	Methods/tools used	Outcomes	Summary of findings
Altemimi 2021	Premenopausal women with PCOS, in Faiha Specialized Diabetes, Endocrine, and Metabolism Center (FDEMC), University of Basrah, Iraq	Cross sectional	129 Premenopausal women with PCOS	2-h OGTT HbA1c test FPG	Glycaemic disorders (IGT, prediabetes, T2D, FPG)	Screening of glycaemic disorders is crucial for PCOS by using 2-h OGTT regardless of risk factor and HbA1c seems to be an unsatisfactory screening tool to predict glycaemic disorders in women with PCOS
Lerchbaum 2013	Women with PCOS, in Medical University of Graz, Austria	Cross sectional	671 women with PCOS	2-h OGTT HbA1c test FPG	Glucose metabolism (prediabetes, T2D)	Our findings do not support the recommendation that FG or HbA1c can be used for the screening of prediabetes in women with PCOS. For such women, OGTT should be performed for screening of prediabetes.
Li 2015	Women with (PCOS), Family Planning Association of Hong Kong and the Department of Obstetrics and Gynaecology, Queen Mary Hospital	Cross sectional	467 women with PCOS	OGTT FPG	Dysglycemia	A full OGTT should be recommended as the screening method for dysglycaemia in women with PCOS, regardless of BMI or family history of diabetes mellitus (DM)
Magnussen 2011	Premenopausal women with PCOS, Odense University Hospital, Odense, Denmark	Retrospective observational study	208 premenopausal women with PCOS	2h OGTT HbA1c	IGT, T2D	Haemoglobin A1c is a relatively poor diagnostic marker
Ortiz-Flores_2019	Women with PCOS, in Hospital Universitario Ramón y Cajal, Spin	Retrospective observational study	400 women with PCOS	OGTT FPG	Dysglycemia (IFG), Diabetes	An OGTT is the most accurate method for the diagnosis of disorders of glucose tolerance in women with PCOS at the clinical setting. FPG, on the contrary, is less accurate in predicting IGT and diabetes in these women
Zhen 2014	Women with PCOS in the Fifth Affiliated Hospital of Zhengzhou	Cross sectional	161 women with PCOS	OGTT HbA1c	Prediabetes (IGT), DM	Overall, FPG or HbA1C were not the perfect indicator for screening abnormal glucose metabolism. However, their combination may reduce the misdiagnosis rate of glucose metabolic disorders to some extent. High-risk groups may still need to be subjected to OGTT to confirm the diagnosis

6. DATA EXTRACTION TABLES

INDEX TEST:						OUTCOME TYPE: Binary (Yes/No)								
COMPARISON (if applicable):														
Author, year	Unit of outcome	Method of measurement	N(sample size)	Outcome	n(outcome)	Threshold cut-off	TP	FP	TN	FN	Sensitivity (95% CI)	Specificity (95%CI)	AUC	Precision
Altemimi et al. 2021	Count	2-h OGTT	129	IGT	21	140-199 mg/dL (7.8-11.0 mmol/L)								
			129	T2D	3	≥200 mg/dL (11.1 mmol/L)								
		HbA1c test	129	prediabetes	25	5.55% (37.2 mmol/mol)					56.5%	74.3%	0.645	
			129	T2D	1	≥6.5% (48 mmol/mol)								
		FPG	129	FPG	34	100-125 mg/dL (5.6-6.9 mmol/L)								
			129	T2D	2	≥126 mg/dL (7 mmol/L)								
Lerchbaum 2013	Count	2-h OGTT	671	prediabetes	76(12.8%)	140 mg/ dl-199 mg/dl								
				T2DM	9(1.5%)	≥ 200 mg/dl								
		HbA1c test	671	prediabetes	19(3.2%)	5.7 –6.4%					25.0%	100%		
				T2DM	6(0.9%)	≥6.5%					66.70%	100%		
		FPG	671	prediabetes	31(5.2%)	100–125 mg/dl					40.8%	100.00%		
				T2DM	7(1%)	≥126 mg/dl					66.70%	100%		
Li 2015	Count	OGTT	467	Dysglycemia	58 (12.4%)	≥ 7.8 mmol/l								
			467	Prediabetes	46 (9.8%)	7.8 -11.1 mmol/l								
				Diabetes	12	≥11.1 mmol/l								
		FPG	467	Prediabetes	21	5.6 -7 mmol/l					45.7			
			467	Diabetes	11	≥ 7 mmol/l					87.5			
Mognussen 2011	Count	2h OGTT	208	IGT	36(17.31%)	7.8–11.0 mmol/L								
			208	T2D	20(9.61%)	> 11.1 mmol/L								
		HbA1c	208	IGT	10(4.80%)	6–6.5%					99%			
			208	T2D	8(3.84%)	> 6.5%					35%			
Ortiz-Flores_2019	Count	OGTT	400	Dysglycemia (IFG)	98(24.5%)	≥ 7.8 mmol/l							0.91	
			400	Diabetes	10	≥ 11.1 mmol/l								

		FPG	400	Dysglycemia (IFG)	57 (14.3%)	≥ 5.6 mmol/l							0.86	
			400	Diabetes	0	≥ 7 mmol/l								
Zhen 2014	Count	OGTT	161	Pre-diabetes(IGT)	12(7.5%)	7.8-11.0 mmol/l								
			161	DM	9(5.6%)	≥ 11.1 mmol/l								
		HbA1c	161	pre-diabetes	17(10.6%)	5.7% - 6.4%					76.7	89.5	0.968	
			161	DM	7 (4.3%)	≥ 6.5%.								

7. QUALITY APPRAISAL SUMMARY TABLE

Study id	Study country	External validity	Internal validity						
			Patient selection/spectrum bias	Classification/ verification/ incorporation/ review bias	Detection bias	Attrition bias	Report bias	Other issues – applicability/ comparability/ variation	What is the overall risk of bias?
Altemimi 2021	Iraq	High	High	High	Low	NA	Low	High	High
Lerchbaum 2013	Austria	High	Low	High	Low	NA	Low	Medium	High
Li 2015	China	High	Medium	Medium	NR	NA	Low	Medium	Medium
Magnussen 2011	Denmark	High	Medium	High	NR	NA	Low	Medium	High
Ortiz-Flores_2019	Spain	High	Medium	Medium	NR	NA	Low	High	High
Zhen 2014	China	High	High	High	NR	NA	low	High	High

NB: External validity – is this study and its results generalizable to my systematic review question? Internal validity – has this study been conducted rigorously in order to reduce bias?

8. GRADE ASSESSMENTS

Comparison of: OGTT, FGT, HbA1c								
Outcome: T2D								
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Favours	Certainty	Importance
6	Cross sectional and retrospective observational study	Very serious	No serious inconsistencies	No serious inconsistencies	No serious inconsistencies	OGTT	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Dysglycemia (IFG)								
6	Cross sectional and retrospective observational study	Very serious	No serious inconsistencies	No serious inconsistencies	No serious inconsistencies	OGTT	⊕◯◯◯ VERY LOW	CRITICAL

APPENDIX. QUALITY APPRAISAL

Study ID	***Altemimi 2021***	
Study Citation	***Altemimi MT, Musa AK, Mansour AA. The Performance of Glycated Hemoglobin vs. Oral Glucose Tolerance Test in the Diagnosis of Glycemic Disorders among Women with Polycystic Ovary Syndrome in Southern Iraq. The Indonesian Biomedical Journal. 2021 Jun 14;13(2):178-85.***	
Study Country	**Iraq**	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	**A cross sectional study was carried out in on 129 *premenopausal women who were diagnosed with PCOS***	
PCOS diagnostic criteria	***Rotterdam***	
N per group	***PCOS: 129***	
Setting	***Faiha Specialized Diabetes, Endocrine, and Metabolism Center (FDEMC), University of Basrah, Iraq, during September 2019 to September 2020***	
Index test	***2-h OGTT, HbA1c test, FPG, fasting insulin***	
Reference Standard	***ADA criteria***	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	***Accuracy (comparison with the reference standard test) - Sensitivity and specificity, Likelihood ratios, Area under the ROC curve***	
Inclusion and exclusion criteria reported?	**Yes Partial No Not reported**	***Yes***
Does the study have a clearly focused question?	**Yes Partial No Not reported**	***Yes***
Summary Result/s	**The result of 2-h OGTT test showed that there were 21 subjects (16.1%) showed to have IGT. The result of HbA1c test showed that 25 subjects (19.4%) were diagonised with prediabetes. Meanwhile FPG test result showed that 34 subjects (26.4%) were having IFG (Table 2). Fourteen subjects (66.7%) of truly IGT were misdiagnosed as normal glycemic state by HbA1c test and 17 subjects (16%) were misinterpreted to be prediabetes by HbA1c test despite they had normal glycemic state by 2-h OGTT. The comparison between 2-h OGTT and HbA1c tests showed a significance difference (p=0.021), so does the comparison between 2-h OGTT and FPG tests (p<0.001). *Prediabetes was diagnosed by either HbA1c or FPG in around one-fifth of women diagnosed with PCOS which was higher than that detected by 2-h OGTT, but more than half of prediabetes were having a normal glucose status by 2 h OGTT and around two-third of women with IGT were misinterpreted as normal glucose by HbA1c. The pattern of strikethrough diabetes and prediabetes diagnosis in this study by HbA1c might underestimate T2DM and overestimate prediabetes among women with PCOS.* These findings suggest that FPG could be a weak tool to screen for dysglycemia in women with PCOS.**	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

PATIENT SELECTION/SPECTRUM BIAS	**Was the spectrum of patients representative of the patients who will receive the test in practice?**	**Yes Partial No Not reported**	***Yes***
	Was a consecutive or random sample of patients enrolled? (Q-2)	**Yes Partial No Not reported**	***No***
	Was a case-control design avoided? (Q-2)	**Yes Partial No Not reported**	***No***
	Did the study avoid inappropriate exclusions? (Q-2)	**Yes Partial No Not reported**	***No***
CLASSIFICATION/ VERIFICATION/ INCORPORATION/ REVIEW BIAS	**Were all participants assessed with both index test and reference standard?**	**Yes Partial No Not reported**	***Yes***
	Did all patients receive the same reference standard? (Q-2)	**Yes Partial No Not reported**	***Yes***
	Is the reference standard likely to correctly classify the target condition? (Q-2)	**Yes Partial No Not reported**	**Partial**
	Was the reference standard independent of the index test (ie. the index test did not form part of the reference standard)?	**Yes Partial No Not reported**	***Yes***
	Were the reference standard results interpreted without knowledge of the results of the index test?	**Yes Partial No Not reported**	***Not reported***
	Were the index test results	**Yes Partial**	***Not reported***

	interpreted without knowledge of the results of the reference standard test?	**No Not reported**	
	If a threshold was used, was it pre-specified?	**Yes Partial No Not reported**	***Yes***
DETECTION BIAS	**Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?**	**Yes Partial No Not reported**	***Yes***
ATTRITION BIAS	**Were withdrawals from the study explained?**	***X% treatment X% control/ comparison***	***NR***
REPORT BIAS	**Were uninterruptable/ intermediate test results reported?**	**Yes Partial No Not reported**	***Yes***
OTHER ISSUES – APPLICABILITY/ COMPARABILITY/ VARIATION	**Was the execution of all tests described in sufficient detail to permit replication of the tests?**	**Yes Partial No Not reported**	***Yes***
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	**Yes Partial No Not reported**	***Not reported***
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	**Yes Partial No Not reported**	***Not reported***
	Were there any conflicts of interest in the writing or funding of this study?	**Yes Partial No Not reported**	***No***

	If statistical analysis was undertaken, was this appropriate?	**Yes** **Partial** **No** **Not reported**	***Partial*** ***the statistical analysis was planned a priori*** ***the data were analysed accordingly to the study protocol.*** ***Not all Diagnostic accuracy and measures of statistical uncertainty (eg. 95%CI) presented:*** ***· Sensitivity and specificity*** ***· Area under the ROC curve***
COMMENTS		***This study aimed to evaluate the performance of HbA1c vs. 2-h OGTT in the diagnosis of glycemic disorders in women with PCOS and to evaluate the correlation between glycemic disorders, insulin resistance, and anthropometric measures of women with PCOS. The results used for this guideline evidence review are secondary aims.***	
What is the overall risk of bias?		***High***	***Few criteria have been fulfilled and the conclusions of the study are likely to be affected.***
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		***No***	

Study ID	***Lerchbaum 2013***	
Study Citation	***Lerchbaum E, Schwetz V, Giuliani A, Obermayer-Pietsch B. Assessment of glucose metabolism in polycystic ovary syndrome: HbA1c or fasting glucose compared with the oral glucose tolerance test as a screening method. Human Reproduction. 2013 Sep 1;28(9):2537-44.***	
Study Country	**Austria**	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	**A cross sectional study was carried out in on 671 *women who were diagnosed with PCOS***	
PCOS diagnostic criteria	***Rotterdam***	
N per group	***PCOS: 671***	
Setting	***The study cohort consisted of 671 women with PCOS, aged 16– 45 years who were routinely referred to our outpatient clinic(*Medical University of Graz*) for PCOS evaluation from 2006 to 2012***	
Index test	***HbA1c test, FPG***	
Reference Standard	***ADA criteria (2-h OGTT)***	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	***Accuracy (comparison with the reference standard test) - Sensitivity and specificity, Likelihood ratios, Area under the ROC curve***	
Inclusion and exclusion criteria reported?	**Yes** **Partial** **No** **Not reported**	***Yes***

Does the study have a clearly focused question?		**Yes Partial No Not reported**	***Yes***
Summary Result/s		**According to the ADA criteria, we found prediabetes and T2DM in 12.8% (n ¼ 76) and 1.5% (n ¼ 9) of PCOS women, respectively. When using elevated HbA1c (5.7 –6.4%) for defining prediabetes, 19 (3.2%) of all PCOS women had prediabetes with a k-index of 0.36. When using elevated FG (100–125 mg/dl) for defining prediabetes, 31 (5.2%) of all the PCOS women were diagnosed with prediabetes with a k-index of 0.05. Further, elevated HbA1c (≥6.5% defining T2DM) was found in six (0.9%) PCOS women (k-index 0.80), and elevated FG (≥126 mg/dl diagnosing T2DM) was found in seven PCOS women (1%; k-index 0.82). Our findings do not support the recommendation that FG or HbA1c can be used for the screening of prediabetes in women with PCOS. For such women, OGTT should be performed for screening of prediabetes.**	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
PATIENT SELECTION/SPECTRUM BIAS	**Was the spectrum of patients representative of the patients who will receive the test in practice?**	**Yes Partial No Not reported**	***Yes***
	Was a consecutive or random sample of patients enrolled? (Q-2)	**Yes Partial No Not reported**	***Yes***
	Was a case-control design avoided? (Q-2)	**Yes Partial No Not reported**	***Yes***
	Did the study avoid inappropriate exclusions? (Q-2)	**Yes Partial No Not reported**	***Yes***
	Were all participants assessed with both index test and reference standard?	**Yes Partial No Not reported**	***Yes***
	Did all patients receive the same reference standard? (Q-2)	**Yes Partial No Not reported**	***Yes***

CLASSIFICATION/ VERIFICATION/ INCORPORATION/ REVIEW BIAS	**Is the reference standard likely to correctly classify the target condition? (Q-2)**	**Yes Partial No Not reported**	**Partial**
	Was the reference standard independent of the index test (ie. the index test did not form part of the reference standard)?	**Yes Partial No Not reported**	***Yes***
	Were the reference standard results interpreted without knowledge of the results of the index test?	**Yes Partial No Not reported**	***Not reported***
	Were the index test results interpreted without knowledge of the results of the reference standard test?	**Yes Partial No Not reported**	***Not reported***
	If a threshold was used, was it pre-specified?	**Yes Partial No Not reported**	***Yes***
DETECTION BIAS	**Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?**	**Yes Partial No Not reported**	***Yes***
ATTRITION BIAS	**Were withdrawals from the study explained?**	***X% treatment X% control/ comparison***	***No***
REPORT BIAS	**Were uninterruptable/ intermediate test results reported?**	**Yes Partial No Not reported**	***Yes***

OTHER ISSUES – APPLICABILITY/ COMPARABILITY/ VARIATION	**Was the execution of all tests described in sufficient detail to permit replication of the tests?**	**Yes Partial No Not reported**	***No***
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	**Yes Partial No Not reported**	***Not reported***
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	**Yes Partial No Not reported**	***Not reported***
	Were there any conflicts of interest in the writing or funding of this study?	**Yes Partial No Not reported**	***No***
	If statistical analysis was undertaken, was this appropriate?	**Yes Partial No Not reported**	***Partial*** ***- if the statistical analysis was planned a priori - if the data were analysed accordingly to the study protocol.*** ***Diagnostic accuracy and measures of statistical uncertainty (eg. 95%CI) presented:*** ***· Sensitivity and specificity*** ***· Area under the ROC curve***
COMMENTS		***The study aimed to examine the utility of HbA1c and FG in estimating the risk of prediabetes and T2DM in a large cohort including 671 PCOS women from Austria diagnosed with the Rotterdam criteria. FG are insufficient screening tools for prediabetes. Further, performing OGTT only in PCOS women with risk factors as suggested by the AES in 2010 was not sufficient in our large PCOS cohort. Our data strongly suggest that OGTTs should be*** **performed in all women with PCOS, which is in line with the 2007 AES recommendation**	
What is the overall risk of bias?		***High***	***Few criteria have been fulfilled and the conclusions of the study are likely to be affected.***
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		***No***	

Study ID	***Li 2015***	
Study Citation	***Li HW, Lam KS, Tam S, Lee VC, Yeung TW, Cheung PT, Yeung WS, Ho PC, Ng EH. Screening for dysglycaemia by oral glucose tolerance test should be recommended in all women with polycystic ovary syndrome. Human Reproduction. 2015 Sep 1;30(9):2178-83.***	
Study Country	**China**	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	**467 Chinese women diagnosed with PCOS during January 2010 to December 2013. They were patients attending the Family Planning Association of Hong Kong and the Department of Obstetrics and Gynaecology, Queen Mary Hospital with symptoms of oligo-amenorrhoea and/or subfertility. They were all non-pregnant at the time of recruitment**	
PCOS diagnostic criteria	***PCOS was diagnosed when two of the following conditions were met: i) clinical hyperandrogenism and/or biochemical hyperandrogenism; ii) chronic oligo- or anovulation; and iii) polycystic ovarian morphology assessed on ultrasound, provided that secondary aetiologies were excluded by appropriate testing, including Cushing disease, thyroid dysfunction, hyperprolactinemia and non-classic congenital adrenal hyperplasia***	
N per group	***PCOS: 400 Control: 147***	
Setting	***The study was done at a university hospital in Hong Kong***	
Index test	***FPG, OGTT***	
Reference Standard	***ADA criteria (2-h OGTT)***	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	***Accuracy (comparison with the reference standard test) - Sensitivity and specificity, Likelihood ratios, Area under the ROC curve***	
Inclusion and exclusion criteria reported?	**Yes Partial No Not reported**	***Yes***
Does the study have a clearly focused question?	**Yes Partial No Not reported**	***Yes***
Summary Result/s	**The OGTT detected dysglycemia in 24.5% of patients, whereas only 14.3% women would have been diagnosed using FPG levels alone. The latter missed as many as 40% of women with dysglycemia in our series, including all cases of diabetes. Diagnostic agreement between both algorithms was only 0.55 (= 0.103; 95% CI: 0.05 – 0.16). Areas under the receiver operating characteristic curve for dysglycemia were 0.86 (95%CI: 0.81 – 0.91) for FPG and 0.91 (95%CI = 0.87 – 0.95) for 120-min plasma glucose during the OGTT. FPG was not accurate in predicting dysglycemia in women with PCOS regardless of the presence of insulin resistance, weight excess, hyperandrogenemia and age.**	

		Principal conclusions: Relying on FPG alone is not adequate for the screening of disorders of glucose tolerance in women with PCOS; such diagnosis should rely on the results of an OGTT regardless of age, weight and/or androgen concentrations.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
PATIENT SELECTION/SPECTRUM BIAS	**Was the spectrum of patients representative of the patients who will receive the test in practice?**	**Yes Partial No Not reported**	***Partial***
	Was a consecutive or random sample of patients enrolled? (Q-2)	**Yes Partial No Not reported**	***Yes***
	Was a case-control design avoided? (Q-2)	**Yes Partial No Not reported**	***Yes***
	Did the study avoid inappropriate exclusions? (Q-2)	**Yes Partial No Not reported**	***Yes***
CLASSIFICATION/ VERIFICATION/ INCORPORATION/ REVIEW BIAS	**Were all participants assessed with both index test and reference standard?**	**Yes Partial No Not reported**	***Yes***
	Did all patients receive the same reference standard? (Q-2)	**Yes Partial No Not reported**	***Yes***
	Is the reference standard likely to correctly classify the target condition? (Q-2)	**Yes Partial No Not reported**	**Partial**
	Was the reference standard independent of the index test (ie. the index test did not form part of the reference standard)?	**Yes Partial No Not reported**	***Yes***

	Were the reference standard results interpreted without knowledge of the results of the index test?	**Yes Partial No Not reported**	***Not reported***
	Were the index test results interpreted without knowledge of the results of the reference standard test?	**Yes Partial No Not reported**	***Not reported***
	If a threshold was used, was it pre-specified?	**Yes Partial No Not reported**	***Yes***
DETECTION BIAS	**Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?**	**Yes Partial No Not reported**	***Not reported***
ATTRITION BIAS	**Were withdrawals from the study explained?**	***X% treatment X% control/ comparison***	***NA***
REPORT BIAS	**Were uninterruptable/ intermediate test results reported?**	**Yes Partial No Not reported**	***Yes***
OTHER ISSUES – APPLICABILITY/	**Was the execution of all tests described in sufficient detail to permit replication of the tests?**	**Yes Partial No Not reported**	***No***
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	**Yes Partial No Not reported**	***Not reported***

	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	**Yes Partial No Not reported**	***Partial***
	Were there any conflicts of interest in the writing or funding of this study?	**Yes Partial No Not reported**	***No***
	If statistical analysis was undertaken, was this appropriate?	**Yes Partial No Not reported**	***Partial*** ***- if the statistical analysis was planned a priori - if the data were analysed accordingly to the study protocol.*** ***Diagnostic accuracy and measures of statistical uncertainty (eg. 95%CI) presented:*** ***· Sensitivity and specificity*** ***· Area under the ROC curve***
COMMENTS		***Primary objective was to establish the diagnostic agreement between the two most commonly used diagnostic algorithms for disordered glucose tolerance in non-pregnant* women with PCOS: i) using FPG alone, or ii) relying on plasma glucose concentrations at fasting and after 120-min of a 75-g OGTT**	
What is the overall risk of bias?		***High***	***Few criteria have been fulfilled and the conclusions of the study are likely to be affected.***
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		***No***	

Study ID	***Mognussen 2011***		
Study Citation	***Magnussen LV, Mumm H, Andersen M, Glintborg D. Hemoglobin A1c as a tool for the diagnosis of type 2 diabetes in 208 premenopausal women with polycystic ovary syndrome. Fertility and sterility. 2011 Nov 1;96(5):1275-80.***		
Study Country	**Denmark**		
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/ participants	**All premenopausal women referred to the outpatient clinic at the Odense University Hospital Department of Endocrinology during 1997–2010 with a diagnosis of PCOS were included**		
PCOS diagnostic criteria	***Rotterdam criteria***		
N per group	***PCOS: 208***		
Setting	***The study was done at a Odense University Hospital in Denmark***		
Index test	***HbA1c***		
Reference Standard	***ADA criteria (2-h OGTT)***		
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	***Accuracy (comparison with the reference standard test) - Sensitivity and specificity***		
Inclusion and exclusion criteria reported?	**Yes Partial No Not reported**	***Yes***	
Does the study have a clearly focused question?	**Yes Partial No Not reported**	***Yes***	
Summary Result/s	**In the present study we tested HbA1c for the diagnosis of T2D in 208 patients with PCOS. Twenty patients were diagnosed with type 2 diabetes during OGTT. The sensitivity and specificity of HbA1c R6.5% for the diagnosis of diabetes were 35% and 99%, respectively, compared with the diagnosis established by OGTT. The clinical utility of HbA1c for diagnosing impaired glucose tolerance and type 2 diabetes in PCOS in daily practice is low.**		
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
PATIENT SELECTION/SPECTRUM	**Was the spectrum of patients representative of the patients who will receive the test in practice?**	**Yes Partial No Not reported**	***Partial***
	Was a consecutive or random sample of patients enrolled? (Q-2)	**Yes Partial No Not reported**	***Yes***

	Was a case-control design avoided? (Q-2)	**Yes** **Partial** **No** **Not reported**	***Yes***
	Did the study avoid inappropriate exclusions? (Q-2)	**Yes** **Partial** **No** **Not reported**	***Partial***
CLASSIFICATION/ VERIFICATION/ INCORPORATION/ REVIEW BIAS	**Were all participants assessed with both index test and reference standard?**	**Yes** **Partial** **No** **Not reported**	***Yes***
	Did all patients receive the same reference standard? (Q-2)	**Yes** **Partial** **No** **Not reported**	***Yes***
	Is the reference standard likely to correctly classify the target condition? (Q-2)	**Yes** **Partial** **No** **Not reported**	**Partial**
	Was the reference standard independent of the index test (ie. the index test did not form part of the reference standard)?	**Yes** **Partial** **No** **Not reported**	***Yes***
	Were the reference standard results interpreted without knowledge of the results of the index test?	**Yes** **Partial** **No** **Not reported**	***Not reported***
	Were the index test results interpreted without knowledge of the results of the reference standard test?	**Yes** **Partial** **No** **Not reported**	***Not reported***
	If a threshold was used, was it pre-specified?	**Yes** **Partial** **No** **Not reported**	***Yes***
DETECTION BIAS	**Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?**	**Yes** **Partial** **No** **Not reported**	***Not reported***
ATTRITION	**Were withdrawals from the study explained?**	***X% treatment*** ***X% control/ comparison***	***NA***
REPORTING BIAS	**Were uninterruptable/ intermediate test results reported?**	**Yes** **Partial** **No** **Not reported**	***Yes***

OTHER ISSUES – APPLICABILITY/ COMPARABILITY/ VARIATION	**Was the execution of all tests described in sufficient detail to permit replication of the tests?**	**Yes** **Partial** **No** **Not reported**	***No***
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	**Yes** **Partial** **No** **Not reported**	***Not reported***
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	**Yes** **Partial** **No** **Not reported**	***Partial***
	Were there any conflicts of interest in the writing or funding of this study?	**Yes** **Partial** **No** **Not reported**	***No***
	If statistical analysis was undertaken, was this appropriate?	**Yes** **Partial** **No** **Not reported**	***Partial*** ***-the statistical analysis was planned a priori*** ***-the data were analysed accordingly to the study protocol.*** ***Diagnostic accuracy and measures of statistical uncertainty (eg. 95%CI) presented:*** ***· Sensitivity and specificity*** ***But no Area under the ROC curve***
COMMENTS		***the study wanted to establish the value of HbA1c for the diagnosis of T2D and as a cardiovascular risk marker in women with PCOS. The clinical utility of HbA1c for diagnosing impaired glucose tolerance and type 2 diabetes in PCOS in daily practice is low.***	
What is the overall risk of bias?		***High***	***Few criteria have been fulfilled and the conclusions of the study are likely to be affected.***
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		***No***	

Study ID	***Ortiz-Flores_2019***

Study Citation	***Ortiz-Flores AE, Luque-Ramírez M, Fernández-Durán E, Alvarez-Blasco F, Escobar-Morreale HF. Diagnosis of disorders of glucose tolerance in women with polycystic ovary syndrome (PCOS) at a tertiary care center: fasting plasma glucose or oral glucose tolerance test? Metabolism. 2019 Apr;93:86-92. doi: 10.1016/j.metabol.2019.01.015. Epub 2019 Jan 30. PMID: 30710572.***	
Study Country	**Spain**	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	**At a tertiary care center, we conducted a retrospective, observational study including 400 women with PCOS submitted to an OGTT.**	
PCOS diagnostic criteria	***PCOS was diagnosed when two of the following conditions were met: i) clinical hyperandrogenism and/or biochemical hyperandrogenism; ii) chronic oligo- or anovulation; and iii) polycystic ovarian morphology assessed on ultrasound, provided that secondary aetiologies were excluded by appropriate testing, including Cushing disease, thyroid dysfunction, hyperprolactinemia and non-classic congenital adrenal hyperplasia***	
N per group	***PCOS: 400*** ***Control: 147***	
Setting	***Hospital Universitario Ramón y Cajal & Universidad de Alcalá & Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS) & Centro de Investigación Biomédica en Red Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM),*** **the outpatient Reproductive Endocrinology clinic of tertiary care center**	
Index test	***FPG, OGTT***	
Reference Standard	***ADA criteria (2-h OGTT)***	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	***Accuracy (comparison with the reference standard test) - Sensitivity and specificity, Likelihood ratios, Area under the ROC curve***	
Inclusion and exclusion criteria reported?	**Yes** **Partial** **No** **Not reported**	***Yes***
Does the study have a clearly focused question?	**Yes** **Partial** **No** **Not reported**	***Yes***
Summary Result/s	**The OGTT detected dysglycemia in 24.5% of patients, whereas only 14.3% women would have been diagnosed using FPG levels alone. The latter missed as many as 40% of women with dysglycemia in our series, including all cases of diabetes. Diagnostic agreement between both algorithms was only 0.55 (= 0.103; 95% CI: 0.05 – 0.16). Areas under the receiver operating characteristic curve for dysglycemia were 0.86 (95%CI: 0.81 – 0.91) for FPG and 0.91 (95%CI = 0.87 – 0.95) for 120-min plasma glucose during the OGTT. FPG was not accurate in predicting dysglycemia in women with PCOS regardless of the presence of insulin resistance, weight excess, hyperandrogenemia and age.**	

		Principal conclusions: Relying on FPG alone is not adequate for the screening of disorders of glucose tolerance in women with PCOS; such diagnosis should rely on the results of an OGTT regardless of age, weight and/or androgen concentrations.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
PATIENT SELECTION/SPECTRUM BIAS	**Was the spectrum of patients representative of the patients who will receive the test in practice?**	**Yes Partial No Not reported**	***Partial***
	Was a consecutive or random sample of patients enrolled? (Q-2)	**Yes Partial No Not reported**	***Yes***
	Was a case-control design avoided? (Q-2)	**Yes Partial No Not reported**	***Yes***
	Did the study avoid inappropriate exclusions? (Q-2)	**Yes Partial No Not reported**	***Yes***
CLASSIFICATION/ VERIFICATION/ INCORPORATION/ REVIEW BIAS	**Were all participants assessed with both index test and reference standard?**	**Yes Partial No Not reported**	***Yes***
	Did all patients receive the same reference standard? (Q-2)	**Yes Partial No Not reported**	***Yes***
	Is the reference standard likely to correctly classify the target condition? (Q-2)	**Yes Partial No Not reported**	**Partial**
	Was the reference standard independent of the index test (ie. the index test did not form part of the reference standard)?	**Yes Partial No Not reported**	***Yes***

	Were the reference standard results interpreted without knowledge of the results of the index test?	**Yes Partial No Not reported**	***Not reported***
	Were the index test results interpreted without knowledge of the results of the reference standard test?	**Yes Partial No Not reported**	***Not reported***
	If a threshold was used, was it pre-specified?	**Yes Partial No Not reported**	***Yes***
DETECTION BIAS	**Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?**	**Yes Partial No Not reported**	***Not reported***
ATTRITION BIAS	**Were withdrawals from the study explained?**	***X% treatment X% control/ comparison***	***NA***
REPORT BIAS	**Were uninterruptable/ intermediate test results reported?**	**Yes Partial No Not reported**	***Yes***
OTHER ISSUES – APPLICABILITY/	**Was the execution of all tests described in sufficient detail to permit replication of the tests?**	**Yes Partial No Not reported**	***No***
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	**Yes Partial No Not reported**	***Not reported***

	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	**Yes Partial No Not reported**	***Partial***
	Were there any conflicts of interest in the writing or funding of this study?	**Yes Partial No Not reported**	***No***
	If statistical analysis was undertaken, was this appropriate?	**Yes Partial No Not reported**	***Partial*** ***- if the statistical analysis was planned a priori - if the data were analysed accordingly to the study protocol.*** ***Diagnostic accuracy and measures of statistical uncertainty (eg. 95%CI) presented:*** ***· Sensitivity and specificity*** ***· Area under the ROC curve***
COMMENTS		***Primary objective was to establish the diagnostic agreement between the two most commonly used diagnostic algorithms for disordered glucose tolerance in non-pregnant* women with PCOS: i) using FPG alone, or ii) relying on plasma glucose concentrations at fasting and after 120-min of a 75-g OGTT**	
What is the overall risk of bias?		***High***	***Few criteria have been fulfilled and the conclusions of the study are likely to be affected.***
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		***No***	

Study ID	***Zhen 2014***
Study Citation	***Zhen Y, Yang P, Dong R, Wu Y, Sang Y, Du X, Wang Y, Song Q, Yu L, Rao X. Effect of HbA1C detection on the diagnostic screening for glucose metabolic disorders in polycystic ovary syndrome. Clinical and Experimental Obstetrics & Gynecology. 2014 Feb 10;41(1):58-61.***
Study Country	**China**
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	**Patients with PCOS**
PCOS diagnostic criteria	***Rotterdam criteria***
N per group	***PCOS: 161***
Setting	***The study was done at Fifth Affiliated Hospital of Zhengzhou University***

Index test	***HbA1c***		
Reference Standard	***ADA criteria (2-h OGTT)***		
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	***Accuracy (comparison with the reference standard test) - Sensitivity and specificity***		
Inclusion and exclusion criteria reported?	**Yes Partial No Not reported**	***Yes***	
Does the study have a clearly focused question?	**Yes Partial No Not reported**	***Yes***	
Summary Result/s	**Based on the traditional standards of blood sugar, the prevalence of type 2 diabetes was 5.6%, and the pre-diabetes prevalence was 7.5%. Based on the HbA1C standards, 4.3% of patients were diagnosed with type 2 diabetes, and 10.6% of the diabetic patients can be considered as high-risk populations. Based on the combined standards of OGTT and HbA1C, the prevalence of type 2 diabetes was 6.2%, and the pre-diabetes prevalence was 12.4%. OGTT is considered the gold standard for identifying abnormal glucose tolerance, and HbA1C detection is considered to be stronger than FPG. The areas under the ROC curves of HbA1C and FPG were 0.968 and 0.672, respectively ($p < 0.01$). The American Diabetes Association (ADA) recommends the cut-off value of HbAlc ≥ 5.7% and FPG ≥ 5.6 mmol/l for identifying abnormal glucose tolerance. The sensitivity and specificity were 76.7% and 89.5% for HBA1C, as well as 40.5% and 94.3% for FPG, respectively. The positive and negative likelihood ratios were 7.3 and 0.26 for HbA1C, as well as 7.1 and 0.63 for FPG, respectively. Conclusion: HbA1C detection can be used as a method for diagnosis and screening.**		
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
PATIENT SELECTION/SPECTRUM BIAS	**Was the spectrum of patients representative of the patients who will receive the test in practice?**	**Yes Partial No Not reported**	***Not reported***
	Was a consecutive or random sample of patients enrolled? (Q-2)	**Yes Partial No Not reported**	***Not reported***
	Was a case-control design avoided? (Q-2)	**Yes Partial No Not reported**	***Yes***
	Did the study avoid inappropriate exclusions? (Q-2)	**Yes Partial No Not reported**	***Partial***
	Were all participants assessed with both index test and reference standard?	**Yes Partial No Not reported**	***Yes***

CLASSIFICATION/ VERIFICATION/ INCORPORATION/ REVIEW BIAS	Did all patients receive the same reference standard? (Q-2)	Yes Partial No Not reported	*Yes*
	Is the reference standard likely to correctly classify the target condition? (Q-2)	Yes Partial No Not reported	Partial
	Was the reference standard independent of the index test (ie. the index test did not form part of the reference standard)?	Yes Partial No Not reported	*Yes*
	Were the reference standard results interpreted without knowledge of the results of the index test?	Yes Partial No Not reported	*Not reported*
	Were the index test results interpreted without knowledge of the results of the reference standard test?	Yes Partial No Not reported	*Not reported*
	If a threshold was used, was it pre-specified?	Yes Partial No Not reported	*Yes*
DETECT ION	Is the time period between tests short enough to be reasonably sure that the target condition did not change between the two tests?	Yes Partial No Not reported	*Not reported*
AT TR	Were withdrawals from the study explained?	*X% treatment* *X% control/ comparison*	*NA*
REPORT BIAS	Were uninterruptable/ intermediate test results reported?	Yes Partial No Not reported	*Yes*
OTHER ISSUES – APPLICABILITY/	Was the execution of all tests described in sufficient detail to permit replication of the tests?	Yes Partial No Not reported	*No*
	Were the clinicians undertaking the tests representative of the clinicians who will be undertaking the tests in the clinical setting?	Yes Partial No Not reported	*Not reported*
	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes Partial No Not reported	*Partial*
	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial	*No*

		No **Not reported**	
	If statistical analysis was undertaken, was this appropriate?	**Yes** **Partial** **No** **Not reported**	***Partial*** ***-the statistical analysis was planned a priori*** ***-the data were analysed accordingly to the study protocol.*** ***Diagnostic accuracy and measures of statistical uncertainty (eg. 95%CI) presented:*** ***· Sensitivity and specificity*** ***Area under the ROC curve***
COMMENTS		***Overall, FPG or HbA1C was not the perfect indicator for screening abnormal glucose metabolism. However, their combination may reduce the misdiagnosis rate of glucose metabolic disorders to some extent. High-risk groups may still need to be subjected to OGTT to confirm the diagnosis***	
What is the overall risk of bias?		***High***	***Few criteria have been fulfilled and the conclusions of the study are likely to be affected.***
Did risk of bias differ by outcome ***(eg. primary outcome was low risk but rest were high)?***		***No***	

PART 2

RECOMMENDATIONS

Compiled by key contact(s)

GDG 1

Question 1.9.2

Q.1.9.2. In women with PCOS, what is the most effective tool/method to assess risk of type 2 diabetes mellitus?

BACKGROUND:

Prevalence and Problem

Diagnostic criteria for diabetes can be based on i) elevated fasting glucose, ii) elevated 2 hr glucose during a 75g OGTT, iii) elevated HbA1c, or iv) elevated random glucose if in the presence of symptoms and signs of diabetes (1). Use of HbA1c for the diagnosis of diabetes has been an area of controversy and debate, though the diagnosis of diabetes using HbA1c has recently been accepted by the World Health Organization (1). Use of HbA1c for diagnosis of diabetes may be inaccurate in certain settings, such as haemoglobinopathy, renal failure, anaemia, and conditions with increased red blood cell turnover. HbA1c has the advantage of not requiring a fasting state, and has been reported to have less intra-individual variability compared to plasma glucose. If elevated levels are detected in asymptomatic subjects, repeat testing, preferably with the same test, is recommended to confirm the diagnosis of diabetes (1).

Clinical practice gap: need for guidance

Whilst the oral glucose tolerance test has been recommended as the test of choice to detect dysglycaemia in PCOS, the practical difficulties of arranging OGTTs have limited its utilization in different healthcare settings. It is therefore important to seek any evidence on the use of other glycaemic parameters for the evaluation of type 2 diabetes in PCOS. In the last version of the International PCOS Guidelines, no study was identified which specifically addressed this question. Whether fasting plasma glucose (FPG), or HbA1c, can replace OGTT as a test of impaired glucose regulation, is of great clinical importance.

Summary of key information

Six studies were identified which provided some information comparing different tests of glycaemia. All studies used OGTT as the “reference”. Results suggest that FPG or HbA1c cannot replace OGTT, which remains the preferred method of evaluating glycaemia in PCOS.

GRADE EVIDENCE CERTAINTY	
Comparison	**GRADE for critical outcomes**
o OGTT versus FG versus HbA1c	⊕◯◯◯ VERY LOW

Evidence to Recommendations Framework

COMPARISONS (option versus other option)

OGTT vs FG vs HbA1c

EVIDENCE-BASED RECOMMENDATION(S)

EBR: Health professionals and women with PCOS should recommend the 75-g oral glucose tolerance test (OGTT) as the most accurate test to assess glycaemic status in PCOS, regardless of BMI.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

EBR: If an OGTT cannot be performed, fasting plasma glucose and/or HbA1c could be considered noting significantly reduced accuracy.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

EBR: An OGTT should be considered in all women with PCOS and without pre-existing diabetes, when planning pregnancy or seeking fertility treatment, given the high risk of hyperglycaemia and the associated comorbidities in pregnancy. If not performed preconception, an OGTT could be offered at the first prenatal visit and all women with PCOS should be offered the test at 24-28 weeks gestation.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

PRACTICE POINT(S)
Insulin resistance is a pathophysiological factor in PCOS, however, clinically available insulin assays are of limited clinical relevance and should not be used in routine care. (refer to recommendation 3.1.10)
GRADE CONSIDERATIONS
Justifications: The quality of evidence is low though there are consistent findings from the studies. This would support a recommendation for OGTT as the preferred tool for evaluating risk of diabetes in PCOS.
Subgroup considerations: Evidence is only available in adults and may not be applicable to other subgroups (different ethnicities, menopausal status etc.)
Implementation considerations: Practical considerations to conduct OGTT among all women with PCOS, especially in low resource settings.
Monitoring and evaluation considerations: Percentage of women with PCOS who have received glycaemic evaluation with OGTT, as well as frequency of repeat evaluation.
Research priorities: There is a need for more research to compare different diagnostic tests against OGTT, and for alternative strategies of glucose testing incorporating a combination of parameters to simplify glycaemic evaluation in settings where regular OGTT may not be practical. Ethnicity. Menopause status.

GRADE framework

GRADE DECIDE **Interactive Evidence to Decision Framework**

● DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

OGTT is more sensitive.

● UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

Judgement:

☐ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☒ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Similar, no definite undesirable effects other than more labour intensive to carry out as a test

● CERTAINTY OF THE EVIDENCE

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☐ Very low	☒ Low	☐ Moderate	☐ High

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

[key contact to draft discussion points and justification for above judgement]

Low level of evidence

● VALUES

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☐ Important uncertainty or variability	☒ Possibly important uncertainty or variability	☐ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Research evidence:

No research evidence was identified

Panel discussion:

Unclear but potential uncertainty in value of favouring OGTT given logistic issues and variability in access. Education of health professionals and women with PCOS on metabolic risk is critical.

● BALANCE OF EFFECTS

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:

[key contact to draft discussion points and justification for above judgement]

Given the long-standing recommendation to use OGTT as the preferred test to evaluate dyglycaemia, balance between desirable and undesirable effects probably favour OGTT

● COSTS

How large are the resource requirements (costs)?

Judgement:

☐ Don't know	☐ Varies	☐ Large costs	☒ Moderate costs	☐ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:

No research evidence was identified

Panel discussion:

Varies according to healthcare settings.

Balance of cost and benefits on prevention.

● CERTAINTY OF COST EVIDENCE

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

No research evidence was identified

Panel discussion:

Not evaluated

● COST-EFFECTIVENESS

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

No research evidence was identified

Panel discussion:

No evidence identified.

● EQUITY

What would be the impact on health equity?

Judgement:

☐ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☒ Probably increased	☐ Increased

Research evidence:

No research evidence was identified

Panel discussion:

● ACCEPTABILITY

Is the option acceptable to key stakeholders?

Judgement:

☐ Don't know	☒ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Some women and healthcare professionals may find OGTT inconvenient and costly compared to other tests.

● FEASIBILITY

Is the option feasible to implement?

Judgement:

☐ Don't know	☒ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Feasibility high though varies according to local healthcare settings.

REFERENCES:

1. World Health Organization. Classification of diabetes mellitus. 2019 21 April 2019. License: CC BY-NC-SA 3.0 IGO. Report No.: ISBN 978-92-4-151570-2.Available at: https://apps.who.int/iris/handle/10665/325182. Accessed: 07 Feb 2023

PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by ECR Lead: Anuradhaa Subramanian
Other Members: Siang Ing Lee

Supervised, edited and supported by the Evidence Team

GDG 1

Question 1.10.

Are women with PCOS at increased risk for sleep apnea?

1. SELECTION CRITERIA

Table 1. PICO Criteria for Inclusion – Not to be adapted To be used by evidence team to decide which studies will be included when screening search results.	
Question	Q 1.10) Are women with PCOS at increased risk for sleep apnea? CLINICAL PRACTICE POINT: What is the method/tool most effective to screen for sleep apnea in PCOS?
Clinical leads (key contacts)	A/Prof Darren Mansfield Respiratory physician Monash Health, Monash University, Australia Prof Helena Teede Endocrinologist Monash University, Australia
Allocation ranking	Level 2- updated systematic review

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(language, year)*
Inclusion	Females of any age, ethnicity, weight. Note subgroup by BMI <30 and >=30 kg/m2	Women with a diagnosis of any phenotype of PCOS (diagnosed by Rotterdam, NIH or AES)	Women without PCOS	Sleep apnea on formal sleep studies Level 1, inlab, level 2, same set up in home or level 3 ambulatory limited channel Polysomography prevalence and severity of obstructive sleep apnea (including obstructive sleep apnoea, sleep apnea, sleep apnoea, sleep disordered breathing, snoring) on 1. Apnea hypopnea index (AHI) >5 events per hour and 2. sleep apnea syndrome > 5 + symptoms Severity by AHI diagnostic categories Mild 5-14 Mod > 15-29 Severe > 30	Evidence based guidelines, systematic reviews, randomised controlled trials, controlled cohort studies, case control studies	English language
Exclusion	Studies of other population groups	Studies with self-reported PCOS diagnosis	Studies without a control or comparison arm	Studies without clinical outcomes (mechanistic studies) Studies not reporting validated sleep outcomes Studies describing sleep apnea symptoms through questionnaires without formal measurement Studies with self-reported or doctor diagnosed OSA without formal measurement		

2. SEARCH STRATEGY

Table 2.1. Search details

Evidence source	Date of search
Medline (Ovid)	2nd August 2022 Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations <1946 to July 29, 2022>
PsychInfo (Ovid)	2nd August 2022 APA PsycArticles Full Text APA PsycInfo <1967 to July Week 4 2022> APA PsycInfo <1806 to 1966>
EMBASE (Ovid)	2nd August 2022 Embase <1974 to 2022 July 29>
All EBM (Ovid)	2nd August 2022 EBM Reviews - Cochrane Database of Systematic Reviews <2005 to July 27, 2022> EBM Reviews - ACP Journal Club <1991 to July 2022> EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016> EBM Reviews - Cochrane Clinical Answers <July 2022> EBM Reviews - Cochrane Central Register of Controlled Trials <June 2022> EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012> EBM Reviews - Health Technology Assessment <4th Quarter 2016> EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>
CINAHL	2nd August 2022
Any subsequent updates - enter database and date:	

Table 2.2. Questions addressed by this search *(add more rows as needed)*:

GDG	Q#	Question
1	1.10	Are women with PCOS at increased risk for sleep apnea?

Table 2.3. Search strings used in OVID or other database/s

OVID Medline, All EBM, PsychInfo, EMBASE (results=996, 286, 247, 2272)	CINAHL (results=)	**Other (results=NA)**

#	Query
1	exp polycystic ovary syndrome/
2	polycystic ovar*.mp.
3	poly-cystic ovar*.mp.
4	PCO*.mp.
5	(stein-leventhal or leventhal).mp.
6	anovulation/
7	anovulat*.mp.
8	oligo-ovulat*.mp.
9	oligoovulat*.mp.
10	(ovar* adj5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*)).mp.
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12	exp Sleep Apnea, Obstructive/
13	exp Sleep Apnea Syndromes/
14	exp Obesity Hypoventilation Syndrome/
15	exp Sleep Apnea, Central/
16	exp Polysomnography/
17	exp Snoring/
18	sleep apn*.mp.
19	apn*-hypopn*.mp.
20	sleep hypopn*.mp.
21	sleep hypoventilation.mp.
22	obesity hypoventilation.mp.
23	apnoea.mp.
24	apnea.mp.
25	apneic.mp.
26	apnoeic.mp.
27	hypopneic.mp.
28	hypopnoeic.mp.
29	sleep disordered breathing.mp.
30	sleep-disordered breathing.mp.
31	(sleep and breathing).mp.
32	(sleep and respiratory).mp.
33	upper-airway resistance.mp.
34	upper airway resistance.mp.
35	(sleep adj5 (apn* or hypopn* or hypoventilation or breathing or respiratory)).mp.
36	polysomnography.mp.
37	snoring.mp.
38	snore.mp.
39	SDB.mp.
40	OSA.mp.
41	OSAS.mp.
42	SAHS.mp.
43	OSAHS.mp.
44	SAS.mp.
45	SHS.mp.
46	pickwickian.mp.
47	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46
48	11 and 47

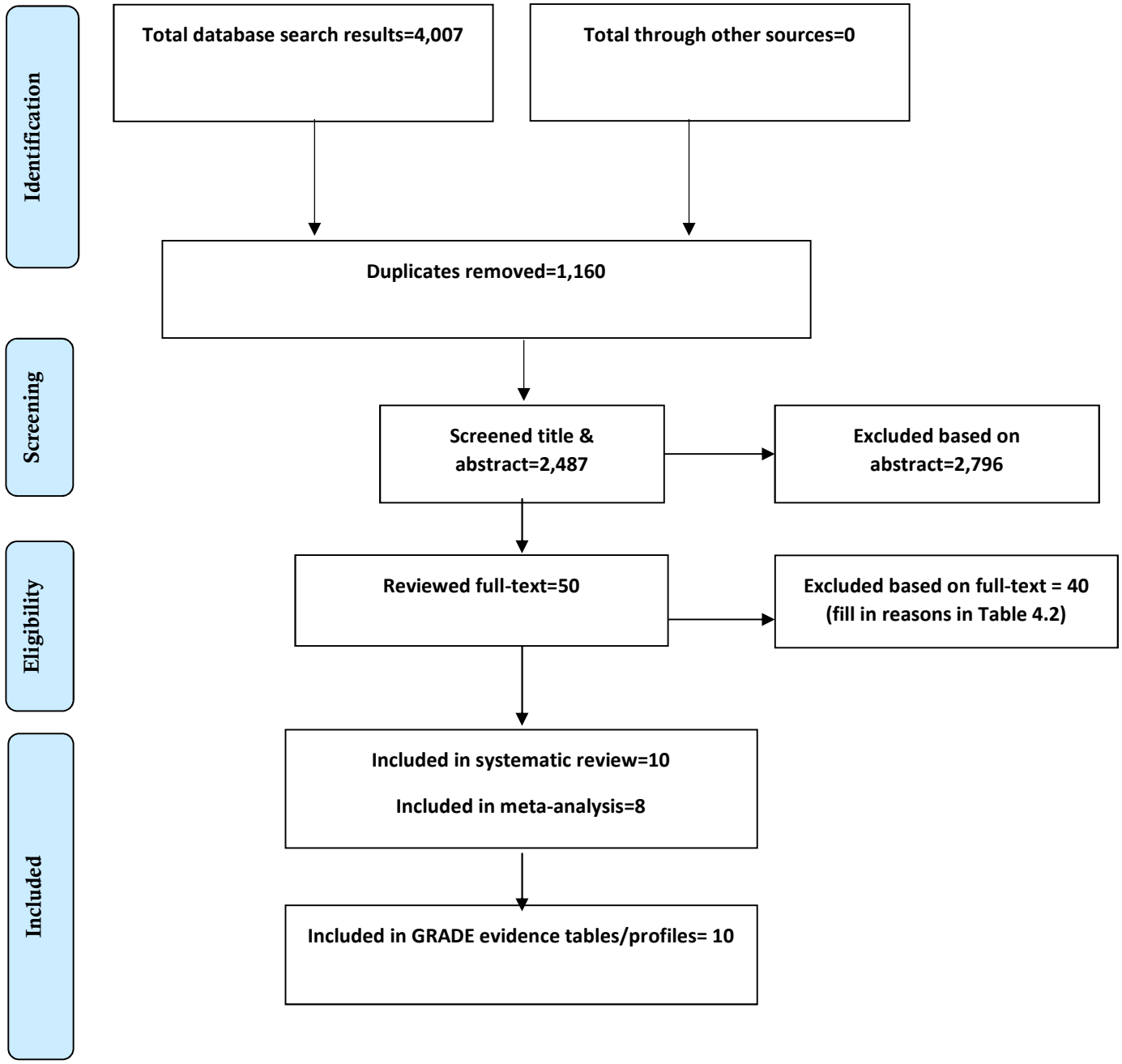
Similar search

#	Query
1	SU polycystic ovary syndrome
2	"polycystic ovar*"
3	"poly-cystic ovar*"
4	"PCO*"
5	"stein-leventhal or leventhal"
6	SU anovulation
7	SU ovarian cysts
8	"anovulat*"
9	"oligo-ovulat*"
10	"oligoovulat*"
11	"ovar* N5 sclerocystic or ovar* N5 polycystic or ovar* N5 poly-cystic or ovar* N5 degenerat* or ovar* N5 hyperandrogen* or ovar* N5 hyperandrogen*"
12	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11
13	SU Sleep Apnea, Obstructive
14	SU Sleep Apnea Syndromes
15	SU Obesity Hypoventilation Syndrome
16	SU Sleep Apnea, Central
17	SU Polysomnography
18	SU Snoring
19	"sleep apn*"
20	"apn*-hypopn*"
21	"sleep hypopn*"
22	"sleep hypoventilation"
23	"obesity hypoventilation"
24	"apnoea"
25	"apnea"
26	"apneic"
27	"apnoeic"
28	"hypopneic"
29	"hypopnoeic"
30	"sleep disordered breathing"
31	"sleep-disordered breathing"
32	"sleep and breathing"
33	"sleep and respiratory"
34	"upper-airway resistance"
35	"upper airway resistance"
36	"sleep N5 apn* or sleep N5 hypopn* or sleep N5 hypoventilation or sleep N5 breathing or sleep N5 respiratory"
37	"polysomnography"
38	"snoring"
39	"snore"
40	"SDB"
41	"OSA"
42	"OSAS"
43	"SAHS"
44	"OSAHS"

	45 "SAS" 46 "SHS" 47 "pickwickian" S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR 48 S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OT S45 OR S46 OR S47 49 S12 AND S48	

Evidence processing: Studies were selected and appraised by two reviewer/s in consultation with the evidence team/ key contact using study selection and appraisal criteria (PICO above) established a priori. The articles were reviewed by title and abstract by two reviewers. When a decision could not be made based on title and abstract alone, full text was retrieved. **Ten studies met inclusion criteria for this review**

3. SEARCH RESULTS - PRISMA flowchart



4. STUDY INCLUSION

Table 4.1. Included Studies (full citation with doi)

de Sousa G, Schlüter B, Menke T, Trowitzsch E, Andler W, Reinehr T. Relationships between polysomnographic variables, parameters of glucose metabolism, and serum androgens in obese adolescents with polycystic ovarian syndrome. J Sleep Res. 2011 Sep;20(3):472-8. doi: 10.1111/j.1365-2869.2010.00902.x. Epub 2010 Dec 29. PMID: 21199038.
Fogel RB, Malhotra A, Pillar G, Pittman SD, Dunaif A, White DP. Increased prevalence of obstructive sleep apnea syndrome in obese women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2001 Mar;86(3):1175-80. doi: 10.1210/jcem.86.3.7316. PMID: 11238505.
Hachul H, Polesel DN, Tock L, Carneiro G, Pereira AZ, Zanella MT, Tufik S, Togeiro SM. Sleep disorders in polycystic ovary syndrome: influence of obesity and hyperandrogenism. Rev Assoc Med Bras (1992). 2019 Mar;65(3):375-383. doi: 10.1590/1806-9282.65.3.375. Epub 2019 Apr 11. PMID: 30994836.
Helvaci N, Karabulut E, Demir AU, Yildiz BO. Polycystic ovary syndrome and the risk of obstructive sleep apnea: a meta-analysis and review of the literature. Endocr Connect. 2017 Oct;6(7):437-445. doi: 10.1530/EC-17-0129. Epub 2017 Jul 24. PMID: 28739562; PMCID: PMC5574283.
Nandalike K, Agarwal C, Strauss T, Coupey SM, Isasi CR, Sin S, Arens R. Sleep and cardiometabolic function in obese adolescent girls with polycystic ovary syndrome. Sleep Med. 2012 Dec;13(10):1307-12. doi: 10.1016/j.sleep.2012.07.002. Epub 2012 Aug 23. PMID: 22921588; PMCID: PMC3509263..
Suri J, Suri JC, Chatterjee B, Mittal P, Adhikari T. Obesity may be the common pathway for sleep-disordered breathing in women with polycystic ovary syndrome. Sleep Med. 2016 Aug;24:32-39. doi: 10.1016/j.sleep.2016.02.014. Epub 2016 Aug 16. PMID: 27810183.
Tasali E, Van Cauter E, Hoffman L, Ehrmann DA. Impact of obstructive sleep apnea on insulin resistance and glucose tolerance in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2008 Oct;93(10):3878-84. doi: 10.1210/jc.2008-0925. Epub 2008 Jul 22. PMID: 18647805; PMCID: PMC2579653.
Vgontzas AN, Legro RS, Bixler EO, Grayev A, Kales A, Chrousos GP. Polycystic ovary syndrome is associated with obstructive sleep apnea and daytime sleepiness: role of insulin resistance. J Clin Endocrinol Metab. 2001 Feb;86(2):517-20. doi: 10.1210/jcem.86.2.7185. PMID: 11158002.
Yang HP, Kang JH, Su HY, Tzeng CR, Liu WM, Huang SY. Apnea-hypopnea index in nonobese women with polycystic ovary syndrome. Int J Gynaecol Obstet. 2009 Jun;105(3):226-9. doi: 10.1016/j.ijgo.2009.02.004. Epub 2009 Apr 5. PMID: 19345941.
Kahal H, Kyrou I, Uthman OA, Brown A, Johnson S, Wall PDH, Metcalfe A, Parr DG, Tahrani AA, Randeva HS. The prevalence of obstructive sleep apnoea in women with polycystic ovary syndrome: a systematic review and meta-analysis. Sleep Breath. 2020 Mar;24(1):339-350. doi: 10.1007/s11325-019-01835-1. Epub 2019 May 20. PMID: 31111411; PMCID: PMC7127997.

Table 4.2. Excluded Studies (on full text assessment)

Reference	Reason
UNDERLAND, Lisa J., Lisa KENIGSBERG FECHTER, Chhavi AGARWAL, Sanghun SIN, Netra PUNJABI, Rubina HEPTULLA, and others, 'Insulin Sensitivity and Obstructive Sleep Apnea in Adolescents with Polycystic Ovary Syndrome', Minerva Endocrinology, 2022 <https://doi.org/10.23736/S2724-6507.22.03619-3>	Unable to access full text
H.-P., Yang, Kang J.-H., Su H.-Y., and Huang S.-Y., 'A Pilot Study of Heart Rate Variability and Apneic-Hypopneic Events in Non-Obese Women with Polycystic Ovary Syndrome during Sleep', Nutritional Sciences Journal, 35.1 (2010), 9–21 <http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=364374196>	Study outcome - only reporting mean (SD) of AHI /obstructive apnoea events
Mokhlesi, Babak, Susan Sam, and David A Ehrmann, 'Obstructive Sleep Apnea and Polycystic Ovary Syndrome: Cause or Association?', Sleep Medicine, 2017, 170–71 <https://doi.org/10.1016/j.sleep.2017.01.001>	Commentary
Su, Nianjun, Chongyang Du, Yuemei Zhang, Lian Deng, Ting Tang, Baoding Zhuang, and others, 'Retrospective Investigation and Analysis of Sleep Disorders on Occurrence of Polycystic Ovary Syndrome', Biomedical Research, 28.2 <https://www.alliedacademies.org/articles/retrospective-investigation-and-analysis-of-sleep-disorders-on-occurrence-of-polycystic-ovary-syndrome.html>	Study outcome - through questionnaire without formal assessment
K.A., Temple, Watson S., Whitmore H., Van Cauter E., and Ehrmann D A, 'Obstructive Apnea in Women with Polycystic Ovary Syndrome Increases the Risk of Abnormal Glucose Tolerance', Endocrine Reviews, 94th Annual Meeting and Expo of the Endocrine Society, ENDO 2012. Houston, TX United States., 33.3 MeetingAbstracts (2012) <http://edrv.endojournals.org/cgi/content/meeting_abstract/33/03_MeetingAbstracts/OR47-4?sid=7df6b636-33d8-4446-9edf-1632dfebd249>	Conference Proceeding

L.L., Morselli, Temple K.A., Mokhlesi B., Tasali E., Chapotot F., Van Cauter E., and others, 'Effects of Polycystic Ovary Syndrome (PCOS) on REM and Non-REM Sleep in African-American (AA) Women', Endocrine Reviews, 95th Annual Meeting and Expo of the Endocrine Society, ENDO 2013. San Francisco, CA United States., 34.3 SUPPL. 1 (2013) <http://press.endocrine.org/doi/abs/10.1210/endo-meetings.2013.RE.5.SAT-543>	Conference Proceeding
H., Hachul, Tock L., Carneiro G., Zanella T., Togeiro S.M., and Tuik S, 'Polycystic Ovary Syndrome: A Comparative Study of Sleep Parameters in Patients with and without Hyperandrogenemia', Sleep, 26th Annual Meeting of the Associated Professional Sleep Societies, LLC, SLEEP 2012. Boston, MA United States., 35.SUPPL. 1 (2012), A421 <http://www.journalsleep.org/Resources/Documents/2012abstractsupplement.pdf>	Conference Proceeding
S., Ioja, Leondires M., and Weir I, 'Insomnia and Obstructive Sleep Apnea in Women Seeking Infertility Treatment in an Assisted Reproduction Clinic', *Sleep*, 27th Annual Meeting of the Associated Professional Sleep Societies, LLC, SLEEP 2013. Baltimore, MD United States., 36.SUPPL. 1 (2013), A403 <http://www.journalsleep.org/Resources/Documents/2013AbstractSupplement.pdf>	Conference Proceeding
G., De Sousa, Schluter B., Menke T., Trowitzsch E., Andler W., and Reinehr T, 'Longitudinal Analyses of Polysomnographic Variables, Serum Androgens, and Parameters of Glucose Metabolism in Obese Adolescents with Polycystic Ovarian Syndrome', *Sleep and Breathing*, 16.4 (2012), 1139–46 <https://doi.org/https://dx.doi.org/10.1007/s11325-011-0620-z>	Study outcome - only reporting mean (SD) of AHI /obstructive apnoea events
Bajuk Studen, Katica, Mojca Jensterle Sever, and Marija Pfeifer, 'Cardiovascular Risk and Subclinical Cardiovascular Disease in Polycystic Ovary Syndrome.', Frontiers of Hormone Research, 40 (2013), 64–82 <https://doi.org/https://dx.doi.org/10.1159/000341838>	Narrative review
K., Kolaczynski, Ibrahim S., Flyckt R., and Tantibhedhyangkul J, 'The Risk of Obstructive Sleep Apnea (OSA) in Infertile Women with and without Polycystic Ovarian Syndrome', *Sleep*, 27th Annual Meeting of the Associated Professional Sleep Societies, LLC, SLEEP 2013. Baltimore, MD United States., 36.SUPPL. 1 (2013), A403 <http://www.journalsleep.org/Resources/Documents/2013AbstractSupplement.pdf>	Conference Proceeding
K.A., Temple, Leproult R., Whitmore H., Mokhlesi B., Van Cauter E., and Ehrmann D A, 'Adiponectin Levels in Obese Women with and without PCOS: Impact of Obstructive Sleep Apnea', *Endocrine Reviews*, 95th Annual Meeting and Expo of the Endocrine Society, ENDO 2013. San Francisco, CA United States., 34.3 SUPPL. 1 (2013) <http://press.endocrine.org/doi/abs/10.1210/endo-meetings.2013.RE.5.SAT-544>	Conference Proceeding
de Sousa, Gideon, Bernhard Schluter, Dirk Buschatz, Thomas Menke, Eckardt Trowitzsch, Werner Andler, and others, 'The Impact of Insulin Resistance and Hyperandrogenemia on Polysomnographic Variables in Obese Adolescents with Polycystic Ovarian Syndrome.', Sleep & Breathing = Schlaf & Atmung, 16.1 (2012), 169–75 <https://doi.org/https://dx.doi.org/10.1007/s11325-010-0469-6>	Study outcome - only reporting mean (SD) of AHI /obstructive apnoea events
Sirmans, Susan M, Roy C Parish, Sandra Blake, and Xiaojun Wang, 'Epidemiology and Comorbidities of Polycystic Ovary Syndrome in an Indigent Population.', Journal of Investigative Medicine (Decker Publishing), 62.6 (2014), 868–74 <https://doi.org/10.1097/01.JIM.0000446834.90599.5d>	Study outcome - self-reported or doctor diagnosed without validation
Lin, Ting-Yang, Pei-Yin Lin, Wen-Hang Chang, Tung-Ping Su, Cheng-Ta Li, Wei-Chen Lin, and others, 'Risk of Developing Obstructive Sleep Apnea among Women with Polycystic Ovarian Syndrome: A Nationwide Longitudinal Follow-up Study.', Sleep Medicine, 2017, 165–69 <https://doi.org/10.1016/j.sleep.2016.12.029>	Study outcome - self-reported or doctor diagnosed without validation
Ehrmann, David A, 'Metabolic Dysfunction in Pcos: Relationship to Obstructive Sleep Apnea.', Steroids, 77.4 (2012), 290–94 <https://doi.org/https://dx.doi.org/10.1016/j.steroids.2011.12.001>	Narrative review
Stankiewicz, M, and R Norman, 'Diagnosis and Management of Polycystic Ovary Syndrome: A Practical Guide.', Drugs, 66.7 (2006), 903–12 <https://doi.org/10.2165/00003495-200666070-00002>	Narrative review
Mokhlesi, B, B Scoccia, T Mazzone, S Sam, Babak Mokhlesi, Bert Scoccia, and others, 'Risk of Obstructive Sleep Apnea in Obese and Nonobese Women with Polycystic Ovary Syndrome and Healthy Reproductively Normal Women.', Fertility & Sterility, 97.3 (2012), 786–91 <https://doi.org/10.1016/j.fertnstert.2011.12.024>	Study outcome - through questionnaire without formal assessment
J., Zea-Hernandez, Sin S., Graw-Panzer K., and Arens R, 'Sleep Disordered Breathing in Adolescent Girls with Polycystic Ovary Syndrome', American Journal of Respiratory and Critical Care Medicine, American Thoracic Society International Conference, ATS 2014. San Diego, CA United States., 189.MeetingAbstracts (2014) <http://www.atsjournals.org/doi/pdf/10.1164/ajrccm-conference.2014.189.1_MeetingAbstracts.A1279>	Conference Proceeding

K., Nandalike, Agarwal C., Coupey S., Sin S., and Arens R, 'Polysomnographic Findings in Adolescent Girls with Polycystic Ovarian Syndrome', American Journal of Respiratory and Critical Care Medicine, American Thoracic Society International Conference, ATS 2010. New Orleans, LA United States., 181.1 MeetingAbstracts (2010) <http://ajrccm.atsjournals.org/cgi/reprint/181/1_MeetingAbstracts/A2430?sid=3e7c2a96-b78a-4696-9ab6-4ef5ed8d119a>	Conference Proceeding
MARTINI, ANNE E, and M A E W HEALY, 'Polycystic Ovarian Syndrome: Impact on Adult and Fetal Health.', Clinical Obstetrics & Gynecology, 64.1 (2021), 26–32 <https://doi.org/10.1097/GRF.0000000000000593>	Narrative review
S., Sam, and Tasali E, 'Role of Obstructive Sleep Apnea in Metabolic Risk in PCOS', Current Opinion in Endocrine and Metabolic Research, 17 (2021), 46–51 <https://doi.org/https://dx.doi.org/10.1016/j.coemr.2021.01.002>	Narrative review
G., de Sousa, Schluter B., Buschatz D., Menke T., Trowitzsch E., Andler W., and others, 'The Impact of Insulin Resistance and Hyperandrogenemia on Polysomnographic Variables in Obese Adolescents with Polycystic Ovarian Syndrome', Sleep and Breathing, 2011, 1–7 <https://doi.org/https://dx.doi.org/10.1007/s11325-010-0469-6>	Study outcome - only reporting mean (SD) of AHI /obstructive apnoea events
G., De Sousa, Schluter B., Menke T., Trowitzsch E., Andler W., and Reinehr T, 'A Comparison of Polysomnographic Variables between Adolescents with Polycystic Ovarian Syndrome with and without the Metabolic Syndrome', Metabolic Syndrome and Related Disorders, 9.3 (2011), 191–96 <https://doi.org/https://dx.doi.org/10.1089/met.2010.0081>	Study outcome - only reporting mean (SD) of AHI /obstructive apnoea events
Zhang, Bingqian, Wei Zhou, Yuhua Shi, Jun Zhang, Linlin Cui, and Zi-Jiang Chen, 'Lifestyle and Environmental Contributions to Ovulatory Dysfunction in Women of Polycystic Ovary Syndrome.', BMC Endocrine Disorders, 20.1 (2020), 1–7 <https://doi.org/10.1186/s12902-020-0497-6>	Study outcome - through questionnaire without formal assessment
Nandalike, K, T Strauss, C Agarwal, Coupey SM, S Sin, S Rajpathak, and others, 'Screening for Sleep-Disordered Breathing and Excessive Daytime Sleepiness in Adolescent Girls with Polycystic Ovarian Syndrome.', Journal of Pediatrics, 159.4 (2011), 591–96 <https://doi.org/10.1016/j.jpeds.2011.06.043>	Study outcome - through questionnaire without formal assessment
Morton, A, 'Don't Forget OSA with PCOS!.', BJOG : An International Journal of Obstetrics and Gynaecology, Comment on: BJOG. 2007 Aug;114(8):922-32 PMID: 17635486 [https://www.ncbi.nlm.nih.gov/pubmed/17635486], 115.1 (2008), 131–32 <http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med7&NEWS=N&AN=18053115>	Commentary
D.M., Wootton, Luo H., Yazdani A., Sin S., McDonough J., Isasi C.R., and others, 'Increased Cfd Pharyngeal Airway Flow Resistance in Adolescent Girls with Polycystic Ovarian Syndrome and Obstructive Sleep Apnea Syndrome', American Journal of Respiratory and Critical Care Medicine, American Thoracic Society International Conference, ATS 2017. Washington, DC United States., 195 (2017) <https://doi.org/https://dx.doi.org/10.1164/ajrccm-conference.2017.D30>	Conference Proceeding
Kumarendran, Balachandran, Dana Sumilo, Michael W. O'Reilly, Konstantinos A. Toulis, Krishna M. Gokhale, Chandrika N. Wijeyaratne, and others, 'Increased Risk of Obstructive Sleep Apnoea in Women with Polycystic Ovary Syndrome: A Population-Based Cohort Study', European Journal of Endocrinology, 180.4 (2019), 265 <https://doi.org/10.1530/EJE-18-0693>	Study outcome - self-reported or doctor diagnosed
'Polycystic Ovary Syndrome (PCOS) and Sleep Apnea', Sleep, Metabolic, and Cardiovascular Dysfunction in Polycystic Ovary Syndrome, 2005 <http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=cctr&NEWS=N&AN=CN-01510943>	Clinical Trial
Eisenberg, Esther, Richard S Legro, Michael P Diamond, Hao Huang, Louise M O'Brien, Yolanda R Smith, and others, 'Sleep Habits of Women With Infertility.', Journal of Clinical Endocrinology & Metabolism, 106.11 (2021), e4414–26 <https://doi.org/10.1210/clinem/dgab474>	Study outcome - through questionnaire without formal assessment
A., Thannickal, Brutocao C., Alsawas M., Morrow A., Zaiem F., Murad M.H., and others, 'Eating, Sleeping and Sexual Function Disorders in Women with Polycystic Ovary Syndrome (PCOS): A Systematic Review and Meta-Analysis', Clinical Endocrinology, 92.4 (2020), 338–49 <https://doi.org/https://dx.doi.org/10.1111/cen.14153>	No pooled analysis
A., Gateva, Kamenov Z., Mondeshki Ts., Bilyukov R., and Georgiev O, '[Polycystic ovarian syndrome and obstructive sleep apnea]', Akusherstvo i ginekologiia, 52.3 (2013), 63–68 <http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed14&NEWS=N&AN=603396089>	Language not English
K.A., Temple, Tasali E., Mokhlesi B., Whitmore H., Watson S., Van Cauter E., and others, 'Abnormal Glucose Tolerance in Women with Polycystic Ovary Syndrome (PCOS): Role of Sex Steroids and Obstructive Sleep Apnea', Diabetes, 73rd Scientific Sessions of the American	Conference Proceeding

Diabetes Association. Chicago, IL United States., 62.SUPPL. 1 (2013), A377 <https://doi.org/https://dx.doi.org/10.2337/db13-1395-1677>	
A., Desai, and Subramanian S, 'Polycystic Ovarian Syndrome and Obstructive Sleep Apnea', Current Respiratory Medicine Reviews, 3.4 (2007), 278–81 <https://doi.org/https://dx.doi.org/10.2174/157339807782359887>	Narrative Review
de Sousa, Gideon, Bernhard Schluter, Dirk Buschatz, Thomas Menke, Eckardt Trowitzsch, Werner Andler, and others, 'A Comparison of Polysomnographic Variables between Obese Adolescents with Polycystic Ovarian Syndrome and Healthy, Normal-Weight and Obese Adolescents.', Sleep & Breathing = Schlaf & Atmung, 14.1 (2010), 33–38 <https://doi.org/https://dx.doi.org/10.1007/s11325-009-0276-0>	Study outcome - only reporting mean (SD) of AHI /obstructive apnoea events
Eisenberg, E, O'Brien LM, S Jin, He AL, H Huang, Smith YR, and others, 'Sleep Habits of Infertile Women', Endocrine Reviews, 36 (2015) <http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=cctr&NEWS=N&AN=CN-01293771>	Conference Proceeding
T., Strauss, Nandalike K., Sin S., and Arens R, 'Upper Airway Structure and Body Fat Composition in Obese Adolescents with PCOS', American Journal of Respiratory and Critical Care Medicine, American Thoracic Society International Conference, ATS 2011. Denver, CO United States., 183.1 MeetingAbstracts (2011) <http://ajrccm.atsjournals.org/cgi/reprint/183/1_MeetingAbstracts/A3697?sid=c7e8ba23-da43-43b2-bef0-dad1707633e9>	Conference Proceeding
M.D., Caltekin, Hamamci M., Onat T., Kirmizi D.A., Baser E., and Melike Demir; ORCID: https://orcid.org/0000-0001-8797-7794 Yalvac E.S. AO - Caltekin, 'Evaluation of Sleep Quality, Restless Legs Syndrome, Anxiety and Depression in Polycystic Ovary Syndrome', Journal of Turkish Sleep Medicine, Polikistik over Sendromunda Uyku Kalitesi, Huzursuz Bacaklar Sendromu, Anksiyete ve Depresyonun Degerlendirilmesi, 8.3 (2021), 243–49 <https://doi.org/https://dx.doi.org/10.4274/JTSM.GALENOS.2021.85057>	Study outcome - through questionnaire without formal assessment
L.A., Allen, Shrikrishnapalasuriyar N., and Dafydd Aled; ORCID: https://orcid.org/0000-0002-1165-9092 Rees D.A. AO - Rees, 'Long-Term Health Outcomes in Young Women with Polycystic Ovary Syndrome: A Narrative Review', Clinical Endocrinology, 97.2 (2022), 187–98 <https://doi.org/https://dx.doi.org/10.1111/cen.14609>	Narrative review

5. STUDY CHARACTERISTICS TABLE

Author, year, country	Population/ Setting	Study Design	Sample Size per group	Intervention/ exposure details	Comparison/ control details	Follow up Duration	Outcomes	Summary of findings
deSousa et al. 2011, Germany	Obese adolescents, outpatient Obesity and Endocrine Department of the Vestische Children's Hospital	Cross sectional	Women with PCOS = 31 Women without PCOS = 19	The diagnosis of PCOS was based on the 1992 NIH criteria	All control patients had normal menstrual cycles (28–35 days) and no clinical signs of androgen excess, thereby excluding PCOS by NIH definition	NA	OSA: AHI≥5	No difference between exposed and control. No OSAS in both groups.
Fogel et al. 2001, USA	Overweight (Body Mass Index > 28 kg/m^2) women aged 18-45. Advertisement within community (controls) or from the Division of Women's Health at the Brigham and Women's Hospital and the Reproductive Endocrine Unit of the Massachusetts General Hospital (cases).	Cross-sectional	Women with PCOS = 18 Women without PCOS = 18	Exposure diagnosed as chronic oligomenorrhea (six or fewer menses per year) along with elevated serum androgen levels (total or biologically available testosterone levels).	Control defined as women having normal menstrual cycles (28–35 days), no clinical signs of androgen excess, and normal serum levels of androgens.	NA	OSA: AHI>5 OSA: AHI>10 OSA: AHI>15 OSAS: AHI>5 + Epworth Sleepiness Score =>10	Obese women with PCOS are at increased risk of OSA when compared with age and weight matched reproductively normal women
Hachul et al. 2019, Brazil	A total of 44 subjects were selected to participate in the study. The volunteers, ranging in age from 16 to 45 years, were recruited from the	Cross-sectional	Women with PCOS = 30 Women without PCOS = 14	The diagnosis of PCOS was based on the latest 2003 Rotterdam consensus	The control group was comprised of 14 women with a regular menstrual cycle of 28-30 days, normal BMI and in the follicular phase of the menstrual cycle.	NA	OSAS: (AHI≥5+ sleep complaints) or AHI≥15	Only the PCOS group had obstructive sleep apnea diagnosis in this study.

	Endocrinology Division of the Federal University of São Paulo, Brazil							
Helvaci et al. 2017, Turkey	Adults and adolescents	Systematic review and meta-analysis	Systematic review: 13 studies (8 adult, 5 adolescent) Meta-analyses: 6 studies (4 adult, 2 adolescent)	Any diagnostic criteria of PCOS	Implied as non-PCOS patients	NA	OR (95% CI) of outcome OSA among adult and adolescent women with PCOS compared to controls	
Kahal et al. 2020, UK	All women with PCOS	Systematic review and meta-analysis	Prevalence of OSA in PCOS women: 17 studies OR for OSA in PCOS vs control: 8 studies	Any diagnostic criteria of PCOS	Implied as non-PCOS patients	NA	OR (95% CI) of outcome OSA among women with PCOS compared to controls	OSA prevalence was markedly higher in obese versus lean women with PCOS, and in women with PCOS compared to controls (odds ratio = 3.83, 95% CI 1.43–10.24, eight studies, 957 participants (349 PCOS and 608 controls))
Nandalike et al. 2012, USA	28 adolescent girls aged 13–18 years diagnosed with PCOS at Children's Hospital at Montefiore (CHAM), between January 2006 and December 2009, and 28 age and BMI z-score matched control women who	Cross-sectional	Women with PCOS = 28 Women without PCOS = 28	The diagnosis of PCOS was based on the latest 2003 Rotterdam consensus	Charts of females chosen as controls through the sleep – disorders centre database were verified and any girl with any history of oligomenorrhea (less than nine menstrual cycles in a year) or amenorrhoea, or any documented	NA	OSA: (AHI > 5) or apnoea index >1	The authors report a higher prevalence of OSA and metabolic dysfunction in a selected group of obese girls with PCOS referred with sleep-related complaints compared to BMI-matched control girls without PCOS.

	underwent overnight polysomnography (PSG)				clinical signs of hyperandrogenism such as acne or hirsutism or biochemical evidence of hyperandrogenemia, was excluded from the study.			
Suri et al. 2016, India	Patients with PCOS who attended the Gynecology Outpatient Department (OPD) and Reproductive Endocrinology Clinic of Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India who met inclusion and exclusion criteria and consented to take part in the study	Cross-sectional	Women with PCOS = 50 Women without PCOS = 100	The diagnosis of PCOS was based on the latest 2003 Rotterdam consensus	Age-matched women who attended the gynecology OPD with other complaints such as vaginal discharge, dysuria, and pelvic organ prolapse were recruited as control subjects after obtaining the required consent. All of these women experienced regular menstrual cycles and did not meet the standard diagnostic criteria for PCOS.	NA	SDB: (RDI ≥ 5 + symptoms such as EDS, choking, witnessed apneic spell, nocturia,) or RDI > 15	SDB was seen in 66% of the case patients and in 4% of control group with (odds ratio [OR] = 46.5, 95% confidence interval [CI] = 14.6–148.4; p < 0.001). After adjustment for body mass index (BMI) and waist circumference (WC), the difference was not significant (p = 0.993 and p = 0.931, respectively)
Tasali et al. 2008, USA	52 women with PCOS aged between 18 and 40 yr old were consecutively recruited from the Endocrinology Clinics at the University of Chicago between	Cross-sectional	Women with PCOS = 21 Women without PCOS = 21	A diagnosis of PCOS required 1) the presence of oligo/amenorrhea; 2) hyperandrogenemia, defined by a supranormal plasma free testosterone level	21 overweight (BMI>25 kg/m2 but <30 kg/m2) and obese (BMI ≥30 kg/m2) women aged between 18 and 40 yr old who were otherwise healthy were recruited through	NA	OSA: AHI≥5	Twenty-nine women (56%) with PCOS had OSA compared with four controls (19%) (adjusted odds ratio 7.1; 95% confidence interval, 1.7–45.7; P<0.01).

	February 1, 2004, and September 30, 2007.			(>10 pg/ml); 3) hyperandrogenism, as evidenced by infertility, hirsutism, acne, or androgenetic alopecia; and 4) exclusion of nonclassic 21-hydroxylase deficiency, congenital adrenal hyperplasia, Cushing's syndrome, hypothyroidism, or significant elevations in serum prolactin.	public advertisements in the local community.			
Vgontzaz et al. 2001, USA	Fifty-three premenopausal women with PCOS [age range, 16–45 yr; body mass index (BMI) range, 24.3–67.7] were prospectively studied in the sleep laboratory.	Cross sectional	Women with PCOS = 53 Women without PCOS = 452	The diagnosis of PCOS was made by the presence of chronic anovulation (six or fewer menstrual periods per year) in association with elevated circulating androgen levels (total testosterone more than 201.1 nmol/L and/or free and weakly bound testosterone more than 55.5 nmol/L).	Control women were 452 premenopausal women 42 yr of age or younger (age range, 20-42 yr; BMI range, 16.1–59.9) selected from a general randomized sample.	NA	SDB: AHI >10 + symptoms such as daytime sleepiness, hypertension, or other cardiovascular complication	OSA was much more prevalent in premenopausal women with PCOS than in normal controls (ratio, 30:1). This difference remained significant, even when we corrected for BMI differences between the two groups
Yang et al. 2009	Women with PCOS aged 18–45 years and with a BMI of	Cross-sectional	Women with PCOS = 18	The Rotterdam criteria were used for the initial	Ten age-matched and BMI-matched women who did not	NA	AHI≥5	There was no difference between the PCOS and the

	less than 27 were consecutively recruited after initial screening for PCOS when they presented with oligomenorrhea at the Obstetric and Gynecology Clinic of Taipei Medical University Hospital between May 2006 and January 2007.		Women without PCOS = 10	diagnosis of PCOS. To make the phenotype more consistent, we included patients who had both biochemical hyperandrogenemia and polycystic ovaries.	have PCOS were recruited as a control group from the same community during the same period. Women were excluded from the control group if they had irregular menstruation or oligomenorrhea, abnormal serum thyroid stimulating hormone or prolactin, or biochemical hyperandrogenemia			control groups in any of the other polysomnographic variables. None of the 28 women had an AHI greater than 5, which is the standard for OSA.

PCOS: Polycystic Ovary syndrome; OSA: Obstructive Sleep Apnoea; AHI: Apnoea Hypopnea Index; OR: Odds Ratio

6. FINDINGS

- **EVIDENCE SUMMARY:**

The developed search strategy was used to extract systematic reviews, randomised controlled trials, cross-sectional studies, controlled cohort studies and case control studies from Medline, PsychInfo, EMBASE, and Evidence Based Medicine Reviews which resulted in 996, 247, 2272 and 286 hits respectively. Following title and abstract screening and full text screening, 10 articles were included in the systematic review, of which 8 were primary research studies conducted using a cross-sectional study design, and 2 were secondary research studies (systematic reviews) by Helavci et al., and Kahal et al. Two of the primary research studies (Hachul et. al., and Suri et. al.) were not included in either of the secondary research studies found. Therefore, a new systematic review and meta-analysis was conducted as an update.

While 3 primary research studies included women of all groups, 3 and 2 studies were restricted to women of reproductive age between 16 and 45 years old, and adolescent girls restrictively. Five out of eight primary research studies had moderate to low risk of bias, and three studies had high risk of bias.

Composite outcome: AHI > 5 / AHI > 5 along with specific symptoms / AHI > 10

The findings from all the 8 primary research studies were pooled together using meta-analysis. In the meta-analysis, a total of 280 women with PCOS were compared to 662 women without PCOS and the pooled relative odds of obstructive sleep apnoea was estimated. OSA was defined variably according to the primary study's definitions as (1) AHI > 5, (2) AHI > 5 along with specific symptoms, or (3) AHI > 10. A total of 109 (38.9%) and 22 (3.3%) women with and without PCOS had OSA respectively.

A further subgroup analysis of women with BMI in the overweight or obesity range (including estimates from deSouza et al., Fogel et al., Tasali et al., and Vgontzaz et al.,) was conducted.

Outcome: AHI > 5

The findings from all the 4 primary research studies (deSouza et al., Fogel et al., Tasali et al., and Yang et al.) were pooled together using meta-analysis of 119 women with PCOS compared to 68 women without PCOS. The pooled relative odds of obstructive sleep apnoea defined as AHI > 5 was estimated. A total of 42 (35.3%) and 11 (16.2%) women with and without PCOS had AHI > 5 respectively.

A further subgroup analysis of women with BMI in the overweight or obesity range (excluding the study by Yang et al.,) was conducted.

Outcome: AHI > 5 along with specific symptoms

The findings from all the 4 primary research studies (Fogel et al., Hachul et al., Nandalike et al., and Suri et al.) were pooled together using meta-analysis of 126 women with PCOS compared to 160 women without PCOS. The pooled relative odds of obstructive sleep apnoea defined as AHI > 5 along with specific symptoms was estimated. A total of 66 (52.4%) and 9 (5.6%) women with and without PCOS had OSA respectively.

▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

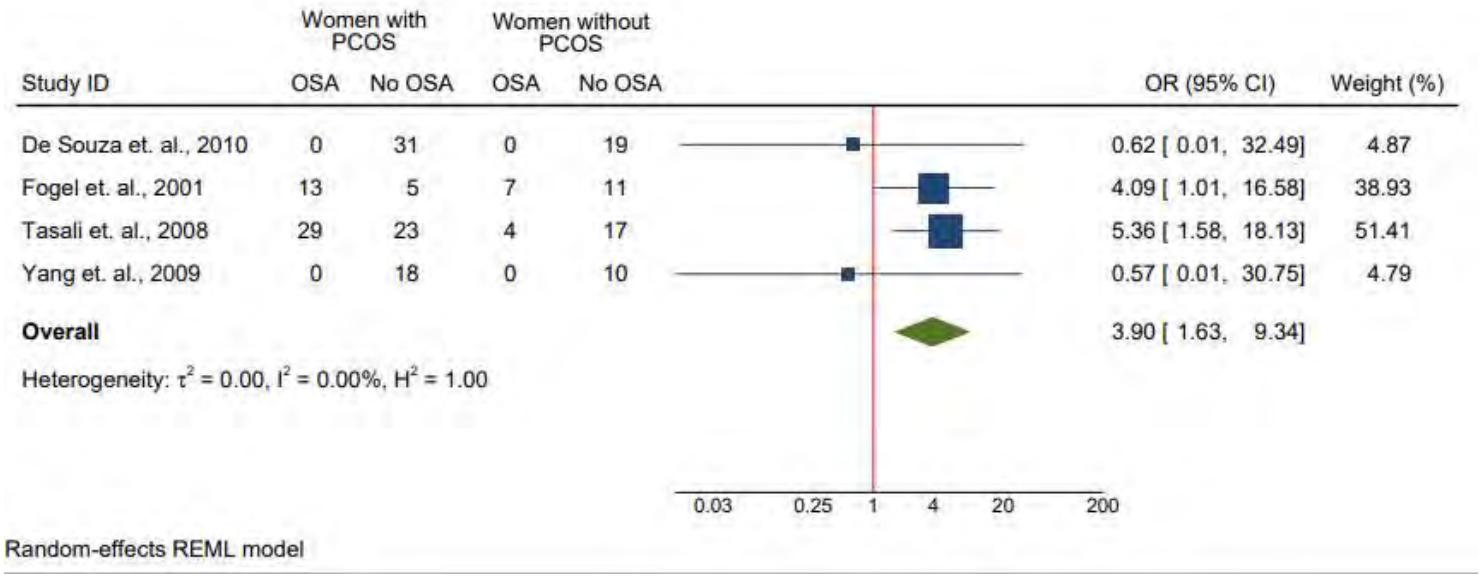
Pooled analysis suggested that women with PCOS were nearly at a 10 times higher risk of OSA (AHI>5 or AHI> 5 along with specific symptoms or AHI>10) compared to women without OSA [aOR: 9.52 (3.90-23.26)]. The association was more profound when when considering the more severe definition of OSA - AHI > 5 was considered alongside presentation of specific symptoms) [OR: 17.95 (95% CI 6.17-52.22)]. The magnitude of effect estimate was relatively smaller when considering the relatively less severe outcome definition - AHI > 5 only [OR: 3.90 (95% CI 1.63-9.34)].

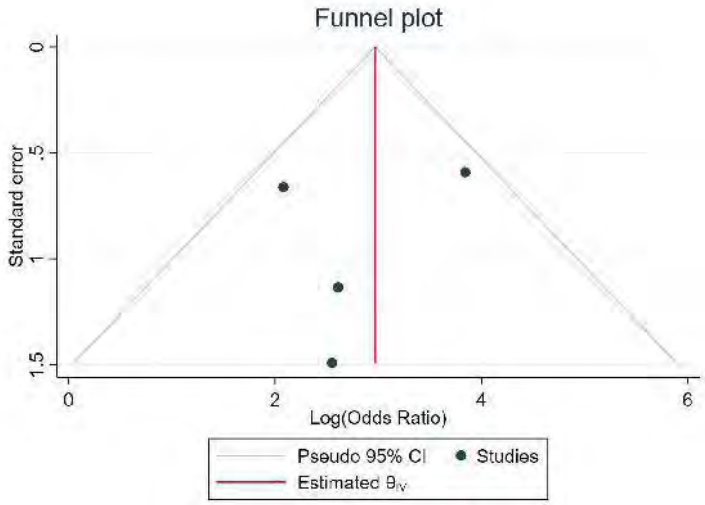
In a subgroup analysis of women with BMI in the overweight or obesity range, there was a 7.1 times and 4.3 times higher risk of (1) AHI>5 or AHI>5 along with specific symptoms or AHI>10 and (2) AHI>5 among women with PCOS compared to women without PCOS respectively [OR: 7.10 (95% CI 2.13-23.65) and 4.29 (95% CI 1.75-10.52) respectively].

▪ RESULTS TABLES and PLOTS:

OUTCOME: Apnea hypopnea index (AHI) >5 events per hour					**OUTCOME TYPE: Dichotomous**			
COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
deSousa et al. 2011	Count	Polysomnography	0	31	0	19	Crude	NA
Fogel et al. 2001	count	Polysomnography	AHI>5 – NR (72%) AHI>10 – NR (66.67%) AHI>15 – NR (44.44%)	AHI>5 - 18 AHI>10 - 18 AHI>15 - 18	AHI>5 – NR (39%) AHI>10 – NR (16.67%) AHI>15 – NR (5.5%)	AHI>5 - 18 AHI>10 - 18 AHI>15 - 18	Crude	NA (but age and weight matched)

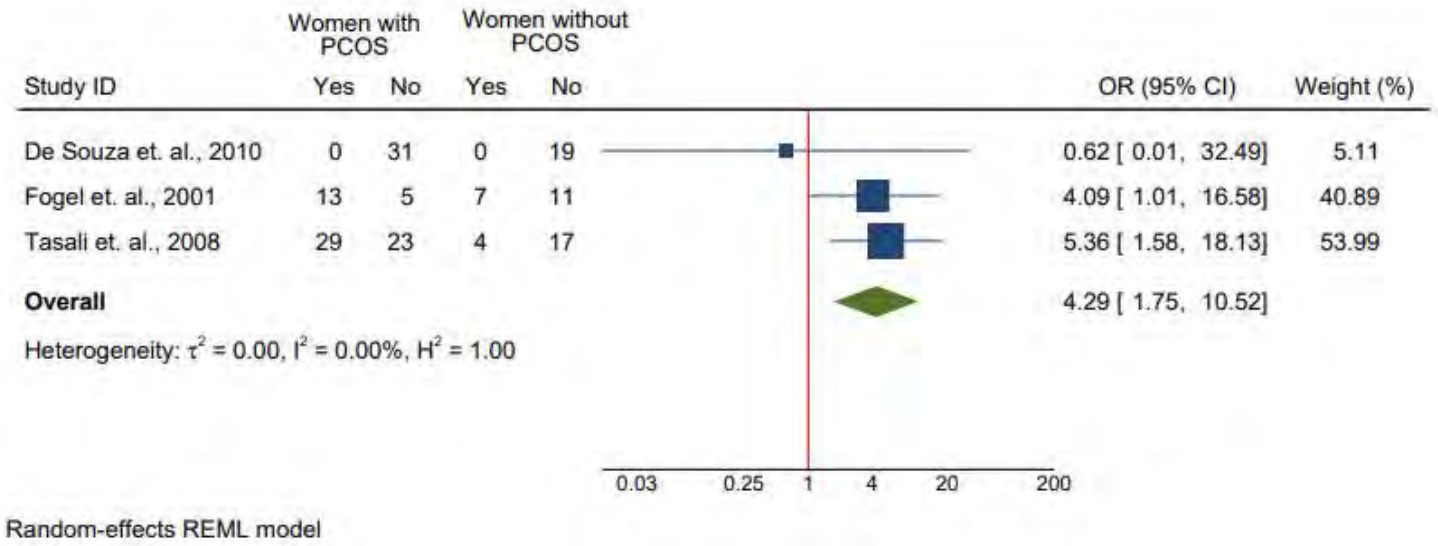
Tasali et al. 2008	Count	Polysomnography	AHI≥5 – 29 (56%)	AHI≥5 – 52	AHI≥5 – 4 (19%)	AHI≥5 – 21	Adjusted	Age, BMI, and ethnicity
Yang et al. 2009	Count	Polysomnogrpahy	AHI≥5 – 0 (0%)	AHI≥5 – 18	AHI≥5 – 0 (0%)	AHI≥5 – 10	Crude	NA (but age and BMI matched)

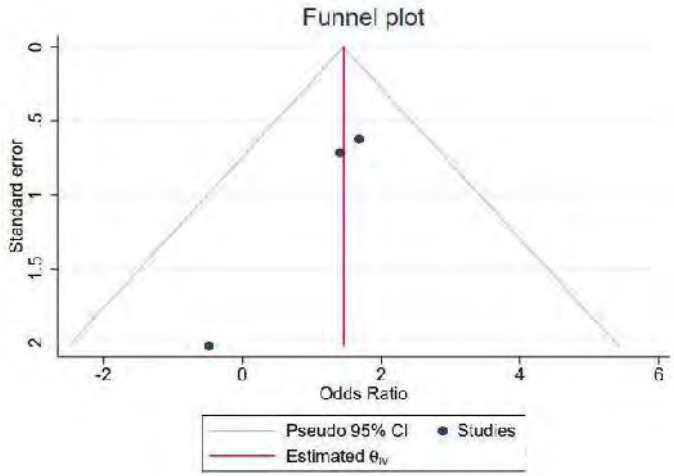




Eggers test for publication bias: Z= -0.43; p=0.6657

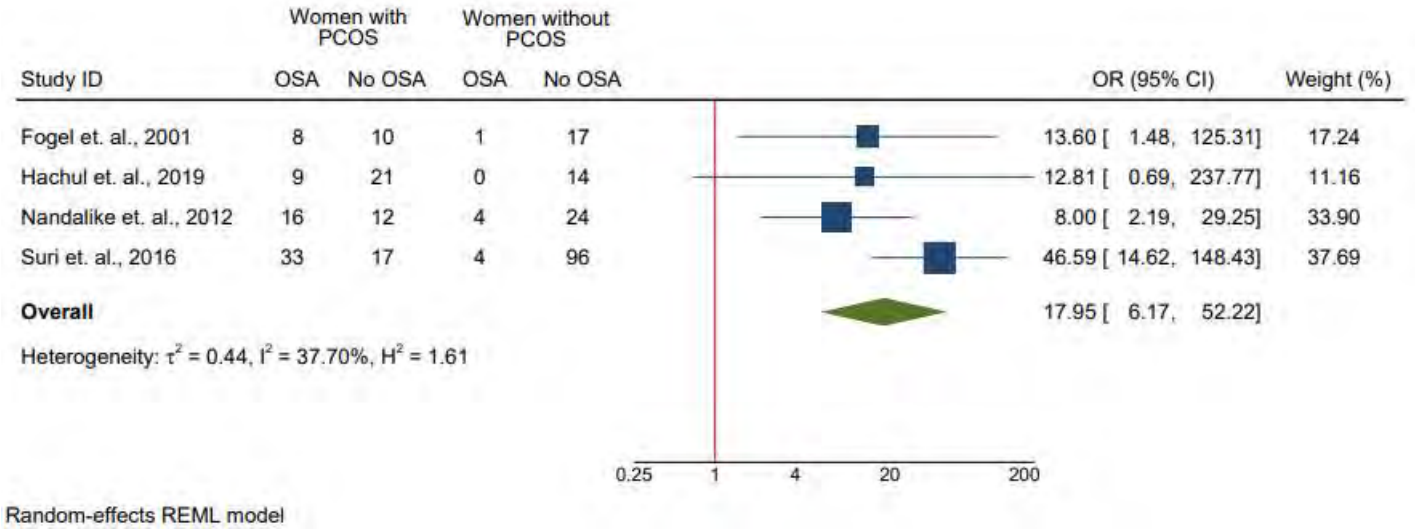
OUTCOME: Apnea hypopnea index (AHI) >5 events per hour				**OUTCOME TYPE: Dichotomous**				
COMPARISON (if applicable): PCOS vs non-PCOS in a subgroup of women who are overweight/obese								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
deSousa et al. 2011	Count	Polysomnography	0	31	0	19	Crude	NA
Fogel et al. 2001	count	Polysomnography	AHI>5 – NR (72%) AHI>10 – NR (66.67%) AHI>15 – NR (44.44%)	AHI>5 - 18 AHI>10 - 18 AHI>15 - 18	AHI>5 – NR (39%) AHI>10 – NR (16.67%) AHI>15 – NR (5.5%)	AHI>5 - 18 AHI>10 - 18 AHI>15 - 18	Crude	NA (but age and weight matched)
Tasali et al. 2008	Count	Polysomnography	AHI≥5 – 29 (56%)	AHI≥5 – 52	AHI≥5 – 4 (19%)	AHI≥5 – 21	Adjusted	Age, BMI, and ethnicity

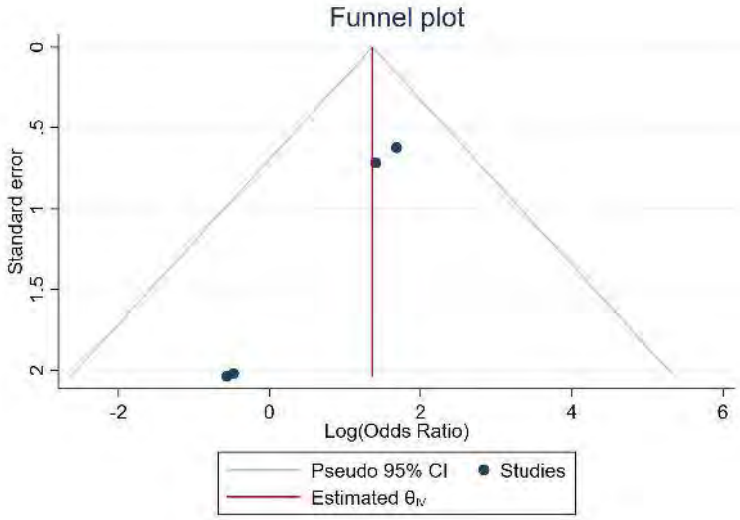




Eggers test for publication bias: Z= -1.02; p=0.3098

OUTCOME: sleep apnea syndrome – AHI > 5 + symptoms				**OUTCOME TYPE: Dichotomous**				
COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Fogel et al. 2001	Count	Polysomnography + self-report from questionnaire to assess excessive daytime sleepiness	AHI>5 & Epworth sleepiness score≥10 - NR (44.44%)	AHI>5 & Epworth sleepiness score≥10 - 18	AHI>5 & Epworth sleepiness score≥10 - NR (5.5%)	AHI>5 & Epworth sleepiness score≥10 - 18	Crude	NA (but age and weight matched)
Hachul et al. 2019	Count	Polysomnography + self-reported sleep complaint	AHI≥5 & sleep complaints (OR) AHI≥15 - 9 (30.0%)	AHI≥5 & sleep complaints (OR) AHI≥15 - 30	AHI≥5 & sleep complaints (OR) AHI≥15 - 0 (0.0%)	AHI≥5 & sleep complaints (OR) AHI≥15 - 14	Crude	NA
Nandalike et al. 2012	Count	Polysomnography	AHI>5 or Apnoea index>1 – 16 (57%)	AHI>5 or Apnoea index>1 – 28	AHI>5 or Apnoea index>1 – 4 (14.3%)	AHI>5 or Apnoea index>1 – 28	Crude	NA (But age and BMI z score matched)
Suri et al. 2016	Count	Polysomnography + self-report from questionnaire	(RDI≥5 + symptoms) or RDI>15 – 33 (66%)	(RDI≥5 + symptoms) or RDI>15 – 50	(RDI≥5 + symptoms) or RDI>15 – 4 (4%)	(RDI≥5 + symptoms) or RDI>15 – 100	Adjusted	BMI or waist circumference (Also age and BMI z score matched)



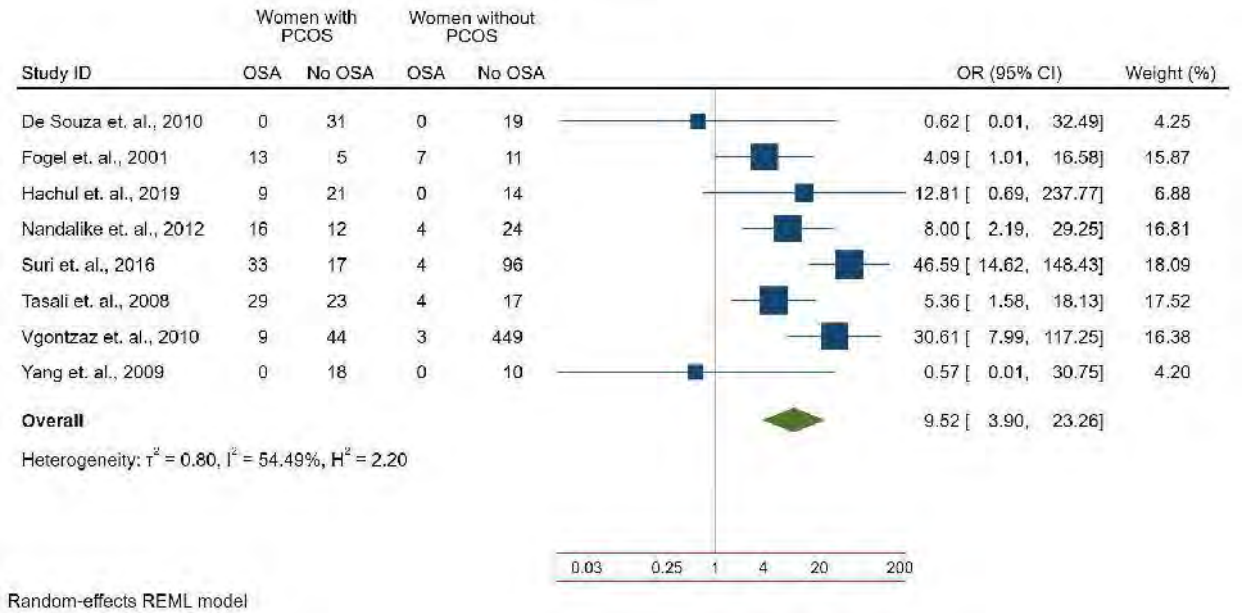


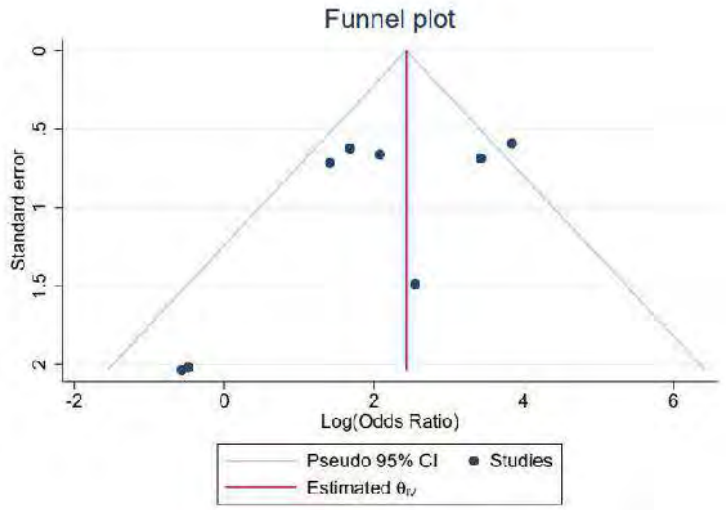
Eggers test for publication bias: Z= -1.40; p=0.1603

OUTCOME: sleep apnea syndrome – AHI > 10 + symptoms				**OUTCOME TYPE: Dichotomous**				
COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Vgontzaz et al. 2001	Count	Polysomnography + self-report from questionnaire	(AHI>10 + symptoms) – 9 (17%) Subgroup <32.2 kg/m^2 – 1 (8.3%) Subgroup ≥32.2 kg/m^2 – 8 (19.5%)	(AHI>10 + symptoms) – 53 Subgroup <32.2 kg/m^2 – 12 Subgroup ≥32.2 kg/m^2 – 41	(AHI>10 + symptoms) – 3 (0.6%) Subgroup <32.2 kg/m^2 – 0 (0%) Subgroup ≥32.2 kg/m^2 – 3 (4.5%)	(AHI>10 + symptoms) – 452 Subgroup <32.2 kg/m^2 – 386 Subgroup ≥32.2 kg/m^2 – 66	Crude	NA

OUTCOME: sleep apnea – AHI > 5 or AHI > 5 + symptoms or AHI > 10				OUTCOME TYPE: Dichotomous				
COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
deSousa et al. 2011	Count	Polysomnography	0	31	0	19	Crude	NA
Fogel et al. 2001	count	Polysomnography	AHI>5 – NR (72%) AHI>10 – NR (66.67%) AHI>15 – NR (44.44%)	AHI>5 - 18 AHI>10 - 18 AHI>15 - 18	AHI>5 – NR (39%) AHI>10 – NR (16.67%) AHI>15 – NR (5.5%)	AHI>5 - 18 AHI>10 - 18 AHI>15 - 18	Crude	NA (but age and weight matched)
Hachul et al. 2019	Count	Polysomnography + self-reported sleep complaint	AHI≥5 & sleep complaints (OR) AHI≥15 - 9 (30.0%)	AHI≥5 & sleep complaints (OR) AHI≥15 - 30	AHI≥5 & sleep complaints (OR) AHI≥15 - 0 (0.0%)	AHI≥5 & sleep complaints (OR) AHI≥15 - 14	Crude	NA
Nandalike et al. 2012	Count	Polysomnography	AHI>5 or Apnoea index>1 – 16 (57%)	AHI>5 or Apnoea index>1 – 28	AHI>5 or Apnoea index>1 – 4 (14.3%)	AHI>5 or Apnoea index>1 – 28	Crude	NA (But age and BMI z score matched)
Suri et al. 2016	Count	Polysomnography + self-report from questionnaire	(RDI≥5 + symptoms) or RDI>15 – 33 (66%)	(RDI≥5 + symptoms) or RDI>15 – 50	(RDI≥5 + symptoms) or RDI>15 – 4 (4%)	(RDI≥5 + symptoms) or RDI>15 – 100	Adjusted	BMI or waist circumference (Also age and BMI z score matched)
Tasali et al. 2008	Count	Polysomnography	AHI≥5 – 29 (56%)	AHI≥5 – 52	AHI≥5 – 4 (19%)	AHI≥5 – 21	Adjusted	Age, BMI, and ethnicity
Vgontzaz et al. 2001	Count	Polysomnography + self-report from questionnaire	(AHI>10 + symptoms) – 9 (17%)	(AHI>10 + symptoms) – 53	(AHI>10 + symptoms) – 3 (0.6%)	(AHI>10 + symptoms) – 452	Crude	NA

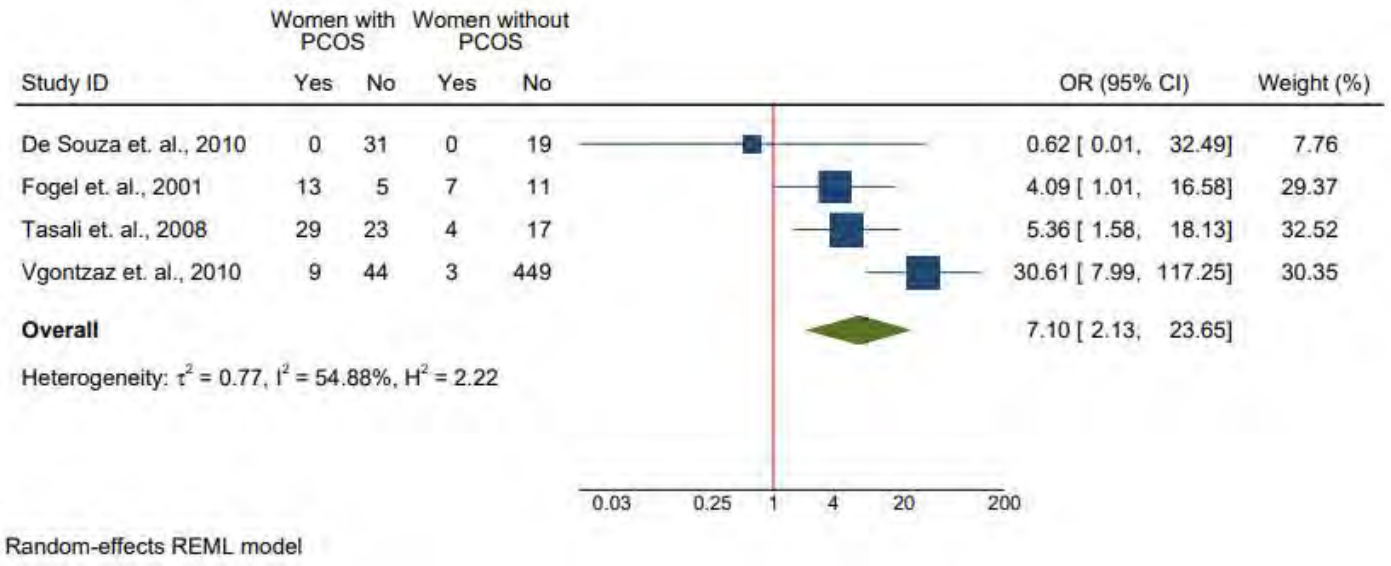
			Subgroup <32.2 kg/m^2 – 1 (8.3%) Subgroup ≥32.2 kg/m^2 – 8 (19.5%)	Subgroup <32.2 kg/m^2 – 12 Subgroup ≥32.2 kg/m^2 – 41	Subgroup <32.2 kg/m^2 – 0 (0%) Subgroup ≥32.2 kg/m^2 – 3 (4.5%)	Subgroup <32.2 kg/m^2 – 386 Subgroup ≥32.2 kg/m^2 – 66		
Yang et al. 2009	Count	Polysomnogrpahy	AHI≥5 – 0 (0%)	AHI≥5 – 18	AHI≥5 – 0 (0%)	AHI≥5 – 10	Crude	NA (but age and BMI matched)

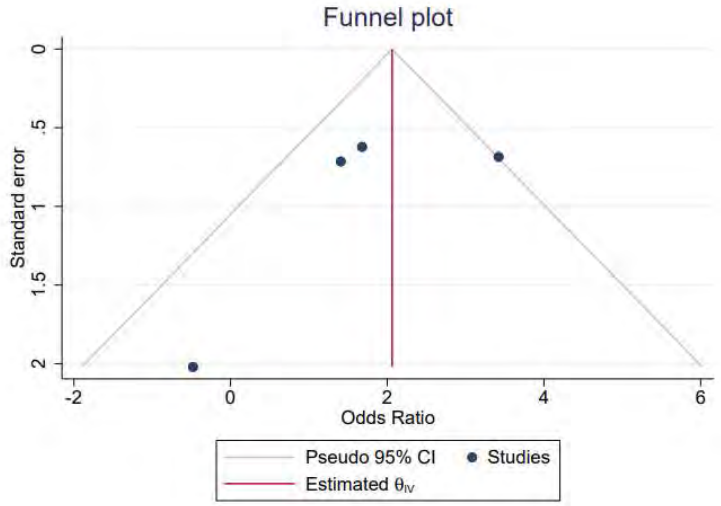




Egger test for funnel plot asymmetry: No significant publication bias; z= -1.16; p=0.1018

OUTCOME: sleep apnea – AHI > 5 or AHI > 5 + symptoms or AHI > 10				OUTCOME TYPE: Dichotomous				
COMPARISON (if applicable): PCOS vs non-PCOS in a subgroup of women who are overweight/obese								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
deSousa et al. 2011	Count	Polysomnography	0	31	0	19	Crude	NA
Fogel et al. 2001	count	Polysomnography	AHI>5 – NR (72%) AHI>10 – NR (66.67%) AHI>15 – NR (44.44%)	AHI>5 - 18 AHI>10 - 18 AHI>15 - 18	AHI>5 – NR (39%) AHI>10 – NR (16.67%) AHI>15 – NR (5.5%)	AHI>5 - 18 AHI>10 - 18 AHI>15 - 18	Crude	NA (but age and weight matched)
Tasali et al. 2008	Count	Polysomnography	AHI≥5 – 29 (56%)	AHI≥5 – 52	AHI≥5 – 4 (19%)	AHI≥5 – 21	Adjusted	Age, BMI, and ethnicity
Vgontzaz et al. 2001	Count	Polysomnography + self-report from questionnaire	(AHI>10 + symptoms) – 9 (17%) Subgroup <32.2 kg/m^2 – 1 (8.3%) Subgroup ≥32.2 kg/m^2 – 8 (19.5%)	(AHI>10 + symptoms) – 53 Subgroup <32.2 kg/m^2 – 12 Subgroup ≥32.2 kg/m^2 – 41	(AHI>10 + symptoms) – 3 (0.6%) Subgroup <32.2 kg/m^2 – 0 (0%) Subgroup ≥32.2 kg/m^2 – 3 (4.5%)	(AHI>10 + symptoms) – 452 Subgroup <32.2 kg/m^2 – 386 Subgroup ≥32.2 kg/m^2 – 66	Crude	NA





Egger test for funnel plot asymmetry: No significant publication bias; z= -1.13; p=0.2568

OUTCOME: Obstructive sleep apnoea (based on polysomnography)			**OUTCOME TYPE: Dichotomous**					
COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Helvaci et al. 2017	Count Proportion Odds ratio	Standard overnight polysomnography in all included studies	Adult Yang,2009 n=0 Tasali,2008 n=29 Fogel,2001 n=8 Vgontzas,2001 n=9 Adolescent Nandalike,2012 n=16 De Sousa,2011 N=0	Adult Yang,2009 n=18 Tasali,2008 n=52 Fogel,2001 n=18 Vgontzas,2001 n=53 Adolescent Nandalike,2012 n=28 De Sousa,2011 n=14	Adult Yang,2009 n=0 Tasali,2008 n=4 Fogel,2001 n=1 Vgontzas,2001 n=3 Adolescent Nandalike,2012 n=4 De Sousa,2011 n=0	Adult Yang,2009 n=10 Tasali,2008 n=21 Fogel,2001 n=18 Vgontzas,2001 n=452 Adolescent Nandalike,2012 n=28 De Sousa,2011 n=19	Crude Yang,2009 OR=0.57 (0.01,30.75) Tasali,2008 OR=5.36 (1.58-18.13) Fogel,2001 OR=13.6 (1.48-125.3) Vgontzas,2001 OR=30.61 (7.99-117.25 Pooled OR= 9.74 (2.76-34.41) Adolescent Nandalike,2012 OR=8.0 (2.19-29.25) De Sousa,2011 OR=0.62 (0.01-32.49) Pooled OR= 4.54 (0.56-36.43)	The studies by Yang et. Al., and De Souza et. Al., report 0 outcomes.
Kahal et al. 2020	Count Proportion Odds ratio	polysomnography	de Sousa,2012 0% Fogel,2001 72%	de Sousa,2012 N=35 Fogel,2001 N=18	de Sousa,2012 0% Fogel,2001 39%	de Sousa,2012 N=19 Fogel,2001 N=18	Crude de Sousa,2012 NA Fogel,2001 4.09 (1.01-16.58)	

			Nandalike,2012 57.1% Tasali,2008 55.8% Temple,2013 48.1% Vgontzas,2001 11.3% Wootton,2017 50% Yang,2009 0%	Nandalike,2012 N=28 Tasali,2008 N=52 Temple,2013 N=129 Vgontzas,2001 N=53 Wootton,2017 N=16 Yang,2009 N=18	Nandalike,2012 14.3% Tasali,2008 19% Temple,2013 41% Vgontzas,2001 0.4% Wootton,2017 57.1% Yang,2009 0%	Nandalike,2012 N=28 Tasali,2008 N=21 Temple,2013 N=46 Vgontzas,2001 N=452 Wootton,2017 N=14 Yang,2009 N=10	Nandalike,2012 8.00 (2.19-29.25) Tasali,2008 5.36 (1.58-18.13) Temple,2013 1.32 (0.67-2.60) Vgontzas,2001 28.72 (5.64-146.35) Wootton,2017 0.75 (0.18-3.17) Yang,2009 NA Pooled OR= 3.83 (1.43-10.24)	

7. GRADE ASSESSMENTS AND EVIDENCE PROFILE

COMPARISON: PCOS vs non-PCOS												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Women with PCOS	Women without PCOS	Effect, fixed [95% CI]	Favours	Certainty	Importance
Outcome: AHI>5												
4	Cross-sectional	no serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[7]	none	119	68	OR: 3.90 (1.63-9.34)	Increased odds of apnea among women with PCOS	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: AHI>5 + symptoms												
4	Cross-sectional	serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	none	126	160	OR: 17.95 (6.17-52.22)	Increased odds of apnea among women with PCOS	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: AHI>5 / AHI>5 + symptoms / AHI>10												
8	Cross-sectional	serious[1]	no serious inconsistency	no serious indirectness	serious imprecision[1]	none	280	662	OR: 9.52 (3.90-23.26)	Increased odds of apnea among women with PCOS	⊕⊕⊕◯ MODERATE	CRITICAL

COMPARISON: Overweight/Obese PCOS vs Overweight/Obese non-PCOS												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Women with PCOS	Women without PCOS	Effect, fixed [95% CI]	Favours	Certainty	Importance
Outcome: AHI>5												
3	Cross-sectional	no serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[9]	none	101	58	OR:4.29 (1.75-10.52)	Increased odds of apnea among women with PCOS	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: AHI>5 / AHI>5 + symptoms / AHI>10												
4	Cross-sectional	serious[1]	no serious inconsistency	no serious indirectness	serious imprecision[1]	none	154	510	OR: 7.10 (2.13-23.65)	Increased odds of apnea among women with PCOS	⊕⊕⊕◯ MODERATE	CRITICAL

[7] Two of the included studies in the pooled analysis have no outcome events
[8] Downgraded once as the majority of evidence is at moderate or high risk of bias
[9] Two of the included studies in the pooled analysis have no outcome events

APPENDIX. QUALITY APPRAISAL: CROSS-SECTIONAL or CASE-CONTROL STUDIES

Study ID	Desouza, 2011	
Study Citation	de Sousa G, Schlüter B, Menke T, Trowitzsch E, Andler W, Reinehr T. Relationships between polysomnographic variables, parameters of glucose metabolism, and serum androgens in obese adolescents with polycystic ovarian syndrome. J Sleep Res. 2011 Sep;20(3):472-8. doi: 10.1111/j.1365-2869.2010.00902.x. Epub 2010 Dec 29. PMID: 21199038.	
Study Country	Germany	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	We studied 31 obese adolescents aged 13–16 years with PCOS (mean age 15.0 years ± 1.0, mean BMI 32.7 kg per m2 ± 6.2, mean SDS–BMI 2.5 ± 0.8). The study group consisted of 13 new subjects and 18 others who had been part of our previous study group (de Sousa et al., 2010). Recruited form the outpatient Obesity and Endocrine Department of the Vestische Children's Hospital, Datteln, Germany	
Control population	19 healthy obese adolescents without PCOS aged 13–17 years (mean age 15.2 years ± 1.1, mean BMI 32.4 kg per m2 ± 4.0, mean SDS–BMI 2.5 ± 0.5). Recruited from the outpatient Obesity and Endocrine Department of the Vestische Children's Hospital, Datteln, Germany.	
PCOS diagnostic criteria	NIH 1992; Conditions such as non-classical adrenal 21-hydroxylase deficiency, androgen-secreting tumours and Cushing's syndrome were excluded by appropriate tests before the diagnosis of PCOS was made.	
N per group	PCOS group – 31 Non-PCOS group – 19	
Setting	Hospital outpatient	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary outcomes: - Obstructive sleep apnoea syndrome (AHI =>5) [n (%)] Outcomes not relevant: - Apnoea index [mean (SD)] -Hypopnoea index [mean (SD)] -Apnoea – hypopnoea index [mean (SD)] -Absolute number of obstructive apnoea [mean (SD)] -Sleep Stage 1 (%) [mean (SD)] -Sleep Stage 2 (%) [mean (SD)] -Sleep Stage 3 and 4 (%) [mean (SD)] - REM sleep (%) [mean (SD)] - Time in bed (min) [mean (SD)] -Total sleep time [mean (SD)] -Sleep efficiency (%) [mean (SD)] -Sleep onset latency (min) [mean (SD)] -Total wake time (TWT) (min) [mean (SD)] -Wakefulness after sleep onset (WASO) [mean(SD)]	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes The aim of this study was to compare polysomnographic variables of obese adolescents with polycystic ovarian syndrome (PCOS) to those of healthy controls

Inclusion criteria		Yes Partial No Not reported	Partial Partial generalisability as limited to obese adolescents aged 13–16 years
Exclusion criteria		Yes Partial No Not reported	Yes, Conditions such as non-classical adrenal 21-hydroxylase deficiency, androgen-secreting tumours and Cushing's syndrome were excluded by appropriate tests before the diagnosis of PCOS was made. The control patients were all healthy and had no history pointing towards sleep-related breathing disorders. All control patients had normal menstrual cycles (28–35 days) and no clinical signs of androgen excess, thereby excluding PCOS by NIH definition (Zawadski and Dunaif, 1992). All participants were without evidence of other diseases, including conditions which are common causes of apnoea in children and adolescents, such as adenotonsillar hypertrophy, craniofacial abnormalities or neuromuscular disease. Furthermore, all participants were not currently taking any medications.
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Yes, This study is cross-sectional
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Not relevant (the study is cross-sectional in nature)
Was matching performed?		Yes Partial No Not reported	No
Summary Result/s		PCOS was not associated with respiratory polysomnographic variables.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	Yes Both recruited from outpatient Obesity and Endocrine Department of the Vestische Children's Hospital
SELECTION BIAS	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes The diagnosis of PCOS was based on the definition of the NIH (Zawadski and Dunaif, 1992). Conditions such as non-classical adrenal 21-hydroxylase deficiency, androgen-secreting tumours and Cushing's syndrome were excluded by appropriate tests before the diagnosis of PCOS was made.

	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes The control patients were all healthy and had no history pointing towards sleep-related breathing disorders. All control patients had normal menstrual cycles (28–35 days) and no clinical signs of androgen excess, thereby excluding PCOS by NIH definition (Zawadski and Dunaif, 1992).
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	Yes Menstrual history was obtained from all the patients. All patients underwent physical examination. Percentage body fat was calculated in all participants. Serum insulin and glucose concentrations were measured in all participants in the fasting status. An oral glucose tolerance test (OGTT) was performed in all girls. All girls underwent overnight 12-channel polysomnography.
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	Yes Menstrual history was obtained from all the patients. All patients underwent physical examination. All girls underwent overnight 12-channel polysomnography
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes All girls underwent overnight 12-channel polysomnography.
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes All polysomnographic records were evaluated by experienced paediatric somnologists (B. S. and D. B.). Sleep was staged according to standard criteria (Rechtschaffen and Kales, 1968). Arousals and respiratory events were defined according to the guidelines of the American Academy of Sleep Medicine (AASM, 1992, 1999).
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	Not relevant to cross-sectional study
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Not reported
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	Not reported No protocol or PROSPERO

CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	Yes The girls in the study group and in the control group did not differ significantly in respect of age (P = 0.46), weight in kg (P = 0.70), BMI (P = 0.84), SDS–BMI (P = 0.74), waist circumference (P = 0.51), fasting glucose (P = 0.13), fasting insulin (P = 0.26), HOMA (P = 0.38), QUICKI (P = 0.95), 2-h glucose in oGTT (P = 0.08), serum dehydroepiandrosterone sulphate (P = 0.52) and serum androstendione (P = 0.08). Total testosterone was significantly higher in the girls with PCOS (P = 0.04) – but this is related to PCOS.
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes Comparisons between the cases and controls were performed by t-test for unpaired observations.
COMMENTS		Small sample size	
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

Study ID	Fogel 2001
Study Citation	Fogel RB, Malhotra A, Pillar G, Pittman SD, Dunaif A, White DP. Increased prevalence of obstructive sleep apnea syndrome in obese women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2001 Mar;86(3):1175-80. doi: 10.1210/jcem.86.3.7316. PMID: 11238505.
Study Country	USA
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	Women with untreated PCOS were recruited from the Division of Women's Health at the Brigham and Women's Hospital and the Reproductive Endocrine Unit of the Massachusetts General Hospital. All women were overweight (Body Mass Index > 28 kg/m2), healthy and between the ages of 18 and 45 yr. They were not currently taking any medications. No woman had an elevated plasma PRL level. Women in both groups were without evidence of other diseases including diabetes and hypertension.

Control population	Age- and weight-matched control women were recruited by means of advertisement within the community and had normal menstrual cycles (28–35 days), no clinical signs of androgen excess, and normal serum levels of androgens	
PCOS diagnostic criteria	AES 2016 Chronic oligomenorrhea (six or fewer menses per year) along with elevated serum androgen levels (total or biologically available testosterone levels). Nonclassical 21-hydroxylase deficiency was excluded by a 1-h ACTH stimulation test.	
N per group	PCOS group – 18 Non-PCOS group – 18	
Setting	Hospital for cases, community based recruitment through adverts for controls	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary outcomes: Polysomnography records classified according to American Academy of Sleep Medicine - AHI >5 [n (%)] - AHI >10 [n (%)] - AHI >15 [n (%)] Outcomes not relevant: - Epworth Sleepiness Score (ESS questionnaire) [mean (SEM)] - Sleep onset latency [mean (SEM)] - Sleep efficiency (%) [mean (SEM)] - REM sleep (%) [mean (SEM)] - AHI (all sleep stages) [mean (SEM)] - AHI (REM sleep) [mean (SEM)]	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes
Inclusion criteria	Yes Partial No Not reported	Partial Overweight women (Body Mass Index > 28 kg/m2) Between the ages of 18 and 45 yr For controls - normal menstrual cycles (28–35 days), and normal serum levels of androgens Generalisable to overweight BMI =>28 PCOS women on no medication and no other disease
Exclusion criteria	Yes Partial No Not reported	Yes, Not currently taking medication No other disease No elevated PRL No nonclassical 21-hydroxylase deficiency For controls - no clinical signs of androgen excess
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No	Yes, This study is cross-sectional

		Not reported	
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Not relevant (the study is cross-sectional in nature)
Was matching performed?		Yes Partial No Not reported	Yes, Age and weight
Summary Result/s		Obese women with PCOS are at increased risk of OSA when compared with matched reproductively normal women.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	No Control women were recruited by means of advertisement within the community. Women with untreated PCOS were recruited from the Division of Women's Health at the Brigham and Women's Hospital and the Reproductive Endocrine Unit of the Massachusetts General Hospital.
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes Case definition – (AES criteria) - Chronic oligomenorrhea (six or fewer menses per year) along with elevated serum androgen levels (total or biologically available testosterone levels). A single fasting blood sample for hormone analysis was obtained between 0800 and 1000 h. Assays for serum Testosterone (T) and de-hydroepiandrosterone sulfate (DHEAS) were performed by using diagnostic Products (Los Angeles, CA) Coat-A-Count kits.
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes Control definition - Control women had normal menstrual cycles (28–35 days), no clinical signs of androgen excess, and normal serum levels of dndrogens. A single fasting blood sample for hormone analysis was obtained between 0800 and 1000 h. Assays for serum Testosterone (T) and de-hydroepiandrosterone sulfate (DHEAS) were performed by using diagnostic Products (Los Angeles, CA) Coat-A-Count kits.
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	Yes Both groups were recruited consecutively, and, to avoid any potential recruitment bias no questions regarding symptoms of any sleep disorder were asked.
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	Yes A single fasting blood sample for hormone analysis was obtained between 0800 and 1000 h. Assays for serum Testosterone (T) and

			de-hydroepiandrosterone sulfate (DHEAS) were performed by using diagnostic Products (Los Angeles, CA) Coat-A-Count kits. Polysomnography was performed according to standard laboratory protocol. Data recorded included four channels of EEG (two central and two occipital), two channels of EOG, submental EMG, arterial oxygen saturation (Healthdyne, Model 930, Marietta, GA.), nasal-oral airflow (thermistor), nasal pressure (Validyne Engineering Corp., Northridge CA), EKG, chest and abdominal wall motion (piezo electrodes, Pro-Tech Services, Woodinville, WA) bilateral anterior tibialis EMG, snoring (tracheal microphone) and body position (mercury gauge). All signals were simultaneously recorded and stored using the ALICE 3 digital polysomnography system (Respironics, Inc., Murraysville, PA). Bedtime was set between 2200 and 2300 h, and waketime occurred between 0600 and 0700 h.
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Yes All of the polysomnographic records were scored by one of the authors (SDP) who was blinded to all subjects' diagnosis.
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes Polysomnography was performed according to standard laboratory protocol. Data recorded included four channels of EEG (two central and two occipital), two channels of EOG, submental EMG, arterial oxygen saturation (Healthdyne, Model 930, Marietta, GA.), nasal-oral airflow (thermistor), nasal pressure (Validyne Engineering Corp., Northridge CA), EKG, chest and abdominal wall motion (piezo electrodes, Pro-Tech Services, Woodinville, WA) bilateral anterior tibialis EMG, snoring (tracheal microphone) and body position (mercury gauge). All signals were simultaneously recorded and stored using the ALICE 3 digital polysomnography system (Respironics, Inc., Murraysville, PA). Bedtime was set between 2200 and 2300 h, and waketime occurred between 0600 and 0700 h.
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes All of the polysomnographic records were scored by one of the authors (SDP) who was blinded to all subjects' diagnosis.
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	Not relevant to cross-sectional study
ATTRITION BIAS	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	0% All those who completed the sleep study were included in the study, regardless of the results.
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	Not reported No protocol or PROSPERO

CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	Yes Limited baseline demographic variables reported (age, BMI, waist-hip ratio, testosterone, non-SHBG bound testosterone) PCOS and control women were well matched for age and BMI. However, as can be seen, women with PCOS had a significantly higher waist-hip ratio (WHR) than control women (0.88 ± 0.02 vs. 0.82 ± 0.01, P <0.001). Women with PCOS also had significantly higher circulating testosterone (94.44 ± 8.5 ng/dl vs. 22.77 ± 2.5 ng/dl, P < 0.001) and unbound testosterone levels (34.06 ± 2.3 ng/dl vs. 5.05 ± 0.8 ng/dl P < 0.001) than controls
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	Not reported
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Yes First, the sample size is relatively small. However, the group differences were sufficiently robust that a larger sample size was not required to demonstrate substantial and significant differences
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Not reported Only descriptive statistics reported
COMMENTS		Possible selection bias: Case and control group were recruited differently Did not report absolute number for OSA, only reported %	
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

Study ID	Hachul 2019
Study Citation	Hachul H, Polesel DN, Tock L, Carneiro G, Pereira AZ, Zanella MT, Tufik S, Togeiro SM. Sleep disorders in polycystic ovary syndrome: influence of obesity and hyperandrogenism. Rev Assoc Med Bras (1992). 2019 Mar;65(3):375-383. doi: 10.1590/1806-9282.65.3.375. Epub 2019 Apr 11. PMID: 30994836.
Study Country	Brazil
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	A total of 44 subjects were selected to participate in the study. The volunteers, ranging in age from 16 to 45 years, were recruited from the Endocrinology Division of the Federal University of São Paulo, Brazil
Control population	The control group was comprised of 14 women (17 women were originally eligible, of which 3 excluded because of missing data on PSQI and BMI).

	Inclusion criteria: a regular menstrual cycle of 28-30 days, normal BMI and in the follicular phase of the menstrual cycle. Exclusion criteria: neurologic conditions and/or being under psychiatric treatment; use of medication for chronic diseases that might interfere with the study results; participation in another clinical study or having participated in a clinical study within a period of 3 months; being a carrier of a disease; having a history of stroke; use of hypnotic, psychotropic, psychostimulant, and/or analgesic drugs; use of hormonal contraceptives; and presence of dysmenorrhea or endometriosis that may interfere with sleep patterns.	
PCOS diagnostic criteria	Rotterdam 2003 The diagnosis of PCOS was based on the latest 2003 Rotterdam consensus, requiring the presence of at least two of the following features: (1) oligomenorrhea or chronic anovulation, (2) clinical and/or biochemical hyperandrogenism, and (3) ultrasound appearance of polycystic ovaries.	
N per group	PCOS were classified according to presence and absence of hyperandrogenism (Total n = 30) - With hyperandrogenism (n=14) - Without hyperandrogenism (n=16) Non-PCOS group (n=14)	
Setting	Hospital	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary outcomes: - Meet criteria for OSA: (AHI≥5+ sleep complaints) or AHI≥15 (full night polysomnography) [n (%)] Outcomes not relevant: - High risk of OSA (Berlin Questionnaire) [n (%)] - High daytime sleepiness (Epworth Sleepiness Scale, score≥10) [n (%)] - Poor sleep quality (PSQI, score>5) [n (%)] - Reported snoring [n (%)] - Epworth Sleepiness Score (ESS Questionnaire) [Mean (SD)] - Pittsburgh Sleep Quality Index score [Mean (SD)] - Sleep latency (min) [Mean (SD)] - REM latency (min) [Mean (SD)] - Total sleep time (min) [Mean (SD)] - Sleep efficiency (%) [Mean (SD)] - N1 sleep stage (% TST) [Men (SD)] - N2 sleep stage (% TST) [Mean (SD)] - N3 sleep stage (% TST) [Mean (SD)] - REM sleep stage (% TST) [Mean (SD)] - Wake After Sleep Onset (WASO) (min) [Mean (SD)] - Arousal index (events/h) [Mean (SD)] - Apnoea Hypopnoea Index (AHI) (events/h) [Mean (SD)] - Basal Oxygen Saturation [Mean (SD)] - Mean Oxygen Saturation [Mean (SD)] - Minimum Oxygen Saturation [Mean (SD)]	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes

Inclusion criteria		Yes Partial No Not reported	Yes The volunteers, ranging in age from 16 to 45 years, were recruited from the Endocrinology Division of the Federal University of São Paulo, Brazil.
Exclusion criteria		Yes Partial No Not reported	Yes Subjects with other known causes of hyperandrogenism (such as congenital adrenal hyperplasia, androgen-secreting tumors and Cushing's syndrome), using oral contraceptives, corticosteroids, antidiabetic or lipid-lowering drugs in the previous 3 months, having a history of liver disease (such as viral hepatitis B and C, hemochromatosis and autoimmune hepatitis), diabetes mellitus, untreated hypothyroidism, renal, hepatic, cardiac or pulmonary disease, receiving treatment for sleep apnea using medications that alter liver enzymes, with a daily ingestion of more than 20 grams of ethanol, using drugs (sympathomimetics, sympatholytics, and β-blockers), with depression or with chronic diseases were excluded
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Partial Partial generalizability due to exclusion of patients using oral contraceptives, and other concurrent comorbidity diagnoses that commonly co-exist among women with PCOS
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Yes This study is cross-sectional
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Not relevant (the study is cross-sectional in nature)
Was matching performed?		Yes Partial No Not reported	No
Summary Result/s		Only the PCOS group had obstructive sleep apnoea diagnosis in this study.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	Yes The volunteers (exposed and unexposed), ranging in age from 16 to 45 years, were recruited from the Endocrinology Division of the Federal University of São Paulo, Brazil
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes The diagnosis of PCOS was based on the latest 2003 Rotterdam consensus,18 requiring the presence of at least two of the following features: (1) oligomenorrhea or chronic anovulation, (2) clinical and/or biochemical hyperandrogenism, and (3) ultrasound appearance of polycystic ovaries.

	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes As above
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	Yes
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	Yes Questionnaires were used to document clinical history, including regularity and length of menstrual cycles, and ovulation status. Signs of androgen excess (hirsutism, alopecia, acne) were noted in the physical examination. Hirsutism with a Ferriman-Gallwey score of 8 or above was considered clinical evidence of androgen excess. All subjects underwent an ultrasound examination of the pelvis by the same radiologist. LOGIQ P5 (GE Healthcare®, Wauwatosa, WI) with an 8 MHz transvaginal transducer was used for the ultrasound of the pelvis
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Partial Full-night polysomnography (PSG) was performed, using a digital system (EMBLA® S700®, Embla Systems Inc, Broomfield, CO) at the sleep laboratory for one night. Trained technicians visually scored all of the PSG data according to standardized criteria for investigating sleep. Electroencephalogram arousals and sleep-related respiratory events were scored following the criteria outlined in the American Academy of Sleep Medicine Manual for Scoring Sleep and Associated Events. OSA classification was defined according to the AHI. Participants were diagnosed with OSA if they presented an AHI≥5 and sleep complaints. Participants with an AHI≥15 were diagnosed with OSA, regardless of whether they had any additional complaint. Unclear what was considered as a sleep complaint
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Partial No report of independent outcome assessment, i.e., blinding outcome assessors to patient's exposure status. However, trained technicians visually scored all of the PSG data according to standardized criteria for investigating sleep.
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	Not relevant to cross-sectional study

	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	20% overall From a total of 55 women initially included in the study, 11 individuals were excluded because of missing data (8 related to the PSQI and 3 to BMI).
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	Yes The study was approved by the Ethics Committee for Research of the Federal University of Sao Paulo (#0588/2010)
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	Yes The authors observed a higher BMI in the PCOS group (F1,42=36,404; P<0.001) compared to the control group.
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes Pearson's chi-squared test was performed to determine the association between categorical variables. BMI and age were used as adjustment factors in evaluating the effect of PCOS and hyperandrogenism on sleep, respectively. The results were submitted to adjustment only when the groups had significant statistical differences in age or BMI.
COMMENTS		Selection bias due to 20% patients excluded from the analysis Outcome assessment was not completely objective, and no report of blinding the outcome assessors to patient's exposure status	
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

Study ID	Nandalike 2012
Study Citation	Nandalike K, Agarwal C, Strauss T, Coupey SM, Isasi CR, Sin S, Arens R. Sleep and cardiometabolic function in obese adolescent girls with polycystic ovary syndrome. Sleep Med. 2012 Dec;13(10):1307-12. doi: 10.1016/j.sleep.2012.07.002. Epub 2012 Aug 23. PMID: 22921588; PMCID: PMC3509263..
Study Country	United States of America
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	

Patient/population/ participants	28 adolescent girls aged 13–18 years diagnosed with PCOS and followed at Children's Hospital at Montefiore (CHAM), between January 2006 and December 2009, who were subsequently referred for an overnight polysomnography (PSG) at CHAM to rule out OSA, because of sleep-related complaints such as snoring, trouble breathing or excessive daytime sleepiness. Referral for PSG was through the adolescent medicine, endocrine, otolaryngology and pulmonary clinics for sleep-related complaints such as snoring, trouble breathing at night or excessive daytime sleepiness. Participants were first identified by an electronic medical information database (Clinical Looking Glass, CLG).
Control population	Age- and body mass index (BMI) Z-score-matched females without PCOS (n=28) and BMI Z-score matched males (n=28) who underwent PSG during the same time period were identified through the sleep–disorders centre database (referred to sleep disorder centre for sleep related complaints). Charts of females chosen as controls were verified and any girl with any history of oligomenorrhea (less than nine menstrual cycles in a year) or amenorrhoea, or any documented clinical signs of hyperandrogenism such as acne or hirsutism or biochemical evidence of hyperandrogenemia, was excluded from the study.
PCOS diagnostic criteria	Rotterdam 2003 Diagnosis of PCOS was made as per the modified Rotterdam criteria. Accordingly, at least two of the following three features existed: (1) oligomenorrhea/amenorrhea, (2) clinical or biochemical evidence of hyperandrogenemia and (3) polycystic ovaries documented on ultrasonography. In our sample, all of the patients fulfilled the first two criteria and only a few had ultrasonography performed, as the interpretation of the sonographic findings is different for adolescents who may have multicystic ovaries as a normal peripubertal finding. Other conditions that could mimic PCOS such as Cushing's syndrome, late onset adrenal hyperplasia or androgen producing neoplasm were excluded.
N per group	Women with PCOS (n=28) Control women (n=28) Control men (n=28)
Setting	Hospital
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary outcomes: - OSA: OSA was diagnosed if the apnoea hypopnoea index (AHI) was more than 5/h or if the apnoea index was more than 1/h [n (%)] Outcomes not relevant: - Sleep onset latency (minutes) [Mean (SD)] - Sleep efficiency (%) [Mean (SD)] - Arousal awakening index (events/h) [Mean (SD)] - AHI (events/h) [Mean (SD)] - Baseline oxygen (%) [Mean (SD)] - Lowest oxygen (%) [Mean (SD)] - Peak $ETCO_2$ (mmHg) [Mean (SD)] - MetS (n) (%) [Mean (SD)] - Fasting glucose (mg/dL) [Mean (SD)] - Fasting insulin (IU) [Mean (SD)] - HOMA-IR>4 [n (%)] - Fasting TG (mg/dL) [Mean (SD)] - Fasting HDL (mg/dL) [Mean (SD)]

		- Systolic blood pressure (mmHg) [Mean (SD)] - Diastolic blood pressure (mmHg) [Mean (SD)]	
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	Yes
Inclusion criteria		Yes Partial No Not reported	Partial, Limited to adolescents aged 13–18 years, and only those who were referred for a polysomnography to rule out OSA as they had sleep related complaints (so biased towards those who already had possible symptoms of OSA).
Exclusion criteria		Yes Partial No Not reported	Yes Patients with significant co-morbid conditions contributing to OSA, such as Trisomy 21, craniofacial anomalies and cerebral palsy were also excluded from the study.
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Yes, This study is cross-sectional
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Not relevant (the study is cross-sectional in nature)
Was matching performed?		Yes Partial No Not reported	Yes, age- and body mass index (BMI) Z-score-matched
Summary Result/s		The authors report a higher prevalence of OSA and metabolic dysfunction in a selected group of obese girls with PCOS referred with sleep-related complaints compared to BMI-matched control girls without PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	Partial Exposed patients were first identified by an electronic medical information database (Clinical Looking Glass, CLG) who were referred to the sleep-disorders centre for PSG. Unexposed patients were directly identified through the sleep –disorders centre database.
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes Participants were first identified by an electronic medical information database (Clinical Looking Glass, CLG). Accordingly,

			the PCOS ICD-9 code-256.4 was queried, and the diagnosis was verified by reviewing each patient's electronic patient file (EPF). Later, individual charts were reviewed to identify the individuals who underwent PSG during the study period.
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Partial Charts of females chosen as controls were verified and any girl with any history of oligomenorrhea (less than nine menstrual cycles in a year) or amenorrhoea, or any documented clinical signs of hyperandrogenism such as acne or hirsutism or biochemical evidence of hyperandrogenemia, was excluded from the study The androgen profile was not available for any of the female controls as they had no menstrual irregularities or clinical hyperandrogenism and were not biochemically tested for excess androgen
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	No This is a retrospective chart review of routine health records, so we cannot be sure the groups were treated the same.
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	Partial Conducted as part of routine care The data on total and free-serum testosterone level were collected on all the subjects in whom it was available. Total testosterone level was available on all girls with PCOS and free testosterone level was available on 25/28 girls with PCOS. The androgen profile was not available for any of the female controls as they had no menstrual irregularities or clinical hyperandrogenism and were not biochemically tested for excess androgens.
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Partial Conducted as part of routine care PSG data (via Xltek, Oakville, ON, Canada) were extracted from the electronic records of the sleep-disorders centre at CHAM. Only 28/240 girls with PCOS were referred by their primary care physicians for a PSG to evaluate for OSAS. Information on any sleep-related complaints or any screening measures for OSA on the 212 girls with PCOS not referred for PSG was unavailable.
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes Sleep staging and scoring of arousals were performed as per standard criteria. OSA was diagnosed if the apnoea hypopnoea index (AHI) was more than 5/h or if the apnoea index was more than 1/h.

ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	Not relevant to cross-sectional study
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	88.33% of the girls with PCOS Only 28/240 girls with PCOS were referred by their primary care physicians for a PSG to evaluate for OSAS.
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	Not reported No protocol or PROSPERO
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	No Compared to the study group girls with PCOS, the female control group had a higher proportion of African Americans (5/28(17.9%) vs. 13/28(46.4%). Also, a greater proportion of girls from the PCOS group were prescribed metformin compared to the female control groups (10/28 (35.7%) vs. 3/28 (10.7%). Similarly, a higher proportion of girls from the PCOS group had a history of adenotonsillectomy prior to PSG compared to the female control groups (9/28 (32.1%) vs. 3/28 (10.7%)).
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes Mean and standard deviation were used to summarise continuous variables. Analysis of variance (ANOVA) was used to compare PSG findings, cardiometabolic profiles and other continuous variables between the PCOS subjects and control groups. Differences in proportions were assessed with the Chi-square test.
COMMENTS		Only women who were referred for PSG were included Highly susceptible to referral bias	
What is the overall risk of bias?		Low Moderate High Insufficient information	High
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

Study ID	Suri 2016

Study Citation	Suri J, Suri JC, Chatterjee B, Mittal P, Adhikari T. Obesity may be the common pathway for sleep-disordered breathing in women with polycystic ovary syndrome. Sleep Med. 2016 Aug;24:32-39. doi: 10.1016/j.sleep.2016.02.014. Epub 2016 Aug 16. PMID: 27810183.	
Study Country	India	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	50 patients with PCOS who attended the Gynecology Outpatient Department (OPD) and Reproductive Endocrinology Clinic of Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India who met inclusion and exclusion criteria and consented to take part in the study	
Control population	A total of 100 age-matched women who attended the gynecology OPD with other complaints such as vaginal discharge, dysuria, and pelvic organ prolapse were recruited as control subjects after obtaining the required consent. All of these women experienced regular menstrual cycles and did not meet the standard diagnostic criteria for PCOS.	
PCOS diagnostic criteria	Rotterdam 2003 PCOS was defined by the Rotterdam criteria, namely, the presence of any two of the following three features: (1) chronic oligomenorrhea (six or fewer spontaneous menses per year), (2) biochemical or clinical evidence of hyperandrogenism, and (3) polycystic ovaries on ultrasonography.	
N per group	Women with PCOS (n=50) Control women (n=100)	
Setting	Hospital	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary outcomes: - Sleep disordered breathing (Polysomnography) SDB was defined as an RDI≥ along with symptoms such as EDS, choking, witnessed apneic spell, nocturia, or an RDI>15 with or without associated symptoms. Outcomes not relevant: - Snoring (patient reported) - Respiratory Distress Index (RDI) [Mean (SD)] - Snoring (PSG document) [n (%)] - Sleep onset [Mean (SD)] - Total Sleep Time [Mean (SD)] - Wake After Sleep Onset (WASO) [Mean (SD)] - Rapid Eye Movement (REM) [Mean (SD)] - Non-Rapid Eye Movement (NREM) [Mean (SD)] - Sleep Efficiency (SE) (%) [Mean (SD)] - Epworth Sleepiness Scale (ESS) [Mean (SD)	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes
Inclusion criteria	Yes Partial No Not reported	Partial Mention of inclusion criteria, but not clearly reported. Those who gave consent to take part in the study
Exclusion criteria	Yes Partial No	Yes

		Not reported	Women taking any form of treatment for PCOS were not included in the study. Patients with thyroid disorders, hyperprolactinemia, and congenital adrenal hyperplasia, with history of smoking, and with neurological or psychiatric disorders were also excluded from the study.
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Partial Unclear why women taking treatment for PCOS and with comorbidities were excluded from the study
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Yes, This study is cross-sectional
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Not relevant (the study is cross-sectional in nature)
Was matching performed?		Yes Partial No Not reported	Yes, age
Summary Result/s		SDB was seen in 66% of the case patients and in 4% of control group with (odds ratio [OR] = 46.5, 95% confidence interval [CI] = 14.6–148.4; p < 0.001). After adjustment for body mass index (BMI) and waist circumference (WC), the difference was not significant (p = 0.993 and p = 0.931, respectively)	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	Yes Both cases and controls attended the Gynecology Outpatient Department (OPD).
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes PCOS was defined by the Rotterdam criteria, namely, the presence of any two of the following three features: (1) chronic oligomenorrhea (six or fewer spontaneous menses per year), (2) biochemical or clinical evidence of hyperandrogenism, and (3) polycystic ovaries on ultrasonography.
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes Control women experienced regular menstrual cycles and did not meet the standard diagnostic criteria for PCOS. All women underwent clinical evaluation, physical examination, and hormonal tests (including testosterone and DHEAS dehydroepiandrostenedione sulfate)

PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	No Keeping in mind the cost and difficulty of convincing a normal asymptomatic woman to undergo a sleep study, we did not find it practical to subject all of the controls to the overnight PSG. Instead, only those women who reported snoring underwent the overnight PSG, as snoring was considered to be a surrogate marker for SDB Not all control participants had polysomnography, only 16 / 100 who reported snoring had it done due to costs and difficulty consenting
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	Partial Overnight in-laboratory polysomnography (PSG), the hormonal and biochemical assays of all case patients and control subjects were done on the second or third day of the menstrual cycle. PSG was done in all 50 women with PCOS, whereas in the control group, it was done only in the 16 women who reported snoring. PSG data that were recorded included a three-channel electroencephalography (EEG), two-channel electrooculography, anterior tibialis and submental electromyography, nasal airflow by thermistor, nasal pressure by pressure cannula, thoracic and abdominal efforts by strain gauges, oxygen saturation by pulse oximeter, and tracheal sound with microphone attached to the neck. The EEG channels used were F3M2, C3M2, and O1M2. ALICE 5 digital polysomnography system (Respironics, Murrysville, PA) was used for recording and storing all of the signals. A length of at least seven hours of sleep was recorded in each subject.
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	No PSG was done in all 50 women with PCOS, whereas in the control group, it was done only in the 16 women who reported snoring. Apnea was defined as a drop in the peak thermal sensor excursion by more than 90% of the baseline lasting for ten seconds or more. Hypopnea was the drop of nasal pressure signal excursions by more than 30% of the baseline lasting for more than ten seconds and was accompanied by a drop in 3% or more of oxygen saturation from the pre-event baseline or an arousal. Respiratory effort–related arousal (RERA) was termed as an event of increasing the respiratory effort or flattening nasal pressure waveform for more than ten seconds, followed by an arousal from sleep, which does not meet the criteria for apnea or hypopnea. Respiratory distress Index (RDI) was defined as the number of obstructive apneas, hypopneas, and RERAs per hour of sleep. This was calculated by dividing the total number of respiratory events by the total sleep time in hours

	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes SDB was defined as an RDI of five or more along with symptoms such as EDS, choking, witnessed apneic spell, nocturia, or an RDI >15 with or without associated symptoms. The severity of SDB was defined according to the RDI as mild (5–15/h), moderate (16–30/h), and severe (>30/h). Polysomnography all scored by an experienced sleep medicine consultant.
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	Not relevant to cross-sectional study
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	16.66% in the treatment group Of the 60 patients who fulfilled the criteria, 50 gave their consent to take part in the study.
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	Not reported No protocol or PROSPERO
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	Yes The mean age of the two groups was comparable. However, the BMI and waist circumference were significantly higher in the case patients when compared with the control subjects ($p < 0.001$; Table 1).
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes The difference in prevalence of snoring and OSA categories between patients with PCOS and control subjects was assessed using the chi-square test (SPSS, version 19; SPSS Inc., Chicago, IL). Multivariate regression analysis was used for eliminating the confounding effect of BMI and waist circumference.
COMMENTS		PSG was done in all 50 women with PCOS, whereas in the control group, it was done only in the 16 women who reported snoring.	
What is the overall risk of bias?		Low Moderate High Insufficient information	High

Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?	Yes Secondary outcome not requiring PSG such as ESS have low risk of bias.

Study ID	Tasali 2009	
Study Citation	Tasali E, Van Cauter E, Hoffman L, Ehrmann DA. Impact of obstructive sleep apnea on insulin resistance and glucose tolerance in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2008 Oct;93(10):3878-84. doi: 10.1210/jc.2008-0925. Epub 2008 Jul 22. PMID: 18647805; PMCID: PMC2579653.	
Study Country	United States of America	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	Women with PCOS aged between 18 and 40 years old were consecutively recruited from the Endocrinology Clinics at the University of Chicago between February 1, 2004, and September 30, 2007.	
Control population	During the same period of time, overweight (BMI >25 kg/m2 but <30 kg/m2) and obese (BMI ≥30 kg/m2) women who were otherwise healthy were recruited through public advertisements in the local community.	
PCOS diagnostic criteria	NIH 1990 A diagnosis of PCOS required 1) the presence of oligo/amenorrhea; 2) hyperandrogenemia, defined by a supranormal plasma free testosterone level (>10 pg/ml); 3) hyperandrogenism, as evidenced by infertility, hirsutism, acne, or androgenetic alopecia; and 4) exclusion of nonclassic 21-hydroxylase deficiency, congenital adrenal hyperplasia, Cushing's syndrome, hypothyroidism, or significant elevations in serum prolactin	
N per group	Women with PCOS (n=52) Control women (n=21)	
Setting	Hospital	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary outcomes: - OSA (AHI≥5) - Mild OSA (AHI>5 and AHI<15) - Moderate OSA (AHI>15 and AHI<30) - Severe OSA (AHI≥30)	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes
Inclusion criteria	Yes Partial No Not reported	Yes, Sleep complaints or symptoms of OSA were not used as selection criteria for the study. Only women between 18 and 40 yr of age were recruited to reduce the impact of age upon ovarian function and glucose tolerance.
Exclusion criteria	Yes Partial No Not reported	Yes, Subjects were excluded if they smoked cigarettes; were diabetic or hypertensive; had a history of cardiac, psychiatric, neurological, or

			endocrine disease; or were taking any medications at the time of the study.
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Yes, This study is cross-sectional
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Not relevant (the study is cross-sectional in nature)
Was matching performed?		Yes Partial No Not reported	Yes, age and BMI
Summary Result/s		Twenty-nine women (56%) with PCOS had OSA compared with four controls (19%) (adjusted odds ratio 7.1; 95% confidence interval, 1.7–45.7; P<0.01).	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	No Women with PCOS aged between 18 and 40 years old were consecutively recruited from the Endocrinology Clinics at the University of Chicago between February 1, 2004, and September 30, 2007. During the same period of time, overweight (BMI >25 kg/m2 but <30 kg/m2) and obese (BMI ≥30 kg/m2) women who were otherwise healthy were recruited through public advertisements in the local community.
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes A complete medical history was obtained, and a physical examination was conducted in all subjects. A fasting blood sample was drawn for routine laboratory tests and the measurement of serum concentrations of total testosterone, free testosterone, SHBG, and dehydroepiandrosterone sulfate (DHEAS). All testing was performed in the follicular phase of the menstrual cycle in normally cycling women. Progesterone levels were measured on a fasting blood sample to confirm the phase of the menstrual cycle
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes As above

PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	Yes
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	Yes A complete medical history was obtained, and a physical examination was conducted in all subjects. Overnight laboratory polysomnography was performed to establish the presence and the severity of OSA. The following morning, a fasting blood sample was drawn for routine laboratory tests and the measurement of serum concentrations of total testosterone, free testosterone, SHBG, and dehydroepiandrosterone sulfate (DHEAS). All testing was performed in the follicular phase of the menstrual cycle in normally cycling women. Progesterone levels were measured on a fasting blood sample to confirm the phase of the menstrual cycle
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes Overnight polysomnography (Neurofax EEG 1100 digital acquisition system; Nihon Kohden, Foothill Ranch, CA) included recordings of two central and two occipital electroencephalogram channels, bilateral electrooculograms, submental electromyogram, leg movements by bilateral anterior tibialis electromyogram, electrocardiogram, oronasal airflow by thermistor, chest and abdominal wall motion by piezo electrodes, and arterial oxygen saturation by pulse oximeter.
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes Sleep recordings were visually scored in 30-sec epochs in stages 1, 2, 3, and 4 of non-rapid eye movement sleep and in rapid eye movement sleep according to standard criteria. Obstructive respiratory events (i.e. apneas and hypopneas) and microarousals were scored according to established criteria. The apnea-hypopnea index (AHI) was calculated as the total number of obstructive respiratory events per hour of sleep
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	Not relevant to cross-sectional study
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Not reported
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	Not reported No protocol or PROSPERO

CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	Yes The control group was comprised of two overweight and 19 obese women. The mean BMI among controls was 36.0±1.5 kg/m2 (range, 27.7– 48.8 kg/m2). The PCOS group had two lean, two overweight, and 48 obese women. The mean BMI in the PCOS group was 39.2±1.0 kg/m2 (range, 23.2–58.8 kg/m2). The control group had a higher proportion of women of African-American or Hispanic descent (86 vs. 62%; P=0.054) who have a higher risk of insulin resistance and type 2 diabetes than White women.
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes Using logistic regression, the odds ratio (with 95% confidence intervals) for having OSA in PCOS women compared with control women was calculated after adjustment for age, BMI, and ethnicity-based diabetes risk (Whites, low risk; African-Americans and Hispanics, high risk)
COMMENTS		Control women were recruited separately through public advertisements in the local community.	
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

Study ID	Vgontzaz 2001
Study Citation	Vgontzas AN, Legro RS, Bixler EO, Grayev A, Kales A, Chrousos GP. Polycystic ovary syndrome is associated with obstructive sleep apnea and daytime sleepiness: role of insulin resistance. J Clin Endocrinol Metab. 2001 Feb;86(2):517-20. doi: 10.1210/jcem.86.2.7185. PMID: 11158002.
Study Country	United States of America
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	Fifty-three premenopausal women with PCOS [age range, 16–45 yr; body mass index (BMI) range, 24.3–67.7] were prospectively studied in the sleep laboratory.

	PCOS women were recruited randomly from a larger PCOS population, and it is possible that a selection bias exists, in that those patients with sleep problems were more likely to volunteer to participate in the study	
Control population	Control women were 452 premenopausal women 42 yr of age or younger (age range, 20-42 yr; BMI range, 16.1–59.9) selected from a general randomized sample. The sample for this epidemiological study was obtained using a 2-stage strategy. In the first stage of this study, a sample of women (age ≥ 20 yr) was randomly selected from telephone households, and 12,219 completed a telephone interview. In the second phase of this study, a random sample from those previously interviewed by telephone was selected for study in our sleep laboratory, to assess for sleep apnea. This selection was based on risk factors reported in the telephone interview (snoring, daytime sleepiness, obesity, hypertension, and menopause), and those with a higher risk for sleep apnea were oversampled. The sleep laboratory sample consisted of 1,000 women. For analysis purposes, compensatory weights were developed to obtain estimates of prevalence of the original target population of women.	
PCOS diagnostic criteria	AES criteria 2016 The diagnosis of PCOS was made by the presence of chronic anovulation (six or fewer menstrual periods per year) in association with elevated circulating androgen levels (total testosterone more than 201.1 nmol/L and/or free and weakly bound testosterone more than 55.5 nmol/L). Non classic adrenal 21-hydroxylase deficiency, hyperprolactinemia, and androgen-secreting tumors were excluded by appropriate tests before the diagnosis of PCOS was made.	
N per group	Women with PCOS (n=53) Control women (n=452)	
Setting	Unclear (likely to be sleep research and treatment centre or hospital based on author affiliations)	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary outcomes: - AHI>10 per hour of sleep plus the presence of clinical symptomatology, e.g. daytime sleepiness, hypertension, or other cardiovascular complication (PSG + questionnaire) [n (%)] Outcomes not relevant: - Sleep apnoea (subjective diagnosis based on requiring immediate treatment) [n (%)] - Upper airway resistance syndrome (PSG + questionnaire) [n (%)] - Sleep latency (min) [Mean (D)] - Wake Time After Sleep Onset (WTASO) (min) [Mean (SD)] - Total Wake Time (min) [Mean (SD)] - % Sleep Time [Mean (SD)] - % Slow Wave [Mean (SD)] - % Rapid Eye Movement [Mean (SD)]	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes
Inclusion criteria	Yes Partial No Not reported	Yes, Premenopausal and 42 yr of age or younger.

Exclusion criteria		Yes Partial No Not reported	No
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Yes, This is a cross-sectional study
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Not relevant (the study is cross-sectional in nature)
Was matching performed?		Yes Partial No Not reported	No
Summary Result/s		OSA was much more prevalent in premenopausal women with PCOS than in normal controls (ratio, 30:1). This difference remained significant, even when we corrected for BMI differences between the two groups	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	No Unclear how women with PCOS were recruited. Control women were obtained using a 2-stage strategy
SELECTION BIAS	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes All of the PCOS women had oligo/amenorrhea and polycystic ovaries, by ultrasound examination. Seventy five percent were hirsute and nulliparous.
SELECTION BIAS	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	No Control subjects were not specifically screened for the presence of PCOS
PERFORM ANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	Not reported
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	Yes Assays for testosterone were performed using Diagnostic Products (Los Angeles, CA) Coat-A-Count kits; the interassay coefficients of variation (CVs) were 8% and 5%, respectively. Unbound testosterone was measured by a modification of the procedure of Tremblay and Dube; the interassay CV was 7%

	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes All subjects were evaluated for 1 night in the sleep laboratory in sound-attenuated, light- and temperature-controlled rooms. During this evaluation, they were continuously monitored for 8 h using 16-channel polygraphs (model 78d, Grass Instrument, Quincy, MA). The three-channel electroencephalogram, three-channel electrooculogram, and an electromyogram were recorded. The sleep records were subsequently scored independently, according to standardized criteria. Respiration was monitored throughout the night by use of thermocouples at the nose and mouth (model TCT 1R, Grass Instrument) and thoracic strain gauges. All-night recordings of hemoglobin oxygen saturation (SaO2) were obtained with an oximeter (Model 8800, Noonin Medical, Plymouth, MN) attached to the finger
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes An apnea was considered present if a breath cessation exceeded 10 sec. Each apnea was categorized in terms of obstructive (chest wall movement present) or central (chest wall movement absent). In addition, hypopneas were considered present when a reduction in airflow of approximately 50% was indicated at the nose or mouth and was associated with a reduction of 4% SaO2. OSA was diagnosed using Sleep Disorders Clinic criteria, which employed sleep laboratory plus clinical findings. This diagnosis was made by a Sleep Disorders Medicine specialist (A. N.Vgontzas) based on whether immediate treatment was considered appropriate. This diagnosis required an apnea/hypopnea index ≥ 10 per hour of sleep plus the presence of clinical symptomatology, e.g. daytime sleepiness, hypertension, or other cardiovascular complication. Daytime sleepiness was assessed subjectively using a sleep questionnaire on a 4-point scale (none, mild, moderate, or severe)
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	Not relevant to cross-sectional study
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	54.8% of the women with PCOS The sleep laboratory sample consisted of 1,000 women. For analysis purposes, compensatory weights were developed to obtain estimates of prevalence of the original target population of women. 452 control patients were included in the study

REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	Yes
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	Yes Controls (n = 452) and PCOS (n = 53) patients were similar in terms of age [32.1 6 0.3 vs. 30.4 6 0.9 yr, respectively, not significant (NS)], whereas PCOS women were heavier than the controls, as indicated by mean BMI values (38.7 ± 1.1 vs. 26.4 ± 0.3, P < 0.01).
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	Not reported
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes For comparisons between two groups, a Student's t test was used. Odds ratios (ORs) were calculated to evaluate differences between prevalences. To assess which variables were significant predictors of the presence of sleep disordered breathing (SDB) in PCOS women, we used logistic regression analysis, with age, BMI, testosterone, insulin, and glucose-to-insulin ratio as independent variables. The values are expressed as the mean ± se. All five independent variables were included as continuous variables in this analysis. The statistical confidence level selected for all analyses was P < 0.05.
COMMENTS		Control subjects were not specifically screened for the presence of PCOS PCOS women with sleep problems may be more likely to volunteer to participate. Control participants were more likely to have been selected if they were at high risk of SDB	
What is the overall risk of bias?		Low Moderate High Insufficient information	High
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

Study ID	*Yang 2009*
Study Citation	*Yang HP, Kang JH, Su HY, Tzeng CR, Liu WM, Huang SY. Apnea-hypopnea index in nonobese women with polycystic ovary syndrome. Int J Gynaecol Obstet. 2009 Jun;105(3):226-9. doi: 10.1016/j.ijgo.2009.02.004. Epub 2009 Apr 5. PMID: 19345941.*
Study Country	*Taiwan*

CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with PCOS aged 18–45 years and with a BMI of less than 27 were consecutively recruited after initial screening for PCOS when they presented with oligomenorrhea at the Obstetric and Gynecology Clinic of Taipei Medical University Hospital between May 2006 and January 2007.*	
Control population	*Ten age-matched and BMI-matched women who did not have PCOS were recruited as a control group from the same community during the same period. Women were excluded from the control group if they had irregular menstruation or oligomenorrhea, abnormal serum thyroid stimulating hormone or prolactin, or biochemical hyperandrogenemia*	
PCOS diagnostic criteria	*Rotterdam 2003* *The Rotterdam criteria were used for the initial diagnosis of PCOS. To make the phenotype more consistent, we included patients who had both biochemical hyperandrogenemia and polycystic ovaries.*	
N per group	*Women with PCOS (n=18)* *Control women (n=10)*	
Setting	*Hospital*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcomes:* *- AHI≥5 (Polysomnography)* *Outcomes not relevant:* *- Sleep efficiency, % [Mean (SD)]* *- Sleep latency, s [Mean (SD)]* *- REM percentage [Mean (SD)]* *- REM latency, min [Mean (SD)]* *- AHI (total) [Mean (SD)]* *- AHI (REM) [Mean (SD)]* *- AHI (NREM) [Mean (SD)]* *- ARI (total) [Mean (SD)]* *- ARI (REM) [Mean (SD)]* *- ARI (NREM) [Mean (SD)]* *- ARI (spontaneous) [Mean (SD)]* *- ARI (PLM-related) [Mean (SD)]* *- PLM index, per h [Mean (SD)]* *- ESS [Mean (SD)]*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes,* *Women aged 18–45 years and with a BMI of less than 27*
Exclusion criteria	Yes Partial No Not reported	*Yes,* *Exclusion criteria were women who had taken any medication affecting the hypothalamic–pituitary–ovarian axis within the last 6 months, women who had been pregnant within the last year, and women with diabetes, hypertension, other diseases associated with obesity, hyperprolactinemia, abnormal thyroid function tests, and congenital adrenal hyperplasia.*

If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Partial* *Women with comorbidities were excluded which reduces the generalizability of the population*
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	*Yes* *This is a cross-sectional study*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Not relevant (the study is cross-sectional in nature)*
Was matching performed?		Yes Partial No Not reported	*Yes, age and BMI*
Summary Result/s		*There was no difference between the PCOS and the control groups in any of the other polysomnographic variables. None of the 28 women had an AHI greater than 5, which is the standard for OSA.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Partial* *Control patients were recruited from the community. However, exposed patients were recruited from the hospital when the presented with oligomenorrhea.*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes* *Total testosterone (TT) was measured by radioimmunoassay using a DSL-4000 kit (Diagnostic System Laboratories, Webster, TX, USA) with a lower limit of sensitivity at 0.08 ng/mL. The inter-assay coefficient of variation (CV) ranged from 8.4% to 9.1%, whereas the intra-assay CV ranged from 7.8% to 9.6%. Androstenedione (AS) was measured by radioimmunoassay using a DSL-3800 kit (Diagnostic System Laboratories) with a sensitivity of 0.03 ng/mL. The inter-assay CV ranged from 6.0% to 9.8%, whereas the intra-assay CV ranged from 2.8% to 5.6%. Biochemical hyperandrogenemia was defined as a high serum concentration of TT (N0.8 ng/mL) or AS (N2.44 ng/mL). The presence of polycystic ovaries was determined by pelvic ultrasound performed by a single qualified technician. Hirsutism was confirmed by the same doctor when the Ferriman-Gallwey score was greater than 8. Ferriman Gallwey method scores the degree of hirsutism and reflects the clinical manifestations of hyperandrogenism in patients with PCOS [1,2]. Serum levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were measured by electro-chemoluminescence assay (ECLIA).* *Prolactin (ECLIA, Elecsys 2010 analyzer; Roche Diagnostics, Indianapolis, USA), thyroid stimulating hormone (MEIA technology; Abbott Laboratories, Abbott Park, IL, USA), dehydroepiandrosterone sulfate (radioimmunoassay; Diagnostic System Laboratories), and 17-hydroxyprogesterone*

			(radioimmunoassay; Diagnostic System Laboratories) levels were also evaluated.
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes* *Ten age-matched and BMI-matched women who did not have PCOS were recruited as a control group from the same community during the same period. Women were excluded from the control group if they had irregular menstruation or oligomenorrhea, abnormal serum thyroid stimulating hormone or prolactin, or biochemical hyperandrogenemia*
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Not reported* *Insufficient information*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes* *Blood samples were obtained between 08:00 and 10:00 AM after an overnight fast on the third to fifth days of the menstrual cycle or after a progestogen-induced bleed.*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes* *All patients were recorded for one full night by standard polysomnography using a computerized sleep-scoring system (Sandman; Tyco Ltd, Ottawa, ON, Canada) in the sleep laboratory of Taipei Medical University Hospital. We recorded 4 channels of the electroencephalogram (C3/A2, C4/A1, O1/ A2, and Fpz/A1–A2), right and left channels of the electrooculogram, 1 channel of the electrocardiogram (modified V2 lead), 1 channel of submentalis and 2 channels of anterior tibilalis muscles, and 1 set of chest/abdomen movements. Heart rate and pulse oximetry were also continuously monitored by a finger probe. Airflow was detected through a nasal cannula pressure transducer and a mouth thermistor. In addition, body position sensors and neck microphones were applied. Whole-night data were analyzed manually in 30-second epochs by the same trained physician and technician. At least 7 hours of recordings were available for each woman.*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes* *Whole-night data were analyzed manually in 30-second epochs by the same trained physician and technician. At least 7 hours of recordings were available for each woman.*

			AHI is defined by the number of obstructive apneic and/or hypopneic events lasting more than 10 seconds of sleep that result in either arousal or 4% oxyhemoglobin desaturation. Apnea is defined as a cessation in airflow, whereas hypopnea is defined as a reduction in airflow of 30%. An AHI of 5 or more on polysomnography is defined as OSA. The total arousal index (ARI) is defined as the number of arousals on the electroencephalogram per hour. Daytime sleepiness was assessed subjectively using a validated Chinese version of the Epworth Sleepiness Scale (ESS) questionnaire provided by Ning-Hung Chen (Chang Gung Memorial Hospital, Taipei, Taiwan.
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant to cross-sectional study*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*33.33% of the women with PCOS* *Twenty-seven women were eligible for inclusion originally. Women who were subsequently found to have undiagnosed diabetes (n=1), hyperprolactinemia that did not show up on the initial test (n=1), pelvic endometriosis (n=2), women who did not demonstrate polycystic ovaries on pelvic ultrasound (n=3), and women who had only hyperandrogenism but not hyperandrogenemia (n=2) were also excluded. This left 18 PCOS patients eligible for the study.*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*No* *The experimental protocol was approved by the Ethics and Research Committee of the Institutional Review Board for Human Investigation of the Taipei Medical University.*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Yes* *Nonobese women with PCOS had a higher waist circumference, waist-to-hip ratio, free androgen index, Ferriman Gallwey score, LH/FSH ratio, serum levels of AS and TT, LH, prolactin, and hsCRP compared with the age- and BMI-matched control group who did not have PCOS. The women in the PCOS group also had lower sex hormone-binding globulin levels than the women in the control group.*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*No* *The study had no outcome event recorded in both the group of women with and without PCOS*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No	*Yes* *No statistical analysis undertaken*

		Not reported	
COMMENTS		*Low sample size - The study had no outcome event recorded in both the group of women with and without PCOS*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Template for SYSTEMATIC REVIEWS

Study ID	*Helvaci 2017*
Study Citation	*Helvaci N, Karabulut E, Demir AU, Yildiz BO. Polycystic ovary syndrome and the risk of obstructive sleep apnea: a meta-analysis and review of the literature. Endocr Connect. 2017 Oct;6(7):437-445. doi: 10.1530/EC-17-0129. Epub 2017 Jul 24. PMID: 28739562; PMCID: PMC5574283.*
SR Country	*Turkey*
SYSTEMATIC REVIEW'S PICO	
Patient/population/ participants	*Adults and adolescents*
PCOS diagnostic criteria	*Any PCOS diagnostic criteria* *One study did not specifiy the criteria used to diagnose PCOS. In two studies, PCOS was defined by the presence of any two of the following three features: chronic oligomenorrhea, biochemical or clinical evidence of hyperandrogenism and polycystic ovaries on ultrasonography. In the rest of the included studies, presence of both chronic anovulation/oligo-amenorrhea and hyperandrogenemia was the main criteria for PCOS diagnosis.*
N	*13 studies* *Eight studies conducted in adults and five studies conducted in adolescents including a total of 404 PCOS patients and 611 control subjects were identified.*
Setting	*Not specified*
Intervention/indicator	*Exposure – PCOS* *Control – (implied as patients without PCOS)*
Comparison/control	
Outcomes (primary and other)	*Primary outcome: Risk of OSA among women with PCOS compared to women without PCOS* *Secondary outcome: Subgroup analysis* *Risk of OSA among adults with PCOS compared to adults without PCOS* *Risk of OSA among adolescents with PCOS compared to adolescents without PCOS* *Other outcomes:* *Prevalence of PCOS among women with PCOS*
Study Inclusion Criteria	*Original studies reported in English and published as full text articles were included in the analysis. There were no*

		country restrictions. All included studies used an objective measurement to assess the presence of OSA. Those studies using questionnaire-based methods for the presence of OSA were excluded.	
Summary Result/s		*Risk of OSA was significantly increased in adult patients with PCOS (odds ratio (OR) 9.74, 95% CI: 2.76–34.41).* *Risk of OSA was not significantly increased in adolescents (OR: 4.54, 95% CI:0.56–36.43).*	
INTERNAL VALIDITY – HAS THIS SYSTEMATIC REVIEW BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were reviewers blind to authors, institutions and affiliations?	Yes Partial No Not reported	*Not reported*
	Does the review have a clearly- focused question?	Yes Partial No Not reported	*Yes*
	Does the review have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
	If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
	Were 2 or more independent reviewers used for application of inclusion criteria to assess eligibility of studies?	Yes Partial No Not reported	*Not reported* *A systematic literature search was performed independently by two investigators to identify all studies published before September 2015 that investigated the association between PCOS and OSA.*
SAMPLING BIAS	Does the review document a comprehensive search strategy?	Yes Partial No Not reported	*Yes*
	Were unpublished studies searched for?	Yes Partial No Not reported	*Not reported*
OUTCOME BIAS	Were 2 or more independent reviewers used for extraction of data from study reports?	Yes Partial No Not reported	*Not reported*
	Was the validity of included trials appraised using appropriate criteria?	Yes Partial No Not reported	*Not applicable.* *No trials included*

	Were 2 or more independent reviewers used for appraisal of study quality?	Yes Partial No Not reported	*No*
REPORTING BIAS	Is there a summary of the results of individual studies?	Yes Partial No Not reported	*Yes*
	Were the strengths and limitations of included studies and potential impact on the results discussed?	Yes Partial No Not reported	*Partial (no predefined appraisal)* *Most of the included studies are cross-sectional in design and have a small sample size* *one study in adolescents was based on patients referred for polysomnography*
	If meta-analyses were conducted, was it reasonable to do so?	Yes Partial No Not reported	*Partial* *OSA outcome definition varying across the included studies.* *6 studies: 4 adults, 2 adolescents*
	If meta-analyses were conducted, was it done appropriately?	Yes Partial No Not reported	*Yes* *Cochrane Q test and Higgins I2 test were used to assess the heterogeneity among studies. When significant heterogeneity was observed among studies, random effects analysis based on the DerSimonian and Laird method was used to estimate the pooled odds ratios and 95% confidence intervals. Sensitivity analysis was performed by removing one study at a time and the meta-analysis was repeated to assess whether any individual study significantly affected pooled estimates.*
	Were appropriate conclusions made?	Yes Partial No Not reported	*Yes*
FUNDING BIAS	Were there any conflicts of interest in the writing or funding of this review?	Yes Partial No Not reported	*No*
COMMENTS		No appraisal of included studies. OSA outcome definition varying across the studies. Inclusion if studies with both-armed zero-event in meta-analysis. Included many studies from same authors when pooling the prevalence of OSA which are likely to have overarching population	
What is the overall risk of bias?		Low Moderate High Insufficient information	High
Did risk of bias differ by outcome?		Not applicable as one outcome	

Study ID	*Kahal 2020*
Study Citation	*Kahal H, Kyrou I, Uthman OA, Brown A, Johnson S, Wall PDH, Metcalfe A, Parr DG, Tahrani AA, Randeva HS. The prevalence of obstructive sleep apnoea in women with polycystic ovary syndrome: a systematic review and meta-analysis. Sleep Breath. 2020 Mar;24(1):339-350. doi: 10.1007/s11325-019-01835-1. Epub 2019 May 20. PMID: 31111411; PMCID: PMC7127997.*
SR Country	*United Kingdom*
SYSTEMATIC REVIEW'S PICO	
Patient/population/ participants	*All women regardless of age (adults (premenopausal and postmenopausal) and adolescents (postmenarchal)) and ethnicity*
PCOS diagnostic criteria	*Any diagnostic criteria* *(7 studies utilized Rotterdam diagnostic criteria for PCOS, 4 studies utilized NIH diagnostic criteria for PCOS, 6 studies did not report the diagnostic criteria employed to diagnose PCOS)*
N	*648 patients from 17 studies in total.* *OSA risks in PCOS compared to controls estimated and effect estimates pooled from eight studies totalling 957 participants (349 PCOS and 608 controls)*
Setting	*Not limited to any setting*
Intervention/indicator	*Exposed: Women with PCOS* *Unexposed: Implied as women without PCOS*
Comparison/control	
Outcomes (primary and other)	*Primary outcome: Risk of OSA among women with PCOS compared to women without PCOS* *Secondary outcome: Pooled prevalence of OSA among women with PCOS* *Subgroup analysis* *Pooled prevalence of OSA among women with PCOS as published in conference abstracts* *Pooled prevalence of OSA among women with PCOS as published in journal articles* *Pooled prevalence of OSA among women with PCOS based on published between 2011-2009* *Pooled prevalence of OSA among women with PCOS based on articles published between 2010-2018* *Pooled prevalence of OSA among women with PCOS based on articles published in USA* *Pooled prevalence of OSA among articles published elsewhere* *Pooled prevalence of OSA among women with PCOS based on studies with sample size <25* *Pooled prevalence of OSA among women with PCOS based on studies with sample size 25+* *Pooled prevalence of OSA among women with PCOS based on studies including adolescent patients* *Pooled prevalence of OSA among women with PCOS based on studies including adult patients* *Pooled prevalence of OSA among women with PCOS based on studies including mixed patients* *Pooled prevalence of OSA among women with PCOS based on NIH definition* *Pooled prevalence of OSA among women with PCOS based on Rotterdam definition* *Pooled prevalence of OSA among women with PCOS based on unreported definition* *Risk of OSA among women with PCOS and obesity compared to women with PCOS without obesity*

Study Inclusion Criteria			*Inclusion* *- Human studies, interventional or observational, that examined the presence of OSA in women with PCOS* *- studies that used polysomnography or level III devices to diagnose OSA, regardless of the cut-offs used.* *- Conference abstracts and published studies were included.* *- All women with PCOS were included regardless of age (adults (premenopausal and postmenopausal) and adolescents (postmenarchal)), ethnicity, or PCOS diagnostic criteria.* *Exclusion* *- conditions with presentation similar to PCOS including congenital adrenal hyperplasia, Cushing's syndrome, prolactinomas, thyroid disease,and androgen-secreting tumours.*
Summary Result/s			*OSA prevalence was markedly higher in women with PCOS compared to controls (odds ratio = 3.83, 95% CI 1.43–10.24, eight studies, 957 participants (349 PCOS and 608 controls))*
INTERNAL VALIDITY – HAS THIS SYSTEMATIC REVIEW BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were reviewers blind to authors, institutions and affiliations?	Yes Partial No Not reported	*Not reported*
	Does the review have a clearly- focused question?	Yes Partial No Not reported	*Yes*
	Does the review have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
	If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
	Were 2 or more independent reviewers used for application of inclusion criteria to assess eligibility of studies?	Yes Partial No Not reported	*Yes* *Two authors (HK and IK) independently screened titles and abstracts*
SAMPLING BIAS	Does the review document a comprehensive search strategy?	Yes Partial No Not reported	*Yes*
	Were unpublished studies searched for?	Yes Partial No Not reported	*Yes* *Open Grey, abstracts from major conferences were included*
OUTCOME BIAS	Were 2 or more independent reviewers used for extraction of data from study reports?	Yes Partial No Not reported	*Yes* *Two authors (HK and IK) independently extracted data*

	Was the validity of included trials appraised using appropriate criteria?	Yes Partial No Not reported	*Yes* *Risk of Bias Assessment Tool for Non-Randomised Studies (RoBANS) was used*
	Were 2 or more independent reviewers used for appraisal of study quality?	Yes Partial No Not reported	*Yes*
REPORTING BIAS	Is there a summary of the results of individual studies?	Yes Partial No Not reported	*Yes*
	Were the strengths and limitations of included studies and potential impact on the results discussed?	Yes Partial No Not reported	*Yes*
	If meta-analyses were conducted, was it reasonable to do so?	Yes Partial No Not reported	*NA*
	If meta-analyses were conducted, was it done appropriately?	Yes Partial No Not reported	*Partial* *Reporting of the meta-analysis for the primary outcome to generate pooled OR is not mentioned.* *The authors mention that they pooled the prevalence estimates using the DerSimonian– Laird random effects model, assessed the between study variations in prevalence estimates using the Higgins I2 statistic, and, as recommended, a value of greater than 50% was considered for moderate heterogeneity.*
	Were appropriate conclusions made?	Yes Partial No Not reported	*Yes*
FUNDING BIAS	Were there any conflicts of interest in the writing or funding of this review?	Yes Partial No Not reported	*No*
COMMENTS		Effect estimates from conference proceedings have been included in the meta-analysis [(Wootton et. al., 2017 and Temple et. al., 2013) with effect estimates of OR 0.75 (0.18-3.17) and 1.32 (0.67-2.60) respectively and a weight of 15.5% and 20.9% respectively]	
What is the overall risk of bias?		Low Moderate High Insufficient information	Low
Did risk of bias differ by outcome?		No	

PART 2

RECOMMENDATIONS

Compiled by key contact(s)

GDG 1

Question 1.10.

Are women with PCOS at increased risk for sleep apnea?

BACKGROUND:

Prevalence and problem

Obstructive sleep apnoea (OSA) is a condition characterised by repetitive occlusions of the upper airway during sleep leading to futile ventilatory efforts, oxygen desaturations, terminating in arousal from sleep. This condition may lead to sleep fragmentation, non-restorative sleep and daytime sleepiness. The postulated longer term health consequences of these repeated sleep related physiological derangements are linked to cardiovascular disease, diabetes, cognitive decline and dementia. However, these associations are yet to be causally demonstrated through rigorous controlled trials.

The prevalence of OSA among general western adult populations based on polysomnographic criteria of an apnoea hypopnoea index of 5 or more respiratory events per hour varies across cohorts between 9 and 38% (1). More than half of these will be minimally symptomatic. The prevalence is higher in men, increases with greater body mass index and advancing age. The diagnostic cut off of 5 apnoeas/hypopnoeas per hour is an arbitrary point along a continuum which evolved from historic rather than evidenced based criteria and is further affected by varied definitional and measurement-based factors. Unlike conditions such as hypertension and diabetes where clinical sequelae are measurable at a particular cut off point that inform treatment decisions, there is no established cut off point at which OSA warrants treatment. In the absence of such guiding parameters the treatment process requires a personalised care plan that factors in symptomatology and the disruptive impact of associated snoring. Although not well quantified, the potential long term health sequelae still remain an important consideration in the treatment decision and treatment is usually offered routinely to severe cases (2). Addressing the public health implications of OSA are challenged by the magnitude of its prevalence, the complexity of the diagnostic process as well as the suboptimal effectiveness of device-based treatments such as continuous positive airway pressure (CPAP).

Summary of key information

Randomised controlled intervention studies demonstrate benefits of treatment on symptoms, quality of life, mood and productivity (3). There are important observational trials demonstrating an association with the severe spectrum of obstructive sleep apnoea and adverse cardiovascular outcomes and death (4). Intervention trials have shown that treating OSA may lead to favourable outcomes in some surrogate endpoints such has blood pressure (5), however the effect overall is modest at 1-3mmHg, with a greater effect for more severe OSA and pre-existing hypertension. The relationship between OSA and diabetes and insulin resistance has shown mixed results across observational trials and smaller intervention studies (6-9). . A larger randomised controlled trial of the use of CPAP for moderate to severe OSA and coexistent diabetes failed to demonstrate improvements in measures of glycaemic control (10). Three randomised controlled trials exploring the treatment effect of obstructive sleep apnoea as secondary prevention for cardiovascular events and/or death have failed to demonstrate a benefit of CPAP treatment on these endpoints (3, 11, 12). The largest of these, the SAVE trial (3), enrolled 2717 subjects with moderate to severe OSA. Whilst they demonstrated treatment improvements in quality of life, mood and work-related productivity, the lack of effect on the primary endpoint of cardiovascular events or death was unexpected. These studies conclude there is insufficient evidence to support a case for screening for OSA among patients with diabetes or cardiovascular disease intending to modify the consequences of these conditions.

A recent systematic review and meta-analysis of 22 studies including non-peer review/unpublished studies, revealed a prevalence of OSA to be 35% among women with PCOS (13). Four the subgroup of studies in which a control group was included, women with PCOS were 3.8 times more likely to have OSA compared to controls. Another recent large study revealed subjectively determined symptoms of OSA. Snoring and

sleepiness and sleep disturbance were four times more prevalent among women with PCOS compared to a control group of infertile women without PCOS (14). The explanation for this high prevalence is not known. There is evidence that the relative androgenised state may contribute to the pathogenesis of OSA (15). Another hypothesis is that if OSA were to directly contribute to the metabolic syndrome (16) it might explain an over-representation of this condition among a PCOS patient cohort where features of the metabolic syndrome may facilitate the clinical presentation.

Some groups have advocated for screening of OSA among PCOS populations (17). However, this is no evidence base to justify screening of general populations, particularly if they are minimally symptomatic (18). Targeted screening is more recently appearing in general population guidelines and position statements where OSA may have high prevalence (19). Patients with PCOS may have features of the metabolic syndrome that expose them to increased cardiovascular diabetes and other health risks. However, the extent to which OSA contributes additionally to this risk is not yet supported by robust clinical trials. There are a number of screening questionnaires that are validated for general populations including the STOP BANG (20), OSA50 (21) or Berlin Questionnaire (22). Currently there is no OSA screening questionnaire validated for young women with and without PCOS. Although the Berlin questionnaire performs less well in general, as opposed to sleep clinic, populations (22) it may be the preferred choice among populations that include younger women as it does not include gender or age criteria in determining the risk prediction. Although most screening questionnaires all make some limited enquiry into symptomatology they tend to focus on BMI and snoring/apnoea detection for predictive power. Therefore, these questionnaires are designed to predict for the presence of OSA and do not necessarily inform the case for treatment. Questionnaires are simple to complete and inexpensive to administer. They can be a useful rule out tool. Nevertheless, the value of managing an isolated positive screening questionnaire for consideration of further evaluation with ambulatory or in-laboratory polysomnography is not well described for a PCOS population. Additional screening for a symptomatic subset may help to direct treatment to those more likely to obtain benefit. This is best achieved through history taking (2). Alternatively, the functional outcomes of sleep questionnaire (FOSQ) is a 30-item questionnaire focusing of symptoms of sleep disturbance that is potentially applicable for clinicians not proficient in taking a sleep apnoea symptom history (23).

The most compelling case for treating OSA relates to the improving symptoms of non-restorative sleep, daytime fatigue and sleepiness. These symptoms may contribute to mood disturbance, especially anxiety and depression (3). PCOS is a condition in which mood disturbance is common. The extent to which co-existent OSA may additional contribute to mood disturbance is an important area for future exploration. Currently there is insufficient evidence to support a case for screening for OSA among women with PCOS with the intention of improving features of the metabolic syndrome, measures of diabetic control or longer term cardiovascular health. However, the available evidence does indicate that a higher prevalence of OSA may exist in PCOS and the potential for symptom benefit to be achieved through identification and effective therapy of OSA is likely to be worthwhile. Therefore, it would seem that questionnaire-based screening for OSA may be an appropriate strategy when combined with a thorough sleep apnoea history that target the symptomatic subgroup.

GRADE EVIDENCE CERTAINTY	
Comparison	**GRADE for critical outcomes**
Comparison 1. PCOS versus Controls	⨁⨁⨁◯ MODERATE

Evidence to Recommendations Framework

COMPARISONS (option versus other option)

To identify the odds of women with PCOS having obstructive sleep apnea (OSA) compared to women without PCOS.

EVIDENCE-BASED RECOMMENDATION(S)

EBR: Health professionals should be aware that women with PCOS have significantly higher prevalence of obstructive sleep apnea compared to women without PCOS, independent of BMI.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

EBR: Women with PCOS should be assessed for symptoms of obstructive sleep apnea (i.e. snoring in combination with waking unrefreshed from sleep, daytime sleepiness or fatigue) and if present, screen with validated tools or refer for assessment.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

PRACTICE POINT(S)

Simple obstructive sleep apnea screening questionnaires (such as the Berlin questionnaire validated in general population) can assist in the identification of obstructive sleep apnea in women with PCOS, but formal diagnosis requires formal sleep study.
Goals of treatment should target obstructive sleep apnearelated symptom burden.

GRADE CONSIDERATIONS

Justification:
Four studies demonstrated that symptomatic OSA was 17.95 times more likely to be present among women with PCOS than controls.
This finding is established from 8 peer reviewed publications that included a control group for which OSA was determined polysomnographically and considered to be present if the apnea/hypopnea index was > 5 events per hour
There is currently no sleep apnea screening questionnaire validated for use in women with PCOS. The Berlin questionnaire is an easily administered tool that avoids using a scores for sex or age as part of the risk prediction. Although well validated for a sleep clinic population, it performs less well for general populations although retains a moderate level of sensitivity and specificity.

Subgroup considerations:
Three studies compared women with PCOS with controls over a healthy weight and demonstrated that OSA was 4.25 times more likely to be present among women with PCOS.
No studies identified for adolescent groups.

Implementation considerations:
The increased risk of having OSA among women with PCOS, especially among symptomatic cases is very high. Nevertheless pooled sample size remains small and some caution in the interpretation of these findings is required. Not all studies were matched or adjusted for BMI. Nevertheless the available data points to over-representation of OSA among women with PCOS and should be considered as a possible contributor to symptoms of poor quality or non-restorative sleep, daytime fatigue, excessive sleepiness and mood disturbances.

Primary care clinicians are likely to be familiar with sleep apnea screening but education is likely required for other healthcare professionals working with women with PCOS.
All women with PCOS need to be aware of symptoms related to obstructive sleep apnea.

Monitoring and evaluation considerations:
Follow up to ensure screening and treatment occurs in practice.

Research priorities:
- Validated existing screening tools for obstructive sleep apnea in PCOS.
- Understanding the mechanisms underlying obstructive sleep apnea in women with PCOS and their relationships with metabolic and psychological features.
- Examination of the adherence and effectiveness of treatment for obstructive sleep apnea in women with PCOS, including the impact this has on the process and outcome of PCOS treatment and management.
- Including more studies in adolescents.
- Long term research on obstructive sleep apnea and PCOS.

GRADE framework

GRADE DECIDE **Interactive Evidence to Decision Framework**

● DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Small sample size and no adolescent studies.

● UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

Judgement:

☐ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☒ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

None

● CERTAINTY OF THE EVIDENCE

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☐ Very low	☐ Low	☒ Moderate	☐ High

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

None

● VALUES

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☐ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☒ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Research evidence:

No research evidence was identified

Panel discussion:

None

● BALANCE OF EFFECTS

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:

None

● COSTS

How large are the resource requirements (costs)?

Judgement:

☐ Don't know	☒ Varies	☐ Large costs	☐ Moderate costs	☐ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:

No research evidence was identified

Panel discussion:

None

● CERTAINTY OF COST EVIDENCE

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

No research evidence was identified

Panel discussion:

No evidence.

● COST-EFFECTIVENESS

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

No research evidence was identified

Panel discussion:

No evidence

● EQUITY

What would be the impact on health equity?

Judgement:

☐ Don't know	☒ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☐ Probably increased	☐ Increased

Research evidence:

No research evidence was identified

Panel discussion:

Access to screening and treatment may be limited in some settings.

● ACCEPTABILITY

Is the option acceptable to key stakeholders?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Consumer perspective was it should be screened.

● FEASIBILITY

Is the option feasible to implement?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Simple clinical screening is possible but further assessment and treatment may be variable.

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11. Peker Y, Glantz H, Eulenburg C, Wegscheider K, Herlitz J, Thunstrom E. Effect of Positive Airway Pressure on Cardiovascular Outcomes in Coronary Artery Disease Patients with Nonsleepy Obstructive Sleep Apnea. The RICCADSA Randomized Controlled Trial. American journal of respiratory and critical care medicine. 2016;194(5):613-20.
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14. Eisenberg E, Legro RS, Diamond MP, Huang H, O'Brien LM, Smith YR, Coutifaris C, Hansen KR, Santoro N, Zhang H. Sleep Habits of Women With Infertility. J Clin Endocrinol Metab. 2021 Oct 21;106(11):e4414-e4426. doi: 10.1210/clinem/dgab474. PMID: 34180998; PMCID: PMC8530742.
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18. US Preventive Services Task Force, Mangione CM, Barry MJ, Nicholson WK, Cabana M, Chelmow D, Rucker Coker T, Davidson KW, Davis EM, Donahue KE, Jaén CR, Kubik M, Li L, Ogedegbe G, Pbert L, Ruiz JM, Stevermer J, Wong JB. Screening for Obstructive Sleep Apnea in Adults: US Preventive Services Task Force Recommendation Statement. JAMA. 2022 Nov 15;328(19):1945-1950. doi: 10.1001/jama.2022.20304. PMID: 36378202.
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21. Chai-Coetzer CL, Antic NA, Rowland LS, Catcheside PG, Esterman A, Reed RL, et al. A simplified model of screening questionnaire and home monitoring for obstructive sleep apnoea in primary care. Thorax. 2011;66(3):213-9.
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PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by the Evidence Team: Aya Mousa, Jillian Tay

Other Members: Loyal Pattuwage, Darren Rajit, Uday Pratap Singh

GDG 1

Question 1.11.

Are women with PCOS at increased risk of endometrial cancer?

1. STUDY SELECTION

Table 1. PICO Criteria for Inclusion	
Question	1.11 Are women with PCOS at increased risk of endometrial cancer? CLINICAL PRACTICE POINT: What methods/tools can be used to screen for endometrial cancer in women with PCOS?
Clinical leads (key contacts)	Duru Shah
Allocation ranking	Level 1 – New systematic review

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(language, year)*
Inclusion	Females of any age, ethnicity, weight or phenotype of PCOS (diagnosed by any criteria including Rotterdam, NIH or AES, self-report, ICD codes etc).	None	Females without PCOS	incidence/prevalence of endometrial hyperplasia, complex endometrial hyperplasia, endometrial cancer.	Evidence based guidelines, systematic reviews, health technology assessments, randomised controlled trials, prospective and retrospective cohort studies, cross-sectional and case-control studies.	English language. Human studies
Exclusion	None	None	Studies without a control or comparison arm	None	case reports, commentaries, letters to editor.	None

2. SEARCH STRATEGY

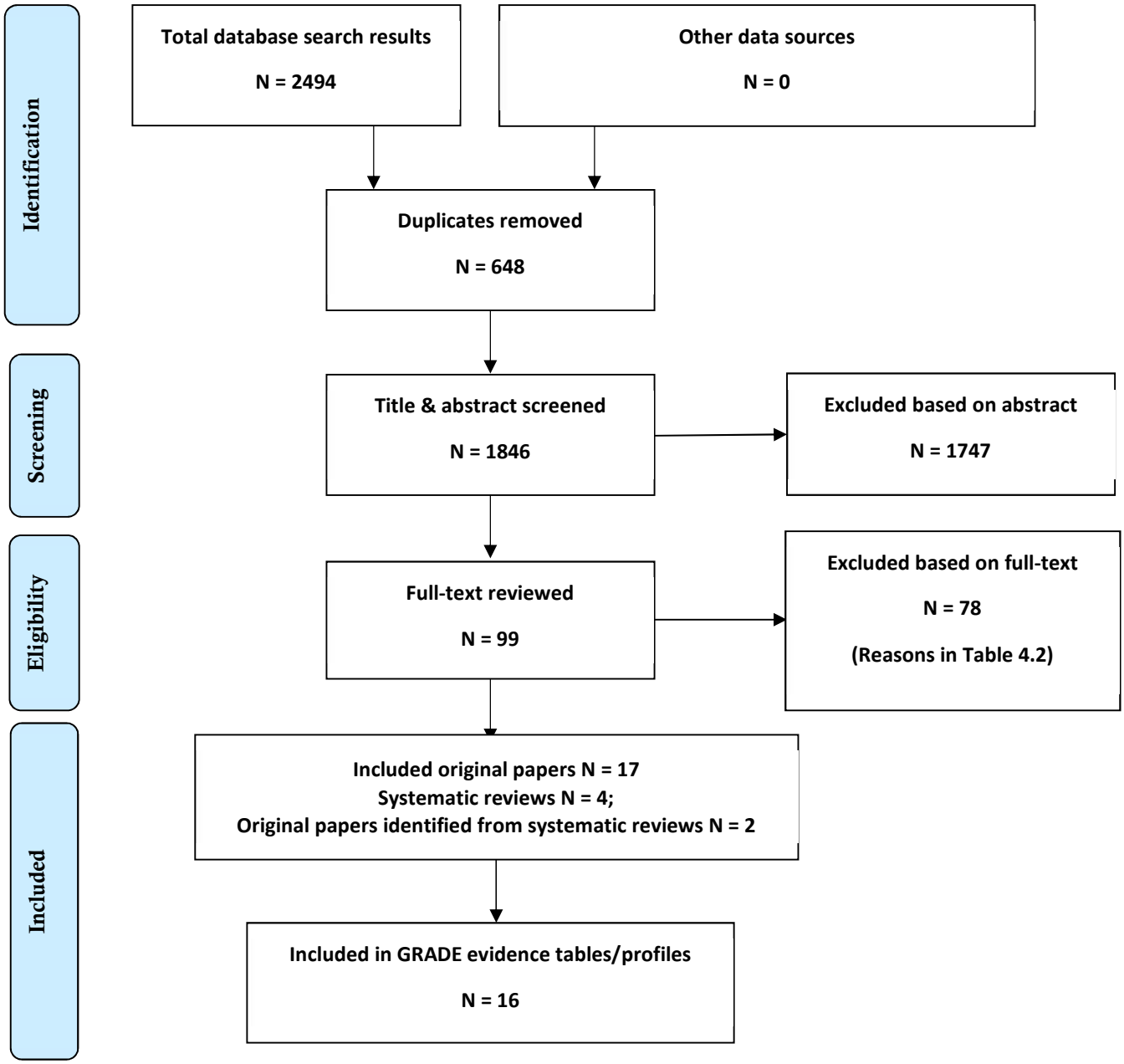
Search details	
Search strategy source: not applicable	
Evidence source	Date of search (day/month/year)
Medline (Ovid)	Inception until 18/8/22
PsychInfo (Ovid)	Inception until 18/8/22
EMBASE	Inception until 18/8/22
All EBM (Ovid)	Inception until 18/8/22
CINAHL	Inception until 18/8/22
Any subsequent updates - enter database and date: not applicable	

Questions addressed by this search:		
GDG	**Q#**	**Question**
1	1.11	1.11 Are women with PCOS at increased risk of endometrial cancer? CLINICAL PRACTICE POINT: What methods/tools can be used to screen for endometrial cancer in women with PCOS?

OVID Medline, All EBM, EMBASE, PsychInfo	CINAHL
1 exp polycystic ovary syndrome/ 2 polycystic ovar*.mp. 3 poly-cystic ovar*.mp. 4 PCO*.mp. 5 (stein-leventhal or leventhal).mp. 6 anovulation/ 7 anovulat*.mp. 8 oligo-ovulat*.mp. 9 oligoovulat*.mp. 10 (ovar* adj5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*)).mp. 11 or/1-10 12 exp Endometrial Neoplasms/ 13 (endom* adj5 (cancer* or neoplas* or carcinom* or adenocarcinom* or malignan* or tumor* or tumour* or hyperplasia* or lesion* or abnormal* or disease*)).ti,ab,kw. 14 ((uter* and lining) adj5 (cancer* or neoplas* or carcinom* or adenocarcinom* or malignan* or tumor* or tumour* or lesion* or abnormal* or disease*)).ti,ab,kw. 15 ((womb or corpus uter*) adj5 (cancer* or neoplas* or carcinom* or adenocarcinom* or malignan* or tumor* or tumour* or lesion* or abnormal* or disease*)).ti,ab,kw. 16 Endometrial Hyperplasia/ 17 or/12-16 18 11 and 17 19 limit 18 to (english language and humans) 20 limit 19 to yr="1990 -Current"	S1 (MM "Polycystic Ovary Syndrome") S2 TX polycystic ovar* S3 TX poly-cystic ovar* S4 TX PCO* S5 TX (stein-leventhal or leventhal) S6 (MM "Anovulation") S7 TX anovulati* S8 TX oligoovulat* S9 TX oligo-ovulat* S10 TX (ovar* N5 (scelerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*)). S11 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 S12 (MM "Endometrial Neoplasms") S13 TX ((endom* N5 (cancer* or neoplas* or carcinom* or adenocarcinom* or malignan* or tumor* or tumour* or hyperplasia* or lesion* or abnormal* or disease*))) S14 TX ((uter* and lining) N5 (cancer* or neoplas* or carcinom* or adenocarcinom* or malignan* or tumor* or tumour* or lesion* or abnormal* or disease*)) S15 TX ((womb or corpus uter*) N5 (cancer* or neoplas* or carcinom* or adenocarcinom* or malignan* or tumor* or tumour* or lesion* or abnormal* or disease*)) S16 (MH "Hyperplasia+") S17 TX endometrial cancer or endometrial carcinoma S18 S16 AND S17 S19 S12 OR S13 OR S14 OR S15 OR S18 S20 S11 AND S19 Limiters - Publication Year: 1990- 2022; English Language; Human Search modes - Boolean/Phrase

Evidence processing: Studies were selected and appraised by one reviewer using study selection and appraisal criteria (PICO above) established a priori. The articles were reviewed by title and abstract by one reviewer. When a decision could not be made based on title and abstract alone, full text was retrieved. A total of 19 studies met inclusion criteria for this review.

3. SEARCH RESULTS - PRISMA flowchart



4. STUDY INCLUSION

4.1 Included studies

Original studies included:

Aldarazi K, Omran H, Jassim NM. Endometrial hyperplasia in asymptomatic subfertile population. J Gynecol Obstet Hum Reprod. 2022 Apr;51(4):102337. doi: 10.1016/j.jogoh.2022.102337. Epub 2022 Feb 10. PMID: 35151930.

Beavis AL, Najjar O, Cheskin LJ, Mangal R, Rositch AF, Langham G, Fader AN. Prevalence of endometrial cancer symptoms among overweight and obese women presenting to a multidisciplinary weight management center. Gynecol Oncol Rep. 2020 Sep 11;34:100643. doi: 10.1016/j.gore.2020.100643. PMID: 32995455; PMCID: PMC7502818.

Ding DC, Chen W, Wang JH, Lin SZ. Association between polycystic ovarian syndrome and endometrial, ovarian, and breast cancer: A population-based cohort study in Taiwan. Medicine (Baltimore). 2018 Sep;97(39):e12608. doi: 10.1097/MD.0000000000012608.

Elfayomy AK, Soliman BS. Risk Factors Associated with the Malignant Changes of Symptomatic and Asymptomatic Endometrial Polyps in Premenopausal Women. J Obstet Gynaecol India. 2015 May;65(3):186-92. doi: 10.1007/s13224-014-0576-6. Epub 2014 Jun 1. PMID: 26085741; PMCID: PMC4464569.

Escobedo LG, Lee NC, Peterson HB, Wingo PA. Infertility-associated endometrial cancer risk may be limited to specific subgroups of infertile women. Obstet Gynecol. 1991 Jan;77(1):124-8. PMID: 1984211.

Fearnley EJ, Marquart L, Spurdle AB, Weinstein P, Webb PM; Australian Ovarian Cancer Study Group and Australian National Endometrial Cancer Study Group. Polycystic ovary syndrome increases the risk of endometrial cancer in women aged less than 50 years: an Australian case-control study. Cancer Causes Control. 2010 Dec;21(12):2303-8. doi: 10.1007/s10552-010-9658-7. Epub 2010 Oct 17. PMID: 20953904.

Gottschau M, Kjaer SK, Jensen A, Munk C, Mellemkjaer L. Risk of cancer among women with polycystic ovary syndrome: a Danish cohort study. Gynecol Oncol. 2015 Jan;136(1):99-103. doi: 10.1016/j.ygyno.2014.11.012. Epub 2014 Nov 20. PMID: 25451694.

Hachisuga T, Fukuda K, Iwasaka T, Hirakawa T, Kawarabayashi T, Tsuneyoshi M. Endometrioid adenocarcinomas of the uterine corpus in women younger than 50 years of age can be divided into two distinct clinical and pathologic entities based on anatomic location. Cancer. 2001 Nov 15;92(10):2578-84. doi: 10.1002/1097-0142(20011115)92:10<2578::aid-cncr1610>3.0.co;2-v. PMID: 11745192.

Ho SP, Tan KT, Pang MW, Ho TH. Endometrial hyperplasia and the risk of endometrial carcinoma. Singapore Med J. 1997 Jan;38(1):11-5. PMID: 9269346.

Iatrakis G, Zervoudis S, Saviolakis A, et al. Women younger than 50 years with endometrial cancer. Eur J Gynaecol Oncol 2006; 27: 399–400.

Kilicdag EB, Haydardedeoglu B, Cok T, Parlakgumus AH, Simsek E, Bolat FA. Polycystic ovary syndrome and increased polyp numbers as risk factors for malignant transformation of endometrial polyps in premenopausal women. Int J Gynaecol Obstet. 2011 Mar;112(3):200-3. doi: 10.1016/j.ijgo.2010.10.014. Epub 2011 Jan 17. PMID: 21247566.

Okamura Y, Saito F, Takaishi K, Motohara T, Honda R, Ohba T, Katabuchi H. Polycystic ovary syndrome: early diagnosis and intervention are necessary for fertility preservation in young women with endometrial cancer under 35 years of age. Reprod Med Biol. 2016 Dec 5;16(1):67-71. doi: 10.1002/rmb2.12012. PMID: 29259453; PMCID: PMC5715875.

Pillay OC, Te Fong LF, Crow JC, Benjamin E, Mould T, Atiomo W, Menon PA, Leonard AJ, Hardiman P. The association between polycystic ovaries and endometrial cancer. Hum Reprod. 2006 Apr;21(4):924-9. doi: 10.1093/humrep/dei420. Epub 2005 Dec 16.

Rosen, Monica W., Tasset, Julia, Kobernik, Emily K., Smith, Yolanda R., Johnston, Carolyn, & Quint, Elisabeth H. (2019). Risk Factors for Endometrial Cancer or Hyperplasia in Adolescents and Women 25 Years Old or Younger. *Journal of Pediatric & Adolescent Gynecology*, *32*(5), 546- 549.

Shu XO, Brinton LA, Zheng W, Gao YT, Fan J, Fraumeni JF Jr. A population-based case-control study of endometrial cancer in Shanghai, China. Int J Cancer. 1991 Aug 19;49(1):38-43. doi: 10.1002/ijc.2910490108. PMID: 1874568.

Uehara, T., Mitsuhashi, A., & Shozu, M. (2020). The impact of pre-existing polycystic ovary syndrome on endometrial cancer recurrence. *European Journal Of Gynaecological Oncology*, *41*(5), 668. doi: 10.31083/j.ejgo.2020.05.5038

Zucchetto A, Serraino D, Polesel J, Negri E, De Paoli A, Dal Maso L, Montella M, La Vecchia C, Franceschi S, Talamini R. Hormone-related factors and gynecological conditions in relation to endometrial cancer risk. Eur J Cancer Prev. 2009 Aug;18(4):316-21. doi: 10.1097/cej.0b013e328329d830. PMID: 19554665.

Systematic review identified:

Barry JA, Azizia MM, Hardiman PJ. Risk of endometrial, ovarian and breast cancer in women with polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update. 2014 Sep-Oct;20(5):748-58. doi: 10.1093/humupd/dmu012. Epub 2014 Mar 30.

Chittenden BG, Fullerton G, Maheshwari A, Bhattacharya S. Polycystic ovary syndrome and the risk of gynaecological cancer: a systematic review. Reprod Biomed Online. 2009 Sep;19(3):398-405. doi: 10.1016/s1472-6483(10)60175-7. PMID: 19778486.

Haoula Z, Salman M, Atiomo W. Evaluating the association between endometrial cancer and polycystic ovary syndrome. Hum Reprod. 2012 May;27(5):1327-31. doi: 10.1093/humrep/des042. Epub 2012 Feb 24. PMID: 22367984.

Li Z, Wang YH, Wang LL, Hu DT, Teng Y, Zhang TY, Yan ZY, Wang F, Zou YF. Polycystic ovary syndrome and the risk of endometrial, ovarian and breast cancer: An updated meta-analysis. Scott Med J. 2022 Aug;67(3):109-120. doi: 10.1177/00369330221107099.

Additional original studies identified from systematic reviews:

Niwa K, Imai A, Hashimoto M, Yokoyama Y, Mori H, Matsuda Y, Tamaya T. A case-control study of uterine endometrial cancer of pre- and post-menopausal women. Oncol Rep. 2000 Jan-Feb;7(1):89-93. PMID: 10601598.

Wild S, Pierpoint T, Jacobs H, et al. Long-term consequences of polycystic ovary syndrome: results of a 31 year follow-up study. Hum Fertil (Camb) 2000; 3: 101–105.

4.2. Excluded studies (on full text assessment)

#	Title	Author/year	Journal	Volume	Issue	Pages	Reason
1	A five-year prevalence and characteristics of polycystic ovary syndrome (PCOS) in Filipino women diagnosed with endometrial cancer	Ortega 2017	Journal of Obstetrics and Gynaecology Research	43(Supplement 1)		146-147	Abstract
2	Polycystic ovarian syndrome, insulin resistance and thickness of the endometrium	Iatrakis 2006	European Journal of Obstetrics, Gynecology, & Reproductive Biology	127	2	218-21	Wrong outcome
3	Risk factors in young reproductive women with endometrial cancer: An observational study	Sumanth 2021	International Journal of Gynecological Cancer	31(SUPPL 1)		A131	Abstract
4	Atlas of causal risk factors for epithelial ovarian cancer risk: A Mendelian randomization analysis in up to 66 450 women	Yarmolinsky 2018	ESMO Open	3(Supplement 2)		A253-A254	Abstract
5	Histopathological findings of endometrial specimens in abnormal uterine bleeding	Soleymani 2014	Archives of Gynecology & Obstetrics	289	4	845-9	Wrong outcome
6	Evaluation of sensitivity and specificity of endometrial thickness on transvaginal ultrasound and baseline risk factors as a predictor for endometrial abnormalities in symptomatic and asymptomatic postmenopausal women	Yerrisani 2017	BJOG: An International Journal of Obstetrics and Gynaecology	124(Supplement 1)		168-169	Abstract
7	Polycystic ovarian syndrome: A risk factor for endometrial carcinoma? A retrospective cross sectional case control study in a busy unit in Srilanka	Shah 2014	BJOG: An International Journal of Obstetrics and Gynaecology	2)		59	Abstract
8	Appraising the role of previously reported risk factors in epithelial ovarian cancer risk: A Mendelian randomization analysis	Yarmolinsky 2019	PLoS Medicine	16(8) (no pagination)			Wrong outcome
9	Polycystic ovarian syndrome - association and risk factors between endometrial polyp and infertility. A retrospective study	Rshoud 2022	Przeglad Menopauzalny	21(2)		106-110	Wrong comparison
10	Risk factors for endometrial cancer or hyperplasia in adolescents and young women under 25 years old	Rosen 2018	Journal of Pediatric and Adolescent Gynecology	31(2)		214	Abstract
11	The percentages of endometrial hyperplasia and endometrial cancer among polycystic ovary syndrome (PCOS) patients presenting with abnormal menstrual pattern	Prakansamut 2014	Journal of the Medical Association of Thailand	97	2	159-64	Wrong comparison
12	Association between genetically predicted polycystic ovary syndrome and ovarian cancer: A Mendelian randomization study	Harris 2019	International Journal of Epidemiology	48(3)		822-830	Wrong population
13	Premenopausal women with endometrial cancer. Risk factors analysis	Guerra 2011	International Journal of Gynecological Cancer	3)		S1190	No full text
14	Causes of endometriosis and prevalent infertility in patients undergoing laparoscopy without achieving pregnancy	DeOliveira 2016	Minerva Ginecologica	68(3)		250-258	No full text
15	Risk factors for endometrial cancer in Japanese women	Hachisuga 1998	International Journal of Gynecological Cancer	8(4)		292-297	No full text
16	Characteristics of Women with Pcos Who Undergo Endometrial Biopsies	Goldrick 2020	Fertility and Sterility	114(3 SUPPL)		e407-e408	Abstract
17	Endometrial abnormalities in infertile women	Kurabayashi 2003	Journal of Reproductive Medicine	48	6	455-9	No full text
18	Frequency of endometrial cancer and atypical hyperplasia in infertile women undergoing hysteroscopic polypectomy	Kuribayashi 2017	Journal of Obstetrics and Gynaecology Research	43(9)		1465-1471	Wrong outcome
19	Association between prolactin receptor expression and proliferation in the endometrium of obese women with polycystic ovary syndrome	Paulson 2020	Gynecological Endocrinology	36	3	226-232	Wrong outcome
20	Comparison of endometrial histology and clinical features in lean and obese Korean women with poly-cystic ovary syndrome	Park 2011	Fertility and Sterility	1)		S131	Wrong comparison
21	Carcinoma Endometrium in Women aged 30 Years and Younger: An Unusual Age of Presentation	Dalal 2020	Indian Journal of Gynecologic Oncology	18(2) (no pagination)			Wrong outcome

22	Incidence of endometrial hyperplasia in polycystic ovary syndrome	Brennan 2011	Reproductive Sciences	1)		252A-253A	Wrong outcome
23	Endometrial carcinoma; ovarian dysfunction - A risk factor in young women	Dahlgren 1991	European Journal of Obstetrics Gynecology and Reproductive Biology	41(2)		143-150	Wrong outcome
24	Factors associated with synchronous ovarian and endometrial cancer: A population-based case control study	AlHilli 2011	Journal of Clinical Oncology. Conference: ASCO Annual Meeting	29	15 SUPPL. 1		Wrong outcome
25	Significance of histopathological evaluation in the diagnosis of endometrial lesions in premenopausal and postmenopausal women	Bodepudi 2021	European Journal of Molecular and Clinical Medicine	8(4)		1111-1114	Wrong outcome
26	Detecting endometrial hyperplasia and cancer in women <45 years old: who warrants an endometrial biopsy?	Beavis 2021	Gynecologic Oncology	162(Supplement 1)		S125-S126	Wrong outcome
27	Genetic analyses of gynecological disease identify genetic relationships between uterine fibroids and endometrial cancer, and a novel endometrial cancer genetic risk region at the WNT4 1p36.12 locus	Kho 2021	Human Genetics	140(9)		1353-1365	Wrong comparison
28	Endometrial neoplasia in reproductive-aged Thai women with polycystic ovary syndrome	Indhavivadhana 2018	International Journal of Gynaecology & Obstetrics	142	2	170-175	Wrong outcome
29	The Genetic Association of Polycystic Ovary Syndrome and the Risk of Endometrial Cancer: A Mendelian Randomization Study	Chen 2021	Frontiers in Endocrinology	12		756137	Wrong comparison
30	The prevalence of endometrial cancer symptoms in overweight and obese women presenting to a multidisciplinary weight management clinic	Beavis 2019	Journal of Women's Health	28(11)		1581	Abstract
31	Are young adult women with polycystic ovary syndrome slipping through the healthcare cracks?	Dokras 2014	Journal of Clinical Endocrinology & Metabolism	99	5	1583-5	Wrong outcome
32	Diagnosis of simple endometrial hyperplasia in a woman with polycystic ovary syndrome with use of hysterosalpingography	Sindi 2002	Fertility & Sterility	77	5	1069-70	case report
33	Endometrial thickness predicts endometrial hyperplasia in patients with polycystic ovary syndrome	McCormick 2011	Fertility & Sterility	95	8	2625-7	Wrong outcome
34	Does polycystic ovary syndrome independently affect oncologic and reproductive outcomes in patients with endometrial cancer receiving fertility-sparing treatment?	Harada 2021	Journal of Gynecologic Oncology	32	5	e80	Wrong outcome
35	Bariatric Surgery: Does It Play a Role in Fertility-Preserving Treatment Among Obese Young Women With Endometrial Cancer?	Benito 2015	Journal of Minimally Invasive Gynecology	22	5	906-9	case report
36	The risk of breast and gynecological cancer in women with a diagnosis of infertility: a nationwide population-based study	Lundberg 2019	European Journal of Epidemiology	34	5	499-507	Wrong outcome
37	Histopathological and Clinical Study of Effect on Polycystic Ovary Syndrome (Pcos) Cancer Risks	Alboaklah 2021	Biochemical and Cellular Archives	21(2)		3125-3132	Wrong outcome
38	Is age a risk factor for endometrial hyperplasia or cancer in young women with abnormal bleeding?	Kim 2015	Obstetrics and Gynecology	1)		24S-25S	Abstract
39	Awareness of Polycystic ovarian disease among females of age group 18-30 years	PriyankaShenoy 2016	Journal of Pharmaceutical Sciences and Research	8(8)		813-816	Wrong outcome
40	Polycystic ovary syndrome and endometrial cancer	Navaratnarajah 2008	Seminars in Reproductive Medicine	26	1	62-71	Narrative review
41	Screening tests for endometrial cancer in the general population	Njoku 2021	Cochrane Database of Systematic Reviews	2021(1) (no pagination)			Wrong outcome
42	Infertility and risk of incident endometrial carcinoma: A pooled analysis from the Epidemiology of Endometrial Cancer Consortium	Yang 2014	Cancer Research. Conference: 105th Annual Meeting of the American Association for Cancer Research, AACR	74	19 SUPPL. 1		Abstract
43	PCO and endometrial adenocarcinoma	Cianci 1994	European Journal of Obstetrics and Gynecology and Reproductive Biology	55(1)		32	Wrong design
44	The Risk of Endometrial Hyperplasia and Malignancy May be Increased in Patients with Endometriosis	Hur 2021	Journal of Minimally Invasive Gynecology	28(11 Supplement)		S148	Abstract

45	Association of Stein - Leventhal syndrome with the incidence of postmenopausal breast carcinoma in a large prospective study of women in Iowa [3]	Parazzini 1997	Cancer	80(7)		1360-1362	Wrong outcome
46	Assessment of risk factors for endometrial cancer in AGC population: A prospective case series study	Jiang 2017	Journal of Lower Genital Tract Disease	21(2 Supplement 1)		S42	Wrong outcome
47	Polycystic Ovarian Morphology may be a Positive Prognostic Factor in Patients with Endometrial Cancer who Achieved Complete Remission after Fertility-Sparing Therapy with Progestin	Fukui 2017	Asian Pacific journal of cancer prevention : APJCP	18(11)		3111-3116	Wrong outcome
48	Polycystic ovary syndrome and endometrial carcinoma	Hardiman 2003	Lancet	361(9371)		1810-1812	Wrong outcome
49	The relationship between androgens, the menstrual cycle, and endometrial cancer in premenopausal women	Hertzmark 2010	Dissertation Abstracts International: Section B: The Sciences and Engineering	70	12-B	7470	Wrong outcome
50	Hysteroscopy, endometrial cancer and risk factor	Coco 2012	International Journal of Gynecology and Obstetrics	3)		S652-S653	Wrong outcome
51	Progestins and menopause: epidemiological studies of risks of endometrial and breast cancer	Pike 2000	Steroids	65	10-11	659-64	Wrong population
52	ART and gynecological cancer: Report of our experiences and literature review	Karimi-Zarchi 2013	International Journal of Fertility and Sterility	1)		109-110	Abstract
53	Analysis on reverse of Atypical endometrial hyperplasia by drugs in patients with polycystic ovary syndrome	Lou 2013	Journal of Reproduction and Contraception	24(4)		205-214	Wrong outcome
54	Prevalence of endometrial cancer or atypical hyperplasia diagnosed incidentally in infertility clinic	Tohma 2018	American Journal of Obstetrics and Gynecology	219(5)		503-505	No full text
55	Assisted reproduction in the treatment of polycystic ovarian syndrome	Urman 2004	Reproductive Biomedicine Online	8	4	419-30	Narrative review
56	Assessing and validating housekeeping genes in normal, cancerous, and polycystic human ovaries	Asiabi 2020	Journal of Assisted Reproduction & Genetics	37	10	2545-2553	Wrong outcome
57	Assisted reproductive technology treatment and risk of ovarian cancer - A nationwide population-based cohort study	Vassard 2019	Human Reproduction	34(11)		2290-2296	Wrong outcome
58	Using genetics to understand the relationship between non-cancerous gynaecological diseases and endometrial cancer risk	O'Mara 2020	European Journal of Human Genetics	28(SUPPL 1)		511-512	Wrong outcome
59	The prevalence of endometrial hyperplasia and endometrial cancer in women with polycystic ovary syndrome or hyperandrogenism	Holm 2012	Acta Obstetricia et Gynecologica Scandinavica	91	10	1173-6	Wrong comparison
60	Hysteroscopic Findings in Ovarian Polycystic and Unexplained Infertile Women						Clinical trial registration
61	A pilot study comparing a low glycaemic index diet with low calorie healthy eating to reduce risk of endometrial cancer in polycystic ovary syndrome	Atiomo 2009	International journal of gynaecology and obstetrics	107		2009-10	Abstract
62	Factors associated with endometrial hyperplasia or cancer symptoms in overweight and obese premenopausal women	Cheskin 2020	Journal of Women's Health	29(12)		A6	Abstract
63	Risk of endometrial cancer in women treated with ovary-stimulating drugs for subfertility	Skalkidou 2017	Cochrane Database of Systematic Reviews	3		CD010931	Wrong population
64	Histopathological findings of the endometrium in patients with dysfunctional uterine bleeding	Vakiani 1996	Clinical and Experimental Obstetrics and Gynecology	23(4)		236-239	No full text
65	Comparing endometrial hysteroscopic and histological findings of infertile women with polycystic ovary syndrome and unexplained infertility: A cross-sectional study	Amooee 2020	International Journal of Reproductive BioMedicine	18(1)		33-40	Wrong outcome
66	Polycystic ovary syndrome predicts prognosis in endometrial cancer patients	Uehara 2014	International Journal of Gynecological Cancer	4)		1508	No full text
67	A novel risk-scoring model for prediction of premalignant and malignant lesions of uterine endometrium among symptomatic premenopausal women	Srinivas 2020	International Journal of Women's Health	12		883-891	Wrong outcome
68	Clinical characteristics and prognosis of young Filipino women ages 30 and below with endometrial cancer: A ten-year retrospective cohort study	Macaurog 2018	International Journal of Gynecological Cancer	28 (Supplement 2)		1127-1128	Wrong outcome

69	Statistical meta-analysis of risk factors for endometrial cancer and development of a risk prediction model using an artificial neural network algorithm	Hutt 2021	Cancers	13(15) (no pagination)			Wrong outcome
70	Progestin therapy of endometrial cancer in young women and the preliminary study on risk factors of recurrence	Yu 2012	International Journal of Gynecological Cancer	3)		E1220	No full text
71	Are patients with PCOS appropriately screened for associated CO morbidities?	Dongerkery 2018	Endocrine Reviews. Conference: 100th Annual Meeting of the Endocrine Society, ENDO	39	2 Supplement 1		Wrong outcome
72	Association of endometrial carcinoma with obesity and diabetes mellitus	Begum 2020	Bangladesh Medical Research Council Bulletin	46(2)		120-127	Wrong population
73	Association of Insulin Resistance and Elevated Androgen Levels with Polycystic Ovarian Syndrome (PCOS): A Review of Literature	Xu 2022	Journal of Healthcare Engineering	2022		9240569	Wrong comparison
74	Review of Mendelian Randomization Studies on Endometrial Cancer	Guo 2022	Frontiers in Endocrinology	13 (no pagination)			Wrong outcome
75	No. 291-Epidemiology and Investigations for Suspected Endometrial Cancer	Renaud 2018	Journal of Obstetrics and Gynaecology Canada	40(9)		e703-e711	No full text
76	Frequency of endometrial cancer and atypical hyperplasia in infertile women undergoing hysteroscopic endometrial polypectomy	Kuribayshi 2016	Human Reproduction	31(Supplement 1)		i466-i467	Abstract
77	Association of Endometrial Cancer Risk with Postmenopausal Bleeding in Women: A Systematic Review and Meta-analysis	Clarke 2018	Obstetrical and Gynecological Survey	73(12)		687-688	Wrong population
78	Risk factors for young premenopausal women with endometrial cancer	Soliman 2005	Obstetrics and Gynaecology	105	3	575-580	Wrong comparison

5. STUDY CHARACTERISTICS TABLE FOR INCLUDED STUDIES

Author, year, country	Study design	Setting	PCOS criteria	PCOS sample size	Control sample size	Population description	Outcomes	Methods of measurement	Follow up Duration	Summary of findings	Pooled in MA?	RoB
Aldarazi 2022, Kingdom of Bahrain	Cross-sectional	infertility clinic	Rotterdam	108 age = 29.91 (5.70)	31 age = 32.54 (5.09)	18-43yo infertile women	Endometrial hyperplasia	Histology	NA	endometrial hyperplasia was found in 12 cases (11%) and atypical hyperplasia was detected in one patient (0.9%). All cases of and endometrial hyperplasia with or without atypia were reported among women with polycystic ovary syndrome	**Yes**	**Low**
Beavis 2020, USA	Cross-sectional	Weight management centre	Self-reported	9	94	overweight or obese women	Endometrial hyperplasia, endometrial cancer	Self reported	NA	A history of polycystic ovarian syndrome (RR:1.72, 95% CI 1.24–2.38) was associated with EH/EC symptoms, while being postmenopausal was not (RR:0.32, 95%CI: 0.12–0.87)	**No, no extractable outcome**	**High**
Ding 2018, Taiwan	Cohort	Community	ICD codes	8155 age = 27.7 (7.0)	32620 age = 27.5 (7.9)	Taiwanese government National Health Insurance Program, the Longitudinal Health Insurance Database, National Health Research Institute Databse. Women 16-49yo. Controls were randomly selected by 4-fold size matched with PCOS group by sex, age, and index year.	Endometrial cancer	ICD code	Mean (SD) PCOS = 6.0 (4.0) control = 6.3 (4.0)	A statistically significant higher risk of endometrial cancer was found in the PCOS cohort (adjusted HR [aHR] = 17.7, 95% CI = 4.9–64.2) than in the comparison cohort. However, no association was observed between PCOS and ovarian (aHR = 1.64, 95% CI: 0.63–4.27) or breast cancer (aHR=0.98, 95% CI: 0.58–1.65).	**No**	**Low**
Elfayomy 2014, India	Cross-sectional	Hospital	Self-reported	21	129	Premenopausal women who had endometrial polyp	premalignant or malignant endometrial polyp	Histology	NA	On logistic regression analysis, the premalignant and malignant lesions were influenced by polycystic ovary syndrome (p \ 0.001; OR 4.61; CI 1.9–27), polyp volume [10 ml (p \ 0.001; OR 5.83; CI 4.31–9.17), and multiple polyps (p = 0. 01; OR 2.05; CI 1.09–3.76).	**Yes**	**Mod**
Escobedo 1991, USA	Case-control	Community	Self-reported	30	3593	Cases were 437 women with endometrial cancer who resides in areas covered by Surveillance, Epidemiology and End Results centres. Control women were 20-54yo women match to the age distribution of the women with breast cancer enrolled in the study	endometrial cancer	histology	N/A	Women with PCOS had an increased adjusted OR for endometrial cancer [aOR 5.4 (2.4-12.3)]	**Yes**	**Mod**
Fearnley 2010, Australia	Case-control	Community	Self-reported	32	517	Cases were 18-79yo Australian women with histologically concerned epithelial cancer.	endometrial cancer	histology	N/A	Women with PCOS had a four fold increased risk of endometrial cancer compared to women without PCOS (OR 4.0, 95% CI 1.7-	**Yes**	**Mod**

						Control women with matched to state and age distribution in 2 waves from the national electoral roll.				9.3). This association was attenuated when additionally adjusted for body mass index (OR 2.2, 95%CI0.9-5.7)		
Gottschau 2015, Denmark	Cohort	Community	ICD codes	12070	national cancer incidence rates	Danish National Patient Register, Danish Cancer Registry, age 9-49 years at first hospital admission or visit for PCOS	Endometrial cancer	Cancer registry	median = 5.7 years	Cancer was diagnosed in 279 women with PCOS (SIR = 1.19; 95% CI = 1.06–1.34). We found an almost fourfold increased risk for endometrial cancer (numbers observed (N) = 16, SIR = 3.9; 95% CI = 2.2–6.3), the large majority of cases being type 1 (N = 14, SIR = 4.7; 95% CI = 2.6–7.9)	**No**	**Low**
Hachisuga 2001, Japan	Cross-sectional	Hospital	Medical records	20	68	Women <50yo with endometrial cancer who undergone surgery.	Endometrial cancer	Histology	NA	In comparison to carcinomas of the LUS, carcinomas of the CMP were more strongly associated with reproductive risk factors including parity (P 0.01) and polycystic ovary syndrome (P 0.02)	**Yes**	**Low**
Ho 1997, Singapore	Cross-sectional	Hospital	Medical records	4	112	Database of the histopathological lab. All patients had endometrial hyperplasia (simple, complex or mixed), with or without atypica.	Endometrial hyperplasia, endometial cancer	Histology	NA	No significant histological differences that could predict carcinoma were found.	**Yes**	**High**
Iatrakis 2006, Greece	Case-control	Hospital/clinic	Unclear. Stated confirmed diagnosis	3	178	Cases: histologicaly concefirmed endometrial cancer control: randomly selected women from gynaecology clinic (43-48yo)	Endometrial cancer	Histology	NA	With the exception of hypertension and ovarian cancer (probably related to small numbers) all other comparisons were statistically insignificant (although some only marginally).	**Yes**	**High**
Kilicdag 2011, Turkey	Cross-sectional	Hospital/clinic	Rotterdam	52	365	All 417 women had endometrial polups. All women are premenopausal	Endometrial hyperplasia, endometrial cancer	Histology	NA	Polycystic ovary syndrome (PCOS) and the presence of 2 or more polyps were associated with significant pre-malignant or malignant changes	**Yes**	**High**
Niwa 2000, Japan	Case-control	Mix - hospital and community	Ultrasound PCO	<40 yo = 5	<40 yo = 28	only those <40yo has usable data Cases: Women with endometrial cancer Control: healthy women visiting Gifu Health Promotion Centre			NA	Frequency of irregular menses, polycystic ovary syndrome (PCOS) and obesity in the EC patients under 40-year old was significantly higher than the control group.	**Yes**	**Mod**
Okamura 2016, Japan	Cross-sectional	Hospital	Japanese Society of Obstetrics and Gynaecology 2007 criteria	14 age = 29.4 (3.3) BMI = 33.9 (9.1)	11 age = 28.8 (3.2) BMI = 25.0 (8.4)	<35yo, all women with pathological diagnosis of endometrial cancer or atypical endometrial hyperplasia	Endometrial cancer, atypical endometrial hyperplasia	Histology	NA	Although both the patients with and without PCOS had irregular men- struation, the patients with PCOS were less likely to have fertility-sparing surgery than the patients without PCOS because they had more advanced disease or failed to re- spond to medroxyprogesterone acetate therapy.	**Yes**	**High**
Pillay 2006, UK	Case-control	Hospital	Histology PCO	18	211	Cases: All patients with diagnosed endometrial cancer with endometrial tissue available.	Endometrial cancer	Histology	NA	Overall, the prevalence of PCO was comparable in women with EC or benign gynaecological conditions [11 of 128 (8.6%)	**Yes**	**High**

						Control: age matched, patients with benign gynaecological conditions operated in the hospital in the same time period				versus 7 of 83 (8.4%), respectively, P = 1.00].. When subjects were divided into two groups aged <50 years and ≥50 years (50 years being the average age of menopause), the prevalence of PCO in patients aged <50 years was greater in those with EC than in controls [10 of 16 (62.5%) versus 6 of 22 (27.3%), respectively, P = 0.033; β = 0.153 by post hoc power analysis]. No difference was noted in PCO prevalence in patients aged ≥50 years.		
Rosen 2019, USA	Cross-sectional	Hospital	Unclear	6	61	Women undergoing endometrial sampling for abnormal uterine bleeding	Endometrial cancer or hyperplasia	ICD code	NA	The proportion of patients with a history of polycystic ovary syndrome (PCOS) and smoking was also significantly different between groups (30.8% vs 3.7%; P ! .01). Although smoking or PCOS alone was not related to endometrial hyperplasia or cancer in this small cohort study, there might be a relationship between endometrial abnormalities and multiple exposures, including smoking and BMI greater than 30 or smoking and a history of PCOS.	**Yes**	**High**
Shu 1991, China	Case-control	Community	Self-reported	NR	NR	Cases: 18-74yo female residents of Shanghai with endometrial cancer from a population-based registry. Controls: age-matched through random selections at the Shanghai Residents' Registry	Endometrial cancer	Cancer registry, 98.5% histologically confirmed	NA	Examination of risk in relation to various physician- diagnosed diseases occurring more than one year prior to diagnosis showed significantly elevated risks for women with histories of polycystic ovaries (OR = 4.8, 95% CI = 1.0- 23.1)	**Yes**	**Mod**
Uehara 2020, Japan	Cohort	hospital	Rotterdam	9	37	Premenopausal women (<50yo) with endometrial cancer who underwent surgery.	Endometrial cancer recurrence	chart review	median 65.5 months	Four of the nine PCOS patients developed recurrence of EC, three of whom died of the disease, whereas only one of 37 patients who did not have PCOS developed EC recurrence (44.4% and 2.7%, respectively; p = 0.003). Univariate analysis showed that the progression-free and overall survival of the patients with pre-existing PCOS was worse than that of patients without pre-existing PCOS (p = 0.008 and p = 0.029, respectively). Multivariate analysis revealed that PCOS was a poor prognostic factor for progression-free survival and a marginal poor prognostic factor for overall survival (p = 0.011 and p = 0.061, respectively)	**Yes**	**High**

Wild 2000, UK	Cohort	Mix - hospital and community	hospital records	319	1060	PCOS: Women with PCOS were identified from hospital records. Control: 3 age-matched control women requested from GP, identified as adjacent to the cohort member on the age-sex register of the practice after exclusion of reatives of the cohort member	Endometrial cancer	questionnaire	average 31 years	Lifetime prevalence of endometrial cancer is 2.2% vs 0.4% in women with and without PCOS (p<0.001) [OR 5.3, 95%CI 1.5-18.6].	**Yes**	**High**
Zucchetto 2009, Italy	Case-control	Hospital	Self-reported	68	1287	Cases were 454 women (median age 60 years, range 18–79 years) with histo- logically confirmed diagnosis of endometrial cancer and no earlier diagnosis of cancer. Only women diagnosed less than 1 year before hospitalization were eligible as cases. Controls were 908 women (median age 61 years, range 19–79 years) admitted to the same network of hospitals of cases for a wide spectrum of non-neoplastic, acute illnesses. Cases and controls were frequency matched won study centre and quinquennia of age, with 1:2 ratio.	Endometrial cancer	histology	NR	Endometrial cancer risk was inversely associated with age at menarche (OR=0.7,95%CI=0.5–1.0,for Z14vs. <12years),and directly associated with age at menopause (OR = 1.8, 95%CI=1.1–2.7,for Z55vs. <50years)and years of menstruation (OR = 2.4, 95% CI = 1.7–3.4, for highest vs. lowest tertile). Multiparity strongly reduced the risk among women under 60 years of age (OR = 0.3, 95% CI = 0.2–0.6, for Z 3 deliveries vs. < 2). Oral contraceptive use conferred a 40% reduced risk (95% CI = 0.4–1.0), irrespective of time since cessation. Although based on small numbers, women with a history of treated infertility (OR = 2.7, 95% CI = 1.1–6.4) or endometriosis (OR = 4.0, 95% CI = 1.0–15.5) were at increased risks. No significant associations with endometrial cancer risk emerged for age at first/last birth, breastfeeding, menopausal status, hormone replacement therapy, and history of uterine fibromyomas or polycystic ovary	**Yes**	**High**

6. FINDINGS

Comparisons included:

- **Comparison 1: PCOS versus non-PCOS**

Outcomes included:

- **Outcome 1. Composite endometrial cancer and/or endometrial hyperplasia**
- **Outcome 2. Endometrial cancer**
- **Outcome 3. Endometrial hyperplasia or atypia**

Comparison 1: PCOS versus non-PCOS

▪ EVIDENCE SUMMARY:

Composite endometrial cancer and/or endometrial hyperplasia

Fifteen studies were suitable for meta-analysis for composite outcomes of endometrial cancer and/or endometrial hyperplasia in women with and without PCOS. Three of the studies were cohort studies (Ding 2018, Uehara 2020 and Wild 2000), six were cross-sectional studies (Aldarazi 2022, Elfayomy, Ho 1997, Kilicdag 2011, Okamura 2017 and Rosen 2019) and six were case control studies (Escobedo 1991, Fearnley 2010, Iatrakis 2006, Niwa 2000, Pilay 2005 and Zucchetto 2009). Most of the studies were judged as high risk of bias (n = 9) and only two studies were judged as low risk of bias, while the rest were moderate risk of bias (n = 4).

Endometrial cancer

Ten studies were included in the meta-analysis for endometrial outcomes in women with and without PCOS. Two studies were cohort studies (Ding 2018 and Wild 2000), two were cross-sectional studies (Ho 1997 and Okamura 2017), the rest were case control studies (Escobedo 1991, Feranley 2010, Iatrakis 2006, Niwa 2000, Shu 1991 and Zucchetto 2009). Only one study was judged as low risk of bias, the rest were moderate (n = 4) and high (n = 5) risk of bias.

Four longitudinal studies examined endometrial cancer in women with and without PCOS (Ding 2018, Gottschau 2015, Uehara 2020 and Wild 2000) but the outcomes were not suitable for meta-analysis. Ding 2018 and Gottschau 2015 were judged as low risk of bias while Uehara 2020 and Wild 2000 were judged as high risk of bias.

Endometrial hyperplasia or atypia

Only two cross-sectional studies reported specifically endometrial hyperplasia or atypia in women with and without PCOS (Aldarazi 2022 and Okamura 2017). Meta-analysis was not performed due to significant study population difference. Aldarazi 2022 examined women recruited from infertility clinic and was judged as low risk of bias; whereas Okamura 2016 recruited women with known endometrial cancer or atypical endometrial hyperplasia and was judged as high risk of bias.

▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

In all groups of meta-analysis, women with PCOS have significantly higher odds of composite endometrial cancer and/or hyperplasia and higher odds of endometrial cancer than women without PCOS. The quality of evidence of these outcomes are low to moderate due to the observational design of included studies and evidence quality being upgraded for their large effect size.

Only two studies reported on endometrial hyperplasia alone and their results were non-consistent. Aldarazi 2022 reported higher prevalence of endometrial hyperplasia in infertile women with than without PCOS but Okamura 2016 reported that prevalence of endometrial hyperplasia was lower in women with PCOS than women without PCOS after treatment of primary endometrial cancer.

All longitudinal studies reported higher risk of endometrial cancer in women with than without

PCOS.

Outcome	Studies	PCOS n	Control n	Effect Estimate; OR [95% CI], M-H, random	Favours	Certainty
Composite endometrial cancer and/or hyperplasia						
Overall	15	8859	40225	6.01 (3.38 – 10.70)	Higher in PCOS	⊕○○○ Very low
<50 age	6	176	3996	5.78 (3.12 – 10.71)	Higher in PCOS	⊕⊕○○ Low
Unbiased population	10	8733	36173	6.37 (2.96 – 13.72)	Higher in PCOS	⊕⊕○○ Low
Endometrial cancer						
Overall	10	8646	39428	7.08 (4.05 – 12.38)	Higher in PCOS	⊕⊕○○ Low
<50 age	5	68	3832	4.70 (2.52 – 8.77)	Higher in PCOS	⊕⊕⊕○ Moderate
Unbiased population	9	8616	35835	8.07 (4.42 – 14.73)	Higher in PCOS	⊕⊕⊕○ Moderate
Endometrial hyperplasia/atypia						
Overall	2	122	42	MA not performed	No difference	⊕○○○ Very low

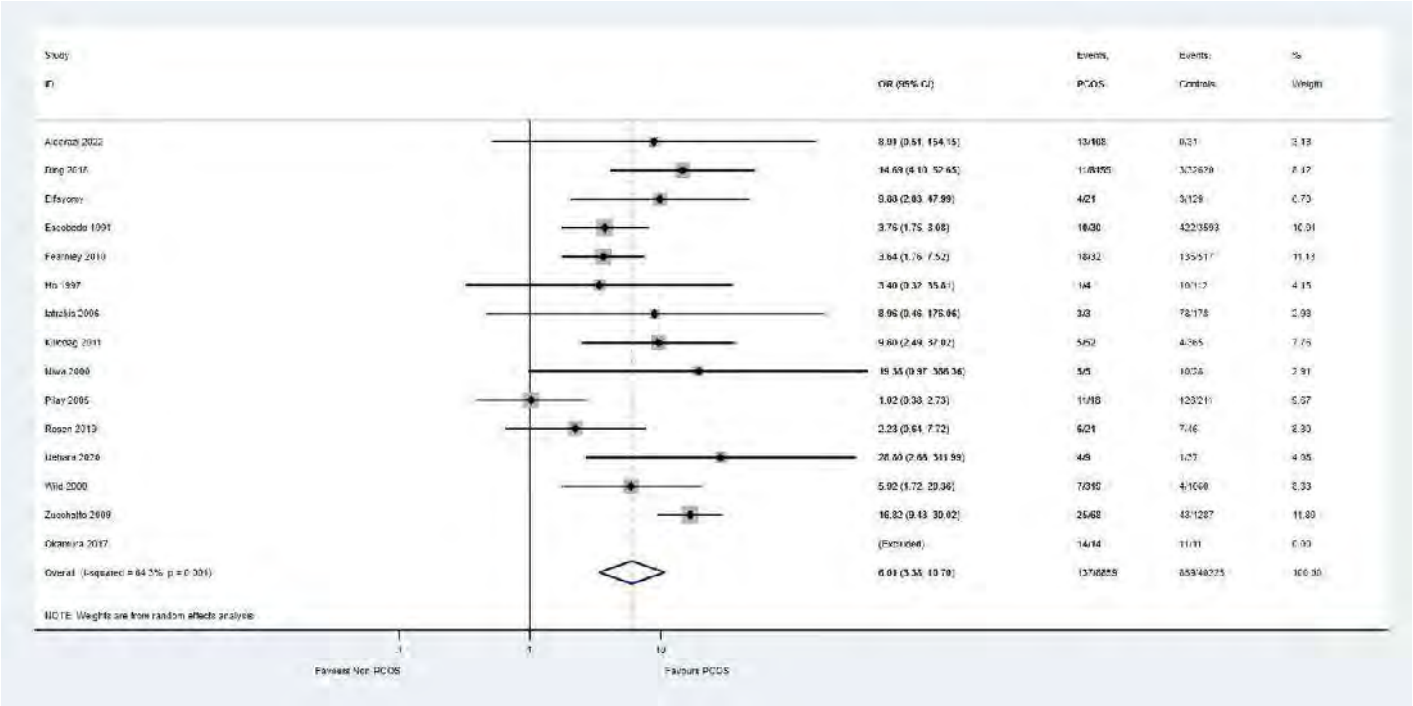
OUTCOME 1. Composite endometrial cancer and/or hyperplasia

1.1.1 Individual Study Data Table

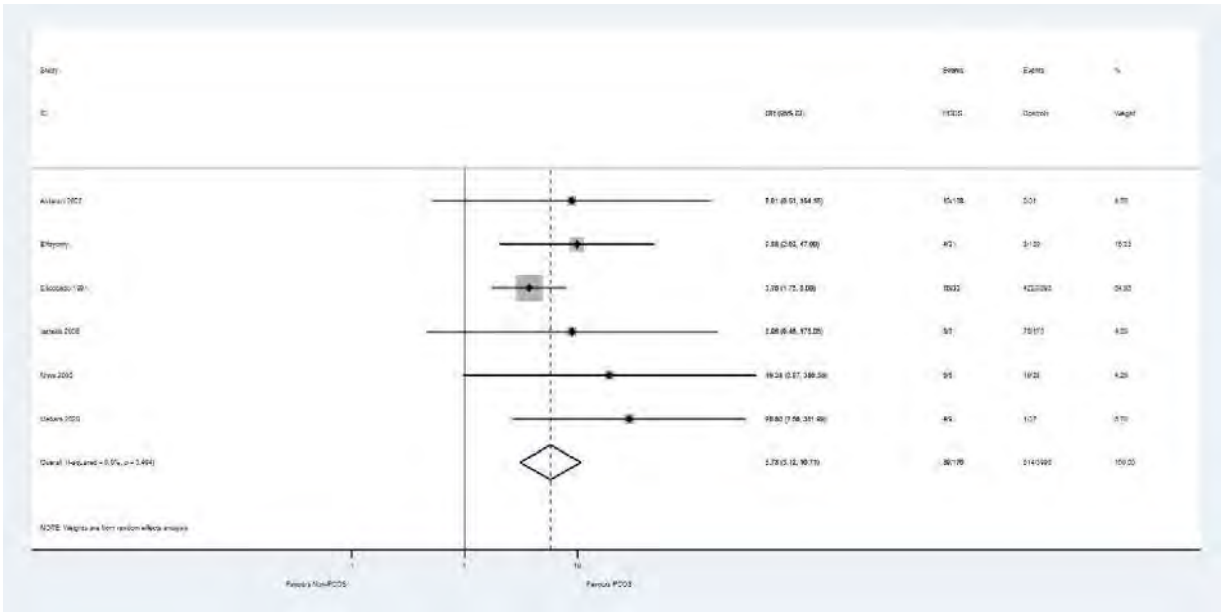
OUTCOME: Composite endometrial cancer and/or hyperplasia						OUTCOME TYPE: Dichotomous		
COMPARISON (if applicable): PCOS and control								
Author, year	Study design	PCOS criteria	Age group	N events in PCOS	N total in PCOS	N events in control	N total in control	Crude OR (95% CI)
Aldarazi 2022	Cross-sectional	Rotterdam	<50	13	108	0	31	.
Ding 2018	Cohort	ICD code	no limit	11	8155	3	32620	.
Elfayomy	Cross-sectional	Self report	premenopausal <52	4	21	3	129	.
Escobedo 1991	Case control	Self report	20-24	10	30	422	3593	.
Fearnley 2010	Case control	Self-report	18-79	18	32	135	517	4 (1.7 – 9.3)
Gottschau 2016	Cohort	ICD code	<50	16	12070	.	.	.
Hachisuga 2001	Cross-sectional	Medical records	<50	20	.	68	.	.
Ho 1997	Cross-sectional	Medical records	no limit	1	4	10	112	.
Iatrakis 2006	Case control	Medical records	<50	3	3	78	178	.
Kilicdag 2011	Cross-sectional	Rotterdam	no limit	5	52	4	365	9.6 (2.5 – 37)
Niwa 2000	Case control	Ultrasound PCO	<40	5	5	10	28	.
Okamura 2017	Cross-sectional	Japanese Society of O&G 2007 criteria	<35	14	14	11	11	.
Pilay 2005	Case control	Histology PCO	No limit <50	11 10	18 16	128 6	211 22	.
Rosen 2019	Cross-sectional	Unclear	no limit	6	21	7	46	.

Shu 1991	Case control	Self report	no limit	.	.	.	.	4.8 (1 – 23.1)
Uehara 2020	Cohort	Medical records	<50	4	9	1	37	.
Wild 2000	Cohort	Medical records	no limit	7	319	4	1060	5.3 (1.5 – 18.6)
Zucchetto 2009	Case control	Self report	no limit	25	68	43	1287	.

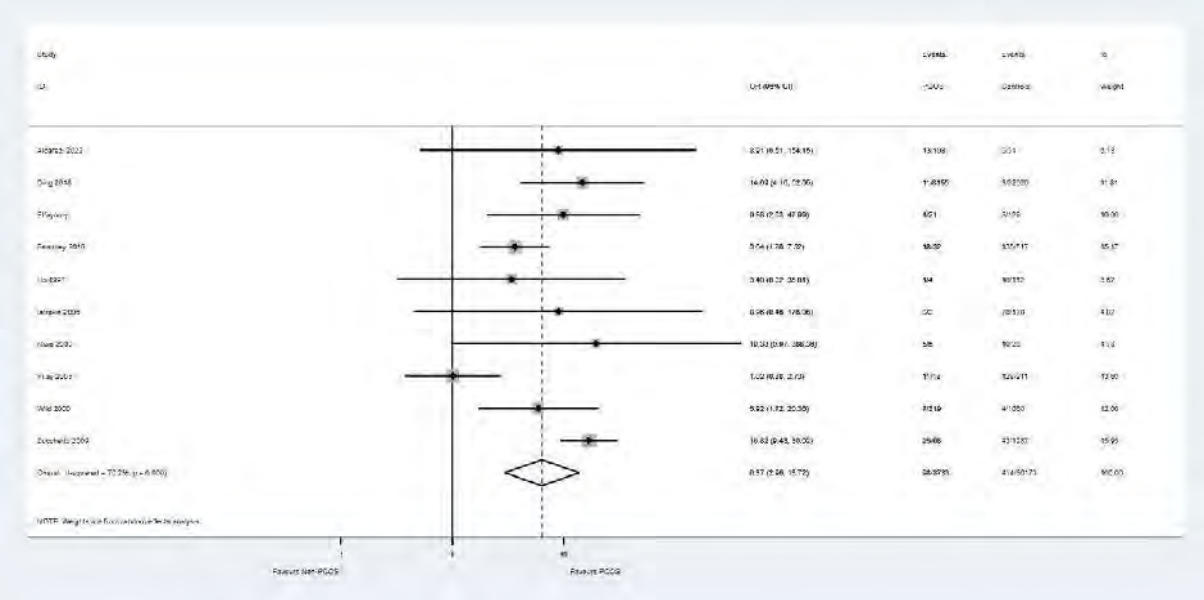
1.1.2 Forest plots for composite endometrial cancer and/or hyperplasia – Overall



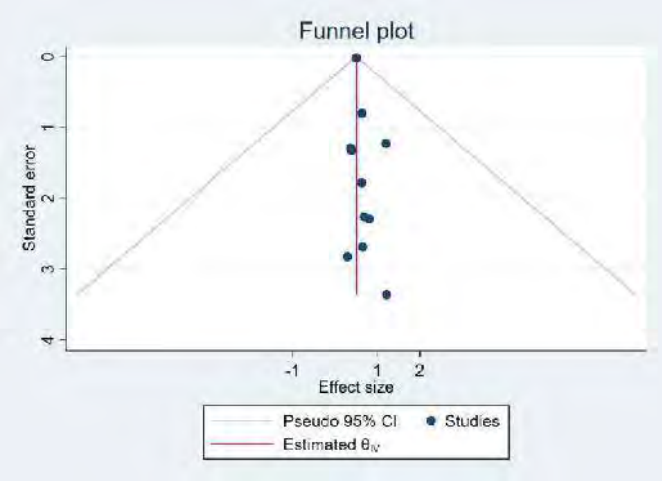
1.1.3 Forest plots for composite endometrial cancer and/or hyperplasia – <50 age



1.1.4 Forest plots for composite endometrial cancer and/or hyperplasia – unbiased population



1.1.5 Funnel plots for composite endometrial cancer and/or hyperplasia



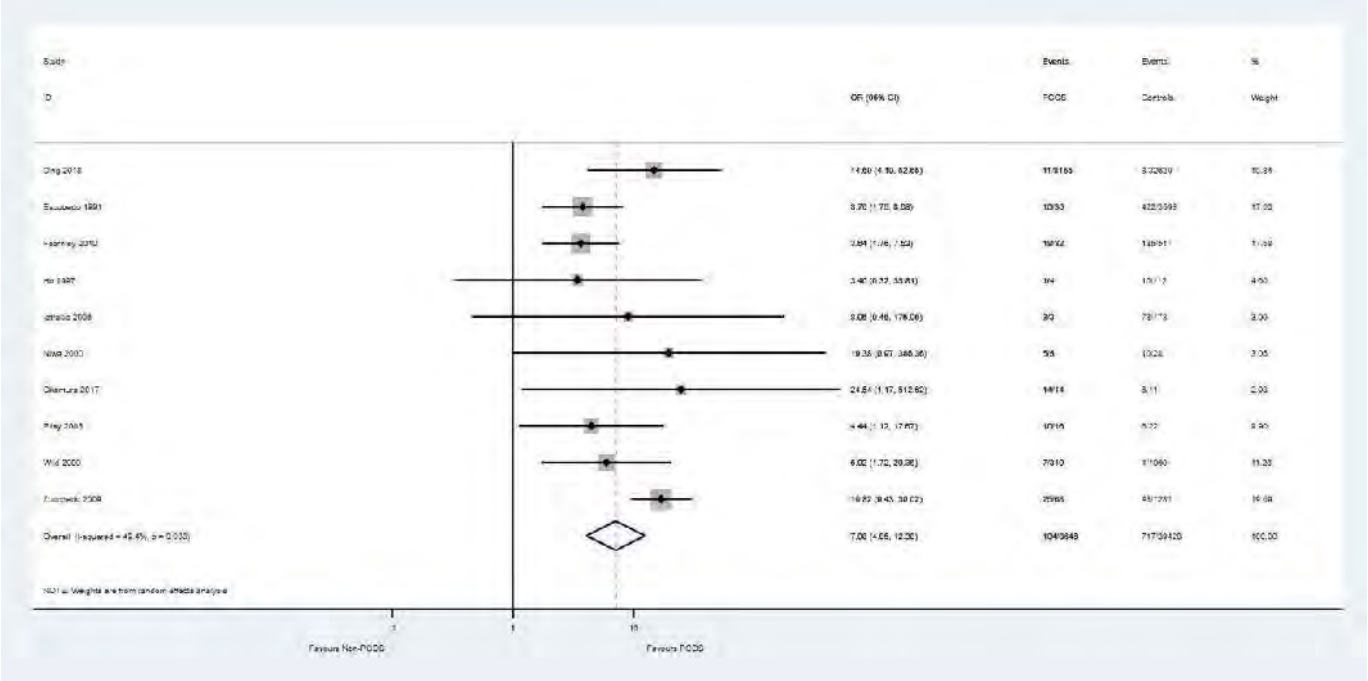
OUTCOME 2. Endometrial cancer

1.2.1 Individual Study Data Table

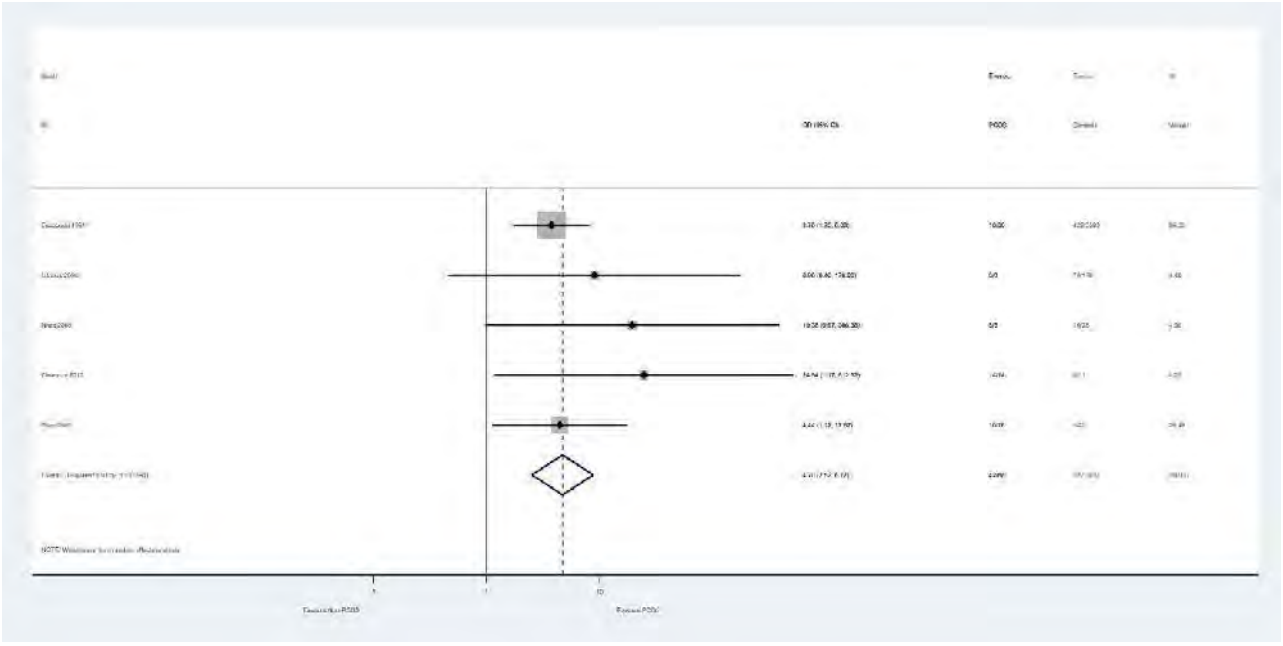
OUTCOME: Endometrial cancer				OUTCOME TYPE: Dichotomous				
COMPARISON (if applicable): PCOS and control								
Author, year	Study design	PCOS criteria	Age group	N events in PCOS	N total in PCOS	N events in control	N total in control	Crude OR (95% CI)
Ding 2018	Cohort	ICD code	no limit	11	8155	3	32620	.
Escobedo 1991	Case control	Self report	20-24	10	30	422	3593	.
Fearnley 2010	Case control	Self-report	18-79	18	32	135	517	4 (1.7 – 9.3)
Gottschau 2016	Cohort	ICD code	<50	16	12070	.	.	.

Hachisuga 2001	Cross-sectional	Medical records	<50	20	.	68	.	.
Ho 1997	Cross-sectional	Medical records	no limit	1	4	10	112	.
Iatrakis 2006	Case control	Medical records	<50	3	3	78	178	.
Niwa 2000	Case control	Ultrasound PCO	<40	5	5	10	28	.
Shu 1991	Case control	Self report	no limit	.	.	.	.	4.6 (1 – 23.1)
Wild 2000	Cohort	Medical records	no limit	7	319	4	1060	5.2 (1.5 – 18.6)
Zucchetto 2009	Case control	Interviews and questionnaires	no limit	25	68	43	1287	.
Okamura 2017	Cross-sectional	Japanese Society of O&G 2007 criteria	<35	14	14	6	11	.
Pilay 2005	Case control	Histology PCO	no limit <50	11 10	18 16	128 6	211 22	.

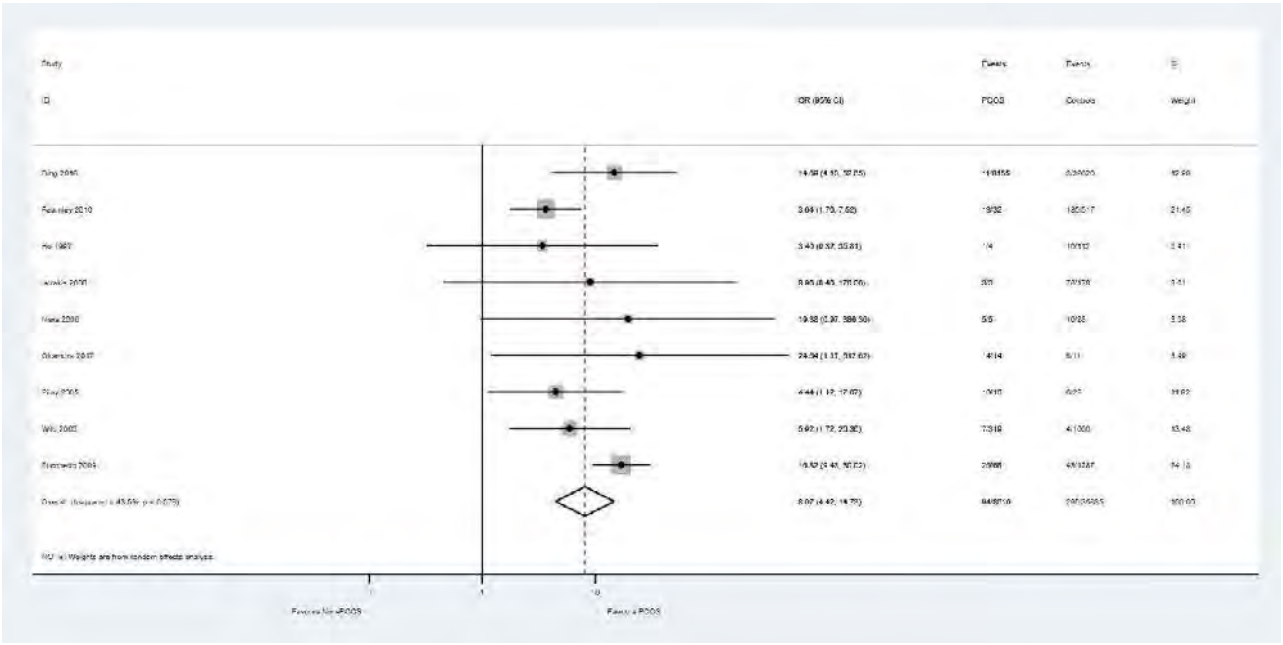
1.2.2 Forest plots for endometrial cancer – Overall



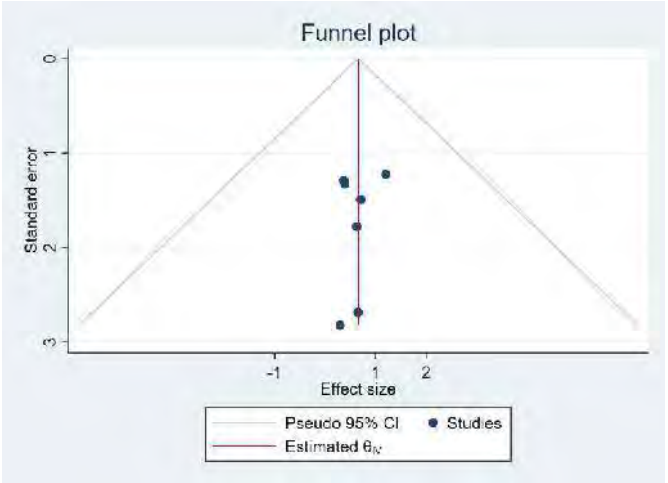
1.2.3 Forest plots for endometrial cancer – <50 age



1.2.4 Forest plots for endometrial cancer – unbiased population



1.2.5 Funnel plots for composite endometrial cancer



OUTCOME 3. Endometrial hyperplasia or atypia

1.3.1 Individual Study Data Table

OUTCOME: Endometrial hyperplasia or atypia				OUTCOME TYPE: Dichotomous				
COMPARISON (if applicable): PCOS and control								
Author, year	Study design	PCOS criteria	Age group	N events in PCOS	N total in PCOS	N events in control	N total in control	Crude OR (95% CI)
Aldarazi 2022	Cross-sectional	Rotterdam	<50	13	108	0	31	.
Okamura 2017	Cross-sectional	Japanese Society of O&G 2007 criteria	<35	0	14	5	11	.

Not suitable for meta-analysis

7. GRADE ASSESSMENTS AND EVIDENCE PROFILE

COMPARISON 1: PCOS vs control													
	Quality assessment						No. participants						
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Subgroup**	**PCOS**	**Controls**	**Effect estimate OR (95% CI)**	**Favours**	**Certainty**	**Importance**
Outcome: Composite endometrial cancer and/or hyperplasia													
15	Observational	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	Overall	8859	40225	6.01 (3.38 – 10.70)	Higher in PCOS	⨁◯◯◯ VERY LOW	CRITICAL
6	Observational	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	<50yo	176	3996	5.78 (3.12 – 10.71)	Higher in PCOS	⨁⨁◯◯ LOW	CRITICAL
10	Observational	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	none	unbiased	8733	36173	6.37 (2.96 – 13.72)	Higher in PCOS	⨁⨁◯◯ LOW	CRITICAL
Outcome: Endometrial cancer													
10	Observational	serious[1]	serious[3]	no serious indirectness	no serious imprecision	none	Overall	8646	39428	7.08 (4.05 – 12.38)	Higher in PCOS	⨁⨁◯◯ LOW	CRITICAL
5	Observational	no serious risk of bias	serious[3]	no serious indirectness	no serious imprecision	none	<50yo	68	3832	4.70 (2.52 – 8.77)	Higher in PCOS	⨁⨁⨁◯ MODERATE	CRITICAL
9	Observational	no serious risk of bias	serious[3]	no serious indirectness	no serious imprecision	none	unbiased	8616	35835	8.07 (4.42 – 14.73)	Higher in PCOS	⨁⨁⨁◯ MODERATE	CRITICAL
Outcome: Endometrial hyperplasia/atypia													
2	Observational	serious[4]	very serious[5]	very serious[6]	very serious[6]	none	Overall	122	42	MA not performed	No difference	⨁◯◯◯ VERY LOW	CRITICAL

[1] Downgraded once as some study populations are from biased populations (i.e. women with endometrial polyps or cancer)
[2] Downgraded once due to heterogeneity
[3] Upgraded once for very large effect and inconsistent result
[4] Downgraded once as outcome of interest was present at the start of the study
[5] Downgraded twice as findings were in different directions
[6] Downgraded twice as study populations are very biased and/or wide confidence intervals

APPENDIX. QUALITY APPRAISAL OF INCLUDED STUDIES

Study ID	*Aldarazi 2022*	
Study Citation	Aldarazi K, Omran H, Jassim NM. Endometrial hyperplasia in asymptomatic subfertile population. J Gynecol Obstet Hum Reprod. 2022 Apr;51(4):102337. doi: 10.1016/j.jogoh.2022.102337. Epub 2022 Feb 10. PMID: 35151930.	
Study Country	*Kingdom of Bahrain*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Subfertile women between ages of 18 and 43 with or without the diagnosis of PCOS were recruited after an informed consent. Subfer- tility was defined as one year of unwanted non-conception with unprotected intercourse in the fertile phase of the menstrual cycles.*	
Control population	*As above.*	
PCOS diagnostic criteria	*Rotterdam 2003*	
N per group	*PCOS 108* *Non-PCOS 31*	
Setting	*outpatient clinic of a tertiary hospital*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary:* *Endometrial thickness measurement using transvaginal ultrasound.* *Secondary:* *LH, FSH, TSH, estradiol, testosterone, SHBG, free androgen index, DHEA, androsten- dione, 17-OH progesterone and homocysteine. Prolactin and proges- terone was evaluated on day 21 of the same cycle. Lipid profile, GTT.* *Endometrial biopsy.*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* *This study aimed to establish the prevalence of endometrial hyperplasia in asymptomatic subfertile women, identify the group at risk, predict the clinical factors associated with EH and determine the predictive cut-off value of endometrial thickness.*
Inclusion criteria	Yes Partial No Not reported	*Yes.*
Exclusion criteria	Yes Partial No Not reported	*Yes.* *Patients who received hormonal treatment 3 months prior to the study, needed to undergo endometrial biopsy for abnormal uterine bleeding were excluded. Moreover, to properly diagnose PCOS; thy- roid malfunction, hyperprolactinaemia, premature ovarian failure and ovarian cyst were eliminated.*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*

Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	*Yes, cross-sectional*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Not applicable*
Was matching performed?		Yes Partial No Not reported	*No*
Summary Result/s		*In asymptomatic subfertile population, PCOS women at risk to develop endometrial hyperpla- sia & atypical hyperplasia. Selective endometrial biopsy recommended with BMI ≥ 30, in presence of insulin resistance and with endometrial thickness ≥7.5 mm*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Yes.* *All participants were recruited from the same outpatient clinic.*
SELECTION BIAS	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
SELECTION BIAS	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
PERFORM ANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
DEDETECTION BIAS	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	Were outcomes assessed objectively and independently?	Yes Partial No	*Yes*

		Not reported	
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant to cross-sectional study*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*All participants were included*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*No*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Yes* *Baseline characteristics were similar between groups.*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS		*Unknown where they recruited healthy volunteer in control group*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*Low*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Beavis 2020*
Study Citation	Beavis AL, Najjar O, Cheskin LJ, Mangal R, Rositch AF, Langham G, Fader AN. Prevalence of endometrial cancer symptoms among overweight and obese women presenting to a multidisciplinary weight management center. Gynecol Oncol Rep. 2020 Sep 11;34:100643. doi: 10.1016/j.gore.2020.100643. PMID: 32995455; PMCID: PMC7502818.
Study Country	*USA*
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	

Patient/population/ participants	Overweight or obese (BMI > 25 kg/ m2) women presenting to the	
Control population	*As above.*	
PCOS diagnostic criteria	*Self-reported*	
N per group	*103*	
Setting	Johns Hopkins Weight Management Center (JHWMC) in Baltimore, MD from May 2018-October 2019	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary:* any EH/EC bleeding symptom, assessed in women who had not undergone hysterectomy who were both pre- and post-menopausal. In premenopausal women, the following were considered potential EH/EC symptoms: irregular periods, abnormal cycle length, passing clots during menses, “heavy” or “very heavy” menses, or bleeding between periods. In postmenopausal women, vaginal bleeding or discharge were considered EH/EC symptoms. *Secondary:* Secondary outcomes addressing work-up for symptoms were examined in women with EH/EC symptoms, including 1) reporting prior discussion of symptoms with a gynecologist, and 2) having undergone an endo- metrial biopsy (EMB) in the past.	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* Study aimed to determine the prevalence of abnormal bleeding symptoms associated with EH/EC in an at-risk population, and deter- mine the proportion who had sought care.
Inclusion criteria	Yes Partial No Not reported	*Partial*
Exclusion criteria	Yes Partial No Not reported	*Not reported*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Partial*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes – retrospective cohort*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Not applicable*
Was matching performed?	Yes Partial No	*No*

		Not reported	
Summary Result/s		*A total of 103 women were included, and 4 (4%) had a history of EH/EC. Of the 84 (n = 82%) of women with no prior hysterectomy, 57% (n = 33/58) of premenopausal women reported any EH/EC symptom compared to 15% (n = 15/26) of postmenopausal women (p <0.001). Two-thirds of symptomatic premenopausal women had two or more symptoms, most commonly heavy menses (49% (n = 25/51)) and irregular periods (39% (n = 17/44)). Sixty percent (n = 20/33) had discussed these with a gynecologist, and one third had undergone an endometrial biopsy. A history of polycystic ovarian syndrome (RR:1.72, 95% CI 1.24–2.38) was associated with EH/EC symptoms, while being postmenopausal was not (RR:0.32, 95%CI: 0.12–0.87).*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Yes.* *All participants were recruited from the same outpatient clinic.*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Partial*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*Not reported*
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Partial (recall bias)*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Partial*
ATTRITION BIAS	What percentage of the individuals recruited into	X% treatment X% control/ comparison Not reported	*Not relevant*

	each arm of the study were lost to follow up?		
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*All participants were included*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Not reported – no comparison group*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS		*No clear comparison group (ie: individuals who are not overweight, assessment of outcomes, and comorbidities / baseline characteristics in population vulnerable to recall bias*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*High*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Ding 2018*
Study Citation	Ding DC, Chen W, Wang JH, Lin SZ. Association between polycystic ovarian syndrome and endometrial, ovarian, and breast cancer: A population-based cohort study in Taiwan. Medicine (Baltimore). 2018 Sep;97(39):e12608. doi: 10.1097/MD.0000000000012608. PMID: 30278576; PMCID: PMC6181615.
Study Country	*Taiwan*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*National Health Insurance (NHI) program in 1995, and it covers >99% of Taiwan's population*
PCOS diagnostic criteria	*ICD-9 PCOS*

N per group	○ *PCOS = 8155* ○ *Controls = 32620*	
Setting	*USA not otherwise specified*	
Intervention/ indicator	Not applicable	
Comparison/ Control	*Women without PCOS from the NHI program.* *The comparison group of this study was randomly selected from women without PCOS and was 4-fold size matched with the PCOS group by sex, age, and index year*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Breast, endometrial and ovarian cancer	
Inclusion criteria reported?	*Yes*	*PCOS based on having both oligomenorrhea and hyperandrogenism. "Oligomenorrhea was defined as irregular menstrual cycles at age 20-30, as reported by women at the year 16 exam. Hyperandrogenism was defined as either hirsutism or increased levels of serum testosterone. Hirsutism was considered present if a woman reported having excess unwanted hair at age 20-30*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes* *We excluded patients who had received diagnoses of breast cancer (ICD-9-CM code 174 and 175), endometrial cancer (ICD-9-CM code 182), or ovarian cancer (ICD-9-CM code 183) and those who had withdrawn from the insurance program before the index date. We also excluded patients who had received a diagnosis of cancer either before the diagnosis of PCOS or within one year after receiving the diagnosis of PCOS and also in the comparison group before the index date.*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*

Was matching performed?		Yes Partial No Not reported	*Yes* *The comparison group of this study was randomly selected from women without PCOS and was 4-fold size matched with the PCOS group by sex, age, and index year*
Summary of Result/s		*The incidence of endometrial cancer was 226 and 15 per 100,000 person-years in the PCOS and comparison groups, respectively. A statistically significant higher risk of endometrial cancer was found in the PCOS cohort (adjusted HR [aHR] = 17.7, 95% CI = 4.9–64.2) than in the comparison cohort. However, no association was observed between PCOS and ovarian (aHR = 1.64, 95% CI: 0.63–4.27) or breast cancer (aHR=0.98, 95% CI: 0.58–1.65).*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Other than the exposure under investigation, were the groups selected from similar populations?	Yes Partial No Not reported	*Yes*
	Was the exposed cohort truly representative?	Yes Partial No Not reported	*Yes*
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	*Yes*
PERFORMANCE BIAS	Aside from the exposure, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	Was exposure measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes* *In addition to ICD-9 code for PCOS, Valid diagnoses were based on blood tests for luteinizing hormone, follicle-stimulating hormone, and testosterone (NHI codes: 09078B2, 09126B, 09126C, 09078B1, 09125B, 09125C, 09064B2, 09121B, and 09121C) or ultrasonography (NHI code: 19003C) or both.*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	What percentage of the individuals recruited into each		*All participants selected had outcomes reported*

	arm of the study were lost to follow up?		
	What percentage of the individuals were not included in the analysis?	*X% treatment X% control/ comparison Not reported*	*As above*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Yes*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS			
What is the overall risk of bias?		*Low*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Elfayomy 2014*
Study Citation	Elfayomy AK, Soliman BS. Risk Factors Associated with the Malignant Changes of Symptomatic and Asymptomatic Endometrial Polyps in Premenopausal Women. J Obstet Gynaecol India. 2015 May;65(3):186-92. doi: 10.1007/s13224-014-0576-6. Epub 2014 Jun 1. PMID: 26085741; PMCID: PMC4464569.
Study Country	*India*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	A series of premenopausal women with or without AUB admitted to the department of obstetrics and gynecology over 31 months, from May 2011 to August 2013, with endometrial polyp
PCOS diagnostic criteria	*Rotterdam*
N per group	○ *150 women with endometrial polyps* ○ *57 with AUB (Abnormal Uterine Bleeding), 93 with no AUB*

Setting	Ouhd Hospital (a Taibah University Teaching Hospital)	
Intervention/ indicator	Not applicable	
Comparison/ Control	*Not reported*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Main / Primary outcome: Pathologic report of endometrial polyp	
Inclusion criteria reported?	*Yes*	*Partial :* premenopausal women with or without AUB, with endometrial polyp
Exclusion criteria reported?	Yes Partial No Not reported	*Yes* Patients were excluded if they were older than 52 years, had reached menopause, had submucosal uterine leiomyomas, or had adenomyosis.
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	*Partial – states is a prospective cohort study, but seems to be more of a cross-sectional study*
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Follow-up not reported*
Was matching performed?	Yes Partial No Not reported	*No*
Summary of Result/s	Among women with endometrial polyps, 62 % had asymptomatic polyps. The prevalence of premalignant and malignant polyps comprised 4.6 % of cases (3.3 % hyperplasia with atypia and 1.3 % carcinomatous polyps). The presence of abnormal uterine bleeding was not a predictor of premalignant and malignant changes in the polyp. On logistic regression analysis, the premalignant and	

		malignant lesions were influenced by polycystic ovary syndrome (p \ 0.001; OR 4.61; CI 1.9–27), polyp volume [10 ml (p \ 0.001; OR 5.83; CI 4.31–9.17), and multiple polyps (p = 0. 01; OR 2.05; CI 1.09–3.76). Notably, the odds ratio of polyp volume [10 ml was 5.83. This additional risk confirms the importance of polyp volume in the detection of malignant transformation rather than associating bleeding in premenopausal women.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Other than the exposure under investigation, were the groups selected from similar populations?	Yes Partial No Not reported	*Yes*
	Was the exposed cohort truly representative?	Yes Partial No Not reported	*Yes*
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	*No*
PERFORMANCE BIAS	Aside from the exposure, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	Was exposure measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?		*All participants selected had outcomes reported*

	What percentage of the individuals were not included in the analysis?	*X% treatment X% control/ comparison Not reported*	*As above*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Yes*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS		Medium risk of bias as unclear whether outcome (malignant / benign polyp) had arisen before or after exposures (AUB / PCOS / Obesity etc.) – states it is a prospective cohort study but seems to be closer to a cross-sectional study.	
What is the overall risk of bias?		*Low* *Medium* *High* *Not enough information*	*Medium*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Escobedo 1991*
Study Citation	Escobedo LG, Lee NC, Peterson HB, Wingo PA. Infertility-associated endometrial cancer risk may be limited to specific subgroups of infertile women. Obstet Gynecol. 1991 Jan;77(1):124-8. PMID: 1984211.
Study Country	*USA*
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Cancer and Steroid Hormone Study: case and control women were enrolled from six areas participating in the Surveillance, Epidemiology, and End Results program of the National Cancer Institute: Atlanta, Detroit, San Francisco, Seattle, Connecticut, and Iowa.*

	826 women 20-54 years of age who resided in areas covered by one of the six SEER centers, and who had primary endometrial cancer newly diagnosed between December 1, 1980 and December 31, 1982. Of these 826 women, 606 were interviewed, histology slides were retrieved for 575. 437 women were classified as having epithelial endometrial cancer.	
Control population	*20-54 years of age, chosen randomly by a method of telephoning selected households in the same six geographic areas. Control women in each 5-year age group were selected to match the age distribution of the women with breast cancer who were enrolled in the study. Of the 5209 women selected as controls, 4352 were interviewed.*	
PCOS diagnostic criteria	*Self-reported*	
N per group	*Cases = 399 (endometrial cancer)* *Controls = 3040*	
Setting	*Population based*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcomes:* *Relationship between infertility and endometrial cancer*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes*
Exclusion criteria	Yes Partial No Not reported	*Yes,* *Among the 437 women with epithelial endometrial cancer interviewed, we excluded 38 who had never married and had never been pregnant. We also excluded 157 control women who had never married and had never been pregnant, as well as three women who reported their fertility status as unknown. We also excluded 1152 control women who had had a D&C of unknown outcome or a hysterectomy.*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes, case control*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Not relevant to this study*
Was matching performed?	Yes Partial No Not reported	*Yes*

Summary Result/s		*Factors such as anovulation may explain much of the increased risk of endometrial cancer found among subgroups of infertile women.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Yes*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes.* *Histological slides of the cases were retrieved and reviewed.*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*No. PCOS was established through self reporting.*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant to this study*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*Not reported*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Not reported*

CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Partial.* *Cases were older, had higher adiposity index, more often had hypertension.*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS		*Unknown where they recruited healthy volunteer in control group*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Fearnley 2010*
Study Citation	Fearnley EJ, Marquart L, Spurdle AB, Weinstein P, Webb PM; Australian Ovarian Cancer Study Group and Australian National Endometrial Cancer Study Group. Polycystic ovary syndrome increases the risk of endometrial cancer in women aged less than 50 years: an Australian case-control study. Cancer Causes Control. 2010 Dec;21(12):2303-8. doi: 10.1007/s10552-010-9658-7. Epub 2010 Oct 17. PMID: 20953904.
Study Country	*Australia*
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Cases were women aged 18-79 years living in Australia with histologically confirmed epithelial endometrial cancer newly diagnosed between July 2005 and December 2007….2231 women were invited to participate and of there 1497 agreed to take part. 39 women were excluded because they did not have primary endometrial cancer or were diagnosed outside the study period. Leaving 1458 cases f whom 1399 completed an interview. The present analysis were restricted to the 156 women <50 years of age at diagnosis.*
Control population	*Control women without endometrial cancer were sampled in 2 waves from the national electoral roll to match the state and age distribution (in 5 year bands) of the cases.*
PCOS diagnostic criteria	*Self-reported doctor diagnosed PCOS or PCOS symptoms*
N per group	*Cases = 156 (endometrial cancer)* *Controls = 398*

Setting		*Population based*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)		*Primary outcomes:* *Relationship between PCOS and endometrial cancer*	
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	*Yes*
Inclusion criteria		Yes Partial No Not reported	*Yes*
Exclusion criteria		Yes Partial No Not reported	*Yes,* *Cases 0 physicians redused permission to contact, too sick to give informed consent, language difficulties, mental incapacity.* *Control - Excluded women who reported a prior hysterectomy or endometrial cancer in the control.*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	*Yes, case control*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Not relevant to this study*
Was matching performed?		Yes Partial No Not reported	*Yes*
Summary Result/s		*Women with PCOS had a 4-fold increased risk of endometrial cancer compared to women without PCOS. This association was attenuated when additionally adjusted for BMI.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Yes*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes.* *Histological slides of the cases were retrieved and reviewed.*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No	*Yes*

		Not reported	
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Partial. PCOS was established through self reporting of doctor diagnosis and PCOS symptoms.*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant to this study*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*All included*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Partial.* *Cases were more likely to be nulliparous, not using OCP.*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No	*Yes*

		Not reported	
COMMENTS		*Unknown where they recruited healthy volunteer in control group*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Gottschau 2014*	
Study Citation	Gottschau M, Kjaer SK, Jensen A, Munk C, Mellemkjaer L. Risk of cancer among women with polycystic ovary syndrome: a Danish cohort study. Gynecol Oncol. 2015 Jan;136(1):99-103. doi: 10.1016/j.ygyno.2014.11.012. Epub 2014 Nov 20. PMID: 25451694.	
Study Country	*Denmark*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	women who had received a main or a secondary diagnosis of PCOS (Danish version of the International Classification of Diseases (ICD) ICD-8 = 256.90 during 1977–1993, and ICD-10 = E28.2 during 1994–2012) and were registered in the Danish National Patient Register [12] during 1977–2012.	
PCOS diagnostic criteria	(Danish version of the International Classification of Diseases (ICD) ICD-8 = 256.90 during 1977–1993, and ICD-10 = E28.2 during 1994–2012)	
N per group	*PCOS = 12070*	
Setting	*Danish National Patient Register (Outpatient visits and hospitalisations)*	
Intervention/ indicator	Not applicable	
Comparison/ Control	*National cancer incidence rates* *(Expected number of cancer cases was calculated by multiplying national cancer incidence rates for fe- males in 5-year age groups and calendar periods by the number of person-years at risk for the study cohort in corresponding strata and summing up these strata. The SIRs were based on the assumption that the observed number of cancer cases in a specific category followed a Poisson distribution [15], and the confidence limits were calculated by Byar's approximation [16]. The analyses were stratified on age at first contact for PCOS (9–29, 30–39 and 40–49 years), age at cancer (b 50 and ≥50 years), time since PCOS (b 1, 1–4, 5–9 and ≥10 years), patient type (in- or outpatients) and calendar year at first PCOS (b1995, 1995–2003 and 2004–2012) for selected cancer types. The excess absolute risk was calculated as the observed minus the expected rate per 100,000 person-years.*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Cancer risk*	
Inclusion criteria reported?	*Yes*	*Yes*

Exclusion criteria reported?		Yes Partial No Not reported	*Yes* .
Does the study have a clearly focused question?		Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?		Yes Partial No Not reported	*Yes*
Does the study have specified inclusion/ exclusion criteria?		Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?		Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Yes* - The cohort was followed for a total of 91,036 person-years, with a median follow-up time of 5.7 years (10th percentile, 1.0 years; 90th percentile, 16.1 years).
Was matching performed?		Yes Partial No Not reported	*No*
Summary of Result/s		Cancer was diagnosed in 279 women with PCOS (SIR = 1.19; 95% CI = 1.06–1.34). We found an almost fourfold increased risk for endometrial cancer (numbers observed (N) = 16, SIR = 3.9; 95% CI = 2.2–6.3), the large majority of cases being type 1 (N = 14, SIR = 4.7; 95% CI = 2.6–7.9). We found no association between PCOS and breast (N = 59, SIR = 1.1; 95% CI = 0.8–1.4) or ovarian cancer (N = 10, SIR = 1.8; 95% CI = 0.8–3.2); however, significantly increased risks were found for kidney, colon and brain cancers.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Other than the exposure under investigation, were the groups selected from similar populations?	Yes Partial No Not reported	*Yes*
	Was the exposed cohort truly representative?	Yes Partial No Not reported	*Yes*

	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	*Yes*
PERFORMANCE BIAS	Aside from the exposure, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	Was exposure measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes – assuming classification system is reliable*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?		*All participants selected had outcomes reported*
	What percentage of the individuals were not included in the analysis?	*X% treatment X% control/ comparison Not reported*	*As above*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Yes*
	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*

OTHER BIAS	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS			
What is the overall risk of bias?		*Low* *Medium* *High* *Not enough information*	*Low*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Hachisuga 2001*	
Study Citation	Hachisuga T, Fukuda K, Iwasaka T, Hirakawa T, Kawarabayashi T, Tsuneyoshi M. Endometrioid adenocarcinomas of the uterine corpus in women younger than 50 years of age can be divided into two distinct clinical and pathologic entities based on anatomic location. Cancer. 2001 Nov 15;92(10):2578-84. doi: 10.1002/1097-0142(20011115)92:10<2578::aid-cncr1610>3.0.co;2-v. PMID: 11745192.	
Study Country	*Japan*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	The study examined the clinical profiles of 88 Japanese women younger than 50 years of age with endometrial carcinoma who had undergone surgery at Fukuoka University Hospital, Kyushu University Hospital, Saga Medical School Hospital, and related hospitals in the Northern Kyushu district between 1974 and 1996	
Control population	*As above*	
PCOS diagnostic criteria	Medical records and reports from patients' gynecologists	
N per group	*Patients with endometrial carcinoma: 88*	
Setting	Fukuoka University Hospital, Kyushu University Hospital, Saga Medical School Hospital, and related hospitals in the Northern Kyushu district between 1974 and 1996.	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Clinicopathologic profile of the corpus mucosa proper (CMS) and Lower uterine segment (LUS), including surgical stage of tumor*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*

Inclusion criteria		Yes Partial No Not reported	*Yes*
Exclusion criteria		Yes Partial No Not reported	*No*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Partial*
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Not relevant to this study*
Was matching performed?		Yes Partial No Not reported	*No*
Summary Result/s		*The mean ages of women with carcinomas of the CMP and LUS were 41.2 and 39.0 years, respectively. In comparison to carcinomas of the LUS, carcinomas of the CMP were more strongly associated with reproductive risk factors including parity (P = 0.01) and polycystic ovary syndrome (P = 0.02). There was no significant difference in body mass index or the incidence of diabetes mellitus and hypertension between women presenting with carcinomas of the CMP and LUS. Histologically, carcinomas of the LUS more frequently showed a high-grade endometrioid tumor (P = 0.02) with deep myometrial invasion (P<, 0.01) and were less associated with endometrial hyperplasia (P < 0.01) than those of the CMP*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Yes*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*Not reported*
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*

DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant to cross-sectional study*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*All included*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
CONFOUN DING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Not reported*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS			
What is the overall risk of bias?		Low Moderate	*Low*

	High Insufficient information	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*No*	

Study ID	*Ho 1997*	
Study Citation	*Ho SP, Tan KT, Pang MW, Ho TH. Endometrial hyperplasia and the risk of endometrial carcinoma. Singapore Med J. 1997 Jan;38(1):11-5. PMID: 9269346.*	
Study Country	*Singapore*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	Patients were selected by screening the database of the histopathological laboratory at Kandang Kerbao Hospital for all cases of endometrial hyperplasia with or without cytological atypia on either endometrial biopsy or curettage.	
Control population	*None*	
PCOS diagnostic criteria	Not described	
N per group	*Total N = 185*	
Setting	Kandang Kerbau Hospital	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Endometrial carcinoma (type of endometrial carcinoma, stage and grade of endometrial carcinoma, presence or absence of myometrial invasion and percentage of invasion).*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* *Complex and mixed hyperplasia with or without cytological atypia*
Exclusion criteria	Yes Partial No Not reported	*Yes.* *Patients with coexisting adenocarcinoma at the time of uterine sampling were excluded.* *Cases of simple hyperplasia were not reviewed as there were no cases of cytological atypia among these cases and the risk of carcinoma from simple hyperplasia is very low.*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No	*Partial. The aim of the study was to determine the incidence of endometrial carcinoma, but only prevalence was reported.*

		Not reported	
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Not relevant to this study*
Was matching performed?		Yes Partial No Not reported	*No*
Summary Result/s		*Incidence of endometrial carcinoma was 27.6% in those with atypia and 3.4% in those without atypia. All were stage 1 adenocarcinomas. PCOS and subfertility were found significantly in the cases with cytological atypia, however they were not significant in the cases with carcinoma.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Yes*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Not reported*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*

ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant to cross-sectional study*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*All included*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Not reported*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*Not reported*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS		*Highly selected population where all participants had endometrial hyperplasia and the definition of PCOS (the exposure) was unclear.*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*High.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Iatrakis 2006*
Study Citation	*Iatrakis G, Zervoudis S, Saviolakis A, et al. Women younger than 50 years with endometrial cancer. Eur J Gynaecol Oncol 2006; 27: 399–400.*
Study Country	*Greece*
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	

Patient/population/ participants	*81 patients with histologically confirmed endometrial cancer were included. 100 patients randomly selected from the gynaecological clinic (inclusion criteria 43-48yo) without any endometrial cancer diagnosis were evaluated for the same factors.*	
Control population	*As above*	
PCOS diagnostic criteria	*Not reported*	
N per group	*PCOS = 81* *Controls = 100*	
Setting	*Hospital*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcomes:* *Factors related to endometrial cancer:* *BMI, parity, hypertension, diabetes, oral contraception, PCOS, irregular menstrual cycles (intervals more than 40 days or less than 20 days on at least 5 occasions) and personal or family history of cancer.*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* *To evaluate if known risk factors for endometrial cancer in menopausal women are also related to endometrial cancer in younger ages.*
Inclusion criteria	Yes Partial No Not reported	*Partial.* *Inclusion criteria or exclusion criteria of controls unclear.*
Exclusion criteria	Yes Partial No Not reported	*Partial.* *Exclusion criteria of controls unclear.*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Partisl*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Not relevant to this study*
Was matching performed?	Yes Partial No Not reported	*No*
Summary Result/s	*BMI, parity, type of menstrual cycles, history of PCOS and diabetes are possibly related to endometrial cancer in women yonger than 50 years of age, and the strongest relation was found with increased BMI.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Partial*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*Partial.* *Just reported patients randomly selected from gynaecological clinic.*
PERFORM ANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Not reported*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Not reported.* *Unclear if potential risk factors were identified from ICD codes or medical records.*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant to cross-sectional study*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*All included*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
CONFOUN DING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Not reported*

OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*Not reported*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Partial* *Only Chi2 test was undertaken to test for subgroup differences.*
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*High*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Kilicdag 2011*	
Study Citation	Kilicdag EB, Haydardedeoglu B, Cok T, Parlakgumus AH, Simsek E, Bolat FA. Polycystic ovary syndrome and increased polyp numbers as risk factors for malignant transformation of endometrial polyps in premenopausal women. Int J Gynaecol Obstet. 2011 Mar;112(3):200-3. doi: 10.1016/j.ijgo.2010.10.014. Epub 2011 Jan 17. PMID: 21247566.	
Study Country	*Turkey*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Clinical records of operative office hysteroscopic and resectoscopic procedures for endometrial polyps in 417 women from Baskent University were examined over a retrospective period of 30 months. Only premenopausal women were included in the study, and patients who had been on tamoxifen were excluded*	
Control population	*As above*	
PCOS diagnostic criteria	*Rotterdam 2003*	
N per group	*PCOS = 52* *Controls = 365*	
Setting	*Hospital*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcomes:* *Prevalence of premalignant and malignant lesions in endometrial polyps resected by surgical hysteroscopy in premenopausal women.*	
Does the study have a clearly focused question and/or PICO?	Yes Partial	*Yes*

		No Not reported	*The aim of the present study was to determine the prevalence of pre-malignant and malignant lesions in endometrial polyps resected by surgical hysteroscopy in premenopausal women, and to evaluate the association of pre-malignancy and malignancy with abnormal bleeding, infertility, polycystic ovary syndrome (PCOS), and some clinical characteristics, with a view to identifying factors related to the malignancy of polyps.*
Inclusion criteria		Yes Partial No Not reported	*Yes* *clinical records of operative office hysteroscopic and resectoscopic procedures for endometrial polyps in 417 women from Baskent University were examined over a retrospective period of 30 months.*
Exclusion criteria		Yes Partial No Not reported	*Yes* *Only premenopausal women were included in the study, and patients who had been on tamoxifen were excluded.*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	*Partial,* *This is a cross-sectional study. Case-control might be better for a less selected population.*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Not relevant to this study*
Was matching performed?		Yes Partial No Not reported	*No*
Summary Result/s		*In 97.8% of women, histology showed benign endometrial pathology. In 2.2% of women, pre-malignant or malignant conditions were found in the polyp. Polycystic ovary syndrome (PCOS) and the presence of 2 or more polyps were associated with significant pre-malignant or malignant changes*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Yes*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*

PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant to cross-sectional study*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*All included*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Not reported*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Partial* *Simple logistic regression undertaken without any adjustments for potential confounders*

COMMENTS	*This is a biased group where all participants had endometrial polyps. Effects of exposure may be exaggerated.*	
What is the overall risk of bias?	Low Moderate High Insufficient information	*High*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*No*	

Study ID	*Niwa 2000*	
Study Citation	*Niwa K, Imai A, Hashimoto M, Yokoyama Y, Mori H, Matsuda Y, Tamaya T. A case-control study of uterine endometrial cancer of pre- and post-menopausal women. Oncol Rep. 2000 Jan-Feb;7(1):89-93. PMID: 10601598.*	
Study Country	*Japan*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*From Jan 1988 to Dec 1997, 42 premenopausal and 92 post menopausal women with endometrial cancer were referred to the Department of Obstetrics and Gynecology, Gifu University Hospital, Japan.*	
Control population	*The controls were sampled from healthy women visiting Gifu Health Promotion Center for the purpose of health screening, including gynaecologic malignancy. The 376 controls were randomly selected, at the rate of one per five women, from 1880 healthy women visiting the Gifu Health Promotion center.*	
PCOS diagnostic criteria	*Unclear*	
N per group	*Cases = 134 (endometrial cancer)* *Controls = 376*	
Setting	*Population based*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcomes:* *Epidemiological factors and expressions of tumor suppressor gene p53, estrogen receptor and progesterone receptor in endometrial cancers of different ages in Japanese women.*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes*
Exclusion criteria	Yes Partial No Not reported	*Yes,* *No gynecological malignancies.*

If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	*Yes, case control*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Not relevant to this study*
Was matching performed?		Yes Partial No Not reported	*Not reported*
Summary Result/s		*Untreated ovarian dysfunction such as PCOS with unopposed estrogenic action in the endometrium may be associated with development and growth of EC in younger women.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Yes*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes.* *Histological slides of the cases were retrieved and reviewed.*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Not reported. No mention of how PCOS diagnosis was established.*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*

	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant to this study*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*All included*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Not reported*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*No.* *Baseline characteristics including nulliparity, BMI, hypertension and diabetes were different between groups.*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*Not reported*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Partial. Not all exposures had logistic regression person. Also did not explain how the variables in multivariate logistic regression were chosen.*
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Okamura 2016*
Study Citation	Okamura Y, Saito F, Takaishi K, Motohara T, Honda R, Ohba T, Katabuchi H. Polycystic ovary syndrome: early diagnosis and intervention are necessary for fertility preservation in young women with endometrial cancer under 35 years of age. Reprod Med Biol. 2016 Dec 5;16(1):67-71. doi: 10.1002/rmb2.12012. PMID: 29259453; PMCID: PMC5715875.
Study Country	*Japan*

CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Between January 2001 and December 2013, hospital records were used to identify a cohort of patients who were under 35 years of age, who had been diagnosed with EC and/or AEH, and who had been treated at Kumamoto University Hospital, Japan*	
Control population	*As above*	
PCOS diagnostic criteria	*revised criteria that were proposed by the Japanese Society of Obstetrics and Gynecology (JSOG) in 2007*	
N per group	*PCOS = 14* *Controls = 11*	
Setting	*Hospital*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcomes:* *clinical characteristics included the participants' age, parity, height, weight, menstruation regularity, and clinical stage of EC and/or AEH. endocrine profiles included the plasma glucose, insulin, luteinizing hormone (LH), follicle-stimulating hormone, free testosterone, and prolactin (PRL) levels.*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* *the current study aimed to elucidate the risk of developing EC and/or AEH in patients with PCOS who are under 35 years of age and to identify preventive measures for this group.*
Inclusion criteria	Yes Partial No Not reported	*Yes* *under 35 years of age, who had been diagnosed with EC and/or AEH*
Exclusion criteria	Yes Partial No Not reported	*Not reported*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Partial,* *This is a cross-sectional study. Case-control might be better for a less selected population.*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Not relevant to this study*
Was matching performed?	Yes Partial No Not reported	*No*
Summary Result/s	*Although both the patients with and without PCOS had irregular men- struation, the patients with PCOS were less likely to have fertility-sparing surgery than the patients without PCOS because they had more advanced disease or failed to re- spond to medroxyprogesterone acetate therapy.*	

INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Yes*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*No. Treatment will differ depending on clinical stage of endometrial cancer and response to medroxyprogesterone acetate therapy.*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Not reported*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Not reported*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant to cross-sectional study*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*All included*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*

CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Partial.* *BMI was higher in PCOS group*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*No* *Only summary statistics was presented.*
COMMENTS		*This is a biased group where all participants had endometrial cancer. Effects of exposure may be exaggerated.*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*High*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	
Study ID		*Pillay 2005*	
Study Citation		*Pillay OC, Te Fong LF, Crow JC, Benjamin E, Mould T, Atiomo W, Menon PA, Leonard AJ, Hardiman P. The association between polycystic ovaries and endometrial cancer. Hum Reprod. 2006 Apr;21(4):924-9. doi: 10.1093/humrep/dei420. Epub 2005 Dec 16. PMID: 16361289.*	
Study Country		*UK*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/ participants		The experimental group (*n* = 128) comprised all patients who had been diagnosed with EC, for whom archived ovaries and endometrial tissue were available, following total hysterectomy and bilateral salpingo-oophorectomy at the Royal Free Hospital (RFH), London, between July 1987 and July 2003 or University College Hospital (UCH), London, between July 2000 and July 2003.	
Control population		The con- trol subjects (*n* = 83) were age matched (□5 years) to the experimental subjects and were derived from a larger group of patients with benign gynaecological conditions operated on in the hospitals above over the same time periods, for whom archived ovaries and, in most cases, endometrium were available. Controls had also undergone total hyster- ectomy and bilateral salpingo-oophorectomy or bilateral oophorectomy. No other selection criteria were applied, and patients with gynaeco- logical cancers other than EC were excluded.	

PCOS diagnostic criteria	PCO morphology in subjects operated on for EC or for benign gynaecological conditions was assessed by examination of archived haematoxylin–eosin-stained 5 m ovarian sections	
N per group	*Cases = 134 (endometrial cancer)* *Controls = 376*	
Setting	*Hospital*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcomes:* differences in the prevalence of PCO morphology, as a marker of PCOS, were investigated in ovarian sections from women who underwent hysterectomy for EC or for benign conditions. To investigate prognosis, p53, Ki67, Bcl2 and cyclin D1 protein expression was investigated by immunohistochemistry in endometrial carcinomas removed from women with PCO or normal ovaries	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes*
Exclusion criteria	Yes Partial No Not reported	*Yes,*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes, cross-sectional*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Not relevant to this study*
Was matching performed?	Yes Partial No Not reported	*No*
Summary Result/s	Overall, PCO were similarly prevalent in women with EC (8.6%) and benign controls (8.4%); however, in women aged <50 years, PCO were more prevalent in women with EC (62.5 versus 27.3%, *P* = 0.033). Cyclin D1-expressing endometrial tumours tended to be more prevalent in women with PCO compared to normal ovaries (36.4 versus 6.25%, respectively, *P* = 0.071). Bcl2-, p53- and Ki67-expressing tumours were similarly prevalent	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Yes*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Not reported*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant to this study*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*All included*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Not reported*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Partial. Only Ethnicity data available*

OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*High* *Conclusion was drawn on PCOS based on ovarian histology assessment only.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Rosen 2019*
Study Citation	Rosen, Monica W., Tasset, Julia, Kobernik, Emily K., Smith, Yolanda R., Johnston, Carolyn, & Quint, Elisabeth H. (2019). Risk Factors for Endometrial Cancer or Hyperplasia in Adolescents and Women 25 Years Old or Younger. *Journal of Pediatric & Adolescent Gynecology*, *32*(5), 546–549. https://doi.org/10.1016/j.jpag.2019.06.004
Study Country	*USA*
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	Retrosepctive chart review of 10-25years aged women with ICD-9 revision and 10th revision codes for endometrial cancer of hyperplasia who underwent an endometrial sampling between February 1, 2006 and August 8, 2017, using the University of Michigan's DataDirect software system
Control population	Retrosepctive chart review of 10-25years aged women without ICD-9 revision and 10th revision codes for endometrial cancer of hyperplasia who underwent an endometrial sampling between February 1, 2006 and August 8, 2017, using the University of Michigan's DataDirect software system
PCOS diagnostic criteria	*Not reported*
N per group	*Cases = 13 (endometrial cancer)* *Controls = 54*
Setting	*Hospital*
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcomes:* characteristics of young women with endometrial hyperplasia or cancer to identify risk factors that might warrant endometrial sam- pling in women aged 25 years and younger.

		All of the charts were evaluated for demographic characteristics; gynecological, medical, surgical, and social histories; sur- gical pathology; and treatments. Body mass index (BMI) was calculated in absolute numbers (as opposed to per- centages).	
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	*Partial* The purpose of this study was to assess characteristics of young women with endometrial hyperplasia or cancer to identify risk factors that might warrant endometrial sam- pling in women aged 25 years and younger.
Inclusion criteria		Yes Partial No Not reported	*Yes*
Exclusion criteria		Yes Partial No Not reported	*Partial* Exclusion criteria included a history of Lynch syndrome, because this condition increases the risk of developing endometrial cancer by 15%-44%, depending on which specific genetic mutation is present . Unclear how this is identified.
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	*Yes, cross-sectional*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Not relevant to this study*
Was matching performed?		Yes Partial No Not reported	*No.*
Summary Result/s		women aged 25 years and younger with endometrial sampling, a BMI greater than 30 was statistically more common in patients with endometrioid intraepithelial neoplasia or cancer. Although smoking or PCOS alone was not related to endometrial hyper- plasia or cancer in this small cohort study, there might be a relationship between endometrial abnormalities and multiple exposures, including smoking and BMI greater than 30 or smoking and a history of PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Yes*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*

	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*No. Through chart review, unclear all factors that were extracted.*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant to this study*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*All included*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Not reported*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*No.* *Baseline BMI different between groups.*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*

	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*High*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Shu 2016*	
Study Citation	Shu, X.-O., Brinton, L.A., Zheng, W., Gao, Y.T., Fan, J. and Fraumeni, J.F., JR. (1991), A population-based case-control study of endometrial cancer in shanghai, china. Int. J. Cancer, 49: 38-43. https://doi.org/10.1002/ijc.2910490108	
Study Country	*China*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	All female residents of urban Shanghai aged 18-74 years who were newly diagnosed with endometrial cancer during the period April 1, 1988, to January 30, 1990. eligible cases were accrued from a population-based cancer registry in Shanghai during the study period.	
Control population	*As above*	
PCOS diagnostic criteria	*Self reported*	
N per group	*Patients with endometrial cancer: 268* *Control: 268*	
Setting	population-based cancer registry in Shanghai during the study period. This registry, established in 1963, has complete ascertainment of practically all cancer cases occurring in the urban Shanghai area.	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Associations between endometrial cancer risk and various exposure factors (demographic characteristics, reproductive characteristics, menstrual characteristics, contraceptive methods used, smoking and drinking)	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes*
Exclusion criteria	Yes Partial No	*Partial*

		Not reported	Cases: 26 (8.8%) were excluded because of refusal (2 cases), death (13 cases), inability to locate (6 cases) and other miscellaneous reasons (5 cases). (Misc. reasons unstated) *Controls:* One woman was excluded because of a prior hysterectomy, while 9 could not be located
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	*Yes (case-control)*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Not relevant to this study*
Was matching performed?		Yes Partial No Not reported	*Yes (age-matched)*
Summary Result/s		*The risk of endometrial cancer was significantly elevated among nulligravidas (OR = 5.4, 95% CI = 2.0-14.6) and decreased with number of pregnancies (p < 0.0 I). Late age at menopause was associated with increased risk, while early age at menarche was unrelated. Use of oral contraceptives for more than 2 years was associated with a reduction in endometrial cancer risk (OR = 0.4, 95% C I = 0.1-1.2). while short-term use of oral contraceptives and other methods of contraception were unrelated. Obesity was a strong predictor of risk, with women in the highest quartile of weight having 2.5 times the risk of those in the lowest quartile. In contrast to many other studies, cigarette smokers were at elevated risk (OR = 1.7. 95% C I = 0.9-3.0). Risk was also elevated among women reporting a history of gall-bladder disease, polycystic ovaries, menstrual symptoms, and non-estrogen hormone use.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Yes*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*

PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Partial (relied on self-report)*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Not reported*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Not reported*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant to cross-sectional study*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*All included*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Partial. – BMI was higher in the case group*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*

COMMENTS	*Medium risk of bias due to potential for recall bias in assessing risk factors / exposures, and lack of sufficient matching beyond age.*	
What is the overall risk of bias?	Low Moderate High Insufficient information	*Medium*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*No*	

Study ID	*Uehara 2020*	
Study Citation	Uehara, T., Mitsuhashi, A., & Shozu, M. (2020). The impact of pre-existing polycystic ovary syndrome on endometrial cancer recurrence. *European Journal Of Gynaecological Oncology*, *41*(5), 668. doi: 10.31083/j.ejgo.2020.05.5038	
Study Country	*Japan*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Premenopausal women (aged 50 years or younger) with endometrial cancer who underwent surgery at Chiba University Hospital between 2009 and 2013 were eligible for par- ticipation in this study*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	*The number of participants that were:* ○ *Screened 85* ○ *Enrolled 46* ○ *Allocated/randomised: PCOS= 9, controls= 37* ○ *Assessed (at f/u): PCOS= 9, controls= 37* ○ *Followed up 65.5 months*	
Setting	Chiba University Hospital, Japan	
Intervention/ indicator	N/A	
Comparison/ Control	*N/A*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Endometrial cancer recurrence*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes*
Exclusion criteria reported?	Yes Partial No Not reported	*Not reported*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes* *To clarify the impact of pre-existing PCOS on the recurrence of EC, the present authors compared the re- currence ratio of surgically treated EC between patients with and those without pre-existing PCOS.*

Is a cohort study the appropriate design to answer this question?		Yes Partial No Not reported	*Yes*
Does the study have specified inclusion/ exclusion criteria?		Yes Partial No Not reported	*Partial - Only inclusion criteria reported*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?		Yes Partial No Not reported	*Not reported.*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Yes*
Was matching performed?		Yes Partial No Not reported	*No*
Summary of Result/s		*Univariate analysis showed that the progression-free and overall survival of the patients with pre-existing PCOS was worse than that of patients without pre-existing PCOS (p = 0.008 and p = 0.029, respectively). Multivariate analysis revealed that PCOS was a poor prognostic factor for progression-free survival and a marginal poor prognostic factor for overall survival (p = 0.011 and p = 0.061, respectively)*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Other than the exposure under investigation, were the groups selected from similar populations?	Yes Partial No Not reported	*No* *Significant differences such as BMI, age, child birth etc exist between the groups*
SELECTION BIAS	Was the exposed cohort truly representative?	Yes Partial No Not reported	*Not reported*
SELECTION BIAS	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	*No* *All patients had endometrial cancer to start with. No clear definition how recurrence was detected.*
PERFORMANCE BIAS	Aside from the exposure, were the groups treated the same?	Yes Partial No Not reported	*No. Treatment differs depending on stage of cancer and response to treatment.*
DEDETECT	Was exposure measured in a	Yes Partial	*Not reported*

	standard, valid and reliable way?	No Not reported	
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Not reported*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Not reported*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?		*All included*
	What percentage of the individuals were not included in the analysis?	*X% treatment X% control/ comparison Not reported*	*As above*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*No*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS		Highly biased study population.	
What is the overall risk of bias?		*High*	*Few criteria have been fulfilled and the conclusions of the study are likely to be affected.*

Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*No* *All outcomes high risk of bias*

Study ID	*Wild 2000*	
Study Citation	*Wild S, Pierpoint T, Jacobs H, et al. Long-term consequences of polycystic ovary syndrome: results of a 31 year follow-up study. Hum Fertil (Camb) 2000; 3: 101–105.*	
Study Country	*UK*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	1028 women diagnosed with PCOS before 1979 in the United Kingdom were identified from hospital records. A total of 54% of these women were initially identified from histopathology records, and a further 22% were identified from operating theatre records of women who had undergone laparoscopy, wedge resection or ovarian biopsy. Further sources of information included hospital admission and discharge rec- ords (16% of cases) and diagnostic indexes.	
PCOS diagnostic criteria	Women included in the cohort were classified as either: (i) definite PCOS (62%), histological evidence of PCO with clin- ical evidence of ovarian dysfunction; or (ii) possible PCOS, his- tological evidence of PCO with clinical evidence not available (19%) or macroscopic evidence of PCO with clinical evidence of ovarian dysfunction (10%) or clinical diagnosis (9%).	
N per group	*The number of participants that were:* ○ *Screened 1028* ○ *Enrolled 786* ○ *Allocated/randomised: PCOS= 345* ○ *Assessed (at year 20 examination): PCOS= 319, matched controls 1060* ○ *Followed up 31 years*	
Setting	*Hospital*	
Intervention/ indicator	N/A	
Comparison/ Control	three age-matched control women was requested from the GP for 204 surviving cohort members for whom no baseline clinical information was available	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Not specified. Included questionnaire responses and doctors' records on on infertility, malignant disease, coronary heart disease, hypertension, diabetes, hypercholesterolemia, age at menarche, menopause, wasit hip circumferences, ethnic origin.*	
Inclusion criteria reported?	*Yes*	*Yes*
Exclusion criteria reported?	Yes Partial No Not reported	*Not reported*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Partial, Stated long term consequences of PCOS were investigated.*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*

Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Partial - Only inclusion criteria reported*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Partial. Combination of questionnaire and medical records.*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	*Yes, age*
Summary of Result/s	All-cause mortality in the cohort did not differ from that of the general population of women. Women with PCOS were not at significantly in- creased risk of mortality or morbidity from breast cancer but were at increased risk of endometrial cancer. Women with a history of PCOS had higher levels of several cardiovascular risk factors including diabetes, hypertension, raised plasma cholesterol and body mass index > 30 kg m^2. Mortality and morbidity from coronary heart disease did not differ sig- nificantly between the women with PCOS and comparison groups. Control of obesity is likely to be particularly im- portant for women with a history of PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS – Other than the exposure under investigation, were the groups selected from similar populations?	*Yes*	*Yes*
SELECTION BIAS – Was the exposed cohort truly representative?	Yes Partial No Not reported	*Partial. Combination of definitive and possible PCOS.*
SELECTION BIAS – Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	*No*
PERFORMANCE BIAS – Aside from the exposure, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS – Was exposure measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*

	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Partial. Combination of questionnaire and medical records.*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	*PCOS= 14%* *Controls= 14%*	*Original cohort 1028, final analysed 319. PCOS = 69% lost to f/u*
	What percentage of the individuals were not included in the analysis?	*X% treatment X% control/ comparison Not reported*	*As above*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Not reported*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*No.* *Significant differences in reproductive and gynaecological history.*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*Not reported*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Partial. Despite being a cohort study for PCOS women, controls were not followed up but rather a newly matched group, therefore limiting longitudinal analysis.*
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Zucchetto 2009*	
Study Citation	Zucchetto A, Serraino D, Polesel J, Negri E, De Paoli A, Dal Maso L, Montella M, La Vecchia C, Franceschi S, Talamini R. Hormone-related factors and gynecological conditions in relation to endometrial cancer risk. Eur J Cancer Prev. 2009 Aug;18(4):316-21.	
Study Country	*Italy*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	Cases were 454 women (median age 60 years, range 18–79 years) with histo- logically confirmed diagnosis of endometrial cancer and no earlier diagnosis of cancer. Only women diagnosed less than 1 year before hospitalization were eligible as cases.	
Control population	Controls were 908 women (median age 61 years, range 19–79 years) admitted to the same network of hospitals of cases for a wide spectrum of non-neoplastic, acute illnesses. Women admitted for gynecological or hormone-related onditions were not eligible as controls and women with a history of hysterectomy were excluded from the control group. Controls were admitted for traumas (36%), other orthopedic disorders (32%), acute surgical conditions (9%), and miscellaneous other illnesses, including eye, nose, ear, skin, or dental disorders (23%). Less than 5% of cases and controls approached refused the interview. Cases and controls were frequency matched on study center and quinquennia of age, with a 1 : 2 ratio.	
PCOS diagnostic criteria	*Not reported, via questionnaire*	
N per group	*Cases = 454 (endometrial cancer)* *Controls = 908*	
Setting	*Hospital*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcomes: not specified but collected via questionnaire*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Partial* We thus explored the role of hormone-related factors on endometrial cancer risk,
Inclusion criteria	Yes Partial No Not reported	*Yes*
Exclusion criteria	Yes Partial No Not reported	*Yes,*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes, case-control*

Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Not relevant to this study*
Was matching performed?		Yes Partial No Not reported	*No. Only match to frequency of cases.*
Summary Result/s		Endometrial cancer risk was inversely associated with age at menarche (OR=0.7,95%CI=0.5–1.0,for Z14vs. <12years),and directly associated with age at menopause (OR = 1.8, 95%CI=1.1–2.7,for Z55vs. <50years)andyearsof menstruation (OR = 2.4, 95% CI = 1.7–3.4, for highest vs. lowest tertile). Multiparity strongly reduced the risk among women under 60 years of age (OR = 0.3, 95% CI = 0.2–0.6, for Z 3 deliveries vs. < 2). Oral contraceptive use conferred a 40% reduced risk (95% CI = 0.4–1.0), irrespective of time since cessation. Although based on small numbers, women with a history of treated infertility (OR = 2.7, 95% CI = 1.1–6.4) or endometriosis (OR = 4.0, 95% CI = 1.0–15.5) were at increased risks. No significant associations with endometrial cancer risk emerged for age at first/last birth, breastfeeding, menopausal status, hormone replacement therapy, and history of uterine fibromyomas or polycystic ovary.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Not reported*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Partial*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Partial. Through questionnaire by trained interviewers.*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Not reported*

	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant to this study*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*All included*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Not reported*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Not reported*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*High*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 1

Question 1.11.

Are women with PCOS at increased risk of endometrial cancer?

BACKGROUND:

Prevalence and Problem:

Endometrial Hyperplasia (EH) and Cancer (EC) are on the rise globally. Whilst Endometrial Cancer is more common in developed countries, it has been on an increasing trend even in developing countries due to urbanization and changing lifestyles of reproductive age women (1).

Various risk factors have been associated with endometrial hyperplasia, the most prominent being unopposed Estrogen, both endogenous as in higher weight, PCOS and exogenous as in estrogen therapy. In women with an intact uterus, unopposed Estrogen is known to increase mitotic activity of endometrial cells, resulting in DNA replication and somatic mutations. These changes are clinically manifested as Endometrial Hyperplasia and Carcinoma (2-4). The other risk factors include previous pelvic irradiation, Diabetes Mellitus, use of Tamoxifen, Hypertension, increasing age, high socio-economic status and family history of uterine malignancy (Lynch Syndrome) (5). A recent systematic review showed that the risk of EC was three times higher in women with PCOS compared to women without the disease (6).

Endometrial hyperplasia (EH) is a relatively common condition that affects women of all age groups. It is diagnosed three times more commonly than endometrial cancer and is classified into three different categories based on the microscopic appearance into simple, complex non-atypical or atypical complex hyperplasia (7). World Health Organization guidelines in 2014 have re-classified EH by categorizing it as hyperplasia without atypia and hyperplasia with atypia. Without any intervention, EH is less than 1% for women with simple hyperplasia, 3% for complex non-atypical hyperplasia, and up to 29% for women with atypical complex hyperplasia progress to endometrial cancer (7). Endometrial tumors display a variety of histologic features and can be classified into two main subtypes, endometrioid (Type I) and non-endometrioid (Type II) (8, 9). with approximately 70–80% of endometrial cancers being Type I tumors. A slightly stronger association between PCOS and endometrial cancer has been observed when limited to Type I EC (OR all cases = 2.2; 95% CI 0.9–5.7 vs. OR Type I cases = 2.4; 95% CI = 1.0–6.2) (10, 11).

Type 1 endometrial cancers comprise 80% of uterine cancers and are estrogen responsive and mostly seen in pre- or perimenopausal age group. They are of endometrioid histology and are usually well differentiated. These tumours are usually linked with chronic and unopposed estrogen exposure as seen in women with higher weight, anovulatory cycles, (PCOS) and estrogen-secreting tumors[2] and have a favorable prognosis and >90% 5-year survival rate (12). They are characterized by K-RAS over expression, PTEN, PiK3CA, K-RAS mutations, and microsatellite instability.

Type 2 endometrial cancers comprise the remaining 10-20% of cases, are estrogen independent and usually arise in an atrophic endometrial background. They occur in women who are older, postmenopausal, multiparous, smokers, and tamoxifen users. Type 2 EC are aggressive tumors and often show deep myometrial invasion and extrauterine spread (13), with a recurrence rate of 50% and overall survival rate of 35% (12). They are associated with genetic alteration in E-cadherin, p53 and HER2/neu expression.

Next generation sequencing has shown four molecular subtypes of endometrial cancer beyond the histological phenotypes, but it is not cost-effective. Testing has been made practical with immunohistochemistry (iHC) based surrogate typing of the endometrial cancer. The four types of endometrial cancer proposed by the Cancer Genome Atlas (TCGA) in the ProMisE study showed a new reproducible way of classification of endometrial cancer based on numbers of mutations and alterations (14, 15).

Several systematic reviews compared the increased risk of endometrial cancer in women with PCOS vs. non-PCOS women (11, 16-19). The data indicates that women with PCOS of all ages are at a higher risk of endometrial cancer, while this risk is increased it must be noted that it is judged in the context of its relatively low incidence in the general population. A cross sectional study of infertile PCOS women diagnosed by Rotterdam Criteria, with ages between 18-43 years found EH in 12/108 women (11%) at a mean age of 29.91

years versus a control group of 31 non PCOS women at a mean age of 32.54 years of which only 1 patient (0.9%) was detected with EH (20).

Diagnosis of Endometrial Cancer

Diagnosis is based on initial clinical assessment, imaging and histology. Transvaginal sonography with color doppler is the first triage modality. The ultrasound features may be the same as those of a leiomyoma, or there may be an irregularly vascularized myometrial mass lesion with an irregular or regular margin often with anechoic areas of necrosis (21). Contrast enhanced MRI has a better predictive accuracy. The most common MRI finding is the presence of a large heterogeneous mass. On T1-weighted images, there may be a high signal intensity indicative of hemorrhagic necrosis in the sarcomas, not seen in other lesions, and on T2-weighted images, they are of intermediate to high signal intensity (22). On diffusion weighted imaging (DW1) high intensity signals along with diffusion restriction might be suggestive. PET-CT has limited utility as even benign lesions may show increased FDG uptake. However, for clarifying ambiguous findings, PET-CT is a useful modality (23). To summarize, there are no definitive imaging findings that can diagnose sarcoma reliably. CT pelvis, abdomen and chest are useful to confirm extra pelvic metastasis of disease. For further management metastasis to distant sites should be ruled out.

In another cross-section study which included 129 women with polyps and self-reported PCOS, the analysis was based on the histopathological diagnosis of EH or EC. On logistic regression analysis it was observed that the premalignant and malignant lessons were influenced by PCOS (0.001) with an odds Ratio of 4.61 (CI 1.9 - 27) with a polyp volume of more than 10 ml p = 0.001 OR 5.83 (CI 4.31 – 9.17) and presence of multiple polyps p=0.01 OR 2.05 (CI: 1.09 – 3.76). Though there was a moderate risk of bias, the evidence seems to suggest that Polyps are frequently present in PCOS women, and are more likely to be larger in volume and multiple in number (24).

In order to assess the effect of PCOS on reproductive centers, Ding et al conducted a large cohort study in a community setting including 8155 women between 16- 44 years, (mean age 27.7 years) from the National Health Databases in Taiwan and compared them with 32620 controls (4 fold) of women with a similar mean age, sex and index. A statistically significant higher risk of endometrial cancer was found in the PCOS cohort (adjusted HR [aHR] = 17.7, 95% CI = 4.9–64.2) than in the Control Cohort. No association was found with ovarian or breast cancer (aHR=0.98, 95% CI: 0.58–1.65) (25).

To determine whether higher weight increased the risk of EC in PCOS women Fearnley et.al. selected a population of 32 self- reported Australian PCOS women with endometrial cancer between ages 18 -79 years with age and stage, included from the national electoral roll. Women with PCOS had a 4 fold increased risk of EC compared to women without PCOS (OR 4.0. 95% CI 1.7 – 9.3) On removing the confounding factor of higher weight, the risk decreased to OR 2.2, (9.5% CI 0.9-5.7) There was a moderate Risk of Bias as these affected women had self- reported PCOS (10).

These observations are limited by the small number of events (reflecting the low incidence in young women in the general population), self-reported diagnosis, case-control designs and a failure to adjust for important confounders such as higher weight, which is a risk factor for endometrial cancer in its own right. Despite these uncertainties, clinicians and patients should be aware of a potentially increased risk of endometrial carcinoma in women with PCOS (26) and seek to prevent endometrial hyperplasia, especially in patients with prolonged time intervals between cycles (27).

Therapy

The epidemiologic data examining the relation between metformin and endometrial cancer have generally suggested no association or a protective association between metformin and endometrial cancer (28, 29). Yet, many epidemiological studies on diabetic patients show a potential preventative role of metformin in endometrial cancer patients, though data regarding its therapeutic role is still limited. So far, most of attention has been paid to the concept of metformin use in fertility sparing treatment of early-stage cancer. Another investigated

alternative is its application in patients with primary advanced or recurrent disease (30). A large study of 478,921 Taiwanese women with diabetes showed a significantly decreased incidence of endometrial cancer (hazard ratio [HR] 0.675, 95% CI 0.614–0.742) in metformin users compared to never users (31). Additionally, a meta-analysis by Tang and colleagues found that metformin use was associated with a decreased risk of endometrial cancer incidence (RR 0.87, 95% CI 0.80–0.95) (32). Endometrial cancer has been the least studied of the hormone related cancers in relation to clomiphene use. An association has been hypothesized since clomiphene has chemical properties similar to tamoxifen, a drug that has been associated with endometrial cancer risk. However, most previous studies of clomiphene and endometrial cancer have been limited by power. In one of the largest studies to date Brinton et al. reported a slight non-significant increase in risk of endometrial cancer among clomiphene users (HR=1.4;95% CI= 1.0-2.0) (33). Letrozole, an aromatase inhibitor, has more recently been considered as an additional treatment option for anovulatory infertility. A pilot study by Zhang et. al, included six endometrial cancer patients with a BMI over 30, who wished to preserve their fertility, treatment regimen consisted of GnRH agonist and letrozole, with none of the patients having recurrences after a median follow-up of 4.0 years (range, 1.3-7.0 years), and pregnancy rate and live birth rate was 50.0% and 75.0%, respectively (34). The LE-FSH-COS regimen was used in four women with endometrial carcinoma in five IVF cycles. The protocol maintained peak E_2 levels close to those of unstimulated cycles, at least in theory, offering a wider safety margin for endometrial cancer patients (35). While longitudinal data does not yet exist to adequately examine the association between letrozole use for ovulatory infertility and endometrial cancer risk, letrozole is currently used as an adjuvant treatment for hormone receptor positive postmenopausal breast cancer, thus it could be hypothesized that it would likely decrease hormonal related cancer risk (36) .

Clinical practice gap: need for guidance

The associations between PCOS and endometrial cancer are complex, requiring consideration of PCOS diagnostic criteria, etiologic heterogeneity of cancer subtypes, confounding and mediating factors, menopausal status, comorbid conditions such as infertility, type II diabetes and metabolic syndrome as well as treatment options that may also influence cancer risk. In addition, the rarity of endometrial cancers make these cancers even more difficult to study. Larger well-designed studies, or pooled analyses, may help clarify these complex associations (12, 37) .

Summary of key information

The associations between PCOS and endometrial cancer is complex, with the need to consider many methodological issues in future analyses.

Endometrial surveillance by transvaginal ultrasound or endometrial biopsy is indicated for those women with PCOS who have thickened endometrium, prolonged amenorrhea, unopposed estrogen exposure or abnormal vaginal bleeding, based upon clinical suspicion (37) .

GRADE EVIDENCE CERTAINTY	
Comparison	**GRADE for critical outcomes**
o PCOS versus non-PCOS Controls	⨁◯◯◯ VERY LOW

Evidence to Recommendations Framework

COMPARISONS (option versus other option)

PCOS (option) vs. non-PCOS women (other option)

EVIDENCE-BASED RECOMMENDATION(S)

EBR: Health professionals should be aware that premenopausal women with PCOS have markedly higher risk of developing endometrial hyperplasia and endometrial cancer.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

PRACTICE POINT(S)

Women with PCOS should be informed about the increased risk of endometrial hyperplasia and endometrial cancer, acknowledging that the overall chance of developing endometrial cancer is low, therefore routine screening is not recommended.

Long-standing untreated amenorrhoea, higher weight, type 2 diabetes and persistent thickened endometrium are additional to PCOS as risk factors for endometrial hyperplasia and endometrial cancer.

Women with PCOS should be informed of preventative strategies which include weight management, cycle regulation and regular progestogen therapy.

When endometrial thickness is detected, a progestogen induced withdrawal bleeding is indicated, and further follow-up is required.

GRADE CONSIDERATIONS

Justifications:
The collective data shows a higher prevalence of endometrial cancer in women with PCOS than those without PCOS which is inversely associated with the age at menarche and positively associated with the age at menopause (33, 34). The reduced risk for endometrial cancer is 40% with oral contraceptive use irrespective of the time since cessation (34). The protective effects according to different endometrial tumor types and oral contraceptive formulations remain unknown. Endometrial cancer remains very uncommon in premenopausal women and an 8-fold increased risk is still very low in absolute numbers.

Subgroup considerations:
In women with PCOS who are under the age of 50 years, the risk for endometrial cancer seems to be elevated (35). Women who are above the healthy weight range have a higher risk of developing endometrial cancer. There is also a relationship of risk of endometrial cancer in PCOS and external exposures like smoking (36). Oral contraceptive use conferred a relative decreased risk of EC, irrespective of the time since cessation (34). No significant associations emerged for age at first/last birth, breastfeeding, menopausal status, hormone replacement therapy, and history of uterine fibromyomas.
Ethnicity should be a consideration.

Implementation considerations:
Implementing the 2023 International PCOS Guideline should be according to the specific guidelines of national and international professional societies. It is imperative to monitor the extent to which these recommendations are being implemented in clinical practice during quality control audits.

Monitoring and evaluation considerations:
Monitoring of the implementation of the recommendation in clinical practice.

Research priorities:
The long-term natural history of endometrial hyperplasia and the impact of treatment.
The impact of androgen excess on endometrial cancer development.
The incidence/prevalence of endometrial cancer in different ethnicities.

GRADE framework

GRADE DECIDE **Interactive Evidence to Decision Framework**

• DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Evidence suggests a higher chance of developing endometrial hyperplasia in women with PCOS, whilst women without PCOS are at a lower risk since the absolute risk of the cancer is relatively low due to its rarity.

● UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

Judgement:

☐ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☒ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Lack of awareness

Inappropriate/complete lack of testing

Easily preventable cancer, often goes undiagnosed due to the above points.

● CERTAINTY OF THE EVIDENCE

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☒ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

As per the GRADE Assessment and Evidence profile, the mean of the overall certainty of the evidence came out to be Low. The Evidence Summary also states that the quality of evidence of the outcomes of the selected studies are low to moderate.

● VALUES

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☐ Important uncertainty or variability	☒ Possibly important uncertainty or variability	☐ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Research evidence:

No research evidence was identified

Panel discussion:

Patients and health professionals would probably value this. The uncertainty lies in the low absolute risk may increase psychological distress for some women.

● BALANCE OF EFFECTS

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:

Although the risk of endometrial hyperplasia is high in women with PCOS, it does not diminish the chance of women without PCOS to develop the same, hence it would be desirable to use the opportunity to screen are PCOS women.

● COSTS

How large are the resource requirements (costs)?

Judgement:

☒ Don't know	☐ Varies	☐ Large costs	☐ Moderate costs	☐ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:

No research evidence was identified

Panel discussion:

The panel has mixed views on cost savings versus spending.

● CERTAINTY OF COST EVIDENCE

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

No research evidence was identified

Panel discussion:

As above

● COST-EFFECTIVENESS

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

No research evidence was identified

Panel discussion:

Uncertain

● EQUITY

What would be the impact on health equity?

Judgement:

☐ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☒ Probably increased	☐ Increased

Research evidence:

No research evidence was identified

Panel discussion:

No research evidence.

● ACCEPTABILITY

Is the option acceptable to key stakeholders?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Common cancer but uncommon in premenopausal women.

● FEASIBILITY

Is the option feasible to implement?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

The knowledge base of non-gynecologist health professionals regarding assessment of the endometrium is variable. Health system and resource variability will impact on feasibility.

Prescribing OCP's cyclic Progestogens or Levonorgestrel containing IUD's could be done either by GP's or (reproductive) endocrinologist or gynecologists.

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PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by ECR Lead: Su Jen Chua
Other Members: Tahani Al-Kindi, Xin Yi Wu
Supervised, edited and supported by the Evidence Team

GDG 1
Question 1.12.

What is the risk of PCOS and cardiometabolic outcomes (CVD, T2D) in relatives of women with PCOS?

1. SELECTION CRITERIA

Table 1. PICO Criteria for Inclusion – Not to be adapted To be used by evidence team to decide which studies will be included when screening search results.	
Question	Q 1.12) What is the risk of PCOS and related cardiometabolic outcomes (CVD, T2D) in relatives of women with PCOS?
Clinical leads (key contacts)	Dr Anju Joham Endocrinologist Monash Health, Monash University, Australia Anju.Joham@monash.edu
Allocation ranking	Level 1 - New systematic review

	P	I	C	O	S
Inclusion criteria PCOS	First degree relatives (only women) of women with PCOS (diagnosed by Rotterdam, NIH or AES) of any age, ethnicity, weight or phenotype of PCOS	PCOS (diagnosed by Rotterdam, NIH or AES)	General population	Prevalence of PCOS in first degree relatives of women with PCOS	Evidence based guidelines, systematic reviews, health technology assessments, randomised controlled trials, comparative cohort studies. Can include cross sectional or case control if it compares PCOS and non-PCOS
Inclusion criteria CVD	First degree relatives (both men and women) of women with PCOS (diagnosed by Rotterdam, NIH or AES) of any age, ethnicity, weight or phenotype of PCOS	Diagnosed CVD – defined as a CVD event including: • angina (heart pain), heart attack, stroke, peripheral vascular disease, CVD-related death	General population	Prevalence of cardiovascular disease and cardiovascular risk factors in first degree relatives of women with PCOS Secondary: CVD risk factors • Waist circumference • Waist-to-hip ratio (WHR) • BMI • Lipid profile (triglycerides, total cholesterol, HDL, LDL) • Blood pressure	Evidence based guidelines, systematic reviews, health technology assessments, randomised controlled trials, comparative cohort studies. Can include cross sectional or case control if it compares CVD events in PCOS and non-PCOS
Inclusion criteria IGT or T2DM	First degree relatives (both men and women) of women with PCOS (diagnosed by Rotterdam, NIH or AES) of any age, ethnicity, weight or phenotype of PCOS	Diagnosed IGT or T2DM	General population	Prevalence of IGT or T2DM in first degree relatives of women with PCOS Other outcomes: Waist circumference • Waist-to-hip ratio (WHR) • BMI	Evidence based guidelines, systematic reviews, health technology assessments, randomised controlled trials, comparative cohort studies and cross sectional or case control if it compares IGT or T2DM in PCOS and non-PCOS

				• Fasting glucose • Glucose tolerance test	
Exclusion criteria	Non blood or second degree or greater relatives of women with PCOS	None	None		Non-evidence based guidelines, non-systematic reviews, non- comparative cohort studies, case series, editorials, letters, commentaries.

2. SEARCH STRATEGY

Table 2.1. Search details

Search strategy source:	
Evidence source	Date of search
Medline (Ovid)	2/8/22: 4558
PsychInfo (Ovid)	2/8/22: 275
EMBASE (Ovid)	2/8/22: 8432
All EBM (Ovid)	2/8/22: 1012
Web of Science	2/8/22: 3738
Clinicaltrials.gov	2/8/22: 13
WHO ICTRP	2/8/22: 2
Any subsequent updates - enter database and date:	

Table 2.2. Questions addressed by this search *(add more rows as needed)*:

GDG	Q#	Question
1	1	What is the risk of PCOS in first degree relatives of women with PCOS?
1	2	What is the risk of T2DM / IGT in first degree relatives of women with PCOS?
1	3	What is the risk of cardiovascular disease (MI, heart failure, stroke, PVD) in first degree relatives of women with PCOS?
1	4	What is the risk of surrogate markers of cardiovascular risk (hypertension and hyperlipidaemia) in first degree relatives of women with PCOS?

Table 2.3. Search strings used in OVID or other database/s

OVID Medline / PsychInfo / All EBM

1. exp Polycystic Ovary Syndrome/
2. (polycystic adj5 ovar$).tw.
3. (PCOS or PCO).tw.
4. PCOD.tw.
5. ("stein-leventhal" or leventhal).tw.
6. PCOM.tw.
7. anovulation/
8. anovulat*.mp.
9. oligo-ovula*.mp.

10. oligoovulat*.mp.
11. (ovar* adj5 (sclerocystic or polycystic or poly?cystic or degenerat* or hyperandrogen* or hyperandrogen*)).mp.
12. Or/1-11
13. exp Diabetes Mellitus, Type 2/
14. (MODY or NIDDM or T2DM or T2D).tw.
15. (non insulin* depend* or noninsulin* depend* or noninsulin?depend* or non insulin?depend*).tw.
16. ((typ? 2 or typ? II or typ?2 or typ?II) adj3 diabet*).tw.
17. (((late or adult* or matur* or slow or stabl*) adj3 onset) and diabet*).tw.
18. exp Glucose Intolerance/
19. exp Insulin Resistance/
20. (diabet* adj6 (diagnos* or prevention* or control*)).tw,ot.
21. (impaired adj6 glucose toleranc*).tw,ot.
22. insulin resistanc*.tw,ot.
23. glucose intoleranc*.tw,ot.
24. Prediabetic state/
25. (prediabet* or pre diabet*).tw.
26. intermediate hyperglyc?emi*.tw.
27. ((impaired fasting adj2 glucose) or IFG or impaired FPG).tw.
28. glucose intolerance.tw.
29. ((impaired glucose adj (tolerance or metabolism)) or IGT).tw.
30. ((risk or progress* or prevent* or inciden* or conversion or develop* or delay*) adj4 (diabetes or T2D* or NIDDM or "type 2" or "type II")).tw.
31. Or/13-30
32. exp Diabetes Insipidus/
33. diabet* insipidus.tw.
34. 32 or 33
35. 31 not 34
36. Cardiovascular Diseases/
37. Cardiovascular disease*.tw.
38. (CVD or ASCVD).tw.
39. coronary disease/ or coronary artery disease/
40. (Coronary adj2 disease*).tw.
41. CAD.tw.
42. Acute Coronary Syndrome/
43. acute coronary syndrome.tw.
44. ACS.tw.
45. exp Myocardial Infarction/
46. myocardial infarction*.tw.
47. heart attack*.tw.
48. exp Angina Pectoris/
49. angina.tw.
50. exp Heart Diseases/
51. heart disease*.tw.
52. (CHD or IHD).tw.
53. revasculari?ation.tw.
54. exp Coronary Artery Bypass/
55. coronary artery bypass.tw.
56. CABG.tw.
57. exp Percutaneous Coronary Intervention/
58. (Percutaneous adj2 coronary).tw.
59. PCI.tw.
60. exp Angioplasty/
61. Angioplast*.tw.
62. Peripheral Arterial Disease/
63. peripheral arter* disease*.tw.
64. Heart Failure/
65. ((heart or cardiac) adj2 failure).tw.
66. (HF or CHF or CCF).tw.
67. HFpEF.tw.
68. HFrEF.tw.

69. exp Hypertension/
70. hypertensi*.tw.
71. ((high or increased or elevated) adj2 blood pressure).tw.
72. exp Hyperlipidemias/
73. hyperlipid*.tw.
74. hyperlip?emia*.tw.
75. hypercholesterol*.tw.
76. hypercholester?emia*.tw.
77. hyperlipoprotein?emia*.tw.
78. hypertriglycerid?emia*.tw.
79. exp Arteriosclerosis/
80. exp Cholesterol/
81. cholesterol.tw.
82. Blood Pressure/
83. blood pressure.tw.
84. cerebrovascular disorders/ or basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp carotid artery diseases/ or exp cerebral small vessel diseases/ or exp intracranial arterial diseases/ or exp "intracranial embolism and thrombosis"/ or exp intracranial hemorrhages/ or stroke/ or exp brain infarction/ or stroke, lacunar/ or vasospasm, intracranial/ or vertebral artery dissection/
85. (stroke$ or poststroke or apoplex$ or cerebral vasc$ or brain vasc$ or cerebrovasc$ or cva$ or SAH).tw.
86. ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or "middle cerebral artery" or MCA$ or "anterior circulation" or "posterior circulation" or "basilar artery" or "vertebral artery" or "space-occupying") adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.
87. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or basal gangli$ or putaminal or putamen or posterior fossa or hemispher$ or subarachnoid) adj5 (h?emorrhag$ or h?ematoma$ or bleed$)).tw.
88. hemiplegia/ or exp paresis/ or exp Gait Disorders, Neurologic/
89. (hemipleg$ or hemipar$ or paresis or paraparesis or paretic).tw.
90. or/35-89
91. family history.tw,ot.
92. exp Family/
93. exp Genetic Predisposition to Disease/
94. (familial or inherit$ or heredit$ or predispos$ or susceptib$).mp.
95. Parent* OR father* OR mother* OR sister* OR brother* OR sibling* OR daughter* OR son* OR children OR twin* OR offspring OR relative* OR kindred* OR proband OR generation.mp.
96. Or/91-95
97. (12 and 90 and 96) or (12 and 96)
98. exp Animals/ not (Humans/ and exp Animals/)
99. 97 not 98

limit 99 to english language

EMBASE

1. exp ovary polycystic disease/
2. (polycystic adj5 ovar$).tw.
3. (PCOS or PCO).tw.
4. leventhal.tw.
5. PCOD.tw.
6. anovulation/
7. anovulat*.mp.
8. oligoovulat*.mp. OR oligo-ovulat*.mp.
9. (ovar* adj5 (sclerocystic or polycystic or poly?cystic or degenerat* or hyperandrogen* or hyperandrogen*)).mp.
10. or/1-9
11. exp diabetes mellitus/
12. exp glucose intolerance/
13. exp insulin resistance/
14. (diabet* adj6 (diagnos* or prevention* or control*)).tw,ot.
15. (impaired adj6 glucos* toleranc*).tw,ot.
16. (insulin resistanc* or glucose intoleranc*).tw,ot.
17. Prediabetic state/
18. (prediabet* or pre diabet*).tw.

19. intermediate hyperglyc?emi*.tw.
20. ((impaired fasting adj2 glucose) or IFG or impaired FPG).tw.
21. glucose intolerance.tw.
22. ((impaired glucose adj (tolerance or metabolism)) or IGT).tw.
23. ((risk or progress* or prevent* or inciden* or conversion or develop* or delay*) adj4 (diabetes or T2D* or NIDDM or "type 2" or "type II")).tw.
24. or/11-23
25. exp Diabetes Insipidus/
26. diabet* insipidus.tw.
27. 25 or 26
28. 24 not 27
29. cardiovascular disease/
30. Cardiovascular disease*.tw.
31. (CVD or ASCVD).tw.
32. coronary artery disease/
33. (Coronary adj2 disease*).tw.
34. CAD.tw.
35. acute coronary syndrome/
36. acute coronary syndrome.tw.
37. ACS.tw.
38. exp heart infarction/
39. myocardial infarction*.tw.
40. heart attack*.tw.
41. exp angina pectoris/
42. angina.tw.
43. exp heart disease/
44. heart disease*.tw.
45. (CHD or IHD).tw.
46. revasculari?ation.tw.
47. exp coronary artery bypass graft/
48. coronary artery bypass.tw.
49. CABG.tw.
50. exp percutaneous coronary intervention/
51. (Percutaneous adj2 coronary).tw.
52. PCI.tw.
53. exp angioplasty/
54. Angioplast*.tw.
55. peripheral occlusive artery disease/
56. peripheral arter* disease*.tw.
57. heart failure/
58. ((heart or cardiac) adj2 failure).tw.
59. (HF or CHF or CCF).tw.
60. HFpEF.tw.
61. HFrEF.tw.
62. exp Hypertension/
63. hypertensi*.tw.
64. ((high or increased or elevated) adj2 blood pressure).tw.
65. exp Hyperlipidemias/
66. hyperlipid*.tw.
67. hyperlip?emia*.tw.
68. hypercholesterol*.tw.
69. hypercholester?emia*.tw.
70. hyperlipoprotein?emia*.tw.
71. hypertriglycerid?emia*.tw.
72. exp Arteriosclerosis/
73. exp Cholesterol/
74. cholesterol.tw.
75. "coronary risk factor* ".tw.
76. Blood Pressure/
77. blood pressure.tw.

78. cerebrovascular disease/ or brain disease/ or exp basal ganglion hemorrhage/ or exp brain hemangioma/ or exp brain hematoma/ or exp brain hemorrhage/ or exp brain infarction/ or exp brain ischemia/ or exp carotid artery disease/ or exp cerebral artery disease/ or exp cerebrovascular accident/ or exp cerebrovascular malformation/ or exp intracranial aneurysm/ or exp occlusive cerebrovascular disease/ or exp vertebrobasilar insufficiency/
79. (stroke$ or poststroke or apoplex$ or cerebral vasc$ or brain vasc$ or cerebrovasc$ or cva$ or SAH).tw.
80. ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or "middle cerebral artery" or MCA$ or "anterior circulation" or "posterior circulation" or "basilar artery" or "vertebral artery" or "space-occupying") adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.
81. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or basal gangli$ or putaminal or putamen or posterior fossa or hemispher$ or subarachnoid) adj5 (h?emorrhag$ or h?ematoma$ or bleed$)).tw.
82. exp hemiplegia/ or exp paresis/
83. neurologic gait disorder/
84. (hemipleg$ or hemipar$ or paresis or paraparesis or paretic).tw.
85. or/28-84
86. (familial or inherit$ or heredit$ or predispos$ or susceptib$).mp.
87. exp genetic predisposition/
88. Parent* OR father* OR mother* OR sister* OR brother* OR sibling* OR daughter* OR son* OR children OR twin* OR offspring OR relative* OR kindred* OR proband OR generation.mp.
89. family history.tw,ot.
90. exp Family/
91. exp Genetic Predisposition to Disease/
92. or/86-91
93. (10 and 85 and 92) or (10 and 92)
94. (animal/ or nonhuman/) not exp human/
95. 93 not 94

limit 95 to english language

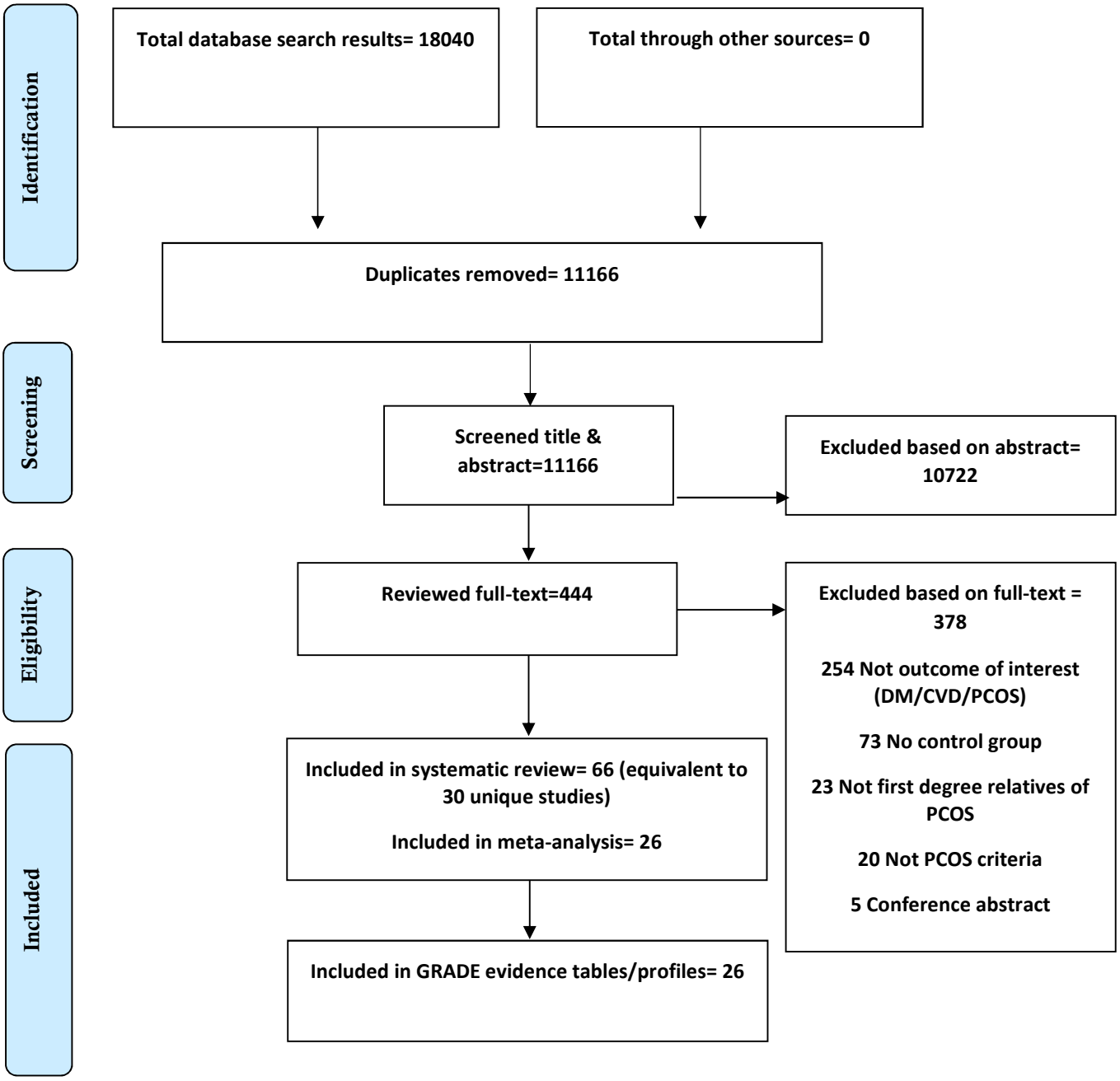
Web of Science

TI = (polycyst* NEAR/5 ovar*)
TS = polycystic ovar*
TS = leventhal
#3 OR #2 OR #1
TS= (diabet* or "noninsulin*-depend*" or "non-insulin*-depend*" or "noninsulin*depend*" or "non-insulin*depend*") OR TS= ("fasting glucose" or "plasma glucose" or "glucose tolerance test* "or (glyc$emic NEAR/2 control*)) OR TS= (HbA1c or A1C or A1c or hba1c or ((glycated or glycosylated) NEAR/1 h$emoglobin*)) OR TS= (IDDM or NIDDM or MODY or T1DM or T2DM or T1D or T2D)
TS= ("diabet* insipidus")
#5 NOT #6
TS=(stroke or poststroke or post-stroke or apoplex* or cerebral vasc* or brain vasc* or cerebrovasc* or cva or SAH)
TS=((brain or cerebr* or cerebell* or vertebrobasil* or hemispher* or intracran* or intracerebral or infratentorial or supratentorial or “middle cerebral artery” or MCA* or “anterior circulation” or “posterior circulation” or “basilar artery” or “vertebral artery” or “space-occupying”) NEAR/5 (isch$emi* or infarct* or thrombo* or emboli* or occlus* or hypoxi*))
TS=((brain* or cerebr* or cerebell* or intracerebral or intracran* or parenchymal or intraparenchymal or intraventricular or infratentorial or supratentorial or “basal gangli*” or putaminal or putamen or “posterior fossa” or hemispher* or subarachnoid) NEAR/5 (h$emorrhage* or h$ematoma* or bleed*))
TS=(hemipleg* or hemipar* or paresis or paraparesis or paretic)
TS=(hyperlipid* OR hyperlip?emia* OR hypercholesterol* OR hypercholester?emia* OR hyperlipoprotein?emia* OR hypertriglycerid?emia*)
TS=(antihypertens* OR hypertens* OR prehypertens* OR "blood pressur*")
TS=(HFpEF or HFrEF) OR TS=(HF or CHF or CCF) OR TS=((heart or cardiac) NEAR/2 failure)
TS=peripheral arter* disease*
TS=(PCI or Angioplast*) OR TS=(Percutaneous NEAR/2 coronary) OR TS=CABG OR TS=coronary artery bypass OR TS=revasculari?ation
TS=(CHD or IHD) OR TS=heart disease* OR TS=angina OR TS=heart attack* OR TS=myocardial infarction* OR TS=ACS OR TS=acute coronary syndrome OR TS=CAD OR TS=(Coronary NEAR/2 disease*)
TS=(CVD or ASCVD) OR TS=Cardiovascular disease*
#18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7
TS=(Parent* OR father* OR mother* OR sister* OR brother* OR sibling* OR daughter* OR son* OR children OR twin* OR offspring OR relative* OR kindred* OR proband OR generation OR familial or inherit$ or heredit$ or predispos$ or susceptib$)

(#4 AND #19 AND #20) OR (#4 AND #20) TI=(rat or rats or mice or mouse) #21 not #22 and English (Languages)
Clinicaltrials.gov Condition: Polycystic ovary Other terms: Family
WHO ICTRP Condition: polycystic ovary Title: family OR relative OR relatives

Evidence processing: Studies were selected and appraised by 2 reviewer/s in consultation with the evidence team/ key contact using study selection and appraisal criteria (PICO above) established a priori. The articles were reviewed by title and abstract by 2 reviewers. When a decision could not be made based on title and abstract alone, full text was retrieved. **In total, 30 studies met inclusion criteria for this review.**

3. SEARCH RESULTS - PRISMA flowchart



4. STUDY INCLUSION

Table 4.1. Included Studies

Baillargeon JP, Carpentier AC. Brothers of women with polycystic ovary syndrome are characterised by impaired glucose tolerance, reduced insulin sensitivity and related metabolic defects. Diabetologia. 2007 Dec;50(12):2424-32. doi: 10.1007/s00125-007-0831-9. Epub 2007 Sep 27. PMID: 17898989; PMCID: PMC3846531.
Coviello AD, Sam S, Legro RS, Dunaif A. High prevalence of metabolic syndrome in first-degree male relatives of women with polycystic ovary syndrome is related to high rates of obesity. J Clin Endocrinol Metab. 2009 Nov;94(11):4361-6. doi: 10.1210/jc.2009-1333. Epub 2009 Oct 16. PMID: 19837913; PMCID: PMC2775643.
Crisosto N, Echiburú B, Maliqueo M, Luchsinger M, Rojas P, Recabarren S, Sir-Petermann T. Reproductive and metabolic features during puberty in sons of women with polycystic ovary syndrome. Endocr Connect. 2017 Nov;6(8):607-613. doi: 10.1530/EC-17-0218. Epub 2017 Sep 14. PMID: 28912339; PMCID: PMC5640572. (primary citation) SIR-PETERMANN, T., VANTMAN, N., CONCHA, F., ECHIBURU, B., PEREIRA, C., DE GUEVARA, A. L., CRISOSTO, N. R., PEREZ-BRAVO, F. A. & SANTOS, J. L. 2014. Metabolic Profile and Eating Behavior Score in Prepubertal and Early Pubertal Sons of Women with Polycystic Ovary Syndrome. Endocr. Rev., 35, 2.
Crisosto N, Ladrón de Guevara A, Echiburú B, Maliqueo M, Cavada G, Codner E, Paez F, Sir-Petermann T. Higher luteinizing hormone levels associated with antimüllerian hormone in postmenarchal daughters of women with polycystic ovary syndrome. Fertil Steril. 2019 Feb;111(2):381-388. doi: 10.1016/j.fertnstert.2018.10.011. Epub 2018 Dec 7. PMID: 30527840.
deWilde MA, Eising JB, Gunning MN, Koster MPH, Evelein AMV, Dalmeijer GW, Uiterwaal CSPM, Eijkemans MJC, Ent CKV, Meijboom FJ, Fauser BCJM. Cardiovascular and Metabolic Health of 74 Children From Women Previously Diagnosed With Polycystic Ovary Syndrome in Comparison With a Population-Based Reference Cohort. Reprod Sci. 2018 Oct;25(10):1492-1500. doi: 10.1177/1933719117749761. Epub 2018 Jan 10. PMID: 29320957.
Diamanti-Kandarakis E, Alexandraki K, Bergiele A, Kandarakis H, Mastorakos G, Aessopos A. Presence of metabolic risk factors in non-obese PCOS sisters: evidence of heritability of insulin resistance. J Endocrinol Invest. 2004 Nov;27(10):931-6. doi: 10.1007/BF03347535. PMID: 15762040.
Harnois-Leblanc S, Trottier A, Leblanc S, Battista MC, Geller DH, Baillargeon JP. Evolution of metabolic alterations 5 Years after early puberty in a cohort of girls predisposed to polycystic ovary syndrome. Reprod Biol Endocrinol. 2017 Jul 24;15(1):56. doi: 10.1186/s12958-017-0275-0. PMID: 28738839; PMCID: PMC5525344. (primary citation) Leblanc, S. H., Leblanc, S., Battista, M. C., Geller, D. H., & Baillargeon, J. P. (2016). Evolution of metabolic alterations 5 years after peri-pubertal years in young girls genetically predisposed to polycystic ovary syndrome compared to age-matched control girls. Endocrine Reviews, 37(2 Supplement 1). doi:https://dx.doi.org/10.1210/endo-meetings.2016.RE.5.SUN-156
Joharatnam J, Barber TM, Webber L, Conway GS, McCarthy MI, Franks S. Determinants of dyslipidaemia in probands with polycystic ovary syndrome and their sisters. Clin Endocrinol (Oxf). 2011 Jun;74(6):714-9. doi: 10.1111/j.1365-2265.2011.03983.x. PMID: 21521255; PMCID: PMC4625580. (primary citation) Franks S, Webber LJ, Goh M, Valentine A, White DM, Conway GS, Wiltshire S, McCarthy MI. Ovarian morphology is a marker of heritable biochemical traits in sisters with polycystic ovaries. J Clin Endocrinol Metab. 2008 Sep;93(9):3396-402. doi: 10.1210/jc.2008-0369. Epub 2008 Jun 17. PMID: 18559912.
Karthik S, Vipin VP, Kapoor A, Tripathi A, Shukla M, Dabadghao P. Cardiovascular disease risk in the siblings of women with polycystic ovary syndrome. Hum Reprod. 2019 Aug 1;34(8):1559-1566. doi: 10.1093/humrep/dez104. PMID: 31299073. (primary citation) Subramaniam K, Tripathi A, Dabadghao P. Familial clustering of metabolic phenotype in brothers of women with polycystic ovary syndrome. Gynecol Endocrinol. 2019 Jul;35(7):601-603. doi: 10.1080/09513590.2019.1566451. Epub 2019 Feb 6. PMID: 30727783. Karthik, S, Vipin, VP, Kapoor, A, Tripathi, A, Shukla, M & Dabadghao, P 2019, 'Cardiovascular disease risk in the siblings of women with polycystic ovary syndrome', Human Reproduction, vol. 34, no. 8, pp. 1559–1566.
Kent SC, Gnatuk CL, Kunselman AR, Demers LM, Lee PA, Legro RS. Hyperandrogenism and hyperinsulinism in children of women with polycystic ovary syndrome: a controlled study. J Clin Endocrinol Metab. 2008 May;93(5):1662-9. doi: 10.1210/jc.2007-1958. Epub 2008 Feb 12. PMID: 18270257; PMCID: PMC2386683.
Krysiak R, Basiak M, Szkróbka W, Okopień B. The Impact of Telmisartan on Cardiometabolic Risk Factors in Hypertensive Male Siblings of Women With Polycystic Ovary Syndrome. J Clin Pharmacol. 2021 Sep;61(9):1165-1173. doi: 10.1002/jcph.1872. Epub 2021 Jun 17. PMID: 33837974.
Krysiak R, Szkróbka W, Okopień B. The impact of atorvastatin on cardiometabolic risk factors in brothers of women with polycystic ovary syndrome. Pharmacol Rep. 2021 Feb;73(1):261-268. doi: 10.1007/s43440-020-00135-w. Epub 2020 Jul 21. Erratum in: Pharmacol Rep. 2021 Oct;73(5):1481. PMID: 32696349; PMCID: PMC8149333.

Kulshreshtha B, Sharma N, Pant S, Prasad A, Chitkara A, Pahuja B, Pahuja I. Predictors of Metabolic Syndrome among Polycystic Ovary Syndrome Sisters. J Hum Reprod Sci. 2019 Oct-Dec;12(4):334-340. doi: 10.4103/jhrs.JHRS_172_18. Epub 2019 Dec 17. PMID: 32038085; PMCID: PMC6937762.
Legro RS, Kunselman AR, Stetter CM, Gnatuk CL, Estes SJ, Brindle E, Vesper HW, Botelho JC, Lee PA, Dodson WC. Normal Pubertal Development in Daughters of Women With PCOS: A Controlled Study. J Clin Endocrinol Metab. 2017 Jan 1;102(1):122-131. doi: 10.1210/jc.2016-2707. PMID: 27778640; PMCID: PMC5413094.
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Lidaka, L., Grasmane, A., Lazdane, G., Dzivite-Krisane, I., Gailite, L., & Viberga, I. (2021). Can a mother's polycystic ovary syndrome (PCOS)-related symptoms be used to predict the future clinical profile of PCOS in her adolescent daughter? A pilot study. *Eur. J. Contracept. Reprod. Health Care, 26*(1), 17-22. doi:10.1080/13625187.2020.1795118	No control group
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Errayya, D., Sreegiri, S., Padmavathi, C., & Madhavi, B. D. (2022). Risk Factors For Polycystic Ovarian Syndrome Among Adolescent Girls In Urban Visakhapatnam. European Journal of Molecular and Clinical Medicine, 9(3), 28-35. Retrieved from https://ejmcm.com/article_17043_a038dd01d4fc994e44806c19d3d4c4d1.pdfhttp://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emexa&NEWS=N&AN=2017197032	Not 1st degree relatives
Hahn, S., Tan, S., Elsenbruch, S., Quadbeck, B., Herrmann, B. L., Mann, K., & Janssen, O. E. (2005). Clinical and biochemical characterization of women with polycystic ovary syndrome in North Rhine-Westphalia. Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme, 37(7), 438-444. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med6&NEWS=N&AN=16034717	Not 1st degree relatives
Hahn, S., Tan, S., Sack, S., Kimmig, R., Quadbeck, B., Mann, K., & Janssen, O. E. (2007). Prevalence of the metabolic syndrome in German women with polycystic ovary syndrome. Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association, 115(2), 130-135. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med6&NEWS=N&AN=17318774	Not 1st degree relatives
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Tang, W., Wang, Y., Jiang, H., Liu, C., Dong, C., Chen, S., . . . Gu, H. (2015). Insulin receptor substrate-1 (IRS-1) rs1801278G>A polymorphism is associated with polycystic ovary syndrome susceptibility: a meta-analysis. International journal of clinical and experimental medicine, 8(10), 17451-17460. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=pmnm3&NEWS=N&AN=26770335	Not 1st degree relatives
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Witwit, S. J. (2019). The prevalence of polycystic ovarian syndrome and it's associated symptoms in selected samples of women in Al-Hilla city, Iraq. Indian Journal of Public Health Research and Development, 10(8), 2548-2552. doi:https://dx.doi.org/10.5958/0976-5506.2019.02250.2	Not 1st degree relatives
Yang, Y., Qiao, J., Tang, R.-X., & Li, M.-z. (2010). Genotype and haplotype determination of interleukin (IL) 1 beta (g. -511C>T and g. +3954C>T) and IL-1RN in polycystic ovary syndrome. Fertility and Sterility, 94(1), 384-386. doi:https://dx.doi.org/10.1016/j.fertnstert.2009.09.042	Not 1st degree relatives
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Xu, S., & Guo, Y. (2018). A singleton pregnancy recommendation for women with polycystic ovary syndrome undergoing invitro fertili zation/intracytoplasmic sperm injection: A propensity score matching study. Journal of Assisted Reproduction and Genetics, 35(11), 2105. doi:https://dx.doi.org/10.1007/s10815-018-1321-3	Not outcome of interest
Xu, S., & Yihong, G. (2019). No increased risk of adverse perinatal outcomes in singleton pregnancy of polycystic ovary syndrome(PCOS): a propensity score matching study. Human Reproduction, 34(SUPPL 1), i433. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emexa&NEWS=N&AN=637583440	Not outcome of interest
Yalamanchi, S. K., Redman, L., & Dunaif, A. (2012). Male first-degree relatives of women with polycystic ovary syndrome have defects in insulin action and energy expenditure. Endocrine Reviews, 33(3 MeetingAbstracts). Retrieved from http://edrv.endojournals.org/cgi/content/meeting_abstract/33/03_MeetingAbstracts/SUN-26?sid=55109b17-d131-4fbe-a1e9-9fa9303e99a8http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed13&NEWS=N&AN=70833223	Not outcome of interest
Yilmaz, B., Vellanki, P., Ata, B., & Yildiz, B. O. (2018a). Diabetes mellitus and insulin resistance in mothers, fathers, sisters, and brothers of women with polycystic ovary syndrome: a systematic review and meta-analysis. *Fertil. Steril., 110*(3), 523-+. doi:10.1016/j.fertnstert.2018.04.024	Not outcome of interest
Yilmaz, B., Vellanki, P., Ata, B., & Yildiz, B. O. (2018b). Metabolic syndrome, hypertension, and hyperlipidemia in mothers, fathers, sisters, and brothers of women with polycystic ovary syndrome: a systematic review and meta-analysis. *Fertil. Steril., 109*(2), 356-+. doi:10.1016/j.fertnstert.2017.10.018	Not outcome of interest
Yu, H., Liang, Z., Cai, R., Jin, S., Xia, T., Wang, C., & Kuang, Y. (2022). Association of adverse birth outcomes with in vitro fertilization after controlling infertility factors based on a singleton live birth cohort. Scientific reports, 12(1), 4528. doi:https://dx.doi.org/10.1038/s41598-022-08707-x	Not outcome of interest
Zhang, F.-F., Zhang, Q., Wang, Y.-L., Wang, F.-F., Hardiman, P. J., & Qu, F. (2021). Intergenerational Influences between Maternal Polycystic Ovary Syndrome and Offspring: An Updated Overview. The Journal of pediatrics, 232, 272-281. doi:https://dx.doi.org/10.1016/j.jpeds.2021.01.018	Not outcome of interest
Zhao, C. C., Zhou, Y., Shen, X., Gong, M., Lu, Y. F., Fang, C., . . . Ju, R. (2020). Circular RNA expression profiling in the fetal side of placenta from maternal polycystic ovary syndrome and circ_0023942 inhibits the proliferation of human ovarian granulosa cell. *Arch. Gynecol. Obstet., 301*(4), 963-971. doi:10.1007/s00404-020-05495-5	Not outcome of interest
Zhao, N. PCOS related to fetal origins of disease. Journal of Assisted Reproduction and Genetics, 30(2), 169. doi:https://dx.doi.org/10.1007/s10815-013-9940-1	Not outcome of interest
Zhou, S., Lu, D., Wen, S., Sheng, Y., Kang, D., & Xu, L. (2022). Elevated Anti-Mullerian Hormone Levels in Newborns of Women with Polycystic Ovary Syndrome: a Systematic Review and Meta-analysis Based on Observational Studies. Reproductive sciences (Thousand Oaks, Calif.), 29(1), 301-311. doi:https://dx.doi.org/10.1007/s43032-021-00652-w	Not outcome of interest
Zhou, S., Wen, S., Sheng, Y., Kang, D., & Xu, L. (2021). NEWBORNS OF WOMEN WITH POLYCYSTIC OVARY SYNDROME (PCOS) HAVE HIGHER ANTI-MULLERIAN HORMONE (AMH) LEVELS: A SYSTEMATIC REVIEW AND META-ANALYSIS. Fertility and Sterility, 116(3 SUPPL), e123-e124. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emexa&NEWS=N&AN=638129893	Not outcome of interest
Zhu, Y., You, J., Xu, C., & Gu, X. (2019). Pathogenicity of the homoplasmic C3275T, T4363C and A8343G variant requires confirmation. Gene, 680, 97-98. doi:https://dx.doi.org/10.1016/j.gene.2018.09.001	Not outcome of interest
Ackerman, C. M., Lowe, L. P., Lee, H., Chen, F., Hughes, E., Cholod, P., . . . Urbanek, M. (2010). The role of the polycystic ovary syndrome susceptibility locus D19S884 allele 8 in maternal glycemia and fetal size. Journal of Clinical Endocrinology and Metabolism, 95(7), 3242-3250. doi:https://dx.doi.org/10.1210/jc.2009-2718	Not fulfilling diagnostic criteria for PCOS
Akbarzadeh, M., Moradi, F., Dabbaghmaneh, M. H., Parsanezhad, M. E., & Jafary, P. (2010). A survey of abnormal blood pressure and hyperandrogenemia in first degree relatives of women with polycystic ovarian syndrome referring to gynecology clinics of Shiraz Medical University. Iranian Journal of Reproductive Medicine, 8(SUPPL. 1), 66. Retrieved from http://www.ssu.ac.ir/ijrm/index.php/ijrm/article/view/157/140http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=72056122	Not fulfilling diagnostic criteria for PCOS
Akbarzadeh, M., Moradi, F., Dabbaghmanesh, M. H., Jafari, P., & Parsanezhad, M. E. (2013). A survey of metabolic syndrome in first-degree relatives (fathers) of patients with polycystic ovarian syndrome. *J. Endocrinol. Metab. Diabetes . S. Afr., 18*(2), 98-103. doi:10.1080/22201009.2013.10872312	Not fulfilling diagnostic criteria for PCOS
Akram, M., & Roohi, N. (2015). Endocrine Correlates of Polycystic Ovary Syndrome in Pakistani Women. *JCPSP-J. Coll. Physicians Surg., 25*(1), 22-26. Retrieved from <Go to ISI>://WOS:000349877100007	Not fulfilling diagnostic criteria for PCOS
Battaglia, C., Mancini, F., Cianciosi, A., Busacchi, P., Persico, N., Paradisi, R., . . . de Aloysio, D. (2009). Cardiovascular risk in normal weight, eumenorrheic, nonhirsute daughters of patients with polycystic ovary syndrome: a pilot study. *Fertil. Steril., 92*(1), 240-249. doi:10.1016/j.fertnstert.2008.05.018	Not fulfilling diagnostic criteria for PCOS
Battaglia, C., Regnani, G., Mancini, F., Iughetti, L., Flamigni, C., & Venturoli, S. (2002). Polycystic ovaries in childhood: a common finding in daughters of PCOS patients. A pilot study. *Hum. Reprod., 17*(3), 771-776. doi:10.1093/humrep/17.3.771	Not fulfilling diagnostic criteria for PCOS

Bell, G. A., Sundaram, R., Mumford, S. L., Park, H., Broadney, M., Mills, J. L., . . . Yeung, E. H. (2018). Maternal polycystic ovarian syndrome and offspring growth: the Upstate KIDS Study. *J. Epidemiol. Community Health, 72*(9), 852-855. doi:10.1136/jech-2017-210004	Not fulfilling diagnostic criteria for PCOS
Cesta, C., Kuja-Halkola, R., Lehto, K., & Iliadou, A. (2017). Polycystic ovary syndrome, personality, and depression: a twin study. *Eur. Neuropsychopharmacol., 27*, S752-S752. doi:10.1016/s0924-977x(17)31377-9	Not fulfilling diagnostic criteria for PCOS
Chen, X., Koivuaho, E., Piltonen, T. T., Gissler, M., & Lavebratt, C. (2021). Association of maternal polycystic ovary syndrome or anovulatory infertility with obesity and diabetes in offspring: a population-based cohort study. Human reproduction (Oxford, England), 36(8), 2345-2357. doi:https://dx.doi.org/10.1093/humrep/deab112	Not fulfilling diagnostic criteria for PCOS
Cooper, H. E., Spellacy, W. N., Prem, K. A., & Cohen, W. D. (1968). Hereditary factors in the Stein-Leventhal syndrome. American Journal of Obstetrics and Gynecology, 100(3), 371-387. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med1&NEWS=N&AN=15782458	Not fulfilling diagnostic criteria for PCOS
Davies, M. J., Marino, J. L., Willson, K. J., March, W. A., & Moore, V. M. (2011). Intergenerational Associations of Chronic Disease and Polycystic Ovary Syndrome. *PLoS One, 6*(10), 4. doi:10.1371/journal.pone.0025947	Not fulfilling diagnostic criteria for PCOS
Finnbogadottir, S. K., Glintborg, D., Jensen, T. K., Kyhl, H. B., Nohr, E. A., & Andersen, M. (2017). Insulin resistance in pregnant women with and without polycystic ovary syndrome, and measures of body composition in offspring at birth and three years of age. *Acta Obstet. Gynecol. Scand., 96*(11), 1307-1314. doi:10.1111/aogs.13200	Not fulfilling diagnostic criteria for PCOS
Fornes, R., Simin, J., Nguyen, M. H., Cruz, G., Crisosto, N., van der Schaaf, M., . . . Brusselaers, N. (2022). Pregnancy, perinatal and childhood outcomes in women with and without polycystic ovary syndrome and metformin during pregnancy: a nationwide population-based study. *Reprod. Biol. Endocrinol., 20*(1), 12. doi:10.1186/s12958-022-00905-6	Not fulfilling diagnostic criteria for PCOS
Govind, A., Obhrai, M. S., & Clayton, R. N. (1999). Polycystic ovaries are inherited as an autosomal dominant trait: Analysis of 29 polycystic ovary syndrome and 10 control families. *J. Clin. Endocrinol. Metab., 84*(1), 38-43. doi:10.1210/jc.84.1.38	Not fulfilling diagnostic criteria for PCOS
Hunter, A., Vimplis, S., Sharma, A., Eid, N., & Atiomo, W. (2007). To determine whether first-degree male relatives of women with polycystic ovary syndrome are at higher risk of developing cardiovascular disease and type II diabetes mellitus. *J. Obstet. Gynaecol., 27*(6), 591-596. doi:10.1080/01443610701497520	Not fulfilling diagnostic criteria for PCOS
Kaushal, R., Parchure, N., Bano, G., Kaski, J. C., & Nussey, S. S. (2004). Insulin resistance and endothelial dysfunction in the brothers of Indian subcontinent Asian women with polycystic ovaries. *Clin. Endocrinol., 60*(3), 322-328. doi:10.1111/j.1365-2265.2004.01981.x	Not fulfilling diagnostic criteria for PCOS
Lunde, O., Magnus, P., Sandvik, L., & Hoglo, S. (1989). FAMILIAL CLUSTERING IN THE POLYCYSTIC OVARIAN SYNDROME. *Gynecol.Obstet.Invest., 28*(1), 23-30. doi:10.1159/000293493	Not fulfilling diagnostic criteria for PCOS
Noroozzadeh, M., Rahmati, M., Behboudi-Gandevani, S., & Tehrani, F. R. (2022). Maternal hyperandrogenism is associated with a higher risk of type 2 diabetes mellitus and overweight in adolescent and adult female offspring: a long-term population-based follow-up study. *J. Endocrinol. Invest., 45*(5), 963-972. doi:10.1007/s40618-021-01721-2	Not fulfilling diagnostic criteria for PCOS
Wang, E. T., Cirillo, P. M., Kao, C. N., Cohn, B. A., & Cedars, M. I. (2013). Birth weight and childhood growth in daughters of women with irregular menstrual cycles. *Gynecol. Endocrinol., 29*(6), 615-618. doi:10.3109/09513590.2013.788638	Not fulfilling diagnostic criteria for PCOS
Zhu, J., Wittemans, L., Lindgren, C., Hirschhorn, J., & Chan, Y. M. (2021). Genetic risk factors for polycystic ovary syndrome: Evidence from men for ovary-independent effects. Hormone Research in Paediatrics, 94(SUPPL 2), 140. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emexa&NEWS=N&AN=637233387	Not fulfilling diagnostic criteria for PCOS

Studies excluded from meta-analysis

Reference	Reason
Crisosto N, Echiburú B, Maliqueo M, Luchsinger M, Rojas P, Recabarren S, Sir-Petermann T. Reproductive and metabolic features during puberty in sons of women with polycystic ovary syndrome. Endocr Connect. 2017 Nov;6(8):607-613. doi: 10.1530/EC-17-0218. Epub 2017 Sep 14. PMID: 28912339; PMCID: PMC5640572. (primary citation) SIR-PETERMANN, T., VANTMAN, N., CONCHA, F., ECHIBURU, B., PEREIRA, C., DE GUEVARA, A. L., CRISOSTO, N. R., PEREZ-BRAVO, F. A. & SANTOS, J. L. 2014. Metabolic Profile and Eating Behavior Score in Prepubertal and Early Pubertal Sons of Women with Polycystic Ovary Syndrome. Endocr. Rev., 35, 2.	Median and IQR reported
Recabarren SE, Smith R, Rios R, Maliqueo M, Echiburú B, Codner E, Cassorla F, Rojas P, Sir-Petermann T. Metabolic profile in sons of women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2008 May;93(5):1820-6. doi: 10.1210/jc.2007-2256. Epub 2008 Jan 29. PMID: 18230657. (Primary source) Recabarren SE, Sir-Petermann T, Rios R, Maliqueo M, Echiburú B, Smith R, Rojas-García P, Recabarren M, Rey RA. Pituitary and testicular function in sons of women with polycystic ovary syndrome from infancy to adulthood. J Clin Endocrinol Metab. 2008 Sep;93(9):3318-24. doi: 10.1210/jc.2008-0255. Epub 2008 Jun 10. PMID: 18544620. Recabarren SE et al. (2008) Metabolic profile in sons of women with polycystic ovary syndrome (PCOS). J Clin Endocrinol Metab doi:10.1210/jc.2007-2256.	Median and IQR reported
Sir-Petermann T, Cartes A, Maliqueo M, Vantman D, Gutiérrez C, Toloza H, Echiburú B, Recabarren SE. Patterns of hormonal response to the GnRH agonist leuprolide in brothers of women with polycystic ovary syndrome: a pilot study. Hum Reprod. 2004 Dec;19(12):2742-7. doi: 10.1093/humrep/deh512. Epub 2004 Sep 9. PMID: 15358722.	Mean and range reported
Torchen LC, Fogel NR, Brickman WJ, Paparodis R, Dunaif A. Persistent apparent pancreatic β-cell defects in premenarchal PCOS relatives. J Clin Endocrinol Metab. 2014 Oct;99(10):3855-62. doi: 10.1210/jc.2014-1474. Epub 2014 Jul 16. PMID: 25029420; PMCID: PMC4184072. (primary citation) TORCHEN, L., FOGEL, N. R., BRICKMAN, W., PAPARODIS, R. & DUNAIF, A. 2013. Persistent defects in pancreatic beta-cell function in early pubertal female relatives of women with polycystic ovary syndrome in a three year longitudinal study. Endocrine Reviews, 34. TORCHEN, L. C., FOGEL, N. R., BRICKMAN, W. J., MAURAS, N. & DUNAIF, A. 2012. Beta-cell dysfunction and hyperandrogenemia in PCOS early pubertal female relatives. Endocrine Reviews, 33.	Median and IQR reported

5. STUDY CHARACTERISTICS TABLE

Author, year, country	Population/ Setting	Country / Ethnicity	Study Design	Method of deriving Control group	Sample Size per group	FDR details	Age (years) / BMI (kg/m^2) of FDRs	Diagnostic criteria for PCOS / DM	Outcomes	Summary of findings	Source of funding / conflict of interest
Baillargeon 2007	Brothers of women with PCOS / Academic hospital / single centre/ timeframe not defined	Canada	Case control	Hospital personnel, university students, local newspaper advertisement	FDR group = 17 Control = 28	Brothers	Age: 31±9 BMI: 27.6±3.7	NICHD (PCOS) / NCEP/ATPIII criteria (metabolic syndrome)	BMI, BP, waist circumference, glucose, lipids, metabolic syndrome	Brothers of women with PCOS had insulin resistance compared to age and BMI matched controls	Yes (government funding)
Coviello 2009	Fathers and brothers of women with PCOS / Academic hospital / multicenter / timeframe not defined	USA	Cross-sectional	Nationwide database NHANES III	FDR group = 211 Control = 1153	Fathers, brothers (data for brothers not extracted as duplicated in Sam 2008 study)	Fathers Age: 57 ±9; BMI: 30.2 ± 5.6	NICHD (PCOS) / NCEP/ATPIII criteria (metabolic syndrome)	Metabolic syndrome	Fathers and brothers of women with PCOS had higher rates of obesity and metabolic syndrome	No
Crisosto 2017	Sons of women with PCOS by Tanner stage / Academic hospital / single center / timeframe not defined	Chile	Cross-sectional	Not defined	FDR group = 69 Control = 84	Sons	Tanner I age: median 9.1 / range 8.4-9.6; BMI: median 18.7 / range 17.3-22.4 Tanner II-III age: median 10.8 / range 10.3-11.6; BMI: median 21 / range 18.4-24.8 Tanner IV-V age: median 14.4 / range 13-16.1; BMI: median 23 / range 20-26.2	NICHD (PCOS) / ADA criteria (glucose intolerance)	WHR, glucose, lipids	Son of women with PCOS had higher rates of hyperlipidaemia and central adiposity	Yes (government / foundation funding)
Crisosto 2019	Postmenarcheal daughters of women with PCOS / Academic hospital/ single center / timeframe not defined	Chile	Case control	Not defined	FDR group = 43 Control = 28	Daughters	Age: median 15.42 / IQR 14.17–16.17 BMI: median 25.28 / IQR 21.70–28.72 BMI z score: median 1.24 (IQR 0.48-2.07)	NICHD (PCOS)	BP, glucose, lipids	No difference in any parameter was found.	Yes (government funding)

deWilde2018	Offspring of women with PCOS / Academic hospital / multicenter / Feb 2013 - July 2014	Netherlands	Prospective cohort	Healthy newborns from a different population follow-up study recruited from same geographical regions	FDR group = 74 Control = 298	Daughters, sons	Age: 3.3 ±0.6; BMI: 15.9 ± 1.6 (younger subgroup) Age: 7.0 ±0.8; BMI: 15.3 ± 1.5 (older subgroup)	Rotterdam (PCOS)	BP, glucose, lipids	Offspring of women with PCOS had higher rates of hyperlipidaemia than healthy controls	Yes (government / university / pharmaceutical company funding)
Diamanti-Kandarakis 2004	Sisters of women with PCOS / Academic hospital / Single center / timeframe not defined	Greece	Case control	Not defined	FDR group = 17 Control = 20	Sisters	Age: 22.88 ±0.93; BMI: 22.98 ± 1.16	NICHD (PCOS)	WHR, glucose, lipids	Sisters of women with PCOS had higher rates of insulin resistance	Not reported
Harnois-Leblanc 2017	Late / postpubertal first degree relatives of women with PCOS / Academic hospital / Single center / 2007-2015 / 4-6 years follow-up	Canada	Prospective cohort	Paediatric endocrine clinic	FDR group = 8 Control = 8	Daughters, sisters	Median age: 17.5 IQR: 14.4-20.1; Median BMI: 22.7 IQR (21.5-30.8)	AE-PCOS (PCOS)	BMI, WHR, glucose, lipids	Late/post pubertal female first degree relatives of women with PCOS had similar rates of insulin resistance	Yes (medical foundation funding)
Joharatnam 2011	Sisters of women with PCOS / Academic hospital / multicenter / timeframe not defined	United Kingdom	Retrospective cohort	Not defined	FDR group = 214 Control = 76	Sisters	Age: 31.3 ±6; BMI: 25.1 ± 0.6 (subgroup with polycystic ovaries) Age:37.8 ±7.7; BMI: 24.5 ± 1.1 (subgroup without polycystic ovaries)	Rotterdam (PCOS)	BMI, WHR, glucose, lipids	Sisters of women with PCOS had higher rates of hyperlipidaemia than healthy controls	Yes (government / medical foundation funding)
Karthik 2019	Siblings of women with PCOS / Academic hospital / single center / January 2016 - July 2017	India	Case control	Hospital staff / relatives of patients	FDR group = 76 Control = 76	Sisters, brothers	Sisters age: median 24; BMI: median 21.2 Brothers age: 23.3 ±4.3; BMI: 23.7 ± 4.2	Rotterdam (PCOS)	BP, WHR, glucose, lipids	Siblings of women with PCOS had higher rates of metabolic syndrome and hyperlipidaemia than healthy controls	Yes (university funding)
Kent 2008	Children of women with PCOS / Academic hospital / single center / timeframe not defined	USA	Case control	Not defined	FDR group = 32 Control = 38	Sons, daughters (data for daughters not extracted as	Daughters Age: 9.1 ±3.4; BMI: 20.0 ± 5.3 Sons Age: 9.7 ±3.4; BMI: 20.9 ± 5.1	NICHD (PCOS) / de Ferranti criteria (metabolic syndrome)	BMI, BP, WHR, glucose, lipids, metabolic syndrome	Children of women with PCOS had higher rates of metabolic syndrome	Yes (university funding)

						duplicated in Legro 2017 study)					
Kulshreshtha 2019	Sisters of women with PCOS / Academic hospital / single center / 2013-2016	India	Case control	Hospital staff and their family members	FDR group = 200 Control = 99	Sisters	Age: 25.4 ±8; BMI: 24.3 ± 5.0	Rotterdam (PCOS)	BMI, BP, WHR, glucose, lipids, metabolic syndrome	Sisters of women with PCOS had higher rates of metabolic syndrome than healthy controls	Yes (government funding)
Krysiak 2021	Hypertensive brothers of women with PCOS / Academic hospital / single center / timeframe not defined	Poland	Interventional cohort	Hypertensive men treated in community centers	FDR group = 24 Control = 26	Brothers	Age: 39 ±8; BMI: 28.3 ± 4.2	Rotterdam (PCOS)	BMI, BP, glucose, lipids	Hypertensive brothers of women with PCOS had higher rates of hyperlipidaemia and insulin resistance than hypertensive controls	No
Krysiak 2021 2	Hypercholesterolaemic brothers of women with PCOS / Academic hospital / single center / timeframe not defined	Poland	Interventional cohort	Hypercholesterolaemic men treated in community centers	FDR group = 20 Control = 20	Brothers	Age: 50 ±12; BMI: 28.5 ± 4.8	Rotterdam (PCOS)	BMI, BP, glucose, lipids	Hypercholesterolaemic brothers of women with PCOS had higher rates of insulin resistance than controls	Yes (government funding)
Legro 2017	Daughters of women with PCOS / Academic hospital / single center / timeframe not defined	USA	Case control	Not defined	FDR group = 76 Control = 80	Daughters	Tanner I age: 7.02 ±1.96; BMI: 17.66 ± 3.43 Tanner II-III age: 11.46 ±1.33; BMI: 21.37 ± 5.63 Tanner IV-V age: 15.24 ±1.17; BMI: 27.56 ± 8.7	NICHD (PCOS)	BMI, BP, waist hip circumference	Daughters of women with PCOS had similar rates of insulin resistance	Yes (government funding)
Lenarcik 2011	Siblings of women with PCOS / Academic hospital / single center / timeframe not defined	Poland	Case control	Not defined	FDR group = 200 Control = 99	Sisters, brothers	Sisters Age: 25.52 ±5.78; BMI: 24.22 ± 6.09 Brothers Age: 23.52 ±5.05; BMI: 24.44 ± 4.00	Rotterdam (PCOS)	WHR, glucose, lipids	Siblings of women with PCOS had higher rates of glucose intolerance and hyperlipidaemia	No
Li 2020	Young children of women with PCOS / Academic hospital / single center / timeframe not defined	China	Case control	Same hospital as experimental group	FDR group = 172 Control = 529	Daughters, sons	Age 4.65 ± 1.34 BMI z score: median 0.2 IQR -0.5-0.6 (Zhang 2021 substudy)	Rotterdam (PCOS)	BMI, Glucose, lipids	Offspring of women with PCOS had higher rates of insulin resistance.	Yes (government funding)

Raissouni 2012	Premenarchal first degree relatives of women with PCOS / Academic hospital / multicenter / timeframe not defined	Multinational (USA/Canada/Chile)	Cross-sectional	School-based study (USA centers)	FDR group = 18 Control = 21	Daughters, sisters	Age: 11.6 ± 1.4; BMI: 21.5 ± 3.5	NICHD (PCOS)	BMI, waist circumference	Premenarchal first degree relatives of women with PCOS had higher rates of insulin resistance	Yes (government / university funding)
Recabarren 2008	Sons of women with PCOS / Academic hospital / timeframe not defined	Chile	Case control	Not defined	FDR group = 80 Control = 56	Sons (infancy, childhood, adulthood)	Infancy median Age: 2.0; IQR 2.0 –3.0 months Childhood median age: 6.0 IQR (4.0 –7.5 years; median BMI: 17.4 IQR 14.9 –24.7 Adulthood median age: 22.0 IQR 18.0 – 29.0; median BMI: 25.1 IQR 20.0 – 45.4	NICHD (PCOS)	BMI, weight, waist circumference, glucose, lipids	If unadjusted for BMI, sons of PCOS women have higher weight during early infancy; higher weight, BMI, waist circumference, total cholesterol and LDL during childhood and adulthood.	Yes (1 author received pharmaceutical company funding)
Sam 2005	Sisters of women with PCOS / Academic hospital / multicenter / timeframe not defined	USA	Case control	Not defined	FDR group = 385 Control = 125	Sisters	Age: 28 ±7; BMI: 32.9 ± 7.0	NICHD (PCOS) ATPIII criteria (metabolic syndrome)	BMI, BP, waist circumference, glucose, metabolic syndrome	Sisters of women with PCOS had higher rates of metabolic syndrome	Yes (government funding)
Sam 2006	Mothers of women with PCOS / Academic hospital / multicenter / 1993-2004	USA	Case control	2 control groups (Not defined / NHANES III)	FDR group = 215 Control = 62	Mothers	Age: 52 ±8; BMI: 29.9 ± 7.0	NICHD (PCOS) NCEP/ATPIII criteria (metabolic syndrome) WHO (glucose intolerance)	BMI, BP, waist circumference, glucose, lipids	Mothers of women with PCOS had higher rates of dyslipidaemia and insulin resistance	Yes (government funding)
Sam 2008	Brothers of women with PCOS / Academic hospital / multicenter / January 1995 - October 2005	USA	Case control	Not defined	FDR group = 196 Control = 169	Brothers	Age: 30 ±8; BMI: 28.4 ± 5.7	NICHD (PCOS)	BMI, BP, waist circumference, glucose	Brothers of women with PCOS had higher rates of hyperlipidaemia and insulin resistance	Yes (government funding)
Sir-Peterman 2004	Brothers of women with PCOS / Academic hospital / 2002-2003	Chile	Case control	Brothers of healthy women in similar geographical region / socioeconomic	FDR group = 22 Control = 14	Brothers	Age: 23 ±8; BMI: 28.4 ± 5.7	NICHD / Rotterdam (PCOS)	BMI, weight, waist circumference, glucose, lipids	If unadjusted for BMI, sons of PCOS women have higher weight during early infancy; higher weight, BMI, waist circumference,	No

				status. University students, hospital staff.						total cholesterol and LDL during childhood and adulthood.	
Sir-Peterman n 2012	Daughters of women with PCOS / Academic hospital / single center / timeframe not defined	Chile	Case control	Not defined	FDR group = 135 Control = 93	Daughters	Tanner I age: mean ± SEM = 8.6 ± 0.2; BMI: mean ± SEM = 19.4 ± 0.8 Tanner II age: mean ± SEM = 9.9 ± 0.2; BMI: mean ± SEM = 19.8 ± 0.6 Tanner III age: mean ± SEM = 10.8 ± 0.2; BMI: mean ± SEM = 20.6 ± 0.9 Tanner IV age: mean ± SEM =12.2 ± 0.3; BMI: mean ± SEM = 20.8 ± 0.7 Tanner V age: mean ± SEM = 13.2 ± 0.3; BMI: mean ± SEM = 22.4 ± 0.8	NICHD (PCOS) / ADA criteria (glucose intolerance)	BMI, weight, waist circumference, WHR, glucose, lipids	No difference in any parameter was found.	Yes (government / foundation funding)
Torchen 2014	Early pubertal female relatives of women with PCOS / Academic hospital / single center / timeframe not defined	USA	Case control	Local media / online advertisement	FDR group = 12 Control = 10	Daughters, sisters	Median age: 10.4	NICHD (PCOS)	BMI, BP, waist hip circumference	Early pubertal female relatives of women with PCOS had similar rates of insulin resistance	Yes (government funding)
Torchen 2016	Daughters of women with PCOS / Academic hospital / single center / timeframe not defined	USA	Case control	Local media / online advertisement	FDR group = 21 Control = 36	Daughters	Age: 1.7 ±0.6; Weight for length Z score: 0.43 ± 1.04	NICHD (PCOS)	BMI, BP, waist hip circumference	Daughters of women with PCOS had higher weight and different levels of androgen metabolites	Yes (government / health institution funding)
Unluhizarci 2007	Female first degree relatives of women with PCOS / Academic hospital / single center / timeframe not defined	Turkey	Case control	Not defined	FDR group = 70 Control = 20	Sisters, mothers	All Female first degree relatives age: mean ± SEM = 27.3 ± 0.8, range 16-42; BMI: mean ± SEM = 24.4 ± 0.3, range 20–31	Rotterdam (PCOS)	BMI, glucose,	Female first degree relatives have similar BMI but higher fasting glucose and 2hr glucose.	Not reported

							Sisters age: mean ± SEM = 26.5 ± 0.8, range 16-42; BMI: mean ± SEM = 24.4 ± 0.8, range 20–31				
Vipin 2016	Parents of women with PCOS / Academic hospital / single center / November 2012 - November 2014	India	Case control	Hospital staff / relatives of patients	FDR group = 86 Control = 86	Fathers, mothers	Fathers age: 53.1 ±5.1; BMI: 25.6 ± 2.9 Mothers age: 47.9 ±4.9; BMI: 27.4 ± 4.4	Rotterdam (PCOS) / ADA (DM) / JNC (hypertension) / IDF (metabolic syndrome)	BMI, BP, WHR, glucose, lipids	Parents of women with PCOS had higher rates of metabolic syndrome and cardiovascular disease than healthy controls	Yes (university funding)
Wang 2021	Children of women with PCOS / Academic hospital / single center / June 2018 - January 2019	China	Case control	Same hospital as experimental group	FDR group = 29 Control = 116	Daughters, sons	Age 1.82 ± 0.23; BMI: 15.84 ± 1.23	Rotterdam (PCOS)	BMI	Children of women with PCOS had lower BMI than healthy controls	Yes (government funding)
Yildiz 2003	First degree relatives of women with PCOS / Academic hospital / single center / timeframe not defined	Turkey	Case control	Not defined	FDR group = 102 Control = 82	Fathers, mothers, sisters brothers	Fathers Age: 50.4 ±4.0; BMI: 27.5 ± 3.2 Mothers Age: 44.5 ±3.3; BMI: 28.5 ± 4.6 (premenopausal) Mothers Age: 50.4 ±4.9; BMI: 29.3 ± 3.7 (postmenopausal) Sisters Age: 25.1 ±5.7; BMI: 22.9 ± 4.9 Brothers Age: 23.8 ±5.3; BMI: 22.6 ± 2.8	NICHD (PCOS) / ADA (DM)	WHR, Glucose, lipids	First degree relatives of women with PCOS had higher rates of glucose intolerance, hypertension and hyperlipidaemia.	Not reported
Yilmaz 2005	First degree relatives of women with PCOS / Academic hospital / single center / timeframe not defined	Turkey	Case control	Not defined	FDR group = 120 Control = 75	Fathers, mothers, sisters brothers	Fathers Age: 51.87 ±8.54; BMI: 26.94 ± 4.22 Mothers Age: 46.38 ±7.95; BMI: 30.46 ± 6.89 Sisters Age: 23.50 ±7.56; BMI: 26.35 ± 6.32	Rotterdam (PCOS) / ADA (DM)	Glucose, lipids	First degree relatives of women with PCOS had higher rates of glucose intolerance, hypertension and hyperlipidaemia.	Not reported

							Brothers Age: 29.0 ±11.1; BMI: 22.97 ± 4.58				
Zhang 2022	Offspring of women with PCOS / Academic hospital / Single center / 2007-2015 / 4-6 years follow-up	China	Prospective cohort	Similar hospital as FDR group	FDR group = 198 Control = 227	Daughters, sons	Age 3 months to 6 years	Rotterdam (PCOS)	BMI	Offspring of women with PCOS had higher BMI	Yes (government funding)

Keywords: ADA = American Diabetes Association; AE-PCOS = Androgen Excess and PCOS Society criteria; BMI = body mass index; BP = blood pressure; FDR = first degree relative; IDF = International Diabetes Federation; JNC = Joint National Committee; NCEP/ATP III = National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III; NICHD = National Institute of Child Health and Human Development criteria; OGTT = oral glucose tolerance test; PCOS = polycystic ovarian syndrome; WHO = World Health Organisation; WHR = Waist hip ratio

6. FINDINGS

- **EVIDENCE SUMMARY:**

All outcomes
31 studies were included in the systematic review and 27 in the meta-analysis. These consisted of 25 cross sectional and 6 cohort studies. One study was assessed as low risk of bias (Wang 2021), one study was assessed as high risk of bias (Lenarcik 2011) and all other studies were judged as moderate risk of bias.

Metabolic Syndrome
Six studies were suitable for meta-analysis for the outcome of metabolic syndrome in first degree relatives of women with PCOS. All studies were cross sectional studies. All studies were judged as moderate risk of bias (Baillargeon 2007; Coviello 2009; Karthik 2019; Kent 2008; Kulshreshtha 2019; Vipin 2016).

Obesity
Two studies were suitable for meta-analysis for the outcome of obesity in first degree relatives of women with PCOS (Harnois-Leblanc 2017; Sir Petermann 2012). One study was a cohort study (Harnois-Leblanc 2017), while the other was a cross sectional study (Sir Petermann 2012). All studies were judged as moderate risk of bias.

Hypertension
Two studies were suitable for meta-analysis for the outcome of hypertension in first degree relatives of women with PCOS (Kent 2008; Vipin 2016). All studies were cross sectional studies. All studies were judged as moderate risk of bias.

Diabetes
Three studies were suitable for meta-analysis for the outcome of diabetes in first degree relatives of women with PCOS (Kent 2008; Vipin 2016; Yilmaz 2005). All studies were cross sectional studies. All studies were judged as moderate risk of bias.

PCOS
Two studies were suitable for meta-analysis for the outcome of PCOS in first degree relatives of women with PCOS (Crisosto 2019; Karthik 2019).All studies were cross sectional studies. All studies were judged as moderate risk of bias.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

When compared to first degree relatives of normal control women, first degree relatives of women with PCOS were more likely to suffer from metabolic syndrome, hypertension, diabetes and PCOS. The quality of evidence for these outcomes were low due to the small number of studies resulting in serious imprecision, with exception of metabolic syndrome, which was of moderate quality due to larger numbers of studies.

On subgroup analysis, fathers of women with PCOS were more likely to suffer from metabolic syndrome, hypertension and diabetes, while mothers of women with PCOS were more likely to suffer from metabolic syndrome. Brothers of women with PCOS were more likely to suffer from metabolic syndrome but not sisters. Offspring of women with PCOS did not appear to have higher incidence of diabetes, obesity or metabolic syndrome. These analysis were moderate to low quality due to low numbers of participants and different ages and short follow-up times due to the cross sectional nature of a majority of the studies. Additionally, not all studies captured the outcome of diabetes and hypertension (particularly for siblings and children of women with PCOS). When analysing by subgroup, daughters and sisters of women with PCOS did not appear to be at risk of PCOS, however this was confounded by serious imprecision driven by very small numbers of participants.

In summary, more longitudinal studies with follow-up from infancy to adulthood are required to thoroughly capture the cardiometabolic risk for first degree relatives of women with PCOS.

7. GRADE ASSESSMENTS AND EVIDENCE PROFILE

Female first degree relatives versus normal controls[10]												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	FDR	Control	Effect, random [95% CI]	Results	Certainty	Importance
Outcome: BMI												
1	Observational	serious[11]	not applicable	serious indirectness	moderate imprecision	none	70	20	MD 0.10 [-0.88, 1.08]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Waist circumference												
1	Observational	serious[2]	not applicable	serious indirectness	serious imprecision	none	18	21	MD -4.00 [-10.26, 2.26]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Fasting glucose												
1	Observational	serious[2]	not applicable	serious indirectness	not serious imprecision	none	70	20	MD 0.70 [0.44, 0.96]	Higher in FDR vs control	⊕◯◯◯ VERY LOW	CRITICAL
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**FDR**	**Control**	**Effect, fixed [95% CI]**	**Results**	**Certainty**	**Importance**
Outcome: Obesity												
1	Observational	serious[2]	not applicable	serious indirectness	serious imprecision	none	8	8	OR 1.00 [0.10, 9.61]	No difference	⊕◯◯◯ VERY LOW	CRITICAL

Parents versus normal controls												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	FDR	Control	Effect, random [95% CI]	Results	Certainty	Importance
Outcome: Total cholesterol												
1	Observational	serious[2]	not applicable	serious indirectness	not serious imprecision	none	86	86	MD 0.23 [-0.07, 0.53]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Metabolic syndrome												
1	Observational	serious[2]	not applicable	serious indirectness	serious imprecision	none	86	86	OR 4.09 [2.17, 7.74]	Higher in FDR vs control	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Hypertension												

[10] Analysis of studies which report a female FDR cohort as a whole (not meta analysis combining daughters / mothers / sisters)
[11] Downgraded twice as majority of evidence is at very high risk of bias (inconsistency and indirectness because single study).

1	Observational	serious[2]	not applicable	serious indirectness	serious imprecision	none	86	86	OR 2.61 [1.15, 5.92]	Higher in FDR vs control	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Diabetes												
1	Observational	serious[2]	not applicable	serious indirectness	serious imprecision	none	86	86	OR 5.81 [1.89, 17.92]	Higher in FDR vs control	⊕◯◯◯ VERY LOW	CRITICAL

Fathers versus normal controls												
	Quality assessment						**No. participants**					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**FDR**	**Control**	**Effect, random [95% CI]**	**Results**	**Certainty**	**Importance**
Outcome: BMI												
1	Observational	serious[12]	not applicable	serious indirectness	moderate imprecision	none	211	1153	MD 3.20 [2.40, 4.00]	Higher in FDR vs control	⊕⊕◯◯ LOW	CRITICAL
Outcome: Weight												
1	Observational	serious[3]	not applicable	serious indirectness	moderate imprecision	none	211	1153	MD 11.00 [8.42, 13.58]	Higher in FDR vs control	⊕⊕◯◯ LOW	CRITICAL
Outcome: Waist circumference												
1	Observational	serious[3]	not applicable	serious indirectness	moderate imprecision	none	211	1153	MD 4.00 [1.99, 6.01]	Higher in FDR vs control	⊕⊕◯◯ LOW	CRITICAL
Outcome: Waist hip ratio												
2	Observational	serious[13]	serious inconsistency	serious indirectness	not serious imprecision	none	62	32	MD 0.02 [-0.05, 0.09]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Systolic blood pressure												
2	Observational	moderate[14]	serious	not serious	serious	none	249	1173	MD 6.40 [-	No difference	⊕⊕◯◯	CRITICAL

[12] Downgraded twice as majority of evidence is at very high risk of bias (inconsistency and indirectness because single study but large numbers).
[13] Downgraded twice as majority of evidence is at very high risk of bias (inconsistency because conflicting conclusions, indirectness because same country, similar age, one used NICHD, the other used Rotterdam, method if deriving control group not reported).
[14] Downgraded once as both evidence is at moderate risk of bias (inconsistency because conflicting conclusions, indirectness because two countries and multicentre, one used NHANES cohort which is a nationwide study as a control group hence upgraded, however overall low certainty as NHANES cohort used was in early 2000 where metabolic syndrome rates where lower).

			inconsistency	indirectness	imprecision				10.96, 23.76]		LOW	
Outcome: Diastolic blood pressure												
2	Observational	moderate[15]	not serious inconsistency	not serious indirectness	moderate imprecision	none	249	1173	MD 4.42 [-1.32, 10.15]	No difference	⊕⊕◯◯ VERY LOW	CRITICAL
Outcome: LDL												
1	Observational	serious[2]	not applicable	serious indirectness	not serious imprecision	none	38	20	MD 1.35 [1.01, 1.69]	Higher in FDR vs control	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: HDL												
1	Observational	serious[2]	not applicable	serious indirectness	not serious imprecision	none	38	20	MD -0.29 [-0.43, -0.15]	Lower in FDR vs control	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Triglycerides												
1	Observational	serious[2]	not applicable	serious indirectness	not serious imprecision	none	38	20	MD 0.67 [0.34, 1.00]	Higher in FDR vs control	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Total cholesterol												
2	Observational	serious[16]	serious inconsistency	moderate indirectness	moderate imprecision	none	79	62	MD 0.68 [-0.62, 1.97]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Metabolic syndrome												
2	Observational	moderate[17]	not serious inconsistency	moderate indirectness	moderate imprecision	none	252	1195	OR 1.76 [1.33, 2.34]	Higher in FDR vs control	⊕⊕◯◯ LOW	CRITICAL
Outcome: Hypertension												
1	Observational	serious[2]	not applicable	serious indirectness	serious imprecision	none	41	42	OR 4.19 [1.06, 16.56]	Higher in FDR vs control	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Diabetes												

[15] Downgraded once as both evidence is at moderate risk of bias (inconsistency because similar conclusions between studies, confidence intervals relatively narrow, indirectness because two countries and multicentre, one used NHANES cohort which is a nationwide study as a control group hence upgraded, however overall low certainty as NHANES cohort used was in early 2000 where metabolic syndrome rates where lower). .

[16] Downgraded twice as majority of evidence is at very high risk of bias (inconsistency because one study showed no difference while the other showed higher TG in FDR, indirectness because 2 countries, difference PCOS criteria used, similar age of fathers)

[17] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because similar conclusions, indirectness because two countries and multicentre, one used NHANES cohort which is a nationwide study as a control group hence upgraded, however overall low certainty as NHANES cohort used was in early 2000 where metabolic syndrome rates where lower)

2	Observational	serious[2]	not applicable	serious indirectness	serious imprecision	none	79	62	OR 14.54 [2.83, 74.71]	Higher in FDR vs control	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Impaired fasting glucose												
1	Observational	serious[2]	not applicable	serious indirectness	serious imprecision	none	38	20	OR 1.06 [0.09, 12.40]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Impaired glucose tolerance												
1	Observational	serious[2]	not applicable	serious indirectness	serious imprecision	none	38	20	OR 6.79 [0.80, 57.48]	No difference	⊕◯◯◯ VERY LOW	CRITICAL

Mothers versus normal controls												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	FDR	Control	Effect, random [95% CI]	Results	Certainty	Importance
Outcome: Waist circumference												
1	Observational	serious[3]	not applicable	serious indirectness	moderate imprecision	none	215	62	MD 3.00 [-1.30, 7.30]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Waist hip ratio												
3	Observational	moderate[18]	not serious inconsistency	moderate indirectness	not serious imprecision	none	119	88	MD 0.05 [0.03, 0.07]	Higher in FDR vs control	⊕⊕◯◯ LOW	CRITICAL
Outcome: Systolic blood pressure												
3	Observational	moderate[19]	not serious inconsistency	not serious indirectness	moderate imprecision	none	300	126	MD 8.49 [2.97, 14.01]	Higher in FDR vs control	⊕⊕◯◯ LOW	CRITICAL
Outcome: Diastolic blood pressure												
2	Observational	serious[20]	moderate inconsistency	moderate indirectness	moderate imprecision	none	255	82	MD 4.38 [-4.57, 13.33]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Fasting glucose												

[18] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because all studies had the same conclusion, indirectness because 2 countries involved, NICHD/Rotterdam criteria used, Turkish studies did not describe method of deriving control cohort)
[19] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because studies have the same conclusion, indirectness because 3 countries, different PCOS criteria used, however control group method of derivation not described)
[20] Downgraded twice as majority of evidence is at very high risk of bias (inconsistency because one study reported no difference while the other smaller study reported higher dBP, indirectness because 2 different countries, different criteria for PCOS used, mothers similar age, method of deriving control group not described)

1	Observational	serious[3]	not applicable	serious indirectness	not serious imprecision	none	215	62	MD 0.40 [0.20, 0.60]	Higher in FDR vs control	⊕⊕◯◯ LOW	CRITICAL
Outcome: LDL												
3	Observational	moderate[21]	moderate inconsistency	not serious indirectness	not serious imprecision	none	300	126	MD 0.62 [0.26, 0.98]	Higher in FDR vs control	⊕⊕◯◯ LOW	CRITICAL
Outcome: HDL												
2	Observational	serious[22]	not serious inconsistency	moderate indirectness	not serious imprecision	none	255	82	MD -0.01 [-0.12, 0.10]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Triglycerides												
2	Observational	serious[23]	not serious inconsistency	moderate indirectness	not serious imprecision	none	255	82	MD 0.44 [0.22, 0.66]	Higher in FDR vs control	⊕⊕◯◯ LOW	CRITICAL
Outcome: Total cholesterol												
3	Observational	moderate[24]	moderate inconsistency	not serious indirectness	not serious imprecision	none	300	126	MD 0.77 [0.33, 1.21]	Higher in FDR vs control	⊕⊕◯◯ LOW	CRITICAL
Outcome: Metabolic syndrome												
1	Observational	serious[2]	not applicable	serious indirectness	serious imprecision	none	45	44	OR 3.24 [1.35, 7.80]	Higher in FDR vs control	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Hypertension												
1	Observational	serious[2]	not applicable	serious indirectness	serious imprecision	none	45	44	OR 1.92 [0.68, 5.46]	No difference	⊕◯◯◯ VERY LOW	CRITICAL

[21] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because studies have the same conclusion but I^2 76%, indirectness because 3 countries, different PCOS criteria used, however control group method of derivation not described) (inconsistency because studies have the same conclusion, indirectness because 3 countries, different PCOS criteria used, however control group method of derivation not described)

[22] Downgraded twice as majority of evidence is at very high risk of bias (inconsistency because one study reported no difference while the other smaller study reported lower HDL but I^2 0%, indirectness because 2 different countries, different criteria for PCOS used, mothers similar age, method of deriving control group not described)

[23] Downgraded twice as majority of evidence is at very high risk of bias (inconsistency because similar conclusions, indirectness because 2 different countries, different criteria for PCOS used, mothers similar age, method of deriving control group not described)

[24] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because similar conclusions, but I2 76% indirectness because 2 different countries, different criteria for PCOS used, mothers similar age, method of deriving control group not described)

Outcome: Diabetes												
2	Observational	serious[25]	not serious inconsistency	moderate indirectness	serious imprecision	none	85	64	OR 1.90 [0.62, 5.85]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Impaired fasting glucose												
1	Observational	serious[2]	not applicable	serious indirectness	serious imprecision	none	40	20	OR 2.66 [0.12, 58.12]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Impaired glucose tolerance												
1	Observational	serious[2]	not applicable	serious indirectness	serious imprecision	none	40	20	OR 1.91 [0.36, 10.17]	No difference	⊕◯◯◯ VERY LOW	CRITICAL

Brothers versus normal controls												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	FDR	Control	Effect, random [95% CI]	Results	Certainty	Importance
Outcome: Waist circumference												
2	Observational	serious[26]	serious inconsistency	moderate indirectness	serious imprecision	none	213	197	MD -0.25 [-6.95, 6.45]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Waist hip ratio												
4	Observational	moderate[27]	not serious inconsistency	not serious indirectness	not serious imprecision	none	133	108	MD 0.00 [-0.02, 0.02]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Systolic blood pressure												
3	Observational	moderate[28]	not serious inconsistency	not serious indirectness	not serious imprecision	none	230	212	MD 2.01 [-0.48, 4.50]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Diastolic blood pressure												

[25] Downgraded twice as majority of evidence is at very high risk of bias (inconsistency because both studies showed no difference, indirectness because 2 different countries, similar criteria for PCOS, similar age of mothers, method of deriving control group not described for one study)
[26] Downgraded twice as majority of evidence is at very high risk of bias (inconsistency - both studies had different conclusions, indirectness because USA/Canada, both NICHD criteria, age similar)
[27] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I2 0% similar conclusions, indirectness because multiple countries, different PCOS criteria, broad range of ages)
[28] Downgraded once as the majority of evidence is at moderate (inconsistency because I2 0% similar conclusions, indirectness because multiple countries, different PCOS criteria, broad range of ages)

4	Observational	moderate[29]	moderate inconsistency	not serious indirectness	not serious imprecision	none	271	253	MD 2.61 [0.79, 4.44]	Higher in FDR vs control	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Fasting glucose												
6	Observational	moderate[30]	serious inconsistency	not serious indirectness	not serious imprecision	none	340	314	MD 0.14 [-0.10, 0.39]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: OGTT - 2 hour glucose												
2	Observational	serious[31]	moderate inconsistency	moderate indirectness	moderate imprecision	none	59	58	MD 1.40 [0.07, 2.74]	Higher in FDR vs control	⊕⊕◯◯ LOW	CRITICAL
Outcome: LDL												
5	Observational	moderate[32]	moderate inconsistency	not serious indirectness	not serious imprecision	none	140	139	MD 0.28 [0.03, 0.53]	Higher in FDR vs control	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: HDL												
5	Observational	moderate[33]	moderate inconsistency	not serious indirectness	not serious imprecision	none	140	139	MD -0.03 [-0.13, 0.07]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Triglycerides												
3	Observational	serious[34]	serious inconsistency	not serious indirectness	not serious imprecision	none	83	71	MD 0.38 [-0.05, 0.81]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Total cholesterol												
3	Observational	serious[35]	serious inconsistency	not serious indirectness	moderate imprecision	none	83	71	MD 0.69 [0.11, 1.27]	Higher in FDR vs control	⊕⊕◯◯ LOW	CRITICAL

[29] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I2 24% slightly dissimilar conclusions, indirectness because multiple countries, different PCOS criteria, broad range of ages)
[30] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I2 85% slightly dissimilar conclusions, indirectness because multiple countries, different PCOS criteria, broad range of ages)
[31] Downgraded twice as majority of evidence is at very high risk of bias (inconsistency because I2 89% but similar conclusions, indirectness because different countries, different PCOS criteria, small numbers however)
[32] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I2 52% slightly dissimilar conclusions, indirectness because multiple countries, different PCOS criteria, broad range of ages)
[33] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I2 48% slightly dissimilar conclusions, indirectness because two countries, similar PCOS criteria, broad range of ages but small numbers)
[34] Downgraded twice as majority of evidence is at very high risk of bias (inconsistency because I2 81% slightly dissimilar conclusions, indirectness because multiple countries, different PCOS criteria, broad range of ages)
[35] Downgraded twice as majority of evidence is at very high risk of bias (inconsistency because I2 77% slightly dissimilar conclusions, indirectness because multiple countries, different PCOS criteria, broad range of ages)

Outcome: Metabolic syndrome												
2	Observational	serious[36]	not serious inconsistency	moderate indirectness	serious imprecision	none	58	69	OR 5.14 [1.57, 16.91]	Higher in FDR vs control	⊕⊕◯◯ LOW	CRITICAL
Outcome: Impaired fasting glucose												
1	Observational	serious[2]	not applicable	serious indirectness	serious imprecision	none	41	41	OR 1.59 [0.41, 6.10]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Impaired glucose tolerance												
1	Observational	serious[2]	not applicable	serious indirectness	serious imprecision	none	17	28	OR 13.76 [0.66, 284.73]	No difference	⊕◯◯◯ VERY LOW	CRITICAL

Sisters versus normal controls												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	FDR	Control	Effect, random [95% CI]	Results	Certainty	Importance
Outcome: BMI												
3[37]	Observational	moderate[38]	no serious inconsistency	no serious indirectness	no serious imprecision	none	419	195	MD 0.82 [0.14, 1.49]	Higher in FDR vs control	⊕⊕⊕◯ MODERATE	CRITICAL
3[39]	Observational	serious[40]	no serious inconsistency	no serious indirectness	no serious imprecision	none	327	195	MD 0.55 [-0.13, 1.24]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Waist circumference												

[36] Downgraded twice as majority of evidence is at very high risk of bias (inconsistency because I2 0% similar conclusions, indirectness because multiple countries, different PCOS criteria, broad range of ages but small numbers)
[37] Joharatnam 2011 - subgroup with polycystic ovaries (duplicate control group)
[38] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I2 0% similar conclusions, indirectness because multiple countries, similar PCOS criteria, broad range of ages)
[39] Joharatnam 2011 - subgroup without polycystic ovaries (duplicate control group)
[40] Downgraded twice as majority of evidence is at very high risk of bias (inconsistency because I2 0% similar conclusions, indirectness because multiple countries, similar PCOS criteria, broad range of ages)

1[41]	Observational	serious[2]	not applicable	serious indirectness	serious imprecision	none	38	125	MD -4.00 [-9.53, 1.53]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
1[42]	Observational	serious[3]	not applicable	serious indirectness	serious imprecision	none	143	125	MD -9.00 [-12.52, -5.48]	Lower in FDR group	⊕⊕◯◯ LOW	CRITICAL
Outcome: Waist hip ratio												
7[43]	Observational	moderate[44]	moderate inconsistency	not serious indirectness	not serious imprecision	none	493	351	MD -0.00 [-0.01, 0.01]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
7[45]	Observational	moderate[46]	moderate inconsistency	not serious indirectness	not serious imprecision	none	401	351	MD -0.00 [-0.01, 0.01]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Systolic blood pressure												
3[47]	Observational	moderate[48]	not serious inconsistency	serious indirectness	not serious imprecision	none	263	244	MD 0.32 [-1.42, 2.05]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
3[49]	Observational	moderate[50]	not serious inconsistency	serious indirectness	serious imprecision	none	368	244	MD -0.44 [-2.05, 1.16]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL

[41] Sam 2005 subgroup with hyperandrogenism (duplicated control group)
[42] Sam 2005 subgroup without PCOS features (duplicated control group)
[43] Joharatnam 2011 - subgroup with polycystic ovaries (duplicate control group)
[44] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I2 51% slightly dissimilar conclusions, indirectness because multiple countries, multiple PCOS criteria, broad range of ages)
[45] Joharatnam 2011 - subgroup without polycystic ovaries (duplicate control group)
[46] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I2 50% slightly dissimilar conclusions, indirectness because multiple countries, multiple PCOS criteria, broad range of ages)
[47] Sam 2005 subgroup with hyperandrogenism (duplicated control group)
[48] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I2 0% similar conclusions, indirectness because multiple countries, multiple PCOS criteria, broad range of ages)
[49] Sam 2005 subgroup without PCOS features (duplicated control group)
[50] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I2 0% similar conclusions, indirectness because multiple countries, multiple PCOS criteria, broad range of ages)

Outcome: Diastolic blood pressure											
4[51]	Observational	moderate[52]	moderate inconsistency	not serious indirectness	not serious imprecision	none	298	279	MD 0.26 [-1.32, 1.83]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
4[53]	Observational	moderate[54]	serious inconsistency	not serious indirectness	not serious imprecision	none	403	279	MD -0.18 [-2.49, 2.12]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Fasting glucose											
5[55]	Observational	moderate[56]	serious inconsistency	not serious indirectness	not serious imprecision	none	365	334	MD 0.15 [-0.14, 0.44]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
5[57]	Observational	moderate[58]	serious inconsistency	not serious indirectness	not serious imprecision	none	470	334	MD 0.18 [-0.10, 0.45]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: OGTT - 2 hour glucose											
3	Observational	moderate[59]	not serious inconsistency	moderate indirectness	not serious imprecision	none	279	204	MD 0.30 [0.02, 0.57]	Higher in FDR vs control	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: LDL											

[51] Sam 2005 subgroup with hyperandrogenism (duplicated control group)
[52] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I2 24% similar conclusions, indirectness because multiple countries, multiple PCOS criteria, broad range of ages)
[53] Sam 2005 subgroup without PCOS features (duplicated control group)
[54] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I2 66% dissimilar conclusions, indirectness because multiple countries, multiple PCOS criteria, broad range of ages)
[55] Sam 2005 subgroup with hyperandrogenism (duplicated control group)
[56] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I2 94% dissimilar conclusions, indirectness because multiple countries, multiple PCOS criteria, broad range of ages)
[57] Sam 2005 subgroup without PCOS features (duplicated control group)
[58] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I2 95% dissimilar conclusions, indirectness because multiple countries, multiple PCOS criteria, broad range of ages)
[59] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I2 0% similar conclusions, indirectness because two countries, similar PCOS criteria, similar range of ages)

5[60]	Observational	moderate[61]	serious inconsistency	not serious indirectness	not serious imprecision	none	439	285	MD 0.06 [-0.15, 0.27]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
5[62]	Observational	moderate[63]	serious inconsistency	not serious indirectness	not serious imprecision	none	347	285	MD 0.02 [-0.14, 0.19]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: HDL												
6[64]	Observational	moderate[65]	not serious inconsistency	not serious indirectness	not serious imprecision	none	474	320	MD 0.03 [-0.01, 0.06]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
6[66]	Observational	moderate[67]	moderate inconsistency	not serious indirectness	not serious imprecision	none	382	320	MD 0.04 [-0.01, 0.09]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Triglycerides												
6[68]	Observational	moderate[69]	moderate inconsistency	not serious indirectness	not serious imprecision	none	474	320	MD 0.05 [-0.03, 0.13]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL

[60] Joharatnam 2011 - subgroup with polycystic ovaries (duplicate control group)
[61] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I2 82% dissimilar conclusions, indirectness because multiple countries, multiple PCOS criteria, broad range of ages)
[62] Joharatnam 2011 - subgroup without polycystic ovaries (duplicate control group)
[63] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I2 70% dissimilar conclusions, indirectness because multiple countries, multiple PCOS criteria, broad range of ages)
[64] Joharatnam 2011 - subgroup with polycystic ovaries (duplicate control group)
[65] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I2 6% similar conclusions, indirectness because multiple countries, multiple PCOS criteria, broad range of ages)
[66] Joharatnam 2011 - subgroup without polycystic ovaries (duplicate control group)
[67] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I2 40% slightly dissimilar conclusions, indirectness because multiple countries, multiple PCOS criteria, broad range of ages)
[68] Joharatnam 2011 - subgroup with polycystic ovaries (duplicate control group)
[69] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I2 69% dissimilar conclusions, indirectness because multiple countries, multiple PCOS criteria, broad range of ages)

6[70]	Observational	moderate[71]	serious inconsistency	serious indirectness	not serious imprecision	none	382	320	MD 0.03 [-0.06, 0.12]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Total cholesterol												
5[72]	Observational	moderate[73]	moderate inconsistency	not serious indirectness	not serious imprecision	none	439	285	MD 0.20 [-0.00, 0.40]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
5[74]	Observational	moderate[75]	moderate inconsistency	not serious indirectness	not serious imprecision	none	347	285	MD 0.19 [-0.01, 0.39]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Metabolic syndrome												
2	Observational	serious[76]	moderate inconsistency	serious indirectness	serious imprecision	none	235	134	OR 0.94 [0.56, 1.58]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Impaired fasting glucose												
1	Observational	serious[2]	not applicable	serious indirectness	serious imprecision	none	35	35	OR 1.00 [0.13, 7.53]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: PCOS												
1	Observational	serious[2]	not applicable	serious indirectness	serious imprecision	none	35	35	OR 10.14 [0.53, 195.91]	No difference	⊕◯◯◯ VERY LOW	CRITICAL

[70] Joharatnam 2011 - subgroup without polycystic ovaries (duplicate control group)
[71] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I2 74% dissimilar conclusions, indirectness because multiple countries, multiple PCOS criteria, broad range of ages)
[72] Joharatnam 2011 - subgroup with polycystic ovaries (duplicate control group)
[73] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I2 75% dissimilar conclusions, indirectness because multiple countries, multiple PCOS criteria, broad range of ages)
[74] Joharatnam 2011 - subgroup without polycystic ovaries (duplicate control group)
[75] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I2 74% dissimilar conclusions, indirectness because multiple countries, multiple PCOS criteria, broad range of ages)
[76] Downgraded twice as majority of evidence is at very high risk of bias (inconsistency because I2 23% slightly dissimilar conclusions, indirectness because single country, similar PCOS criteria, similar control group, similar study design)

All offspring versus normal controls												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	FDR	Control	Effect, random [95% CI]	Results	Certainty	Importance
Outcome: BMI												
3[77]	Observational	moderate[78]	serious inconsistency	moderate indirectness	not serious imprecision	none	301	641	MD -0.33 [-0.80, 0.13]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
3[79]	Observational	moderate	serious inconsistency	moderate indirectness	not serious imprecision	none	301	641	MD -0.32 [-0.82, 0.17]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
3[80]	Observational	moderate	serious inconsistency	moderate indirectness	not serious imprecision	none	301	641	MD -0.32 [-0.82, 0.18]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
3[81]	Observational	moderate	serious inconsistency	moderate indirectness	not serious imprecision	none	301	641	MD -0.32 [-0.84, 0.21]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
3[82]	Observational	moderate	serious inconsistency	moderate indirectness	not serious imprecision	none	301	641	MD -0.32 [-0.83, 0.19]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
3[83]	Observational	moderate	serious inconsistency	moderate indirectness	not serious imprecision	none	301	641	MD -0.34 [-0.79, 0.11]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL

[77] Zhang 2022 - age 3 months
[78] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I2 >70% dissimilar conclusions, indirectness because two countries, similar PCOS criteria, broad range of ages, method of control group defined)
[79] Zhang 2022 - age 6 months
[80] Zhang 2022 - age 8 months
[81] Zhang 2022 - age 12 months
[82] Zhang 2022 - age 18 months
[83] Zhang 2022 - age 24 months

3[84]	Observational	moderate	serious inconsistency	moderate indirectness	not serious imprecision	none	301	641	MD -0.35 [-0.77, 0.08]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
3[85]	Observational	moderate	serious inconsistency	moderate indirectness	not serious imprecision	none	301	641	MD -0.35 [-0.76, 0.06]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
3[86]	Observational	moderate	serious inconsistency	moderate indirectness	not serious imprecision	none	301	641	MD -0.32 [-0.81, 0.16]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
3[87]	Observational	moderate	serious inconsistency	moderate indirectness	not serious imprecision	none	301	641	MD -0.30 [-0.83, 0.22]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
3[88]	Observational	moderate	serious inconsistency	moderate indirectness	not serious imprecision	none	301	641	MD -0.30 [-0.83, 0.22]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Weight												
2[89]	Observational	serious[90]	serious inconsistency	moderate indirectness	moderate imprecision	none	272	525	MD -1.48 [-3.22, 0.26]	No difference	⊕⊕◯◯ LOW	CRITICAL
2[91]	Observational	serious	serious inconsistency	moderate indirectness	moderate imprecision	none	272	525	MD -1.48 [-3.23, 0.27]	No difference	⊕⊕◯◯ LOW	CRITICAL
2[92]	Observational	serious	serious inconsistency	moderate indirectness	moderate imprecision	none	272	525	MD -1.47 [-3.25, 0.32]	No difference	⊕⊕◯◯ LOW	CRITICAL
2[93]	Observational	serious	serious inconsistency	moderate indirectness	moderate imprecision	none	272	525	MD -1.45 [-3.28, 0.38]	No difference	⊕⊕◯◯ LOW	CRITICAL

[84] Zhang 2022 - age 30 months
[85] Zhang 2022 - age 3 years
[86] Zhang 2022 - age 4 years
[87] Zhang 2022 - age 5 years
[88] Zhang 2022 - age 6 years
[89] Zhang 2022 - age 3 months
[90] Downgraded twice as majority of evidence is at very high risk of bias (inconsistency because I2 >90% dissimilar conclusions, indirectness because two countries, similar PCOS criteria, broad range of ages, method of control group defined)
[91] Zhang 2022 - age 6 months
[92] Zhang 2022 - age 8 months
[93] Zhang 2022 - age 12 months

2[94]	Observational	serious	serious inconsistency	moderate indirectness	moderate imprecision	none	272	525	MD -1.47 [-3.26, 0.33]	No difference	⊕⊕◯◯ LOW	CRITICAL
2[95]	Observational	serious	serious inconsistency	moderate indirectness	moderate imprecision	none	272	525	MD -1.47 [-3.26, 0.32]	No difference	⊕⊕◯◯ LOW	CRITICAL
2[96]	Observational	serious	serious inconsistency	moderate indirectness	moderate imprecision	none	272	525	MD -1.46 [-3.29, 0.37]	No difference	⊕⊕◯◯ LOW	CRITICAL
2[97]	Observational	serious	serious inconsistency	moderate indirectness	moderate imprecision	none	272	525	MD -1.44 [-3.32, 0.45]	No difference	⊕⊕◯◯ LOW	CRITICAL
2[98]	Observational	serious	serious inconsistency	moderate indirectness	moderate imprecision	none	272	525	MD -1.40 [-3.40, 0.59]	No difference	⊕⊕◯◯ LOW	CRITICAL
2[99]	Observational	serious	serious inconsistency	moderate indirectness	moderate imprecision	none	272	525	MD -1.33 [-3.54, 0.87]	No difference	⊕⊕◯◯ LOW	CRITICAL
2[100]	Observational	serious	serious inconsistency	moderate indirectness	moderate imprecision	none	272	525	MD -1.37 [-3.53, 0.80]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Weight z score												
1	Observational	serious[2]	not applicable	serious indirectness	serious imprecision	none	70	71	MD -0.40 [-0.75, -0.05]	Lower in FDR vs control	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Waist circumference												
1	Observational	serious[3]	not applicable	serious indirectness	serious imprecision	none	74	298	MD -2.54 [-4.69, -0.38]	Lower in FDR vs control	⊕⊕◯◯ LOW	CRITICAL
Outcome: Systolic blood pressure												
1	Observational	serious[3]	not applicable	serious indirectness	not serious imprecision	none	63	265	MD -1.54 [-3.39, 0.30]	No difference	⊕⊕◯◯ LOW	CRITICAL

[94] Zhang 2022 - age 18 months
[95] Zhang 2022 - age 24 months
[96] Zhang 2022 - age 30 months
[97] Zhang 2022 - age 3 years
[98] Zhang 2022 - age 4 years
[99] Zhang 2022 - age 5 years
[100] Zhang 2022 - age 6 years

Outcome: Diastolic blood pressure											
1	Observational	serious[3]	not applicable	serious indirectness	not serious imprecision	none	63	265	MD -0.51 [-3.45, 2.43]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Fasting glucose											
2	Observational	moderate[101]	not serious inconsistency	moderate indirectness	not serious imprecision	none	137	625	MD 0.04 [-0.04, 0.12]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: LDL											
2	Observational	moderate[102]	not serious inconsistency	moderate indirectness	not serious imprecision	none	137	625	MD -0.02 [-0.14, 0.09]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: HDL											
2	Observational	moderate[103]	not serious inconsistency	moderate indirectness	not serious imprecision	none	137	625	MD 0.03 [-0.02, 0.08]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Triglycerides											
2	Observational	moderate[104]	serious inconsistency	moderate indirectness	not serious imprecision	none	137	625	MD 0.10 [-0.07, 0.28]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Total cholesterol											
2	Observational	serious[105]	moderate inconsistency	moderate indirectness	not serious imprecision	none	137	625	MD 0.14 [-0.27, 0.54]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Metabolic syndrome											

[101] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I2 0% similar conclusions, indirectness because two countries, similar PCOS criteria, broad range of ages, method of control group defined, majority of numbers came from one study)
[102] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I2 0% similar conclusions, indirectness because two countries, similar PCOS criteria, broad range of ages, method of control group defined, majority of numbers came from one study)
[103] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I2 0% similar conclusions, indirectness because two countries, similar PCOS criteria, broad range of ages, method of control group defined, majority of numbers came from one study)
[104] Downgraded twice as majority of evidence is at very high risk of bias (inconsistency because I2 87% dissimilar conclusions, indirectness because two countries, similar PCOS criteria, broad range of ages, method of control group defined, majority of numbers came from one study)
[105] Downgraded twice as majority of evidence is at very high risk of bias (inconsistency because I2 44% slightly dissimilar conclusions, indirectness because two countries, similar PCOS criteria, broad range of ages, method of control group defined, majority of numbers came from one study)

1	Observational	serious[2]	not applicable	serious indirectness	serious imprecision	none	15	12	OR 5.50 [0.55, 55.49]	No difference	⨁◯◯◯ VERY LOW	CRITICAL
Outcome: Hypertension												
1	Observational	serious[2]	not applicable	serious indirectness	serious imprecision	none	32	28	OR 1.36 [0.44, 4.25]	No difference	⨁◯◯◯ VERY LOW	CRITICAL

Daughters versus normal controls												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	FDR	Control	Effect, random [95% CI]	Results	Certainty	Importance
Outcome: BMI												
3[106]	Observational	moderate[107]	not serious inconsistency	not serious indirectness	not serious imprecision	none	318	284	MD 0.38 [0.10, 0.66]	Higher in FDR vs control	⨁⨁⨁◯ MODERATE	CRITICAL
3[108]	Observational	moderate	not serious inconsistency	not serious indirectness	not serious imprecision	none	318	284	MD 0.27 [-0.04, 0.57]	No difference	⨁⨁⨁◯ MODERATE	CRITICAL
3[109]	Observational	moderate	not serious inconsistency	not serious indirectness	not serious imprecision	none	318	284	MD 0.36 [0.05, 0.67]	Higher in FDR vs control	⨁⨁⨁◯ MODERATE	CRITICAL
3[110]	Observational	moderate	not serious inconsistency	not serious indirectness	not serious imprecision	none	318	284	MD 0.32 [0.05, 0.60]	Higher in FDR vs control	⨁⨁⨁◯ MODERATE	CRITICAL
3[111]	Observational	moderate	not serious inconsistency	not serious indirectness	not serious imprecision	none	318	284	MD 0.19 [-0.06, 0.45]	No difference	⨁⨁⨁◯ MODERATE	CRITICAL

[106] Zhang 2022 - age 3 months
[107] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I2 0% similar conclusions, indirectness because three countries, different PCOS criteria, broad range of ages)
[108] Zhang 2022 - age 6 months
[109] Zhang 2022 - age 8 months
[110] Zhang 2022 - age 12 months
[111] Zhang 2022 - age 18 months

3[112]	Observational	moderate	not serious inconsistency	not serious indirectness	not serious imprecision	none	318	284	MD 0.16 [-0.11, 0.42]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
3[113]	Observational	moderate	not serious inconsistency	not serious indirectness	not serious imprecision	none	318	284	MD 0.12 [-0.13, 0.37]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
3[114]	Observational	moderate	not serious inconsistency	not serious indirectness	not serious imprecision	none	318	284	MD 0.16 [-0.11, 0.43]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
3[115]	Observational	moderate	not serious inconsistency	not serious indirectness	not serious imprecision	none	318	284	MD 0.35 [0.04, 0.66]	Higher in FDR vs control	⊕⊕⊕◯ MODERATE	CRITICAL
3[116]	Observational	moderate	not serious inconsistency	not serious indirectness	not serious imprecision	none	318	284	MD 0.37 [0.02, 0.73]	Higher in FDR vs control	⊕⊕⊕◯ MODERATE	CRITICAL
3[117]	Observational	moderate	not serious inconsistency	not serious indirectness	not serious imprecision	none	318	284	MD 0.38 [-0.01, 0.77]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: BMI z score												
1	Observational	serious[3]	not applicable	serious indirectness	not serious imprecision	none	135	93	MD 0.01 [-0.22, 0.23]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Weight												
2[118]	Observational	moderate[119]	not serious inconsistency	moderate indirectness	not serious imprecision	none	243	202	MD 0.18 [0.02, 0.34]	Higher in FDR vs control	⊕⊕◯◯ LOW	CRITICAL
2[120]	Observational	moderate	not serious inconsistency	serious indirectness	not serious imprecision	none	243	202	MD 0.17 [-0.04, 0.38]	No difference	⊕⊕◯◯ LOW	CRITICAL

[112] Zhang 2022 - age 24 months
[113] Zhang 2022 - age 30 months
[114] Zhang 2022 - age 3 years
[115] Zhang 2022 - age 4 years
[116] Zhang 2022 - age 5 years
[117] Zhang 2022 - age 6 years
[118] Zhang 2022 - age 3 months
[119] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I2 0% similar conclusions, indirectness because two countries, different PCOS criteria, broad range of ages, method of control group derivation not defined in one study)
[120] Zhang 2022 - age 6 months

2[121]	Observational	moderate	not serious inconsistency	serious indirectness	not serious imprecision	none	243	202	MD 0.29 [0.05, 0.52]	Higher in FDR vs control	⨁⨁◯◯ LOW	CRITICAL
2[122]	Observational	moderate	not serious inconsistency	serious indirectness	not serious imprecision	none	243	202	MD 0.30 [0.06, 0.55]	Higher in FDR vs control	⨁⨁◯◯ LOW	CRITICAL
2[123]	Observational	moderate	not serious inconsistency	serious indirectness	not serious imprecision	none	243	202	MD 0.26 [-0.01, 0.54]	No difference	⨁⨁◯◯ LOW	CRITICAL
2[124]	Observational	moderate	not serious inconsistency	serious indirectness	not serious imprecision	none	243	202	MD 0.21 [-0.11, 0.53]	No difference	⨁⨁◯◯ LOW	CRITICAL
2[125]	Observational	moderate	not serious inconsistency	serious indirectness	not serious imprecision	none	243	202	MD 0.30 [-0.06, 0.65]	No difference	⨁⨁◯◯ LOW	CRITICAL
2[126]	Observational	moderate	not serious inconsistency	serious indirectness	not serious imprecision	none	243	202	MD 0.41 [0.03, 0.80]	Higher in FDR vs control	⨁⨁◯◯ LOW	CRITICAL
2[127]	Observational	moderate	not serious inconsistency	serious indirectness	not serious imprecision	none	243	202	MD 0.47 [-0.04, 0.97]	No difference	⨁⨁◯◯ LOW	CRITICAL
2[128]	Observational	moderate	not serious inconsistency	serious indirectness	not serious imprecision	none	243	202	MD 0.69 [0.01, 1.38]	Higher in FDR vs control	⨁⨁◯◯ LOW	CRITICAL
2[129]	Observational	moderate	not serious inconsistency	serious indirectness	not serious imprecision	none	243	202	MD 0.75 [-0.07, 1.56]	No difference	⨁⨁◯◯ LOW	CRITICAL
Outcome: Weight z score												

[121] Zhang 2022 - age 8 months
[122] Zhang 2022 - age 12 months
[123] Zhang 2022 - age 18 months
[124] Zhang 2022 - age 24 months
[125] Zhang 2022 - age 30 months
[126] Zhang 2022 - age 3 years
[127] Zhang 2022 - age 4 years
[128] Zhang 2022 - age 5 years
[129] Zhang 2022 - age 6 years

2	Observational	serious[130]	moderate inconsistency	moderate indirectness	not serious imprecision	none	156	129	MD 0.09 [-0.18, 0.37]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Waist circumference												
1	Observational	serious[2]	not applicable	serious indirectness	moderate imprecision	none	135	93	MD 0.01 [-2.10, 2.12]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Waist hip ratio												
1	Observational	serious[2]	not applicable	serious indirectness	moderate imprecision	none	75	79	MD 0.03 [0.00, 0.05]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Systolic blood pressure												
1	Observational	serious[2]	not applicable	serious indirectness	moderate imprecision	none	74	81	MD -0.87 [-4.73, 2.99]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Diastolic blood pressure												
1	Observational	serious[2]	not applicable	serious indirectness	moderate imprecision	none	74	81	MD 0.29 [-2.03, 2.62]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Fasting glucose												
1	Observational	serious[3]	not applicable	serious indirectness	not serious imprecision	none	135	93	MD -0.13 [-0.39, 0.12]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: OGTT - 2 hour glucose												
1	Observational	serious[3]	not applicable	serious indirectness	not serious imprecision	none	135	93	MD 0.18 [-0.12, 0.48]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Obesity												
1	Observational	serious[3]	not applicable	serious indirectness	serious imprecision	none	135	93	OR 1.23 [0.49, 3.06]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: PCOS												
1	Observational	serious[2]	not applicable	serious indirectness	serious imprecision	none	43	28	OR 11.71 [0.64, 213.79]	No difference	⊕◯◯◯ VERY LOW	CRITICAL

[130] Downgraded twice as majority of evidence is at very high risk of bias (inconsistency because I2 37% slightly dissimilar conclusions, indirectness because two countries, similar PCOS criteria, broad range of ages, method of control group derivation not defined in one study, most numbers from one study)

Sons versus normal controls												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	FDR	Control	Effect, random [95% CI]	Results	Certainty	Importance
Outcome: BMI												
2[131]	Observational	serious[132]	not serious inconsistency	serious indirectness	not serious imprecision	none	105	135	MD -0.01 [-0.37, 0.35]	No difference	⊕⊕◯◯ LOW	CRITICAL
2[133]	Observational	serious	not serious inconsistency	serious indirectness	not serious imprecision	none	105	135	MD 0.22 [-0.13, 0.56]	No difference	⊕⊕◯◯ LOW	CRITICAL
2[134]	Observational	serious	not serious inconsistency	serious indirectness	not serious imprecision	none	105	135	MD 0.11 [-0.21, 0.42]	No difference	⊕⊕◯◯ LOW	CRITICAL
2[135]	Observational	serious	not serious inconsistency	serious indirectness	not serious imprecision	none	105	135	MD 0.20 [-0.09, 0.50]	No difference	⊕⊕◯◯ LOW	CRITICAL
2[136]	Observational	serious	not serious inconsistency	serious indirectness	not serious imprecision	none	105	135	MD 0.30 [0.03, 0.56]	Higher in FDR vs control	⊕⊕◯◯ LOW	CRITICAL
2[137]	Observational	serious	not serious inconsistency	serious indirectness	not serious imprecision	none	105	135	MD 0.17 [-0.10, 0.44]	No difference	⊕⊕◯◯ LOW	CRITICAL
2[138]	Observational	serious	not serious inconsistency	serious indirectness	not serious imprecision	none	105	135	MD 0.14 [-0.15, 0.43]	No difference	⊕⊕◯◯ LOW	CRITICAL

[131] Zhang 2022 - age 3 months
[132] Downgraded twice as majority of evidence is at very high risk of bias (inconsistency because I2 0% similar conclusions, indirectness because two countries, similar PCOS criteria, broad range of ages, method of control group derivation not defined, most numbers from one study)
[133] Zhang 2022 - age 6 months
[134] Zhang 2022 - age 8 months
[135] Zhang 2022 - age 12 months
[136] Zhang 2022 - age 18 months
[137] Zhang 2022 - age 24 months
[138] Zhang 2022 - age 30 months

2[139]	Observational	serious	not serious inconsistency	serious indirectness	not serious imprecision	none	105	135	MD 0.03 [-0.26, 0.33]	No difference	⊕⊕◯◯ LOW	CRITICAL
2[140]	Observational	serious	not serious inconsistency	serious indirectness	not serious imprecision	none	105	135	MD 0.09 [-0.26, 0.43]	No difference	⊕⊕◯◯ LOW	CRITICAL
2[141]	Observational	serious	not serious inconsistency	serious indirectness	not serious imprecision	none	105	135	MD 0.37 [-0.15, 0.89]	No difference	⊕⊕◯◯ LOW	CRITICAL
2[142]	Observational	serious	not serious inconsistency	serious indirectness	not serious imprecision	none	105	135	MD 0.40 [-0.10, 0.90]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Weight												
1[143]	Observational	serious[3]	not applicable	serious indirectness	not serious imprecision	none	90	118	MD -0.04 [-0.24, 0.16]	No difference	⊕⊕◯◯ LOW	CRITICAL
1[144]	Observational	serious	not applicable	serious indirectness	not serious imprecision	none	90	118	MD -0.02 [-0.25, 0.21]	No difference	⊕⊕◯◯ LOW	CRITICAL
1[145]	Observational	serious	not applicable	serious indirectness	not serious imprecision	none	90	118	MD -0.02 [-0.28, 0.24]	No difference	⊕⊕◯◯ LOW	CRITICAL
1[146]	Observational	serious	not applicable	serious indirectness	not serious imprecision	none	90	118	MD 0.08 [-0.17, 0.33]	No difference	⊕⊕◯◯ LOW	CRITICAL
1[147]	Observational	serious	not applicable	serious indirectness	not serious imprecision	none	90	118	MD 0.03 [-0.25, 0.31]	No difference	⊕⊕◯◯ LOW	CRITICAL

[139] Zhang 2022 - age 3 years
[140] Zhang 2022 - age 4 years
[141] Zhang 2022 - age 5 years
[142] Zhang 2022 - age 6 years
[143] Zhang 2022 - age 3 months
[144] Zhang 2022 - age 6 months
[145] Zhang 2022 - age 8 months
[146] Zhang 2022 - age 12 months
[147] Zhang 2022 - age 18 months

1[148]	Observational	serious	not applicable	serious indirectness	not serious imprecision	none	90	118	MD 0.07 [-0.26, 0.40]	No difference	⊕⊕◯◯ LOW	CRITICAL
1[149]	Observational	serious	not applicable	serious indirectness	not serious imprecision	none	90	118	MD 0.14 [-0.25, 0.53]	No difference	⊕⊕◯◯ LOW	CRITICAL
1[150]	Observational	serious	not applicable	serious indirectness	not serious imprecision	none	90	118	MD 0.14 [-0.32, 0.60]	No difference	⊕⊕◯◯ LOW	CRITICAL
1[151]	Observational	serious	not applicable	serious indirectness	not serious imprecision	none	90	118	MD 0.42 [-0.16, 1.00]	No difference	⊕⊕◯◯ LOW	CRITICAL
1[152]	Observational	serious	not applicable	serious indirectness	not serious imprecision	none	90	118	MD 0.78 [-0.23, 1.79]	No difference	⊕⊕◯◯ LOW	CRITICAL
1[153]	Observational	serious	not applicable	serious indirectness	not serious imprecision	none	90	118	MD 0.55 [-0.62, 1.72]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Waist hip ratio												
1	Observational	serious[2]	not applicable	serious indirectness	not serious imprecision	none	15	17	Not estimable	Not estimable	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Systolic blood pressure												
1	Observational	serious[2]	not applicable	serious indirectness	serious imprecision	none	15	17	MD 3.20 [-7.10, 13.50]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Diastolic blood pressure												
1	Observational	serious[2]	not applicable	serious indirectness	serious imprecision	none	15	17	MD 0.80 [-4.79, 6.39]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Fasting glucose												
1	Observational	serious[2]	not applicable	serious indirectness	moderate imprecision	none	10	6	MD 0.13 [-0.34, 0.60]	No difference	⊕◯◯◯ VERY LOW	CRITICAL

[148] Zhang 2022 - age 24 months
[149] Zhang 2022 - age 30 months
[150] Zhang 2022 - age 3 years
[151] Zhang 2022 - age 4 years
[152] Zhang 2022 - age 5 years
[153] Zhang 2022 - age 6 years

Outcome: OGTT - 2 hour glucose												
1	Observational	serious[2]	not applicable	serious indirectness	moderate imprecision	none	10	6	MD 0.20 [-0.54, 0.94]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: LDL												
1	Observational	serious[2]	not applicable	serious indirectness	moderate imprecision	none	10	6	MD 0.01 [-0.54, 0.56]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: HDL												
1	Observational	serious[2]	not applicable	serious indirectness	not serious imprecision	none	10	6	MD 0.30 [-0.03, 0.63]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Triglycerides												
1	Observational	serious[2]	not applicable	serious indirectness	not serious imprecision	none	10	6	MD -0.34 [-0.63, -0.05]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Total cholesterol												
1	Observational	serious[2]	not applicable	serious indirectness	moderate imprecision	none	10	6	MD 0.17 [-0.38, 0.72]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	FDR	Control	Effect, fixed [95% CI]	Results	Certainty	Importance
Outcome: Diabetes												
1	Observational	serious[2]	not applicable	serious indirectness	serious imprecision	none	10	6	Not estimable (no events)	Not estimable	⊕◯◯◯ VERY LOW	CRITICAL

All first degree relatives versus normal controls												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	FDR	Control	Effect, random [95% CI]	Results	Certainty	Importance
Outcome: BMI												
10[154]	Observational	moderate[155]	serious inconsistency	not serious indirectness	not serious imprecision	none	1068	2181	MD 0.39 [-0.18, 0.95]	No difference	⊕⊕⊕◯	CRITICAL

[154] Zhang 2022 - age 6 subgroup; Joharatnam 2011 - subgroup without polycystic ovaries used

[155] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 81% dissimilar conclusions,

											MODERATE	
Outcome: Weight												
4[156]	Observational	moderate[157]	serious inconsistency	not serious indirectness	not serious imprecision	none	618	1771	MD 0.67 [-1.72, 3.06]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Waist circumference												
8[158]	Observational	moderate[159]	serious inconsistency	not serious indirectness	not serious imprecision	none	1009	1949	MD -0.87 [-2.92, 1.19]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Waist hip ratio												
10[160]	Observational	moderate[161]	serious inconsistency	not serious indirectness	not serious imprecision	none	790	658	MD 0.01 [0.00, 0.02]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Systolic blood pressure												
9[162]	Observational	moderate[163]	moderate inconsistency	not serious indirectness	not serious imprecision	none	795	863	MD 0.04 [-1.15, 1.24]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Diastolic blood pressure												
11[164]	Observational	moderate[165]	serious inconsistency	not serious indirectness	not serious imprecision	none	1330	2150	MD 1.37 [0.15, 2.58]	Higher in FDR vs control	⊕⊕⊕◯ MODERATE	CRITICAL

indirectness because multiple countries, different PCOS criteria, broad range of ages and genders, method of control group not described for many studies)

[156] Zhang 2022 - age 6 subgroup used

[157] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 92% dissimilar conclusions, indirectness because multiple countries, different PCOS criteria, broad range of ages and genders)

[158] Sam 2005 - subgroup without PCOS features used

[159] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 82% dissimilar conclusions, indirectness because multiple countries, different PCOS criteria, broad range of ages and genders)

[160] Joharatnam 2011 - subgroup without polycystic ovaries used

[161] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 61% dissimilar conclusions, indirectness because multiple countries, different PCOS criteria, broad range of ages and genders)

[162] Sam 2005 - subgroup without PCOS features used

[163] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 16% some differences between subgroups, indirectness because multiple countries, different PCOS criteria, broad range of ages and genders, no data for age >50 however)

[164] Sam 2005 - subgroup without PCOS features used

[165] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 66% dissimilar conclusions, indirectness because multiple countries, different PCOS criteria, broad range of ages and genders)

Outcome: Fasting glucose												
15[166]	Observational	moderate[167]	serious inconsistency	not serious indirectness	not serious imprecision	none	1311	1434	MD 0.09 [-0.02, 0.21]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: OGTT - 2 hour glucose												
6	Observational	moderate[168]	serious inconsistency	not serious indirectness	not serious imprecision	none	483	361	MD 0.44 [0.13, 0.74]	Higher in FDR vs control	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: LDL												
13[169]	Observational	moderate[170]	serious inconsistency	not serious indirectness	not serious imprecision	none	987	1201	MD 0.36 [0.17, 0.55]	Higher in FDR vs control	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: HDL												
12[171]	Observational	moderate[172]	serious inconsistency	not serious indirectness	not serious imprecision	none	962	1192	MD 0.00 [-0.05, 0.05]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Triglycerides												
11[173]	Observational	moderate[174]	serious inconsistency	not serious indirectness	not serious imprecision	none	905	1124	MD 0.13 [0.04, 0.21]	Higher in FDR vs control	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Total cholesterol												

[166] Sam 2005 - subgroup without PCOS features used
[167] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 87% dissimilar conclusions, indirectness because multiple countries, different PCOS criteria, broad range of ages and genders)
[168] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 64% dissimilar conclusions, indirectness because multiple countries, different PCOS criteria, broad range of ages and genders but no data for age >50)
[169] Joharatnam 2011 - subgroup without polycystic ovaries used
[170] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 89% dissimilar conclusions, indirectness because multiple countries, different PCOS criteria, broad range of ages and genders)
[171] Joharatnam 2011 - subgroup without polycystic ovaries used
[172] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 63% dissimilar conclusions, indirectness because multiple countries, different PCOS criteria, broad range of ages and genders)
[173] Joharatnam 2011 - subgroup without polycystic ovaries used
[174] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 81% dissimilar conclusions, indirectness because multiple countries, different PCOS criteria, broad range of ages and genders)

11[175]	Observational	moderate[176]	serious inconsistency	not serious indirectness	not serious imprecision	none	956	1175	MD 0.42 [0.24, 0.61]	Higher in FDR vs control	⊕⊕⊕◯ MODERATE	CRITICAL
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	FDR	Control	Effect, fixed [95% CI]	Results	Certainty	Importance
Outcome: Metabolic syndrome												
6	Observational	moderate[177]	moderate inconsistency	not serious indirectness	not serious imprecision	none	605	1454	OR 1.72 [1.37, 2.17]	Higher in FDR vs control	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Obesity												
2	Observational	serious[178]	not serious inconsistency	serious indirectness	serious imprecision	none	143	101	OR 1.19 [0.51, 2.78]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Hypertension												
2	Observational	serious[179]	not serious inconsistency	serious indirectness	serious imprecision	none	118	114	OR 2.10 [1.09, 4.06]	Higher in FDR vs control	⊕⊕◯◯ LOW	CRITICAL
Outcome: Diabetes												
3	Observational	moderate[180]	moderate inconsistency	moderate indirectness	serious imprecision	none	174	132	OR 4.74 [2.01, 11.17]	Higher in FDR vs control	⊕⊕◯◯ LOW	CRITICAL
Outcome: Impaired fasting glucose												

[175] Joharatnam 2011 - subgroup without polycystic ovaries used

[176] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 84% dissimilar conclusions, indirectness because multiple countries, different PCOS criteria, broad range of ages and genders)

[177] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 65% dissimilar conclusions, indirectness because multiple countries, different PCOS criteria, broad range of ages and genders)

[178] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 0% similar conclusions, indirectness because 2 countries, different PCOS criteria, largest study predominantly from Chile and daughters, second study very small numbers, female only, not broad range of ages)

[179] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 0% similar conclusions, indirectness because 2 countries, different PCOS criteria, not broad range of ages)

[180] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 50% slightly dissimilar conclusions, indirectness because 3 countries, different PCOS criteria, only parents and sons)

2	Observational	serious[181]	not serious inconsistency	serious indirectness	serious imprecision	none	154	116	OR 1.43 [0.55, 3.74]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Impaired glucose tolerance												
2	Observational	serious[182]	not serious inconsistency	serious indirectness	serious imprecision	none	95	68	OR 4.32 [1.34, 13.91]	Higher in FDR vs control	⊕⊕◯◯ LOW	CRITICAL
Outcome: PCOS												
2	Observational	serious[183]	not serious inconsistency	serious indirectness	serious imprecision	none	78	63	OR 10.98 [1.38, 87.61]	Higher in FDR vs control	⊕⊕◯◯ LOW	CRITICAL

[181] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 0% similar conclusions, indirectness because 2 countries, similar PCOS criteria, only parents and siblings)
[182] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 0% similar conclusions, indirectness because 2 countries, different PCOS criteria, only parents and brothers, small numbers)
[183] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 0% similar conclusions, indirectness because 2 countries, different PCOS criteria, small numbers)

All female first degree relatives versus normal controls[184]												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	FDR	Control	Effect, random [95% CI]	Results	Certainty	Importance
Outcome: BMI												
6[185]	Observational	moderate[186]	not serious inconsistency	not serious indirectness	not serious imprecision	none	649	479	MD 0.39 [0.07, 0.72]	Higher in FDR vs control	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Weight												
2[187]	Observational	moderate[188]	not serious inconsistency	serious indirectness	not serious imprecision	none	243	202	MD 0.75 [-0.07, 1.56]	No difference	⊕⊕◯◯ MODERATE	CRITICAL
Outcome: Waist circumference												
4[189]	Observational	moderate[190]	serious inconsistency	moderate indirectness	not serious imprecision	none	511	301	MD -1.12 [-4.37, 2.13]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Waist hip ratio												
9[191]	Observational	moderate[192]	serious inconsistency	not serious indirectness	not serious imprecision	none	595	518	MD 0.01 [0.00, 0.03]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Systolic blood pressure												

[184] Includes all studies with female FDRs (including mother, sister, daughter)
[185] Zhang 2022 - age 6 subgroup; Joharatnam 2011 - subgroup without polycystic ovaries used
[186] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 0% similar conclusions, indirectness because multiple countries, different PCOS criteria, broad range of age, no data for age >50 however)
[187] Zhang 2022 - age 6 subgroup used
[188] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 0% similar conclusions, indirectness because 2 countries, different PCOS criteria, age up to 20 only)
[189] Sam 2005 - subgroup without PCOS features used
[190] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 74% dissimilar conclusions, indirectness because multiple countries, similar PCOS criteria - all NICHD, broad range of age)
[191] Joharatnam 2011 - subgroup without polycystic ovaries used
[192] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 69% dissimilar conclusions, indirectness because multiple countries, different PCOS criteria, broad range of age)

6[193]	Observational	moderate[194]	serious inconsistency	not serious indirectness	not serious imprecision	none	742	451	MD 2.23 [-0.62, 5.08]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Diastolic blood pressure												
6[195]	Observational	moderate[196]	serious inconsistency	not serious indirectness	not serious imprecision	none	732	442	MD 0.90 [-0.99, 2.79]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Fasting glucose												
7[197]	Observational	moderate[198]	serious inconsistency	not serious indirectness	not serious imprecision	none	824	489	MD 0.07 [-0.12, 0.26]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: OGTT - 2 hour glucose												
4	Observational	moderate[199]	not serious inconsistency	moderate indirectness	not serious imprecision	none	414	297	MD 0.24 [0.04, 0.45]	Higher in FDR vs control	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: LDL												
7[200]	Observational	moderate[201]	serious inconsistency	moderate indirectness	not serious imprecision	none	647	411	MD 0.24 [0.01, 0.47]	Higher in FDR vs control	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: HDL												

[193] Sam 2005 - subgroup without PCOS features used
[194] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 70% dissimilar conclusions, indirectness because multiple countries, different PCOS criteria, broad range of age)
[195] Sam 2005 - subgroup without PCOS features used
[196] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 69% dissimilar conclusions, indirectness because multiple countries, different PCOS criteria, broad range of age)
[197] Sam 2005 - subgroup without PCOS features used
[198] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 70% dissimilar conclusions, indirectness because multiple countries, different PCOS criteria, broad range of age)
[199] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 0% similar conclusions, indirectness because multiple countries, different PCOS criteria, only one study explored age <20 years and no data for age >50)
[200] Joharatnam 2011 - subgroup without polycystic ovaries used
[201] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 88% dissimilar conclusions, indirectness because multiple countries, different PCOS criteria, data only for age 20 and above, broad range of degree of relative and genders)

7[202]	Observational	moderate[203]	moderate inconsistency	moderate indirectness	not serious imprecision	none	637	402	MD 0.04 [-0.00, 0.08]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Triglycerides												
7[204]	Observational	moderate[205]	serious inconsistency	moderate indirectness	not serious imprecision	none	637	402	MD 0.08 [-0.01, 0.18]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Total cholesterol												
7[206]	Observational	moderate[207]	serious inconsistency	moderate indirectness	not serious imprecision	none	647	411	MD 0.37 [0.15, 0.60]	Higher in FDR vs control	⊕⊕⊕◯ MODERATE	CRITICAL
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	FDR	Control	Effect, fixed [95% CI]	Results	Certainty	Importance
Outcome: Metabolic syndrome												
3	Observational	moderate[208]	serious inconsistency	serious indirectness	not serious imprecision	none	280	178	OR 1.31 [0.84, 2.03]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Obesity												
2	Observational	serious[209]	not serious inconsistency	serious indirectness	not serious imprecision	none	143	101	OR 1.19 [0.51, 2.78]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Hypertension												
1	Observational	serious[2]	not applicable	serious indirectness	serious imprecision	none	45	44	OR 1.92 [0.68, 5.46]	No difference	⊕◯◯◯ VERY LOW	CRITICAL

[202] Joharatnam 2011 - subgroup without polycystic ovaries used
[203] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 27% slightly dissimilar conclusions, indirectness because multiple countries, different PCOS criteria, data only for age 20 and above, broad range of degree of relative)
[204] Joharatnam 2011 - subgroup without polycystic ovaries used
[205] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 76% dissimilar conclusions, indirectness because multiple countries, different PCOS criteria, data only for age 20 and above, broad range of degree of relative)
[206] Joharatnam 2011 - subgroup without polycystic ovaries used
[207] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 84% dissimilar conclusions, indirectness because multiple countries, different PCOS criteria, data only for age 20 and above, broad range of degree of relative
[208] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 72% dissimilar conclusions, indirectness because only from single country, similar PCOS criteria, data only mothers and sisters, all women >age 20)
[209] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 0% similar conclusions, indirectness because 2 countries, different PCOS criteria, data only predominantly from one study of daughters)

Outcome: Diabetes												
2	Observational	serious[210]	not serious inconsistency	serious indirectness	serious imprecision	none	85	64	OR 1.90 [0.62, 5.85]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Impaired fasting glucose												
2	Observational	serious[211]	not serious inconsistency	serious indirectness	serious imprecision	none	75	55	OR 1.41 [0.28, 7.21]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Impaired glucose tolerance												
1	Observational	serious[2]	not applicable	serious indirectness	serious imprecision	none	40	20	OR 1.91 [0.36, 10.17]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: PCOS												
2	Observational	serious[212]	not serious inconsistency	serious indirectness	serious imprecision	none	78	63	OR 10.98 [1.38, 87.61]	Higher in FDR vs control	⊕⊕◯◯ LOW	CRITICAL

[210] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 0% similar conclusions, indirectness because 2 countries, similar PCOS criteria, data only for mothers of similar age)
[211] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 0% similar conclusions, indirectness because 2 countries, similar PCOS criteria, data only for mothers and sisters)
[212] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 0% similar conclusions, indirectness because 2 countries, different PCOS criteria, small numbers)

All male first degree relatives versus normal controls												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	FDR	Control	Effect, random [95% CI]	Results	Certainty	Importance
Outcome: BMI												
3[213]	Observational	moderate [214]	serious inconsistency	serious indirectness	not serious imprecision	none	316	1288	MD 1.70 [-0.60, 4.01]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Weight												
2[215]	Observational	serious[216]	serious inconsistency	serious indirectness	serious imprecision	none	301	1271	MD 5.71 [-4.53, 15.95]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Waist circumference												
3	Observational	moderate [217]	serious inconsistency	serious indirectness	serious imprecision	none	424	1350	MD 1.43 [-3.94, 6.81]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Waist hip ratio												
4	Observational	moderate [218]	moderate inconsistency	serious indirectness	not serious imprecision	none	195	140	MD 0.01 [-0.01, 0.03]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Systolic blood pressure												

[213] Zhang 2022 - age 6 subgroup used
[214] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 94% dissimilar conclusions, indirectness because different countries, different PCOS criteria, no analysis for age 20-50, only parents and children)
[215] Zhang 2022 - age 6 subgroup used
[216] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 98% dissimilar conclusions, indirectness because 2 countries, different PCOS criteria, no analysis for age 20-50, only parents and children)
[217] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 87% dissimilar conclusions, indirectness because 2 countries, same PCOS criteria - all NICHD, no analysis for age <20)
[218] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 27% some dissimilar conclusions, indirectness because 3 countries, different PCOS criteria, no analysis for age <20)

5	Observational	moderate [219]	serious inconsistency	not serious indirectness	not serious imprecision	none	494	1402	MD 2.98 [-1.15, 7.12]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Diastolic blood pressure												
6	Observational	moderate [220]	moderate inconsistency	not serious indirectness	not serious imprecision	none	535	1443	MD 2.65 [1.24, 4.06]	Higher in FDR vs control	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Fasting glucose												
7	Observational	moderate [221]	not serious inconsistency	not serious indirectness	not serious imprecision	none	350	320	MD 0.14 [-0.08, 0.37]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: OGTT - 2 hour glucose												
3	Observational	moderate [222]	serious inconsistency	serious indirectness	not serious imprecision	none	69	64	MD 1.01 [-0.03, 2.06]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: LDL												
6	Observational	moderate [223]	serious inconsistency	not serious indirectness	not serious imprecision	none	188	165	MD 0.43 [0.03, 0.83]	Higher in FDR vs control	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: HDL												
6	Observational	moderate [224]	serious inconsistency	not serious indirectness	not serious imprecision	none	188	165	MD -0.05 [-0.17, 0.08]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL

[219] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 73% dissimilar conclusions, indirectness because multiple countries, different PCOS criteria, broad range of age - no analysis for age 10-20 however)
[220] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 32% dissimilar conclusions, indirectness because multiple countries, different PCOS criteria, broad range of age)
[221] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 83% dissimilar conclusions, indirectness because multiple countries, different PCOS criteria, broad range of age)
[222] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 87% dissimilar conclusions, indirectness because multiple countries, different PCOS criteria, no data for age >50)
[223] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 87% dissimilar conclusions, indirectness because multiple countries, different PCOS criteria, broad range for age)
[224] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 88% dissimilar conclusions,

Outcome: Triglycerides												
4	Observational	moderate [225]	serious inconsistency	not serious indirectness	not serious imprecision	none	131	97	MD 0.29 [-0.11, 0.70]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Total cholesterol												
5	Observational	moderate [226]	serious inconsistency	not serious indirectness	not serious imprecision	none	172	139	MD 0.60 [0.15, 1.06]	Higher in FDR vs control	⊕⊕⊕◯ MODERATE	CRITICAL
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	FDR	Control	Effect, fixed [95% CI]	Results	Certainty	Importance
Outcome: Metabolic syndrome												
4	Observational	moderate [227]	serious inconsistency	moderate indirectness	not serious imprecision	none	310	1264	OR 1.89 [1.44, 2.48]	Higher in FDR vs control	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Hypertension												
1	Observational	serious[2]	not applicable	serious indirectness	serious imprecision	none	41	42	OR 4.19 [1.06, 16.56]	Higher in FDR vs control	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Diabetes												
3	Observational	serious[228]	moderate inconsistency	serious indirectness	serious imprecision	none	89	68	OR 14.54 [2.83, 74.71]	Higher in FDR vs control	⊕⊕◯◯ LOW	CRITICAL
Outcome: Impaired fasting glucose												

indirectness because multiple countries, different PCOS criteria, broad range for age)

[225] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 75% dissimilar conclusions, indirectness because multiple countries, different PCOS criteria, broad range for age)

[226] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 82% dissimilar conclusions, indirectness because multiple countries, different PCOS criteria, broad range for age)

[227] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 70% dissimilar conclusions, indirectness because multiple countries, different PCOS criteria, no data for children however)

[228] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 34% some dissimilar conclusions, indirectness because multiple countries, similar PCOS criteria, only data for fathers as data for sons not estimable due to no events)

2	Observational	moderate [229]	not serious inconsistency	serious indirectness	moderate imprecision	none	79	61	OR 1.44 [0.44, 4.72]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Impaired glucose tolerance												
2	Observational	moderate [230]	not serious inconsistency	serious indirectness	serious imprecision	none	55	48	OR 8.47 [1.47, 48.81]	Higher in FDR vs control	⊕⊕◯◯ LOW	CRITICAL

[229] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 0% similar conclusions, indirectness because 2 countries, similar PCOS criteria, data only for adults)
[230] Downgraded once as the majority of evidence is at moderate or high risk of bias (inconsistency because I^2 0% similar conclusions, indirectness because 2 countries, different PCOS criteria, data only for adults)

9. SUMMARY TABLES

Female first degree relatives versus normal controls						
Outcome or Subgroup	**Studies**	**n**	**Effect Estimate: OR [95% CI], M-H, fixed**	**P**	**Favours**	**Certainty**
Obesity	1	16	OR 1.00 [0.10, 9.61]	P = 1.00	No difference	⊕◯◯◯ VERY LOW

Parents versus normal controls						
Outcome or Subgroup	**Studies**	**n**	**Effect Estimate: OR [95% CI], M-H, fixed**	**P**	**Favours**	**Certainty**
Metabolic syndrome	1	172	OR 4.09 [2.17, 7.74]	P < 0.0001	Higher in FDR vs control	⊕◯◯◯ VERY LOW
Hypertension	1	172	OR 2.61 [1.15, 5.92]	P = 0.02	Higher in FDR vs control	⊕◯◯◯ VERY LOW
Diabetes	1	172	OR 5.81 [1.89, 17.92]	P = 0.002	Higher in FDR vs control	⊕◯◯◯ VERY LOW

Fathers versus normal controls						
Outcome or Subgroup	**Studies**	**n**	**Effect Estimate: OR [95% CI], M-H, fixed**	**P**	**Favours**	**Certainty**

Metabolic syndrome	2	1447	OR 1.76 [1.33, 2.34]	P<0.0001 I^2 = 85%	Higher in FDR vs control	⊕⊕◯◯ LOW
Hypertension	1	83	OR 4.19 [1.06, 16.56]	P = 0.04	Higher in FDR vs control	⊕◯◯◯ VERY LOW
Diabetes	2	141	OR 14.54 [2.83, 74.71]	P = 0.001 I^2 = 34%	Higher in FDR vs control	⊕◯◯◯ VERY LOW
Impaired fasting glucose	1	58	OR 1.06 [0.09, 12.40]	P = 0.97	No difference	⊕◯◯◯ VERY LOW
Impaired glucose tolerance	1	58	OR 6.79 [0.80, 57.48]	P = 0.08	No difference	⊕◯◯◯ VERY LOW

Mothers versus normal controls						
Outcome or Subgroup	**Studies**	**n**	**Effect Estimate: OR [95% CI], M-H, fixed**	**P**	**Favours**	**Certainty**
Metabolic syndrome	1	89	OR 3.24 [1.35, 7.80]	P = 0.009	Higher in FDR vs control	⊕◯◯◯ VERY LOW
Hypertension	1	89	OR 1.92 [0.68, 5.46]	P = 0.22	No difference	⊕◯◯◯ VERY LOW
Diabetes	2	149	OR 1.90 [0.62, 5.85]	P = 0.26 I^2 = 0%	No difference	⊕⊕◯◯ LOW

Impaired fasting glucose	1	60	OR 2.66 [0.12, 58.12]	P = 0.53	No difference	⊕◯◯◯ VERY LOW
Impaired glucose tolerance	1	60	OR 1.91 [0.36, 10.17]	P = 0.45	No difference	⊕◯◯◯ VERY LOW

Brothers versus normal controls						
Outcome or Subgroup	**Studies**	**n**	**Effect Estimate: OR [95% CI], M-H, fixed**	**P**	**Favours**	**Certainty**
Metabolic syndrome	2	127	OR 5.14 [1.57, 16.91]	P = 0.007 I^2 = 0%	Higher in FDR vs control	⊕⊕◯◯ LOW
Impaired fasting glucose	1	82	OR 1.59 [0.41, 6.10]	P = 0.50	No difference	⊕◯◯◯ VERY LOW
Impaired glucose tolerance	1	45	OR 13.76 [0.66, 284.73]	P = 0.09	No difference	⊕◯◯◯ VERY LOW

Sisters versus normal controls						
Outcome or Subgroup	**Studies**	**n**	**Effect Estimate: OR [95% CI], M-H, fixed**	**P**	**Favours**	**Certainty**
PCOS	1	70	OR 10.14 [0.53, 195.91]	P = 0.13	No difference	⊕◯◯◯ VERY LOW
Metabolic syndrome	2	369	OR 0.94 [0.56, 1.58]	P = 0.82	No difference	⊕⊕◯◯

				I^2 = 23%		LOW
Impaired fasting glucose	1	70	OR 1.00 [0.13, 7.53]	P = 1.00	No difference	⊕◯◯◯ VERY LOW

All offspring versus normal controls						
Outcome or Subgroup	**Studies**	**n**	**Effect Estimate: OR [95% CI], M-H, fixed**	**P**	**Favours**	**Certainty**
Metabolic syndrome	1	27	OR 5.50 [0.55, 55.49]	P = 0.15	No difference	⊕◯◯◯ VERY LOW
Hypertension	1	60	OR 1.36 [0.44, 4.25]	P = 0.59	No difference	⊕◯◯◯ VERY LOW

Daughters versus normal controls						
Outcome or Subgroup	**Studies**	**n**	**Effect Estimate: OR [95% CI], M-H, fixed**	**P**	**Favours**	**Certainty**
PCOS	1	71	OR 11.71 [0.64, 213.79]	P = 0.10	No difference	⊕◯◯◯ VERY LOW
Obesity	1	228	OR 1.23 [0.49, 3.06]	P = 0.66	No difference	⊕⊕◯◯ LOW

Sons versus normal controls						
Outcome or Subgroup	**Studies**	**n**	**Effect Estimate: OR [95% CI], M-H, fixed**	**P**	**Favours**	**Certainty**
Diabetes	1	16	Not estimable (no events)	Not applicable	Not estimable	⊕◯◯◯ VERY LOW

All first degree relatives versus normal controls						
Outcome or Subgroup	**Studies**	**n**	**Effect Estimate: OR [95% CI], M-H, fixed**	**P**	**Favours**	**Certainty**
PCOS	2	141	OR 10.98 [1.38, 87.61]	P = 0.02 I^2 = 0%	Higher in FDR vs control	⊕⊕◯◯ LOW
Metabolic syndrome	6	2059	OR 1.72 [1.37, 2.17]	P < 0.00001 I^2 = 65%	Higher in FDR vs control	⊕⊕⊕◯ MODERATE
Obesity	2	244	OR 1.19 [0.51, 2.78]	P = 0.68 I^2 = 0%	No difference	⊕⊕◯◯ LOW
Hypertension	2	232	OR 2.10 [1.09, 4.06]	P = 0.03 I^2 = 0%	Higher in FDR vs control	⊕⊕◯◯ LOW
Diabetes	3	306	OR 4.74 [2.01, 11.17]	P = 0.0004 I^2 = 50%	Higher in FDR vs control	⊕⊕◯◯ LOW
Impaired fasting glucose	2	270	OR 1.43 [0.55, 3.74]	P = 0.46 I^2 = 0%	No difference	⊕⊕◯◯ LOW
Impaired glucose tolerance	2	163	OR 4.32 [1.34, 13.91]	P = 0.01 I^2 = 0%	Higher in FDR vs control	⊕⊕◯◯ LOW

All female first degree relatives versus normal controls						
Outcome or Subgroup	**Studies**	**n**	**Effect Estimate: OR [95% CI], M-H, fixed**	**P**	**Favours**	**Certainty**
PCOS	2	141	OR 10.98 [1.38, 87.61]	P =	Higher in FDR vs	⊕⊕◯◯

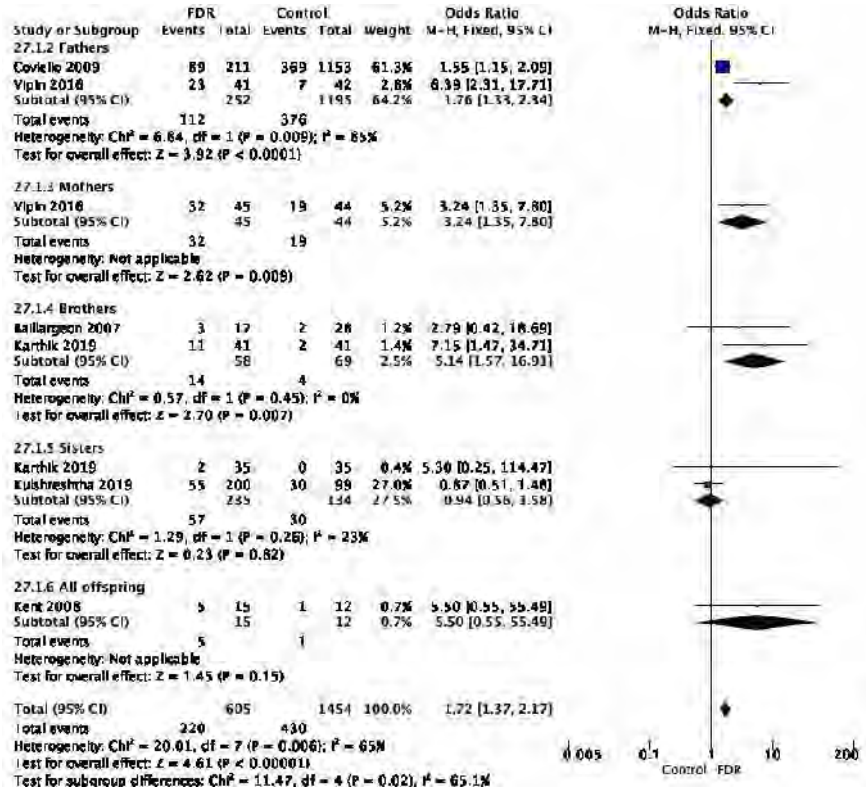
				0.02 I^2 = 0%	control	LOW
Metabolic syndrome	3	458	OR 1.31 [0.84, 2.03]	P = 0.24 I^2 = 72%	No difference	⊕⊕◯◯ LOW
Obesity	2	244	OR 1.19 [0.51, 2.78]	P = 0.68 I^2 = 0%	No difference	⊕⊕◯◯ LOW
Hypertension	1	89	OR 1.92 [0.68, 5.46]	P = 0.22	No difference	⊕◯◯◯ VERY LOW
Diabetes	2	149	OR 1.90 [0.62, 5.85]	P = 0.26 I^2 = 0%	No difference	⊕⊕◯◯ LOW
Impaired fasting glucose	2	130	OR 1.41 [0.28, 7.21]	P = 0.68 I^2 = 0%	No difference	⊕⊕◯◯ LOW
Impaired glucose tolerance	1	60	OR 1.91 [0.36, 10.17]	P = 0.45	No difference	⊕◯◯◯ VERY LOW

All male first degree relatives versus normal controls						
Outcome or Subgroup	**Studies**	**n**	**Effect Estimate: OR [95% CI], M-H, fixed**	**P**	**Favours**	**Certainty**
Metabolic syndrome	4	1574	OR 1.89 [1.44, 2.48]	P < 0.00001 I^2 = 70%	Higher in FDR vs control	⊕⊕⊕◯ MODERATE

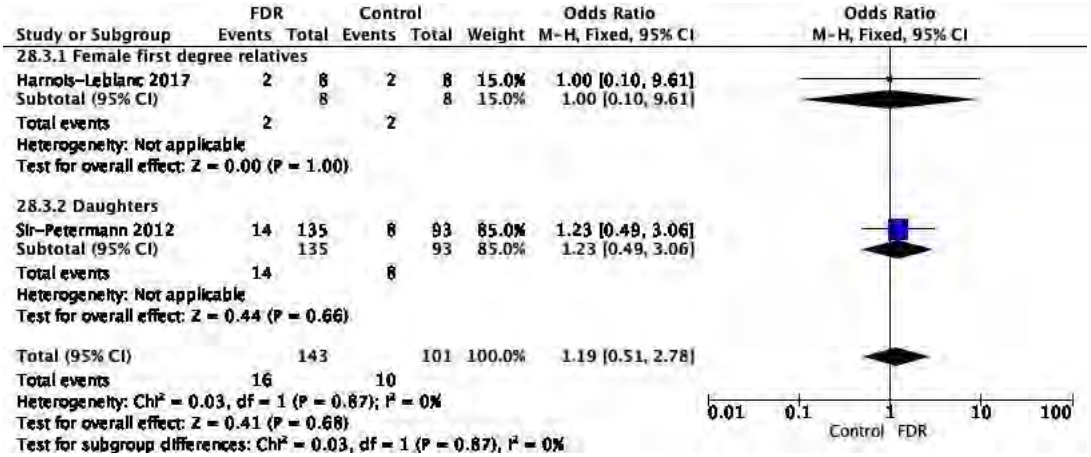
Hypertension	1	83	OR 4.19 [1.06, 16.56]	P = 0.04	Higher in FDR vs control	⊕◯◯◯ VERY LOW
Diabetes	3	157	OR 14.54 [2.83, 74.71]	P = 0.001 I^2 = 34%	Higher in FDR vs control	⊕⊕◯◯ LOW
Impaired fasting glucose	2	140	OR 1.44 [0.44, 4.72]	P = 0.54 I^2 = 0%	No difference	⊕⊕◯◯ LOW
Impaired glucose tolerance	2	103	OR 8.47 [1.47, 48.81]	P = 0.02 I^2 = 0%	Higher in FDR vs control	⊕⊕◯◯ LOW

10. Forest Plots

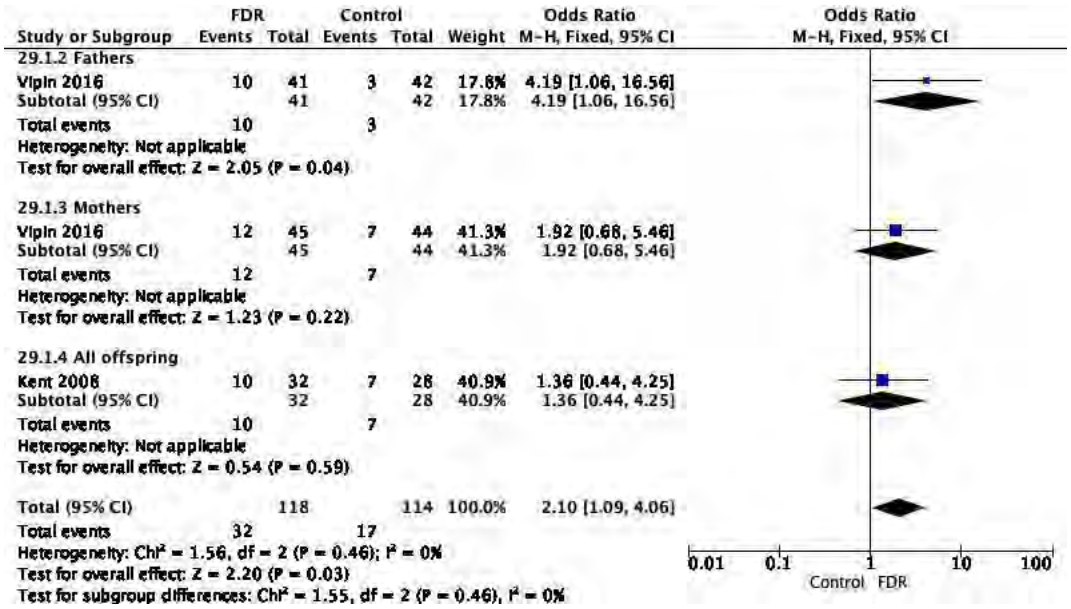
Prevalence of metabolic syndrome



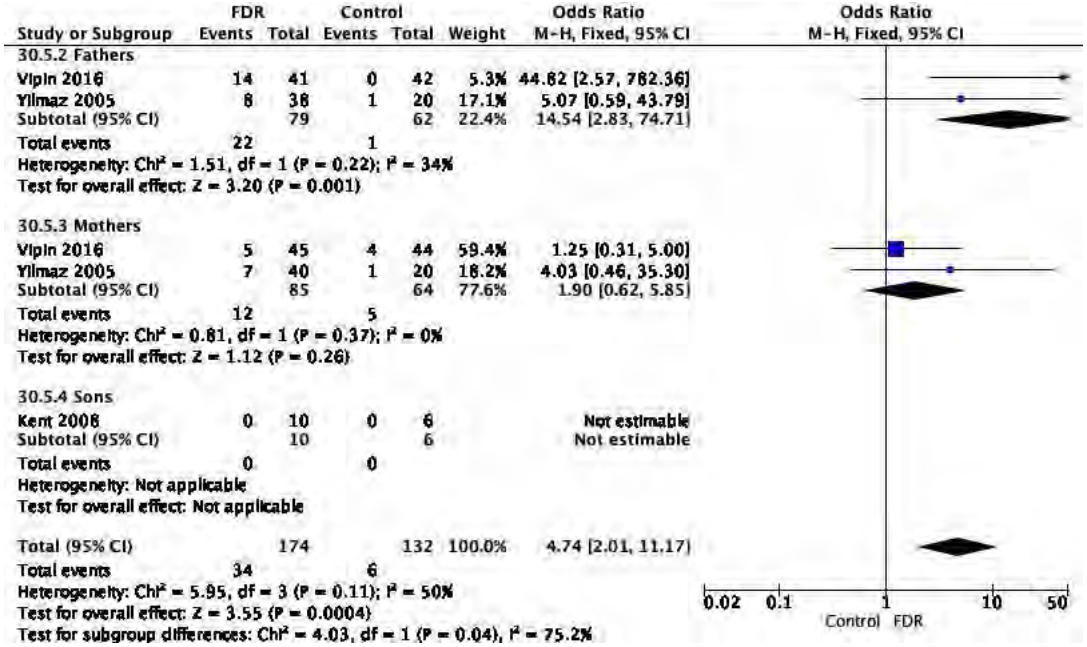
Prevalence of obesity



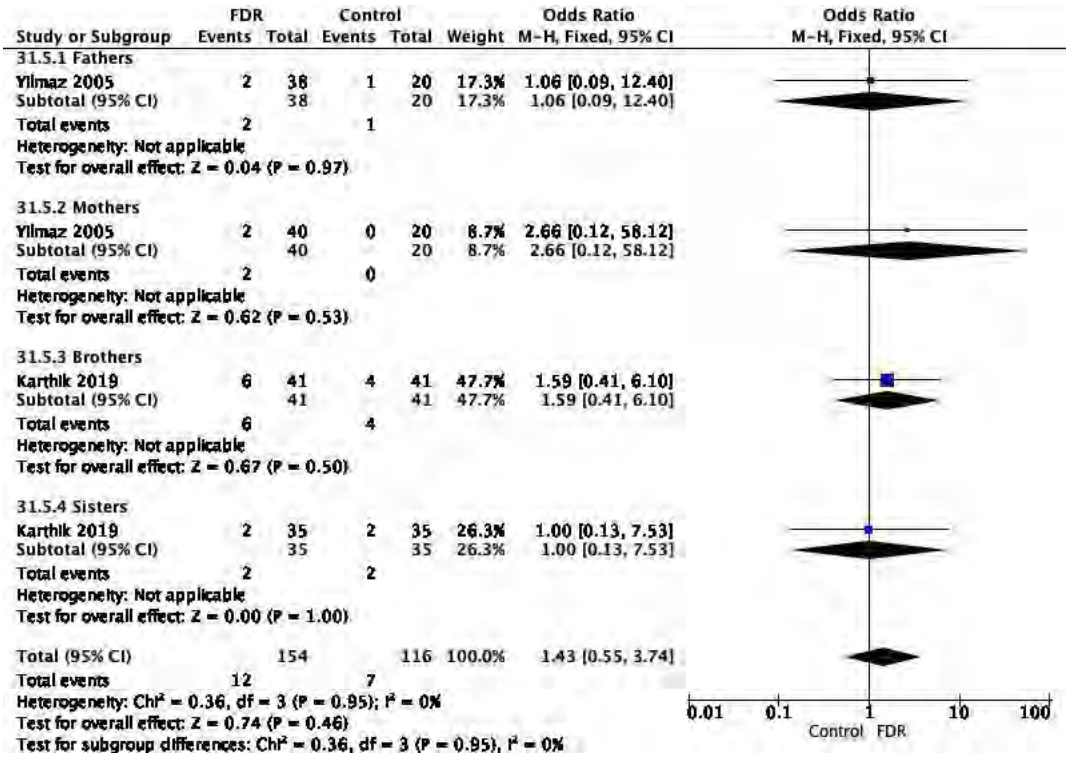
Prevalence of hypertension



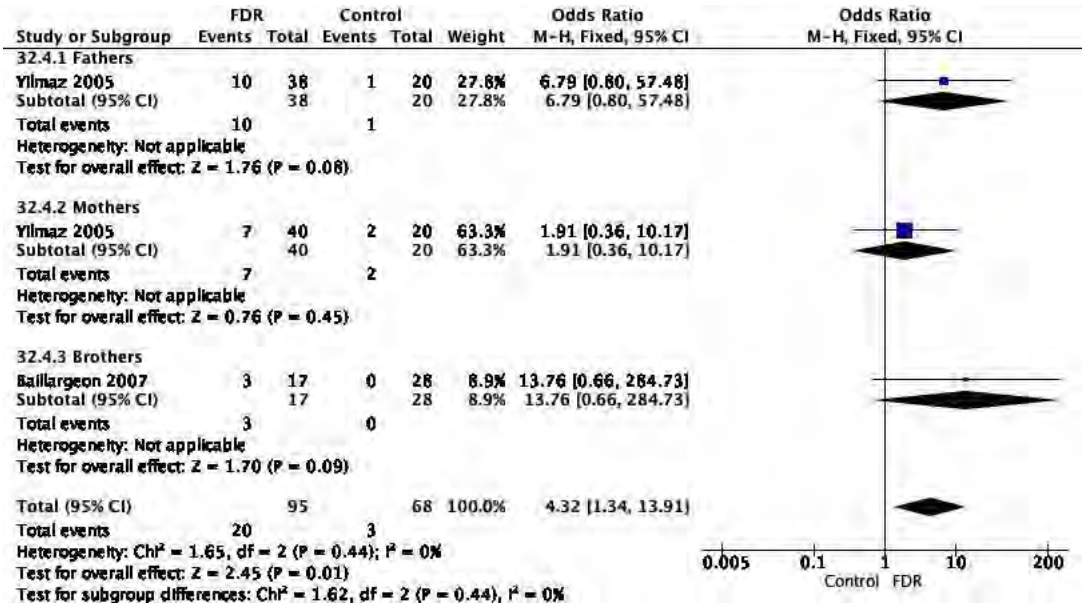
Prevalence of diabetes



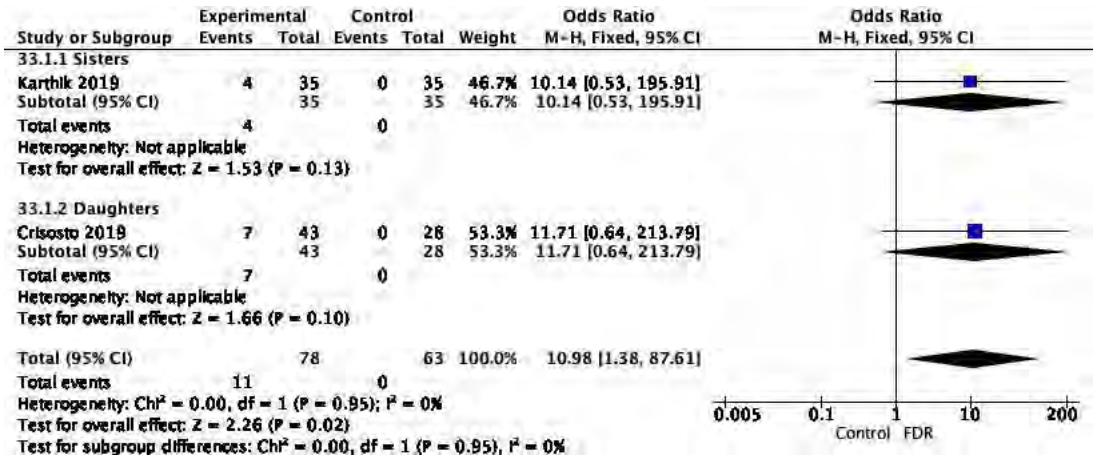
Prevalence of impaired fasting glucose



Prevalence of impaired glucose tolerance



Prevalence of PCOS



11. DATA EXTRACTION TABLES – DICHOTOMOUS OUTCOMES

OUTCOME: Metabolic syndrome				OUTCOME TYPE: Dichotomous				
Parents								
Author, year	Unit of outcome	Method of measurement	N events in First Degree Relatives	N total in First Degree Relatives	N events in control group	N total in control group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Vipin 2016	Prevalence	IDF criteria	55	86	26	86	Crude	Age and BMI matched (mean age 50.4 ± 5.6 years)
Fathers								
Author, year	Unit of outcome	Method of measurement	N events in First Degree Relatives	N total in First Degree Relatives	N events in control group	N total in control group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Coviello 2009	Prevalence	NCEP/ATPIII criteria	89	211	369	1153	Crude	Age range similar, however mean age varied (Mean age 57 ± 9 years), ethnicity matched
Vipin 2016	Prevalence	IDF criteria	23	41	7	42	Crude	Age and BMI matched (mean age 53.1 ± 5.1 years)
Mothers								
Author, year	Unit of outcome	Method of measurement	N events in First Degree Relatives	N total in First Degree Relatives	N events in control group	N total in control group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Vipin 2016	Prevalence	IDF criteria	32	45	19	44	Crude	Age and BMI matched (mean age 47.9 ± 4.9 years)
Brothers								
Author, year	Unit of outcome	Method of measurement	N events in First Degree Relatives	N total in First Degree Relatives	N events in control group	N total in control group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Baillargeon 2007	Prevalence	NCEP/ATPIII	3	17	2	28	Crude	Age and BMI matched (mean age 31 ± 9 years)
Karthik 2019	Prevalence	NCEP/ATPIII	11	41	2	41	Crude	Age and BMI matched (mean age 23.3 ± 4.3 years)
Sisters								
Author, year	Unit of outcome	Method of measurement	N events in First Degree Relatives	N total in First Degree Relatives	N events in control group	N total in control group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?

Karthik 2019	Prevalence	NCEP/ATPIII	2	35	0	35	Crude	Age and BMI matched (median age 24; IQR 19-27 years)
Kulshreshtha 2019	Prevalence	NCEP/ATPIII criteria	55	200	30	99	Crude	Age matched (Mean age 25.42 ± 7.89 years)
All offspring								
Author, year	Ufnit of outcome	Method of measurement	N events in First Degree Relatives	N total in First Degree Relatives	N events in control group	N total in control group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Kent 2008	Prevalence	de Ferranti criteria (for adolescents)	5	15	1	12	Crude	Tanner stage matched (mean age 9.3 ± 3.1 years)

OUTCOME: Obesity				OUTCOME TYPE: Dichotomous				
Female first degree relatives								
Author, year	Unit of outcome	Method of measurement	N events in First Degree Relatives	N total in First Degree Relatives	N events in control group	N total in control group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Harnois-Leblanc 2017	Prevalence	>95th centile	2	8	2	8	Crude	Age matched. (median age 17.5 years; IQR 14.4-20.1 years)
Daughters								
Author, year	Unit of outcome	Method of measurement	N events in First Degree Relatives	N total in First Degree Relatives	N events in control group	N total in control group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Slr-Petermann 2012	Prevalence	>95th centile	14	135	8	93	Crude	Age matched. (median age 17.5 years; IQR 14.4-20.1 years)

OUTCOME: Hypertension				OUTCOME TYPE: Dichotomous				
Parents								
Author, year	Unit of outcome	Method of measurement	N events in First Degree Relatives	N total in First Degree Relatives	N events in control group	N total in control group	Are these values	If adjusted, what variables were included in the model?

							adjusted or crude?	
Vipin 2016	Prevalence	JNC criteria	22	86	10	86	Crude	Age and BMI matched (mean age 50.4 ± 5.6 years)
Fathers								
Author, year	Unit of outcome	Method of measurement	N events in First Degree Relatives	N total in First Degree Relatives	N events in control group	N total in control group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Vipin 2016	Prevalence	JNC criteria	10	41	3	42	Crude	Age and BMI matched (mean age 53.1 ± 5.1 years)
Mothers								
Author, year	Unit of outcome	Method of measurement	N events in First Degree Relatives	N total in First Degree Relatives	N events in control group	N total in control group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Vipin 2016	Prevalence	JNC criteria	12	45	7	44	Crude	Age and BMI matched (mean age 47.9 ± 4.9 years)
All offspring								
Author, year	Unit of outcome	Method of measurement	N events in First Degree Relatives	N total in First Degree Relatives	N events in control group	N total in control group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Kent 2008	Prevalence	de Ferranti criteria (for adolescents)	10	32	7	28	Crude	Tanner stage matched (mean age 9.3 ± 3.1 years)

OUTCOME: Diabetes					OUTCOME TYPE: Dichotomous			
Parents								
Author, year	Unit of outcome	Method of measurement	N events in First Degree Relatives	N total in First Degree Relatives	N events in control group	N total in control group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Vipin 2016	Prevalence	ADA criteria	19	86	4	86	Crude	Age and BMI matched (mean age 50.4 ± 5.6 years)
Fathers								
Author, year	Unit of outcome	Method of measurement	N events in First Degree Relatives	N total in First Degree Relatives	N events in control group	N total in control group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Vipin 2016	Prevalence	ADA criteria	14	41	0	42	Crude	Age and BMI matched (mean age 53.1 ± 5.1 years)

Yilmaz 2005	Prevalence	ADA 2003 (OGTT)	8	38	1	20	Crude	Age and weight matched (mean age 51.87 ± 8.54 years)
Mothers								
Author, year	Unit of outcome	Method of measurement	N events in First Degree Relatives	N total in First Degree Relatives	N events in control group	N total in control group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Vipin 2016	Prevalence	ADA criteria	5	45	4	44	Crude	Age and BMI matched (mean age 47.9 ± 4.9 years)
Yilmaz 2005	Prevalence	ADA 2003 (OGTT)	7	40	1	20	Crude	Age and weight matched (mean age 46.38 ± 7.95 years)
Sons								
Author, year	Unit of outcome	Method of measurement	N events in First Degree Relatives	N total in First Degree Relatives	N events in control group	N total in control group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Kent 2008	Prevalence	de Ferranti criteria (fasting glucose >6.1mmol/L)	0	10	0	6	Crude	Tanner stage, Age 9.7 ± 3.4 years (FDR)

OUTCOME: Impaired fasting glucose				OUTCOME TYPE: Dichotomous				
Fathers								
Author, year	Unit of outcome	Method of measurement	N events in First Degree Relatives	N total in First Degree Relatives	N events in control group	N total in control group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Yilmaz 2005	Prevalence	ADA 2003 (OGTT)	2	38	1	20	Crude	Age and weight matched (mean age 51.87 ± 8.54 years)
Mothers								
Author, year	Unit of outcome	Method of measurement	N events in First Degree Relatives	N total in First Degree Relatives	N events in control group	N total in control group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Yilmaz 2005	Prevalence	ADA 2003 (OGTT)	2	40	0	20	Crude	Age and weight matched (mean age 46.38 ± 7.95 years)
Brothers								

Author, year	Unit of outcome	Method of measurement	N events in First Degree Relatives	N total in First Degree Relatives	N events in control group	N total in control group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Karthik 2019	Prevalence	ADA 2019 (OGTT)	6	41	4	41	Crude	Age and BMI matched (mean age 23.3 ± 4.3 years)
Sisters								
Author, year	Unit of outcome	Method of measurement	N events in First Degree Relatives	N total in First Degree Relatives	N events in control group	N total in control group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Karthik 2019	prevalence	ADA 2019	2	35	2	35	Crude	Age and BMI matched (Median age 24 years; IQR 19-27)

OUTCOME: Impaired glucose tolerance				OUTCOME TYPE: Dichotomous				
Fathers								
Author, year	Unit of outcome	Method of measurement	N events in First Degree Relatives	N total in First Degree Relatives	N events in control group	N total in control group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Yilmaz 2005	Prevalence	ADA 2003 (OGTT)	10	38	1	20	Crude	Age and weight matched (mean age 51.87 ± 8.54 years)
Mothers								
Author, year	Unit of outcome	Method of measurement	N events in First Degree Relatives	N total in First Degree Relatives	N events in control group	N total in control group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Yilmaz 2005	Prevalence	ADA 2003 (OGTT)	7	40	2	20	Crude	Age and weight matched (mean age 46.38 ± 7.95 years)
Brothers								
Author, year	Unit of outcome	Method of measurement	N events in First Degree Relatives	N total in First Degree Relatives	N events in control group	N total in control group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Baillargeon 2007	Prevalence	Not defined	3	17	0	28	Crude	Age and BMI matched (mean age 31 ± 9 years)

OUTCOME: PCOS	OUTCOME TYPE: Dichotomous

Sisters								
Author, year	Unit of outcome	Method of measurement	N events in First Degree Relatives	N total in First Degree Relatives	N events in control group	N total in control group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Karthik 2019	Prevalence	Rotterdam 2003	4	35	0	35	Crude	Age and BMI matched (Median age 24 years; IQR 19-27)
Daughters								
Author, year	Unit of outcome	Method of measurement	N events in First Degree Relatives	N total in First Degree Relatives	N events in control group	N total in control group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Crisosto 2019	Prevalence	NICHD 1990	7	43	0	28	Crude	Age, gynecologic age, menarchal age, BMI, waist, WHR, and birth weight matched. Age median (IQR): 15.42 (14.17–16.17)

12. DATA EXTRACTION TABLES – CONTINUOUS OUTCOMES

OUTCOME: BMI						OUTCOME TYPE: Continuous				
Female first degree relatives										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Harnois-Leblanc 2017	kg/m^2	Not reported	Median = 22.7	IQR = 21.5-30.8	8	Median = 22.4	IQR = 19.1-27.8	8	Crude	Age matched. (median age 17.5 years; IQR 14.4-20.1 years)
Harnois-Leblanc 2017	z score	Not reported	Median = 0.63	IQR = 0.02-1.71	8	Median = 0.26	IQR = -0.96-1.52	8	Crude	Age matched. (median age 17.5 years; IQR 14.4-20.1 years)
Unluhizarci 2007	kg/m^2	Not reported	24.4	SEM = 0.3 Range = 20–31 SD=2.51	70	24.3	SEM = 0.4 Range = 21–28 SD=1.79	20	Crude SD recalculated from SEM	No matching performed. Mean age 27.3 ± 0.8 years

Fathers										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Coviello 2009	kg/m^2	Not reported	30.2	5.6	211	27.0	4.4	1153	Crude	Age range similar, however mean age varied (Mean age 57 ± 9 years), ethnicity matched
Sisters										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Joharatnam 2011	kg/m^2	Not reported	25.1	0.6	153	24	4.5	76	Crude	Mean age 31.3 ± 6 years-subgroup with polycystic ovaries (duplicate control group)
Joharatnam 2011	kg/m^2	Not reported	24.5	1.2	61	24	4.5	76	Crude	Mean age 37.8 ± 7.7 years - subgroup without polycystic ovaries (duplicate control group)
Kulshreshtha 2019	kg/m^2	Not reported	24.28	5.01	200	23.51	4.05	99	Crude	Age matched (Mean age 25.42 ± 7.89 years)
Unluhizarci 2007	kg/m^2	Not reported	24.4	SEM = 0.8 SD=6.5 Range = 20–31	66	24.3	SEM = 0.4 SD=1.8 Range = 21–28	20	Crude SD recalculated from SEM	No matching performed. Mean age 26.5 ± 0.8 years Similar subgroup to female FDR analysis
All offspring										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure:	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95%	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?

				IQR, SE or 95% CI) in Fist Degree Relatives			CI) in control group			
deWilde 2018	kg/m^2	Stadiometer, digital scales	15.9	1.6	42	16.4	1.3	168	Crude	Age 3.3 ± 0.6 years (FDR)
deWilde 2018	kg/m^2	Stadiometer, digital scales	15.3	1.5	32	15.8	1.7	130	Crude	Age 7.0 ± 0.8 years (FDR)
Li 2020	z score	Not reported	Median = 0.2	IQR = -0.5-0.6	70	Median = 0.4	IQR = -0.5-1.3	71	Crude	Maternal age and BMI matched (median age 3.51; IQR 3.2-5.16 years)
Wang 2021	kg/m^2	Not reported	15.84	1.23	29	16.49	1.37	116	Crude	Age and socioeconomic status matched (mean age 1.82 ± 0.23 years)
Zhang 2022	kg/m^2	Stadiometer, digital scales	17.35	1.29	198	17.19	1.21	227	Crude	Age 3 months
Zhang 2022	kg/m^2	Stadiometer, digital scales	17.91	1.39	198	17.70	1.15	227	Crude	Age 6 months
Zhang 2022	kg/m^2	Stadiometer, digital scales	17.83	1.32	198	17.62	1.13	227	Crude	Age 8 months
Zhang 2022	kg/m^2	Stadiometer, digital scales	17.26	1.21	198	17.02	0.97	227	Crude	Age 12 months
Zhang 2022	kg/m^2	Stadiometer, digital scales	16.45	1.10	198	16.24	0.90	227	Crude	Age 18 months
Zhang 2022	kg/m^2	Stadiometer, digital scales	15.98	1.11	198	15.86	1.00	227	Crude	Age 24 months
Zhang 2022	kg/m^2	Stadiometer, digital scales	15.83	1.10	198	15.75	0.95	227	Crude	Age 30 months
Zhang 2022	kg/m^2	Stadiometer, digital scales	15.63	1.17	198	15.57	0.97	227	Crude	Age 3 years
Zhang 2022	kg/m^2	Stadiometer, digital scales	15.64	1.43	198	15.44	1.13	227	Crude	Age 4 years
Zhang 2022	kg/m^2	Stadiometer, digital scales	15.79	1.98	198	15.47	1.45	227	Crude	Age 5 years
Zhang 2022	kg/m^2	Stadiometer, digital scales	15.91	2.00	198	15.58	1.60	227	Crude	Age 6 years
Daughters (Infancy)										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure:	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95%	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?

				IQR, SE or 95% CI) in Fist Degree Relatives			CI) in control group			
Zhang 2022	kg/m^2	Stadiometer, digital scales	17.25	1.23	108	16.86	1.05	109	Crude	Age 3 months
Zhang 2022	kg/m^2	Stadiometer, digital scales	17.79	1.43	108	17.54	1.10	109	Crude	Age 6 months
Zhang 2022	kg/m^2	Stadiometer, digital scales	17.79	1.39	108	17.43	1.18	109	Crude	Age 8 months
Zhang 2022	kg/m^2	Stadiometer, digital scales	17.14	1.23	108	16.82	0.96	109	Crude	Age 12 months
Daughters (Childhood)										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Legro 2017	kg/m^2	Not reported	17.66	3.43	46	16.59	3.75	39	Crude	Tanner stage matched. (Tanner stage I) Mean age 7.02 ±1.96 years
Legro 2017	kg/m^2	Not reported	21.37	5.63	16	21.13	3.87	27	Crude	Tanner stage matched. (Tanner stage II/III) Mean age 11.46 ±1.33 years
Legro 2017	kg/m^2	Not reported	27.56	8.7	13	25.68	6.62	16	Crude	Tanner stage matched. (Tanner stage IV/V) Mean age 15.24 ±1.17 years
Sir-Petermann 2012	kg/m^2	Not reported	19.4	SEM=0.8 SD = 4.38	30	18.6	SEM=0.5 SD = 2.29	21	Crude SD recalculated from SEM	Tanner stage matched. (Tanner stage I) Mean age 8.6 ± 0.2 years (*SEM=0.2)
Sir-Petermann 2012	kg/m^2	Not reported	19.8	SEM=0.6 SD = 3.06	26	19.4	SEM=0.8 SD=3.30	17	Crude SD recalculated from SEM	Tanner stage matched. (Tanner stage II) Mean age 9.9 ± 0.2 years (*SEM=0.2)
Sir-Petermann 2012	kg/m^2	Not reported	20.6	SEM=0.9 SD=4.59	26	20.7	SEM=0.9 SD=3.92	19	Crude SD recalculated from SEM	Tanner stage matched. (Tanner stage III) Mean age 10.8 ± 0.2 years (*SEM=0.2)

Sir-Petermann 2012	kg/m^2	Not reported	20.8	SEM=0.7 SD=3.77	29	21.7	SEM=0.5 SD=2.06	17	Crude SD recalculated from SEM	Tanner stage matched. (Tanner stage IV) Mean age 12.2 ± 0.3 years (*SEM=0.3)
Sir-Petermann 2012	kg/m^2	Not reported	22.4	SEM=0.8 SD = 3.92	24	22.0	SEM=0.6 SD = 2.62	19	Crude SD recalculated from SEM	Tanner stage matched. (Tanner stage V) Mean age 13.2 ± 0.3 years (*SEM=0.3)
Sir-Petermann 2012	SDS	Not reported	1.0	SEM=0.2 SD=1.10	30	0.8	SEM=0.2 SD=0.92	21	Crude SD recalculated from SEM	Tanner stage matched. (Tanner stage I) Mean age 8.6 ± 0.2 years (*SEM=0.2)
Sir-Petermann 2012	SDS	Not reported	0.8	SEM=0.2 SD=1.02	26	0.8	SEM=0.2 SD=0.82	17	Crude SD recalculated from SEM	Tanner stage matched. (Tanner stage II) Mean age 9.9 ± 0.2 years (*SEM=0.2)
Sir-Petermann 2012	SDS	Not reported	0.7	SEM=0.2 SD=1.02	26	0.7	SEM=0.2 SD=0.87	19	Crude SD recalculated from SEM	Tanner stage matched. (Tanner stage III) Mean age 10.8 ± 0.2 years (*SEM=0.2)
Sir-Petermann 2012	SDS	Not reported	0.8	SEM=0.2 SD=1.08	29	0.9	SEM=0.1 SD=0.41	17	Crude SD recalculated from SEM	Tanner stage matched. (Tanner stage IV) Mean age 12.2 ± 0.3 years (*SEM=0.3)
Sir-Petermann 2012	SDS	Not reported	0.8	SEM=0.2 SD=0.98	24	0.8	SEM=0.1 SD=0.44	19	Crude SD recalculated from SEM	Tanner stage matched. (Tanner stage V) Mean age 13.2 ± 0.3 years (*SEM=0.3)
Zhang 2022	kg/m^2	Stadiometer, digital scales	16.27	1.12	108	16.10	0.91	109	Crude	Age 18 months
Zhang 2022	kg/m^2	Stadiometer, digital scales	15.85	1.2	108	15.72	0.93	109	Crude	Age 24 months
Zhang 2022	kg/m^2	Stadiometer, digital scales	15.65	1.02	108	15.56	0.95	109	Crude	Age 30 months
Zhang 2022	kg/m^2	Stadiometer, digital scales	15.55	1.17	108	15.42	0.98	109	Crude	Age 3 years
Zhang 2022	kg/m^2	Stadiometer, digital scales	15.53	1.52	108	15.18	0.97	109	Crude	Age 4 years
Zhang 2022	kg/m^2	Stadiometer, digital scales	15.56	1.84	108	15.18	1.14	109	Crude	Age 5 years
Zhang 2022	kg/m^2	Stadiometer, digital scales	15.64	2.02	108	15.25	1.39	109	Crude	Age 6 years
Sons (Infancy)										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?

				95% CI) in Fist Degree Relatives						
Zhang 2022	kg/m^2	Stadiometer, digital scales	17.46	1.35	90	17.49	1.28	118	Crude	Age 3 months
Zhang 2022	kg/m^2	Stadiometer, digital scales	18.05	1.34	90	17.85	1.18	118	Crude	Age 6 months
Zhang 2022	kg/m^2	Stadiometer, digital scales	17.88	1.23	90	17.79	1.06	118	Crude	Age 8 months
Zhang 2022	kg/m^2	Stadiometer, digital scales	17.40	1.19	90	17.21	0.94	118	Crude	Age 12 months
Sons (Childhood)										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Crisosto 2017	kg/m^2	U.S. Growth Charts BMI for age	Median = 18.7	IQR = 17.3–22.4	23	Median = 19.8	IQR = 16.4–22.5	20	Crude	Tanner stage matched. (Tanner stage I) Age median (IQR): 9.1 (8.4–9.6) years
Crisosto 2017	kg/m^2	U.S. Growth Charts BMI for age	Median = 21	IQR = 18.4–24.8	26	Median = 20.2	IQR = 18.2–23.1	31	Crude	Tanner stage matched. (Tanner stage II/III) Age median (IQR): 10.8 (10.3–11.6) years
Crisosto 2017	kg/m^2	U.S. Growth Charts BMI for age	Median = 23	IQR = 20–26.2	20	Median = 22.7	IQR = 20.3–24.5	33	Crude	Tanner stage matched. (Tanner stage IV/V) Age median (IQR): 14.4 (13–16.1) years
Crisosto 2017	SDS	U.S. Growth Charts BMI for age	Median = 1.44	IQR = 0.4–2.6	23	Median = 1.6	IQR = −0.1 – 2.4	20	Crude	Tanner stage matched. (Tanner stage I) Age median (IQR): 9.1 (8.4–9.6) years
Crisosto 2017	SDS	U.S. Growth Charts BMI for age	Median = 1.6	IQR = 0.8–2.5	26	Median = 1.5	IQR = 0.6–2.l	31	Crude	Tanner stage matched. (Tanner stage II/III) Age median (IQR): 10.8 (10.3–11.6) years

Crisosto 2017	SDS	U.S. Growth Charts BMI for age	Median = 1.6	IQR = 0.4–2.0	20	Median = 1.2	IQR = 0.6–1.8	33	Crude	Tanner stage matched. (Tanner stage IV/V) Age median (IQR): 14.4 (13–16.1) years
Kent 2008	kg/m^2	Not reported	20.9	5.1	15	19.4	3.3	17	Crude	Tanner stage, Age 9.7 ± 3.4 years (FDR)
Recabarren 2008	kg/m^2	U.S. Growth Charts BMI for age	Median = 17.4	Range = 14.9 –24.7	31	Median = 15.1	Range = 13.8 – 18.8	17	Crude	Age median 6.0 (range 4.0 – 7.5) years and socio-economic status matched.
Recabarren 2008	SDS	U.S. Growth Charts BMI for age	Median = 1.2	Range = -0.7-2.9	31	Median = -0.2	Range = -1.9-2.1	17	Crude	Age median 6.0 (range 4.0 – 7.5) years and socio-economic status matched.
Zhang 2022	kg/m^2	Stadiometer, digital scales	16.67	1.03	90	16.38	0.88	118	Crude	Age 18 months
Zhang 2022	kg/m^2	Stadiometer, digital scales	16.14	0.97	90	15.98	1.04	118	Crude	Age 24 months
Zhang 2022	kg/m^2	Stadiometer, digital scales	16.05	1.17	90	15.92	0.92	118	Crude	Age 30 months
Zhang 2022	kg/m^2	Stadiometer, digital scales	15.72	1.17	90	15.70	0.95	118	Crude	Age 3 years
Zhang 2022	kg/m^2	Stadiometer, digital scales	15.77	1.31	90	15.70	1.21	118	Crude	Age 4 years
Zhang 2022	kg/m^2	Stadiometer, digital scales	16.07	2.12	90	15.73	1.63	118	Crude	Age 5 years
Zhang 2022	kg/m^2	Stadiometer, digital scales	16.23	1.95	90	15.86	1.72	118	Crude	Age 6 years
Sons (Adulthood)										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Recabarren 2008	kg/m^2	U.S. Growth Charts BMI for age	Median = 25.1	Range = 20.0 – 45.4	29	Median = 22.9	Range = 19.4 – 29.1	19	Crude	Age median 22.0 (range 18.0 – 29.0) years and socio-economic status matched.

OUTCOME: Weight				OUTCOME TYPE: Continuous						
Female first degree relatives										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Harnois-Leblanc 2017	kg	Not reported	Median = 57.4	IQR = 45.7-77.6	8	Median = 58.5	IQR = 54.2-73.9	8	Crude	Age matched. (median age 17.5 years; IQR 14.4-20.1 years)
Harnois-Leblanc 2017	z score	Not reported	Median = 0.63	IQR = 0.02–1.71	8	Median = 0.26	QR = −0.96–1.52	8	Crude	Age matched. (median age 17.5 years; IQR 14.4-20.1 years)
Fathers										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Coviello 2009	kg	Not reported	94	18	211	83	15	1153	Crude	Age range similar, however mean age varied (Mean age 57 ± 9 years), ethnicity matched
All offspring										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
deWilde 2018	kg	Digital scales	16.1	2.6	42	17.1	2.3	168	Crude	Age 3.3 ± 0.6 years (FDR)

deWilde 2018	kg	Digital scales	23.8	4.3	32	27.9	4.2	130	Crude	Age 7.0 ± 0.8 years (FDR)
Li 2020	z score	Not reported	0.3	1.0	70	0.7	1.1	71	Crude	Maternal age and BMI matched (median age 3.51; IQR 3.2-5.16 years)
Zhang 2022	kg	Digital scales	6.73	0.74	198	6.69	0.67	227	Crude	Age 3 months
Zhang 2022	kg	Digital scales	8.34	0.9	198	8.29	0.78	227	Crude	Age 6 months
Zhang 2022	kg	Digital scales	9.08	1.01	198	8.98	0.85	227	Crude	Age 8 months
Zhang 2022	kg	Digital scales	10.07	1.02	198	9.9	0.88	227	Crude	Age 12 months
Zhang 2022	kg	Digital scales	11.28	1.11	198	11.17	1.00	227	Crude	Age 18 months
Zhang 2022	kg	Digital scales	12.51	1.29	198	12.41	1.21	227	Crude	Age 24 months
Zhang 2022	kg	Digital scales	13.86	1.47	198	13.70	1.35	227	Crude	Age 30 months
Zhang 2022	kg	Digital scales	15.01	1.71	198	14.77	1.48	227	Crude	Age 3 years
Zhang 2022	kg	Digital scales	17.11	2.19	198	16.71	1.90	227	Crude	Age 4 years
Zhang 2022	kg	Digital scales	19.82	3.59	198	19.12	2.80	227	Crude	Age 5 years
Zhang 2022	kg	Digital scales	22.51	4.16	198	21.89	3.44	227	Crude	Age 6 years
Daughters (Infancy)										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Torchen 2016	Weight for length z score	Not reported	0.43	1.04	21	-0.29	0.99	36	Crude	Age and ethnicity matched. Mean age 1.7 ± 0.6 years (FDR)
Zhang 2022	kg	Digital scales	6.57	0.65	108	6.39	0.55	109	Crude	Age 3 months
Zhang 2022	kg	Digital scales	8.16	0.87	108	7.99	0.70	109	Crude	Age 6 months
Zhang 2022	kg	Digital scales	8.92	0.98	108	8.63	0.76	109	Crude	Age 8 months
Zhang 2022	kg	Digital scales	9.88	1.01	108	9.57	0.81	109	Crude	Age 12 months
Daughters (Childhood)										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?

Sir-Petermann 2012	kg	Not reported	33.5	SEM=1.8 SD=9.86	30	32.0	SEM=1.3 SD=5.96	21	Crude SD recalculated from SEM	Tanner stage matched. (Tanner stage I) Mean age 8.6 ± 0.2 years (*SEM=0.2)
Sir-Petermann 2012	kg	Not reported	37.4	SEM=1.4 SD=7.14	26	37.8	SEM=2.0 SD=8.25	17	Crude SD recalculated from SEM	Tanner stage matched. (Tanner stage II) Mean age 9.9 ± 0.2 years (*SEM=0.2)
Sir-Petermann 2012	kg	Not reported	43.6	SEM=2.6 SD=13.26	26	44.3	SEM=2.3 SD=10.03	19	Crude SD recalculated from SEM	Tanner stage matched. (Tanner stage III) Mean age 10.8 ± 0.2 years (*SEM=0.2)
Sir-Petermann 2012	kg	Not reported	48.5	SEM=2.1 SD=11.31	29	51.0	SEM=1.4 SD=5.77	17	Crude SD recalculated from SEM	Tanner stage matched. (Tanner stage IV) Mean age 12.2 ± 0.3 years (*SEM=0.3)
Sir-Petermann 2012	kg	Not reported	53.3	SEM=2.7 SD=13.23	24	52.6	SEM=1.5 SD=6.54	19	Crude SD recalculated from SEM	Tanner stage matched. (Tanner stage V) Mean age 13.2 ± 0.3 years (*SEM=0.3)
Sir-Petermann 2012	SDS	Not reported	0.7	SEM=0.2 SD=1.10	30	0.4	SEM=0.2 SD=0.92	21	Crude SD recalculated from SEM	Tanner stage matched. (Tanner stage I) Mean age 8.6 ± 0.2 years (*SEM=0.2)
Sir-Petermann 2012	SDS	Not reported	0.5	SEM=0.2 SD=1.02	26	0.7	SEM=0.2 SD=0.82	17	Crude SD recalculated from SEM	Tanner stage matched. (Tanner stage II) Mean age 9.9 ± 0.2 years (*SEM=0.2)
Sir-Petermann 2012	SDS	Not reported	0.6	SEM=0.2 SD=1.02	26	0.6	SEM=0.2 SD=0.87	19	Crude SD recalculated from SEM	Tanner stage matched. (Tanner stage III) Mean age 10.8 ± 0.2 years (*SEM=0.2)
Sir-Petermann 2012	SDS	Not reported	0.6	SEM=0.2 SD=1.08	29	0.7	SEM=0.1 SD=0.41	17	Crude SD recalculated from SEM	Tanner stage matched. (Tanner stage IV) Mean age 12.2 ± 0.3 years (*SEM=0.3)
Sir-Petermann 2012	SDS	Not reported	0.5	SEM=0.2 SD=0.98	24	0.6	SEM=0.2 SD=0.87	19	Crude SD recalculated from SEM	Tanner stage matched. (Tanner stage V) Mean age 13.2 ± 0.3 years (*SEM=0.3)
Zhang 2022	kg	Digital scales	11.07	1.12	108	10.80	0.94	109	Crude	Age 18 months
Zhang 2022	kg	Digital scales	12.25	1.33	108	12.03	1.08	109	Crude	Age 24 months
Zhang 2022	kg	Digital scales	13.57	1.37	108	13.26	1.32	109	Crude	Age 30 months
Zhang 2022	kg	Digital scales	14.77	1.58	108	14.34	1.33	109	Crude	Age 3 years
Zhang 2022	kg	Digital scales	16.78	2.11	108	16.28	1.76	109	Crude	Age 4 years
Zhang 2022	kg	Digital scales	19.32	3.13	108	18.54	2.20	109	Crude	Age 5 years
Zhang 2022	kg	Digital scales	22.00	3.71	108	21.12	2.76	109	Crude	Age 6 years
Sons (Infancy)										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in	SD (or specify if other	Sample size	Mean (specify if median) or	SD (or specify if other measure: SE, IQR or 95%	Sample size	Are these values	If adjusted, what variables were included in the model?

			First Degree Relatives	measure: IQR, SE or 95% CI) in Fist Degree Relatives		median in control group	CI) in control group		adjusted or crude?	
Recabarren 2008	kg	Not reported	Median = 6.1	Range = 4.9 – 8.4	20	Median = 5.6	Range = 5.0 – 7.5	20	Crude	Age median 2.0 (range 2.0 - 3.0) months and socio-economic status matched.
Recabarren 2008	SDS	Not reported	Median = 0.5	Range = -0.9 - 3.0	20	Median = 0.3	Range = -0.8 - 2.0	20	Crude	Age median 2.0 (range 2.0 - 3.0) months and socio-economic status matched.
Zhang 2022	kg	Digital scales	6.92	0.80	90	6.96	0.65	118	Crude	Age 3 months
Zhang 2022	kg	Digital scales	8.56	0.89	90	8.58	0.75	118	Crude	Age 6 months
Zhang 2022	kg	Digital scales	9.28	1.02	90	9.30	0.80	118	Crude	Age 8 months
Zhang 2022	kg	Digital scales	10.30	0.98	90	10.22	0.82	118	Crude	Age 12 months
Sons (Childhood)										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Crisosto 2017	kg	Not reported	Median = 34	IQR = 30–42	23	Median = 36	IQR = 27–39	20	Crude	Tanner stage matched. (Tanner stage I) Age median (IQR): 9.1 (8.4–9.6) years
Crisosto 2017	kg	Not reported	Median = 41	IQR = 36–55	26	Median = 39	IQR = 35–48	31	Crude	Tanner stage matched. (Tanner stage II/III) Age median (IQR): 10.8 (10.3–11.6) years
Crisosto 2017	kg	Not reported	Median = 64	IQR = 55–76	20	Median = 58	IQR = 52–73	33	Crude	Tanner stage matched. (Tanner stage IV/V) Age median (IQR): 14.4 (13–16.1) years
Recabarren 2008	kg	Not reported	Median = 23.0	Range = 14.3 – 38.7	31	Median = 19.4	Range = 14.5 – 24.0	17	Crude	Age median 6.0 (range 4.0 – 7.5) years and socio-economic status matched.

Recabarren 2008	SDS	Not reported	Median = 1.0	Range = -1.3-2.8	31	Median = -0.3	Range = -1.6-1.6	17	Crude	Age median 6.0 (range 4.0 – 7.5) years and socio-economic status matched.
Zhang 2022	kg	Digital scales	11.54	1.05	90	11.51	0.94	118	Crude	Age 18 months
Zhang 2022	kg	Digital scales	12.82	1.16	90	12.75	1.22	118	Crude	Age 24 months
Zhang 2022	kg	Digital scales	14.23	1.52	90	14.09	1.26	118	Crude	Age 30 months
Zhang 2022	kg	Digital scales	15.30	1.81	90	15.16	1.50	118	Crude	Age 3 years
Zhang 2022	kg	Digital scales	17.55	2.22	90	17.13	1.94	118	Crude	Age 4 years
Zhang 2022	kg	Digital scales	20.43	4.01	90	19.65	3.17	118	Crude	Age 5 years
Zhang 2022	kg	Digital scales	23.12	4.58	90	22.57	3.84	118	Crude	Age 6 years
Sons (Adulthood)										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Recabarren 2008	kg	Not reported	Median = 78.0	Range = 56.2–139.0	29	Median = 72.5	Range = 54.0 – 86.0	19	Crude	Age median 22.0 (range 18.0 – 29.0) years and socio-economic status matched.

OUTCOME: Waist circumference						OUTCOME TYPE: Continuous				
Female first degree relatives										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Harnois-Leblanc 2017	z score	Anatomical landmarks reported	Median = -0.38	IQR = -1.25--0.38	8	Median = -0.98	IQR = -1.50-0.50	8	Crude	Age matched. (median age 17.5 years; IQR 14.4-20.1 years)

Raissouni 2012	cm	Anatomical landmarks reported	72	10.9	18	76	8.7	21	Crude	Age, weight and Tanner stage matched. (mean age 11.6 ± 1.4 years)
Fathers										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Coviello 2009	cm	Not reported	104	14	211	100	12	1153	Crude	Age range similar, however mean age varied (Mean age 57 ± 9 years), ethnicity matched
Mothers										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Sam 2006	cm	Not reported	92	16	215	89	15	62	Crude	Age, weight, ethnicity matched (mean age 52 ± 8 years)
Brothers										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Baillargeon 2007	cm	Anatomical landmarks reported	92	12	17	88	11	28	Crude	Age and BMI matched (mean age 31 ± 9 years)

Sam 2008	cm	Not reported	93	15	196	96	14	169	Crude	Age, BMI, and ethnicity matched (mean age 30 ± 8 years)
Sir-Petermann 2004	cm	Anatomical landmarks reported	87.6	Range = 60.0 - 106.0	22	88.1	Range = 77-114	14	Crude	Age and BMI (mean age 23 years, range 19-39 years)
Sisters										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Sam 2005	cm	Not reported	87	15	38	91	16	125	Crude	Weight and ethnicity matched, Mean age 26 ± 6 years -subgroup with hyperandrogenism (duplicated control group)
Sam 2005	cm	Not reported	82	13	143	91	16	125	Crude	Weight and ethnicity matched, Mean age 31± 9 years -subgroup without PCOS features (duplicated control group)
All offspring										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
deWilde 2018	cm	Anatomical landmarks reported	51.3	3.8	42	52.8	3.5	168	Crude	Age 3.3 ± 0.6 years (FDR)
deWilde 2018	cm	Anatomical landmarks reported	54.5	4.1	32	58.2	4.7	130	Crude	Age 7.0 ± 0.8 years (FDR)
Daughters (Childhood)										

Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Sir-Petermann 2012	cm	Not reported	64.2	SEM=2.2 SD=12.0	30	60.6	SEM=1.4 SD=6.4	21	Crude SD recalculated from SEM	Tanner stage matched. (Tanner stage I) Mean age 8.6 ± 0.2 years (*SEM=0.2)
Sir-Petermann 2012	cm	Not reported	65.7	SEM=1.7 SD=8.7	26	65.3	SEM=2.1 SD=8.7	17	Crude SD recalculated from SEM	Tanner stage matched. (Tanner stage II) Mean age 9.9 ± 0.2 years (*SEM=0.2)
Sir-Petermann 2012	cm	Not reported	69.0	SEM=2.3 SD=11.7	26	69.3	SEM=1.8 SD=7.8	19	Crude SD recalculated from SEM	Tanner stage matched. (Tanner stage III) Mean age 10.8 ± 0.2 years (*SEM=0.2)
Sir-Petermann 2012	cm	Not reported	68.1	SEM=1.5 SD=8.1	29	70.1	SEM=1.1 SD=4.5	17	Crude SD recalculated from SEM	Tanner stage matched. (Tanner stage IV) Mean age 12.2 ± 0.3 years (*SEM=0.3)
Sir-Petermann 2012	cm	Not reported	70.9	SEM=1.9 SD=9.3	24	70.7	SEM=1.5 SD=6.5	19	Crude SD recalculated from SEM	Tanner stage matched. (Tanner stage/V) Mean age 13.2 ± 0.3 years (*SEM=0.3)
Sons (Childhood)										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Crisosto 2017	cm	Not reported	Median = 63	IQR = 60–70	23	Median = 63	IQR = 59–68	20	Crude	Tanner stage matched. (Tanner stage I) Age median (IQR): 9.1 (8.4–9.6) years

Crisosto 2017	cm	Not reported	Median = 71	IQR = 66–79	26	Median = 66	IQR = 61–75	31	Crude	Tanner stage matched. (Tanner stage II/III) Age median (IQR): 10.8 (10.3–11.6) years
Crisosto 2017	cm	Not reported	Median = 78	IQR = 71–84	20	Median = 74	IQR = 70–81	33	Crude	Tanner stage matched. (Tanner stage IV/V) Age median (IQR): 14.4 (13–16.1) years
Recabarren 2008	cm	Not reported	Median = 57.5	Range = 47.0 – 70.0	31	Median = 51.0	Range = 46.0 – 61.5	17	Crude	Age median 6.0 (range 4.0 – 7.5) years and socio-economic status matched.
Sons (Adulthood)										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Recabarren 2008	cm	Not reported	Median = 87.0	Range = 65.0 –129.0	29	Median = 82.0	Range = 71.0 – 95.0	19	Crude	Age median 22.0 (range 18.0 – 29.0) years and socio-economic status matched.

OUTCOME: Waist hip ratio						OUTCOME TYPE: Continuous				
All first degree relatives										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Yilmaz 2005	Ratio (no units)	Ratio of waist to hip circumference (anatomical	0.84	0.08	84	0.83	0.07	73	Crude	Age and weight matched (mean age 43.78 ± 13.14 years)

		landmarks defined)								
Female first degree relatives										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Harnois-Leblanc 2017	z score	Ratio of waist to hip circumference (anatomical landmarks defined)	Median = -0.41	IQR = -1.04-0.57	8	Median = -0.88	IQR = -1.06-0.54	8	Crude	Age matched. (median age 17.5 years; IQR 14.4-20.1 years)
Raissouni 2012	Ratio (no units)	Ratio of waist to hip circumference (anatomical landmarks defined)	Median = 0.83	IQR = 0.77-0.86	9	Median = 0.77	IQR = 0.71-0.82	10	Crude	Age matched. (median age 12.1; IQR 9.7-13.7 years) - extracted from Trottier substudy
Parents										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Vipin 2016	Ratio (no units)	Ratio of waist to hip circumference (anatomical landmarks defined)	Median = 0.98	IQR = 0.91-1.01	86	Median = 0.92	IQR = 0.89-0.97	86	Crude	Age and BMI matched (mean age 50.4 ± 5.6 years)
Fathers										

Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Vipin 2016	Ratio (no units)	Ratio of waist to hip circumference (anatomical landmarks defined)	Median = 1	IQR = 0.96-1.03	41	Median = 0.92	IQR = 0.88-0.97	42	Crude	Age and BMI matched (mean age 53.1 ± 5.1 years)
Yildiz 2003	Ratio (no units)	Ratio of waist to hip circumference (anatomical landmarks defined)	0.95	0.1	24	0.97	0.09	12	Crude	Age and weight matched (mean age 50.4 ± 4.0 years)
Yilmaz 2005	Ratio (no units)	Ratio of waist to hip circumference (anatomical landmarks defined)	0.84	0.08	38	0.79	0.07	20	Crude	Age (mean age 51.87 ± 8.54 years) and weight matched
Mothers										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Vipin 2016	Ratio (no units)	Ratio of waist to hip circumference (anatomical landmarks defined)	0.95	0.06	45	0.93	0.48	44	Crude	Age and BMI matched (mean age 47.9 ± 4.9 years)

Yildiz 2003	Ratio (no units)	Ratio of waist to hip circumference (anatomical landmarks defined)	0.83	0.06	23	0.78	0.04	16	Crude	Age and weight matched (mean age 44.5 ± 3.3 years) - premenopausal subgroup
Yildiz 2003	Ratio (no units)	Ratio of waist to hip circumference (anatomical landmarks defined)	0.85	0.06	11	0.77	0.05	8	Crude	Age and weight matched (mean age 50.4 ± 4.9 years) - postmenopausal subgroup
Yilmaz 2005	Ratio (no units)	Ratio of waist to hip circumference (anatomical landmarks defined)	0.87	0.08	40	0.83	0.07	20	Crude	Age (mean age 46.38 ± 7.95 years) and weight matched
Brothers										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Karthik 2019	Ratio (no units)	WHO criteria	Median = 0.88	IQR = 0.83 - 0.94	41	Median = 0.89	IQR = 0.86 - 0.93	41	Crude	Age and BMI matched (mean age 23.3 ± 4.3 years)
Lenarcik 2011	Ratio (no units)	Not reported	0.89	0.07	42	0.88	0.06	30	Crude	Age (mean age 23.52 ± 5.05 years) and weight matched
Sam 2008	Ratio (no units)	Not reported	0.91	0.07	49	0.91	0.08	48	Crude	Age, BMI, and ethnicity matched (mean age 30 ± 8 years)
Yildiz 2003	Ratio (no units)	Ratio of waist to hip circumference (anatomical	0.84	0.07	25	0.86	0.07	15	Crude	Age and weight matched (mean age 23.8 ± 5.3 years)

		landmarks defined)								
Yilmaz 2005	Ratio (no units)	Ratio of waist to hip circumference (anatomical landmarks defined)	0.80	0.08	17	0.80	0.07	15	Crude	Age (mean age 29.00 ± 11.10 years) and weight matched
Sisters										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Diamanti-Kandarakis 2004	Ratio (no units)	Not reported	0.72	0.014	17	0.72	0.015	20	Crude	Age (Mean age 22.88 ± 0.93 years) and BMI matched
Joharatnam 2011	Ratio (no units)	Not reported	0.78	0.01	153	0.78	0.08	76	Crude	Mean age 31.3 ± 6 years-subgroup with polycystic ovaries (duplicate control group)
Joharatnam 2011	Ratio (no units)	Not reported	0.78	0.02	61	0.78	0.08	76	Crude	Mean age 37.8 ± 7.7 years - subgroup without polycystic ovaries (duplicate control group)
Karthik 2019	Ratio (no units)	WHO standards	0.84	0.07	35	0.84	0.05	35	Crude	Age and BMI matched (Median age 24 years; IQR 19-27)
Kulshreshtha 2019	Ratio (no units)	Ratio of waist to hip circumference (anatomical landmarks defined)	0.84	0.005	200	0.85	0.06	99	Crude	Age matched (Mean age 25.42 ± 7.89 years)
Lenarcik 2011	Ratio (no units)	Not reported	0.79	0.05	44	0.81	0.06	70	Crude	Age (mean age 25.52 ± 5.78 years) and weight matched

Yildiz 2003	Ratio (no units)	Ratio of waist to hip circumference (anatomical landmarks defined)	0.77	0.08	19	0.72	0.04	31	Crude	Age and weight matched (mean age 25.1 ± 5.7 years)
Yilmaz 2005	Ratio (no units)	Ratio of waist to hip circumference (anatomical landmarks defined)	0.82	0.08	25	0.81	0.07	20	Crude	Age (mean age 23.50 ± 7.56 years) and weight matched
Daughters (Childhood)										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Legro 2017	Ratio (no units)	Ratio of waist to hip circumference (anatomical landmarks defined)	0.90	0.07	47	0.87	0.07	36	Crude	Tanner stage matched. (Tanner stage I) Mean age 7.02 ±1.96 years
Legro 2017	Ratio (no units)	Ratio of waist to hip circumference (anatomical landmarks defined)	0.88	0.09	16	0.85	0.06	27	Crude	Tanner stage matched. (Tanner stage II/III) Mean age 11.46 ±1.33 years
Legro 2017	Ratio (no units)	Ratio of waist to hip circumference (anatomical landmarks defined)	0.86	0.05	12	0.84	0.08	16	Crude	Tanner stage matched. (Tanner stage IV/V) Mean age 15.24 ±1.17 years
Sir-Petermann 2012	Ratio (no units)	Not reported	0.9	SEM=0.0 SD=0	30	0.9	SEM=0.0 SD=0	21	Crude	Tanner stage matched. (Tanner stage I) Mean age

									SD recalculated from SEM	8.6 ± 0.2 years (*SEM=0.2)
Sir-Petermann 2012	Ratio (no units)	Not reported	0.9	SEM=0.0 SD=0	26	0.9	SEM=0.0 SD=0	17	Crude SD recalculated from SEM	Tanner stage matched. (Tanner stage II) Mean age 9.9 ± 0.2 years (*SEM=0.2)
Sir-Petermann 2012	Ratio (no units)	Not reported	0.9	SEM=0.0 SD=0	26	0.9	SEM=0.0 SD=0	19	Crude SD recalculated from SEM	Tanner stage matched. (Tanner stage III) Mean age 10.8 ± 0.2 years (*SEM=0.2)
Sir-Petermann 2012	Ratio (no units)	Not reported	0.8	SEM=0.0 SD=0	29	0.8	SEM=0.0 SD=0	17	Crude SD recalculated from SEM	Tanner stage matched. (Tanner stage IV) Mean age 12.2 ± 0.3 years (*SEM=0.3)
Sir-Petermann 2012	Ratio (no units)	Not reported	0.8	SEM=0.0 SD=0	24	0.8	SEM=0.0 SD=0	19	Crude SD recalculated from SEM	Tanner stage matched. (Tanner stage/V) Mean age 13.2 ± 0.3 years (*SEM=0.3)
Sons (Childhood)										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Crisosto 2017	Ratio (no units)	Not reported	Median = 0.91	IQR = 0.9–0.96	23	Median = 0.9	IQR = 0.86–0.93	20	Crude	Tanner stage matched. (Tanner stage I) Age median (IQR): 9.1 (8.4–9.6) years
Crisosto 2017	Ratio (no units)	Not reported	Median = 0.94	IQR = 0.93–0.96	26	Median = 0.92	IQR = 0.88–0.94	31	Crude	Tanner stage matched. (Tanner stage II/III) Age median (IQR): 10.8 (10.3–11.6) years
Crisosto 2017	Ratio (no units)	Not reported	Median = 0.91	IQR = 0.88–0.96	20	Median = 0.91	IQR = 0.88–0.94	33	Crude	Tanner stage matched. (Tanner stage IV/V) Age median (IQR): 14.4 (13–16.1) years

Kent 2008	Ratio (no units)	Not reported	0.9	0.1	15	0.8	0.0	17	Crude	Tanner stage, Age 9.7 ± 3.4 years (FDR)

OUTCOME: Systolic blood pressure				OUTCOME TYPE: Continuous						
Parents										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Vipin 2016	mmHg	Standardised	Median = 130	IQR = 120-136	86	Median = 121	IQR = 110-128	86	Crude	Age and BMI matched (mean age 50.4 ± 5.6 years)
Fathers										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Coviello 2009	mmHg	Not reported	131	17	211	133	18	1153	Crude	Age range similar, however mean age varied (Mean age 57 ± 9 years), ethnicity matched
Vipin 2016	mmHg	Standardised	Median = 130	IQR = 122-136	41	Median = 120	IQR = 110-130	42	Crude	Age and BMI matched (mean age 53.1 ± 5.1 years)
Yilmaz 2005	mmHg	Not reported	145.92	19.71	38	130.18	12.64	20	Crude	Age (mean age 51.87 ± 8.54 years) and weight matched
Mothers										

Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Sam 2006	mmHg	Not reported	125	17	215	120	15	62	Crude	Age, weight, ethnicity matched (mean age 52 ± 8 years)
Vipin 2016	mmHg	Standardised	128	14	45	121	10	44	Crude	Age and BMI matched (mean age 47.9 ± 4.9 years)
Yilmaz 2005	mmHg	Not reported	144.39	21.18	40	128.12	10.83	20	Crude	Age (mean age 46.38 ± 7.95 years) and weight matched
Brothers										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Baillargeon 2007	mmHg	Standardised measurement	124	19	17	120	13	28	Crude	Age and BMI matched (mean age 31 ± 9 years)
Karthik 2019	mmHg	Automated measurement	Median = 120	IQR = 110 - 126	41	Median = 116	IQR = 110 - 122	41	Crude	Age and BMI matched (mean age 23.3 ± 4.3 years)
Sam 2008	mmHg	Standardised measurement	125	15	196	123	12	169	Crude	Age, BMI, and ethnicity matched (mean age 30 ± 8 years)
Yilmaz 2005	mmHg	Not reported	126.19	9.75	17	124.98	9.77	15	Crude	Age (mean age 29.00 ± 11.10 years) and weight matched
Sisters										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First	SD (or specify if other	Sample size	Mean (specify if median) or	SD (or specify if other measure: SE, IQR or 95%	Sample size	Are these values	If adjusted, what variables were included in the model?

			Degree Relatives	measure: IQR, SE or 95% CI) in Fist Degree Relatives		median in control group	CI) in control group		adjusted or crude?	
Karthik 2019	mmHg	Automated measurement	Median = 110	IQR = 104 - 120	35	Median = 108	IQR = 100 - 120	35	Crude	Age and BMI matched (Median age 24 years; IQR 19-27)
Kulshreshtha 2019	mmHg	Not reported	118.56	10.74	200	118.74	6.9	99	Crude	Age matched (Mean age 25.42 ± 7.89 years)
Sam 2005	cm	Not reported	118	12	38	115	11	125	Crude	Weight and ethnicity matched, Mean age 26 ± 6 years -subgroup with hyperandrogenism (duplicated control group)
Sam 2005	cm	Not reported	114	14	143	115	11	125	Crude	Weight and ethnicity matched, Mean age 31± 9 years -subgroup without PCOS features (duplicated control group)
Yilmaz 2005	mmHg	Not reported	124.12	9.69	25	124.62	9.72	20	Crude	Age (mean age 23.50 ± 7.56 years) and weight matched
All offspring										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
deWilde 2018	mmHg	Not reported	93	7	31	94	7	136	Crude	Age 3.3 ± 0.6 years (FDR)
deWilde 2018	mmHg	Not reported	103	6	32	105	8	129	Crude	Age 7.0 ± 0.8 years (FDR)
Li 2020	mmHg	Not reported	Median = 90	IQR = 88-96	70	Median = 90	IQR = 88-100	71	Crude	Maternal age and BMI matched (median age 3.51; IQR 3.2-5.16 years)
Daughters (Childhood)										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First	SD (or specify if other	Sample size	Mean (specify if median) or	SD (or specify if other measure: SE, IQR or 95%	Sample size	Are these values	If adjusted, what variables were included in the model?

			Degree Relatives	measure: IQR, SE or 95% CI) in Fist Degree Relatives		median in control group	CI) in control group		adjusted or crude?	
Crisosto 2019	mmHg	Not reported	Median = 100.0	IQR = 90.0–110.0	43	Median = 100.0	IQR = 90.0–110.0	28	Crude	Age, gynecologic age, menarchal age, BMI, waist, WHR, and birth weight matched. Age median (IQR): 15.42 (14.17–16.17)
Legro 2017	mmHg	Standardised measurement	100.42	12.73	45	101.74	11.61	38	Crude	Tanner stage matched. (Tanner stage I) Mean age 7.02 ±1.96 years
Legro 2017	mmHg	Standardised measurement	107.25	12.26	16	108.04	9.2	27	Crude	Tanner stage matched. (Tanner stage II/III) Mean age 11.46 ±1.33 years
Legro 2017	mmHg	Standardised measurement	114.85	14.49	13	114.25	12.79	16	Crude	Tanner stage matched. (Tanner stage IV/V) Mean age 15.24 ±1.17 years
Sons (Childhood)										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) First Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Kent 2008	mmHg	Standardised measurement	110.6	18.1	15	107.4	9.9	17	Crude	Tanner stage, Age 9.7 ± 3.4 years (FDR)

OUTCOME: Diastolic blood pressure			OUTCOME TYPE: Continuous							
Parents										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?

				Fist Degree Relatives						
Vipin 2016	mmHg	Standardised	Median = 82	IQR = 80-88	86	Median = 80	IQR = 78-82	86	Crude	Age and BMI matched (mean age 50.4 ± 5.6 years)
Fathers										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Coviello 2009	mmHg	Not reported	79	10	211	77	10	1153	Crude	Age range similar, however mean age varied (Mean age 57 ± 9 years), ethnicity matched
Vipin 2016	mmHg	Standardised	Median = 84	IQR = 80-88	41	Median = 80	IQR = 70-82	42	Crude	Age and BMI matched (mean age 53.1 ± 5.1 years)
Yilmaz 2005	mmHg	Not reported	87.19	11.57	38	79.23	8.65	20	Crude	Age (mean age 51.87 ± 8.54 years) and weight matched
Mothers										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Sam 2006	mmHg	Not reported	74	10	215	74	9	62	Crude	Age, weight, ethnicity matched (mean age 52 ± 8 years)
Vipin 2016	mmHg	Standardised	Median = 82	IQR = 80-86	45	Median = 80	IQR = 78-82	44	Crude	Age and BMI matched (mean age 47.9 ± 4.9 years)

Yilmaz 2005	mmHg	Not reported	86.12	9.86	40	76.98	7.47	20	Crude	Age (mean age 46.38 ± 7.95 years) and weight matched
Brothers										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Baillargeon 2007	mmHg	Standardised measurement	74	12	17	68	10	28	Crude	Age and BMI matched (mean age 31 ± 9 years)
Karthik 2019	mmHg	Automated measurement	76	6	41	72	6	41	Crude	Age and BMI matched (mean age 23.3 ± 4.3 years)
Krysiak 2021	mmHg	Not reported	95	3	24	94	3	26	Crude	Age, BP, BMI, body composition matched (mean age 39 ± 8 years)
Krysiak 2021 2	mmHg	Not reported	85	8	20	84	8	20	Crude	Age, BP, BMI, lipid level (mean age 50 ± 12 years)
Sam 2008	mmHg	Standardised measurement	77	10	196	75	9	169	Crude	Age, BMI, and ethnicity matched (mean age 30 ± 8 years)
Yilmaz 2005	mmHg	Not reported	76.48	6.53	17	76.73	6.54	15	Crude	Age (mean age 29.00 ± 11.10 years) and weight matched
Sisters										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Karthik 2019	mmHg	Automated measurement	71	8	35	69	8	35	Crude	Age and BMI matched (Median age 24 years; IQR 19-27)

Kulshreshtha 2019	mmHg	Not reported	72.97	7.2	200	72.02	6.7	99	Crude	Age matched (Mean age 25.42 ± 7.89 years)
Sam 2005	mmHg	Standardised measurement	71	7	38	73	10	125	Crude	Weight and ethnicity matched, Mean age 26 ± 6 years -subgroup with hyperandrogenism (duplicated control group)
Sam 2005	mmHg	Standardised measurement	70	9	143	73	10	125	Crude	Weight and ethnicity matched, Mean age 31± 9 years -subgroup without PCOS features (duplicated control group)
Yilmaz 2005	mmHg	Not reported	76.23	6.28	25	76.37	6.49	20	Crude	Age (mean age 23.50 ± 7.56 years) and weight matched
All offspring										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
deWilde 2018	mmHg	Not reported	48	6	31	50	5	136	Crude	Age 3.3 ± 0.6 years (FDR)
deWilde 2018	mmHg	Not reported	55	6	32	54	6	129	Crude	Age 7.0 ± 0.8 years (FDR)
Li 2020	mmHg	Not reported	Median = 58	IQR = 54-60	70	Median = 58	IQR = 52-60	71	Crude	Maternal age and BMI matched (median age 3.51; IQR 3.2-5.16 years)
Daughters (Childhood)										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Crisosto 2019	mmHg	Not reported	Median = 60.0	IQR = 60.0–70.0	43	Median = 60.0	IQR = 60.0–70.0	28	Crude	Age, gynecologic age, menarchal age, BMI, waist, WHR, and birth

										weight matched. Age median (IQR): 15.42 (14.17–16.17)
Legro 2017	mmHg	Standardised measurement	62.67	6.55	45	62.74	6.93	38	Crude	Tanner stage matched. (Tanner stage I) Mean age 7.02 ±1.96 years
Legro 2017	mmHg	Standardised measurement	65.81	7.07	16	66.00	7.72	27	Crude	Tanner stage matched. (Tanner stage II/III) Mean age 11.46 ±1.33 years
Legro 2017	mmHg	Standardised measurement	71.08	10.23	13	67.25	9.64	16	Crude	Tanner stage matched. (Tanner stage IV/V) Mean age 15.24 ±1.17 years
Sons (Childhood)										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) First Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Kent 2008	mmHg	Standardised measurement	65.6	8.5	15	64.8	7.5	17	Crude	Tanner stage, Age 9.7 ± 3.4 years (FDR)

OUTCOME: Fasting glucose				OUTCOME TYPE: Continuous						
Female first degree relatives										
Author, year	Unit of outcome	Method of measurement	Mean in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) First Degree Relatives	Sample size	Mean or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Harnois-Leblanc 2017	mmol/L	Glucose hexokinase	Median = 4.6	IQR = 4.4-4.8	8	Median = 5.0	IQR = 4.6-5.3	8	Crude	Age matched. (median age 17.5 years; IQR 14.4-20.1 years)
Raissouni 2012	mg/dL	Glucose hexokinase	Median = 86	IQR = 83-90	9	Median = 85	IQR = 79-88	10	Crude	Age matched. (median age 12.1; IQR 9.7-13.7 years) - extracted from Trottier substudy
	mmol/L conversion		Median = 4.78	IQR = 4.61-5	9	Median = 4.72	IQR = 4.39-4.89	10		
Torchen 2014	mg/dL		Median = 92	IQR = 89-95	12	Median = 90	IQR = 88-90	10	Crude	

	mmol/L conversion	Glucose oxidase	Median = 5.11	Range = 4.94-5.28	12	Median = 5.0	IQR = 4.89-5	10		Age, BMI, visceral adiposity and breast Tanner stage matched. Median age 10.4 years (IQR 8.8-12.1 years)
Unluhizarci 2007	mg/dL	Not reported	77.1	SEM = 2.0 SD=16.7 Range =40–120	70	64.5	SEM = 2.2 SD=9.8 Range = 46–85	20	Crude SD recalculated from SEM	No matching performed. Mean age 27.3 ± 0.8 years
	mmol/L conversion		4.3	SEM = 0.1 SD=0.8 Range =2.2 - 6.7	70	3.6	SEM = 0.1 SD=0.4 Range = 2.6 - 4.7	20		
Parents										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Vipin 2016	mg/dL	Glucose oxidase	Median = 99	IQR = 83-112	86	Median = 92	IQR = 78-103	86	Crude	Age and BMI matched (mean age 50.4 ± 5.6 years)
	mmol/L conversion		Median = 5.5	IQR = 4.61-6.22	86	Median = 5.11	IQR = 4.33-5.72	86		
Fathers										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Vipin 2016	mg/dL	Glucose oxidase	Median = 101	IQR = 82-121	41	Median = 83	IQR = 72-95	42	Crude	Age and BMI matched (mean age 53.1 ± 5.1 years)
	mmol/L conversion		Median = 5.61	IQR = 4.56-6.72	41	Median = 4.61	IQR = 4-5.28	42		
Mothers										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?

Sam 2006	mmol/L	Glucose oxidase	5.3	1.2	215	4.9	0.5	62	Crude	Age, weight, ethnicity matched (mean age 52 ± 8 years)
Vipin 2016	mg/dL	Glucose oxidase	Median = 98	IQR = 83-109	45	Median=98	IQR = 84-111	44	Crude	Age and BMI matched (mean age 47.9 ± 4.9 years)
	mmol/L conversion		Median= 5.44	IQR = 4.61-6.06	45	Median= 5.44	IQR = 4.67-6.17	44		
Brothers										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Baillargeon 2007	mmol/l	Glucose hexokinase	5.14	0.30	17	4.70	0.67	28	Crude	Age and BMI matched (mean age 31 ± 9 years)
Karthik 2019	mg/dL	Glucose oxidase	86	16	41	84	11	41	Crude	Age and BMI matched (mean age 23.3 ± 4.3 years)
	mmol/L conversion		4.78	0.89	41	4.67	0.61	41		
Krysiak 2021	mg/dL	Glucose oxidase	96	12	24	92	11	26	Crude	Age, BP, BMI, body composition matched (mean age 39 ± 8 years)
	mmol/L conversion		5.33	0.67	24	5.11	0.61	26		
Krysiak 2021 2	mg/dL	Glucose oxidase	95	14	20	91	16	20	Crude	Age, BP, BMI, lipid level (mean age 50 ± 12 years)
	mmol/L conversion		5.28	0.78	20	5.06	0.89	20		
Lenarcik 2011	mg/dL	Glucose oxidase	89.33	6.08	42	85.93	6.37	30	Crude	Age (mean age 23.52 ± 5.05 years) and weight matched
	mmol/L conversion		4.96	0.34	42	4.77	0.35	30		
Sam 2008	mmol	Glucose oxidase	4.9	0.5	196	5.1	0.4	169	Crude	Age, BMI, and ethnicity matched (mean age 30 ± 8 years)
Sir-Petermann 2004	mg/dL	Glucose oxidase	83.7	Range = 73-94	10	87.4	Range = 78-96.5	14	Crude	Age and BMI (mean age 22 years) Subgroup = control group duplicated
	mmol/L conversion		4.65	Range = 4.06-5.22	10	4.86	Range = 4.33-5.36	14		
Sir-Petermann 2004	mg/dL	Glucose oxidase	83.6	Range = 65-99	12	87.4	Range = 78-96.5	14	Crude	Age and BMI (mean age 23.8 years)

	mmol/L conversion		4.64	Range = 3.61-5.5	12	4.86	Range = 4.33-5.36	14		Subgroup = control group duplicated
Sisters										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Diamanti-Kandarakis 2004	mmol/L	Glucose oxidase	4.6	0.15	17	4.83	0.13	20	Crude	Age (Mean age 22.88 ± 0.93 years) and BMI matched
Karthik 2019	mg/dL	Glucose oxidase	Median = 84	IQR = 78-90	35	Median = 88	IQR = 78-91	35	Crude	Age and BMI matched (Median age 24 years; IQR 19-27)
	mmol/L conversion		Median = 4.67	IQR = 4.33-5	35	Median = 4.89	IQR = 4.33-5.06	35		
Kulshreshtha 2019	mg/dL	Glucose oxidase	84.26	22.78	200	84.04	9.52	99	Crude	Age matched (Mean age 25.42 ± 7.89 years)
	mmol/L conversion		4.68	1.27	200	4.67	0.53	99		
Lenarcik 2011	mg/dL	Glucose oxidase	87.23	7.14	44	81.69	8.32	70	Crude	Age (mean age 25.52 ± 5.78 years) and weight matched
	mmol/L conversion		4.85	0.40	44	4.54	0.46	70		
Sam 2005	mg/dL	Glucose oxidase	84	8	38	84	8	125	Crude	Weight and ethnicity matched, Mean age 26 ± 6 years -subgroup with hyperandrogenism (duplicated control group)
	mmol/L conversion		4.67	0.44	38	4.67	0.44	125		
Sam 2005	mg/dL	Glucose oxidase	87	8	143	84	8	125	Crude	Weight and ethnicity matched, Mean age 31± 9 years -subgroup without PCOS features (duplicated control group)
	mmol/L conversion		4.83	0.44	143	4.67	0.44	125		
Unluhizarci 2007	mg/dL	Not reported	76.6	SEM = 1.9 SD=15.4 Range = 40 - 120	66	64.5	SEM = 2.2 SD=9.8 Range = 46–85	20	Crude SD recalculated from SEM	No matching performed. Similar control group as female FDR analysis. Mean age 26.5 ± 0.8 years
	mmol/L conversion		4.3	SEM = 0.1 SD = 0.8 Range =2.2 - 6.7	66	3.6	SEM = 0.1 SD=0.4 Range = 2.6 - 4.7	20		

All offspring										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
deWilde 2018	mmol/L	Not reported	4.7	0.4	14	4.6	0.3	130	Crude	Age 7.0 ± 0.8 years (FDR)
Li 2020	mmol/L	Glucose oxidase method	5.03	0.45	123	5.00	0.48	495	Crude	Age matched (mean age 4.65 ± 1.34 years)
Daughters (Childhood)										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Crisosto 2019	mg/dl	Glucose oxidase method	Median = 82.5	IQR= 74.0 - 91.0	43	Median= 83.0	IQR= 75.0 - 91.0	28	Crude	Age, gynecologic age, menarchal age, BMI, waist, WHR, and birth weight matched. Age median (IQR): 15.42 (14.17–16.17)
	mmol/L conversion		Median= 4.6	IQR= 4.1 - 5.1	43	Median= 4.6	IQR= 4.2 - 5.1	28		
Sir-Petermann	mg/dl	Glucose oxidase method	87.5	SEM=2.1	30	84.1	SEM=2.7	21	Crude SD recalculated from SEM	Tanner stage matched. (Tanner stage I) Mean age 8.6 ± 0.2 years (*SEM=0.2)
	mmol/L conversion		4.9	SEM=0.1 SD=0.5	30	4.7	SEM=0.2 SD = 0.9	21		
Sir-Petermann	mg/dl	Glucose oxidase method	81.7	SEM=2.6	26	84.8	SEM=3.4	17	Crude SD recalculated from SEM	Tanner stage matched. (Tanner stage II) Mean age 9.9 ± 0.2 years (*SEM=0.2)
	mmol/L conversion		4.5	SEM=0.1 SD=0.5	26	4.7	SEM=0.2 SD=0.8	17		
Sir-Petermann	mg/dl	Glucose oxidase method	81.3	SEM=2.3	26	89.5	SEM=2.1	19	Crude SD recalculated from SEM	Tanner stage matched. (Tanner stage III) Mean age 10.8 ± 0.2 years (*SEM=0.2)
	mmol/L conversion		4.5	SEM=0.1 SD=0.5	26	5.0	SEM=0.1 SD=0.4	19		
Sir-Petermann	mg/dl	Glucose oxidase method	85.6	SEM=2.4	29	83.9	SEM=2.4	17	Crude SD recalculated from SEM	Tanner stage matched. (Tanner stage IV) Mean age 12.2 ± 0.3 years (*SEM=0.3)
	mmol/L conversion		4.8	SEM=0.1 SD=0.5	29	4.7	SEM=0.1 SD=0.4	17		
Sir-Petermann	mg/dl	Glucose oxidase method	82.9	SEM=2.1	24	86.1	SEM=2.6	19	Crude SD recalculated from SEM	Tanner stage matched. (Tanner stage/V) Mean age 13.2 ± 0.3 years (*SEM=0.3)
	mmol/L conversion		4.6	SEM=0.1 SD=0.5	24	4.8	SEM=0.1 SD=0.4	19		

Sons (Infancy)										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Recabarren 2008	mg/dl	Glucose oxidase method	Median = 102.5	Range = 87.0 – 117.0	20	Median = 100.0	Range = 88.0 – 119.0	20	Crude	Age median 2.0 (range 2.0 - 3.0) months and socio-economic status matched.
	mmol/L conversion		Median = 5.7	Range = 4.8 – 6.5	20	Median = 5.6	Range = 4.9 – 6.6	20		
Sons (Childhood)										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Crisosto 2017	mg/dl	Glucose-oxidase method	Median = 84	IQR = 78–89	23	Median = 80	IQR = 77.2–85	20	Crude	Tanner stage matched. (Tanner stage I) Age median (IQR): 9.1 (8.4–9.6) years
	mmol/L conversion		Median = 4.7	IQR = 4.3–4.9	23	Median = 4.4	IQR = 4.3–4.7	20		
Crisosto 2017	mg/dl	Glucose-oxidase method	Median = 87	IQR = 81–94	26	Median = 84	IQR = 76–90	31	Crude	Tanner stage matched. (Tanner stage II/III) Age median (IQR): 10.8 (10.3–11.6) years
	mmol/L conversion		Median = 4.8	IQR = 4.5–5.2	26	Median = 4.7	IQR = 4.2–5.0	31		
Crisosto 2017	mg/dl	Glucose-oxidase method	Median = 83	IQR = 78–86	20	Median = 83	IQR = 76–90	33	Crude	Tanner stage matched. (Tanner stage IV/V) Age median (IQR): 14.4 (13–16.1) years
	mmol/L conversion		Median = 4.6	IQR = 4.3–4.8	20	Median = 4.6	IQR = 4.2–5.0	33		
Kent 2008	mg/dl	Glucose-oxidase method	79.6	6.4	10	77.3	9.3	6	Crude	Tanner stage, Age 11.1 ± 2.1 years (FDR)
	mmol/L conversion		4.42	0.36	10	4.29	0.52	6		
Recabarren 2008	mg/dl	Glucose oxidase method	Median = 90.2	Range = 59.0 – 115.0	31	Median = 85.0	Range = 64.0 – 109.2	17	Crude	Age median 6.0 (range 4.0 – 7.5) years and socio-economic status matched.
	mmol/L conversion		Median = 5.0	Range = 3.3 – 6.4	31	Median = 4.7	Range = 3.6 – 6.1	17		

Sons (Adulthood)										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Recabarren 2008	mg/dl	Glucose oxidase method	Median = 85.4	Range = 65.9 – 105.4	29	Median = 86.3	Range = 65.6 – 108.6	19	Crude	Age median 22.0 (range 18.0 – 29.0) years and socio-economic status matched.
	mmol/L conversion		Median = 4.7	Range = 3.7 – 5.9	29	Median = 4.8	Range = 3.6 – 6.0	19		

Blood glucose level conversion based on formula: 1 mmol/L = 18 mg/dL

OUTCOME: OGTT - 2 hour glucose				OUTCOME TYPE: Continuous						
Female first degree relatives										
Author, year	Unit of outcome	Method of measurement	Mean in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) First Degree Relatives	Sample size	Mean or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Harnois-Leblanc 2017	mmol/L	Glucose hexokinase	Median = 5.8	IQR = 5.3-6.8	8	Median = 5.7	IQR = 5.1-7.3	8	Crude	Age matched. (median age 17.5 years; IQR 14.4-20.1 years)
Raissouni 2012	mg/dL	Glucose hexokinase	Median = 112	IQR = 97-124	9	Median = 110	IQR = 86-128	10	Crude	Age matched. (median age 12.1; IQR 9.7-13.7 years) - extracted from Trottier substudy
	mmol/L conversion		Median = 6.22	IQR = 5.39-6.89	9	Median = 6.11	IQR = 4.78-7.11	10		
Torchen 2014	mg/dL	Glucose oxidase	Median = 121	IQR = 108-136	12	Median = 108	IQR = 96-120	10	Crude	Age, BMI, visceral adiposity and breast Tanner stage matched. Median age 10.4 years (IQR 8.8-12.1 years)
	mmol/L conversion		Median = 6.72	Range = 6-7.56	12	Median = 6.0	IQR = 5.33-6.67	10		
Parents										

Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Vipin 2016	mg/dL	Glucose oxidase	Median = 130	IQR = 107-176	86	Median = 110	IQR = 91-136	86	Crude	Age and BMI matched (mean age 50.4 ± 5.6 years)
	mmol/L conversion		Median = 7.22	IQR = 5.94-9.78	86	Median = 6.11	IQR = 5.06-7.56	86		
Fathers										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Vipin 2016	mg/dL	Glucose oxidase	Median = 132	IQR = 102-222	41	Median = 98	IQR = 86-110	42	Crude	Age and BMI matched (mean age 53.1 ± 5.1 years)
	mmol/L conversion		Median = 7.33	IQR = 5.67-12.33	41	Median = 5.44	IQR = 4.78-6.11	42		
Mothers										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Vipin 2016	mg/dL	Glucose oxidase	Median = 128	IQR = 113-153	45	Median=132	IQR = 109-145	44	Crude	Age and BMI matched (mean age 47.9 ± 4.9 years)
	mmol/L conversion		Median= 7.11	IQR = 6.28-8.5	45	Median= 7.33	IQR = 6.06-8.06	44		

Brothers										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Baillargeon 2007	mmol/l	Glucose hexokinase	6.64	1.08	17	4.54	1.27	28	Crude	Age and BMI matched (mean age 31 ± 9 years)
Karthik 2019	mg/dL	Glucose oxidase	Median = 109	IQR = 93-137	41	Median = 107	IQR = 97-123	41	Crude	Age and BMI matched (mean age 23.3 ± 4.3 years)
	mmol/L conversion		Median = 6.06	IQR = 5.17-7.61	41	Median = 5.94	IQR = 5.39-6.83	41		
Lenarcik 2011	mg/dL	Glucose oxidase	84.98	19.70	42	71.60	22.84	30	Crude	Age (mean age 23.52 ± 5.05 years) and weight matched
	mmol/L conversion		4.72	1.09	42	3.98	1.27	30		
Sir-Petermann 2004	mg/dL	Glucose oxidase	72.7	Range = 40.0–91.0	10	92.3	Range = 65-122	14	Crude	Age and BMI (mean age 22 years) Subgroup = control group duplicated
	mmol/L conversion		4.04	Range = 2.22-5.06	10	5.13	Range = 3.61-6.78	14		
Sir-Petermann 2004	mg/dL	Glucose oxidase	96.1	Range = 60-129	12	92.3	Range = 65-122	14	Crude	Age and BMI (mean age 23.8 years) Subgroup = control group duplicated
	mmol/L conversion		5.34	Range = 3.33-7.17	12	5.13	Range = 3.61-6.78	14		
Sisters										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Karthik 2019	mg/dL	Glucose oxidase	117	24	35	108	22	35	Crude	

	mmol/L conversion		6.5	1.33	35	6	1.22	35		Age and BMI matched (Median age 24 years; IQR 19-27)
Kulshreshtha 2019	mg/dL	Glucose oxidase	104.65	41.98	200	100.05	22.04	99	Crude	Age matched (Mean age 25.42 ± 7.89 years)
	mmol/L conversion		5.81	2.33	200	5.56	1.22	99		
Lenarcik 2011	mg/dL	Glucose oxidase	87.23	26.05	44	83.07	19.50	70	Crude	Age (mean age 25.52 ± 5.78 years) and weight matched
	mmol/L conversion		4.85	1.45	44	4.62	1.08	70		
Daughters (Childhood)										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Crisosto 2019	mg/dl	Glucose oxidase method	Median = 94.5	IQR= 76.0 - 114.0	43	Median = 85.5	IQR= 80.5 - 107.0	28	Crude	Age, gynecologic age, menarchal age, BMI, waist, WHR, and birth weight matched. Age median (IQR): 15.42 (14.17–16.17)
	mmol/L conversion		Median = 5.3	IQR= 4.2 - 6.3	43	Median = 4.8	IQR= 4.5 - 5.9	28		
Sir-Petermann 2012	mg/dl	Glucose oxidase method	95.5	SEM=3.5	30	91.6	SEM=4.8	21	Crude	Tanner stage matched. (Tanner stage I) Mean age 8.6 ± 0.2 years (*SEM=0.2)
	mmol/L conversion		5.3	SEM=0.2 SD=1.1	30	5.1	SEM=0.3 SD=1.4	21		
Sir-Petermann 2012	mg/dl	Glucose oxidase method	100.3	SEM=4.0	26	96.8	SEM=6.1	17	Crude	Tanner stage matched. (Tanner stage II) Mean age 9.9 ± 0.2 years (*SEM=0.2)
	mmol/L conversion		5.6	SEM=0.2 SD=1.0	26	5.4	SEM=0.3 SD=1.2	17		
Sir-Petermann 2012	mg/dl	Glucose oxidase method	103.1	SEM=4.2	26	99.8	SEM=3.2	19	Crude	Tanner stage matched. (Tanner stage III) Mean age 10.8 ± 0.2 years (*SEM=0.2)
	mmol/L conversion		5.7	SEM=0.2 SD=1.0	26	5.5	SEM=0.2 SD=0.9	19		

Sir-Petermann 2012	mg/dl	Glucose oxidase method	89.5	SEM=4.0	29	88.5	SEM=4.7	17	Crude	Tanner stage matched. (Tanner stage IV) Mean age 12.2 ± 0.3 years (*SEM=0.3)
	mmol/L conversion		5.0	SEM=0.2 SD=1.1	29	4.9	SEM=0.3 SD=1.2	17		
Sir-Petermann 2012	mg/dl	Glucose oxidase method	100.2	SEM=5.1	24	96.9	SEM=4.2	19	Crude	Tanner stage matched. (Tanner stage/V) Mean age 13.2 ± 0.3 years (*SEM=0.3)
	mmol/L conversion		5.6	SEM=0.3 SD=1.5	24	5.4	SEM=0.2 SD=0.9	19		
Sons (Childhood)										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Crisosto 2017	mg/dl	Glucose-oxidase method	Median = 96	IQR = 86–113	23	Median = 91	IQR = 81–101.3	20	Crude	Tanner stage matched. (Tanner stage I) Age median (IQR): 9.1 (8.4–9.6) years
	mmol/L conversion		Median = 5.3	IQR = 4.8–6.3	23	Median = 5.1	IQR = 4.5–5.6	20		
Crisosto 2017	mg/dl	Glucose-oxidase method	Median = 102	IQR = 93–113	26	Median = 96	IQR = 87–114	31	Crude	Tanner stage matched. (Tanner stage II/III) Age median (IQR): 10.8 (10.3–11.6) years
	mmol/L conversion		Median = 5.7	IQR = 5.2–6.3	26	Median = 5.3	IQR = 4.8–6.3	31		
Crisosto 2017	mg/dl	Glucose-oxidase method	Median = 95	IQR = 82–107	20	Median = 97	IQR = 83–106	33	Crude	Tanner stage matched. (Tanner stage IV/V) Age median (IQR): 14.4 (13–16.1) years
	mmol/L conversion		Median = 5.3	IQR = 4.6–5.9	20	Median = 5.4	IQR = 4.6–5.9	33		
Kent 2008	mg/dl	Glucose-oxidase method	90.3	10.1	10	86.8	14.7	6	Crude	Tanner stage, Age 11.1 ± 2.1 years (FDR)
	mmol/L conversion		5.02	0.56	10	4.82	0.82	6		

Recabarren 2008	mg/dl	Glucose oxidase method	Median = 100.5	Range = 69.0 –139.0	31	Median = 91.4	Range = 65.0 – 121.0	17	Crude	Age median 6.0 (range 4.0 – 7.5) years and socio-economic status matched.
	mmol/L conversion		Median = 5.6	Range = 3.8 – 7.7	31	Median = 5.1	Range = 3.6 – 6.7	17		
Sons (Adulthood)										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Recabarren 2008	mg/dl	Glucose oxidase method	Median = 89.2	Range = 57.0 –155.0	29	Median = 79.6	Range = 54.9 – 105.5	19	Crude	Age median 22.0 (range 18.0 – 29.0) years and socio-economic status matched.
	mmol/L conversion		Median = 5.0	Range = 3.2 – 8.6	29	Median = 4.4	Range = 3.1 – 5.9	19		

OUTCOME: LDL						OUTCOME TYPE: Continuous				
Female first degree relatives										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Torchen 2014	mg/dL	Standard colorimetric assays (Friedewald)	Median = 88	IQR = 69-98	12	Median = 87	IQR = 82-97	10	Crude	Age, BMI, visceral adiposity and breast Tanner stage matched. Median age 10.4 years (IQR 8.8-12.1 years)
	mmol/L conversion		Median = 2.28	Range = 1.78-2.53	12	Median = 2.25	IQR = 2.12-2.51	10		
Parents										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in	SD (or specify if other	Sample size	Mean (specify if median) or	SD (or specify if other measure: SE, IQR or 95%	Sample size	Are these values	If adjusted, what variables were included in the model?

			First Degree Relatives	measure: IQR, SE or 95% CI) in Fist Degree Relatives		median in control group	CI) in control group		adjusted or crude?	
Vipin 2016	mg/dL	Standard colorimetric assays (Friedewald)	Median = 115	IQR = 86-136	86	Median = 96	IQR = 76-127	86	Crude	Age and BMI matched (mean age 50.4 ± 5.6 years)
	mmol/L conversion		Median = 2.97	IQR = 2.22-3.52	86	Median = 2.48	IQR = 1.97-3.28	86		
Fathers										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Vipin 2016	mg/dL	Standard colorimetric assays (Friedewald)	Median = 111	IQR = 85-127	41	Median = 92	IQR = 69-133	42	Crude	Age and BMI matched (mean age 53.1 ± 5.1 years)
	mmol/L conversion		Median = 2.87	IQR = 2.20-3.28	41	Median = 2.38	IQR = 1.78-3.44	42		
Yilmaz 2005	mg/dL	Standard colorimetric assays (Friedewald)	142.69	26.83	38	90.41	22.38	20	Crude	Age (mean age 51.87 ± 8.54 years) and weight matched
	mmol/L conversion		3.69	0.69	38	2.34	0.58	20		
Mothers										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Sam 2006	mmol/L	Standard colorimetric assays (Friedewald)	3.58	0.97	215	3.11	0.66	62	Crude	Age, weight, ethnicity matched (mean age 52 ± 8 years)

Vipin 2016	mg/dL	Standard colorimetric assays (Friedewald)	118	35	45	103	29	44	Crude	Age and BMI matched (mean age 47.9 ± 4.9 years)
	mmol/L conversion		3.05	0.91	45	2.66	0.75	44		
Yilmaz 2005	mg/dL	Standard colorimetric assays (Friedewald)	120.81	38.02	40	80.59	17.42	20	Crude	Age (mean age 46.38 ± 7.95 years) and weight matched
	mmol/L conversion		3.12	0.98	40	2.08	0.45	20		
Brothers										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Baillargeon 2007	mmol/l	Chemiluminescent immunoassay(Friedewald)	2.99	0.78	16	2.87	1.06	27	Crude	Age and BMI matched (mean age 31 ± 9 years)
Karthik 2019	mg/dL	Standard laboratory assays (Friedewald)	96	27	41	94	26	41	Crude	Age and BMI matched (mean age 23.3 ± 4.3 years)
	mmol/L conversion		2.48	0.70	41	2.43	0.67	41		
Krysiak 2021	mg/dL	Standard laboratory assays (Friedewald)	134	20	24	128	17	26	Crude	Age, BP, BMI, body composition matched (mean age 39 ± 8 years)
	mmol/L conversion		3.47	0.52	24	3.31	0.44	26		
Lenarcik 2011	mg/dL	Standard colorimetric assays (Friedewald)	105.68	39.88	42	88.53	26.47	30	Crude	Age (mean age 23.52 ± 5.05 years) and weight matched
	mmol/L conversion		2.73	1.03	42	2.29	0.68	30		
Yilmaz 2005	mg/dL	Standard colorimetric assays (Friedewald)	124.15	38.73	17	90.74	18.19	15	Crude	Age (mean age 29.00 ± 11.10 years) and weight matched
	mmol/L conversion		3.21	1.00	17	2.35	0.47	15		
Sisters										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in	SD (or specify if other	Sample size	Mean (specify if median) or	SD (or specify if other measure: SE, IQR or 95%	Sample size	Are these values	If adjusted, what variables were included in the model?

			First Degree Relatives	measure: IQR, SE or 95% CI) in Fist Degree Relatives		median in control group	CI) in control group		adjusted or crude?	
Diamanti-Kandarakis 2004	mmol/L	Friedewald	2.55	0.25	17	2.67	0.24	20	Crude	Age (Mean age 22.88 ± 0.93 years) and BMI matched
Joharatnam 2011	mmol/L	Not reported	3.00	0.14	153	2.7	0.71	76	Crude	Mean age 31.3 ± 6 years- subgroup with polycystic ovaries (duplicate control group)
Joharatnam 2011	mmol/L	Not reported	2.87	0.21	61	2.7	0.71	76	Crude	Mean age 37.8 ± 7.7 years - subgroup without polycystic ovaries (duplicate control group)
Karthik 2019	mg/dL	Standard colorimetric assays (Friedewald)	Median = 93	IQR = 72-108	35	Median = 89	IQR = 70-101	35	Crude	Age and BMI matched (Median age 24 years; IQR 19-27)
	mmol/L conversion		Median = 2.41	IQR = 1.86-2.79	35	Median = 2.30	IQR = 1.81-2.61	35		
Kulshreshtha 2019	mg/dL	Standard colorimetric assays (Friedewald)	88.65	25.73	200	94.86	28.20	99	Crude	Age matched (Mean age 25.42 ± 7.89 years)
	mmol/L conversion		2.29	0.67	200	2.45	0.73	99		
Lenarcik 2011	mg/dL	Standard colorimetric assays (Friedewald)	107.54	30.42	44	95.81	29.74	70	Crude	Age (mean age 25.52 ± 5.78 years) and weight matched
	mmol/L conversion		2.78	0.79	44	2.48	0.77	70		
Yilmaz 2005	mg/dL	Standard colorimetric assays (Friedewald)	90.58	18.53	25	90.26	16.88	20	Crude	Age (mean age 23.50 ± 7.56 years) and weight matched
	mmol/L conversion		2.34	0.48	25	2.33	0.44	20		
All offspring										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?

				Fist Degree Relatives						
deWilde 2018	mmol/L	Not reported	3.1	1.3	14	2.8	0.6	130	Crude	Age 7.0 ± 0.8 years (FDR)
Li 2020	mmol/L	Standard colorimetric assays	2.58	0.60	123	2.61	0.54	495	Crude	Age matched (mean age 4.65 ± 1.34 years)
Daughters (Childhood)										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Crisosto 2019	mg/dl	Standard colorimetric assays (Friedewald)	Median = 127.5	IQR = 110.9 - 138.8	43	Median =119.0	IQR = 96.1 - 138.3	28	Crude	Age, gynecologic age, menarchal age, BMI, waist, WHR, and birth weight matched. Age median (IQR): 15.42 (14.17–16.17)
	mmol/L conversion		Median =3.30	IQR = 2.87 - 3.59	43	Median = 3.08	IQR = 2.49 - 3.58	28		
Sons (Infancy)										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Recabarren 2008	mg/dl	Standard colorimetric assays (Friedewald)	Median = 57.8	Range = 9.9 –101.7	20	Median = 66.6	Range = 20.3 – 152.1	20	Crude	Age median 2.0 (range 2.0 - 3.0) months and socio-economic status matched.
	mmol/L conversion		Median = 1.49	Range = 0.26 – 2.63	20	Median = 1.72	Range = 0.53 – 3.93	20		
Sons (Childhood)										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?

				Fist Degree Relatives						
Crisosto 2017	mg/dl	Standard colorimetric assays (Friedewald)	Median = 89	IQR = 70–108	23	Median = 74	IQR = 57–82	20	Crude	Tanner stage matched. (Tanner stage I) Age median (IQR): 9.1 (8.4–9.6) years
	mmol/L conversion		Median = 2.30	IQR = 1.81–2.79	23	Median = 1.91	IQR = 1.47–2.12	20		
Crisosto 2017	mg/dl	Standard colorimetric assays (Friedewald)	Median = 93	IQR = 79–104	26	Median = 80	IQR = 58–93	31	Crude	Tanner stage matched. (Tanner stage II/III) Age median (IQR): 10.8 (10.3–11.6) years
	mmol/L conversion		Median = 2.41	IQR = 2.04–2.69	26	Median = 2.07	IQR = 1.5–2.41	31		
Crisosto 2017	mg/dl	Standard colorimetric assays (Friedewald)	Median = 78	IQR = 58 – 101	20	Median = 55	IQR = 45–77	33	Crude	Tanner stage matched. (Tanner stage IV/V) Age median (IQR): 14.4 (13–16.1) years
	mmol/L conversion		Median = 2.02	IQR = 1.5–2.61	20	Median = 1.42	IQR = 1.16–1.99	33		
Kent 2008	mg/dl	Standard colorimetric assays (Friedewald)	90.6	21.0	10	90.0	21.1	6	Crude	Tanner stage, Age 11.1 ± 2.1 years (FDR)
	mmol/L conversion		2.34	0.54	10	2.33	0.55	6		
Recabarren 2008	mg/dl	Standard colorimetric assays (Friedewald)	Median = 106.8	Range = 52.6 –224.3	31	Median = 94.0	Range = 60.4 – 142.5	17	Crude	Age median 6.0 (range 4.0 – 7.5) years and socio-economic status matched.
	mmol/L conversion		Median = 2.76	Range = 1.36 – 5.80	31	Median = 2.43	Range = 1.56 – 3.69	17		
Sons (Adulthood)										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Recabarren 2008	mg/dl	Standard colorimetric	Median = 114.5	Range = 39.6 –169.2	29	Median = 97.2	Range = 84.1–185.5	19	Crude	Age median 22.0 (range 18.0 – 29.0) years and

	mmol/L conversion	assays (Friedewald)	Median = 2.96	Range = 1.02 – 4.38	29	Median = 2.51	Range = 2.18 – 4.80	19		socio-economic status matched.

Conversion for TC (total cholesterol), HDL (high density lipoprotein) and LDL (low density lipoprotein): from mg/dL to mmol/L multiply by 0.02586

OUTCOME: HDL				OUTCOME TYPE: Continuous						
Female first degree relatives										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Raissouni 2012	mmol/L	Standard colorimetric assays	Median = 0.38	IQR = 0.29-0.44	9	Median = 0.35	IQR = 0.28-0.47	10	Crude	Age matched. (median age 12.1; IQR 9.7-13.7 years) - extracted from Trottier substudy
Torchen 2014	mg/dL	Standard colorimetric assays	Median = 41	IQR = 38-45	12	Median = 41	IQR = 32-49	10	Crude	Age, BMI, visceral adiposity and breast Tanner stage matched. Median age 10.4 years (IQR 8.8-12.1 years)
	mmol/L conversion		Median = 1.06	Range = 0.98-1.16	12	Median = 1.06	IQR = 0.83-1.27	10		
Parents										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Vipin 2016	mg/dL	Standard colorimetric assays	Median = 42	IQR = 36-51	86	Median = 41	IQR = 33-51	86	Crude	Age and BMI matched (mean age 50.4 ± 5.6 years)
	mmol/L conversion		Median = 1.09	IQR = 0.93-1.32	86	Median = 1.06	IQR = 0.85-1.32	86		
Fathers										

Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Vipin 2016	mg/dL	Standard colorimetric assays (Friedewald)	Median = 40	IQR = 34-48	41	Median = 41	IQR = 32-50	42	Crude	Age and BMI matched (mean age 53.1 ± 5.1 years)
	mmol/L conversion		Median = 1.03	IQR = 0.88-1.24	41	Median = 1.06	IQR = 0.83-1.29	42		
Yilmaz 2005	mg/dL	Standard colorimetric assays	41.26	9.08	38	52.64	10.35	20	Crude	Age (mean age 51.87 ± 8.54 years) and weight matched
	mmol/L conversion		1.07	0.23	38	1.36	0.27	20		
Mothers										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Sam 2006	mmol/L	Standard colorimetric assays	1.24	0.56	215	1.24	0.44	62	Crude	Age, weight, ethnicity matched (mean age 52 ± 8 years)
Vipin 2016	mg/dL	Standard colorimetric assays	Median = 46	IQR = 37-53	45	Median = 43	IQR = 33-54	44	Crude	Age and BMI matched (mean age 47.9 ± 4.9 years)
	mmol/L conversion		Median = 1.19	IQR = 0.96-1.37	45	Median = 1.11	IQR = 0.85-1.40	44		
Yilmaz 2005	mg/dL	Standard colorimetric assays	55.32	18.01	40	56.74	11.46	20	Crude	Age (mean age 46.38 ± 7.95 years) and weight matched
	mmol/L conversion		1.43	0.47	40	1.47	0.30	20		
Brothers										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure:	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95%	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?

				IQR, SE or 95% CI) in Fist Degree Relatives			CI) in control group			
Baillargeon 2007	mmol/l	Chemiluminescent immunoassay(Friedewald)	1.15	0.34	16	1.24	0.25	27	Crude	Age and BMI matched (mean age 31 ± 9 years)
Karthik 2019	mg/dL	Standard laboratory assays	41	11	41	39	9	41	Crude	Age and BMI matched (mean age 23.3 ± 4.3 years)
	mmol/L conversion		1.06	0.28	41	1.01	0.23	41		
Krysiak 2021	mg/dL	Standard laboratory assays	43	11	24	50	9	26	Crude	Age, BP, BMI, body composition matched (mean age 39 ± 8 years)
	mmol/L conversion		1.11	0.28	24	1.29	0.23	26		
Sir-Petermann 2004	mg/dL	Standard laboratory assays	43.5	Range = 33.7–58.3	10	39.2	Range = 29.3–48.5	14	Crude	Age and BMI (mean age 22 years) Subgroup = control group duplicated
	mmol/L conversion		1.13	Range = 0.87-1.51	10	1.01	Range = 0.76-1.25	14		
Sir-Petermann 2004	mg/dL	Standard laboratory assays	36.6	Range = 25.4–45.3	12	39.2	Range = 29.3–48.5	14	Crude	Age and BMI (mean age 23.8 years) Subgroup = control group duplicated
	mmol/L conversion		0.95	Range = 0.66-1.17	12	1.01	Range = 0.76-1.25	14		
Lenarcik 2011	mg/dL	Standard colorimetric assays	59.95	14.81	42	57.73	14.84	30	Crude	Age (mean age 23.52 ± 5.05 years) and weight matched
	mmol/L conversion		1.55	0.38	42	1.49	0.38	30		
Yilmaz 2005	mg/dL	Standard colorimetric assays	51.25	11.17	17	51.76	10.38	15	Crude	Age (mean age 29.00 ± 11.10 years) and weight matched
	mmol/L conversion		1.33	0.29	17	1.34	0.27	15		
Sisters										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?

				Fist Degree Relatives						
Diamanti-Kandarakis 2004	mmol/L	Not reported	1.25	0.09	17	1.19	0.11	20	Crude	Age (Mean age 22.88 ± 0.93 years) and BMI matched
Joharatnam 2011	mmol/L	Not reported	1.35	0.06	153	1.33	0.28	76	Crude	Mean age 31.3 ± 6 years- subgroup with polycystic ovaries (duplicate control group)
Joharatnam 2011	mmol/L	Not reported	1.43	0.09	61	1.33	0.28	76	Crude	Mean age 37.8 ± 7.7 years - subgroup without polycystic ovaries (duplicate control group)
Karthik 2019	mg/dL	Standard colorimetric assays	45	14	35	49	10	35	Crude	Age and BMI matched (Median age 24 years; IQR 19-27)
	mmol/L conversion		1.16	0.36	35	1.27	0.26	35		
Kulshreshtha 2019	mg/dL	Direct method	47.71	11.41	200	46.85	9.85	99	Crude	Age matched (Mean age 25.42 ± 7.89 years)
	mmol/L conversion		1.23	0.30	200	1.21	0.25	99		
Lenarcik 2011	mg/dL	Standard colorimetric assays	67.30	16.65	44	63.27	16.18	70	Crude	Age (mean age 25.52 ± 5.78 years) and weight matched
	mmol/L conversion		1.74	0.43	44	1.64	0.42	70		
Yilmaz 2005	mg/dL	Standard colorimetric assays	54.50	10.67	25	54.63	10.95	20	Crude	Age (mean age 23.50 ± 7.56 years) and weight matched
	mmol/L conversion		1.41	0.28	25	1.41	0.28	20		
All offspring										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
deWilde 2018	mmol/L	Not reported	1.5	0.3	14	1.4	0.2	130	Crude	Age 7.0 ± 0.8 years (FDR)

Li 2020	mmol/L	Standard colorimetric assays	1.36	0.28	123	1.34	0.25	495	Crude	Age matched (mean age 4.65 ± 1.34 years)
Daughters (Childhood)										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Crisosto 2019	mg/dl	Standard colorimetric assays	Median = 39.70	IQR = 35.90 - 44.10	43	Median = 39.35	IQR = 32.45 - 42.15	28	Crude	Age, gynecologic age, menarchal age, BMI, waist, WHR, and birth weight matched. Age median (IQR): 15.42 (14.17–16.17)
	mmol/L conversion		Median = 1.03	IQR = 0.93 - 1.14	43	Median = 1.02	IQR = 0.84 - 1.09	28		
Sons (Infancy)										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Recabarren 2008	mg/dl	Standard colorimetric assays	Median = 55.1	Range = 33.6 – 68.1	20	Median = 51.6	Range = 35.6 – 67.5	20	Crude	Age median 2.0 (range 2.0 - 3.0) years and socio-economic status matched.
	mmol/L conversion		Median = 1.43	Range = 0.87 – 1.76	20	Median = 1.33	Range = 0.92 – 1.75	20		
Sons (Childhood)										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?

Crisosto 2017	mg/dl	Standard colorimetric assays	Median = 40	IQR = 37–50	23	Median = 44	IQR = 39–53	20	Crude	Tanner stage matched. (Tanner stage I) Age median (IQR): 9.1 (8.4–9.6) years
	mmol/L conversion		Median = 1.03	IQR = 0.96–1.29	23	Median = 1.14	IQR = 1.01–1.37	20		
Crisosto 2017	mg/dl	Standard colorimetric assays	Median = 42	IQR = 38–52	26	Median = 42	IQR = 37–45	31	Crude	Tanner stage matched. (Tanner stage II/III) Age median (IQR): 10.8 (10.3–11.6) years
	mmol/L conversion		Median = 1.09	IQR = 0.98–1.34	26	Median = 1.09	IQR = 0.96–1.16	31		
Crisosto 2017	mg/dl	Standard colorimetric assays	Median = 39	IQR = 34–44	20	Median = 38	IQR = 32–43	33	Crude	Tanner stage matched. (Tanner stage IV/V) Age median (IQR): 14.4 (13–16.1) years
	mmol/L conversion		Median = 1.01	IQR = 0.88–1.14	20	Median = 0.98	IQR = 0.83–1.11	33		
Kent 2008	mg/dl	Standard colorimetric assays (Friedewald)	44.3	8.0	10	32.8	14.6	6	Crude	Tanner stage, Age 11.1 ± 2.1 years (FDR)
	mmol/L conversion		1.15	0.21	10	0.85	0.38	6		
Recabarren 2008	mg/dl	Standard colorimetric assays	Median = 44.2	Range = 29.8 – 58.3	31	Median = 41.5	Range = 31.6 – 73.6	17	Crude	Age median 6.0 (range 4.0 – 7.5) years and socio-economic status matched.
	mmol/L conversion		Median = 1.14	Range = 0.77 – 1.51	31	Median = 1.07	Range = 0.82 – 1.90	17		
Sons (Adulthood)										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Recabarren 2008	mg/dl	Standard colorimetric assays	Median = 41.3	Range = 29.1 – 64.9	29	Median = 41.9	Range = 28.7 – 64.1	19	Crude	Age median 22.0 (range 18.0 – 29.0) years and socio-economic status matched.
	mmol/L conversion		Median = 1.07	Range = 0.75 – 1.68	29	Median = 1.08	Range = 0.74 – 1.66	19		

Conversion for TC (total cholesterol), HDL (high density lipoprotein) and LDL (low density lipoprotein): from mg/dL to mmol/L multiply by 0.02586

OUTCOME: Triglycerides				OUTCOME TYPE: Continuous						
Female first degree relatives										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Harnois-Leblanc 2017	mmol/L	Standard colorimetric assays	Median = 0.7	IQR = 0.6–0.9	8	Median = 1.2	IQR = 0.7–1.6	8	Crude	Age matched. (median age 17.5 years; IQR 14.4-20.1 years)
Raissouni 2012	mg/dL	Standard colorimetric assays	Median = 59	IQR = 39-73	9	Median = 64	IQR = 45-96	10	Crude	Age matched. (median age 12.1; IQR 9.7-13.7 years) - extracted from Trottier substudy
	mmol/L conversion		Median = 0.67	IQR = 0.44-0.82	9	Median = 0.72	IQR = 0.51-1.08	10		
Torchen 2014	mg/dL	Standard colorimetric assays	Median = 75	IQR = 65-98	12	Median = 48	IQR = 37-86	10	Crude	Age, BMI, visceral adiposity and breast Tanner stage matched. Median age 10.4 years (IQR 8.8-12.1 years)
	mmol/L conversion		Median = 0.85	Range = 0.73-1.11	12	Median = 0.54	IQR = 0.42-0.97	10		
Parents										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Vipin 2016	mg/dL	Standard colorimetric assays	Median = 126	IQR = 93-161	86	Median = 120	IQR = 80-154	86	Crude	Age and BMI matched (mean age 50.4 ± 5.6 years)
	mmol/L conversion		Median = 1.42	IQR = 1.05-1.82	86	Median = 1.35	IQR = 0.90-1.74	86		
Fathers										

Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Vipin 2016	mg/dL	Standard colorimetric assays	Median = 123	IQR = 88-161	41	Median = 116	IQR = 85-157	42	Crude	Age and BMI matched (mean age 53.1 ± 5.1 years)
	mmol/L conversion		Median = 1.39	IQR = 0.99-1.82	41	Median = 1.31	IQR = 0.96-1.77	42		
Yilmaz 2005	mg/dL	Standard colorimetric assays	160.18	69.52	38	101.04	43.62	20	Crude	Age (mean age 51.87 ± 8.54 years) and weight matched
	mmol/L conversion		1.81	0.78	38	1.14	0.49	20		
Mothers										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Sam 2006	mmol/L	Standard colorimetric assays	1.89	1.69	215	1.48	0.96	62	Crude	Age, weight, ethnicity matched (mean age 52 ± 8 years)
Vipin 2016	mg/dL	Standard colorimetric assays	Median = 132	IQR = 95-157	45	Median = 127	IQR = 75-153	44	Crude	Age and BMI matched (mean age 47.9 ± 4.9 years)
	mmol/L conversion		Median = 1.49	IQR = 1.07-1.77	45	Median = 1.43	IQR = 0.85-1.73	44		
Yilmaz 2005	mg/dL	Standard colorimetric assays	139.79	61.95	40	98.32	40.29	20	Crude	Age (mean age 46.38 ± 7.95 years) and weight matched
	mmol/L conversion		1.58	0.70	40	1.11	0.45	20		
Brothers										

Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Baillargeon 2007	mmol/l	Chemiluminescent immunoassay	Geometric mean = 1.66	IQR = 0.94–2.64	16	Geometric mean = 0.99	IQR = 0.70–1.32	27	Crude (log transformed)	Age and BMI matched (mean age 31 ± 9 years)
Karthik 2019	mg/dL	Standard laboratory assays	Median = 100	IQR = 70-162	41	Median = 109	IQR = 71-145	41	Crude	Age and BMI matched (mean age 23.3 ± 4.3 years)
	mmol/L conversion		Median = 1.13	IQR = 0.79-1.83	41	Median = 1.23	IQR = 0.80-1.64	41		
Krysiak 2021	mg/dL	Standard laboratory assays	195	48	24	163	40	26	Crude	Age, BP, BMI, body composition matched (mean age 39 ± 8 years)
	mmol/L conversion		2.20	0.54	24	1.84	0.45	26		
Lenarcik 2011	mg/dL	Standard colorimetric assays	91.71	44.32	42	91.0	59.81	30	Crude	Age (mean age 23.52 ± 5.05 years) and weight matched
	mmol/L conversion		1.04	0.50	42	1.03	0.68	30		
Sir-Petermann 2004	mg/dL	Standard laboratory assays	112.4	Range = 65.0–164.0	10	113.2	Range = 66.0–189.0	14	Crude	Age and BMI (mean age 22 years) Subgroup = control group duplicated
	mmol/L conversion		1.27	Range = 0.73-1.85	10	1.28	Range = 0.75-2.13	14		
Sir-Petermann 2004	mg/dL	Standard laboratory assays	151.9	Range = 77.0–411.0	12	113.2	Range = 66.0–189.0	14	Crude	Age and BMI (mean age 23.8 years) Subgroup = control group duplicated
	mmol/L conversion		1.72	Range = 0.87-4.64	12	1.28	Range = 0.75-2.13	14		
Yilmaz 2005	mg/dL	Standard colorimetric assays	175.12	65.27	17	101.39	38.94	15	Crude	Age (mean age 29.00 ± 11.10 years) and weight matched
	mmol/L conversion		1.98	0.74	17	1.14	0.44	15		
Sisters										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First	SD (or specify if other	Sample size	Mean (specify if median) or	SD (or specify if other measure: SE, IQR or 95%	Sample size	Are these values	If adjusted, what variables were included in the model?

			Degree Relatives	measure: IQR, SE or 95% CI) in Fist Degree Relatives		median in control group	CI) in control group		adjusted or crude?	
Diamanti-Kandarakis 2004	mmol/L	Not reported	0.78	0.09	17	0.62	0.05	20	Crude	Age (Mean age 22.88 ± 0.93 years) and BMI matched
Joharatnam 2011	mmol/L	Not reported	0.98	0.06	153	0.91	0.39	76	Crude	Mean age 31.3 ± 6 years-subgroup with polycystic ovaries (duplicate control group)
Joharatnam 2011	mmol/L	Not reported	0.92	0.10	61	0.91	0.39	76	Crude	Mean age 37.8 ± 7.7 years - subgroup without polycystic ovaries (duplicate control group)
Karthik 2019	mg/dL	Standard colorimetric assays	89	31	35	94	31	35	Crude	Age and BMI matched (Median age 24 years; IQR 19-27)
	mmol/L conversion		1.00	0.35	35	1.06	0.35	35		
Kulshreshtha 2019	mg/dL	Standard colorimetric assays	106.43	58.17	200	101.10	48.45	99	Crude	Age matched (Mean age 25.42 ± 7.89 years)
	mmol/L conversion		1.20	0.66	200	1.14	0.55	99		
Lenarcik 2011	mg/dL	Standard colorimetric assays	75.50	34.77	44	86.43	60.19	70	Crude	Age (mean age 25.52 ± 5.78 years) and weight matched
	mmol/L conversion		0.85	0.39	44	0.98	0.68	70		
Yilmaz 2005	mg/dL	Standard colorimetric assays	89.56	21.68	25	85.14	20.76	20	Crude	Age (mean age 23.50 ± 7.56 years) and weight matched
	mmol/L conversion		1.01	0.24	25	0.96	0.23	20		
All offspring										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?

deWilde 2018	mmol/L	Not reported	0.7	0.2	14	0.5	0.2	130	Crude	Age 7.0 ± 0.8 years (FDR)
Li 2020	mmol/L	Standard colorimetric assays	0.84	0.31	123	0.82	0.29	495	Crude	Age matched (mean age 4.65 ± 1.34 years)
Daughters (Childhood)										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Crisosto 2019	mg/dl	Standard colorimetric assays	Median = 131.0	IQR = 93.0 - 163.0	43	Median = 112.0	IQR = 81.5 - 146.5	28	Crude	Age, gynecologic age, menarchal age, BMI, waist, WHR, and birth weight matched. Age median (IQR): 15.42 (14.17–16.17)
	mmol/L conversion		Median = 1.5	IQR = 1.1 - 1.8	43	Median = 1.3	IQR = 0.9 - 1.7	28		
Sons (Infancy)										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Recabarren 2008	mg/dl	Standard colorimetric assays	Median = 121.5	Range = 70.0 –239.0	20	Median = 149.0	Range = 75.0 – 258.0	20	Crude	Age median 2.0 (range 2.0 - 3.0) years and socio-economic status matched.
	mmol/L conversion		Median = 1.37	Range = 0.79 – 2.70	20	Median = 1.68	Range = 0.85 – 2.91	20		
Sons (Childhood)										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?

Crisosto 2017	mg/dl	Standard colorimetric assays	Median = 104	IQR = 81–137	23	Median = 108	IQR = 86–132	20	Crude	Tanner stage matched. (Tanner stage I) Age median (IQR): 9.1 (8.4–9.6) years
	mmol/L conversion		Median = 1.17	IQR = 0.91–1.55	23	Median = 1.22	IQR = 0.97–1.49	20		
Crisosto 2017	mg/dl	Standard colorimetric assays	Median = 126	IQR = 89–151	26	Median = 106	IQR = 82–141	31	Crude	Tanner stage matched. (Tanner stage II/III) Age median (IQR): 10.8 (10.3–11.6) years
	mmol/L conversion		Median = 1.42	IQR = 1.00–1.70	26	Median = 1.20	IQR = 0.93–1.59	31		
Crisosto 2017	mg/dl	Standard colorimetric assays	Median = 123	IQR = 91–149	20	Median = 124	IQR = 87–141	33	Crude	Tanner stage matched. (Tanner stage IV/V) Age median (IQR): 14.4 (13–16.1) years
	mmol/L conversion		Median = 1.39	IQR = 1.03–1.68	20	Median = 1.4	IQR = 0.98–1.59	33		
Kent 2008	mg/dl	Standard colorimetric assays	78.6	23.6	10	108.6	26.7	6	Crude	Tanner stage, Age 11.1 ± 2.1 years (FDR)
	mmol/L conversion		0.89	0.27	10	1.23	0.30	6		
Recabarren 2008	mg/dl	Standard colorimetric assays	Median = 101.0	Range = 63.0 –174.0	31	Median = 86.0	Range = 59.0 – 130.0	17	Crude	Age median 6.0 (range 4.0 – 7.5) years and socio-economic status matched.
	mmol/L conversion		Median = 1.14	Range = 0.71 – 1.96	31	Median = 0.971	Range = 0.67–1.47	17		
Sons (Adulthood)										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Recabarren 2008	mg/dl	Standard colorimetric assays	Median = 112.0	Range = 69.0 –340.0	29	Median = 117.5	Range = 69.0 – 345.0	19	Crude	Age median 22.0 (range 18.0 – 29.0) years and socio-economic status matched.
	mmol/L conversion		Median = 1.26	Range = 0.78 – 3.84	29	Median = 1.33	Range = 0.78–3.90	19		

Conversion for TG (triglycerides):from mg/dL to mmol/L, multiply by 0.01129

OUTCOME: Total cholesterol				OUTCOME TYPE: Continuous						
Female first degree relatives										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Torchen 2014	mg/dL	Standard colorimetric assays	Median = 146	IQR = 128-152	12	Median = 148	IQR = 134-154	10	Crude	Age, BMI, visceral adiposity and breast Tanner stage matched. Median age 10.4 years (IQR 8.8-12.1 years)
	mmol/L conversion		Median = 3.78	Range = 3.31-3.93	12	Median = 3.83	IQR = 3.47-3.98	10		
Parents										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Vipin 2016	mg/dL	Standard colorimetric assays	184	36	86	175	41	86	Crude	Age and BMI matched (mean age 50.4 ± 5.6 years)
	mmol/L conversion		4.76	0.93	86	4.53	1.06	86		
Fathers										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?

				Fist Degree Relatives						
Vipin 2016	mg/dL	Standard colorimetric assays	173	32	41	172	45	42	Crude	Age and BMI matched (mean age 53.1 ± 5.1 years)
	mmol/L conversion		4.47	0.83	41	4.45	1.16	42		
Yilmaz 2005	mg/dL	Standard colorimetric assays	214.72	35.72	38	162.78	32.56	20	Crude	Age (mean age 51.87 ± 8.54 years) and weight matched
	mmol/L conversion		5.55	0.92	38	4.21	0.84	20		
Mothers										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Sam 2006	mmol/L	Standard colorimetric assays	5.65	1.06	215	4.99	0.84	62	Crude	Age, weight, ethnicity matched (mean age 52 ± 8 years)
Vipin 2016	mg/dL	Standard colorimetric assays	193	37	45	177	37	44	Crude	Age and BMI matched (mean age 47.9 ± 4.9 years)
	mmol/L conversion		4.99	0.96	45	4.58	0.96	44		
Yilmaz 2005	mg/dL	Standard colorimetric assays	208.65	46.13	40	157.12	30.87	20	Crude	Age (mean age 46.38 ± 7.95 years) and weight matched
	mmol/L conversion		5.40	1.19	40	4.06	0.80	20		
Brothers										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Krysiak 2021	mg/dL		220	31	24	211	29	26	Crude	

	mmol/L conversion	Standard laboratory assays	5.69	0.80	24	5.46	0.75	26		Age, BP, BMI, body composition matched (mean age 39 ± 8 years)
Lenarcik 2011	mg/dL	Standard colorimetric assays	184.31	40.22	42	161.17	32.71	30	Crude	Age (mean age 23.52 ± 5.05 years) and weight matched
	mmol/L conversion		4.77	1.04	42	4.17	0.85	30		
Sir-Petermann 2004	mg/dL	Standard laboratory assays	162.2	Range = 102.0–253.0	10	171.5	Range = 112.0–223.0	14	Crude	Age and BMI (mean age 22 years) Subgroup = control group duplicated
	mmol/L conversion		4.19	Range = 2.64-6.54	10	4.44	Range = 2.90-5.77	14		
Sir-Petermann 2004	mg/dL	Standard laboratory assays	167.2	Range = 124.0–198.0	12	171.5	Range = 112.0–223.0	14	Crude	Age and BMI (mean age 23.8 years) Subgroup = control group duplicated
	mmol/L conversion		4.32	Range = 3.21-5.12	12	4.44	Range = 2.90-5.77	14		
Yilmaz 2005	mg/dL	Standard colorimetric assays	212.76	42.04	17	160.72	23.84	15	Crude	Age (mean age 29.00 ± 11.10 years) and weight matched
	mmol/L conversion		5.50	1.09	17	4.16	0.62	15		
Sisters										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Diamanti-Kandarakis 2004	mmol/L	Not reported	4.63	0.31	17	4.22	0.18	20	Crude	Age (Mean age 22.88 ± 0.93 years) and BMI matched
Joharatnam 2011	mmol/L	Not reported	4.9	0.17	153	4.6	0.80	76	Crude	Mean age 31.3 ± 6 years-subgroup with polycystic ovaries (duplicate control group)
Joharatnam 2011	mmol/L	Not reported	4.85	0.18	61	4.6	0.80	76	Crude	Mean age 37.8 ± 7.7 years - subgroup without polycystic ovaries (duplicate control group)

Kulshreshtha 2019	mg/dL	Standard colorimetric assays	158.23	31.97	200	161.78	33.89	99	Crude	Age matched (Mean age 25.42 ± 7.89 years)
	mmol/L conversion		4.09	0.83	200	4.18	0.88	99		
Lenarcik 2011	mg/dL	Standard colorimetric assays	189.45	34.40	44	177.04	34.37	70	Crude	Age (mean age 25.52 ± 5.78 years) and weight matched
	mmol/L conversion		4.90	0.89	44	4.58	0.89	70		
Yilmaz 2005	mg/dL	Standard colorimetric assays	162.50	21.04	25	161.38	19.06	20	Crude	Age (mean age 23.50 ± 7.56 years) and weight matched
	mmol/L conversion		4.20	0.54	25	4.17	0.49	20		
All offspring										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
deWilde 2018	mmol/L	Not reported	4.9	1.3	14	4.4	0.7	130	Crude	Age 7.0 ± 0.8 years (FDR)
Li 2020	mmol/L	Standard colorimetric assays	4.11	0.74	123	4.09	0.65	495	Crude	Age matched (mean age 4.65 ± 1.34 years)
Daughters (Childhood)										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Crisosto 2019	mg/dl	Standard colorimetric assays	Median = 135.0	IQR = 127.0 - 155.0	43	Median = 132.5	IQR = 107.5 - 157.5	28	Crude	Age, gynecologic age, menarchal age, BMI, waist, WHR, and birth weight matched. Age median (IQR): 15.42 (14.17–16.17)
	mmol/L conversion		Median = 3.5	IQR = 3.3 - 4.0	43	Median = 3.4	IQR = 2.8 - 4.1	28		
Sons (Infancy)										

Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Recabarren 2008	mg/dl	Standard colorimetric assays	Median = 145.1	Range = 103.0 – 183.0	20	Median = 155.7	Range = 89.0 – 224.0	20	Crude	Age median 2.0 (range 2.0 - 3.0) months and socio-economic status matched.
	mmol/L conversion		Median = 3.75	Range = 2.66 – 4.73	20	Median = 4.03	Range = 2.30 – 5.79	20		
Sons (Childhood)										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Crisosto 2017	mg/dl	Standard colorimetric assays	Median = 155	IQR = 129–176	23	Median = 141	IQR = 133–164	20	Crude	Tanner stage matched. (Tanner stage I) Age median (IQR): 9.1 (8.4–9.6) years
	mmol/L conversion		Median = 4.01	IQR = 3.34–4.55	23	Median = 3.65	IQR = 3.44–4.24	20		
Crisosto 2017	mg/dl	Standard colorimetric assays	Median = 164	IQR = 142–179	26	Median = 140	IQR = 130–159	31	Crude	Tanner stage matched. (Tanner stage II/III) Age median (IQR): 10.8 (10.3–11.6) years
	mmol/L conversion		Median = 4.24	IQR = 3.67–4.63	26	Median = 3.62	IQR = 3.36–4.11	31		
Crisosto 2017	mg/dl	Standard colorimetric assays	Median = 140	IQR = 118–166	20	Median = 120	IQR = 106–140	33	Crude	Tanner stage matched. (Tanner stage IV/V) Age median (IQR): 14.4 (13–16.1) years
	mmol/L conversion		Median = 3.62	IQR = 3.05–4.29	20	Median = 3.10	IQR = 2.74–3.62	33		

Kent 2008	mg/dl	Standard colorimetric assays	150.8	27.0	10	144.4	16.1	6	Crude	Tanner stage, Age 11.1 ± 2.1 years (FDR)
	mmol/L conversion		3.9	0.70	10	3.73	0.42	6		
Recabarren 2008	mg/dl	Standard colorimetric assays	Median = 171.0	Range = 129.0 – 262.0	31	Median = 155.0	Range = 110.0 –199.0	17	Crude	Age median 6.0 (range 4.0 – 7.5) years and socio-economic status matched.
	mmol/L conversion		Median = 4.42	Range = 3.34 – 6.78	31	Median = 4.01	Range = 2.84– 5.15	17		
Sons (Adulthood)										
Author, year	Unit of outcome	Method of measurement	Mean (specify if median) in First Degree Relatives	SD (or specify if other measure: IQR, SE or 95% CI) in Fist Degree Relatives	Sample size	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Recabarren 2008	mg/dl	Standard colorimetric assays	Median = 182.0	Range = 102.0 – 240.0	29	Median = 163.0	Range = 106.0 – 208.0	19	Crude	Age median 22.0 (range 18.0 – 29.0) years and socio-economic status matched.
	mmol/L conversion		Median = 4.71	Range = 2.64 – 6.21	29	Median = 4.22	Range = 2.74 – 5.38	19		

Conversion for TC (total cholesterol), HDL (high density lipoprotein) and LDL (low density lipoprotein): from mg/dL to mmol/L multiply by 0.02586

APPENDIX. QUALITY APPRAISAL TEMPLATES

CROSS-SECTIONAL or CASE-CONTROL STUDIES

Study ID	Baillargeon 2007
Study Citation	Baillargeon JP, Carpentier AC. Brothers of women with polycystic ovary syndrome are characterised by impaired glucose tolerance, reduced insulin sensitivity and related metabolic defects. Diabetologia. 2007 Dec;50(12):2424-32. doi: 10.1007/s00125-007-0831-9. Epub 2007 Sep 27. PMID: 17898989; PMCID: PMC3846531.
Study Country	Canada
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	17 brothers of women with PCOS diagnosed with PCOS according to1990 NICHD criteria.
Control population	28 control males, matched for age and BMI
PCOS diagnostic criteria	NICHD 1990
N per group	FDR: 17 brothers of women with PCOS Control: 28 control males
Setting	Academic hospital / Single center / timeframe not defined
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary outcome: insulin clamp Other outcomes of interest: - Metabolic syndrome (NCEP–ATP III guidelines) - Waist circumference Measured with a flexible tape midway between the last rib and iliac crest, at the end of a normal expiration. - Systolic BP (mmHg) BP was recorded following a 5 min rest period in the sitting position. - Diastolic BP (mmHg) - Lipid profile (chemiluminescent immunoassay, Freidewald for LDL) Includes triacylglycerol, HDL, LDL, - Fasting plasma glucose (Glucose hexokinase) - OGTT - 2h glucose (Glucose hexokinase) At approximately 09:00 hours, a standard OGTT was performed by administering 75 g glucose orally - Glucose intolerance (not defined) Outcomes not relevant: - BMI (kg/m^2) - not extracted as controls are matched for BMI - Percentage total fat mass (by standing electrical bioimpedance) - AUC glucose AUC for glucose response curves were calculated by the trapezoidal rule using absolute values. - Fasting hormonal studies Total testosterone, androstenedione, 17α-hydroxyprogesterone levels, DHEAS (RIA) SHBG (IRMA) Calculated free testosterone Calculated by the method of Sodergard et al. using a serum albumin concentration of 40 g/l (4.0 g/dl) Oestradiol, progesterone, folliclestimulating hormone, luteinising hormone, thyrotrophin and prolactin (chemiluminescent immunoassay) - Total cholesterol:HDL-cholesterol ratio

	- hsCRP (ELISA) - PAI-1 (ELISA) - Fibrinogen (modified Clauss technique) - Factor VIII (ELISA) - Fasting insulin - AUC insulin AUC for insulin response curves were calculated by the trapezoidal rule using absolute values. - M value Participants were instructed to maintain an isocaloric standard diet for 48 h prior to the euglycaemic–hyperinsulinaemic clamp. At least 2 days later, after a 12 h overnight fast, insulin sensitivity was directly determined. An insulin dose of 40 mU m−2 min−1 was used and total-body carbohydrate metabolism (M value, μmol kg−1 min−1) was calculated as follows: glucose infusion rate during the last 30 min of the clamp (μmol/min) divided by the participant's weight (kg) - Total-body carbohydrate oxidation In an unselected subgroup of participants, the rates of O2 consumption VO2 and CO2 production VCO2 were measured during a 40 min baseline period and during the last 40 min of the clamp to determine total-body carbohydrate oxidation by indirect calorimetry - Basal and insulin-stimulated total-body oxidative carbohydrate metabolisms Calculated as: (25.196 x VCO2=weight) - (17.749 x VO2/weight) - (0.21349 x 1.047 x 10^-4 x weight) - Insulin-stimulated total-body non-oxidative carbohydrate metabolism Calculated as: M value−CHox *All procedures were performed at the Centre de Recherche Clinique Etienne-Le Bel of the CHUS.	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes. Insulin clamp data.
Inclusion criteria	Yes Partial No Not reported	Yes. PCOS proband: normal serum prolactin and thyroid function tests. All participants were white of European origin, in good health, aged between 18 and 40 years, with BMI between 19 and 40 kg/m2
Exclusion criteria	Yes Partial No Not reported	Yes. All participants: type 2 diabetes according to interview, fasting glucose or 75 g OGTT PCOS proband: Late-onset congenital adrenal hyperplasia All participants had never used insulin-sensitising drugs or medications that affect insulin sensitivity. No control individual had any first-degree relatives with a known diagnosis of PCOS, or features of PCOS, based on interview.
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes

Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Yes, case control
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Not relevant to this systematic review
Was matching performed?		Yes Partial No Not reported	Yes, age and BMI.
Summary Result/s		After adjusting for BMI and age, brothers of PCOS women have higher 2h glucose compared to controls.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	Partial Controls were recruited from hospital personnel, students at the Université de Sherbrooke or following an advertisement in Sherbrooke city newspapers. IGT is relatively rare in this age group (7.8% in NHANES II), but we might have unintentionally selected healthier control individuals than expected Whereas brothers of PCOS women were recruited as their PCOS probands were initially treated at the academic hospital.
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes. PCOS defined.
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes.
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	Yes.
DE DETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	Partial. T2DM status was self-reported. BMI measurement may be subject to more variability than laboratory measurements.
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported

	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes.
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Not reported
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	Not relevant to case control study
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	3 brothers and 1 control participant with type 2 diabetes (self-reported) were excluded for fasting glucose or 75 g OGTT analyses. 1 brother and 1 control participant were on a lipid-lowering drug (statin), and their lipid profiles were excluded from all analyses.
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	No protocol registration. No ethics approval.
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	Partial.
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	No conflict of interest. Funding: Fonds de la Recherche en Santé du Québec (FRSQ; Quebec Health Research Funds; J.-P. Baillargeon, no. 2834) and the Canadian Institutes for Health Research (CIHR; A. C. Carpentier, no. MOP 53094). The Centre de Recherche Etienne-Le Bel is an FRSQ-funded research centre. J.-P. Baillargeon is a Junior 2 Clinical Investigator of the FRSQ and A. C. Carpentier is a Junior 2 Investigator of the FRSQ.
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Yes. 88%.
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes.
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate.

Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?	Yes. T2DM status was self-reported, therefore more prone to risk of bias. BMI measurement may be subject to more variability than laboratory measurements.

Study ID	Coviello 2009	
Study Citation	Coviello AD, Sam S, Legro RS, Dunaif A. High prevalence of metabolic syndrome in first-degree male relatives of women with polycystic ovary syndrome is related to high rates of obesity. J Clin Endocrinol Metab. 2009 Nov;94(11):4361-6. doi: 10.1210/jc.2009-1333. Epub 2009 Oct 16. PMID: 19837913; PMCID: PMC2775643.	
Study Country	USA	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	211 fathers, 58 brothers of 237 women with PCOS diagnosed with PCOS according to1990 NICHD criteria.	
Control population	1153 and 582 men from an age and ethnicity matched control population derived from Third National Health and Nutrition Survey (NHANES III)	
PCOS diagnostic criteria	NICHD 1990	
N per group	FDR: 211 Fathers; 53 brothers Control: 1153 / 582 age and ethnicity matched	
Setting	Hospital / Multicentre (3 centers)	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary outcomes: - Metabolic syndrome - Weight (kg) - BMI (kg/m^2) - Waist circumference - Systolic BP (mmHg) - Diastolic BP (mmHg) - Fasting plasma glucose - data not published - Metabolic syndrome (NCEP/ATPIII criteria): Waist circumference >102cm Impaired fasting glucose (>110mg/dL) Hypertriglycerdiaemia (≥150mg/dL) Hypertension (sBP ≥130 / dBP ≥85) Outcomes not relevant: - Testosterone (radioimmunometric assay with interassay coefficients of variation (CVs) of 5%) - Sex hormone binding globulin - DHEAS (radioimmunometric assay with interassay coefficients of variation (CVs) were 8%) Outcomes for brothers not extracted as duplicate data found in another study: SAM, S., COVIELLO, A. D., SUNG, Y.-A., LEGRO, R. S. & DUNAIF, A. 2008. Metabolic phenotype in the brothers of women with polycystic ovary syndrome. Diabetes care, 31, 1237-41.	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes

Inclusion criteria		Yes Partial No Not reported	Yes, Brothers were <40 years old, in the event multiple brothers from one family participated in the study, the youngest brother with complete data was selected. Probands fulfilled diagnostic criteria for PCOS.
Exclusion criteria		Yes Partial No Not reported	Not reported
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Yes, cross-sectional
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Not relevant to this systematic review
Was matching performed?		Yes Partial No Not reported	Yes, age and ethnicity. Fathers were on average younger than control men 57 ±9 years compared with 63 ±13 years (P < 0.0001)
Summary Result/s		Fathers and brothers of women with PCOS had higher rates of metabolic syndrome compared to age and ethnicity matched controls	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	Partial Control group using healthy volunteer participants from a different population than the FDR population
SELECTION BIAS	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes. PCOS defined.
SELECTION BIAS	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Partial.
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	Partial.
DETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	Yes

	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes.
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes.
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	Not relevant to cross-sectional study
ATTRITION BIAS	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Not reported
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	Not reported No protocol registration. Ethics approval obtained
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	Yes Demographic difference between group in age of fathers
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	No
OTHER BIAS	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
OTHER BIAS	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes.
COMMENTS		Control group was derived from a different population	
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate

Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?	Yes. Laboratory measurements are less subject to bias than measurements of blood pressure from different populations.

Study ID	Crisosto 2017
Study Citation	Crisosto N, Echiburú B, Maliqueo M, Luchsinger M, Rojas P, Recabarren S, Sir-Petermann T. Reproductive and metabolic features during puberty in sons of women with polycystic ovary syndrome. Endocr Connect. 2017 Nov;6(8):607-613. doi: 10.1530/EC-17-0218. Epub 2017 Sep 14. PMID: 28912339; PMCID: PMC5640572. (primary citation) SIR-PETERMANN, T., VANTMAN, N., CONCHA, F., ECHIBURU, B., PEREIRA, C., DE GUEVARA, A. L., CRISOSTO, N. R., PEREZ-BRAVO, F. A. & SANTOS, J. L. 2014. Metabolic Profile and Eating Behavior Score in Prepubertal and Early Pubertal Sons of Women with Polycystic Ovary Syndrome. Endocr. Rev., 35, 2.
Study Country	Chile
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	69 sons of women with PCOS between age 7 and 18 years of age, subgroup by Tanner stage. Similar cohort present in Recabarren 2008 study however different age
Control population	84 sons of control women without hyperandrogenism between age 7 and 18 years of age, matched by Tanner stage
PCOS diagnostic criteria	NICHD 1990
N per group	Sons of PCOS women: N = 69 - Tanner I (median age 9.1 years): N = 23 - Tanner II - III (median age 10.8 years): N = 26 - Tanner IV-V (median age 14.4 years): N = 20 Sons of control women: N = 84 - Tanner I (median age 9.0 years): N = 20 - Tanner II - III (median age 10.3 years): N = 31 - Tanner IV-V (median age 13.9 years): N = 33
Setting	Academic clinic / single center
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Outcomes: - Weight (kg) - BMI (kg/m^2) Calculated by the Growth Analyzer Program using the U.S. Growth Charts BMI for age (previously shown to be applicable to the Chilean population) - Waist circumference - Waist hip ratio - Obesity (defined as body weight >95th percentile) - Lipid profile (standard colorimetric assays) LDL calculated by Friedewald's formula - Fasting glucose (glucose oxidase method) - OGTT - 2 hour glucose (glucose oxidase method) After a 12-h overnight fast, an oral glucose tolerance test was performed by giving 1.75 g/kg, up to a maximum of 75 g glucose in 250 ml water. 5 ml blood samples were obtained at baseline and 30, 60 and 120 min after glucose administration. Glucose tolerance defined by ADA criteria

		Outcomes not relevant: - Insulin (radioimmunometric assay) - Testicular volume (Prader orchidometer by a single endocrinologist) - HOMA-IR (standardised calculation) - Insulin sensitivity composite index (ISI) (standardised calculation) - Fasting SHBG (radioimmunometric assay) - Fasting adiponectin (radioimmunometric assay) - Fasting leptin (radioimmunometric assay) - CRP (ultrasensitive immunoturbidimetric assay) - Hormonal studies: LH, FSH, SHBG, testosterone, androstenedione, 17-OH progesterone, AMH (enzyme immunoassay) - Lipid profile	
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	Yes
Inclusion criteria		Yes Partial No Not reported	Yes. All PCOS sons were born at term after spontaneous conceptions, singletons. Control women have a history of singleton pregnancies, regular 28 to 32 day menstrual cycles.
Exclusion criteria		Yes Partial No Not reported	Yes. PCOS probands: Patients with hyperprolactinemia, androgen-secreting neoplasms, Cushing's syndrome, and late-onset 21-hydroxylase deficiency as well as thyroid disease. Control women: hirsutism, other manifestations of hyperandrogenism, history of infertility or pregnancy complications.
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Partial, case control. No follow-up for future cardiovascular events
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Not relevant to this systematic review
Was matching performed?		Yes Partial No Not reported	Yes, Tanner stage.
Summary Result/s		Sons of women with PCOS had higher rates of dyslipidaemia during puberty compared to controls matched by Tanner stage	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	Partial Method of control women recruitment not specified.

BIAS	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Partial. National Institutes of Health consensus criteria.
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes.
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	Yes.
DE DETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes.
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Partial. Tanner stage determined by a single endocrinologist.
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	Not relevant to cross-sectional study
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Not reported
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	Partial. Ethics approval, protocol not registered prospectively.
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	Partial Method of control women recruitment not specified.

OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	No. Funded by Fondo Nacional de Desarrollo Científico y Tecnológico (National Fund for Scientific and Technological Research; Fondecyt; Grants 1030487-1151531), and the Alexander von Humboldt Foundation.
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Partial. Propensity matching. Median and interquartile range reported, but not mean nor standard deviation.
COMMENTS		Method of control women recruitment not specified.	
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate - Non-specified recruitment method of control group. - Single endocrinologist
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No.	

Study ID	Crisosto 2019
Study Citation	Crisosto N, Ladrón de Guevara A, Echiburú B, Maliqueo M, Cavada G, Codner E, Paez F, Sir-Petermann T. Higher luteinizing hormone levels associated with antimüllerian hormone in postmenarchal daughters of women with polycystic ovary syndrome. Fertil Steril. 2019 Feb;111(2):381-388. doi: 10.1016/j.fertnstert.2018.10.011. Epub 2018 Dec 7. PMID: 30527840.
Study Country	Chile
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	43 postmenarcheal daughters of women with PCOS 1.5-6 years after menarche
Control population	28 postmenarcheal daughters of women without hyperandrogenism 1.5-6 years after menarche matched by age, gynecologic age, menarchal age, BMI, waist, WHR, and birth weight
PCOS diagnostic criteria	NICHD 1990
N per group	FDR: 43 daughters Control: 28 daughters
Setting	Academic hospital / Single centre / timeframe not specified
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary outcomes: - Waist circumference - not extracted as matched for WHR - Hip circumference - not extracted as matched for WHR - OGTT - 2 hour glucose (glucose oxidase method) After a 12-h overnight fast, an oral glucose tolerance test was performed by giving 1.75 g/kg, up to a maximum of 75 g glucose in 250 ml water. 5 ml blood samples were obtained at baseline and 30, 60 and 120 min after glucose administration.

	Glucose tolerance defined by ADA criteria - Fasting plasma glucose (glucose oxidase method) - PCOS (NICHD criteria) - Lipid profile Total cholesterol, triglycerides, LDL, and HDL-C - Systolic blood pressure - Diastolic blood pressure BP measurement method not defined. - Weight (kg) (could not extract due to weight matching) - Height (m) - BMI (kg/m^2) (could not extract due to weight matching) Calculated by the Growth Analyzer Program using the U.S. Growth Charts BMI for age (previously shown to be applicable to the Chilean population) - Obesity (could not extract due to lack of individual data to extract) Defined as a body weight >95th percentile Outcomes not relevant: - Tanner stage (single observer) - Hirsutism (determining the presence of terminal hair using the modified Ferriman-Gallway score) - Acne and acanthosis nigricans - HOMA-IR - Whole-body insulin sensitivity composite index (ISI) - LH, FSH (electrochemiluminiscence) - SHBG (radioimmunometric assay) - AMH (enzyme immunoassay) - FAI Basal serum testosterone to SHBG ratio x 100 - Ovarian volume (transabdominal ultrasonography - blinded observer) - Cycles per year - GnRH agonist test 10 mg/kg subcutaneous leuprolide acetate administered between 8:00 and 9:00 a.m. Serum LH and FSH levels were measured before and 3 hours after leuprolide injection Serum Testosterone, androstenedione, 17a-hydroxyprogesterone (17-OHP) (radioimmunometric assay) and estradiol concentrations (electrochemiluminiscence) were determined at baseline and 24 hours - Fasting insulin (radioimmunometric assay) Biochemistry studied during the early follicular phase of the menstrual cycle (day 3–7) or whenever feasible in those with amenorrhea	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes
Inclusion criteria	Yes Partial No Not reported	Yes. All participants:11–17 years old, gynecologic age (years after menarche) of 1.5–6 years, born from singleton pregnancies Control mothers of similar socioeconomic level with a history of singleton pregnancies and regular 28–32-day menstrual cycles.
Exclusion criteria	Yes Partial No Not reported	Yes. All participants: any chronic diseases, history of early puberty,precocious pubarche, previously diagnosed with PCOS,

			oral contraceptives or any other medication during the 6 months before the study Mothers of control girls: hirsutism, clinical manifestations of hyperandrogenism, infertility, pregnancy complications during their early reproductive age were excluded.
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Yes, case control.
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Not relevant to this systematic review
Was matching performed?		Yes Partial No Not reported	Yes, propensity matching for age, gynecologic age, menarchal age, BMI, waist, WHR, and birth weight matched.
Summary Result/s		No difference in fasting glucose and insulin and 2-hour glucose levels, between daughters of PCOS mothers and age, gynecologic age, menarchal age, BMI, waist, WHR, and birth weight matched controls of children of mothers without PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	Partial Method of control group recruitment not specified.
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes. National Institutes of Health consensus criteria.
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Partial Method of control group recruitment not specified.
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	Yes.
DE DETECTION	Were measurements (for exposures or outcomes) carried out and calculated in	Yes Partial No Not reported	Partial.

BIAS	a standard, valid and reliable way?		- Measurement biases can occur with weight, height, waist and hip circumferences, as well as the systolic and diastolic blood pressures (method not specified)
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported.
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes.
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Partial. Blinded observer for ultrasound. Single observer for Tanner staging. Other outcomes not reported.
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	Not relevant to case control study
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Not relevant to case control study
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	Partial. No protocol registration. Ethics approval obtained.
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	Yes.
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	No conflict of interest. Funding source: National Fund for Scientific and Technological Development (FONDECYT) grants 1071007 and 1151531.
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported.
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Partial. Median and interquartile range reported, but not mean nor standard deviation.
COMMENTS			
What is the overall risk of bias?		Low Moderate	Moderate. Method of deriving control group not reported.

	High Insufficient information	
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?	Yes. Systolic and diastolic blood pressures, waist and hip circumferences, and thus the waist to hip ratio were more prone to measurement biases.	

Study ID	Diamanti-Kandarakis 2004	
Study Citation	Diamanti-Kandarakis E, Alexandraki K, Bergiele A, Kandarakis H, Mastorakos G, Aessopos A. Presence of metabolic risk factors in non-obese PCOS sisters: evidence of heritability of insulin resistance. J Endocrinol Invest. 2004 Nov;27(10):931-6. doi: 10.1007/BF03347535. PMID: 15762040.	
Study Country	Greece	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	17 sisters of 54 women with PCOS diagnosed with PCOS according to1990 NICHD criteria.	
Control population	20 healthy control women, matched for age and BMI	
PCOS diagnostic criteria	NICHD 1990	
N per group	FDR: 17 sisters of PCOS women Control: 20 women	
Setting	Hospital / Single center	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary outcomes: - Metabolic syndrome - Weight (kg) - not extracted as matched for BMI - BMI (kg/m^2) - not extracted as matched for BMI - Waist circumference - Systolic BP (mmHg) (measured in the morning in the seated position in the right arm after a 5-min rest period. The average of three measurements taken 2 min apart) - Diastolic BP (mmHg) - Hypertension (blood pressure >90th percentile age, height, and gender, as defined by the National High Blood Pressure Education Program for Children and Adolescents) - Fasting plasma glucose (glucose oxidase method) - Lipid profile (enzymatic assay, Freidewald for LDL) - OGTT (glucose oxidase method) After a 12-h overnight fast, glucose load of 1.7 g/kg. In children <8 years old, salivary samples collected at 0, 30, 60, 90, and 120 min to measure salivary insulin levels. In children > 8 years old, blood was drawn at baseline and 120 min after glucose administration for glucose and insulin levels Outcomes not relevant: - Fasting insulin (radioimmunometric assay) - Fasting hormonal studies: testosterone, DHEAS, gonadotropins, SHBG (radioimmunometric assay) - HOMA-IR - QUICKI - Uric acid	
Does the study have a clearly focused question and/or PICO?	Yes Partial	Partial. “Metabolic and hormonal ”

		No Not reported	
Inclusion criteria		Yes Partial No Not reported	Yes. Sisters of women with PCOS diagnosed with NICHD criteria All women had regular ovulatory cycles
Exclusion criteria		Yes Partial No Not reported	Yes. PCOS probands and sisters: non classical congenital adrenal hyperplasia, androgen secreting neoplasm, hyperprolactinaemia, thyroid disease All groups: confounding medications known to affect sex steroids or insulin action. Clinical hyperandrogenism (hirsutism, acne, alopecia), treatment for menstrual disturbances, inferility or hirsutism
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Yes, case control
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Not relevant to this systematic review
Was matching performed?		Yes Partial No Not reported	Yes, age and BMI
Summary Result/s		Sisters of women with PCOS had higher rates of insulin resistance compared to age and BMI matched controls	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	Partial Control group method of derivation not described
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes. PCOS defined.
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Partial. Control group method of derivation not described

PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	Yes.
DE DETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	Partial. Anatomical landmarks for waist and hip circumference not reported. Laboratory measurements described with coefficient of variance.
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes.
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Not reported
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	Not relevant to case control study
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	All included
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	Not reported No protocol registration. Ethics approval obtained
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	Partial. Method of deriving control cohort not described
OTHER	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	Not reported.
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported

BIAS	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes.
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate. Control group method of derivation not reported.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		Yes. Waist hip measurements may be subject to more variability than laboratory measurements.	

Study ID	Karthik 2019
Study Citation	Karthik S, Vipin VP, Kapoor A, Tripathi A, Shukla M, Dabadghao P. Cardiovascular disease risk in the siblings of women with polycystic ovary syndrome. Hum Reprod. 2019 Aug 1;34(8):1559-1566. doi: 10.1093/humrep/dez104. PMID: 31299073. (primary citation) Subramaniam K, Tripathi A, Dabadghao P. Familial clustering of metabolic phenotype in brothers of women with polycystic ovary syndrome. Gynecol Endocrinol. 2019 Jul;35(7):601-603. doi: 10.1080/09513590.2019.1566451. Epub 2019 Feb 6. PMID: 30727783. Karthik, S, Vipin, VP, Kapoor, A, Tripathi, A, Shukla, M & Dabadghao, P 2019, 'Cardiovascular disease risk in the siblings of women with polycystic ovary syndrome', Human Reproduction, vol. 34, no. 8, pp. 1559–1566.
Study Country	India
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	35 unrelated sisters and 41 unrelated brothers of 76 women with PCOS diagnosed with PCOS according to Rotterdam 2003 criteria
Control population	35 women and 41 men age and BMI matched
PCOS diagnostic criteria	Rotterdam 2003
N per group	FDR: 35 sisters; 41 brothers Control: 35 / 41 age and BMI matched controls
Setting	Hospital / Single centre / January 2016 - July 2017
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary outcomes: - Carotid intima media thickness (2 independent observers, ultrasound, standardised protocol) - Brachial artery flow-mediated dilatation (2 independent observers, ultrasound, standardised protocol) Other outcomes: - Weight (kg) (single observer) - not extracted as matched for BMI - Height (m) (single observer) - BMI (kg/m^2) (automated BP measurement) - not extracted as matched for BMI - Waist circumference ((WHO standards)

	- Hip circumference (WHO standards) - Systolic BP (mmHg) (automated BP measurement) - Diastolic BP (mmHg) - Fasting plasma glucose - OGTT (75g loading) ADA criteria 2019 to evaluate glucose tolerance - Lipid profile (standard colorimetric assays) - Metabolic syndrome (NCEP/ATPIII criteria) Outcomes not relevant: - HOMA-IR - QUICKI - DHEAS, testosterone (radioimmunoassay) - C-peptide (ELISA) - High sensitivity CRP (chemiluminescence) - Hypertension (not published) - Diabetes (ADA 2019 criteria) - not all data published - Fasting insulin (ELISA)	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes
Inclusion criteria	Yes Partial No Not reported	Yes. First degree relatives of women with PCOS diagnosed by the Rotterdam 2003 criteria. Age 12-40
Exclusion criteria	Yes Partial No Not reported	Yes. Siblings: chronic systemic medical illness, acute illness in past 3 months, pregnant, attending endocrine clinic for metabolic health
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	Yes, case control
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	Not relevant to this systematic review
Was matching performed?	Yes Partial No Not reported	Yes, age and BMI.
Summary Result/s	Siblings of women with PCOS had higher rates of metabolic syndrome and insulin resistance than age and weight matched controls	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	Partial Control group using outpatient department staff and relatives of patients admitted in the endocrine ward.
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes. Rotterdam criteria.
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Partial. Family members of patients attending endocrine clinic potentially have a family history of diabetes.
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	Yes.
DE DETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	Yes. Method of blood pressure measurement not described
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Yes (for the primary outcome).
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes.
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Partial. Single observer for BMI, BP and waist measurements.
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	Not relevant to case control study
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Not relevant to case control study
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	No protocol registration. Ethics approval obtained

CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	Partial. Only age and weight matched
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	No. Funded by university grant - Intramural Research Grant (PGI/DIR/RC/943/2013)
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Yes. Powered for carotid intima media thickness and flow-mediated dilatation
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes. Only one sibling from each family recruited. Some data in median, IQR.
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate. Method of derivation of control cohort.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		Yes. Laboratory measurements are less subject to bias than measurements of blood pressure / weight / height.	

Study ID	Kent 2008
Study Citation	Kent SC, Gnatuk CL, Kunselman AR, Demers LM, Lee PA, Legro RS. Hyperandrogenism and hyperinsulinism in children of women with polycystic ovary syndrome: a controlled study. J Clin Endocrinol Metab. 2008 May;93(5):1662-9. doi: 10.1210/jc.2007-1958. Epub 2008 Feb 12. PMID: 18270257; PMCID: PMC2386683.
Study Country	USA
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	32 children of 27 women with PCOS diagnosed with PCOS according to1990 NICHD criteria.
Control population	38 children from control women, subgroup by Tanner stage
PCOS diagnostic criteria	NICHD 1990
N per group	FDR: 17 sons, 15 daughters of women with PCOS Control: 21 sons, 17 daughters of control women recruited by local advertisement Data for daughters not extracted as duplicate of other studies
Setting	Hospital / Single center / June-Dec 2005

Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary outcomes: - Weight (kg) - BMI (kg/m^2) - Waist circumference - Systolic BP (mmHg) (measured in the morning in the seated position in the right arm after a 5-min rest period. The average of three measurements taken 2 min apart) - Diastolic BP (mmHg) - Hypertension (blood pressure >90th percentile age, height, and gender, as defined by the National High Blood Pressure Education Program for Children and Adolescents) - Fasting plasma glucose (glucose oxidase method) - Lipid profile (enzymatic assay, Freidewald for LDL) - OGTT (glucose oxidase method) After a 12-h overnight fast, glucose load of 1.7 g/kg. In children <8 years old, salivary samples collected at 0, 30, 60, 90, and 120 min to measure salivary insulin levels. In children > 8 years old, blood was drawn at baseline and 120 min after glucose administration for glucose and insulin levels - Metabolic syndrome (Ferranti criteria for adolescents); at least 3 of: Waist circumference more than the 75th percentile Hypertension defined by either systolic or diastolic blood pressure more than the 90th percentile Fasting triglyceridesmore than or equal to 97.3mg/dl Fasting HDL-C less than 50.2 mg/dl Fasting glucose more than or equal to 110mg/dl. Outcomes not relevant: - Insulin (double antibody method) Salivary insulin levels from children correlated with 30 control adults - Hormonal studies: testosterone, DHEAS, gonadotropins (radioimmunoassay) - HOMA-IR - Ovarian size and morphology on transabdominal ultrasound - Tanner staging (assessed by nursing personnel) - Gestational age - Birthweight Outcomes for daughters not extracted as duplicate data found in another study: Legro RS, Kunselman AR, Stetter CM, Gnatuk CL, Estes SJ, Brindle E, Vesper HW, Botelho JC, Lee PA, Dodson WC. Normal Pubertal Development in Daughters of Women With PCOS: A Controlled Study. J Clin Endocrinol Metab. 2017 Jan 1;102(1):122-131. doi: 10.1210/jc.2016-2707. PMID: 27778640; PMCID: PMC5413094.	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Partial. “Reproductive and metabolic functions”
Inclusion criteria	Yes Partial No Not reported	Yes. Control group: mothers of control children had a history of regular menstrual cycles
Exclusion criteria	Yes Partial No Not reported	Yes. All groups: confounding medications known to affect sex steroids or insulin action Control children: personal or family history of diabetes, mothers of children with hirsutism
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No	Yes

		Not reported	
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Yes, case control
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Not relevant to this systematic review
Was matching performed?		Yes Partial No Not reported	Yes, Tanner staging
Summary Result/s		Children of women with PCOS had higher rates of metabolic syndrome compared to age and ethnicity matched controls	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	Partial Control group method of derivation not described
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes. PCOS defined.
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Partial. Control group method of derivation not described
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	Yes.
DE DETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	Yes, Blood pressure measurement standardised, clear criteria for metabolic syndrome
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes.

	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Not reported
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	Not relevant to case control study
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Not all children had serum samples. 53% FDR 45% control
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	Not reported No protocol registration. Ethics approval obtained
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	Partial. Method of deriving control cohort not described
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	No. Grant funding from university PHS K24 HD01476, U54 HD034449, General Clinical Research Center Grant MO1 RR 10732, and construction Grant C06 RR016499. One author had pharmaceutical company funding (however no pharmaceutical products used in this study).
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes.
COMMENTS		Control group was derived from a different population	
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No.	

Study ID	Kulshreshtha 2019
Study Citation	Kulshreshtha B, Sharma N, Pant S, Prasad A, Chitkara A, Pahuja B, Pahuja I. Predictors of Metabolic Syndrome among Polycystic Ovary Syndrome Sisters. J Hum Reprod Sci.

	2019 Oct-Dec;12(4):334-340. doi: 10.4103/jhrs.JHRS_172_18. Epub 2019 Dec 17. PMID: 32038085; PMCID: PMC6937762.	
Study Country	India	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	200 sisters of women with PCOS not on treatment for diabetes, hypertension or hyperlipidaemia	
Control population	99 age matched healthy controls who did not meet criteria for PCOS from hospital staff or healthy daughters of hospital staff	
PCOS diagnostic criteria	Rotterdam 2003	
N per group	FDR: N = 200 Control: N = 99	
Setting	Academic hospital / single center / 2013 - 2016	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Outcomes: - Weight (kg) - BMI (kg/m^2) - Waist circumference (measured at the narrowest level between the costal margin and the iliac crest) - Hip circumference (measured at the widest level over the buttocks with the participant standing normally) - Blood pressure (in the seated position in the right arm as the average of two separate readings obtained two min apart after a 5-min rest) - Obesity (defined as BMI >23 kg/m^2) - Lipid profile Standard colorimetric assays for triglycerides / cholesterol Direct method for HDL LDL calculated by Friedewald's formula - Fasting glucose (glucose oxidase) - OGTT - 2 hour glucose After an overnight fast, an oral glucose tolerance test was performed by giving 75 g glucose with blood samples obtained at baseline, 60 and 120 min after glucose administration - Metabolic syndrome (NCEP ATP III criteria) Outcomes not relevant: - Insulin (ELISA) - HOMA-IR (standardised calculation) - Hormonal studies: LH, FSH, testosterone, androstenedione, 17-OH progesterone, thyroid function tests, cortisol, prolactin (chemiluminescence and ELISA) - Transabdominal ultrasound for polycystic ovaries - Hypertension (unable to be extracted as control group selected to not have hypertension) - PCOS (unable to be extracted as control group selected to not have PCOS and criteria not clearly defined for sisters)	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes
Inclusion criteria	Yes Partial	Yes.

		No Not reported	Control women age 15-45 years, regular 27 to 32 day menstrual cycles.
Exclusion criteria		Yes Partial No Not reported	Yes. PCOS sisters: Pregnant, lactating, premenarchal, menopausal, on oral contraceptive pills, oral hypoglycemics, antihypertensives, or lipid-lowering agents Control women: clinical hyperandrogenism (hirsutism, acne, or hair loss), major medical or psychiatric illnesses, hypertension, diabetes, intake of medications known to alter sex hormone metabolism or glucose homeostasis for at least 3 months before the study
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Partial, case control. No follow-up for future cardiovascular events
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Not relevant to this systematic review
Was matching performed?		Yes Partial No Not reported	Yes, age
Summary Result/s		Sisters of women with PCOS have higher risk of metabolic syndrome (especially if they themselves are affected by PCOS) compared to age matched controls	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	No Control group from healthy hospital staff
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Partial. Some of the sisters of women with PCOS likely had PCOS themselves but not clearly defined by Rotterdam criteria
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes.
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	Yes.

DE DETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes.
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Not reported.
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	Not relevant to case-control study. However, 221 PCOS probands recruited with 354 sisters. 154 sisters declined consent / geographically distant or did not meet inclusion criteria (56% sisters included)
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Not reported
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	Partial. Ethics approval, protocol not registered prospectively.
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	Partial. Only age matchced
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	No. Funded by government DST grant number---SR/ FT/LS-37/2011.
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes.
COMMENTS			

What is the overall risk of bias?	Low Moderate High Insufficient information	Moderate - Control group method of derivation dissimilar. - 56% sisters of women with PCOS included
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?	Yes. Measurement of BP likely more subject to bias than laboratory measures	

Study ID	Legro 2017
Study Citation	Legro RS, Kunselman AR, Stetter CM, Gnatuk CL, Estes SJ, Brindle E, Vesper HW, Botelho JC, Lee PA, Dodson WC. Normal Pubertal Development in Daughters of Women With PCOS: A Controlled Study. J Clin Endocrinol Metab. 2017 Jan 1;102(1):122-131. doi: 10.1210/jc.2016-2707. PMID: 27778640; PMCID: PMC5413094.
Study Country	USA
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	76 daughters of women with PCOS diagnosed with PCOS according to 1990 NICHD criteria.
Control population	80 daughters of control mothers, subgroup by Tanner stage
PCOS diagnostic criteria	NICHD 1990
N per group	FDR: 76 daughters Control: 80 daughters of control women
Setting	Hospital / Single center
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Outcomes: - Metabolic syndrome - Weight (kg) (to the nearest 0.1 kg) - Height (cm) (to the nearest 0.1 cm) - BMI (kg/m^2) - Waist circumference (to the nearest 0.1 cm, measured at the level of the umbilicus) - Hip circumference(to the nearest 0.1 cm, measured at the widest diameter) - Systolic BP (mmHg) (average of three measurements in the right arm in the sitting position after a 15-minute rest) - Diastolic BP (mmHg) Outcomes not relevant: - Tanner stage (single trained study coordinator) - Acne (standardised pictorial methods) - Ferriman-Gallwey score - Transabdominal ultrasound - Hormonal studies: testosterone, DHEAS, gonadotropins (radioimmunoassay), urine LH/FSH (ELISA), urine estrogen/androgen (tandem mass spectrometry / isotope dilution liquid chromatography) (Primary outcome of hyperandrogenism) - HOMA-IR - Metabolic syndrome (ATP III criteria) - could not be extracted as control group selected to not have metabolic syndrome - Lipid profile (enzymatic assay, Freidewald for LDL) - not reported

	- PCOS (NICHD criteria) - could not be extracted as control group selected to not have PCOS - OGTT (75g) After a 12-h overnight fast, glucose load of 1.7 g/kg. In children <8 years old, salivary samples collected at 0, 30, 60, 90, and 120 min to measure salivary insulin levels. In children > 8 years old, blood was drawn at baseline and 120 min after glucose administration for glucose and insulin levels - Insulin (double antibody method) Salivary insulin levels from children correlated with 30 control adults	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes. Hyperandrogenism as the primary outcome
Inclusion criteria	Yes Partial No Not reported	Yes. Women were non-Hispanic Caucasian (to avoid confounding effects of ethnicity on metabolic endpoints) Control women: history of regular menstrual cycles (10 to 14 cycles per year), normal circulating androgen levels, normal levels of 17 OH progesterone (i.e., a morning level ,2 ng/mL) or a normal adrenocorticotropic hormone stimulation test if above that level,
Exclusion criteria	Yes Partial No Not reported	Yes. PCOS probands: secondary causes of oligomenorrhea, including thyroid disease, prolactin excess, and congenital adrenal hyperplasia. Daughters of women with PCOS: preexisting diagnosis of type 1 or 2 diabetes, known history of PCOS in the sisters or mother of the father of the child, medications that could affect hormonal levels or glucose tolerance, such as GnRH agonists, hormonal contraceptives, insulin-sensitizing agents, statins, and many antihypertensives, conceived through in vitro fertilization Control women: personal or family history of history of hypertension or diabetes mellitus, oral contraceptive agents in preceding 3 months, suspicion of Cushing syndrome, clinical/biochemical evidence of hyperandrogenism, sister or mother with PCOS, current use of confounding medications that could affect steroid levels, conceived with the use of clomiphene citrate
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	Yes, case control
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	Not relevant to this systematic review
Was matching performed?	Yes Partial No Not reported	Yes, Tanner stage

Summary Result/s		Daughters of women with PCOS had similar rates of hyperandrogenism and insulin resistance compared to pubertal stage matched controls	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	Partial Method of deriving control group not defined
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes. PCOS defined.
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Partial.
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	Partial.
DE DETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	Partial. Blood pressure and laboratory measures standardised. Salivary insulin levels validated in adult cohort
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes.
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Partial. Single assessor for Tanner stage
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	Not relevant to case control study
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	FDR: 74/76 (97%) included for BP measurement; 75/76 (99%) for BMI measurement; 75/76 (99%) for WHR measurement COntrol: 81 daughters included for BP measurement; 82 daughters for BMI measurement; 79 for waist hip ratio (despite total stating to be 80 daughters)

REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	Not reported No protocol registration. Ethics approval obtained
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	No.
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	No. Funded by government grant (Eunice Kennedy Shriver National Institutes of Child Health and Human Development (NICHD), National Center for Research Resources, and the National Center for Advancing Translational Sciences at the National Institutes of Health, through Grants U54 HD034449 (Specialized Cooperative Centers Program in Reproductive & Infertility Research at VCU) and UL1 TR000127 (Pennsylvania State Clinical andTranslational Institute). Partial funding from Eunice Kennedy Shriver NICHD research infrastructure grant, R24HD042828, to the Center for Studiesin Demography & Ecology at the University of Washington. 3 authors receive pharmaceutical company funding (however non interventional study).
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Partial. Multiple daughters from the same mother included if eligible, random effect model used to control for this.
COMMENTS		Control group was derived from a different population	
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate. Some attrition in measurements. No blinding / independent assessment of blood pressure and waist hip ratio.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		Yes. Blood pressure / WHR more subject to bias than laboratory measurements.	

Study ID	Lenarcik 2011
Study Citation	Lenarcik, A., Bidzinska-Speichert, B. and Tworowska-Bardzinska, U. (2011) 'Metabolic Abnormalities in Siblings of Women with Polycystic Ovary Syndrome', ADVANCES IN CLINICAL AND EXPERIMENTAL MEDICINE, 20(2), pp. 165–175.
Study Country	Poland

CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	44 sisters and 42 brothers of women with PCOS	
Control population	70 healthy women and 30 healthy men (age and BMI matched)	
PCOS diagnostic criteria	Rotterdam 2003	
N per group	FDR: 44 sisters; 42 brothers Control: 70 women and 30 men age and BMI matched	
Setting	University Hospital / Single centre	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary outcomes: - Weight (kg) - not extracted as matched for BMI - Height (m) - BMI (kg/m^2) - not extracted as matched for BMI - Waist circumference (anatomical landmarks not described) - Hip circumference (anatomical landmarks not described) - Fasting plasma glucose (glucose oxidase) - OGTT (did not describe protocol) - Lipid profile (Standard colorimetric assays ; Friedewald calculation for LDL Outcomes not relevant: - Fasting insulin (chemiluminescence) - HOMA-IR - Insulin sensitivity index - FIRI - insulin resistance index - QUICKI - MATSUDA index	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Partial. “metabolic parameters”
Inclusion criteria	Yes Partial No Not reported	Yes. First degree relatives of women with PCOS diagnosed by the Rotterdam 2003 criteria. Only occasional alcohol use.
Exclusion criteria	Yes Partial No Not reported	Partial. Hypercortisolemia, hyperprolactinemia, impaired thyroid function, ovarian tumour, adrenal tumor, hormonal treatment, insulin sensitising drugs, special diet, intense physical exercises, smoking >5 cigarettes a day Control group defined as those who’s sisters did not have PCOS, menstrual disturbances or hirsutism
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Partial. No mention of how control group women were defined not to have PCOS in themselves.
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	Yes, case control.

Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Not relevant to this systematic review
Was matching performed?		Yes Partial No Not reported	Yes, age and weight.
Summary Result/s		Siblings of women with PCOS had high rates of hyperlipidaemia and glucose intolerance than age and weight matched controls	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	Partial Method of deriving controls not defined.
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes. Rotterdam criteria.
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Partial. Method of deriving controls not defined.
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	Partial.
DE DETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Partial. Method of measuring BP not mentioned
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Not reported.
ATTRITI	What percentage of the individuals recruited into	X% treatment X% control/ comparison	Not relevant to case control study

ON BIAS	each arm of the study were lost to follow up?	Not reported	
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Not relevant to case control study
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	No protocol registration. Ethics approval obtained
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	Partial. Only age and weight matched
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes.
COMMENTS		Method of deriving control cohort not described	
What is the overall risk of bias?		Low Moderate High Insufficient information	High. Method of deriving cohort not defined
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		Yes. Laboratory measurements are less subject to bias than measurements of blood pressure from different populations.	

Study ID	Li 2020
Study Citation	Li J, Cui L, Jiang X, Zhao H, Zhao S, Shi Y, Wei D, You L, Ma J, Chen ZJ. Transmission of polycystic ovary syndrome susceptibility single-nucleotide polymorphisms and their association with phenotype changes in offspring. Hum Reprod. 2020 Jul 1;35(7):1711-1718. doi: 10.1093/humrep/deaa125. PMID: 32619219. (primary citation) Zhang Z, Liu Y, Lv J, Zhang D, Hu K, Li J, Ma J, Cui L, Zhao H. Differential Lipidomic Characteristics of Children Born to Women with Polycystic Ovary Syndrome. Front Endocrinol (Lausanne). 2021 Aug 9;12:698734. doi: 10.3389/fendo.2021.698734. PMID: 34434168; PMCID: PMC8380809.
Study Country	China

CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	172 children of women with PCOS diagnosed with PCOS according to Rotterdam 2003 criteria	
Control population	529 children of women without PCOS of similar age	
PCOS diagnostic criteria	Rotterdam 2003	
N per group	FDR: 172 children Control: 529 children	
Setting	Academic hospital / Single centre (timeframe not defined)	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary outcomes of interest: association of SNPs and maternal PCOS Other ouutcomes: - Fasting plasma glucose (oxidase method) - Height (z score) - reported in Zhang 2021 substudy (method of assessment not reported) - Weight (z score) - reported in Zhang 2021 substudy (method of assessment not reported) - BMI (z score) - reported in Zhang 2021 substudy (method of assessment not reported) - Blood pressure - reported in Zhang 2021 substudy (method of assessment not reported) - Cholesterol - Triglycerides - HDL - LDL Levels of serum cholesterol, triglycerides, LDL and HDL were measured using the precipitation and enzymatic methods. Outcomes not relevant: - Fasting insulin (chemiluminescence immunoassays) - HOMA-IR, HOMA-beta - FSH, LH, prolactin, DHEA-S, estradiol, testosterone, prolactin, TSH, AMH, free triiodothyronine. free thyroxine A morning fasting blood sample was obtained for examining circulating serum levels of hormones - Antibodies against thyroglobulin and antibodies against thyroperoxidase - 18 SNPs In the DENND1A gene, the SNPs were rs10818854 and 2479106; in the YAP1 gene, the SNPs were rs1894116 and rs11225161; in the THADA gene, the SNPs were rs12478601 and rs13429458; in the FSHR gene, the SNPs were rs2268361 and rs2349415; and in the C9orf3 gene, the SNPs were rs3802457 and rs4385527. In addition, rs4784165 in TOX3, rs6022786 in SUMO1P1, rs705702 in RAB5B, rs13405728 in LHCGR, rs2059807 in INSR, rs9939609 in FTO, rs2272046 in HMGA2 and 1351592 in ERBB4 were also chosen	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes
Inclusion criteria	Yes Partial No Not reported	Yes. All children participants were conceived by ART or artificial insemination, aged 1-8 yr.
Exclusion criteria	Yes Partial No Not reported	Yes. PCOS probands:other causes of oligomenorrhea or hyperandrogenism such as Cushing's syndrome and hypothyroidism

If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Yes, case control.
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Not relevant to this systematic review
Was matching performed?		Yes Partial No Not reported	Similar age.
Summary Result/s		Offspring of women with PCOS had higher rates of insulin resistance compared to age matched controls.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	Yes.
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes. Rotterdam criteria.
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Partial. Recruited from same center but unclear attrition.
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	Yes.
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	Partial. Weight method of measurement not described
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes.

	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Not reported.
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	Not relevant to case control study
ATTRITION BIAS	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	618/701 total population for endocrine and metabolic parameters FDR: 123/172 (72%) Control: 495/529 (94%) BP and BMI reported for the following in Zhang 2021 substudy: FDR: 70/123 (57%) Control: 71/495 (14%)
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	Partial. No protocol registration. No ethics approval.
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	Partial. Age matched.
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	No. Funding source: National Key Research and Development Program of China, National Natural Science Foundation of China, National Natural Science Foundation of Shandong Province, and Shandong Provincial Key Research and Development Program. Conflict of interest not reported.
OTHER BIAS	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Partial. Power analysis performed for association between SNPs and maternal PCOS (80%).
OTHER BIAS	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes.
COMMENTS		Not enough follow-up for clinical cardiovascular outcomes	
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate. Not all participants analysed
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		Yes. Weight and blood pressure measurements method of assessment not mentioned.	

Study ID	Raissouni 2012
Study Citation	Raissouni N, Kolesnikov A, Purushothaman R, Sinha S, Bhandari S, Bhangoo A, Malik S, Mathew R, Baillargeon JP, Hernandez MI, Rosenbaum M, Ten S, Geller D. Altered glucose disposition and insulin sensitivity in peri-pubertal first-degree relatives of women with polycystic ovary syndrome. Int J Pediatr Endocrinol. 2012 May 29;2012(1):14. doi: 10.1186/1687-9856-2012-14. PMID: 22643321; PMCID: PMC3477027. (primary citation) Trottier, A., Battista, M. C., Carpentier, A., Simoneau-Roy, J., Geller, D., & Baillargeon, J. P. (2011). Early metabolic and endocrine perturbations in pre- or peripubertal girls with a first degree relative with polycystic ovary syndrome. Fertility and sterility, 96(3), S129-S129. doi:10.1016/j.fertnstert.2011.07.502 Trottier, A., Battista, M. C., Simoneau-Roy, J., Carpentier, A., Geller, D. H., & Baillargeon, J. P. (2011). Early metabolic and endocrine perturbations in first-degree relative adolescent girls of polycystic ovary syndrome women. Endocrine Reviews, 32(3 Meeting Abstracts). Trottier A, Battista MC, Geller DH, Moreau B, Carpentier AC, Simoneau-Roy J, Baillargeon JP. Adipose tissue insulin resistance in peripubertal girls with first-degree family history of polycystic ovary syndrome. Fertil Steril. 2012 Dec;98(6):1627-34. doi: 10.1016/j.fertnstert.2012.08.025. Epub 2012 Sep 15. PMID: 22985947; PMCID: PMC3902032.
Study Country	Multinational (USA / Canada / Chile)
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	18 premenarchal first degree relatives of women with PCOS (either mother or sister) diagnosed with PCOS according to NICHD 1990
Control population	21 healthy premenarchal girls, matched for age, weight and Tanner stage
PCOS diagnostic criteria	NICHD 1990
N per group	FDR: 18 Control: 21
Setting	Hospital / Multicentre (5 centers)
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Outcomes: - Waist circumference (measured midway between the lower rib margin and the iliac crest) - Weight (kg) - not extracted as matched for weight - Height (cm) - BMI (kg/m^2) - not extracted as matched for weight Reported as z score using National Center for Health Statistics (NCHS) data - Serum glucose (glucose hexokinase) Only reported in substudy by Trottier et al 2012 - OGTT - only reported in substudy by Trottier et al 2012 Blood samples were collected at 15, 5, 0, 15, 30, 60, 90, and 120 minutes after glucose load (40 g/m2 body surface area) for the measurement of glucose, insulin, C-peptide, NEFA, and ghrelin - Lipid profile (enzymatic assay, Freidewald for LDL)

	Outcomes not relevant: - Insulin - Tanner stage (based on DHEAS and E2 levels) - HOMA-IR - QUICKI - AIRg - Glucose disposal index - Body fat composition by bioelectrical impedance - Hormonal studies: DHEAS, E2 (similar assay) - Frequently sampled glucose tolerance test: IV 25% Dextrose at 2 ml/Kg (max 25gm of Dextrose). This was followed by measurements of of serum glucose and insulin at 2, 3, 4 and 5 min after glucose administration	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Partial. Risk of type 2 diabetes measured by insulin sensitivity and reproductive hormones
Inclusion criteria	Yes Partial No Not reported	Yes. All subjects: premenarchal
Exclusion criteria	Yes Partial No Not reported	Yes. PCOS probands: secondary causes of chronic oligomenorrhea or amenorrhea and hyperandrogenism All subjects: medications known to affect either sex steroids or carbohydrate metabolism Mothers of control girls: history of irregular menstrual cycles or hirsutism Control girls: personal history of diabetes or family history of irregular menstruation, diabetes or hirsutism
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Partial. No mention of exclusion of secondary causes of oligoanovulation in PCOS probands (however likely to have been done as similar protocol to other studies by the same group)
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	Yes, case control
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	Not relevant to this systematic review
Was matching performed?	Yes Partial No Not reported	Yes, age, weight and Tanner stage
Summary Result/s	Premenarchal first degree relatives of women with PCOS had higher rates of insulin resistance compared to age matched controls	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	Partial Control group recruited by school based study from centers in USA
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes. PCOS defined.
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Partial. USA centers only
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	Yes.
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	Partial. Laboratory measures standardised. Anthropometric measures method of assessment not described.
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Partial. Anthropometric measures method of assessment not described.
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Partial.
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	Not relevant to case control study
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Not reported
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	Not reported No protocol registration. Ethics approval obtained

CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	No.
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	No. Funded by government and health institution grant AMDeC (Academy for Medical Development and Collaboration) and NIH grant # 1 UL1 RR024156-01.
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes.
COMMENTS		Control group was derived from a different population	
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate. Control group from different population. Laboratory measures standardised.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		Yes. Anthropometric measurements more at risk for bias.	

Study ID	Recabarren 2008
Study Citation	Recabarren SE, Smith R, Rios R, Maliqueo M, Echiburú B, Codner E, Cassorla F, Rojas P, Sir-Petermann T. Metabolic profile in sons of women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2008 May;93(5):1820-6. doi: 10.1210/jc.2007-2256. Epub 2008 Jan 29. PMID: 18230657. (Primary source) Recabarren SE, Sir-Petermann T, Rios R, Maliqueo M, Echiburú B, Smith R, Rojas-García P, Recabarren M, Rey RA. Pituitary and testicular function in sons of women with polycystic ovary syndrome from infancy to adulthood. J Clin Endocrinol Metab. 2008 Sep;93(9):3318-24. doi: 10.1210/jc.2008-0255. Epub 2008 Jun 10. PMID: 18544620. Recabarren SE et al. (2008) Metabolic profile in sons of women with polycystic ovary syndrome (PCOS). J Clin Endocrinol Metab doi:10.1210/jc.2007-2256.
Study Country	Chile
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	80 sons of women with PCOS (20 infants, 31 children, and 29 adults)
Control population	56 sons of control women without hyperandrogenism (20 infants, 17 children, and 19 adults) of similar age and socioeconomic status
PCOS diagnostic criteria	NICHD 1990

N per group	Sons of PCOS women: N = 80. - Infant: N = 20. - Children: N = 31. - Adults: N = 29. Sons of control women: N = 56. - Infant: N = 20. - Children: N = 17. - Adults: N = 19. Definitions: infancy (2–3 months), childhood (4–7 yr), and adulthood (18–30 yr).	
Setting	Academic hospital / single centre / timeframe not defined	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Outcomes: - Weight (kg) - BMI (kg/m^2) Calculated by the Growth Analyzer Program using the U.S. Growth Charts BMI for age - Waist circumference - Total cholesterol (standard colorimetric assays) - LDL (standard colorimetric assays) LDL calculated by Friedewald's formula - HDL (standard colorimetric assays) - Triglycerides (standard colorimetric assays) - Fasting glucose (glucose oxidase method) - OGTT - 2 hour glucose (glucose oxidase method) After a 12-h overnight fast, an oral glucose tolerance test was performed by giving 1.75 g/kg, up to a maximum of 75 g glucose in 250 ml water. In children, 5 ml blood samples were obtained at baseline and 120 min after glucose administration. In adults, blood was withdrawn before and 30, 60, 90, and 120 min after the glucose load. In infants, a 3ml blood sample was obtained in the fasting state. Outcomes not relevant: - Fasting insulin (radioimmunometric assay) - 2 hour insulin (RIA) - Fasting HOMA-IR (homeostatic model assessment for insulin resistance) - Fasting SHBG (radioimmunometric assay) - Fasting adiponectin (RIA) - Fasting leptin (RIA) - CRP (ultrasensitive immunoturbidimetric assay)	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes
Inclusion criteria	Yes Partial No Not reported	Yes. All PCOS sons were born at term after spontaneous conceptions, singletons. Control women have a history of singleton pregnancies, regular 28- to 32-d menstrual cycles. PCOS probands: normoglycaemic All participants: elevated WHR >0.85
Exclusion criteria	Yes Partial No Not reported	Yes.

			PCOS probands: hyperprolactinemia, androgen-secreting neoplasms, Cushing's syndrome, late-onset 21-hydroxylase deficiency, thyroid disease. Control mothers: hirsutism, other manifestations of hyperandrogenism, history of infertility or pregnancy complications. All participants: unrelated (no siblings)
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Yes, case control.
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Not relevant to this systematic review
Was matching performed?		Yes Partial No Not reported	Yes, age and socioeconomic status.
Summary Result/s		When unadjusted for BMI, sons of PCOS women have higher weight during early infancy; higher weight, BMI, waist circumference, total cholesterol and LDL during childhood and adulthood compared to sons of women without hyperandrogenism.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	Partial Method of control women recruitment not specified.
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Partial. Because the range definition for childhood (4–7 yr), and adulthood (18–30 yr) are relatively big and can exhibit unanalysed effects of confounding variables.
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Partial. - Because the range definition for childhood (4–7 yr), and adulthood (18–30 yr) are relatively big and can exhibit unanalysed effects of confounding variables. - Non-specific recruitment method for the control group.
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	Yes.
DETECT	Were measurements (for exposures or outcomes)	Yes Partial	Yes

	carried out and calculated in a standard, valid and reliable way?	No Not reported	
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes.
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes.
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	Not relevant to cross-sectional study
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Not reported
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	Partial. Ethics approval, protocol not registered prospectively.
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	Partial Method of control women recruitment not specified.
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	Partial. One author has received lecture fees from Pfizer and Novo-Nordisk.
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Partial. Median and range reported, but not mean nor standard deviation. (Sample size quite small).
COMMENTS		Method of control women recruitment not specified.	
What is the overall risk of bias?		Low Moderate	Moderate

	High Insufficient information	- Non-specified recruitment method of control group. - Range definition for childhood (4–7 yr), and adulthood (18–30 yr) are relatively big and can exhibit unanalysed effects of confounding variables.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?	No.	

Study ID	Sam 2005
Study Citation	Sam S, Legro RS, Bentley-Lewis R, Dunaif A. Dyslipidemia and metabolic syndrome in the sisters of women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2005 Aug;90(8):4797-802. doi: 10.1210/jc.2004-2217. Epub 2005 May 17. PMID: 15899949; PMCID: PMC4428585. (primary citation) Legro RS, Driscoll D, Strauss JF 3rd, Fox J, Dunaif A. Evidence for a genetic basis for hyperandrogenemia in polycystic ovary syndrome. Proc Natl Acad Sci U S A. 1998 Dec 8;95(25):14956-60. doi: 10.1073/pnas.95.25.14956. PMID: 9843997; PMCID: PMC24557. Legro RS, Bentley-Lewis R, Driscoll D, Wang SC, Dunaif A. Insulin resistance in the sisters of women with polycystic ovary syndrome: association with hyperandrogenemia rather than menstrual irregularity. J Clin Endocrinol Metab. 2002 May;87(5):2128-33. doi: 10.1210/jcem.87.5.8513. PMID: 11994352; PMCID: PMC4429513.
Study Country	USA
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	385 sisters women with PCOS diagnosed with PCOS according to1990 NICHD criteria. Subgrouped by phenotype: diagnosis of PCOS (n=51) / hyperandrogenism (n=38) / no features of PCOS (n=143) / unknown (n=153)
Control population	125 healthy controls with normal ovulatory cycles weight matched
PCOS diagnostic criteria	NICHD 1990
N per group	FDR: 385 sisters Control: 125 weight and ethnicity matched women
Setting	Hospital / Multicentre (3 centers)
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary outcomes: - Weight (kg) (some self-reported with validation study) - not extracted as matched for weight - Height (cm) (some self-reported with validation study) - BMI (kg/m^2) - not extracted as matched for weight - Waist circumference - Systolic BP (mmHg) (measured in seated position in the right arm as the average of three separate readings obtained 2 min apart after a 5-min rest) - Diastolic BP (mmHg) - Fasting plasma glucose (glucose oxidase) - OGTT (75g) (glucose oxidase) After a 12-h overnight fast and 3 day carbohydrate diet, 75g glucose load was administered Blood was drawn for glucose and insulin at baseline and 2 h Glucose tolerance defined by WHO criteria

	Outcomes not relevant: - Insulin (double antibody method) - Hormonal studies: testosterone, DHEAS, gonadotropins (radioimmunoassay) - HOMA-IR - Metabolic syndrome (ATP III criteria) - could not be extracted as control group selected to not have metabolic syndrome - Lipid profile (enzymatic assay, Freidewald for LDL) - not reported - PCOS (NICHD criteria) - could not be extracted as control group selected to not have PCOS - Metabolic syndrome (could not be extracted as control group selected to not have metabolic syndrome)	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes. Metabolic syndrome and dyslipidaemia
Inclusion criteria	Yes Partial No Not reported	Yes. Women were non-Hispanic Caucasian (to avoid confounding effects of ethnicity on metabolic endpoints) Control women: good health, sedentary
Exclusion criteria	Yes Partial No Not reported	Yes. PCOS probands: other causes of anovulation and hyperandrogenaemia by laboratory testing Control women: personal or family history of history of hypertension or diabetes mellitus, oral contraceptive agents in preceding 3 months, hypertensive medications or insulin-sensitizing medications in preceding 1 month, clinical/biochemical evidence of hyperandrogenism
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	Yes, case control
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	Not relevant to this systematic review
Was matching performed?	Yes Partial No Not reported	Yes, ethnicity and weight.
Summary Result/s	Sisters of women with PCOS had higher rates of metabolic syndrome compared to weight and ethnicity matched controls	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS: Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	Partial Method of deriving control group not defined

	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes. PCOS defined.
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Partial.
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	Partial.
DETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	Partial. Blood pressure and laboratory measures standardised. However self-report for height and weight
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Partial. Self report for height and weight.
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes.
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	Not relevant to case control study
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Not all participants could be assessed for metabolic syndrome (34% FDR included 131/385)
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	Not reported No protocol registration. Ethics approval obtained
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	No. Some age differences.

OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	No. Funded by government grant (National Institutes of Health Grants U54 HD34449, P50 HD44405, K12 RR017707, M01 RR00048, M01 RR10732, and M01 RR02635)
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Partial. To control for the overrepresentation of families with multiple sisters, the data from sisters with the same phenotype was averaged to yield one value per phenotype per family
COMMENTS		Control group was derived from a different population	
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate. Some outcomes self reported
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		Yes. Some outcomes self reported but metabolic syndrome diagnosis relied on measurements on site by investigators	

Study ID	Sam 2006
Study Citation	Sam S, Legro RS, Essah PA, Apridonidze T, Dunaif A. Evidence for metabolic and reproductive phenotypes in mothers of women with polycystic ovary syndrome. Proc Natl Acad Sci U S A. 2006 May 2;103(18):7030-5. doi: 10.1073/pnas.0602025103. Epub 2006 Apr 21. PMID: 16632599; PMCID: PMC1459013. (primary citation) Taylor MC, Reema Kar A, Kunselman AR, Stetter CM, Dunaif A, Legro RS. Evidence for increased cardiovascular events in the fathers but not mothers of women with polycystic ovary syndrome. Hum Reprod. 2011 Aug;26(8):2226-31. doi: 10.1093/humrep/der101. Epub 2011 Apr 19. PMID: 21505042; PMCID: PMC3137384.
Study Country	USA
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	215 mothers of women with PCOS diagnosed with PCOS according to 1990 NICHD criteria.
Control population	62 healthy controls of similar age, weight and ethnicity
PCOS diagnostic criteria	NICHD 1990
N per group	FDR: 215 mothers Control: 62 age, weight and ethnicity matched women
Setting	Hospital / Multicenter / NHANES III (1998-1994) / FDR (1993-2004)

Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary outcome: LDL level Other outcomes: - Weight (kg) (some self-reported with validation study) - Height (cm) (some self-reported with validation study) - not extracted as matched for weight - BMI (kg/m^2) - not extracted as matched for weight - Waist circumference (some self-reported with validation study) - Systolic BP (mmHg) (measured in seated position in the right arm as the average of three separate readings obtained 2 min apart after a 5-min rest) - Diastolic BP (mmHg) - Fasting plasma glucose (glucose oxidase) - Lipid profile (enzymatic assay, Freidewald for LDL) Outcomes not relevant: - Insulin (double antibody method) - Hormonal studies: testosterone, DHEAS, gonadotropins, SHBG (radioimmunoassay) - HOMA-IR - Metabolic syndrome (NCEP/ATP III criteria) - data could not be extracted as there was no sample size for the NHANES III population used - Diabetes (ADA criteria) - data could not be extracted as control group selected to not have diabetes - OGTT (75g) (glucose oxidase) - could not be extracted as data for control group not reported After a 12-h overnight fast and 3 day carbohydrate diet, 75g glucose load was administered Blood was drawn for glucose and insulin at baseline and 2 h Glucose tolerance defined by WHO criteria	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes. Metabolic syndrome and dyslipidaemia
Inclusion criteria	Yes Partial No Not reported	Yes. Women were non-Hispanic Caucasian (to avoid confounding effects of ethnicity on metabolic endpoints) Control women: regular 27- to 35-day menstrual cycles throughout their reproductive life, normal glucose tolerance according to the World Health Organization criteria
Exclusion criteria	Yes Partial No Not reported	Yes. PCOS probands: other causes of anovulation and hyperandrogenaemia by laboratory testing Control women: hypertension, personal or family history of history of diabetes mellitus, hormonal, antihypertensive antidiabetic medications, clinical/biochemical evidence of hyperandrogenism
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	Yes, case control
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial	Not relevant to this systematic review

		No Not reported	
Was matching performed?		Yes Partial No Not reported	Yes, age, ethnicity and weight.
Summary Result/s		Mothers of women with PCOS had higher rates of hyperlipidaemia and insulin resistance compared to weight and ethnicity matched controls	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	Partial. Control women for biochemical measures were a different cohort than control population for metabolic syndrome (method of deriving cohort not defined) NHANES III population (collected at 1988 to 1994 where the prevalence of metabolic syndrome may have been lower) as comparison for metabolic syndrome.
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes. PCOS defined.
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Partial. NHANES III population does not have data on PCOS.
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	Partial.
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	Partial. Blood pressure and laboratory measures standardised. However self-report for height and weight
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Partial. Self report for height and weight and waist circumference.
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes.

ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	Not relevant to case control study
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	All control women and 21% of mothers (n = 45) underwent a 75-g oral glucose tolerance test with fasting and 2-h postchallenge blood sampling for glucose and insulin levels.
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	Not reported No protocol registration. Ethics approval obtained
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	No. Some age differences despite age matching.
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	No. Funded by government grant (National Institutes of Health Grants U54 HD34449, P50 HD44405, K12 RR017707, M01 RR00048, M01 RR10732, and M01 RR02635)
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Yes. Powered for LDL
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes.
COMMENTS		2 control groups, of which one was derived from a nationwide registry population (NHANES III) and the other the method of derivation was not reported	
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate. Some outcomes self reported
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		Yes. Some outcomes self reported	

Study ID	Sam 2008
Study Citation	Sam S, Coviello AD, Sung YA, Legro RS, Dunaif A. Metabolic phenotype in the brothers of women with polycystic ovary syndrome. Diabetes Care. 2008 Jun;31(6):1237-41. doi: 10.2337/dc07-2190. Epub 2008 Mar 10. PMID: 18332151; PMCID: PMC2897239. (primary citation) Legro RS, Roller RL, Dodson WC, Stetter CM, Kunselman AR, Dunaif A. Associations of birthweight and gestational age with reproductive and metabolic phenotypes in women with

	polycystic ovarian syndrome and their first-degree relatives. J Clin Endocrinol Metab. 2010 Feb;95(2):789-99. doi: 10.1210/jc.2009-1849. Epub 2009 Dec 4. PMID: 19965924; PMCID: PMC2840854. Legro RS, Kunselman AR, Demers L, Wang SC, Bentley-Lewis R, Dunaif A. Elevated dehydroepiandrosterone sulfate levels as the reproductive phenotype in the brothers of women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2002 May;87(5):2134-8. doi: 10.1210/jcem.87.5.8387. PMID: 11994353; PMCID: PMC4428582. Sam S, Sung YA, Legro RS, Dunaif A. Evidence for pancreatic beta-cell dysfunction in brothers of women with polycystic ovary syndrome. Metabolism. 2008 Jan;57(1):84-9. doi: 10.1016/j.metabol.2007.08.010. PMID: 18078863; PMCID: PMC2710887.	
Study Country	USA	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	196 brothers of 158 women with PCOS diagnosed with PCOS according to1990 NICHD criteria.	
Control population	169 healthy controls matched for age, BMI and ethnicity	
PCOS diagnostic criteria	NICHD 1990	
N per group	FDR: 196 brothers Control: 169 unrelated control men	
Setting	Hospital / Multicentre (3 centers) / January 1995 - October 2005	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary outcomes: - Metabolic syndrome - Weight (kg) (some self-reported with validation study) - not extracted as matched for BMI - Height (cm) (some self-reported with validation study) - BMI (kg/m^2) - not extracted as matched for BMI - Waist circumference (some self-reported with validation study, calibrated tape measure provided) - WHR (data in Legro 2002 study) - Systolic BP (mmHg) (measured in seated position in the right arm single reading after 5-min rest) - Diastolic BP (mmHg) - Fasting plasma glucose (glucose oxidase) - OGTT (75g) (glucose oxidase) After a 12-h overnight fast and 3 day carbohydrate diet, 75g glucose load was administered Blood was drawn for glucose and insulin at baseline and 2 h Glucose tolerance defined by WHO criteria Outcomes not relevant: - Insulin (double antibody method) - Hormonal studies: testosterone, DHEAS, gonadotropins (radioimmunoassay) - HOMA-IR - Metabolic syndrome (ATP III criteria) - could not be extracted as control group selected to not have metabolic syndrome - Lipid profile (enzymatic assay, Freidewald for LDL) - not reported	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes.

Inclusion criteria		Yes Partial No Not reported	Yes. Men were non-Hispanic Caucasian (to avoid confounding effects of ethnicity on metabolic endpoints) Control men:normal glucose tolerance (WHO criteria),
Exclusion criteria		Yes Partial No Not reported	Yes. PCOS probands: nonclassic 21-hydroxylase deficiency, hyperprolactinemia, and androgen-secreting tumors All men: medications known to alter sex hormone metabolism or glucose homeostasis for at least 1 month before the study Control men: major medical / psychiatric illnesses, hypertension, diabetes, family history of diabetes
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Partial. Unable to screen control men for family history of PCOS (not all have female first degree relatives of reproductive age, unknown history, PCOS often remains undiagnosed). Assuming in power calculations that ~7% male control subjects will have a first degree relative with PCOS (general population prevalence)
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Yes, case control
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Not relevant to this systematic review
Was matching performed?		Yes Partial No Not reported	Yes. Age, BMI and ethnicity
Summary Result/s		Brothers of women with PCOS had higher rates of dyslipidaemia and insulin resistance compared to age, BMI and ethnicity matched controls	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	Partial Method of deriving control group not defined
SELECTION BIAS	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes. PCOS defined.
SELECTION BIAS	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Partial. Control men may have first degree relatives with PCOS.
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	Partial. Different sites used for measurements with validation studies.

DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	Partial. Blood pressure and laboratory measures standardised. However self-report for height and weight
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Partial. Self report for height and weight.
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes.
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	Not relevant to case control study
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Not reported
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	Not reported No protocol registration. Ethics approval obtained
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	No. Some age differences - brothers significantly younger than control men.
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	No. Funded by government grant (National Institutes of Health Grants U54 HD34449, P50 HD44405, K12 RR017707, M01 RR00048, M01 RR10732, and M01 RR02635)
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Yes. Power calculation to account for control men potentially having a first degree relative with PCOS
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Partial. In families with multiple brothers, the brothers' data were averaged to yield one mean value per family.
COMMENTS		Control group method of derivation not described	

What is the overall risk of bias?	Low Moderate High Insufficient information	Moderate. Some outcomes self reported (validation studies performed)
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?	Yes. Some outcomes self reported (validation studies performed)	

Study ID	Sir-Petermann 2004	
Study Citation	Sir-Petermann T, Cartes A, Maliqueo M, Vantman D, Gutiérrez C, Toloza H, Echiburú B, Recabarren SE. Patterns of hormonal response to the GnRH agonist leuprolide in brothers of women with polycystic ovary syndrome: a pilot study. Hum Reprod. 2004 Dec;19(12):2742-7. doi: 10.1093/humrep/deh512. Epub 2004 Sep 9. PMID: 15358722.	
Study Country	Chile	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	22 unrelated brothers of 22 women with PCOS between age 20 and 30 years of age	
Control population	14 brothers of normal cycling women matched for age and BMI	
PCOS diagnostic criteria	NICHD criteria; Rotterdam 2003	
N per group	Brothers of PCOS women: N = 22 Brothers of control women: N = 14	
Setting	Academic clinic / single center / 2002-2003	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Outcomes: - Weight (kg) - not extracted as matched for BMI - BMI (kg/m^2) - not extracted as matched for BMI - Waist circumference (to the nearest 0.5 cm at the point of narrowing (as viewed from behind) between the umbilicus and xiphoid process) - Lipid profile (standard colorimetric assays) LDL calculated by Friedewald's formula - Fasting glucose (glucose oxidase method) - OGTT - 2 hour glucose (glucose oxidase method) After a 3 days of a diet containing 300 g of carbohydrate per day and an overnight fast of 10 h, an oral glucose tolerance test was performed by giving 75 g glucose. Blood samples were obtained at baseline and 30, 60, 90 and 120 min after glucose administration. Glucose tolerance defined by WHO criteria Outcomes not relevant: - Insulin (radioimmunometric assay) - Testicular volume (Prader orchidometer by a single endocrinologist) - HOMA-IR (standardised calculation) - Insulin sensitivity composite index (ISI) (standardised calculation) - Hormonal studies: LH, FSH, SHBG, testosterone, DHEAS, 17-OH progesterone, AMH (radioimmunometric) - Leuprolide acetate test - Premature male pattern baldness (Hamilton scale)	
Does the study have a clearly focused question and/or PICO?	Yes Partial No	Yes. Response to leuprolide, OGTT and lipid profile

		Not reported	
Inclusion criteria		Yes Partial No Not reported	Yes. PCOS probands: anovulatory as indicated by progesterone measurements and ultrasound examinations Control brothers: normal medical history and physical examination, sisters with regular 28 to 32 day menstrual cycles,
Exclusion criteria		Yes Partial No Not reported	Yes. PCOS probands: Patients with hyperprolactinemia, androgen-secreting neoplasms, Cushing's syndrome, and late-onset 21-hydroxylase deficiency as well as thyroid disease. Control brother: sisters with hirsutism, other manifestations of hyperandrogenism, history of infertility or pregnancy complications.
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Partial, case control. No follow-up for future cardiovascular events
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Not relevant to this systematic review
Was matching performed?		Yes Partial No Not reported	Yes, age and BMI match
Summary Result/s		Sons of women with PCOS had higher rates of dyslipidaemia during puberty compared to controls matched by Tanner stage	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	Partial Method of control recruitment were control women recruited from hospital staff and university students in the same city area as the PCOS patients, with the same socio-economic status, and thne contact of their brothers.
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes. National Institutes of Health consensus criteria.
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes.

PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	Yes.
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	Partial. No report on method of measurement of weight and height
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Partial. No report on method of measurement of weight and height
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Not reported.
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	Not relevant to case control study
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Not reported
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	Partial. Ethics approval, protocol not registered prospectively.
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	Partial Control brothers from similar geographic region and socioeconomic status
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	No. Funded by Fondo Nacional de Desarrollo Científico y Tecnológico (National Fund for Scientific and Technological Research; Fondecyt; Grants 1030487-1151531), and the Alexander von Humboldt Foundation.
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported

	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Partial. Mean and range reported. Subgroup by response to leuprolide
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		Yes. Measurement of height and weight not reported.	

Study ID	Sir-Petermann 2012
Study Citation	Sir-Petermann T, Ladrón de Guevara A, Codner E, Preisler J, Crisosto N, Echiburú B, Maliqueo M, Sánchez F, Perez-Bravo F, Cassorla F. Relationship between anti-Müllerian hormone (AMH) and insulin levels during different tanner stages in daughters of women with polycystic ovary syndrome. Reprod Sci. 2012 Apr;19(4):383-90. doi: 10.1177/1933719111424444. Epub 2012 Feb 16. PMID: 22344736. (primary source) Maliqueo M, Sir-Petermann T, Pérez V, Echiburú B, de Guevara AL, Gálvez C, Crisosto N, Azziz R. Adrenal function during childhood and puberty in daughters of women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2009 Sep;94(9):3282-8. doi: 10.1210/jc.2009-0427. Epub 2009 Jun 30. PMID: 19567527. Crisosto N, Codner E, Maliqueo M, Echiburú B, Sánchez F, Cassorla F, Sir-Petermann T. Anti-Müllerian hormone levels in peripubertal daughters of women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2007 Jul;92(7):2739-43. doi: 10.1210/jc.2007-0267. Epub 2007 May 8. PMID: 17488788. Maliqueo M, Galgani JE, Pérez-Bravo F, Echiburú B, de Guevara AL, Crisosto N, Sir-Petermann T. Relationship of serum adipocyte-derived proteins with insulin sensitivity and reproductive features in pre-pubertal and pubertal daughters of polycystic ovary syndrome women. Eur J Obstet Gynecol Reprod Biol. 2012 Mar;161(1):56-61. doi: 10.1016/j.ejogrb.2011.12.012. Epub 2012 Jan 23. PMID: 22277163. Sir-Petermann T, Angel B, Maliqueo M, Carvajal F, Santos JL, Pérez-Bravo F. Prevalence of Type II diabetes mellitus and insulin resistance in parents of women with polycystic ovary syndrome. Diabetologia. 2002 Jul;45(7):959-64. doi: 10.1007/s00125-002-0836-3. Epub 2002 Apr 26. PMID: 12136394. Sir-Petermann, T.; Angel, B.; Maliqueo, M.; Perez-Bravo, F. Glucose tolerance, insulin secretion and insulin resistance in parents of women with polycystic ovary sindrome. Diabetologia 2001;44:A86-A86. Sir-Petermann T, Codner E, Maliqueo M, Echiburú B, Hitschfeld C, Crisosto N, Pérez-Bravo F, Recabarren SE, Cassorla F. Increased anti-Müllerian hormone serum concentrations in prepubertal daughters of women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2006 Aug;91(8):3105-9. doi: 10.1210/jc.2005-2693. Epub 2006 May 23. PMID: 16720659. Sir-Petermann T, Codner E, Pérez V, Echiburú B, Maliqueo M, Ladrón de Guevara A, Preisler J, Crisosto N, Sánchez F, Cassorla F, Bhasin S. Metabolic and reproductive features before and during puberty in daughters of women with polycystic ovary syndrome.

	J Clin Endocrinol Metab. 2009 Jun;94(6):1923-30. doi: 10.1210/jc.2008-2836. Epub 2009 Feb 17. PMID: 19223518; PMCID: PMC2730345. Echiburú B, Pérez-Bravo F, Maliqueo M, Ladrón de Guevara A, Gálvez C, Crisosto N, Sir-Petermann T. CAG repeat polymorphism of androgen receptor gene and X-chromosome inactivation in daughters of women with polycystic ovary syndrome (PCOS): relationship with endocrine and metabolic parameters. Gynecol Endocrinol. 2012 Jul;28(7):516-20. doi: 10.3109/09513590.2011.650744. Epub 2012 Feb 17. PMID: 22724574. Sir-Petermann T, Maliqueo M, Codner E, Echiburú B, Crisosto N, Pérez V, Pérez-Bravo F, Cassorla F. Early metabolic derangements in daughters of women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2007 Dec;92(12):4637-42. doi: 10.1210/jc.2007-1036. Epub 2007 Sep 11. PMID: 17848407.
Study Country	Chile
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	135 daughters of women with PCOS between age 8 and 16 years of age, subgroup by Tanner stage
Control population	93 daughters of control women without hyperandrogenism between age 8 and 16 years of age, matched by Tanner stage and maternal age
PCOS diagnostic criteria	NICHD 1990
N per group	Daughters of PCOS women: N = 135 - Tanner I (mean age 8.6 years): N = 30 - Tanner II (mean age 9.9 years): N = 26 - Tanner III (mean age 10.8 years): N = 26 - Tanner IV (mean age 12.2 years): N = 29 - Tanner V (mean age 13.2 years): N = 24 Daughters of control women: N = 93 - Tanner I (mean age 8.6 years): N = 21 - Tanner II (mean age 9.9 years): N = 17 - Tanner III (mean age 10.8 years): N = 19 - Tanner IV (mean age 12.2 years): N = 17 - Tanner V (mean age 13.2 years): N = 19
Setting	Academic hospital/ Single centre / timeframe not specified
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary outcomes: AMH and stimulated insulin Other outcomes: - Weight (kg) - BMI (kg/m^2) Calculated by the Growth Analyzer Program using the U.S. Growth Charts BMI for age (previously shown to be applicable to the Chilean population) - Waist circumference - WHR - OGTT - 2 hour glucose (glucose oxidase method) After a 12-h overnight fast, an oral glucose tolerance test was performed by giving 1.75 g/kg, up to a maximum of 75 g glucose in 250 ml water. 5 ml blood samples were obtained at baseline and 30, 60 and 120 min after glucose administration. Glucose tolerance defined by ADA criteria - Fasting plasma glucose (glucose oxidase method) - Fasting insulin (radioimmunometric assay)

	- Obesity Defined as a body weight >95th percentile. Outcomes not relevant: - Hirsutism (determining the presence of terminal hair using the modified Ferriman-Gallway score) - Acne and acanthosis nigricans - HOMA-IR - Whole-body insulin sensitivity composite index (ISI) - LH, FSH, estradiol (electrochemiluminiscence) - Testosterone, androstenedione, 17-OHP, SHBG (radioimmunometric assay) - AMH (enzyme immunoassay) - FAI Basal serum testosterone to SHBG ratio x 100 - Ovarian volume (transabdominal ultrasonography plus the simplified formula for a prolate ellipsoid)	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes
Inclusion criteria	Yes Partial No Not reported	Yes. All girls were born at term from singleton pregnancies; only evaluated in 1 Tanner stage. Control mothers comparable in age with PCOS mothers, had a history of regular 28- to 32-day menstrual cycles.
Exclusion criteria	Yes Partial No Not reported	Yes. Girls taking oral contraceptives or any other medications. Control mothers with hirsutism or other manifestations of hyperandrogenism, or with a history of infertility or pregnancy complications were excluded.
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	Yes, case control.
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	Not relevant to this systematic review
Was matching performed?	Yes Partial No Not reported	Yes, both experimental and control group girls were matched using the Tanner stage score for breast development. Control mothers matched in age,

Summary Result/s		No difference in fasting glucose, fasting insulin, OGTT, weight or waist-to-hip ratio between daughters of PCOS and control of women.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	Partial Method of control group recruitment not specified.
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes. National Institutes of Health consensus criteria.
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Partial Method of control group recruitment not specified. But Tanner stage matched.
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	Yes.
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	Partial. - Measurement biases can occur with weight, height, waist and hip circumferences (method not specified)
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported.
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes.
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Not reported.
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	Not relevant to case control study
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Not relevant to case control study

REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	Partial. No protocol registration. Obtained ethics approval.
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	Partial. Method of deriving control group not defined
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	No conflict of interest. Funding source: a grant from FONDECYT 1071007 and by the Alexander von Humboldt foundation.
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported.
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Partial. Mean and SEM reported.
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		Yes. Waist and hip circumferences, and thus the waist to hip ratio were more prone to measurement biases.	

Study ID	Torchen 2014
Study Citation	Torchen LC, Fogel NR, Brickman WJ, Paparodis R, Dunaif A. Persistent apparent pancreatic β-cell defects in premenarchal PCOS relatives. J Clin Endocrinol Metab. 2014 Oct;99(10):3855-62. doi: 10.1210/jc.2014-1474. Epub 2014 Jul 16. PMID: 25029420; PMCID: PMC4184072. (primary citation) TORCHEN, L., FOGEL, N. R., BRICKMAN, W., PAPARODIS, R. & DUNAIF, A. 2013. Persistent defects in pancreatic beta-cell function in early pubertal female relatives of women with polycystic ovary syndrome in a three year longitudinal study. Endocrine Reviews, 34. TORCHEN, L. C., FOGEL, N. R., BRICKMAN, W. J., MAURAS, N. & DUNAIF, A. 2012. Beta-cell dysfunction and hyperandrogenemia in PCOS early pubertal female relatives. Endocrine Reviews, 33.
Study Country	USA
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	

Patient/population/ participants	12 premenarchal first degree relatives of women with PCOS (either mother or sister) diagnosed with PCOS according to 1990 NICHD criteria.	
Control population	10 daughters of control mothers, matched for age, BMI, visceral adipose tissue and Tanner stage	
PCOS diagnostic criteria	NICHD 1990	
N per group	FDR: 12 premenarchal first degree relatives Control: 10 daughters of control women	
Setting	Hospital / Single center	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Outcomes: - Weight (kg) (to the nearest 0.1 kg) - not extracted as matched for BMI - Height (cm) (to the nearest 0.1 cm) - BMI (kg/m^2) - reported as z score - not extracted as matched for BMI - OGTT (75g) After a 12-h overnight fast, glucose load of 1.7 g/kg, followed by blood samples collected at 0, 30, 60, 90, and 120 min - Lipid profile (enzymatic assay, Freidewald for LDL) Outcomes not relevant: - Insulin (double antibody method) - Tanner stage (single trained study coordinator) - ISI - Acute insulin response to glucose (AIRg) - Disposition index - Glucose clearance - Hormonal studies: AMH, DHEAS, gonadotropins (radioimmunoassay), LH/FSH (ELISA), testosterone (tandem mass spectrometry / isotope dilution liquid chromatography) - Frequently sampled glucose tolerance test (Glucose (0.3 g/kg) was administered iv at time 0 and 0.03 U/kg regular insulin was administered iv at time 20 minutes. This was followed by frequent blood samples for 15 minutes before and 180 minutes after the iv glucose) - Visceral adipose tissue (measured by MRI) - Impaired fasting glucose / impaired glucose tolerance - not extracted as control group selected to not have dysglycaemia	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes. Insulin sensitivity and reproductive hormones
Inclusion criteria	Yes Partial No Not reported	Yes. All subjects: well, age 8 –12 years, Tanner Stage I-III breast development, and 85th to 98th BMI percentile Mothers of control girls: regular menses every 27–35 days
Exclusion criteria	Yes Partial No Not reported	Yes. All subjects: medications known to alter reproductive hormone metabolism or glucose homeostasis for at least 1 month prior to study Mothers of control girls: history of reproductive disorders, signs or symptoms of androgen excess by validated questionnaire

			Control girls: Dysglycemia [fasting glucose 100 mg/dL and/or 2 h postglucose challenge glucose 140 mg/dL
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Partial. No mention of exclusion of secondary causes of oligoanovulation in PCOS probands (however likely to have been done as similar protocol to other studies by the same group)
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Yes, case control
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Not relevant to this systematic review
Was matching performed?		Yes Partial No Not reported	Yes, age, BMI, Tanner stage, visceral adiposity
Summary Result/s		Daughters of women with PCOS had higher rates of insulin resistance compared to age, BMI and pubertal stage matched controls	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	Partial Control group recruited by local media and online advertisements
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes. PCOS defined.
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Partial. Hyperandrogenism in mothers of control women screened by validated questionnaire
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	Partial.
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	Partial. Laboratory measures standardised. Testosterone levels validated in adult cohort
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported

	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes.
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Partial.
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	Not relevant to case control study
ATTRITION BIAS	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Screened: 14 FDR, 25 control Enrolled: 12 FDR, 10 control (due to not meeting inclusion criteria / not tolerating study procedures) Analysed: 7 FDR, 8 control (completed biochemistry) 2 year follow-up: 6 FDR, 8 control
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	Not reported No protocol registration. Ethics approval obtained
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	No.
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	No. Funded by government and health institution grant R01 DK073411, P50 HD044405, UL1 TR000150, U54 HD28934.
OTHER BIAS	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
OTHER BIAS	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Partial. Median and IQR as data not normally distributed
COMMENTS		Control group was derived from a different population	
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate. Some attrition in measurements. No blinding / independent assessment of BMI. Laboratory measures standardised.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No.	

Study ID	Torchen 2016	
Study Citation	Torchen LC, Idkowiak J, Fogel NR, O'Neil DM, Shackleton CH, Arlt W, Dunaif A. Evidence for Increased 5α-Reductase Activity During Early Childhood in Daughters of Women With Polycystic Ovary Syndrome. J Clin Endocrinol Metab. 2016 May;101(5):2069-75. doi: 10.1210/jc.2015-3926. Epub 2016 Mar 18. PMID: 26990942; PMCID: PMC4870855.	
Study Country	USA	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	21 daughters of women with PCOS diagnosed with PCOS according to 1990 NICHD criteria.	
Control population	36 daughters of control mothers, matched for age and ethnicity	
PCOS diagnostic criteria	NICHD 1990	
N per group	FDR: 21 daughters Control: 36 daughters of control women	
Setting	Hospital / Single center	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Outcomes: - Weight (kg) (to the nearest 0.1 kg) - reported as weight for length z-score (US Centers for Disease Control and Prevention 2000 growth charts) Outcomes not relevant: - Hormonal studies: cortisol / cortisone / androgen / mineralocorticoid metabolites (quantitative gas chromatography-mass spectrometry)	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes. Ratio of 5-reduced tetrahydrocortisol (5THF) to its 5-reduced metabolite, THF (5THF/THF), a measure of 5-reductase activity
Inclusion criteria	Yes Partial No Not reported	Yes. All subjects: well, age 1-3 years Mothers of control girls: regular menses every 27–35 days
Exclusion criteria	Yes Partial No Not reported	Yes. PCOS proband: other reproductive disorders causing anovulation All subjects: medications known to alter reproductive hormone metabolism Mothers of control girls: signs or symptoms of androgen excess by validated questionnaire
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Partial.

Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Yes, case control
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Not relevant to this systematic review
Was matching performed?		Yes Partial No Not reported	Yes, age and ethnicity
Summary Result/s		Daughters of women with PCOS had higher weight different levels of androgen metabolites compared to age and ethnicity matched controls	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	Partial Control group recruited by local media and online advertisements
SELECTION BIAS	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes. PCOS defined.
SELECTION BIAS	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Partial. Hyperandrogenism in mothers of control women screened by validated questionnaire
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	Partial. Weight self reported
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	Partial. Laboratory measures standardised. Urine steroid metabolites with recalculation of average 24 hour excretion rates. Weight self reported
DEDETECTION BIAS	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported
DEDETECTION BIAS	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes.
DEDETECTION BIAS	Were outcomes assessed objectively and independently?	Yes Partial No	Partial. Weight self reported

		Not reported	
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	Not relevant to case control study
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Not reported
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	Not reported No protocol registration. Ethics approval obtained
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	No.
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	No. Funded by government and health institution grant P50 HD044405, K12 HD055884, G1001964, 092283
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Yes, urine metabolites.
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes.
COMMENTS		Control group was derived from a different population	
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate. Control group from a different population. Weight self reported
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		Yes. Weight self reported	

Study ID	Unluhizarci 2007
Study Citation	Unlühizarci K, Ozocak M, Tanriverdi F, Atmaca H, Keleştimur F. Investigation of hypothalamo-pituitary-gonadal axis and glucose intolerance among the first-degree female relatives of women with polycystic ovary syndrome. Fertil Steril. 2007 Jun;87(6):1377-82. doi: 10.1016/j.fertnstert.2006.11.075. Epub 2007 Mar 6. PMID: 17336975.
Study Country	Turkey

CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	70 Female first degree relatives of women with PCOS	
Control population	20 control women without hyperandrogenism	
PCOS diagnostic criteria	Rotterdam 2003	
N per group	Female first degree relatives of PCOS women: N = 70 - Sisters (mean age 26.5 years): N = 66 - All Female first degree relatives (mean age 27.3 years): N = 70 Control women: N = 20 - Mean age 26.5 years	
Setting	Academic hospital / single center / timeframe not defined	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Outcomes: - BMI (kg/m^2) - extracted as not specified that matched by BMI - OGTT - 2 hour glucose Glucose level expressed as area under the curve (AUC) estimated by the trapezoidal rule An oral glucose tolerance test (OGTT) was performed between 8:00 and 10:00 AM after 11–12 hours of fasting. A 300-g carbohydrate diet was given for 3 days before the OGTT. After a basal blood sample was obtained, a 75-g glucose load was administered orally and blood samples were obtained at 30-minute intervals for 2 hours for the measurement of glucose and insulin. - Fasting glucose Outcomes not relevant: - Impaired glucose tolerance (Outcome could not be extracted due to lack of data for control group) Glucose tolerance was evaluated by using the criteria of ADA IGT defined as 2-hour post-load glucose 140 mg/dL and 200 mg/dL - PCOS (Outcome could not be extracted as control population selected to not have PCOS) - Rotterdam criteria - Fasting and OGTT insulin (RIA) - HOMA score Calculated with the formula: fasting serum insulin (U/mL) x fasting plasma glucose (mmol/L)/22.5 - Insulinogenic index Calculated as a ratio of the increment of serum insulin 30 minutes after the oral glucose load to blood glucose concentration 30 minutes after the glucose load ([30-min insulin fasting insulin]/[30-min glucose fasting glucose]) - Baseline LH, FSH, estradiol, free testosterone, DHEAS, SHBG, androstenedione, 17-OH progesterone FSH, LH, and estradiol levels measured by automated chemiluminescence system Free testosterone and DHEAS measured by RIA SHBG level measured by IRMA - Hormonal level in buserelin testing: LH, FSH, estradiol, 17-OH progesterone Serum samples for hormone levels were drawn after an overnight fast in the follicular phase of the menstrual cycle.	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes

Inclusion criteria	Yes Partial No Not reported	Yes. Control women: healthy premenopausal eumenorrheic; normal ovarian appearance on ultrasonography.
Exclusion criteria	Yes Partial No Not reported	Yes. PCOS proband: nonclassic adrenal hyperplasia, Cushing's syndrome, thyroid dysfunction, hyperprolactinemia Control women: personal or family history of hirsutism, endocrine disorder, or diabetes. All participants: any medication known to alter carbohydrate metabolism or hormonal investigations.
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	Yes, case control.
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	Not relevant to this systematic review
Was matching performed?	Yes Partial No Not reported	Not reported. BMI appeared similar but unclear if this is by design
Summary Result/s	Female first degree relatives have similar BMI but significantly higher fasting glucose and 2hr glucose than control women. No conclusion about IGT prevalence can be made due to lack of data presented for control group.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS – Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	Partial Method of control women recruitment not specified.
SELECTION BIAS – Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes. Rotterdam criteria
SELECTION BIAS – Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Partial. No matching performed.

PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	Yes.
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	Partial. Method of BMI measurement not specified.
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Partial Method of BMI measurement not specified.
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Not reported.
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	Not relevant to case-control study
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Not reported.
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	Partial. Not registered. No ethical approval.
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	Partial Method of control women recruitment not specified.
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	Not reported.
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported.

	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes.
COMMENTS		Method of control women recruitment not specified.	
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate - Non-specified recruitment method of control group. - Single endocrinologist
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		Yes. BMI more prone to measurement biases.	

Study ID	Vipin 2016
Study Citation	Vipin VP, Dabadghao P, Shukla M, Kapoor A, Raghuvanshi AS, Ramesh V. Cardiovascular disease risk in first-degree relatives of women with polycystic ovary syndrome. Fertil Steril. 2016 May;105(5):1338-1344.e3. doi: 10.1016/j.fertnstert.2016.01.024. Epub 2016 Feb 4. PMID: 26852421.
Study Country	India
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	41 fathers and 45 mothers of 47 women with PCOS diagnosed with PCOS according to Rotterdam 2003 criteria
Control population	42 men and 44 women age and BMI matched
PCOS diagnostic criteria	Rotterdam 2003 (28/47 fulfilled NIH criteria)
N per group	FDR: 41 fathers; 45 mothers Control: 42 / 44 age and BMI matched controls
Setting	University Hospital / Single centre / November 2012 - November 2014
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary outcomes: - Carotid intima media thickness (single blinded observer, ultrasound, standardised protocol) - Brachial artery flow-mediated dilatation (single blinded observer, ultrasound, standardised protocol) Other outcomes: - Weight (kg) (single observer) - not extracted as matched for BMI - Height (m) (single observer) - BMI (kg/m^2) (automated BP measurement) - not extracted as matched for BMI - Waist circumference (measured at midpoint between the iliac crest and lower rib margin at the end of normal expiration) - Hip circumference (measured at the widest level of the greater trochanters) - Systolic BP (mmHg) (measured three times in a sitting position) - Diastolic BP (mmHg) - Fasting plasma glucose (glucose oxidase) - OGTT (75g loading) ADA criteria 2019 to evaluate glucose tolerance - Lipid profile (standard colorimetric assays)

	- Metabolic syndrome (IDF criteria) - T2DM (ADA criteria) - Hypertension (JNC 7 criteria) - IFG (ADA criteria) - IGT (ADA criteria) Outcomes not relevant: - HOMA-IR - QUICKI - DHEAS, testosterone (radioimmunoassay) - C-peptide (ELISA) - High sensitivity CRP, FSH, LH, TSH, prolactin, SHBG (chemiluminescence) - Fasting insulin (ELISA)	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes
Inclusion criteria	Yes Partial No Not reported	Yes. First degree relatives of women with PCOS diagnosed by the Rotterdam 2003 criteria. Age <70 years
Exclusion criteria	Yes Partial No Not reported	Yes. PCOS probands: attending medical services for metabolic health Parents: >70 years old, had liver or renal failure, malignancy, or any acute medical illness in recent past (within 3 months), attending endocrine clinic for metabolic health
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	Yes, case control
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	No. Insufficient follow-up for clinical cardiovascular events
Was matching performed?	Yes Partial No Not reported	Yes, age and BMI.
Summary Result/s	Siblings of women with PCOS had higher rates of metabolic syndrome and insulin resistance than age and weight matched controls	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS: Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	Partial Control group using hospital staff and relatives of other endocrine clinic patients

	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes. Rotterdam criteria.
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Partial. Family members of patients attending endocrine clinic potentially have a family history of diabetes.
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	Yes.
DETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	Yes.
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Yes (for the primary outcome).
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes.
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes for primary outcome. Other outcomes not reported
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	Not relevant to case control study
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	50 families recruited. 47 PCOS probands had parents who consented to participate.
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	Partial. No protocol registration. Ethics approval obtained
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	Partial. Only age and BMI matched

OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	No. Funded by university grant - Intramural Research Grant (PGI/DIR/RC/943/2013)
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Yes. Powered for carotid intima media thickness and flow-mediated dilatation
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes. Some data in median, IQR.
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate. Method of derivation of control cohort.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		Yes. Laboratory measurements are less subject to bias than measurements of blood pressure / weight / height.	

Study ID	Wang 2021
Study Citation	Wang Y, Guo L, Jiang J, Wang F, Hardiman PJ, Qu F. Development of 1-2 years Offspring Born to Mothers with Polycystic Ovary Syndrome. J Coll Physicians Surg Pak. 2021 Oct;31(10):1186-1190. doi: 10.29271/jcpsp.2021.10.1186. PMID: 34601839.
Study Country	China
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	29 children of women with PCOS diagnosed with PCOS according to Rotterdam 2003 criteria
Control population	116 children of women without PCOS
PCOS diagnostic criteria	Rotterdam 2003
N per group	FDR: 29 children Control: 116 children Matched by socioeconomic status / age 4:1
Setting	Academic hospital / Single centre / June 2018 - January 2019
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary outcomes: - BMI - Denver developmental screening test (DDST) - not extracted Outcomes not relevant: - Demographic characteristics of mothers: age, BMI, employment, education, parity, material weight gain, pregnancy complications, mode of delivery - Neonatal outcomes: gestational age, birth weight, Apgar score

		- Head circumference	
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	Yes
Inclusion criteria		Yes Partial No Not reported	Yes. Control mothers: regular 28- to 32-day menstrual cycles All participants: singleton pregnancy
Exclusion criteria		Yes Partial No Not reported	Yes. PCOS women with other causes of oligomenorrhea or hyperandrogenism such as Cushing's syndrome and hypothyroidism were excluded. All participants: < 37-week gestational age, < 2500-g birth weight, missing data, birth asphyxia, congenital diseases Control mothers: hirsutism, other manifestations of hyperandrogenism
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Yes, case control.
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Not relevant to this systematic review. Not enough follow-up for cardiovascular disease.
Was matching performed?		Yes Partial No Not reported	Yes. Age and socioeconomic status
Summary Result/s		1-2 year old children of women with PCOS were of lower BMI than age and socioeconomic status matched controls	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	Yes.
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes. Rotterdam criteria.

	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes.
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	Yes.
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	Partial. No method of measurement described for BMI
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Yes. Blinding performed
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes.
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes.
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	Not relevant to case control study
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Not reported
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	Partial. No protocol registration. No ethics approval.
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	Partial. Not matched for gender.
	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	No. Funded by government grant (National Natural Science Foundation of China (81874480; 81873837), the Zhejiang Province Science Foundation for Distinguished Young Scholars (LR16H0 40001))

OTHER BIAS	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes.
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Low. Method of outcome assessment not fully described but independently assessed and blinded.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No. Independent blinded assessment	

Study ID	Yildiz 2003
Study Citation	Yildiz BO, Yarali H, Oguz H, Bayraktar M. Glucose intolerance, insulin resistance, and hyperandrogenemia in first degree relatives of women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2003 May;88(5):2031-6. doi: 10.1210/jc.2002-021499. PMID: 12727950.
Study Country	Turkey
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	26 fathers, 37 mothers, 19 sisters and 25 brothers of 52 women with PCOS diagnosed with PCOS according to NICHD 1990 criteria
Control population	Family members of 35 women who come for routine check-up between the age of 18-35 years with no prior family history of PCOS and DM (75 controls age and weight matched)
PCOS diagnostic criteria	NICHD 1990
N per group	FDR: 24 fathers; 34 mothers; 19 sisters; 25 brothers Control: 12 / 24 / 31 / 15 age and weight matched controls by the above subgroups Mothers subgrouped by pre or postmenopausal state
Setting	Hospital / Single centre
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary outcomes: - Weight (kg) - not extracted as matched for weight - Height (m) - BMI (kg/m^2) - not extracted as matched for weight - Waist circumference (measured at midway between the lower rib margin and the iliac crest) - Hip circumference (measured at the widest circumference over the great trochanters) Outcomes not relevant: - Fasting insulin (chemiluminescence) - OGTT (glucose oxidase) - ADA criteria - baseline and 2 hour glucose not reported

	Between 0800–1000 h after a 3-d, 300-g carbohydrate diet and an overnight fast of 10–14 h 75 g load Blood samples for glucose and insulin determinations were collected at 0, 30, 60, 90, and 120 min - HOMA-IR - Insulin, LH, FSH, Estradiol, testosterone, androstenedione, and DHEAS (radioimmunoassay) - PCOS / DM / IGT IFG (cannot be extracted as control group selected to not have the outcome of interest)	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes
Inclusion criteria	Yes Partial No Not reported	Yes. Female controls: pre-menopausal, regular ovulatory cycles (every 27-35 days) All participants: All medications, including oral contraceptives, known to alter sex hormone metabolism or insulin action and/or kinetics discontinued for at least 3 months
Exclusion criteria	Yes Partial No Not reported	Yes. PCOS probands: Cushing's syndrome, nonclassical 21-hydroxylase deficiency, hyperprolactinemia, thyroid dysfunction, androgen-secreting tumors Female controls with personal history of PCOS / hyperandrogenism Controls: family history of PCOS or DM
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	Yes, case control.
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	Not relevant to this systematic review
Was matching performed?	Yes Partial No Not reported	Yes, age and weight.
Summary Result/s	First degree relatives of women with PCOS had high rates of glucose intolerance than age and weight matched controls	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	Partial Method of deriving control group not defined
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes. NICHD criteria.
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Partial. Method of deriving control group not defined
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	Partial.
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	Partial. Method of measurement of height and weight not described.
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Partial. Method of measurement of height and weight not described.
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	No. Single assessor.
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	Not relevant to case control study
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Available and living: 51 mothers, 52 fathers, 34 sisters, and 45 brothers Consented to participate: 37 mothers (73%), 26 fathers (50%), 19 sisters (56%), and 25 brothers (56%)
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	No protocol registration. Ethics approval obtained

CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	Partial. Only age and weight matched
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	No. Funded by government grant (Scientific and Technical Research Council of Turkey)
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes.
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate. Single assessor non blinded.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		Yes. Laboratory measurements are less subject to bias than measurements of BMI/height/weight.	

Study ID	Yilmaz 2005
Study Citation	Yilmaz M, Bukan N, Ersoy R, Karakoç A, Yetkin I, Ayvaz G, Cakir N, Arslan M. Glucose intolerance, insulin resistance and cardiovascular risk factors in first degree relatives of women with polycystic ovary syndrome. Hum Reprod. 2005 Sep;20(9):2414-20. doi: 10.1093/humrep/dei070. Epub 2005 May 12. PMID: 15890734. (primary citation) Yilmaz M, Ergün MA, Karakoç A, Yurtçu E, Yetkin I, Ayvaz G, Cakir N, Arslan M. Pro12Ala polymorphism of the peroxisome proliferator-activated receptor-gamma gene in first-degree relatives of subjects with polycystic ovary syndrome. Gynecol Endocrinol. 2005 Oct;21(4):206-10. doi: 10.1080/09513590500231593. PMID: 16316841.
Study Country	Turkey
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	38 fathers, 40 mothers, 25 sisters and 17 brothers of 55 women with PCOS diagnosed with PCOS according to Rotterdam 2003 criteria Substudy with 120 family members analysed as a whole group reported in another publication
Control population	Family members of 35 women who come for routine check-up between the age of 18-35 years with no prior family history of PCOS and DM (75 controls age and weight matched)
PCOS diagnostic criteria	Rotterdam 2003

N per group	FDR: 38 fathers; 40 mothers; 25 sisters; 17 brothers Control: 20 / 20 / 20 / 15 age and weight matched controls by the above subgroups	
Setting	Hospital / Single centre	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary outcomes: - Weight (kg) - not extracted as matched for weight - Height (m) - BMI (kg/m^2) - not extracted as matched for weight - Waist circumference (measured at the narrowest level between the costal margin and the iliac crest) - Hip circumference (measured at the widest level over the buttocks with the subject standing and breathing normally) - Systolic BP (mmHg) - Diastolic BP (mmHg) - Fasting plasma glucose - OGTT (75g loading) ADA criteria 2003 to evaluate glucose tolerance - Lipid profile (standard colorimetric assays) Outcomes not relevant: - Fasting insulin (chemiluminescence) - HOMA-IR - Insulin sensitivity index - QUICKI - Lipoprotein (a), Aproprotein A, Apoprotein B (nephelometric assay) - FSH, LH, prolactin, DHEA-S, insulin, cortisol, TSH (chemiluminescence) - 17-OH progesterone, free testosterone, androstenedione (radioimmunoassay) - B12 (chemiluminescence) - Folate (autoanalyser) - Adiponectin (enzyme-linked immunosorbent assay) - Resistin (competitive enzyme immunoassay) - Homocysteine (high performance liquid chromatography)	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes
Inclusion criteria	Yes Partial No Not reported	Yes. First degree relatives of women with PCOS diagnosed by the Rotterdam 2003 criteria. Control group age range of 18-35 years. Female controls who were pre-menopausal had regular ovulatory cycles (every 21-35 days)
Exclusion criteria	Yes Partial No Not reported	Yes. PCOS probands with DM, hyperprolactinaemia, congenital adrenal hyperplasia, thyroid disorders, Cushing disease, hypertension, hepatic or renal dysfunction were excluded. Female controls with personal history of PCOS / hirsutism (Ferriman Gallwey score >8) / acne were excluded. Controls had no family history of PCOS or DM
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes

Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Yes, case control.
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Not relevant to this systematic review
Was matching performed?		Yes Partial No Not reported	Yes, age and weight.
Summary Result/s		First degree relatives of women with PCOS had high rates of hypertension, hyperlipidaemia and glucose intolerance than age and weight matched controls	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	Partial Control group using healthy family members of women presenting for routine care for other reasons.
SELECTION BIAS	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes. Rotterdam criteria.
SELECTION BIAS	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Partial.
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	Partial.
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
DEDETECTION BIAS	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported
DEDETECTION BIAS	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes.
DEDETECTION BIAS	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Not reported.

ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	Not relevant to case control study
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Not relevant to case control study
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	No protocol registration. Ethics approval obtained
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	Partial. Only age and weight matched
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	Not reported
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes.
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		Yes. Laboratory measurements are less subject to bias than measurements of blood pressure from different populations.	

6.3. Template for COHORT STUDIES

Study ID	deWilde 2018
Study Citation	deWilde MA, Eising JB, Gunning MN, Koster MPH, Evelein AMV, Dalmeijer GW, Uiterwaal CSPM, Eijkemans MJC, Ent CKV, Meijboom FJ, Fauser BCJM. Cardiovascular and Metabolic Health of 74 Children From Women Previously Diagnosed With Polycystic Ovary Syndrome in Comparison With a Population-Based Reference Cohort. Reprod Sci. 2018 Oct;25(10):1492-1500. doi: 10.1177/1933719117749761. Epub 2018 Jan 10. PMID: 29320957.
Study Country	Netherlands

EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	Offspring of women with PCOS (n=74) compared to healthy offspring from a prospective cohort recruited from the same geographical region (n=298) subgroup by age Younger subgroup Age= FDR: 3.3±0.6 years, controls: 3.7±0.2 years (younger subgroup inclusion age range 2.5-4 Years) BMI= FDR: 15.9±1.6kg/m², controls: 16.4±1.3 kg/m² Older subgroup Age= FDR: 7.0±0.8 years, controls: 8.1±0.5 years (older subgroup inclusion age range 6-8 Years) BMI= FDR: 15.3±1.5kg/m², controls: 15.8±1.7 kg/m²	
PCOS diagnostic criteria	Rotterdam 2003	
N per group	The number of participants that were: Screened: 113 proband women with PCOS (excluded n=39 did not consent; n=1 T1DM in child); control cohort ongoing recruitment with aim of 2000 newborns Enrolled: FDR = 74, controls= 298 Allocated: FDR = 74, controls= 298 Assessed and followed up: FDR = 74, controls= 298	
Setting	Prospective cohort study FDR: single center; PCOS proband delivered a newborn between January 2005 and December 2010 asked to participate; screening took place February 2013 to July 2014 Control: multicenter; all healthy newborns born since 2001 in similar geographical region invited in follow-up study	
Intervention/ indicator	Offspring of women with PCOS	
Comparison/ Control	Healthy newborns (however PCOS criteria during preconception could not be determined) No matching performed outside of age range inclusion criteria and recruitment from same geographical regiom	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Primary outcome: Pulse wave velocity of aorta by arteriography Outcomes measured: - Height (stadiometer) - Weight (digital scale) - BMI (calculated as weight / height^2) - Waist circumference (measured twice after expiration between the > superior iliac anterior spine and the lowest rib) - Blood pressure (arteriography and non invasive measurements) - Fasting glucose - Lipid profile (autoanalyser / standard enzymatic assay, Friedewald equation) Outcomes not relevant: - Fasting insulin (chemiluminescence immunoassays) - Breast circumference - Transthoracic echocardiogram (1 observer blinded for clinical measurements of children) - Carotid intima media thickness (1 observer) - HOMA-IR - C reactive protein	
Inclusion criteria reported?	Yes	Yes.
Exclusion criteria reported?	Yes Partial	Yes.

		No Not reported	FDR: heart defect, type I diabetes, or a respiratory infection less than 2 weeks before screening Control: gestational age <36 weeks, major congenital abnormalities, or neonatal respiratory disease Unable to assess PCOS status of mothers of control children
Does the study have a clearly focused question?		Yes Partial No Not reported	Yes.
Is a cohort study the appropriate design to answer this question?		Yes Partial No Not reported	Yes
Does the study have specified inclusion/ exclusion criteria?		Yes Partial No Not reported	Yes.
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Partial. PCOS status of the mothers of control children unable to be assessed.
Were the outcomes measured appropriate?		Yes Partial No Not reported	Partial. Pulse wave velocity of the aorta as a primary outcome is not a typically used clinical measure of cardiovascular risk, however
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	No. Duration of follow-up likely not long enough to capture cardiovascular disease
Was matching performed?		Yes Partial No Not reported	No.
Summary of Result/s		Offspring of women with PCOS had higher rates of dyslipidaemia compared to a reference cohort.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Other than the exposure under investigation, were the groups selected from similar populations?	Yes	No. Control cohort came from a prospective study of healthy newborns recruited from the same geographical region of which PCOS status of the mothers could not be ascertained.
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Partial. (35% of screened participants were included)
	Is it clear that the outcome of interest	Yes Partial No	Yes.

	was not present at the start of study?	Not reported	
PERFORMANCE BIAS	Aside from the exposure, were the groups treated the same?	Yes Partial No Not reported	Yes
DETECTION BIAS	Was exposure measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes.
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	Yes.
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes.
	Were outcomes assessed objectively and independently?	Yes Yes Partial No Not reported	Yes..
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	PCOS= 14% Controls= 14%	FDR= 0% Controls= 0%
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Blood pressure FDR= 15% Controls= 11% Blood assessments for glucose and lipid profile FDR= 15% Controls= 11%
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	Yes. Ethics approval present. Study registration for included cohorts present (trial number NCT01767051 and NCT02309047)
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	Partial. Not matched and no possibility of ascertaining PCOS status.
	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	No. Multiple sources of funding disclosed (university grant, heart foundation grant, medical council grant). Pharmaceutical company funding disclosed but no involvement of pharmaceutical company in publication of study.

OTHER BIAS	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Power calculation for pulse wave velocity
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes. Single imputation for missing data.
COMMENTS		Control cohort difficult to ascertain if mothers had no PCOS	
What is the overall risk of bias?		High	Moderate. Difficult to ascertain control cohort. Independent assessment of outcomes.
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		No All outcomes low risk of bias.	

Study ID	Harnois-Leblanc 2017
Study Citation	Harnois-Leblanc S, Trottier A, Leblanc S, Battista MC, Geller DH, Baillargeon JP. Evolution of metabolic alterations 5 Years after early puberty in a cohort of girls predisposed to polycystic ovary syndrome. Reprod Biol Endocrinol. 2017 Jul 24;15(1):56. doi: 10.1186/s12958-017-0275-0. PMID: 28738839; PMCID: PMC5525344. (primary citation) Leblanc, S. H., Leblanc, S., Battista, M. C., Geller, D. H., & Baillargeon, J. P. (2016). Evolution of metabolic alterations 5 years after peri-pubertal years in young girls genetically predisposed to polycystic ovary syndrome compared to age-matched control girls. Endocrine Reviews, 37(2 Supplement 1). doi:https://dx.doi.org/10.1210/endo-meetings.2016.RE.5.SUN-156
Study Country	Canada
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	Female first degree relatives of women with PCOS (n=8) compared to age-matched controls without family history of PCOS (n=8). Median Age: 17.5 years; IQR: 14.4-20.1 years Median BMI: 22.7 kg/m²; IQR: 21.5-30.8 kg/m²
PCOS diagnostic criteria	AE-PCOS 2009
N per group	The number of participants that were: Screened: 7 proband women with PCOS; 9 FDR (6 daughters, 1 sister); control cohort (n=10) Enrolled: FDR = 7, controls= 8 Allocated: FDR = 8 (newly recruited FDR), controls= 8 Assessed and followed up (5 year follow-up cohort): FDR = 7, controls= 8
Setting	Prospective cohort study. University Hospital, 2007-2015, Single center, median follow-up 5.4 years
Intervention/ indicator	Sisters / daughters of women with PCOS
Comparison/ Control	Controls without history of PCOS Age matched

Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Primary outcomes: - Frequently sampled intravenous glucose tolerance test (FSivGTT)-derived insulin sensitivity (IS) and beta-cell function (disposition index, DIFSivGTT) - NEFA suppression during FSivGTT (logn-linear slope of NEFA and T50 of NEFA suppression). Outcomes measured: - Height - Weight - BMI (calculated as weight / height^2) / z score (Center for Disease Control and Prevention growth charts) - Obesity (defined as age and sex adjusted BMI zscore ≥ 95th percentile) - Waist circumference (measured between the inferior costal margin and the iliac crest in standing position) - z score reported - Hip circumference (level of the femoral trochanters) - Waist hip ratio (z score reported) - Fasting glucose (glucose hexokinase) - 75g OGTT Glucose, insulin and NEFA were collected at times −15, −5, 0, 15, 30, 60, 90 and 120 min after glucose load (40 g/m2 body surface area) - Lipid profile (colorimetric assays, Friedewald equation) Only triglycerides reported Outcomes not relevant: - Fasting insulin (electrochemiluminescence) - Lean mass percentage (foot-to-foot bioimpedance) - Hirsutism (modified Ferriman-Gallwey score) - HOMA-IR - C reactive protein - Adiponectin (RIA) - Leptin (ELISA) - Matsuda insulin sensivity index - Corrected insulin response to glucose at 30 min - Disposition index	
Inclusion criteria reported?	Yes	Yes. Oral contraceptives allowed.
Exclusion criteria reported?	Yes Partial No Not reported	Yes. PCOS proband: nonclassical congenital adrenal hyperplasia, abnormal thyroid function, hyperprolactinemia, evidence of androgensecreting tumours, Cushing's syndrome, acromegaly, the use of medications known to affect levels of testosterone or 17OHPg within 3 months of testing. All participants: precocious puberty, medication known to affect glucose homeostasis such as insulin sensitizers, having diabetes or other uncontrolled metabolic disorder or following a highlyrestrictive diet or intense physical activity program
Does the study have a clearly focused question?	Yes Partial No Not reported	Yes.
Is a cohort study the appropriate design to answer this question?	Yes Partial No	Yes.

		Not reported	
Does the study have specified inclusion/ exclusion criteria?		Yes Partial No Not reported	Partial. OCP allowed - unethical to withhold OCP
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes.
Were the outcomes measured appropriate?		Yes Partial No Not reported	Partial. Surrogate markers for beta cell function and not clinical diabetes.
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	No. Duration of follow-up likely not long enough to capture cardiovascular disease
Was matching performed?		Yes Partial No Not reported	Age matched
Summary of Result/s		Female first degree relatives of women with PCOS who are late/post-puberty have similar surrogate markers of beta cell function with age matched controls.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Other than the exposure under investigation, were the groups selected from similar populations?	Yes	No. Control cohort from paediatric endocrine clinic with a stable condition
SELECTION BIAS	Was the exposed cohort truly representative?	Yes Partial No Not reported	Partial. Very small numbers
SELECTION BIAS	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes.
PERFORMANCE BIAS	Aside from the exposure, were the groups treated the same?	Yes Partial No Not reported	Yes.
DEDETECTION BIAS	Was exposure measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes.
DEDETECTION BIAS	Were outcome assessors blind to the exposure?	Yes Partial No	Not reported.

		Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes.
	Were outcomes assessed objectively and independently?	Yes Yes Partial No Not reported	Not reported.
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	PCOS= 14% Controls= 14%	FDR= 12% Controls= 10%
ATTRITION BIAS	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	FDR= 12% Controls= 10% (additional FDR recruited separate from original cohort)
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	Partial. Ethics approval present. No protocol registration
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	Partial. Control population derived from different cohort.
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	No. Funded by medical foundation (La Fondation des étoiles (Montréal, Québec)
OTHER BIAS	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported. No power calculation
OTHER BIAS	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Partial. Median and interquartile range. Data could not be adjusted due to small sample size.
COMMENTS			
What is the overall risk of bias?		High	Moderate. Small sample size
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		Yes Laboratory measurements likely low risk for bias, however measurements of waist hip ratio might be subject of bias.	

Study ID	Joharatnam 2011

Study Citation	Joharatnam J, Barber TM, Webber L, Conway GS, McCarthy MI, Franks S. Determinants of dyslipidaemia in probands with polycystic ovary syndrome and their sisters. Clin Endocrinol (Oxf). 2011 Jun;74(6):714-9. doi: 10.1111/j.1365-2265.2011.03983.x. PMID: 21521255; PMCID: PMC4625580. (primary citation) Franks S, Webber LJ, Goh M, Valentine A, White DM, Conway GS, Wiltshire S, McCarthy MI. Ovarian morphology is a marker of heritable biochemical traits in sisters with polycystic ovaries. J Clin Endocrinol Metab. 2008 Sep;93(9):3396-402. doi: 10.1210/jc.2008-0369. Epub 2008 Jun 17. PMID: 18559912.	
Study Country	United Kingdom	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	Sisters of women with PCOS (n=214) compared to controls without polycystic ovaries on sonography with normal ovulatory cycles (n=76). Proband women with PCOS (n=157) also included in study but data not extracted Age= FDR with polycystic ovaries: 3.3±0.6 years, FDR without polycystic ovaries: 3.3±0.6 years; controls: 3.7±0.2 years BMI= FDR with polycystic ovaries: 15.9±1.6kg/m²; FDR without polycystic ovaries: 15.9±1.6kg/m²; controls: 16.4±1.3 kg/m²	
PCOS diagnostic criteria	Rotterdam 2003 (all PCOS probands); NIH criteria (69% PCOS probands)	
N per group	The number of participants that were: Screened: 157 proband women with PCOS; 248 sisters; control cohort (n=76) Enrolled: FDR = 214 (86%), controls= 76 Allocated: FDR = 214, controls= 76 Assessed and followed up: FDR = 214, controls= 76	
Setting	Retrospective cohort study. University Hospital, timeframe not specified, multicenter (2 centers)	
Intervention/ indicator	Sisters of women with PCOS	
Comparison/ Control	Controls without history of PCOS No matching performed	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Primary outcome not defined Outcomes measured: - Height - Weight - BMI (calculated as weight / height^2) - Waist hip circumference (anatomical landmarks not reported) - Fasting glucose - Lipid profile (autoanalyser, standard enzymatic assay, Friedewald equation) - PCOS (Rotterdam criteria) Outcome could not be extracted as control population selected to not have PCOS Outcomes not relevant: - Fasting insulin (ELISA) - Hirsutism (assessed by one examiner using the modified Ferriman-Gallwey score in which a score >8 indicates hirsutism) - Hormonal studies (LH, FSH, E2, Testosterone, androstenedione, Sex hormone–binding globulin, free androgen index) - HOMA-IR - C reactive protein	
Inclusion criteria reported?	Yes	Yes.

			Control women had ultrasound-proven normal ovarian morphology, regular menstrual cycles
Exclusion criteria reported?		Yes Partial No Not reported	Yes. PCOS proband: estrogen-deficient amenorrhea, hyperprolactinemia, Cushing's syndrome, and late-onset 21-hydroxylase deficiency Control: family history of PCOS, clinical hyperandrogenism
Does the study have a clearly focused question?		Yes Partial No Not reported	Yes.
Is a cohort study the appropriate design to answer this question?		Yes Partial No Not reported	Yes. Some attrition in sister data - PCOS diagnosis in sisters may be affected by this.
Does the study have specified inclusion/ exclusion criteria?		Yes Partial No Not reported	Yes.
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes. Method of deriving control cohort not described
Were the outcomes measured appropriate?		Yes Partial No Not reported	Yes
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	No. Duration of follow-up likely not long enough to capture cardiovascular disease
Was matching performed?		Yes Partial No Not reported	No.
Summary of Result/s		Sisters of women with PCOS had higher rates of hyperlipidemia compared to healthy controls without PCOS. When adjusted for BMI, sisters did not have higher rates of hyperlipidaemia to women without PCOS	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Other than the exposure under investigation, were the groups selected from similar populations?	Yes	No. Control cohort derivation not defined
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Yesl. (86% of screened participants were included)

	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes.
PERFORMANCE BIAS	Aside from the exposure, were the groups treated the same?	Yes Partial No Not reported	Yes
DEDETECTION BIAS	Was exposure measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes.
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	Not reported.
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Partial. Waist circumference method not reported
	Were outcomes assessed objectively and independently?	Yes Yes Partial No Not reported	Not reported.
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	PCOS= 14% Controls= 14%	FDR= 0% Controls= 0%
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	FDR= 0% Controls= 0%
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	Partial. Ethics approval present. No protocol registration
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	Partial. Not matched and method of deriving control cohort not described
	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	No. Medical Research Council (G9710020) and a Project Grant from Wellbeing of Women (RG944)

OTHER BIAS	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported. No power calculation
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes.
COMMENTS			
What is the overall risk of bias?		High	Moderate. Control cohort method of derivation not reported. Only 86% sisters included
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		Yes Laboratory measurements likely low risk for bias, however measurements of waist hip ratio might be subject of bias and assessment of PCOS status	

Study ID	Krysiak 2021
Study Citation	Krysiak R, Basiak M, Szkróbka W, Okopień B. The Impact of Telmisartan on Cardiometabolic Risk Factors in Hypertensive Male Siblings of Women With Polycystic Ovary Syndrome. J Clin Pharmacol. 2021 Sep;61(9):1165-1173. doi: 10.1002/jcph.1872. Epub 2021 Jun 17. PMID: 33837974.
Study Country	Poland
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	Hypertensive brothers of women with PCOS (n=24) compared to hypertensive controls without family history of PCOS (n=26). Age= FDR: 33±8 years, controls: 41±7 years BMI= FDR: 28.3±4.2kg/m²; controls: 27.8±4.7 kg/m²
PCOS diagnostic criteria	Rotterdam 2003
N per group	The number of participants that were: Screened: Men aged 20-55 years with grade 1 hypertension (n = 188) Enrolled: Meeting inclusion criteria (n=82) Allocated: FDR = 24, controls= 26 Assessed and followed up: FDR = 24, controls= 24 (unclear reason for why 2 participants excluded from analysis)
Setting	Prospective intervention cohort study. University Hospital, timeframe not specified, single center
Intervention/ indicator	Brothers of women with PCOS
Comparison/ Control	Controls without family history of PCOS Matching for age, blood pressure, BMI and fat free mass index
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Primary outcome not defined Outcomes measured: - Height - Weight - not extracted as cohorts matched - BMI (calculated as weight / height^2) - not extracted as cohorts matched - Fasting glucose

	- Lipid profile (autoanalyser, standard enzymatic assay, Friedewald equation) Outcomes not relevant: - Fasting insulin (electrochemiluminescence) - not published - Body composition (bioelectrical impedance analysis) - HOMA-IR - Fasting hormonal studies: testosterone, SHBG (electrochemiluminescence) - Vitamin D (electrochemiluminescence) - Homocysteine - Uric acid (routine laboratory techniques) - High sensitivity CRP (chemiluminescence) - Post treatment with telmisartan outcomes not extracted	
Inclusion criteria reported?	Yes	Yes. Age 20-55 years, grade 1 arterial hypertension (systolic blood pressure between 140 and 159 mm Hg and/or diastolic blood pressure between 90 and 99 mm Hg on 2 different days), 12 weeks of non pharmacological treatment of hypertension, ASCVD risk calculator <10% 10 year risk. All participants instructed on lifestyle and exercise changes. Medication adherence by pill count.
Exclusion criteria reported?	Yes Partial No Not reported	Yes. Coronary artery disease, myocardial infarction or stroke within 6 months preceding the study, heart failure, diabetes, thyroid disorders, other endocrine disorders, impaired renal or hepatic function, malabsorption syndromes, poor patient compliance, treated within 6 months preceding the study with any prescription or over-the-counter drug for more than a week
Does the study have a clearly focused question?	Yes Partial No Not reported	Partial. Defined as effect of telmisartan on blood pressure and “cardiometabolic” outcomes
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial. RCT design more appropriate
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes.
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes.
Were the outcomes measured appropriate?	Yes Partial No Not reported	Yes.
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	No. Duration of follow-up likely not long enough to capture cardiovascular disease. 12 week follow-up
Was matching performed?	Yes	Yes. Age, BP, BMI, body composition

		Partial No Not reported	
Summary of Result/s		Brothers of women with PCOS had higher rates of hyperlipidemia and insulin resistance compared to controls at baseline.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Other than the exposure under investigation, were the groups selected from similar populations?	Yes	Yes.
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Partial. (44% of screened participants were included)
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Partial. Participants were hypertensive at baseline.
PERFORMANCE BIAS	Aside from the exposure, were the groups treated the same?	Yes Partial No Not reported	Yes
DEDETECTION BIAS	Was exposure measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes.
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	Partial, laboratory data carried out in duplicate by technicians blinded to patient data.
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Partial, laboratory data carried out in duplicate by technicians blinded to patient data.
	Were outcomes assessed objectively and independently?	Yes Yes Partial No Not reported	Partial, laboratory data carried out in duplicate by technicians blinded to patient data.
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	PCOS= 14% Controls= 14%	FDR= 0% Controls= 0%
	What percentage of the individuals were not	X% treatment X% control/	FDR= 0% Controls= 8%

	included in the analysis?	comparison Not reported	
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	Partial. Ethics approval present. No protocol registration
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	Yes
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	No.
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Partial. Power calculation reported but primary outcome for power calculation not reported.
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Partial. For subjects younger than 40 years at presentation, an age of 40 years was assigned.
COMMENTS			
What is the overall risk of bias?		High	Moderate. Not randomised. Not all screened population enrolled and some loss to follow-up in control grouwp.
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		Yes Laboratory measurements low risk for bias, however measurements of waist hip ratio / blood pressure might be subject of bias	

Study ID	Krysiak 2021 2
Study Citation	Krysiak R, Szkróbka W, Okopień B. The impact of atorvastatin on cardiometabolic risk factors in brothers of women with polycystic ovary syndrome. Pharmacol Rep. 2021 Feb;73(1):261-268. doi: 10.1007/s43440-020-00135-w. Epub 2020 Jul 21. Erratum in: Pharmacol Rep. 2021 Oct;73(5):1481. PMID: 32696349; PMCID: PMC8149333.
Study Country	Poland
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	Hypercholesterolaemic brothers of women with PCOS (n=20) compared to hypercholesterolaemic controls without family history of PCOS (n=20). Age= FDR: 50±12 years, controls: 52±10 years BMI= FDR: 28.5±4.8kg/m²; controls: 28.1±5.0 kg/m²
PCOS diagnostic criteria	Rotterdam 2003
N per group	The number of participants that were:

	Screened: Not described Enrolled: Not described Allocated: FDR = 20, controls= 20 Assessed and followed up: FDR = 20, controls= 20	
Setting	Prospective interventional cohort study. University Hospital, timeframe not specified, single center	
Intervention/ indicator	Brothers of women with PCOS	
Comparison/ Control	Controls without family history of PCOS Matching for age, blood pressure, BMI and plasma lipid levels	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Primary outcome not defined Outcomes measured: - Height - Weight - not extracted as cohorts matched - BMI (calculated as weight / height^2) - not extracted as cohorts matched - Fasting glucose - Lipid profile (autoanalyser, standard enzymatic assay, Friedewald equation) - not extracted as cohorts matched Outcomes not relevant: - Fasting insulin (electrochemiluminescence) - Body composition (bioelectrical impedance analysis) - HOMA-IR - Fasting hormonal studies: testosterone, SHBG (electrochemiluminescence) - Vitamin D (electrochemiluminescence) - Homocysteine - Uric acid (routine laboratory techniques) - High sensitivity CRP (chemiluminescence) - Fibrinogen (clauss) - Estimated glomerular filtration rate (MDRD) - Post treatment with atorvastatin outcomes not extracted	
Inclusion criteria reported?	Yes	Yes. Age 30-70 years, total cholesterol > 200 mg/dL and low-density lipoprotein (LDL) cholesterol > 130 mg/dL, 12 weeks of lifestyle modification All participants instructed on lifestyle, dietary and exercise changes. Medication adherence by pill count.
Exclusion criteria reported?	Yes Partial No Not reported	Yes. cardiovascular disease (with the exception of mild arterial hypertension), diabetes, thyroid disorders, acute and chronic infammatory processes, kidney or liver failure, malabsorption syndromes, any pharmacotherapy
Does the study have a clearly focused question?	Yes Partial No Not reported	Partial. Defined as effect of atorvastatin and “cardiometabolic” outcomes
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial. RCT design more appropriate

Does the study have specified inclusion/ exclusion criteria?		Yes Partial No Not reported	Yes.
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes.
Were the outcomes measured appropriate?		Yes Partial No Not reported	Yes.
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	No. Duration of follow-up likely not long enough to capture cardiovascular disease. 6 month follow-up
Was matching performed?		Yes Partial No Not reported	Yes. Age, BP, BMI, lipid profile
Summary of Result/s		Brothers of women with PCOS had higher rates of insulin resistance compared to controls at baseline.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Other than the exposure under investigation, were the groups selected from similar populations?	Yes	Yes.
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Partial. Unclear how many screened were enrolled
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Partial. Participants were hypercholesterolaemic at baseline.
PERFORMANCE BIAS	Aside from the exposure, were the groups treated the same?	Yes Partial No Not reported	Yes
DE DETECTION	Was exposure measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes.

BIAS	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes.
	Were outcomes assessed objectively and independently?	Yes Yes Partial No Not reported	Not reported
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	PCOS= 14% Controls= 14%	FDR= 0% Controls= 0%
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	FDR= 0% Controls= 0%
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	Partial. Ethics approval present. No protocol registration
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	Yes
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	No. Government funding for publication.
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		High	Moderate. Not randomised. Unclear how representative the cohort is
Did risk of bias differ by outcome *(eg. primary outcome*		No	

was low risk but rest were high)?	

Study ID	Zhang 2022	
Study Citation	Zhang F, Ying L, Zhang Q, Wang F, Qu F. Association between maternal polycystic ovary syndrome and early childhood growth: a continuous observation from 3 months to 6 years of age. J Assist Reprod Genet. 2022 Feb;39(2):461-471. doi: 10.1007/s10815-021-02378-9. Epub 2022 Jan 20. Erratum in: J Assist Reprod Genet. 2022 Jan 31;: PMID: 35048272; PMCID: PMC8956758.	
Study Country	China	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	Children of women with PCOS (n=198) compared to children born to health mothers (n=227) followed from 3 months to 6 years of age	
PCOS diagnostic criteria	Rotterdam 2003	
N per group	The number of participants that were: Screened: Not reported Enrolled: Not reported Allocated: Not reported Assessed and followed up: FDR = 198, controls= 227	
Setting	Prospective cohort study. University Hospital, October 2012-July 2015, single center	
Intervention/ indicator	Children of women with PCOS	
Comparison/ Control	Control children of mothers without history of PCOS Matched for age and gender	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Primary outcome not defined Outcomes measured: - Height (Standardized children's meters) - Weight (Standardised weight scales, participants wore lightweight clothes and stood barefoot naturally during the measurement) - BMI (calculated as weight / height^2) Outcomes not relevant: - Head circumference - Tooth eruption (defined as any part of the tooth exposed to the gingiva during the examination) - Feeding patterns of children within age 1 year (self report e.g breastfeeding, mixed feeding, and artificial feeding) - Characteristics of mothers: age, height, weight, BMI, employment, education, gravidity, mode of delivery	
Inclusion criteria reported?	Yes	Yes. Control mothers had regular menstrual cycles
Exclusion criteria reported?	Yes Partial No Not reported	Yes. Control mothers: hyperandrogenism, chronic hypertension, diabetes, thyroid disease, other pregnancy complications

			All participants: multiple pregnancies, preterm births, and children with a birth weight of less than 2,500 g or more than 4,500 g
Does the study have a clearly focused question?		Yes Partial No Not reported	Partial. Primary outcome not reported.
Is a cohort study the appropriate design to answer this question?		Yes Partial No Not reported	Yes.
Does the study have specified inclusion/ exclusion criteria?		Yes Partial No Not reported	Partial. No mention of exclusion of secondary causes of oligoamenorrhea in PCOS mothers.
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes.
Were the outcomes measured appropriate?		Yes Partial No Not reported	Yes
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	No. Duration of follow-up likely not long enough to capture cardiovascular disease
Was matching performed?		Yes Partial No Not reported	Yes. Analysed by age and gender
Summary of Result/s		Children of women with PCOS had higher BMI compared to children of women without PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Other than the exposure under investigation, were the groups selected from similar populations?	Yes	Yes.
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Partial. Single center, no flowchart of participants excluded.
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes.

PERFORMANCE BIAS	Aside from the exposure, were the groups treated the same?	Yes Partial No Not reported	Yes.
DETECTION BIAS	Was exposure measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes. Standardised
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	Not reported.
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes. Standardised
	Were outcomes assessed objectively and independently?	Yes Yes Partial No Not reported	Not reported.
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	PCOS= 14% Controls= 14%	Not reported
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Not reported
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	Partial. Ethics approval present. No protocol registration
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	Partial. Unclear how much attrition in cohort.
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	No. National Natural Science Foundation of China (81874480; 82074476; 81873837), and the Zhejiang Province Science Foundation for Key Program (LZ21H270001)
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported. No power calculation
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No	Yes.

		Not reported	
COMMENTS			
What is the overall risk of bias?		High	Moderate. Unclear attrition.
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		No. Only one outcome of interest	

Abbreviations: ADA = American Diabetes Association; AE-PCOS = Androgen Excess and PCOS Society criteria; AIRg = acute insulin response to glucose; AMH = anti Mullerian hormone; ART = assisted reproductive technology; AUC = area under the curve; BMI = body mass index; BP = blood pressure; CRP = C-reactive protein; DHEAS = Dehydroepiandrosterone sulfate; DM = diabetes mellitus; E2 = estradiol; ELISA/EIA = enzyme-linked immunosorbent assay; FAI = free androgen index; FIRI = Fasting insulin resistance index; FDR = first degree relative; FSH = follicle stimulating hormone; HDL = high density lipoprotein; HOMA-IR = Homeostatic Model Assessment for Insulin Resistance; IDF = International Diabetes Federation; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; ISI = Insulin sensitivity index; JNC = Joint National Committee; LDL = low density lipoprotein; LH = luteinising hormone; NCEP/ATP III = National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III; NICHD = National Institute of Child Health and Human Development criteria; OGTT = oral glucose tolerance test; PCOS = polycystic ovarian syndrome; QUICKI = quantitative insulin-sensitivity check index; RIA = radioimmunoassay; SDS = Standard deviation score; T1DM = Type 1 Diabetes Mellitus; T2DM = Type 2 Diabetes Mellitus; TSH = Thyroid stimulating hormone; WHO = World Health Organisation; WHR = Waist hip ratio

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 1

Question 1.12.

What is the risk of PCOS and cardiometabolic outcomes (CVD, T2D) in relatives of women with PCOS?

BACKGROUND:

Women with PCOS have a 1.9-fold increased risk of metabolic syndrome (1) and clustering of cardiovascular risk factors; however, the risk of metabolic complications in first-degree relatives (FDR) of PCOS women is unclear (2, 3). Other studies showed that first degree relatives of women with PCOS had higher rates of glucose intolerance, hypertension and hyperlipidaemia (4). There are thought to be significant adverse impacts on children of affected mothers (5).

Family studies suggest a 2.3-fold increased risk for T2DM and a 1.4-fold increased risk for metabolic syndrome in fathers of women with PCOS (6) and a 3.9-fold increased risk for dyslipidaemia (7) in brothers of women with PCOS. Studies suggest a genetically defined, ovarian-independent, male cardiometabolic equivalent for PCOS (8). PCOS propensity risk scoring was associated with obesity, T2DM, dyslipidaemia, coronary artery disease, androgenic alopecia, free androgen index and sex hormone binding globulin in men, with the effect mediated by BMI (8).

GRADE EVIDENCE CERTAINTY	
Comparison	**GRADE for critical outcomes***
o Female first degree relatives versus normal controls	⨁◯◯◯ VERY LOW
o Parents versus normal controls	⨁◯◯◯ VERY LOW
o Fathers versus normal controls	⨁◯◯◯ VERY LOW
o Mothers versus normal controls	⨁◯◯◯ VERY LOW
o Brothers versus normal controls	⨁◯◯◯ VERY LOW
o Sisters versus normal controls	⨁◯◯◯ VERY LOW
o All offspring versus normal controls	⨁◯◯◯ VERY LOW
o Daughters versus normal controls	⨁◯◯◯ VERY LOW
o Sons versus normal controls	⨁◯◯◯ VERY LOW
o All first-degree relatives versus normal controls	⨁⨁◯◯ LOW
o All female first-degree relatives versus normal controls	⨁◯◯◯ VERY LOW
o All male first-degree relatives versus normal controls	⨁◯◯◯ VERY LOW

* based on the lowest certainty for risk of PCOS, diabetes, metabolic syndrome, IGT, IFG, hypertension, or higher weight, rather than surrogate markers (e.g. lipids, FBG, etc).

Evidence to Recommendations Framework

COMPARISONS (option versus other option)

Summary of evidence and comparisons

o Female first degree relatives versus normal controls

Early pubertal female relatives of women with PCOS had similar rates of insulin resistance (9).

o Parents versus normal controls

Parents of women with PCOS had higher rates of metabolic syndrome and cardiovascular disease than healthy controls (2).

o Fathers versus normal controls

First degree relatives (including fathers) of women with PCOS had higher rates of glucose intolerance, hypertension and hyperlipidaemia (4).

First degree relatives (including fathers) of women with PCOS had higher rates of glucose intolerance, hypertension and hyperlipidaemia (10).

o Mothers versus normal controls

Mothers of women with PCOS had higher rates of dyslipidaemia and insulin resistance (11).

o Brothers versus normal controls

Brothers of women with PCOS had insulin resistance compared to age and BMI matched controls (Baillargeon 2007)

Brothers of women with PCOS had higher rates of hyperlipidaemia and insulin resistance (Sam 2008)

Hypertensive brothers of women with PCOS had higher rates of hyperlipidaemia and insulin resistance than hypertensive controls (12).

Hypercholesterolaemic brothers of women with PCOS had higher rates of insulin (13).

o Sisters versus normal controls

Sisters of women with PCOS had higher rates of insulin resistance (14).

Sisters of women with PCOS had higher rates of hyperlipidaemia than healthy controls (15).

Sisters of women with PCOS had higher rates of metabolic syndrome (16).

Sisters of women with PCOS had higher rates of metabolic syndrome than healthy controls (17).

Siblings of women with PCOS had higher rates of metabolic syndrome and hyperlipidaemia than healthy controls (18).

Siblings (both brothers and sisters) of women with PCOS had higher rates of glucose intolerance and hyperlipidaemia (19).

o All offspring versus normal controls

Offspring of women with PCOS had higher rates of hyperlipidaemia than healthy controls (20).

Children of women with PCOS had higher rates of metabolic syndrome (21).

Children of women with PCOS had lower BMI than healthy controls (22).

Offspring of women with PCOS had higher BMI (23).

o Daughters versus normal controls

No difference in post menarcheal daughters - median age 15.42 years (24).

Daughters of women with PCOS had similar rates of insulin resistance (26).

Daughters of women with PCOS – no difference – included pre-menarcheal girls (26).

Daughters of women with PCOS had higher weight and different levels of androgen metabolites (27).

Daughters of women with PCOS had similar rates of insulin resistance (28).

o Sons versus normal controls

Sons of women with PCOS had higher rates of hyperlipidaemia and central adiposity (29).

If unadjusted for BMI, sons of PCOS women have higher weight during early infancy; higher weight, BMI, waist circumference, total cholesterol and LDL during childhood and adulthood (30, 31).

If unadjusted for BMI, sons of PCOS women have higher weight during early infancy; higher weight, BMI, waist circumference, total cholesterol and LDL during childhood and adulthood (32).

o All first-degree relatives versus normal controls

First degree relatives of women with PCOS had higher rates of glucose intolerance, hypertension and hyperlipidaemia (4).

First degree relatives of women with PCOS had higher rates of glucose intolerance, hypertension and hyperlipidaemia (10, 33).

o All female first-degree relatives versus normal controls

Late/post pubertal female first degree relatives of women with PCOS had similar rates of insulin resistance (34).

Premenarchal first degree relatives (daughters, sisters) of women with PCOS had higher rates of insulin resistance (35).

Female first-degree relatives have similar BMI but higher fasting glucose and 2-hour glucose (36).
o All male first-degree relatives versus normal controls
Fathers and brothers of women with PCOS had higher rates of higher weight and metabolic syndrome (37).

EVIDENCE-BASED RECOMMENDATION(S)

EBR: Healthcare professionals could consider that fathers and brothers of women with PCOS may have increased prevalence of metabolic syndrome, type 2 diabetes and hypertension.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

PRACTICE POINT

The cardiometabolic risk in female first degree relatives of women with PCOS remains inconclusive.

GRADE CONSIDERATIONS

Justifications:
First degree male relatives of women with PCOS had a moderately increased risk of metabolic syndrome. Quality of evidence: very low to low.

Subgroup considerations:
Evidence in mothers, daughters and sisters of women with PCOS was very limited due to small number of studies and participants.

Implementation considerations:
It is unclear how often healthcare professionals should screen male first-degree relatives of women with PCOS.

Monitoring and evaluation considerations:
As above.

Research priorities:
More studies in families of women with PCOS and across all age groups, including mechanisms.
Studies including daughters of women with PCOS studied at least 8 years post menarche.

GRADE framework

GRADE DECIDE Interactive Evidence to Decision Framework

● DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

● UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

● CERTAINTY OF THE EVIDENCE

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☒ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Very low level of evidence

Very disparate studies

● VALUES

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☒ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☐ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Research evidence:

No research evidence was identified

Panel discussion:

● BALANCE OF EFFECTS

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:

● COSTS

How large are the resource requirements (costs)?

Judgement:

☒ Don't know	☐ Varies	☐ Large costs	☐ Moderate costs	☐ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:

No research evidence was identified

Panel discussion:

There will be a cost for implementing screening of diabetes but this may be offset by prevention of complications.

● CERTAINTY OF COST EVIDENCE

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

No research evidence was identified

Panel discussion:

[key contact to draft discussion points and justification for above judgement]

● COST-EFFECTIVENESS

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

No research evidence was identified

Panel discussion:

● EQUITY

What would be the impact on health equity?

Judgement:

☒ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☐ Probably increased	☐ Increased

Research evidence:

No research evidence was identified

Panel discussion:

● ACCEPTABILITY

Is the option acceptable to key stakeholders?

Judgement:

☒ Don't know	☐ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

● FEASIBILITY

Is the option feasible to implement?

Judgement:

☒ Don't know	☐ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

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9856-2012-14. PMID: 22643321; PMCID: PMC3477027. (primary citation)

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GUIDELINE DEVELOPMENT GROUP 2

Prevalence, screening and management of psychological features and models of care

	Clinical Questions
2.1	1) In women with PCOS, what is the prevalence and severity of reduced QoL? 2) In women with PCOS, what dimensions of QoL are most affected? *CLINICAL PRACTICE POINTS:* *- Should QoL be assessed as part of standard care?* *- In women with PCOS, what tools/methods can be used to assess quality of life?*
2.2	In women with PCOS, what is the prevalence and severity of depression and anxiety? *CLINICAL PRACTICE POINTS:* *- Should anxiety and depression be assessed as part of standard care?* *- In women with PCOS, what tools/methods can be used to assess depression and/or anxiety?*
2.3	In women with PCOS what is the prevalence and severity of psychosexual dysfunction? *CLINICAL PRACTICE POINTS:* *- Should psychosexual dysfunction be assessed as part of standard care?* *- In women with PCOS, what tools/methods can be used to assess psychosexual dysfunction?*
2.4	In women with PCOS, what is the prevalence and severity of body image distress? *CLINICAL PRACTICE POINTS:* *- Should body image distress be screened as part of standard care?* *- In women with PCOS, what tools/methods can be used to assess body image distress?*
2.5	In women with PCOS what is the prevalence and severity of disordered eating? *CLINICAL PRACTICE POINT:* *- Should disordered eating be assessed as part of standard care?* *- In women with PCOS, what tools/methods can be used to assess disordered eating?*
2.6	1) What are the information, resource and education needs of women, adolescents, CALD groups and healthcare providers regarding PCOS? 2) What are the characteristics of available models of care implemented in PCOS clinic or service? 3) How can we best support women to navigate the impact of PCOS on family and interpersonal relationships? 4) What are the key challenges for those with PCOS when interacting with healthcare professionals about polycystic ovary syndrome and related features?
2.7	Is psychological therapy effective for management and support of depression and/or anxiety, disordered eating, body image distress, self-esteem, feminine identity or psychosexual dysfunction in women with PCOS?
2.8	Are anti-depressants and anxiolytics effective for management and support of depression and/or anxiety or disordered eating in women with PCOS?

PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by ECR Lead: Jodie Avery

Other Members: Stephanie Pirotta

Supervised, edited and supported by the Evidence Team (Jillian Tay, Aya Mousa)

GDG 2

Question 2.1.

1) In women with PCOS, what is the prevalence and severity of reduced QoL?

2) In women with PCOS, what dimensions of QoL are most affected? (Narrative Review)

1. STUDY SELECTION

Table 1. PICO Criteria for Inclusion	
Question	Q 2.1) In women with PCOS, what is the prevalence and severity of reduced QoL? Q 2.2) In women with PCOS, what dimensions of QoL are most affected? CLINICAL PRACTICE POINTS: Should QoL be screened as part of standard care? In women with PCOS, what tools/methods can be used to assess quality of life?
Clinical leads (key contacts)	Rhonda Garad
Allocation ranking	Level 2- updated systematic review

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits (language, year)
Inclusion	Females of any age, ethnicity and weight. Subgroups: Adolescents Ethnicity Phenotype	Quality of life measured in women with PCOS (diagnosed by Rotterdam, NIH or AES – phenotypes will be captured).	Quality of life measured in a non-PCOS group. Same QoL tool as that used in women with PCOS must be used.	Prevalence and severity of impaired quality of life. Sensitivity, specificity, PPV and NPV of each assessment tool. AUC (when comparing two methods). Acceptability to users/patients. Self- esteem. Timing of assessment. Assessment intervals	Evidence based guidelines, systematic reviews, comparative prospective cohort studies and comparative cross-sectional studies.	English language. New search.
Exclusion				NA	Non-evidence-based guidelines or any study lower than a comparative cross-sectional study.	

2. SEARCH STRATEGY

2.1 Search details

Search strategy source: 2018 PCOS guideline technical report: QoL evidence review for GDG 2: Emotional wellbeing

Evidence source	Date of search
Medline (Ovid)	1/01/2017 - 17/07/22
PsychInfo (Ovid)	1/01/2017 - 17/07/22
EMBASE (Ovid)	1/01/2017 - 17/07/22
All EBM (Ovid)	1/01/2017 - 18/07/22
CINAHL	1/01/2017 - 17/07/22
Any subsequent updates - enter database and date: not applicable	

2.2 Questions addressed by this search:

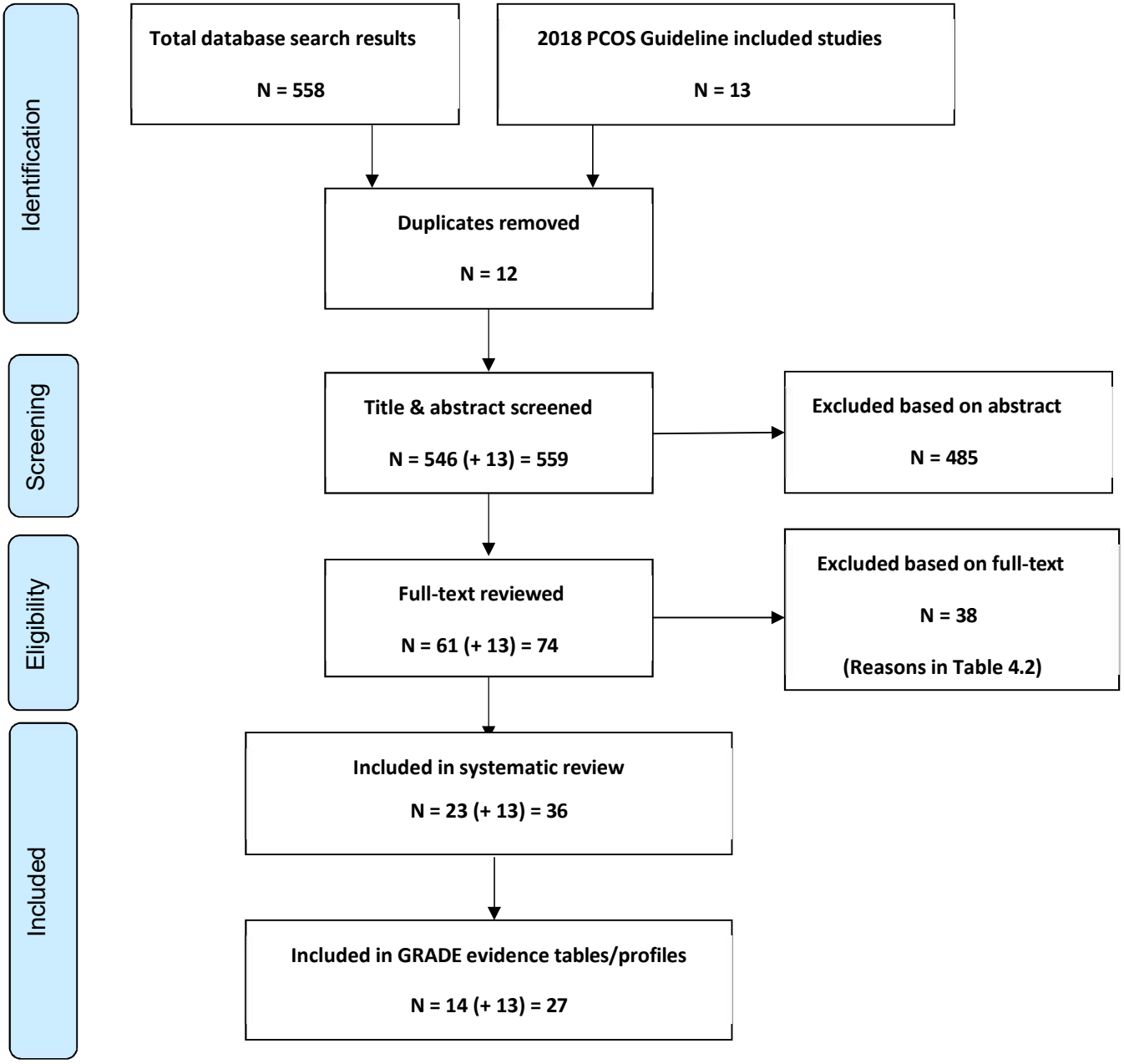
GDG	Q#	Question
2	2.1.1	In women with PCOS, what is the prevalence and severity of reduced QoL?
2	2.1.2	2) In women with PCOS, what dimensions of QoL are most affected?
		CLINICAL PRACTICE POINTS: Should QoL be assessed as part of standard care? In women with PCOS, what tools/methods can be used to assess quality of life?

OVID Medline, All EBM, PsychInfo, EMBASE	CINAHL
1 exp polycystic ovary syndrome/	S1. SU polycystic ovary syndrome
2 polycystic ovar*.mp.	S2. polycystic ovar*
3 poly-cystic ovar*.mp.	S3. poly-cystic ovar*
4 PCO*.mp.	S4. PCO*
5 (stein-leventhal or leventhal).mp.	S5. stein-leventhal or leventhal
6 anovulation/	S6. SU ovarian cysts
7 anovulat*.mp.	S7. SU anovulation
8 oligo-ovulat*.mp.	S8. oligo-ovulat*
9 oligoovulat*.mp.	S9. oligoovulat*
10 (ovar* adj5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*)).mp.	S10. ovar* N5 sclerocystic or. ovar* N5 polycystic or ovar* N5 poly-cystic or S1. ovar* N5 degenerat* or ovar* N5 hyperandrogen* or ovar* N5 hyperandrogen
11 or/1-10	S11. S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10
12 "Quality of Life"/	S12. (MH "Quality of Life+")
13 Quality of life.mp.	S13. quality of life
14 Sickness Impact Profile/	S14. (MH "Sickness Impact Profile")
15 Sickness impact profile.mp.	S15. sickness impact profile
16 Polycystic Ovar* Syndrome Questionnaire.mp.	S16. (MH "Quality of Life (Iowa NOC)") OR (MH " Health and Life Quality (Iowa NOC)+")
17 (short form and ("21" or "36")).mp.	S17. Polycystic Ovar* Syndrome Questionnaire
18 (World Health Organization quality of life scale or WHO brief).mp.	S18. (short form AND ("12" or "36"))
19 (Quality of well?being or quality of well being).mp.	S19. World Health Organization quality of life scale OR WHO brief
20 General health questionnaire.mp.	S20. Quality of well?being OR quality of well being
21 Spitzer quality of life index.mp.	S21. General health questionnaire
22 Medical outcomes study short form health survey.mp.	S22. Spitzer quality of life index
23 "Work and social adjustment scale".mp.	S23. Medical outcomes study short form health survey
24 "The quality of life enjoyment and satisfaction questionnaire".mp.	S24. "Work and social adjustment scale"
25 Nottingham health profile.mp.	S25. "The quality of life enjoyment and satisfaction questionnaire"
26 Medical outcomes scale.mp.	S26. Nottingham health profile
27 Assessment of quality of life.mp.	S27. Medical outcomes scale
28 EuroQol.mp.	S28. Assessment of quality of life
29 PaedsQL.mp.	S29. EuroQol
30 (HRQOL or HRQL or PCOSQ or MPCOSQ or SF-36 or SF36 or SF-12 or SF12 or SIP or QWB or GHQ28 or WHO-QOL or WHOQOL or AQOL or SQLI or EQ-5D).mp.	S30. pedsql
31 or/12-30	

32 11 and 31 33 limit 32 to (english language and humans) 34 33 35. limit 34 to yr="2017-Current"	S31. TX PaedsQL S32. HRQOL OR HRQL OR PCOSQ OR MPCOSQ OR SF-36 OR SF36 OR SF-12 OR SF12 OR SIP OR QWB OR GHQ28 OR WHOQOL OR WHOQOL OR AQOL OR SQLI OR EQ-5D S33. S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 S34. S11 AND S33

Evidence processing: Studies were selected and appraised by two reviewer/s in consultation with the evidence team/ key contact using study selection and appraisal criteria (PICO above) established a priori. The articles were reviewed by title and abstract by two reviewers. When a decision could not be made based on title and abstract alone, full text was retrieved. A total of 31 studies and 5 reviews met inclusion criteria for this review.

3. SEARCH RESULTS - PRISMA flowchart



4. STUDY INCLUSION

4.1 Included studies

Original studies from 2022 search:

Bazarganipour, F.; Taghavi, S. A.; Asemi, Z.; Allan, H.; Khashavi, Z.; Safarzadeh, T.; Pourchangiz, S.; Zare, F.; Ghasemi, S.; Karimi, Z.; Azizi Kutenaee, M. The impact of irritable bowel syndrome on health-related quality of life in women with polycystic ovary syndrome. Health & Quality of Life Outcomes Jul 13 2020;18(1):226 2020 Jul 13

Boivin, M. J.; Fatehi, F.; Phillips-Chan, A. E.; Richardson, J. R.; Summers, A. N.; Foley, S. A. Exploratory study of a screening measure for polycystic ovarian syndrome, quality of life assessment, and neuropsychological evaluation BMC Women's Health 06 23 2020;20(1):132 2 020 06 23

Borghi, L.; Leone, D.; Vegni, E.; Galiano, V.; Lepadatu, C.; Sulpizio, P.; Garzia, E. Psychological distress, anger and quality of life in polycystic ovary syndrome: associations with biochemical, phenotypical and socio- demographic factors. Journal of Psychosomatic Obstetrics & Gynecology 06 2018;39(2):128-137 2018 06

Coban OG, Tulaci OD, Adanir AS, Onder A. Psychiatric disorders, self-esteem, and quality of life in adolescents with polycystic ovary syndrome. J. Pediatr. Adolesc. Gynecol. 2019; 32: 600–4.

Donbaloglu, Z.; Tuhan, H.; Coban, O. G.; Kizilay, D. O.; Ismailoglu, E.; Onder, A.; Acar, S.; Bedel, A.; Cetiner, E. B.; Singin, B.; Erdem, H.; Parlak, M. Hyperandrogenism correlates with psychological symptoms in adolescents with polycystic ovary syndrome. Clinical Pediatric Endocrinology 05 Apr 2022;31(2)():68-76 2022 05 Apr

Jose, S. A.; Ravi, R.; Murthy, M. K. Quality of life in women with polycystic ovarian syndrome: Requisite of clinical pharmacist intervention. Asian Journal of Pharmaceutical and Clinical Research. Conference: 3rd International Conference on Academic and Industrial Innovations: Transitions in Pharmaceutical, Medical and Biosciences, INNOPHARM 2018;11(11): 2018

Kahal, H.; Kilpatrick, E.; Rigby, A.; Coady, A.; Atkin, S. The effects of treatment with liraglutide on quality of life and depression in young obese women with PCOS and controls. Gynecological Endocrinology Feb 2019;35(2):142-145 2019 Feb

Kaluzna, M.; Nomejko, A.; Slowinska, A.; Wachowiak-Ochmanska, K.; Pikosz, K.; Ziemnicka, K.; Ruchala, M. Lower sexual satisfaction in women with polycystic ovary syndrome and metabolic syndrome. Endocrine connections September 2021;10(9)():1035-1044 2021 September

Karjula, S.; Morin-Papunen, L.; Franks, S.; Auvinen, J.; Jarvelin, M. R.; Tapanainen, J. S.; Jokelainen, J.; Miettunen, J.; Piltonen, T. T. Population-based Data at Ages 31 and 46 Show Decreased HRQoL and Life Satisfaction in Women with PCOS Symptoms. Journal of Clinical Endocrinology & Metabolism 06 01 2020;105(6):01 2020 06 01

Kutlu, O. Evaluation of quality of life of patients with hirsutism among Turkish women: A single-center cross- sectional study. Journal of Cosmetic Dermatology Nov 2020;19(11):3053-3057

Lidaka, L.; Lazdane, G.; Kivite-Urtane, A.; Gailite, L.; Dzivite-Krisane, I.; Stokenberga, I. Health-related quality of life and binge eating among adolescent girls with PCOS. Clinical and Experimental Obstetrics and Gynecology 2019;46(5)():831-832

Ozcan Dag, Z.; Alpua, M.; Isik, Y.; Buturak, S. V.; Tulmac, O. B.; Turkel, Y. The evaluation of temperament and quality of life in patients with polycystic ovary syndrome Gynecological Endocrinology Mar 2017;33(3):250-253 2017 Mar

Panico A, Messina G, Lupoli GA, et al. Quality of life in overweight (obese) and normal-weight women with polycystic ovary syndrome. Patient Prefer Adherence. 2017;11:423–429

Rzonca, E.; Bien, A.; Wdowiak, A.; Szymanski, R.; Iwanowicz-Palus, G. Determinants of Quality of Life and Satisfaction with Life in Women with Polycystic Ovary Syndrome. International Journal of Environmental Research & Public Health [Electronic Resource] 02 22 2018;15(2):22

Sanchez-Ferrer, M. L.; Adoamnei, E.; Prieto-Sanchez, M. T.; Mendiola, J.; Corbalan-Biyang, S.; Monino-Garcia, M.; Palomar-Rodriguez, J. A.; Torres-Cantero, A. M. Health-related quality of life in women with polycystic ovary syndrome attending to a tertiary hospital in Southeastern Spain: a case-control study. Health & Quality of Life Outcomes Jul 16 2020;18(1):232.

Stevanovic, D.; Bozic-Antic, I.; Stanojlovic, O.; Vojnovic Milutinovic, D.; Bjekic-Macut, J.; Jancic, J.; Macut, D. Health-related quality of life questionnaire for polycystic ovary syndrome (PCOSQ-50): a psychometric study with the Serbian version. Women & Health 10 2019;59(9):1015-1025

Tan, J.; Wang, Q. Y.; Feng, G. M.; Li, X. Y.; Huang, W. Increased Risk of Psychiatric Disorders in Women with Polycystic Ovary Syndrome in Southwest China. Chinese Medical Journal 02 05 2017;130(3):262-266.

Wang, Z.; Groen, H.; Cantineau, A. E. P.; van Elten, T. M.; Karsten, M. D. A.; van Oers, A. M.; Mol, B. W. J.; Roseboom, T. J.; Hoek, A. Dietary Intake, Eating Behavior, Physical Activity, and Quality of Life in Infertile Women with PCOS and Obesity Compared with Non-PCOS Obese Controls. Nutrients Oct 08 2021;13(10):08

Reviews from 2022 search:

Behboodi Moghadam, Z.; Fereidooni, B.; Saffari, M.; Montazeri, A. Measures of health-related quality of life in pcos women: A systematic review. International Journal of Women's Health 2018;10():397-408

Castelo-Branco, C.; Naumova, I. Quality of life and sexual function in women with polycystic ovary syndrome: a comprehensive review. Gynecological Endocrinology Feb 2020;36(2):96-103

Dokras, A.; Stener-Victorin, E.; Yildiz, B. O.; Li, R.; Ottey, S.; Shah, D.; Epperson, N.; Teede, H. Androgen Excess-Polycystic Ovary Syndrome Society: position statement on depression, anxiety, quality of life, and eating disorders in polycystic ovary syndrome. Fertility & Sterility 05 2018;109(5):888-899 2018 05

Wilson, N. A.; Pena, A. S. Quality of life in adolescent girls with polycystic ovary syndrome Journal of Paediatrics & Child Health Sep 2020;56(9):1351-1357. 2020 Sep

Yin, X.; Ji, Y.; Chan, C. L. W.; Chan, C. H. Y. The mental health of women with polycystic ovary syndrome: a systematic review and meta-analysis Archives of Women's Mental Health 02 2021;24(1):11-27 2021 02

Original studies from 2018 PCOS Guideline:

Acmaz G, Albayrak E, Acmaz B, Bager M, Soyak M, ZararsJz G, and Ipekmüderris I (2013). "Level of anxiety, depression, self-esteem, social anxiety, and quality of life among the women with polycystic ovary syndrome." The Scientific World Journal 2013: 851815.

Benetti-Pinto, C. L., Ferreira S. R. Antunes Jr. A. Yela D. A. (2015). "The influence of body weight on sexual function and quality of life in women with polycystic ovary syndrome." Archives of Gynecology & Obstetrics 291(2): 451-455.

Benson, S., Janssen O.E., Hahn S. Tan S. Dietz T. Mann K. Pleger K. Schedlowski M. Arck PC. Elsenbruch S (2008). "Obesity, depression, and chronic low-grade inflammation in women with polycystic ovary syndrome." Brain, Behavior, & Immunity 22(2): 177-184.

Drosdzol, A., Skrzypulec V, Mazur B, Pawliñska-Chmara R (2007). "Quality of life and marital sexual satisfaction in women with polycystic ovary syndrome." Folia Histochemica et Cytobiologica 45 Suppl 1: S93-97.

Elsenbruch, S., Hahn, S., Kowalsky, D., Offner, A. H., Schedlowski, M., Mann, K. and Janssen, O. E. 2003 Quality of life, psychosocial well-being, and sexual satisfaction in women with polycystic ovary syndrome. Journal of Clinical Endocrinology & Metabolism. 88 [12]: 5801-7.

Hahn, S., Janssen OE, Tan S, Pleger K, Mann K, Schedlowski M, Kimmig R, Benson S, Balamitsa E and Elsenbruch S(2005). "Clinical and psychological correlates of quality-of-life in polycystic ovary syndrome." European Journal of Endocrinology 153(6): 853-860.

Kumarapeli, V., Seneviratne R de A, Wijeyaratnec CN. (2011). "Health-related quality of life and psychological distress in polycystic ovary syndrome: a hidden facet in South Asian women." BJOG: An International Journal of Obstetrics & Gynaecology 118(3): 319-328.

Ozcan Dag, Z., Alpua M, Isik Y, S. Buturak V, Ozlem B., Tulmac & Yakup Turkel (2016). "The evaluation of temperament and quality of life in patients with polycystic ovary syndrome." Gynecological Endocrinology: 1-4.

Ozcan Dag, Z., Oguzturk O, Isik Y, Turkel Y & Bulcun E (2015). "Personality profile in patients with polycystic ovary syndrome." Gynecological Endocrinology 31(7): 540-542.

Ramos, F. K., Lara LS, Kogure GS, Silva RC, Ferriani RA, de Sá MFS, dos Reis RM (2016). "Quality of Life in Women with Polycystic Ovary Syndrome after a Program of Resistance Exercise Training." Revista Brasileira de Ginecologia e Obstetricia 38(7): 340-347.

Shafti, V. and S. Shahbazi (2016). "Comparing Sexual Function and Quality of Life in Polycystic Ovary Syndrome and Healthy Women." Journal of Family & Reproductive Health 10(2): 92-98.

Shishehgar F, Tehrani FR, Mirmiran P, Hajian S, Baghestani AR (2016). "Comparison of the Association of Excess Weight on Health Related Quality of Life of Women with Polycystic Ovary Syndrome: An Age- and BMI- Matched Case Control Study." PLoS ONE [Electronic Resource] 11(10): e0162911.

Trent, M. E Rich M, Austin B, Gordon C (2002). "Quality of life in adolescent girls with polycystic ovary syndrome." Archives of Pediatrics & Adolescent Medicine 156(6): 556-560.

4.2 Excluded Studies (on full text assessment 2022 search)

	Reference	Reason
1	**#59 - Abdalla 2021** Abdalla, M. A.; Deshmukh, H.; Mohammed, I.; Atkin, S.; Reid, M.; Sathyapalan, T. The Effect of Free Androgen Index on the Quality of Life of Women With Polycystic Ovary Syndrome: A Cross-Sectional Study Frontiers in Physiology 24 May 2021;12 (no pagination)(): doi: 10.3389/fphys.2021.652559	Wrong patient population
2	**#60 - Abdollahi 2019** Abdollahi, L.; Mirghafourvand, M.; Babapour, J. K.; Mohammadi, M. Effectiveness of cognitive-behavioral therapy (CBT) in improving the quality of life and psychological fatigue in women with polycystic ovarian syndrome: a randomized controlled clinical trial Journal of Psychosomatic Obstetrics & Gynecology 12 2019;40(4):283-293 doi: 10.1080/0167482X.2018.1502265	Wrong patient population
3	**#73 - Al-Naqeeb 2022** Al-Naqeeb, Aaag; Zedian, M. A.; Mohammad, A. Impact of Polycystic Ovarian Syndrome on General Health Related-Quality of Life among a Sample at "Maternity and Children Teaching Hospital" in Diwaniyah City-Iraq. Wiadomosci Lekarskie 2022;75(4 pt 1):836-841 doi: 10.36740/WLek202204116	Wrong patient population
4	**#77 - Alghadeer 2020** Alghadeer, S.; Algarawi, A.; Abu-Rkybah, F.; Alshebly, M. M.; Alruthia, Y. The translation and validation of the Arabic Version of the Polycystic Ovary Syndrome Health-Related Quality of Life Questionnaire (AR-PCOSQ) BMC Women's Health 10 29 2020;20(1):244 2020 10 29 doi: 10.1186/s12905-020-01108-0	Wrong patient population
5	**#78 - Alhussain 2020** Alhussain, F.; Alruthia, Y.; Al-Mandeel, H.; Bellahwal, A.; Alharbi, F.; Almogbel, Y.; Awwad, O.; Dala'een, R.; Alharbi, F. A. Metformin improves the depression symptoms of women with polycystic ovary syndrome in a lifestyle modification program Patient Preference and Adherence 2020;14():737-746 2020 doi: 10.2147/PPA.S244273	Wrong patient population
6	**#80 - Alkoudsi 2019** Alkoudsi, K. T.; Al-Qudah, R.; Basheti, I. A. Assessing the effectiveness of a pharmaceutical care service on the quality of life of women with polycystic ovarian syndrome living in war and non-war countries Journal of evaluation in clinical practice 2019;(): 2019 doi: 10.1111/jep.13310	Wrong patient population
7	**#86 - Amiri 2019** Amiri, M.; Bidhendi Yarandi, R.; Nahidi, F.; Tohidi, M.; Ramezani Tehrani, F. The relationship between clinical and biochemical characteristics and quality of life in patients with polycystic ovary syndrome Clinical Endocrinology 01 2019;90(1):129-137 2019 01 doi: 10.1111/cen.13858	Wrong patient population
8	**#87 - Amiri 2020** Amiri, M.; Nahidi, F.; Yarandi, R. B.; Khalili, D.; Tohidi, M.; Tehrani, F. R. Effects of oral contraceptives on the quality of life of women with polycystic ovary syndrome: a crossover randomized controlled trial Health & Quality of Life Outcomes Aug 31 2020;18(1):293 doi: 10.1186/s12955-020-01544-4	Wrong patient population
9	**#93 - Arentz 2019** Arentz, S.; Smith, C.; Abbott, J.; Bensoussan, A. Herbal medicine plus lifestyle for overweight women with polycystic ovary syndrome: A randomised control trial Australian Journal of Herbal and Naturopathic Medicine March 2019;31(1)():38 2019 March doi: 10.1186/1472-6882-14-511.	Wrong patient population
10	**#106 - Barbosa 2018** Barbosa, C. I. B.; Caldas, C. E.; Fernando, F. Jl; Browne, R. A. V.; Ferezini De Sa, J. C.; Keith, S. N. Aerobic Training Improves Quality of Life in Women with Polycystic Ovary Syndrome Medicine and science in sports and exercise 2018;Vol.50(7):1357-1366p 2018	Wrong patient population

	doi: 10.1249/MSS.0000000000001579.	
11	**#114 - BehboodiMoghadam 2018** Behboodi Moghadam, Z.; Fereidooni, B.; Saffari, M.; Montazeri, A Polycystic ovary syndrome and its impact on Iranian women's quality of life: a population-based study. BMC Women's Health 10 11 2018;18(1):164 2018 10 11 doi: 10.1186/s12905-018-0658-1	Wrong patient population
12	**#128 - Bottcher 2018** Bottcher, B.; Fessler, S.; Friedl, F.; Toth, B.; Walter, M. H.; Wildt, L.; Riedl, D. Health-related quality of life in patients with polycystic ovary syndrome: validation of the German PCOSQ-G Archives of Gynecology & Obstetrics 04 2018;297(4):1027-1035 2018 04 doi: 10.1007/s00404-017-4623-2	Wrong patient population
13	**#134 - Budharam 2020** Budharam, S.; Veeramreddy, S.; Goluguri, D. S.; Rajani, A. A study on identification of risk factors of polycystic ovarian syndrome by conducting survey and minimizing them through patient counseling and its impact on quality of life International Journal of Pharmaceutical Sciences and Research November 2020;11(11)():5747-5752 2020 doi: 10.13040/IJPSR.0975-8232.11%2811%29.5747-52	Wrong outcomes
14	**#164 - D'Souza 2022** D'Souza, P.; Rodrigues, D. E.; Kaipangala, R. G.; Leena, K. C. Effectiveness of Multimodular Interventions of Lifestyle Modification on Symptoms of Polycystic Ovarian Syndrome and Quality of Life among Women- A Quasi-experimental Study. Journal of Clinical and Diagnostic Research February 2022;16(2)():LC27-LC31 doi: 10.7860/JCDR/2022/50394.16030	Wrong study design
15	**#172 – Desai 2019** Desai, H. J.; Gundabattula, S. R. Quality of life in Indian women with fertility problems as assessed by the FertiQoL questionnaire: a single center cross sectional study Journal of Psychosomatic Obstetrics & Gynecology Mar 2019;40(1):82-87 doi: 10.1080/0167482X.2017.1405257	Wrong patient population - have not reported PCOS results separately from control
16	**#187 - Dorgham 2021** Dorgham, N.; Sharobim, A.; Haggag, H.; El-Kalioby, M.; Dorgham, D. Adding Combined Oral Contraceptives or Metformin to Laser Treatment in Polycystic Ovarian Syndrome Hirsute Patients Journal of Drugs in Dermatology: JDD 03 01 2021;20(3):302-306 doi: 10.36849/JDD.5652	Wrong patient population
17	**#202 – Eyupoglu 2022** Eyupoglu, N. D.; Aksun, S.; Ozturk, M.; Yildiz, B. O. Impact of social isolation during COVID-19 pandemic on health behaviors and weight management in women with polycystic ovary syndrome Eating & Weight Disorders: EWD Feb 23 2022;23():23 2022 Feb 23 doi: 10.1007/s40519-022-01369-8	Wrong patient population - only reports PCOSQ on PCOS women and no quality of life results for whole group
18	**211 - Forslund 2019** Forslund, M.; Landin-Wilhelmsen, K.; Krantz, E.; Trimpou, P.; Schmidt, J.; Brannstrom, M.; Dahlgren, E. No difference in quality of life or depression/anxiety diagnosis between middle-aged women with PCOS and age-matched controls Maturitas 2019;124(154):2019-05 doi: 10.1016/j.maturitas.2019.04.125	Wrong study design: abstract
19	**#230 - Greenwood 2018** Greenwood, E. A.; Pasch, L. A.; Cedars, M. I.; Legro, R. S.; Huddleston, H. G. Association among depression, symptom experience, and quality of life in polycystic ovary syndrome American journal of obstetrics and gynecology United States Mosby Inc 2018;Vol.219(3):279.e1- 279.e7p 2018 United States Mosby Inc doi: 10.1016/j.ajog.2018.06.017	Wrong patient population

20	**#276 - Kaboudi 2018** Kaboudi, M.; Jalilian, F.; Montazeri, A.; Zadeh, M. T. The effect of cognitive behavioral counseling on quality of life in women with polycystic ovarian syndrome Journal of reproduction and infertility April - June 2018;19(2 Supplement 2)():169 Doi: N/A	Wrong patient population - abstract
21	**279 - Kahal 2020** Kahal, H.; Tahrani, A. A.; Kyrou, I.; Dimitriadis, G. K.; Kimani, P. K.; Barber, T. M.; Nicholls, M.; Ali, A.; Weickert, M. O.; Randeva, H. S , The relationship between obstructive sleep apnoea and quality of life in women with polycystic ovary syndrome: a cross-sectional study. Therapeutic Advances in Endocrinology and Metabolism 2020;11(no pagination):2020 doi: 10.1177/2042018820906689	Wrong patient population
22	**#286 - Kazemi 2020** Kazemi, M.; McBreairty, L. E.; Zello, G. A.; Pierson, R. A.; Gordon, J. J.; Serrao, S. B.; Chilibeck, P. D.; Chizen, D. R. A pulse-based diet and the Therapeutic Lifestyle Changes diet in combination with health counseling and exercise improve health-related quality of life in women with polycystic ovary syndrome: secondary analysis of a randomized controlled trial Journal of Psychosomatic Obstetrics & Gynecology 06 2020;41(2):144-153 2020 06 doi: 10.1080/0167482X.2019.1666820	Wrong patient population
23	**#289 - Kiel 2022** Kiel, I. A.; Lionett, S.; Parr, E. B.; Jones, H.; Roset, M. A. H.; Salvesen, O.; Hawley, J. A.; Vanky, E.; Moholdt, T. High-Intensity Interval Training in Polycystic Ovary Syndrome: A Two-Center, Three-Armed Randomized Controlled Trial Medicine & Science in Sports & Exercise 05 01 2022;54(5):717-727 doi: 10.1249/MSS.0000000000002849	Wrong patient population
24	**#309 - Lara 2018** Lara, L.; Lopes, I. P.; Dos Reis, R. M.; Ribeiro, V. B.; De Souza, H. C. D.; Silva, R. C. Aerobic physical training improves sexual function and qol of pcos women: randomized conrrolled tria International journal of gynaecology and obstetrics 2018;143():357-358 2018 doi: 10.1002/ijgo.12582	Wrong patient population
25	**#312 – Lee 2017** Lee, I.; Cooney, L. G.; Saini, S.; Smith, M. E.; Sammel, M. D.; Allison, K. C.; Dokras, A. Increased risk of disordered eating in polycystic ovary syndrome Fertility & Sterility 03 2017;107(3):796-802 2017 03 doi:10.3390/ijerph15020376	Wrong patient population - does not compare quality of life scores with controls, only within PCOS group
26	**#361 - Mei 2022** Mei, L. L.; Abu, M. A.; Chew, K. T.; Ismail, A.; Zainuddin, A. A.; Nur Azurah, A. G. The Reliability and Validity of the Malay Version of Polycystic Ovarian Syndrome Health-Related Quality of Life Questionnaire Frontiers in Endocrinology 2022;13():848860. 2022 doi: 10.3389/fendo.2022.848860	Wrong patient population
27	**#386 - Naumova 2021** Naumova, I.; Castelo-Branco, C.; Kasterina, I.; Casals, G. Quality of Life in Infertile Women with Polycystic Ovary Syndrome: a Comparative Study Reproductive Sciences 07 2021;28(7):1901-1909 doi: 10.1007/s43032-020-00394-1	Wrong patient population
28	**#387 - Naz 2020** Naz, Marzieh Saei Ghare; Tehrani, Fahimeh Ramezani; Lak, Tahereh Behroozi; Mohammadzadeh, Farnaz; Nasiri, Malihe; Badr, Farahnaz Kholosi; Ozgoli, Giti Quality of life and emotional states of depression, anxiety and stress in adolescents with polycystic ovary syndrome: A cross-sectional study Psychology Research and Behavior Management Vol 13 2020, ArtID 203-209 Feb 2020;13(): 2020 Feb doi: N/A	Wrong patient population
29	**#418 - Patten 2021** Patten, R. K.; Pascoe, M. C.; Moreno-Asso, A.; Boyle, R. A.; Stepto, N. K.; Parker, A. G. Effectiveness of exercise interventions on mental health and health-related quality of life in women with polycystic ovary syndrome: a systematic review	Wrong patient population

	BMC Public Health 12 20 2021;21(1):2310\. 2021 12 20 doi: 10.1186/s12889-021-12280-9	
30	**#434 - Ribeiro 2021** Ribeiro, V. B.; Lopes, I. P.; Dos Reis, R. M.; Silva, R. C.; Mendes, M. C.; Melo, A. S.; de Souza, H. C. D.; Ferriani, R. A.; Kogure, G. S.; Lara, Lads Continuous versus intermittent aerobic exercise in the improvement of quality of life for women with polycystic ovary syndrome: A randomized controlled trial Journal of Health Psychology 08 2021;26(9):1307-1317. 2021 08 doi: 10.1177/1359105319869806	Wrong patient population
31	**#466 - Sidra 2019** Sidra, S.; Tariq, M. H.; Farrukh, M. J.; Mohsin, M. Evaluation of clinical manifestations, health risks, and quality of life among women with polycystic ovary syndrome PLoS ONE [Electronic Resource] 2019;14(10):e0223329 Medicine Mar 2020;99(12):e19427 2020 Mar doi: 10.1097/MD.0000000000019427	Wrong patient population
32	**#473 - Soriano-Maldonado** Soriano-Maldonado, A.; Martinez-Forte, S.; Ferrer-Marquez, M.; Martinez-Rosales, E.; Hernandez-Martinez, A.; Carretero-Ruiz, A.; Villa-Gonzalez, E.; Barranco-Ruiz, Y.; Rodriguez-Perez, M. A.; Torrente-Sanchez, M. J 2020 Physical Exercise following bariatric surgery in women with Morbid obesity: Study protocol clinical trial (SPIRIT compliant) Doi: 10.1097/MD.0000000000019427	Wrong study design: study protocol
33	**#486 - Tabassum 2020** Tabassum, F.; Sinha, H. H.; Dhar, K.; Jyoti, C.; Akhtar, M. S.; Chopra, V. S. Assessment of psycho-emotional distress due to age, body mass index, and marital status in polycystic ovary syndrome in North Indian population International Journal of Women's Health and Reproduction Sciences October 2020;8(4)():368-375 2020 October doi: 10.15296/ijwhr.2020.59	Wrong patient population
34	**#492 - Thakur 2021** Thakur, D.; Saurabh Singh, D. S.; Tripathi, D. M.; Lufang, D. Effect of yoga on polycystic ovarian syndrome: A systematic review Journal of Bodywork & Movement Therapies Jul 2021;27():281-286 2021 Jul doi: 10.1016/j.jbmt.2021.02.018	Wrong outcomes
35	**#514 - Vidhya 2020** Vidhya, M.; Bindhu, C.; Mounika, G.; Harika, K A prospective observational study on evaluation of complications in women with polycystic ovarian syndrome International Research Journal of Pharmacy 2020;11(7)():10-12 doi: 10.7897/2230-8407.110768	Wrong patient population
36	**#518 - Wang 2019** Wang, Z.; Dong, H.; Wang, Q.; Zhang, L.; Wu, X.; Zhou, Z.; Yang, L.; Huang, D. Effects of electroacupuncture on anxiety and depression in unmarried patients with polycystic ovarian syndrome: secondary analysis of a pilot randomised controlled trial Acupuncture in Medicine 02 2019;37(1):40-46 2019 02 doi: 10.1136/acupmed-2017-011615	Wrong patient population
37	**#528 - Williams 2018** Williams, Sophie; Sheffield, David; Knibb, Rebecca C. The polycystic ovary syndrome quality of life scale (PCOSQOL): Development and preliminary validation Health Psychology Open Vol 5(2), 2018, doi: N/A	Wrong patient population
	Reviews	
38	**#547 - Zehravi 2021** Zehravi, M.; Maqbool, M.; Ara, I. Depression and anxiety in women with polycystic ovarian syndrome: a literature survey. International Journal of Adolescent Medicine & Health Aug 23 2021;33(6):367-373 2021 Aug 23 DOI: 10.1515/ijamh-2021-0092 doi: 10.1515/ijamh-2021-0092	Wrong outcome - only concerns mental health

5. STUDY CHARACTERISTICS TABLE FOR INCLUDED STUDIES

Author, year, country	Population/ Setting	Study Design	Sample Size per group	Intervention/ exposure details	Comparison/ control details	Outcomes	BMI (kg/m2)]	Hirsutism (FGI/S)	Acne	Summary of findings
Acmaz 2013 Turkey	Hospital	Cross-sectional	C: n = 47 P/OH: n = 35 P/I: n = 22 P/W: n = 29	SF-36	SF-36	SF-36	C: 23.37 ± 3.13 P/OH: 24.45 ± 2.75 P/I: 24.35 ± 3.48 P/W: 33.59 ± 2.61	C: 0% P/OH: 60% P/I: 36.4% P/W: 37.9%	C: 6.4% P/OH: 85.7% P/I: 40.9% P/W: 55.2%	Although there were significant differences in all of these parameters compared to the healthy group, the most affected group was oligomenorrhea-hirsutism group in terms of PF, PRF, pain, SF, ERF, and EWB, but it was obesity group that was affected by GH most and it was infertility group that was affected by vitality most.
Bazarganipour 2020 Iran	Women with PCOS according to the Rotterdam criteria who attended an infertility clinic (n = 101)	Cross Sectional	PCOS n= 101 Control n = 100	Completed IBS-QOL	Completed IBS-QOL	IBS-QOL	PCOS: 25.52 ± 4.70 No PCOS: 24.53 ± 3.88	PCOS: 3.35 ± 3.15 No PCOS 0.58 ± 1.39	PCOS: 4.20 ± 5.01 No PCOS 1.76 ± 3.8	Having PCOS and an increased level of LH/FSH tends to cause IBS symptoms. IBS + PCOS women experience significant impaired quality of life scores particularly in relation to worries about health and food avoidance.
Benetti- Pinto 2015 Brazil	University O+G department	Cross-sectional	PCOS: 52 Control: 102	WHOQOL-BREF	WHOQOL-BREF	WHOQOL-BREF	C: 28.5 ± 5.4 P: 31.9 ± 8.5	FGI: 10.4 ± 4.5 (85.7%)	NR	Women with PCOS had a worse sexual function and self-assessment of health condition in comparison to controls. The body weight as isolated symptom was correlated to the worsening in quality of life, but not with the worsening of sexual function.
Benson 2008 Germany	Uni clinics, private practice, community	Cross-sectional	PCOS: 57 Control: 28	SF-36	SF-36	SF-36	C: 23.6 ± 0.7 P: 29.6 ± 1 (SEM)	P: 10.2 ± 5.6 (SEM)	NR	PCOS may be unique in that BMI does not appear to be the major correlate of depression. Other factors, such as infertility or hirsutism, may play a greater role in emotional well-being.
Boivin 2020 USA	Total: 120 undergraduate psychology women 18 to 41 years of age, n = 10 PCOS patients diagnosed medically in a manner consistent with	Cross Sectional	PCOS patients diagnosed medically: n = 10 Screened negative on a 12-item PCOS symptoms	Completed PCOS Quality-of-Life (PCOSQ) questionnaire,	Completed PCOS Quality-of-Life (PCOSQ) questionnaire,	PCOSQ	NA	NA	NA	The PCOS-confirmed women scored more poorly than the screen-negative (reference) and screen-positive groups on all the measures of physical, emotional, social, and spiritual well-being measures.

	evidence-based diagnostic guidelines. 2nd year psychology course at Indiana Wesleyan University, students were given the option to participate in our study for academic extra credit		inventory: n = 74 screened positive on a 12-item PCOS symptoms inventory: n = 25							
Borghi 2018 Italy	Convenience sample of 30 PCOS women referring to an outpatient clinic of Gynecological Endocrinology of a University Hospital in northern Italy during a period of four months	Cross Sectional	PCOS n= 30 Control n= 30	Completed Short Form Health Survey (SF-36)	Completed Short Form Health Survey (SF-36)	Short Form Health Survey (SF- 36)	PCOS: 33.35 ± 5.85 No PCOS: 23.46 ± 3.43	PCOS: 12.13 ± 7.51 No PCOS: 5.87 ± 3.08	NA	PCOS patients had significantly lower scores on SF-36 scales of physical functioning and bodily pain.
Coban 2019 Turkey	Female adolescents aged 13-18 years with and without PCOS from Department of medicine and local high school	Cross Sectional	adolescent with PCOS n = 28 age- and sex-matched healthy peers n = 31	Completed PedsQL	Completed PedsQL	Pediatric Quality of Life Inventory (PedsQL)	PCOS: 22.68 ± 5.21 No PCOS: 20.06 ±1.83	NA	NA	There were no significant differences in the PCOS and control groups in terms of PedsQL scores.
Donbaloglu 2022 Turkey	100 participants aged 13-18 yr were included in the study. Adolescent girls who were diagnosed with PCOS and admitted to the pediatric endocrinology clinic of Çiğli Regional Training Hospital and Akdeniz University Hospital.	Cross Sectional	PCOS group, n=51 control group, n=49	Completed PedsQL	Completed PedsQL	Pediatric Quality of Life Inventory (PedsQL)	PCOS: 24.3 ± 5.1 No PCOS: 20.6 ± 2.48	PCOS: 26 (51%) No PCOS: NA	PCOS: 12 (23.5%) No PCOS: NA	Adolescent girls diagnosed with PCOS demonstrated higher depressive and anxiety symptoms and lower psychosocial quality of life scores than their healthy counterparts
Drosdzol 2007 Poland	Uni O&G/ GE clinics,	Cross-sectional	PCOS: n=50 Control: n=40	SF-36	SF-36	SF-36	C: 22.1 ± 2.9 P: 24.6 ± 3.8	C: 2.7 ± 2.1 P: 12.7 ± 6.1	NR	Quality of life parameters for women with PCOS were lower than for the controls in the aspect of: general health, limitations due to physical health, limitations due to emotional problems, social functioning, energy/fatigue and emotional wellbeing. Studied women showed worse marital sexual functioning. PCOS decreases quality of life and marital sexual functioning among women. A negative effect of hirsutism

										severity on general well-being and marital sexual life is also observed.
Elsenbruch 2003 Germany	Uni clinic & employees	Case-control	PCOS: n= 50 Control: n=50	German SF- 36	German SF-36	German SF- 36	C: 24.4 ± 5.3 P: 30.1 ± 9.8	C: 3 ± 2 P: 12 ± 5	NR	Health related quality of life measured with the 36- revealed significantly decreased scores for physical role function, bodily pain, vitality, social function, emotional role function, and mental health in patients with PCOS.
Hahn 2005 Germany	Uni dep clinics, public ads	Case-control	PCOS: n=50 Control: n=120	SF-36	SF-36	SF-36	C: 24 ± 5.3 P: 31 ± 9.3	C: 3.0 ± 2.0 P: 9.2 ± 5.8	NR	In PCOS, changes in appearance, particularly obesity and hirsutism, reduce physical dimensions of quality-of-life
Jose 2018 India	173 subjects were recruited. average age 23.9±4.5 years. Age range 10 to 40 years	Cohort study	PCOS n= 83, controls n= 90	Completed WHOQOL-BREF	Completed WHOQOL-BREF	WHOQOL-BREF	NA	NA	NA	Women suffering from PCOS exhibit varied symptoms which affect both physical and psychological health. The key factor in management is to create awareness on the complications of the disease and the lifestyle modification to minimize severity and progression. The study findings reveal that women with PCOS showed an improved QOL post participation in awareness programs imparted by the clinical pharmacists.
Kahal 2019	PCOS were recruited from endocrine clinic. Controls via newspaper advertisement	Cross sectional	PCOS, n=19 controls n=17	Completed WHOQOL-BREF	Completed WHOQOL-BREF	WHOQOL-BREF	PCOS: 37.9 (5.0) No PCOS: 36.5 (4.6)	NA	NA	PCOS was not independently associated with reduced QoL, and/or depression, in the presence of obesity.
Kaluzna 2021 Poland	Not reported	Cross sectional	PCOS: n =190 age-matched CON: n=197	Completed WHOQOL-BREF	Completed WHOQOL-BREF	WHOQOL-BREF	PCOS: 25.46 (5.91) No PCOS: 23.14 (4.93)	PCOS: 91 (54.5) No PCOS: 12 (22.2)	PCOS: 95 (56.9) No PCOS: 12 (22.6)	There were no significant differences in the level of SS, presence of depressive symptoms, or HRQoL between PCOS and CON.
Karjula et al. 2022, Finland	Women with self-reported oligomenorrhea and hirsutism and those without aged 31-46 years	Cohort study	PCOS= 75 Control= 1,382	Completed 15-D Health Related Quality of Life Questionnaire and clinical examination	Completed 15-D Health Related Quality of Life Questionnaire and clinical examination	15-D Health Related Quality of Life score	PCOS: 27.3 ± 6.9 No PCOS: 23.8 ± 4.3	NA	NA	Quality of life was lower at ages 31 and 46 in women with PCOS than controls. PCOS was an independent risk factor for low quality of life, with decreases in quality of life in women with PCOS and other chronic conditions being similar. The risk for low quality of life in PCOS remained significant after adjusting for body mass index, hyperandrogenism, and socioeconomic status.
Kumarapeli 2011 Sri Lanka	Community in a district	Case-control	PCOS: n=146 Control: n=170	WHOQOL-BREF, GHQ30	WHOQOL-BREF, GHQ30	WHOQOL-BREF, GHQ30	C: NR P: BMI ≥ 25: 43.8% BMI ≥ 30: 17.8%	C: NR P: 53.4%	C: NR P: 25.3%	PCOS occurring in South Asians adversely affects their psychological wellbeing and HRQoL. Their psychological distress is related to hirsutism rather than to obesity, which affects white Europeans with PCOS.

Kutlu et al. 2020, Turkey	Individuals diagnosed with hirsutism, unknown	Cross-sectional	PCOS: n= 16 Controls: n= 41	Completed Dermatologist Life Quality Index Questionnaire	Completed Dermatologist Life Quality Index Questionnaire	Dermatologist Life Quality Index	NA	NA	NA	No difference between in quality of life between individuals with PCOS and others with or without acne, seborrhea, androgenetic alopecia, menstrual irregularity, and acanthosis nigricans.
Lidaka et al, 2022, Latvia	Adolescents aged 13 and 18 years, at least a year after menarche, who attended the out-patient paediatric gynaecology clinic at the Children's Clinical University Hospital.	Case-control	PCOS: n= 63 Control: n= 66	Completed PCOSQ	Completed PCOSQ	PCOSQ score	P: 89.9 (46.7) C: 46.9 (46.3)	PCOS: 10.0 (6.0) No PCOS: 1.0 (2.3)	PCOS:20 (33.3) No PCOS: 3 (4.7)	The total PCOSQ score and the results in all the subscales, with the exception of one (menstrual problems), were significantly lower in the PCOS group than in the control group. Despite the PCOS group showing a significantly lower quality of life for the infertility domain than the control group, both groups recorded a high score in this domain (above 6), indicating this particular domain to be of fairly low concern in our adolescent population. The body hair domain had the lowest result (4.0) in the PCOS group.
Ozcan Dag 2015 & 2016 Turkey	Uni clinic	Cross-sectional	PCOS: n=53 Control: n =38	SF-36	SF-36	SF-36	C: 20.83 ± 3.16 P: 23.26 ± 4.44	NR	NR	Patients with PCOS had lower SF-36 physical and mental health summary scores
Ozcan et al, 2017, Turkey	Adults attending the University Gynaecology Clinic at Kirikkale University	Case-control	PCOS: n=53 Controls: n=38	Completed SF-36 questionnaire	Completed SF-36 questionnaire	SF-36 score	P: 23.26±4.44 C: 20.83±3.16	NA	NA	The PCOS patients had significantly lower mean SF-36 health summary scores.
Panico et al, 2017, Italy	Mediterranean – details not reported	Case-control	PCOS: n=100 Controls: n=40	Completed SF-36 and PCOSQ	Completed SF-36 and PCOSQ	SF-36 and PCOSQ scores	NA	NA	NA	Patients with PCOS had significantly worse quality of life compared to those without PCOS, with the greatest reduction in patients with PCOS and obesity compared to controls and those with lean PCOS.
Ramos 2016 Brazil	Uni hospital clinic	Case-control	PCOS: n=43 Control: n=51	SF-36	SF-36	SF-36	C: 25.99 ± 5.49 P: 27.91 ± 5.51	NR	NR	There was a weak correlation between social aspects of the SF-36 domain and testosterone levels in PCOS women
Rzonca et al. 2018, Poland	Women using health care services (primary care, specialist outpatient care, and inpatient/hospital	Cross-sectional	PCOS: n=250 Controls: n=254	Completed WHOQOL-BREF questionnaire	Completed WHOQOL-BREF questionnaire	WHOQOL-BREF scores - overall and domains	PCOS: 26.41 No PCOS: 24.33	NA	NA	Patients with PCOS had a lower overall QoL, worse perceived health and lower QoL in all specific domains: physical, psychological, environmental and social compared with controls.

	care) in four regions of Poland: Lublin, Podkarpacie, Pomerania, and Greater Poland Provinces.									
Sanchez-Ferrer et al, 2020, Serbia	Women attending out-patient gynaecology clinical for regular check-up at the University Clinical Hospital.	Case-control	PCOS: n=117 Control: n=153	Completed SF-36 v2	Completed SF-36 v2	Completed SF-36 v2 scores – adjusted 0-100	PCOS: 25.5 (5.9) No PCOS: 23.3 (4.3)	NA	NA	Women with PCOS scored significantly lower in the scales, except for physical functioning, social functioning and mental health.
Shafti 2016 Iran	Hospital, infertility clinics and public	Case-control	PCOS: n=129 Control: n=125	WHOQOL	WHOQOL	WHOQOL	NR	NR	NR	All of quality of life subscales except environment domain were significantly lower in PCOS than healthy group. Women with PCOS in term of some quality of life parameters have lower performance than healthy women.
Shishehgar 2016 Iran	Uni and clinics	Case-control	PCOS: n=142 Control: n=140	SF-36	SF-36	SF-36	C: 26.0 ± 4.8 P: 26.6 ± 5.7	C: 0 (0-1) P: 6 (3-10)	NR	Women with PCOS had significantly lower scores for both, the physical and the mental component summary scales, compared to controls
Stevanovic et al, 2019, Serbia	Women attending the Clinic of Endocrinology, Diabetes and Metabolic Disorders between 2016 and 2017 who were investigated for irregular menstrual bleeding, hirsutism or acne	Cross-sectional	PCOS: n=76 Control: n=28	Completed PCOSQ-50, WHOQOL-BREF and clinical assessment	Completed PCOSQ-50 and WHOQOL-BREF	PCOSQ-50 and WHOQOL-BREF scores	PCOS: 24.79 (6.24) No PCOS: 23.25 (3.19)	PCOS: 7.75 (6.23) No PCOS: 3.68 (1.79)	NA	Women with PCOS had significantly lower scores than healthy women for hirsutism, obesity and menstrual disorders and the total PCOSQ-50 scale score, but not for the psychosocial and emotional, fertility, sexual function, and coping scales.
Tan et al, 2017, China	Women aged 18-35 years from the local community and universities in Chengdu.	Cross-sectional	PCOS: n=120 Control: n= 100	Completed SF-36	Completed SF-36	SF-36 score	PCOS: 21.4 ± 3.0 No PCOS: 20.8 ± 1.9	PCOS: 3 (0, 6) No PCOS: 1 (0, 4)	PCOS: 2 (0, 4) No PCOS: 0	Patients with PCOS had decreased quality of life.
Trent 2002 USA	Primary care clinics	Cross-sectional	PCOS: n=97 Control: n=186 Adolescents	CHQ-CF87	CHQ-CF87	CHQ-CF87	C: 23.5 ± 4.2 P: 31.7 ± 8.4	C: 2.7 ± 4.8 P: 13.5 ± 9.2	C: 1.8 ± 3.2 P: 4.4 ± 4.7	Adolescents with PCOS scored lower on subscales measuring general health perceptions, physical functioning, general behavior, and limitations in family activities because of illness. Patients scored higher on the change in health in the last year subscale, and most had been diagnosed and initiated treatment for PCOS in the last

										year. Patients who had higher self-perceived severity of illness also scored lower on the general health perceptions subscale, but clinical severity was not associated with differences in HRQL.
Wang et al., 2021, The Netherlands	Women who took part in the LIFEstyle multicentre RCT between 2009 and 1012 aged 18-39 years	RCT	At baseline: PCOS n=170 Controls: n=321 At 3 and 6 months: PCOS=97 Controls=191	6-month lifestyle intervention followed by 18 months of infertility treatment (PCOS and controls)	6-month lifestyle intervention followed by 24 months of infertility treatment (PCOS and controls)	SF-36 scores	PCOS: 36.0 ± 3.5 No PCOS: 36.0 ±3.3	NA	NA	Women with PCOS and controls had similar physical and mental health quality of life scores. Physical quality of life scores were lower in women with PCOS than controls at 3 months but not at 6 months. Mental quality of life scores did not differ between groups.
C: Control, P: PCOS P/OH: PCOS oligomenorrhea-hirsutism, P/I: PCOS Infertility, P/W: PCOS obesity,										

6. FINDINGS

COMPARISONS INCLUDED:

Comparison 1. Adult women with PCOS vs controls
Intervention 1.1 Short-Form Health Survey 36 (SF 36)
Intervention 1.2 WHO Quality of Life-BREF (WHOQOL-BREF)
Intervention 1.3 PCOS Health related Quality of Life Questionnaire (PCOSQ)

Comparison 2. Adolescent females with PCOS vs controls
Intervention 2.1 Paediatric Quality of Life Inventory

COMPARISON 1: Adult women with PCOS vs control

EVIDENCE SUMMARY:

Health Related Quality of life (HRQoL) is a well-recognised and important health outcome, especially in chronic disease and relates to the patient reported physical, social and emotional effects of a condition and its associated treatments. HRQoL is patient reported subjective perception of wellbeing, has multiple dimensions and is time dependent.

Assessment is based on patient reported outcomes and can be measured through a variety of tools. Commonly used generic tools for screening HRQoL such as the Short Form -36 (SF-36)[1] and WHO- BREF[2] are limited by specificity for PCOS features and are not ideal for PCOS overall as they have a significant focus on unrelated health issues such as mobility, impact on work, pain, environment and propensity to infective illnesses. They also do not measure the impact of key dimensions of PCOS such as infertility and hirsutism. However, the use of these tools is the only way to assess QoL across women with PCOS and women without PCOS.

Condition specific tools have therefore been developed which in PCOS include the PCOSQ[3] and modified PCOSQ (MPCOSQ)[4]. The PCOSQ has 26 items, measuring emotions (8 items), body hair (5 items), weight (5 items), infertility difficulties (4 items) and menstrual problems (4 items). Each item is graded with a seven-point scale ranging from 1 (maximum impairment) to 7 (no problems or difficulties). The MPCOSQ is similar to the PCOSQ and in addition to four more items on acne. The PCOSQ-50[5] was developed to overcome the measurement shortcomings of the above questionnaire and measures PCOS-related HRQOL aspects and well-being and includes two domains important for these women, but overlooked in the previous measures, namely sexual functioning and hirsutism. The PCOSQ-50 has 50 items in six scales: psychosocial and emotional (12 items), fertility (9 items), sexual function (7 items), obesity and menstrual disorder (9 items), hirsutism (6 items), and coping (7 items). Studies in PCOS increasingly use the PCOSQ and the MPCOSQ which have also been adapted and tested in different ethnic populations including in China[6]. However, although these tools are not designed to be used to show how QoL in PCOS differs to non PCOS women, a number of studies have used them to compare PCOS and Non PCOS women.

[1] Ware Jr J E, Sherbourne C D. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. . Med Care 1992 Jun;30(6):473-83.

[2] Skevington, S. M., M. Lotfy, and K. A. O'Connell. 2004. The World Health Organization's WHOQOL-BREF quality of life assessment: Psychometric properties and results of the international field trial. A report from the WHOQOL group. Quality of Life Research 13 (2):299–310. doi:10.1023/B:QURE.0000018486.91360.00.e

[3] Cronin, L., G. Guyatt, L. Griffith, E. Wong, R. Azziz, W. Futterweit, D. Cook, and A. Dunaif. 1998. Development of a health-related quality-of-life questionnaire (PCOSQ) for women with polycystic ovary syndrome (PCOS). Journal of Clinical Endocrinology & Metabolism 83 (6):1976–87.

[4] Bazarganipour F, Ziaei S, Montazeri A, Faghihzadeh S, Frozanfard F. Psychometric properties of the Iranian version of modified polycystic ovary syndrome health-related quality-of-life questionnaire. Hum Reprod. 2012;27(9):2729-36.

[5] Nasiri-Amiri, F., F. R. Tehrani, M. Simbar, A. Montazeri, and R. A. Mohammadpour.. Healthrelated quality of life questionnaire for polycystic ovary syndrome (PCOSQ-50): Development and psychometric properties. Quality of Life Research 2016. 25 (7):1791–801. doi:10.1007/s11136-016-1232-7.

[6] Ou HT, Wu MH, Lin CY, Chen PC. Development of Chinese Version of Polycystic Ovary Syndrome Health-Related Quality of Life Questionnaire (Chi-PCOSQ). PLoS One. 2015;10(10):e0137772

Additionally, PCOS has different implications for quality of life around the globe[7] and the most significant predictors of lower perceived health status include self-esteem, body image, and sexual dysfunction[6]. It is well known that symptoms associated with PCOS have a great effect on self-perceived health, and that this is also associated with depression and anxiety. In a study regarding patient perceptions of PCOS, the most common response was that women felt "frustration" (67%), followed by "anxiety" (16.3%)8. Often worsening, as a function of the number of comorbid mental disorders9, health related quality of life is recognised as an important health outcome providing information on the physical, social and emotional impacts of a disease/disorder, such as PCOS.

Women with PCOS have been found to have a lower perceived health status (alternatively known as health-related quality of life (HRQoL)), on both on generic self-perceived health scales, such as the Short Form 36[3] and the Short Form 12[10,] as well as PCOS specific scales such as the validated PCOSQ5. The PCOSQ, developed by Cronin et al, encompasses construct addressing the physical, emotional and social consequences of the disease. This questionnaire includes five domains: emotions, body hair, weight problems, menstrual problems and infertility. Each question is associated with a seven-point scale, in which a score of 7 denotes no problems or difficulties and one indicates maximum impairment. Domain scores are calculated using the mean score of all items in a domain. Lower scores indicate a lower health status5. This questionnaire is useful to asses within group treatment or outcomes on women with PCOS, however, it is difficult to use specific PCOS scales to measure the health status of women with PCOS in comparison with other chronic conditions, or alternatively individual risk factors within groups of women with PCOS.

The PCOSQ has been validated against generic health status scales in different populations6,8,11. These studies have been mostly derived from gynaecological or infertility clinics, and usually within a specific age group. Most also do not use controls. Interesting one study has modified the PCOS specific scale comparing women with PCOS against controls specifically for acne (MPCOSQ), but predictably finding comparatively lower health status in the PCOS population[12.] Another study regarding acne also used the specific scale on 34 women from a gynaecology clinic, illustrating the worth of specific scales in a more severe PCOS population undergoing treatment, but not across less severe presentations or the general community as a whole[13].

One study by Coffey et al, specifically comparing the PCOSQ with the SF36 for women with a number of different chronic conditions, recruited twenty-two women with PCOS from an outpatient clinic and 96 control women from a family planning clinic[13]. Although women with PCOS scored lower in both summary scores of the SF-36 and in all domains of the PCOSQ, after adjusting for body mass index, the differences in health status between the groups in the SF-36 disappeared, while those in the PCOSQ remained. When compared with asthma, epilepsy, diabetes, back pain, arthritis and coronary heart disease, the PCOS group had the same or better physical health status but poorer psychological health status[13]. These results are interesting, however the use of the PCOSQ in the control group does not really suit its purpose, the sample size is quite small, and the sample is selected from a clinical population, thus reflecting a group of women with more severe presentations of PCOS.

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8 Sills ES, Perloe M, Tucker MJ, Kaplan CR, Genton MG, Schattman GL. Diagnostic and treatment characteristics of polycystic ovary syndrome: descriptive measurements of patient perception and awareness from 657 confidential self-reports. BMC Womens Health. 2001;1(1):3.

9 Gonzalez-Blanch C, Hernandez-de-Hita F, Munoz-Navarro R, Ruiz-Rodriguez P, Medrano LA, Cano-Vindel A. The association between different domains of quality of life and symptoms in primary care patients with emotional disorders. Sci Rep. 2018;8(1):11180.

10 Ware J, Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Medical Care. 1996;34(3):220-3

11 Coffey S, Bano G, Mason HD. Health-related quality of life in women with polycystic ovary syndrome: a comparison with the general population using the Polycystic Ovary Syndrome Questionnaire (PCOSQ) and the Short Form-36 (SF-36). Gynecol Endocrinol.

2006;22(2):80-6.

12 Barnard L, Ferriday D, Guenther N, Strauss B, Balen AH, Dye L. Quality of life and psychological well being in polycystic ovary syndrome. Hum Reprod. 2007;22(8):2279-86.

13 De Frene V, Verhofstadt L, Lammertyn J, Stuyver I, Buysse A, De Sutter P. Quality of Life and Body Mass Index in Overweight Adult Women with Polycystic Ovary Syndrome During a Lifestyle Modification Program. J Obstet Gynecol Neonatal Nurs. 2015;44(5):587- 99.

Another study using both the PCOSQ and the SF36 on 203 PCOS patients from an endocrinological clinic, with no controls, found SF-36 scores were significantly lower than the age- and sex-matched Australian population, including the overweight subset, and health status using the PCOSQ was similar to other published studies[14]. Other clinical studies using the PCOSQ with varying samples sizes found differing results, however these are possibly due to the age range selected. One study with 36 PCOS women aged 17-35 years found the main complaints of the patients were hirsutism and irregular menses. Menstrual and hirsutism problems were the most serious concerns followed by emotional problems on the PCOSQ[15.] Another study with 128 women with PCOS found the most common health status concern reported by women with PCOS was weight, followed in descending order by menstrual problems, infertility, emotions, and body hair[16.] A more comprehensive version of the PCOSQ, the PCOSQ-50 has been developed, as the original is thought to neglect acne and sexuality. This has been compared with the SF36 in a clinical population of 200 women with PCOS, however more studies are needed to ensure its validity[7].

Health status has also been discussed in relation to a number of different comorbidities, health and psychosocial risk factors associated with PCOS. However generally samples obtained of women with PCOS and their controls, often come from infertility or gynaecology clinics, which can only inform us about women with extreme presentations of the syndrome. One study from a gynaecological clinic, administered both the SF36 and the PCOSQ, and found that PCOS did have a negative impact on self- perceived health status even when compared with other serious health conditions[13]. When compared with asthma, epilepsy, diabetes, back pain, arthritis and coronary heart disease, it was found that the PCOS group had the same or better physical health status but poorer psychological health status.

It is noted that generic patient-reported outcome (PRO) measures underestimate the impact of polycystic ovary syndrome (PCOS) on HRQoL[17.] However, the majority of self-perceived health status literature around PCOS, concerns fertility specific or PCOS specific measurement scales, rather than generic such as the SF36 or the SF12. The women in these studies are often retained from infertility clinics. This only enables comparison within a group of affected women, such that they have PCOS or infertility, and does not enable comparison to be made with women with other chronic conditions in the community.

Short Form 36 Health Related Quality of Life

Two studies, Dag 2017 and Wang 2021 used Version 1 of the SF36[1], however Sanchez-Ferrer et al, 2020 used V2, so when combined, although both measure the Physical Component Summary (PCS) and the Mental Component Summary (MCS)– the studies were very heterogeneous. Traditionally the PCS and MCS are scored using norms-based scoring, which did not seem to be the case with the Dag 2017 study, however removing the Dag 2017 from the analysis made no difference to the heterogeneity.

Other studies reported the individual dimensions of the SF36 including Physical Function (PF), Physical Role Function (RF), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Function (SF), Emotional Role Function (RE), Mental Health (SM).

Borghi 2018 reported median scores and interquartile ranges which is a highly unusual way of reporting SF36 scores. So, the median was used for mean and standard deviations were calculated using the

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[15] Cinar N, Harmanci A, Demir B, Yildiz BO. Effect of an oral contraceptive on emotional distress, anxiety and depression of women with polycystic ovary syndrome: a prospective study. Hum Reprod. 2012;27(6):1840-5.

[16] McCook JG, Reame NE, Thatcher SS. Health-related quality of life issues in women with polycystic ovary syndrome. J Obstet Gynecol Neonatal Nurs. 2005;34(1):12-20.

[17] Malik-Aslam A, Reaney MD, Speight J. The suitability of polycystic ovary syndrome-specific questionnaires for measuring the impact of PCOS on quality of life in clinical trials. Value Health. 2010;13(4):440-6.

IQR. Panico 2017 and Borghi 2018 also did not used norms-based scoring. Combing these studies with the Sanchez-Ferrer et al, 2020 could also contribute to the high heterogeneity scores.

The World Health Organization's WHOQOL-BREF quality of life assessment (WHOQoL Bref)[2]

Seven studies including 1834 women assessed quality of life using the WHOQoL Bref, which included four domains Physical Health, Psychological Health, Social Relationships, and Environmental. These studies scored the questionnaires similarly, and used very similar versions, however some used extra questions and domains.

Quality-of-life questionnaire (PCOSQ) for women with polycystic ovary syndrome (PCOS).

Lidaka et al 2022, was concerned with adolescents median age 16 and 17, and used the PCOSQ[3] in Latvian or Russian. Panico et al 2017 used the 26 item PCOSQ with an added Acne domain. Stevanovic et al 2019 used the Serbian version PCOSQ-50, which has similar domains.

As acknowledged in guideline development meetings, quality of life is not necessarily diagnosed and instead is assessed using tools that measure the level of impairment of quality of life. Therefore, we are unable to determine the 'prevalence' of quality of life in women with PCOS as this would require evidence about the number of women diagnosed with impaired quality of life in those with and without PCOS.

Here we have compared the level/severity of impairment of quality of life in women with and without PCOS. Based on studies of low quality and certainty; and with some statistical heterogeneity, the evidence suggests that women with PCOS have lower quality of life compared to women without PCOS. This may suggest the value of quality of life assessment as part of standard care in order to address the aspects leading to reduced quality of life.

No evidence was identified by our search to determine the most effective tool to assess quality of life. A clinical expert recommendation may be made about tools used in the general population such as SF- 36 and WHOQOL or the PCOS specific, PCOSQ.

META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

The following summarises the meta-analysis results by health related quality of life domains.

Quality of Life – Physical

This was measured by SF36 Physical Component Summary, based on data from 1219 patients in 5 studies, SF36 Physical Function, Based on data from 1166 patients in 8 studies, as well as the WHO QoL BREF Physical Health Based on data from 1894 patients in 7 studies.

With a P<0.00001 and a heterogeneity of over 90%, evidence suggests that while scores for the SF36 quality of life domain of Physical Component Summary and as the WHO QoL BREF Physical Health are lower in women with PCOS compared to women without PCOS, high heterogeneity means the results should be interpreted with caution. The SF36 Physical Function had a P=0.08 and a heterogeneity of 60%, evidence suggests that scores for SF36 quality of life domain of Physical Component Summary are lower in women with PCOS compared to women without PCOS, but this is not statistically significant.

QoL Mental

This was measured by SF36 Mental Component summary based on data from 1219 patients in 5 studies, the SF36 Mental Health, cased on data from 1166 patients in 8 studies and the WHO QoL BREF Psychological Health, based on data from 1894 patients in 7 studies.

With a P<0.00001 and a heterogeneity of over 80%, evidence suggests that while scores for the SF36 quality of life domain of Mental Component Summary, and Mental Health and as the WHO QoL BREF Psychological Health are lower in women with PCOS compared to women without PCOS, high heterogeneity means the results should be interpreted with caution.

QoL Emotions / Psychosocial

This was measured by SF36 Emotional role (RE) - High better, Based on data from 1166 patients in 8 studies, SF36 Social function (SF) -High better, Based on data from 1166 patients in 8 studies, PCOSQ Emotions (EMOT) - High better, Based on data from 330 patients in 3 studies, and WHO QoL BREF Social Relationships High better, Based on data from 1894 patients in 7 studies.

The domains from the SF36 and the WHOQol Bref, were all significant but With a high heterogeneity of 88%, evidence suggests that while scores for the SF36 quality of life domain of Emotional role rea lower in women with PCOS compared to women without PCOS, high heterogeneity means the results should be interpreted with caution. The PCOSQ Emotions domain With a P=0.08 and a heterogeneity of 66 %, evidence suggests that scores for the PCOSQ quality of life domain of Emotions are lower in women with PCOS compared to women without PCOS.

QoL Environment

This was measured by the WHO QoL BREF Environment High better, based on data from 1894 patients in 7 studies. With a P<0.00001 and a heterogeneity of 96 %, evidence suggests that while scores for the WHO QoL BREF quality of life domain of Environment are lower in women with PCOS compared to women without PCOS high heterogeneity means the results should be interpreted with caution.

QoL Bodily pain

This was measured by the SF36 Bodily pain (BP) based on data from 1166 patients in 8 studies. With a P=0.0008 and a heterogeneity of 86 %, evidence suggests that while scores for the SF36 quality of life domain of Bodily pain are lower in women with PCOS compared to women without PCOS high heterogeneity means the results should be interpreted with caution.

QoL General Health

This was measured by the SF36 General health (GH) based on data from 1166 patients in 8 studies, With a P<0.00001 and a heterogeneity of 91 %, evidence suggests that while scores for the SF36 quality of life domain of General health are lower in women with PCOS compared to women without PCOS high heterogeneity means the results should be interpreted with caution.

QoL Vitality

This was measured by the SF36 Vitality (VT) based on data from 1166 patients in 8 studies. With a P=0.007 and a heterogeneity of 80%, evidence suggests that while scores for the SF36 quality of life domain of Vitality are lower in women with PCOS compared to women without PCOS high heterogeneity means the results should be interpreted with caution.

QoL Hirsutism

This was measured by the PCOSQ Hirsutism (HIRS) based on data from 1166 patients in 8 studies, With a P<0.00001 and a heterogeneity of 96%, evidence suggests that while scores for the PCOSQ quality of life domain of Hirsutism are lower in women with PCOS compared to women without PCOS high heterogeneity means the results should be interpreted with caution.

QoL Body Weight

This was measured by the PCOSQ Body Weight (BW) based on data from 1166 patients in 8 studies, With a P<0.00001 and a heterogeneity of 97%, evidence suggests that while scores for the PCOSQ quality of life domain of Body Weight are lower in women with PCOS, compared to women without PCOS, high heterogeneity means the results should be interpreted with caution.

QoL Infertility

This was measured by the PCOSQ Infertility (INF) based on data from 1166 patients in 8 studies, With a P<0.00001 and a heterogeneity of 98%, evidence suggests that scores for the PCOSQ quality of life domain of Infertility are lower in women with PCOS compared to women without PCOS.

QoL Menstrual Disorders

This was measured by the PCOSQ Menstrual Disorders (MD) based on data from 1166 patients in 8 studies, With a P<0.00001 and a heterogeneity of 98%, evidence suggests that while scores for the PCOSQ quality of life domain of Menstrual Disorders are lower in women with PCOS compared to women without PCOS high heterogeneity means the results should be interpreted with caution.

Outcome or Subgroup	Studies	n	Effect Estimate; OR [95% CI], M-H, random	P	Favours	Certainty
SF-36 Physical Component Summary (PCS)	5[1]	1219	1.28 [-2.38,-0.17]	P<0.00001 I^2= 98%	Lower scores in PCOS	⊕⊕◯◯ LOW
SF-36 Mental Component Summary (MCS)	5[1]	1219	-1.63 [-3.15,-0.11]	P<0.00001 I^2 =99%	Lower scores in PCOS	⊕◯◯◯ VERY LOW
SF-36 Physical Function (AF)	8[2]	1166	-0.52 [-0.86,-0.17]	P<0.0001 I^2 = 78%	Lower scores in PCOS	⊕⊕◯◯ LOW
SF-36 Physical Role Function (RF)	8[2]	1166	-0.74 [-1.28,-0.19]	P<0.00001 I^2 = 94%	Lower scores in PCOS	⊕◯◯◯ VERY LOW
SF-36 Bodily Pain (BP)	8[2]	1166	-0.80 [-1.52,-0.08]	P<0.00001 I^2 = 97%	Lower scores in PCOS	⊕⊕◯◯ LOW
SF-36 General Health (GH)	8[2]	1166	-1.02 [-1.93,-0.11]	P<0.00001 I^2 = 98%	Lower scores in PCOS	⊕⊕◯◯ LOW
SF-36 Vitality (VT)	8[2]	1166	-0.80 [-1.07,-0.53]	P<0.00001 I^2 = 78%	Lower scores in PCOS	⊕⊕◯◯ LOW
SF-36 Social Function (SF)	8[2]	1166	-0.77 [-1.68, 0.13]	P<0.00001 I^2 = 98%	Lower scores in PCOS	⊕◯◯◯ VERY LOW
SF-36 Emotional Role Function (RE)	8[2]	1166	-0.86 [-1.27,-0.46]	P<0.00001 I^2 = 90%	Lower scores in PCOS	⊕◯◯◯ VERY LOW
SF-36 Mental Health (SM)	8[2]	1166	-1.56 [-2.66,-0.46]	P<0.00001 I^2= 98%	Lower scores in PCOS	⊕⊕◯◯ LOW
WHOQOL-BREF Physical Health	7[3]	1834	-0.28 [-0.52,-0.04]	P<0.00001 I^2 = 83%	Lower scores in PCOS	⊕⊕◯◯ LOW
WHOQOL-BREF Psychological Health	7[3]	1834	-0.46 [-0.79,-0.12]	P<0.00001 I^2 = 91%	Lower scores in PCOS	⊕⊕◯◯ LOW

WHOQOL-BREF Social Relationships	7[3]	1834	-0.32 [-0.62-,0.03]	P<0.00001 I^2 = 89%	Lower scores in PCOS	⊕⊕◯◯ LOW
WHOQOL-BREF Environmental:	7[3]	1834	-0.34 [-0.73,0.05]	P<0.00001 I^2 =94%	Lower scores in PCOS	⊕⊕◯◯ LOW
PCOS Health related Quality of Life Questionnaire (PCOSQ) Total	2[4]	233	-0.96 [-1.46,-0.46]	P=0.08 I^2 = 66%	No difference	⊕⊕◯◯ LOW
PCOSQ score Emotions (EMOT)	3[5]	330	-1.65 [-2.93,-0.36]	P<0.00001 I^2 = 96%	Lower scores in PCOS	⊕◯◯◯ VERY LOW
PCOSQ score Hirsutism (HIRS)	3[5]	330	-2.09 [-3.49,-0.70]	P<0.00001 I^2 = 96%	Lower scores in PCOS	⊕◯◯◯ VERY LOW
PCOSQ score Body Weight (BW)	3[5]	330	-1.79 [-3.45,-0.12]	P<0.00001 I^2 = 97%	Lower scores in PCOS	⊕◯◯◯ VERY LOW
PCOSQ score Infertility (INF)	3[5]	330	-1.66 [-3.44,-0.11]	P<0.00001 I^2 = 98%	Lower scores in PCOS	⊕◯◯◯ VERY LOW
PCOSQ score Menstrual Disorders (MD)	3[5]	330	-1.63 [-3.45,0.19]	P<0.00001 I^2 = 98%	Lower scores in PCOS	⊕◯◯◯ VERY LOW

Benson 2008, Dag et al, 2015, 2016,2017 (V1), Sanchez-Ferrer et al, 2020 (V2), Shishehgar 2016, Wang et al, 2021 (V1).
Borghi 2018 (V1), Drosdzol 2007, Elsenbruch 2003, Hahn 2005, Panico et al 2017 (V1), Ramos 2016, Sanchez- Ferrer et al, 2020 (V2), Shishehgar 2016.
Benetti-Pinto 2015,Jose 2018, Kahal 2019, Kaluzna 2021, Kumarapeli 2011, Rzonca 2018, Shafti 2016
Lidaka et al, 2022, (Adolescents), Stevanovic et al, 2019 (PCOSQ-50)
Lidaka et al, 2022, (Adolescents), Panico et al 2017, Stevanovic et al, 2019 (PCOSQ-50)

OUTCOME 1.1. Short-Form Health Survey 36 (SF 36)

Individual Study Data Tables

OUTCOME: SF36 V1 and V2					**OUTCOME TYPE: Continuous**				
Comparison: Adult women with PCOS vs control									
Author, year	**Method of measurement**	**Mean (specify if median) in intervention / exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Acmaz 2013	SF36 Physical functioning Vitality Bodily pain General health Social functioning Physical role functioning Emotional role functioning Mental health	 Medians only Medians only Medians only Medians only Medians only P/OH: 70.8 P/I: 73.5 P/W: 79.8 P/OH: 75.2 P/I: 79.0 P/W: 79.6 P/OH: 58.2 P/I: 61.0 P/W: 66.9	 ±7.4 ±8.0 ±5.4 ±7.10 ±8.8 ±8.0 ±8.9 ±6.9 ±5.6	P/OH=35 P/I=22 P/W=29	 Medians only Medians only Medians only Medians only Medians only C: 90.7 C: 95.1 C: 79.8	 ±1.9 ±2.3 ±4.2	47	Crude	NA
Benson 2008	SF36 Physical Component Summary Mental Component Summary	 48.9 39.9	 ±15.1 ±12.1	57	 57.1 45.4	 ±3.7 ±10.6	28	Crude	NA
Borghi 2018 (V1)	SF36 Physical functioning Physical role functioning Bodily pain	**Median score** 90 100 61	**IQR** 77-96.25 75-100 48.75-84	30	**Median score** 100 100 84	**IQR** 95-100 87.5-100 74-100	30	crude	n/a

Median and IQR (converted to SD)	General health Vitality Social functioning Emotional role functioning Mental health	72 60 87 100 66	50.75-83 45-70 62-87 57.75-100 52-84		76 65 100 100 76	67-82 52.5-75 68-100 66-100 58-88			
Drosdzol 2007	SF36 Physical functioning Physical role functioning Bodily pain General health Vitality Social functioning Emotional role functioning Mental health	 89.9 73.5 64.8 46.3 57.3 70.6 67.7 57.5	 ±11.1 ±30.8 ±25.1 ±15.9 ±16.4 ±21.5 ±28.6 ±17.9	50	 93.7 87.5 72.6 60.1 71.2 82.6 95.8 69.9	 ±8.1 ±22.6 ±19.8 ±18.9 ±17.7 ±17.8 ±11.4 ±15.1	40	Crude	NA
Elsenbruch 2003	SF36 Physical functioning Physical role functioning Bodily pain General health Vitality Social functioning Emotional role functioning Mental health	 71 NR 73 NR 43 66 49 53	 ±37 NR ±30 NR ±20 ±30 ±44 ±20	50	 90 NR 85 NR 60 80 87 70	 ±21 NR ±26 NR ±20 ±27 ±27 ±18	50	Crude	NA
Hahn 2005	SF36 Physical functioning Physical role functioning Bodily pain General health Vitality Social functioning Emotional role functioning Mental health	 81 76 74 62 43 67 62 57	 ±21 ±32 ±28 ±20 ±20 ±24 ±40 ±20	50	 88 90 85 62 60 80 87 70	 ±20 ±21 ±26 ±18 ±20 ±27 ±27 ±19	120	Crude	NA
Ozcan Dag 2015 & 2016	SF36 Physical Component Summary Mental Component Summary	 67.3 52.7	 ± 12.9 ± 15.3	53	 79.6 62.6	 ± 11.8 ± 20.6	38	Crude	NA
Ozcan Dag, 2017 (V1)	SF36 V1 Physical Component Summary Mental Component Summary	 67.31 52.74	 12.91 15.29	53	 79.61 62.63	 11.85 20.56	38	crude	n/a

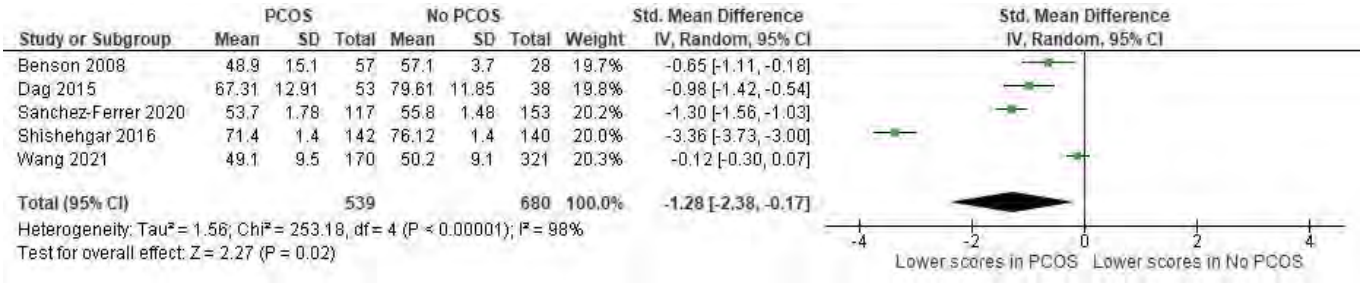
Panico 2017 (V1)	SF36 V1 Physical functioning Physical role functioning Bodily pain General health Vitality Social functioning Emotional role functioning Mental health	 90.1 80.1 94.1 72.6 53.4 57.1 52.3 47.5	 6.2 16.3 6.2 6.5 12.1 23.8 27.6 13.7	50	 97.3 86.9 95.0 74.9 65.2 77.8 75.6 68.0	 6.2 5.5 7.4 1.6 2.5 8.0 6.1 3.9	50	crude	n/a
Ramos 2016	SF36 V1 Physical Component Summary Mental Component Summary	 67.3 52.7	 ± 12.9 ± 15.3	43	 79.6 62.6	 ± 11.8 ± 20.6	51	Crude	NA
Sanchez-Ferrer 2020 (V2)	SF36 V2 Physical Component Summary Mental Component Summary Physical functioning Physical role functioning Bodily pain General health Vitality Social functioning Emotional role functioning Mental health	**Median score** 53.7 44.2 53.5 50.1 51.1 48.9 51.6 47.5 44.0 45.9	**IQR/range SD** 52.5-54.9 ±1.78 42.4-46.1 ±2.74 52.3-54.6 1.70 48.8-51.5 ±2.00 49.5-52.7 ±2.37 47.4-50.5 ±2.30 50.0-53.2 ±2.37 45.7-49.3 ±2.67 42.2-45.9 ±2.74 44.1-47.7 ±2.60	117	**Median score** 55.8 46.2 54.4 53.3 53.3 51.8 53.8 49.0 47 47.3	**IQR/range SD** 54.8-56.8 ± 1.48 44.7-47.8 ±2.30 53.4-55.3 1.41 52.2-54.5 ±1.70 51.9-54.6 ±2.00 50.5-53.1 ±1.93 52.5-55.1 ±1.93 47.5-50.5 ±2.22 45.4-48.6 ±2.37 45.7-48.9 ±2.37	153	crude	n/a
Shishehgar 2016	SF36 V1 Physical Component Summary Mental Component Summary Physical functioning Physical role functioning Bodily pain General health Vitality Social functioning	 71.4 61.2 80.3 71.7 70.9 63.04 52.2 70.9 66.8	 ±1.4 ±1.5 ±1.9 ±2.8 ±2.1 ±1.5 ±1.3 ±2.1 ±2.8	142	 76.2 71.0 82.4 76.2 77.5 68.7 64.6 79.4 71.3±2.8	 ±1.4 ±1.5 ±1.9 ±2.8 ±2.1 ±1.6 ±1.7 ±2.1	140	Crude	NA

	Emotional role functioning Mental health	55.0	±1.9		68.8	±1.9			
Wang 2021 (V1)	SF36 V1 Physical Component Summary Mental Component Summary	 49.1 50.2	 ±9.5 ±9.1	170	 : 50.2 49.4	 ±8.5 ±10.4	321	Crude	NA

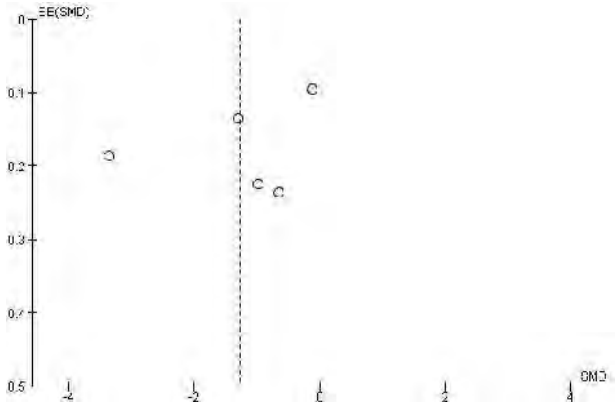
SF36: Short-Form Health Survey
Numbers are presented as mean (SD) unless otherwise stated. IQR Interquartile range

Results of original studies in meta-analyses of QoL using SF 36

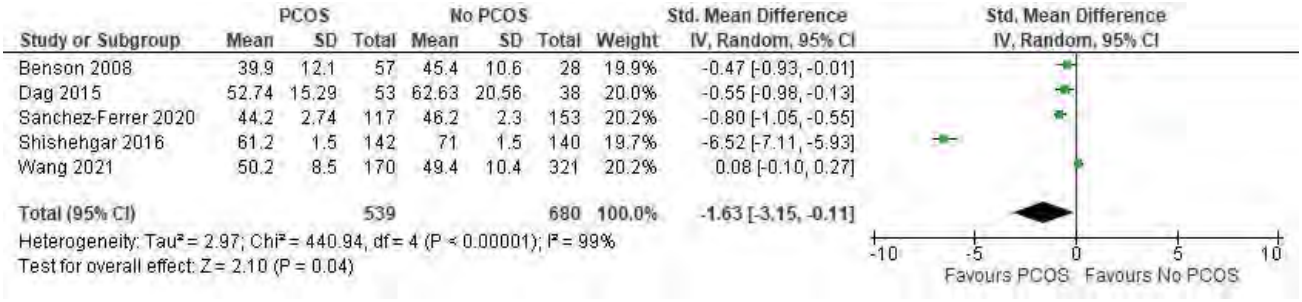
Forest plot for Physical Component Summary



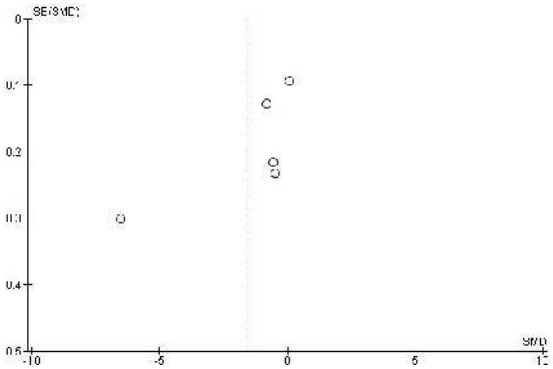
Funnel plot for assessment of publication bias for Physical Component Summary



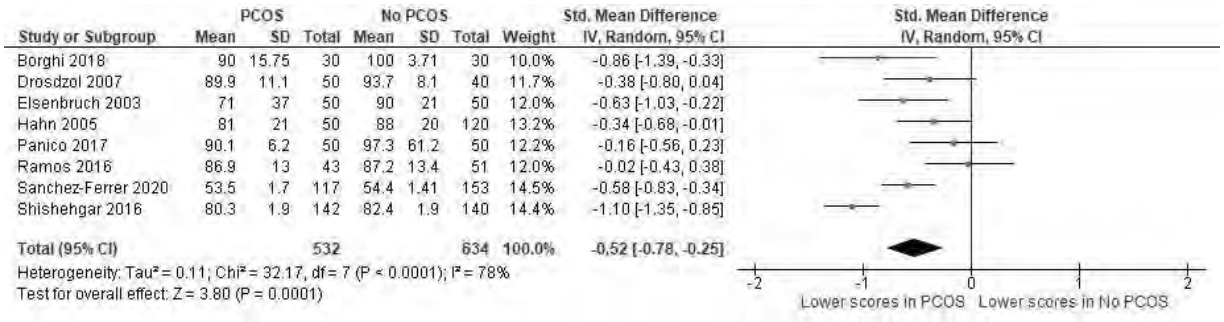
Forest plot for Mental Component Summary



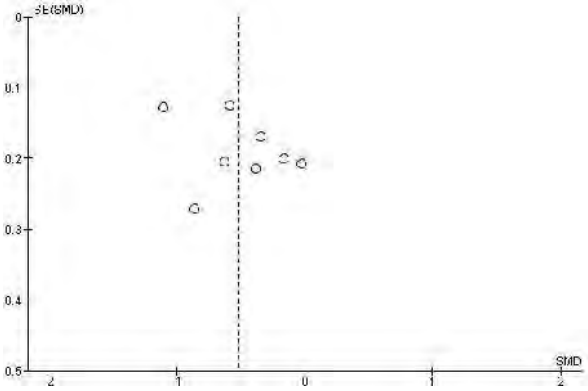
Funnel plot for assessment of publication bias for Mental Component Summary



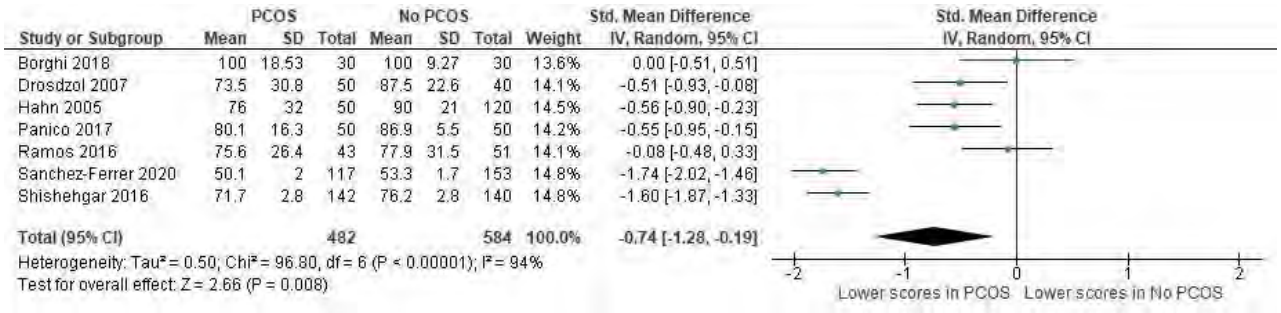
Forest plot for Physical Function



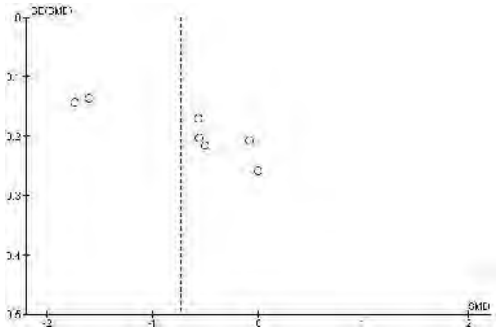
Funnel plot for assessment of publication bias for Physical Function



Forest plot for Physical Role Function



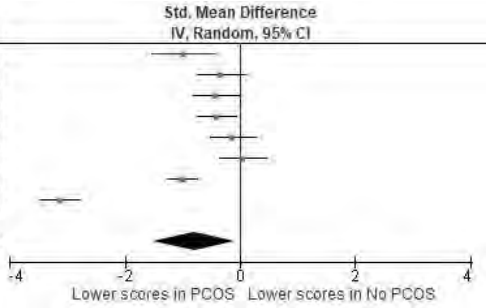
Funnel plot for assessment of publication bias for Physical Role Function



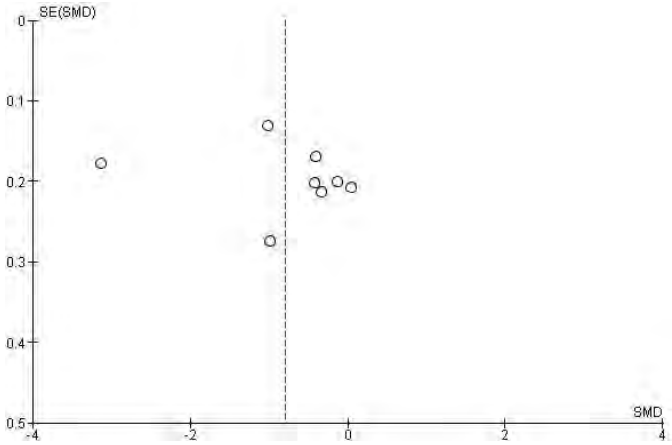
Forrest plot for Bodily Pain

Study or Subgroup	PCOS Mean	PCOS SD	PCOS Total	No PCOS Mean	No PCOS SD	No PCOS Total	Weight	Std. Mean Difference IV, Random, 95% CI
Borghi 2018	61	26.13	30	84	19.27	30	12.1%	-0.99 [-1.53, -0.45]
Drosdzol 2007	64.8	25.1	50	72.6	19.8	40	12.4%	-0.34 [-0.76, 0.08]
Elsenbruch 2003	73	30	50	85	26	50	12.5%	-0.42 [-0.82, -0.03]
Hahn 2005	74	28	50	85	26	120	12.6%	-0.41 [-0.74, -0.08]
Panico 2017	94.1	6.2	50	95	7.4	50	12.5%	-0.13 [-0.52, 0.26]
Ramos 2016	68.6	23.2	43	67.6	21.6	51	12.5%	0.04 [-0.36, 0.45]
Sanchez-Ferrer 2020	51.1	2.37	117	53.3	2	153	12.8%	-1.01 [-1.27, -0.76]
Shishehgar 2016	70.9	2.1	142	77.5	2.1	140	12.6%	-3.13 [-3.48, -2.78]
Total (95% CI)			**532**			**634**	**100.0%**	**-0.80 [-1.52, -0.08]**

Heterogeneity: Tau² = 1.04; Chi² = 213.80, df = 7 (P < 0.00001); I² = 97%
Test for overall effect: Z = 2.18 (P = 0.03)



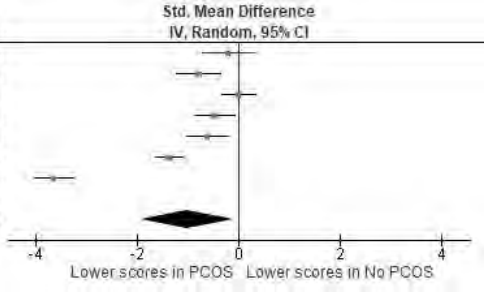
Funnel plot for assessment of publication bias for Bodily Pain



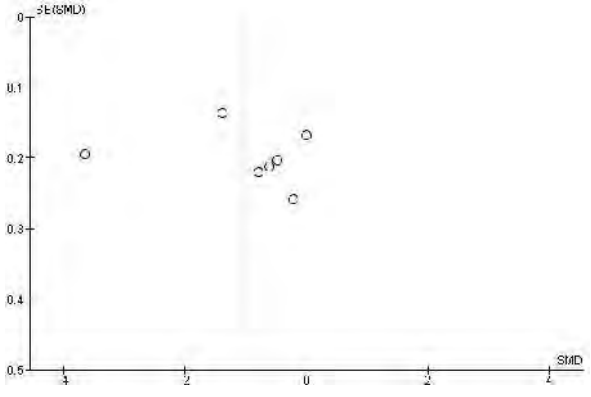
Forest plot for General Health

Study or Subgroup	PCOS Mean	PCOS SD	PCOS Total	No PCOS Mean	No PCOS SD	No PCOS Total	Weight	Std. Mean Difference IV, Random, 95% CI
Borghi 2018	72	23.91	30	76	11.12	30	14.0%	-0.21 [-0.72, 0.30]
Drosdzol 2007	46.3	15.9	50	60.1	18.9	40	14.2%	-0.79 [-1.22, -0.36]
Hahn 2005	62	20	50	62	18	120	14.4%	0.00 [-0.33, 0.33]
Panico 2017	72.6	6.5	50	74.9	1.6	50	14.3%	-0.48 [-0.88, -0.08]
Ramos 2016	58.5	17.8	43	70.6	20.8	51	14.2%	-0.62 [-1.03, -0.20]
Sanchez-Ferrer 2020	48.9	2.3	117	51.8	1.93	153	14.5%	-1.38 [-1.65, -1.11]
Shishehgar 2016	63.04	1.5	142	68.7	1.6	140	14.3%	-3.64 [-4.02, -3.26]
Total (95% CI)			**482**			**584**	**100.0%**	**-1.02 [-1.93, -0.11]**

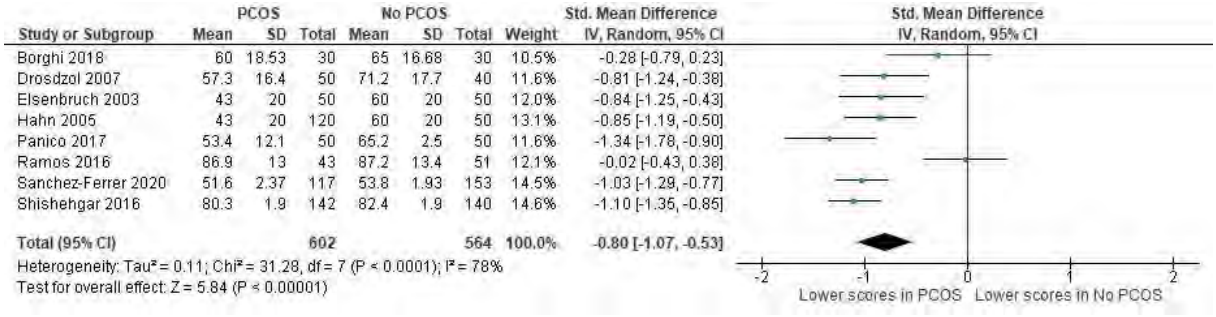
Heterogeneity: Tau² = 1.46; Chi² = 244.82, df = 6 (P < 0.00001); I² = 98%
Test for overall effect: Z = 2.21 (P = 0.03)



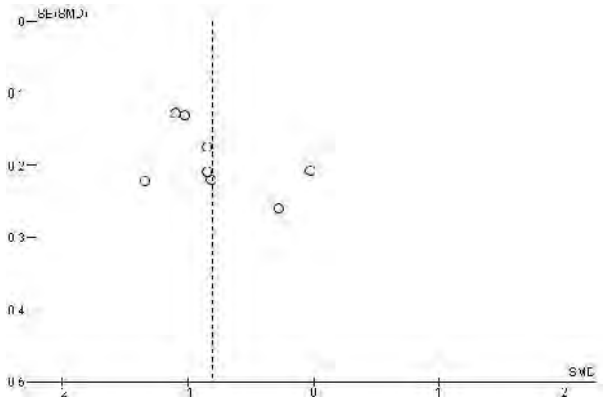
Funnel plot for assessment of publication bias for General Health



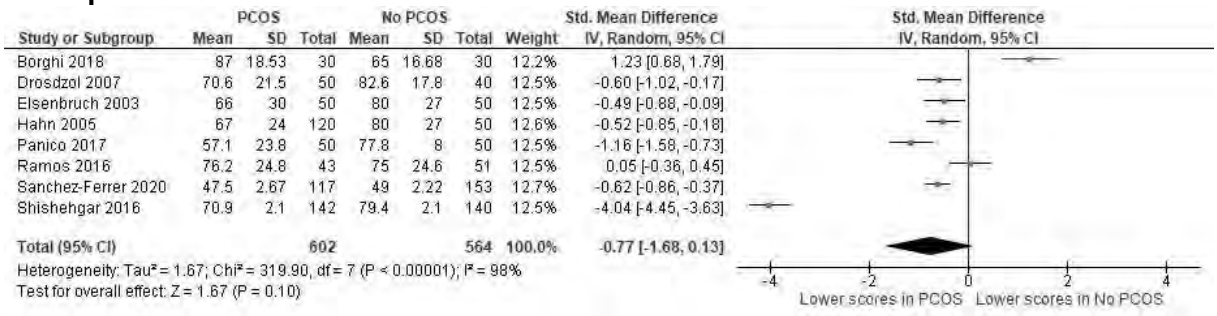
Forest plot for Vitality



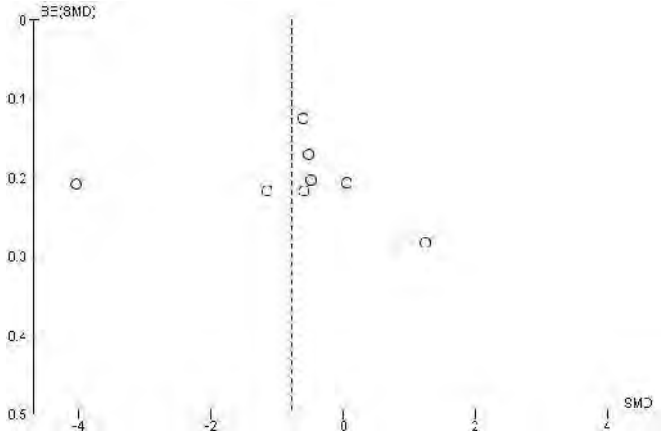
Funnel plot for assessment of publication bias for Vitality



Forest plot for Social Function



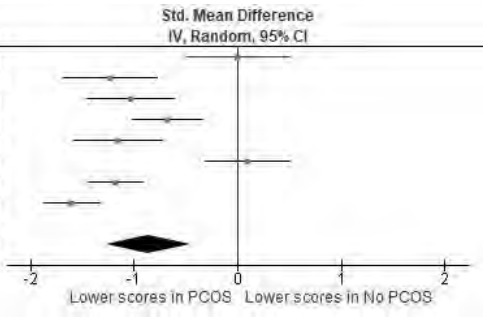
Funnel plot for assessment of publication bias for Social Function



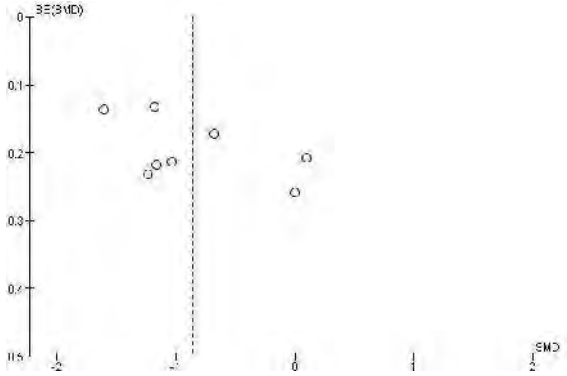
Forest plot for Emotional Role Function

Study or Subgroup	PCOS Mean	PCOS SD	PCOS Total	No PCOS Mean	No PCOS SD	No PCOS Total	Weight	Std. Mean Difference IV, Random, 95% CI
Borghi 2018	100	31.39	30	100	25.2	30	11.6%	0.00 [-0.51, 0.51]
Drosdzol 2007	67.7	28.6	50	95.8	11.4	40	12.0%	-1.23 [-1.68, -0.78]
Elsenbruch 2003	49	44	50	87	27	50	12.3%	-1.03 [-1.45, -0.61]
Hahn 2005	62	40	120	87	27	50	12.9%	-0.68 [-1.02, -0.34]
Panico 2017	52.3	27.6	50	75.6	6.1	50	12.2%	-1.16 [-1.58, -0.73]
Ramos 2016	72.8	31.1	43	69.3	38.8	51	12.4%	0.10 [-0.31, 0.50]
Sanchez-Ferrer 2020	44	2.74	117	47	2.37	153	13.4%	-1.18 [-1.44, -0.92]
Shishehgar 2016	66.8	2.8	142	71.3	2.8	140	13.3%	-1.60 [-1.87, -1.33]
Total (95% CI)			**602**			**564**	**100.0%**	**-0.86 [-1.27, -0.46]**

Heterogeneity: Tau² = 0.30; Chi² = 69.23, df = 7 (P < 0.00001); I² = 90%
Test for overall effect: Z = 4.17 (P < 0.0001)



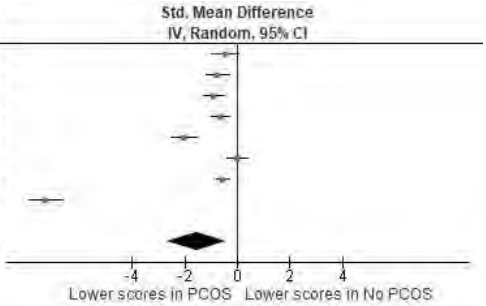
Funnel plot for assessment of publication bias for Emotional Role Function



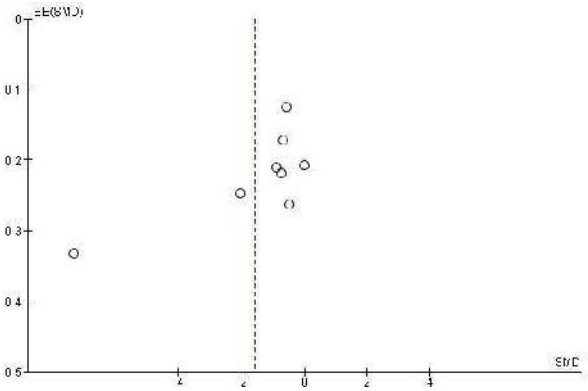
Forest plot for Mental Health

Study or Subgroup	PCOS Mean	PCOS SD	PCOS Total	No PCOS Mean	No PCOS SD	No PCOS Total	Weight	Std. Mean Difference IV, Random, 95% CI
Borghi 2018	66	19.27	30	76	22.24	30	12.4%	-0.47 [-0.99, 0.04]
Drosdzol 2007	57.5	17.9	50	69.9	15.1	40	12.5%	-0.74 [-1.17, -0.31]
Elsenbruch 2003	53	20	50	70	18	50	12.5%	-0.89 [-1.30, -0.48]
Hahn 2005	57	20	120	70	19	50	12.6%	-0.66 [-0.99, -0.32]
Panico 2017	47.5	13.7	50	68	3.9	50	12.5%	-2.02 [-2.50, -1.53]
Ramos 2016	68.4	23.9	43	68.2	20.5	51	12.5%	0.01 [-0.40, 0.41]
Sanchez-Ferrer 2020	45.9	2.67	117	47.3	2.37	153	12.7%	-0.56 [-0.80, -0.31]
Shishehgar 2016	55	1.9	142	68.9	1.9	140	12.2%	-7.30 [-7.95, -6.65]
Total (95% CI)			**602**			**564**	**100.0%**	**-1.56 [-2.66, -0.46]**

Heterogeneity: Tau² = 2.47; Chi² = 423.53, df = 7 (P < 0.00001); I² = 98%
Test for overall effect: Z = 2.78 (P = 0.006)



Funnel plot for assessment of publication bias for Mental Health



OUTCOME 1.2. WHO Quality of Life-BREF (WHOQOL-BREF)

Individual Study Data Tables

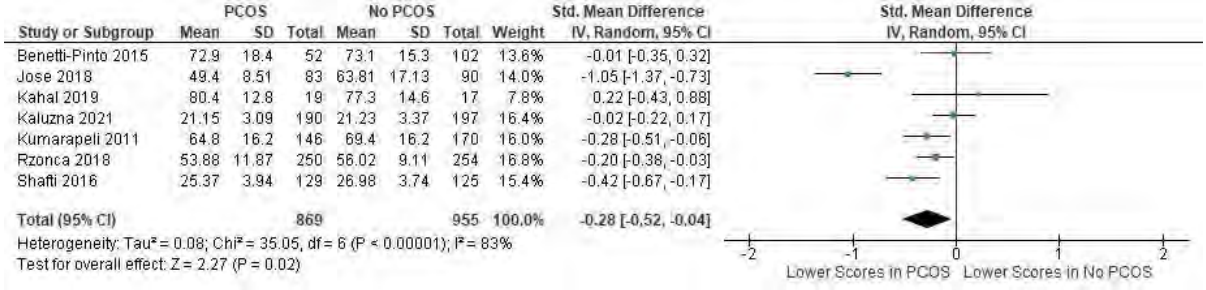
OUTCOME: WHO Quality of Life-BREF (WHOQOL-BREF)					OUTCOME TYPE: Continuous				
Comparison: Adult women with PCOS vs control									
Author, year	Method of measurement	Mean (specify if median) in intervention / exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Benetti-Pinto 2015	WHOQOL-BREF Physical health Psychological Social relationships Environment	 72.9 62.4 69.5 61.1	 18.4 19.2 20.5 13.3	 n=52	 73.1 66.6 69.5 59.9	 15.3 16.7 16.1 13.3	 N=102	 Crude	 NA
Jose 2018	WHOQOL-BREF Physical health Psychological Social relationships Environment	 49.40 43.67 48.36 47.12	 8.51 10.68 15.17 9.90	 n = 83	 63.81 65.81 66.84 66.03	 17.13 14.28 13.57 11.86	 n= 90	 Crude	 NA
Kahal 2019	WHOQOL-BREF Physical health Psychological Social relationships Environment	 80.4 59.1 73.7 71.5	 12.8 9.7 12.5 12.3	 n = 19 3	 77.3 55.7 68 73.3	 14.6 21.9 20.5 16.9	 n = 17	 Crude	 NA
Kaluzna 2021 Sexual	WHOQOL-BREF Physical health Psychological Social relationships Environment	 21.15 20.43 7.80 29.58	 3.09 3.15 1.46 4.37	 n =190	 21.23 21.00 7.78 29.77	 3.37 3.07 1.61 3.90	 n=197	 Crude	 NA
Kumarapeli 2011	WHOQOL-BREF Physical health Psychological Social relationships Environment	 64.8 64.9 60.5 60.8	16.2 17.2 21.4 17.4	 n=146	 69.4 68.8 66.8 63.3	 15.4 14.4 20.7 15.0	 n=170	 Crude	 NA

Rzonca et al, 2018	WHOQOL-BREF Physical Health Psychological Social relationships Environment	 53.88 59.88 67.12 63.35	 11.87 15.09 18.18 14.90	n = 250	 56.02 66.23 74.37 70.21	 9.11 10.27 15.90 12.61	n = 254	Crude	NA
Shafti 2016	WHOQOL-BREF Physical health Psychological Social relationships Environment	 25.37 21.59 11.24 27.61	 3.94 3.41 2.19 5.37	n=129	 26.98 22.79 12.05 28.77	 3.74 2.88 1.82 3.90	n=125	Crude	NA
Stevanovic et al, 20191	World Health Organization Quality of Life-BREF	Not reported	Not reported		Not reported	Not reported			

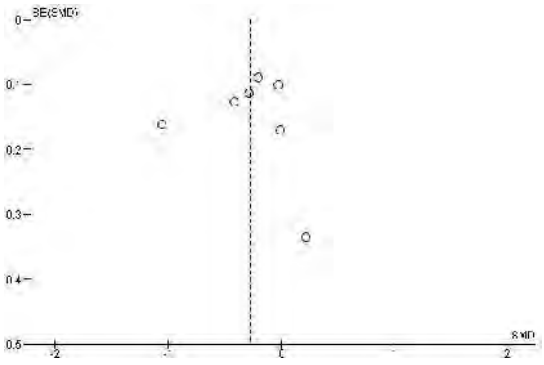
1. Stevanovic et al, 2019 not included in meta analysis as scores were not reported for the WHOQoL BREF

Results of individual studies in meta-analyses of quality of life in women with and without PCOS using WHOQOL Bref

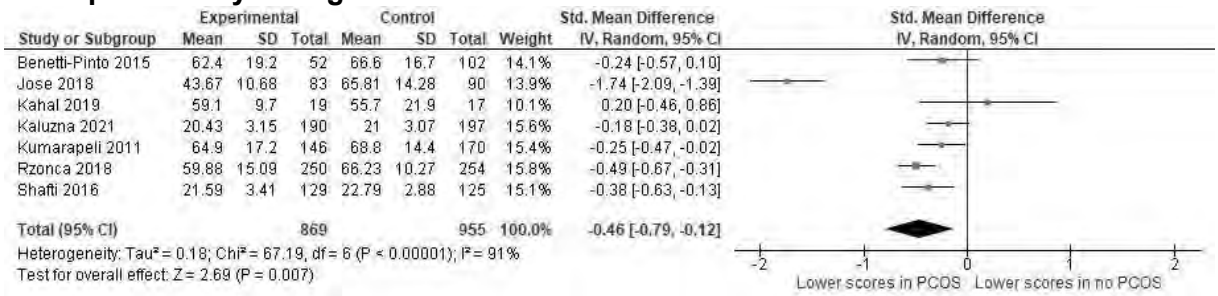
Forest plot for Physical Health:



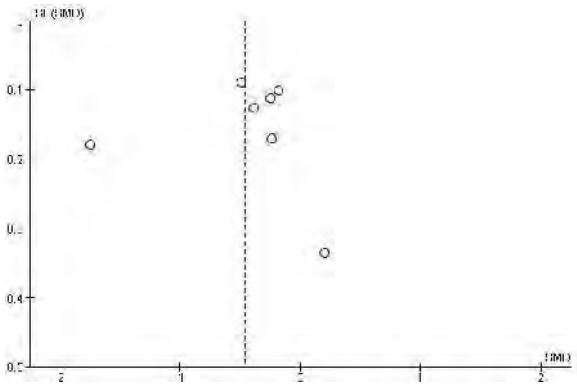
Funnel plot for assessment of publication bias for Physical Health



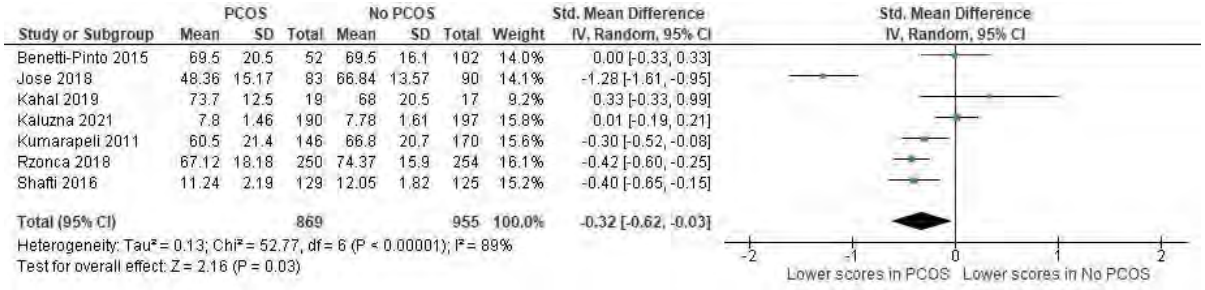
Forest plot for Psychological Health:



Funnel plot for assessment of publication bias for Psychological Health:



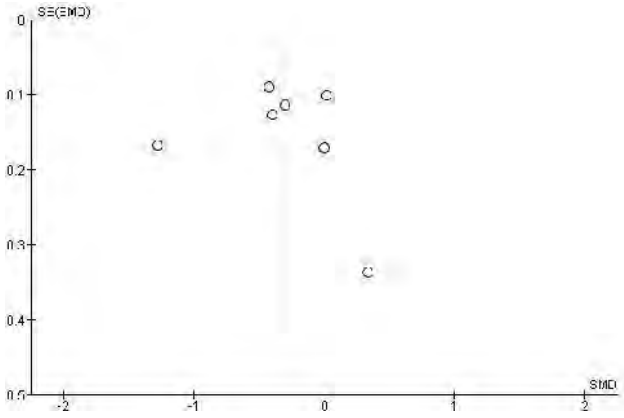
Forest plot for Social Relationships: P<0.00001 I2 = 89%



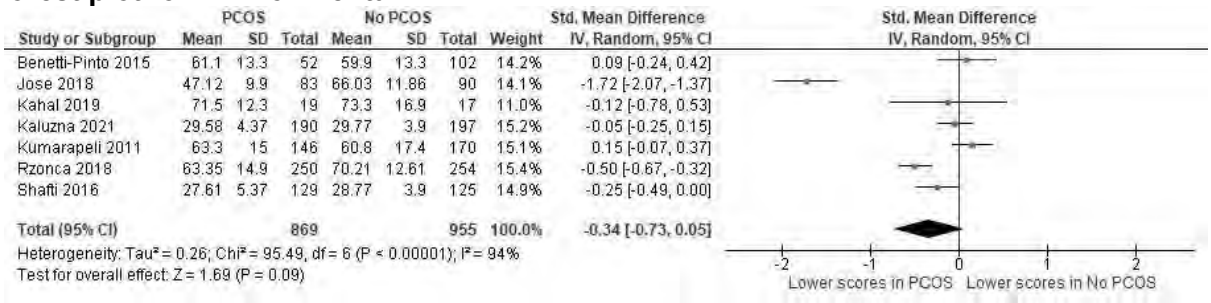
Study or Subgroup	PCOS Mean	PCOS SD	PCOS Total	No PCOS Mean	No PCOS SD	No PCOS Total	Weight	Std. Mean Difference IV, Random, 95% CI
Benetti-Pinto 2015	69.5	20.5	52	69.5	16.1	102	14.0%	0.00 [-0.33, 0.33]
Jose 2018	48.36	15.17	83	66.84	13.57	90	14.1%	-1.28 [-1.61, -0.95]
Kahal 2019	73.7	12.5	19	68	20.5	17	9.2%	0.33 [-0.33, 0.99]
Kaluzna 2021	7.8	1.46	190	7.78	1.61	197	15.8%	0.01 [-0.19, 0.21]
Kumarapeli 2011	60.5	21.4	146	66.8	20.7	170	15.6%	-0.30 [-0.52, -0.08]
Rzonca 2018	67.12	18.18	250	74.37	15.9	254	16.1%	-0.42 [-0.60, -0.25]
Shafti 2016	11.24	2.19	129	12.05	1.82	125	15.2%	-0.40 [-0.65, -0.15]
Total (95% CI)			869			955	100.0%	-0.32 [-0.62, -0.03]

Heterogeneity: Tau² = 0.13; Chi² = 52.77, df = 6 (P < 0.00001); I² = 89%
Test for overall effect: Z = 2.16 (P = 0.03)

Funnel plot for assessment of publication bias for Social Relationships:



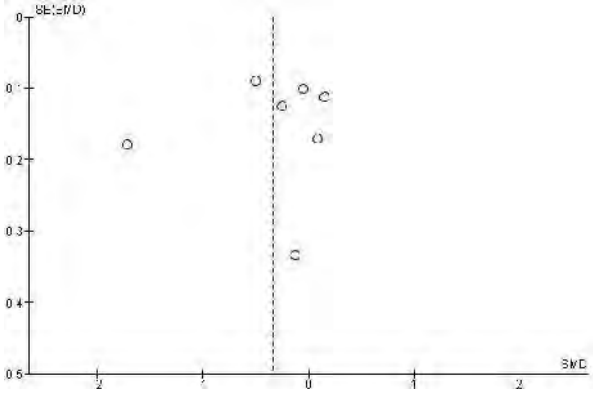
Forest plot for Environmental:



Study or Subgroup	PCOS Mean	PCOS SD	PCOS Total	No PCOS Mean	No PCOS SD	No PCOS Total	Weight	Std. Mean Difference IV, Random, 95% CI
Benetti-Pinto 2015	61.1	13.3	52	59.9	13.3	102	14.2%	0.09 [-0.24, 0.42]
Jose 2018	47.12	9.9	83	66.03	11.86	90	14.1%	-1.72 [-2.07, -1.37]
Kahal 2019	71.5	12.3	19	73.3	16.9	17	11.0%	-0.12 [-0.78, 0.53]
Kaluzna 2021	29.58	4.37	190	29.77	3.9	197	15.2%	-0.05 [-0.25, 0.15]
Kumarapeli 2011	63.3	15	146	60.8	17.4	170	15.1%	0.15 [-0.07, 0.37]
Rzonca 2018	63.35	14.9	250	70.21	12.61	254	15.4%	-0.50 [-0.67, -0.32]
Shafti 2016	27.61	5.37	129	28.77	3.9	125	14.9%	-0.25 [-0.49, 0.00]
Total (95% CI)			869			955	100.0%	-0.34 [-0.73, 0.05]

Heterogeneity: Tau² = 0.26; Chi² = 95.49, df = 6 (P < 0.00001); I² = 94%
Test for overall effect: Z = 1.69 (P = 0.09)

Funnel plot for assessment of publication bias for Environmental:



OUTCOME 1.3. PCOS Health related Quality of Life Questionnaire (PCOSQ)

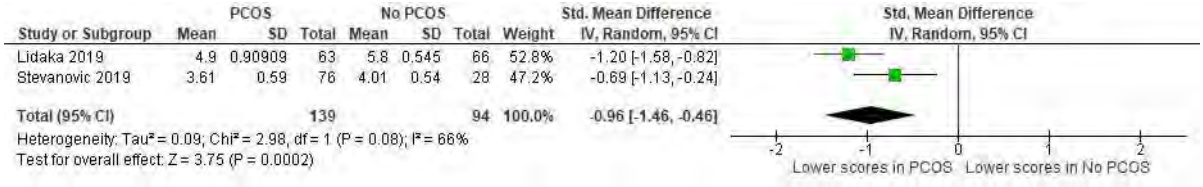
Individual Study Data Tables

OUTCOME: PCOS QOL					OUTCOME TYPE: Continuous				
Comparison: Adult women with PCOS vs control									
Author, year	**Method of measurement**	**Mean (specify if median) in exposure group**	**SD (or specify if other: IQR, SE or 95% CI) in exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control group**	**SD (or specify if other: SE, IQR or 95% CI) in control group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Boivin et al 2020[1]	PCOSQ Questionnaire score Total Total	 8.80 13.72	 5.02 3.29	n = 10 PCOS diagnosed medically n = 25 PCOS +ve	 12.67	 3.54	n = 74 PCOS -ve	Crude	NA
Lidaka et al, 2022[2]	PCOSQ Questionnaire score Total Emotions (EMOT) Hirsutism (HIRS) Body Weight (BW) Infertility (INF) Menstrual Disorders (MD)	 Median = 4.9 5.1 4.0 4.3 6.3 4.5	 IQR=1.5 1.3 2.7 3.7 1.6 1.3	n = 60	 Median=5.8 6.3 6.4 5.6 6.8 4.8	 IQR=0.9 0.5 1.4 2.1 0.5 2.1	n = 66	Crude	NA
Panico et al 2017	PCOSQ score Emotions (EMOT) Hirsutism (HIRS) Body Weight (BW) Infertility (INF) Acne Menstrual Disorders (MD)	 4.7 3.6 3.6 3.7 3.7 3.7	 1.1 1.0 1.2 1.1 1.0 1.0	n = 50	 6.7 6.2 7.0 6.9 5.6 6.5	 0.1 0.1 0.1 0.2 0.3 0.1	n = 50	Crude	NA
Stevanovic et al, 2019	PCOSQ-50 score Total Psychosocial and emotional Fertility Sexual function	 3.61 3.76 3.88 3.83	 0.59 0.68 0.83 0.90	n = 76	 4.01 4.03 4.15 3.83	 0.54 0.78 0.65 0.71	N = 28	NA	NA
	Obesity and menstrual disorder Hirsutism Coping	3.37 3.49 3.40	0.84 1.35 0.63		3.99 4.49 3.48	0.73 0.08 0.92			

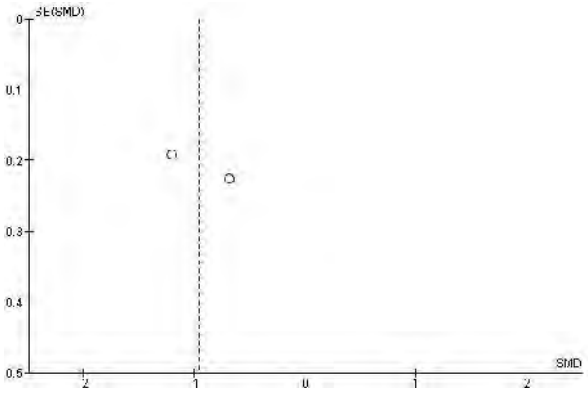
1. Boivin 2020 not included in metanalysis because 3 groups were compared, with different PCOS definitions 2. Lidaka 2022 concerns adolescent women using the PCOS-Q

Results of individual studies in meta-analyses of quality of life in women with and without PCOS using PCOSQ

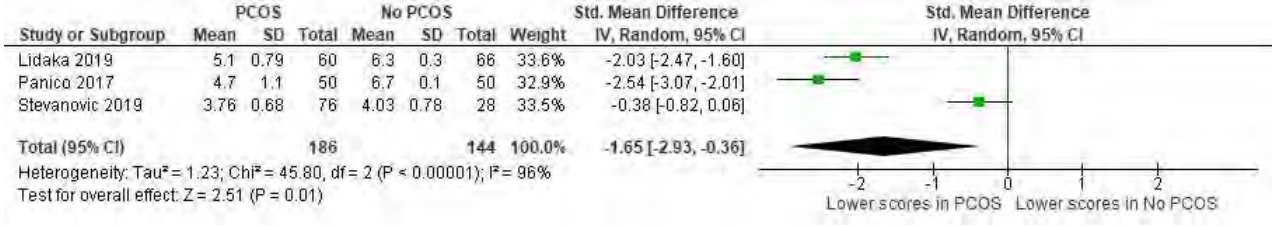
Forest Plot for Total



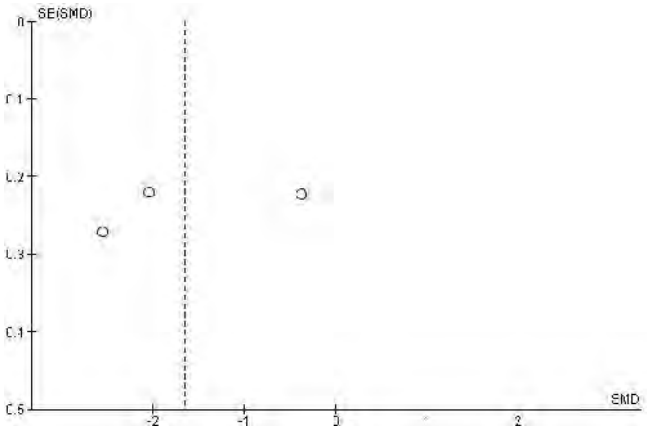
Funnel plot for assessment of publication bias for Total



Forest Plot for Emotions

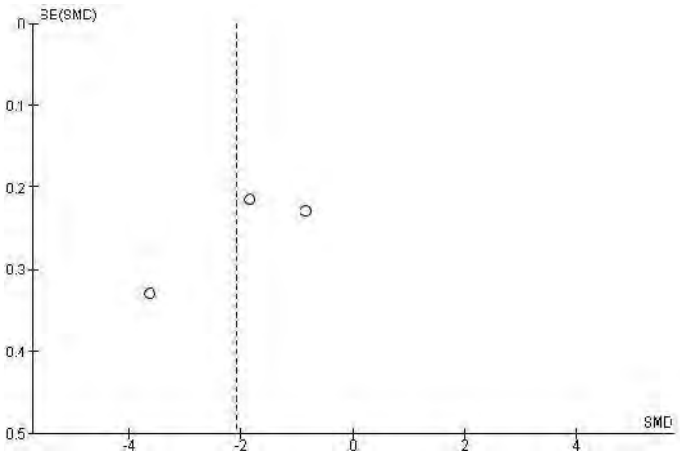


Funnel plot for assessment of publication bias for Emotions

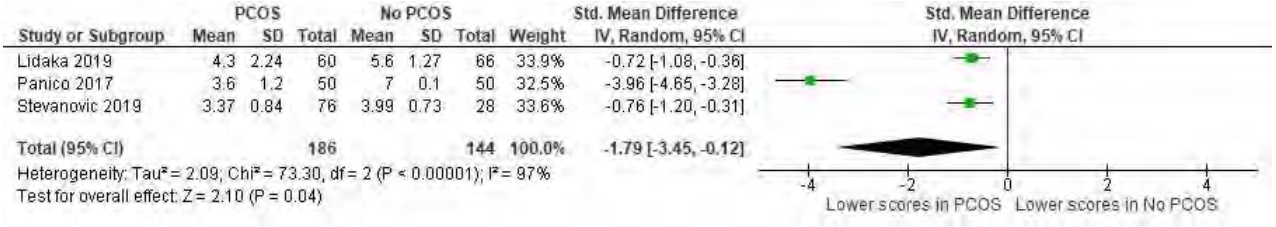


Forest Plot for Hirsutism

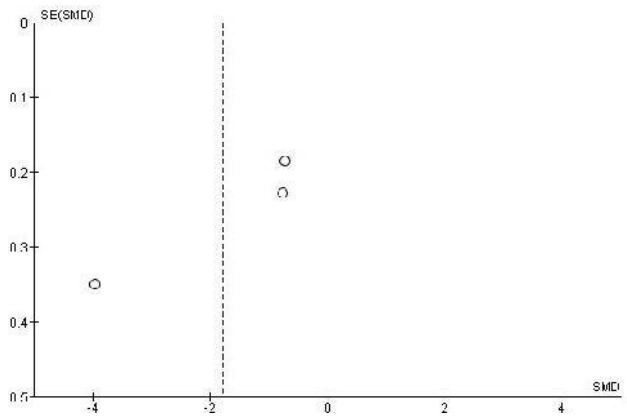
Funnel plot for assessment of publication bias for Hirsutism:



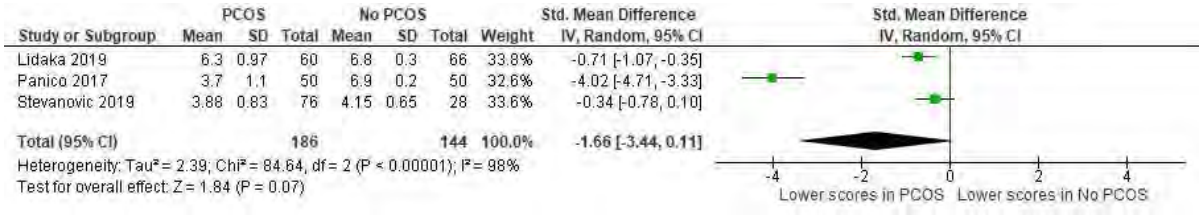
Forest Plot for Body Weight



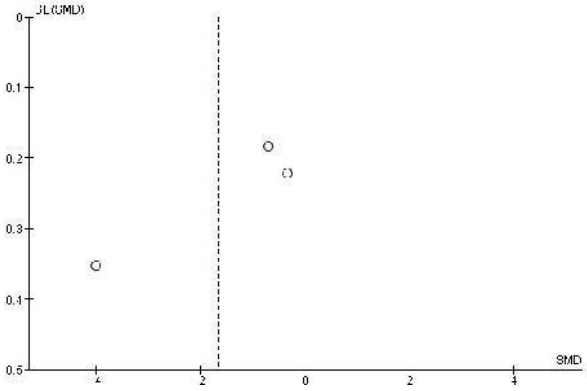
Funnel plot for assessment of publication bias for Body Weight:



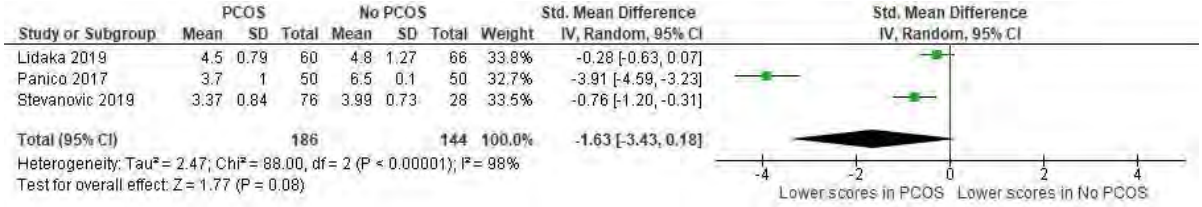
Forest Plot for Infertility: P<0.00001 I2 = 98%



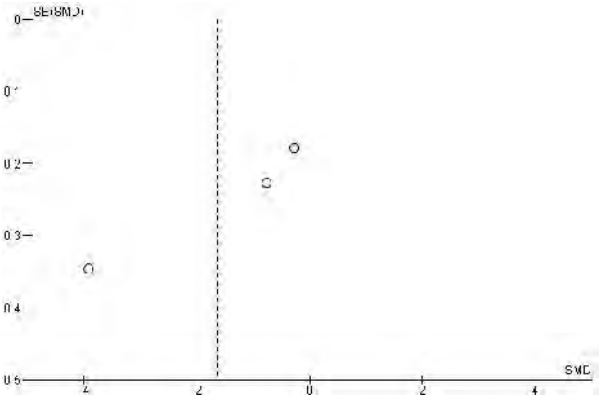
Funnel plot for assessment of publication bias for Infertility



Forest Plot for Menstrual disorders



Funnel plot for assessment of publication bias for Menstrual disorders



COMPARISON 2: Adolescent female with PCOS vs control

EVIDENCE SUMMARY:

The PEDSQL has also be used in populations of younger women with PCOS[18].
The Pediatric Quality of Life Inventory (PedsQL) questionnaires were the same for both Coban 2019 and Donbaloglu 2022.

META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

QoL Physical

Measured by PedsQL Physical Function- With a P=0.04 and a heterogeneity of 76%, evidence suggests that while scores for the PEDSQoL domain of Physical Function are lower in adolescent women with PCOS compared to adolescent women without PCOS, moderate heterogeneity means the results should be interpreted with caution.

QoL Psychosocial

Measured by PedsQL Psychosocial function and based on data from 169 patients in 2 studies. With a P=0.83 and a heterogeneity of 0 %, evidence suggests that scores for the PedsQL quality of life domain of Psychosocial function are lower in adolescent women with PCOS compared to adolescent women without PCOS.

QoL Total (Adolescence)

Measured by the PedsQL Total and based on data from 169 patients in 2 studies. With a P=0.47 and a heterogeneity of 0%, evidence suggests that while scores for the PEDsQoL total quality of life domain are lower in women with PCOS compared to women without PCOS, however this is not statistically significant.

Outcome or Subgroup	Studies	n	Effect Estimate; OR [95% CI], M-H, random	P	Favours	Certainty
Paediatric Quality of Life Inventory: Total	21	169	-0.07 [-0.37,0.23]	P=0.47 I^2 = 0%	No difference	⊕⊕◯◯ LOW
PedSQL Physical function	21	169	-0.15 [-0.79,0.48]	P=0.04 I^2 = 76%	No difference	⊕◯◯◯ VERY LOW
PedSQL Psychosocial function	21	169	-0.06 [-0.36,0.24]	P=0.83 I^2 = 0 %	No difference	⊕⊕◯◯ LOW
1. Coban 2019, Donbaloglu 2022						

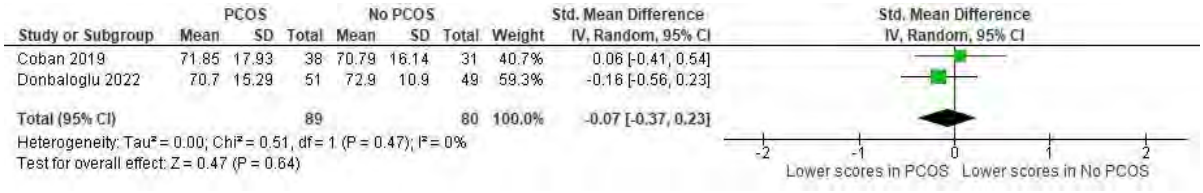
[18] Varni JW, Seid M, Rode CA: The PedsQL: measurement model for the Pediatric Quality of Life Inventory. Med Care 1999; 37:126

OUTCOME 2.1. Pediatric Quality of Life Inventory (PedSQL)
Individual Study Data Tables

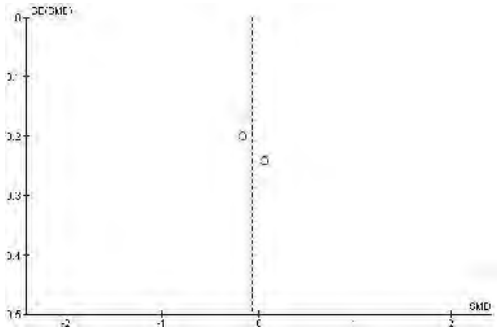
OUTCOME: Pediatric Quality of Life Inventory (PedsQL)					OUTCOME TYPE: Continuous				
Comparison: Adolescents women with PCOS vs control									
Author, year	**Method of measurement**	**Mean (specify if median) in intervention / exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Coban 2019	Pediatric Quality of Life Inventory (PedsQL) Total Physical function Psychosocial function	 71.85 72.32 71.60	 17.93 18.70 19.58	n = 38	 70.79 68.54 71.98	 16.14 22.15 15.76	n = 31	Crude	NA
Donbaloglu 2022	Pediatric Quality of Life Inventory (PedsQL) ○Total Physical function Psychosocial function	 70.70 68.29 71.40	 15.29 18.5 11.60	n = 51	 72.9 76.10 72.65	 10.90 14.55 16.41	n = 49	Crude	NA

Results of individual studies in meta-analyses of quality of life in women with and without PCOS using PedsQL

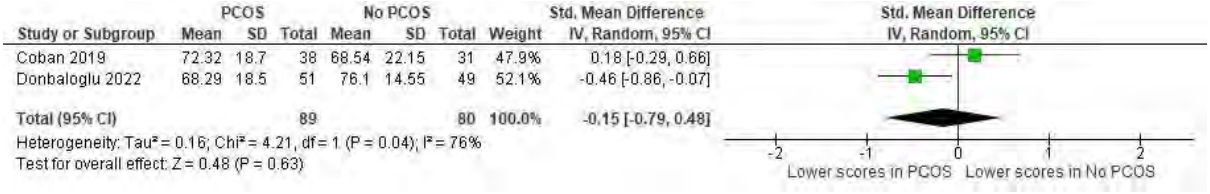
Forest Plot for Total



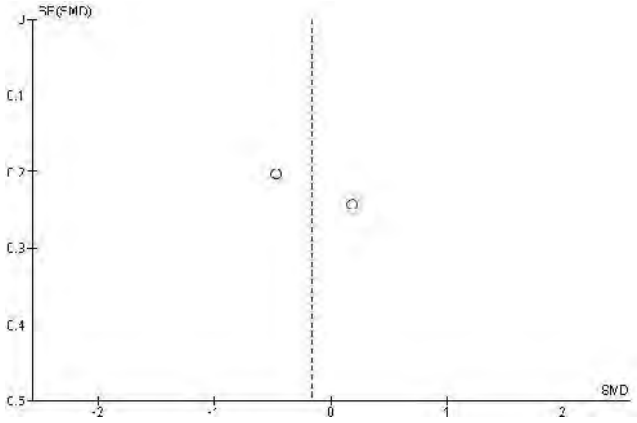
Funnel plot for assessment of publication bias for Total:



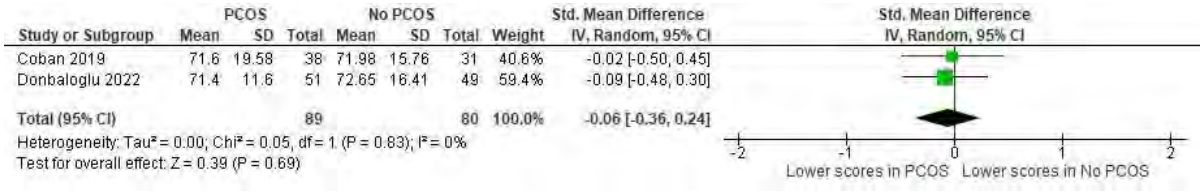
Forest Plot for Physical Function:



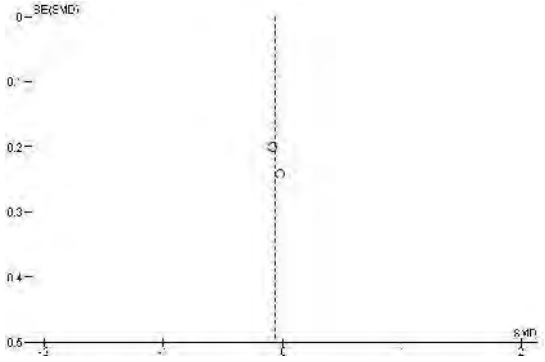
Funnel plot for assessment of publication bias for Physical Function



Forest Plot for Psychosocial Function



Funnel plot for assessment of publication bias for Psychosocial Function



7 GRADE ASSESSMENTS AND EVIDENCE PROFILE

7.1 Adult Women with PCOS

Short-Form Health Survey 36 (SF-36)

COMPARISON: PCOS vs No PCOS												
	Quality assessment						No. participants					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**PCOS**	**No PCOS**	**Effect, fixed [95% CI]** MD	**Favours**	**Certainty**	**Importance**
Outcome: SF-36 Physical Component Summary (PCS)												
5[1]	Cross-sectional studies	No serious limitations[2]	Serious Inconsistency[3]	Serious indirectness[4]	No serious Imprecision	None	539	680	-1.28 [-2.38,-0.17]	Lower scores in PCOS	⊕⊕◯◯ LOW	IMPORTANT
Outcome: SF-36 Mental Component Summary (MCS)												
5[1]	Cross-sectional studies	No serious limitations[2]	Very Serious Inconsistency[5]	Serious indirectness[4]	No serious Imprecision	None	539	680	-1.63 [-3.15,-0.11]	Lower scores in PCOS	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: SF-36 Physical Function (AF)												
8[6]	Cross-sectional studies	Serious limitations[7]	Serious Inconsistency[8]	Serious indirectness[10]	No serious Imprecision	None	532	634	-0.52 [-0.86,-0.17]	Lower scores in PCOS	⊕⊕◯◯ LOW	IMPORTANT
Outcome: SF-36 Physical Role Function (RF)												
8[6]	Cross-sectional studies	Serious limitations[7]	Very Serious Inconsistency[9]	Serious indirectness[10]	No serious Imprecision	None	532	634	-0.74 [-1.28,-0.19]	Lower scores in PCOS	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: SF-36 Bodily Pain (BP)												
8[6]	Cross-sectional studies	Serious limitations[7]	Serious Inconsistency[8]	Serious indirectness[10]	No serious Imprecision	None	532	634	-0.80 [-1.52,-0.08]	Lower scores in PCOS	⊕⊕◯◯ LOW	IMPORTANT
Outcome: SF-36 General Health (GH)												
8[6]	Cross-sectional studies	Serious limitations[7]	Serious Inconsistency[8]	Serious indirectness[10]	No serious Imprecision	None	532	634	-1.02 [-1.93,-0.11]	Lower scores in PCOS	⊕⊕◯◯ LOW	IMPORTANT
Outcome: SF-36 Vitality (VT)												
8[6]	Cross-sectional studies	Serious limitations[7]	Serious Inconsistency[8]	Serious indirectness[10]	No serious Imprecision	None	532	634	-0.80 [-1.07,-0.53]	Lower scores in PCOS	⊕⊕◯◯ LOW	IMPORTANT

Outcome: SF-36 Social Function (SF)											
8[6]	Cross-sectional studies	Serious limitations[7]	Very Serious Inconsistency[9]	Serious indirectness[10]	No serious Imprecision	None	532	634	-0.77 [-1.68,0.13]	Lower scores in PCOS	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: SF-36 Emotional Role Function (RE)											
8[6]	Cross-sectional studies	Serious limitations[7]	Very Serious Inconsistency[9]	Serious indirectness[10]	No serious Imprecision	None	532	634	-0.86 [-1.27,-0.46]	Lower scores in PCOS	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: SF-36 Mental Health (SM)											
8[6]	Cross-sectional studies	Serious limitations[7]	Serious Inconsistency[8]	Serious indirectness[10]	No serious Imprecision	None	532	634	-1.56 [-2.66,-0.46]	Lower scores in PCOS	⊕⊕◯◯ LOW	IMPORTANT

1. Benson 2008, Dag et al, 2015, 2016,2017 (V1), Sanchez-Ferrer et al, 2020 (V2), Shishehgar 2016, Wang et al, 2021 (V1).
2. Not downgraded as the majority of evidence is at low or moderate risk of bias.
3. Downgraded by one due to statistical heterogeneity.
4. Downgraded twice (very serious) due to the effect sizes (mean difference) being on different sides of the line of no effect with no overlap of CIs and statistical heterogeneity is high.
5. Downgraded by one due to outcome dissimilarity as one study used a different version of survey, and different scoring systems used

6. Borghi 2018 (V1), Drosdzol 2007, Elsenbruch 2003, Hahn 2005, Panico et al 2017 (V1), Ramos 2016, Sanchez-Ferrer et al, 2020 (V2), Shishehgar 2016**.**
7. Downgraded once as although the majority of evidence is at low risk of bias, one study was high.
8. Downgraded by one due to statistical heterogeneity.
9. Downgraded twice due to statistical heterogeneity, Confidence intervals vary widely/do not overlap
10. Downgraded by one due to outcome dissimilarity as one study used a different version of survey, and different scoring systems used

WHO QoL BREF

COMPARISON: PCOS vs No PCOS												
	Quality assessment						No. participants					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**PCOS**	**No PCOS**	**Effect, fixed [95% CI]** MD	**Favours**	**Certainty**	**Importance**
Outcome: WHO QoL BREF Physical Health												
7[1]	Cross-sectional or cohort studies	No serious limitations[2]	Very Serious Inconsistency[3]	Serious indirectness[4]	No serious Imprecision	None	869	955	-0.28 [-0.52,-0.04]	Lower scores in PCOS	⊕⊕◯◯ LOW	IMPORTANT
Outcome: WHO QoL BREF Psychological												
7[1]	Cross-sectional or cohort studies	No serious limitations[2]	Very Serious Inconsistency[3]	Serious indirectness[4]	No serious Imprecision	None	869	955	-0.46 [-0.79,-0.12]	Lower scores in PCOS	⊕⊕◯◯ LOW	IMPORTANT
Outcome: WHO QoL BREF Social relationships												
7[1]	Cross-sectional or cohort studies	No serious limitations[2]	Very Serious Inconsistency[3]	Serious indirectness[4]	No serious Imprecision	None	869	955	-0.32 [-0.62-,0.03]	Lower scores in PCOS	⊕⊕◯◯ LOW	IMPORTANT
Outcome: WHO QoL BREF Environment												
7[1]	Cross-sectional or cohort studies	No serious limitations[2]	Serious Inconsistency[5]	Serious indirectness[4]	No serious Imprecision	None	869	955	-0.34 [-0.73,0.05]	Lower scores in PCOS	⊕⊕◯◯ LOW	IMPORTANT

1. Benetti-Pinto 2015,Jose 2018, Kahal 2019, Kaluzna 2021, Kumarapeli 2011, Rzonca 2018, Shafti 2016
2. Not downgraded as the majority of evidence is at low or moderate risk of bias.
3. Downgraded twice (very serious) due to the effect sizes (mean difference) being on different sides of the line of no effect with no overlap of CIs and statistical heterogeneity is high.
4. Downgraded by one due to outcome dissimilarity as one study used a different scoring system used
5. Downgraded by one due to statistical heterogeneity.

PCOS Health Related Quality of Life Questionnaire (PCOSQ)

COMPARISON: PCOS vs No PCOS												
	Quality assessment						No. participants					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**PCOS**	**No PCOS**	**Effect, fixed [95% CI]** MD	**Favours**	**Certainty**	**Importance**
Outcome: PCOSQ Total												
2[1]	Cross-sectional studies	No serious limitations[2]	Serious Inconsistency[3]	Serious Indirectness[4]	No serious Imprecision	None	139	94	-0.96 [-1.46,-0.46]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: PCOSQ Emotions (EMOT),												
3[5]	Cross-sectional studies	Serious limitations[6]	Very Serious Inconsistency[7]	Serious Indirectness[8]	No serious Imprecision	None	186	144	-1.65 [-2.93,-0.36]	Lower scores in PCOS	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: PCOSQ Hirsutism (HIRS),												
3[5]	Cross-sectional studies	Serious limitations[6]	Very Serious Inconsistency[7]	Serious Indirectness[8]	No serious Imprecision	None	186	144	-2.09 [-3.49,-0.70]	Lower scores in PCOS	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: PCOSQ Body Weight (BW)												
3[5]	Cross-sectional studies	Serious limitations[6]	Very Serious Inconsistency[7]	Very Serious Indirectness[9]	No serious Imprecision	None	186	144	-1.79 [-3.45,-0.12]	Lower scores in PCOS	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: PCOSQ Infertility (INF),												
3[5]	Cross-sectional studies	Serious limitations[6]	Very Serious Inconsistency[7]	Serious Indirectness[8]	No serious Imprecision	None	186	144	-1.66 [-3.44,-0.11]	Lower scores in PCOS	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: PCOSQ Menstrual Disorders (MD)												
3[5]	Cross-sectional studies	Serious limitations[6]	Very Serious Inconsistency[7]	Very serious Indirectness[9]	No serious Imprecision	None	186	144	-1.63 [-3.45,0.19]	Lower scores in PCOS	⊕◯◯◯ VERY LOW	IMPORTANT

1. Lidaka et al, 2022, (Adolescents), Stevanovic et al, 2019 (PCOSQ-50)
2. Not downgraded as the majority of evidence is at moderate risk of bias.
3. Downgraded by one due to statistical heterogeneity
4. Downgraded by one due to outcome dissimilarity as one study used a different population (adolescents), and another study used a different version of survey, with different scoring systems used
5. Lidaka et al, 2022, (Adolescents), Panico et al 2017, Stevanovic et al, 2019 (PCOSQ-50)
6. Downgraded by one due to the majority of evidence is at moderate to high risk of bias.
7. Downgrade twice (very serious) due to the effect sizes (mean difference) having no overlap of CIs and statistical heterogeneity is high
8. Downgraded by one due to outcome dissimilarity as one study used a different population (adolescents), and another study used a different version of survey, with different scoring systems
9. Downgraded twice due to outcome dissimilarity as one study used a different version of survey, and different scoring systems used (Stevanovic 2019 had Obesity and Menstrual disorders combined)

7.2. Adolescent girls with PCOS

Pediatric Quality of Life Inventory (PedsQL)

COMPARISON: PCOS vs No PCOS												
	Quality assessment						No. participants					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**PCOS**	**No PCOS**	**Effect, fixed [95% CI]** MD	**Favours**	**Certainty**	**Importance**
Outcome: PedsQL Total												
2[1]	Cross-sectional studies	No serious limitations[2]	No serious inconsistency	No serious indirectness	No serious Imprecision	none	89	80	-0.07 [-0.37,0.23]	No difference	⨁⨁◯◯ LOW	IMPORTANT
Outcome: PedsQL Physical function												
2[1]	Cross-sectional studies	No serious limitations[2]	Very Serious inconsistency[3]	No serious indirectness	No serious Imprecision	none	89	80	-0.15 [-0.79,0.48]	No difference	⨁◯◯◯ VERY LOW	IMPORTANT
Outcome: PedsQL Psychosocial function												
2[1]	Cross-sectional studies	No serious limitations[2]	No Serious inconsistency	No serious indirectness	No serious Imprecision	none	89	80	-0.06 [-0.36,0.24]	No difference	⨁⨁◯◯ LOW	IMPORTANT

1. Coban 2019 (Adolescents), Donbaloglu 2022(Adolescents)
2. Not downgraded as the majority of evidence is at moderate risk of bias.
3. Downgraded twice (very serious) due to the effect sizes (mean difference) being on different sides of the line of no effect with no overlap of CIs and statistical heterogeneity is high.

APPENDIX. STUDY CHARACTERISTICS AND QUALITY APPRAISAL

Study ID		**Acmaz 2013**	
Study Citation		Açmaz, G., Albayrak, E., Acmaz, B., Başer, M., Soyak, M., Zararsız, G., & İpekMüderris,I (2013). Level of anxiety, depression, self-esteem, social anxiety, and quality of life among the women with polycystic ovary syndrome. The Scientific World Journal,	
Study Country		Turkey	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/ participants		86 patients diagnosed with PCOS according to 2003 Rotterdam Criteria, had no physical disease but PCOS, did not receive any treatment (before the treatment) for PCOS and had at least primary school degree. Those who had thyroid disorders, DM, Cushing' disease, positive malignancy, congenital adrenal hyperplasia, psychotic disorders and used antidepressants or steroidal hormone drugs and mood stabilizers were excluded. Patients with personality disorders assessed by SCID-I and SCID-II were not included.	
Control population		47 healthy volunteer participants in reproductive age.	
PCOS diagnostic criteria		Rotterdam	
N per group		PCOS were classified according to the complaints at the time of polyclinic admission. - Infertility group (concern with having child) - Oligomenorrhea-hirsutism group (concerns with hirsutism) - Overweight-obesity group (concerns with losing weight and had a BMI 30 or more)	
Setting		Hospital	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)		Primary outcomes: - SF-36 Quality of Life Scale (Short-Form 36) Outcomes not relevant: - LSAS (Liebowitz' Social Anxiety Scale) - RSES (Rosenberg' Self-Esteem Scale) - Beck Anxiety Inventory (BAI) - Beck Depression Inventory (BDI)	
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	Yes
Inclusion criteria		Yes Partial No Not reported	Yes
Exclusion criteria		Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Yes
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Not relevant to this systematic review
Was matching performed?		Yes Partial No Not reported	Not reported
Summary Result/s		Although there were significant differences in all of these parameters compared to the healthy group, the most affected group was oligomenorrhea-hirsutism group in terms of PF, PRF, pain, SF, ERF, and EWB, but it was obesity group that was affected by GH most and it was infertility group that was affected by vitality most.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes Partial No Not reported	Partial Control group using healthy volunteer participants in reproductive age, unknown whether also recruit at the hospital.
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Was the control status established in a standard, valid and	Yes Partial No	Yes.

	reliable way?	Not reported	
PERFORMANCE	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes
DEDETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Partial because of nature of study
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Partial because of nature of study
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	X% treatment X% control/ comparison Not reported	Not relevant to cross-sectional study
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Not reported
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes Demographic difference between group in marital status, number of children, obesity due to the aim of the study
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Partial Some reported in median and percentiles without stating reasons.
COMMENTS		Unknown where to recruit healthy volunteer in control group	
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

Study ID	**Bazarganipour 2020**
Study Citation	Bazarganipour, F.; Taghavi, S. A.; Asemi, Z.; Allan, H.; Khashavi, Z.; Safarzadeh, T.; Pourchangiz, S.; Zare, F.; Ghasemi, S.; Karimi, Z.; Azizi Kutenaee, M. The impact of irritable bowel syndrome on health-related quality of life in women with polycystic ovary syndrome. Health & Quality of Life Outcomes Jul 13 2020;18(1):226 2020 Jul 13 Doi: 10.1186/s12955-020-01428-7
Study Country	Hormozgan Province, Iran
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	Women with PCOS according to the Rotterdam criteria who attended an infertility clinic (n = 101)

Control population	Control group of healthy women whose partners had a diagnosis of male infertility (n = 100)	
PCOS diagnostic criteria	Rotterdam diagnostic criteria	
N per group	PCOS n= 101 Control n = 100	
Setting	infertility clinic at a hospital	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary outcomes: IBS-QOL questionnaire was designed by Patrick, et al., (1998) and contains 34 items with a five degree Likert scale. There are eight domains: dysphoria, relationships, sexual concern, health worry, social reaction, body image, food avoidance, and interference with activity. Scores were between 0 to 100; a higher score in this tool represents a worse quality of life. The validity and reliability of these tools are approved in Iran. Outcomes not relevant: Menstrual history: BMI Body hair: Ferriman-Gallwey Scoring System (F/G score). Acne: Global Acne Grading System (GAGS) Socio-demographic status Laboratory measures ROME III diagnostic criteria: IBS. 9. Bristol scale stool consistency	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes To investigate the prevalence of IBS in women with PCOS compared to healthy women and to compare QOL in a group of women with PCOS and healthy women.
Inclusion criteria	Yes Partial No Not reported	Yes being 15–40 years of age; married; having two of the following Rotterdam diagnostic criteria: Polycystic ovaries visualized on ultrasound scan (presence of 12 follicles or more in one or both ovaries and/or increased ovarian volume i.e., > 10 ml), Clinical signs of hyperandrogenism (hirsutism score based on hirsutism score greater than 7 or obvious acne), having an interval between menstrual periods > 35 days and/or amenorrhea, defined as the absence of vaginal bleeding for at least 6 months (i.e. 199 days).
Exclusion criteria	Yes Partial No Not reported	Yes absence of non-classic adrenal hyperplasia, thyroid dysfunction, hyperprolactinemia; non-smoking; absence of following warning signs that rejected IBS included extreme weight loss over the past few months, fever, nocturnal symptoms, severe chronic constipation, diarrhea, frequent vomiting, progressive dysphasia, a history of travel to areas of parasitic infections, family history of colon cancer, inflammatory bowel disease; not having cough (bronchitis) during the last 3 months; no problems in speaking or listening; Iranian; not taking any prescription medication (except allergy medications and occasional pain medications) for at least 3 months before entering the study;
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	Yes
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	Yes 6 months
Was matching performed?	Yes Partial No Not reported	No
Summary Result/s	Having PCOS and an increased level of LH/FSH tends to cause IBS symptoms. IBS + PCOS women experience significant impaired quality of life scores particularly in	

		relation to worries about health and food avoidance.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes Partial No Not reported	Yes – women with PCOS and women whose partners had infertility from the same infertility clinic in Iran
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
PERFORMANCE	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes
DEDETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	The women were requested to complete the study measures in clinic - no mention of blinding
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes, via questionnaire
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	X% treatment X% control/ comparison Not reported	Nil
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	0%
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Yes
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No. The research grant provided by Research Deputy of Hormozgan University of Medical Sciences (HUMS). The role of the funding body was collection and analysis.
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	The sample size (201) was calculated using previous study on PCOS Mathur, et al., (2010) information.
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Low
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

Study ID	Benetti-Pinto 2015
Study Citation	Benetti-Pinto, C. L., Ferreira, S. R., Antunes, A., & Yela, D. A. (2015). The influence of body weight on sexual function and quality of life in women with polycystic ovary syndrome. Archives of gynecology and obstetrics, 291(2), 451- 455.
Study Country	Brazil

CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/ participants		150 women aged between 18 and 40 years presenting PCOS diagnosis according to Rotterdam criteria for which they must submit 2 of the 3 characteristics: oligoamenorrhea or amenorrhea, clinical and/or biochemical signs of hyperandrogenism with polycystic ovaries and ultrasound assisted for a period of 10 months. Only 56 women fulfil inclusion criteria.	
Control population		102 women with regular menstrual cycles every 24-35 days, without signs of clinical hyperandrogenism, assisted in the same institution. For both case and control groups, women with any type of cognitive deficiency that could jeopardize the understanding of the study instruments were excluded. Women with arterial hypertension, type 1 or 2 diabetes, autoimmune disease, neoplasia or those were taking antidepressants, anxiolytics medication and pregnant were also excluded.	
PCOS diagnostic criteria		Rotterdam	
N per group		Case group: 150 women for screening for inclusion criteria, 56 women included. Control group: 102 volunteer in the same institution.	
Setting		University O&G department, Brazil	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)		Primary outcomes: - Quality of life using WHOQOL-bref Not relevant: - Female Sexual Functional Index	
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	Yes
Inclusion criteria		Yes Partial No Not reported	Yes
Exclusion criteria		Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Yes
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Yes Only included patients who have symptoms for 10 months.
Was matching performed?		Yes Partial No Not reported	Not reported
Summary Result/s		Women with PCOS had a worse sexual function and self-assessment of health condition in comparison to controls. The body weight as isolated symptom was correlated to the worsening in quality of life, but not with the worsening of sexual function.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes Partial No Not reported	Yes
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes Clarified definition of PCOS
	Was the control status established in a	Yes Partial	Yes Control group only included people with regular menstrual

	standard, valid and reliable way?	No Not reported	cycle
PERFORMANCE	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes Partial No Not reported	Not applicable to this study since there is no intervention
DEDETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported.
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes, Measurement of quality of life is validated.
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Partial Measurement of quality of life is subjective by itself.
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	X% treatment X% control/ comparison Not reported	Not relevant since it is a cross sectional study.
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Not relevant since it is a cross sectional study. All participants consented to study were analysed.
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not known because no protocol available.
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No, may be due to nature of PCOS disease. BMI of PCOS group was significantly higher than the control group (31.9 ± 8.5 vs 28.5 ± 5.4 kg/m2) The control group had significantly higher age than the PCOS group (26.9 ± 4.9 vs 35.6 ± 7.3 years old)
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No.
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported.
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?			

Study ID		**Benson 2008**	
Study Citation		Benson, S., Janssen O.E., Hahn S. Tan S. Dietz T. Mann K. Pleger K. Schedlowski M. Arck PC. Elsenbruch S (2008). "Obesity, depression, and chronic low-grade inflammation in women with polycystic ovary syndrome." Brain, Behavior, & Immunity 22(2): 177-184.	
Study Country		Germany	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/ participants		PCOS women (untreated) with a mean age of 28.9±0.7 yrs and BMI of 29.6±1 kg/m2	
Control population		Healthy women with a mean age of 29.9±1.2 yrs and BMI of 23.6±0.7 kg/m2	
PCOS diagnostic criteria		Cases were diagnosed by NIH & Rotterdam criteria	
N per group		57 women with PCOS and 28 healthy women	
Setting		Cases were recruited from outpatient clinics of the University Hospital and Private Practice whereas controls were from the general community, Germany.	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)		Health related quality of life (SF-36) Non relevant outcomes Clinical parameters including anthropometric measures Inflammatory markers Psychological assessments particularly levels of depression	
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	Yes
Inclusion criteria		Yes Partial No Not reported	Not reported
Exclusion criteria		Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Yes
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Not applicable
Was matching performed?		Yes Partial No Not reported	Not applicable
Summary Result/s		PCOS may be unique in that BMI does not appear to be the major correlate of depression. Other factors, such as infertility or hirsutism, may play a greater role in emotional well-being.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes Partial No Not reported	No Cases were recruited from the hospital while controls were from the community.
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes Cases were diagnosed by NIH & Rotterdam criteria
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes PCOS diagnosis criteria performed on everyone. Similar criteria was applied to exclude PCOS in controls
PERFORMANCE BIAS	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes Partial No Not reported	No Insulin resistance level of the control group was not measured and so similarity of the groups on this regard is not known. Although the control group had a lower BMI than the cases, there is still a possibility that lean people can also be insulin resistant.
DEDETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes They were measured objectively using a validated criteria

	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Yes Almost all of the outcomes were assessed objectively by laboratory tests. Previously validated tools were used for the subjective outcomes
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes, Established case definition and validated tools were used.
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Partial
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	X% treatment X% control/ comparison Not reported	Not applicable
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Not applicable
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported This is difficult to determine if there isn't a protocol.
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Partial The groups were different in BMI, but the authors didn't adjust all the outcomes for this factor. E.g. comparison of psychological parameters (BDI and SF-36) between cases and controls were not adjusted for BMI. Level of insulin resistance in controls and cases was not compared.
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	Not reported
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Partial. Sample size determination was not reported, but clinically significant difference was observed between cases and controls.
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Partial - Potential confounders such as BMI was not adjusted for psychological parameters between cases and controls. - the level of significance was not adjusted for multiple comparisons
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

Study ID	**Boivin 2020**
Study Citation	Boivin, M. J.; Fatehi, F.; Phillips-Chan, A. E.; Richardson, J. R.; Summers, A. N.; Foley, S. A. Exploratory study of a screening measure for polycystic ovarian syndrome, quality of life assessment, and neuropsychological evaluation BMC Women's Health 06 23 2020;20(1):132 2 020 06 23 Doi:10.1186/s12905-020-00994-8
Study Country	USA Indiana Wesleyan University
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	

Patient/population/ participants	Total: 120 undergraduate psychology women 18 to 41 years of age, n = 10 PCOS patients diagnosed medically in a manner consistent with the Teede et al. (2018) evidence-based diagnostic guidelines	
Control population	n = 74 “screened negative” on a 12-item PCOS symptoms inventory. n = 25 “screened positive” on a 12-item PCOS symptoms inventory	
PCOS diagnostic criteria	PCOS patients diagnosed medically in a manner consistent with the Teede et al. (2018) evidence-based diagnostic guidelines	
N per group	n = 10 PCOS patients diagnosed medically n = 74 screened negative on a 12-item PCOS symptoms inventory. n = 25 screened positive on a 12-item PCOS symptoms inventory	
Setting	2nd year psychology course at Indiana Wesleyan University, students were given the option to participate in our study for academic extra credit.	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary Outcomes: **The PCOS Quality-of-Life Scale** was devised by researchers at Brigham and Women’s Hospital, Boston, MA and validated with a sample of 100 clinically diagnosed PCOS women. As described above, the present version consists of 26 items provided a composite total PCOS QoL score as an overall item average on a scale from 1 to 10, with a higher score indicating a better QoL. Outcomes not relevant **Foley polycystic ovarian syndrome screening scale (FPCOS)** The PCOS Foley Screening Instrument was developed by SAF to assess the medical risk for PCOS. **Zung self-rating depression scale** assess depression in individuals in a general medical setting. **State-Trait Anxiety Inventory (STAI)** is a 40-item measure that looks at both state (in the moment" and trait (chronic) anxiety. **Fatigue symptom inventory (FSI)** this is a 14-item self-report measure for measuring the intensity, frequency, and impact of symptoms of fatigue on a woman’s quality of life. Higher scores indicate more fatigue symptoms.	
	Bottomley social support scale (BSS) This is a seven-item scale originally designed for cancer patients. **Spiritual beliefs inventory (SBI)** This is a well validated15-item questionnaire that is a brief, yet robust measure of the more universal aspects of religious spiritual and community social support while coping with a life-threatening illness as well as the subsequent quality of life (QoL) issues, particularly in the context of cancer care. **Automated Neuropsychological Assessment Metric (ANAM)** is a computerized neuropsychological assessment for a PC laptop in the hospital or clinic setting. **Bilateral Field Advantage (BFA)** task of interhemispheric brain integration is a computerized assessment.	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Partial. Evaluate the utility of the FPCOS as a screening instrument for clinical practice.
Inclusion criteria	Yes Partial No Not reported	Partial: confirmed to have PCOS following analysis of a blood draw for insulin resistance markers, blood androgen levels, as well as elevated cholesterol and triglyceride level (N = 11, PCOS confirmed group).
Exclusion criteria	Yes Partial No Not reported	Not reported
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Not reported
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	Yes
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	Yes
Was matching performed?	Yes Partial No Not reported	No

Summary Result/s		The PCOS-confirmed women scored more poorly than the screen-negative (reference) and screen-positive groups on all the measures of physical, emotional, social, and spiritual well-being measures. On the ANAM neuropsychological battery, PCOS-confirmed women did more poorly on Sternberg Memory and Stimulus Response throughput measures. They also had slower correct response speed for both the unilateral and bilateral dot- and letter-matching tachistoscopic stimulus presentations. However, the bilateral field advantage throughput performance ratio did not differ among groups, which is a global measure of bilateral versus unilateral brain/behavior asymmetries.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes Partial No Not reported	Yes
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
PERFORMANCE	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes
DEDETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	X% treatment X% control/ comparison Not reported	Difficult to ascertain as the final numbers don't add up completely and there is no flow chart. Eight of the IWU psychology students scored high enough on the Foley PCOS screening questionnaire for medical follow- up but declined to participate and remained in the "screen positive" group in the present study.
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Five women scored negative on the PCOS screening measure but did not attend their appointments for completing the other study assessments and were not included in this study.
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Yes
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	The authors declare that they have no competing interests
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Partial, Unfortunately, the PCOS medically confirmed sample size (N = 11) from the base sample of 120 women is too small to compute a sensitivity or specificity analysis for our FPCOS screening measure, assuming a disease prevalence of 10% or less and a power of 0.80 at a 5% significance level. Statistical analyses could only be correlational in nature, as a preliminary evaluation of the possible utility of this screening tool in a university population of young women.

If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS		
What is the overall risk of bias?	Low Moderate High Insufficient information	Moderate
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?	No	

Study ID	**Borghi 2018**	
Study Citation	Borghi, L.; Leone, D.; Vegni, E.; Galiano, V.; Lepadatu, C.; Sulpizio, P.; Garzia, E. Psychological distress, anger and quality of life in polycystic ovary syndrome: associations with biochemical, phenotypical andsocio-demographic factors. Journal of Psychosomatic Obstetrics & Gynecology 06 2018;39(2):128-137 2018 06	
	Doi: 10.1080/0167482X.2017.1311319	
Study Country	Milan, Italy	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	Convenience sample of 30 PCOS women referring to an outpatient clinic of Gynecological Endocrinology of a University Hospital in northern Italy during a period of four months	
Control population	Infertile non pcos women from same clinic	
PCOS diagnostic criteria	NIH criteria.	
N per group	n= 30 PCOS women n= 30 control women	
Setting	Reproductive Medicine Unit for infertility	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary outcomes: **Quality of life (QoL)** Health-related QoL was assessed using the Italian version of the Short Form Health Survey (SF-36) an instrument composed by eight subscales, namely Physical Functioning, Physical Role Function, Bodily Pain, General Health, Vitality, Social Functioning, Emotional Role Function and Mental Health. The subscales scores range between 0 and 100, with lower scores indicating poorer QoL and a higher concern in the specific domain. Outcomes not relevant: Socio-demographic data **Psychological distress Symptom Checklist-90-Revision (SCL-90-R)** a multidimensional, self-report questionnaire of 90 items on a 5-point Likert scale (ranging from “0: no problem” to “4: very serious”). **Anger and aggressiveness:** Participants’ trait anger and aggressiveness were evaluated using the State-Trait-Anger-Expression-Inventory, version 2 (STAXI-2), a self-report questionnaire of 57-items on a 4-point scale. **Phenotypical and biochemical features** As regards the phenotypical features, BMI (kg/m2) was calculated from height and weight measurements. Abdominal circumference (AC) was recorded and waist-to-hip (W/H) ratio calculated. Hirsutism scoring was done using the modified Ferriman–Gallwey score (mFG score). Nine body areas were scored on a 0–4 scale for facial and body terminal hair growth distribution, with a mFG score of _6 considered to be hirsutism. Presence of acne and/or acanthosis nigricans was noted.	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	To investigate the association between polycystic ovary syndrome (PCOS) and psychological disturbances, including anger. To analyze whether the biochemical/phenotypical features of PCOS play a role in the type and severity of psychological disorders
Inclusion criteria	Yes Partial No Not reported	Selected PCOS patients who met the more strict and conservative NIH diagnostic criteria which include the presence of oligomenorrhea (cycles lasting >35 days) or amenorrhea (no periods in 6 months) and
		hyperandrogenemia/hyperandrogenism (hirsutism or obvious

			acne or pronounced alopecia). Enrolled PCOS patients that were all infertile at the moment they filled out the questionnaires, in order to control for the potential confounding role of infertility on psychological outcomes. Control group of 30 women, age matched with the PCOS women, from consecutive women seen in the same outpatient clinic who met the following inclusion criteria: history of regular menstrual cycle, absence of severe gynecologic and nongynecologic diseases. Women of both groups have had spontaneous onset of puberty and regular sexual development.
Exclusion criteria		Yes Partial No Not reported	In both groups, included a prior psychiatric diagnosis, current use of psychiatric medications and difficulties with Italian language comprehension.
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Yes
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Yes
Was matching performed?		Yes Partial No Not reported	Yes
Summary Result/s		Compared with control women, women with PCOS reported significantly higher scores on SCL-90-R scales of somatization, anxiety, hostility, psychoticism, overall psychological distress and a number of symptoms. At STAXI-2, patients with PCOS scored higher in trait-anger and in the outward expression of anger, while lower in outward anger-control; **PCOS patients had significantly lower scores on SF-36 scales of physical functioning and bodily pain.** Hirsutism was directly associated with anxiety. Regarding the associations between phenotypical/biochemical features and psychological distress in PCOS patients, results showed that waist-to-hip ratio is inversely related to anxiety, psychoticism, hostility and to the indexes of psychological distress; such inverse relationship was also seen between plasmatic levels of testosterone and trait- anger, and between total cholesterol and hostility.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes Partial No Not reported	Yes
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
PERFORMANCE	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes
DETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported

	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	X% treatment X% control/ comparison Not reported	Out of 43 PCOS women who met study criteria, 30 agreed to participate with a response rate of 70%, and Out of 40 control women who met study criteria, 30 agreed to participate with a response rate of 75%.
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Yes, all outcomes reported
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	The authors report no conflicts of interest.
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Partial: The sample size of patients was small and only one center was involved, which may limit the possibility of generalizing.
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Low
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

Study ID	**Coban 2019**	
Study Citation	Coban OG, Tulaci OD, Adanir AS, Onder A. Psychiatric disorders, selfesteem, and quality of life in adolescents with polycystic ovary syndrome. J. Pediatr. Adolesc. Gynecol. 2019; 32: 600–4.	
Study Country	Turkey	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	Female adolescents aged 13-18 years with and without PCOS	
Control population	age- and sex-matched healthy peers	
PCOS diagnostic criteria	previously been diagnosed as having PCOS	
N per group	n = 28 adolescent with PCOS n = 31 age- and sex-matched healthy peers were recruited	
Setting	University School of Medicine, Local high school	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary outcomes: Health-related quality of life was measured using the Pediatric Quality of Life Inventory (PedsQL) Outcomes Not relevant: Assessment of psychiatric disorders through a semistructured interview (Schedule for Affective Disorders and Schizophrenia for School Age Children) conducted by a child and adolescent psychiatrist. self-esteem was measured using the Rosenberg Self-Esteem Scale (RSES).	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	To assess psychiatric disorders in adolescents with PCOS and evaluate HRQoL and selfesteem in this group.

Inclusion criteria		Yes Partial No Not reported	Aged 13-19 years who had previously been diagnosed as having PCOS and who voluntarily agreed to participate in the study. The inclusion criteria for the controls were as follows: absence of severe gynecologic and nongynecologic diseases, and history of regular menstrual bleeding.
Exclusion criteria		Yes Partial No Not reported	Exclusion criteria were the lack of consent for the participation in the study and having difficulty in understanding the questionnaires.
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Yes.
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Yes
Was matching performed?		Yes Partial No Not reported	Yes
Summary Result/s		There were no significant differences in the PCOS and control groups in terms of PedsQL scores. Adolescents with PCOS frequently experience psychiatric disorders. Physicians should be aware that adolescents with PCOS are at a high risk for major depression and anxiety disorders.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes Partial No Not reported	Yes
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
PERFORMANCE	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes
DEDETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported Each interview was administered by a child and adolescent psychiatrist
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	X% treatment X% control/ comparison Not reported	0%
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	0%
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Yes

CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	Not reported
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

Study ID	**Donbaloglu 2022**
Study Citation	Donbaloglu, Z.; Tuhan, H.; Coban, O. G.; Kizilay, D. O.; Ismailoglu, E.; Onder, A.; Acar, S.; Bedel, A.; Cetiner, E. B.; Singin, B.; Erdem, H.; Parlak, M. Hyperandrogenism correlates with psychological symptoms in adolescents with polycystic ovary syndrome. Clinical Pediatric Endocrinology 05 Apr 2022;31(2)():68-76 2022 05 Apr Doi: 10.1297/cpe.31.2022-0010
Study Country	Turkey
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	100 participants (PCOS group, 51; control group, 49) aged 13–18 yr were included in the study. n = 51 Adolescent girls who were diagnosed with PCOS and admitted to the pediatric endocrinology clinic of Çiğli Regional Training Hospital and Akdeniz University Hospital.
Control population	n = 49 age matched healthy volunteers who visited our hospitals for primary health-care services (e.g., vaccination). Participants in the control group had no menstrual irregularity or psychiatric disease and no clinical evidence of hyperandrogenism.
PCOS diagnostic criteria	The PCOS diagnostic criteria used in adults are not applied in adolescents. The diagnosis was made in patients who had at least 2 yr since menarche and were admitted to the endocrine clinic with menstrual irregularity (oligomenorrhea: menstrual cycle > 45 d) and hyperandrogenism (biochemical: free testosterone [fT] level higher than the reference levels of our laboratory; clinical: physical examination findings of hyperandrogenism, such as a modified Ferriman–Gallwey [mFG] score of > 8). Pelvic ultrasound was not used for the diagnosis of PCOS in adolescent patients who had < 8 yr since menarche because of the psychological multifollicular appearance of the ovaries during this period (7).
N per group	PCOS n= 51 Control n=49
Setting	Cross-sectional, multicenter, case–control study, pediatric endocrinology clinic
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary outcomes: **Pediatric Quality of Life Inventory (PedsQL):** This inventory was designed by Varni et al. to assess the HRQoL of children and adolescents. The 23-item PedsQL scale assesses physical and psychosocial functioning. Items are rated on a five-point Likert-type scale. The reliability and validity of the scale has been confirmed by Cakin Memik et al. Outcomes Not relevant: **Clinical and laboratory investigations. Beck Depression Inventory (BDI):**

		BDI is a self-assessment measure consisting of 21 items that evaluate the severity of somatic, emotional, mental, and motivational symptoms of depression. In this inventory, each item is scored between 0 and 3. High test scores indicate an increase in depressive symptoms. Total scores of 0–9 indicate no or minimal depressive symptoms; 10–18, mild depressive symptoms; 19–29, moderate depressive symptoms; and 30–63, severe depressive symptoms. The validity and reliability coefficients of the Turkish version of the scale are similar to those of the original form. **State–Trait Anxiety Inventory (STAI):** This 40-item self-report scale assesses separate dimensions of anxiety: "state" (STAI-S) and "trait" (STAI-T). Items are rated on a four-point Likert-type scale. Scores range from 20 to 80 for each subtest, with higher scores indicating higher anxiety levels (17). The Turkish version of this inventory has been proven valid and reliable in the adolescent age group.
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	To analyze the depressive and anxiety states of adolescent girls with polycystic ovary syndrome (PCOS) The psychological features of the PCOS group were compared with those of the control group. The relationship between clinical/biochemical parameters and psychiatric scores was also investigated in the PCOS group
Inclusion criteria		Yes Partial No Not reported	Girls aged 13–18 yrs
Exclusion criteria		Yes Partial No Not reported	Adolescent girls who had previously visited the psychiatry clinic and who had been diagnosed with any psychiatric disease and were using psychiatric medications were excluded from the control group. The other exclusion criteria for both the PCOS and control groups were as follows: hyperprolactinemia, thyroid dysfunction, Cushing's syndrome, androgen-secreting tumors, late-onset congenital adrenal hyperplasia, cognitive disability, and presence of any other coexisting chronic illness. Participants who were using any medication that may affect the psychological evaluation, such as antidepressants, melatonin, or stimulant drugs, were also excluded from the study. Participants who were born small for gestational age or premature were also excluded because they may have several other accompanying problems.
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Yes
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Yes
Was matching performed?		Yes Partial No Not reported	No, the control participants were not BMI-matched to the patients with PCOS.
Summary Result/s		Adolescent girls diagnosed with PCOS demonstrated higher depressive and anxiety symptoms and lower psychosocial quality of life scores than their healthy counterparts. A relationship was found between the fT level and all psychological measures.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes Partial No Not reported	Yes
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes

PERFORMANCE BIAS	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes
DEDETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Not reported
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	X% treatment X% control/ comparison Not reported	0%
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	0%
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Yes
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	The authors declare no conflicts of interest.
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

Study ID	Drosdzol 2007
Study Citation	Drosdzol, A., Skrzypulec, V., Mazur, B., & Pawlińska-Chmara, R. (2007). Quality of life and marital sexual satisfaction in women with polycystic ovary syndrome. Folia Histochem Cytobiol, 45(Suppl 1), S93-7.
Study Country	Poland
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	PCOS group: Age: 28.9±5.6 BMI: 24.6±3.8 Marital status: single (38%); married (52%); divorced (10%) Education: vocational (14%); secondary (42%); higher (44%) Previous pregnancy and children delivery: 24% Miscarriage experience: 6% Diagnosed and treated for infertility: 50%

Control population	Control group: Age: 30.5±5.3 BMI: 22.1±2.9 Marital status: single (22.5%); married (67.5%); divorced (10.0%) Education: vocational (15%); secondary (52.5%); higher (32.5%) Previous pregnancy and children delivery: 82.5% Miscarriage experience: 0% Diagnosed and treated for infertility: 0%		
PCOS diagnostic criteria	Validated guidelines of the Polish Society of Endocrinology (PSE) and European Society of Human Reproduction (ESHRE)		
N per group	PCOS group: Screened: 100 Enrolled: 73 (27 lack of consent for participation) Completed: 50 (23 incomplete filling out of the questionnaire) Control group: 40 healthy women aged 19-40 who reported to Outpatient Gynaecological Clinics.		
Setting	Same questionnaires were given to participants to fill in voluntarily and anonymously.		
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Relevant: SF-36 Not relevant: Index of Sexual Satisfaction (evaluate marital sexual satisfaction)		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes	
Inclusion criteria	Yes Partial No Not reported	Yes Aged between 19 and 40 diagnosed with PCOS	
Exclusion criteria	Yes Partial No Not reported	Yes Incomplete filling out of the questionnaire	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Partial Unknown reason of why questionnaire incomplete. Selection bias: might be different demographic between participants	
		who completed questionnaire and who did not?	
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	Yes	
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	Not relevant to this study measuring their quality of life	
Was matching performed?	Yes Partial No Not reported	Not reported	
Summary Result/s	Quality of life parameters for women with PCOS were lower than for the controls in the aspect of: general health, limitations due to physical health, limitations due to emotional problems, social functioning, energy/fatigue and emotional wellbeing. Studied women showed worse marital sexual functioning. PCOS decreases quality of life and marital sexual functioning among women. A negative effect of hirsutism severity on general well-being and marital sexual life is also observed		
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes Partial No Not reported	Yes Both case and control groups were recruited from the same clinics
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes PCOS cases were defined according to validated guidelines of Polish Society of Endocrinology and European Society of Human Reproduction.
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes PCOS diagnosis criteria performed on everyone
PERFORMANCE	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes
DEDETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes Validated questionnaire used.
	Were outcome assessors	Yes Partial No	Not reported

	blind to case and control status?	Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Partial because of nature of study
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Partial because of nature of study
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	X% treatment X% control/ comparison Not reported	Not relevant to the study design
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	PCOS group: 50% (27 women lack of consent for participation; 23 women incomplete filling out of the questionnaire) Control group: not reported
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported No protocol or PROSPERO
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Not reported Only mentioned 'NS' in table without stating exact figure
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	Not reported
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Partial Some did not provide results of statistical test, only stated 'NS' in the table.
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

Study ID	Elsenbruch 2003
Study Citation	Elsenbruch, S., Hahn, S., Kowalsky, D., Offner, A. H., Schedlowski, M., Mann, K. and Janssen, O. E. 2003 Quality of life, psychosocial well-being, and sexual satisfaction in women with polycystic ovary syndrome. Journal of Clinical Endocrinology & Metabolism. 88 [12]: 5801-7.
Study Country	Germany
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	Women with PCOS Age: 28.4 ± 5.0 BMI: 30.1 ± 9.8
Control population	Healthy aged matched women Age: 29.9 ± 5.7 BMI: 24.4 ± 5.3
PCOS diagnostic criteria	National Institutes of Health
N per group	50 PCOS and 50 controls
Setting	"..outpatient clinics of the Division of Endocrinology, Department of Medicine at the University of Essen, based on referrals from gynecologists in the surrounding area or patients attracted by the clinic's home page." "Age-matched healthy controls were recruited from a health screening program for employees instituted at the University of Essen" Germany

Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)		German version of the 36-item short-form health survey (SF-36) Not relevant: Psychological disturbances using the German version of the symptom checklist revised (SCL-90-R); Sexuality using a 100-mm visual analog scale (VAS)	
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	Yes
Inclusion criteria		Yes Partial No Not reported	Yes
Exclusion criteria		Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Yes
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	N/A
Was matching performed?		Yes Partial No Not reported	
Summary Result/s		Health related quality of life measured with the 36- revealed significantly decreased scores for physical role function, bodily pain, vitality, social function, emotional role function, and mental health in patients with PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes Partial No Not reported	Yes
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	NIH
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
PERFORMANCE	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes Partial No Not reported	N/A
DEDETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes Measurements and questionnaires were performed on all participants.
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Yes “personal interview, physical examination, and measurement of hormone parameters”
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Not reported
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Partial Some outcomes rely on others.
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	X% treatment X% control/ comparison Not reported	N/A
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Not reported
REPORT	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported No protocol

CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Partial BMI and unfulfilled wish to conceive higher in PCOS group. "This difference was very likely to be related to a selection bias/self-selection for specialized medical treatment because 30% of patients were referred specifically because of infertility problems, and almost all patients had previously been diagnosed with PCOS and thus aware of potential infertility problems."
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	Not reported
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate Most of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?			

Study ID	**Hahn 2005**	
Study Citation	Hahn, S., Janssen OE, Tan S, Pleger K, Mann K, Schedlowski M, Kimmig R, Benson S, Balamitsa E and Elsenbruch S(2005). "Clinical and psychological correlates of quality-of-life in polycystic ovary syndrome." European Journal of Endocrinology 153(6): 853-860.	
Study Country	Germany	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	PCOS women with a mean (SD) age of 29 (5.4) yrs and BMI of 31 (9.3) kg/m	
Control population	Healthy women with a mean (SD) age of 30 (5.7) yrs and BMI of 24 (5.3) kg/m2	
PCOS diagnostic criteria	NIH Criteria	
N per group	120 women with PCOS and 50 healthy women	
Setting	Cases were recruited from the outpatient clinics of the Department of Medicine whereas controls (historical) were from a health screening program and by public advertisement, University of Duisburg-Essen, Germany.	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Health related quality of life (SF-36) Non relevant outcomes psychological distress sexual satisfaction clinical parameters	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes
Inclusion criteria	Yes Partial No Not reported	Yes Women with PCOS (cases), diagnosed based on the 1990 NIH criteria. - Healthy women from a previously studied control group (historical control), not diagnosed with PCOS by the NIH- PCOS criteria
Exclusion criteria	Yes Partial No Not reported	Yes Taking any prescription medication or any known medical condition
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Partial No information reported whether study participants were included/excluded based on their age, BMI and ethnicity

Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Yes as the main aim of the study was to explore the correlation of major PCOS symptoms with quality-of-life, psychosocial well-being and sexual satisfaction
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Yes
Was matching performed?		Yes Partial No Not reported	Not applicable
Summary Result/s		In PCOS, changes in appearance, particularly obesity and hirsutism, reduce physical dimensions of quality-of-life	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes Partial No Not reported	No Cases were recruited from the outpatient clinics whereas controls were from the previous study.
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes Cases were diagnosed by the 1990 PCOS-NIH criteria
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes Similar criteria was applied to exclude PCOS in controls
PERFORMANCE	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes
DEDETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes Validated tools and laboratory tests were used to measure the the exposures and outcomes.
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Yes Previously validated tools were used to measure subjective outcomes in addition to the laboratory tests
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes Established case definition and validated tools were used.
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Partial
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	X% treatment X% control/ comparison Not reported	Not reported
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Not reported
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Not reported Women with PCOS had significantly higher BMI and HOMA-IR than the controls
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	Not reported
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Partial Sample size determination was not reported, however, a difference in statistical significance was observed in QoL and other outcomes between the groups.
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes V
COMMENTS			

What is the overall risk of bias?	Low Moderate High Insufficient information	Moderate - Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?	No	

Study ID	**Jose 2018**	
Study Citation	Jose, S. A.; Ravi, R.; Murthy, M. K. Quality of life in women with polycystic ovarian syndrome: Requisite of clinical pharmacist intervention. Asian Journal of Pharmaceutical and Clinical Research. Conference: 3rd International Conference on Academic and Industrial Innovations: Transitions in Pharmaceutical, Medical and Biosciences, INNOPHARM 2018;11(11): 2018 Doi: 10.22159/ajpcr.2019.v12i11.34426	
Study Country	India	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	A total of 173 subjects were recruited for the study, average age of study participants was 23.9±4.5 years. Patients were recruited based on inclusion criteria from the outpatient clinics of the department of endocrinology based on referrals from gynecologists and dermatologists Age range 10 to 40 years	
PCOS diagnostic criteria	1990 National Institutes of Health conference for diagnosis of the PCOS	
N per group	The number of participants that were: Screened Enrolled n = 173 Allocated/randomised: PCOS= 83, controls= 90 Assessed (at 3 month examination): PCOS=83, controls=90 Followed up	
Setting	Hospital-based prospective observational study was carried out for a period of 6 months at a tertiary care hospital in Bengaluru.	
Intervention/ indicator	Patients were recruited based on inclusion criteria from the outpatient clinics of the department of endocrinology based on referrals from gynecologists and dermatologists	
Comparison/ Control	Healthy Controls	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Primary outcomes: The World Health Organization BREF, a validated, reliable tool to assess QOL was administered in two phases of the study, pre-interventional, and post-interventional phase. Outcomes Not relevant:	
Inclusion criteria reported?	Yes	While patients in the test group were included, if they presented with either oligomenorrhea (cycles lasting longer than 35 days) or amenorrhea (absence of menstrual cycles in the past 6 months) or clinical signs of hyperandrogenism (hirsutism with a Ferriman/Gallwey score of more than 7 or obvious acne) or an elevated total testosterone (normal range – 2.0 nmol/l).
Exclusion criteria reported?	Yes Partial No Not reported	Patients with pituitary, adrenal, or ovarian diseases were excluded as they mimic the symptoms of PCOS
Does the study have a clearly focused question?	Yes Partial No Not reported	To study the present QOL status in woman with PCOS in our setup.
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Yes
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes

Were the outcomes measured appropriate?		Yes Partial No Not reported	Yes
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Yes
Was matching performed?		Yes Partial No Not reported	No
Summary of Result/s		Women suffering from PCOS exhibit varied symptoms which affect both physical and psychological health. The key factor in management is to create awareness on the complications of the disease and the lifestyle modification to minimize severity and progression. The study findings reveal that women with PCOS showed an improved QOL post participation in awareness programs imparted by the clinical pharmacists.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Yes
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	No
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	Yes
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Yes Partial No Not reported	Partial
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	PCOS= Controls=	0%
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	0%
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Yes
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes

OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	The authors declare that they have no conflicts of interest.
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		Low Moderate High	Moderate
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

Study ID	**Kahal 2019**	
Study Citation	Kahal, H.; Kilpatrick, E.; Rigby, A.; Coady, A.; Atkin, S. The effects of treatment with liraglutide on quality of life and depression in young obese women with PCOS and controls. Gynecological Endocrinology Feb 2019;35(2):142-145 2019 Feb Doi: 10.1080/09513590.2018.1505848	
Study Country	United Kingdom	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	Interventional case-control study of women with PCOS and obesity, and age- and weight-matched controls.	
Control population	36 women were recruited (19 PCOS, 17 controls), age 33.9 ± 6.7 vs. 33.5 ± 7.1 yr, and weight 102.1 ± 17.1 vs. 100.4 ± 15.1 kg, respectively	
PCOS diagnostic criteria	Rotterdam criteria	
N per group	19 PCOS, 17 controls	
Setting	Women with PCOS were recruited from the endocrine clinic and controls were recruited through an advertisement in the local newspaper.	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary outcomes: **Quality of life** QoL was measured using the short version of the World Health Organization QoL questionnaire (WHOQOL-BREF), which includes 26 questions to assess four major domains (subscales): physical, psychological, social and environment Outcomes Not relevant: Anthropometric measurements Biochemical investigations Depression	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	To determine the effect of six months treatment of liraglutide on weight loss in PCOS compared to weight matched controls, including an assessment of QoL.
Inclusion criteria	Yes Partial No Not reported	Body mass index (BMI) between 30–45 kg/m2, and were between 18 and 45 years of age.
Exclusion criteria	Yes Partial No Not reported	Previous history of hypothyroidism, pancreatitis, heart failure, renal failure, type 2 diabetes, alcohol consumption of >14 units/week, and pregnant or breast feeding women.
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	Yes

Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Yes
Was matching performed?		Yes Partial No Not reported	Yes
Summary Result/s		PCOS was not independently associated with reduced QoL, and/or depression, in the presence of obesity. Six months treatment with liraglutide resulted in significant reduction in weight and improvement in QoL in young women with PCOS and obesity.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes Partial No Not reported	Yes
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
PERFORMANCE	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes
DEDETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	X% treatment X% control/ comparison Not reported	Twenty five women, 69%, completed the study (13 PCOS, and 12 controls).
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	25 participants completed the study; intention-to-treat analysis was performed, including all 36 study participants, with the last observation carried forward.
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Yes
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No potential conflict of interest was reported by the authors.
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported No prior power calculation was undertaken the data presented represents secondary outcomes to another study
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Low

Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?	No

Study ID	**Kaluzna 2021**	
Study Citation	Kaluzna, M.; Nomejko, A.; Slowinska, A.; Wachowiak-Ochmanska, K.; Pikosz, K.; Ziemnicka, K.; Ruchala, M. Lower sexual satisfaction in women with polycystic ovary syndrome and metabolic syndrome. Endocrine connections September 2021;10(9)():1035-1044 2021 September Doi: 10.1530/EC-21-0257	
Study Country	Poland	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	n =190 patients with PCOS (mean age 26.34 ± 5.47 years)	
Control population	n=197 age-matched CON (mean age 27.12 ± 4.97 years)	
PCOS diagnostic criteria	Rotterdam criteria and the latest international evidence-based guidelines for the assessment and management of PCOS	
N per group	n=190 PCOS n=197 Controls	
Setting	Not reported	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary outcomes: WHO Quality of Life-BREF (WHOQOL-BREF) Outcomes Not relevant: Polish version of the Sexual Satisfaction Questionnaire (SSQ), and the Center for Epidemiologic Studies Depression Scale-Revised (CESD-R) questionnaire. Fasting blood samples were collected to assess hormonal, lipid, and glucose profiles. Anthropometric measures were collected. Metabolic syndrome (MS) was evaluated according to the IDF-AHA/NHLBI criteria.	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	This study aimed to assess sexual satisfaction (SS) in PCOS patients and eumenorrheic controls (CON). The relationships between SS, depressive symptoms, health-related quality of life (HRQoL), and hormonal and metabolic profiles were evaluated.
Inclusion criteria	Yes Partial No Not reported	PCOS diagnosis. Eumenorrheic healthy individuals without reported problems concerning endocrine disorders, sexual development, and maturation.
Exclusion criteria	Yes Partial No Not reported	Excluded if they had severe psychiatric disorders (schizophrenia, bipolar disorder, severe depression), diabetes, severe liver or kidney disease, the use of oral contraceptive or anti-androgen therapy in the last 3 months or current pregnancy or diagnosed and/ or treated infertility.
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	Yes
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	Yes
Was matching performed?	Yes Partial No Not reported	Yes: age-matched
Summary Result/s	There were no significant differences in the level of SS, presence of depressive symptoms, or HRQoL between PCOS and CON. Sexual Satisfaction in PCOS women appears to be undisturbed. However, Metabolic Syndrome in PCOS patients could negatively influence Sexual Satisfaction. The level of Sexual Satisfaction should be assessed in PCOS women, especially if Metabolic Syndrome is present.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS **Were the cases and controls taken from comparable populations?**	Yes Partial No Not reported	Yes

	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
PERFORMANCE	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes
DETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	No – self report for questionnaires
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	X% treatment X% control/ comparison Not reported	O%
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	PCOS 8/190 = 4% CON 3/197 = 2%
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Yes all outcomes reported
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes
OTHER	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Low
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

Study ID	**Karjula 2020**
Study Citation	Karjula, S.; Morin-Papunen, L.; Franks, S.; Auvinen, J.; Jarvelin, M. R.; Tapanainen, J. S.; Jokelainen, J.; Miettunen, J.; Piltonen, T. T. Population-based Data at Ages 31 and 46 Show Decreased HRQoL and Life Satisfaction in Women with PCOS Symptoms. Journal of Clinical Endocrinology & Metabolism 06 01 2020;105(6):01 2020 06 01 doi:10.1210/clinem/dgz256
Study Country	Finland
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	

Patient/population/ participants		Women aged 31-46 years. BMI: Controls (at age 31 years) = 23.8±4.3kg/m^2 PCOS (at age 31 years) = 27.1±6.9kg/m^2	
PCOS diagnostic criteria		Self-report of having both oligomenorrhea and hirsutism	
N per group		The number of participants that were: Screened: n= 5,889 Enrolled: n=2,306 Allocated/randomised: PCOS=125, controls=2181 Assessed (at year 1996-1997 examination): PCOS=74, controls=1,382 Followed up: 2013 (46 years old) PCOS=75, controls=1,412	
Setting		Clinical	
Intervention/ indicator		Completed 15D Quality of Life Questionnaire	
Comparison/ Control		PCOS/control	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)		Primary outcomes: 15 Quality of Life Questionnaire Score and clinical examination completed Outcomes Not relevant:	
Inclusion criteria reported?		Yes	Yes
Exclusion criteria reported?		Yes Partial No Not reported	Yes
Does the study have a clearly focused question?		Yes Partial No Not reported	Yes – Does the health burden experienced by women with PCOS differ to that experienced by women with other chronic conditions e.g. asthma, migraine, rheumatoid arthritis, depression?
Is a cohort study the appropriate design to answer this question?		Yes Partial No Not reported	Yes
Does the study have specified inclusion/ exclusion criteria?		Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Were the outcomes measured appropriate?		Yes Partial No Not reported	Yes
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Yes
Was matching performed?		Yes Partial No Not reported	No
Summary of Result/s		HRQoL was lower at ages 31 and 46 in women with PCOS or H than in the controls. PCOS was an independent risk factor for low HRQoL, and the decrease in HRQoL in PCOS was similar to that of women with other chronic conditions, such as asthma, migraine, rheumatoid arthritis, and depression. The risk for low HRQoL in PCOS remained significant after adjusting for body mass index, hyperandrogenism, and socioeconomic status.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Partial - minimal ethnic, geographic, and age variations, and socioeconomic diversity is low, largely as a result of the availability of free health care and education in Finland.
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	Yes
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	Partial – further examinations to truly meet Rotterdam criteria for PCOS could have been completed. Self- report of hirsutism and oligomenorrhea and testosterone measured

	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Yes Partial No Not reported	Yes
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	PCOS= Controls=	PCOS = 20/75= 27% Controls= 430/1382= 31%
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	As above- 15D scored of drop-outs compared to follow ups overall.
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Yes
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		High	low
Did risk of bias differ by outcome (e.g. primary outcome was low risk but rest were high)?		No	

Study ID	**Kumarapeli 2011**	
Study Citation	Kumarapeli, V., Seneviratne R de A, Wijeyaratnec CN. (2011). "Health-related quality of life and psychological distress in polycystic ovary syndrome: a hidden facet in South Asian women." BJOG: An International Journal of Obstetrics & Gynaecology 118(3): 319-328.	
Study Country	Sri Lanka.	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	Newly diagnosed women with PCOS aged between 15-39 years	
Control population	Healthy women aged between 15 -39 years (age matched controls)	
PCOS diagnostic criteria	Cases were diagnosed by the revised Rotterdam criteria	
N per group	146 women with PCOS and 170 controls	
Setting	Both cases and controls were selected from the same cluster (district of Gampaha)	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Health related quality of life were measured by the World Health Organization Quality of Life questionnaire (WHOQOL-BREF) and General Health Questionnaire (GHQ30) Non relevant outcomes - psychological distress	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes

Inclusion criteria		Yes Partial No Not reported	Yes - Cases were diagnosed based on the revised Rotterdam criteria. - Age-matched controls were not diagnosed with PCOS by the above criteria.
Exclusion criteria		Yes Partial No Not reported	Yes Any known medical condition
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Partial No information reported whether study participants were included/excluded based other criteria such as BMI and family income.
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Yes
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Yes
Was matching performed?		Yes Partial No Not reported	Not applicable
Summary Result/s		PCOS occurring in South Asians adversely affects their psychological wellbeing and HRQoL. Their psychological distress is related to hirsutism rather than to obesity, which affects white Europeans with PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes Partial No Not reported	Yes
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes Cases were diagnosed by the revised Rotterdam criteria
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes Similar criteria was applied to exclude PCOS in controls
PERFORMANCE	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes
DEDETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes Partial No Not reported	yes previously validated tools in that community were used to assess the outcomes.
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Yes Previously validated tools were used.
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes Established case definition and validated tools were used
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Partial
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	X% treatment X% control/ comparison Not reported	Not applicable
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Not reported

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	yes
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	yes
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	no
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Yes
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Low All of the criteria have been fulfilled or where criteria have not been fulfilled it is very unlikely the conclusions of the study would be affected.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?			

Study ID	**Kutlu 2020**	
Study Citation	Kutlu, O. Evaluation of quality of life of patients with hirsutism among Turkish women: A single-center cross-sectional study. Journal of Cosmetic Dermatology Nov 2020;19(11):3053-3057 2020 Nov Doi: 10.1111/jocd.13563	
Study Country	Turkey	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	Patients with hirsutism BMI: PCOS = 23.71±5.71 kg/m^2 ; Controls =25.30±5.16 kg/m^2	
Control population	Women with hirsutism according to the Modified Ferriman-Gallwey	
PCOS diagnostic criteria	2003 Rotterdam criteria diagnosed by an onstretician-gynecologist	
N per group	PCOS= 16 Controls= 41	
Setting	Unknown	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary outcomes: Dermatological Life Quality Index – 10 questions designed specifically for dermatological diseases. Unknown if self-reported or completed with clinician. Outcomes Not relevant:	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Partial
Inclusion criteria	Yes Partial No Not reported	Partial
Exclusion criteria	Yes Partial No Not reported	Partial – those who presented with hirsutism but with mFG score less than eight, hypertrichosis, who performed procedures such as epilation or depilation at the time of admission, or who had mental retardation were excluded from the study.
If there were specified inclusion/ exclusion criteria,	Yes Partial	Yes

were these appropriate?		No Not reported	
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Yes
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	NA – cross-sectional
Was matching performed?		Yes Partial No Not reported	Not reported
Summary Result/s		There was no statistically significant difference for patients with PCOS in terms of mean DLQI score for those with acne, seborrhea, androgenetic alopecia, menstrual irregularity, and acanthosis nigricans and those without acne, seborrhea, androgenetic alopecia, menstrual irregularity, and acanthosis nigricans (P values were .760, .913, .455, .456, and .957, respectively).	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes Partial No Not reported	Not reported
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
PERFORMANCE	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes
DETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes Partial No Not reported	Partial – no description of tests used to measure clinical examinations
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Not reported
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	X% treatment X% control/ comparison Not reported	NA- cross-sectional study
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	0% treatment 0% control
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Yes
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this	Yes Partial No Not reported	Yes

	appropriate?		
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		Nil	

Study ID		**Lidaka 2019**	
Study Citation		Lidaka, L.; Lazdane, G.; Kivite-Urtane, A.; Gailite, L.; Dzivite-Krisane, I.; Stokenberga, I. Health-related quality of life and binge eating among adolescent girls with PCOS. Clinical and Experimental Obstetrics and Gynecology 2019;46(5)():831-832 2019 doi:10.3390/ijerph15020376	
Study Country		Latvia	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/ participants		Not reported	
Control population		Adolescent patients aged 13-18 years at least 1- year post menarche without PCOS	
PCOS diagnostic criteria		PCOM and hirsutism according to ESHRE 2018 guidelines.	
N per group		PCOS= 63 Control= 66	
Setting		Out patient paediatric gynaecology clinic at the Children's University Hospital	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)		Primary outcomes: Quality of life using the PCOSQ – 26 item questionnaires Self-reported Outcomes Not relevant:	
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	Yes – How does PCOS and its associated factors, including binge eating, affect the HRQoL of adolescent girls?
Inclusion criteria		Yes Partial No Not reported	Partial – attending in-patient clinic
Exclusion criteria		Yes Partial No Not reported	Partial - patients who did not fulfil the new diagnostic criteria for PCOS were excluded from the study. None other described.
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Yes
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	NA
Was matching performed?		Yes Partial No Not reported	Yes – age matched
Summary Result/s		HRQoL was significantly lower in adolescents with PCOS than controls (4.9 (interquartile range (IQR) 1.5) vs. 5.8 (IQR 0.9) points).	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes Partial No Not reported	Yes
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
PERFORMANCE	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes
DETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated**	Yes Partial No Not reported	Yes

	in a standard, valid and reliable way?		
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	No
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Not reported
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	X% treatment X% control/ comparison Not reported	PCOS=0% Control=0%
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	PCOS=0% Control=0%
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Yes
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

Study ID	**Ozcan Dag 2015** (the same study as Ozcan dag 2016 except the small sample size)	
Study Citation	Ozcan Dag, Z., Oguzturk O, Isik Y, Turkel Y & Bulcun E (2015). "Personality profile in patients with polycystic ovary syndrome." Gynecological Endocrinology 31(7): 540-542.	
Study Country	Turkey.	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	Adult women with PCOS	
Control population	Healthy women	
PCOS diagnostic criteria	Rotterdam criteria.	
N per group	Enrolled = 49 women with PCOS and 34 controls Assessed = 45 women with PCOS and 32 controls	
Setting	Both cases and controls were referred from the Kirikale University Gynecology Clinic, Turkey.	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Health related quality of life (SF-36 version 1.0) Non relevant outcomes Psychometric evaluation Anxiety and depression levels	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes

Inclusion criteria		Yes Partial No Not reported	Yes- Cases were diagnosed based on the Rotterdam criteria. Age-matched controls were not diagnosed with PCOS by the above criteria.
Exclusion criteria		Yes Partial No Not reported	Yes Any known medical condition, taking any medications, pregnancy and lactation
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Partial No information reported whether study participants were included/excluded based other criteria such as family income and ethnicity.
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	yes - as the aim of the study was to investigate to investigate the effect of PCOS on personality using Minnesota Multiphasic Personality Inventory
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Not applicable
Was matching performed?		Yes Partial No Not reported	Yes
Summary Result/s		Patients with PCOS had lower SF-36 physical and mental health summary scores	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes Partial No Not reported	Yes Both cases and aged-matched controls were selected from the hospital.
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes Cases were diagnosed by the revised Rotterdam criteria
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes Similar criteria was applied to exclude PCOS in controls
PERFORMANCE	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes
DEDETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes Validated tools were used to assess the outcomes.
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Yes Previously validated tools were used.
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes Established case definition and validated tools were used.
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	PArtial
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	X% treatment X% control/ comparison Not reported	Not applicable
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Cases = 4/49 = 8% Controls = 2/34 = 5%
REPORT	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Partial The PCOS group had higher mean BMI score than the control group. And no data reported on participants' economic status
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No

	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Partial No report on sample size determination however statistical significance was observed in key outcomes such as QoL.
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes Adjustment for BMI was done.
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

Study ID		**Ozcan Dag 2016** (the same study as Ozcan dag 2015 except the larger sample size)	
Study Citation		Ozcan Dag, Z., Alpua M, Isik Y, S. Buturak V, Ozlem B., Tulmac & Yakup Turkel (2016). "The evaluation of temperament and quality of life in patients with polycystic ovary syndrome." Gynecological Endocrinology: 1-4.	
Study Country		Turkey	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/ participants		Adult women with PCOS with a BMI of 23.26 (4.44) kg/m2	
Control population		Age-matched healthy women with a BMI of 20.83(3.16) kg/m2	
PCOS diagnostic criteria		Rotterdam	
N per group		Assessed = 53 women with PCOS and 38 controls	
Setting		Both cases and controls were referred from the Kirikale University Gynecology Clinic, Turkey.	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)		Health related quality of life (SF-36 version 1.0) Non relevant outcomes Temperament evaluation Anxiety and depression levels	
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	Yes
Inclusion criteria		Yes Partial No Not reported	Yes - Cases were diagnosed based on the Rotterdam criteria. Age-matched controls were not diagnosed with PCOS by the above criteria.
Exclusion criteria		Yes Partial No Not reported	Yes Any known medical condition, taking any medications, pregnancy and lactation
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Partial No information reported whether study participants were included/excluded based other criteria such as family income and ethnicity.
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	No - as the aim of the study was to investigate the affective temperaments of PCOS patients and the **effects of those temperament** characteristics on the QoL.
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Not applicable
Was matching performed?		Yes Partial No Not reported	Yes
Summary Result/s		Patients with PCOS had lower SF-36 physical and mental health summary scores	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes Partial No Not reported	Yes Both cases and aged-matched controls were selected from the hospital.
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes Cases were diagnosed by the revised Rotterdam criteria

	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes Similar criteria was applied to exclude PCOS in controls
PERFORMANCE	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes
DEDETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes Validated tools were used to assess the outcomes.
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Yes Previously validated tools were used.
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes Established case definition and validated tools were used
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Partial
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	X% treatment X% control/ comparison Not reported	Not applicable
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Not applicable
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Partial The PCOS group had higher mean BMI score than the control group. And no data reported on participants' economic status.
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Partial No report on sample size determination however statistical significance was observed in key outcomes such as QoL
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes Adjustment for BMI was done.
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

Study ID	**Ozcan Dag 2017**(the same study as Ozcan Dag 2015, 2016
Study Citation	Zeynep Ozcan Dag, Murat Alpua, Yuksel Isik, S. Visal Buturak, Ozlem, B. Tulmac & Yakup Turkel (2017) The evaluation of temperament and quality of life in patients with polycystic ovary syndrome, Gynecological Endocrinology, 33:3, 250-253, DOI: 10.1080/09513590.2016.1254610
Study Country	Turkey
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	Adults attending the University Gynecology Clinic at the Kirikale University
Control population	Do not meet Rotterdam criteria for PCOS
PCOS diagnostic criteria	Rotterdam criteria
N per group	PCOS= 53 Control=38

Setting		Gynaecology clinic	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)		Primary outcomes: SF-36 score Outcomes Not relevant:	
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	Yes
Inclusion criteria		Yes Partial No Not reported	Yes - did not have any cognitive impairments or psychiatric disorders that disrupted their perceptions of reality.
Exclusion criteria		Yes Partial No Not reported	Yes - those with menstrual irregularities, those who were pregnant or breastfeeding; those with intercurrent illnesses, hypothyroidism, or diabetes, and those who were on hormonal therapy or medications.
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Yes
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	NA
Was matching performed?		Yes Partial No Not reported	Yes= age-matched
Summary Result/s		The PCOS patients had significantly lower mean SF-36 health summary scores.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes Partial No Not reported	Yes
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes
DEDETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Not reported
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	X% treatment X% control/ comparison Not reported	PCOS = 0% Control=0%
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	PCOS = 0% Control=0%

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Yes
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Partial
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Yes
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

Study ID	**Panico 2017**	
Study Citation	Panico A, Messina G, Lupoli GA, et al. Quality of life in overweight (obese) and normal-weight women with polycystic ovary syndrome. Patient Prefer Adherence. 2017; 11:423–429	
Study Country	Italy	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	PCOS and controls – not reported	
Control population	Do not meet Rotterdam criteria for PCOS	
PCOS diagnostic criteria	Rotterdam criteria	
N per group	PCOS = 100 Controls = 40	
Setting	Not reported	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Quality of Life – PCOSQ and SF-36	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Partial
Inclusion criteria	Yes Partial No Not reported	Partial: 100 Mediterranean women with PCOS aged 17.2–29 years. Controls = no PCOS of healthy weight.
Exclusion criteria	Yes Partial No Not reported	No reported
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Partial
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	Partial
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	Not reported
Was matching performed?	Yes Partial	Yes – age matched and similar socioeconomic background
	No Not reported	

Summary Result/s		A considerable worsening of HRQoL in PCOS patients (A) compared with controls (B). In addition, patients with PCOS and BMI <25 (A1) showed a significant and more marked reduction in scores, suggesting a lower quality of life, compared with controls (B) and with normal-weight PCOS patients (A2).	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes Partial No Not reported	Partial – relate to matching. Demographic data not reported
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes
DEDETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Not reported
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	X% treatment X% control/ comparison Not reported	Not reported
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Not reported
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	**Yes**
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	High
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

Study ID		Ramos 2016	
Study Citation		Ramos, F. K., Lara LS, Kogure GS, Silva RC, Ferriani RA, de Sá MFS, dos Reis RM (2016). "Quality of Life in Women with Polycystic Ovary Syndrome after a Program of Resistance Exercise Training." Revista Brasileira de Ginecologia e Obstetricia 38(7): 340-347.	
Study Country		Brazil	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/ participants		Women with PCOS aged 18 to 37 years and had a BMI of 18 to 39.9 kg/m2	
Control population		Healthy women aged 18 to 37 years and had a BMI of 18 to 39.9 kg/m2	
PCOS diagnostic criteria		Rotterdam	
N per group		Screened = 350 women Enrolled = 124 women Assessed = 43 women with PCOS and 51 controls Followed up = 43 women with PCOS and 51 controls	
Setting		Cases were recruited from the Endocrine Genecology Outpatient Clinic of the Universidade de Hospital whereas controls were from the community, São Paulo.	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)		Health related quality of life (SF-36) Non relevant outcomes Anthropometric and Clinical Measurements	
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	Yes
Inclusion criteria		Yes Partial No Not reported	Yes Cases, diagnosed based on the Rotterdam criteria. Controls, not diagnosed with PCOS by the above criteria.
Exclusion criteria		Yes Partial No Not reported	Yes Any known medical condition, taking any medications, any regular physical activity
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Yes
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Yes 16 weeks
Was matching performed?		Yes Partial No Not reported	
Summary Result/s		There was a weak correlation between social aspects of the SF-36 domain and testosterone levels in PCOS women	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes Partial No Not reported	No Cases were from the hospital whereas controls were from the community
SELECTION BIAS	**Was the case definition adequate and established in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes Cases were diagnosed by the revised Rotterdam criteria
SELECTION BIAS	**Was the control status established in a standard, valid and reliable way?**	Yes Partial No Not reported	**Yes** Similar criteria was applied to exclude PCOS in controls
PERFORMANCE	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes
DEDETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a**	Yes Partial No Not reported	Yes Validated tools were used to assess the outcomes.

	standard, valid and reliable way?		
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Yes Previously validated tools were used.
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes Established case definition and validated tools were used
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Partial Not reported
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	X% treatment X% control/ comparison Not reported	Not reported
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Not reported
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Partial No report on sample size determination however statistical and clinical significance was observed in key outcomes such as QoL.
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	yes
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

Study ID	**Rzonca 2018**
Study Citation	Rzonca, E.; Bien, A.; Wdowiak, A.; Szymanski, R.; Iwanowicz-Palus, G. Determinants of Quality of Life and Satisfaction with Life in Women with Polycystic Ovary Syndrome. International Journal of Environmental Research & Public Health [Electronic Resource] 02 22 2018;15(2):22 2018 02 22 doi:10.3390/ijerph15020376
Study Country	Poland
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	Women using healthcare services (primary care, specialist outpatient care, and inpatient/hospital care) in four regions of Poland: Lublin, Podkarpacie, Pomerania, and Greater Poland.
Control population	Do not meet PCOS criteria
PCOS diagnostic criteria	Rotterdam criteria

N per group		PCOS= 250 Control=254	
Setting		Clinical	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)		Primary outcomes: Outcomes Not relevant: World Health Organization Quality of Life-BREF (WHOQOL-BREF) questionnaire scores	
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	Yes
Inclusion criteria		Yes Partial No Not reported	Yes - age over 18 years, PCOS diagnosis made based on the Rotterdam criteria, and use of health care services in Poland.
Exclusion criteria		Yes Partial No Not reported	Yes - cancer diagnosis and psychiatric disorders.
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Yes
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	NA – cross sectional
Was matching performed?		Yes Partial No Not reported	Not reported
Summary Result/s		Patients with PCOS had a lower overall QoL (p = 0.000), worse perceived health (p = 0.000), and lower QoL in all specific domains: physical (p = 0.023), psychological (p = 0.000), environmental (p = 0.000), and social (p = 0.000), compared with controls.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes Partial No Not reported	Yes
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
PERFORMANC	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes
DEDETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	No
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Not reported
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	X% treatment X% control/ comparison Not reported	PCOS= 16.7% Control= 15.33%

	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	PCOS=0% Control=0%
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Yes
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Yes - All tests used in the study had high statistical power: 98–100% for regression analysis, 99–100% for WHOQOL- BREF score comparisons
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	**Yes**
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Low
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

Study ID	**Sanchez-Ferrer 2020**	
Study Citation	Sanchez-Ferrer, M. L.; Adoamnei, E.; Prieto-Sanchez, M. T.; Mendiola, J.; Corbalan-Biyang, S.; Monino-Garcia, M.; Palomar-Rodriguez, J. A.; Torres- Cantero, A. M. Health-related quality of life in women with polycystic ovary syndrome attending to a tertiary hospital in Southeastern Spain: a case-control study. Health & Quality of Life Outcomes Jul 16 2020;18(1):232. 2020 Jul 16 DOI: 10.1186/s12955-020-01484-z	
Study Country	Spain	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	Age: PCOS=27.4±5.0 Controls= 30.6±5.9 BMI: PCOS=25.5±5.9 Controls=23.3±4.3	
Control population	Women attending the gynaecological outpatient clinic for routine examination at the University Clinical Hospital.	
PCOS diagnostic criteria	Rotterdam criteria which included a complete medical history with a modified Ferriman-Galwey (mF-G) score, transvaginal ultrasound (TVUS) and serum sexual hormones.	
N per group	PCOS=117 Control=153	
Setting	Clinical – outpatient gynaecological clinic	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary outcomes: SF-36 score Outcomes Not relevant:	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes
Inclusion criteria	Yes Partial No Not reported	Yes - Women with PCOS (n = 117) were women attending the gynaecology unit of the hospital, and included newly diagnosed cases as well as prevalent ones.
Exclusion criteria	Yes Partial No Not reported	Yes - Women were excluded if they: were < 18 and > 40 years old, had endocrine disorders (e.g. Cushing's syndrome, congenital adrenal hyperplasia, androgen-secreting tumours, hyperprolactinemia and hyper and hypothyroidism) or were taking any hormonal medication
		(including contraception) during the 3 months prior to the study; were pregnant or lactating; had been exposed to oncological treatment; or had genitourinary prolapse.

If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Yes- case control
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Yes
Was matching performed?		Yes Partial No Not reported	Not reported
Summary Result/s		Quality of life of women with PCOS, especially, anovulatory PCOS- was significantly decreased compared to controls. In adjusted analyses, five scales showed significantly lower scores for all PCOS versus controls (role physical, bodily pain, general health, vitality and role emotional, having this last one the lowest score 44.0 vs.47.0; p = 0.02). The physical score was also significantly lower in all PCOS women versus controls (53.7 vs. 55.8; p = 0.01).	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes Partial No Not reported	Partial - PCOS women were younger, had higher BMI, more infertility problems, and showed lower educational and current occupation level than controls. Regarding marital status and other lifestyle factors both groups were comparable.
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
PERFORMANCE	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes
DEDETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	X% treatment X% control/ comparison Not reported	PCOS = 0% Controls=0%
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	0%
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Yes
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the	Yes Partial No Not reported	Yes - controls. For an of alpha error of 0.05 and 80% statistical power to detect differences, a minimum of 90 women would be required in each group.

	groups?		
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Low
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

Study ID	**Shafti 2016**	
Study Citation	Shafti, V. and S. Shahbazi (2016). "Comparing Sexual Function and Quality of Life in Polycystic Ovary Syndrome and Healthy Women." Journal of Family & Reproductive Health 10(2): 92-98	
Study Country	Iran	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	Married women with polycystic ovary syndrome aged between 18-45 years	
Control population	Healthy married women aged between 18-45 years	
PCOS diagnostic criteria	Rotterdam	
N per group	Assessed = 129 women with PCOS and 125 healthy women	
Setting	Cases were selected from Shahid Rajaee Hospital and infertility clinics while controls were from clinic's employees and patients' companions, Tonekabon, Iran	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	WHO quality of life (26-question brief form)	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes
Inclusion criteria	Yes Partial No Not reported	Yes Inclusion of the cases were decided by specialist's diagnosis, medical records and individual's self-report. For control group, it was done based on individual's self- report
Exclusion criteria	Yes Partial No Not reported	Yes Any known chronic diseases including psychological disorders, intake of treatments
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	No - similar method of diagnosing PCOS was not used in both groups
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	Yes as the aim of this study was to compare sexual function and quality of life of women with PCOS with normal women
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	Not applicable
Was matching performed?	Yes Partial No Not reported	
Summary Result/s	All of quality of life subscales except environment domain were significantly lower in PCOS than healthy group. Women with PCOS in term of some quality of life parameters have lower performance than healthy women**.**	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS **Were the cases and controls taken from comparable populations?**	Yes Partial No Not reported	No Hospital cases were compared with both hospital and special controls
SELECTION BIAS **Was the case definition adequate and established in a standard, valid and reliable way?**	Yes Partial No Not reported	Partial Specialist's diagnosis was used in addition to the individuals medical record and self-report

	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	No Only individuals' self-report was used to rule out PCOS in controls
PERFORMANCE	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes Partial No Not reported	No
DEDETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Yes A validated tool was used
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes A validated tool was used
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	X% treatment X% control/ comparison Not reported	Partial
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Not reported
REPORT	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Not reported Unable to judge as the participants' sociodemographic variables were not reported.
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Partial Statistical significance was observed between the groups, but no information reported on sample size determination.
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Not reported Unable to judge as there were no reported data on participants' sociodemographic characteristics, missing values, normality assumptions
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	High
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?			

Study ID	**Shishehgar 2016**
Study Citation	Shishehgar F, Tehrani FR, Mirmiran P, Hajian S, Baghestani AR (2016). "Comparison of the Association of Excess Weight on Health Related Quality of Life of Women with Polycystic Ovary Syndrome: An Age- and BMI-Matched Case Control Study." PLoS ONE [Electronic Resource] 11(10): e0162911.
Study Country	Iran
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	Women with PCOS aged 18–40 years
Control population	Age- and BMI-matched healthy women
PCOS diagnostic criteria	AE PCOS riteria

N per group		Screened = 300 women (1:1 case-control ratio) Enrolled = 282 women (142 cases and 140 controls) Assessed = 282 women (142 cases and 140 controls)	
Setting		Cases were recruited from the Reproductive Endocrinology Research Centre of Shahid Beheshti University of Medical Sciences while controls were from among women attending gynaecologic centres affiliated to Shahid Beheshti University of Medical Sciences in Tehran	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)		Health related quality of life SF-36	
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	Not applicable
Inclusion criteria		Yes Partial No Not reported	Yes Criteria of the Androgen Excess Society (AES) was used to diagnose PCOS. None of the women in the control group had any specific complaint.
Exclusion criteria		Yes Partial No Not reported	Yes Any medical illness, intake of contraceptives and medications, pregnancy, lactating
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Partial - Not clear as to whether the same criteria was applied in the control group
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Yes as the aim of the study was to compare the effects of excess body weight on HRQOL between women with PCOS and their age and BMI matched counterparts
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Not applicable
Was matching performed?		Yes Partial No Not reported	No
Summary Result/s			
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes Partial No Not reported	Yes Both cases and controls were selected from the hospital
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes the Androgen Excess Society (AES) criteria was used to diagnose cases
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Not reported Not clear as to whether the same criteria was applied in the control group
PERFORMANCE	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes Partial No Not reported	Partial
DETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes A previously validated tool was used in both cases and controls
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Yes
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Partial
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	X% treatment X% control/ comparison Not reported	Zero for both groups

	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	2 (1.3%) participants each in cases and controls
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes Groups were comparable with respect to sociodemographic characteristics such as age, BMI, educational level, marital status, etc.
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Yes - Sample size was appropriately determined using adequate power (95%)
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?			

Study ID	**Stevanovic 2019**	
Study Citation	Stevanovic, D.; Bozic-Antic, I.; Stanojlovic, O.; Vojnovic Milutinovic, D.; Bjekic-Macut, J.; Jancic, J.; Macut, D. Health-related quality of life questionnaire for polycystic ovary syndrome (PCOSQ-50): a psychometric study with the Serbian version. Women & Health 10 2019;59(9):1015-1025 2019 10 DOI: 10.1080/03630242.2019.1587664	
Study Country	Serbia	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	Women aged 18 years and above referred to the daily hospital of the Clinic of Endocrinology, Diabetes and Metabolic Disorders between October 2016 and March 2017 who were investigated for irregular menstrual bleeding, hirsutism or acne.	
Control population	Women aged 18 years and above who were referred to the clinic for different health conditions requiring endocrinologic evaluation, such as irregular menstrual bleeding, hirsutism, specific endocrinologic conditions and others.	
PCOS diagnostic criteria	Rotterdam consensus criteria	
N per group	PCOS=76 Control=28	
Setting	Gynaecology clinic	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary outcomes: Quality of life: PCOSQ-50 and WHOQOL-BREF scores. Only PCOSQ-50 scores compared to controls. Outcomes Not relevant:	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes
Inclusion criteria	Yes Partial No Not reported	Yes - women with diagnosed PCOS who had not initiated therapy.

Exclusion criteria		Yes Partial No Not reported	Yes - exclusion criteria: adolescent age below 18 years, pregnancy, Cushing's syndrome, hyperprolactinemia, thyroid dysfunction and other endocrine disorders, psychiatric, and/or neurological disorder and inability to read and write Serbian. Patients with non-classical 21-hydroxylase deficiency, hyperprolactinemia, Cushing's disease, untreated hypothyroidism, and androgen secreting tumours were excluded.
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Yes
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Yes
Was matching performed?		Yes Partial No Not reported	Not reported
Summary Result/s		Women with PCOS had significantly lower PCOSQ-50 scores than healthy control women in the hirsutism (Mean (SD) controls = 4.49 (0.08); t (df) = −3.62 (102), p < .001), obesity and menstrual disorder (Mean (SD) controls = 3.99 (0.73); t (df) = −3.41 (102), p = .001), and total PCOSQ-50 scores (Mean (SD) controls = 4.01 (0.54); t (df) = −3.09 (102), p = .03), but not for the psychosocial and emotional (Mean (SD) controls = 4.03 (0.78); t (df) = −1.69 (102), p = .09), fertility (Mean (SD) controls = 4.15 (0.65); t (df) = −1.49 (102), p = .14), sexual function (Mean (SD) controls = 3.83 (0.71); t (df) = 0.05 (70), p = .96), and coping scores (Mean (SD) controls = 3.48 (0.92); t (df) = −0.51 (102), p = .61).	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes Partial No Not reported	Partial – age differences only
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes – met criteria from the clinic database with no hyperandrogenism.
PERFORMANCE	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes
DEDETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	No
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	X% treatment X% control/ comparison Not reported	PCOS=6.2% Controls= 44%

	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	PCOS=0% Control=0%
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Yes
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	Not reported
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Partially- significantly different in age
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

Study ID	**Tan 2017**	
Study Citation	Tan, J.; Wang, Q. Y.; Feng, G. M.; Li, X. Y.; Huang, W. Increased Risk of Psychiatric Disorders in Women with Polycystic Ovary Syndrome in Southwest China. Chinese Medical Journal 02 05 2017;130(3):262-266. 2017 02 05 doi: 10.4103/0366-6999.198916	
Study Country	China	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	Outpatient women Age: PCOS=24.8±3.8; Controls=25.0±3.5 BMI: PCOS=21.4±3.0; Controls=20.8±1.9	
Control population	Women from the local community and universities in Chengdu	
PCOS diagnostic criteria	2003 Rotterdam criteria	
N per group	PCOS=120 Controls= 100	
Setting	Outpatient clinic at the Reproductive Endocrinology Division of West China Second University Hospital,	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary outcomes: SF-36 questionnaire Outcomes Not relevant:	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes
Inclusion criteria	Yes Partial No Not reported	Controls - (1) a regular menstrual cycle of 28–35 days after menarche; (2) being aged between 18 and 35 years; and (3) agreeing to participate in this survey voluntarily.
Exclusion criteria	Yes Partial No Not reported	PCOS - (1) suffering from any other conditions affecting fertility; (2) receiving treatment for psychiatric disorders; and (3) a body mass index (BMI) of <18 or >30.
		Controls - (1) suffering any other conditions except infertility; (2) being in treatment for psychiatric disorders; (3) being pregnant or lactating; and (4) a BMI of <18 or >30.
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	Cross-sectional - yes

Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	NA
Was matching performed?		Yes Partial No Not reported	Yes – age and educational experience
Summary Result/s		Patients with PCOS had decreased quality of life (p<0.001).	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes Partial No Not reported	Yes
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
PERFORMANCE	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes
DEDETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	X% treatment X% control/ comparison Not reported	PCOS=0% Controls=0%
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	PCOS=0% Controls=0%
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Yes
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Low
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

Study ID		Trent 2002	
Study Citation		Trent, M. E Rich M, Austin B, Gordon C (2002). "Quality of life in adolescent girls with polycystic ovary syndrome." Archives of Pediatrics & Adolescent Medicine 156(6): 556-560.	
Study Country		USA	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/ participants		Adolescent girls with PCOS (aged 13 to 22 years)	
Control population		Healthy adolescent girls (aged 13 to 22 years)	
PCOS diagnostic criteria		Adolescent – hyperandrogenism and menstrual irregularity	
N per group		Screened = 413 adolescents Enrolled = 293 adolescents (101 cases and 192 controls) Assessed = 283 adolescents (97 cases and 186 controls)	
Setting		Cases were recruited from the primary care practice and referral base. Healthy female adolescents presenting for routine or sports physicals, routine gynaecologic care, contraceptive management, or follow-up of a minor medical issue were selected as controls.	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)		The Child Health Questionnaire–Child Self-Report Form (CHQ-CF87)	
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	Yes
Inclusion criteria		Yes Partial No Not reported	Yes Diagnosis of PCOS was decided by hyperandrogenism (clinical or laboratory diagnosis) and menstrual irregularity
Exclusion criteria		Yes Partial No Not reported	Yes Any medical illness, pregnancy and language difficulties
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Partial - not clearly reported as to whether the same diagnostic criteria was applied to exclude PCOS in controls
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Yes - as the aims of this study were to examine HRQL in adolescents with PCOS, compared with healthy adolescents, and to determine whether clinically assessed or self-perceived severity of illness affects HRQL
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Not applicable
Was matching performed?		Yes Partial No Not reported	
Summary Result/s		Adolescents with PCOS scored lower on subscales measuring general health perceptions, physical functioning, general behavior, and limitations in family activities because of illness. Patients scored higher on the change in health in the last year subscale, and most had been diagnosed and initiated treatment for PCOS in the last year. Patients who had higher self-perceived severity of illness also scored lower on the general health perceptions subscale, but clinical severity was not associated with differences in HRQL.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes Partial No Not reported	Yes Both cases and controls were selected from the hospital
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes a previously validated criteria was used to diagnose cases
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Not reported - not clearly reported as to whether the same diagnostic criteria was applied to exclude PCOS in controls
PERFORMANCE	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes

DEDETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Yes
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes - a previously validated criteria was used
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Partial
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	X% treatment X% control/ comparison Not reported	Not applicable
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	3.9% (n=4) among cases and 3.1% (n=6) in controls
REPORT	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes Both groups were comparable in key prognostic variables such as age, BMI, ethnicity and insurance status
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	Not reported
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported. Although significant difference was observed between the groups, there was no report on sample size determination
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

Study ID	**Wang 2021**
Study Citation	Wang, Z.; Groen, H.; Cantineau, A. E. P.; van Elten, T. M.; Karsten, M. D. A.; van Oers, A. M.; Mol, B. W. J.; Roseboom, T. J.; Hoek, A. Dietary Intake, Eating Behavior, Physical Activity, and Quality of Life in Infertile Women with PCOS and Obesity Compared with Non-PCOS Obese Controls. Nutrients Oct 08 2021;13(10):08 2021 Oct 08 doi:10.3390/nu13103526
Study Country	The Netherlands
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	Women of childbearing age as part of the LIFEstyle study attending a participating fertility centre
Control population	Women attending a participating fertility centre
PCOS diagnostic criteria	Two of the three Rotterdam criteria were met
N per group	PCOS=170 Controls=321
Setting	Clinical

Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)		Primary outcomes: Outcomes Not relevant: Quality of life: SF-36	
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	Yes
Inclusion criteria		Yes Partial No Not reported	Partial – further explained in original RCT paper that is cited.
Exclusion criteria		Yes Partial No Not reported	Partial – further explained in original RCT paper that is cited.
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Cross-sectional
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	NA
Was matching performed?		Yes Partial No Not reported	No
Summary Result/s		Both the physical quality of life (mean difference: −1.26, 95% CI: −3.29 to 0.76, p = 0.22) and mental quality of life scores (mean difference: 0.45, 95% CI: −1.72 to 2.62, p = 0.69) were similar between the groups.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes Partial No Not reported	Yes
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
PERFORMANCE	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes
DEDETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Yes
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	X% treatment X% control/ comparison Not reported	PCOS= 0% Control=0%
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	O% O%
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Yes
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Partial – age was significantly different between groups

OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	Yes – person in conflict did not collect data, complete analysis, data interpretation or write the report.
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	**Yes**
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Low
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 2

Question 2.1.

1) In women with PCOS, what is the prevalence and severity of reduced QoL?

2) In women with PCOS, what dimensions of QoL are most affected?

BACKGROUND:

Health-related quality of life (HRQoL), a multidimensional construct, encompassing impacts of health, illness, and treatment on an individual's quality of life (1). QoL has consistently been shown to be poorer in women with PCOS when compared to women without PCOS (2, 3, 4). Global variation in the manifestations (5), suggests impacts are strongly underpinned by socio-cultural influences.

Women with PCOS consistently report higher prevalence and severity of reduced QoL compared to women without PCOS. Dimensional variability reported according to measurement tools used and between populations studied.

QoL tools are generally divided into generic measures that have broad application across different types and severity of diseases, and, disease-specific measures designed to assess particular diseases or patient populations (6).

Both generic and PCOS specific tools are used to measure HRQoL in the women with PCOS. Generic tools include the Short Form -36 (SF-36) (8) and, the WHO- BREF (9). Designed for use in the general population, these tools primarily focus on issues such as mobility, impact on work, pain, environment and vulnerability illnesses. An important limitation of generic tools is the lack of sensitivity to PCOS specific features such as infertility and hirsutism; however, they do enable QoL comparisons across affected and non-affected populations of women.

Commonly used PCOS specific tools include PCOSQ (9) and the modified PCOSQ (MPCOSQ) (4) and the PCOSQ-50 (10). The PCOSQ has 26 items, measuring emotions (8 items), body hair (5 items), weight (5 items), infertility difficulties (4 items) and menstrual problems (4 items) and graded on a seven-point scale. The MPCOSQ is similar to the PCOSQ with an additional four more items on acne. The PCOSQ-50 was developed to overcome the measurement shortcomings and measures PCOS-related HRQOL aspects and well-being and includes two domains important for these women, but overlooked in the previous measures, namely sexual functioning and hirsutism.

The main criticisms of these tools are that they are do not capture QoL impacts beyond the physical manifestations, with calls for the development of tools based on a broader conceptual model of QoL. Commonly used tools are limited by a narrow conceptual model of QoL. Further work is needed to strengthen HRQoL tools, to enable a comprehensive determination on the HRQoL in women with PCOS.

GRADE EVIDENCE CERTAINTY	
Comparison	GRADE for critical outcomes
Comparison 1. Women with PCOS versus controls	QoL -Physical (hirsutism, weight, menstrual irregularities, infertility) Mental health Emotional/psychological Bodily pain Vitality Environment Social functioning Sexual health General health

Evidence to Recommendations Framework

COMPARISONS (option versus other option)

Comparison 1. Adult women with PCOS vs controls
o Intervention 1.1 Short-Form Health Survey 36 (SF 36)
o Intervention 1.2 WHO Quality of Life-BREF (WHOQOL-BREF)
o Intervention 1.3 PCOS Health related Quality of Life Questionnaire (PCOSQ)

Comparison 2. Adolescent females with PCOS vs controls
o Intervention 2.1 Paediatric Quality of Life Inventory

EVIDENCE-BASED RECOMMENDATION(S)

- **EBR:** Health professionals and women should recognise the adverse impact of PCOS and/or PCOS features on quality of life in adults.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

PRACTICE POINT

- Women with PCOS should be asked about their perception of PCOS-related symptoms, impact on quality of life, key concerns and priorities for management.

GRADE CONSIDERATIONS

Justifications:
Despite significant limitations with current tools, there is consistent evidence of lower quality of life in PCOS.
The GDG 2 panel did not consider that population level differences in dimension scores are important to the individual woman.

Subgroup considerations:
Adolescents with PCOS may have different quality of life concerns and there is limited evidence in this population.

Implementation considerations:
Need for education and awareness about quality of life for women with PCOS, and health professionals.

Monitoring and evaluation considerations:
No monitoring and evaluation in clinical settings.

Research priorities:
Further research is required in adolescents and adults to develop a PCOS specific HRQoL tool that addresses the limitations of current tools. Current screening tools are too generic or too focused on symptoms to identify QoL impacts.

GRADE framework

GRADE DECIDE **Interactive Evidence to Decision Framework**

● DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:
See Part 1- Evidence Summary and GRADE document.

Panel discussion:
-What is the purpose of measuring QoL in women with PCOS?
It is acknowledged that understanding QoL can potentially inform policy-makers, direct treatment and requires the use of generic and PCOS specific tools.

● UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:
See Part 1- Evidence Summary and GRADE document.

Panel discussion:

● CERTAINTY OF THE EVIDENCE

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☐ Very low	☒ Low	☐ Moderate	☐ High

Research evidence:
See Part 1- Evidence Summary and GRADE document.

Panel discussion:
Certainty of evidence is low based on observational data but evidence is consistent across disease specific and generic tools.

● VALUES

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☐ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☒ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Research evidence:
No research evidence was identified

Panel discussion:

● BALANCE OF EFFECTS

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☒ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:
It is considered imperative for health professionals to ask and to understand the impact of features on quality of life for shared decision making and to inform treatment priorities.

● COSTS

How large are the resource requirements (costs)?

Judgement:

☒ Don't know	☐ Varies	☐ Large costs	☐ Moderate costs	☐ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:
No research evidence was identified

Panel discussion:

● CERTAINTY OF COST EVIDENCE

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:
No research evidence was identified

Panel discussion:

● COST-EFFECTIVENESS

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:
No research evidence was identified

Panel discussion:

● EQUITY

What would be the impact on health equity?

Judgement:

☐ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☐ Probably increased	☒ Increased

Research evidence:
No research evidence was identified

Panel discussion:

● ACCEPTABILITY

Is the option acceptable to key stakeholders?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

Research evidence:
No research evidence was identified

Panel discussion:

● FEASIBILITY

Is the option feasible to implement?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

Research evidence:
No research evidence was identified

Panel discussion:

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PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by the Evidence Team (Aya Mousa, Jillian Tay)

Other Members: Loyal Pattuwage, Tusyita Menon, Ladan Yeganeh, Darren Rajit, Shrinkhala Dawadi

GDG 2

Question 2.2.

In women with PCOS, what is the prevalence and severity of depression and anxiety?

1. STUDY SELECTION

Table 1. PICO Criteria for Inclusion	
Question	2.2 In women with PCOS, what is the prevalence and severity of depression and anxiety? CLINICAL PRACTICE POINTS: - Should anxiety and depression be assessed as part of standard care? - In women with PCOS, what tools/methods can be used to assess depression and/or anxiety?
Clinical leads (key contacts)	Anuja Dokras, Melanie Gibson-Helm
Allocation ranking	Level 2 - systematic review update

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(language, year)*
Inclusion	Women with PCOS. PCOS diagnosed by Rotterdam criteria/ National Institutes of Health/ Androgen Excess and PCOS society criteria	Validated screening tool for anxiety or depression. Note down tools. Diagnosis of depression.	Women without PCOS.	Prevalence or incidence of anxiety or depression. Scores on anxiety or depression tools.	Systematic reviews. Observational studies.	English language. Full text publication. Human studies.
Exclusion	Unrelated to PCOS. PCOS induced by valproate use PCOS in combination with other diseases. Idiopathic hyperandrogenism. Hyperandrogenism caused by other diseases	None	None	Health related quality of life Quality of life Mental health Psychological distress	Full text not available Abstracts Posters PhD theses Narrative reviews, letter to editor, editorials etc.	

2. SEARCH STRATEGY

Search details	
Search strategy source: update from Cooney LG, Lee I, Sammel MD, Dokras A. High prevalence of moderate and severe depressive and anxiety symptoms in polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod. 2017 May 1;32(5):1075-1091. doi: 10.1093/humrep/dex044. PMID: 28333286.	
Evidence source	**Date of search**
Medline (Ovid)	04/08/2022
PsychInfo (Ovid)	04/08/2022
EMBASE	04/08/2022
All EBM (Ovid)	04/08/2022
CINAHL	Not conducted (not included in Coonet et al., 2017)
Any subsequent updates - enter database and date: not applicable	

Questions addressed by this search:		
GDG	Q#	Question
2	2.2	In women with PCOS, what is the prevalence and severity of depression and anxiety?
		CLINICAL PRACTICE POINTS: - Should anxiety and depression be assessed as part of standard care? - In women with PCOS, what tools/methods can be used to assess depression and/or anxiety?

Search strategy

Search strategy used by Cooney et al., 2017 was followed to retrieve studies from 2016 onwards.
[Cooney LG, Lee I, Sammel MD, Dokras A. High prevalence of moderate and severe depressive and anxiety symptoms in polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod. 2017 May 1;32(5):1075-1091. doi: 10.1093/humrep/dex044. PMID: 28333286.]

Medline

1 Polycystic Ovary Syndrome/
2 pcos.mp.
3 polycyst$ ovar$.mp.
4 Stein Leventhal Syndrome/
5 stein leventhal$.mp.
6 or/1-5
7 exp Depression/
8 exp Depressive Disorder/
9 depress$.mp.
10 exp Anxiety/
11 exp Anxiety Disorder/
12 (anxiet$ or anxious$).mp.
13 exp Mental Disorders/
14 (panic or phobi$ or nervous).mp.
15 exp Mood Disorders/
16 (bipolar or cyclothym$ or dysthym$ or affective).mp.
17 or/7-16
18 6 and 17
19 limit 18 to (english language and humans and yr="2016 -Current")

Embase

1 Polycystic Ovary Syndrome/
2 pcos.mp.
3 polycyst$ ovar$.mp.
4 Stein Leventhal Syndrome/
5 stein leventhal$.mp.
6 or/1-5
7 exp major depression/
8 exp Depressive Disorder/
9 depress$.mp.
10 exp Anxiety/

11	exp Anxiety Disorder/
12	(anxiet$ or anxious$).mp.
13	exp Mental Disorders/
14	(panic or phobi$ or nervous).mp.
15	exp Mood Disorders/
16	(bipolar or cyclothym$ or dysthym$ or affective).mp.
17	or/7-16
18	6 and 17
19	limit 18 to (english language and humans and yr="2016 -Current")

PsycINFO

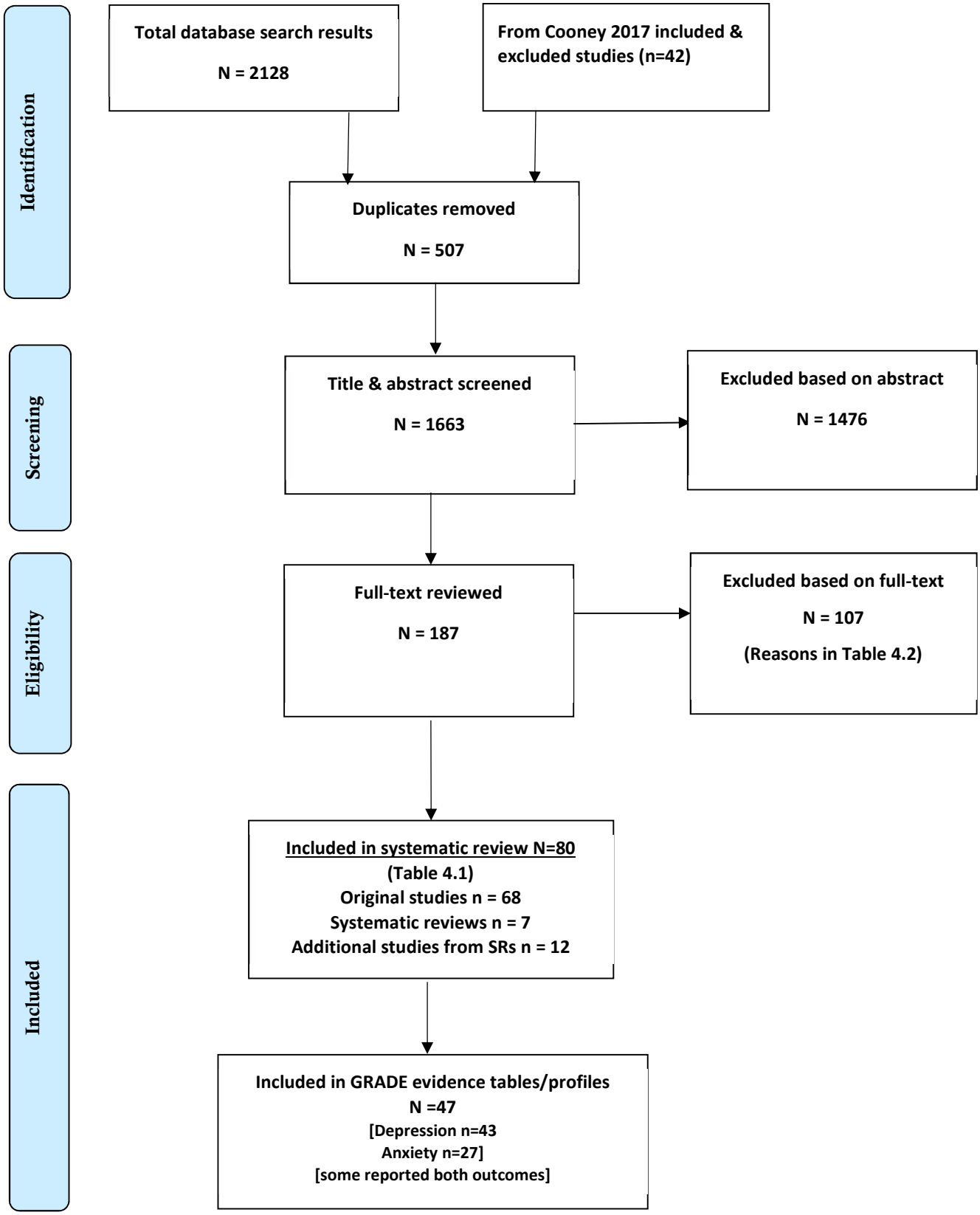
1	exp Endocrine Sexual Disorders/
2	pcos.mp.
3	polycyst* ovar*.mp.
4	stein leventhal*.mp.
5	or/1-4
6	exp major depression/
7	exp "Depression (Emotion)"/
8	depress$.mp.
9	exp Anxiety/
10	exp Anxiety Disorder/
11	(anxiet$ or anxious$).mp.
12	exp Mental Disorders/
13	(panic or phobi$ or nervous).mp.
14	exp Mood Disorders/
15	(bipolar or cyclothym$ or dysthym$ or affective).mp.
16	or/6-15
17	5 and 16
18	limit 17 to (human and english language and yr="2016 -Current")

EBM Reviews

1	Polycystic Ovary Syndrome/
2	pcos.mp.
3	polycyst$ ovar$.mp.
4	Stein Leventhal Syndrome/
5	stein leventhal$.mp.
6	or/1-5
7	exp Depression/
8	exp Depressive Disorder/
9	depress$.mp.
10	exp Anxiety/
11	exp Anxiety Disorder/
12	(anxiet$ or anxious$).mp.
13	exp Mental Disorders/
14	(panic or phobi$ or nervous).mp.
15	exp Mood Disorders/
16	(bipolar or cyclothym$ or dysthym$ or affective).mp.
17	or/7-16
18	6 and 17
19	limit 18 to (english language and humans and yr="2016 -Current")

Evidence processing: Studies were selected and appraised by 2 reviewers using study selection and appraisal criteria (PICO above) established a priori. The articles were reviewed by title and abstract by 2 reviewers. When a decision could not be made based on title and abstract alone, full text was retrieved. **A total of 80 studies met inclusion criteria for this review.**

3. SEARCH RESULTS - PRISMA flowchart



4. STUDY INCLUSION

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4.2 Excluded studies (on full text assessment)

#	Title	Author/year	Journal	Vol	Pages	Notes
1	Quality of life and emotional states of depression, anxiety and stress in adolescents with polycystic ovary syndrome: A cross-sectional study	Naz 2020	Psychology Research and Behavior Management Vol 13 2020, ArtID 203-209	13		Wrong comparator
2	An evaluation of psychosocial and socio-demographic factors associated with metabolic syndrome and cardiovascular risk in polycystic ovary syndrome cases and controls	Cipkala-Gaffiin 2021	Dissertation Abstracts International: Section B: The Sciences and Engineering	82		Wrong study design
3	Frequency and predictors of comorbid depression in polycystic ovary syndrome	Hasan 2020	Endocrine Practice	26(SUPPL 2)	237	conference abstract/protocol/trial register
4	Increased risk of eating disorders in women with polycystic ovary syndrome	Lee 2016	Fertility and Sterility	106(Supp 3)	e260-e261	conference abstract/protocol/trial register
5	The effect of depression and anxiety on cognitive performance in women with polycystic ovary syndrome	Mehrabadi 2016	International Journal of Fertility and Sterility	10(Supp 1)	95	conference abstract/protocol/trial register
6	Healthcare providers' knowledge, diagnosis and management of polycystic ovary syndrome (PCOS) in Europe, North America and internationally	Gibson-Helm 2017	Human Reproduction	32(Supplement 1)	i33-i34	conference abstract/protocol/trial register
7	Assessment of Psychological Distress in Polycystic Ovarian Syndrome Infertile Patients at a Tertiary Level Infertility Care Centre in India	Nayar 2019	Fertility and Sterility	112(3 SUPPL)	e394	conference abstract/protocol/trial register
8	The Correlation between Mental Health and Number of Symptoms Endorsed on a Review of Systems Form in Polycystic Ovary Syndrome	Sundaram 2018	Fertility and Sterility	110(4 SUPPL)	e114	conference abstract/protocol/trial register
9	Polycystic ovary syndrome, personality, and depression: A twin study	Cesta 2017	European Neuropsychopharmacology	27(Supplement 4)	S752	conference abstract/protocol/trial register
10	Psychiatric disorders in reproductive age women with polycystic ovarian syndrome: A literature review	Azizi 2017	Journal of Reproduction and Infertility	18(2 Supplement 2)	202	conference abstract/protocol/trial register
11	Prevalence of psychological distress in polycystic ovarian syndrome (PCOS) infertile patients and non PCOS infertile controls and their relationship with clinical-biochemical parameters of the syndrome	Nayar 2019	Human Reproduction	34(SUPPL 1)	i411	conference abstract/protocol/trial register
12	Disordered Eating Pathology in Polycystic Ovary Syndrome: Prevalence and Predictors in a Longitudinal Cohort	Greenwood 2018	Fertility and Sterility	110(4 SUPPL)	e7	conference abstract/protocol/trial register
13	The predictors of quality of life in women with polycystic ovarian syndrome	Aliasghari 2017	International Journal of Nursing Practice	23		Wrong comparator
14	Depression and anxiety in women with polycystic ovary syndrome and its biochemical associates	Batool 2016	Journal of SAFOG	8(1)	44-47	Wrong patient population
15	Polycystic Ovary Syndrome Is Associated With Adverse Mental Health and Neurodevelopmental Outcomes	Berni 2018	Journal of Clinical Endocrinology & Metabolism	103	2116-2125	Wrong patient population
16	Polycystic ovary syndrome and psychiatric disorders: Co-morbidity and heritability in a nationwide Swedish cohort	Cesta 2016	Psychoneuroendocrinology	73	196-203	Wrong patient population

17	Depression and Anxiety in Polycystic Ovary Syndrome: Etiology and Treatment	Cooney 2017	Current Psychiatry Reports	19	83	Wrong study design
18	Depression, anxiety and perceived stress in women with and without PCOS: a community-based study	Damone 2019	Psychological Medicine	49	1510-1520	Wrong patient population
19	Association among depression, symptom experience, and quality of life in polycystic ovary syndrome	Greenwood 2018	American Journal of Obstetrics and Gynecology	219(3)	279.e1 - 279.e7	Wrong study design
20	Female infertility, infertility-associated diagnoses, and comorbidities: a review	Hanson 2017	Journal of Assisted Reproduction & Genetics	34	167-177	Wrong patient population
21	A mixed-methods study of coping and depression in adolescent girls with polycystic ovary syndrome	Hopkins 2019	Journal of the American Association of Nurse Practitioners	31	189-197	Wrong comparator
22	How Common are Depressive-Anxiety States, Body Image Concerns and Low Self-Esteem in Patients of PCOS?	Joshi 2022	Journal of Obstetrics and Gynecology of India	72(1)	72-77	Wrong comparator
23	Depression symptoms and quality of life in women with polycystic ovary syndrome	Kocak 2022	Perspectives in psychiatric care.	23		Wrong comparator
24	Body image and its relationships with sexual functioning, anxiety, and depression in women with polycystic ovary syndrome	Kogure 2019	Journal of Affective Disorders	253	385-393	Wrong comparator
25	Risk of developing major depressive disorder in polycystic ovary syndrome: a retrospective cohort study	Lee 2021	Journal of Obstetrics & Gynaecology	41	1157-1161	Wrong study design
26	Psychological Distress in Women Living with Polycystic Ovary Syndrome: The Role of Illness Perceptions	Light 2021	Womens Health Issues	31	177-184	Wrong study design
27	The Prevalence and Factors Associated With Anxiety-Like and Depression-Like Behaviors in Women With Polycystic Ovary Syndrome	Lin 2021	Frontiers in Psychiatry	12 (no pagination)		Wrong study design
28	Predictors of Depression in Iranian Women with Polycystic Ovarian Syndrome	Mirghafourv and 2018	Community Mental Health Journal	54	1274-1283	Wrong comparator
29	Clinician vs Self-ratings of Hirsutism in Patients With Polycystic Ovarian Syndrome: Associations With Quality of Life and Depression	Pasch 2016	JAMA Dermatology	152	783-8	Wrong comparator
30	Obesity and psychological wellbeing in patients undergoing fertility treatment	Rodino 2016	Reproductive Biomedicine Online	32	104-12	Wrong patient population
31	Young women's psychological distress after a diagnosis of polycystic ovary syndrome or endometriosis	Rowlands 2016	Human Reproduction	31	2072-81	Wrong patient population
32	A study on physical and physiological impact of polycystic ovary syndrome	SathishKumar 2021	International Journal of Pharmaceutical Sciences Review and Research	69(2)	145-149	Wrong patient population
33	Psychiatric comorbidities and adverse childhood experiences in women with self-reported polycystic ovary syndrome: An Australian population-based study	Tay 2020	Psychoneuroendocrinology Vol 116 2020, ArtID 104678	116		Wrong patient population
34	Polycystic Ovary Syndrome: Personality and Temperamental Characteristics	Urban 2022	Journal of Obstetrics & Gynaecology Canada: JOGC	44	813-818	Wrong patient population
35	Polycystic ovarian syndrome: Prevalence and impact on the wellbeing of Australian women 16-29 years	Varanasi 2017	Australian and New Zealand Journal of Obstetrics and Gynaecology	57(Supplement 1)	28	conference abstract/protocol/trial register
36	The mental health of Chinese women with polycystic ovary syndrome is related to sleep disorders, not disease status	Yang 2021	Journal of Affective Disorders	282	51-57	Wrong comparator

37	The mental health of women with polycystic ovary syndrome: a systematic review and meta-analysis	Yin 2020	Human Reproduction	35(SUPPL 1)	i395	conference abstract/protocol/trial register
38	Phenotypic features and fertility outcomes of women with polycystic ovary syndrome: The effect of quality of life	Zhang 2021	Journal of Obstetrics and Gynaecology Research	47(1)	233-242	Wrong comparator
39	Motivational interviewing in obese women with polycystic ovary syndrome - a pilot study	Moeller 2019	Gynecological Endocrinology	35	76-80	Wrong comparator
40	Increased prevalence of eating disorders, low self-esteem, and psychological distress in women with polycystic ovary syndrome: a community-based cohort study	Tay 2019	Fertility & Sterility	112	353-361	Wrong patient population
41	Metformin improves the depression symptoms of women with polycystic ovary syndrome in a lifestyle modification program	Alhussain 2020	Patient Preference and Adherence	14	737-746	Wrong comparator
42	Sexual functioning as predictor of depressive symptoms and life satisfaction in females with polycystic ovary syndrome (Pcos)	Shakil 2020	Pakistan Journal of Medical Sciences	36(7)	1500-1504	Wrong comparator
43	Free testosterone is related to aspects of cognitive function in women with and without polycystic ovary syndrome	Sukhapure 2022	Archives of Women's Mental Health	25	87-94	Wrong patient population
44	Evaluation of depression and anxiety in women with polycystic ovary syndrome by physician trainees	Pakhdikian 2020	Journal of Investigative Medicine	68(1)	A168	Wrong patient population
45	The impact of peer-led support groups on health-related quality of life, coping skills and depressive symptomatology for women with PCOS	Ranasinghe 2021	Psychology, health & medicine		1-10	Wrong study design
46	Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome	Teede 2018	Clinical Endocrinology	89(3)	251-268	Wrong study design
47	Enduring Depression in Polycystic Ovary Syndrome: Results of a Longitudinal Study	Greenwood 2018	Fertility and Sterility	110(4 SUPPL)	e66	Wrong comparator
48	Evaluation of clinical manifestations, health risks, and quality of life among women with polycystic ovary syndrome	Sidra 2019	PLoS ONE [Electronic Resource]	14	e0223329	Wrong comparator
49	An exploration of the hypothesis that testosterone is implicated in the psychological functioning of women with polycystic ovary syndrome (PCOS)	Barry 2018	Medical Hypotheses	110	42-45	Wrong study design
50	Exploratory study of a screening measure for polycystic ovarian syndrome, quality of life assessment, and neuropsychological evaluation	Boivin 2020	BMC Women's Health	20	132	Wrong patient population
51	Factors affecting the adoption of health-promoting behaviours in patients with polycystic ovary syndrome: a cross-sectional study	Guo 2022	BMJ Open	12	e056478	Wrong comparator
52	The feasibility of progressive resistance training in women with polycystic ovary syndrome: A pilot randomized controlled trial	Vizza 2016	BMC Sports Science, Medicine and Rehabilitation	8(1) (no pagination)		Wrong study design
53	Inositol treatment for psychological symptoms in Polycystic Ovary Syndrome women	Cantelmi 2021	European Review for Medical & Pharmacological Sciences	25	2383-2389	Wrong study design
54	Insulin resistance is associated with depression risk in polycystic ovary syndrome	Greenwood 2018	Fertility and Sterility	110(1)	27-34	Wrong study design
55	Objectification and ambiguity of body image in women with Polycystic Ovary Syndrome: A mixed-method study	Yin 2022	Journal of Affective Disorders	310	296-303	Wrong comparator
56	The impact of depression, self-esteem, and body image on sleep quality in patients with PCOS: a cross-sectional study	AziziKutenaee 2020	Sleep & Breathing	24	1027-1034	Wrong patient population

57	Loss of attributes of femininity, anxiety and value crisis. Women with polycystic ovary syndrome compared to women after mastectomy and in menopause	Macik 2016	Health Psychology Report	4	1-11	Wrong patient population
58	Mental health and body image in polycystic ovary syndrome	Lee 2020	Current Opinion in Endocrine and Metabolic Research	12	85-90	Wrong study design
59	Higher incidence of postpartum complications in women with polycystic ovary syndrome	Alur-Gupta 2019	Fertility and Sterility	112(3 Supplement)	e39	Wrong study design
60	Association between depression risk and polycystic ovarian syndrome in young women: a retrospective nationwide population-based cohort study (1998-2013)	Harnod 2019	Human Reproduction	34	1830-1837	Wrong patient population
61	Psychosomatic aspects of polycystic ovarian syndrome: A review	Azizi 2017	Iranian Journal of Psychiatry and Behavioral Sciences	11(2)		Wrong study design
62	Understanding and supporting women with polycystic ovary syndrome: A qualitative study in an ethnically diverse UK sample	Hadjiconstantinou 2017	Endocrine Connections	6(5)	323-330	Wrong study design
63	Prevalence and associated risk factors for mental health problems among patients with polycystic ovary syndrome in Bangladesh: A nationwide cross-Sectional study	Hasan 2022	PLoS ONE [Electronic Resource]	17	e0270102	Wrong patient population
64	Prevalence of anxiety and depression among women with Polycystic Ovary Syndrome living in war versus non-war zone countries: A randomized controlled trial assessing a pharmacist intervention	Alkoudsi 2020	Research In Social & Administrative Pharmacy	16	689-698	Wrong study design
65	Polycystic ovary syndrome and postpartum depression symptoms: a population-based cohort study	Koric 2021	American Journal of Obstetrics & Gynecology	224	591.e1 - 591.e12	Wrong patient population
66	The polycystic ovary syndrome quality of life scale (PCOSQOL): Development and preliminary validation	Williams 2018	Health Psychology Open Vol 5(2), 2018, ArtID 2055102918788195	5		Wrong outcomes
67	Perinatal mental health in women with polycystic ovary syndrome: A cross-sectional analysis of an australian population-based cohort	Tay 2019	Journal of Clinical Medicine	8(12) (no pagination)		Wrong patient population
68	Endocrine evaluation and management of anovulutaory infertility in females	Balasubramanian 2017	Journal of Endocrinology, Metabolism and Diabetes of South Africa	22(1)	21	Wrong study design
69	Evaluation of the Clinical and Psychological Impact of Vitamin D Replacement in Adolescent Females at Risk for Polycystic Ovarian Syndrome (PCOS)					Wrong study design
70	Insulin resistance and anti-mullerian hormone impact depression risk in PCOS	Greenwood 2017	Fertility and Sterility	108(3 Supplement 1)	e70	Wrong study design
71	An Integrated Self-Management Intervention for Adolescents With Polycystic Ovary Syndrome					Wrong study design
72	IRIS: Methodological assessment of psychopathological disease in a cohort of hirsute women	Javor 2017	Giornale Italiano di Dermatologia e Venereologia	152(2)	132-139	Wrong patient population
73	Patient-reported impact of hirsutism on health-related quality of life, mood and self-esteem in patients with polycystic ovary syndrome	He 2016	Journal of the American Academy of Dermatology	1)	AB66	Wrong comparator

74	A mixed methods study of coping and depression in adolescent girls with polycystic ovary syndrome	Hopkins 2017	Dissertation Abstracts International: Section B: The Sciences and Engineering	78		Wrong comparator
75	Impaired olfactory function in patients with PCOS	Koseotlu 2016	Journal of the Turkish German Gynecology Association	17(Supplement 1)	S155	Wrong outcomes
76	Polycystic Ovary Syndrome in adolescents: A qualitative study	Naz 2019	Psychology Research and Behavior Management Vol 12 2019, ArtID 715-723	12		Wrong study design
77	Depression and anxiety in women with polycystic ovarian syndrome: a literature survey	Zehravi 2021	International Journal of Adolescent Medicine & Health	33	367-373	Wrong study design
78	Health related quality of life and psychological parameters in different polycystic ovary syndrome phenotypes: a comparative cross-sectional study	Fatemeh 2021	Journal of ovarian research	14	57	Wrong comparator
79	Polycystic Ovary Syndrome and Risk of Five Common Psychiatric Disorders Among European Women: A Two-Sample Mendelian Randomization Study	Jin 2021	Frontiers in Genetics	12 (no pagination)		Wrong intervention
80	Association among Depression, Symptom Experience, and Quality of Life in Polycystic Ovary Syndrome	Greenwood 2018	Obstetrical and Gynecological Survey	73(12)	691-692	Wrong study design
81	Obstructive Sleep Apnea Risk Is Associated with Lower Health-Related Quality of Life in Women with Polycystic Ovary Syndrome	Zhou 2021	Fertility and Sterility	116(3 SUPPL)	e122	conference abstract/protocol/trial register
82	Blue Morpho Survey: Increased anxiety, depression and body dysmorphia in PCOS	Sheikh 2021	BJOG: An International Journal of Obstetrics and Gynaecology	128(SUPPL 2)	247	conference abstract/protocol/trial register
83	Androgen Excess- Polycystic Ovary Syndrome Society: position statement on depression, anxiety, quality of life, and eating disorders in polycystic ovary syndrome	Dokras 2018	Fertility & Sterility	109	888-899	Wrong study design
84	Fundamental concepts and novel aspects of polycystic ovarian syndrome: Expert consensus resolutions	Aversa 2020	Frontiers in Endocrinology	11 (no pagination)		Wrong study design
85	Outcomes of a Mindfulness-Based Healthy Lifestyle Intervention for Adolescents and Young Adults with Polycystic Ovary Syndrome	Young 2022	Journal of Pediatric and Adolescent Gynecology	35(3)	305-313	Wrong intervention
86	Body Image Distress (Bid) Contributes to Increased Risk of Anxiety and Depressive Symptoms in Women with Polycystic Ovary Syndrome (Pcos)	Alur-Gupta 2018	Fertility and Sterility	110(4 SUPPL)	e114-e115	conference abstract/protocol/trial register
87	Evaluation of quality of life of patients with hirsutism among Turkish women: A single-center cross-sectional study	Kutlu 2020	Journal of Cosmetic Dermatology	19	3053-3057	Wrong intervention
88	Oral carnitine supplementation influences mental health parameters and biomarkers of oxidative stress in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial	Jamilian 2017	Gynecological Endocrinology	33	442-447	Wrong intervention
89	Increased risk of psychiatric disorders in PCOS women in southwest China	Huang 2016	Gynecological Endocrinology	32(Supplement 1)	128	conference abstract/protocol/trial register
90	Motivational interviewing in obese women with polycystic ovary syndrome;a pilot study	Moeller 2019	Gynecological Endocrinology	Vol.35	76-80p	Wrong intervention
91	The facial expression of emotions recognition in patients with polycystic ovary syndrome	Czyzyk 2016	Gynecological Endocrinology	32(Supplement 1)	78	conference abstract/protocol/trial register

92	Correlates and prevalence of anxiety disorders among women with polycystic ovarian syndrome (PCOS): a Malaysian cross-sectional study	Francis 2018	European Psychiatry	48(Supplement 1)	S220	conference abstract/protocol/trial register
93	Is there the relationship between anxiety and depression level and clinical presentation of polycystic ovary syndrome in adolescent girls?	Zachurzok 2019	Hormone Research in Paediatrics	91(Supplement 1)	192	conference abstract/protocol/trial register
94	Psychiatric aspects in endocrinolgical disorders: Identifying depressive and anxiety in endocrine patients attending outpatient department - A study from general hospital in Kashmir (India)	Shoib 2016	British Journal of Medical Practitioners	9(3) (no pagination)		Wrong patient population
95	Endocrine disorders and psychiatric manifestations	Salvador 2021	Endocrinology (Switzerland)		311-345	Wrong study design
96	Factors affecting the prevalence of depressive symptoms in women with PCOS	Banaszewska 2016	Gynecological Endocrinology	32(Supplement 1)	132	conference abstract/protocol/trial register
97	International evidence-based guideline for the assessment and management of polycystic ovary syndrome-Lifestyle management and models of care Guideline Development Group	Moran 2019	Obesity Research and Clinical Practice	13(3)	323	conference abstract/protocol/trial register
98	No difference in quality of life or depression/anxiety diagnosis between middle-aged women with PCOS and age-matched controls	Forslund 2019	Maturitas	124	154	conference abstract/protocol/trial register
99	Women with polycystic ovary syndrome are at increased risk of postnatal depression	Davies 2018	Human Reproduction	33(Supplement 1)	i321-i322	conference abstract/protocol/trial register
100	Polycystic ovarian syndrome-related depression in adolescent girls: A Review	Sadeeqa 2018	Journal of Pharmacy and Bioallied Sciences	10(2)	55-59	Wrong study design
101	Infertility-related stress and quality of life among infertile women with polycystic ovary syndrome: Does body mass index matter?	Li 2022	Journal of Psychosomatic Research	158 (no pagination)		Wrong intervention
102	Empowering women with PCOS	TheLancet 2019	The Lancet Diabetes and Endocrinology	7(10)	737	Wrong study design
103	Sex hormones, mood, cognitive function and emotion processing in women	Sukhapure 2017	New Zealand Medical Journal	130(1459)	80	conference abstract/protocol/trial register
104	Clinical course of depression symptoms and predictors of enduring depression risk in women with polycystic ovary syndrome: Results of a longitudinal study	Greenwood 2019	Fertility & Sterility	111	147-156	Wrong comparator
105	Characterization of Depression Phenotypes in Women with Polycystic Ovary Syndrome	Dayo 2021	Fertility and Sterility	116(3 SUPPL)	e110-e111	Wrong comparator
106	Quality of life and psychological wellbeing in polycystic ovary syndrome.	Bernard 2007	Hum Reprod.	22 (8)	2279-86	Self-reported PCOS
107	Sleep and Psychological Well-Being: Is Obstructive Sleep Apnea Associated with Depression and anxiety In women with polycystic Ovary Syndrome?	Zhou 2020	Fertility and Sterility	114(3 SUPPL)	e61	Wrong comparator

5. STUDY CHARACTERISTICS TABLE

#	First author, Year, Country	PCOS diagnosis/ Setting	Study design	N, Age (yrs), BMI (kg/m^2)		Outcomes assessed / Screening tool	Depression score Mean (SD) (Unless reported otherwise)		Depression (n) prevalence		Anxiety Score Mean (SD) (Unless reported otherwise)		Anxiety (n) prevalence	
				PCOS	Comparison		PCOS	Comparison	PCOS	Comparison	PCOS	Comparison	PCOS	Comparison
1	Acmaz, 2013 Turkey	Rotterdam/ Education and Research Hospital of Medicine	Cross sectional	86 3 PCOS sub groups: Hirsutism- acnea n=35 Age = 26.14 ± 4.98 BMI = 24.45 ± 2.75 Infertility: n = 22 24.32 ± 4.59 24.35 ± 3.48 Obesity: n=29 Age = 26.00 ± 6.58 BMI = 33.59 ± 2.61	47 Healthy volunteers in reproductive age/ Community Age = 27.77 ± 6.49 BMI = 23.37 ± 3.13	Depression BDI (Turkish version) Anxiety BAI	n=35 Hirsutism-acnea: 24.46 (9.76) n=22 Infertility:30.59 (11.31) n=29 Obesity:19.10 (8.52)	12.28 (6.35)	NR	NR	Median (IQR): Hirsutism-acnea: 20.00 (14-26) Infertility: 13.50 (10.00-21.00) Obesity: (24.00)	Median (IQR) 12 (9.00–16.00)	NR	NR
2	Adali, 2008 Turkey	Rotterdam/ Outpatient clinics	Case control	42 Age = 23.54 ± 3.13 BMI = 28.42 ± 4.30	42 Age-matched healthy women Age (19-29) yrs Age = 24.45 ± 2.47 BMI = 24.11 ± 4.14	Depression BDI (Turkish version) Anxiety NA	11.69 (9.49)	5.8 (4.58)	BDI score ≥11: 14 (BDI ≥11-16 mild, ≥17 moderate to severe)	BDI score ≥11: 5 (BDI ≥11-16 mild, ≥17 moderate to severe)	NA	NA	NA	NA
3	Ahmadi 2020 Iran	Rotterdam/ Infertility clinic	Case control	201 Age = 25 (5) Age 18-25 =55 Age 26-30 =76 Age 31-35 =46 Age 36-47 =24	199 Matched for age, education, infertility period Age = 30 (5) Age 18-25 = 36 Age 26-30 = 63 Age 31-35 = 61 Age 36-47 = 39	Depression Millon Clinical Multi-axial Inventory-III (MCMI-III) Anxiety Millon Clinical Multi-axial Inventory-III (MCMI-III)	42 (23)	35 (24)	OR = 1.01 (95% CI 1.001-1.02) crude OR	NR	53 (21)	49 (22)	NR	NR

4	Akdag Cirik 2016 Turkey	Rotterdam/ clinic	cross-sectional	101 Two subgroups: NIH phenotype n=54 Age = 24.70 ± 4.39 BMI = 25.84 ± 4.81 non-NIH phenotype n=47 Age = 24.15 ± 4.08 BMI = 23.88 ± 8.45	49 Age = 26.29 ± 5.17 BMI = 24.44 ± 3.88	Depression HADS Anxiety HADS	Overall = 7.00 (4.0) NIH = 7.00 (3.25) non-NIH = 7.00 (4.0)	6.0 (2.0)	Overall = 47 (46.5%) NIH = 25 (46.3%) non-NIH = 22 (46.8)	10 (20.4)	Overall = 10.00 (5.0) NIH = 10.00 (4.0) non-NIH = 10.00 (4.0)	8.0 (3.0)	Overall = 34 (33.7%) NIH = 17 (31.5%) non-NIH = 17 (36.2)	6 (12.2%)
5	Aksu 2019 Turkey	Rotterdam/ Clinic [excluded: BMI >25, previous or present psychiatric diagnosis]	Case control	50	42 age = 33.26 (5.59) Matched for age and BMI	Anxiety State-Trait Anxiety Inventory -1 and -2	NA	NA	NA	NA	STAI-1 = 54.80 (7.235) STAI-2 = 53.93 (5.821)	STAI-1 = 46.31 (6.949) STAI-2 = 50.74 (8.148)	-	-
6	Almis 2021 Turkey	Rotterdam/ Clinic [Exclusion - hx of chronic diseases, psychiatric diagnosis, anatomic anomalies, malignancy etc.,]	case control (matched for age)	153 Adolescents (13-18 yrs) Age = 15.57 ± 1.11 BMI = 21.84 ± 3.47	161 Adolescents (13-18 yrs) Age = 15. ± 1.05 BMI = 20.53 ± 2.75	Depression Children's Depression Inventory (CDI) Anxiety Piers-Harris Children's Self-Concept Scales (PHCSCS) State-Trait Anxiety Inventory for children (STAI-C) # #Consists of 2 subscales: State Anxiety Subscale (SAS) and Trait Anxiety Subscale (TAS)	CDI score = 17.6 (8.45)	CDI score = 11.75 (7.35)	CDI >=19 = 60 (39.2%)	CDI >=19 = 34 (21.1)	PHCSCS Anxiety score = 6.12 (3.34) STAI-C = 78.94 (14.52) TAS = 39.07 (7.88) SAS = 39.86 (7.8)	PHCSCS Anxiety score = 8.97 (11.16) STAI-C = 68.02 (11.16) TAS = 34.13 (5.84) SAS = 33.99 (7.01)	TAS 20-39 = 77 (50.3%) TAS 40-60 = 76 (49.7%) SAS 20-39 = 80 (52.3%) SAS 40-60 = 73 (47.7%)	TAS 20-39 = 130 (80.7%) TAS 40-60 = 31 (19.3%) SAS 20-39 = 130 (80.7%) SAS 40-60 = 31 (19.3%)

7	Altinkaya 2014 Turkey	Rotterdam/ University faculty	Case control	50 Age = 23.7 ± 5.3 BMI = 25.1 ± 3.7	50 Age matched women who had regular menses and no clinical or biochemical hyper-androgenism or PCO Age = 24.4 ± 5.7 BMI = 22.1 ± 2.7	Depression BDI (Turkish version) Anxiety BAI	Median (IQR) 8.5 (4-20)	Median (IQR) 6 (2-20)	Minimal 31 (62.0%) Mild 4 (8.0%) Moderate 15 (30.0%) Severe 0(0)	Minimal 45 (90.0%) Mild 2 (4.0%) Moderate 3 (6.0%) Severe 0(0)	median (IQR) 8 (3-26)	median (IQR) 5 (4-18)	Minimal 24 (48.0%) Mild 9 (18.0%) Moderate 15 (30.0%) Severe 2 (4.0%)	Minimal 24 (48.0%) Mild 1 (2.0%) Moderate 4 (30.0%) Severe 0 (0)
8	Alur-Gupta 2019 USA	Rotterdam/ Clinic	Cross-sectional	189 Age (median and range) = 29.3 (18.1-47.4) BMI (median and range) = 32.1 (17.8-57.1)	225 Age (median and range) = 32.1 (19.7-49.8) BMI (median and range) = 30.9 (17.3-54.4) [Enrollment was targeted to recruit women of similar BMI to the PCOS group]	Depression HADS >=8 Anxiety HADS >=8	5.1 (NR)	4.5 (NR)	HAD >=8 = 28%	HAD >=8 = 19.2%	10.1 (NR)	8.4 (NR)	HAD >=8 = 76.5%	HAD >=8 = 56.5%
9	Annagür, 2014 Turkey	Rotterdam/ Gyn clinic	Case control	83 Age = 22.27±1.84 BMI = 23.85±4.67	64 Age = 22.85 ± 2.06 22.00±2.43 [Healthy women/ employees at University Hospital]	Depression BDI (Turkish version) Anxiety NA	14.6 (8.54)	6.07 (3.85)	NR	NR	NR	NR	NA	NA
10	Asdag 2020 Saudi Arabia	Rotterdam/ clinic	Case-control	82 Age <=25 = 21 (25.6) Age 26-35 = 31 (37.8) Age >=36 = 30 (36.6) BMI = NR	85 Age <=25 = 14 (16.5) Age 26-35 = 54 (63.5) Age >= 36 = 17 (20) BMI = NR	Depression Depression, Anxiety and Stress Scale 21 Anxiety Depression, Anxiety and Stress Scale 21	NR	NR	Depression 57 (69.5%) Mild 17 (29.82%) Moderate 37 (64.91) Severe 3 (5.26)	Depression 40 (47.1%) mild 37 (92.5) Moderate 3 (7.5) Severe 0	NR	NR	Anxiety 54 (65.9%) Mild 2 (3.7) Moderate 17 (31.48) Severe 35 (64.81)	Anxiety 39 (45.9%) Mild 4 (10.25) Moderate 35 (89.74) Severe 0

11	Asik, 2015 Turkey	Rotterdam/ Endocrine outpatient clinic	Case control	71 Age = Median (range) 22 (18–32) BMI = 27 (17–47)	50 Healthy controls Age = Median (range) 24 (18–37) BMI = 21 (16-37)	Depression HADS Anxiety HADS	6.1 (3.75)	3.54 (2.79)	30	7	8.59 (4.52)	5.98 (3.05)	25	6
12	Balikci 2014 Turkey	Rotterdam/ NR	Case-control	44 Age = 27.4 ± 6.1 BMI = 24.2 ± 4.3 [excluded - smoking or had type 2 diabetes mellitus	44 Age = 27.3 ± 5.6 BMI = 21.1 ± 2.3 BMI matched healthy women	Depression Beck Depression Inventory (BDI) [BDI <9 = no depression BDI 10-15 = mild BDI 17-23 = medium BDI >=17 = depression] Anxiety Beck Anxiety Inventory (BAI)	14 (4)	9 (2)	NR	NR	14 (4)	9 (6)	NR	NR
13	Barry 2011 UK	Rotterdam/ Gyn clinic	Case control	76	49 Women with fertility issues not related to PCOS	Depression HADS [Mild: 8–10 Moderate: 11–14 Clinical: 15–21] Anxiety HADS [Mild: 8–10 Moderate: 11–14 Clinical: 15–21]	4.88 (1.98)	2.76 (2.04)	NR	NR	9.99 (4.56)	7.57 (4.12)	NR	NR
14	Basirat 2019 Iran	Rotterdam/ Clinic	Case control	120 Age = 29.55 ± 5.17 BMI = <25 41 ± 34.2 25-29.99 45 ± 37.5 ≥30 34 ± 28.3	120 Age = 29.33 ± 6.23 BMI = <25 29 ± 24.2 25-29.99 52 ± 43.3 ≥30 39 ± 32.5 (matched for age, level of education, duration of infertility)	Depression Beck Depression Inventory II [0-13: minimal depression 14-19: mild depression 20-28: moderate depression 29-63: severe depression] Anxiety NA	18.06 (12.03)	15.65 (11.76)	Minimum 31 (26.1%) Mild 35 (29.4%) Moderate 33 (27.7) Severe 20 (16.8)	Minimum 46 (39.0) Mild 27 (22.9) Moderate 33 (28.0) Severe 12 (10.1)	NA	NA	NA	NA

15	Basirat 2020 Iran	Rotterdam/ Clinic	Case control	135 Age = 29.5 ± 5.62 BMI = NR	122 Age = 29.46 ± 5.16 BMI = NR (matched for duration of infertility, level of education, age)	Depression NA Anxiety State-Trait Anxiety Inventory	NA	NA	NA	NA	TAS = 46.19 (5.25) SAS =. 49.55 (5.10)	TAS = 44.49 (5.13) SAS = 49.22 (4.66)	aOR TAS 1.063 (1.013-1.116) aOR SAS 0.956 (0.894-1.022) variables adjusted unclear	NA
16	Battaglia 2008 Italy	Rotterdam/ /NR	Case control	25 Age = 27.7 ± 5.4 BMI = 21.6 ± 2.4	18 Age = 30.7 ± 3.9 BMI = 21.2 ± 2.0 Healthy Caucasian (native Italians), non-hirsute heterosexual volunteers	Depression BDI [10–18 mild/moderate depression; 19–29 moderate/severe depression; 30–63 severe depression] Anxiety NA	NR	NR	5 (mild to mod) 1 (mod to severe)	3 (mild to mod) 1 (mod to severe)	NA	NA	NA	NA
17	Benson 2009 Germany	NIH/ Endocrine outpatient clinics	Case-control	32 Age = 30.1 ± 0.9 BMI = 29.8 ± 1.6 [50% on metformin, 50% not on metformin. Antidepressants were excluded]	32 Age = 31.5 ± 1.1 BMI = 28.7 ± 1.5 (BMI matched)	Depression Global Severity Score (GSS) Positive Symptom Distress Index (PSDI) Beck Depression Inventory (BDI) [BDI >=11-17 = mild-mod depression BDI >=18 severe depression] Anxiety NA	GSS = 53 (1.9) PSDI = 54 (2.1) BDI= 9.7 (1.4)	GSS = 48 (1.5) PSDI = 49 (1.7) BDI = 4.9 (0.9)	Mild-mod = 13 (44.8%) Severe = 5 (17.2%)	Mild-mod = 3 (9.4%) Severe = 0	NA	NA	NA	NA

18	Benson 2020 USA	NIH/ Tertiary children's hospital	Cross sectional, Retrospective chart review [Age 11-17yrs, obese (BMI >=95th centile for age/sex) or overweight (BMI 85-94 centile for age/sex)]	47 Age (median, IQR) = 15.6 (14.6, 16.8) BMI (median, IQR) = 34.9 (30.9, 41.8)	44 T2DM Age (median, IQR) = 14.51 (12.5, 16.5) BMI (median, IQR) = 34.8 (29.6, 42.6)	Depression Center for Epidemiologic Studies-Depression (CES-D) scale [0-15 none 16-23 mild 24-60 severe any depression = CES-D >= 16] Anxiety NA	NR	NR	PCOS any 60% mild 30% severe 30% PCOS+T2DM any 78% mild 7% severe 71%	T2DM any 39% mild 18% severe 21%	NA	NA	NA	NA
19	Benson 2008 Germany	Aligns with Rotterdam criteria#/ Endocrine clinic #PCOS was established when either oligomenorrhea or amenorrhea and either clinical signs of hyper-androgenism and/or an elevated testosterone	Case control	57 Age = mean ± SEM* 28.9 ± 0.7 BMI <25: 32% BMI ≥25–<30: 20% BMI ≥30: 48% * standard error of mean	28 Healthy women Age = mean ± SEM* 29.9 ± 1.2 BMI <25: 62% BMI ≥25–<30: 31% BMI ≥30: 8% [women with a similar age-range and hormonal and immunological markers in the community]	Depression BDI (score ≥11) Anxiety NA	10.1 (1 SEM)	5.9 (1.4)	26	5	NA	NA	NA	NA

20	Besenek 2021 Turkey	NIH/ clinic	Case control	39 Age (median, IQR) = 17.0 (2.0) BMI (mean, SD) = 24.3 (5.71) 11-18 yrs who did not receive hormonal treatment for PCOS	37 Age (median, IQR) = 17.5 (2) BMI (mean, SD) = 19.6 (3.03) (unsure of matching variables)	Depression Beck Depression Inventory Anxiety State-Trait Anxiety Inventory -1 and -2 [Social Anxiety Scale for adolescents; FNE = Fear of Negative Evaluation; SDA-general = Social Avoidance and Distress in general; SDA-new = Social Avoidance and Distress in new situations]	median (IQR) 13 (10)	median (IQR) 12 (13)	-	-	SAS 41.08 (8.78) TAS 46.21 (9.25) Total 87.28 (16.25) SAS-A FNE median (IQR) 16 (9) SDA-general median (IQR) 9 (6) SDA-mew 16.46 (5.09) Total 44.23 (16.47)	SAS 41.57 (10.61) TAS 47.19 (11.18) Total 88.76 (20.75) SAS-A FNE median (IQR) 4 (8) SDA-general median (IQR) 9 (5) SDA-mew 16.46 (5.25) Total 41.24 (13.07)	-	-
21	Bhattacharya 2010 India	Rotterdam/ Gyn clinic	Cross sectional	117 Age: NR BMI: NR	84 Age: NR BMI: NR Women with regular menses and no hyperandrogenism (21-32 yrs)	Depression PHQ-9 Anxiety NA	NR	NR	75	20	NA	NA	NA	NA
22	Borghi 2018 Italy	NIH/ Clinic	Case control	30 Age = 33.7 (5.7) BMI = 33.35 (5.85) All infertile, 15 taking metformin	30 Age = 35.5 (4.6) BMI 23.46 (3.43) (age matched, non-PCOS women referring to Reproductive Medicine Unit for infertility)	Depression Symptom Checklist-90 Revision Positive Symptom Distress Inndex (PSDI) Anxiety Symptom Checklist-90 Revision Positive Symptom Distress Index (PSDI)	SCL-90-R Depression (median) 0.70 (IQR) 0.21-0.94 PSDI (median) 33 (IQR) 25.75-45.50	SCL-90-R Depression (median) 0.48 (IQR) 0.13-0.98 PSDI (median) 19 (IQR) 13.25-35.75	NR	N R	SCL-90-R Anxiety (median) 0.45 (IQR) 0.20-0.93	SCL-90-R Anxiety (median) 0.20 (IQR) 0.10-0.45	NR	NR

23	Caltekin 2021 Turkey	Rotterdam/ Clinic	Case-control	73 Age = 26.03 ± 5.02 BMI = 25.9 ±4.37	63 Age = 27.35 ± 5.3 BMI = 24.6 ± 4.34 Healthy women volunteers	Depression Beck's Depression Inventory Anxiety Beck's Anxiety Inventory (BAI)	BDI median 15 (range) 5-46	BDI median 5 (range) 0-24	NR	NR	BAI median 14 (range) 2-59	BAI median 6 (range) 1-28	NR	NR
24	Cinar, 2011 Turkey	Rotterdam/ University endocrinology unit	Cross sectional	226 Age = 23.2 + 5.2 BMI = 24.7 + 5.7	85 Age = 24.4 + 4.0 BMI = 23.4 + 5.4 BMI matched healthy women/ community	Depression BDI, Mod≥17 Anxiety HADS, mod≥11	6.4 (4.1)	NR	64	4	9.3 (4.3)	NR	95	5
25	Dag 2017 Turkey	Rotterdam/ Clinic	Case control	53 Age = 22.69 ± 4.54 BMI = 23.36 ± 4.44	38 Age = 2.34 ± 2.12 BMI = 20.83 ± 3.16 Age-matched regularly menstruating and nulliparous women	Depression HADS Anxiety HADS	5.47 (2.97)	5.23 (3.96)	NR	NR	7.67 (4.2)	7.39 (3.88)	NR	NR
26	Davari Tanha 2013 Iran	Rotterdam/ Infertility clinic	Case control	110 Age = 29.59 ± 5.60 BMI = 30.54 ± 4.10	110 Age = 30.99 ± 7.30 BMI = 29.03 ± 3.40 Infertile women with normal menstruation cycles	Depression Evaluation by psychiatrist Anxiety NA	NR	NR	88	96	NA	NA	NA	NA
27	Deeks 2011 Australia	Rotterdam/ survey?	Cross sectional	177 Age = 32.8 ± 7.8 BMI = 31.5 ± 7.9	109 Age = 41.9 ± 15.4 BMI = 24.5 ± 5.4 Healthy women-community and internet advertising	Depression HADS Anxiety HADS	5.7 (3.7)	3.3 (3.1)	NR	NR	9.5 (3.9)	6.5 (3.6)	NR	NR

28	Deniz 2020 Nigeria	PCOS diagnosed by two of the following ESHRE-ASRM criteria: 1) oligo/ amenorrhea; 2) clinical or biochemical hyperandrogenism 3) polycystic ovaries at ultrasound examination when all other endocrine causes are excluded. Clomiphene resistance not stated/ private Gyn & Obs centre	Stated by authors: Cross-sectional study (Naturalistic)	100 [2 case subgroups: with and without fertility, n=50 with infertility n=50 with fertility] Age: PCOS = 32.0 ± 4.0 PCOS + Infertility = 31.7 ± 3.7 BMI: PCOS = 25.1 ± 2.2 PCOS + Infertility = 27.9 ± 2.9	50 Age: 31.0 +/- 4.0, BMI: 25.5 +/- 2.3 Healthy, no PCOS, no infertility	Female Sexual Function NA Depression Beck Depression Inventory Anxiety NA	PCOS: 10.96 (5.12) PCOS + Infertility: 12.74 (4.56)	9.22 (4.24)	NR	NR	NA	NA	NA	NA
29	Dobbaloglu 2022 Turkey	NIH/ Multi-centre study	Case control (13-18 years)	51 Age = 15.72 ± 1.32 BMI = 24.3 ± 5.1	49 Age = 15.53 ± 1.77 BMI = 20.6 ± 2.48 (Age matched healthy volunteers)	Depression Beck's depression inventory [0-9 minimal 10-18 mild 19-29 moderate 30-63 severe] Anxiety State-Trait Anxiety Inventory	13.42 (9.94)	9.56 (6.72)	49 included in analysis minimal 20 mild 15 moderate 12 severe 2	48 included in analysis minimal 29 mild 15 moderate 3 severe 1	SAS 40.77 (10.44) TAS 44.60 (13.16)	SAS 36.64 (6.89) TAS 40.02 (7.61)	NR	NR
30	Dybciak 2022 Poland	Rotterdam/ endocrine clinic	Case control (age matched)	230 Age 2-25 = 86 (37.39%) Age 26-30 = 102 (44.35%) Age 31-40 = 42 (18.26%) underweight = 6 (2.61%) normal weight = 108 (46.96%) overweight = 59 (25.65%) obese = 57 (24.78%)	199 Age 2-25 = 75 (37.69%) Age 26-30 = 90 (45.23%) Age 31-40 = 34 (17.09%) underweight = 15 (7.54%) normal weight = 149 (74.87%) overweight = 30 (15.08%) obese = 5 (2.51%) Healthy controls	Depression HADS 0-7 no issues 8-10 mild 11-14 moderate 15-21 severe Anxiety HADS 0-7 no issues 8-10 mild 11-14 moderate 15-21 severe	6.9 (NR)	4.2 (NR)	none 58.3% mild 23.5% moderate 13.9% severe 4.3%	None 83.9% mild 10.1% moderate 6.0% severe 0	10.6 (NR)	7.3 (NR)	none 25.7% mild 28.3% moderate 26.1% severe 20.0%	none 60.8% mild 13.6% moderate 21.1% severe 4.5%

31	Elsenbruch 2003 Germany	NIH/ Endocrine clinics	Case control	50 Age = 28.4 ± 5.0 BMI = 30.1 ± 9.8	50 Age = 29.9 ± 5.7 BMI = 24.4 ± 5.3 Healthy women/ health screening program for employees	Depression SCL-90 Anxiety SCL-90	NR	NR	NR	NR	NR	NR	NR	NR
32	Emeksiz 2018 Turkey	Rotterdam/ Clinic	Case control (Age 16-19 years)	80 Age = 17.23 ± 1.15 BMI (median, IQR) = 24.7 (21.0, 29.06)	50 Age = 17.00 ± 0.99 BMI (median, IQR) = 24.3 (20.1, 27.3) (Healthy adolescents matched for age and BMI from general population)	Depression Child Depression Inventory Anxiety Screen for Child Anxiety Related Emotional Disorders (SCARED)	CDI median 19 (IQR 13-22)	CDI median 16 (IQR 12-20)	NR	NR	SCARED (median) total 24 (IQR) 19.0-31 Panic disorder 6 (IQR) 4-7 Generalised anxiety disorder 6 (IQR) 5-9 Separation anxiety disorder 4 (IQR) 3-5 Social anxiety disorder 7 (IQR) 4-8 Significant school avoidance 1.5 (IQR) 1-3	SCARED (median) total 21 (IQR) 16-26 Panic disorder 5.5 (IQR) 4-7 Generalised anxiety disorder 5 (IQR) 4-7 Separation anxiety disorder 4 (IQR) 3-5 Social anxiety disorder 5.5 (IQR) 4-7 Significant school avoidance 1 (IQR) 0-2	NR	NR

33	Enjezab 2013 Iran	Rotterdam/ clinic	Cross-sectional	62 Age = 29.97 ± 6.85 BMI = 29.16 ± 6.56	61 Age = 29.49 ± 7.44 BMI = 25.66 ± 5.48 Non-PCOS	Depression Beck Depression Short Inventory (BDI-S) [0-4 no depression 5-7 minimal 8-15 moderate >=16 Severe depression] Anxiety NA	7.47 (5.54)	7.57 (5.77)	Normal = 22 (35.5) Mild = 17 (27.4) Mod = 17 (27.4) Severe = 6 (9.7)	Normal = 24 (39.3) Mild = 15 (24.6) Mod = 12 (19.7) Severe = 10 (16.4)	NA	NA	NA	NA
34	Ercan, 2013 Turkey	Rotterdam/ Gyn clinic	Case control age-matched	32 Age = 27.4 ± 3.3 BMI = 25.5 ± 3.0	32 Age = 27.0 ± 3.2 BMI = 24.4 ± 3.6 Age-matched healthy females	Depression BDI (BDI scores ≥17 have been reported to identify depression Anxiety NA	12.3 (4.1)	8.7 (2.7)	NR	NR	NA	NA	NA	NA
35	Ghazeeri 2013 Lebanon	Rotterdam/ Tertiary care centre	Case control (Adolescent girls aged 14-18 years)	20 Age = 16.7 ± 1.1 BMI = 26.3 ± 4.2	17 Age = 16.4 ± 1.3 BMI = 21.1 ± 2.55 Healthy age-matched girls	Depression BDI Anxiety Screen for Child Anxiety Related Emotional Disorders (SCARED)	16 (11.1)	10 (10.1)	NR	NR	Total SACRED: 6.8 (4.25) SACRED Generalized Anxiety: 4.55 (2.42)	Total SACRED: 5.24 (5.06) SACRED Generalized Anxiety: 4.18 (3.50)	NR	NR
36	Ghazeeri 2022 Lebanon	Rotterdam/ Clinic	cross-sectional	49 Age = 25.0 ± 4.7 BMI = NR	50 Age = 28.1 ± 5.3 BMI = NR	Depression HADS Anxiety HADS	3.3 (2.7)	4.7 (3.4)	NR	NR	5.5 (4)	5.9 (3.7)	NR	NR
37	Glowinska 2020 Poland	Rotterdam/ Clinic	Case control	96 Age = 28.6 ± 0.5 BMI = 26.5 ± 0.6	47 Age = 29.5 ± 0.7 BMI = 23.5 ± 0.7 Healthy women matched for age and social parameters from community	Depression Beck Depression Inventory Anxiety State-Trait Anxiety Inventory 1 = SAS 2 = TAS	10.1 (0.74) SEM	6.4 (0.8) SEM	BDI 10-16 mild = 32.3% BDI > 16 = 12.5%	BDI 10-16 mild = 10.6% BDI >16 = 6.4%	SAS 42.9 (1.1) SEM TAS 45.5 (1.0) SEM	SAS 38.4 (1.3) SEM TAS 42.3 (1.4) SEM	NR	NR

38	Greenwood 2019 USA	NIH/ Multicentre clinic CARDIA study. The study enrolled 5115 men and women ages 18 to 30 years at an initial visit between 1985 and 1986 and followed them for 30 years. Subject recruitment occurred at four study centers across the US	Longitudinal population - based cohort	83 Baseline age = 26.8 (3.7) Baseline BMI = 26.3 (6.8) 33 (40%) Black 50 (60%) White	1044 Baseline age = 27.3 (3.6) Baseline BMI = 25.6 (6.3) Non-PCOS	Depression Centre for Epidemiologic Studies-Depression (CES-D) Anxiety NA	Mixed-effects models to quantify effect of PCOS on lifetime depression symptom scores: adjusted for - age, BMI, race, education, exercise output, and study center crude coef 2.1 (95% CI 1.09, 3.19; P , 0.001) adjusted coef 2.51; 95% CI 1.49, 3.54; P , 0.001; White population crude coef 2.59 (1.32, 3.87) adjusted coef 2.62 (1.37, 3.87) Black population crude coef 2.54 (0.82, 4.26) Adjusted coef 2.25 (0.54, 3.95)		Mixed-effects logistic regression models to examine effect of PCOS Diagnosis on Positive Depression Screens (CES-D ‡ 16) Across the Lifespan adjusted for - age, BMI, race, education, exercise output, and study center crude OR 1.79 (1.02, 3.14) adjusted OR 2.11 (1.24, 3.58)					

39	Hahn 2005 Germany	NIH/ clinic	Cross-sectional	120 Age = 29 ± 5.4 BMI = 31 ± 9.3	50 Age = 30 ± 5.7 BMI = 24 ± 5.3 Healthy women	Depression SCL-90R PSDI Anxiety NA	SCL-90-R scales: Depression = 0.88 (0.72) PSDI = 1.66 (0.77)	SCL-90-R scales: Depression = 0.49 (0.55) PSDI = 1.23 (0.37)	NR	NR	SCL-90-R scales: Anxiety = 0.57 (0.61)	SCL-90-R scales: Anxiety = 0.40 (0.60)	NR	NR
40	Harmanci, 2013 Turkey	Rotterdam/ Gyn clinic	Cross sectional	42 Age = 22.5 ± 3.6 BMI = 22.8 ± 5.5	42 Age = 22.9 ± 3.7 BMI = 22.5 ± 3.7 Healthy women	Depression BSI Anxiety BSI	8.4 (5.9)	5.1 (4.8)	NR	NR	7.6 (6.2)	4.6 (4.4)	NR	NR
41	Harnod,2020 Taiwan	women aged 15–49 years with newly diagnosed PCOS/ NIH or Rotterdam/ Sub-dataset from the National Health Insurance Research Database (NHIRD). This sub-dataset contains 1 million residents randomly selected from all beneficiaries in Taiwan's NHI program. All subjects were followed up until the occurrence of anxiety, death, or withdrawal from the NHI program, or December 31, 2013 reflecting the country's entire population	Retrospective cohort study	7,026 Age = 27.74 ± 6.81 Follow up duration: 5.62 ± 3.94 Infertility (n): 1437, 20.45% [women aged 15–49 years with newly diagnosed PCOS (ICD9 code: 256.4) from 1996 to 2013]	28,104 Age = 27.75 ± 6.82 Follow up duration: 5.59 ± 3.93 Infertility (n): 875, 3.1% [Randomly selected women without histories of PCOS and anxiety as the comparison cohort in which its size was fourfold of that of the PCOS cohort. In addition, the comparison cohort was frequency-matched by birth year, and a year was randomly selected, matching the index year of the PCOS case]	Depression (ICD9 codes: 296.2, 296.3, 300.4, and 311) - as determined from NHIRD claims Anxiety A woman was considered to have anxiety (ICD9 code: 300) if she had at least two related outpatient diagnoses or at least one related inpatient diagnosis by a psychiatrist	-	-	83	235	-	-	606 events at end of follow-up period (15.34 / 1000 person-years)	2017 events at end of follow up period (12.84 / 1000 person-years)
42	Himelein 2006 USA	Rotterdam/ Reproductive endocrinology clinic	Cross sectional	40 Age = NR BMI = NR	100 From Infertility clinic (n=40) & Community control (n=60)	Depression Short form BDI Moderate: ≥13 Anxiety NA	7.85 (7)	Infertility: 4.56 (5.03) Community control: 3.61 (4.08)	11	Infertility: 4 Community control: 1	NA	NA	NA	NA

43	Holinrake 2007 USA	Rotterdam/ Reproductive endocrinology clinic	Case control	103 Age = 29.8 ± 6.2 BMI = 34.9 ± 8.5	103 Age = 30.7 ± 8.5 BMI = 25.4 ± 4.7 Women without PCOS seen during the same time period	Depression PRIME-MD PHQ & BDI Anxiety PRIME-MD PHQ & BDI	11.9 (11.1)	4.5 (5.9)	36	11	NR	NR	14	1
44	Hussain 2015 India	National Institute of Health/National Institute of Child Health and Human Development/ outpatient clinic	Cross sectional	110 Age = 24.77 ± NR	40 Age = 22.65 ± NR Healthy women	Psychiatric Disorders: Depression Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition criteria by means of Mini International Neuro-psychiatric Interview Anxiety Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition criteria by means of Mini International Neuropsychiatric Interview	NR	NR	26	3	NR	NR	17	0
45	Jedel, 2010 Sweden	Rotterdam/ NR	Case control	30 Age = median (min-max) 28.0 (21.0-37.0) BMI = median (min-max) 24.8 (18.2-40.3)	30 Age = median (min-max) 27.8 (22.0–35.0) BMI = median (min-max) 24.7 (19.3-41.6) Women in community without any of the symptoms listed for potential PCOS	Depression Montgomery Asberg Depression Rating Scale (MADRS-S) – cut-off ≥11 Anxiety BSA-S: sum total > 11	median 10 (IQR) NR	median 5.5 (IQR) NR	16	6	median 10.5 (IQR) NR	median 5 (IQR) NR	19	4

46	Karjula 2017 Finland	Self-reported or answered Yes to (1) Is your menstrual cycle longer than 35 days more than twice a year (OA)? AND (2) Do you have excessive body hair (H)? Setting: Northern Finland birth cohort 1966 (NFBC1966), a unique longitudinal data set comprising follow-up of all individuals with expected birth in 1966 in the Northern Finland area (5889 females)	Population-based follow-up. - once at age 31 and at age 46	At first follow up, age 31 (n = 125 at second follow up, age 31 (n = 86) Two subgroups: first follow up at age 31, and at age 46	At first follow up, age 31 (n =2188) at second follow up, age 31 (n= 1628) Two subgroups: first follow up at age 31, and at age 46 Setting: Northern Finland birth cohort 1966 (NFBC1966), a unique longitudinal data set comprising follow-up of all individuals with expected birth in 1966 in the Northern Finland area (5889 females)	Psychological distress (Hopkins Symptom Check List -25, self-reported depression from physician diagnosis, socioeconomic status, BMI, serum testosterone, sex hormone globulin Depression Hopkins Symptom Checklist - 25 Depression Anxiety Hopkins Symptom Checklist - 25 Anxiety	At first follow up, age 31 Median: 1.40 (Q1-Q3: 1.15-1.67) At second follow up, age 46 Median: 1.27 (Q1-Q3: 1.12-1.62)	At first follow up, age 31 Median: 1.27 (Q1-Q3: 1.33-1.53) At second follow up, age 46 Median: 1.27 (Q1-Q3: 1.07-1.59)	At first follow up, age 31: 24 (19.4%) At second follow up, age 46: 11 (17.4%)	At first follow up, age 31: 277 (12.7%) At second follow up, age 46: 245 (15.2%)	At first follow up, age 31 Median: 1.30 (Q1-Q3: 1.20-1.60) At second follow up, age 46 Median: 1.30 (Q1-Q3: 1.11-1.60)	At first follow up, age 31 Median: 1.20 (Q1-Q3: 1.10-1.40) At second follow up, age 46 Median: 1.20 (Q1-Q3: 1.10-1.40)	At first follow up, age 31: 19 (16.1%) At second follow up, age 46: 15 (12.8%)	At first follow up, age 31: 179 (8.2%) At second follow up, age 46: 134 (8.3%)
47	Kirmizi 2020 Turkey	Rotterdam/ Tertiary centre	Not indicated: description suggestive of case-control study	50 Two subgroups: PCOS Fertile: n=20 PCOS Infertile: n=30 PCOS Fertile: Age = 23.8 ± 4.05 BMI = 27.62 ± 3.77 PCOS Infertile: Age = 26.13 ± 4.66 BMI = 26.19 ± 6.02	30 Age = 31.9 ± 4.73 BMI = 25.08 ± 4.84 Healthy volunteers	Depression Beck Depression Inventory (BDI) Anxiety NA	PCOS Fertile: 17 (8.91) PCOS Infertile: 15.63 (5.53)	8.3 (5.57)						
48	Komarowska, 2013 Poland	Rotterdam/ NR	Cross sectional	20 Age = NR BMI + NR	20 Age = NR BMI + NR Healthy women with regular menstrual cycles matched for age, BMI and education	Depression BDI Anxiety STAI	NR	NR	NR	NR	48 (NR)	40 (NR)	NR	NR

49	Koseoglu, 2016 Turkey	Rotterdam/ University Gyn & Obs dept.	Case-control study	30 Age = 24.13 ± 0.01 BMI = NR (excluded BMI >30)	25 Age = 28.5 ± 7.8 BMI = NR Age matched healthy volunteers with regular menses	Depression Beck Depression Inventory (BMI) Anxiety NA	18.7 (4.1)	9.2 (1.3)	NR	NR	-	-	-	-
50	Laggari 2009 Greece	Rotterdam/ Obs & Gyn clinic	Cross sectional (aged≤20 yrs)	22 Age = 16.95 ± 2.00 BMI = 24.63 ± 6.42	22 Age = 17.04 ± 2.16 BMI = 20.70 ± 2.97 Healthy eumenorrheic adolescents-age-matched	Depression BDI Mild: 20-29 Mod: 30-39 Anxiety STAI	12.82 (7.86)	10.32 (7.19)	Mild:6	Mild:2	36.55 (10.44)	31.5 (8.24)	NR	NR
51	Lee 2017 USA	Rotterdam/ PCOS centre	Cross-sectional study	148 Age = 28.12 ± 5.13 BMI: 33.85 ± 8.90	106 Age = 28.12 ± 5.13 BMI: 33.85 ± 8.90 Patients presenting for general gynaecologic care	Depression Hospital Anxiety & Depression Scale Anxiety Hospital Anxiety & Depression Scale	4.84 (4.22)	3.09 (3.21)	18	4	9.41 (5.08)	6.72 (3.87)	61	18
52	Li 2017 China	Rotterdam/ Reproductive Medical Centre	Open-label, prospective, non-randomized, observational study, age matched	103 Age (n) 20 - 25: 18 26 - 30: 51 31 - 35: 25 >=36: 9	110 Age (n) 20 - 25: 18 26 - 30: 51 31 - 35: 25 >=36: 9 Infertile patients with male factor infertility, female factor infertility, with normal ovarian reserve, age-matched	Depression Symptom Checklist-90 (DEP) [Score range: 0 - 4, 4 indicative of worse indications] Anxiety Symptom Checklist-90 (ANX) [Score range: 0 - 4, 4 indicative of worse indications]	16 (0.6)	1.5 (0.5)	-	-	Raw data not reported - only results with significant differences (Depression)	Raw data not reported - only results with significant differences (Depression)	Raw data not reported - only results with significant differences (Depression)	Raw data not reported - only results with significant differences (Depression)

53	Mansson, 2008 Sweden	Rotterdam/ Department of gyn & obs	Case control	49 Age = 35.9 ± 10.4 BMI = 29.1 ± 7.4	49 Age = 35.9 ± 10.4 BMI = 23.5 ± 3.0 Age-matched women with no known PCOS and no oligo- or amenorrhea/ population registry	Depression MINI NPI by Psychiatrist: Any Major Depressive Episodes Anxiety MINI NPI by Psychiatrist: Generalized Anxiety	NR	NR	33	17	NR	NR	6	1
54	Mansson 2011 Sweden	Rotterdam/ Infertility clinic	Cross-sectional	49 (see Mansson 2008 above)	49 (see Mansson 2008 above) Woman born on the same day, identified from the population registry	Depression Psychological general well-being scale (PGWB) Lower scores more severe distress Anxiety Psychological general well-being scale (PGWB)	12.4 (2.7)	13.5 (1.9)	NR	NR	17 (5.9)	18.9 (4)	NR	NR
55	March 2018 Australia	Rotterdam/ Setting: Based on retrospective cohort study women born 1973 - 1975 in a large maternity hospital in Adelaide, SA	Cross-sectional study	52 Age (n) <30 years: 12 >= 30 years: 40 BMI (n) <25: 12 =<25 BMI <30: 8 >= 30: 29	514 Age (n) <30 years: 111 >= 30 years: 403 BMI (n) <25: 227 =<25 BMI <30: 128 >= 30: 137	Current depression: Centre for Epidemiological Studies Depression Scale (CES-D) [≥16 indicates clinical depression] Self-reported post-natal depression Anxiety NA	-	-	CES-D > 16: 22 Self-reported Post-natal depression: 19	CES-D > 16: 157 Self-reported Post-natal depression: 137	-	-	-	-

56	Maya 2020 USA	NIH Criteria or diagnosed with PCOS in electronic medical records/ Adolescent clinic	Not listed, but suggests cross-sectional study	46 Overweight population: Patients were filtered using the following indicators: obese, overweight and BMI greater than 85% from EHR.	392 Overweight population: Patients were filtered using the following indicators: obese, overweight and BMI greater than 85%. From EHR	Diagnosis of depression on EHR and/or positive PHQ-9 score >= 10 Anxiety Diagnosis was made after routine interview by the primary care provider based on diagnostic criteria of anxiety, a positive GAD7 score or documented past medical history if enrolled in mental health care	NR	NR	17	129	-	-	-	-
57	Mehrabadi, 2020 Iran	Rotterdam/ hospital clinic	Cross-sectional study	53 Age = 28.47 ± 6.27 BMI = 28.74 ± 5.33	50 Age = 29.94 ± 6.24 BMI = 27.78 ± 4.45 Matched for age, education level, employment status, parity, marital status, height, and weight.	Depression Beck Depression Inventory Anxiety Beck Anxiety Inventory	20.39 (9.85)	14.46 (8.4)	-	-	17.35 (10.44)	12.2 (9.65)	-	-
58	Moran 2012 Australia	Rotterdam/ community advertising	Cross sectional	54 Two groups: NIH PCOS (n=29) Age = 32.0 ± 1.1 BMI = 36.1 ± 1.6 Non-NIH PCOS (n=25) Age = 33.4 ± 1.2 BMI = 32.5 ± 1.1	27 Age = 36.4 ± 1.7 BMI = 28.7 ± 0.8 Healthy women, above average weight and with normal periods	Depression HADS Anxiety HADS	NR	NR	17	3	NR	NR	32	11

59	Moran 2010 Australia	Rotterdam/ NR [PCOS status was based on a prior established medical diagnosis confirmed using in-depth phone screening]	Cross sectional study (conducted using mailed or online surveys)	24 Age = 22.41 ± 0.39 BMI = 29.17 ± 1.54	22 Age = 21.95 ± 0.47 BMI = 22.05 ± 0.83 Young women without PCOS in the community	Depression HADS Anxiety HADS	median 5.5 (IQR) 2-9.5	median 2.5 (IQR) 1-6)	6	1	median 10.5 (IQR) 7-12	median 7 (IQR) 5-9	9	2
60	Moran 2015 Australia	Rotterdam/ NR [women with at least two of the following three symptoms: menstrual disorders; clinical and/or biochemical hyperandrogenism; polycystic ovaries]	Cross sectional	87 Age = median (IQR) 30.2 (29.9-30.8) BMI = 30.1 (25.1-38.6)	637 Age = median (IQR) 30.2 (29.9-30.9) BMI = 25.4 (22.4-29.9) Non-PCOS	Depression CES-D [Clinical score > 16 indicates the presence of symptoms of clinical depression] Anxiety NA	NR	NR	43	192	NA	NA	NA	NA
61	Mukundan 2018 India	Clinical signs of hyper-androgenism, menstrual irregularity, oligomenorrhea, visualization of polycystic ovaries on ultrasound/ Tertiary care hospital	Case-control study	186 Age = 25.19 ± NR BMI: 23.72 ± 2.96	186 Age: 23.38 ± 4.14 BMI: NR Matched criteria not clear	Depression (PHQ-9) QOL (PCOSQS) Anxiety NA	-	-	132	54	-	-	-	-
62	Naumova 2021 Spain	Rotterdam/ Reproductive medicine unit of the Hospital Clinic	Cross sectional study	37 Age: 32 ± 5.05 BMI: 24.91 ± 3.59	67 Two groups of infertile patients without PCOS: Tubal factor infertility (TFI) TFI: 36 MFI: 31 Age: 30.58 ± 6.27 BMI: 32.12 ± 2.79 Male Factor Infertility (MFI) Age: 31.87 ± 4.55 BMI: 22.49 ± 2.95	Depression Beck Depression Inventory (BDI) Anxiety Hamilton Anxiety Rating Scale (HAM-A)	12.3 (0.91)	TFI: 7.2 (0.77) MFI: 5.8 (0.62)	Total: 18 Mild: 15 Moderate: 3 Severe: 0	Total: 14 TFI Mild: 7 Moderate: 0 Severe: 0 MFI: Mild: 7 Moderate: 0 Severe: 0	10.7 (1.23)	TFI: 5.2 (1.01) MFI: 2.7 (0.62)	Total: 8 Mild to Moderate: 6 Moderate to Severe: 2	Total: 3 TFI: Mild to Moderate: 1 Moderate to Severe: 1 MFI: Mild to Moderate: 1 Moderate to Severe: 0

63	Ozedemir 2017 Turkey	Rotterdam/ Clinic	Case-control	69 Age = 21.95 ± 2.89 BMI = 24.02 ± 5.49 [Included women with diagnosed depression. of 69 px with PCOS, 58 had depression]	49 Age = 22.04 ± 2.38) BMI = 22 57 ± 3.56 Age-matched hospital staff and nursing student	Depression Beck Depression Inventory (BDI) Beck Hopelessness Scale (BHS) Scale for Suicide Ideation (SSI) Structured Clinical Interview for DSM-4 Anxiety Beck Anxiety Inventory (BAI)	BDI = 16.31 (12.18) BHS = 6.17 (5.02) SSI = 5.05 (4.39)	BDI = 9.36 (4.92) BHS = 4.38 (3.01) SSI = 2.97 (2.18)	SCI-DSM4 = 34 (49.3%)	NR	BAI = 19.59 (12.35)	BAI = 11.02 (8.41)	NR	NR
64	Ozenli 2008 Turkey	Rotterdam/ gyn clinic	Cross sectional	35 Age = 27.58 ± 7.66 BMI = 25.43 ± 5.58	35 Age = 26.54 ± 5.16 BMI = 24.76 ± 5.37 Healthy volunteer individuals of friends and family of staff	Depression BDI Anxiety STAI	14.71 (7.67)	10.5 (5.26)	NR	NR	47.8 (8.13)	42.5 (5.47)	NR	NR
65	Ozturk 2020 Turkey	Rotterdam/ University Gyn & Obs unit	Cross sectional study	50 Age: 22.3 ± 4.2 BMI: 24.17 ± 5.01	41 Age: 22.4 ± 3.5 BMI: 23.21 ± 4.02 Age and BMI matched healthy individuals Ferriman Gallwey scores of all control patients were under 8	Depression Beck Depression Inventory Anxiety Beck Anxiety Inventory	14.16 (10)	9.07 (6.5)	-	-	16.48 (12.2)	10.58 (7.9)	-	-

66	Pastore 2011 USA	NICHD/ clinic	Cross sectional	94 Three sub categories: Lean BMI <25 n=33 Age = 24.3 ± 5.2 BMI = 22.5 ± 1.6 Over-weight BMI 25-30 n=11 Age = 26.0 ± 7.5 BMI = 27.9 ± 1.6 Obese BMI >=30 n=50 Age = 29.0 ± 6.1 BMI = 35.9 ± 3.7	96 Age = NA BMI = NA Lean BMI <25 n=34 Overweight BMI 25-30 n=17 Obese BMI >=30 = 45 Non-PCOS control matched by BMI category	Depression Quick Inventory of Depressive Symptomatology Self Report 16 [0-5 = no depression 6-10 = mild sx 11-15 = moderate sx 16-20 = severe sx 21-27 - very severe sx] Anxiety NA	Total = 6.7 (4.3) lean = 5.4 (3.2) overweight = 5.6 (2.9) obese = 7.8 (4.8)	Total = 6.7 (4.4) lean = 4.6 (2.9) overweight = 7.4 (4.3) obese = 8.0 (4.8)	None Total = 47% lean = 57% overweight = 55% obese = 40% Mild Total = 40% lean = 36% overweight = 45% obese = 40% Moderate Total = 6% lean = 6% overweight = 0 obese = 8% Severe Total = 6% lean = 6% overweight = 0 obese = 12%	None Total = 49% lean = 71% overweight = 41% obese = 36% Mild Total = 29% lean = 24% overweight = 29% obese = 33% Moderate Total = 19% lean = 6% overweight = 29% obese = 24% Severe Total = 3% lean = 0 overweight = 0 obese = 7%	-	-	-	-
67	Sahingoz 2013 Turkey	NIH/ Clinic	Cross sectional	73 Age = 23.82 ± 4.99 BMI = NR	73 Age = 24.59 ± 4.71 BMI = NR Hospital personnel and their relatives matched for sociodemographic characteristics of the patients	Major depression, Structured clinical interview for DSM 4 Anxiety Structured clinical interview for DSM 4	NR	NR	Major depression = 6 (8.2%)	Major depression 4 (5.5%)	NR	NR	Generalised anxiety disorder = 8 (11%) Anxiety disorder = 4 (5.5%) Any anxiety disorder = 19 (26%)	Generalised anxiety disorder = 1 (1.4%) Anxiety disorder = 4 (5.5%) Any anxiety disorder = 7 (9.6%)

68	Sari 2020 Turkey	International Consortium Update reports in cases in which all of the following criteria were present: 1. Persistent oligomenorrhea beyond 2 years after menarche 2. Clinical and/or biochemical hyperandrogenemia. 3. Exclusion of secondary causes of hyper-androgenism / University Medical Faculty Paediatric Endocrinology Outpatient Clinic	Cross sectional study	50 Age = 16.01 ± 1.19 BMI = 26.18 ± 5.55	37 Age = 16.0 ± 1.49 BMI = 22.07 ± 4.05 Age-matched non-PCOS volunteer adolescent girls who had no previous psychiatric admission	Depression Children's Depression Inventory (CDI) Anxiety KSADS-PL	13.64 (8.46)	10.08 (6.6)	15	2	-	-	2	2
69	Sayyah-Melli 2015 Iran	Rotterdam/ Academic centre infertility clinic	Case control	742 Age = 23.5 ± 5.2 BMI = 27.4 ± 8.2	798 Age = 27.1 ± 5.9 BMI = 26.8 ± 7.1 Non-PCOS women matched by BMI and menstruation (mid follicular phase)	Depression Screened with MMPI. Confirmed by psychologist – DSM IV Anxiety Screened with MMPI. Confirmed by psychologist – DSM IV 'Anxiety Disorder'	NR	NR	140	63	NR	NR	57	26
70	Shi 2011 China	Rotterdam/ Infertility clinic	Case control	30 Age = 25.40 ± 2.98 BMI = NR	30 Age = 26.70 ± 3.73 BMI = NR Infertility patients without PCOS	Depression SCL-90 Anxiety SCL-91	0.62 (0.47)	0.42 (0.47)	NR	NR	0.46 (0.45)	0.28 (0.4)	NR	NR

71	Sirmans 2014 USA	Women were considered to have probable PCOS if they had at least 1 paid claim for a diagnosis of PCOS (ICD-9 code 256.4) on or before January 1, 2010. Women were also considered to have probable PCOS if they had at least 1 paid claim for oligomenorrhea (ICD-9 code 626.1) or amenorrhea (ICD-9 code 620.0) plus hyperandrogenism. Hyperandrogenism was defined by the diagnosis of hirsutism (ICD-9 code 704.1)/ Louisiana Medicaid claims data	Case control (using Medicaid claim data)	1,689 Age in 2010 = 25.24 ± NR	5,067 Age in 2010 = 25.23 ± NR Healthy women matched for age and race	Depression NR Anxiety NR	NR	NR	438	690	NR	NR	347	648
72	Soyupek 2010 Turkey	Rotterdam/ NR	Cross sectional	40 Age = 24.10 ± 6.13 BMI = 24.17 ± 5.60	39 Age = 26.14 ± 5.67 BMI = 21.81 ± 3.82 Age matched healthy women from hospital staff and other volunteers	Depression BDI: ≥11 Anxiety BAI: ≥11	8.92 (7.73)	5.25 (4.19)	26	4	4.22 (2.94)	1.89 (2.1)	NA	NA
73	Soyupek 2008 Turkey	Rotterdam/ NR	Cross sectional	37 Age = 24.10 ± 6.13 BMI = 24.76 ± 6.48	35 Age = 26.14 ± 5.67 BMI = 22.53 ± 2.62 Age matched healthy /hospital staff and other volunteers	Depression BDI: ≥11 Anxiety NA	9.78 (8.05)	6.42 (5.03)	13	6	NA	NA	NA	NA

74	Sulaiman, 2017 Oman	Rotterdam/ tertiary teaching hospital	Case-control study	52 Age: =< 25 (n): 10 26 - 34 (n): 31 >= 35 (n): 11	60 Age: =< 25 (n): 7 26 - 34 (n): 34 >= 35 (n): 19 Non-menopausal, nonpregnant women with no PCOS with similar ethnicity, culture and quality of care	Depression Depression Anxiety and Stress Scale (DASS)-21 Anxiety DASS-21	-	-	Total: 27 Score > 10, Mild: 9 Score > 14, Moderate: 8 Score > 21, Severe: 10	-	Total: 30 Score > 10, Mild: 7 Score > 14, Moderate: 13 Score > 21, Severe: 10	-	Total: 35 Score > 8, Mild: 5 Score > 10, Moderate: 14 Score > 15, Severe: 16	Total: 36 Score > 8, Mild: 5 Score > 10, Moderate: 8 Score > 15, Severe: 23
75	Tan 2017 China	Rotterdam/ University hospital	Case-control study	120 Age = 24.8 ± 3.8 BMI = 21.4 ± 3.0	100 Age = 25.0 ± 3.5 BMI = 20.8 ± 1.9 Healthy non-PCOS women from the local community and universities in Chengdu	Depression Beck Depression Inventory Anxiety State-Trait Anxiety Inventory (STAI)	12.1 (7.3)	7.8 (5.3)	33	3	SAI score: 42.7 (11.7) TAI score: 43.4 (9.8)	SAI: 34.2 (10.1) TAI: 36.1 (9.4)	16	2
76	Tseng 2021 Taiwan	Rotterdam/ University hospital	Cross-sectional, case-control study (described in the text)	431 Age = 25.3 ± 4.9 BMI = 26.4 ± 6.5	259 Age = 48.4 ± 10.5 BMI = 23.0 ± 12.6 Healthy volunteer women who had come to the same institute for a routine health check-up and were older than or equal to 20 years	Depression Brief Social Rhythm Scale (BSRS)-5 Anxiety BSRS-5	0.87 (0.93)	0.65 (0.8)	49	9	0.88 (0.87)	0.8 (0.71)	49	9

77	Varanasi 2018 Australia	NIH, and Self Report/ NR Participants involved in the Young Female Health Initiative (YFHI) and Safe-D studies - with PCOS Clomiphene resistance not stated, 2 subgroups: non-self-reported PCOS that fulfil NIH Criteria, self-reported PCOS that fulfil NIH criteria	Cross-sectional study	31 (met NIH criteria) Age = Median (IQR) 22 (20 – 24) BMI = Median (IQR) 23.2 (20.5 - 27.4)	233 (did not meet NIH criteria) Age = Median (IQR) 22 (21 – 24) BMI = Median (IQR) 22.9 (21.1 - 25.5)	Depression 'yes' to a question in the original YFHI or Safe--D survey, or as determined by Kessler Score, with score > 20 being presence of mental health disorder. Anxiety NA	-	-	Kessler score >20 Total: 4 Met NIH Criteria but not self-reported PCOS: 4 Met NIH Criteria but did self-report PCOS: 0 Self-reported depression Total: 19 Met NIH Criteria but not self-reported PCOS: 17 Met NIH Criteria and self-report PCOS: 2	Kessler score > 20: 42 Self-reported depression: 61	-	-	-	-
78	Weiner 2004 Germany	NIH/Endocrine clinic and community	Case control	27 Age = 28.19 ± 4.84 BMI = 37.70 ± 8.46	27 Age = 30.07 ± 6.48 BMI = 36.89 ± 7.24 Women without history of abnormal mood associated with the menstrual cycle recruited through community advertising matched for BMI, age, education and race	Depression DACL State and DACL Trait Depression Anxiety STAI	State: 11.30 (6.49) Trait:12.37 (5.89)	State: 6.81 (4.87) Trait: 7.89 (4.77)	NR	NR	State: 37.67 (12.42) Trait: 43.89 (11.68)	State: 32.56 (7.61) Trait: 37.81 (8.94)	NR	NR

79	Zachurzok 2021 Poland	Ibanez criteria: A diagnosis of PCOS was made when both criteria were present: menstrual disturbances (oligomenorrhea, secondary amenorrhea) and clinical or biochemical hyper-androgenism/ Medical university	Case-control study	27 Age = 16.7 ± 1.2 BMI z-score = 1.1 ± 0.9	27 Age = 16.1 ± 1.1 BMI z score = 1.0 ± 1.0 Healthy, regularly menstruating, non-hirsute, age and BMI matched girls	Depression Hospital Anxiety & Depression Scale Anxiety Hospital Anxiety & Depression Scale	4.2 (2.9)	5.1 (3.4)	1	2	7.3 (3.9)	9.6 (3)	5	14
80	Zeuff 2015 Brazil	Rotterdam/ Clinic	Case control	44 Age = 30.1 ± 4.9 BMI = 34.5 ± 3.9 PCOS obese women BMI 30-40	43 Age = 32.6 ± 4.6 BMI = 34.5 ± 3.0 Obese without PCOS	Depression Hospital Anxiety and Depression Scale [>=9 indicates Depression] Anxiety Hospital Anxiety and Depression Scale [>= 8 indicates anxiety]	NR	NR	18.7%	29.5%	NR	NR	52.3%	51.2%

6. QUALITY APPRAISAL TABLE

#	Author, year, country	Does the study have a clearly focused question and/or PICO?	Inclusion criteria	Exclusion criteria	If there were specified inclusion/ exclusion criteria, were these appropriate?	Is a cross sectional or case-control study the appropriate design to answer this question?	Was matching performed?	Selection Bias			Performance bias	Detection bias				Attrition bias		Report bias	Confounding	Other bias			Risk of Bias
								Were the cases and controls taken from comparable populations?	Was the case definition adequate and established in a standard, valid and reliable way?	Was the control status established in a standard, valid and reliable way?	Aside from the exposure/ intervention, were the groups treated the same?	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and	Were outcome assessors blind to case and control status?	Were all outcomes measured in a standard, valid and reliable way?	Were outcomes assessed objectively and independently?	What percentage of the individuals recruited into each arm of the study were lost to follow up?	What percentage of the individuals were not included in the analysis?	Is the paper free of selective outcome reporting?	Are the cohorts comparable on the basis of design or analysis?	Were there any conflicts of interest in the writing or funding of this study?	Was the study sufficiently powered to detect any differences between the groups?	If statistical analysis was undertaken, was this appropriate?	What is the overall risk of bias?
1	Acmaz, 2013 Turkey	Yes	Yes	Yes	Yes	Yes	Yes	Partial	Yes	Yes	Yes	Yes	Not reported	Partial	Partial	Not reported	Not reported	Not reported	Yes	No	Not reported	Partial	Moderate
2	Adali, 2008 Turkey	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	Yes	No	Not reported	Yes	Moderate
3	Ahmadi 2020 Iran	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	Yes	No	Not reported	Yes	Moderate
4	Akdag Cirik 2016 Turkey	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	13%	Not reported	No	Not reported	Yes	Yes	Low
5	Aksu 2019 Turkey	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	Yes	No	Yes	Yes	Low
6	Almis 2021 Turkey	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	100% included	Not reported	Partial	No	Not reported	Yes	Mod
7	Altinkaya 2014 Turkey	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	Yes	Not reported	Not reported	Yes	Low
8	Alur-Gupta 2019 USA	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	No	Not reported	Not reported	Yes	Mod

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9	Annagür, 2014 Turkey	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	Yes	No	Not reported	Yes	Mod
10	Asdag 2020 Saudi Arabia	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	No	No	Not reported	Yes	Mod
11	Asik, 2015 Turkey	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	Yes	No	Not reported	Yes	Mod
12	Balikci 2014 Turkey	Yes	Yes	Yes			Yes	Not reported	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	Partial	No	Not reported	Yes	Mod
13	Barry 2011 UK	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	10/135 (7%)	Not reported	No	No	Not reported	Yes	Mod
14	Basirat 2019 Iran	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	100% included	Not reported	Yes	No	Not reported	Yes	Mod
15	Basirat 2020 Iran	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	100% included	Not reported	Yes	No	Not reported	Yes	Mod
16	Battaglia,2008 Italy	Yes	Yes	Yes	Yes	Yes	Yes	Partial	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	Yes	No	Not reported	Yes	Mod
17	Benson 2009 Germany	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	Yes	No	Not reported	Yes	Mod
18	Benson 2020 USA	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	Yes	No	Not reported	Yes	Low

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19	Benson 2008 Germany	Yes	Yes	Yes	Yes	Yes	Not reported	No	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	Partial	Not reported	Not reported	Yes	Mod
20	Besenek 2021 Turkey	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not relevant	Not reported	Not reported	Yes	No	Yes.	Yes	Low
21	Bhattacharya, 2010 India	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	Yes	No	Yes	Yes	Low
22	Borghi 2018 Italy	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	100% included	Not reported	Partial	No	No	Yes	Mod
23	Caltekin 2021 Turkey	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	Yes	No	Not reported	Yes	Mod
24	Cinar, 2011 Turkey	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	Yes	Not reported	Not reported	Yes	Mod
25	Dag 2017 Turkey	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	100% included	Not reported	Yes	No	Not reported	Yes	Mod
26	Davari Tanha, 2013 Iran	Yes	Yes	Yes	Partial	Yes	Yes	Yes	Yes	Yes	Yes	No	Not reported	No	Yes	Not relevant	Not reported	Not reported	Yes	Not reported	Not reported	Yes	Mod
27	Deeks 2011 Australia	Yes	Yes	Yes	Yes	Yes	No	Not reported	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	No	Not reported	Yes	Yes	Mod

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28	Deniz 2020 Nigeria	Yes	Partial	Partial	Yes	Yes	Not reported	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	36%	Not reported	Yes	No	Yes	Yes	Low
29	Dobbaloglu 2022 Turkey	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	Partial	No	Not reported	Yes	Mod
30	Dybciak 2022 Poland	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	Partial	No	Not reported	Yes	Mod
31	Elsenbruch 2003 Germany	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	100% included	Not reported	Yes	No	Not reported	Yes	Mod
32	Emeksiz 2018 Turkey	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	NR	Not reported	Yes	Not reported	Not reported	Yes	Mod
33	Enjezab 2013 Iran	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	Partial	No	Not reported	Yes	Mod
34	Ercan, 2013 Turkey	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	Yes	No	Partial	Yes	Mod
35	Ghazeeri 2013 Lebanon	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	100% included	Not reported	Partial	No	Not reported	Yes	Mod
36	Ghazeeri 2022 Lebanon	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	Not reported	Not reported	Not reported	Yes	Mod
37	Glowinska 2020 Poland	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	Yes	Not reported	Partial	Yes	Mod

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38	Greenwood 2019 USA	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	Yes	Not reported	Not reported	Yes	Low
39	Hahn 2005 Germany	Yes	Yes	Yes	Yes	Yes	Not reported	No	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	Partial	Not reported	Not reported	Yes	Mod
40	Harmanci, 2013 Turkey	Yes	Yes	Not reported	Yes	Yes	Not reported	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	Yes	Not reported	Not reported	Yes	Low
41	Harnod, 2020 Taiwan	See under quality assessment for cohort studies																					
42	Himelein, 2006 USA	Yes	Yes	Yes	Yes	Yes	Not reported	No	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	Yes	No	Not reported	Partial	Mod
43	Holinrake, 2007 USA	Yes	Yes	Not reported	Partial	Yes	Partial	No	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	Partial	Not reported	Partial	Yes	High
44	Hussain, 2015 India	Yes	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Not reported	Yes	Yes	Not reported	Yes	Yes	Not relevant	100% included	Not reported	Yes	No	Not reported	Not reported	High
45	Jedel, 2010 Sweden	Yes	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	Yes	Not reported	No	Yes	Mod
46	Karjula, 2017 Finland	Yes	Yes	Yes	Partial	Yes	Not reported	Yes	Not reported	Not reported	Yes	Yes	Not reported	Yes	Yes	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Yes	High
47	Kirmizi, 2020 Turkey	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not relevant	100% included	Not reported	Yes	No	Yes	Yes	Low

#	Author, year, country	Does the study have a clearly focused question and/or PICO?	Inclusion criteria	Exclusion criteria	If there were specified inclusion/ exclusion criteria, were these appropriate?	Is a cross sectional or case-control study the appropriate design to answer this question?	Was matching performed?	Selection Bias			Performance bias	Detection bias				Attrition bias		Report bias	Confounding	Other bias			Risk of Bias
								Were the cases and controls taken from comparable populations?	Was the case definition adequate and established in a standard, valid and reliable way?	Was the control status established in a standard, valid and reliable way?	Aside from the exposure/ intervention, were the groups treated the same?	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and	Were outcome assessors blind to case and control status?	Were all outcomes measured in a standard, valid and reliable way?	Were outcomes assessed objectively and independently?	What percentage of the individuals recruited into each arm of the study were lost to follow up?	What percentage of the individuals were not included in the analysis?	Is the paper free of selective outcome reporting?	Are the cohorts comparable on the basis of design or analysis?	Were there any conflicts of interest in the writing or funding of this study?	Was the study sufficiently powered to detect any differences between the groups?	If statistical analysis was undertaken, was this appropriate?	What is the overall risk of bias?
48	Komarowska, 2013 Poland	Yes	Yes	Yes	Partial	Yes	Yes	Not reported	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	100% included	Not reported	Yes	No	Not reported	Partial	High
49	Koseoglu, 2016 Turkey		Yes	Partial	Yes	Yes	Yes	Yes	Yes	Partial	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	Partial	No	Not reported	Yes	Mod
50	Laggari 2009 Greece	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	Not reported	No	Not reported	Yes	High
51	Lee 2017 USA	Yes	Yes	Yes	Yes	Yes	Not reported	No	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	No	Not reported	Yes	Yes	Mod
52	Li 2017 China	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	7.39%	Not reported	Yes	No	Not reported	Yes	Mod
53	Mansson 2011 Sweden	Yes	Yes	Not reported	Yes	Yes	No	NO	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	Partial	No	No	Yes	High
54	Mansson, 2008 Sweden	Yes	Yes	Not reported	Partial	Yes	Yes	No	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	Partial	No	Not reported	Yes	Mod
55	March 2018 Australia	Yes	Yes	Not reported	Partial	Yes	Not reported	Yes	Yes	Partial	Yes	Yes	Not reported	Partial	Yes	Not relevant	Not reported	Not reported	Partial	No	Not reported	Partial	High
56	Maya,2020 USA	Yes	Yes	Not reported	Partial	Yes	Not reported	Yes	Yes	Partial	Yes	Partial	Not reported	Partial	Yes	Not relevant	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	High
57	Mehrabadi, 2020 Iran	Yes	Yes	Not reported	Yes	Yes	Yes	Yes	Yes	Partial	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	Yes	No	Not reported	Yes	Mod

#	Author, year, country	Does the study have a clearly focused question and/or PICO?	Inclusion criteria	Exclusion criteria	If there were specified inclusion/ exclusion criteria, were these appropriate?	Is a cross sectional or case-control study the appropriate design to answer this question?	Was matching performed?	Selection Bias			Performance bias	Detection bias				Attrition bias		Report bias	Confounding	Other bias			Risk of Bias
								Were the cases and controls taken from comparable populations?	Was the case definition adequate and established in a standard, valid and reliable way?	Was the control status established in a standard, valid and reliable way?	Aside from the exposure/ intervention, were the groups treated the same?	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and	Were outcome assessors blind to case and control status?	Were all outcomes measured in a standard, valid and reliable way?	Were outcomes assessed objectively and independently?	What percentage of the individuals recruited into each arm of the study were lost to follow up?	What percentage of the individuals were not included in the analysis?	Is the paper free of selective outcome reporting?	Are the cohorts comparable on the basis of design or analysis?	Were there any conflicts of interest in the writing or funding of this study?	Was the study sufficiently powered to detect any differences between the groups?	If statistical analysis was undertaken, was this appropriate?	What is the overall risk of bias?
58	Moran, 2012 Australia	Yes	Yes	Yes	Yes	Yes	Not reported	Partial	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	No	No	Yes	Yes	Low
59	Moran, 2010 Australia	Yes	Yes	Yes	Yes	Yes	Not reported	Partial	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	18%	Not reported	Partial	No	Yes	Yes	Low
60	Moran, 2015 Australia	Yes	Yes	Yes	Yes	Yes	Yes	Partial	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	Partial	No	Not reported	Yes	Mod
61	Mukundan 2018 India	Yes	Yes	Yes	Yes	Yes	No	Not reported	Yes	Not reported	Yes	Yes	Not reported	Yes	Yes	Not relevant	100% included	Not reported	Not reported	No	Not reported	No	High
62	Naumova, 2021 Spain	Yes	Yes	Not reported	Partial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	18.11%	Not reported	Partial	No	Yes	Yes	Mod
63	Ozedemir 2017 Turkey	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	8.33%	Not reported	Yes	Not reported	Not reported	Yes	Mod
64	Ozenli, 2008 Turkey	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	Yes	Not reported	Not reported	Yes	Mod
65	Ozturk,2020 Turkey	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not relevant	Not reported	Not reported	Yes	No	Not reported	Yes	Mod
66	Pastore 2011 USA	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	No	No	Not reported	Yes	Mod
67	Sahingoz 2013 Turkey	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Not reported	Partial	Yes	Not relevant	5.80%	Not reported	Yes	Not reported	Not reported	Yes	High

#	Author, year, country	Does the study have a clearly focused question and/or PICO?	Inclusion criteria	Exclusion criteria	If there were specified inclusion/ exclusion criteria, were these appropriate?	Is a cross sectional or case-control study the appropriate design to answer this question?	Was matching performed?	Selection Bias			Performance bias	Detection bias				Attrition bias		Report bias	Confounding	Other bias			Risk of Bias
								Were the cases and controls taken from comparable populations?	Was the case definition adequate and established in a standard, valid and reliable way?	Was the control status established in a standard, valid and reliable way?	Aside from the exposure/ intervention, were the groups treated the same?	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and	Were outcome assessors blind to case and control status?	Were all outcomes measured in a standard, valid and reliable way?	Were outcomes assessed objectively and independently?	What percentage of the individuals recruited into each arm of the study were lost to follow up?	What percentage of the individuals were not included in the analysis?	Is the paper free of selective outcome reporting?	Are the cohorts comparable on the basis of design or analysis?	Were there any conflicts of interest in the writing or funding of this study?	Was the study sufficiently powered to detect any differences between the groups?	If statistical analysis was undertaken, was this appropriate?	What is the overall risk of bias?
68	Sari, 2020 Turkey	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	Partial	No	Not reported	Yes	Mod
69	Sayyah-Melli, 2015 Iran	Yes	Yes	Not reported	Partial	Yes	Not reported	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	Partial	No	Not reported	Yes	Mod
70	Shi 2011 China	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	Partial	No	Not reported	Yes	Mod
71	Sirmans, 2014 USA	Yes	Yes	Yes	Yes	Yes	Yes	Not reported	Partial	Partial	Yes	No	Not reported	No	Yes	Not relevant	Not reported	Not reported	Yes	Not reported	Not reported	Yes	High
72	Soyupek, 2010 Turkey	Yes	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	Yes	No	Not reported	Yes	Mod
73	Soyupek, 2008 Turkey	Yes	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	Yes	No	Not reported	Yes	Mod
74	Sulaiman, 2017 Oman	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	100% included	Not reported	Yes	No	Yes	Yes	Low
75	Tan, 2017 China	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	100% included	Not reported	Yes	No	Not reported	Yes	Mod
76	Tseng, 2021 Taiwan	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	2.12%	Not reported	No	No	Partial	Yes	Mod
77	Varanasi, 2018 Australia	Yes	Yes	Yes	Yes	Yes	Not reported	Not reported	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	Yes	No	Not reported	Yes	Mod

#	Author, year, country	Does the study have a clearly focused question and/or PICO?	Inclusion criteria	Exclusion criteria	If there were specified inclusion/ exclusion criteria, were these appropriate?	Is a cross sectional or case-control study the appropriate design to answer this question?	Was matching performed?	Selection Bias			Performance bias	Detection bias				Attrition bias		Report bias	Confounding	Other bias			Risk of Bias
								Were the cases and controls taken from comparable populations?	Was the case definition adequate and established in a standard, valid and reliable way?	Was the control status established in a standard, valid and reliable way?	Aside from the exposure/ intervention, were the groups treated the same?	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and	Were outcome assessors blind to case and control status?	Were all outcomes measured in a standard, valid and reliable way?	Were outcomes assessed objectively and independently?	What percentage of the individuals recruited into each arm of the study were lost to follow up?	What percentage of the individuals were not included in the analysis?	Is the paper free of selective outcome reporting?	Are the cohorts comparable on the basis of design or analysis?	Were there any conflicts of interest in the writing or funding of this study?	Was the study sufficiently powered to detect any differences between the groups?	If statistical analysis was undertaken, was this appropriate?	What is the overall risk of bias?
78	Weiner, 2004 Germany	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	Not reported	Not reported	Yes	Not reported	Not reported	Yes	Mod
79	Zachurzok 2021 Poland	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	100% included	Not reported	Yes	No	Not reported	Yes	Mod
80	Zeuff 2015 Brazil	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not relevant	1/88 (1.13%)	Not reported	Partial	No	Not reported	Yes	Mod

#	Author, year, country	Does the study have a clearly focused question and/or PICO?	Inclusion criteria	Exclusion criteria	If there were specified inclusion/ exclusion criteria, were these appropriate?	Is a cohort study the appropriate design to answer this question?	Was there sufficient duration of follow-up for outcomes to occur?	Was matching performed?	Other than the exposure under investigation, were the groups selected from similar populations?	Was the exposed cohort truly representative?	Is it clear that the outcome of interest was not present at the start of study?	Aside from the exposure/ intervention, were the groups treated the same?	Was exposure measured in a standard, valid and reliable way?	Were outcome assessors blind to case and control status?	Were all outcomes measured in a standard, valid and reliable way?	Were outcomes assessed objectively and independently?	What percentage of the individuals recruited into each arm of the study were lost to follow up?	What percentage of the individuals were not included in the analysis?	Is the paper free of selective outcome reporting?	Are the cohorts comparable on the basis of design or analysis?	Were there any conflicts of interest in the writing or funding of this study?	Was the study sufficiently powered to detect any differences between the groups?	If statistical analysis was undertaken, was this appropriate?	What is the overall risk of bias?
1	Harnod 2020 Taiwan	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NR	Partial	Yes		NR	NR	Yes	No	NR	Yes	Mod

7. FINDINGS

Outcomes included:

- Outcome 1. Prevalence of depression – All studies
- Outcome 2. Prevalence of depression – Adult studies
- Outcome 3. Prevalence of depression – Adolescent studies
- Outcome 4. Prevalence of depression – studies that used clinical interviews
- Outcome 5. Depression scores – All studies
- Outcome 6. Depression scores – Adult studies
- Outcome 7. Depression scores – Adolescent studies
- Outcome 8. Depression scores by screening tools used – All studies
- Outcome 9. Depression scores by screening tools used – Adults
- Outcome 10. Depression scores by screening tools used – Adolescents
- Outcome 11. Prevalence of anxiety – All studies
- Outcome12. Prevalence of anxiety – Adult studies
- Outcome13. Prevalence of anxiety – Adolescent studies
- Outcome 14. Prevalence of anxiety – studies that used clinical interviews
- Outcome 15. Anxiety scores – All studies
- Outcome 16. Anxiety scores – Adult studies
- Outcome 17. Anxiety scores – Adolescent studies
- Outcome 18. Anxiety scores by screening tool used – All studies
- Outcome 19. Anxiety scores by screening tools used – Adults
- Outcome 20. Anxiety scores by screening tools used – Adolescents

▪ EVIDENCE SUMMARY:

Forty-seven studies compared prevalence of depression between women with PCOS versus women without PCOS. Only seven studies were of low risk of bias (Akdag Cirik 2016, Altinkaya 2014, Benson 2020, Bhattacharya 2010, Moran 2010, Moran 2012 and Sulaiman 2017) and the rest were either moderate or high risk of bias. All 47 studies were included in the meta-analysis.

Seventy-three studies reported depression scores between women with PCOS versus women without PCOS. However, only 45 contained sufficient data to be included in the meta-analysis and one study (Mansson 2011) was later excluded from the meta-analysis due to the direction of the effect. Four of those included in the meta-analysis were of low risk of bias (Akdag Cirik 2016, Deniz 2020, Harmanci 2013 and Kirmizi 2020) and the rest were either moderate or high risk of bias.

Twenty-seven studies compared prevalence of anxiety between women with PCOS versus women without PCOS. Only six studies were of low risk of bias (Akdag Cirik 2016, Altinkaya 2014, Harnod 2020, Moran 2010, Moran 2012 and Sulaiman 2014) and the rest were either moderate or high risk of bias. All 27 studies were included in the meta-analysis. One study (Harnod 2020) potentially included both adults and adolescents and therefore only included in the analysis that included all studies.

Fifty studies reported anxiety scores between women with PCOS versus women without PCOS. However, only 28 contained sufficient data to be included in the meta-analysis. Nine of those included in the meta-analysis were of low risk of bias (Akdag Cirik 2016, Aksu 2020, Altinkaya 2014, Besenek 2021, Harmanci 2013, Harnod 2020, Moran 2010, Moran 2012 and Sulaiman 2014) and the rest were either moderate or high risk of bias.

▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

All the studies pointed toward statistically significant high prevalence of depression in PCOS patients compared to women without PCOS. Sub group analysis of adult only and adolescent only studies showed the same trend for depression. Majority of studies were either high or moderate risk of bias.

All the studies pointed toward statistically significant high prevalence of anxiety in PCOS patients compared to women without PCOS. Sub group analysis of adult only and adolescent only studies showed the same trend for anxiety. Majority of studies were either high or moderate risk of bias.

Outcome	Studies	n	Effect Estimate; OR [95% CI]	P	Favours	Certainty
Prevalence of depression – All studies	47	54,352	OR 2.59 [2.11-3.16]	<0.001	PCOS patients	⊕⊕◯◯ LOW
Prevalence of depression – Adult studies	41	53,254	OR 2.63 [2.12-3.28]	<0.001	PCOS patients	⊕⊕◯◯ LOW
Prevalence of depression – Adolescent studies	6	1098	OR 2.26 [1.36-3.76]	<0.001	PCOS patients	⊕⊕⊕◯ MODERATE
Prevalence of depression – studies that used clinical interviews	6	2241	OR 2.33 [1.18 – 4.61]	0.02	PCOS patients	⊕⊕◯◯ LOW
Depression scores – All studies	44	6057	SMD 0.71 [0.55-0.87]	<0.001	PCOS patients	⊕⊕◯◯ LOW
Depression scores – Adult studies	38	5421	SMD 0.76 [0.58-0.94]	<0.001	PCOS patients	⊕⊕◯◯ LOW
Depression scores – Adolescent studies	6	636	SMD 0.41 [0.13-0.70]	0.005	PCOS patients	⊕⊕◯◯ LOW
Depression scores by screening tools used-All studies	44	6123	MD 3.27 [2.69-3.84] SMD 0.69 [0.53-0.86] Overall effect	<0.001	PCOS patients	⊕⊕◯◯ LOW
Depression scores by screening tools used-Adult studies	38	5580	MD 3.36 [2.75-3.98] SMD 0.76 [0.58-0.95] Overall effect	<0.001	PCOS patients	⊕⊕◯◯ LOW
Depression scores by screening tools used-Adolescent studies	6	636	MD 3.26 [0.31-6.20] SMD 0.41 [0.13-0.70] Overall effect	0.03 0.005	PCOS patients	⊕⊕◯◯ LOW
Prevalence of anxiety – All studies	27	50,104	OR 2.68 [2.08-3.44]	<0.001	PCOS patients	⊕⊕◯◯ LOW
Prevalence of anxiety – Adult studies	23	14,519	OR 2.89 [2.27-3.68]	<0.001	PCOS patients	⊕⊕◯◯ LOW
Prevalence of anxiety – Adolescent studies	3	455	OR 0.92 [0.11-7.96]	0.94	None	⊕◯◯◯ VERY LOW
Prevalence of anxiety – studies that used clinical interviews	5	2021	OR 2.70 [1.74-4.18]	<0.001	PCOS patients	⊕⊕⊕◯ MODERATE
Anxiety scores – All studies	30	4540	SMD 0.52 [0.36-0.68]	<0.001	PCOS patients	⊕⊕◯◯ LOW
Anxiety scores – Adult studies	24	3918	SMD 0.58 [0.41-0.76]	<0.001	PCOS patients	⊕⊕◯◯ LOW
Anxiety scores – Adolescent studies	6	622	SMD 0.23 [-0.19-0.64] Trait scores only	<0.001	None	⊕◯◯◯ VERY LOW
Anxiety scores by screening tools used-All studies	30	4540	MD 2.57 [1.93-3.21] SMD 0.52 [0.36-0.68] Overall effect	<0.001	PCOS patients	⊕⊕◯◯ LOW
Anxiety scores by screening tools used-Adult studies	24	3918	SMD 0.58 [0.41-0.76]	<0.001	PCOS patients	⊕⊕◯◯ LOW

			MD 2.67 [1.99-3.35] Overall effect			
Anxiety scores by screening tools used-Adolescent studies	6	622	MD 2.02 [-1.24-5.29] SMD 0.23 [-0.19-0.64] Trait scores only Overall effect	0.022 0.28	None	⨁◯◯◯ VERY LOW

7.1. Depression

OUTCOME 1. Prevalence of depression – All studies

Table 1: Individual Study Data Table - Prevalence of depression – All studies

	OUTCOME: Prevalence of depression – All studies					OUTCOME TYPE: Dichotomous				
	Comparison: Women with PCOS vs. Women without PCOS									
	Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	N events in PCOS group	N total in PCOS group	N events in comparison group	N total in comparison group	Are these values adjusted or crude?	RoB	If adjusted, what variables were in the model?
1	Adali 2008	Score	BDI	14	42	5	42	Crude	Mod	NA
2	Akdag Cirik 2016	Score	HADS	47	101	10	49	Crude	Low	NA
3	Almis 2021	Score	CDI	60	153	34	161	Crude	Mod	NA
4	Altinkaya 2014	Score	BDI	15	50	3	50	Crude	Low	NA
5	Alur-Gupta 2019	Score	HADS	53	189	43	225	Crude	Mod	NA
6	Asdag 2020	Score	DASS-21	40	82	3	85	Crude	Mod	NA
7	Asik 2015	Score	HADS	30	71	7	50	Crude	Mod	NA
8	Basirat 2019	Score	BDI II	53	120	45	120	Crude	Mod	NA
9	Battaglia 2008	Score	BDI	1	25	1	18	Crude	Mod	NA
10	Benson 2009	Score	BDI	5	32	0	32	Crude	Mod	NA
11	Benson 2020	Score	CES-D	24	61	9	44	Crude	Low	NA
12	Benson 2008	Score	BDI	26	57	5	28	Crude	Mod	NA
13	Bhattacharya 2010	Score	PHQ-9	75	117	20	84	Crude	Low	NA
14	Cinar 2011	Score	BDI	64	226	4	85	Crude	Mod	NA
15	Davari Tanha 2013		Evaluation by psychiatrist	88	110	96	110	Crude	Mod	NA
16	Dobbaloglu 2022	Score	BDI	14	51	4	49	Crude	Mod	NA
17	Dybciak 2022	Score	HADS	42	230	12	199	Crude	Mod	NA
18	Enjezab 2013	Score	BDI	23	62	22	61	Crude	Mod	NA
19	Glowinska 2020	Score	BDI	12	96	3	47	Crude	Mod	NA
20	Harnod 2020	ICD9 codes: 296.2, 296.3, 300.4, and 311	as determined from National Health Insurance Research Database (NHIRD) claims	83	7026	235	28104	Crude	Mod	NA

21	Himelein 2006	Score	BDI short form	11	40	5	100	Crude	Mod	NA
22	Holinrake 2007	Score	PHQ	36	103	11	103	Crude	High	NA
23	Hussain 2015	Score	DSM-4	26	110	3	40	Crude	High	NA
24	Jedel 2010	Score	MADRS-S	16	30	6	30	Crude	Mod	NA
25	Karjula 2017	Score	Hopkins Symptom Checklist - 25 Depression	24	125	277	2188	Crude	High	NA
26	Lee 2017	Score	HADS	18	148	4	106	Crude	Mod	NA
27	Mansson 2008	Score	Mini NPI by psychiatrist	33	49	17	49	Crude	Mod	NA
28	March 2018	Score	CES-D	22	52	157	514	Crude	High	NA
29	Maya 2020	Score	PHQ-9	17	46	129	392	Crude	High	NA
30	Moran 2012	Score	HADS	17	52	3	24	Crude	Low	NA
31	Moran 2010	Score	HADS	6	24	1	22	Crude	Low	NA
32	Moran 2015	Score	CES-D Score >16	43	87	192	637	Crude	Mod	NA
33	Mukundan 2018	Score	PHQ-9	132	186	54	186	Crude	High	NA
34	Naumova 2021	Score	BDI	3	37	0 0	36 (tubal factor infertility) 31 (male factor infertility)	Crude	Mod	NA
35	Pastore 2011	Score	QIDS-SR 16	12	94	21	96	Crude	Mod	NA
36	Sahingoz 2013	Score	DSM-4	6	73	4	73	Crude	High	NA
37	Sari 2020	Score	CDI	15	50	2	37	Crude	Mod	NA
38	Sayyah-Melli 2015	Score	MMPI (screening) DSM-4 (confirmation)	140	742	63	798	Crude	Mod	NA
39	Sirmans 2014	Score	Not Reported	438	1689	690	5067	Crude	High	NA
40	Soyupek 2008	Score	BDI	13	37	6	35	Crude	Mod	NA
41	Soyupek 2010	Score	BDI	26	40	4	39	Crude	Mod	NA
42	Sulaiman 2017	Score	DASS-21	18	52	23	60	Crude	Low	NA
43	Tan 2017	Score	BDI	33	120	3	100	Crude	Mod	NA
44	Tseng 2021	Score	BSRS-5	49	431	9	259	Crude	Mod	NA
45	Varanasi 2018	Score	Original YFHI or Safe-D survey	4	31	42	233	Crude	Mod	NA
46	Zachurzok 2021	Score	HADS	1	27	2	27	Crude	Mod	NA

47	Zeuff 2015	Score	HADS	8	44	13	43	Crude	Mod	NA

BDI: Beck Depression Inventory; HADS: Hospital Anxiety and Depression Scale; CDI: Children's Depression Inventory; DASS-21: Depression Anxiety and Stress Scale-21; CES-D: Center for Epidemiologic Studies-Depression scale; PHQ-9: Patient Health Questionnaire – Depression; DSM-4: Diagnostic and Statistical Manual of Mental Disorders; MADRS-S: Montgomery
Asberg Depression Rating Scale; QIDS-SR 16: Quick Inventory of Depressive Symptomatology-Self Report 16; MMPI: Minnesota Multiphasic Personality Inventory; DASS-21: Depression Anxiety and Stress Scale -21; BSRS-5: Brief Social Rhythm Scale – 5; YFHI: Young Female Health Initiative

Figure 1.1: Forest plot for Prevalence of depression – All studies

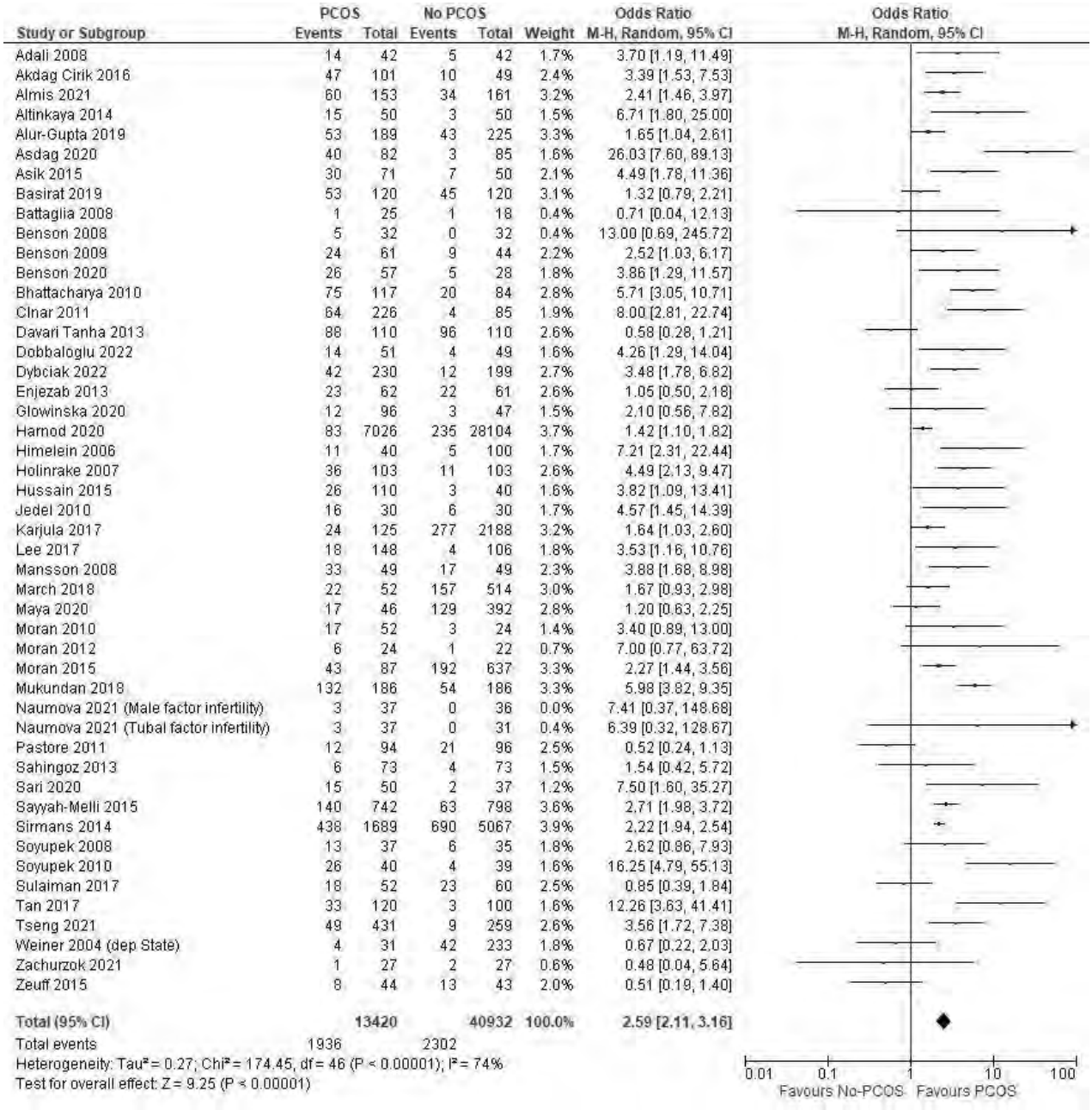
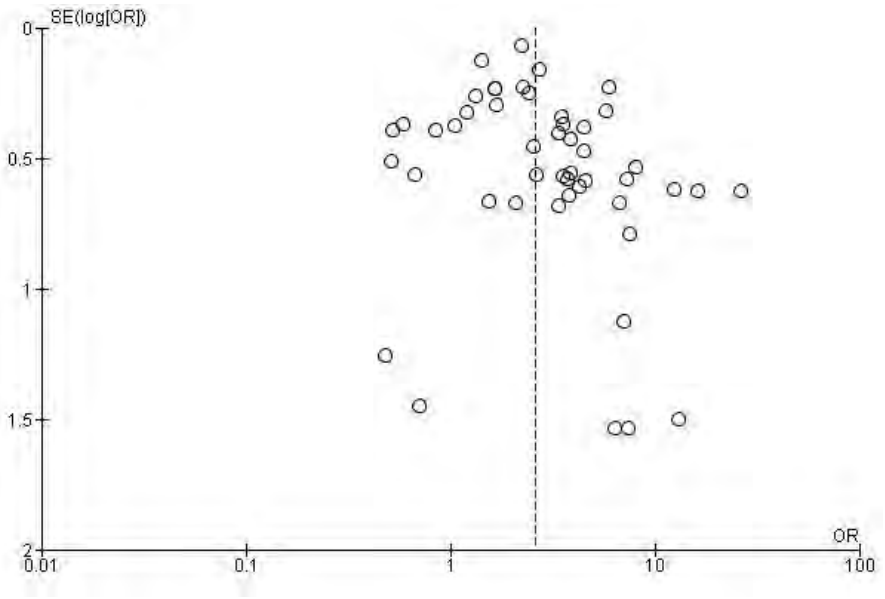


Figure 1.2: Funnel plot for Prevalence of depression – All studies



OUTCOME 2. Prevalence of depression – Adult studies

Table 2: Individual Study Data Table - Prevalence of depression – Adult studies

	OUTCOME: Prevalence of depression – Adult studies					OUTCOME TYPE: Dichotomous				
	Comparison: Adult women with PCOS vs. Adult women without PCOS									
#	Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	N events in PCOS group	N total in PCOS group	N events in comparison group	N total in comparison group	Are these values adjusted or crude?	RoB	If adjusted, what variables were in the model?
1	Adali 2008	Score	BDI	14	42	5	42	Crude	Mod	NA
2	Akdag Cirik 2016	Score	HADS	47	101	10	49	Crude	Low	NA
3	Altinkaya 2014	Score	BDI	15	50	3	50	Crude	Low	NA
4	Alur-Gupta 2019	Score	HADS	53	189	43	225	Crude	Mod	NA
5	Asdag 2020	Score	DASS-21	40	82	3	85	Crude	Mod	NA
6	Asik 2015	Score	HADS	30	71	7	50	Crude	Mod	NA
7	Basirat 2019	Score	BDI II	53	120	45	120	Crude	Mod	NA
8	Battaglia 2008	Score	BDI	1	25	1	18	Crude	Mod	NA
9	Benson 2008	Score	BDI	26	57	5	28	Crude	Mod	NA
10	Benson 2009	Score	BDI	5	32	0	32	Crude	Mod	NA
11	Bhattacharya 2010	Score	PHQ-9	75	117	20	84	Crude	Low	NA

12	Cinar 2011	Score	BDI	64	226	4	85	Crude	Mod	NA
13	Davari Tanha 2013		Evaluation by psychiatrist	88	110	96	110	Crude	Mod	NA
14	Dybciak 2022	Score	HADS	42	230	12	199	Crude	Mod	NA
15	Enjezab 2013	Score	BDI	23	62	22	61	Crude	Mod	NA
16	Glowinska 2020	Score	BDI	12	96	3	47	Crude	Mod	NA
17	Harnod 2020	ICD9 codes: 296.2, 296.3, 300.4, and 311	as determined from National Health Insurance Research Database (NHIRD) claims	83	7026	235	28104	Crude	Mod	NA
18	Himelein 2006	Score	BDI short form	11	40	5	100	Crude	Mod	NA
19	Holinrake 2007	Score	PHQ	36	103	11	103	Crude	High	NA
20	Hussain 2015	Score	DSM-4	26	110	3	40	Crude	High	NA
21	Jedel 2010	Score	MADRS-S	16	30	6	30	Crude	Mod	NA
22	Karjula 2017	Score	Hopkins Symptom Checklist - 25 Depression	24	125	277	2188	Crude	High	NA
23	Lee 2017	Score	HADS	18	148	4	106	Crude	Mod	NA
24	Mansson 2008	Score	Mini NPI by psychiatrist	33	49	17	49	Crude	Mod	NA
25	March 2018	Score	CES-D	22	52	157	514	Crude	High	NA
26	Moran 2012	Score	HADS	17	52	3	24	Crude	Low	NA
27	Moran 2010	Score	HADS	6	24	1	22	Crude	Low	NA
28	Moran 2015	Score	CES-D Score >16	43	87	192	637	Crude	Mod	NA
29	Mukundan 2018	Score	PHQ-9	132	186	54	186	Crude	High	NA
30	Naumova 2021	Score	BDI	3	37	0	36 (tubal factor infertility) 31 (male factor infertility)	Crude	Mod	NA
31	Pastore 2011	Score	QIDS-SR 16	12	94	21	96	Crude	Mod	NA
32	Sahingoz 2013	Score	DSM-4	6	73	4	73	Crude	High	NA
33	Sayyah-Melli 2015	Score	MMPI (screening) DSM-4 (confirmation)	140	742	63	798	Crude	Mod	NA
34	Sirmans 2014	Score	Not Reported	438	1689	690	5067	Crude	High	NA
35	Soyupek 2008	Score	BDI	13	37	6	35	Crude	Mod	NA

36	Soyupek 2010	Score	BDI	26	40	4	39	Crude	Mod	NA
37	Sulaiman 2017	Score	DASS-21	18	52	23	60	Crude	Low	NA
38	Tan 2017	Score	BDI	33	120	3	100	Crude	Mod	NA
39	Tseng 2021	Score	BSRS-5	49	431	9	259	Crude	Mod	NA
40	Varanasi 2018	Score	Original YFHI or Safe-D survey	4	31	42	233	Crude	Mod	NA
41	Zeuff 2015	Score	HADS	8	44	13	43	Crude	Mod	NA

BDI: Beck Depression Inventory; HADS: Hospital Anxiety and Depression Scale; DSM-4: Diagnostic and Statistical Manual of Mental Disorders

Figure 2.1: Forest plot for Prevalence of depression – Adult studies

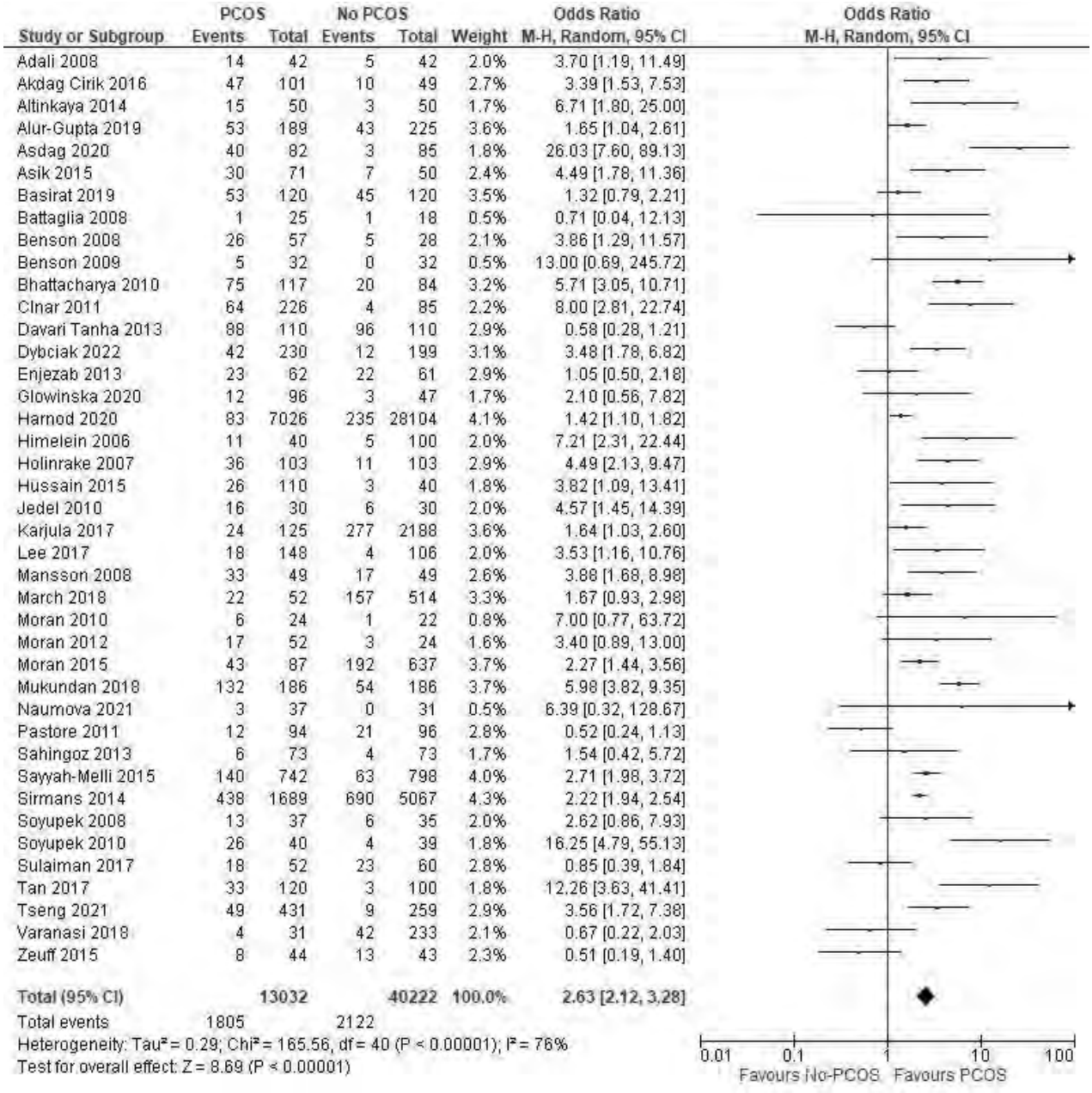
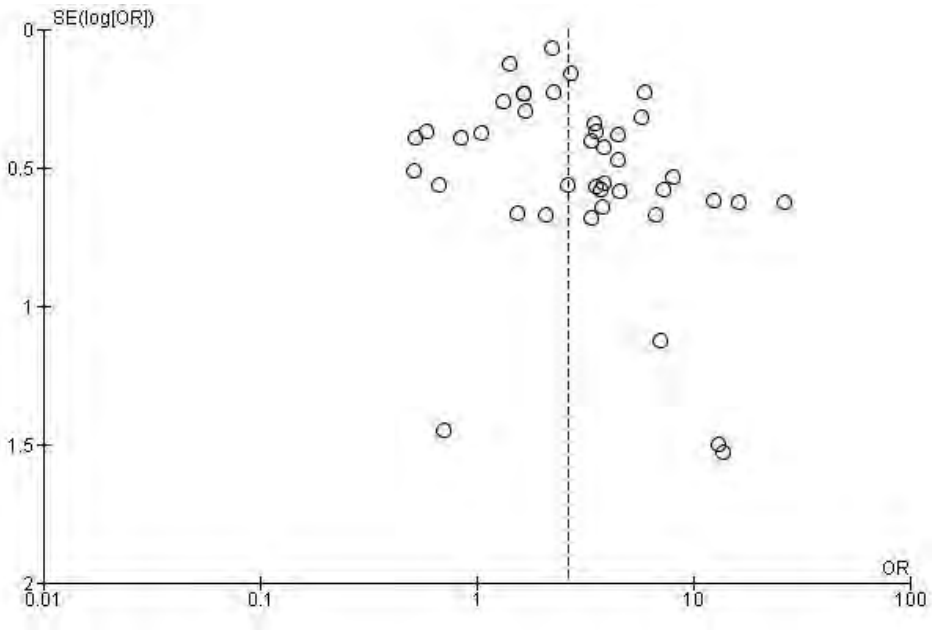


Figure 2.2: Funnel plot for Prevalence of depression – Adult studies



OUTCOME 3. Prevalence of depression – Adolescent studies

Table 3: Individual Study Data Table - Prevalence of depression – Adolescent studies

	OUTCOME: Prevalence of depression – Adolescent studies					OUTCOME TYPE: Dichotomous				
	Comparison: Adolescents with PCOS vs. Adolescents without PCOS									
#	Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	N events in PCOS group	N total in PCOS group	N events in comparison group	N total in comparison group	Are these values adjusted or crude?	RoB	If adjusted, what variables were in the model?
1	Almis 2021	Score	CDI	60	153	34	161	Crude	Mod	NA
2	Benson 2020	Score	CES-D	24	61	9	44	Crude	Low	NA
3	Dobbaloglu 2022	Score	BDI	14	51	4	49	Crude	Mod	NA
4	Maya 2020	Score	PHQ-9 (dep and/or anxiety)	17	46	129	392	Crude	Mod	NA
5	Sari 2020	Score	CDI	15	50	2	37	Crude	Mod	NA
6	Zachurzok 2021	Score	HADS	1	27	2	27	Crude	Mod	NA

CDI: Children's Depression Inventory; CES-D: Center for Epidemiologic Studies-Depression scale; BDI: Beck Depression Inventory;

Figure 3.1: Forest plot for Prevalence of depression – Adolescent studies

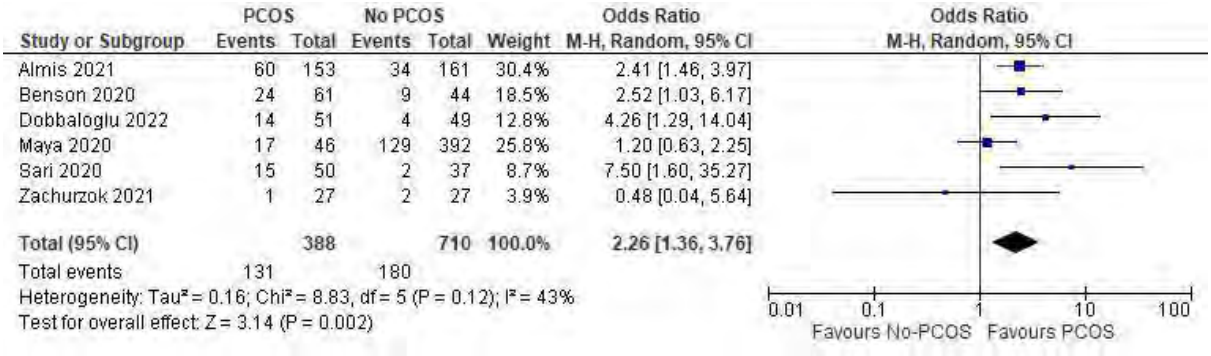
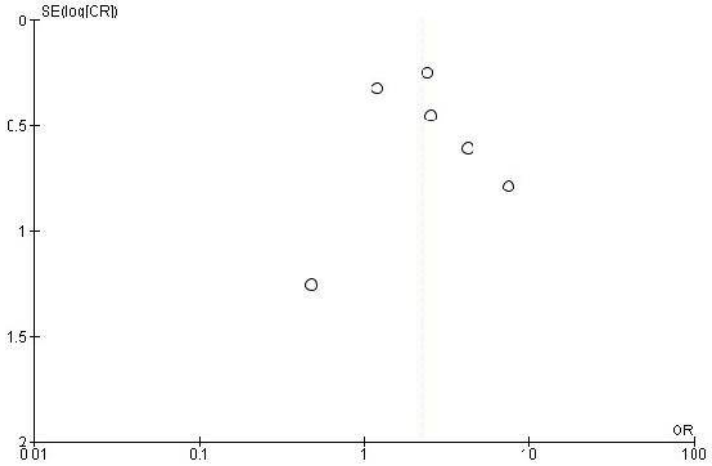


Figure 3.2: Funnel plot for Prevalence of depression – Adolescent studies



OUTCOME 4. Prevalence of depression – studies that used clinical interviews

Table 4. Individual Study Data Table - Prevalence of depression – clinical interview studies

	OUTCOME: Prevalence of depression –studies that used clinical interviews			OUTCOME TYPE: Dichotomous						
	Comparison: PCOS vs. No-PCOS									
#	Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	N events in PCOS group	N total in PCOS group	N events in comparison group	N total in comparison group	Are these values adjusted or crude?	RoB	If adjusted, what variables were in the model?
1	Davari Tanha 2013	-	Evaluation by psychiatrist	88	110	96	110	Crude	Mod	NA
2	Hussain 2015	Score	DSM-4	26	110	3	40	Crude	High	NA
3	Mansson 2008	Score	Mini NPI by psychiatrist	33	49	17	49	Crude	Mod	NA

4	Sahingoz 2013	Score	DSM-4	6	73	4	73	Crude	High	NA
5	Sari 2020	Score	CDI	15	50	2	37	Crude	Mod	NA
6	Sayyah-Melli 2015	Score	MMPI (screening) DSM-4 (confirmation)	140	742	63	798	Crude	Mod	NA

Figure 4.1: Forest plot for prevalence of depression – studies that used clinical interviews

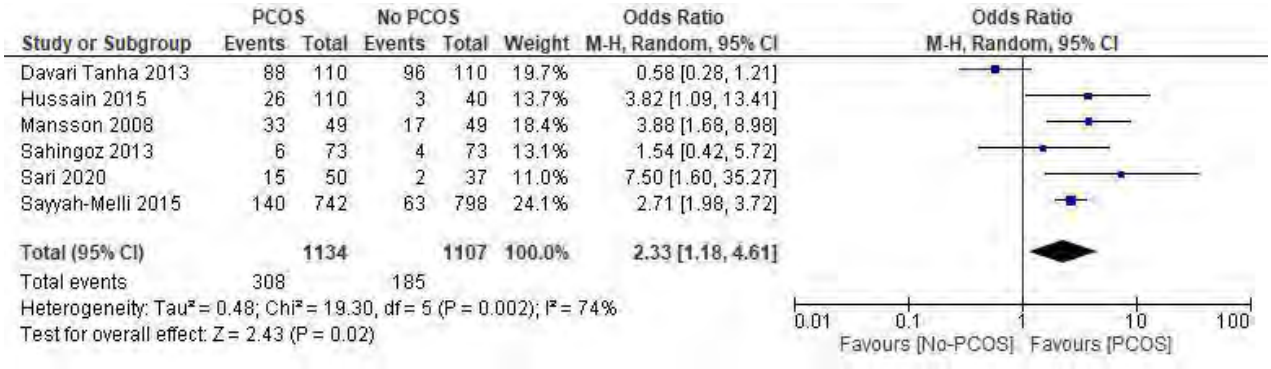
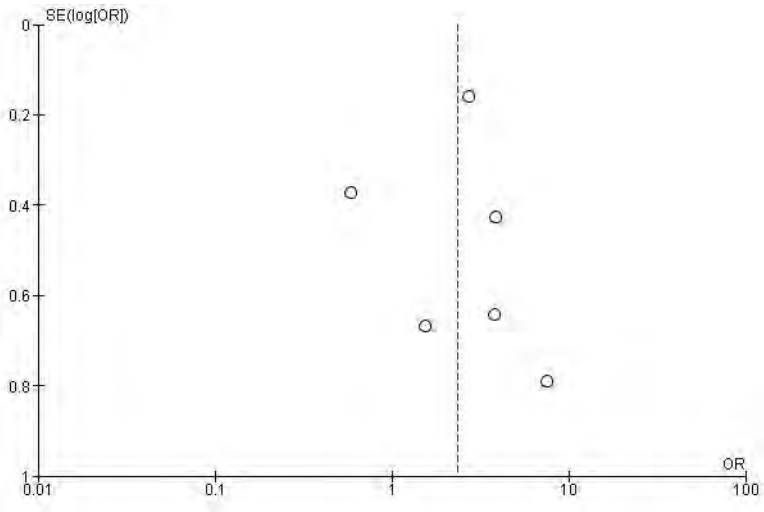


Figure 4.2: Funnel plot for prevalence of depression – studies that used clinical interviews



OUTCOME 5. Depression scores – All studies

Table 5: Individual Study Data Table - Depression scores – All studies

	OUTCOME: Depression scores – All studies	**OUTCOME TYPE: Continuous**
	Comparison: Women with PCOS vs. Women without PCOS	

#	Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (SD) in PCOS group	N total in PCOS group	Mean (SD) in comparison group	N total in comparison group	Are these values adjusted or crude?	RoB	If adjusted, what variables were in the model?
1	Acmaz 2013	Score	BDI	Hirsutism- acnea 12.28 (6.35) n=35 Infertility:30.59 (11.31) n=22 Obesity:19.10 (8.52) n=29	86	12.28 (6.35)	47	Crude	Mod	NA
2	Adali 2008	Score	BDI	11.69 (9.49)	42	5.8 (4.58)	42	Crude	Mod	NA
3	Ahmadi 2020	Score	Millon Clinical Multi-axial Inventory-III (MCMI-III)	42 (23)	201	35 (24)	199	Crude	Mod	NA
4	Akdag Cirik 2016	Score	HADS	7.0 (SEM 4.0) 7 (40.2 calculated)	101	6.0 (SEM 2.0) 6 (14 calculated)	49	Crude	Low	NA
5	Annagur 2014	Score	BDI	14.6 (8.54)	83	6.07 (3.85)	64	Crude	Mod	NA
6	Almis 2021	Score	CDI	17.6 (8.45)	153	11.75 (7.35)	161	Crude	Mod	NA
7	Altinkaya 2014	Score	BDI	median (IQR) 8.5 (4-20)	50	median (IQR) 6 (2-20)	50	Crude	Low	NA
8	Alur-Gupta 2019	Score	HADS	5.1 (NR)	189	4.5 (NR)	225	Crude	Mod	NA
9	Asdag 2020	Score	DASS-21	NR (NR)	82	NR (NR)	85	Crude	Mod	NA
10	Asik 2015	Score	HADS	6.1 (3.75)	71	3.54 (2.79)	50	Crude	Mod	NA
11	Balikci 2014	Score	BDI	14 (4)	44	9 (6)	44	Crude	Mod	NA
12	Barry 2011	Score	BDI	14 (4)	44	9 (6)	44	Crude	Mod	NA
13	Basirat 2019	Score	BDI II	18.06 (12.03)	120	15.65 (11.76)	120	Crude	Mod	NA
14	Battaglia 2008	Score	BDI	NR (NR)	25	NR (NR)	18	Crude	Mod	NA
15	Benson 2009	Score	BDI	9.7 (1.4)	32	4.9 (0.9)	32	Crude	Mod	NA
16	Benson 2020	Score	CES-D	NR (NR)	61	NR (NR)	44	Crude	Low	NA
17	Benson 2008	Score	BDI	10.1 (1 SEM) 10.1 (7.55) calculated	57	5.9 (1.4 SEM) 5.9 (7.41) calculated	28	Crude	Mod	NA
18	Besenek 2021	Score	BDI	Median (IQR)	39	Median (IQR)	37	Crude	Low	NA
19	Bhattacharya 2010	Score	PHQ-9	NR (NR)	117	NR (NR)	84	Crude	Low	NA
20	Cinar 2011	Score	BDI	6.4 (4.1)	226	NR (NR)	85	Crude	Mod	NA

21	Dag 2017	Score	HADS	5.47 (2.97)	53	5.23 (3.96)	38	Crude	Mod	NA
22	Davari Tanha 2013		Evaluation by psychiatrist	NR (NR)	110	NR (NR)	110	Crude	Mod	NA
23	Deeks 2011	Score	HADS	5.7 (3.7)	177	3.3 (3.1)	109	Crude	Mod	NA
24	Deniz 2020	Score	BDI	10.96 (5.12)	50	9.22 (4.24)	50	Crude	Low	NA
25	Dobbaloglu 2022	Score	BDI	13.42 (9.94)	51	9.56 (6.72)	49	Crude	Mod	NA
26	Dybciak 2022	Score	HADS	6.9 (NR)	230	4.2 (NR)	199	Crude	Mod	NA
27	Emeksiz 2018 (16-19 years)	Score	CDI	Median (IQR)	80	Median (IQR)	50	Crude	Mod	NA
28	Enjezab 2013	Score	BDI	7.47 (5.54)	62	7.57 (5.77)	61	Crude	Mod	NA
29	Ercan 2013	Score	BDI	12.3 (4.1)	32	8.7 (2.7)	32	Crude	Mod	NA
30	Ghazeeri 2013	Score	BDI	16 (11.1)	20	10 (10.1)	17	Crude	Mod	NA
31	Ghazeeri 2022	Score	HADS	3.3 (2.7)	49	4.7 (3.4)	50	Crude	Mod	NA
32	Glowinska 2020	Score	BDI	10.1 (0.74 SEM) 10.1 (7.25) calculated	96	6.4 (0.8 SEM) 6.4 (5.48) calculated	47	Crude	Mod	NA
33	Hahn 2005	Score	SCL-90-R	0.88 (0.72)	120	0.49 (0.55)	50	Crude	Mod	NA
34	Harmanci 2013	Score	BSI	8.4 (5.9)	42	5.1 (4.8)	42	Crude	Low	NA
35	Harnod 2020	ICD9 codes: 296.2, 296.3, 300.4, and 311	as determined from National Health Insurance Research Database (NHIRD) claims	NR (NR)	7026	NR (NR)	28104	Crude	Mod	NA
36	Himelein 2006	Score	BDI short form	7.85 (7.0)	40	infertility: 4.56 (5.03) community control: 3.61 (4.08)	100 (infertility group n=40) (community control n=60)	Crude	Mod	NA
37	Holinrake 2007	Score	PHQ	11.9 (11.1)	103	4.5 (5.9)	103	Crude	High	NA
38	Hussain 2015	Score	DSM-4	NR (NR)	110	NR (NR)	40	Crude	High	NA
39	Jedel 2010	Score	MADRS-S	median (IQR) 10 (NR)	30	median (IQR)	30 5.5 (NR)	Crude	Mod	NA
40	Karjula 2017	Score	Hopkins Symptom Checklist - 25 Depression	median (IQR) 1.40 (1.15-1.67) At age 31y	125	median (IQR) 1.27 (1.33-1.53) At age 31 y	2188	Crude	High	NA
41	Kirmizi 2020	Score	BDI	15.63 (5.53)	30 PCOS infertile	8.3 (5.57)	30	Crude	Low	NA
42	Koseoglu 2016	Score	BDI	18.7 (4.1)	30	9.2 (1.3)	25	Crude	Mod	NA
43	Laggari 2009	Score	BDI	12.82 (7.86)	22	10.32 (7.19)	22	Crude	High	NA

44	Lee 2017	Score	HADS	4.84 (4.22)	148	3.09 (3.21)	106	Crude	Mod	NA
45	Li 2017	Score	SCL-90 (DEP)	1.6.0 (0.6)	103	1.5 (0.5)	110	Crude	Mod	NA
46	Mansson 2008	Score	Mini NPI by psychiatrist	NR (NR)	49	NR (NR)	49	Crude	Mod	NA
47	Mansson 2011	Score	PGWB [Lower scores more severe distress]	12.4 (2.7)	49	13.5 (1.9)	49	Crude	High	NA
48	March 2018	Score	CES-D	Self-reported	52	-	514	Crude	High	NA
49	Mehrabadi 2020	Score	BDI	20.39 (9.85)	53	14.46 (8.4)	50	Crude	Mod	NA
50	Maya 2020	Score	PHQ-9	NR	46	NR	392	Crude	High	NA
51	Moran 2012	Score	HADS	NR (NR)	52	NR (NR)	24	Crude	Low	NA
52	Moran 2010	Score	HADS	median (IQR) 5.5 (2-9.5)	24	median (IQR) 2.5 (1-6)	22	Crude	Low	NA
53	Moran 2015	Score	CES-D Score >16	NR (NR)	87	NR (NR)	637	Crude	Mod	NA
54	Mukundan 2018	Score	PHQ-9	NR (NR)	186	NR (NR)	186	Crude	High	NA
55	Naumova 2021	Score	BDI	12.3 (0.91)	37	TFI: 7.2 (0.8) MFI: 5.8 (0.77)	67 (TFI n=36 MFI n=31)	Crude	Mod	NA
56	Ozedemir 2017	Score	BDI	16.91 (12.18)	69	9.36 (4.92)	49	Crude	Mod	NA
57	Ozenil 2008	Score	BDI	14.71 (7.67)	35	10.5 (5.26)	35	Crude	Mod	NA
58	Ozturk 2020	Score	BDI	14.16 (10.0)	50	9.07 (6.5)	41	Crude	Mod	NA
59	Pastore 2011	Score	QIDS-SR 16	6.7 (4.3)	94	6.7 (4.4)	96	Crude	Mod	NA
60	Sahingoz 2013	Score	DSM-4	NR (NR)	73	NR (NR)	73	Crude	High	NA
61	Sari 2020	Score	CDI	13.64 (8.46)	50	10.08 (6.6)	37	Crude	Mod	NA
62	Shi 2011	Score	SCL-90	0.62 (0.47)	30	0.42 (0.47)	30	Crude	Mod	NA
63	Sayyah-Melli 2015	Score	MMPI (screening) DSM-4 (confirmation)	NR (NR)	742	NR (NR)	798	Crude	Mod	NA
64	Sirmans 2014	Score	Not Reported	NR (NR)	1689	NR (NR)	5067	Crude	High	NA
65	Soyupek 2008	Score	BDI	9.78 (8.05)	37	6.42 (5.03)	35	Crude	Mod	NA
66	Soyupek 2010	Score	BDI	8.92 (7.73)	40	5.25 (4.19)	39	Crude	Mod	NA
67	Sulaiman 2017	Score	DASS-21	NR (NR)	52	NR (NR)	60	Crude	Low	NA
68	Tan 2017	Score	BDI	12.1 (7.3)	120	7.8 (5.3)	100	Crude	Mod	NA
69	Tseng 2021	Score	BSRS-5	0.87 (0.93)	431	0.65 (0.8)	259	Crude	Mod	NA
70	Varanasi 2018	Score	Original YFHI or Safe-D survey	NR (NR)	31	NR (NR)	233	Crude	Mod	NA

71	Weiner 2004	Score	DACL	State 11.30 (6.49) Trait 12.37 (5.89)	27	State 6.81 (4.87) Trait 7.89 (4.77)	27	Crude	Mod	NA
72	Zachurzok 2021	Score	HADS	4.2 (2.9)	27	5.1 (3.4)	27	Crude	Mod	NA
73	Zeuff 2015	Score	HADS	NR (NR)	44	NR (NR)	43	Crude	Mod	NA

BDI: Beck Depression Inventory; HADS: Hospital Anxiety and Depression Scale; CDI: Children's Depression Inventory; DASS-21: Depression Anxiety and Stress Scale-21; CES-D: Center for Epidemiologic Studies-Depression scale; PHQ-9: Patient Health Questionnaire – Depression; DSM-4: Diagnostic and Statistical Manual of Mental Disorders; MADRS-S: Montgomery
Asberg Depression Rating Scale; QIDS-SR 16: Quick Inventory of Depressive Symptomatology-Self Report 16; MMPI: Minnesota Multiphasic Personality Inventory; DASS-21: Depression Anxiety and Stress Scale -21; BSRS-5: Brief Social Rhythm Scale – 5; YFHI: Young Female Health Initiative; SEM: standard error of mean

Figure 5.1: Forest plot for depression scores– all studies

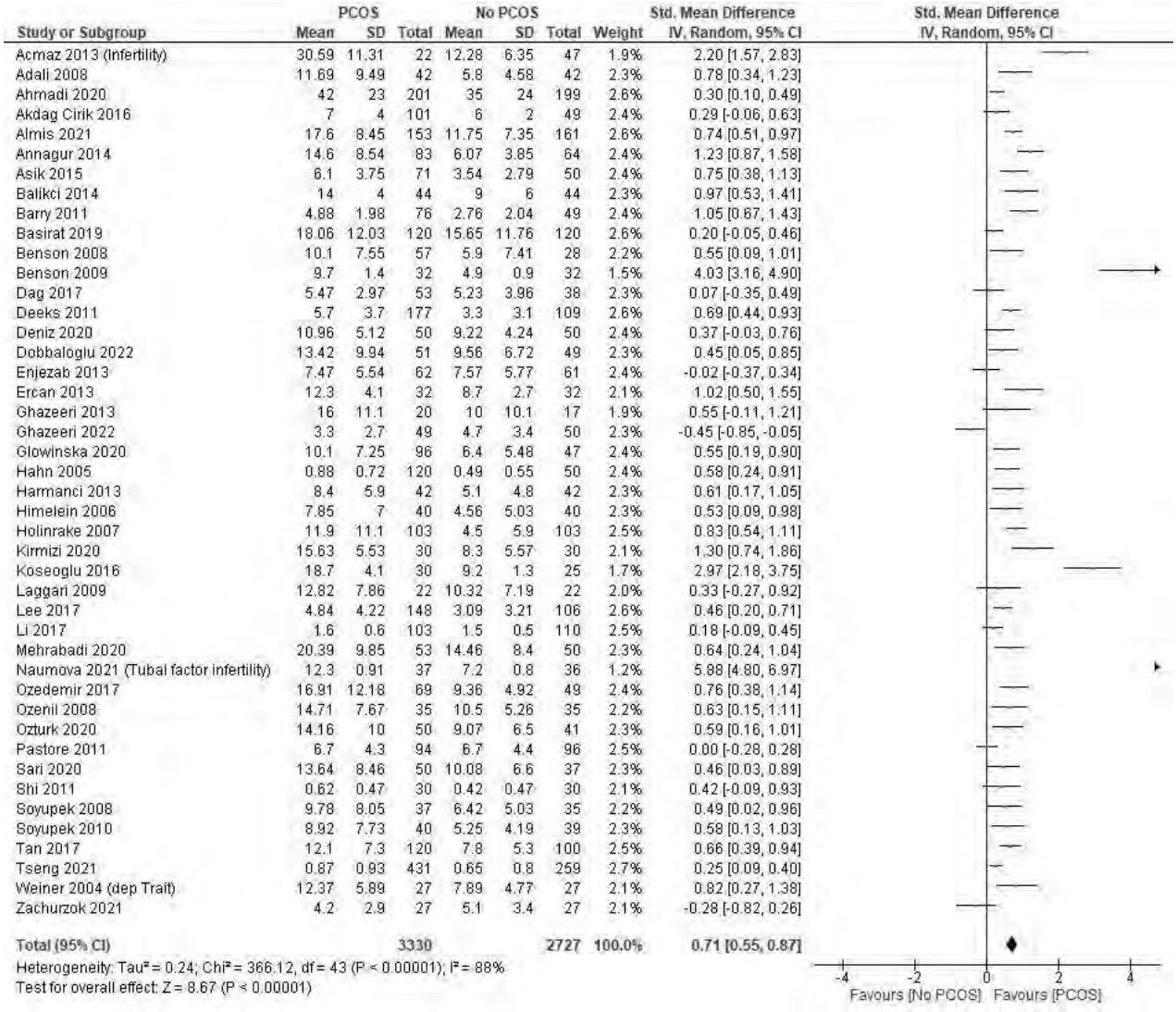
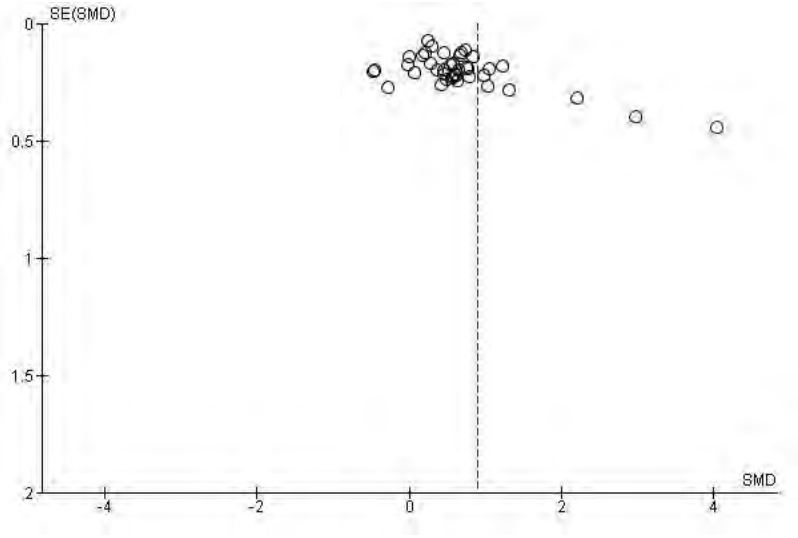


Figure 5.2: Funnel plot for depression scores – all studies



OUTCOME 6. Depression scores – Adult studies

Table 6: Individual Study Data Table - Depression scores – Adult studies

	OUTCOME: Depression scores – Adult studies				**OUTCOME TYPE: Continuous**					
	Comparison: Women with PCOS vs. Women without PCOS									
#	Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (SD) in PCOS group	N total in PCOS group	Mean (SD) in comparison group	N total in comparison group	Are these values adjusted or crude?	RoB	If adjusted, what variables were in the model?
1	Acmaz 2013	Score	BDI	Hirsutism- acnea 12.28 (6.35) n=35 Infertility:30.59 (11.31) n=22 Obesity:19.10 (8.52) n=29	86	12.28 (6.35)	47	Crude	Mod	NA
2	Adali 2008	Score	BDI	11.69 (9.49)	42	5.8 (4.58)	42	Crude	Mod	NA
3	Ahmadi 2020	Score	Millon Clinical Multi-axial Inventory-III (MCMI-III) [higher the worse]	42 (23)	201	35 (24)	199	Crude	Mod	NA
4	Akdag Cirik 2016	Score	HADS	7.0 (4.0)	101	6.0 (2.0)	49	Crude	Low	NA
5	Altinkaya 2014	Score	BDI	median (IQR) 8.5 (4-20)	50	median (IQR) 6 (2-20)	50	Crude	Low	NA
6	Alur-Gupta 2019	Score	HADS	5.1 (NR)	189	4.5 (NR)	225	Crude	Mod	NA
7	Annagur 2014	Score	BDI	14.6 (8.54)	83	6.07 (3.85)	64	Crude	Mod	NA
8	Asdag 2020	Score	DASS-21	NR (NR)	82	NR (NR)	85	Crude	Mod	NA

9	Asik 2015	Score	HADS	6.1 (3.75)	71	3.54 (2.79)	50	Crude	Mod	NA
10	Balikci 2014	Score	BDI	14 (4)	44	9 (6)	44	Crude	Mod	NA
11	Barry 2011	Score	HADS	4.88 (1.98)	76	2.76 (2.04)	49	Crude	Mod	NA
12	Basirat 2019	Score	BDI II	18.06 (12.03)	120	15.65 (11.76)	120	Crude	Mod	NA
13	Battaglia 2008	Score	BDI	NR (NR)	25	NR (NR)	18	Crude	Mod	NA
14	Benson 2009	Score	BDI	9.7 (1.4)	32	4.9 (0.9)	32	Crude	Mod	NA
15	Benson 2008	Score	BDI	10.1 (1 SEM) 10.1 (7.55) calculated	57	5.9 (1.4 SEM) 5.9 (7.41) calculated	28	Crude	Mod	NA
16	Bhattacharya 2010	Score	PHQ-9	NR (NR)	117	NR (NR)	84	Crude	Low	NA
17	Cinar 2011	Score	BDI	6.4 (4.1)	226	NR (NR)	85	Crude	Mod	NA
18	Dag 2017	Score	HADS	5.47 (2.97)	53	5.23 (3.96)	38	Crude	Mod	NA
19	Davari Tanha 2013		Evaluation by psychiatrist	NR (NR)	110	NR (NR)	110	Crude	Mod	NA
20	Deeks 2011	Score	HADS	5.7 (3.7)	177	3.3 (3.1)	109	Crude	Mod	NA
21	Deniz 2020	Score	BDI	10.96 (5.12)	50	9.22 (4.24)	50	Crude	Low	NA
22	Dybciak 2022	Score	HADS	6.9 (NR)	230	4.2 (NR)	199	Crude	Mod	NA
23	Enjezab 2013	Score	BDI	7.47 (5.54)	62	7.57 (5.77)	61	Crude	Mod	NA
24	Ercan 2013	Score	BDI	12.3 (4.1)	32	8.7 (2.7)	32	Crude	Mod	NA
25	Ghazeeri 2022	Score	HADS	3.3 (2.7)	49	4.7 (3.4)	50	Crude	Mod	NA
26	Glowinska 2020	Score	BDI	10.1 (0.74 SEM) 10.1 (7.25) calculated	96	6.4 (0.8 SEM) 6.4 (5.48) calculated	47	Crude	Mod	NA
27	Hahn 2005	Score	SCL-90-R	0.88 (0.72)	120	0.49 (0.55)	50	Crude	Mod	NA
28	Harmanci 2013 (A)	Score	BSI	8.4 (5.9)	42	5.1 (4.8)	42	Crude	Low	NA
29	Harnod 2020	ICD9 codes: 296.2, 296.3, 300.4, and 311	as determined from National Health Insurance Research Database (NHIRD) claims	NR (NR)	7026	NR (NR)	28104	Crude	Mod	NA
30	Himelein 2006	Score	BDI short form	7.85 (7.0)	40	infertility: 4.56 (5.03) community control: 3.61 (4.08)	100 (infertility group n=40) (community control n=60)	Crude	Mod	NA
31	Holinrake 2007	Score	PHQ	11.9 (11.1)	103	4.5 (5.9)	103	Crude	High	NA
32	Hussain 2015	Score	DSM-4	NR (NR)	110	NR (NR)	40	Crude	High	NA

33	Jedel 2010	Score	MADRS-S	median (IQR) 10 (NR)	30	median (IQR)	30 5.5 (NR)	Crude	Mod	NA
34	Karjula 2017	Score	Hopkins Symptom Checklist - 25 Depression	median (IQR) 1.40 (1.15-1.67) At age 31y	125	median (IQR) 1.27 (1.33-1.53) At age 31 y	2188	Crude	High	NA
35	Kirmizi 2020	Score	BDI	15.63 (5.53)	30 PCOS infertile	8.3 (5.57)	30	Crude	Low	NA
36	Koseoglu 2016	Score	BDI	18.7 (4.1)	30	9.2 (1.3)	25	Crude	Mod	NA
37	Lee 2017	Score	HADS	4.84 (4.22)	148	3.09 (3.21)	106	Crude	Mod	NA
38	Li 2017	Score	SCL-90 (DEP)	1.6.0 (0.6)	103	1.5 (0.5)	110	Crude	Mod	NA
39	Mansson 2008	Score	Mini NPI by psychiatrist	NR (NR)	49	NR (NR)	49	Crude	Mod	NA
40	Mansson 2011	Score	PGWB [Lower scores more severe distress]	12.4 (2.7)	49	13.5 (1.9)	49	Crude	High	NA
41	March 2018	Score	CES-D	Self-reported	52	-	514	Crude	High	NA
42	Maya 2020	Score	PHQ-9	NR	46	NR	392	Crude	High	NA
43	Moran 2012	Score	HADS	NR (NR)	52	NR (NR)	24	Crude	Low	NA
44	Moran 2010	Score	HADS	median (IQR) 5.5 (2-9.5)	24	median (IQR) 2.5 (1-6)	22	Crude	Low	NA
45	Moran 2015	Score	CES-D Score >16	NR (NR)	87	NR (NR)	637	Crude	Mod	NA
46	Mehrabadi 2020 (A)	Score	BDI	20.39 (9.85)	53	14.46 (8.4)	50	Crude	Mod	NA
47	Mukundan 2018	Score	PHQ-9	NR (NR)	186	NR (NR)	186	Crude	High	NA
48	Naumova 2021	Score	BDI	12.3 (0.91)	37	TFI: 7.2 (0.8) MFI: 5.8 (0.77)	67 (TFI n=36 MFI n=31)	Crude	Mod	NA
49	Ozedemir 2017	Score	BDI	16.91 (12.18)	69	9.36 (4.92)	49	Crude	Mod	NA
50	Ozenil 2008 (A)	Score	BDI	14.71 (7.67)	35	10.5 (5.26)	35	Crude	Mod	NA
51	Ozturk 2020 (A)	Score	BDI	14.16 (10.0)	50	9.07 (6.5)	41	Crude	Mod	NA
52	Pastore 2011	Score	QIDS-SR 16	6.7 (4.3)	94	6.7 (4.4)	96	Crude	Mod	NA
53	Sahingoz 2013	Score	DSM-4	NR (NR)	73	NR (NR)	73	Crude	High	NA
54	Sayyah-Melli 2015	Score	MMPI (screening) DSM-4 (confirmation)	NR (NR)	742	NR (NR)	798	Crude	Mod	NA
55	Shi 2011	Score	SCL-90	0.62 (0.47)	30	0.42 (0.47)	30	Crude	Mod	NA
56	Sirmans 2014	Score	Not Reported	NR (NR)	1689	NR (NR)	5067	Crude	High	NA
57	Soyupek 2008	Score	BDI	9.78 (8.05)	37	6.42 (5.03)	35	Crude	Mod	NA
58	Soyupek 2010	Score	BDI	8.92 (7.73)	40	5.25 (4.19)	39	Crude	Mod	NA

59	Sulaiman 2017	Score	DASS-21	NR (NR)	52	NR (NR)	60	Crude	Low	NA
60	Tan 2017	Score	BDI	12.1 (7.3)	120	7.8 (5.3)	100	Crude	Mod	NA
61	Tseng 2021	Score	BSRS-5	0.87 (0.93)	431	0.65 (0.8)	259	Crude	Mod	NA
62	Varanasi 2018	Score	Original YFHI or Safe-D survey	NR (NR)	31	NR (NR)	233	Crude	Mod	NA
63	Weiner 2004	Score	DACL	State 11.30 (6.49) Trait 12.37 (5.89)	27	State 6.81 (4.87) Trait 7.89 (4.77)	27	Crude	Mod	NA
64	Zeuff 2015	Score	HADS	NR (NR)	44	NR (NR)	43	Crude	Mod	NA

BDI: Beck Depression Inventory; HADS: Hospital Anxiety and Depression Scale; CDI: Children's Depression Inventory; DASS-21:
Depression Anxiety and Stress Scale-21; CES-D: Center for Epidemiologic Studies-Depression scale; PHQ-9: Patient Health Questionnaire – Depression; DSM-4: Diagnostic and Statistical Manual of Mental Disorders; MADRS-S: Montgomery Asberg Depression Rating Scale; QIDS-SR 16: Quick Inventory of Depressive Symptomatology-Self Report 16; MMPI: Minnesota Multiphasic Personality Inventory; DASS-21: Depression Anxiety and Stress Scale -21; BSRS-5: Brief Social Rhythm Scale – 5; YFHI: Young Female Health Initiative; SEM: standard error of mean

Figure 6.1: Forest plot for depression scores – adult studies

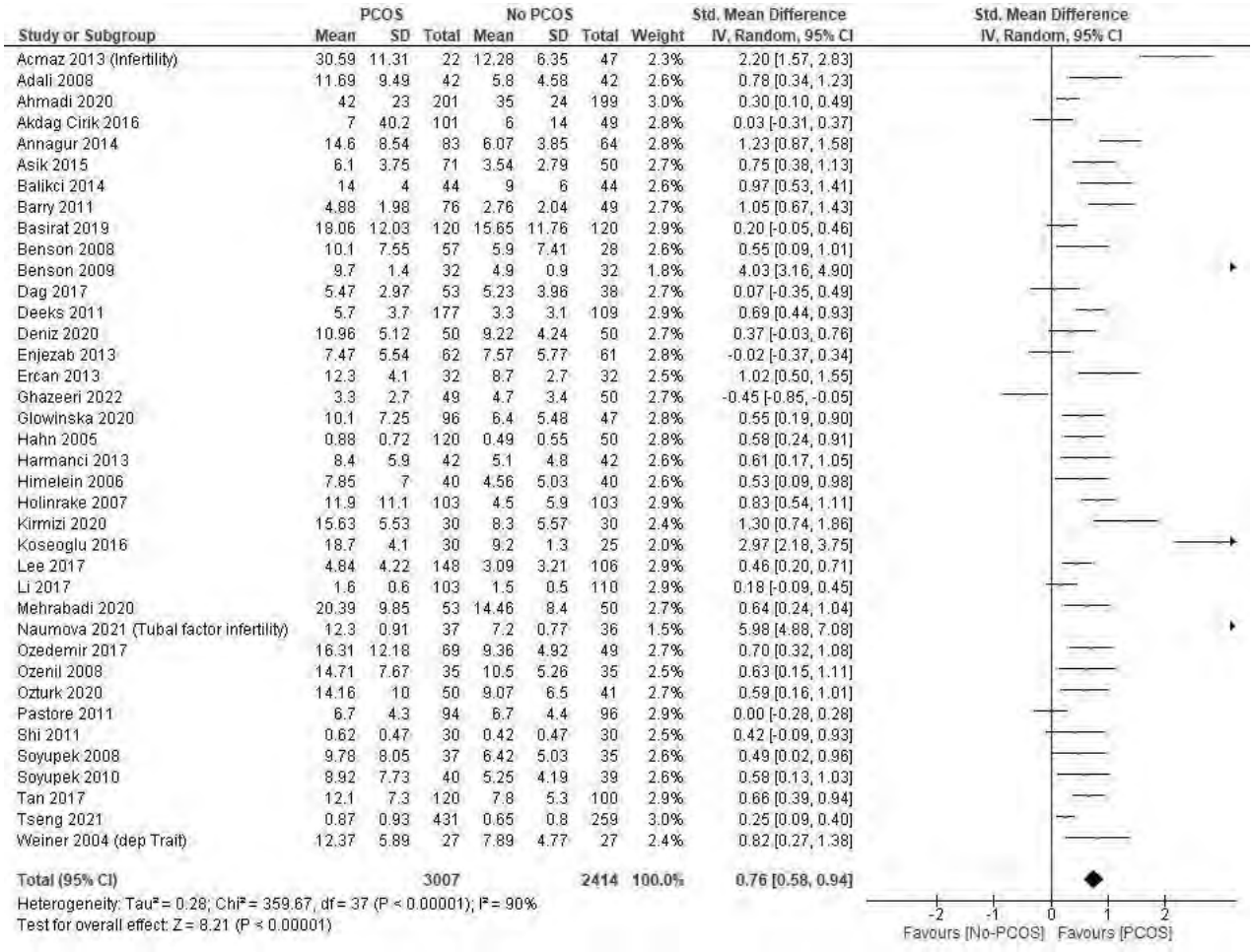
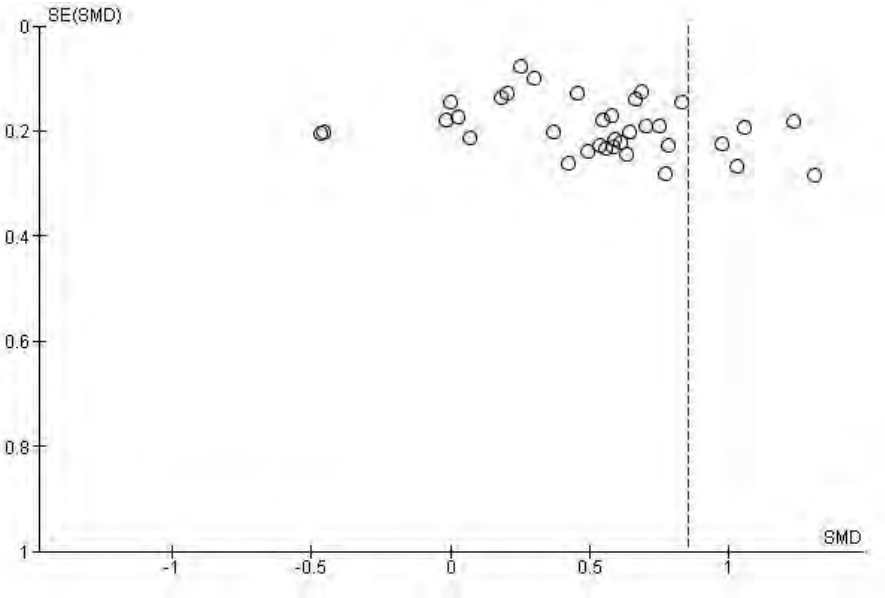


Figure 6.2: Funnel plot for depression scores– adult studies



OUTCOME 7. Depression scores – Adolescent studies

Table 7: Individual Study Data Table - Depression scores – Adolescent studies

	OUTCOME: Depression scores – Adolescent studies					OUTCOME TYPE: Continuous				
	Comparison: Women with PCOS vs. Women without PCOS									
#	Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (SD) in PCOS group	N total in PCOS group	Mean (SD) in comparison group	N total in comparison group	Are these values adjusted or crude?	RoB	If adjusted, what variables were in the model?
1	Almis 2021	Score	CDI	17.6 (8.45)	153	11.75 (7.35)	161	Crude	Mod	NA
2	Benson 2020	Score	CES-D	NR (NR)	61	NR (NR)	44	Crude	Low	NA
3	Besenek 2021	Score	BDI	Median (IQR)	39	Median (IQR)	37	Crude	Low	NA
4	Dobbaloglu 2022	Score	BDI	13.42 (9.94)	51	9.56 (6.72)	49	Crude	Mod	NA
5	Emeksiz 2018 (16-19 years)	Score	CDI	Median (IQR)	80	Median (IQR)	50	Crude	Mod	NA
6	Ghazeeri 2013	Score	BDI	16 (11.1)	20	10 (10.1)	17	Crude	Mod	NA
7	Laggari 2009	Score	BDI	12.82 (7.86)	22	10.32 (7.19)	22	Crude	High	NA
8	Sari 2020	Score	CDI	13.64 (8.46)	50	10.08 (6.6)	37	Crude	Mod	NA
9	Zachurzok 2021	Score	HADS	4.2 (2.9)	27	5.1 (3.4)	27	Crude	Mod	NA

BDI: Beck Depression Inventory; HADS: Hospital Anxiety and Depression Scale; CDI: Children's Depression Inventory; DASS-21:
Depression Anxiety and Stress Scale-21; CES-D: Center for Epidemiologic Studies-Depression scale; SEM: standard error of mean

Figure 7.1: Forest plot for depression scores – adolescent studies

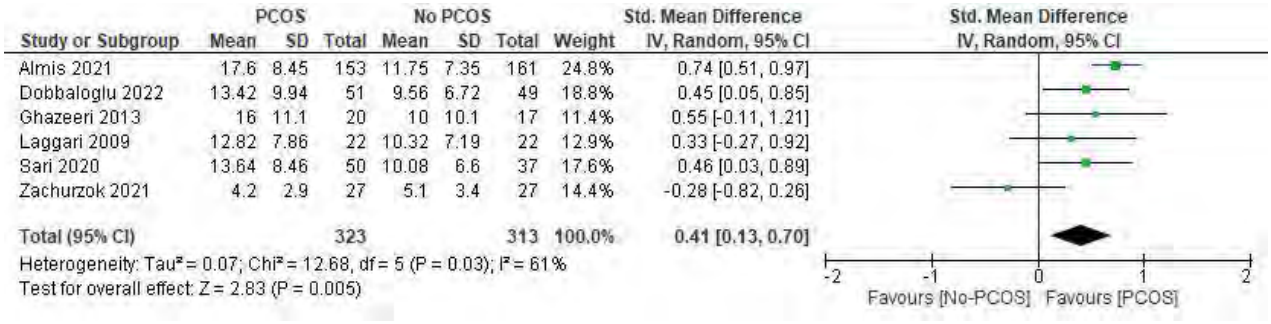
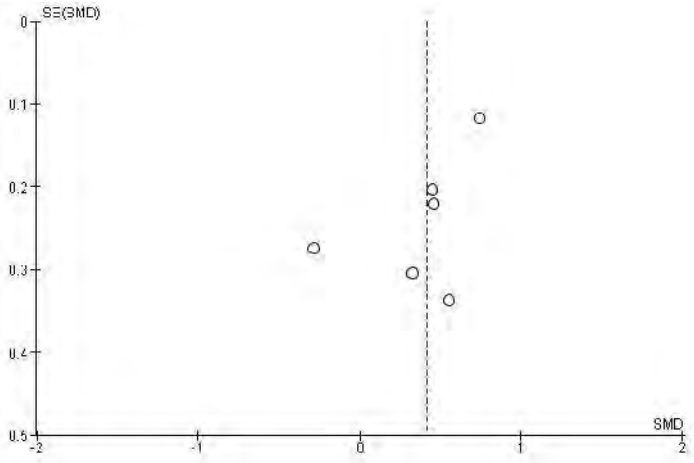


Figure 7.2: Funnel plot for depression scores – adolescent studies



OUTCOME 8. Depression scores by screening tools used – All studies

Table 8: Individual Study data Table – depression scores by screening tools used – All studies

	OUTCOME: Depression scores by screening tools used – All studies							OUTCOME TYPE: Continuous		
	Comparison: Women with PCOS vs. Women without PCOS									
	Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (SD) in PCOS group	N total in PCOS group	Mean (SD) in comparison group	N total in comparison group	Are these values adjusted or crude?	RoB	If adjusted, what variables were in the model?
	BDI									
1	Acmaz 2013	Score	BDI	Infertility:30.59 (11.31) n=22	86	12.28 (6.35)	47	Crude	Mod	NA
2	Adali 2008	Score	BDI	11.69 (9.49)	42	5.8 (4.58)	42	Crude	Mod	NA
3	Altinkaya 2014	Score	BDI	median (IQR)	50	median (IQR)	50	Crude	Low	NA

				8.5 (4-20)		6 (2-20)				
4	Annagur 2014	Score	BDI	14.6 (8.54)	83	6.07 (3.85)	64	Crude	Mod	NA
5	Balikci 2014	Score	BDI	14 (4)	44	9 (6)	44	Crude	Mod	NA
6	Basirat 2019	Score	BDI II	18.06 (12.03)	120	15.65 (11.76)	120	Crude	Mod	NA
7	Besenek 2021	Score	BDI	Median (IQR)	39	Median (IQR)	37	Crude	Low	NA
8	Battaglia 2008	Score	BDI	NR (NR)	25	NR (NR)	18	Crude	Mod	NA
9	Benson 2009	Score	BDI	9.7 (1.4)	32	4.9 (0.9)	32	Crude	Mod	NA
10	Benson 2008	Score	BDI	10.1 (1 SEM) 10.1 (7.55) calculated	57	5.9 (1.4 SEM) 5.9 (7.41) calculated	28	Crude	Mod	NA
11	Cinar 2011	Score	BDI	6.4 (4.1)	226	NR (NR)	85	Crude	Mod	NA
12	Deniz 2020	Score	BDI	10.96 (5.12)	50	9.22 (4.24)	50	Crude	Low	NA
13	Dobbaloglu 2022	Score	BDI	13.42 (9.94)	49	9.56 (6.72)	48	Crude	Mod	NA
14	Enjezab 2013	Score	BDI	7.47 (5.54)	62	7.57 (5.77)	61	Crude	Mod	NA
15	Ercan 2013	Score	BDI	12.3 (4.1)	32	8.7 (2.7)	32	Crude	Mod	NA
16	Ghazeeri 2013	Score	BDI	16 (11.1)	20	10 (10.1)	17	Crude	Mod	NA
17	Glowinska 2020	Score	BDI	10.1 (0.74 SEM) 10.1 (7.25) calculated	96	6.4 (0.8 SEM) 6.4 (5.48) calculated	47	Crude	Mod	NA
18	Himelein 2006	Score	BDI short form	7.85 (7.0)	40	infertility: 4.56 (5.03) community control: 3.61 (4.08)	100 (infertility group n=40) (community control n=60)	Crude	Mod	NA
19	Kirmizi 2020	Score	BDI	15.63 (5.53)	30 PCOS infertile	8.3 (5.57)	30	Crude	Low	NA
20	Koseoglu 2016	Score	BDI	18.7 (4.1)	30	9.2 (1.3)	25	Crude	Mod	NA
21	Laggari 2009	Score	BDI	12.82 (7.86)	22	10.32 (7.19)	22	Crude	High	NA
22	Mehrabadi 2020	Score	BDI	20.39 (9.85)	53	14.46 (8.4)	50	Crude	Mod	NA
23	Naumova 2021	Score	BDI	12.3 (0.91)	37	TFI: 7.2 (0.8) MFI: 5.8 (0.77)	67 (TFI n=36 MFI n=31)	Crude	Mod	NA
24	Ozedemir 2017	Score	BDI	16.91 (12.18)	69	9.36 (4.92)	49	Crude	Mod	NA
25	Ozenil 2008	Score	BDI	14.71 (7.67)	35	10.5 (5.26)	35	Crude	Mod	NA
26	Ozturk 2020	Score	BDI	14.16 (10.0)	50	9.07 (6.5)	41	Crude	Mod	NA
27	Soyupek 2008	Score	BDI	9.78 (8.05)	37	6.42 (5.03)	35	Crude	Mod	NA
28	Soyupek 2010	Score	BDI	8.92 (7.73)	40	5.25 (4.19)	39	Crude	Mod	NA
29	Tan 2017	Score	BDI	12.1 (7.3)	120	7.8 (5.3)	100	Crude	Mod	NA

	CDI									
30	Almis 2021	Score	CDI	17.6 (8.45)	153	11.75 (7.35)	161	Crude	Mod	NA
31	Emeksiz 2018	Score	CDI	Median (IQR)	80	Median (IQR)	50	Crude	Mod	NA
32	Sari 2020	Score	CDI	13.64 (8.46)	50	10.08 (6.6)	37	Crude	Mod	NA
	CES-D									
33	Benson 2020	Score	CES-D	NR (NR)	61	NR (NR)	44	Crude	Low	NA
34	March 2018	Score	CES-D	Self-reported	52	-8.4	514	Crude	High	NA
35	Moran 2015	Score	CES-D Score >16	NR (NR)	87	NR (NR)	637	Crude	Mod	NA
	DASS-21									
36	Asdag 2020	Score	DASS-21	NR (NR)	82	NR (NR)	85	Crude	Mod	NA
37	Sulaiman 2017	Score	DASS-21	NR (NR)	52	NR (NR)	60	Crude	Low	NA
	DSM-4									
38	Hussain 2015	Score	DSM-4	NR (NR)	110	NR (NR)	40	Crude	High	NA
39	Sahingoz 2013	Score	DSM-4	NR (NR)	73	NR (NR)	73	Crude	High	NA
40	Sayyah-Melli 2015	Score	MMPI (screening) DSM-4 (confirmation)	NR (NR)	742	NR (NR)	798	Crude	Mod	NA
	HADS									
41	Akdag Cirik 2016	Score	HADS	7.0 (4.0)	101	6.0 (2.0)	49	Crude	Low	NA
42	Alur-Gupta 2019	Score	HADS	5.1 (NR)	189	4.5 (NR)	225	Crude	Mod	NA
43	Asik 2015	Score	HADS	6.1 (3.75)	71	3.54 (2.79)	50	Crude	Mod	NA
44	Barry 2011	Score	HADS	4.88 (1.98)	76	2.76 (2.04)	49	Crude	Mod	NA
45	Dag 2017	Score	HADS	5.47 (2.97)	53	5.23 (3.96)	38	Crude	Mod	NA
46	Deeks 2011	Score	HADS	5.7 (3.7)	177	3.3 (3.1)	109	Crude	Mod	NA
47	Dybciak 2022	Score	HADS	6.9 (NR)	230	4.2 (NR)	199	Crude	Mod	NA
48	Ghazeeri 2022	Score	HADS	3.3 (2.7)	49	4.7 (3.4)	50	Crude		NA
49	Lee 2017	Score	HADS	4.84 (4.22)	148	3.09 (3.21)	106	Crude	Mod	NA
50	Moran 2012	Score	HADS	NR (NR)	52	NR (NR)	24	Crude	Low	NA
51	Moran 2010	Score	HADS	median (IQR) 5.5 (2-9.5)	24	median (IQR) 2.5 (1-6)	22	Crude	Low	NA
52	Zachurzok 2021 (Adolescents)	Score	HADS	4.2 (2.9)	27	5.1 (3.4)	27	Crude	Mod	NA
53	Zeuff 2015	Score	HADS	NR (NR)	44	NR (NR)	43	Crude	Mod	NA
	SCL-90									
54	Hahn 2005 (A)	Score	SCL-90-R	0.88 (0.72)	120	0.49 (0.55)	50	Crude	Mod	NA
55	Li 2017 (A)	Score	SCL-90 (DEP)	1.6 (0.6)	103	1.5 (0.5)	110	Crude	Mod	NA

56	Shi 2011 (A)	Score	SCL-90	0.62 (0.47)	30	0.42 (0.47)	30	Crude	Mod	NA
	PHQ									
57	Bhattacharya 2010	Score	PHQ-9	NR (NR)	117	NR (NR)	84	Crude	Low	NA
58	Holinrake 2007	Score	PHQ	11.9 (11.1)	103	4.5 (5.9)	103	Crude	High	NA
59	Maya 2020	Score	PHQ-9	NR	46	NR	392	Crude	High	NA
60	Mukundan 2018	Score	PHQ-9	NR (NR)	186	NR (NR)	186	Crude	High	NA
	Others									
61	Ahmadi 2020 (A)	Score	Millon Clinical Multi-axial Inventory-III (MCMI-III)	42 (23)	201	35 (24)	199	Crude	Mod	NA
62	Davari Tanha 2013		Evaluation by psychiatrist	NR (NR)	110	NR (NR)	110	Crude	Mod	NA
63	Harmanci 2013 (A)	Score	BSI	8.4 (5.9)	42	5.1 (4.8)	42	Crude	Low	NA
64	Harnod 2020	ICD9 codes: 296.2, 296.3, 300.4, and 311	as determined from National Health Insurance Research Database (NHIRD) claims	NR (NR)	7026	NR (NR)	28104	Crude	Mod	NA
65	Jedel 2010	Score	MADRS-S	median (IQR) 10 (NR)	30	median (IQR)	30 5.5 (NR)	Crude	Mod	NA
66	Karjula 2017	Score	Hopkins Symptom Checklist - 25 Depression	median (IQR) 1.40 (1.15-1.67) At age 31y	125	median (IQR) 1.27 (1.33-1.53) At age 31 y	2188	Crude	High	NA
67	Mansson 2008	Score	Mini NPI by psychiatrist	NR (NR)	49	NR (NR)	49	Crude	Mod	NA
68	Mansson 2011	Score	PGWB [Lower scores more severe distress]	12.4 (2.7)	49	13.5 (1.9)	49	Crude	High	NA
69	Pastore 2011	Score	QIDS-SR 16	6.7 (4.3)	94	6.7 (4.4)	96	Crude	Mod	NA
70	Sirmans 2014	Score	Not Reported	NR (NR)	1689	NR (NR)	5067	Crude	High	NA
71	Tseng 2021 (A)	Score	BSRS-5	0.87 (0.93)	431	0.65 (0.8)	259			
72	Varanasi 2018	Score	Original YFHI or Safe-D survey	NR (NR)	31	NR (NR)	233	Crude	Mod	NA
73	Weiner 2004 (A)	Score	DACL	State 11.30 (6.49) Trait 12.37 (5.89)	27	State 6.81 (4.87) Trait 7.89 (4.77)	27	Crude	Mod	NA

BDI: Beck Depression Inventory; HADS: Hospital Anxiety and Depression Scale; CDI: Children's Depression Inventory; DASS-21: Depression Anxiety and Stress Scale-21; CES-D: Center for Epidemiologic Studies-Depression scale; PHQ-9: Patient Health Questionnaire – Depression; DSM-4: Diagnostic and Statistical Manual of Mental Disorders; MADRS-S: Montgomery Asberg Depression Rating Scale; QIDS-SR 16: Quick Inventory of Depressive Symptomatology-Self Report 16; MMPI: Minnesota Multiphasic Personality Inventory; DASS-21: Depression Anxiety and Stress Scale -21; BSRS-5: Brief Social Rhythm Scale – 5; YFHI: Young Female Health Initiative; SEM: standard error of mean

Figure 8.1A: Forest plot for depression scores by screening tools – All studies (Mean difference)

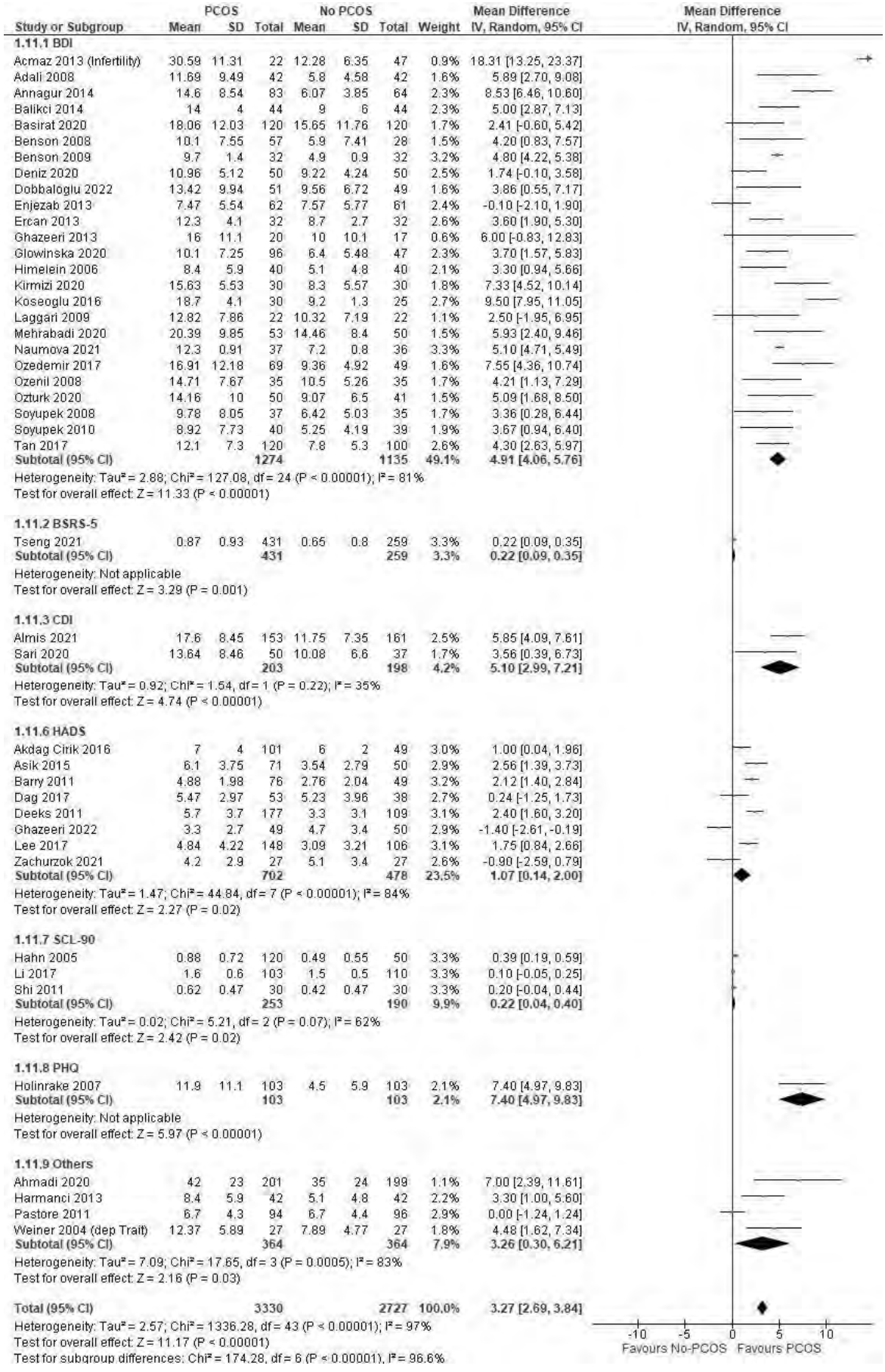


Figure 8.1B: Forest plot for depression scores by screening tools – All studies (Std. Mean difference)

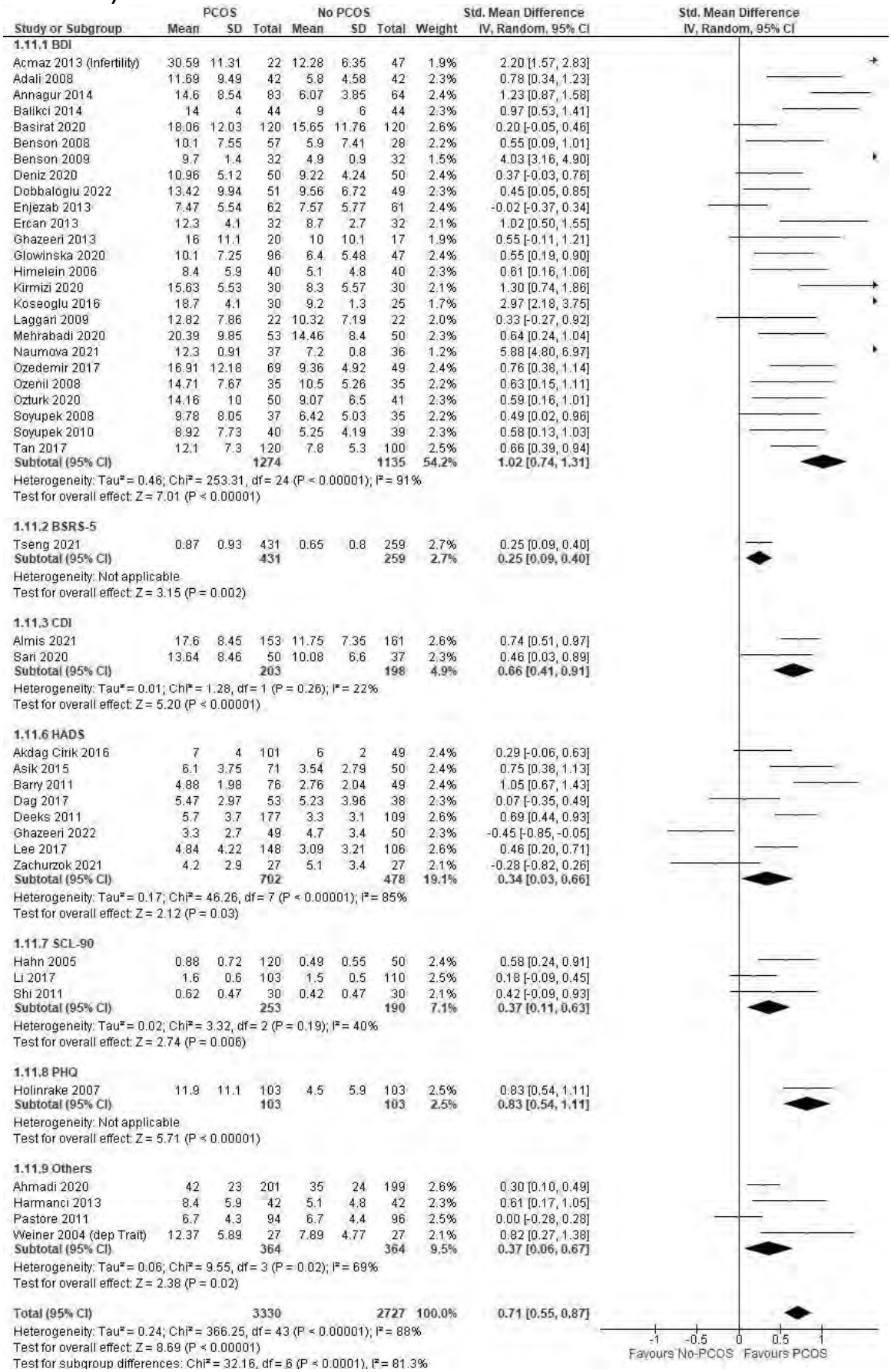
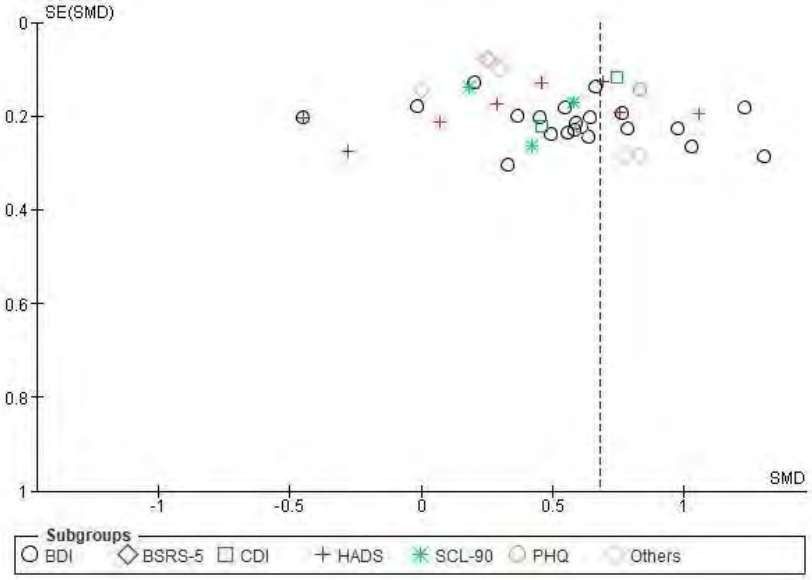


Figure 8.2: Funnel plot for depression scores by screening tools – All studies



OUTCOME 9. Depression scores by screening tools used - Adults

Table 9: Individual Study Data Table - Depression scores – Screening tools used in adults

	OUTCOME: Depression scores – All studies – screening tools in adults							OUTCOME TYPE: Continuous		
	Comparison: Women with PCOS vs. Women without PCOS									
#	Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (SD) in PCOS group	N total in PCOS group	Mean (SD) in comparison group	N total in comparison group	Are these values adjusted or crude?	RoB	If adjusted, what variables were in the model?
	BDI									
1	Acmaz 2013	Score	BDI	Infertility:30.59 (11.31) n=22	86	12.28 (6.35)	47	Crude	Mod	NA
2	Adali 2008	Score	BDI	11.69 (9.49)	42	5.8 (4.58)	42	Crude	Mod	NA
3	Altinkaya 2014	Score	BDI	median (IQR) 8.5 (4-20)	50	median (IQR) 6 (2-20)	50	Crude	Low	NA
4	Annagur 2014 (A)	Score	BDI	14.6 (8.54)	83	6.07 (3.85)	64	Crude	Mod	NA
5	Balikci 2014 (A)	Score	BDI	14 (4)	44	9 (6)	44	Crude	Mod	NA
6	Basirat 2019	Score	BDI II	18.06 (12.03)	120	15.65 (11.76)	120	Crude	Mod	NA
7	Battaglia 2008	Score	BDI	NR (NR)	25	NR (NR)	18	Crude	Mod	NA
8	Benson 2009	Score	BDI	9.7 (1.4)	32	4.9 (0.9)	32	Crude	Mod	NA
9	Benson 2008	Score	BDI	10.1 (1 SEM)	57	5.9 (1.4 SEM) 5.9 (7.41)	28	Crude	Mod	NA

				10.1 (7.55) calculated		calculated				
10	Cinar 2011	Score	BDI	6.4 (4.1)	226	NR (NR)	85	Crude	Mod	NA
11	Deniz 2020	Score	BDI	10.96 (5.12)	50	9.22 (4.24)	50	Crude	Low	NA
12	Enjezab 2013	Score	BDI	7.47 (5.54)	62	7.57 (5.77)	61	Crude	Mod	NA
13	Ercan 2013	Score	BDI	12.3 (4.1)	32	8.7 (2.7)	32	Crude	Mod	NA
14	Glowinska 2020	Score	BDI	10.1 (0.74 SEM) 10.1 (7.25) calculated	96	6.4 (0.8 SEM) 6.4 (5.48) calculated	47	Crude	Mod	NA
15	Himelein 2006	Score	BDI short form	7.85 (7.0)	40	infertility: 4.56 (5.03) community control: 3.61 (4.08)	100 (infertility group n=40) (community control n=60)	Crude	Mod	NA
16	Kirmizi 2020	Score	BDI	15.63 (5.53)	30 PCOS infertile	8.3 (5.57)	30	Crude	Low	NA
17	Koseoglu 2016	Score	BDI	18.7 (4.1)	30	9.2 (1.3)	25	Crude	Mod	NA
18	Mehrabadi 2020	Score	BDI	20.39 (9.85)	53	14.46 (8.4)	50	Crude	Mod	NA
19	Naumova 2021	Score	BDI	12.3 (0.91)	37	TFI: 7.2 (0.8) MFI: 5.8 (0.77)	67 (TFI n=36 MFI n=31)	Crude	Mod	NA
20	Ozedemir 2017	Score	BDI	16.91 (12.18)	69	9.36 (4.92)	49	Crude	Mod	NA
21	Ozenil 2008	Score	BDI	14.71 (7.67)	35	10.5 (5.26)	35	Crude	Mod	NA
22	Ozturk 2020	Score	BDI	14.16 (10.0)	50	9.07 (6.5)	41	Crude	Mod	NA
23	Soyupek 2008	Score	BDI	9.78 (8.05)	37	6.42 (5.03)	35	Crude	Mod	NA
24	Soyupek 2010	Score	BDI	8.92 (7.73)	40	5.25 (4.19)	39	Crude	Mod	NA
25	Tan 2017	Score	BDI	12.1 (7.3)	120	7.8 (5.3)	100	Crude	Mod	NA
	BSRS-5									
26	Tseng 2021	Score	BSRS-5	0.87 (0.93)	431	0.65 (0.8)	259	Crude	Mod	NA
	CES-D									
27	Benson 2020	Score	CES-D	NR (NR)	61	NR (NR)	44	Crude	Low	NA
28	March 2018	Score	CES-D	Self-reported	52		514	Crude	High	NA
29	Moran 2015	Score	CES-D Score >16	NR (NR)	87	NR (NR)	637	Crude	Mod	NA
	DASS-21									
30	Asdag 2020	Score	DASS-21	NR (NR)	82	NR (NR)	85	Crude	Mod	NA
31	Sulaiman 2017	Score	DASS-21	NR (NR)	52	NR (NR)	60	Crude	Low	NA
	DSM-4									
32	Hussain 2015	Score	DSM-4	NR (NR)	110	NR (NR)	40	Crude	High	NA
33	Sahingoz 2013	Score	DSM-4	NR (NR)	73	NR (NR)	73	Crude	High	NA
34	Sayyah-Melli 2015	Score	MMPI (screening) DSM-4 (confirmation)	NR (NR)	742	NR (NR)	798	Crude	Mod	NA
	HADS									

35	Akdag Cirik 2016	Score	HADS	7.0 (4.0)	101	6.0 (2.0)	49	Crude	Low	NA
36	Alur-Gupta 2019	Score	HADS	5.1 (NR)	189	4.5 (NR)	225	Crude	Mod	NA
37	Asik 2015	Score	HADS	6.1 (3.75)	71	3.54 (2.79)	50	Crude	Mod	NA
38	Barry 2011	Score	HADS	4.88 (1.98)	76	2.76 (2.04)	49	Crude	Mod	NA
39	Dag 2017	Score	HADS	5.47 (2.97)	53	5.23 (3.96)	38	Crude	Mod	NA
40	Deeks 2011	Score	HADS	5.7 (3.7)	177	3.3 (3.1)	109	Crude	Mod	NA
41	Dybciak 2022	Score	HADS	6.9 (NR)	230	4.2 (NR)	199	Crude	Mod	NA
42	Ghazeeri 2022	Score	HADS	3.3 (2.7)	49	4.7 (3.4)	50			
43	Lee 2017	Score	HADS	4.84 (4.22)	148	3.09 (3.21)	106	Crude	Mod	NA
44	Moran 2012	Score	HADS	NR (NR)	52	NR (NR)	24	Crude	Low	NA
45	Moran 2010	Score	HADS	median (IQR) 5.5 (2-9.5)	24	median (IQR) 2.5 (1-6)	22	Crude	Low	NA
46	Zeuff 2015	Score	HADS	NR (NR)	44	NR (NR)	43	Crude	Mod	NA
	SCL-90									
47	Hahn 2005 (A)	Score	SCL-90-R	0.88 (0.72)	120	0.49 (0.55)	50	Crude	Mod	NA
48	Li 2017 (A)	Score	SCL-90 (DEP)	1.6.0 (0.6)	103	1.5 (0.5)	110	Crude	Mod	NA
49	Shi 2011 (A)	Score	SCL-90	0.62 (0.47)	30	0.42 (0.47)	30	Crude	Mod	NA
	PHQ									
50	Bhattacharya 2010	Score	PHQ-9	NR (NR)	117	NR (NR)	84	Crude	Low	NA
51	Holinrake 2007	Score	PHQ	11.9 (11.1)	103	4.5 (5.9)	103	Crude	High	NA
52	Maya 2020	Score	PHQ-9	NR	46	NR	392	Crude	High	NA
53	Mukundan 2018	Score	PHQ-9	NR (NR)	186	NR (NR)	186	Crude	High	NA
	Others									
54	Ahmadi 2020 (A)	Score	Millon Clinical Multi-axial Inventory-III (MCMI-III) [higher the worse]	42 (23)	201	35 (24)	199	Crude	Mod	NA
55	Davari Tanha 2013		Evaluation by psychiatrist	NR (NR)	110	NR (NR)	110	Crude	Mod	NA
56	Harmanci 2013 (A)	Score	BSI	8.4 (5.9)	42	5.1 (4.8)	42	Crude	Low	NA
57	Harnod 2020	ICD9 codes: 296.2, 296.3, 300.4, and 311	as determined from National Health Insurance Research Database	NR (NR)	7026	NR (NR)	28104	Crude	Mod	NA

			(NHIRD) claims							
58	Jedel 2010	Score	MADRS-S	median (IQR) 10 (NR)	30	median (IQR)	30 5.5 (NR)	Crude	Mod	NA
59	Karjula 2017	Score	Hopkins Symptom Checklist - 25 Depression	median (IQR) 1.40 (1.15-1.67) At age 31y	125	median (IQR) 1.27 (1.33-1.53) At age 31 y	2188	Crude	High	NA
60	Mansson 2008	Score	Mini NPI by psychiatrist	NR (NR)	49	NR (NR)	49	Crude	Mod	NA
61	Mansson 2011	Score	PGWB							
62	Pastore 2011	Score	QIDS-SR 16	6.7 (4.3)	94	6.7 (4.4)	96	Crude	Mod	NA
63	Tseng 2021 (A)	Score	BSRS-5	0.87 (0.93)	431	0.65 (0.8)	259			
64	Varanasi 2018	Score	Original YFHI or Safe-D survey	NR (NR)	31	NR (NR)	233	Crude	Mod	NA
65	Weiner 2004 (A)	Score	DACL	State 11.30 (6.49) Trait 12.37 (5.89)	27	State 6.81 (4.87) Trait 7.89 (4.77)	27	Crude	Mod	NA

BDI: Beck Depression Inventory; HADS: Hospital Anxiety and Depression Scale; CDI: Children's Depression Inventory; DASS-21: Depression Anxiety and Stress Scale-21; CES-D: Center for Epidemiologic Studies-Depression scale; PHQ-9: Patient Health Questionnaire – Depression; DSM-4: Diagnostic and Statistical Manual of Mental Disorders; MADRS-S: Montgomery Asberg Depression Rating Scale; QIDS-SR 16: Quick Inventory of Depressive Symptomatology-Self Report 16; MMPI: Minnesota Multiphasic Personality Inventory; DASS-21: Depression Anxiety and Stress Scale -21; BSRS-5: Brief Social Rhythm Scale – 5; YFHI: Young Female Health Initiative; SEM: standard error of mean; PGWB: Psychological general well-being scale

Figure 9.1A: Forest plot - Depression scores by screening tools used – Adults (Mean difference)

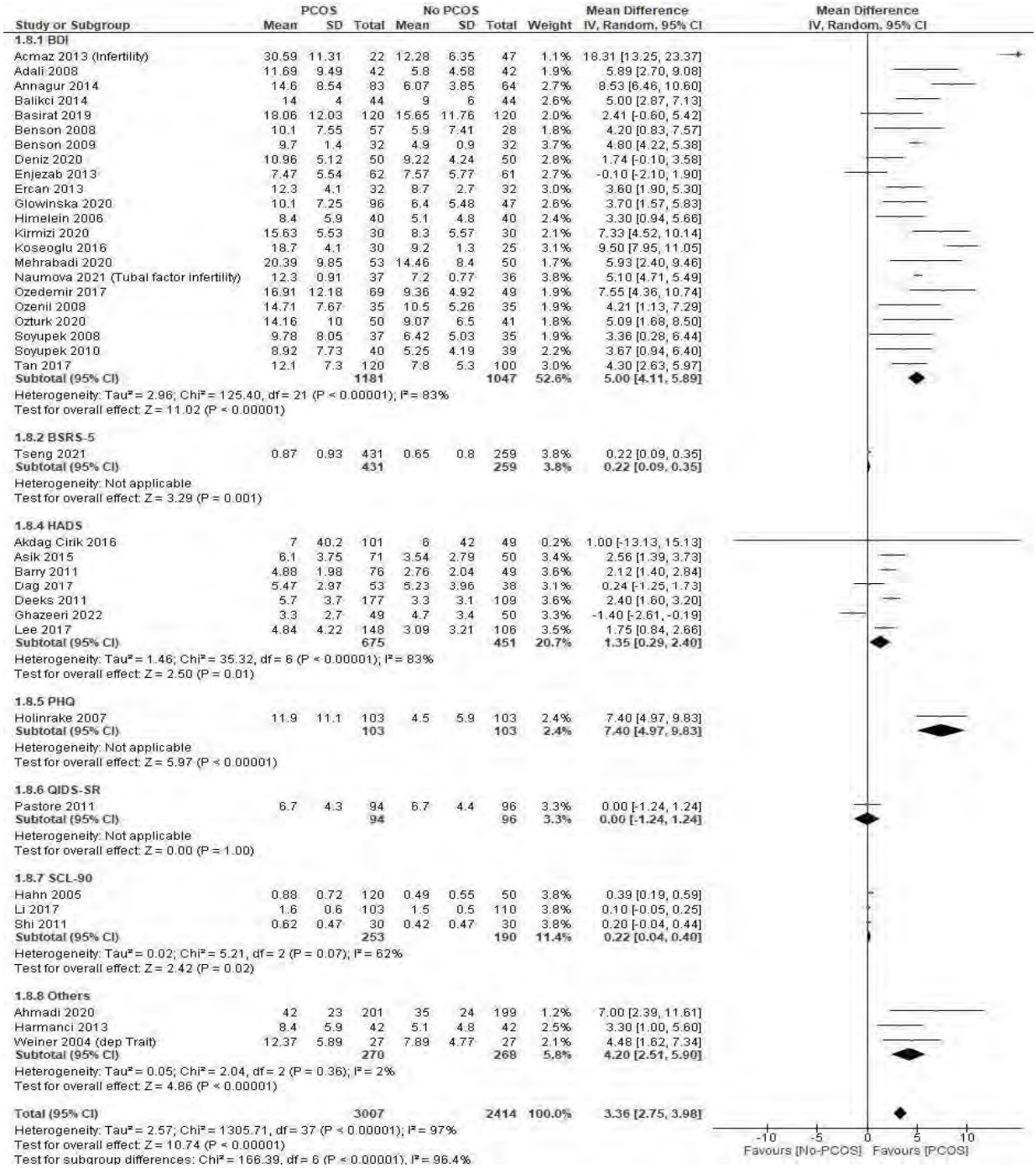


Figure 9.1B: Forest plot - Depression scores by screening tools used – Adults (Std. mean difference)

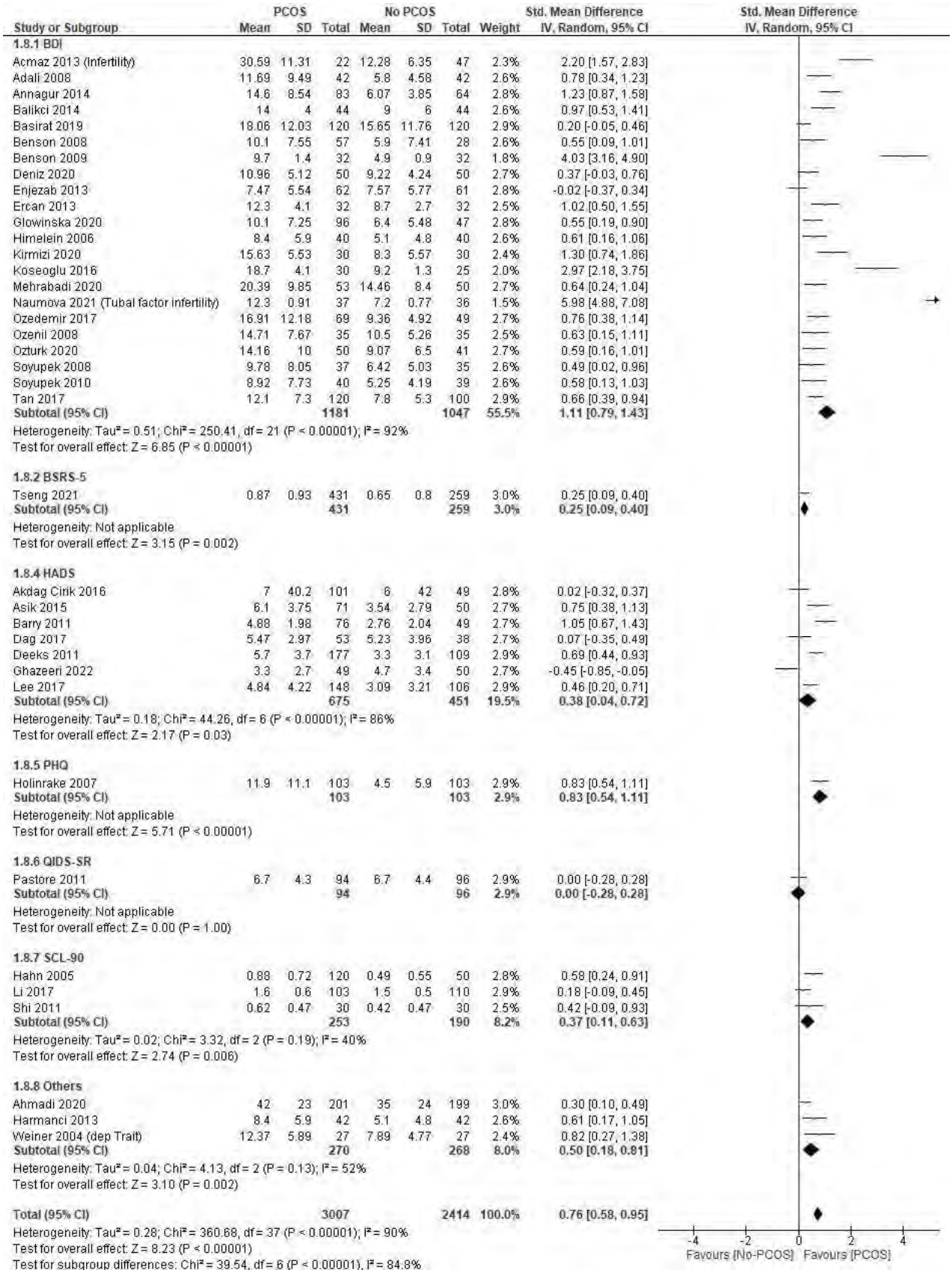
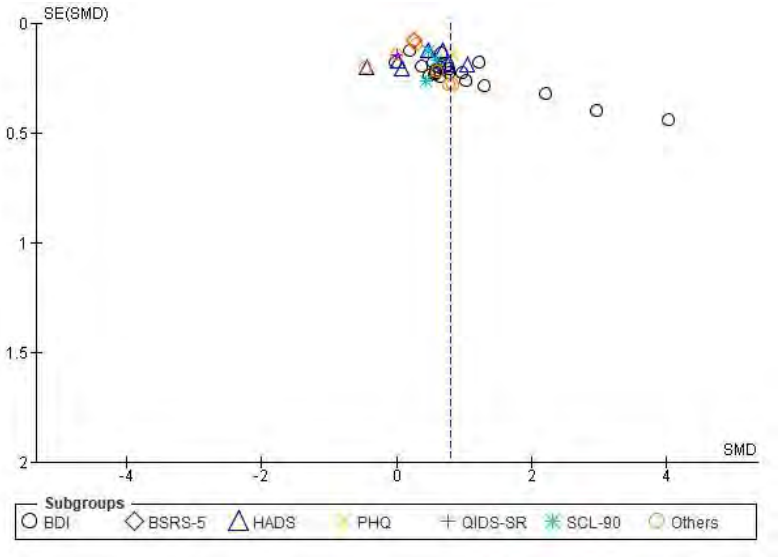


Figure 9.2: Funnel plot – Depression scores by tools used - Adults



OUTCOME 10. Depression scores by Screening tools used - Adolescents

Table 10: Individual Study Data Table - Depression scores – Screening tools used in adolescents

#	Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (SD) in PCOS group	N total in PCOS group	Mean (SD) in comparison group	N total in comparison group	Are these values adjusted or crude?	RoB	If adjusted, what variables were in the model?
1	Besenek 2021 (Adolescents)	Score	BDI	Median (IQR)	39	Median (IQR)	37	Crude	Low	NA
2	Dobbaloglu 2022 (Adolescents)	Score	BDI	13.42 (9.94)	49	9.56 (6.72)	48	Crude	Mod	NA
3	Ghazeeri 2013 (Adolescents)	Score	BDI	16 (11.1)	20	10 (10.1)	17	Crude	Mod	NA
4	Laggari 2009 (Adolescents)	Score	BDI	12.82 (7.86)	22	10.32 (7.19)	22	Crude	High	NA
5	Almis 2021 (Adolescents)	Score	CDI	17.6 (8.45)	153	11.75 (7.35)	161	Crude	Mod	NA
6	Emeksiz 2018 (16-19 years)	Score	CDI	Median (IQR)	80	Median (IQR)	50	Crude	Mod	NA
7	Sari 2020 (Adolescents)	Score	CDI	13.64 (8.46)	50	10.08 (6.6)	37	Crude	Mod	NA
8	Zachurzok 2021 (Adolescents)	Score	HADS	4.2 (2.9)	27	5.1 (3.4)	27	Crude	Mod	NA
9	Benson 2020 (Adolescents)	Score	CES-D	-	-	-	-			
10	Maya 2020 (Adolescents)	Score	PHQ-9 (dep and/or anxiety)	-	-	-	-			

BDI: Beck Depression Inventory; HADS: Hospital Anxiety and Depression Scale; CDI: Children's Depression Inventory; CES-D: Center for Epidemiologic Studies-Depression scale; PHQ-9: Patient Health Questionnaire – Depression; SEM: standard error of mean

Figure 10.1: Forest plot - Depression scores by screening tools used - Adolescents

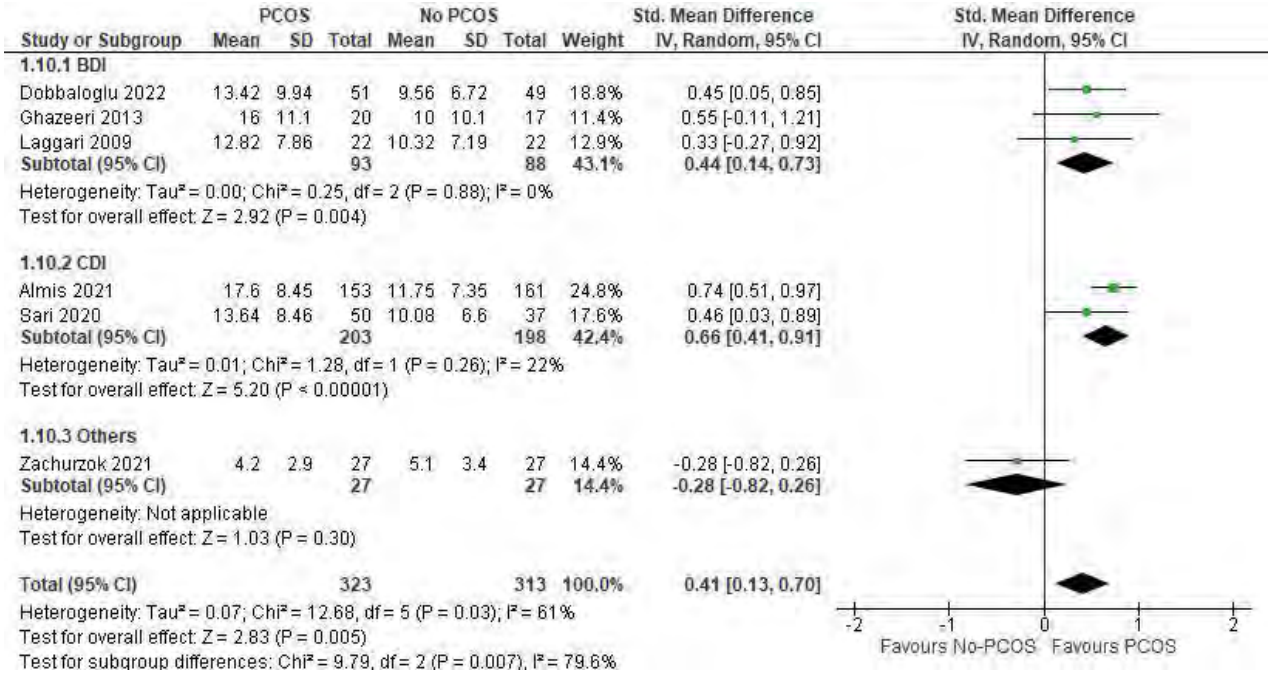
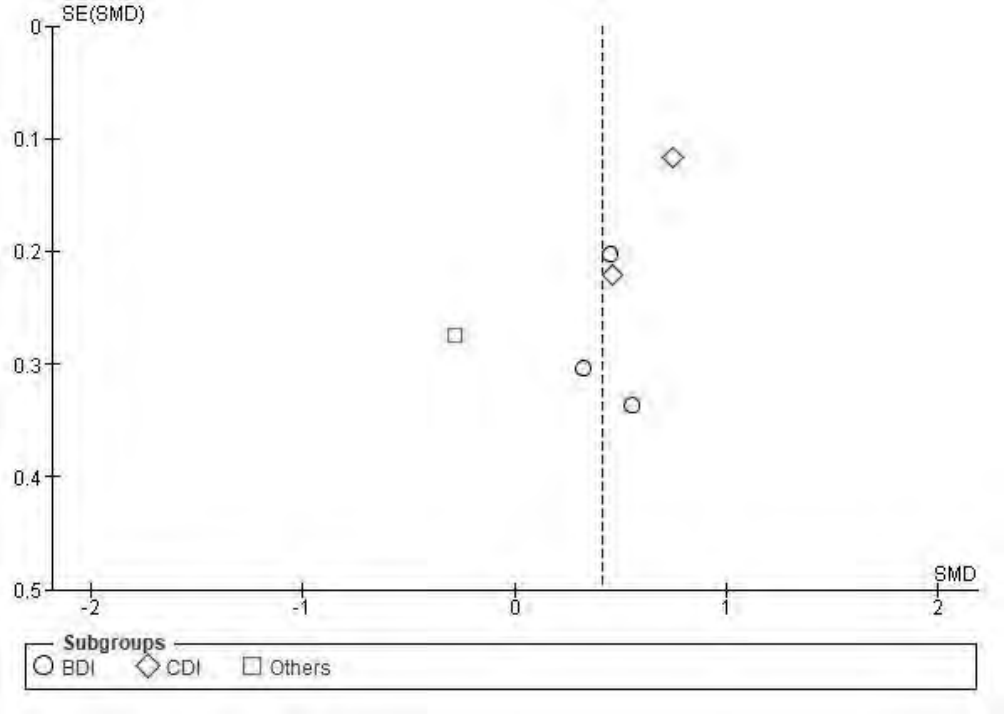


Figure 10.2: Funnel plot - Depression scores by screening tools used - Adolescents



7.2. Anxiety

OUTCOME 11. Prevalence of anxiety – All studies

Table 11: Individual Study Data Table - Prevalence of anxiety – All studies

	OUTCOME: Prevalence of anxiety – All studies					OUTCOME TYPE: Dichotomous				
	Comparison: Women with PCOS vs. Women without PCOS									
#	Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	N events in PCOS group	N total in PCOS group	N events in comparison group	N total in comparison group	Are these values adjusted or crude?	RoB	If adjusted, what variables were in the model?
1	Akdag Cirik 2016	Score	HADS	34	101	6	49	Crude	Low	NA
2	Almis 2021	Score	TAS	76	153	31	161	Crude	Mod	NA
		Score	SAS	73	153	31	161	Crude		NA
3	Altinkaya 2014	Score	BAI	17	50	4	50	Crude	Low	NA
4	Alur-Gupta 2019	Score	HADS	145	189	127	225	Crude	Mod	NA
5	Asdag 2020	Score	DASS-21	52	82	35	85	Crude	Mod	NA
6	Asik 2015	Score	HADS	25	71	6	50	Crude	Mod	NA
7	CInar 2011	Score	HADS	95	226	5	85	Crude	Mod	NA
8	Dybciak 2022	Score	HADS	106	230	51	199	Crude	Mod	NA
9	Harnod 2020 (Potentially included both adults and adolescents)	ICD 9 code: 300	by Psychiatrist	606	7026	2017	28104	Crude	Low	NA
10	Holinrake 2007	Score	PRIME-MD PHQ	14	103	1	103	Crude	High	NA
11	Hussain 2015	Score	DSM-4	17	110	0	40	Crude	High	NA
12	Jedel 2010	Score	BSA-S	19	30	4	30	Crude	Mod	NA
13	Karjula 2017	Score	Hopkins Symptom Checklist - 25 Anxiety	19	125	179	2188	Crude	High	NA
14	Lee 2017	Score	HADS	61	148	18	106	Crude	Mod	NA
15	Mansson 2008	Score	MINI NPI by Psychiatrist	6	49	1	49	Crude	Mod	NA
16	Moran 2012	Score	HADS	32	52	11	24	Crude	Low	NA
17	Moran 2010	Score	HADS	9	24	2	22	Crude	Low	NA
18	Naumova 2021	Score	HAM-A	2	37	2 TFI 1 MFI	36 (tubal factor infertility-TFI) 31 (male factor	Crude	Mod	NA

							infertility-MFI)			
19	Sahingoz 2013	Score	DSM-4	19	73	7	73	Crude	High	NA
20	Sari 2020	Score	KSADS-PL	2	50	2	37	Crude	Mod	NA
21	Sayyah-Melli 2015	Score	DSM-4	57	742	26	798	Crude	Mod	NA
22	Sirmans 2014	Score	Not reported	347	1689	648	5067	Crude	High	NA
23	Sulaiman 2014	Score	DASS-21	30	52	31	60	Crude	Low	NA
24	Tan 2017	Score	STAI	16	120	2	100	Crude	Mod	NA
25	Tseng 2021	Score	BSRS-5	49	431	9	259	Crude	Mod	NA
26	Zachurzok 2021	Score	HADS	5	27	14	27	Crude	Mod	NA
27	Zeuff 2015	Score	HADS	23	44	22	43	Crude	Mod	NA

HADS: Hospital Anxiety and Depression Scale; TAS: Trait Anxiety Score of the State-Trait Anxiety Inventory for Children (STAI-C); SAS: State Anxiety Score of the STAI-C; DASS-21: Depression Anxiety Stress Scale-21; HAM-A: Hamilton Anxiety Rating Scale; BAI: Beck Anxiety Inventory; PRIME-MD PHQ: Primary Care Evaluation of Mental Disorders Patient Health Questionnaire; BSA-S: Brief Scale for Anxiety; MINI NPI: Mini International Neuro-psychiatric Interview; DSM-4: Diagnostic and Statistical Manual of Mental Disorders; KSADS-PL: Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Present and Lifetime Version; STAI: State-Trait Anxiety Inventory; BSRS-5: Brief Social Rhythm Scale-5

Figure 11.1: Forest plot for Prevalence of anxiety – All studies

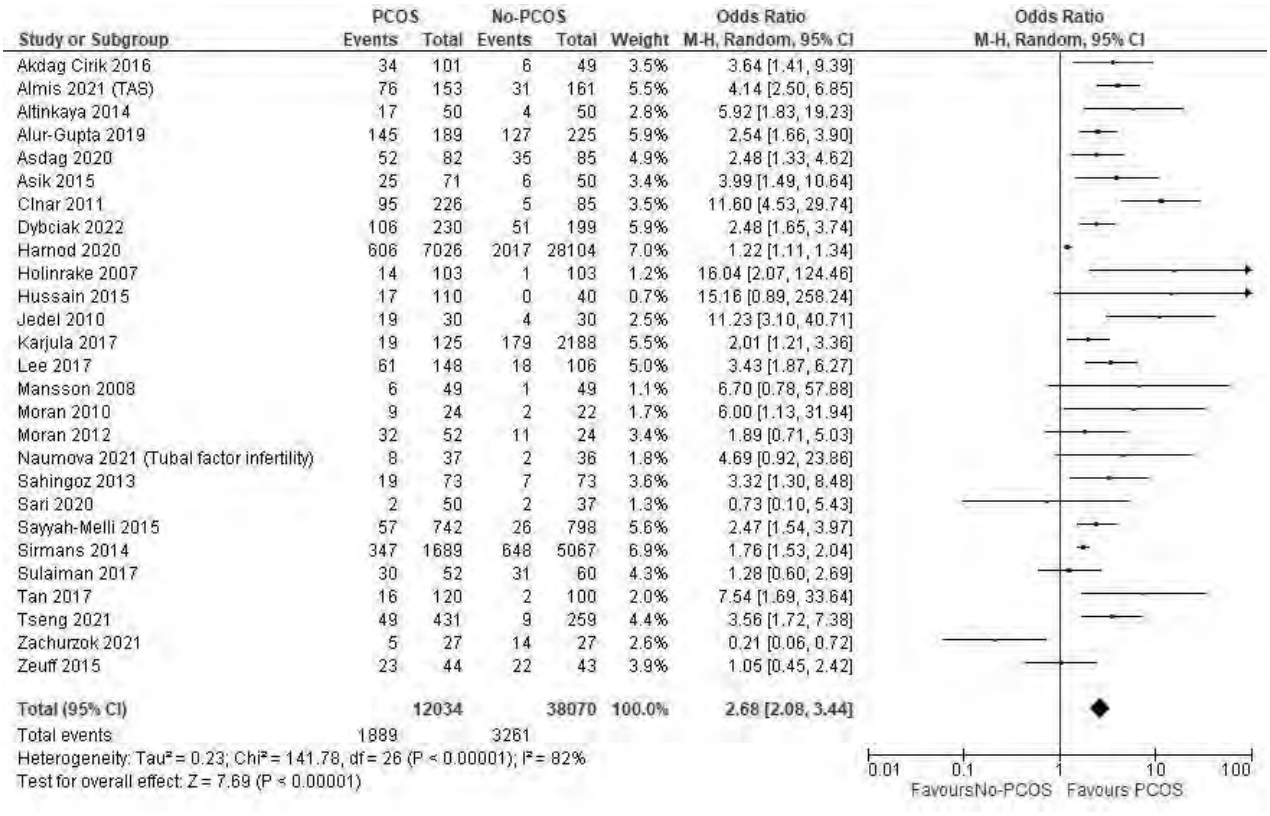
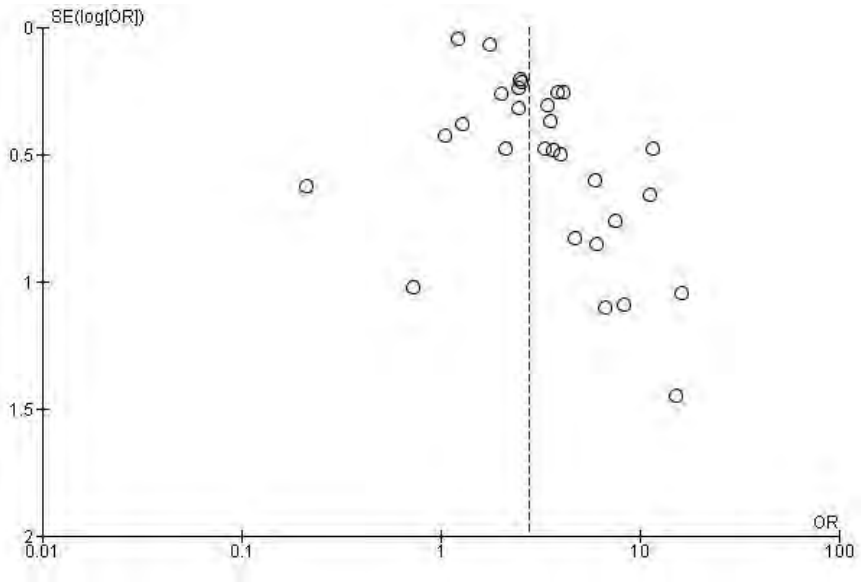


Figure 11.2: Funnel plot for Prevalence of anxiety – All studies



OUTCOME 12. Prevalence of anxiety – Adult studies

Table 12: Individual Study Data Table - Prevalence of anxiety – Adult studies

	OUTCOME: Prevalence of anxiety – Adult studies					OUTCOME TYPE: Dichotomous				
	Comparison: Adult women with PCOS vs. Adult women without PCOS									
#	Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	N events in PCOS group	N total in PCOS group	N events in comparison group	N total in comparison group	Are these values adjusted or crude?	RoB	If adjusted, what variables were in the model?
1	Akdag Cirik 2016	Score	HADS	34	101	6	49	Crude	Low	NA
2	Altinkaya 2014	Score	BAI	17	50	4	50	Crude	Low	NA
3	Alur-Gupta 2019	Score	HADS	145	189	127	225	Crude	Mod	NA
4	Asdag 2020	Score	DASS-21	52	82	35	85	Crude	Mod	NA
5	Asik 2015	Score	HADS	25	71	6	50	Crude	Mod	NA
6	CInar 2011	Score	HADS	95	226	5	85	Crude	Mod	NA
7	Dybciak 2022	Score	HADS	106	230	51	199	Crude	Mod	NA
8	Harnod 2020	ICD 9 code: 300	by Psychiatrist	606	7026	2017	28104	Crude	Low	NA
9	Holinrake 2007	Score	PRIME-MD PHQ	14	103	1	103	Crude	High	NA
10	Hussain 2015	Score	DSM-4	17	110	0	40	Crude	High	NA
11	Jedel 2010	Score	BSA-S	19	30	4	30	Crude	Mod	NA

12	Karjula 2017	Score	Hopkins Symptom Checklist - 25 Anxiety	19	125	179	2188	Crude	High	NA
13	Lee 2017	Score	HADS	61	148	18	106	Crude	Mod	NA
14	Mansson 2008	Score	MINI NPI by Psychiatrist	6	49	1	49	Crude	Mod	NA
15	Moran 2012	Score	HADS	32	52	11	24	Crude	Low	NA
16	Moran 2010	Score	HADS	9	24	2	22	Crude	Low	NA
17	Naumova 2021	Score	HAM-A	2	37	2 TFI 1 MFI	36 (tubal factor infertility-TFI) 31 (male factor infertility-MFI)	Crude	Mod	NA
18	Sahingoz 2013	Score	DSM-4	19	73	7	73	Crude	High	NA
19	Sayyah-Melli 2015	Score	DSM-4	57	742	26	798	Crude	Mod	NA
20	Sirmans 2014	Score	Not reported	347	1689	648	5067	Crude	High	NA
21	Sulaiman 2014	Score	DASS-21	30	52	31	60	Crude	Low	NA
22	Tan 2017	Score	STAI	16	120	2	100	Crude	Mod	NA
23	Tseng 2021	Score	BSRS-5	49	431	9	259	Crude	Mod	NA
24	Zeuff 2015	Score	HADS	23	44	22	43	Crude	Mod	NA

HADS: Hospital Anxiety and Depression Scale; TAS: Trait Anxiety Score of the State-Trait Anxiety Inventory for Children (STAI-C); SAS: State Anxiety Score of the STAI-C; DASS-21: Depression Anxiety Stress Scale-21; HAM-A: Hamilton Anxiety Rating Scale; BAI: Beck Anxiety Inventory; PRIME-MD PHQ: Primary Care Evaluation of Mental Disorders Patient Health Questionnaire; BSA-S: Brief Scale for Anxiety; MINI NPI: Mini International Neuro-psychiatric Interview; DSM-4: Diagnostic and Statistical Manual of Mental Disorders; KSADS-PL: Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Present and Lifetime Version; STAI: State-Trait Anxiety Inventory; BSRS-5: Brief Social Rhythm Scale-5

Figure 12.1: Forest plot for Prevalence of anxiety – Adult studies

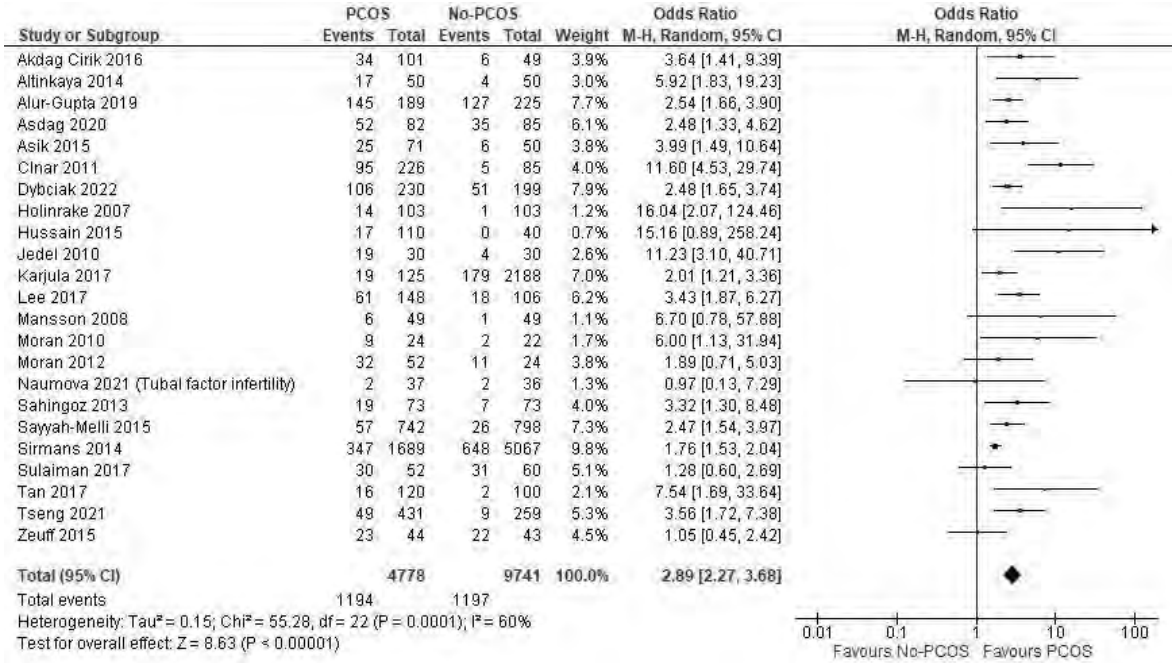
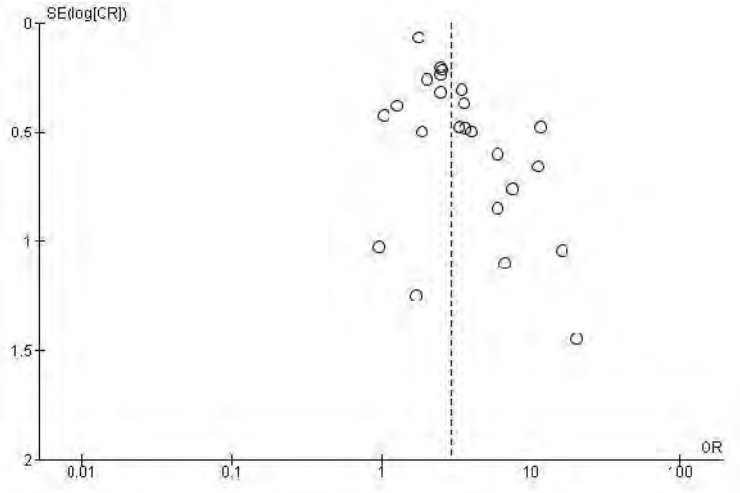


Figure 12.2: Funnel plot for Prevalence of anxiety – Adult studies



OUTCOME 13. Prevalence of anxiety – Adolescents

Table 13: Individual Study Data Table - Prevalence of anxiety – Adolescents

	OUTCOME: Prevalence of anxiety – Adolescent studies			OUTCOME TYPE: Dichotomous						
	Comparison: Adolescents with PCOS vs. Adolescents without PCOS									
	Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	N events in PCOS group	N total in PCOS group	N events in comparison group	N total in comparison group	Are these values adjusted or crude?	RoB	If adjusted, what variables were in the model?
1	Almis 2021	Score	TAS	TAS 40-60 76 (49.7%) SAS 40-60 73 (47.7%)	153	TAS 40-60 31 (19.3%) SAS 40-60 31 (19.3%)	161	Crude	Mod	NA
2	Sari 2020	Score	KSADS-PL	2	50	2	37	Crude	Mod	NA
3	Zachurzok 2021	Score	HADS	5	27	14	27	Crude	Mod	NA

Figure 13.1: Forest plot for Prevalence of anxiety – Adolescents

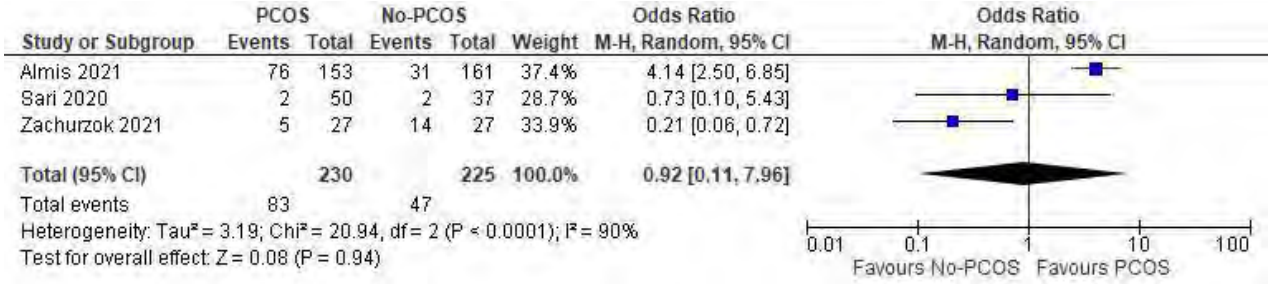
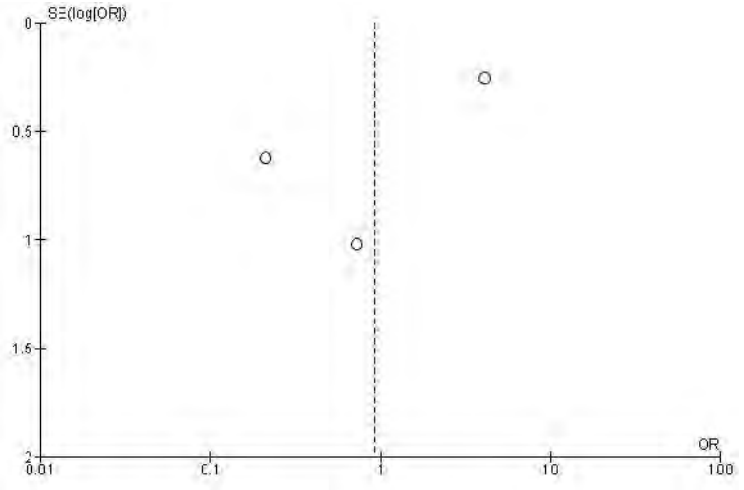


Figure 13.2: Funnel plot for Prevalence of anxiety – Adolescents



OUTCOME 14. Prevalence of anxiety – studies that used clinical interviews

Table 14: Individual Study Data Table - Prevalence of anxiety – Studies that used clinical interviews

	OUTCOME: Prevalence of anxiety – studies that used clinical interviews					OUTCOME TYPE: Dichotomous				
	Comparison: PCOS vs. No-PCOS									
#	Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	N events in PCOS group	N total in PCOS group	N events in comparison group	N total in comparison group	Are these values adjusted or crude?	RoB	If adjusted, what variables were in the model?
1	Hussain 2015	Score	DSM-4	17	110	0	40	Crude	High	NA
2	Mansson 2008	Score	MINI NPI by Psychiatrist	6	49	1	49	Crude	Mod	NA
3	Sahingoz 2013	Score	DSM-4	19	73	7	73	Crude	High	NA
4	Sari 2020	Score	KSADS-PL	2	50	2	37	Crude	Mod	NA
5	Sayyah-Melli 2015	Score	DSM-4	57	742	26	798	Crude	Mod	NA

Figure 14.1: Forest plot for Prevalence of anxiety – studies that used clinical interviews

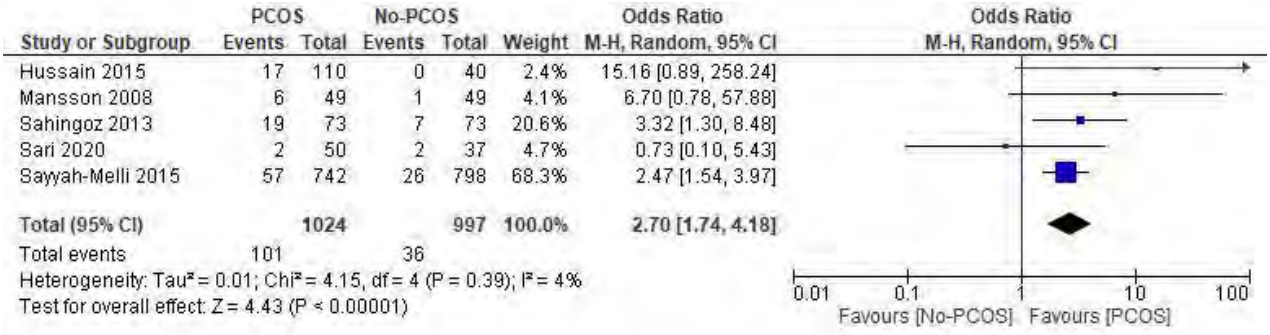
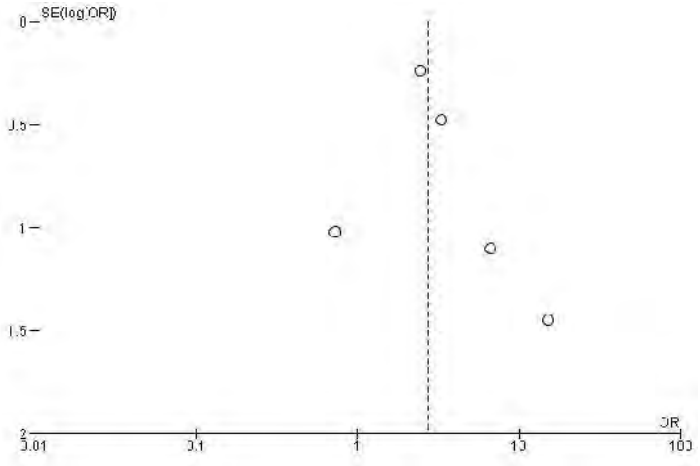


Figure 14.2: Funnel plot for Prevalence of anxiety – studies that used clinical interviews



OUTCOME 15. Anxiety scores – All studies

Table 15: Individual Study Data Table - anxiety scores – All studies

	OUTCOME: Anxiety scores – All studies				OUTCOME TYPE: Continuous					
	Comparison: Women with PCOS vs. Women without PCOS									
#	Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (SD) in PCOS group	N total in PCOS group	Mean (SD) in comparison group	N total in comparison group	Are these values adjusted or crude?	RoB	If adjusted, what variables were in the model?
1	Ahmadi 2020	Score	Millon Clinical Multi-axial Inventory-III (MCMI-III) [higher the worse]	53 (21)	201	49 (22)	199	Crude	Mod	NA
2	Akdag Cirik 2016	Score	HADS	10 (5)	101	8 (3)	49	Crude	Low	NA
3	Aksu 2020	Score	STAI-2 (trait anxiety-baseline)	53.9 (5.8)	50	50.7 (8.1)	42	Crude	Low	NA
4	Almis 2021	Score	TAS	39.07 (7.88)	153	34.13 (5.84)	161	Crude	Mod	NA
		Score	SAS	39.86 (7.8)	153	33.99 (7.01)	161	Crude		NA
5	Altinkaya 2014	Score	BAI	Median (IQR) 8 (3-26)	50	Median (IQR) 5 (4-18)	50	Crude	Low	NA
6	Alur-Gupta 2019	Score	HADS	10.1 (NR)	189	8.4 (NR)	225	Crude	Mod	NA
7	Asdag 2020	Score	DASS-21	NR (NR)	82	NR (NR)	85	Crude	Mod	NA
8	Asik 2015	Score	HADS	8.59 (4.52)	71	5.98 (3.05)	50	Crude	Mod	NA

9	Balikci 2014	Score	BAI	14 (4)	44	9 (6)	44	Crude	Mod	NA
10	Barry 2011	Score	HADS	9.99 (4.56)	76	7.57 (4.12)	49	Crude	Mod	NA
11	Basirat 2020	Score	TAS	46.19 (5.29)	135	44.49 (5.13)	122	Crude	Mod	NA
			SAS	49.55 (5.10)	135	49.22 (4.66)	122			
12	Besenek 2021	Score	TAS	46.21 (9.25)	39	47.19 (11.18)	37	Crude	Low	NA
			SAS	41.08 (8.78)	39	41.57 (10.61)	37			
13	Borghi 2018 (A)	Score	SCL-90-R	Median (IQR)	30	Median (IQR)	30	Crude	Mod	NA
14	Caltekin 2021 (A)	Score	BAI	Median (IQR)	73	Median (IQR)	63	Crude	Mod	NA
15	CInar 2011	Score	HADS	9.3 (4.3)	226	NR (NR)	85	Crude	Mod	NA
16	Dag 2017	Score	HADS	7.67 (4.2)	53	7.39 (3.88)	38	Crude	Mod	NA
17	Deeks 2011	Score	HADS	9.5 (3.9)	177	6.5 (3.6)	109	Crude	Mod	NA
18	Dobbaloglu 2022	Score	TAS	44.60 (13.16)	49	40.02 (7.61)	48	Crude	Mod	NA
			SAS	40.77 (10.44)	49	36.64 (6.89)	48			
19	Dybciak 2022	Score	HADS	10.6 (NR)	230	7.3 (NR)	199	Crude	Mod	NA
20	Ghazeeri 2013	Score	SCARED	6.8 (4.25)	20	5.24 (5.06)	17	Crude	Mod	NA
21	Ghazeeri 2022	Score	HADS	5.5 (4.0)	49	5.9 (3.7)	50	Crude	Mod	NA
22	Glowinska 2020	Score	TAS	45.5 (1.0 SEM) 45.5 (9.8 calculated)	96	42.3 (1.4 SEM) 42.3 (9.6 calculated)	47	Crude	Mod	NA
			SAS	42.9 (1.1 SEM) 42.9 (10.8 calculated)	96	38.4 (1.3 SEM) 38.4 (8.9 calculated)	47			
23	Hahn 2005	Score	SCL-90-R	0.57 (0.61)	120	0.40 (0.60)	50	Crude	Mod	NA
24	Harmanci 2013 (A)	Score	BSI	7.6 (6.2)	42	4.6 (4.4)	42	Crude	Low	NA
25	Harnod 2020	ICD 9 code: 300	by Psychiatrist	NR	7026	NR	28104	Crude	Low	NA
26	Holinrake 2007	Score	PRIME-MD PHQ	NR (NR)	103	NR (NR)	103	Crude	High	NA
27	Hussain 2015	Score	DSM-4	NR (NR)	110	NR (NR)	40	Crude	High	NA
28	Jedel 2010	Score	BSA-S	Median (IQR) 10.5 (NR)	30	Median (IQR) 5.0 (NR)	30	Crude	Mod	NA
29	Karjula 2017	Score	Hopkins Symptom Checklist - 25 Anxiety	Median (IQR) 1.30 (1.20-1.60)	125	Median (IQR) 1.20 (1.10-1.40)	2188	Crude	High	NA
30	Komarowska 2013	Score	STAI [state / trait NR]	48 (NR)	20	40 (NR)	20	Crude	High	NA

31	Laggari 2009	Score	STAI-Gr (STAI-Greek version)	36.55 (10.44)	22	31.5 (8.24)	22	Crude	High	NA
32	Lee 2017	Score	HADS	9.41 (5.08)	148	6.72 (3.87)	106	Crude	Mod	NA
33	Mansson 2008	Score	MINI NPI by Psychiatrist	NR (NR)	49	NR (NR)	49	Crude	Mod	NA
34	Mehrabadi 2020 (A)	Score	BAI	17.35 (10.44)	53	12.2 (9.65)	50	Crude	Mod	NA
35	Moran 2012	Score	HADS	NR (NR)	52	NR (NR)	24	Crude	Low	NA
36	Moran 2010	Score	HADS	Median (IQR) 10.5 (7-12)	24	Median (IQR) 7 (5-9)	22	Crude	Low	NA
37	Naumova 2021	Score	HAM-A	10.7 (1.23)	37	TFI: 5.2 (1.01) MFI: 2.7 (0.62)	67 TFI n=36 MFI n=31	Crude	Mod	NA
38	Ozedemir 2017	Score	BAI	19.59 (12.35)	69	11.02 (8.41)	49	Crude	Mod	NA
39	Ozenil 2008	Score	STAI	47.8 (8.13)	35	42.5 (5.47)	35	Crude	Mod	NA
40	Ozturk 2020	Score	BAI	16.48 (12.2)	50	10.58 (7.9)	41	Crude	Mod	NA
41	Sahingoz 2013	Score	DSM-4	NR (NR)	73	NR (NR)	73	Crude	High	NA
42	Sari 2020	Score	KSADS-PL	NR (NR)	50	NR (NR)	37	Crude	Mod	NA
43	Sayyah-Melli 2015	Score	DSM-4	NR (NR)	742	NR (NR)	798	Crude	Mod	NA
44	Shi 2011	Score	SCL-90	0.46 (0.45)	30	0.28 (0.4)	30	Crude	Mod	NA
45	Sirmans 2014	Score	Not reported	NR (NR)	1689	NR (NR)	5067	Crude	High	NA
46	Soyupek 2010	Score	BAI	4.22 (2.94)	40	1.89 (2.1)	39	Crude	Mod	NA
47	Sulaiman 2014	Score	DASS-21	NR (NR)	52	NR (NR)	60	Crude	Low	NA
48	Tan 2017	Score	STAI	SAI score 42.7 (11.7) TAI score 43.4 (9.8)	120	SAI score 34.2 (10.1) TAI score 36.1 (9.4)	100	Crude	Mod	NA
49	Tseng 2021	Score	BSRS-5	0.88 (0.87)	431	0.8 (0.71)	259	Crude	Mod	NA
50	Weiner 2004	Score	Trait	43.89 (11.68)	27	37.81 (8.94)	27	Crude	Mod	NA
			State17.3	37.67 (12.42)	27	32.56 (7.61)	27			
51	Zachurzok 2021	Score	HADS	7.3 (3.9)	27	9.6 (3.0)	27	Crude	Mod	NA
52	Zeuff 2015	Score	HADS	NR (NR)	44	NR (NR)	43	Crude	Mod	NA

HADS: Hospital Anxiety and Depression Scale; TAS: Trait Anxiety Score of the State-Trait Anxiety Inventory for Children (STAI-C); SAS: State Anxiety Score of the STAI-C; DASS-21: Depression Anxiety Stress Scale-21; HAM-A: Hamilton Anxiety Rating Scale; BAI: Beck Anxiety Inventory; PRIME-MD PHQ: Primary Care Evaluation of Mental Disorders Patient Health Questionnaire; BSA-S: Brief Scale for Anxiety; MINI NPI: Mini International Neuro-psychiatric Interview; DSM-4: Diagnostic and Statistical Manual of Mental Disorders; KSADS-PL: Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Present and Lifetime Version; STAI: State-Trait Anxiety Inventory; BSRS-5: Brief Social Rhythm Scale-5; SCARED: Screen for Child Anxiety Related Emotional Disorders

Figure 15.1: Forest plot for anxiety score – All studies

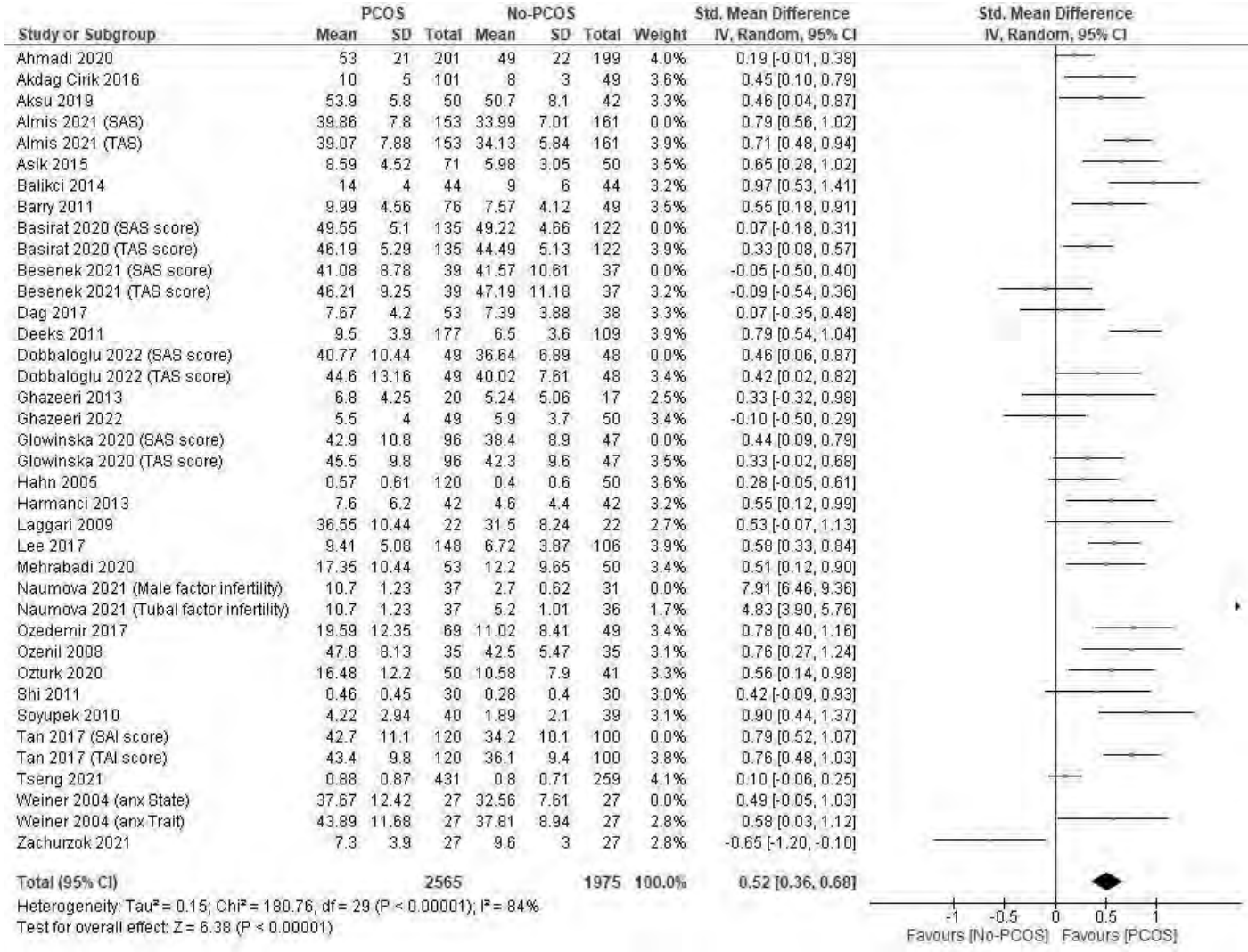
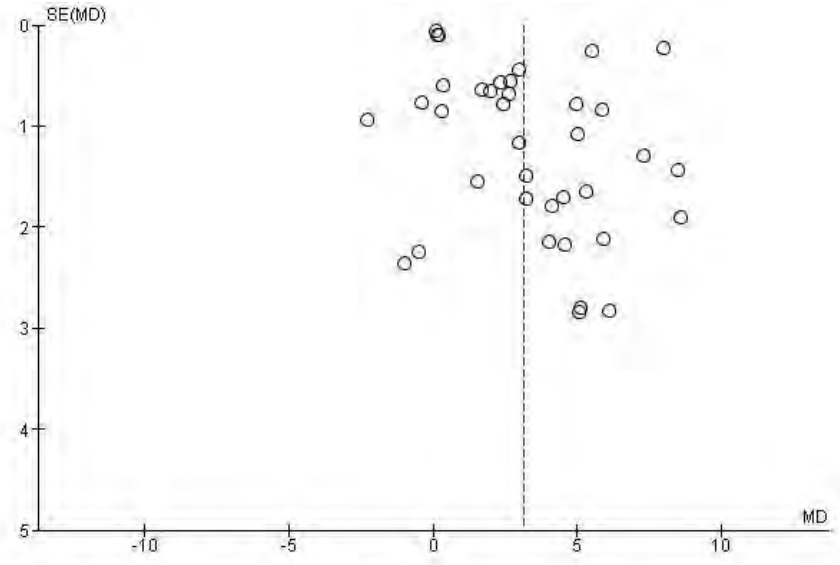


Figure 15.2: Funnel plot for anxiety score – All studies



OUTCOME 16. Anxiety scores – Adult studies

Table 16: Individual Study Data Table - anxiety scores – Adult studies

	OUTCOME: Anxiety scores – Adults studies					OUTCOME TYPE: Continuous				
	Comparison: Women with PCOS vs. Women without PCOS									
#	Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (SD) in PCOS group	N total in PCOS group	Mean (SD) in comparison group	N total in comparison group	Are these values adjusted or crude?	RoB	If adjusted, what variables were in the model?
1	Ahmadi 2020	Score	Millon Clinical Multi-axial Inventory-III (MCMI-III) [higher the worse]	53 (21)	201	49 (22)	199	Crude	Mod	NA
2	Akdag Cirik 2016	Score	HADS	10 (5)	101	8 (3)	49	Crude	Low	NA
3	Aksu 2020	Score	STAI-2 (trait anxiety-baseline)	53.9 (5.8)	50	50.7 (8.1)	42	Crude	Low	NA
4	Altinkaya 2014	Score	BAI	Median (IQR) 8 (3-26)	50	Median (IQR) 5 (4-18)	50	Crude	Low	NA
5	Alur-Gupta 2019	Score	HADS	10.1 (NR)	189	8.4 (NR)	225	Crude	Mod	NA
6	Asdag 2020	Score	DASS-21	NR (NR)	82	NR (NR)	85	Crude	Mod	NA
7	Asik 2015	Score	HADS	8.59 (4.52)	71	5.98 (3.05)	50	Crude	Mod	NA
8	Balikci 2014	Score	BAI	14 (4)	44	9 (6)	44	Crude	Mod	NA
9	Barry 2011	Score	HADS	9.99 (4.56)	76	7.57 (4.12)	49	Crude	Mod	NA
10	Basirat 2020	Score	TAS	46.19 (5.29)	135	44.49 (5.13)	122	Crude	Mod	NA
			SAS	49.55 (5.10)	135	49.22 (4.66)	122			
11	Borghi 2018 (A)	Score	SCL-90-R	Median (IQR)	30	Median (IQR)	30	Crude	Mod	NA
12	Caltekin 2021 (A)	Score	BAI	Median (IQR)	73	Median (IQR)	63	Crude	Mod	NA
13	CInar 2011	Score	HADS	9.3 (4.3)	226	NR (NR)	85	Crude	Mod	NA
14	Dag 2017	Score	HADS	7.67 (4.2)	53	7.39 (3.88)	38	Crude	Mod	NA
15	Deeks 2011	Score	HADS	9.5 (3.9)	177	6.5 (3.6)	109	Crude	Mod	NA
16	Dybciak 2022	Score	HADS	10.6 (NR)	230	7.3 (NR)	199	Crude	Mod	NA
17	Ghazeeri 2022	Score	HADS	5.5 (4.0)	49	5.9 (3.7)	50	Crude	Mod	NA
18	Glowinska 2020	Score	TAS	45.5 (1.0 SEM) 45.5 (9.8 calculated)	96	42.3 (1.4 SEM) 42.3 (9.6 calculated)	47	Crude	Mod	NA
			SAS	42.9 (1.2 SEM)	96	38.4 (1.3 SEM)	47			

				42.9 (10.8 calculated)		38.4 (8.9 calculated)				
19	Hahn 2005	Score	SCL-90-R	0.57 (0.61)	120	0.40 (0.60)	50	Crude	Mod	NA
20	Harmanci 2013 (A)	Score	BSI	7.6 (6.2)	42	4.6 (4.4)	42	Crude	Low	NA
21	Harnod 2020	ICD 9 code: 300	by Psychiatrist	NR	7026	NR	28104	Crude	Low	NA
22	Holinrake 2007	Score	PRIME-MD PHQ	NR (NR)	103	NR (NR)	103	Crude	High	NA
23	Hussain 2015	Score	DSM-4	NR (NR)	110	NR (NR)	40	Crude	High	NA
24	Jedel 2010	Score	BSA-S	Median (IQR) 10.5 (NR)	30	Median (IQR) 5.0 (NR)	30	Crude	Mod	NA
25	Karjula 2017	Score	Hopkins Symptom Checklist - 25 Anxiety	Median (IQR) 1.30 (1.20-1.60)	125	Median (IQR) 1.20 (1.10-1.40)	2188	Crude	High	NA
26	Komarowska 2013	Score	STAI [state / trait NR]	48 (NR)	20	40 (NR)	20	Crude	High	NA
27	Lee 2017	Score	HADS	9.41 (5.08)	148	6.72 (3.87)	106	Crude	Mod	NA
28	Mansson 2008	Score	MINI NPI by Psychiatrist	NR (NR)	49	NR (NR)	49	Crude	Mod	NA
29	Mehrabadi 2020 (A)	Score	BAI	17.35 (10.44)	53	12.2 (9.65)	50	Crude	Mod	NA
30	Moran 2012	Score	HADS	NR (NR)	52	NR (NR)	24	Crude	Low	NA
31	Moran 2010	Score	HADS	Median (IQR) 10.5 (7-12)	24	Median (IQR) 7 (5-9)	22	Crude	Low	NA
32	Naumova 2021	Score	HAM-A	10.7 (1.23)	37	TFI: 5.2 (1.01) MFI: 2.7 (0.62)	67 TFI n=36 MFI n=31	Crude	Mod	NA
33	Ozedemir 2017	Score	BAI	19.59 (12.35)	69	11.02 (8.41)	49	Crude	Mod	NA
34	Ozenil 2008	Score	STAI	47.8 (8.13)	35	42.5 (5.47)	35	Crude	Mod	NA
35	Ozturk 2020	Score	BAI	16.48 (12.2)	50	10.58 (7.9)	41	Crude	Mod	NA
36	Sahingoz 2013	Score	DSM-4	NR (NR)	73	NR (NR)	73	Crude	High	NA
37	Sayyah-Melli 2015	Score	DSM-4	NR (NR)	742	NR (NR)	798	Crude	Mod	NA
38	Shi 2011	Score	SCL-90	0.46 (0.45)	30	0.28 (0.4)	30	Crude	Mod	NA
39	Sirmans 2014	Score	Not reported	NR (NR)	1689	NR (NR)	5067	Crude	High	NA
40	Soyupek 2010	Score	BAI	4.22 (2.94)	40	1.89 (2.1)	39	Crude	Mod	NA
41	Sulaiman 2014	Score	DASS-21	NR (NR)	52	NR (NR)	60	Crude	Low	NA
42	Tan 2017	Score	STAI	SAI score 42.7 (11.7) TAI score 43.4 (9.8)	120	SAI score 34.2 (10.1) TAI score 36.1 (9.4)	100	Crude	Mod	NA
43	Tseng 2021	Score	BSRS-5	0.88 (0.87)	431	0.8 (0.71)	259	Crude	Mod	NA

44	Weiner 2004	Score	Trait	43.89 (11.68)	27	37.81 (8.94)	27	Crude	Mod	NA
			State	37.67 (12.42)	27	32.56 (7.61)	27			
45	Zeuff 2015	Score	HADS	NR (NR)	44	NR (NR)	43	Crude	Mod	NA

HADS: Hospital Anxiety and Depression Scale; TAS: Trait Anxiety Score of the State-Trait Anxiety Inventory for Children (STAI-C); SAS: State Anxiety Score of the STAI-C; DASS-21: Depression Anxiety Stress Scale-21; HAM-A: Hamilton Anxiety Rating Scale; BAI: Beck Anxiety Inventory; PRIME-MD PHQ: Primary Care Evaluation of Mental Disorders Patient Health Questionnaire; BSA-S: Brief Scale for Anxiety; MINI NPI: Mini International Neuro-psychiatric Interview; DSM-4: Diagnostic and Statistical Manual of Mental Disorders; KSADS-PL: Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Present and Lifetime Version; STAI: State-Trait Anxiety Inventory; BSRS-5: Brief Social Rhythm Scale-5

Figure 16.1: Forest plot for anxiety score – adult studies

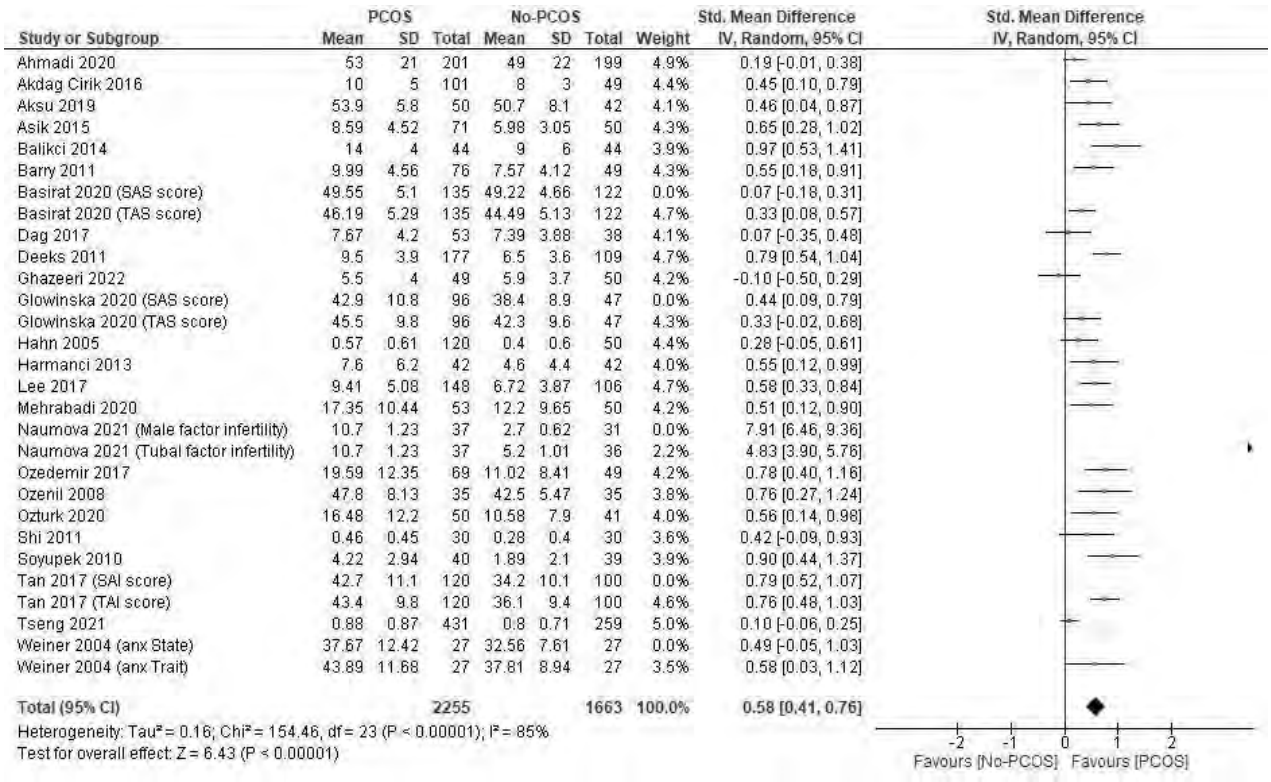
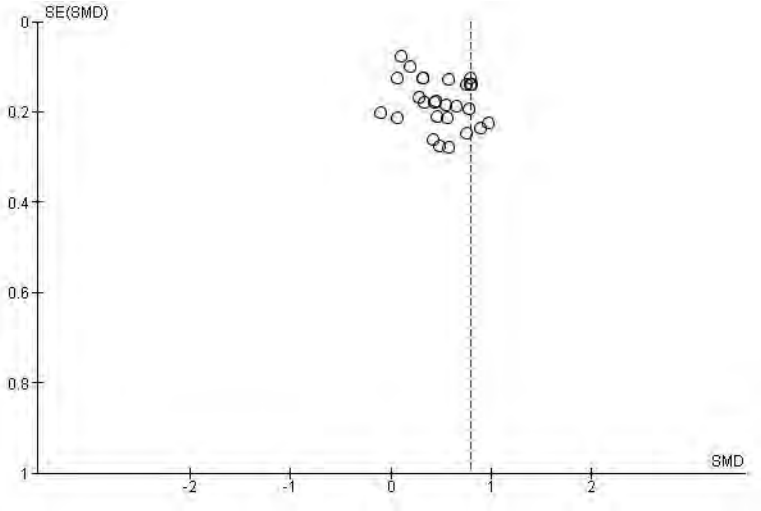


Figure 16.2: Funnel plot for anxiety score – adult studies



OUTCOME 17. Anxiety scores – Adolescent studies

Table 17: Individual Study Data Table - anxiety scores – Adolescent studies

	OUTCOME: Anxiety scores – Adolescent studies					OUTCOME TYPE: Continuous				
	Comparison: Women with PCOS vs. Women without PCOS									
#	Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (SD) in PCOS group	N total in PCOS group	Mean (SD) in comparison group	N total in comparison group	Are these values adjusted or crude?	RoB	If adjusted, what variables were in the model?
1	Almis 2021	Score	TAS	39.07 (7.88)	153	34.13 (5.84)	161	Crude	Mod	NA
			SAS	39.86 (7.8)	153	33.99 (7.01)	161			
2	Besenek 2021	Score	TAS	46.21 (9.25)	39	47.19 (11.18)	37	Crude	Low	NA
			SAS	41.08 (8.78)	39	41.57 (10.61)	37			
3	Dobbaloglu 2022	Score	TAS	44.60 (13.16)	49	40.02 (7.61)	48	Crude	Mod	NA
			SAS	40.77 (10.44)	49	36.64 (6.89)	48			
4	Ghazeeri 2013	Score	SCARED	6.8 (4.25)	20	5.24 (5.06)	17	Crude	Mod	NA
5	Laggari 2009	Score	STAI-Gr (STAI-Greek version)	36.55 (10.44)	22	31.5 (8.24)	22	Crude	High	NA
6	Sari 2020	Score	KSADS-PL	NR (NR)	50	NR (NR)	37	Crude	Mod	NA
7	Zachurzok 2021	Score	HADS	7.3 (3.9)	27	9.6 (3.0)	27	Crude	Mod	NA

TAS: Trait Anxiety Score of the State-Trait Anxiety Inventory for Children (STAI-C); SAS: State Anxiety Score of the STAI-C; KSADS-PL: Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Present and Lifetime Version; Screen for Child Anxiety Related Emotional Disorders, HADS: Hospital Anxiety and Depression Scale; SCARED: Screen for Child Anxiety Related Emotional Disorders

Figure 17.1: Forest plot for anxiety score – adolescent studies

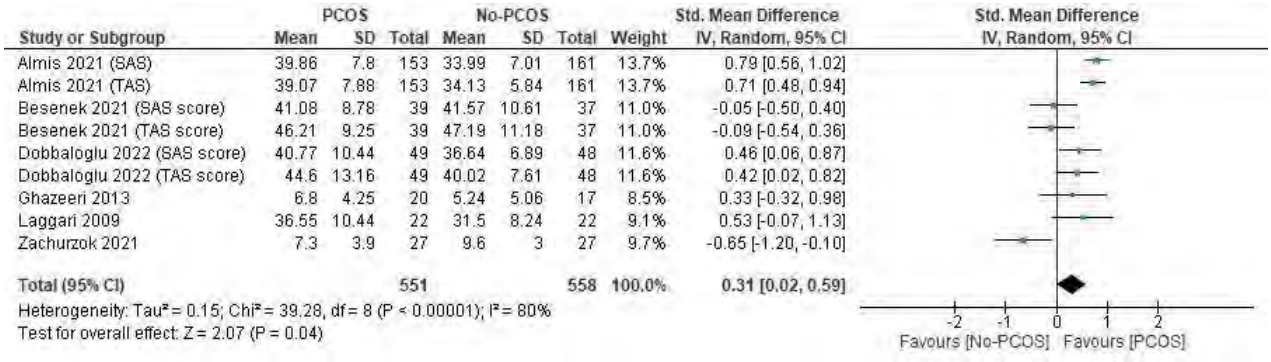


Figure 17.1A: Sensitivity analysis - SAS scores removed

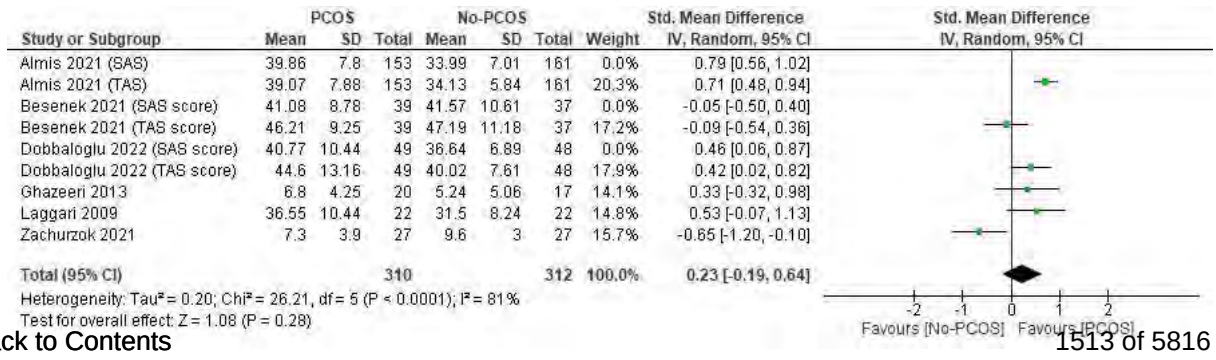


Figure 17.1B: Sensitivity analysis – TAS scores removed

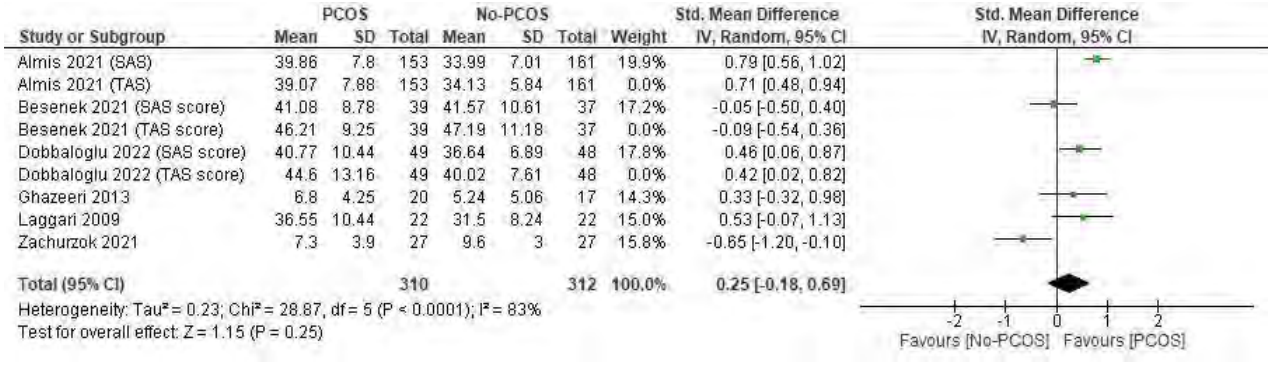
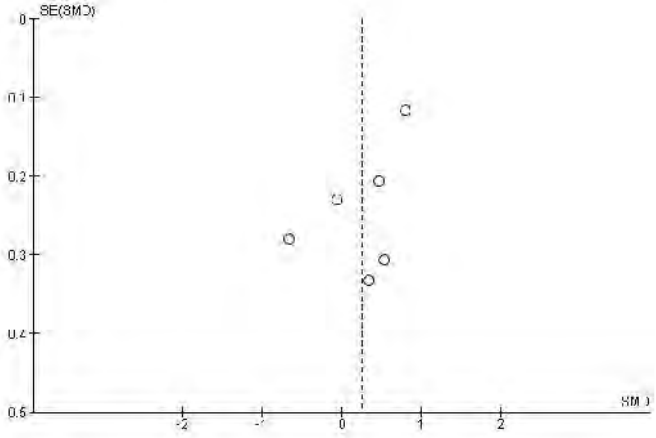


Figure 17.2: Funnel plot for anxiety score – adolescent studies



Outcome 18. Anxiety scores by screening tools used – All studies

Table 18: Individual Study data Table – anxiety scores by screening tools used – All studies

	OUTCOME: Anxiety scores by screening tool – All studies				OUTCOME TYPE: Continuous					
	Comparison: Women with PCOS vs. Women without PCOS									
#	Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (SD) in PCOS group	N total in PCOS group	Mean (SD) in comparison group	N total in comparison group	Are these values adjusted or crude?	RoB	If adjusted, what variables were in the model?
	BAI									
1	Altinkaya 2014	Score	BAI	Median (IQR) 8 (3-26)	50	Median (IQR) 5 (4-18)	50	Crude	Low	NA
2	Balikci 2014 (A)	Score	BAI	14 (4)	44	9 (6)	44	Crude	Mod	NA
3	Caltekin 2021 (A)	Score	BAI	Median (IQR)	73	Median (IQR)	63	Crude	Mod	NA
4	Mehrabadi 2020 (A)	Score	BAI	17.35 (10.44)	53	12.2 (9.65)	50	Crude	Mod	NA
5	Ozedemir 2017 (A)	Score	BAI	19.59 (12.35)	69	11.02 (8.41)	49	Crude	Mod	NA

6	Ozturk 2020 (A)	Score	BAI	16.48 (12.2)	50	10.58 (7.9)	41	Crude	Mod	NA
7	Soyupek 2010 (A)	Score	BAI	4.22 (2.94)	40	1.89 (2.1)	39	Crude	Mod	NA
	BSRS-5									
8	Tseng 2021	Score	BSRS-5	0.88 (0.87)	431	0.8 (0.71)	259	Crude	Mod	NA
	DASS-21									
9	Asdag 2020	Score	DASS-21	NR (NR)	82	NR (NR)	85	Crude	Mod	NA
10	Sulaiman 2014	Score	DASS-21	NR (NR)	52	NR (NR)	60	Crude	Low	NA
	HADS									
11	Akdag Cirik 2016	Score	HADS	10 (5)	101	8 (3)	49	Crude	Low	NA
12	Alur-Gupta 2019	Score	HADS	10.1 (NR)	189	8.4 (NR)	225	Crude	Mod	NA
13	Asik 2015	Score	HADS	8.59 (4.52)	71	5.98 (3.05)	50	Crude	Mod	NA
14	Barry 2011	Score	HADS	9.99 (4.56)	76	7.57 (4.12)	49	Crude	Mod	NA
15	CInar 2011	Score	HADS	9.3 (4.3)	226	NR (NR)	85	Crude	Mod	NA
16	Dag 2017	Score	HADS	7.67 (4.2)	53	7.39 (3.88)	38	Crude	Mod	NA
17	Deeks 2011	Score	HADS	9.5 (3.9)	177	6.5 (3.6)	109	Crude	Mod	NA
18	Dybciak 2022	Score	HADS	10.6 (NR)	230	7.3 (NR)	199	Crude	Mod	NA
19	Ghazeeri 2022	Score	HADS	5.5 (4.0)	49	5.9 (3.7)	50	Crude	Mod	NA
20	Lee 2017	Score	HADS	9.41 (5.08)	148	6.72 (3.87)	106	Crude	Mod	NA
21	Moran 2012	Score	HADS	NR (NR)	52	NR (NR)	24	Crude	Low	NA
22	Moran 2010	Score	HADS	Median (IQR) 10.5 (7-12)	24	Median (IQR) 7 (5-9)	22	Crude	Low	NA
23	Zachurzok 2021	Score	HADS	7.3 (3.9)	27	9.6 (3.0)	27	Crude	Mod	NA
24	Zeuff 2015	Score	HADS	NR (NR)	44	NR (NR)	43	Crude	Mod	NA
	STAI									
25	Aksu 2020 (A)	Score	STAI-2 (trait anxiety-baseline)	53.9 (5.8)	50	50.7 (8.1)	42	Crude		
26	Almis 2021	Score	TAS	39.07 (7.88)	153	34.13 (5.84)	161	Crude	Mod	NA
		Score	SAS	39.86 (7.8)	153	33.99 (7.01)	161			NA
27	Basirat 2020	Score	TAS	46.19 (5.29)	135	44.49 (5.13)	122	Crude	Mod	NA
			SAS	49.55 (5.10)	135	49.22 (4.66)	122			
28	Besenek 2021	Score	TAS	46.21 (9.25)	39	47.19 (11.18)	37	Crude	Low	NA
			SAS	41.08 (8.78)		41.57 (10.61)				
29	Dobbaloglu 2022	Score	TAS	44.60 (13.16)	49	40.02 (7.61)	48	Crude	Mod	NA
			SAS	40.77 (10.44)		36.64 (6.89)				
30	Laggari 2009	Score	STAI-Gr	TAS	22	TAS	22	Crude	High	NA

			(STAI-Greek version)	36.55 (10.44)		31.5 (8.24)				
31	Glowinska 2020 (A)	Score	TAS	45.5 (1.0 SEM) 45.5 (9.8 calculated)	96	42.3 (1.4 SEM) 42.3 (9.6 calculated)	47	Crude	Mod	NA
			SAS	42.9 1.2 SEM) 42.9 (10.8 calculated)	96	38.4 (1.3 SEM) 38.4 (8.9 calculated)	47			
32	Komarowska 2013	Score	STAI [state / trait NR]	48 (NR)	20	40 (NR)	20	Crude	High	NA
33	Ozenil 2008	Score	STAI (TAS)	47.8 (8.13)	35	42.5 (5.47)	35	Crude	Mod	NA
34	Tan 2017	Score	TAS	43.4 (9.8)	120	36.1 (9.4)	100	Crude	Mod	NA
			SAS	42.7 (11.7)	120	34.2 (10.1)	100			
	DSM-4									
35	Hussain 2015	Score	DSM-4	NR (NR)	110	NR (NR)	40	Crude	High	NA
36	Sayyah-Melli 2015	Score	DSM-4	NR (NR)	742	NR (NR)	798	Crude	Mod	NA
37	Sahingoz 2013	Score	DSM-4	NR (NR)	73	NR (NR)	73	Crude	High	NA
	SCL-90									
38	Borghi 2018 (A)	Score	SCL-90-R	Median (IQR)	30	Median (IQR)	30	Crude	Mod	NA
39	Hahn 2005 (A)	Score	SCL-90-R	0.57 (0.61)	120	0.40 (0.60)	50	Crude	Mod	NA
40	Shi 2011	Score	SCL-90	0.46 (0.45)	30	0.28 (0.4)	30	Crude	Mod	NA
	SCARED									
41	Emeksiz 2018	Score	SCARED	Median (IQR)	80	Median (IQR)	50	Crude	Mod	NA
42	Ghazeeri 2013	Score	SCARED	5.5 (4.0)	49	5.9 (3.7)	50	Crude	Mod	NA
	OTHER									
43	Ahmadi 2020 (A)	Score	Millon Clinical Multi-axial Inventory-III (MCMI-III)	53 (21)	201	49 (22)	199	Crude	Mod	NA
44	Harmanci 2013 (A)	Score	BSI	7.6 (6.2)	42	4.6 (4.4)	42	Crude	Low	NA
45	Harnod 2020	ICD 9 code: 300	by Psychiatrist	NR	7026	NR	28104	Crude	Low	NA
46	Holinrake 2007	Score	PRIME-MD PHQ	NR (NR)	103	NR (NR)	103	Crude	High	NA
47	Jedel 2010	Score	BSA-S	Median (IQR) 10.5 (NR)	30	Median (IQR) 5.0 (NR)	30	Crude	Mod	NA
48	Karjula 2017	Score	Hopkins Symptom Checklist - 25 Anxiety	Median (IQR) 1.30 (1.20- 1.60)	125	Median (IQR) 1.20 (1.10- 1.40)	2188	Crude	High	NA
49	Mansson 2008	Score	MINI NPI by Psychiatrist	NR (NR)	49	NR (NR)	49	Crude	Mod	NA

50	Naumova 2021	Score	HAM-A	10.7 (1.23)	37	TFI: 5.2 (1.01) MFI: 2.7 (0.62)	67 TFI n=36 MFI n=31	Crude	Mod	NA
51	Sirmans 2014	Score	Not reported	NR (NR)	1689	NR (NR)	5067	Crude	High	NA

HADS: Hospital Anxiety and Depression Scale; TAS: Trait Anxiety Score of the State-Trait Anxiety Inventory for Children (STAI-C); SAS: State Anxiety Score of the STAI-C; DASS-21: Depression Anxiety Stress Scale-21; HAM-A: Hamilton Anxiety Rating Scale; BAI: Beck Anxiety Inventory; PRIME-MD PHQ: Primary Care Evaluation of Mental Disorders Patient Health Questionnaire; BSA-S: Brief Scale for Anxiety; MINI NPI: Mini International Neuro-psychiatric Interview; DSM-4: Diagnostic and Statistical Manual of Mental Disorders; KSADS-PL: Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Present and Lifetime Version; STAI: State-Trait Anxiety Inventory; BSRS-5: Brief Social Rhythm Scale-5; SCARED: Screen for Child Anxiety Related Disorders

Figure 18.1A: Forest plot for anxiety scores by screening tools – All studies (Mean difference)

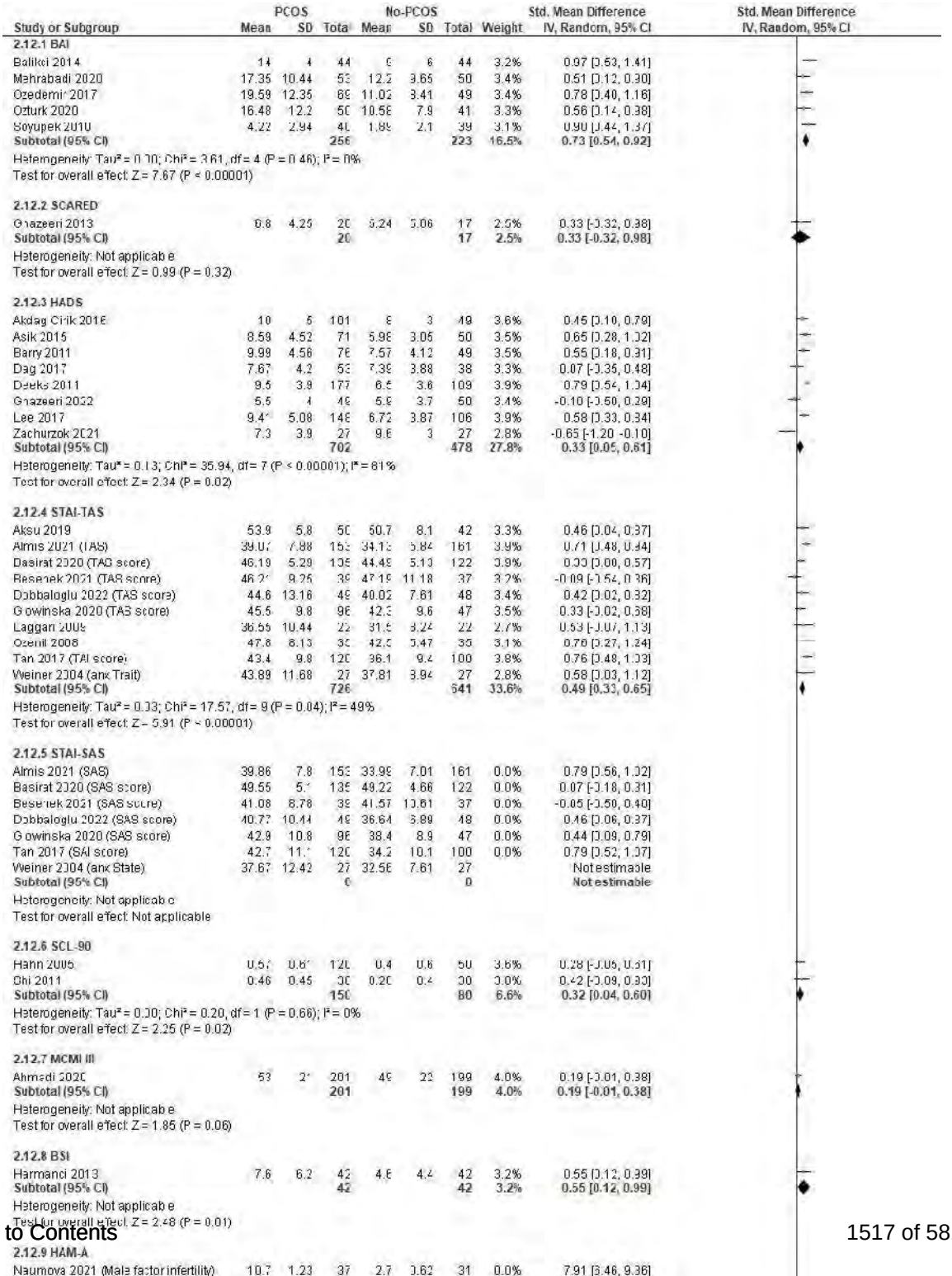


Figure 19.1B: Forest plot for anxiety scores by screening tools – All studies (Std. Mean difference)

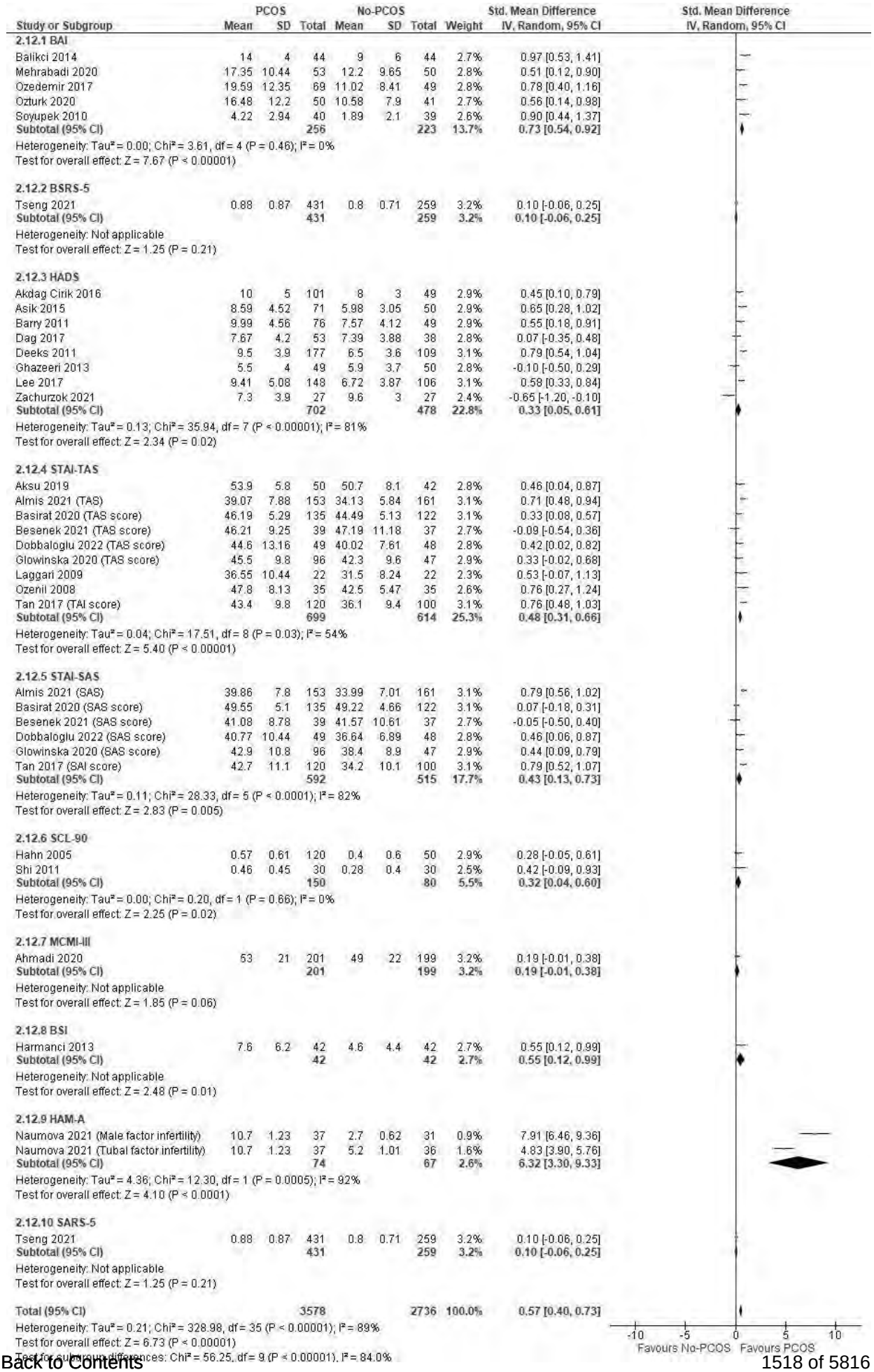
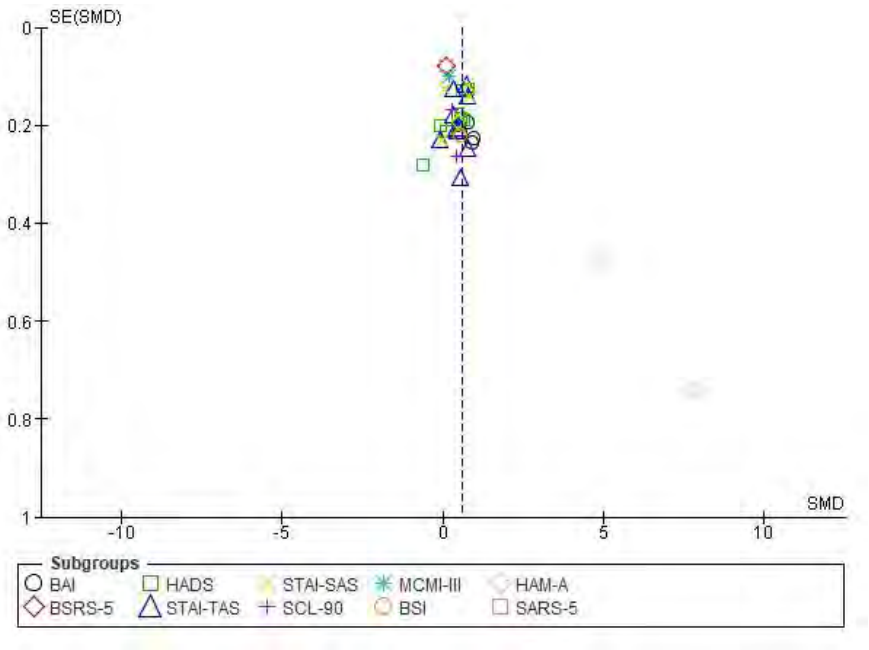


Figure 18.2: Funnel plot for anxiety scores by screening tools – All studies



OUTCOME 19. Anxiety scores by screening tools used - Adults

Table 19: Individual Study Data Table - anxiety scores by screening tool – Adults

	OUTCOME: Anxiety scores by screening tool - Adults				OUTCOME TYPE: Continuous					
	Comparison: Women with PCOS vs. Women without PCOS									
#	Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (SD) in PCOS group	N total in PCOS group	Mean (SD) in comparison group	N total in comparison group	Are these values adjusted or crude?	RoB	If adjusted, what variables were in the model?
	BAI									
1	Altinkaya 2014	Score	BAI	Median (IQR) 8 (3-26)	50	Median (IQR) 5 (4-18)	50	Crude	Low	NA
2	Balikci 2014 (A)	Score	BAI	14 (4)	44	9 (6)	44	Crude	Mod	NA
3	Caltekin 2021 (A)	Score	BAI	Median (IQR)	73	Median (IQR)	63	Crude	Mod	NA
4	Mehrabadi 2020 (A)	Score	BAI	17.35 (10.44)	53	12.2 (9.65)	50	Crude	Mod	NA
5	Ozedemir 2017 (A)	Score	BAI	19.59 (12.35)	69	11.02 (8.41)	49	Crude	Mod	NA
6	Ozturk 2020 (A)	Score	BAI	16.48 (12.2)	50	10.58 (7.9)	41	Crude	Mod	NA
7	Soyupek 2010 (A)	Score	BAI	4.22 (2.94)	40	1.89 (2.1)	39	Crude	Mod	NA
	BSRS-5									
8	Tseng 2021	Score	BSRS-5	0.88 (0.87)	431	0.8 (0.71)	259	Crude	Mod	NA
	DASS-21									

9	Asdag 2020	Score	DASS-21	NR (NR)	82	NR (NR)	85	Crude	Mod	NA
10	Sulaiman 2014	Score	DASS-21	NR (NR)	52	NR (NR)	60	Crude	Low	NA
	HADS									
11	Akdag Cirik 2016	Score	HADS	10 (5)	101	8 (3)	49	Crude	Low	NA
12	Alur-Gupta 2019	Score	HADS	10.1 (NR)	189	8.4 (NR)	225	Crude	Mod	NA
13	Asik 2015	Score	HADS	8.59 (4.52)	71	5.98 (3.05)	50	Crude	Mod	NA
14	Barry 2011	Score	HADS	9.99 (4.56)	76	7.57 (4.12)	49	Crude	Mod	NA
15	CInar 2011	Score	HADS	9.3 (4.3)	226	NR (NR)	85	Crude	Mod	NA
16	Dag 2017	Score	HADS	7.67 (4.2)	53	7.39 (3.88)	38	Crude	Mod	NA
17	Deeks 2011	Score	HADS	9.5 (3.9)	177	6.5 (3.6)	109	Crude	Mod	NA
18	Dybciak 2022	Score	HADS	10.6 (NR)	230	7.3 (NR)	199	Crude	Mod	NA
19	Ghazeeri 2022	Score	HADS	5.5 (4.0)	49	5.9 (3.7)	50	Crude	Mod	NA
20	Lee 2017	Score	HADS	9.41 (5.08)	148	6.72 (3.87)	106	Crude	Mod	NA
21	Moran 2012	Score	HADS	NR (NR)	52	NR (NR)	24	Crude	Low	NA
22	Moran 2010	Score	HADS	Median (IQR) 10.5 (7-12)	24	Median (IQR) 7 (5-9)	22	Crude	Low	NA
23	Zeuff 2015	Score	HADS	NR (NR)	44	NR (NR)	43	Crude	Mod	NA
	STAI									
24	Aksu 2020 (A)	Score	STAI-2 (trait anxiety-baseline)	53.9 (5.8)	50	50.7 (8.1)	42	Crude		
25	Basirat 2020	Score	TAS	46.19 (5.29)	135	44.49 (5.13)	122	Crude	Mod	NA
			SAS	49.55 (5.10)	135	49.22 (4.66)	122			
26	Glowinska 2020 (A)	Score	TAS	45.5 (1.0 SEM) 45.5 (9.8 calculated)	96	42.3 (1.4 SEM) 42.3 (9.6 calculated)	47	Crude	Mod	NA
			SAS	42.9 1.3 SEM) 42.9 (10.8 calculated)	96	38.4 (1.3 SEM) 38.4 (8.9 calculated)	47			
27	Komarowska 2013	Score	STAI [state / trait NR]	48 (NR)	20	40 (NR)	20	Crude	High	NA
28	Ozenil 2008	Score	STAI (TAS)	47.8 (8.13)	35	42.5 (5.47)	35	Crude	Mod	NA
29	Tan 2017	Score	TAS	43.4 (9.8)	120	36.1 (9.4)	100	Crude	Mod	NA
			SAS	42.7 (11.7)	120	43.2 (10.1)	100			

30	Weiner 2004	Score	Trait	43.89 (11.68)	27	37.81 (8.94)	27	Crude	Mod	NA
			State17.3	37.67 (12.42)	27	32.56 (7.61)	27			
	DSM-4									
31	Hussain 2015	Score	DSM-4	NR (NR)	110	NR (NR)	40	Crude	High	NA
32	Sayyah-Melli 2015	Score	DSM-4	NR (NR)	742	NR (NR)	798	Crude	Mod	NA
33	Sahingoz 2013	Score	DSM-4	NR (NR)	73	NR (NR)	73	Crude	High	NA
	SCL-90									
34	Borghi 2018 (A)	Score	SCL-90-R	Median (IQR)	30	Median (IQR)	30	Crude	Mod	NA
35	Hahn 2005 (A)	Score	SCL-90-R	0.57 (0.61)	120	0.40 (0.60)	50	Crude	Mod	NA
36	Shi 2011	Score	SCL-90	0.46 (0.45)	30	0.28 (0.4)	30	Crude	Mod	NA
	OTHER									
37	Ahmadi 2020 (A)	Score	Millon Clinical Multi-axial Inventory-III (MCMI-III)	53 (21)	201	49 (22)	199	Crude	Mod	NA
38	Harmanci 2013 (A)	Score	BSI	7.6 (6.2)	42	4.6 (4.4)	42	Crude	Low	NA
39	Harnod 2020	ICD 9 code: 300	by Psychiatrist	NR	7026	NR	28104	Crude	Low	NA
40	Holinrake 2007	Score	PRIME-MD PHQ	NR (NR)	103	NR (NR)	103	Crude	High	NA
41	Jedel 2010	Score	BSA-S	Median (IQR) 10.5 (NR)	30	Median (IQR) 5.0 (NR)	30	Crude	Mod	NA
42	Karjula 2017	Score	Hopkins Symptom Checklist - 25 Anxiety	Median (IQR) 1.30 (1.20-1.60)	125	Median (IQR) 1.20 (1.10-1.40)	2188	Crude	High	NA
43	Mansson 2008	Score	MINI NPI by Psychiatrist	NR (NR)	49	NR (NR)	49	Crude	Mod	NA
44	Naumova 2021	Score	HAM-A	10.7 (1.23)	37	TFI: 5.2 (1.01) MFI: 2.7 (0.62)	67 TFI n=36 MFI n=31	Crude	Mod	NA
45	Sirmans 2014	Score	Not reported	NR (NR)	1689	NR (NR)	5067	Crude	High	NA

HADS: Hospital Anxiety and Depression Scale; TAS: Trait Anxiety Score of the State-Trait Anxiety Inventory for Children (STAI-C); SAS: State Anxiety Score of the STAI-C; DASS-21: Depression Anxiety Stress Scale-21; HAM-A: Hamilton Anxiety Rating Scale; BAI: Beck Anxiety Inventory; PRIME-MD PHQ: Primary Care Evaluation of Mental Disorders Patient Health Questionnaire; BSA-S: Brief Scale for Anxiety; MINI NPI: Mini International Neuro-psychiatric Interview; DSM-4: Diagnostic and Statistical Manual of Mental Disorders; KSADS-PL: Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Present and Lifetime Version; STAI: State-Trait Anxiety Inventory; BSRS-5: Brief Social Rhythm Scale-5

Figure 19.1: Forest plot for anxiety scores by screening tool - Adults

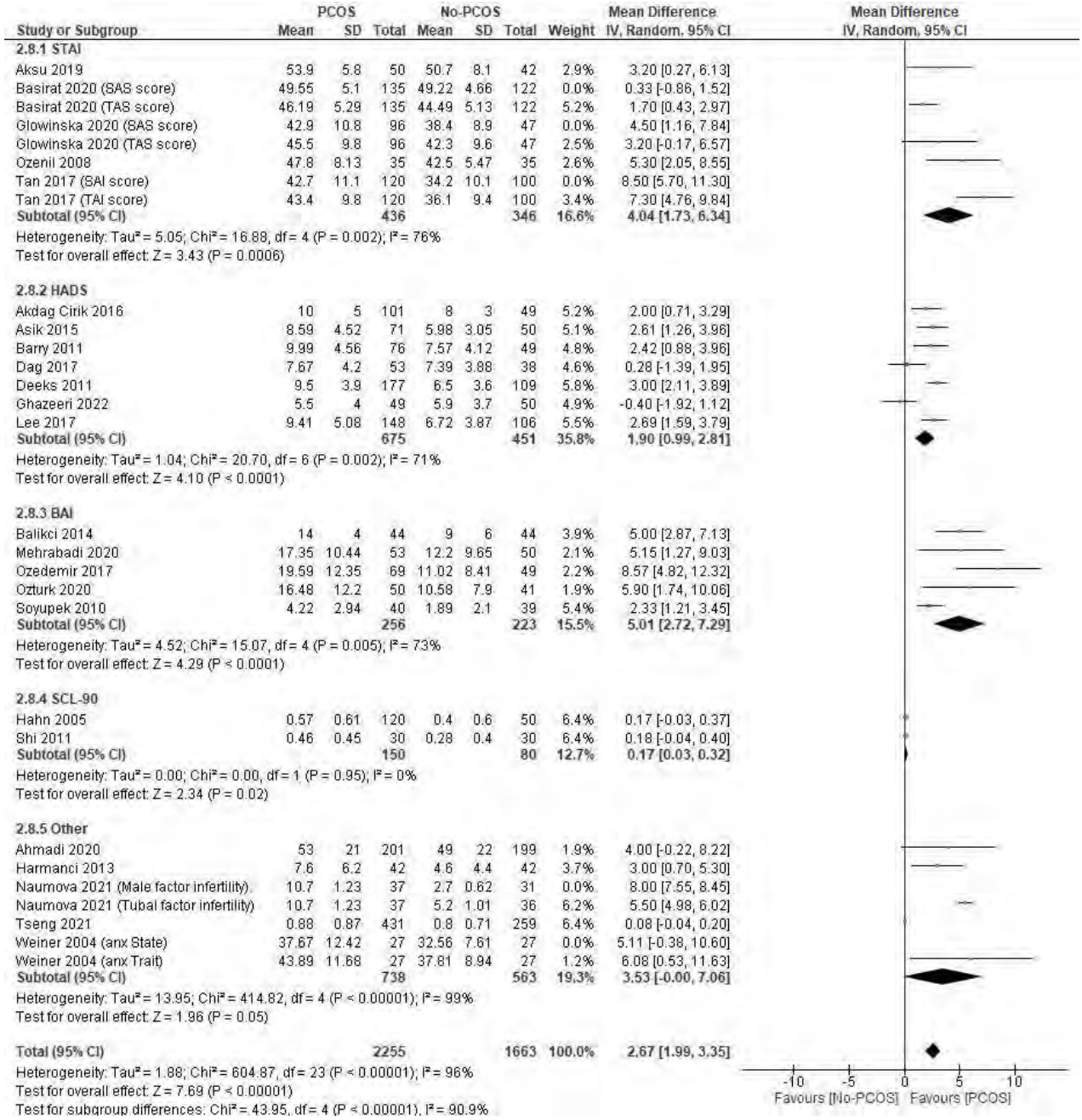


Figure 19.1A: Sensitivity analysis - Adults; STAI with 'trait' scores only

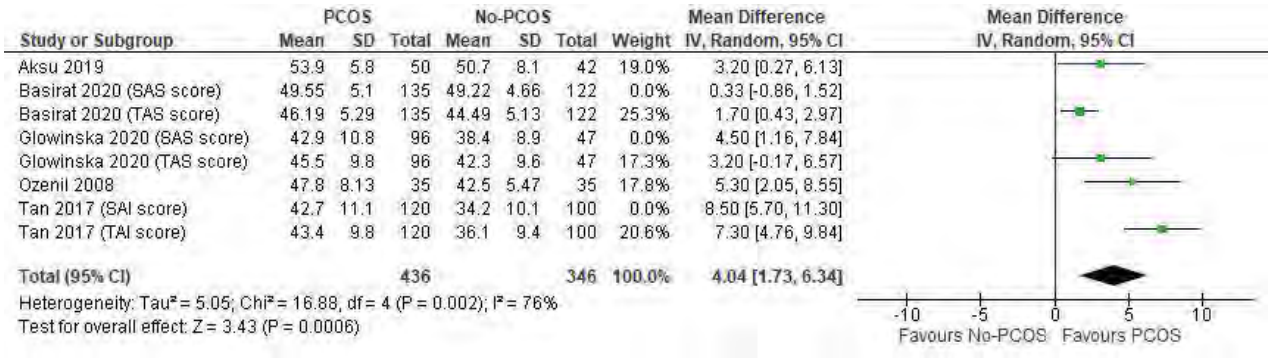


Figure 19.1B: Sensitivity analysis - Adults; STAI with 'state' scores only

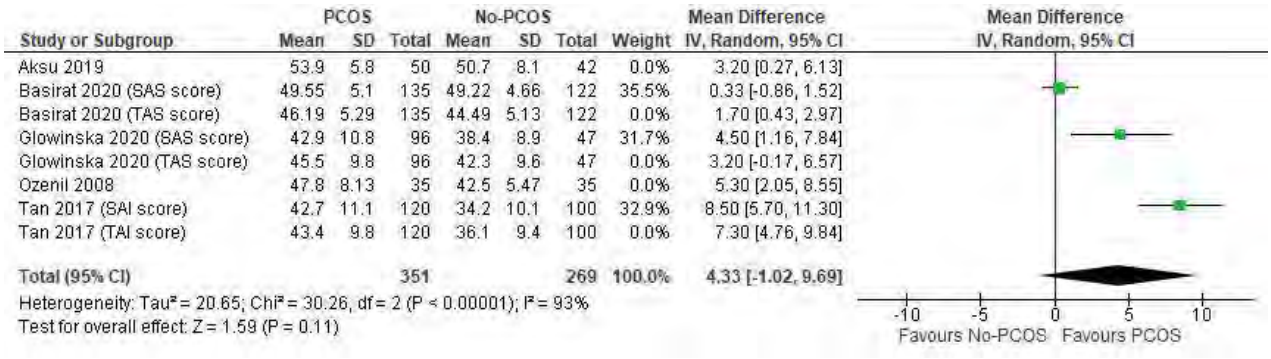
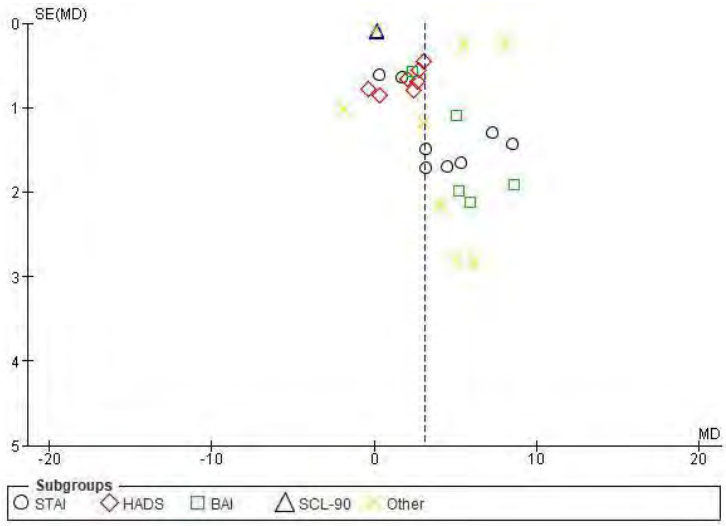


Figure 19.2: Funnel plot for anxiety scores by screening tools - Adults



OUTCOME 20. Anxiety scores by screening tools used - adolescents

Table 20: Individual Study Data Table - anxiety scores by screening tool – Adolescents

#	Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (SD) in PCOS group	N total in PCOS group	Mean (SD) in comparison group	N total in comparison group	Are these values adjusted or crude?	RoB	If adjusted, what variables were in the model?
1	Almis 2021	Score	STAI	TAS 39.07 (7.88) SAS 39.86 (7.8)	153	TAS 34.13 (5.84) SAS 33.99 (7.01)	161	Crude	Mod	NA
2	Besenek 2021	Score	STAI	TAS 46.21 (9.25) SAS 4 41.08 (8.78)	39	TAS 47.19 (11.18) SAS 41.57 (10.61)	37	Crude	Low	NA
3	Dobbaloglu 2022	Score	STAI	TAS 44.60 (13.16) SAS 40.77 (10.44)	49	TAS 40.02 (7.61) SAS 36.64 (6.89)	48	Crude	Mod	NA
4	Laggari 2009	Score	STAI-Gr (STAI-Greek version)	TAS 36.55 (10.44)	22	TAS 31.5 (8.24)	22	Crude	High	NA
5	Emeksiz 2018	Score	SCARED	Median (IQR)	80	Median (IQR)	50	Crude	Mod	NA
6	Ghazeeri 2013	Score	SCARED	5.5 (4.0)	49	5.9 (3.7)	50	Crude	Mod	NA
7	Zachurzok 2021	Score	HADS	7.3 (3.9)	27	9.6 (3.0)	27	Crude	Mod	NA

Figure 20.1: Forest plot for anxiety scores by screening tool - Adolescents

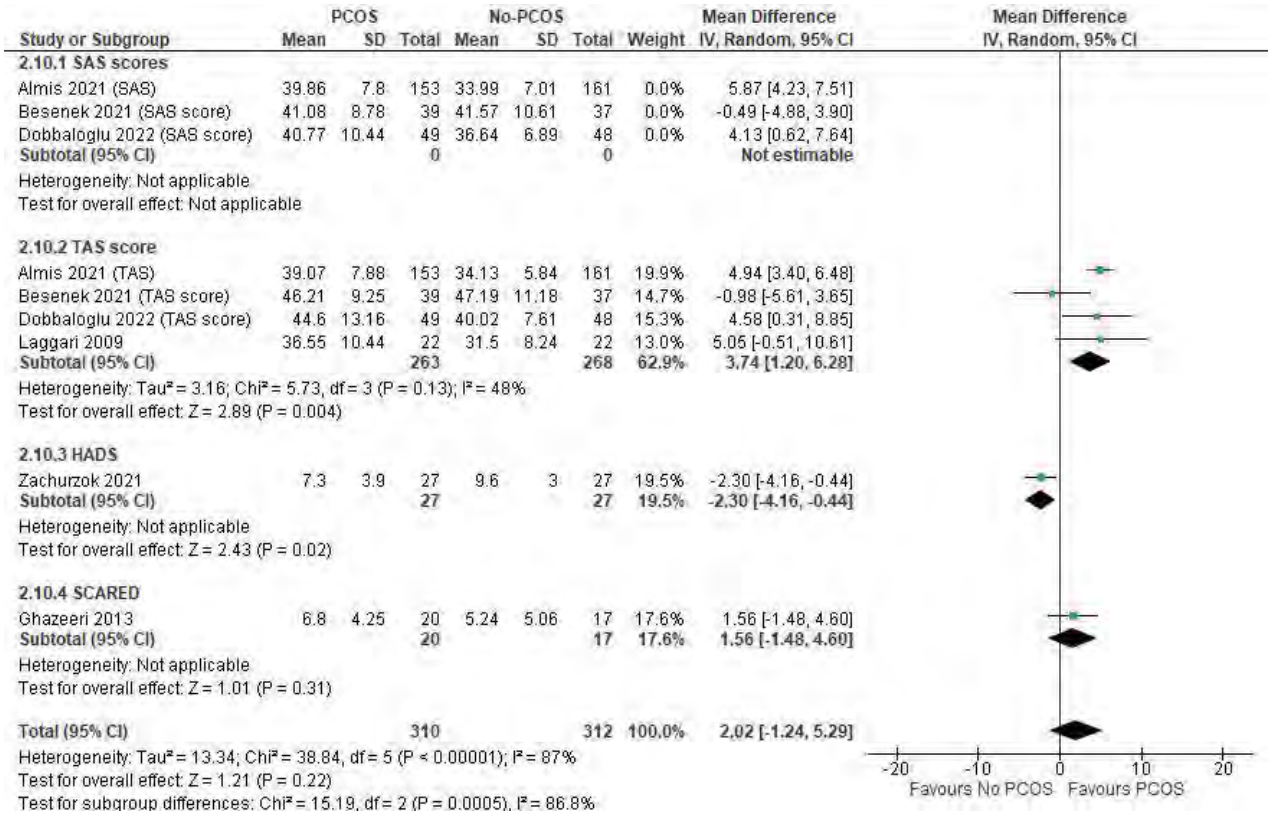
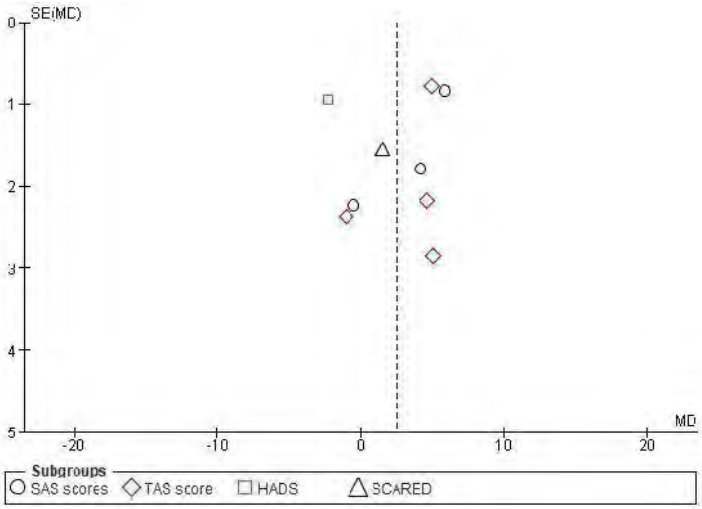


Figure 20.2: Funnel plot for anxiety scores by screening tool - Adolescents



8. GRADE ASSESSMENTS AND EVIDENCE PROFILE

COMPARISON 1: Women with PCOS versus controls												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other (publication bias)	PCOS	Control	Effect Estimate: Odds ratio, (95% CI)	Favours	Certainty	Importance
Outcome: Prevalence of depression – All studies												
47 entries	Observational	serious[1]	serious[2]	serious[3]	no serious imprecision	None	13,420	40,932	2.59 [2.11-3.16]	PCOS	⊕⊕◯◯ LOW	CRITICAL
Outcome: Prevalence of depression – Adult studies												
41 entries	Observational	serious[1]	serious[2]	serious[3]	no serious imprecision	None	13,032	40,222	2.63 [2.12-3.28]	PCOS	⊕⊕◯◯ LOW	CRITICAL
Outcome: Prevalence of depression – Adolescent studies												
6 entries	Observational	serious[1]	no serious inconsistency	serious[3]	no serious imprecision	None	388	710	2.26 [1.36 – 3.76]	PCOS	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Prevalence of depression-studies that used clinical interviews												
6 entries	Observational	serious[1]	serious[2]	serious[2]	no serious imprecision	None	1134	1107	2.33 [1.18 – 4.61]	PCOS	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Depression scores – All studies												
44 entries	Observational	serious[1]	serious[2]	serious[3]	no serious imprecision	None	3330	2727	SMD 0.71 [0.55-0.87]	PCOS	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Depression scores – Adult studies												
38 entries	Observational	serious[1]	serious[2]	serious[3]	no serious imprecision	None	3007	2414	SMD 0.76 (0.58 – 0.94)	PCOS	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Depression scores – Adolescent studies												
6 entries	Observational	serious[1]	serious[2]	serious[3]	no serious imprecision	None	323	313	SMD 0.41 (0.13-0.70)	None	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Depression scores by screening tools used – All studies												
See Depression scores – All studies												
Outcome: Depression scores by screening tools used – Adult studies												
See Depression scores – Adult studies												
Outcome: Depression scores by screening tools used – Adolescent studies												
See Depression scores – Adolescent studies												
Outcome: Prevalence of anxiety – All studies												
27 entries	Observational	serious[1]	serious[2]	serious[3]	no serious imprecision	None	12,034	38,070	2.68 [2.08 – 3.44]	PCOS	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Prevalence of anxiety – Adult studies												
23 entries	Observational	serious[1]	serious[2]	serious[3]	no serious imprecision	None	4,778	9,741	2.89 [2.27 – 3.68]	PCOS	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Prevalence of anxiety – Adolescent studies												
3 entries	Observational	serious[1]	serious[2]	not applicable	serious[4]	None	225	230	0.92 [0.11 – 7.96]	PCOS	⊕◯◯◯	IMPORTANT

											VERY LOW	
Outcome: Prevalence of anxiety-studies that used clinical interviews												
5 entries	Observational	serious[1]	no serious inconsistency	No serious indirectness	no serious imprecision	None	1024	997	2.70 [1.74-4.18]	PCOS	⊕⊕⊕◯ MODERATE	IMPORTANT
Outcome: Anxiety scores – All studies												
30 entries	Observational	serious[1]	serious[2]	serious[3]	no serious imprecision	None	2565	1975	SMD 0.52 (0.36 – 0.68)	PCOS	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Anxiety scores – Adult studies												
24 entries	Observational	serious[1]	serious[2]	serious[3]	no serious imprecision	None	2255	1663	SMD 0.58 [0.41-0.76]	PCOS	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Anxiety scores – Adolescent studies												
6 entries	Observational	serious[1]	serious[2]	serious[3]	serious[4]	None	310	312	SMD 0.23 (-0.19 – 0.64)	None	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Anxiety scores – by screening tools used – All studies												
See Anxiety scores – All studies												
Outcome: Anxiety scores – by screening tools used – Adult studies												
See Anxiety scores – Adult studies												
Outcome: Anxiety scores – by screening tools used – Adolescent studies												
See Anxiety scores – Adolescent studies												

[1] downgraded once for risk of bias due to the observational study design (majority cross-sectional) and most studies being of moderate or high risk of bias
[2] downgraded once for inconsistency due to high heterogeneity measured by the I^2 statistic
[3] downgraded once for indirectness due to different outcome measurements/tools used
[4] downgraded once for imprecision of included studies

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 2

Question 2.2.

In women with PCOS, what is the prevalence and severity of depression and anxiety?

BACKGROUND:

Prevalence and problem

Depression and anxiety are exceptionally common throughout the world with a higher prevalence in women and represent a major public health problem. It is established that women with PCOS are more likely to have depressive symptoms or clinical depression and anxiety symptoms than their healthy counterparts (1). The underlying aetiology and pathophysiology of psychiatric disorders in women with PCOS remain unclear, and the comorbidities are likely a mixture of genetic and environmental factors (2). Twin and familial studies indicate that psychiatric disorders show substantial heritability (3). However, a recent study found no genetic correlation between PCOS and psychiatric disorders implying that genetic factors are secondary phenomena rather than directly triggered in the pathogenesis of PCOS (4). A weak association for depression with PCOS attenuated to null when BMI was considered, indicating a critical role of obesity in both conditions. Non-genetic factors, such as an adverse maternal-fetal environment due to elevated androgens, with or without obesity, negatively affect the growing fetus and are critical for the development of anxiety-like behaviour in the mice offspring (5,6). These data are further supported by epidemiological studies (7-9).

Clinical practice gap – need for guidance

Previous surveys of women with PCOS in North America, Europe and Australia show that less than 10% were satisfied with information regarding long term complications associated with PCOS and less than 5% were satisfied with emotional support and counselling offered [10]. Given the high prevalence of depressive and anxiety symptoms, especially moderate to severe symptoms [11], the 2018 International PCOS Guideline recommended screen women with PCOS routinely and at the time of diagnosis. There is limited information on the prevalence of these symptoms in adolescents and the long-term risk of depressive and anxiety symptoms in adults. Further, there is limited information on perinatal mental health.

Summary of key information

Depression

The most commonly reported symptoms of depression were daily fatigue, sleep disturbances and diminished interest [12]. A meta-analysis of 10 studies including 522 women with PCOS and 475 women without PCOS from 8 countries reported increased depression scores in 44% women in the PCOS group (14-67%) versus 17% in women without PCOS (2-35%) (OR: 4.03, 95% CI: 2.96-5.5, $p<0.01$) [13]. Interestingly, the risk of having an abnormal depression score was still 4-fold increased when PCOS and non-PCOS groups were matched for BMI (number of studies = 5) suggesting that this risk is independent of and exacerbated by higher weight. This meta-analysis reported no evidence of heterogeneity between the included studies. Another meta-analysis with several overlapping studies included 910 women with PCOS and 1347 women without PCOS and reported a standardized mean difference (SMD) of depression scores between the two groups of 0.82 (95% CI: 0.73-0.92), suggesting a higher risk of depression in PCOS [14]. Included studies did not show a significant heterogeneity in this meta-analysis however, it was not clear if the depression scores were clinically significant. A meta-analysis of 26 studies including 4716 participants from 14 different countries was published in 2012 [6]. This paper reported SMD of 0.60 for depression scores between PCOS and non-PCOS groups (95% CI: 0.47-0.73) however, the authors emphasized that scores for women with PCOS were not in a clinically significant range in half of the studies whereas mild

depression was reported in the remaining studies. Further, there was significant heterogeneity between studies (I2-73%, p<0.001). The most recent meta-analysis including 23 studies was conducted with rigorous inclusion criteria including diagnosis of PCOS by a physician and not self-reported, and inclusion of studies that provided prevalence of abnormal depression scores in the study population [16]. This meta-analysis showed the odds ratio of moderate/severe depressive symptoms was 4.18 in women with PCOS (95% CI:2.68-6.52). The median prevalence of depression was 36.6% (IQR: 22.3, 50.0%) in women with PCOS and 14.2% (IQR: 10.7, 22.2%) in women without PCOS. This meta-analysis also confirmed that the increased risk of depressive symptoms was independent of higher weight. Sensitivity analyses showed that both clinic and community recruits had higher depressive scores compared to matched controls. There are some limitations to most studies included in the above meta-analyses including relatively small sample sizes of individual studies and limited confirmation of the diagnosis of depression. For example, in only 3 studies, depression was confirmed with further clinical assessment in individuals who had abnormal screening test scores. Nevertheless, two out of those 3 studies reported increased rates of clinically diagnosed depression in women with PCOS.

A new systematic review and meta-analysis was conducted for the 2023 update of the International PCOS Guideline. The meta-analysis included 47 studies comparing the prevalence of moderate to severe scores or diagnosed depression between women with PCOS and women without PCOS, and showed statistically significant higher prevalence of depression in PCOS (n=54,388 OR 2.6 [95% CI 2.12 – 3.18] <0.001). Only seven studies were of low risk of bias and the rest were either moderate or high risk of bias. Six studies included diagnostic assessment by clinical interviews. A subgroup analysis of adult only studies (n=42 studies) showed a higher prevalence of depression (n=53728, OR 2.58 (95%CI 2.08-3.2). A subgroup analysis of adolescent studies (n=5 studies of low or moderate risk of bias) also showed a higher prevalence (n= 660, OR 2.71 [95% CI 1.75 – 4.19].

A large population-based study using national health registries in Sweden, examined the association between PCOS and psychiatric disorders, as well as risks for psychiatric disorders in female and male siblings of women with PCOS [17]. This study reported a significantly increased adjusted risk of depression in women with PCOS of 1.25 (1.1.9-1.31) than women without PCOS. In another large hospital database in Western Australia, the incidence of depression in women with PCOS (9.8%) was significantly higher compared to women who did not have a diagnosis of PCOS (4.6%) [18]. Overall, these studies confirm that women with PCOS have a higher prevalence of clinically significant depressive symptoms indicating a chronic condition and not episodic events.

Anxiety

Symptoms of anxiety and anxiety disorders are more common in women with PCOS. One meta-analysis published in 2011 including 6 studies and another including 11 studies reported that women with PCOS had significantly higher anxiety scores compared to women without PCOS [14, 15]. Another meta-analysis in the same time period including 4 studies reported a sevenfold increase in the risk of abnormal anxiety scores among women with PCOS [19]. However, there was significant heterogeneity amongst included studies in all three meta-analyses. A recent rigorous meta-analysis identified 10 studies that included prevalence of anxiety symptoms in women with well-defined PCOS diagnosed by physicians using validated screening tools [16]. This study shows an increased odds of high anxiety symptoms compared to women without PCOS (OR: 5.62; 95% CI: 3.22, 9.80) and also an increased odds of moderate and severe anxiety symptoms (OR: 5.38; 95% CI: 2.28, 12.67).

The median prevalence of anxiety was 41.9% (IQR: 13.6, 52.0%) in the PCOS group and 8.5% (IQR: 3.3, 12.0%) in the non-PCOS group. There was however, increased heterogeneity amongst studies.

A new systematic review and meta-analysis was conducted for the 2023 update of the International PCOS Guideline. The meta-analysis included 27 studies comparing the prevalence of anxiety between women with PCOS and women without PCOS and showed a statistically significant higher prevalence of anxiety in women with PCOS (n=50,135, OR 2.67 [2.08 – 3.44]). Only six studies were of low risk of bias and the rest were either moderate or high risk of bias. A subgroup analysis of adults (n=23 studies,) showed statistically significantly higher odds of anxiety in women with PCOS (n= 14,527, OR 2.94 [95% CI 2.31 – 3.75]. In three studies of adolescents, the prevalence of anxiety was not increased (n= 455 OR 0.92 [95% CI 0.11 – 7.96].

In a large population-based study in Sweden, including 24,385 women diagnosed with PCOS matched for sex, year of birth, and county of residence to ten individuals randomly selected from the general population showed an increased adjusted OR for anxiety disorder (1.37, CI: 1.32, 1.43) [17]. Further, sisters of women with PCOS also had higher adjusted OR for anxiety disorder (1.15, CI: 1.07, 1.25). In another large hospital database in Western Australia mentioned in the depression section, the incidence of anxiety in women with PCOS (14%) was significantly higher compared to women who did not have a diagnosis of PCOS (5.9%) [18]. Collectively these studies indicate increased anxiety symptoms and anxiety disorders in women with PCOS, across diverse ethnic groups.

Perinatal anxiety or depression

The current evidence review only included populations with defined PCOS diagnostic criteria and therefore only identified a single study examining postpartum depression in women with PCOS. No meta-analysis could be performed. However, a recent meta-analysis has been conducted of six studies (n=934,922 women) that less rigorously defined PCOS status, e.g. self-report. One study was rated as good quality [20], two as fair [21, 22], and the remainder as low quality [23, 24, 25]. The meta-analysis reported that women with PCOS have a greater likelihood of postpartum depression (OR= 1.45, 95% CI=1.18 to 1.79, p<0.001) compared to women without PCOS (https://doi.org/10.1016/j.jad.2021.12.044). An awareness of these findings is important, but also need to be confirmed in well-characterised PCOS populations.

A range of mental health screening guidelines for the general population, were referred to in considering this question [26, 27, 28,29, 30, 31, 32, 33, 34, 35, 36, 37].

GRADE EVIDENCE CERTAINTY	
Comparison	**GRADE for critical outcomes**
Comparison 1. Women with PCOS versus controls	⨁⨁◯◯ LOW

Evidence to Recommendations Framework

COMPARISONS (option versus other option)

PCOS vs non-PCOS

- Prevalence of depression in all patients - yes/no
- Prevalence of depression in Adults
- Prevalence of depression in adolescents

EVIDENCE-BASED RECOMMENDATION(S)

EBR: Health professionals should be aware of the high prevalence of moderate to severe depressive symptoms and depression in adolescents and adults with PCOS and should screen for depression in all adults and adolescents with PCOS, using regionally validated screening tools.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

- **EBR:** Health professionals should be aware of the high prevalence of moderate to severe anxiety symptoms and anxiety disorders in adults and should screenfor anxiety in all adults with PCOS, using regionally validated screening tools.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

Consensus RECOMMENDATION

If moderate or severe depressive or anxiety symptoms are detected, practitioners should further assess, refer appropriately or offer treatment.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

PRACTICE POINT(S)

- Severity of symptoms and clinical diagnosis of depression or anxiety should guide management. The optimal interval for anxiety and depression screening is not known. A pragmatic approach could include screening at diagnosis with repeat screening based on clinical judgement, risk factors, comorbidities and life events, including the perinatal period.
- Screening for mental health disorders comprises assessment of risk factors, symptoms, and risk of self-harm and suicidal intent.

GRADE CONSIDERATIONS

Justifications:

Systematic reviews, meta-analyses, registries and health service datasets collectively indicate that women with PCOS have a higher prevalence of clinically significant symptoms of depression and anxiety.

Identification of mental health disorders is important for supporting women's overall health, wellbeing and quality of life by facilitating appropriate referral and care. In the context of PCOS, identification of mental health disorders is also crucial for optimising women's ability to engage with lifestyle management and other preventive strategies at the core of PCOS care. Therefore, we recommend routine mental health screening for women with PCOS.

In adolescents, early identification of mental health disorders is crucial to supporting lifelong health. Although there are fewer studies in adolescents, they all indicate an increased prevalence of depression. The evidence for a difference in the prevalence of anxiety is inconclusive. We therefore recommend general mental health screening at diagnosis.

Evidence is based on studies using screening tools and clinical interviews and is inclusive of broad regions.

Subgroup considerations:

Perinatal depression was considered in the literature search but only one study was identified and no meta-analysis is possible.

Adolescents – Depression prevalence summarised above. Only three studies on anxiety with no significant difference.

Implementation considerations:

In many countries it is not usual practice to screen adolescents or adults with PCOS for depression and/or anxiety symptoms and doing so may identify affected patients who would otherwise be missed. Screening may have resource implications such as an impact on length of consultation, however this can be reduced by the use of the screening tools recommended here. If depression and/or anxiety symptoms are detected, intervention may require referral to other health practitioners. Additional time with the patient may also be required to complete an appropriate care plan. Access to appropriate information and appropriately trained and experienced health professionals is important but may be limited. It is the responsibility of all health professionals to understand the impact of PCOS on psychological health and to screen for and manage these disorders.

Feasibility - A pragmatic approach may be to screen all women and adolescents at the time of PCOS diagnosis and where appropriate, at the time of their regular physical health checks for PCOS. Use clinical judgment considering an individual woman's risk factors to inform if additional screening is warranted. Align timing and interval of screening during the antenatal and postnatal periods with the regional general population guidelines.

Partner with mental health professionals to improve feasibility related to referral for further care

The life stage of a woman should also be considered when screening for mental health disorders as risk factors and life events may differ. Consider issues around culture and sexual orientation.
The cultural identity and preferred language of a woman are also important considerations. Be aware of possible variations in presentation of mental health disorders and conduct screening in a culturally sensitive manner.

Translation tools should include:

- Screening can be separated into two levels depending on the competence of the practitioner.
  Step 1: The following questions could be asked [10]:
  Over the last 2 weeks, how often have you been bothered by the following problems?
  1) Feeling down, depressed, or hopeless?
  2) Little interest or pleasure in doing things?
  3) Feeling nervous, anxious or on edge?
  4) Not being able to stop or control worrying?

  Step 2: If any of the responses are positive, further screening should involve:
  Assessment of risk factors and symptoms using tools appropriate for age, culture and region (e.g. the Patient Health Questionnaire (PHQ) or the Generalised Anxiety Disorder Scale (GAD7)) and/or refer to an appropriate professional for further assessment.

Monitoring and evaluation considerations:
The optimal interval for anxiety and depressive symptom screening is not known. A pragmatic approach could include repeat screening using clinical judgement, considering risk factors, comorbidities and life events including the perinatal period.
Ongoing monitoring of women with depressive and anxiety symptoms is important. Change in symptoms with initiation of PCOS related therapies should be monitored.
Monitoring of these recommendations is needed in routine care.

Research priorities:

- Where regions, ethnic, population subgroups and life stages (including perinatal period) have not been adequately included, prevalence studies could be justified. Otherwise, further prevalence studies are not warranted.
- Longitudinal follow up to determine frequency of screening for depressive and anxiety symptoms.
- Examination of the impact of depression or anxiety on the process and outcome of PCOS treatment and management, and the impact of PCOS treatment and management on depression or anxiety.
- Examination of the effectiveness of treatment for depression or anxiety in women with PCOS, including the impact this has on the process and outcome of PCOS treatment and management
- The aetiology and pathophysiology of mental health disorders in PCOS which may inform more targeted therapy.

GRADE framework

GRADE DECIDE **Interactive Evidence to Decision Framework**

● DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

Judgement:

☒ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:
See Part 1- Evidence Summary and GRADE document.

Panel discussion:

● UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

Judgement:

☒ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:
See Part 1- Evidence Summary and GRADE document.

Panel discussion:
The difference between depression or anxiety symptoms to actual clinical diagnosis requiring treatment needs to be appreciated.

● CERTAINTY OF THE EVIDENCE

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☐ Very low	☐ Low	☐ Moderate	☒ High

Research evidence:
See Part 1- Evidence Summary and GRADE document.

Panel discussion:
Anxiety in adolescents and perinatal depression/anxiety are still gaps.

● VALUES

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☐ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☐ Probably no important uncertainty or variability	☒ No important uncertainty or variability

Research evidence:
No research evidence was identified

Panel discussion:

● BALANCE OF EFFECTS

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☒ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:

● COSTS

How large are the resource requirements (costs)?

Judgement:

☐ Don't know	☐ Varies	☐ Large costs	☒ Moderate costs	☐ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:
No research evidence was identified

Panel discussion:
The GDG did have different perspectives on this issue.

● CERTAINTY OF COST EVIDENCE

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:
No research evidence was identified

Panel discussion:
As above in cost.

● COST-EFFECTIVENESS

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:
No research evidence was identified

Panel discussion:
Cannot be rated due to no evidence.

● EQUITY

What would be the impact on health equity?

Judgement:

☐ Don't know	☒ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☐ Probably increased	☐ Increased

Research evidence:
No research evidence was identified

Panel discussion:
Equitable access to appropriately trained health professionals for mental health varies considerably. The cultural identity and preferred language of a woman are also important considerations. Be aware of possible variations in presentation of mental health disorders and conduct screening in a culturally sensitive manner.

- **ACCEPTABILITY**

Is the option acceptable to key stakeholders?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

Research evidence:
No research evidence was identified

Panel discussion:
Workforce training, health system, stigma and resources are all considerations.

- **FEASIBILITY**

Is the option feasible to implement?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

Research evidence:
No research evidence was identified

Panel discussion:
See above in feasibility.

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PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by ECR Lead: Hester Pastoor

Other Members: Wichor Bramer, Hanneke Bolt, Reinier Timman

Supervised, edited and supported by the Evidence Team (Aya Mousa, Jillian Tay)

GDG 2

Question 2.3.

In women with PCOS what is the prevalence and severity of psychosexual dysfunction?

1. STUDY SELECTION

Table 1. PICO Criteria for Inclusion	
Question	**2.3 In women with PCOS what is the prevalence and severity of psychosexual dysfunction?** **CLINICAL PRACTICE POINTS:** **- Should psychosexual dysunfction be assessed as part of standard care?** **- In women with PCOS, what tools/methods can be used to assess psychosexual dysfunction?**
Clinical leads (key contacts)	**Tania Burgert**
Allocation ranking	**Level 1 - new systematic review**

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(language, year)*
Inclusion	• Women with PCOS. • PCOS diagnosed by Rotterdam criteria/ National Institutes of Health/ Androgen Excess and PCOS society criteria • 14 years and older	None.	Women without PCOS. Less than 14-year-old.	Adequate definition of sexual function, operationalized as: desire, arousal, lubrication, orgasm, frequency of intercourse, masturbation frequency, sexual dysfunction, sexual satisfaction, sexual self-image, sexual debut, sexual distress. Validated sexuality questionnaire or VAS scales	Any original study. E.g. case-control, RCT, cross-sectional	English language. Full text publication.
Exclusion	Unrelated to PCOS. PCOS induced by valproate use PCOS in combination with other diseases. Idiopathic hyperandrogenism. Hyperandrogenism caused by other diseases	None	Women without PCOS but with other diseases (endocrine, somatic or psychological) that influence sexual function	Health related quality of life Quality of life Mental health	Reviews	Full text not available Abstracts Posters PhD theses

2. SEARCH STRATEGY

Search details	
Search strategy source: update from Pastoor H, Timman R, de Klerk C, M Bramer W, Laan ET, Laven JS. Sexual function in women with polycystic ovary syndrome: a systematic review and meta-analysis. Reprod Biomed Online. 2018 Dec;37(6):750-760. doi: 10.1016/j.rbmo.2018.09.010. Epub 2018 Oct 19. PMID: 30420168.	
Evidence source	Date of search
Medline (Ovid)	24/08/2022
PsychInfo (Ovid)	24/08/2022
EMBASE	24/08/2022
All EBM (Ovid)	Not searched
CINAHL	24/08/2022
Any subsequent updates - enter database and date: not applicable	

Questions addressed by this search:		
GDG	**Q#**	**Question**
2	2.3	In women with PCOS what is the prevalence and severity of psychosexual dysfunction?
		CLINICAL PRACTICE POINTS: - Should psychosexual dysfunction be assessed as part of standard care? - In women with PCOS, what tools/methods can be used to assess psychosexual dysfunction?

Search strategy

Embase.com
('ovary polycystic disease'/de OR (((polycyst* OR micropolycyst* OR sclerocyst*) NEAR/3 (ovar* OR follic*)) OR ((Stein) NEAR/3 (Leventhal)) OR pcos):ab,ti) AND (sex/de OR sexuality/exp OR 'sexual arousal'/de OR 'sexual dysfunction'/exp OR 'psychosexual disorder'/exp OR sexology/de OR 'sexual counseling'/de OR 'sexual function'/de OR 'Female Sexual Function Index'/de OR (sexual* OR arous* OR anorgas* OR orgas* OR libid* OR abstinen* OR hypersex* OR hyposex* OR dyspareun* OR frigid* OR vaginis* OR psychosex* OR copulation OR coit* OR masturbat* OR virgin*):ab,ti) NOT ([animals]/lim NOT [humans]/lim)

Medline (OvidSP)
("Polycystic Ovary Syndrome"/ OR (((polycyst* OR micropolycyst* OR sclerocyst*) ADJ3 (ovar* OR follic*)) OR ((Stein) ADJ3 (Leventhal)) OR pcos).ab,ti.) AND (exp "sexual behavior"/ OR exp "Sexual Dysfunction, Physiological"/ OR exp "Sexual Dysfunctions, Psychological"/ OR exp sexology/ OR (sexual* OR arous* OR anorgas* OR orgas* OR libid* OR abstinen* OR hypersex* OR hyposex* OR dyspareun* OR frigid* OR vaginis* OR psychosex* OR copulation OR coit* OR masturbat* OR virgin*).ab,ti.) NOT (exp animals/ NOT humans/)

Cochrane
((((polycyst* OR micropolycyst* OR sclerocyst*) NEAR/3 (ovar* OR follic*)) OR ((Stein) NEAR/3 (Leventhal)) OR pcos):ab,ti) AND ((sexual* OR arous* OR anorgas* OR orgas* OR libid* OR abstinen* OR hypersex* OR hyposex* OR dyspareun* OR frigid* OR vaginis* OR psychosex* OR copulation OR coit* OR masturbat* OR virgin*):ab,ti)

Web-of-science
TS=(((((polycyst* OR micropolycyst* OR sclerocyst*) NEAR/3 (ovar* OR follic*)) OR ((Stein) NEAR/3 (Leventhal)) OR pcos)) AND ((sexual* OR arous* OR anorgas* OR orgas* OR libid* OR abstinen* OR hypersex* OR hyposex* OR dyspareun* OR frigid* OR vaginis* OR psychosex* OR copulation OR coit* OR masturbat* OR virgin*)))

Scopus
TITLE-ABS-KEY(((((polycyst* OR micropolycyst* OR sclerocyst*) W/3 (ovar* OR follic*)) OR ((Stein) W/3 (Leventhal)) OR pcos)) AND ((sexual* OR arous* OR anorgas* OR orgas* OR libid* OR abstinen* OR hypersex* OR hyposex* OR dyspareun* OR frigid* OR vaginis* OR psychosex* OR copulation OR coit* OR masturbat* OR virgin*)))

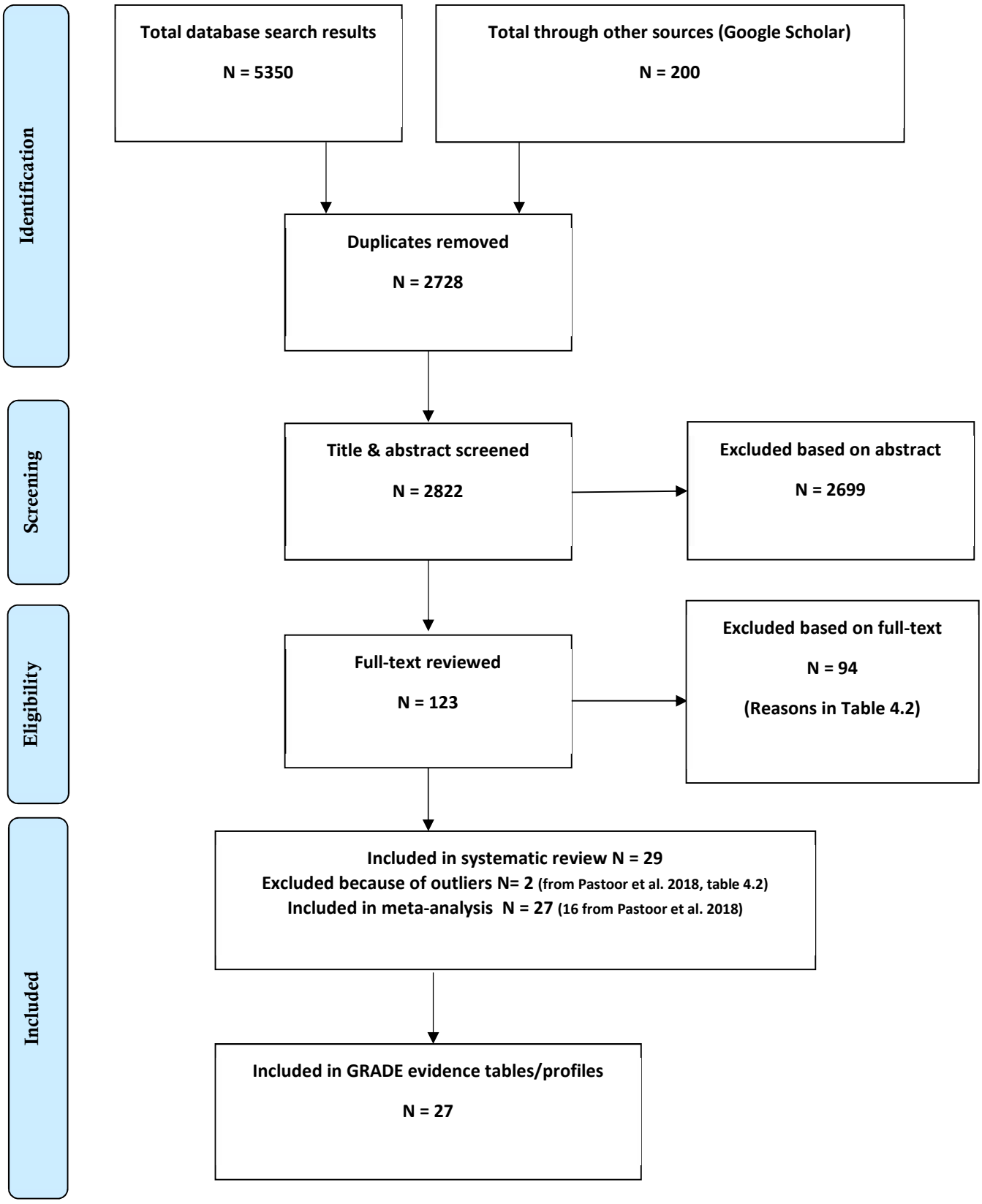
Cinahl
(MH "Polycystic Ovary Syndrome+" OR (((polycyst* OR micropolycyst* OR sclerocyst*) N3 (ovar* OR follic*)) OR ((Stein) N3 (Leventhal)) OR pcos)) AND (MH "sexuality+" OR MH "Sexual and Gender Disorders+" OR MH "Sexual Dysfunction, Female+" OR (sexual* OR arous* OR anorgas* OR orgas* OR libid* OR abstinen* OR hypersex* OR hyposex* OR dyspareun* OR frigid* OR vaginis* OR psychosex* OR copulation OR coit* OR masturbat* OR virgin*)) NOT (MH animals+ NOT MH humans+)

PsycINFO (OvidSP)
((((polycyst* OR micropolycyst* OR sclerocyst*) ADJ3 (ovar* OR follic*)) OR ((Stein) ADJ3 (Leventhal)) OR pcos).ab,ti.) AND (exp "Psychosexual Behavior"/ OR exp "Sexual Function Disturbances"/ OR Sexuality/ OR "Sexual Satisfaction"/ OR "Sex Therapy"/ OR (sexual* OR arous* OR anorgas* OR orgas* OR libid* OR abstinen* OR hypersex* OR hyposex* OR dyspareun* OR frigid* OR vaginis* OR psychosex* OR copulation OR coit* OR masturbat* OR virgin*).ab,ti.) NOT (exp animals/ NOT humans/)

Google Scholar
Pcos
sexual|sexuality|anorgasmia|orgasm|libido|hyposexuality|dyspareunia|frigidity|vaginismus|psychosexual|copulation|coitus|masturbatation

Evidence processing: Studies were selected and appraised by 2 reviewers using study selection and appraisal criteria (PICO above) established a priori. The articles were reviewed by title and abstract by 2 reviewers. When a decision could not be made based on title and abstract alone, full text was retrieved**. A total of 29 studies met inclusion criteria for this review**.

3. SEARCH RESULTS - PRISMA flowchart



4. STUDY INCLUSION

4.1 Included studies

Original studies from Pastoor et al. 2018 search:

1. Benetti-Pinto, C.L., Ferreira, S.R., Antunes Jr, A. and Yela, D.A., (2014). The influence of body weight on sexual function and quality of life in women with polycystic ovary syndrome. Arch Gynecol Obstet. 2014; doi: 10.1007/s00404-014-3423-1.
2. Caruso, S., Rugolo, S., Agnello, C., Romano, M. and Cianci, A., (2009). Quality of sexual life in hyperandrogenic women treated with an oral contraceptive containing chlormadinone acetate. J Sex Med. 2009; 6, 3376-84. doi: 10.1111/j.1743-6109.2009.01529.x.
3. Diamond, M.P., Legro, R.S., Coutifaris, C., Alvero, R., Robinson, R.D., Casson, P.A., Christman, G.M., Huang, H., Hansen, K.R., Baker, V., Usadi, R., Seungdamrong, A., Bates, G.W., Rosen, R.M., Schlaff, W., Haisenleder, D., Krawetz, S.A., Barnhart, K., Trussell, J.C., Santoro, N., Eisenberg, E. and Zhang, H., (2017). Sexual function in infertile women with polycystic ovary syndrome and unexplained infertility. Am J Obstet Gynecol.2017. doi: 10.1016/j.ajog.2017.04.034.
4. Drosdzol, A., Skrzypulec, V., Mazur, B. and Pawlinska-Chmara, R., (2007). Quality of life and marital sexual satisfaction in women with polycystic ovary syndrome. Folia Histochem Cytobiol. 2007; 45, 93-97. doi.org/10.2478/4495.
5. Elkhiat, Y., Zedan, A., Mostafa, M. and Elhalwagi, A., (2015). Sexual desire in a sample of married Egyptian women with polycystic ovarian syndrome. Human Andrology. 2015; 5(3):49-57. DOI:10.1097/01.XHA.0000470182.71509.1b
6. Elsenbruch, S., Hahn, S., Kowalsky, D., Offner, A.H., Schedlowski, M., Mann, K. and Janssen, O.E., (2003). Quality of Life, Psychosocial Well-Being, and Sexual Satisfaction in Women with Polycystic Ovary Syndrome. J Clin Endocrinol Metab 88, 5801-5807. 2013. doi: 10.1210/jc.2003-030562.
7. Ercan, C.M., Coksuer, H., Aydogan, U., Alanbay, I., Keskin, U., Karasahin, K.E. and Baser, I., (2013). Sexual dysfunction assessment and hormonal correlations in patients with polycystic ovary syndrome. Int J Impotence Res. 2013; 25, 127-132. doi: 10.1038/ijir.2013.2.
8. Ferraresi, S.R., Lara, L.A.S., Reis, R.M. and de Sa Rosa e Silva, A.C.J.,(2013). Changes in Sexual Function among Women with Polycystic Ovary Syndrome: A Pilot Study. J Sex Med. 2013; 10, 467-473. DOI: 10.1111/jsm.12011
9. Gateva, A. and Kamenov, Z., (2012). Sexual Function in Patients with PCOS and/or Obesity before and after Metformin Treatment. Advances in Sexual Medicine. 2012. DOI: 10.4236/asm.2012.22005.
10. Hahn, S., Janssen, O.E., Tan, S., Pleger, K., Mann, K., Schedlowski, M., Kimmig, R., Benson, S., Balamitsa, E. and Elsenbruch, S., (2005). Clinical and psychological correlates of quality-of-life in polycystic ovary syndrome. Eur J Endocrinol. 2005, 153, 853-60. doi: 10.1530/eje.1.02024.
11. Kowalczyk, R., Skrzypulec-Plinta, V., Nowosielski, K. and Lew-Starowicz, Z., (2015). Sexuality in women with polycystic ovary syndrome. Ginekol Pol. 2015; 86, 100-106. doi: 10.17772/gp/1995.
12. Lara, L.A.S., Ramos, F.K.P., Kogure, G.S., Costa, R.S., Silva de Sá, M.F., Ferriani, R.A. and dos Reis, R.M.,(2015). Impact of Physical Resistance Training on the Sexual Function of Women with Polycystic Ovary Syndrome. J Sex Med. 2015; 12, 1584-1590. doi: 10.1111/jsm.12909.
13. Mansson, M., Norstrom, K., Holte, J., Landin-Wilhelmsen, K., Dahlgren, E. and Landen, M., (2011). Sexuality and psychological wellbeing in women with polycystic ovary syndrome compared with healthy controls. Eur J Obstet Gynecol Reprod Biol. 2011; 155, 161-5. doi: 10.1016/j.ejogrb.2010.12.012.
14. Noroozzadeh, M., Tehrani, F.R., Mobarakabadi, S.S., Farahmand, M. and Dovom, M.R., (2016). Sexual function and hormonal profiles in women with and without polycystic ovary syndrome: a population-based study. Int J Impotence Res. 2016. doi: 10.1038/ijir.2016.35.
15. Shafti, V. and Shahbazi, S., (2016). Comparing sexual function and quality of life in polycystic ovary syndrome and healthy women. J Fam Reprod Health. 2016; 10, 92-98.
16. Stovall, D.W., Scriver, J.L., Clayton, A.H., Williams, C.D. and Pastore, L.M., (2012). Sexual function in women with polycystic ovary syndrome. J Sex Med 2012; 9, 224-230. doi: 10.1111/j.1743-6109.2011.02539.x.

17. Tan, S., Hahn, S., Benson, S., Janssen, O.E., Dietz, T., Kimmig, R., Hesse-Hussain, J., Mann, K., Schedlowski, M., Arck, P.C. and Elsenbruch, S., (2008). Psychological implications of infertility in women with polycystic ovary syndrome. Hum Reprod. 2008; 23, 2064-71. doi: 10.1093/humrep/den227.
18. Zueff, L.N., Lara, L.A., Vieira, C.S., Martins Wde, P. and Ferriani, R.A., (2015). Body composition characteristics predict sexual functioning in obese women with or without PCOS. J Sex Marital Ther. 2015; 41, 227-37. doi: 10.1080/0092623X.2013.864369.

Original studies from 2022 search:

19. Akbari Sene A, Tahmasbi B, Keypour F, Zamanian H, Golbabaei F, Amini-Tehrani M. (2021) Differences in and correlates of sexual function in infertile women with and without polycystic ovary syndrome. Int J Fertil Steril. 2021; 15(1): 65-72. doi: 10.22074/IJFS.2021.6206.
20. Ashrafi, M., Jahangiri, N., Sadatmahalleh, S.J., Mirzaei, N., Hesari, N.G., Rostami, F., Mousavi, S.S., & Zeinaloo, M. (2022). Does prevalence of sexual dysfunction differ among the most common casuse of infertility? A cross-sectional study. BMC Women's Health, 2022: 22:140. doi.org/10.1186/s12905-022-01708-y
21. Aydogan Kirmizi, D, Base, E, Onat, T, Caltekin, MD, Yalvac, ES, Kara, M & Gocmen, AY. (2020). Sexual function and depression in polycystic ovary syndrome: is it associated with inflammation and neuromdulators? Neuropeptides. 2020; 84. 10.1016/j.npep.2020.102099
22. Basirat, Z, Faramarzi, M, Esmaelzadeh, S, Firoozjai, SA, Mahouti, T, & Geraili, Z. (2019) Stress, depression, sexual function, and alexithymia in infertile females with and without polycystic ovary syndrome: a case-control study. Int J Fert STerl. 2019;13(3):203-208. doi: 10.22074/ijfs.2019.5703.
23. Deniz, A & Kehribar, DY. (2020). Evalulation of sexual functions in infertile women with polycystic ovary syndrome. Niger J Clin Pract, 2020; 23:1548-54. DOI: 10.4103/njcp.njcp_15_20
24. Glowinska, A, Duleba, AJ, Zielona-Jenek, M, Siakoswka, M, Pawelczyk, L, & Banaszweska, B. (2020). Disparate Relationship of sexual satisfaction, self-esteem, anxiety, and depression with endocrine profiles of women with or without PCOS. Reproductive Sciences, 2020; 27:432-44. doi.org/10.1007/s43032-019-00061-0
25. Karsten, MDA, Wekker, V, Groen, H, Painter, RC, Mol, BWJ, Laan, ETM, Roseboom, TJ, & Hoek, A. (2021). The role of PCOS in mental health and sexual function in women with obesity and a history of infertility. Human Reproduction Open. 2021;1:1-11. doi.org/10.1093/hropen/hoab038
26. Kaluzna, M, Nomejko, A, Slowinska, A, Wachowiak-Ochmanska, K, Pikosz, K, Ziemnicka, K, & Ruchala, M. (2021). Lower sexual satisfaction in women with polycystic ovary syndrome and metabolic syndrome. Endocrine connnections. 2021;10(9):1035-1044. doi.org/10.1530/EC-21-0257
27. Mantzou, D, Stamou, MI, Armeni, AK, Roupas, ND, Assimakopoulos, K, Adonakis, G, Georgopoulos, NA & Markantes, GK. (2021). Impaired sexual function in young women with PCOS: the detrimental effect of anovulation. J Sexual Medicine, 2021;18:1872-1879. doi.org/10.1016/j.jsxm.2021.09.004
28. Naumova, I, Castelo-Branco, C, & Casals, G. (2021). Psychological issues and sexual function in women with different infertility causes: focus on polycystic ovary syndrome. Reproductive Sciences. 2021;28:2830-2838. doi.org/10.1007/s43032-021-00546-x
29. Thagavi, SA, Aramesh, S, Azizi-Kutenaee, M, Allan, H, Safarzadeh, T, Taheri, M, Salari, S, Khashavi & Bazarganipour, F. (2021) The influence of infertility on sexual and marital satisfaction in Iranian women with polycystic ovary syndrome: a case-control study. Middel East Fertilty Society Journal. 2021;26(2). doi.org/10.1186/s43043-020-00047-y

4.2 Excluded Studies (on full text assessment)

	Reference	Reason
1	Albani, 2009 J Sex Med p 394	Conference abstract
2	Aloulou, 2012 European …	Conference abstract
3	Aloulou, 2012	Conference abstract, same article

	Eur Psychiatry	
4	Altay, 2014 J Sex Med, p 47	Conference abstract
5	Anger, 2007 J Pelvic Med Surg	No standard deviations presented, no controlgroup
6	Arandara 2005 archive.cmb.ac.lk	Full text not available (title in English)
7	Baez, 2012 Dissertation Abstract: 2012-99120-320	Dissertation, only partly available
8	Basson, 2010 Womens Health p 407-429	not specifically on PCOS
9	Battaglia, 2009 J Sex Med p2707	On anatomy, not sexual function
10	Battaglia 2010 J Sex Med p 2755	On anatomy, not sexual function
11	Battista, 2002 Giornale Italiano Ostetricia	Italian, full text not available (title + abstract in English)
12	Bazarganipour, 2013 J Sex Med	About HRQOL
13	Bazarganipour, 2013 Fert Ster	About HRQOL
14	Benson, 2005 Psychotherapie Psychosomatik, p119	German, Full text not available
15	Bhasin, 2007 Lancet p 597	Not specifically about PCOS
16	Brady, 2009 Drug Heatlhc Patient Staf p9	Not about sexual function
17	Bucuras, 2010 J Sex Med	Conference abstract
18	Chavis, 1989 Int J Gyn obst p 389	Case report
19	Childers, 2003 Fert Ster	Conference abstract
20	Di Vasta, 2013 Contemporary Obgyn.	Full text not available (title in English)
21	Elsenbruch, 2003 Journal of …	Full text not available (title in English)
22	Farkas, 2014 Gynecol Endocrinol p95	Review, only partly about sexual function
23	Fauser, 2012 Fert Ster	Consensus statement, review, only partly about sexuality
24	Ferraresi, 2011 J Sex Med	Conference abstract
25	Gateva, 2011 J Sex Med	Conference abstract
26	Hahn, 2005 Exper and Clinical	Full text not available
27	Himmelein, 2006 Obstet Gynecl Surv	Review, only partly about sexual function
28	Janssen, 2008 Semin Reprod Med	Review, only partly about sexual function
29	Jauca, 2010 Zeitschrift Mediz Psychol	Full text not available (title + abstract in English)
30	McCook, 2002	Dissertation
31	McCook, 2002 Fert steril	Conference abstract
32	Milheiser, 2008 Sex Reprod Menopause	Not about PCOS
33	Moran, 2010	Not about sexual function

	J Psychosom Obstet Gyn	
34	Moreira, 2010 Acta Med Port	Portuguese, review, only partly about sexual function
35	Moreira, 2006 Hum Reprod	Letter to the editor
36	Morris, 2005 Epilepsy Behav	About epilepsy not PCOS
37	Nesbitt, 1968 Fert Ster	Full text not available
38	Nowak, 1988 Wiad Lek	Polish, full text not available
39	Pagidas, 2010 Fert ster	Not about sexual function
40	Raboch, 1982 Cesk Gynekol	Czech , full text not available
41	Raboch, 1982 Cesk Gynekol	Czech, full text not available
42	Rellini, 2010 J Sex Med	Conference abstract
43	Rellini 2010 J Sex Med	Conference abstract
44	Rohr, 2002 Maturitas	Not about PCOS
45	Schattmann, 2006	Dissertation, not available
46	Silva, 2010 Einstein	Full text not available
47	Skrzypulec, 2011 J Sex Med	Conference abstract
48	Stoian, 2013 Eur J Contracept Reprod H	Conference abstract
49	Stovall, 2011 Fert Ster	Conference abstract
50	Thomas, 2013	Book chapter, only partly about sexual function
51	Trent, 2001 J Pediatr Adolesc	Not about sexual function
52	Trent, 2003 J Pediatr Adolesc	Not about sexual function
53	Velet, 2011 endocrine-abstracts.org	Abstract
54	Veras, 2011 Compr Psychiatry	No controlgroup
55	Wierman, 2010 J Sex Med	Review, only partly on PCOS, only partly on sexual function
56	Zueff, 2010 Sexologies	Conference abstract
57	Bazarganipour, 2013 J Sex Med	About HRQOL
58	Bazarganipour, 2013 J Sex Med	About HRQOL, same study
59	Bazarganipour, 2013 Fert ster	About HRQOL
60	Conaglen, 2003 J Sex Marit Ther	Not specifically about PCOS
61	Gorzynski, 1977 Arch Sex Behav	Did not use a validated questionnaire on sexual function
62	Jones, 2011 J Obst Gynel Repr Biol	About HRQOL
63	Raboch, 1985 Arch sex behav	Did not use a validated questionnaire on sexual function

64	Alasiri, 2013 J Sex Med p386	No, conference abstract
65	Alasiri, 2014 J Sex Med p252	No, conference abstract
66	Amini, 2012a Int J Fert Ster p148	Conference abstract/poster
67	Amini, 2012b Int J Fert Ster p153	Conference abstract
68	Amini, 2014 J Mazandar, p212-216	Persian language (abstract + title in English)
69	Bazarganipour, 2013 Iranian J	Is about HRQOL. PCOS is not the main topic.
70	Bazarganipour, 2014 Int J Fertility Sterility	No control group, no scores presented
71	De Frene, 2015 Human Reproduction	No control group
72	De Frene, Posters2view.eu	Conference poster
73	De Frene, 2015 Hum Reprod, p 625-631	Mainly about partnerrelationship instead of sexual function
74	Hahn, ? Experimental and Clinical …	Full text not available (title in English)
75	Hashemi, 2014 Iran J Endocrinol Metab	Persian language (abstract + title in English)
76	Hashemi, 2014 en.journals.sid.ir	Full text not available (title + abstract in English)
77	Lara, 2015 J Sex Med p61	Conference abstract
78	Lara 2014 J Sex Med, p245	Conference abstract
79	Romao, 2014 J Sex Med, p249-250	Conference abstract
80	Stadnicka, 2014 Eur J Contra Reprod H	Conference abstract
81	De Frene, 2015 Library University Gent Belgium	Book, thesis
82	Lara, 2015 Nursing Standard	Full text not available
83	Podfigurna, 2015 Gynecological Endocrinology	Review, not concerning sexuality
84	Taghavi, 2015 BMC Women's Health	Qualitative study, interview, no validated questionnaires
85	De Niet, 2012 Intech.com	Book chapter
86	Noroozzadeh, 2017 Arch Sex Beh	No comparison between PCOS and non-PCOS women
87	Schattmann, 2005 Elibrary.ru	Book
88	Winkelman, 2016 Sex Med	Not about PCOS
89	Hevesi et al. 2017	Validation study
90	Nohr, 2021	No validated questionnaires, no means, no SD
91	Uzel et al. 2021	Control group not healthy
92	Javed et al. 2022	Data missing in full text
93	Battaglia, 2008 J Sex Med	Scores not presented
94	Morotti, 2013 J Sex Med	Presented scores are incomplete

5. STUDY CHARACTERISTICS TABLE FOR INCLUDED STUDIES

Author, year, country	Population/ Setting	Study Design	Sample Size per group	Outcomes	Summary of findings	Other notes
Elsenbruch et al. 2003	Outpatient endocrine clinic, Website clinic; Health screening program university	Cross- sectional	PCOS 50 Controls 50	VAS sexual function	PCOS: less satisfied with sexual life, less attractive, sex life is as important as for controls, body hair impacts sexuality negatively	Elsenbruch, Tan, Hahn and Caruso used the same control group
Hahn et al. 2005	Outpatient endocrine Clinic, Website clinic Health screening program university	Cross-sectional	PCOS 120 Controls 50	VAS sexual function	PCOS: less satisfied with sexual life, less attractive, sex life is as important as for controls, body hair impacts sexuality negatively	Elsenbruch, Tan, Hahn and Caruso used the same control group
Drosdzol et al. 2007	University Hospital Outpatient Gynecological Clinics	Cross-sectional	PCOS 50 Controls 40	ISS questionnaire sexual function	PCOS lower marital sexual function, more marital sexual dysfunction, hirsutism affects sexual function negatively than controls	
Tan et al. 2008	Outpatient endocrine clinic Health screening program university	Cross-sectional	PCOS 115 Controls 50	VAS sexual function	PCOS reduced sexual satisfaction and sexual self-worth compared to controls	Elsenbruch, Tan, Hahn and Caruso used the same control group
Caruso et al. 2009	Family planning center Health screening program university	Prospective intervention	PCOS 94 Controls 50	VAS sexual function	Women with PCOS find themselves less sexual attractive. Body hair impacted sexual function and PCOS had an impact on social relations.	Elsenbruch, Tan, Hahn and Caruso used the same control group Intervention study, we used baseline scores only for this meta-analysis
Mansson et al. 2011	Linne Infertlity Clinic in Uppsale Department of Obstetrics & gynecology and Medicine at Sahlgrenska University Hospital Gothenburg For each woman with PCOS a woman born on the same day, identified from the population registry served as a control.	Case control	PCOS 49 Controls 49	McCoy-FSQ	Despite having the same number of partners and about the same frequency of sexual intercourse, women with PCOS were generally less satisfied with their sex lives compared to the population-based controls. PCOS women scored numerically lower than controls on the McCoy total score, but this difference was not statistically significant.	Not included in MA for outliers see Pastoor et al. 2018

Gateva et al. 2012	Hospitalized patients endocrine clinic Other hospital population	Cross- sectional	PCOS 57 Controls 22	FSFI	PCOS lower sexual function scores then obese controls. Obese PCOS women score better in FSFI than lean PCOS women.	Intervention study, we used baseline scores only for this meta-analysis We only used data for obese women.
Stovall et al. 2012	Convenient, hospital Waiting room university gyn department	Cross- sectional	PCOS 92 Controls 82	CSFQ	PCOS lower orgasm score than controls, higher BMI related to worse orgasm scores, testosterone >1SD above mean better sexual function	
Ercan et al. 2013	Not specified, hospital University hospital, routine check up	Cross-sectional	PCOS 32 Controls 32	FSFI	No differences in sexual function, higher testosterone associated with higher total FSFI score	
Ferraresi et al. 2013	Consecutive sample, tertiary hospital, rr 83/87 total population Primary care same hospital, Regular menses	Cross- sectional	PCOS 48 Controls 35	FSFI	PCOS 50% below cut off FSFI, no significant differences in FSFI total score between PCOS and control	We used both the lean and obese data.
Zueff et al. 2014	Outpatient gyn, contraception program	Case control	PCOS 43 Controls 44	SQ-F	No significant differences in total SQ-F scores	
Benetti-Pinto et al. 2015	Gynecology department university hospital, rr 100%	Cross- sectional	PCOS 56 Controls 102	FSFI	PCOS lower score on FSFI scales except for desire and orgasm	
Elkhiat et al. 2015	Gynecology & Obstetrics Clinic	Cross-sectional	PCOS 85 Controls 63	FSDQ	PCOS lower scores on FSDQ scales except for solitary desire. Normal testosterone levels in PCOS associated with better sexual function.	
Kowalczyk et al. 2015	University hospital: department of Gynecologic Endocrinology	Cross-sectional	PCOS 73 Controls 45	MSQ	Both groups find sexuality equally important. PCOS rates themselves negatively as sexual partner.	
Lara et al. 2015	Endocrine gynecology outpatient clinic, academic medical center	Case control	PCOS 43 Controls 51	FSFI	PCOS more sexual dysfunction at baseline, other scales similar scores between PCOS and controls	Intervention study, we used baseline scores only for this meta-analysis
Noroozzadeh et al. 2016	Stratified-cluster sampling method in four provinces of various geographic regions of Iran	Cross-sectional population based	PCOS 63 Controls 216	FSFI	No significant differences between controls and PCOS on FSFI scores.	

Shafti et al. 2016	Hospital and women infertility clinics Convenient sample	Casual comparative study	PCOS 129 Controls 125	FSFI	No significant differences on FSFI scores between PCOS and controls	
Diamond et al. 2017	Trial PCOS II Trial AMIGOS Women seeking infertility care	Cross sectional secondary data analysis with data from clinical trial	PCOS 733 Controls 865	FSFI	Sexual function scores, as assessed by the Female Sexual Function Inventory, were nearly identical. The Female Sexual Distress Scale total score was higher in women with polycystic ovary syndrome. The mean Female Sexual Function Inventory total score increased slightly as the free androgen index increased, mainly as a result of the desire subscore. This association was more pronounced in the women with unexplained infertility	We only used baseline data for this study. Excluded from MA for being an outlier (see Pastoor et al. 2018)
Basirat et al. 2019	Infertility clinic Fatemeh Azahra Infertility and Reproductive Health Research Center, Babol, Iran	Case control	PCOS 120 Controls 120	FSFI	No significant differences on FSFI scores between PCOS and controls	
Glowinska et al. 2020	Gynecology Clinic at Posnan University Of Medical Sciences Internet advertisements	Cross sectional case control study	PCOS 94 Controls 47	Sexual Satisfaction Scales (physical satisfaction)	No significant difference on this scale between PCOS and controls	We only used scores on the Physical satisfactions scale since we thought these were most comparable with FSFI satisfaction
Deniz et al. 2020	Private Manavgat Obstettrics and Gynecology Center, Antalya, Turkey	Case control	PCOS 50 Controls 50	FSFI	Controls have a significantly higher FSFI total score than women with PCOS	We only used data from PCOS fertile group
Aydogan et al. 2020	A tertiary center	Case control	PCOS 20 Controls 30	FSFI	FSFI lubrication score was significantly higher in the PCOS group. Other scores were not significantly different.	We only used data from PCOS fertile group
Akbari Sene et al. 2021	Two infertility centers in Tehran, Iran	Case control	PCOS 116 Controls 93	FSFI	No significant differences were found between PCOS and controls	
Mantzou et al. 2021	Division of endocrinology of the Universitu Hospital of Patras, Greece	Case control	PCOS 76	FSFI	Women with PCOS scored significantly lower on FSFI domains arousal, lubrication, orgasm and	

	Two workshops on female sexuality conducted in the Universities of Athens and Patras, Greece		Controls 133		satisfaction and on the FSFI total score	
Thagavi et al. 2021	Infertility clinic in Omelila Hospital in Hormozgan province Iran Convenience sampling, patients companions	Case control	PCOS 90 Controls 90	FSFI	Women with PCOS scored significantly lower on all FSFI domains and the FSFI total score	
Kaluzna et al. 2021	Not reported, most likely Poznan University of Medical Sciences	Case control	PCOS 190 Controls 197	Sexual Satisfaction Questionnaire (SSQ)	No significant difference between the groups in SSQ total score	
Naumova et al. 2021	reproductive medicine unit of the Hospital Clinic, Barcelona, Spain	Case control	PCOS 37 Controls 31 (male factor infertility)	FSFI	Women with PCOS scored significantly lower compared to the MFI control group on all FSFI domains except pain and on the FSFI total score	We only used data from the male factor infertility control group
Karsten et al. 2021	Follow up of an RCT (women with obesity and infertility randomized to lifestyle intervention followed by infertility treatment or to prompt infertility treatment)	Cross sectional analysis of data from a follow up study after a multicentre RCT	PCOS 64 (orgasm, lubrication, total) PCOS 73 (sexual interest) PCOS 70 (sexual satisfaction) Controls 79 (orgasm, lubrication, total) Controls 100 (sexual interest) Controls 97 (sexual satisfaction)	MFSQ	No significant differences between PCOS and controls were found on MFSQ scores.	
Ashrafi et al. 2022	Royal Institute and health care centers in Tehran, Iran	Cross sectional	PCOS 80 Controls 80 (male factor infertility)	FSFI	Infertile women with PCOS showed lower scores on all FSFI domains and the FSFI total score compared to women with male factor infertility.	We only used data from the male factor infertility control group

6. FINDINGS

Comparisons included:

- **Comparison 1:** Women with PCOS versus controls

Outcomes included:

- **Outcome 1.** Total sexual function
- **Outcome 2.** Sexual desire
- **Outcome 3.** Sexual arousal
- **Outcome 4.** Lubrication
- **Outcome 5.** Orgasm
- **Outcome 6.** Satisfaction
- **Outcome 7.** Pain
- **Outcome 8.** VAS How many sexual thoughts and fantasies did you have?
- **Outcome 9.** VAS How satisfied were you with your sex life?
- **Outcome 10.** VAS How important is a satisfying sex life for you?
- **Outcome 11.** VAS How often do you experience pain during intercourse?
- **Outcome 12.** VAS how much does excessive body hair impact your sexuality?
- **Outcome 13.** VAS Does your appearance make it difficult to engage in social contact?
- **Outcome 14.** VAS Do you find yourself sexually attractive?

COMPARISON 1: Women with PCOS versus Controls

- **EVIDENCE SUMMARY:**

Twenty-seven studies compared psychosexual dysfunction in women with PCOS versus control. Only six studies were of low risk of bias (Basirat et al. 2019, Benetti Pinto et al. 2015, Ercan et al. 2013, Kowalczyk et al. 2015, Mantzou et al. 2021, Noroozzadeh et al. 2017) and the rest were of moderate risk of bias.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

Pooled analysis showed that there were no differences in sexual desire or pain between women with and without PCOS, but women with PCOS had lower total sexual function, sexual arousal, lubrication, orgasm and satisfaction. The four studies using the VAS tool could not be pooled due to using the same control group, but comparisons within each study showed that women with PCOS had reduced sex life satisfaction and perceptions of sexual attractiveness, while reporting a higher impact of excessive body hair on sexuality and greater difficulties in engaging in social contact due to appearance. No differences were found in the reported frequency of sexual thoughts and fantasies, importance of sexual satisfaction or pain during intercourse between women with PCOS and controls. Evidence for all outcomes was low, due to downgrading for risk of bias (most studies had a moderate risk), inconsistency due to heterogeneity and varying estimates in some pooled analyses, and imprecision due to the small sample size of the control group across the four VAS studies.

Outcome or Subgroup	Studies	n	Effect Estimate; MD [95% CI]	P	Favours	Certainty
Total sexual function	17	2143	-2.42 [-3.26, -1.58]	<0.00001	**Controls** (lower in PCOS)	⊕⊕◯◯ LOW
Sexual desire	16	2498	-0.22 [-0.47, 0.03]	0.08	No difference	⊕⊕◯◯ LOW
Sexual arousal	14	2177	-0.36 [-0.59, -0.13]	0.002	**Controls** (lower in PCOS)	⊕⊕◯◯ LOW
Lubrication	14	2136	-0.47 [-0.75, -0.20]	0.0007	**Controls** (lower in PCOS)	⊕⊕◯◯ LOW
Orgasm	15	2207	-0.35 [-0.52, -0.17]	0.0001	**Controls** (lower in PCOS)	⊕⊕◯◯ LOW
Satisfaction	19	2994	-1.48 [-2.21, -0.75]	<0.0001	**Controls** (lower in PCOS)	⊕⊕◯◯ LOW
Pain	13	2003	-0.27 [-0.57, 0.03]	0.08	No difference	⊕⊕◯◯ LOW
VAS sexual thoughts and fantasies	3	375	NA	NA	No difference	⊕⊕⊕◯ MODERATE
VAS sex life satisfaction	3	377	NA	NA	**Controls** (lower in PCOS)*	⊕⊕◯◯ LOW
VAS importance of sexual satisfaction	3	377	NA	NA	No difference	⊕⊕◯◯ LOW
VAS pain during intercourse	2	282	NA	NA	No difference	⊕⊕⊕◯ MODERATE
VAS body hair impact	4	554	NA	NA	**Controls** (higher in PCOS)*	⊕⊕◯◯ LOW
VAS social contact impact	4	554	NA	NA	**Controls** (higher in PCOS)*	⊕⊕◯◯ LOW
VAS sexual attractiveness	4	554	NA	NA	**Controls** (lower in PCOS)*	⊕⊕⊕◯ MODERATE

*based on statistically significant difference in scores when PCOS was compared with controls within each individual study (since all studies used the same control groups, this effect was not pooled to avoid duplication of the control group in the same analysis).

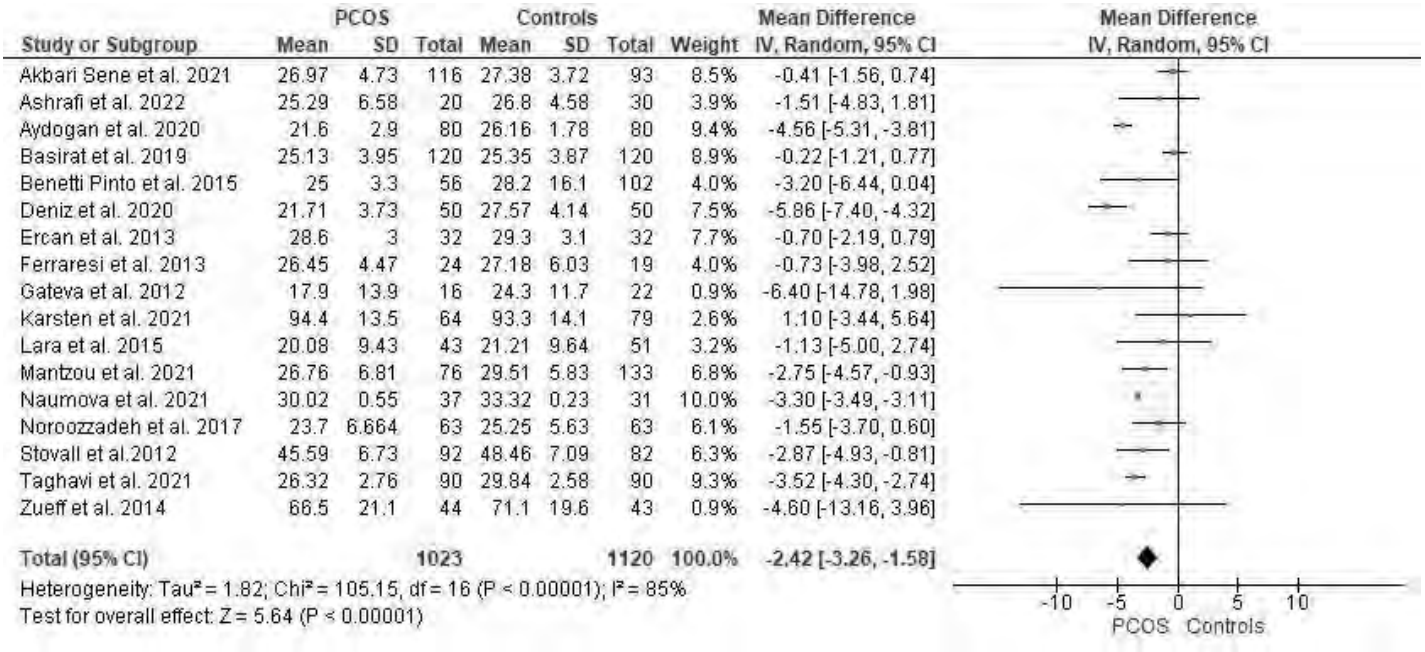
OUTCOME 1. Total sexual function

1.1 Individual Study Data Tables

OUTCOME: total sexual function						OUTCOME TYPE: Continuous				
Comparison: Women with PCOS vs control										
Author, year	**Unit**	**Method of measurement**	**Mean in PCOS group**	**SD in PCOS group**	**Sample size in PCOS group**	**Mean in control group**	**SD in control group**	**Sample size in control group**	**Are these values adjusted or crude?**	**What variables are adjusted for?**
Akbari Sene et al. 2021	Natural number	FSFI	26.97	4.73	116	27.38	3.72	93	Crude	NA
Aydogan et al. 2020	Natural number	FSFI	25.29	6.58	20	26.8	4.58	30	Crude	NA
Ashrafi et al. 2022	Natural number	FSFI	21.6	2.9	80	26.16	1.78	80	Crude	NA
Basirat et al. 2019	Natural number	FSFI	25.13	3.95	120	25.35	3.87	120	Crude	NA
Benetti Pinto et al. 2015	Natural number	FSFI	25	3.3	56	28.2	16.10	102	Crude	NA
Deniz et al. 2020	Natural number	FSFI	21.71	3.73	50	27.57	4.14	50	Crude	NA
Ercan et al. 2013	Natural number	FSFI	28.6	3	32	29.3	3.1	32	Crude	NA
Ferraresi et al. 2013	Natural number	FSFI	26.45	4.47	24	27.18	6.03	19	Crude	NA
Gateva et al. 2012	Natural number	FSFI	17.9	13.9	16	24.3	11.7	22	Crude	NA
Karsten et al. 2021	Natural number	Mc Coy	94.4	13.5	64	93.3	14.1	79	Crude	NA
Lara et al. 2015	Natural number	FSFI	20.08	9.43	43	21.21	9.64	51	Crude	NA
Mantzou et al. 2021	Natural number	FSFI	26.76	6.81	76	29.51	5.83	133	Crude	NA
Naumova et al. 2021	Natural number	FSFI	30.02	0.55	37	33.32	0.23	31	Crude	NA
Noroozzadeh et al. 2017	Natural number	FSFI	23.7	6.664	63	25.25	5.63	63	Crude	NA
Stovall et al.2012	Natural number	CSFQ	45.59	6.73	92	48.46	7.09	82	Crude	NA
Taghavi et al. 2021	Natural number	FSFI	26.32	2.76	90	29.84	2.58	90	Crude	NA
Zueff et al. 2014	Natural number	SQ-F	66.5	21.1	44	71.1	19.6	43	Crude	NA

CSFQ: Changes in Sexual Function Questionnaire, FSDQ: Female Sexual Desire Questionnaire, FSFI: Female Sexual Function Index, ISS: Index of Sexual Satisfaction, MFSQ: Mc Coy Female Sexuality Questionnaire, MSQ: Multidimensional Sexuality Questionnaire, SQ-F: Sexual Quotient Female, VAS: Visual analogue scale.

1.2 Forest plot for total sexual function between women with PCOS compared with controls



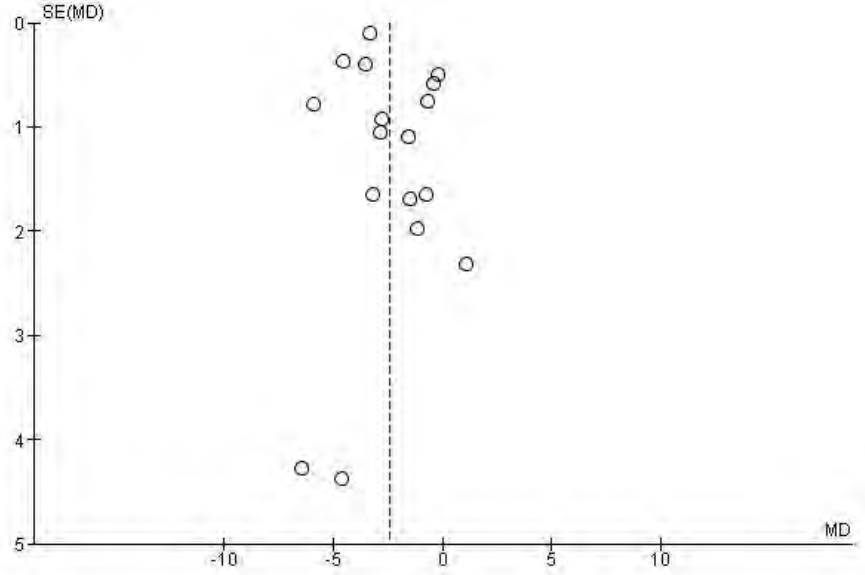
Study or Subgroup	PCOS Mean	PCOS SD	PCOS Total	Controls Mean	Controls SD	Controls Total	Weight	Mean Difference IV, Random, 95% CI
Akbari Sene et al. 2021	26.97	4.73	116	27.38	3.72	93	8.5%	-0.41 [-1.56, 0.74]
Ashrafi et al. 2022	25.29	6.58	20	26.8	4.58	30	3.9%	-1.51 [-4.83, 1.81]
Aydogan et al. 2020	21.6	2.9	80	26.16	1.78	80	9.4%	-4.56 [-5.31, -3.81]
Basirat et al. 2019	25.13	3.95	120	25.35	3.87	120	8.9%	-0.22 [-1.21, 0.77]
Benetti Pinto et al. 2015	25	3.3	56	28.2	16.1	102	4.0%	-3.20 [-6.44, 0.04]
Deniz et al. 2020	21.71	3.73	50	27.57	4.14	50	7.5%	-5.86 [-7.40, -4.32]
Ercan et al. 2013	28.6	3	32	29.3	3.1	32	7.7%	-0.70 [-2.19, 0.79]
Ferraresi et al. 2013	26.45	4.47	24	27.18	6.03	19	4.0%	-0.73 [-3.98, 2.52]
Gateva et al. 2012	17.9	13.9	16	24.3	11.7	22	0.9%	-6.40 [-14.78, 1.98]
Karsten et al. 2021	94.4	13.5	64	93.3	14.1	79	2.6%	1.10 [-3.44, 5.64]
Lara et al. 2015	20.08	9.43	43	21.21	9.64	51	3.2%	-1.13 [-5.00, 2.74]
Mantzou et al. 2021	26.76	6.81	76	29.51	5.83	133	6.8%	-2.75 [-4.57, -0.93]
Naumova et al. 2021	30.02	0.55	37	33.32	0.23	31	10.0%	-3.30 [-3.49, -3.11]
Noroozzadeh et al. 2017	23.7	6.664	63	25.25	5.63	63	6.1%	-1.55 [-3.70, 0.60]
Stovall et al.2012	45.59	6.73	92	48.46	7.09	82	6.3%	-2.87 [-4.93, -0.81]
Taghavi et al. 2021	26.32	2.76	90	29.84	2.58	90	9.3%	-3.52 [-4.30, -2.74]
Zueff et al. 2014	66.5	21.1	44	71.1	19.6	43	0.9%	-4.60 [-13.16, 3.96]
Total (95% CI)			**1023**			**1120**	**100.0%**	**-2.42 [-3.26, -1.58]**

Heterogeneity: Tau² = 1.82; Chi² = 105.15, df = 16 (P < 0.00001); I² = 85%
Test for overall effect: Z = 5.64 (P < 0.00001)

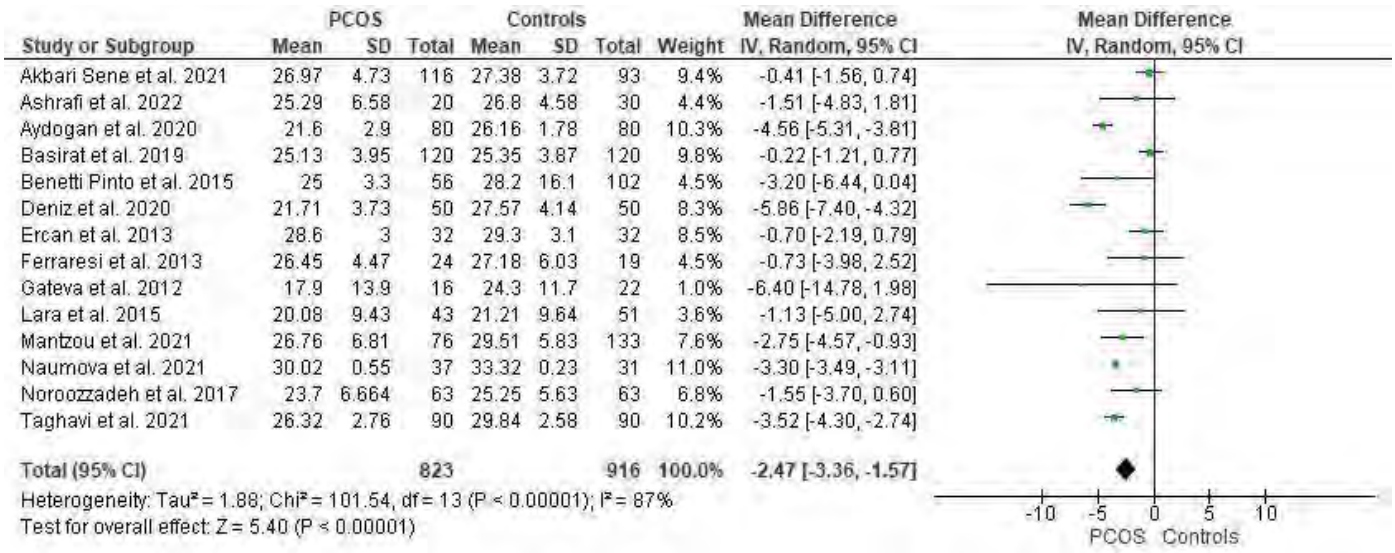
Mean Difference IV, Random, 95% CI

-10 -5 0 5 10
PCOS Controls

1.3 Funnel plot for total sexual function



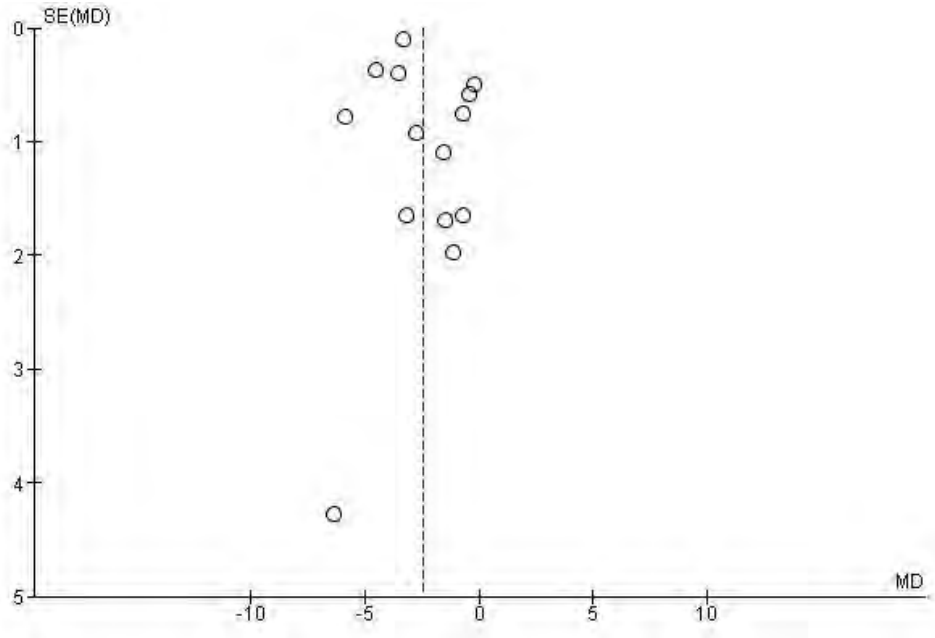
1.4. Sensitivity analysis of only studies using FSFI for total sexual function



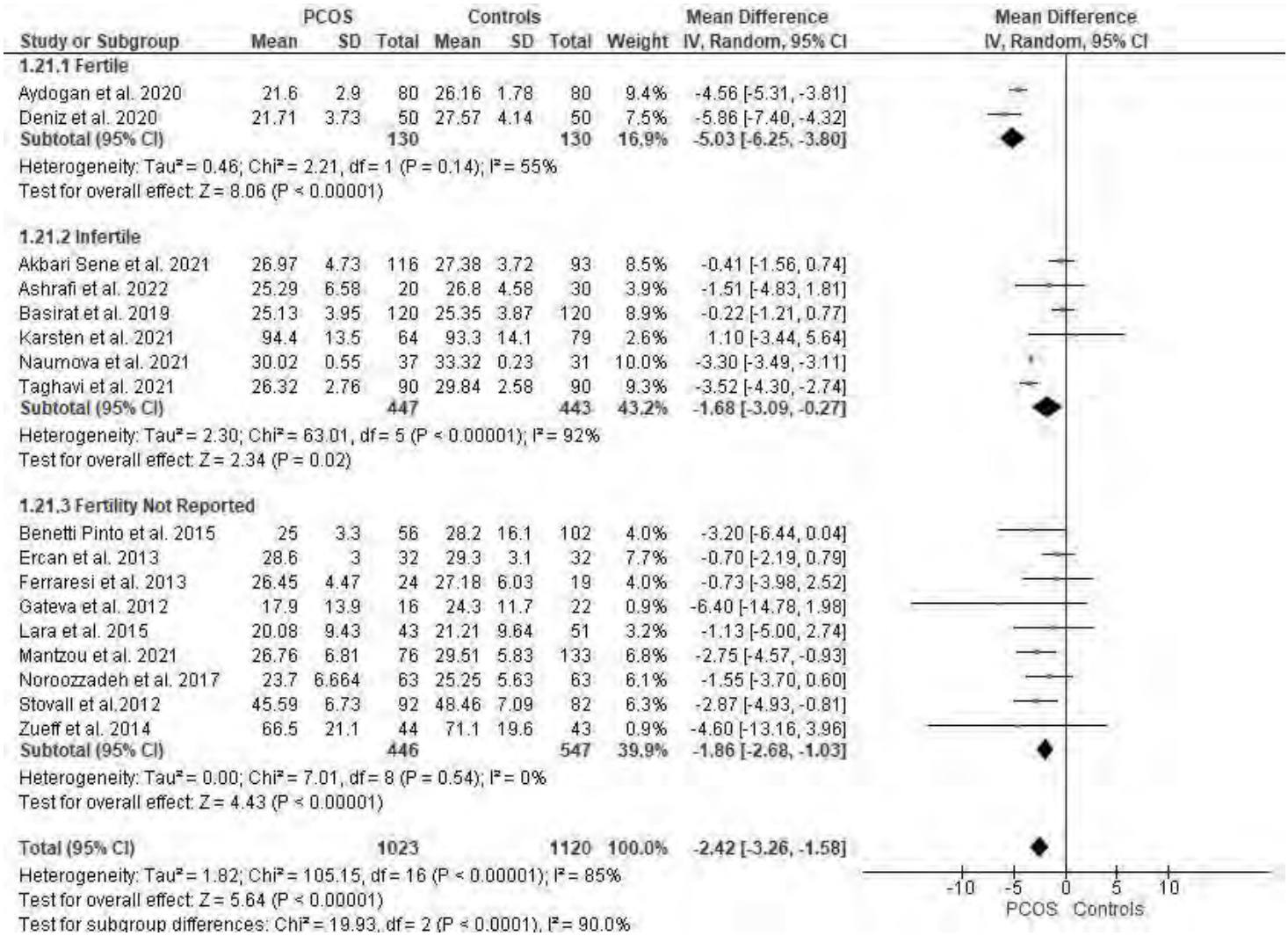
Study or Subgroup	PCOS Mean	PCOS SD	PCOS Total	Controls Mean	Controls SD	Controls Total	Weight	Mean Difference IV, Random, 95% CI
Akbari Sene et al. 2021	26.97	4.73	116	27.38	3.72	93	9.4%	-0.41 [-1.56, 0.74]
Ashrafi et al. 2022	25.29	6.58	20	26.8	4.58	30	4.4%	-1.51 [-4.83, 1.81]
Aydogan et al. 2020	21.6	2.9	80	26.16	1.78	80	10.3%	-4.56 [-5.31, -3.81]
Basirat et al. 2019	25.13	3.95	120	25.35	3.87	120	9.8%	-0.22 [-1.21, 0.77]
Benetti Pinto et al. 2015	25	3.3	56	28.2	16.1	102	4.5%	-3.20 [-6.44, 0.04]
Deniz et al. 2020	21.71	3.73	50	27.57	4.14	50	8.3%	-5.86 [-7.40, -4.32]
Ercan et al. 2013	28.6	3	32	29.3	3.1	32	8.5%	-0.70 [-2.19, 0.79]
Ferraresi et al. 2013	26.45	4.47	24	27.18	6.03	19	4.5%	-0.73 [-3.98, 2.52]
Gateva et al. 2012	17.9	13.9	16	24.3	11.7	22	1.0%	-6.40 [-14.78, 1.98]
Lara et al. 2015	20.08	9.43	43	21.21	9.64	51	3.6%	-1.13 [-5.00, 2.74]
Mantzou et al. 2021	26.76	6.81	76	29.51	5.83	133	7.6%	-2.75 [-4.57, -0.93]
Naumova et al. 2021	30.02	0.55	37	33.32	0.23	31	11.0%	-3.30 [-3.49, -3.11]
Noroozzadeh et al. 2017	23.7	6.664	63	25.25	5.63	63	6.8%	-1.55 [-3.70, 0.60]
Taghavi et al. 2021	26.32	2.76	90	29.84	2.58	90	10.2%	-3.52 [-4.30, -2.74]
Total (95% CI)			**823**			**916**	**100.0%**	**-2.47 [-3.36, -1.57]**

Heterogeneity: Tau² = 1.88; Chi² = 101.54, df = 13 (P < 0.00001); I² = 87%
Test for overall effect: Z = 5.40 (P < 0.00001)

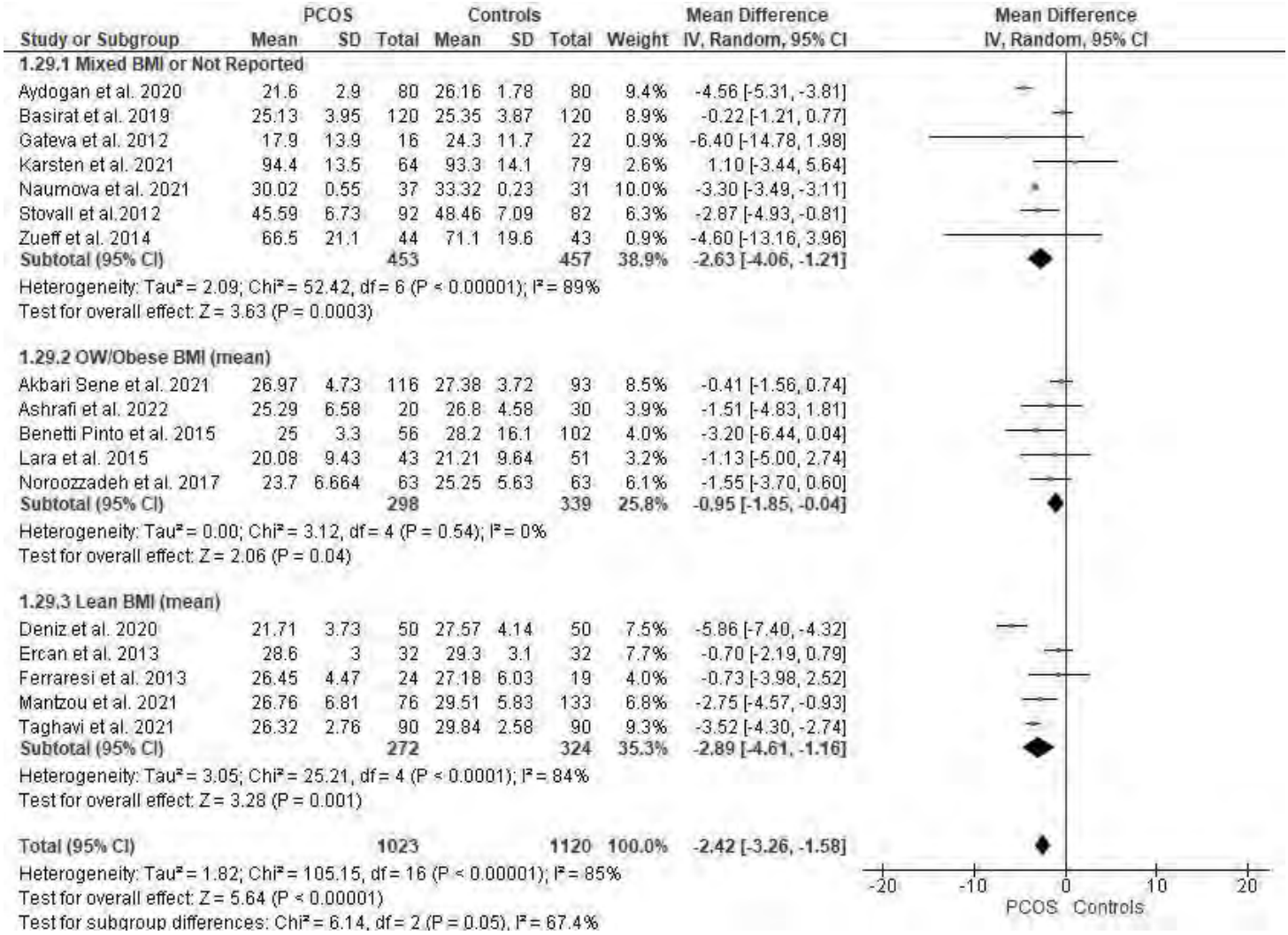
1.5. Funnel plot for sensitivity analysis



1.6. Subgroup Analysis by Fertility Status for total sexual function



1.7. Subgroup analysis by BMI status (mean BMI) for total sexual function



OUTCOME 2. Sexual desire

2.1 Individual Study Data Tables

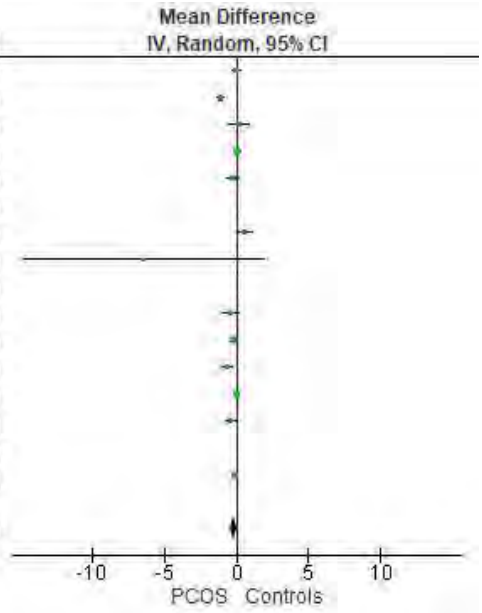
OUTCOME: Sexual desire						OUTCOME TYPE: Continuous				
Comparison: Women with PCOS vs control										
Author, year	**Unit**	**Method of measurement**	**Mean in intervention / exposure group**	**SD in intervention / exposure group**	**Sample size (n within this group)**	**Mean in control / comparison group**	**SD in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**What variables are adjusted for?**
Akbari Sene et al. 2021	Natural number	FSFI	3.78	1.01	116	3.81	1.09	93	Crude	NA
Ashrafi et al. 2022	Natural number	FSFI	3.04	0.74	80	4.11	0.77	80	Crude	NA
Aydogan et al. 2020	Natural number	FSFI	3.86	1.34	20	3.69	0.92	30	Crude	NA
Basirat et al. 2019	Natural number	FSFI	3.94	0.85	120	3.92	0.84	120	Crude	NA
Benetti Pinto et al. 2015	Natural number	FSFI	3.4	1.2	56	3.6	1.2	102	Crude	NA
Elkhiat et al. 2015	Natural number	FSDQ	49.4	11	85	59.4	14.4	63	Crude	NA
Ercan et al. 2013	Natural number	FSFI	4.9	1.1	32	4.3	1.2	32	Crude	NA
Gateva et al. 2012	Natural number	FSFI	17.9	13.9	16	24.3	11.7	22	Crude	NA
Karsten et al. 2021	Natural number	Mc Coy	26.4	6.6	73	25.4	7.4	100	Crude	NA
Lara et al. 2015	Natural number	FSFI	3.28	1.47	43	3.68	1.36	51	Crude	NA
Mantzou et al. 2021	Natural number	FSFI	4.07	0.98	76	4.25	0.95	133	Crude	NA
Naumova et al. 2021	Natural number	FSFI	4.87	0.9	37	5.5	0.5	31	Crude	NA
Noroozzadeh et al. 2017	Natural number	FSFI	3.6	0.816	63	3.6	0.816	216	Crude	NA
Shafti et al. 2016	Natural number	FSFI	6.18	1.56	129	6.55	1.68	125	Crude	NA
Stovall et al.2012	Natural number	CSFQ	8.28	1.64	92	8.43	1.44	82	Crude	NA
Taghavi etal. 2021	Natural number	FSFI	4.3	0.68	90	4.4	0.73	90	Crude	NA

CSFQ: Changes in Sexual Function Questionnaire, FSDQ: Female Sexual Desire Questionnaire, FSFI: Female Sexual Function Index, ISS: Index of Sexual Satisfaction, MFSQ: Mc Coy Female Sexuality Questionnaire, MSQ: Multidimensional Sexuality Questionnaire, SQ-F: Sexual Quotient Female, VAS: Visual analogue scale.

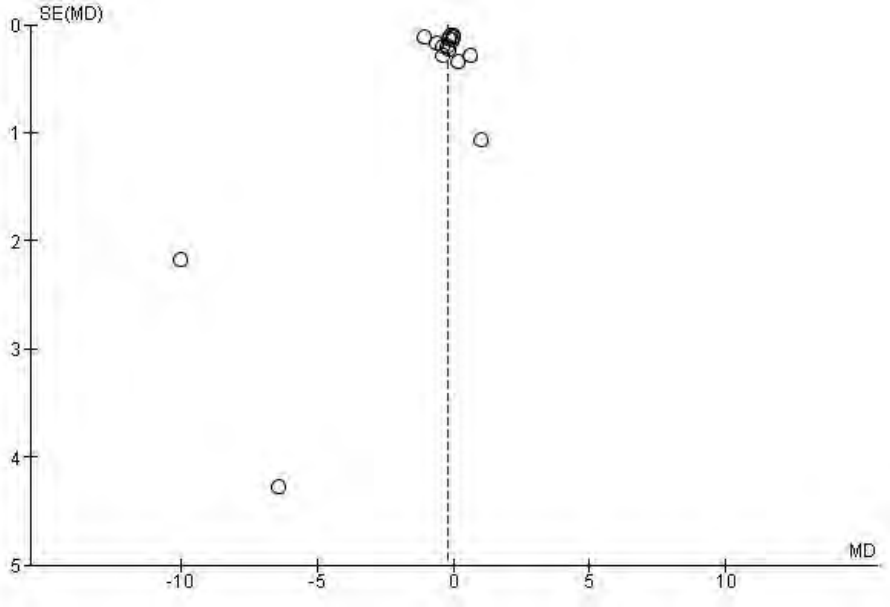
2.2 Forest plot for total sexual desire

Study or Subgroup	PCOS Mean	PCOS SD	PCOS Total	Controls Mean	Controls SD	Controls Total	Weight	Mean Difference IV, Random, 95% CI
Akbari Sene et al. 2021	3.78	1.01	116	3.81	1.09	93	9.0%	-0.03 [-0.32, 0.26]
Ashrafi et al. 2022	3.04	0.74	80	4.11	0.77	80	9.4%	-1.07 [-1.30, -0.84]
Aydogan et al. 2020	3.86	1.34	20	3.69	0.92	30	5.7%	0.17 [-0.50, 0.84]
Basirat et al. 2019	3.94	0.85	120	3.92	0.84	120	9.6%	0.02 [-0.19, 0.23]
Benetti Pinto et al. 2015	3.4	1.2	56	3.6	1.2	102	8.1%	-0.20 [-0.59, 0.19]
Elkhiat et al. 2015	49.4	11	85	59.4	14.4	63	0.0%	-10.00 [-14.26, -5.74]
Ercan et al. 2013	4.9	1.1	32	4.3	1.2	32	6.6%	0.60 [0.04, 1.16]
Gateva et al. 2012	17.9	13.9	16	24.3	11.7	22	0.1%	-6.40 [-14.78, 1.98]
Karsten et al. 2021	26.4	6.6	73	25.4	7.4	100	0.0%	1.00 [-1.10, 3.10]
Lara et al. 2015	3.28	1.47	43	3.68	1.36	51	6.5%	-0.40 [-0.98, 0.18]
Mantzou et al. 2021	4.07	0.98	76	4.25	0.95	133	9.1%	-0.18 [-0.45, 0.09]
Naumova et al. 2021	4.87	0.9	37	5.5	0.5	31	8.6%	-0.63 [-0.97, -0.29]
Noroozzadeh et al. 2017	3.6	0.816	63	3.6	0.816	216	9.5%	0.00 [-0.23, 0.23]
Shafti et al. 2016	6.18	1.56	129	6.55	1.68	125	8.1%	-0.37 [-0.77, 0.03]
Stovall et al.2012	8.28	1.64	92	8.43	1.44	82	0.0%	-0.15 [-0.61, 0.31]
Taghavi et al. 2021	4.3	0.68	90	4.4	0.73	90	9.6%	-0.10 [-0.31, 0.11]
Total (95% CI)			**878**			**1125**	**100.0%**	**-0.21 [-0.45, 0.03]**

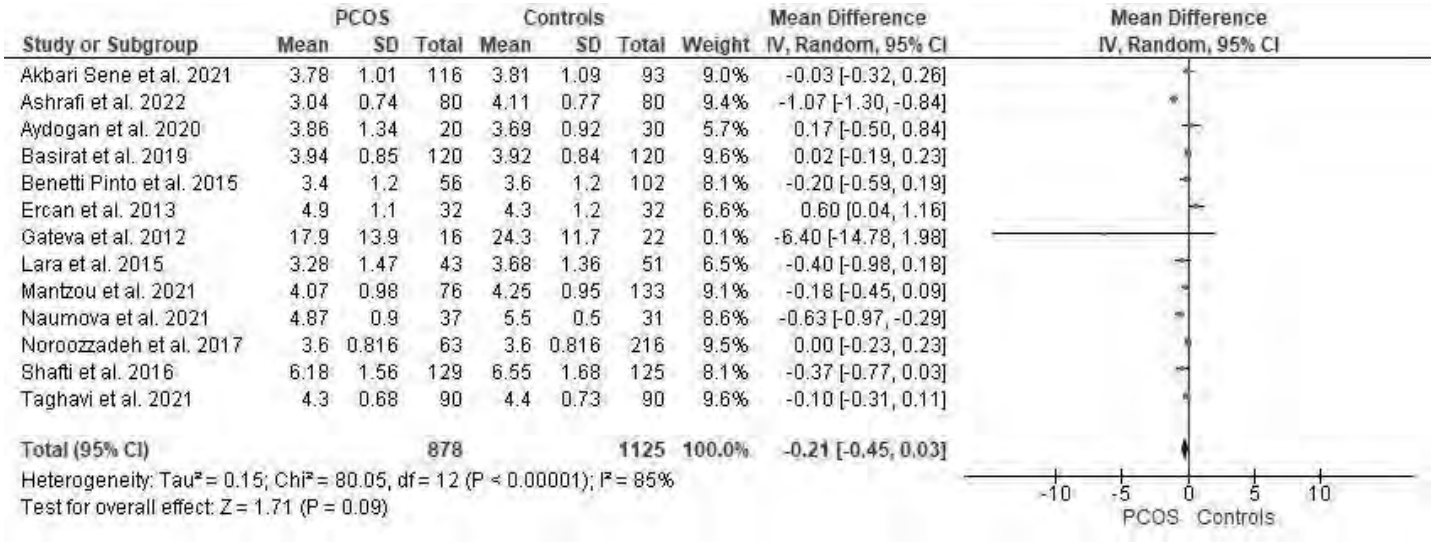
Heterogeneity: Tau² = 0.15; Chi² = 80.05, df = 12 (P < 0.00001); I² = 85%
Test for overall effect: Z = 1.71 (P = 0.09)



2.3 Funnel plot for total sexual desire



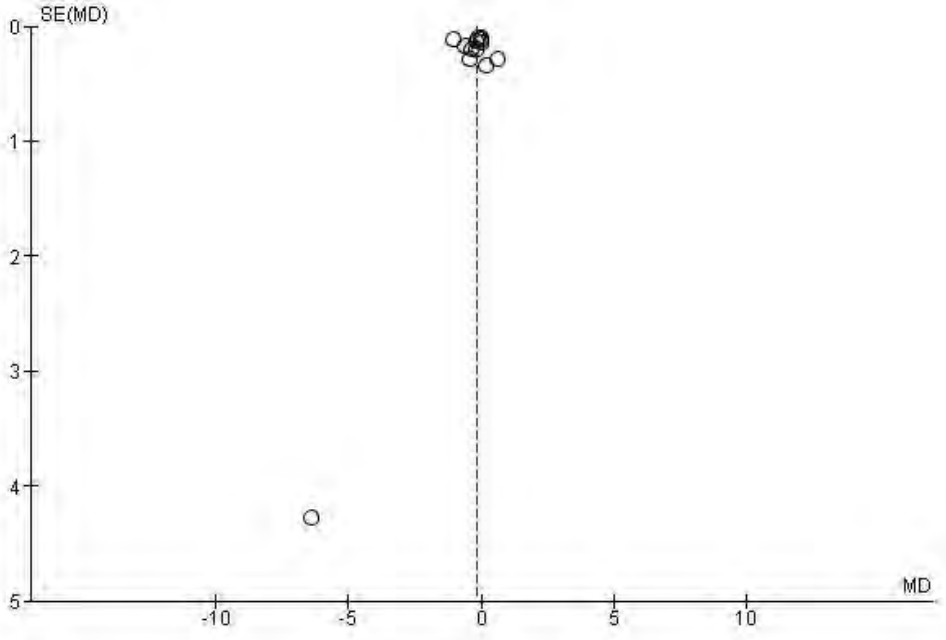
2.4. Sensitivity analysis of only studies using FSFI for total sexual desire



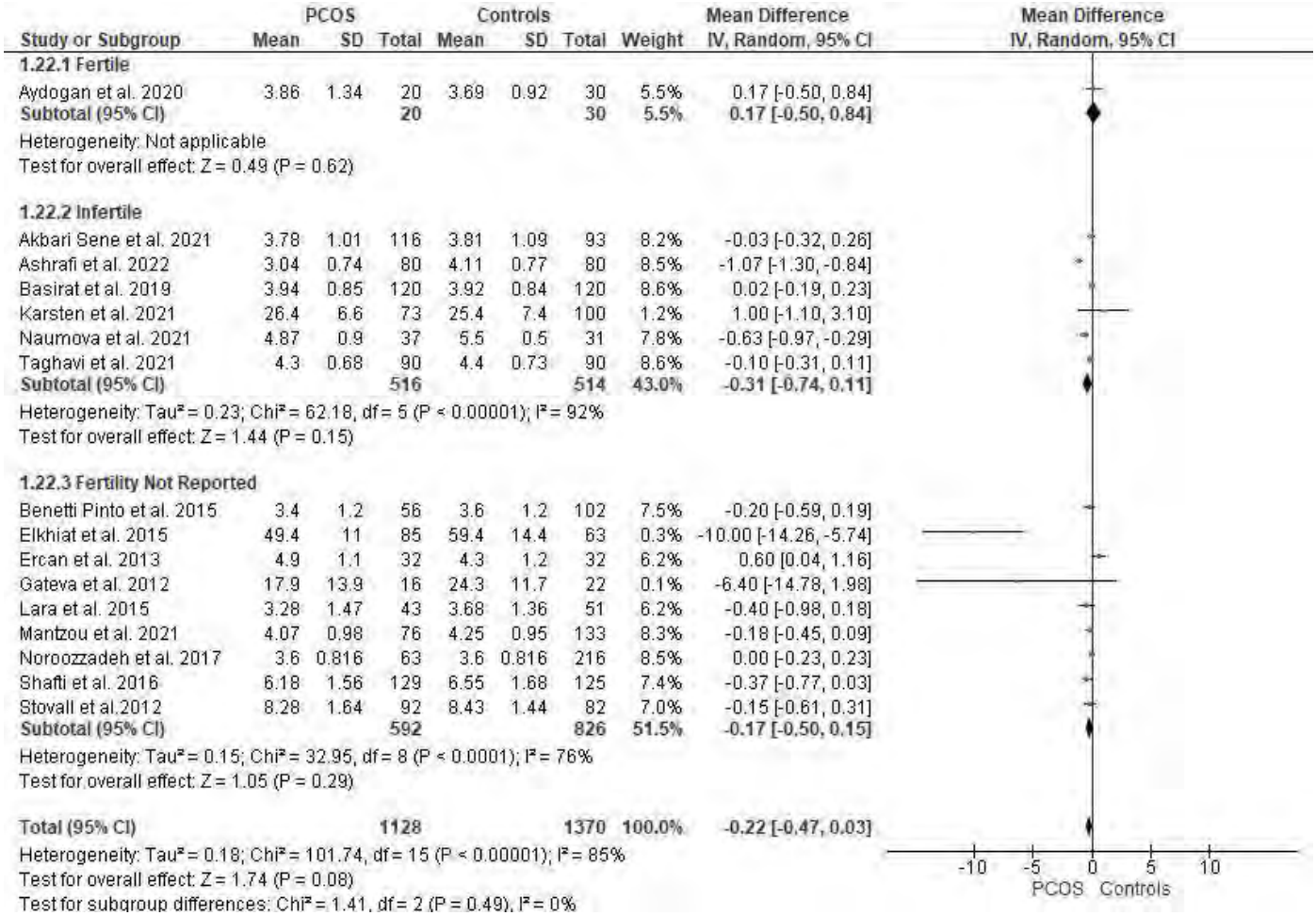
Study or Subgroup	PCOS Mean	PCOS SD	PCOS Total	Controls Mean	Controls SD	Controls Total	Weight	Mean Difference IV, Random, 95% CI
Akbari Sene et al. 2021	3.78	1.01	116	3.81	1.09	93	9.0%	-0.03 [-0.32, 0.26]
Ashrafi et al. 2022	3.04	0.74	80	4.11	0.77	80	9.4%	-1.07 [-1.30, -0.84]
Aydogan et al. 2020	3.86	1.34	20	3.69	0.92	30	5.7%	0.17 [-0.50, 0.84]
Basirat et al. 2019	3.94	0.85	120	3.92	0.84	120	9.6%	0.02 [-0.19, 0.23]
Benetti Pinto et al. 2015	3.4	1.2	56	3.6	1.2	102	8.1%	-0.20 [-0.59, 0.19]
Ercan et al. 2013	4.9	1.1	32	4.3	1.2	32	6.6%	0.60 [0.04, 1.16]
Gateva et al. 2012	17.9	13.9	16	24.3	11.7	22	0.1%	-6.40 [-14.78, 1.98]
Lara et al. 2015	3.28	1.47	43	3.68	1.36	51	6.5%	-0.40 [-0.98, 0.18]
Mantzou et al. 2021	4.07	0.98	76	4.25	0.95	133	9.1%	-0.18 [-0.45, 0.09]
Naumova et al. 2021	4.87	0.9	37	5.5	0.5	31	8.6%	-0.63 [-0.97, -0.29]
Noroozzadeh et al. 2017	3.6	0.816	63	3.6	0.816	216	9.5%	0.00 [-0.23, 0.23]
Shafti et al. 2016	6.18	1.56	129	6.55	1.68	125	8.1%	-0.37 [-0.77, 0.03]
Taghavi et al. 2021	4.3	0.68	90	4.4	0.73	90	9.6%	-0.10 [-0.31, 0.11]
Total (95% CI)			**878**			**1125**	**100.0%**	**-0.21 [-0.45, 0.03]**

Heterogeneity: Tau² = 0.15; Chi² = 80.05, df = 12 (P < 0.00001); I² = 85%
Test for overall effect: Z = 1.71 (P = 0.09)

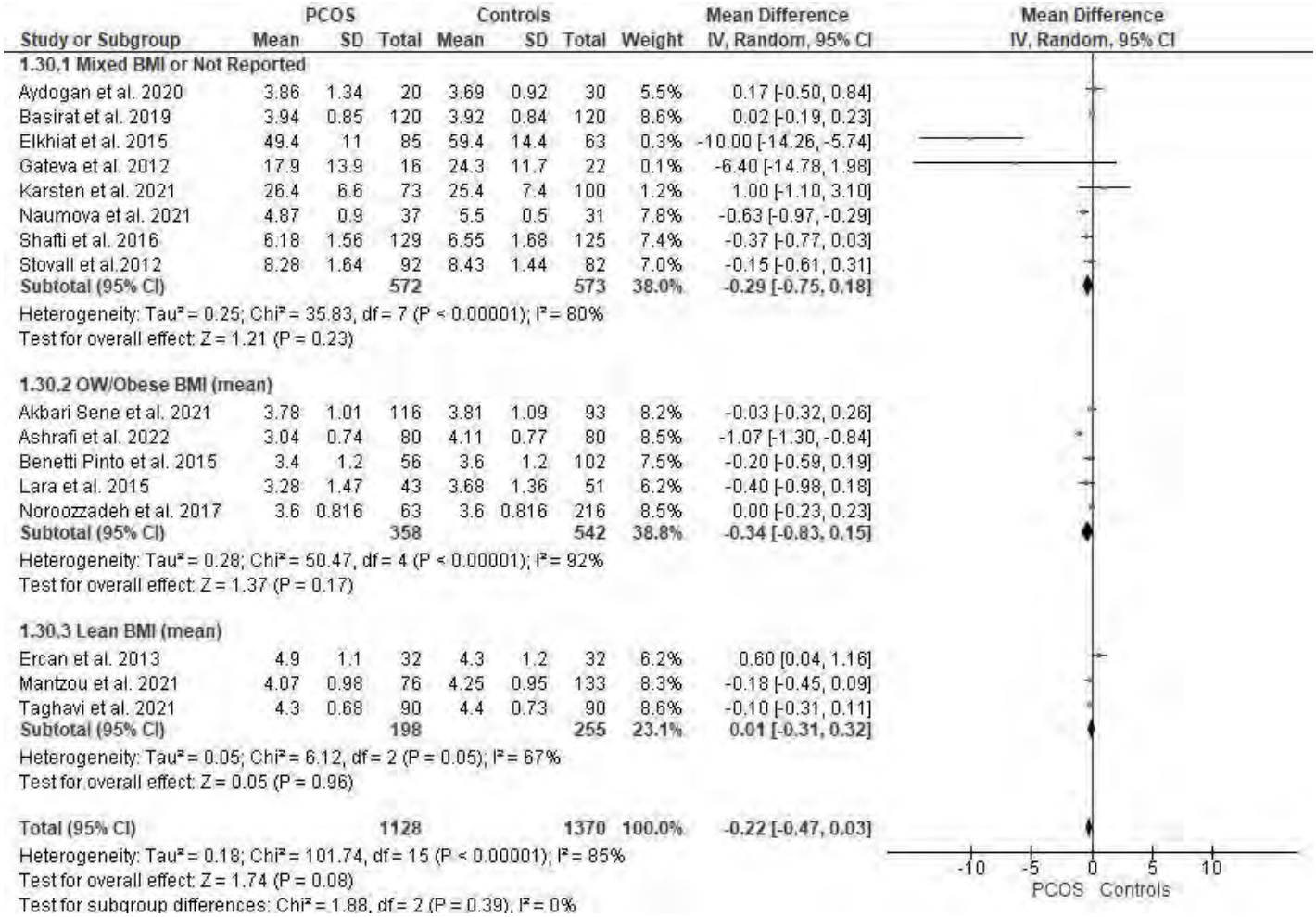
2.5. Funnel plot for sensitivity analysis



2.6. Subgroup Analysis by Fertility Status for total sexual desire



2.7. Subgroup analysis by BMI status (mean BMI) for total sexual desire



OUTCOME 3. Sexual arousal

3.1 Individual Study Data Tables

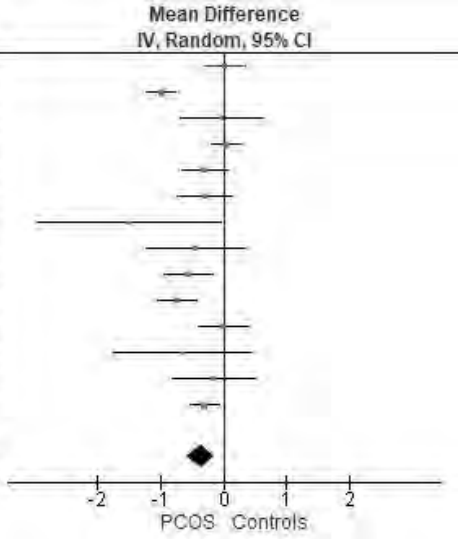
OUTCOME: Sexual arousal						OUTCOME TYPE: Continuous				
Comparison: Women with PCOS vs control										
Author, year	**Unit**	**Method of measurement**	**Mean in PCOS group**	**SD in PCOS group**	**Sample size in PCOS**	**Mean in control group**	**SD in control group**	**Sample size in control group**	**Are these values adjusted or crude?**	**What variables are adjusted for?**
Akbari Sene et al. 2021	Natural number	FSFI	3.69	1.23	116	3.67	1.23	93	Crude	NA
Ashrafi et al. 2022	Natural number	FSFI	3.21	0.75	80	4.2	0.77	80	Crude	NA
Aydogan et al. 2020	Natural number	FSFI	4.07	1.31	20	4.09	0.92	30	Crude	NA
Basirat et al. 2019	Natural number	FSFI	3.92	0.92	120	3.88	0.91	120	Crude	NA
Benetti Pinto et al. 2015	Natural number	FSFI	3.9	1.1	56	4.2	1.1	102	Crude	NA
Ercan et al. 2013	Natural number	FSFI	5	1	32	5.3	0.8	32	Crude	NA
Gateva et al. 2012	Natural number	FSFI	2.6	2.4	16	4.1	2.1	22	Crude	NA
Lara et al. 2015	Natural number	FSFI	2.78	1.92	43	3.22	1.98	51	Crude	NA
Mantzou et al. 2021	Natural number	FSFI	4.48	1.44	76	5.04	1.19	133	Crude	NA
Naumova et al. 2021	Natural number	FSFI	4.95	0.9	37	5.68	0.3	31	Crude	NA
Noroozzadeh et al. 2017	Natural number	FSFI	3.9	1.428	63	3.9	1.578	216	Crude	NA
Shafti et al. 2016	Natural number	FSFI	12.74	3.92	129	13.38	4.873	125	Crude	NA
Stovall et al.2012	Natural number	CSFQ	10.05	2.01	92	10.21	2.41	82	Crude	NA
Taghavi etal. 2021	Natural number	FSFI	4.19	0.79	90	4.49	0.82	90	Crude	NA

CSFQ: Changes in Sexual Function Questionnaire, FSDQ: Female Sexual Desire Questionnaire, FSFI: Female Sexual Function Index, ISS: Index of Sexual Satisfaction, MFSQ: Mc Coy Female Sexuality Questionnaire, MSQ: Multidimensional Sexuality Questionnaire, SQ-F: Sexual Quotient Female, VAS: Visual analogue scale.

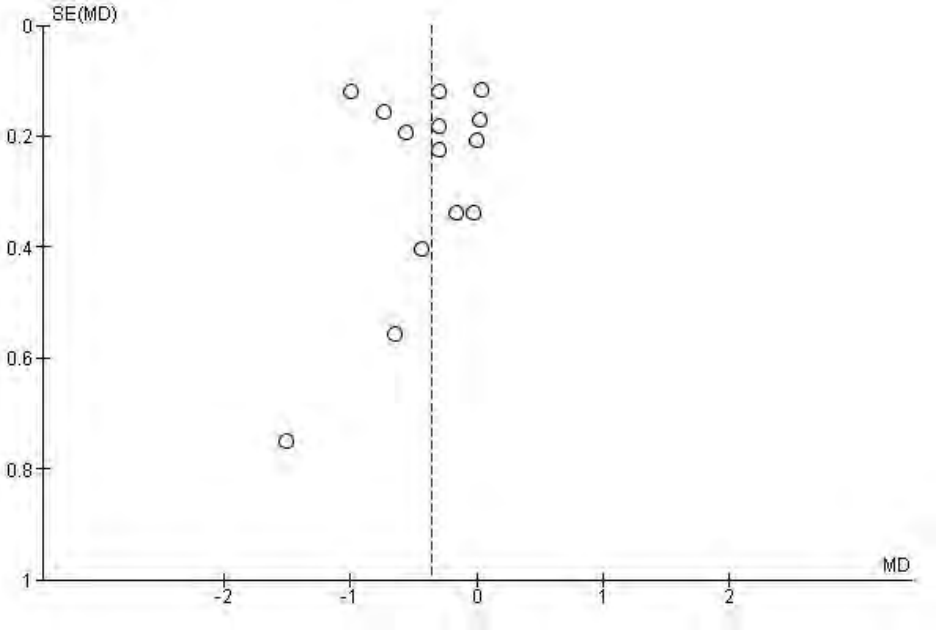
3.2 Forest plot for total sexual arousal

Study or Subgroup	PCOS Mean	PCOS SD	PCOS Total	Controls Mean	Controls SD	Controls Total	Weight	Mean Difference IV, Random, 95% CI
Akbari Sene et al. 2021	3.69	1.23	116	3.67	1.23	93	8.7%	0.02 [-0.32, 0.36]
Ashrafi et al. 2022	3.21	0.75	80	4.2	0.77	80	9.7%	-0.99 [-1.23, -0.75]
Aydogan et al. 2020	4.07	1.31	20	4.09	0.92	30	5.6%	-0.02 [-0.68, 0.64]
Basirat et al. 2019	3.92	0.92	120	3.88	0.91	120	9.7%	0.04 [-0.19, 0.27]
Benetti Pinto et al. 2015	3.9	1.1	56	4.2	1.1	102	8.5%	-0.30 [-0.66, 0.06]
Ercan et al. 2013	5	1	32	5.3	0.8	32	7.6%	-0.30 [-0.74, 0.14]
Gateva et al. 2012	2.6	2.4	16	4.1	2.1	22	1.9%	-1.50 [-2.97, -0.03]
Lara et al. 2015	2.78	1.92	43	3.22	1.98	51	4.7%	-0.44 [-1.23, 0.35]
Mantzou et al. 2021	4.48	1.44	76	5.04	1.19	133	8.3%	-0.56 [-0.94, -0.18]
Naumova et al. 2021	4.95	0.9	37	5.68	0.3	31	9.0%	-0.73 [-1.04, -0.42]
Noroozzadeh et al. 2017	3.9	1.428	63	3.9	1.578	216	8.0%	0.00 [-0.41, 0.41]
Shafti et al. 2016	12.74	3.92	129	13.38	4.873	125	3.1%	-0.64 [-1.73, 0.45]
Stovall et al.2012	10.05	2.01	92	10.21	2.41	82	5.6%	-0.16 [-0.82, 0.50]
Taghavi et al. 2021	4.19	0.79	90	4.49	0.82	90	9.7%	-0.30 [-0.54, -0.06]
Total (95% CI)			**970**			**1207**	**100.0%**	**-0.36 [-0.59, -0.13]**

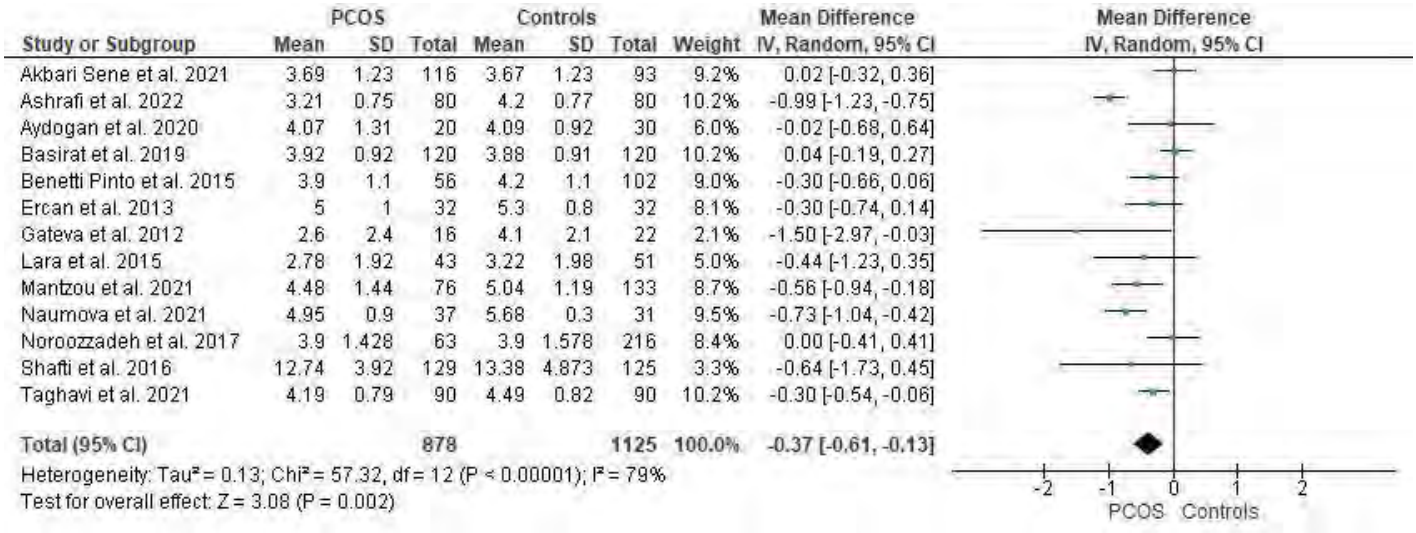
Heterogeneity: Tau² = 0.12; Chi² = 57.73, df = 13 (P < 0.00001); I² = 77%
Test for overall effect: Z = 3.11 (P = 0.002)



3.3 Funnel plot for total sexual arousal



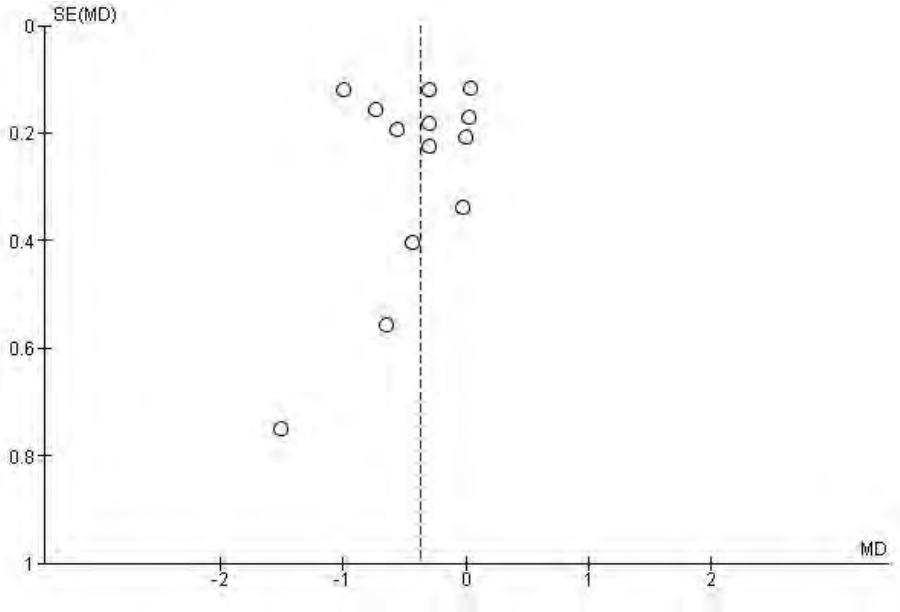
3.4. Sensitivity analysis of only studies using FSFI for total sexual arousal



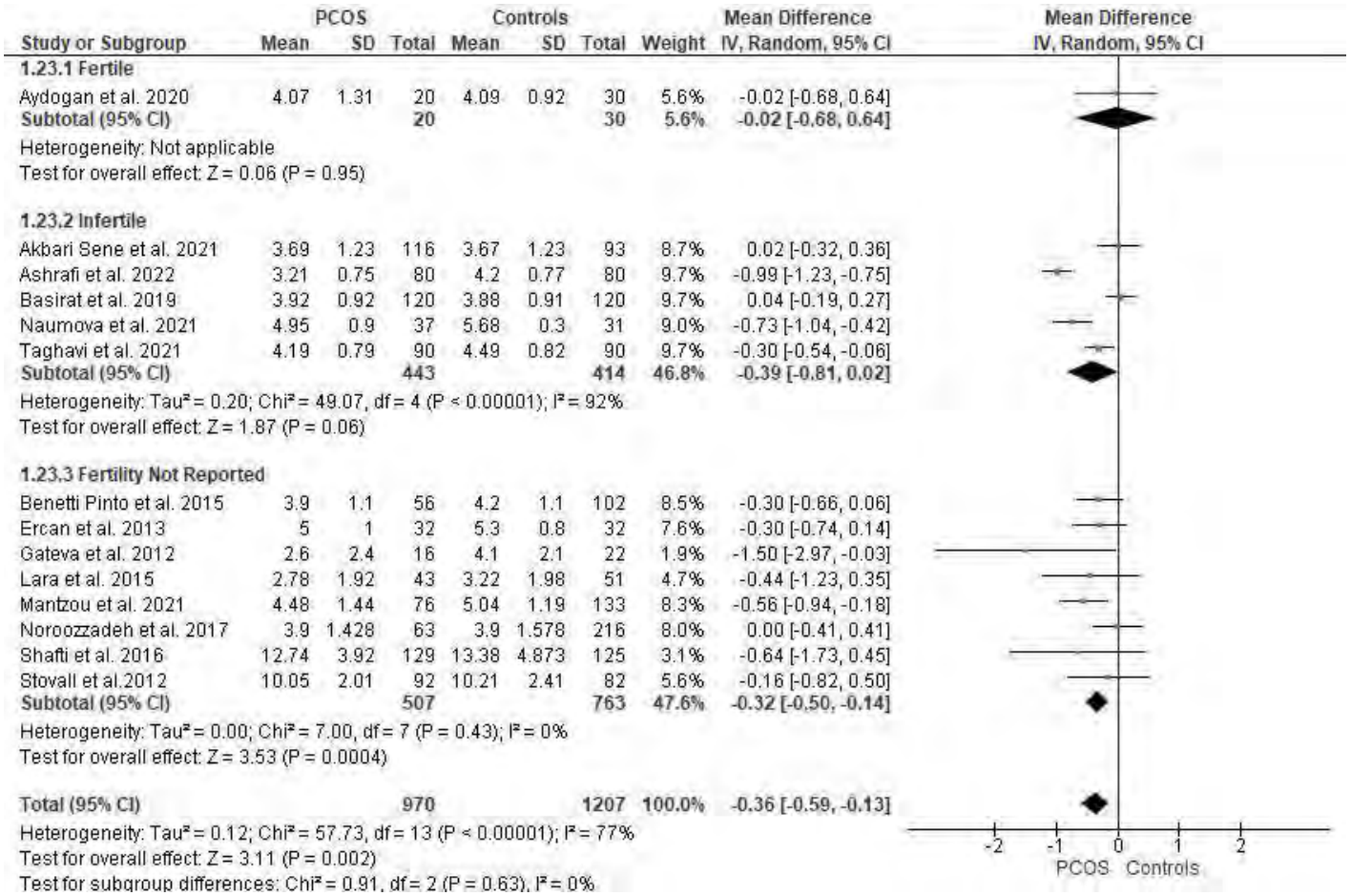
Study or Subgroup	PCOS Mean	PCOS SD	PCOS Total	Controls Mean	Controls SD	Controls Total	Weight	Mean Difference IV, Random, 95% CI
Akbari Sene et al. 2021	3.69	1.23	116	3.67	1.23	93	9.2%	0.02 [-0.32, 0.36]
Ashrafi et al. 2022	3.21	0.75	80	4.2	0.77	80	10.2%	-0.99 [-1.23, -0.75]
Aydogan et al. 2020	4.07	1.31	20	4.09	0.92	30	6.0%	-0.02 [-0.68, 0.64]
Basirat et al. 2019	3.92	0.92	120	3.88	0.91	120	10.2%	0.04 [-0.19, 0.27]
Benetti Pinto et al. 2015	3.9	1.1	56	4.2	1.1	102	9.0%	-0.30 [-0.66, 0.06]
Ercan et al. 2013	5	1	32	5.3	0.8	32	8.1%	-0.30 [-0.74, 0.14]
Gateva et al. 2012	2.6	2.4	16	4.1	2.1	22	2.1%	-1.50 [-2.97, -0.03]
Lara et al. 2015	2.78	1.92	43	3.22	1.98	51	5.0%	-0.44 [-1.23, 0.35]
Mantzou et al. 2021	4.48	1.44	76	5.04	1.19	133	8.7%	-0.56 [-0.94, -0.18]
Naumova et al. 2021	4.95	0.9	37	5.68	0.3	31	9.5%	-0.73 [-1.04, -0.42]
Noroozzadeh et al. 2017	3.9	1.428	63	3.9	1.578	216	8.4%	0.00 [-0.41, 0.41]
Shafti et al. 2016	12.74	3.92	129	13.38	4.873	125	3.3%	-0.64 [-1.73, 0.45]
Taghavi et al. 2021	4.19	0.79	90	4.49	0.82	90	10.2%	-0.30 [-0.54, -0.06]
Total (95% CI)			**878**			**1125**	**100.0%**	**-0.37 [-0.61, -0.13]**

Heterogeneity: Tau² = 0.13; Chi² = 57.32, df = 12 (P < 0.00001); I² = 79%
Test for overall effect: Z = 3.08 (P = 0.002)

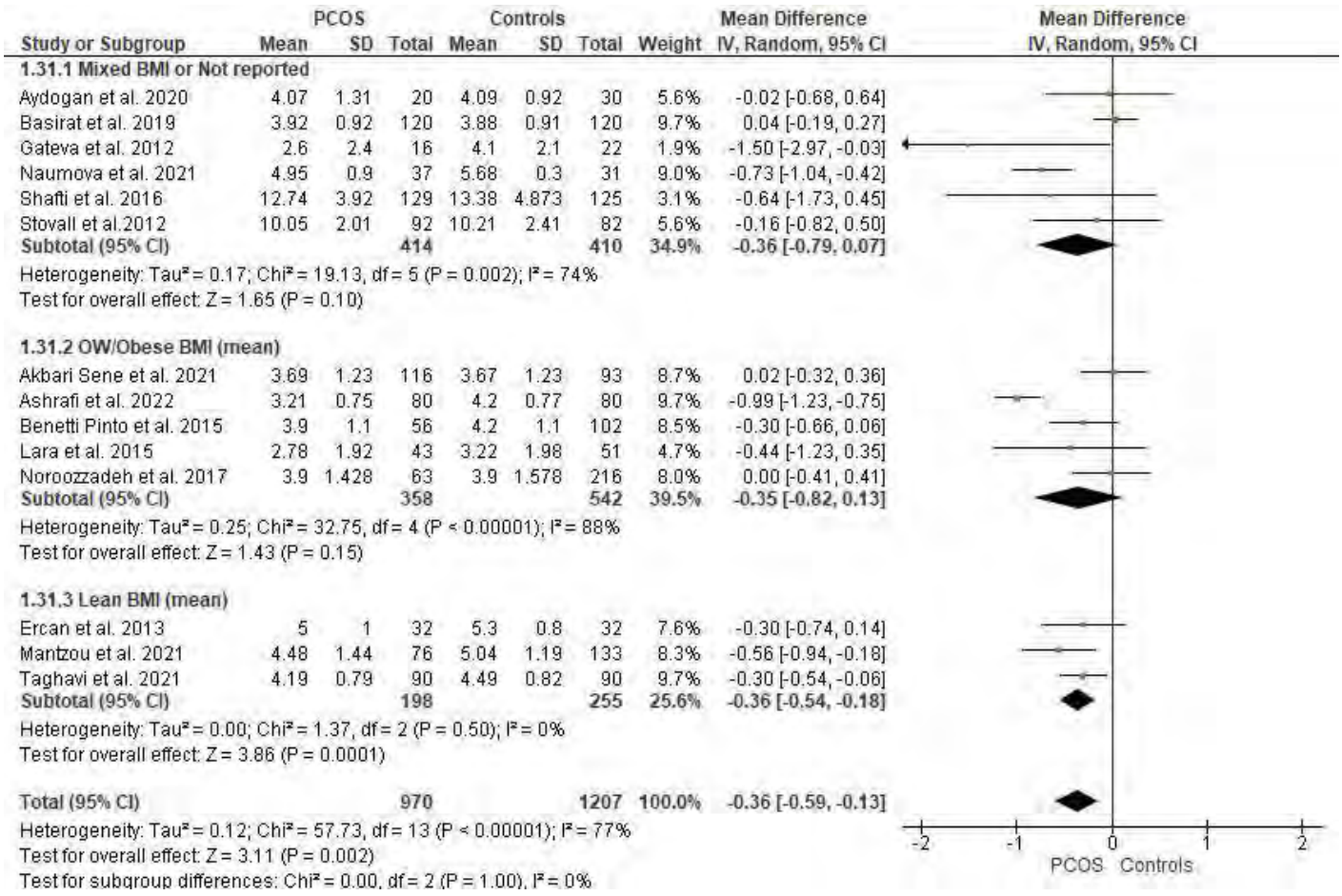
3.5. Funnel plot for sensitivity analysis



3.6. Subgroup Analysis by Fertility Status for sexual arousal



3.7. Subgroup analysis by BMI status (mean BMI) for sexual arousal



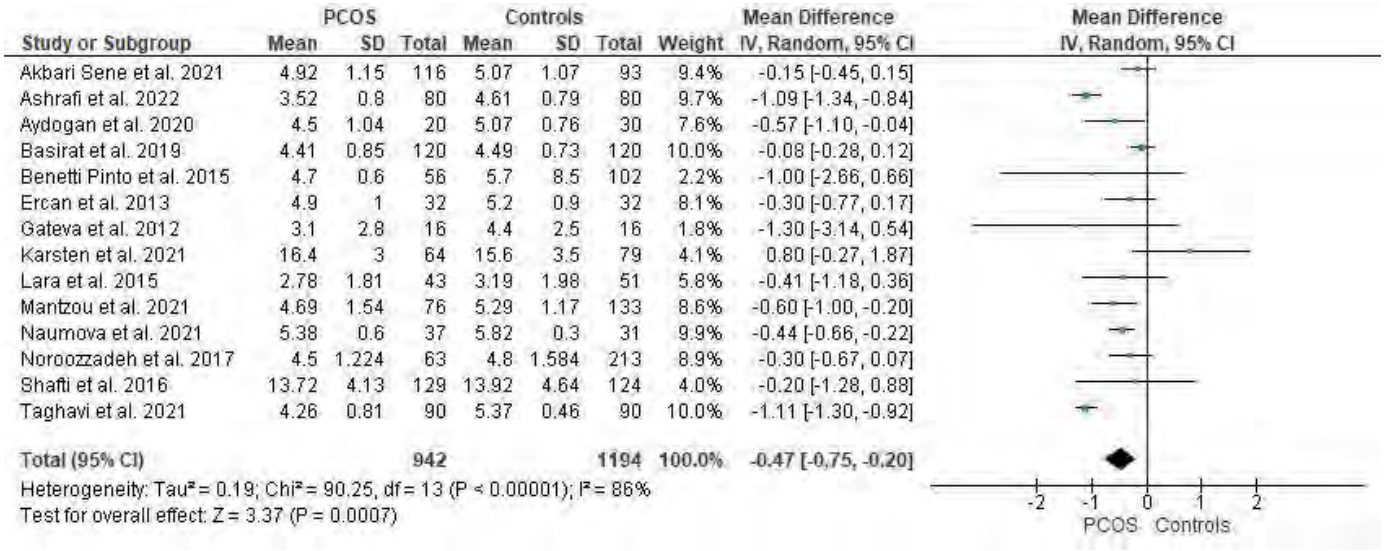
OUTCOME 4. Lubrication

4.1 Individual Study Data Tables

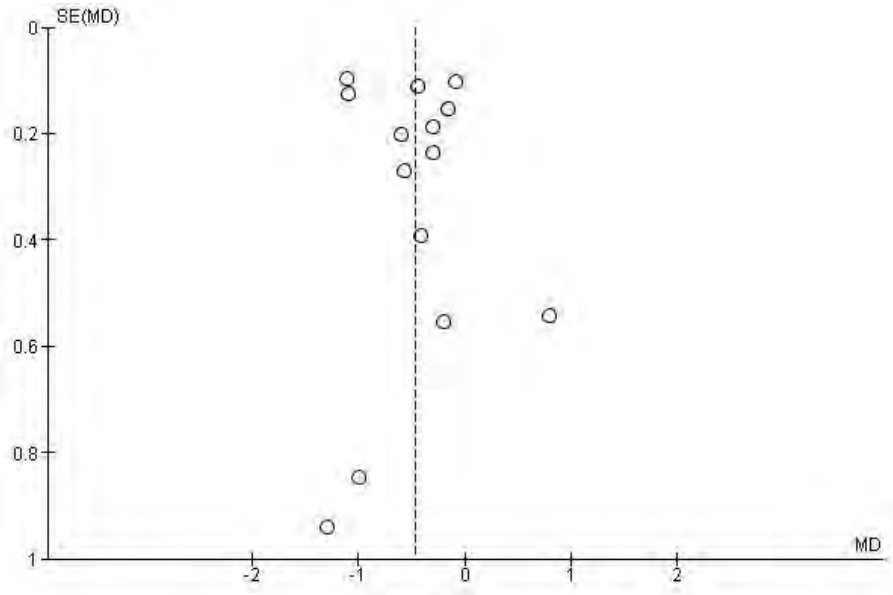
OUTCOME: Lubrication						OUTCOME TYPE: Continuous				
Comparison: Women with PCOS vs control										
Author, year	Unit	Method of measurement	Mean in PCOS group	SD in PCOS group	Sample size in PCOS	Mean in control group	SD in control group	Sample size in control group	Are these values adjusted or crude?	What variables are adjusted for?
Akbari Sene et al. 2021	Natural number	FSFI	4.92	1.15	116	5.07	1.07	93	Crude	NA
Ashrafi et al. 2022	Natural number	FSFI	3.52	0.80	80	4.61	0.79	80	Crude	NA
Aydogan et al. 2020	Natural number	FSFI	4.5	1.04	20	5.07	0.76	30	Crude	NA
Basirat et al. 2019	Natural number	FSFI	4.41	0.85	120	4.49	0.73	120	Crude	NA
Benetti Pinto et al. 2015	Natural number	FSFI	4.7	0.6	56	5.7	8.5	102	Crude	NA
Ercan et al. 2013	Natural number	FSFI	4.9	1	32	5.2	0.9	32	Crude	NA
Gateva et al. 2012	Natural number	FSFI	3.1	2.8	16	4.4	2.5	16	Crude	NA
Karsten et al. 2021	Natural number	Mc Coy	16.4	3	64	15.6	3.5	79	Crude	NA
Lara et al. 2015	Natural number	FSFI	2.78	1.81	43	3.19	1.98	51	Crude	NA
Mantzou et al. 2021	Natural number	FSFI	4.69	1.54	76	5.29	1.17	133	Crude	NA
Naumova et al. 2021	Natural number	FSFI	5.38	0.6	37	5.82	0.3	31	Crude	NA
Noroozzadeh et al. 2017	Natural number	FSFI	4.5	1.224	63	4.8	1.584	213	Crude	NA
Shafti et al. 2016	Natural number	FSFI	13.72	4.13	129	13.92	4.64	124	Crude	NA
Taghavi etal. 2021	Natural number	FSFI	4.26	0.81	90	5.37	0.46	90	Crude	NA

CSFQ: Changes in Sexual Function Questionnaire, FSDQ: Female Sexual Desire Questionnaire, FSFI: Female Sexual Function Index, ISS: Index of Sexual Satisfaction, MFSQ: Mc Coy Female Sexuality Questionnaire, MSQ: Multidimensional Sexuality Questionnaire, SQ-F: Sexual Quotient Female, VAS: Visual analogue scale.

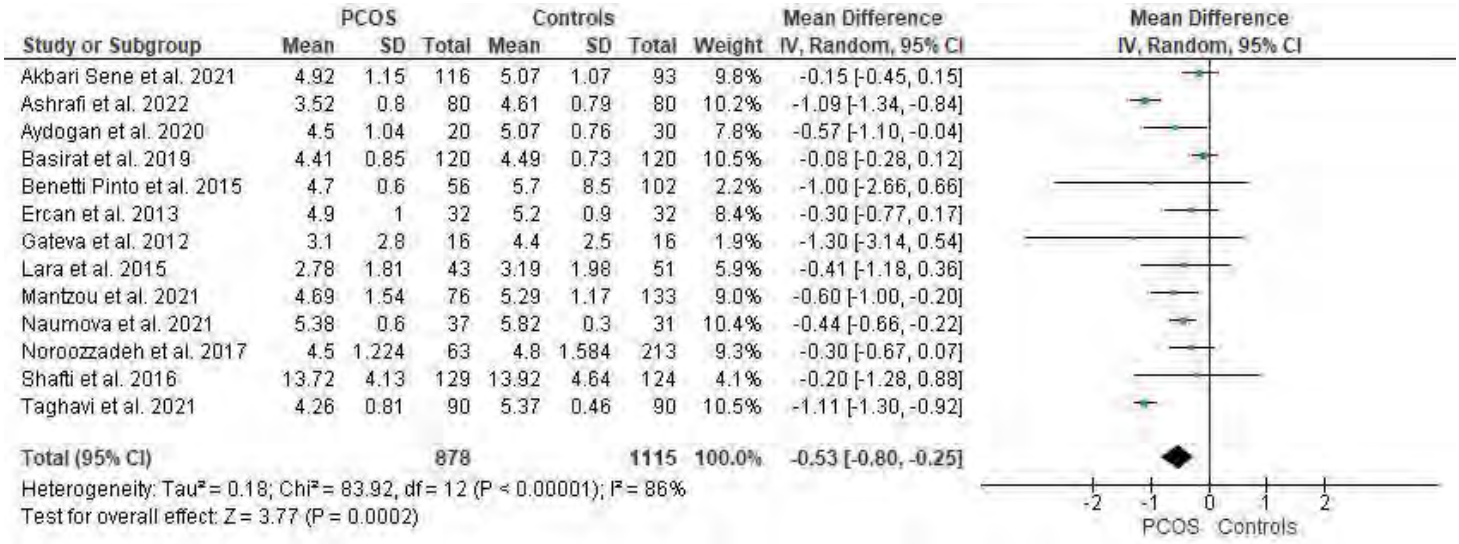
4.2 Forest plot for lubrication



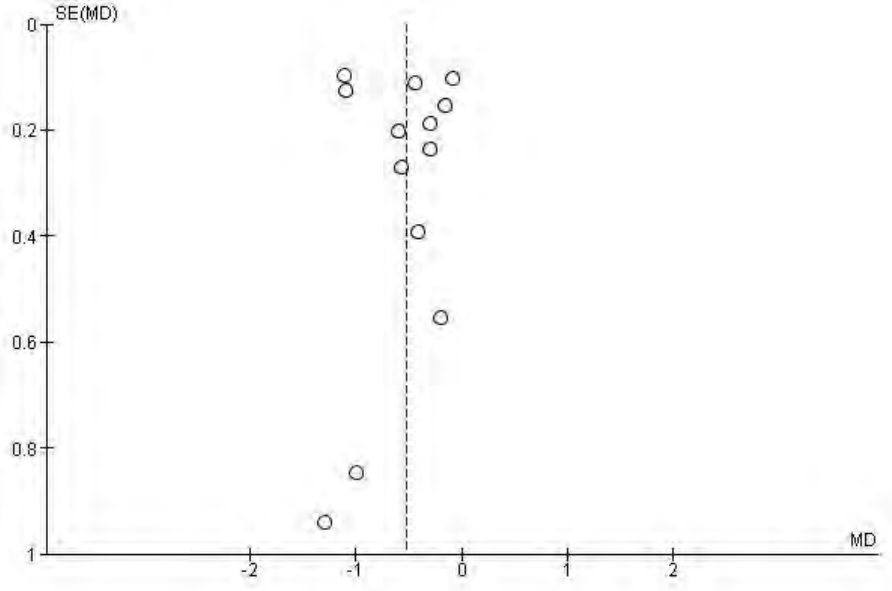
4.3 Funnel plot for lubrication



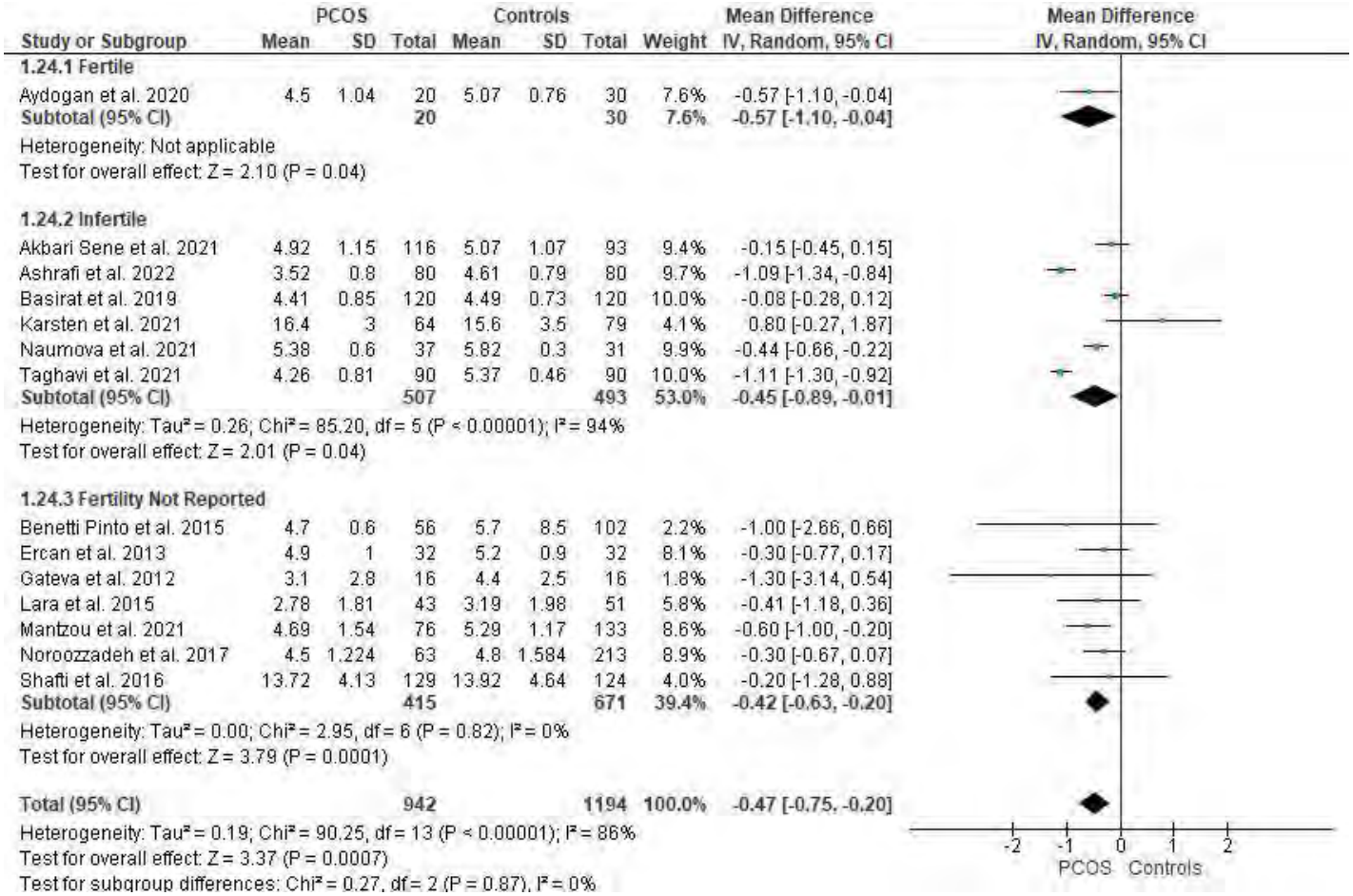
4.4. Sensitivity analysis of only studies using FSFI for lubrication



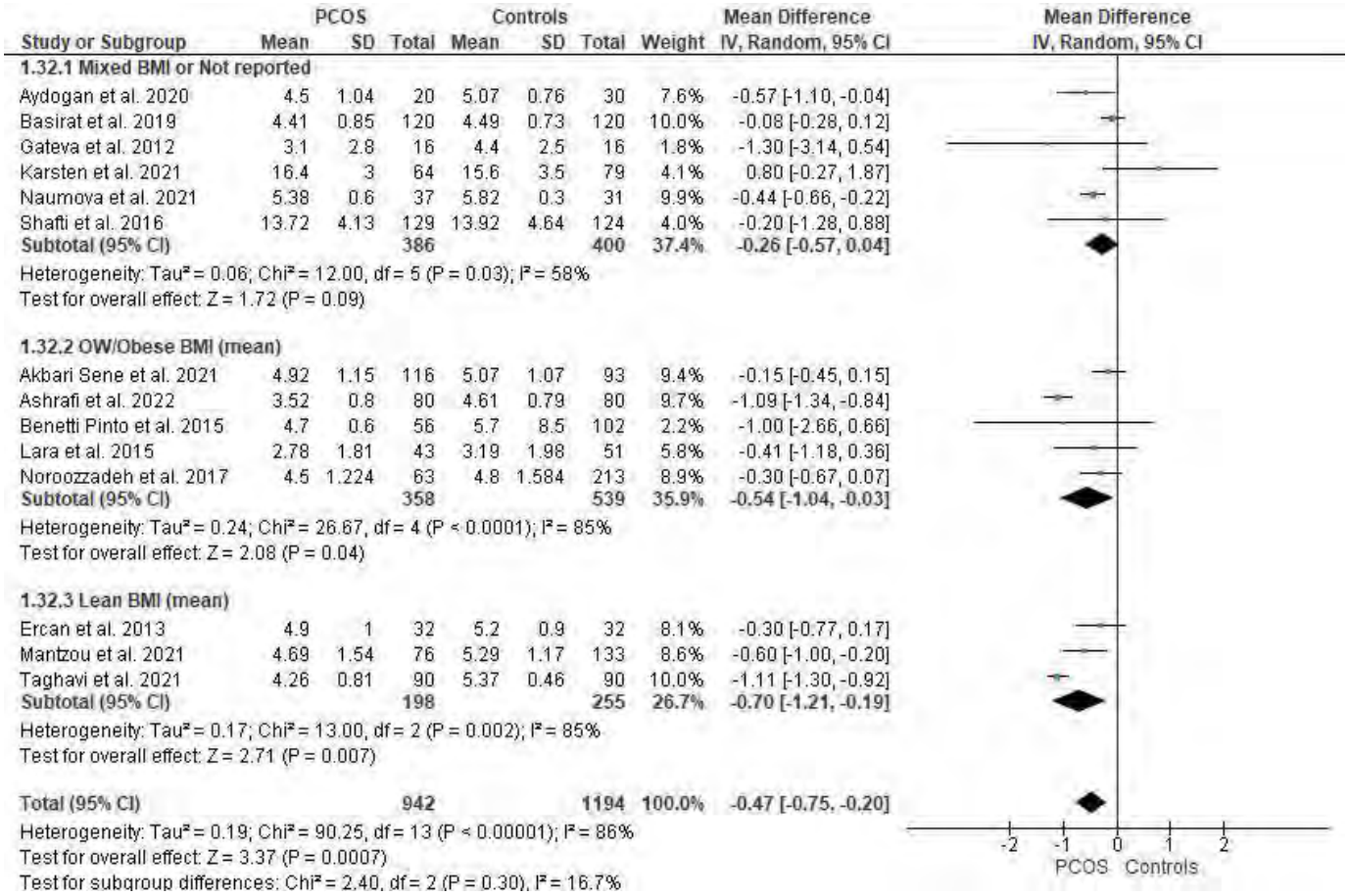
4.5. Funnel plot for sensitivity analysis



4.6. Subgroup Analysis by Fertility Status for lubrication



4.7. Subgroup analysis by BMI status (mean BMI) for lubrication



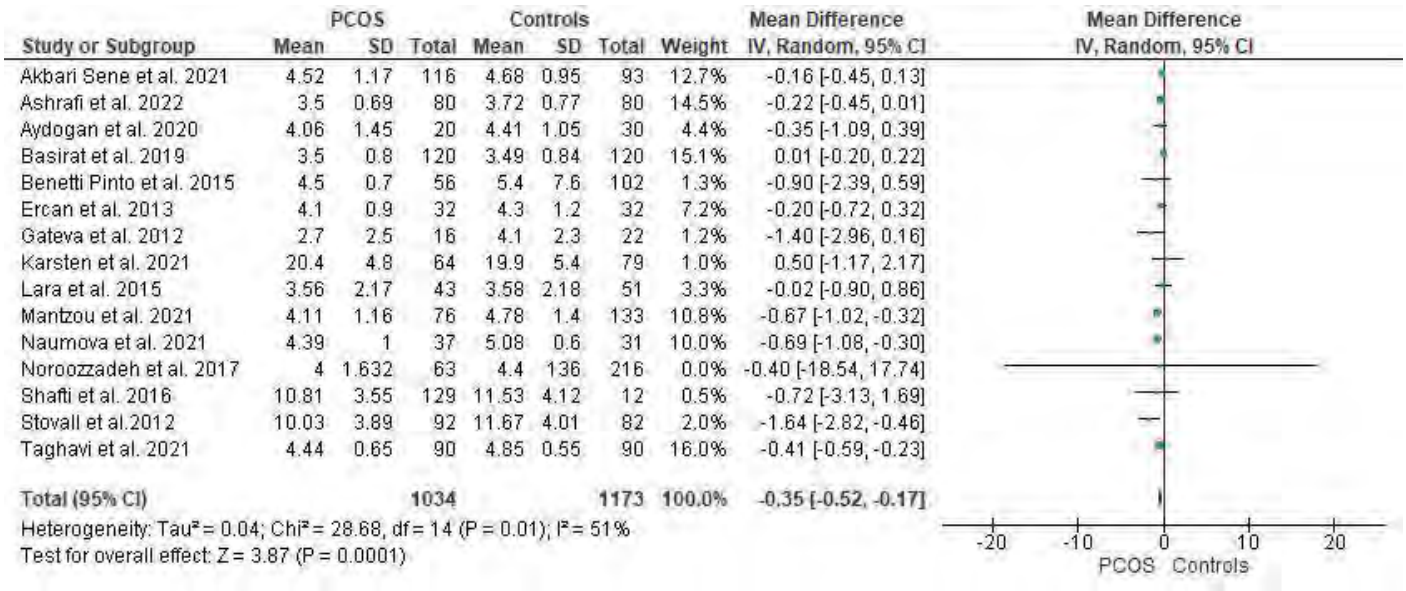
OUTCOME 5. Orgasm

5.1 Individual Study Data Tables

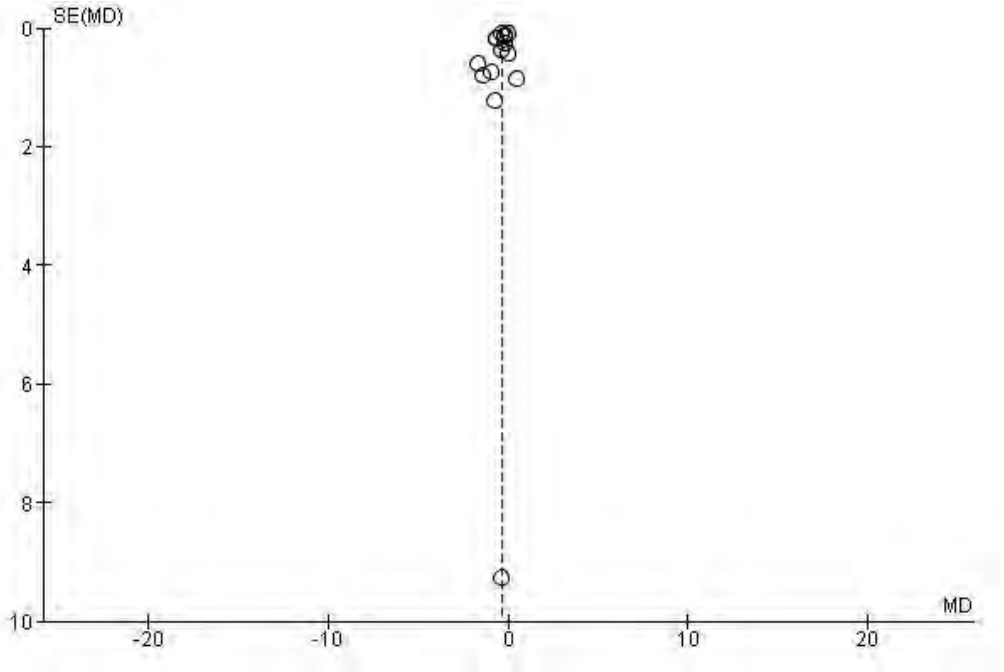
OUTCOME: Orgasm						OUTCOME TYPE: Continuous				
Comparison: Women with PCOS vs control										
Author, year	Unit	Method of measurement	Mean in PCOS group	SD in PCOS group	Sample size in PCOS	Mean in control group	SD in control group	Sample size in control group	Are these values adjusted or crude?	What variables are adjusted for?
Akbari Sene et al. 2021	Natural number	FSFI	4.52	1.17	116	4.68	0.95	93	Crude	NA
Ashrafi et al. 2022	Natural number	FSFI	3.5	0.69	80	3.72	0.77	80	Crude	NA
Aydogan et al. 2020	Natural number	FSFI	4.06	1.45	20	4.41	1.05	30	Crude	NA
Basirat et al. 2019	Natural number	FSFI	3.5	0.8	120	3.49	0.84	120	Crude	NA
Benetti Pinto et al. 2015	Natural number	FSFI	4.5	0.7	56	5.4	7.6	102	Crude	NA
Ercan et al. 2013	Natural number	FSFI	4.1	0.9	32	4.3	1.2	32	Crude	NA
Gateva et al. 2012	Natural number	FSFI	2.7	2.5	16	4.1	2.3	22	Crude	NA
Karsten et al. 2021	Natural number	Mc Coy	20.4	4.8	64	19.9	5.4	79	Crude	NA
Lara et al. 2015	Natural number	FSFI	3.56	2.17	43	3.58	2.18	51	Crude	NA
Mantzou et al. 2021	Natural number	FSFI	4.11	1.16	76	4.78	1.4	133	Crude	NA
Naumova et al. 2021	Natural number	FSFI	4.39	1	37	5.08	0.6	31	Crude	NA
Noroozzadeh et al. 2017	Natural number	FSFI	4	1.632	63	4.4	136	216	Crude	NA
Shafti et al. 2016	Natural number	FSFI	10.81	3.55	129	11.53	4.12	12	Crude	NA
Stovall et al.2012	Natural number	CSFQ	10.03	3.89	92	11.67	4.01	82	Crude	NA
Taghavi etal. 2021	Natural number	FSFI	4.44	0.65	90	4.85	0.55	90	Crude	NA

CSFQ: Changes in Sexual Function Questionnaire, FSDQ: Female Sexual Desire Questionnaire, FSFI: Female Sexual Function Index, ISS: Index of Sexual Satisfaction, MFSQ: Mc Coy Female Sexuality Questionnaire, MSQ: Multidimensional Sexuality Questionnaire, SQ-F: Sexual Quotient Female, VAS: Visual analogue scale.

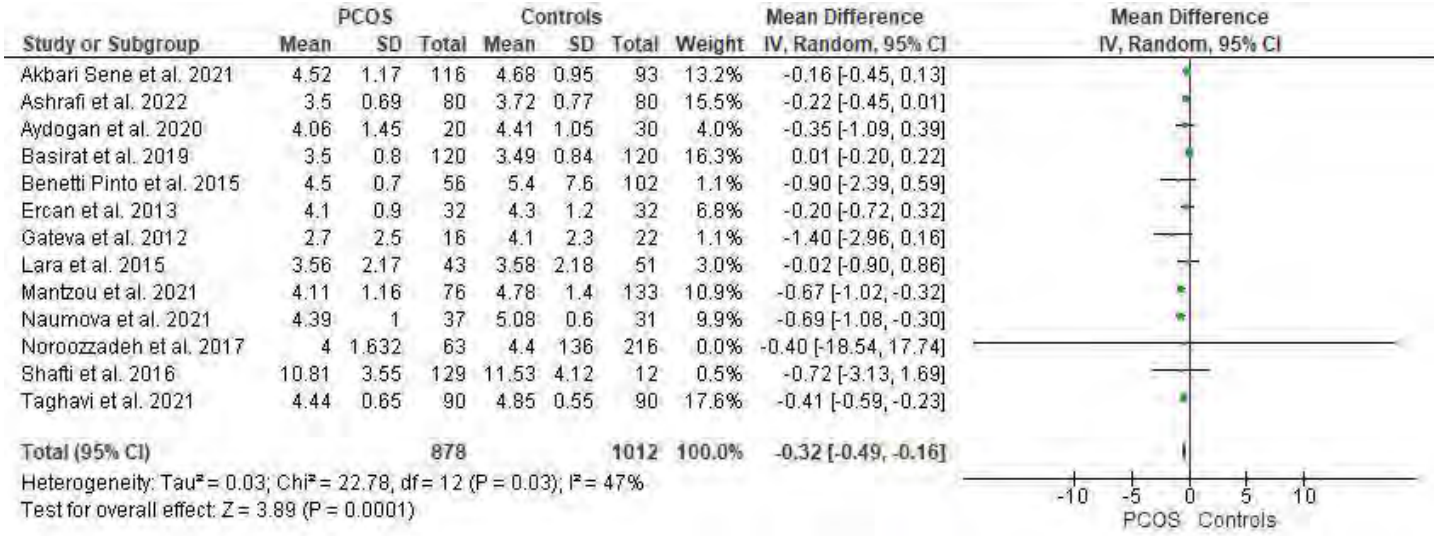
5.2 Forest plot for orgasm



5.3 Funnel plot for orgasm



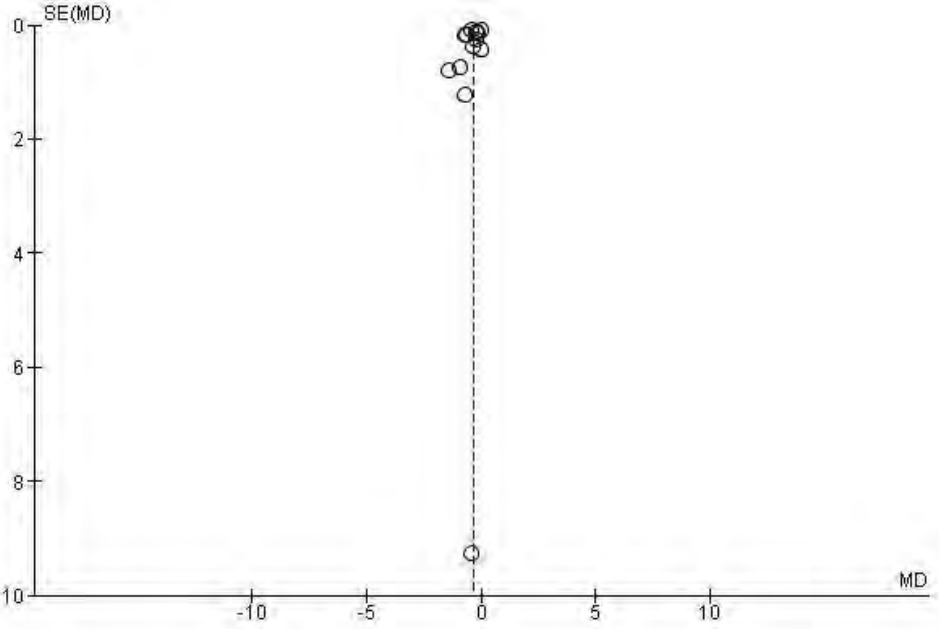
5.4. Sensitivity analysis of only studies using FSFI for orgasm



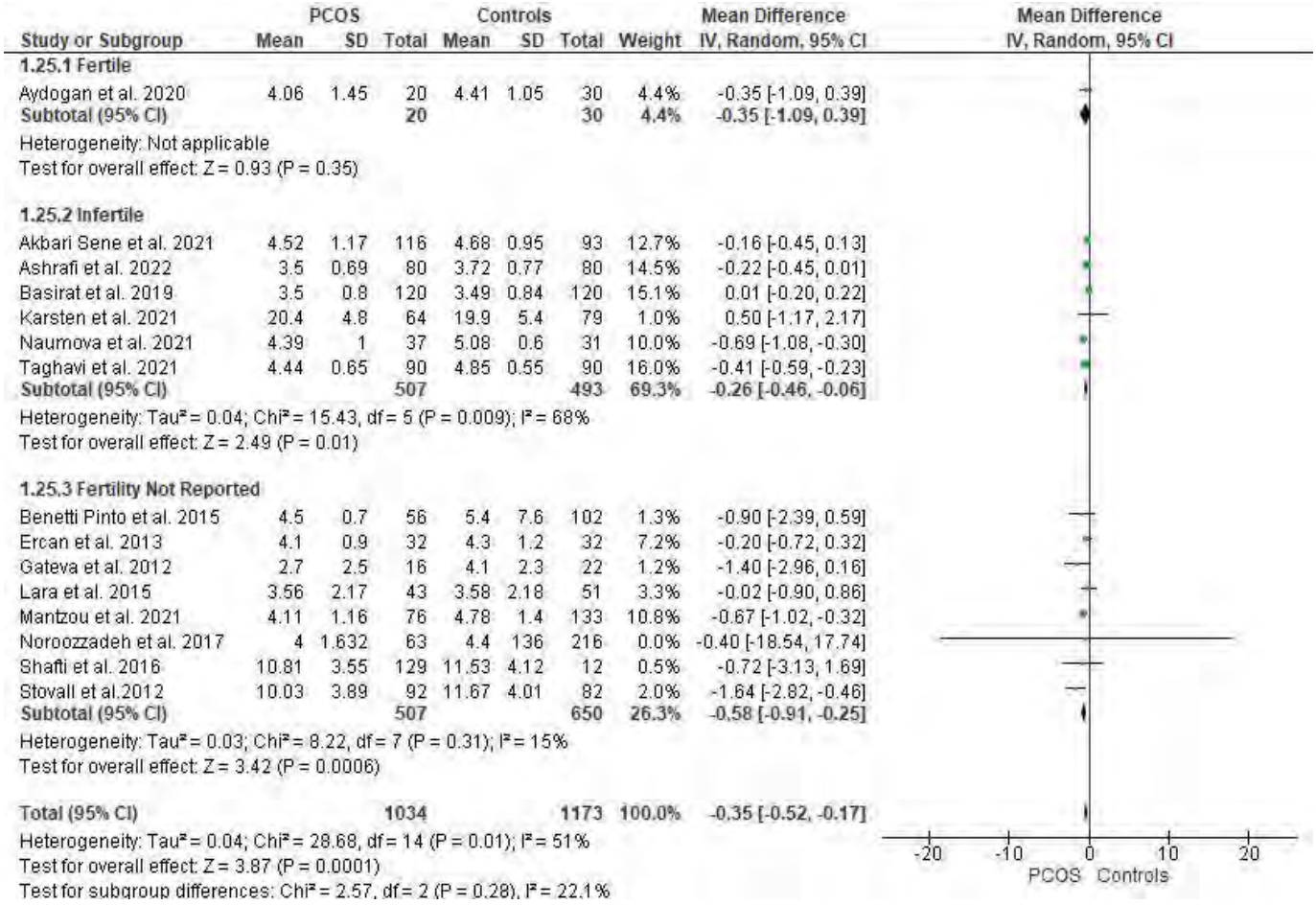
Study or Subgroup	PCOS Mean	PCOS SD	PCOS Total	Controls Mean	Controls SD	Controls Total	Weight	Mean Difference IV, Random, 95% CI
Akbari Sene et al. 2021	4.52	1.17	116	4.68	0.95	93	13.2%	-0.16 [-0.45, 0.13]
Ashrafi et al. 2022	3.5	0.69	80	3.72	0.77	80	15.5%	-0.22 [-0.45, 0.01]
Aydogan et al. 2020	4.06	1.45	20	4.41	1.05	30	4.0%	-0.35 [-1.09, 0.39]
Basirat et al. 2019	3.5	0.8	120	3.49	0.84	120	16.3%	0.01 [-0.20, 0.22]
Benetti Pinto et al. 2015	4.5	0.7	56	5.4	7.6	102	1.1%	-0.90 [-2.39, 0.59]
Ercan et al. 2013	4.1	0.9	32	4.3	1.2	32	6.8%	-0.20 [-0.72, 0.32]
Gateva et al. 2012	2.7	2.5	16	4.1	2.3	22	1.1%	-1.40 [-2.96, 0.16]
Lara et al. 2015	3.56	2.17	43	3.58	2.18	51	3.0%	-0.02 [-0.90, 0.86]
Mantzou et al. 2021	4.11	1.16	76	4.78	1.4	133	10.9%	-0.67 [-1.02, -0.32]
Naumova et al. 2021	4.39	1	37	5.08	0.6	31	9.9%	-0.69 [-1.08, -0.30]
Noroozzadeh et al. 2017	4	1.632	63	4.4	136	216	0.0%	-0.40 [-18.54, 17.74]
Shafti et al. 2016	10.81	3.55	129	11.53	4.12	12	0.5%	-0.72 [-3.13, 1.69]
Taghavi et al. 2021	4.44	0.65	90	4.85	0.55	90	17.6%	-0.41 [-0.59, -0.23]
Total (95% CI)			**878**			**1012**	**100.0%**	**-0.32 [-0.49, -0.16]**

Heterogeneity: Tau² = 0.03; Chi² = 22.78, df = 12 (P = 0.03); I² = 47%
Test for overall effect: Z = 3.89 (P = 0.0001)

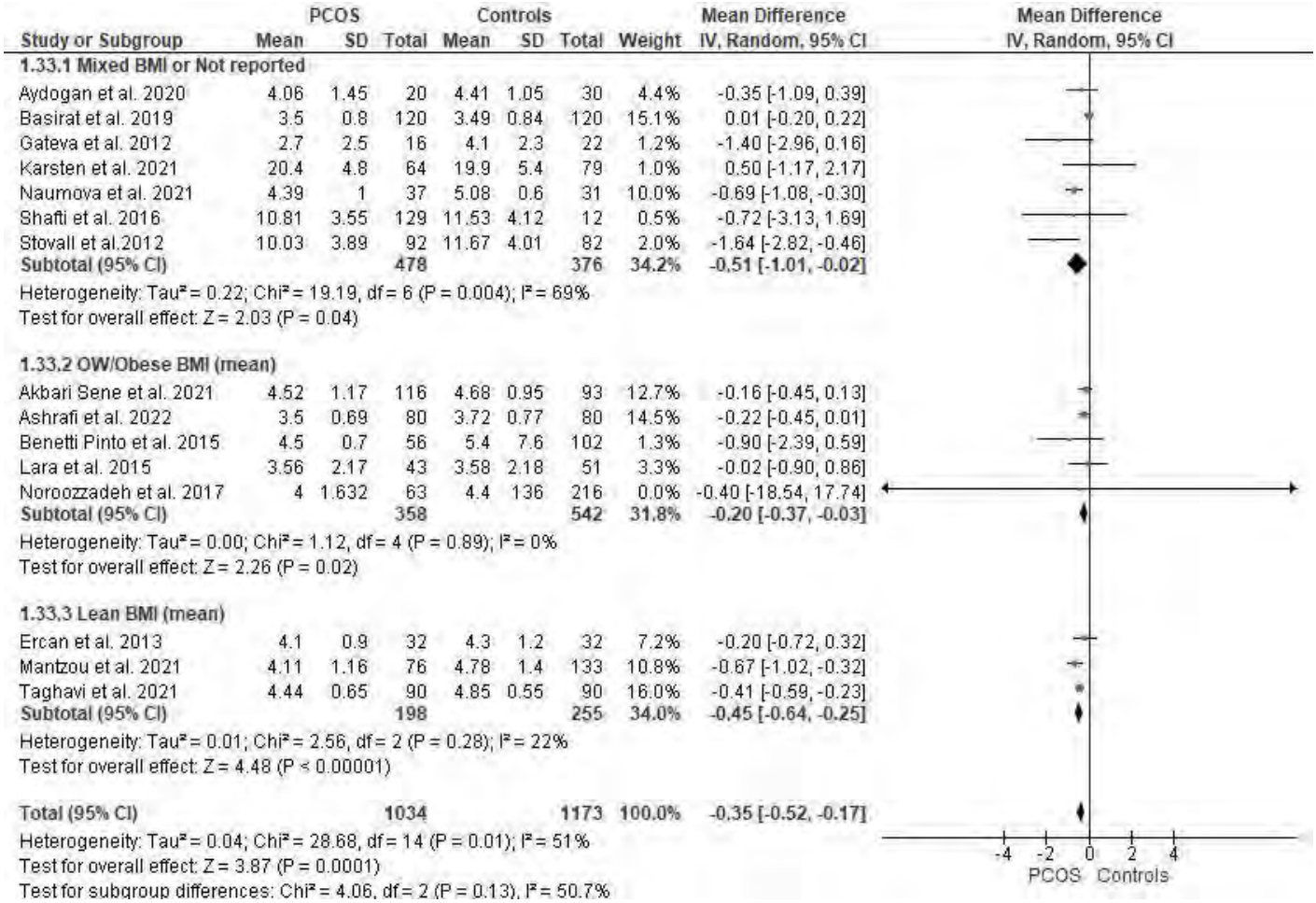
5.5. Funnel plot for sensitivity analysis



5.6. Subgroup Analysis by Fertility Status for orgasm



5.7. Subgroup analysis by BMI status (mean BMI) for orgasm



OUTCOME 6. Satisfaction

6.1 Individual Study Data Tables

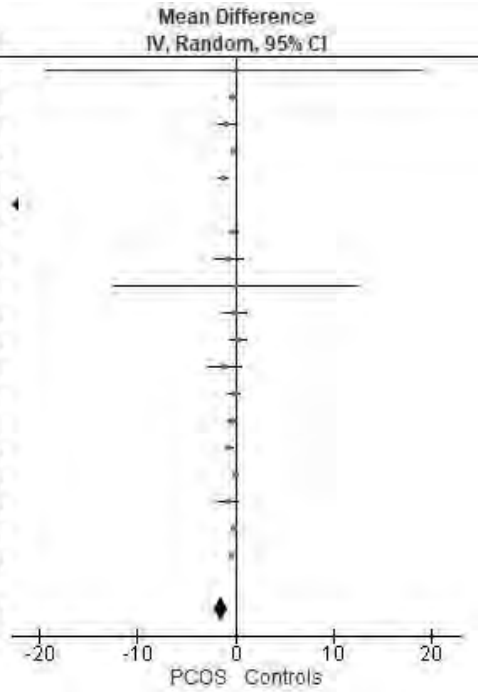
OUTCOME: Satisfaction						OUTCOME TYPE: Continuous				
Comparison: Women with PCOS vs control										
Author, year	**Unit**	**Method of measurement**	**Mean in PCOS group**	**SD in PCOS group**	**Sample size in PCOS**	**Mean in control group**	**SD in control group**	**Sample size in control group**	**Are these values adjusted or crude?**	**What variables are adjusted for?**
Akbari Sene et al. 2021	Natural number	FSFI	5.06	1	116	5.11	095	93	Crude	NA
Ashrafi et al. 2022	Natural number	FSFI	4.16	0.95	80	4.54	0.79	80	Crude	NA
Aydogan et al. 2020	Natural number	FSFI	4.1	1.91	20	4.93	1.5	30	Crude	NA
Basirat et al. 2019	Natural number	FSFI	4.78	1.19	120	4.92	1.05	120	Crude	NA
Benetti Pinto et al. 2015	Natural number	FSFI	2.8	1.2	56	4.1	1.6	102	Crude	NA
Drodszol et al. 2007	Natural number	ISS	20.7	18.5	50	111.2	10.4	40	Crude	NA
Ercan et al. 2013	Natural number	FSFI	4.2	0.9	32	4.4	1	32	Crude	NA
Gateva et al. 2012	Natural number	FSFI	3.4	2.3	16	4.1	2.3	22	Crude	NA
Glowinska et al. 2020	Natural number	Sexual Satisfactionn Scales	38.6	8.81	2	38.6	8.23	47	Crude	NA
Kaluzna et al. 2021	Natural number	Sexual Satisfaction Questionnaire	31.43	6.24	190	31.48	6.22	197	Crude	NA
Karsten et al. 2021	Natural number	Mc Coy	11.2	2.5	70	10.9	3	97	Crude	NA
Kowalczyk et al. 2015	Natural number	MSQ	16.9	4.6	73	18	4.6	45	Crude	NA
Lara et al. 2015	Natural number	FSFI	4	1.39	43	4.12	1.48	51	Crude	NA
Mantzou et al. 2021	Natural number	FSFI	4.78	1.31	76	5.22	1.1	133	Crude	NA
Naumova et al. 2021	Natural number	FSFI	4.75	0.9	37	5.42	0.5	37	Crude	NA
Noroozzadeh et al. 2017	Natural number	FSFI	4.8	1.088	63	4.8	1.36	216	Crude	NA
Shafti et al. 2016	Natural number	FSFI	11.4	3.75	129	12.19	4.18	125	Crude	NA
Stovall et al.2012	Natural number	CSFQ	3.23	0.81	92	3.35	1.01	82	Crude	NA
Taghavi etal. 2021	Natural number	FSFI	5.46	0.59	90	5.8	0.35	90	Crude	NA

CSFQ: Changes in Sexual Function Questionnaire, FSDQ: Female Sexual Desire Questionnaire, FSFI: Female Sexual Function Index, ISS: Index of Sexual Satisfaction, MFSQ: Mc Coy Female Sexuality Questionnaire, MSQ: Multidimensional Sexuality Questionnaire, SQ-F: Sexual Quotient Female, VAS: Visual analogue scale.

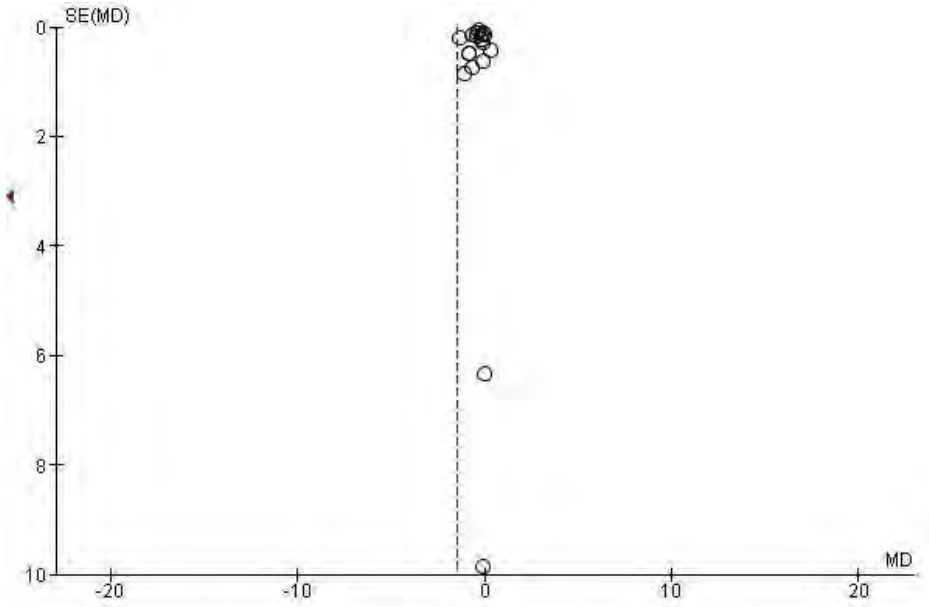
6.2 Forest plot for total satisfaction

Study or Subgroup	PCOS Mean	PCOS SD	PCOS Total	Controls Mean	Controls SD	Controls Total	Weight	Mean Difference IV, Random, 95% CI
Akbari Sene et al. 2021	5.06	1	116	5.11	95	93	0.1%	-0.05 [-19.36, 19.26]
Ashrafi et al. 2022	4.16	0.95	80	4.54	0.79	80	6.5%	-0.38 [-0.65, -0.11]
Aydogan et al. 2020	4.1	1.91	20	4.93	1.5	30	5.9%	-0.83 [-1.82, 0.16]
Basirat et al. 2019	4.78	1.19	120	4.92	1.05	120	6.5%	-0.14 [-0.42, 0.14]
Benetti Pinto et al. 2015	2.8	1.2	56	4.1	1.6	102	6.4%	-1.30 [-1.74, -0.86]
Drodszol et al. 2007	20.7	18.5	50	111.2	10.4	40	1.2%	-90.50 [-96.56, -84.44]
Ercan et al. 2013	4.2	0.9	32	4.4	1	32	6.4%	-0.20 [-0.67, 0.27]
Gateva et al. 2012	3.4	2.3	16	4.1	2.3	22	5.2%	-0.70 [-2.18, 0.78]
Glowinska et al. 2020	38.6	8.81	2	38.6	8.23	47	0.3%	0.00 [-12.43, 12.43]
Kaluzna et al. 2021	31.43	6.24	190	31.48	6.22	197	5.5%	-0.05 [-1.29, 1.19]
Karsten et al. 2021	11.2	2.5	70	10.9	3	97	6.1%	0.30 [-0.54, 1.14]
Kowalczyk et al. 2015	16.9	4.6	73	18	4.6	45	4.8%	-1.10 [-2.81, 0.61]
Lara et al. 2015	4	1.39	43	4.12	1.48	51	6.3%	-0.12 [-0.70, 0.46]
Mantzou et al. 2021	4.78	1.31	76	5.22	1.1	133	6.5%	-0.44 [-0.79, -0.09]
Naumova et al. 2021	4.75	0.9	37	5.42	0.5	37	6.5%	-0.67 [-1.00, -0.34]
Noroozzadeh et al. 2017	4.8	1.088	63	4.8	1.36	216	6.5%	0.00 [-0.32, 0.32]
Shafti et al. 2016	11.4	3.75	129	12.19	4.18	125	5.9%	-0.79 [-1.77, 0.19]
Stovall et al.2012	3.23	0.81	92	3.35	1.01	82	6.5%	-0.12 [-0.39, 0.15]
Taghavi et al. 2021	5.46	0.59	90	5.8	0.35	90	6.6%	-0.34 [-0.48, -0.20]
Total (95% CI)			**1355**			**1639**	**100.0%**	**-1.48 [-2.21, -0.75]**

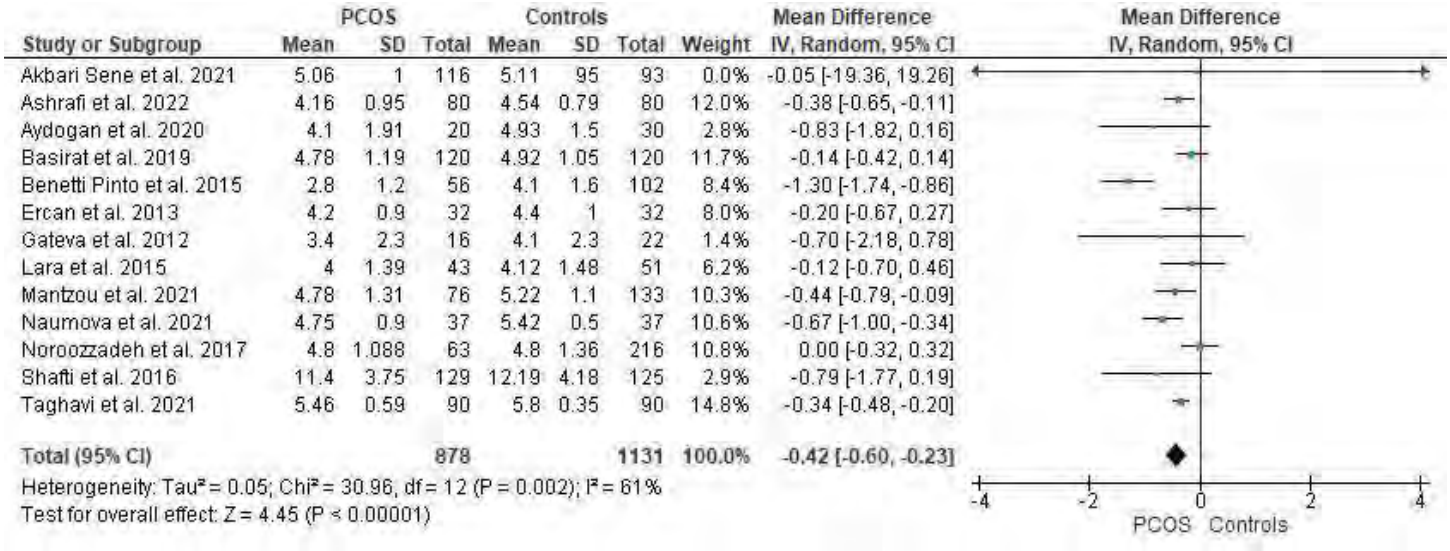
Heterogeneity: Tau² = 2.08; Chi² = 888.19, df = 18 (P < 0.00001); I² = 98%
Test for overall effect: Z = 3.99 (P < 0.0001)



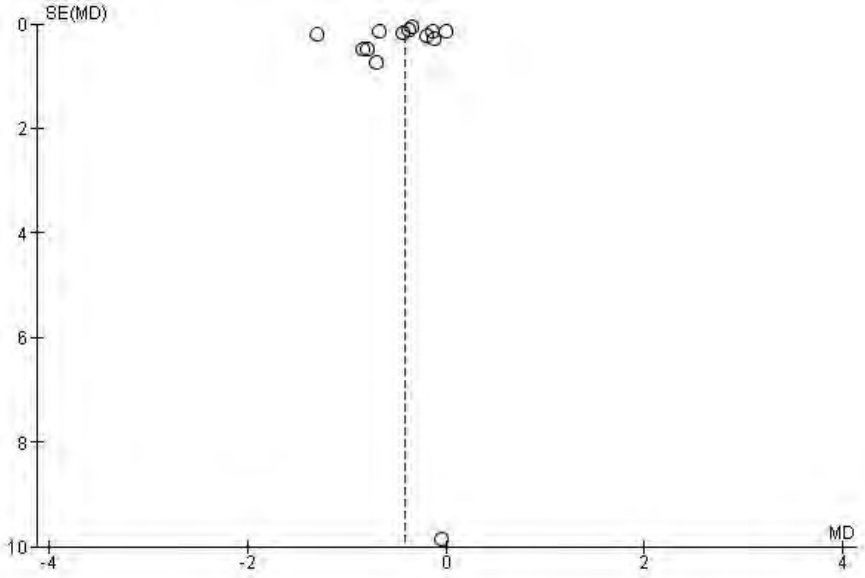
6.3 Funnel plot for total satisfaction



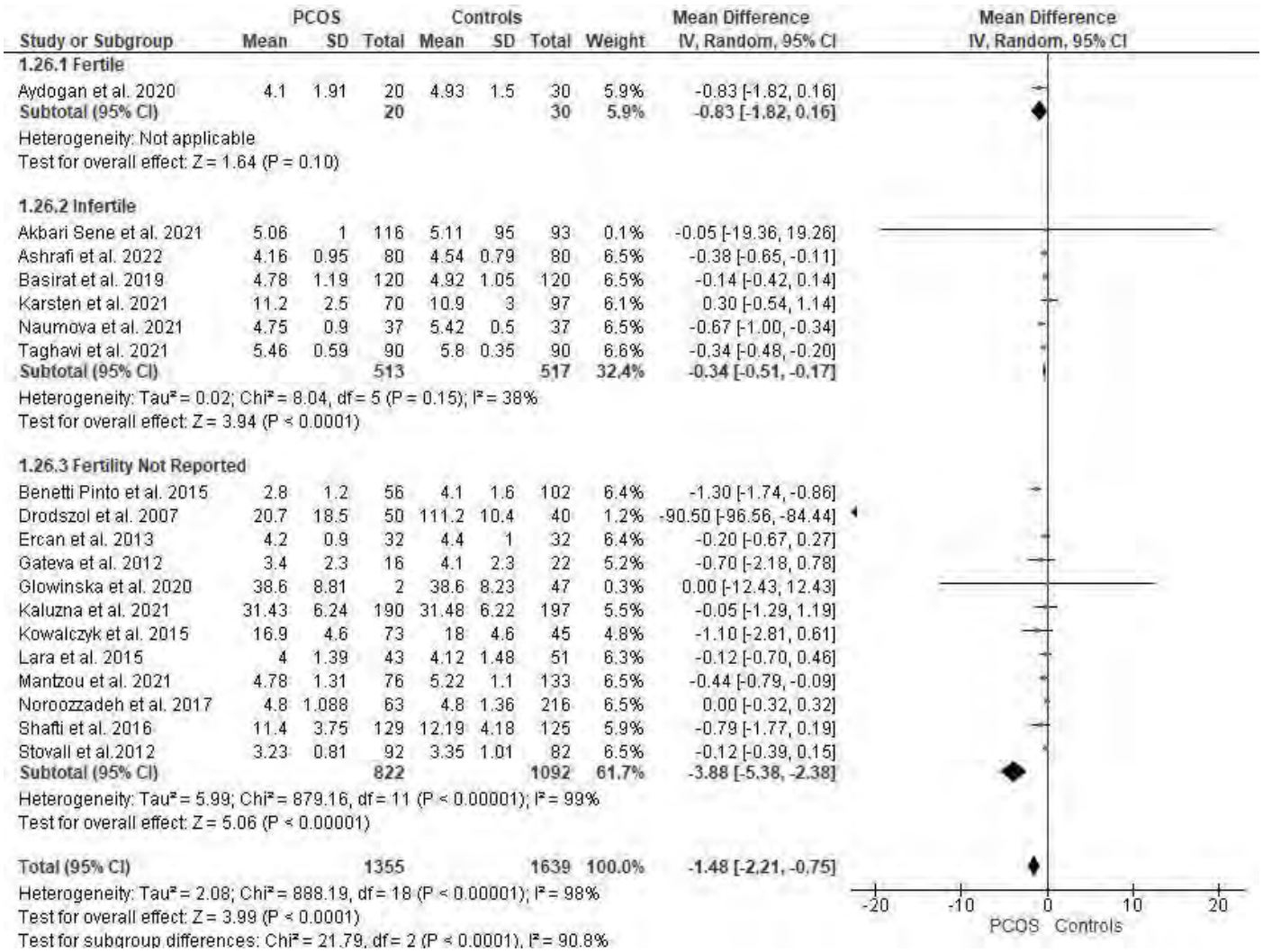
6.4. Sensitivity analysis of only studies using FSFI for total satisfaction



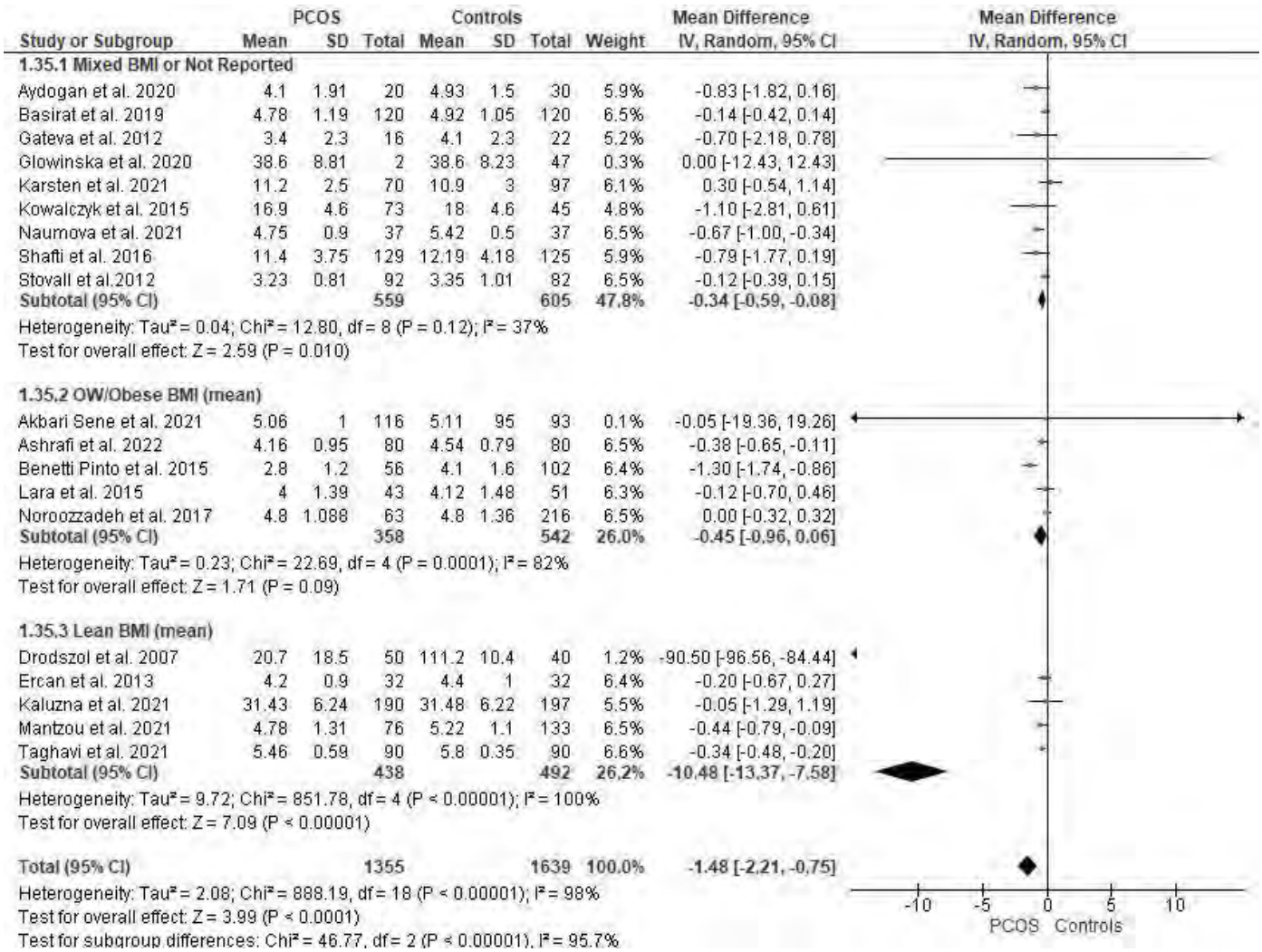
6.5. Funnel plot for sensitivity analysis



6.6. Subgroup Analysis by Fertility Status for total satisfaction



6.7. Subgroup analysis by BMI status (mean BMI) for total satisfaction



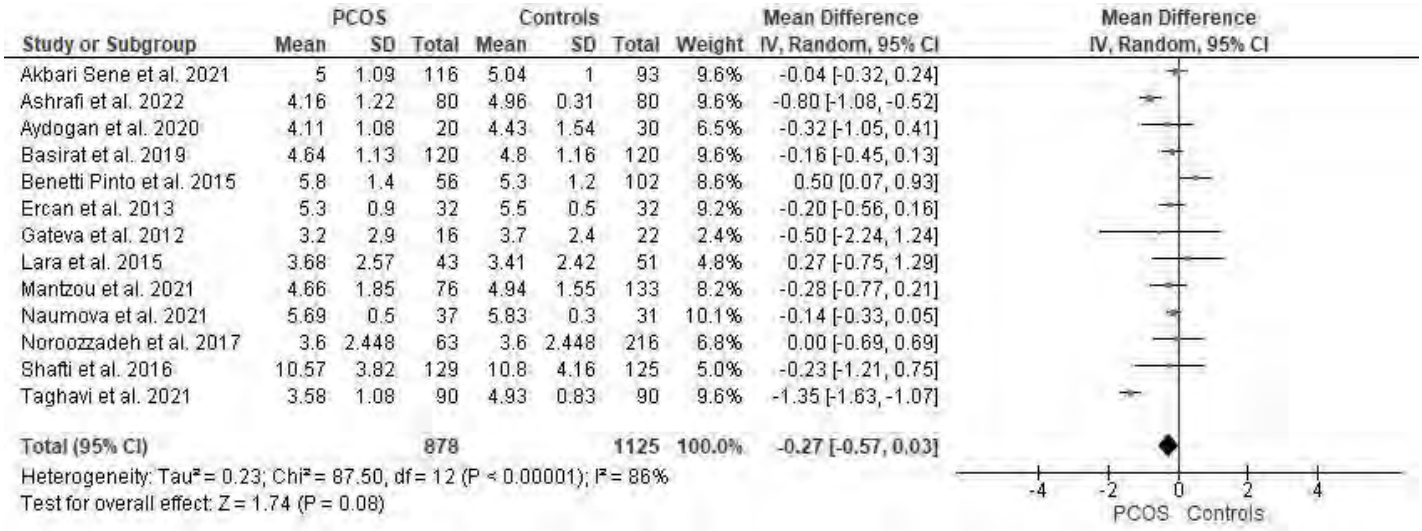
OUTCOME 7. Pain

7.1 Individual Study Data Tables

OUTCOME: Pain						OUTCOME TYPE: Continuous				
Comparison: Women with PCOS vs control										
Author, year	Unit	Method of measurement	Mean in PCOS group	SD in PCOS group	Sample size in PCOS	Mean in control group	SD in control group	Sample size in control group	Are these values adjusted or crude?	What variables are adjusted for?
Akbari Sene et al. 2021	Natural number	FSFI	5	1.09	116	5.04	1	93	Crude	NA
Ashrafi et al. 2022	Natural number	FSFI	4.16	1.22	80	4.96	0.31	80	Crude	NA
Aydogan et al. 2020	Natural number	FSFI	4.11	1.08	20	4.43	1.54	30	Crude	NA
Basirat et al. 2019	Natural number	FSFI	4.64	1.13	120	4.8	1.16	120	Crude	NA
Benetti Pinto et al. 2015	Natural number	FSFI	5.8	1.4	56	5.3	1.2	102	Crude	NA
Ercan et al. 2013	Natural number	FSFI	5.3	0.9	32	5.5	0.5	32	Crude	NA
Gateva et al. 2012	Natural number	FSFI	3.2	2.9	16	3.7	2.4	22	Crude	NA
Lara et al. 2015	Natural number	FSFI	3.68	2.57	43	3.41	2.42	51	Crude	NA
Mantzou et al. 2021	Natural number	FSFI	4.66	1.85	76	4.94	1.55	133	Crude	NA
Naumova et al. 2021	Natural number	FSFI	5.69	0.5	37	5.83	0.3	31	Crude	NA
Noroozzadeh et al. 2017	Natural number	FSFI	3.6	2.448	63	3.6	2.448	216	Crude	NA
Shafti et al. 2016	Natural number	FSFI	10.57	3.82	129	10.8	4.16	125	Crude	NA
Taghavi etal. 2021	Natural number	FSFI	3.58	1.08	90	4.93	0.83	90	Crude	NA

CSFQ: Changes in Sexual Function Questionnaire, FSDQ: Female Sexual Desire Questionnaire, FSFI: Female Sexual Function Index, ISS: Index of Sexual Satisfaction, MFSQ: Mc Coy Female Sexuality Questionnaire, MSQ: Multidimensional Sexuality Questionnaire, SQ-F: Sexual Quotient Female, VAS: Visual analogue scale.

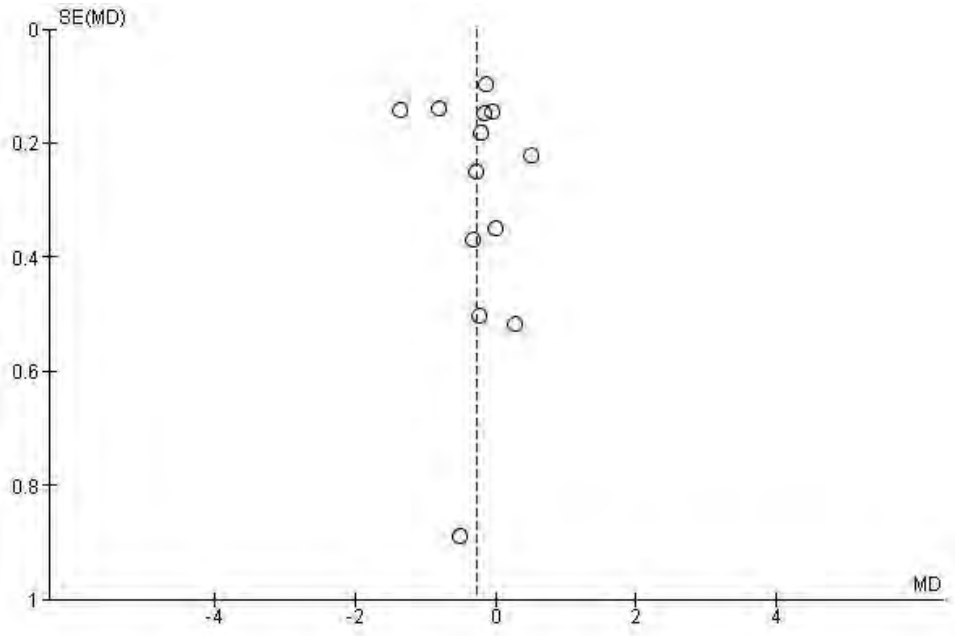
7.2 Forest plot for pain



Study or Subgroup	PCOS Mean	PCOS SD	PCOS Total	Controls Mean	Controls SD	Controls Total	Weight	Mean Difference IV, Random, 95% CI
Akbari Sene et al. 2021	5	1.09	116	5.04	1	93	9.6%	-0.04 [-0.32, 0.24]
Ashrafi et al. 2022	4.16	1.22	80	4.96	0.31	80	9.6%	-0.80 [-1.08, -0.52]
Aydogan et al. 2020	4.11	1.08	20	4.43	1.54	30	6.5%	-0.32 [-1.05, 0.41]
Basirat et al. 2019	4.64	1.13	120	4.8	1.16	120	9.6%	-0.16 [-0.45, 0.13]
Benetti Pinto et al. 2015	5.8	1.4	56	5.3	1.2	102	8.6%	0.50 [0.07, 0.93]
Ercan et al. 2013	5.3	0.9	32	5.5	0.5	32	9.2%	-0.20 [-0.56, 0.16]
Gateva et al. 2012	3.2	2.9	16	3.7	2.4	22	2.4%	-0.50 [-2.24, 1.24]
Lara et al. 2015	3.68	2.57	43	3.41	2.42	51	4.8%	0.27 [-0.75, 1.29]
Mantzou et al. 2021	4.66	1.85	76	4.94	1.55	133	8.2%	-0.28 [-0.77, 0.21]
Naumova et al. 2021	5.69	0.5	37	5.83	0.3	31	10.1%	-0.14 [-0.33, 0.05]
Noroozzadeh et al. 2017	3.6	2.448	63	3.6	2.448	216	6.8%	0.00 [-0.69, 0.69]
Shafti et al. 2016	10.57	3.82	129	10.8	4.16	125	5.0%	-0.23 [-1.21, 0.75]
Taghavi et al. 2021	3.58	1.08	90	4.93	0.83	90	9.6%	-1.35 [-1.63, -1.07]
Total (95% CI)			**878**			**1125**	**100.0%**	**-0.27 [-0.57, 0.03]**

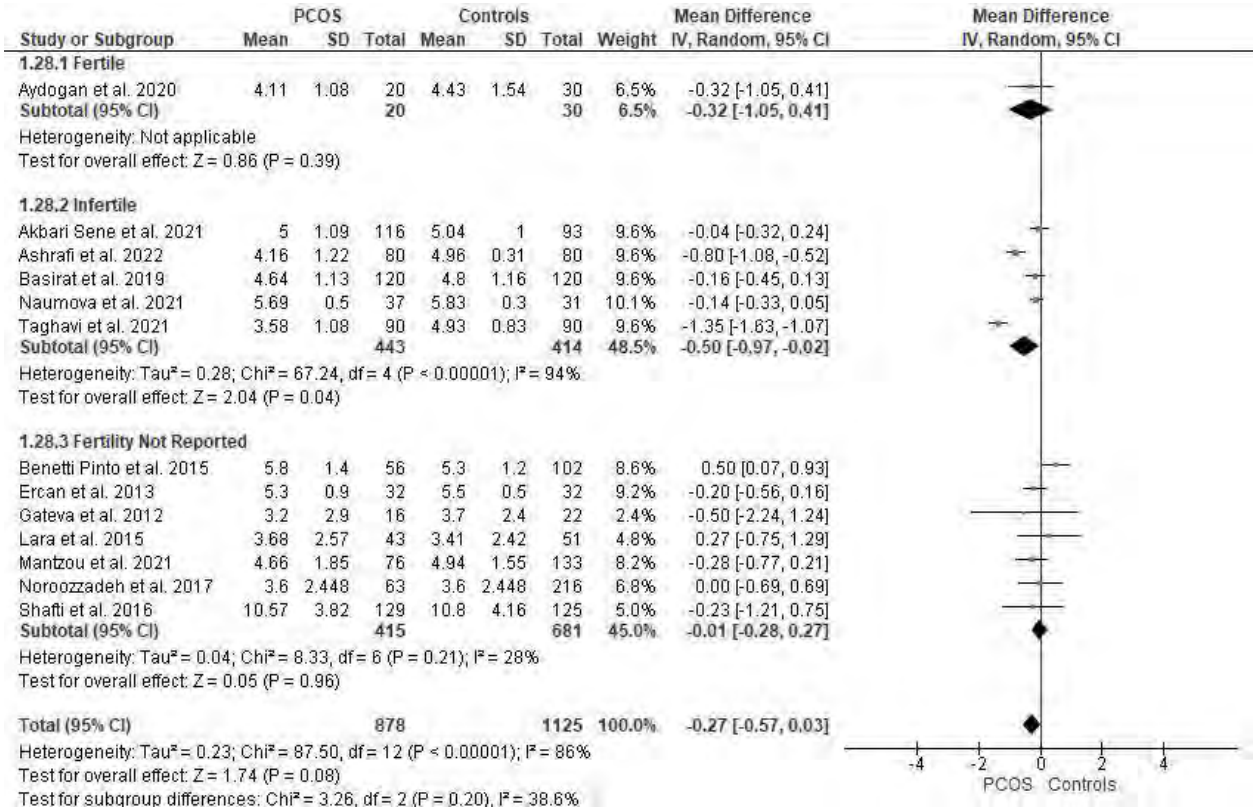
Heterogeneity: Tau² = 0.23; Chi² = 87.50, df = 12 (P < 0.00001); I² = 86%
Test for overall effect: Z = 1.74 (P = 0.08)

7.3 Funnel plot for pain

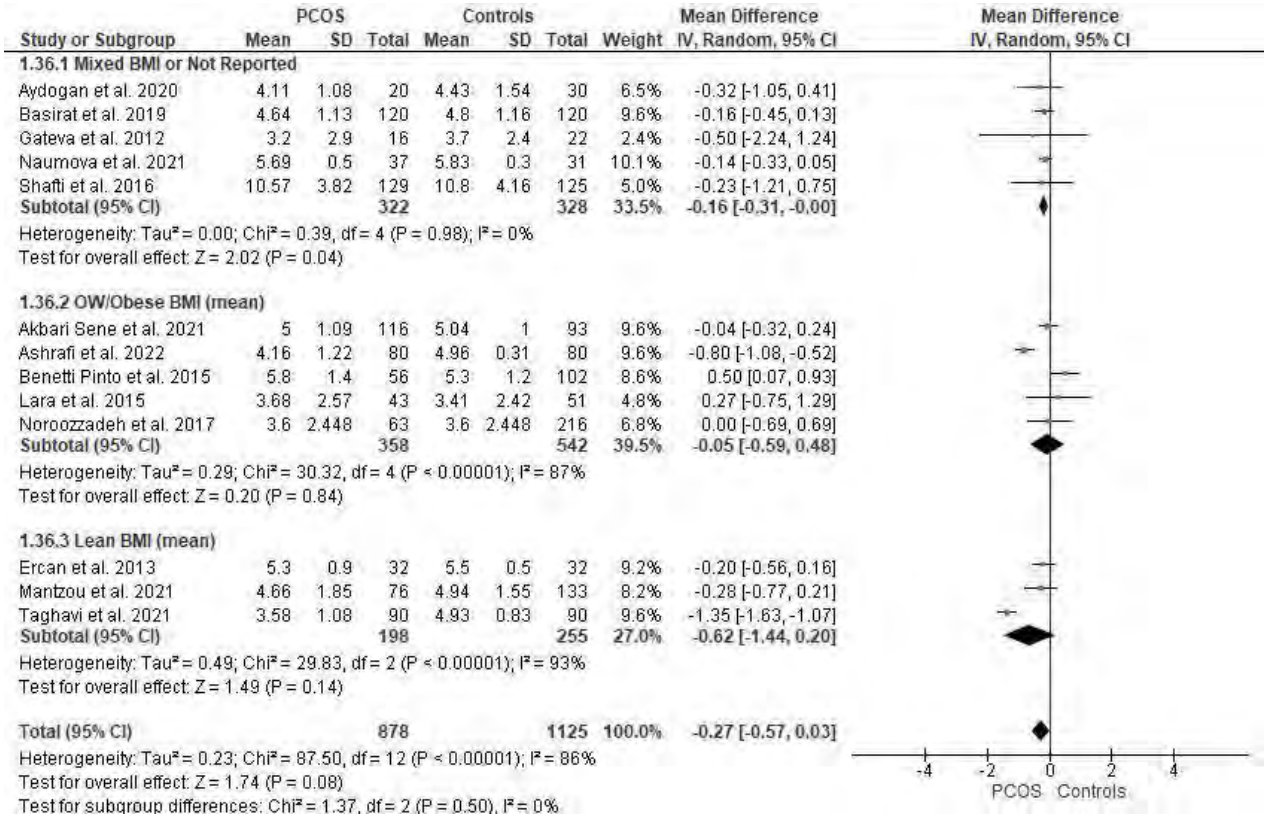


7.4. No sensitivity analysis needed as all studies use FSFI.

7.5. Subgroup Analysis by Fertility Status for pain



7.6. Subgroup analysis by BMI status (mean BMI) for pain



OUTCOME 8. VAS How many sexual thoughts and fantasies did you have?

8.1 Individual Study Data Tables

OUTCOME: VAS How many sexual thoughts and fantasies did you have?						OUTCOME TYPE: Continuous				
Comparison: Women with PCOS vs control										
Author, year	**Unit**	**Method of measurement**	**Mean in PCOS group**	**SD in PCOS group**	**Sample size in PCOS**	**Mean in control group**	**SD in control group**	**Sample size in control group**	**Are these values adjusted or crude?**	**What variables are adjusted for?**
Elsenbruch et al. 2003	Natural number	VAS	47.7	25.8	50	58.0	28.7	50	Crude	NA
Hahn et al. 2005	Natural number	VAS	49	30	120				Crude	NA
Tan et al. 2008	Natural number	VAS	Infertile=51.2 Fertile= 51.3	29.0 28.1	57 55				Crude	NA

CSFQ: Changes in Sexual Function Questionnaire, FSDQ: Female Sexual Desire Questionnaire, FSFI: Female Sexual Function Index, ISS: Index of Sexual Satisfaction, MFSQ: Mc Coy Female Sexuality Questionnaire, MSQ: Multidimensional Sexuality Questionnaire, SQ-F: Sexual Quotient Female, VAS: Visual analogue scale.

OUTCOME 9. VAS How satisfied were you with your sex life?

9.1 Individual Study Data Tables

OUTCOME: VAS How satisfied were you with your sex life?						OUTCOME TYPE: Continuous				
Comparison: Women with PCOS vs control										
Author, year	**Unit**	**Method of measurement**	**Mean in PCOS group**	**SD in PCOS group**	**Sample size in PCOS**	**Mean in control group**	**SD in control group**	**Sample size in control group**	**Are these values adjusted or crude?**	**What variables are adjusted for?**
Elsenbruch et al. 2003	Natural number	VAS	41.3	33.4	50	73.8	27.4	50	Crude	NA
Hahn et al. 2005	Natural number	VAS	46	30	120				Crude	NA
Tan et al. 2008	Natural number	VAS	Infertile= 47.7 Fertile= 37.9	29.7 35.7	57 55				Crude	NA

CSFQ: Changes in Sexual Function Questionnaire, FSDQ: Female Sexual Desire Questionnaire, FSFI: Female Sexual Function Index, ISS: Index of Sexual Satisfaction, MFSQ: Mc Coy Female Sexuality Questionnaire, MSQ: Multidimensional Sexuality Questionnaire, SQ-F: Sexual Quotient Female, VAS: Visual analogue scale

OUTCOME 10. VAS How important is a satisfying sex life for you?

10.1 Individual Study Data Tables

OUTCOME: VAS importance of satisfying sex life						OUTCOME TYPE: Continuous				
Comparison: Women with PCOS vs control										
Author, year	**Unit**	**Method of measurement**	**Mean in PCOS group**	**SD in PCOS group**	**Sample size in PCOS**	**Mean in control group**	**SD in control group**	**Sample size in control group**	**Are these values adjusted or crude?**	**What variables are adjusted for?**
Elsenbruch et al. 2003	Natural number	VAS	76.3	22.0	50	76.3	24.1	50	Crude	NA
Hahn et al. 2005	Natural number	VAS	76	23	120				Crude	NA
Tan et al. 2008	Natural number	VAS	Infertile=79.5 Fertile=75.8	20.2 20.6	57 55				Crude	NA

CSFQ: Changes in Sexual Function Questionnaire, FSDQ: Female Sexual Desire Questionnaire, FSFI: Female Sexual Function Index, ISS: Index of Sexual Satisfaction, MFSQ: Mc Coy Female Sexuality Questionnaire, MSQ: Multidimensional Sexuality Questionnaire, SQ-F: Sexual Quotient Female, VAS: Visual analogue scale.

OUTCOME 11. VAS How often do you experience pain during intercourse?

11.1 Individual Study Data Tables

OUTCOME: VAS pain during intercourse						OUTCOME TYPE: Continuous				
Comparison: Women with PCOS vs control										
Author, year	**Unit**	**Method of measurement**	**Mean in PCOS group**	**SD in PCOS group**	**Sample size in PCOS**	**Mean in control group**	**SD in control group**	**Sample size in control group**	**Are these values adjusted or crude?**	**What variables are adjusted for?**
Elsenbruch et al. 2003	Natural number	VAS	20.8	22.5	50	15.8	23.8	50	Crude	NA
Tan et al. 2008	Natural number	VAS	Infertile=17.1 Fertile= 28.6	23.4 31.1	57 55				Crude	NA

CSFQ: Changes in Sexual Function Questionnaire, FSDQ: Female Sexual Desire Questionnaire, FSFI: Female Sexual Function Index, ISS: Index of Sexual Satisfaction, MFSQ: Mc Coy Female Sexuality Questionnaire, MSQ: Multidimensional Sexuality Questionnaire, SQ-F: Sexual Quotient Female, VAS: Visual analogue scale.

OUTCOME 12. VAS how much does excessive body hair impact your sexuality?

12.1 Individual Study Data Tables

OUTCOME: VAS body hair impact						OUTCOME TYPE: Continuous				
Comparison: Women with PCOS vs control										
Author, year	**Unit**	**Method of measurement**	**Mean in PCOS group**	**SD in PCOS group**	**Sample size in PCOS**	**Mean in control group**	**SD in control group**	**Sample size in control group**	**Are these values adjusted or crude?**	**What variables are adjusted for?**
Elsenbruch et al. 2003	Natural number	VAS	45.8	26.2	50	12.2	33.3	50	Crude	NA
Hahn et al. 2005	Natural number	VAS	39	35	120				Crude	NA
Tan et al. 2008	Natural number	VAS	Infertile=32.7 Fertile=47.3	32.6 42.1	57 55				Crude	NA
Caruso et al. 2009	Natural number	VAS	72.7	4.3	72				Crude	NA

CSFQ: Changes in Sexual Function Questionnaire, FSDQ: Female Sexual Desire Questionnaire, FSFI: Female Sexual Function Index, ISS: Index of Sexual Satisfaction, MFSQ: Mc Coy Female Sexuality Questionnaire, MSQ: Multidimensional Sexuality Questionnaire, SQ-F: Sexual Quotient Female, VAS: Visual analogue scale.

OUTCOME 13. VAS Does your appearance make it difficult to engage in social contact?

13.1 Individual Study Data Tables

OUTCOME: VAS social contact impact						OUTCOME TYPE: Continuous				
Comparison: Women with PCOS vs control										
Author, year	**Unit**	**Method of measurement**	**Mean in PCOS group**	**SD in PCOS group**	**Sample size in PCOS**	**Mean in control group**	**SD in control group**	**Sample size in control group**	**Are these values adjusted or crude?**	**What variables are adjusted for?**
Elsenbruch et al. 2003	Natural number	VAS	28.4	31.7	50	12.7	24.5	50	Crude	NA
Hahn et al. 2005	Natural number	VAS	27	30	120				Crude	NA
Tan et al. 2008	Natural number	VAS	Infertile= 23.2 Fertile=39.5	25.5 32.4	57 55				Crude	NA
Caruso et al. 2009	Natural number	VAS	47.5	3.9	72				Crude	NA

CSFQ: Changes in Sexual Function Questionnaire, FSDQ: Female Sexual Desire Questionnaire, FSFI: Female Sexual Function Index, ISS: Index of Sexual Satisfaction, MFSQ: Mc Coy Female Sexuality Questionnaire, MSQ: Multidimensional Sexuality Questionnaire, SQ-F: Sexual Quotient Female, VAS: Visual analogue scale.

OUTCOME 14. VAS Do you find yourself sexually attractive?

14.1 Individual Study Data Tables

OUTCOME: VAS sexually attractive						OUTCOME TYPE: Continuous				
Comparison: Women with PCOS vs control										
Author, year	**Unit**	**Method of measurement**	**Mean in PCOS group**	**SD in PCOS group**	**Sample size in PCOS**	**Mean in control group**	**SD in control group**	**Sample size in control group**	**Are these values adjusted or crude?**	**What variables are adjusted for?**
Elsenbruch et al. 2003	Natural number	VAS	37.4	27.1	50	58.5	29.3	50	Crude	NA
Hahn et al. 2005	Natural number	VAS	40	26	120				Crude	NA
Tan et al. 2008	Natural number	VAS	Infertile= 31.9 Fertile=33.3	27.7 28.8	57 55				Crude	NA
Caruso et al. 2009	Natural number	VAS	29.6	4.8	72				Crude	NA

CSFQ: Changes in Sexual Function Questionnaire, FSDQ: Female Sexual Desire Questionnaire, FSFI: Female Sexual Function Index, ISS: Index of Sexual Satisfaction, MFSQ: Mc Coy Female Sexuality Questionnaire, MSQ: Multidimensional Sexuality Questionnaire, SQ-F: Sexual Quotient Female, VAS: Visual analogue scale.

8. GRADE ASSESSMENTS AND EVIDENCE PROFILE

COMPARISON 1: Women with PCOS versus controls												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	PCOS	Control	Effect Estimate: MD (95% CI)	Favours	Certainty	Importance
Outcome: Total sexual function												
17	Case control, cross sectional	serious[1]	serious[2]	not serious	not serious	none	1023	1120	-2.42 [-3.26, -1.58]	Controls	⊕⊕◯◯ LOW	CRITICAL
Outcome: Sexual desire												
16	Case control, cross sectional	serious[1]	serious[2]	not serious	not serious	none	1128	1370	-0.22 [-0.47, 0.03]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Sexual arousal												
14	Case control, cross sectional	serious[1]	serious[2]	not serious	not serious	none	970	1207	-0.36 [-0.59, -0.13]	Controls	⊕⊕◯◯ LOW	CRITICAL
Outcome: Lubrication												
14	Case control, cross sectional	serious[1]	serious[2]	not serious	not serious	none	942	1194	-0.47 [-0.75, -0.20]	Controls	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Orgasm												
15	Case control, cross sectional	serious[1]	serious[2]	not serious	not serious	none	1034	1173	-0.35 [-0.52, -0.17]	Controls	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Satisfaction												
19	Case control, cross sectional	serious[1]	serious[2]	not serious	not serious	none	1355	1639	-1.48 [-2.21, -0.75]	Controls	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Pain												
13	Case control, cross sectional	serious[1]	serious[2]	not serious	not serious	none	878	1125	-0.27 [-0.57, 0.03]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: VAS sexual thoughts and fantasies												
3	Case control, cross sectional	serious[1]	not applicable	not applicable	serious[3]	none	225	50	NA	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: VAS sex life satisfaction												
3	Case control, cross sectional	serious[1]	not applicable	not applicable	serious[3]	none	225	50	NA	Controls*	⊕⊕◯◯ LOW	IMPORTANT
Outcome: VAS importance of satisfying sex life												
3	Case control, cross sectional	serious[1]	not applicable	not applicable	serious[3]	none	225	50	NA	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: VAS pain during intercourse												
2	Case control, cross sectional	serious[1]	not applicable	not applicable	serious[3]	none	105	50	NA	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: VAS body hair impact												
4	Case control, cross sectional	serious[1]	not applicable	not applicable	serious[3]	none	297	50	NA	Controls*	⊕⊕◯◯ LOW	IMPORTANT

Outcome: VAS social contact impact												
4	Case control, cross sectional	serious[1]	not applicable	not applicable	serious[3]	none	297	50	NA	Controls*	⊕⊕◯◯ LOW	IMPORTANT
Outcome: VAS sexual attractiveness												
4	Case control, cross sectional	serious[1]	not applicable	not applicable	serious[3]	none	297	50	NA	Controls*	⊕⊕◯◯ LOW	IMPORTANT

[1] **Downgraded once due to most studies being of moderate risk of bias**
[2] **Downgraded once due to high statistical heterogeneity**
[3] **Downgraded once due to small sample size of control group and the same controls used across all studies**

APPENDIX. STUDY CHARACTERISTICS AND QUALITY APPRAISAL TEMPLATES

Study ID	*Benetti Pinto et al. 2015*	
Study Citation	*Benetti-Pinto, C.L., Ferreira, S.R., Antunes Jr, A. and Yela, D.A., (2014). The influence of body weight on sexual function and quality of life in women with polycystic ovary syndrome. Arch Gynecol Obstet. 2014; doi: 10.1007/s00404-014-3423-1.*	
Study Country	*Brazil*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Department of Gynecology and Obstetrics, School of Medicine, State University of Campinas-Unicamp* *Women with PCOS diagnosis, 18-40 years*	
Control population	*Women with regular menstrual cycles every 24-35 days without signs of clinical hyperandrogenism, assisted in the seame institution*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	*PCOS 56* *Control 102*	
Setting	*University hospital*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary: FSFI* *Not relevant: WHOQOL-bref* *All self-report*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* *This study had as objective to assess sexuality and quality of life in Brazilian women with PCOS diagnosis, with emphasis on the role of weight over such parameters.*
Inclusion criteria	Yes Partial No Not reported	*Partial* *Age 18-40* *Sexually active* *PCOS or regular menstrual cycles without clinical hyperandrogenism*
Exclusion criteria	Yes Partial No Not reported	*Yes* *women with any type of cognitive* *deficiency that could jeopardize the understanding of the study instruments were excluded. We also excluded women who with chronic diseases such as: arterial hypertension, diabetes type I or II, autoimmune disease, neoplasia, or those were taking antidepressants, anxiolytics medication and pregnant.*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Partial*

Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Not relevant for the included studies*
Was matching performed?		Yes Partial No Not reported	*Not reported*
Summary Result/s		*Women with PCOS had a worse evaluation to arousal, lubrication, satisfaction, pain and total FSFI, and there was no difference in sexual desire and orgasm.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
Quality assessment based on assessment for Pastoor et al. 2018			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Partial*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*No*
PERFORM ANCE	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No	*Not reported*

		Not reported	
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant for the included studies*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*PCOS 63%* *Control not reported*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Partial*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Partially reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Low*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Caruso et al. 2009*
Study Citation	Caruso, S., Rugolo, S., Agnello, C., Romano, M. and Cianci, A., (2009). Quality of sexual life in hyperandrogenic women treated with an oral contraceptive containing chlormadinone acetate. J Sex Med. 2009; 6, 3376-84. doi: 10.1111/j.1743-6109.2009.01529.x.
Study Country	*Italy*
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	

Patient/population/ participants	*Women aged 18-32 attending the Family Planning Centre, and had been planning to take oral contraceptives for the treatment of their hirsutism for at least 1 year.*	
Control population	*Same as Elsenbruch et al. 2003*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	*PCOS 94* *Control 50*	
Setting	Research Group for Sexology, Department of Microbiological and Gynecological Science, University of Catania, School of Medicine, Catania, Italy	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary:* *VAS sexual satisfaction, impact PCOS characteristics* *Not relevant:* *SF36, SPEQ, Follow up data after starting oral contraptives* *All self-report*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* *to investigate the psychosexual aspects of women affected by clinical signs of androgenization, such a hirsutism, seborrhea and acne, before and under monophasic combined low-dose oral contraceptive intake containing 30 mg EE and 2 mg CMA*
Inclusion criteria	Yes Partial No Not reported	*Partial, only for PCOS* *18-32 years, commited relationship* *had been planning to take oral contraceptives for the treatment of their hirsutism for at least 1 year.*
Exclusion criteria	Yes Partial No Not reported	Partially reported For PCOS: Women with hyperprolactinemia, adrenal hyperplasia, Cushing's syndrome, hypothyroidism or metabolic diseases, or with depressive disorder or other previous psychiatric diagnoses and use of psychiatric drugs, or had taken oral contraceptives or other hormonal medications in the previous 6 months for treating hirsutism or anovulatory menstrual dysfunction were excluded from the study. Moreover, women who used drugs possibly impeding sexual function as well as patients with diagnosed organic causes of sexual disorders were excluded from the study. The body mass index of each woman was _30 kg/m2.
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*

Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Partial* *(since we only used baseline data for the meta-analysis it is appropriate for the meta-analysis).*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Not relevant for the included studies*
Was matching performed?	Yes Partial No Not reported	*Not reported*
Summary Result/s	*Frequency of sexual intercourse and of orgasm by intercourse increased, and the frequency of masturbation decreased during the 6th ($p < 0.05$) and the 9th cycle ($p < 0.001$).*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
Quality assessment based on assessment for Pastoor et al. 2018		
SELECTION BIAS – Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*No*
SELECTION BIAS – the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
SELECTION BIAS – Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*Not reported*
PERFORMANCE BIAS – Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Not reported*
DEDETECTION BIAS – Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*No*
DEDETECTION BIAS – Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
DEDETECTION BIAS – Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*

	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Not reported*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant for the included studies*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*19/91*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*No*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Partial*
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Diamond et al. 2017*
Study Citation	*Diamond, M.P., Legro, R.S., Coutifaris, C., Alvero, R., Robinson, R.D., Casson, P.A., Christman, G.M., Huang, H., Hansen, K.R., Baker, V., Usadi, R., Seungdamrong, A., Bates, G.W., Rosen, R.M., Schlaff, W., Haisenleder, D., Krawetz, S.A., Barnhart, K., Trussell, J.C., Santoro, N., Eisenberg, E. and Zhang, H., (2017). Sexual function in infertile women with polycystic ovary syndrome and unexplained infertility. Am J Obstet Gynecol.2017. doi: 10.1016/j.ajog.2017.04.034*

Study Country	*USA*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*PPCOS II trial* *AMIGOS trial*	
Control population	*PPCOS II trial* *AMIGOS trial*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	*PCOS 733* *Control 865*	
Setting	*multicenter Hospital*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcome:* *FSFI, FSDS* *Not relevant outcomes:* *Medical Outcomes Survey, SF-36, FertiQol* *All self-report*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* *To elucidate sexual dysfunction in well-characterized couples with polycystic ovary syndrome (PCOS) and unexplained infertility (UI) and to assess correlations of sexual function and dysfunction in female partners of infertile couples, we undertook a secondary analysis of data from 2 studies of the Eunice Kennedy Shriver National Institutes of Child Health and Human Development Cooperative Reproductive MedicineNetwork (RMN). Additionally, we sought to test the hypothesis that circulating androgen, as assessed by free androgen index (FAI) in women, would be inversely related to the prevalence of sexual dysfunction.*
Inclusion criteria	Yes Partial No Not reported	*Partial* *All PPCOS II women were seeking infertility care and were between the ages of 18 and 39 years; had oligoovulation, defined by the modified Rotterdam criteria for this disorder; and had exclusion of other disorders that could mimic the syndrome, such as congenital adrenal hyperplasia, hyperprolactinemia, or thyroid disease. All participants were required to have a normal uterine cavity and at least 1 patent fallopian tube. Male partners were required to have at least 14 million sperm per milliliter on screening semen analysis.* *All AMIGOS women were between the ages of 18 and 40 years and had UI,*

			defined as 1 or more years of an infertility history with regular menstrual cycles; had normal results on fertility testing including evidence of normal uterine cavity and at least 1 patent fallopian tube and had a male partner with at least 5 million motile sperm on semen analysis; and were also seeking infertility care.
Exclusion criteria		Yes Partial No Not reported	*Partial* *PPCOS II* *Exclusion of other disorders that could mimic the syndrome, such as congenital adrenal hyperplasia, hyperprolactinemia, or thyroid disease.*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Partial*
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Not relevant for the included studies*
Was matching performed?		Yes Partial No Not reported	*Not reported*
Summary Result/s		*Sexual function scores, as assessed by the Female Sexual Function Inventory, were nearly identical. The Female Sexual Distress Scale total score was higher in women with polycystic ovary syndrome. The mean Female Sexual Function Inventory total score increased slightly as the free androgen index increased, mainly as a result of the desire subscore. This association was more pronounced in the women with unexplained infertility.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
Quality assessment based on assessment for Pastoor et al. 2018			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Yes*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*Not reported*

PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Not reported*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant for the included studies*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*PPCOS II 2.3%* *AMIGOS 3.9%*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*No* *Basic characteristics are significantly different on various factors*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*Partial*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Yes (but not reported)*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*

COMMENTS		
What is the overall risk of bias?	Low Moderate High Insufficient information	*Moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*No*	

Study ID	*Drosdzol et al. 2007*	
Study Citation	Drosdzol, A., Skrzypulec, V., Mazur, B. and Pawlinska-Chmara, R., (2007). Quality of life and marital sexual satisfaction in women with polycystic ovary syndrome. Folia Histochem Cytobiol. 2007; 45, 93-97. doi.org/10.2478/4495.	
Study Country	*Poland*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women between 19 and 40 years old who reported to the Obstetrics and Gynecology and the Gynecological Endocrionology Clinics of the Medical university of Silesia in Katowice, Poland*	
Control population	*Healthy women between 19 and 40 years from the Outpatient Gynecological Clinics*	
PCOS diagnostic criteria	*PSE and ESHRE*	
N per group	*PCOS 50* *Control 40*	
Setting	*University Hosptial*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcome:* *ISS (index of sexual satisfaction)* *Outcomes not relevant:* *SF-36* *All self-report*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	YES to evaluate the effect of polycystic ovary syndrome on quality of life and marital sexual satisfaction among women with diagnosed PCOS and compared with a group of healthy controls.
Inclusion criteria	Yes Partial No Not reported	*Partial :* *PCOS diagnosis vs no PCOS diagnosis*
Exclusion criteria	Yes Partial No Not reported	*Partial* *PCOS:* *Using drugs that impede sexual function or having a organic cause of sexual disorder*

			Controsl not reported
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Partial* *becauselimited*
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Not relevant for the included studies*
Was matching performed?		Yes Partial No Not reported	*Partial* *Age-matched, otherwise not reported*
Summary Result/s		Studied women showed worse marital sexual functioning (p<0.05). Marital sexual dysfunctions were diagnosed in 28.6% of women with polycystic ovary syndrome and in 10.5% of healthy women (p<0.05). Anegative effect of hirsutism severity on general well-being and marital sexual life is also observed.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
Quality assessment based on assessment for Pastoor et al. 2018			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Yes*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*Not reported*
PERFORM ANCE	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*No*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*

	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Not reported*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant for the included studies*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*PCOS 46%*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Partial*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*Not reported*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Partial*
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate to high*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Elkhiat et al. 2015*

Study Citation	*Elkhiat, Y., Zedan, A., Mostafa, M. and Elhalwagi, A., (2015). Sexual desire in a sample of married Egyptian women with polycystic ovarian syndrome. Human Andrology. 2015; 5(3):49-57. DOI:10.1097/01.XHA.0000470182.71509.1b*	
Study Country	*Egypt*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Sexually active women in the childbearing period (21-45y) with PCOS*	
Control population	*Normal women ithout PCOS*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	*PCOS 85* *Control 63*	
Setting	*Gynecology and obstetrics clinic*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary: FSDQ* *Self-report*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* *To assess the sexual desire in a smpale of married women with PCOS using the FSDQ.*
Inclusion criteria	Yes Partial No Not reported	*Partially* *Married, sexually active, 21-45y*
Exclusion criteria	Yes Partial No Not reported	*Yes* *Chronic disabling disease, psycologicsal disorders, endocrine disorders other than PCOS, age above 45y, sexually inactive*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Partial*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Not relevant for the included studies*
Was matching performed?	Yes Partial No Not reported	*Not reported*
Summary Result/s	*The FSDQ score for control women was significantly higher then for women with PCOS (P<0.001), except for solitary desire score which was higher in the PCOS groep (P=0.02).*	

INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
Quality assessment based on assessment for Pastoor et al. 2018			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Partial*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*No*
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Not reported*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant for the included studies*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*Not reported*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*

CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Partial*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Partial*
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Elsenbruch, 2003*
Study Citation	Elsenbruch, S., Hahn, S., Kowalsky, D., Offner, A.H., Schedlowski, M., Mann, K. and Janssen, O.E., (2003). Quality of Life, Psychosocial Well-Being, and Sexual Satisfaction in Women with Polycystic Ovary Syndrome. J Clin Endocrinol Metab 88, 5801-5807. 2013. doi: 10.1210/jc.2003-030562.
Study Country	*Germany*
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Patients from the outpatient clinic of the Division of Endocrinology, Department of Medicine at University of Essen* *By referrals from gynaecologists in surrounding area or patients attracted by clinics home page*
Control population	*Age matched healthy controls from a health screening program for employees of the University of Essen*
PCOS diagnostic criteria	*1990 National Institute of Health Conference*
N per group	*PCOS 50* *Controls 50*
Setting	*Hospital, University*

Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)		*Primary outcome:* *PCOS specific characteristics: VAS scale* *Sexual satisfaction: VAS scale* *Outcomes not relevant:* *Psychological wellbeing: SCL-90* *HRQL: SF-36, Fragenbogen zur Liebenszufriedenheit* *All self- report*	
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	*Yes* *The impact of PCOS on psychosocial and emotional functioning, HRQL, and sexual satisfaction in a German patient sample compared with an age-matched healthy control sample.*
Inclusion criteria		Yes Partial No Not reported	*Partial* *PCOS: Otherwise healthy*
Exclusion criteria		Yes Partial No Not reported	*Partial* *Controls: Any known medical condition of psychological disorder, irregular periods, hormonal disturbances.*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Not relevant for the included studies*
Was matching performed?		Yes Partial No Not reported	*Yes, age-matched* *But not reported how.*
Summary Result/s		*Women with PCOS reported a lower degree of satisfaction with their sex life, found themselves less attractive and reported more social impact of PCOS characteristics.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
Quality assessment based on assessment for Pastoor et al. 2018			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Partial*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Partial*

	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*Partial*
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Partial (only partial reported)*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant for the included studies*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*Not reported*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Partial*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*Not reported*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*

	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Partial*
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Ercan et al. 2013*	
Study Citation	*Ercan, C.M., Coksuer, H., Aydogan, U., Alanbay, I., Keskin, U., Karasahin, K.E. and Baser, I., (2013). Sexual dysfunction assessment and hormonal correlations in patients with polycystic ovary syndrome. Int J Impotence Res. 2013; 25, 127-132. doi: 10.1038/ijir.2013.2.*	
Study Country	*Turkey*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with PCOS, otherwise healthy, faithfully married with an active sexual life*	
Control population	*Age matched healthy regular menstruating non-PCOS women who were admitted to outpatient unit for a routine check up*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	*PCOS 32* *Controls 32*	
Setting	*University hospital*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary: FSFI* *Not relevant: BDI* *All self-report*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* *We aimed to evaluate the sexual function of PCOS patients in comparison with healthy controls*
Inclusion criteria	Yes Partial No Not reported	*Yes* *The inclusion criteria of the study were women who were married, sexually active and between the ages of 20 and 40 who had at least a* *secondary school education, agreed to fill out the Female Sexual Function* *Index (FSFI) and Beck's Depression Inventory (BDI) questionnaire forms,* *and gave informed consent for participation.*

Exclusion criteria		Yes Partial No Not reported	*Yes* *pregnancy, a postpartum period within the past 3 months, gynecologic disorders that might affect female sexual function (that is, pelvic floor disorders, adnexal mass or atrophy, endometriosis), a history of psychological disorders (that is, anxiety states, obsessive-compulsive disorders, vaginismus), a history of internal pathology (that is, hepatic, pulmonary, renal, hematological, or endocrine diseases such as diabetes mellitus, prolactinoma or thyroid dysfunction), menopausal symptoms (including menstrual irregularities or permanent cessation of menses), and no regular sexual intercourse, which was defined as any woman who was not with her husband during the study period. Moreover, patients who did not want to complete the questionnaire forms and patients receiving any medication up to 3 months before the study that could interfere with sexual function (that is, oral contraceptives, estrogens, anti-androgens, sedatives, antidepressants, antidiabetic medications and beta blockers) were excluded due to their possible confounding effects.*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Not relevant for the included studies*
Was matching performed?		Yes Partial No Not reported	*Yes* *Age matched* *Not specified how*
Summary Result/s		*The* *prevalence of sexual dysfunction in the PCOS group was similar to controls (25% vs 19%; P¼0.54). No significant difference was* *found according to each domain score of FSFI.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
Quality assessment based on assessment for Pastoor et al. 2018			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Partial*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No	*Yes*

		Not reported	
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Not reported*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant for the included studies*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*2/34 PCOS* *3/35 control*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Partial*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Partially reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No	*Partial*

	Not reported	
COMMENTS		
What is the overall risk of bias?	Low Moderate High Insufficient information	*Low to moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*No*	

Study ID	*Ferraresi et al. 2013*	
Study Citation	*Ferraresi, S.R., Lara, L.A.S., Reis, R.M. and de Sa Rosa e Silva, A.C.J.,(2013). Changes in Sexual Function among Women with Polycystic Ovary Syndrome: A Pilot Study. J Sex Med. 2013; 10, 467-473. DOI: 10.1111/jsm.12011*	
Study Country	*Brazil*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*sexually active obese and nonobese women with PCOS selected at the Outpatient Clinic of Gynecologic Endocrinology, which is part of the Sector of Human Reproduction, Department of Gynecology and Obstetrics, University Hospital, Faculty of Medicine of Ribeirão Preto (DGO/HCFMRP), University of São Paulo, Ribeirão Preto, São Paulo, Brazil.*	
Control population	*recruited from a primary care center at the same institution.*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	*PCOS 48* *Controls 35*	
Setting	*Tertiary hospital*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary: FSFI* *Self-report*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* *The present study sought to evaluate the sexual function of obese and nonobese women with PCOS compared to that of obese and nonobese women with regular cycles.*
Inclusion criteria	Yes Partial No Not reported	*Partial* *PCOS; diagnosis of PCOS, sexually active* *Control: regular menstrual cycle*
Exclusion criteria	Yes Partial No Not reported	*Yes* *(not reported for which group)* *the use of metformin* *or hormone-based contraceptives in the*

			last 2 months, the use of any anti-androgenic medication (cyproterone acetate or spironolactone) in the last 12 months, or the presence of any psychiatric disorder, endocrinopathy, neuropathy, or gynecologic neoplasia. Any subject exhibiting hyperandrogenism of any other etiology (i.e., congenital adrenal hyperplasia, the presence of an androgen-secreting tumor, Cushing syndrome, or hyperprolactinemia) [17] was also excluded.
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Partial*
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Not relevant for the included studies*
Was matching performed?		Yes Partial No Not reported	*Yes* *On BMI*
Summary Result/s		*Evaluation of the total FSFI scores revealed that obese women without PCOS had below-normal sexual function scores, whereas both obese and nonobese women with PCOS had borderline scores compared to controls, who had normal FSFI findings. No association was observed between body mass index, the presence of PCOS, testosterone level, and FSFI score.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
Quality assessment based on assessment for Pastoor et al. 2018			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Partial*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*No*
PERFORM ANCE	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*

DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Not reported*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant for the included studies*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*Not reported*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Partial*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Partial*
COMMENTS			
What is the overall risk of bias?		Low Moderate	*Moderate*

	High Insufficient information	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*No*	

Study ID	*Gateva et al. 2012*	
Study Citation	Gateva, A. and Kamenov, Z., (2012). Sexual Function in Patients with PCOS and/or Obesity before and after Metformin Treatment. Advances in Sexual Medicine. 2012. DOI: 10.4236/asm.2012.22005.	
Study Country	*Bulgaria*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*patients with PCOS and/or obesity that were recruited from the hospitalized in the Clinic of Endocrinology in Alexandrovska Univer- sity Hospital in Sofia*	
Control population	*Obese women without PCOS*	
PCOS diagnostic criteria	*ESHRE, ASRM*	
N per group	*PCOS 57* *Controls 22*	
Setting	*University Hospital*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary: FSFI* *Not relevant:* *Follow up data after starting metformin* *All self- report*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* *Obese PCOS patients probably have increased rate of sexual dysfunction. These data are not confirmed in lean PCOS patients. Additional studies are necessary to determine if normalizing the androgen excess and insulin resistance would improve the sexual function in PCOS patients*
Inclusion criteria	Yes Partial No Not reported	*Yes* *premenopausal women aged 18 to 45;* *PCOS, diagnosed by ESHRE-ASRM criteria and;* *BMI > 30 kg/m2.*
Exclusion criteria	Yes Partial No Not reported	*Partial* *Pregnancy;* *Serious illnesses as cardiac, renal or liver insuffi-ciency;* *Other endocrine pathology like type 2 diabetes melli-tus, adrenal tumors, hypothyroidism, prolactinomas, hypogonadism, Cushing's disease, congenital adrenal hyperplasia;* *Insulin sensitizing medication (metformin or glita-zones) or combined oral contraceptive (COC, con-taining etinylestradiol and progestin) use less than 4 months prior to the study.*

If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Partial*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Partial* *(since we only used baseline data for the meta-analysis it is appropriate for the meta-analysis).*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Not relevant for the included studies*
Was matching performed?	Yes Partial No Not reported	*Not reported*
Summary Result/s	Obese women without PCOS showed significantly higher scores on total FSFI and all domains except from desire compared to lean PCOS subjects. Although the differences do not reach statistical significance, lean PCOS patients have the lowest scores on all domains. FSFI score correlates negatively only with androstendione levels. Women with and without hy- perandrogenemia do not show differences in FSFI score.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
Quality assessment based on assessment for Pastoor et al. 2018		
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Yes*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*Partial*
PERFORM ANCE	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*

	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant for the included studies*
ATTRITION BIAS	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*Not reported*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Yes*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*Not reported*
OTHER BIAS	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
OTHER BIAS	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Partial*
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Hahn et al. 2005*
Study Citation	Hahn, S., Janssen, O.E., Tan, S., Pleger, K., Mann, K., Schedlowski, M., Kimmig, R., Benson, S., Balamitsa, E. and Elsenbruch, S., (2005). Clinical and psychological

	correlates of quality-of-life in polycystic ovary syndrome. Eur J Endocrinol. 2005, 153, 853-60. doi: 10.1530/eje.1.02024.	
Study Country	*Germany*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Patients from the outpatient clinic of the, Department of Medicine at University of Duisburg-Essen* *By referrals from gynaecologists in surrounding area or patients attracted by clinics home page*	
Control population	*Age matched healthy controls from a health screening program for employees of the University of Essen (same control group as Elsenbruch et al. 2013)*	
PCOS diagnostic criteria	*1990 National Institute of Health Conference*	
N per group	*PCOS 120* *Controls 50*	
Setting	*Hospital, University*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcome:* *PCOS specific characteristics: VAS scale* *Sexual satisfaction: VAS scale* *Outcomes not relevant:* *Psychological wellbeing: SCL-90* *HRQL: SF-36* *All self- report*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* *To explore the correlation of major PCOS symptoms with quality of life, psychoscial well-being and sexual satisfaction.*
Inclusion criteria	Yes Partial No Not reported	*Partial* *PCOS: Otherwise healthy*
Exclusion criteria	Yes Partial No Not reported	*Partial* *PCOS: previous psychiatric diagnoses and use of psychiatric medications including anti- depressants* *Controls: PCOS was excluded, Any known medical condition of psychological disorder.*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial	*Not relevant for the included studies*

		No Not reported	
Was matching performed?		Yes Partial No Not reported	*Yes, age-matched* *But not reported how.*
Summary Result/s		*Women with PCOS reported a lower degree of satisfaction with their sex life, found themselves less attractive and reported more social impact of PCOS characteristics.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
Quality assessment based on assessment for Pastoor et al. 2018			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*No*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Partial*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*Partial*
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*No*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Partial (only partial reported)*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant for the included studies*

	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*Not reported*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*No*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*Not reported*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Partial*
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Kowalczyk et al. 2015*
Study Citation	*Kowalczyk, R., Skrzypulec-Plinta, V., Nowosielski, K. and Lew-Starowicz, Z., (2015). Sexuality in women with polycystic ovary syndrome. Ginekol Pol. 2015; 86, 100-106. doi: 10.17772/gp/1995.*
Study Country	*Poland*
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women who were diagnosed and hospitalized in Department of gynecological endocrinology medical university of Silesia.* *Diagnosis of PCOS.*
Control population	*Healthy women without PCOS* *Gynecological outpatient clinics womens health diagnostic center in Katovwice* *Yearly routine gynecological check up*

PCOS diagnostic criteria	*Rotterdam*	
N per group	*PCOS 73* *Control 45*	
Setting	*University hospital*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary: MSQ* *Not relevant: GHQ12, SS, SAQ, MSSCQ, SFK/K scale* *All self-report*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* *To compare women with PCOS and healthy controls with respect to sexual function, sexual response, attitude toward sexuality and relationships with sexual partners.*
Inclusion criteria	Yes Partial No Not reported	*Partial* *23-42 y* *Abscense of psychological disorders (GHQ12)*
Exclusion criteria	Yes Partial No Not reported	*Yes* *PCOS:Drugs that affect libido , manor gynecological operations* *Control: sever somatic disease, thyroid dysfunctione, diabetes mellituys, liver dysfunction, major gynecologic operation, medications affections sexual function, pregnancy or within 3m post partum, lack of sexual initiation.*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Partial*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Not relevant for the included studies*
Was matching performed?	Yes Partial No Not reported	*Yes* *On sociodemographic profiles*
Summary Result/s	*There were no significant differences in importance of sexual activity between the groups. Mean scores on MSQ were similar, sexual needs and reactions were perceived the same, but women with PCOS rated themselves more frequently negatively as sexual partners.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
Quality assessment based on assessment for Pastoor et al. 2018		

SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Yes*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*No*
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*No*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Not reported*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant for the included studies*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*PCOS: 55/128* *Control: 5/50*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Yes*

OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*Reported but in Polish*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Partial*
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Low*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Lara et al. 2015*
Study Citation	*Lara, L.A.S., Ramos, F.K.P., Kogure, G.S., Costa, R.S., Silva de Sá, M.F., Ferriani, R.A. and dos Reis, R.M.,(2015). Impact of Physical Resistance Training on the Sexual Function of Women with Polycystic Ovary Syndrome. J Sex Med. 2015; 12, 1584-1590. doi: 10.1111/jsm.12909.*
Study Country	*Brazil*
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with PCOS* *Endocrine Gynecology Outpatient Clinic of the Department of Gynecology and Obstetrics, University Hospital, Ribeirão Preto Medical School, University of São Paulo*
Control population	*Control women* *Endocrine Gynecology Outpatient Clinic of the Department of Gynecology and Obstetrics, University Hospital, Ribeirão Preto Medical School, University of São Paulo*
PCOS diagnostic criteria	*Rotterdam*
N per group	*PCOS 43* *Control 51*
Setting	*Academic medical center*

Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primar: FSFI* *Not relevant: HADS* *All self-report*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* *However, the effect of PRT on the sexual function of women with PCOS has not been evaluated. This study therefore assessed the impact of PRT on the sexual function of women with PCOS.*
Inclusion criteria	Yes Partial No Not reported	*Yes* *18-37* *sedentary, were not taking hormones, and had a body mass index (BMI) of 18–39.9 kg/m2.* *control: regular menstrual cyles, no clinical signs of hyperandrogenism*
Exclusion criteria	Yes Partial No Not reported	*Partial* *use of hormonal contraceptives, smoking, pregnancy, and diseases such as congenital adrenal hyperplasia, thyroid disease, and Cushing disease.*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Partial*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Partial* *(since we only used baseline data for the meta-analysis it is appropriate for the meta-analysis).*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Not relevant for the included studies*
Was matching performed?	Yes Partial No Not reported	*Not reported*
Summary Result/s	*Of the 43 women with PCOS, 30 (69.70%) had a basal total FSFI score = 26.55 and 24 of them (58.54%) had a score = 26.55 after PRT (P = 0.08). Of the 51 control women, 32 (62.7%) and 27 (52.9%) had FSFI scores < 26.55 at baseline and after PRT, respectively (P = 0.06).*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
Quality assessment based on assessment for Pastoor et al. 2018		
SELECTION BIAS – Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Yes*

	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*No*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*No*
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Not reported*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant for the included studies*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*Not reported*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Partial*
	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*

OTHER BIAS	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	***Mansson et al. 2011***	
Study Citation	***Mansson, M., Norstrom, K., Holte, J., Landin-Wilhelmsen, K., Dahlgren, E. and Landen, M., (2011). Sexuality and psychological wellbeing in women with polycystic ovary syndrome compared with healthy controls. Eur J Obstet Gynecol Reprod Biol. 2011; 155, 161-5. doi: 10.1016/j.ejogrb.2010.12.012. (not included in meta-analysis)***	
Study Country	***Sweden***	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	***Women with PCOS seeking infertility treatment***	
Control population	***Women without PCOS born on the same day as each woman with PCOS***	
PCOS diagnostic criteria	***Rotterdam***	
N per group	***PCOS 49*** ***Control 49***	
Setting	***Hospital, infertility clinic Uppsala and gynecology department Gothenburg, support community homepage***	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	***Primary: McCoy*** ***Not relevant: PGWB*** ***Self-report***	
Does the study have a clearly focused question and/or PICO?	**Yes** **Partial** **No** **Not reported**	***Yes*** ***The objective of this study was to compare sexual functioning – defined as the integration of physical, socioemotional and intellectual aspects of sexual expression and performance – in PCOS women***

			with a matched population-based control group, and to study potential relationships between serum testosterone levels, psychological wellbeing, and sexual functioning.
Inclusion criteria		**Yes** **Partial** **No** **Not reported**	***Not reported***
Exclusion criteria		**Yes** **Partial No** **Not reported**	***Not reported***
If there were specified inclusion/ exclusion criteria, were these appropriate?		**Yes** **Partial** **No** **Not reported**	***Not reported***
Is a cross sectional or case-control study the appropriate design to answer this question?		**Yes** **Partial** **No** **Not reported**	***Yes***
Was there sufficient duration of follow-up for outcomes to occur?		**Yes** **Partial** **No** **Not reported**	***Not relevant for the included studies***
Was matching performed?		**Yes** **Partial** **No** **Not reported**	***Yes*** ***Control women were born on the same date as women with PCO***
Summary Result/s		***Almost half the women with PCOS reported that the disorder had a great impact on their sex life. Despite having the same number of partners and about the same frequency of sexual intercourse, women with PCOS were generally less satisfied with their sex lives compared to the population-based controls. Within the group of women with PCOS, high body mass index had only a minor effect on sexual functioning, while the total serum level of testosterone correlated positively to sexual satisfaction. PCOS*** ***women scored numerically lower than controls on the McCoy total score, but this difference was not statistically significant.***	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
Quality assessment based on assessment for Pastoor et al. 2018			
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	**Yes** **Partial** **No** **Not reported**	***Partial***
	Was the case definition adequate and established in a standard, valid and reliable way?	**Yes** **Partial** **No** **Not reported**	***Yes***
	Was the control status established in a standard, valid and reliable way?	**Yes** **Partial** **No** **Not reported**	***Partial***

PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Partial* *Not clearly reported*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Not reported*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant for the included studies*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*Not reported*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*No* *Data on endocrine levels not reported* *Not clear if endocrine levels were assessed in control women*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Partial*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Partial*

COMMENTS		
What is the overall risk of bias?	**Low** **Moderate** **High Insufficient information**	***High***
Did risk of bias differ by outcome ***(eg. primary outcome was low risk but rest were high)?***	***Yes*** ***For endocrine levels and regression analysis with it, power in control group was not sufficient***	

Study ID	*Noroozzadeh et al. 2017*	
Study Citation	*Noroozzadeh, M., Tehrani, F.R., Mobarakabadi, S.S., Farahmand, M. and Dovom, M.R., (2016). Sexual function and hormonal profiles in women with and without polycystic ovary syndrome: a population-based study. Int J Impotence Res. 2016. doi: 10.1038/ijir.2016.35.*	
Study Country	*Iran*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with PCOS*	
Control population	*Women without PCOS*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	*PCOS 63* *Control 216*	
Setting	*Iranian PCOS prevalence study, population based study, four provinces of various geographic regions in Iran using stratified cluster sampling*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary: FSFI* *Self-report*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* *We aimed to compare the sexual function in PCOS patients with controls in a population-based study and to assess the association between hormonal profiles (especially androgens) with sexual function in women with PCOS and controls.*
Inclusion criteria	Yes Partial No Not reported	*Not reported* *Published before (Tehrani et al. 2011)*
Exclusion criteria	Yes Partial No Not reported	*Partial* *congenital adrenal hyperplasia, androgen-secreting tumors and Cushing's syndrome based on physical exam and hormonal assessment.*

			excluding women with no partners (n = 210), those with incomplete data (women who refused to fill out the FSFI questionnaire) (n = 70) and those with only oligomenorrhea/amenorrhea (n = 77), only hyperandrogenemia (n = 205) or only polycystic ovaries (n = 74),
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Partially reported*
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Not relevant for the included studies*
Was matching performed?		Yes Partial No Not reported	*Not reported*
Summary Result/s		*A comparison of PCOS women and controls showed no statistically significant difference in total FSFI and each of its specific domain*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
Quality assessment based on assessment for Pastoor et al. 2018			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Yes*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*Not reported*
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*

	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Not reported*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant for the included studies*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*Not reported*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Yes*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Low*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Shafti et al. 2016*	
Study Citation	*Shafti, V. and Shahbazi, S., (2016). Comparing sexual function and quality of life in polycystic ovary syndrome and healthy women. J Fam Reprod Health. 2016; 10, 92-98. (doi not available)*	
Study Country	*Iran*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Married women with PCOS who visited Shahid Rajaee Hospital and selected women infertility clinics in Tonekabon*	
Control population	*Healthy married women who visited Shahid Rajaee Hospital and selected women infertility clinics in Tonekabon*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	*PCOS 129 Control 125*	
Setting	*Hospital*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary: FSFI Not relevant: WHOQOL-bref All self-report*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes the aim of this study is to compare sexual function and quality of life of women with PCOS with normal women and it is hypothesized that the sexual function and quality of life of women with PCOS is lower in comparison with normal women.*
Inclusion criteria	Yes Partial No Not reported	*Partial Married, 18-45 Control: no chronic disease, had regular menstrual cycle and they were selected from clinic's employees and patients' companions by Convenience sampling method.*
Exclusion criteria	Yes Partial No Not reported	*Yes Diagnosed with psychological disorders or use of psychiatric medications or history of hospitalization in Neurology and psychiatry ward, Pregnancy or lactation, any chronic disease (Diabetes, endocrine disorders, receiving treatment for PCOS in the previous two months).*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Partial*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*

Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Not relevant for the included studies*
Was matching performed?		Yes Partial No Not reported	*Not reported*
Summary Result/s		*none of sexual function subscales were significantly different between two groups (p > 0.05).*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
Quality assessment based on assessment for Pastoor et al. 2018			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Yes*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Partial*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*No*
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Not reported*
ATTRITION BIAS	What percentage of the individuals recruited into	X% treatment X% control/ comparison Not reported	*Not relevant for the included studies*

	each arm of the study were lost to follow up?		
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*Not reported*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Partial*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*No*
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate to high*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Stovall et al. 2012*
Study Citation	Stovall, D.W., Scriver, J.L., Clayton, A.H., Williams, C.D. and Pastore, L.M., (2012). Sexual function in women with polycystic ovary syndrome. J Sex Med 2012; 9, 224-230. doi: 10.1111/j.1743-6109.2011.02539.x.
Study Country	*USA*
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*treatment-naive women diagnosed with PCOS (cases) who had agreed to participate in a complementary and alternative therapy randomized clinical trial.*

Control population	*Waiting room university gynaecological department*	
PCOS diagnostic criteria	*NICHD*	
N per group	*PCOS 92* *Controls 82*	
Setting	*Hospital*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary: CSFQ* *Self-report*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* *We evaluated the sexual functioning of women with untreated PCOS in comparison with controls. Furthermore, we examined specific aspects of sexual functioning that might be associated with PCOS. In addition, we evaluated the association of total serum testosterone levels, BMI, hirsutism, and acne with the components of sexual functioning in women with PCOS.*
Inclusion criteria	Yes Partial No Not reported	*PCOS:* *(i) a diagnosis of PCOS using the NICHD criteria of oligomenorrhea, nondiabetic, with self-reported hirsutism and/or acne and/or elevated free testosterone; (ii) age 18 to 43 years; (iii) weight _ 250 pounds (113 kg); and (iv) at least one menses in the past 6 months but no more than eight menstrual periods in the most recent 12 months without hormonal intervention.* *Controls:* *(i) no prior or current diagnosis of PCOS; (ii) age 18 to 45 years; (iii) nondiabetic; (iv) weight _ 250 pounds (113 kg); (v) nonhirsute; and (vi) regular monthly cyclic menses.*
Exclusion criteria	Yes Partial No Not reported	*Partial (not clear if these are for both groups)* *Exclusion criteria: (i) prior or current use of oral hypoglycemic agents or insulin; (ii) the use of hormonal contraceptives or any other hormonal intervention in the 60 days prior to enrollment; (iii) currently pregnant or breastfeeding during the prior 30 days; (iv) immune deficiency; (v) fasting blood glucose level > 125 mg/dL; and (vi) hemoglobin A1C (HgbA1C) level > 6.0%.*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial	*Not relevant for the included studies*

		No Not reported	
Was matching performed?		Yes Partial No Not reported	*Not reported*
Summary Result/s		*Based on total CSFQ scores, sexual dysfunction was present in 27.2% of cases vs. 24.4% of controls (not signifcant).Women with PCOS had a significantly lower orgasm/completion score compared with women in the control group (P < 0.001).*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
Quality assessment based on assessment for Pastoor et al. 2018			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Yes*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*No*
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Not reported*
ATTRITION BIAS	What percentage of the individuals recruited into	X% treatment X% control/ comparison Not reported	*Not relevant for the included studies*

	each arm of the study were lost to follow up?		
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*Not reported*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Yes*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Partial*
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Tan et al. 2008*
Study Citation	Tan, S., Hahn, S., Benson, S., Janssen, O.E., Dietz, T., Kimmig, R., Hesse-Hussain, J., Mann, K., Schedlowski, M., Arck, P.C. and Elsenbruch, S., (2008). Psychological implications of infertility in women with polycystic ovary syndrome. Hum Reprod. 2008; 23, 2064-71. doi: 10.1093/humrep/den227.
Study Country	*Germany*
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*University Hospital of Essen* *(same as Elsenbruch 2003, Hahn 2005)*
Control population	*Same as Elsenbruch et al. 2003*

PCOS diagnostic criteria	*NIH 1990, Rotterdam*	
N per group	*PCOS 115* *Control 50*	
Setting	*University Hospital*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcome:* *VAS sexual function, sexual satisfaction, impact PCOS characteristics* *Not relevant outcomes:* *BDI, SF-36, SCL-90, FKW (desire to have a child)* *All self-report*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* we compared psychosocial functioning in PCOS women with and without a present unfulfilled wish to conceive in order to test the hypothesis that PCOS women with a present unfulfilled wish to conceive would experience more psychological problems, particularly increased rates of depression, lower quality-of-life, and decreased sexual satisfaction and self-worth, when compared with PCOS patients without the present desire to conceive.
Inclusion criteria	Yes Partial No Not reported	*Not reported* *(same as Elsenbruch 2003?)*
Exclusion criteria	Yes Partial No Not reported	*Not reported* *(same as Elsenbruch 2003?)*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Not reported* *(same as Elsenbruch 2003?)*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Not relevant for the included studies*
Was matching performed?	Yes Partial No Not reported	*Not reported*
Summary Result/s	Compared with PCOS patients without the desire for a child,PCOS patients with the present wish to conceive reported a significantly higher frequency of sexual intercourse in the past month. No differences between PCOS groups were observed regarding the amount of sexual thoughts and fantasies, the importance of a satisfying sex life, the actual satisfaction with the sex life or with the perceived	

		sexual attractiveness. However, PCOS women without the current desire for a child indicated to have experienced more pain during sexual intercourse, to experience a more negative effect of excessive body hair on sexuality and to perceive more difficulties forming social contacts due to changes in outer appearance	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
Quality assessment based on assessment for Pastoor et al. 2018			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Not reported*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*Not reported*
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Not reported*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant for the included studies*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*Not reported*

REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Not reported*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*Not reported*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Partial*
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Zueff et al. 2014*
Study Citation	*Zueff, L.N., Lara, L.A., Vieira, C.S., Martins Wde, P. and Ferriani, R.A., (2015). Body composition characteristics predict sexual functioning in obese women with or without PCOS. J Sex Marital Ther. 2015; 41, 227-37. doi: 10.1080/0092623X.2013.864369.*
Study Country	*Brazil*
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*a convenient sample of sexually active obese Brazilian women with PCOS who were participating in a contraception program they were invited as they were admitted for gynecological follow-up at the Outpatient Clinic of the Human Reproduction Sector, Department of Gynecology and Obstetrics at the Faculty of Medicine of Ribeirao Preto, Sao Paolo*
Control population	*a convenient sample of sexually active obese Brazilian women without PCOS who were participating in a contraception program they were invited as they were admitted for gynecological follow-up at the Outpatient Clinic of the Human Reproduction Sector, Department of Gynecology and Obstetrics at the Faculty of Medicine of Ribeirao Preto, Sao Paolo*

PCOS diagnostic criteria	*Rotterdam*	
N per group	*PCOS 43* *Control 44*	
Setting	*Hospital*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary: SQ-F* *Not relevant: HADS* *All self-report*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* *the present study aimed to assess the effect of the PCOS on the sexual functioning of obese women and to determine which body measures can predict sexual functioning among obese women with and without PCOS.*
Inclusion criteria	Yes Partial No Not reported	*Partial* *Obesity was defined as a body mass index ≥ 30 kg/m2 and < 40 kg/m2, based on theWorld Health Organization system*
Exclusion criteria	Yes Partial No Not reported	*Yes* *the presence of chronic diseases such as neoplasias, neuropathy or systemic arterial hypertension; the use of hormonal contraceptives, anticonvulsants, or any antiandrogenic medications (e.g., cyproterone acetate, spironolactone) in the past 12 months; and* *the use of tobacco, alcohol, or illicit drugs*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Partial*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Not relevant for the included studies*
Was matching performed?	Yes Partial No Not reported	*Yes* *On BMI*
Summary Result/s	*No significant difference between groups was observed in weight, waist-hip ratio, body mass index, serum glucose, cholesterol, triglycerides, total testosterone, sex hormone binding globulin, total Sexual Quotient-Female version score, and the total score of ≤ 60 for subjects (risk for sexual dysfunction) and Hospital Anxiety and Depression.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
Quality assessment based on assessment for Pastoor et al. 2018		

SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Yes*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*No*
PERFORMANCE	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	5.Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Not reported*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant for the included studies*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*1/44 control*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Yes*

OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*Not reported*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Partial*
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Akbari Sene et al. 2021*	
Study Citation	*Akbari Sene A, Tahmasbi B, Keypour F, Zamanian H, Golbabaei F, Amini-Tehrani M. (2021) Differences in and correlates of sexual function in infertile women with and without polycystic ovary syndrome. Int J Fertil Steril. 2021; 15(1): 65-72. doi: 10.22074/IJFS.2021.6206.*	
Study Country	*Iran*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Infertile PCOS women visiting a infertility centerin Tehran, Iran*	
Control population	*Infertile non-PCOS women visiting a infertility centerin Tehran, Iran, by convenience sampling*	
PCOS diagnostic criteria	*PCOS guideline 2018*	
N per group	*PCOS 116* *Non-PCOS 93*	
Setting	*Two infertility centers in Tehran, Iran*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary: FSFI* *Self-report*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* *The present study, therefore, investigated the differences between infertile Iranian women with and without PCOS in terms of sexual function. It also aimed to evaluate the degree to which hormonal, anthropomorphic, and hyperandrogenic manifestations may be correlated with the sexual function of these groups of women.*

Inclusion criteria		Yes Partial No Not reported	*Not reported*
Exclusion criteria		Yes Partial No Not reported	*Partial* *Certain disorders, including thyroid disease (based on thyroid-stimulating hormone (TSH) level), hyperprolactinemia (based on prolactin level), and non-classic congenital adrenal hyperplasia (based on 17-hydroxyprogesterone (17-OHP) level), were ruled out by clinical judgment.* *psychiatric disorders; severe emotional problems in the past six months; consumption of oral contraceptive pills, gonadotropin-releasing hormone (GnRH) agonists, or insulin sensitizers in the past six months; chronic cardiovascular diseases; primary or secondary vaginismus and dyspareunia; pelvic mass; active genital infection; external vaginal anomalies; pelvic endometriosis; and partner's sexual dysfunction.*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Partial*
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Not relevant for the included studies*
Was matching performed?		Yes Partial No Not reported	*Not reported*
Summary Result/s		*Eighty-four (40.2%) patients including 42.2% of the PCOS patients and 37.6% of the non-PCOS cases (P>0.05), were suspected of female sexual dysfunction (FSD). The most impaired functions in both groups were desire and arousal. Sexual function was not significantly different between the groups. However, PCOS women had more orgasm problems and acne worsened their sexual function. Total FSFI was positively associated with prolactin level but negatively associated with central obesity in the non-PCOS group; it was negatively correlated with marital duration in the PCOS group. Luteinizing hormone (LH) and pain, prolactin level and lubrication, and central obesity and arousal were correlated in the non-PCOS women. Prolactin level and orgasm, marital duration and arousal, and marital duration and the total FSFI were correlated in the PCOS women.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Yes*
	Was the case definition adequate and established	Yes Partial No	*Yes*

	in a standard, valid and reliable way?	Not reported	
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*Partial* *Not clearly reported*
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Not reported*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant for the included studies*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*7/216* *0.03 of total recruited patients because of not sexually active after FSFI scoring. Not clear if PCO or Non-PCO group.*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Yes* *Small (but statistically significant) demographic difference between group in patients age and spouses age. Confounding effect of age was analysed and no significant changes in the pattern of the comparison emerged.*
	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*

OTHER BIAS	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Yes*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Ashrafi et al. 2022*
Study Citation	*Ashrafi, M., Jahangiri, N., Sadatmahalleh, S.J., Mirzaei, N., Hesari, N.G., Rostami, F., Mousavi, S.S., & Zeinaloo, M. (2022). Does prevalence of sexual dysfunction differ among the most common cause of infertility? A cross-sectional study. BMC Women's Health, 2022: 22:140. doi.org/10.1186/s12905-022-01708-y*
Study Country	*Iran*
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Infertile women were those with primary or secondary infertility and were grouped based on the existence of polycystic ovary syndrome (PCOS), endometriosis and male factor, as the most common causes of infertility.*
Control population	*Fertile women were recruited from the health-care centers in Tehran and all had used a condom as a birth control method;*
PCOS diagnostic criteria	*Rotterdam*
N per group	*PCOS 80* *Control MFI 80 (we only used the MFI group as a comparison)* *Control endometriosis 80* *Control fertile 160*
Setting	*Royan Institute and health care centers in Tehran, Iran.*
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary: FSFI* *Not relevant: HADS* *All self-report*

Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* *Since no study has yet compared sexual function based on the different causes of infertility, the present work compared sexual dysfunction and its prevalence among Iranian females with three most-common infertility etiologies, using a validated questionnaire.*
Inclusion criteria	Yes Partial No Not reported	*Inclusion criteria consisted of an age range of 18 to 45 years, living with the husband, and being Sexually active in the last 4 weeks.*
Exclusion criteria	Yes Partial No Not reported	*Participants who filled the questionnaire incompletely or refused to complete the study were excluded*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Partial*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Not relevant for the included studies*
Was matching performed?	Yes Partial No Not reported	*Not reported*
Summary Result/s	*The prevalence of female sexual dysfunction was 98.8% in women with PCOS, 100.0% in those with endometriosis,and 80.0% in those with male factor infertility. Overall, 36.2% of the enrolled fertile women were suffering from sexual dysfunction.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS – Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Partial* *Control group using fertile volunteer participants from other type of healthcare centres then the ones of the PCOS cases, both in the same city.*
SELECTION BIAS – Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Not reported*
SELECTION BIAS – Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*Not reported*

PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Partial*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Not reported*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant for the included studies*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*0*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Partial* *Small difference in age, big difference in education level and job status. Some difference in BMI.*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Partial*

COMMENTS		
What is the overall risk of bias?	Low Moderate High Insufficient information	*Moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*No*	

Study ID	*Aydogan et al. 2020*	
Study Citation	*Aydogan Kirmizi, D, Base, E, Onat, T, Caltekin, MD, Yalvac, ES, Kara, M & Gocmen, AY. (2020). Sexual function and depression in polycystic ovary syndrome: is it associated with inflammation and neuromdulators? Neuropeptides. 2020; 84. 10.1016/j.npep.2020.102099*	
Study Country	*Turkey*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Fertile women with PCOS* *Infertile women with PCOS*	
Control population	*Healthy women with regular menstrual cycles and without evidence of hyperandrogenism or PCOS were included in the control group.*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	*PCOS 20 (fertile)* *Control 30*	
Setting	*Tertiary center*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary: FSFI* *Not relevant: BDI* *All self-report*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* *This study aimed to evaluate the relationship between depression and sexual dysfunction seen in patients with PCOS and serum GABA, glutamate, BDNF, and inflammatory markers and to contribute to the determination of the etiopathogenesis of PCOS.*
Inclusion criteria	Yes Partial No Not reported	*No*
Exclusion criteria	Yes Partial No Not reported	*Yes* *we excluded all patients in whom secondary etiologies were clinically suspected, including hyperprolactinemia, thyroid*

		dysfunction, Cushing's syndrome, congenital adrenal hyperplasia, and virilizing tumors. The exclusion criteria were: (i) history of any exogenous hormonal agent use in the last 3 months; (ii) chronic systemic diseases (e.g. chronic renal failure, chronic heart failure, chronic liver disease); (iii) use of antidepressants and anti-inflammatory agents (e.g. steroids); (iv) (iv) hormonal therapies and insulin sensitizers related to PCOS, or history of antiandrogen drug use in the last 3 months; (v) any antioxidant supportive therapy (e.g. vitamin C, etc.); and (vi) smoking. Furthermore, after a general psychiatric evaluation conducted by a psychiatrist, patients with bipolar disorder, psychotic symptoms during the current major depressive episode, a history of psychosis other than the mood disorder episode, any eating disorders, post-traumatic stress disorder, or a history of substance use were excluded from the study.
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Partial*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Not relevant for the included studies*
Was matching performed?	Yes Partial No Not reported	*Not reported*
Summary Result/s	*Lubrication was significantly higher in the PCOS groups compared to those in the control group (p = 0.040). There were no statistically significant differences in other FSFI scores between the groups. Although not statistically significant, sexual dysfunction was higher (50%) in the PCOS infertile group*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS – Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Partial* *Control group using healthy volunteer participants in reproductive age, unknown where recruited.*
SELECTION BIAS – Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Partial.* *Ultrasound was abdominally performed in a number of patients (less accurate). Guideline recommends tve or measuring volume. Was not mentioned in article*
SELECTION BIAS – Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*Not clearly reported*

PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Partial* *For blood samples*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Not reported*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant for the included studies*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*Not reported*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Partial*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Yes*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*

COMMENTS		
What is the overall risk of bias?	Low Moderate High Insufficient information	*Moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*No*	

Study ID	*Basirat et al. 2019*	
Study Citation	*Basirat, Z, Faramarzi, M, Esmaelzadeh, S, Firoozjai, SA, Mahouti, T, & Geraili, Z. (2019) Stress, depression, sexual function, and alexithymia in infertile females with and without polycystic ovary syndrome: a case-control study. Int J Fert STerl. 2019;13(3):203-208. doi: 10.22074/ijfs.2019.5703.*	
Study Country	*Iran*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*240 infertile females through census sampling methods (PCOS and control)* *Infertile women with definite diagnosis of PCOS*	
Control population	*Infertile women without PCOS*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	*PCOS 120* *Control 120*	
Setting	*Infertility clinic Fatemeh Azahra Infertility and Reproductive Health Research Center, Babol, Iran*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary: FSFI* *Not relevant: FPI, BDI-II, TAS-20* *All self-report*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* *As differences in psychological profiles between infertile females with PCOS and those without PCOS are not clear yet, the current study aimed at comparing the psychological profile of these two groups. To the authors' best knowledge, it was the first study that compared psychological profiles of infertile females with and with-out PCOS in terms of four domains: infertility stress, depression, female sexual dysfunction, and alexithymia (i.e. the inability to distinguish and describe feelings and the absence of fantasies).*
Inclusion criteria	Yes Partial No Not reported	*Yes* *Inclusion criteria for infertile females with and without PCOS were being 15-45 years old, completion of primary school as the minimum level of education, being married and having an active sex life, and lacking any problems in speaking or understanding the Persian language; also, a definite diagnosis of PCOS was an additional criterion for PCOS group.*

Exclusion criteria		Yes Partial No Not reported	*Yes* *Exclusion criteria for all participants (females with and without PCOS) were diagnosis of the husband with azoospermia or oligospermia, presence of other disorders that could mimic PCOS syndrome such as congenital adrenal hyperplasia, thyroid disease, or hyperprolactinemia.*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Partial*
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Not relevant for the included studies*
Was matching performed?		Yes Partial No Not reported	*Yes* *On age, level of education, duration of infertility*
Summary Result/s		*There was no significant difference between the two groups regarding the mean scores of depression symptoms and sexual function.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Yes* *Infertile women from Infertility clinic Fatemeh Azahra Infertility and Reproductive Health Research Center, Babol, Iran*
SELECTION BIAS	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
SELECTION BIAS	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*Not reported*
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*

	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Not reported*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant for the included studies*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*PCOS 9/129* *Controls 9/129*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Yes*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Low*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Deniz et al. 2020*	
Study Citation	*Deniz, A & Kehribar, DY. (2020). Evalulation of sexual functions in infertile women with polycystic ovary syndrome. Niger J Clin Pract, 2020; 23:1548-54. DOI: 10.4103/njcp.njcp_15_20*	
Study Country	*Turkey*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*This naturalistic, cross-sectional study evaluated 235 women who were admitted to Private Manavgat Obstetrics and Gynecology Center in Antalya, Turkey*	
Control population	*Healthy women without PCOS and without infertility*	
PCOS diagnostic criteria	*ESHRE-ASRM*	
N per group	*PCOS fertile 50* *Control fertile 50*	
Setting	*Hospital*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary: FSFI* *Not relevant: BDI* *All self-report*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* *In the present study, we aimed to investigate the factors affecting sexual functions in women with PCOS and to evaluate differences in sexual functions among women with and without infertility.*
Inclusion criteria	Yes Partial No Not reported	*Partial* *20-45 years*
Exclusion criteria	Yes Partial No Not reported	*Yes* *not having sexual intercourse in the past month, women and their partners having a need for inpatient treatment, women whose partners were absent at the same address in the past month, women and their partners with medical disorders interfering with sexual intercourse, women with alcohol and illicit drug use, women with psychiatric disorders, women with psychiatric drug use, women with a systemic disease complicating or preventing physical activity, women with a genital anatomical anomaly, women with a pathology creating mass formation in the genital and pelvic organs, women with genitourinary infection, and women with an endometriosis diagnosis*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Partial*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No	*Yes*

		Not reported	
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Not relevant for the included studies*
Was matching performed?		Yes Partial No Not reported	*Not reported*
Summary Result/s		*The PCOS plus infertility group showed significantly lower FSFI scores than the PCOS group in terms of desire, lubrication, orgasm, satisfaction, and pain. A significant negative correlation was observed between BMI and BDI scores in the PCOS plus infertility group (r:−0.384, P = 0.04).*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Yes*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Partial* *Ascertainment not reported* *Criteria for infertility were not specified.*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*Not reported*
PERFORM ANCE	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Partial*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Not reported*

ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant for the included studies*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*85/235 were excluded from the study*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Partial* *Because there is no correlation analysis of BDI/FSFI and BMI with the healthy controls (HC).*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Partial* *There is a statistical significant difference in BMI between PCOS+infertility and HC*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Yes*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Glowinska et al. 2020*
Study Citation	*Glowinska, A, Duleba, AJ, Zielona-Jenek, M, Siakoswka, M, Pawelczyk, L, & Banaszweska, B. (2020). Disparate Relationship of sexual satisfaction, self-esteem, anxiety, and depression with endocrine profiles of women with or without PCOS. Reproductive Sciences, 2020; 27:432-44. doi.org/10.1007/s43032-019-00061-0*
Study Country	*Poland*
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with PCOS were recruited from the Gynecology Clinic at the Poznan University of Medical*

	Sciences.	
Control population	*Recruited via internet advertisements*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	*PCOS 96* *Control 47*	
Setting	*University hospital*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary: sexual satisfaction scales* *Not releveant: MSEI, STAI, BDI* *All self-report*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* *In view of the above outlined findings and discordant reports,this study was designed to carry out a comprehensive evaluation of the relationship of sexual satisfaction and other relevant psychological functions with clinical, endocrine, and metabolic profiles of women with and without PCOS. In particular, we focused on the relationship of psychosexual characteristics with BMI and testosterone level.*
Inclusion criteria	Yes Partial No Not reported	*Partial* *3 months before the study none of the study subjects used any form of oral contraceptives, other steroid hormones, or any other medications likely to affect ovarian function, insulin sensitivity, or lipid profile.* *Controls: regular menstruation and no clinical symptoms of hyperandrogenism.*
Exclusion criteria	Yes Partial No Not reported	*Partial* *Congenital adrenal hyperplasia was excluded on the basis of morning follicular phase 17-hydroxyprogesterone below 2 ng/mL. None of the subjects had elevated prolactin,thyroid disease, Cushing disease, diabetes mellitus, or symptoms of any other endocrinopathy.*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Partial*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Not relevant for the included studies*
Was matching performed?	Yes Partial No Not reported	*Yes* *on age and social parameters*

Summary Result/s			*Overall, sexual satisfaction scores were comparable among women with and without PCOS. However, psychosexual function of women with PCOS exhibited distinguishing characteristics. The unconscious aspect of sexuality: frequency of erotic dreams, significantly correlated with free testosterone (ρ = 0.24, P = 0.03) and DHEAS (ρ = 0.31, P = 0.004) only in the PCOS group. In contrast, in women with PCOS, the frequency of masturbation did not correlate with endocrine profiles, but correlated with trait anxiety (ρ = 0.21, P = 0.049) and depression (ρ = 0.21, P = 0.05).*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Partial* *Cases from clinic, receiving fertility treatment, Control from general population.*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*Partial* *Seems as they also received hormonal sreening. Not clear how many of the controls where excluded because of PCOS diagnosis after evaluation.*
PERFORMANCE	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*No* *Sexual questionnaires they used are not validated.*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Not reported*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant for the included studies*

	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*Only report on controls: 16 out of 63 not included=25%.*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Partial* *Because a large proportion of PCOS participants also received infertility treatment compared to the control group (big difference! P=<0.0001)*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Yes*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Karsten et al. 2021*
Study Citation	*Karsten, MDA, Wekker, V, Groen, H, Painter, RC, Mol, BWJ, Laan, ETM, Roseboom, TJ, & Hoek, A. (2021). The role of PCOS in mental health and sexual function in women with obesity and a history of infertility. Human Reproduction Open. 2021;1:1-11. doi.org/10.1093/hropen/hoab038*
Study Country	*The Netherlands*
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with infertility and a BMI of 29 or higher participated in this follow-up study. PCOS was diagnosed by clinicians at entry within the initial trial, based on the Rotterdam 2003 criteria*
Control population	*women with obesity and infertility without PCOS (ovulatory and anovulatory non-PCOS women (WHO class I and II)).*

PCOS diagnostic criteria	*Rotterdam*	
N per group	*PCOS 73* *Control women 100*	
Setting	*University hospital*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary: MSFQ* *Not relevant: HADS, SF-36* *All self-report*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* *The aim of the current study was therefore to investigate whether mental health and sexual function differ between women with or without PCOS with a comparable BMI and fertility characteristics. We therefore compared symptoms of anxiety and depression, quality of* *life and sexual function in women with obesity and a history of infertility with and without PCOS.*
Inclusion criteria	Yes Partial No Not reported	*Yes* *18-39years, infertility, BMI 29 or higher*
Exclusion criteria	Yes Partial No Not reported	*Not reported,* *Reported elsewhere*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Not reported*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Not relevant for the included studies*
Was matching performed?	Yes Partial No Not reported	*Not reported*
Summary Result/s	*Symptoms of anxiety and depression, physical quality of life and sexual function did not differ significantly between obese women with and without PCOS. However, women with PCOS had a worse mental quality of life summary component score (_3.60 [95% CI _6.72 to _0.56]), mainly due to a lower score on the subscale 'role limitations due to emotional problems' (_12.41 [95% CI _22.78 to _2.28]), compared to women without PCOS. However, compared to an age-matched Dutch reference population, the obese infertile women with and without PCOS both scored lower on almost all physical and mental quality of life subscales.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Yes*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Not reported*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*Not reported*
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Not reported*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant for the included studies*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*47/190* *17 did not complete all questionnaires* *9 out of 73 PCOS because of no intercourse= 12,3%* *21 out of 100 Non-PCOS because of no intercourse= 21 %*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Partial* *because of a big difference between the groups in intercourse activity and selectivity in report of the MFSQ.*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Yes*

OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*Partial*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS		*This is a follow up study from a RCT study by the same group. Not all criteria etc are reported in this paper, but are probably reported in previous papers. We did not read those papers.*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate* *(insuffient information?)*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Kaluzna et al. 2021*
Study Citation	*Kaluzna, M, Nomejko, A, Slowinska, A, Wachowiak-Ochmanska, K, Pikosz, K, Ziemnicka, K, & Ruchala, M. (2021). Lower sexual satisfaction in women with polycystic ovary syndrome and metabolic syndrome. Endocrine connnections. 2021;10(9):1035-1044. doi.org/10.1530/EC-21-0257*
Study Country	*Poland*
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*PCOS patients mean age 26.34±5.47 years*
Control population	*A CON group consisted of eumenorrheic healthy Individuals without reported problems concerning endocrine disorders, sexual development, and maturation. Mean age 27.12 ± 4.97 years*
PCOS diagnostic criteria	*Rotterdam, PCOS guideline 2018*
N per group	*PCOS 190* *Control 197*
Setting	*Not reported (probably university hospital)*
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary: Sexual Satisfaction Questionnaire* *Not relevant: WHOQOL-bref, CEDS-R* *All self-report*

Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	*Yes* *This study aimed to screen SS and psychological conditions in PCOS women in comparison to eumenorrheic controls. The relationship of depressive symptoms, HRQoL, and clinical phenotype of PCOS (clinical and biochemical hyperandrogenism (HA), simple and central obesity, insulin resistance (IR), lipid disturbances, metabolic syndrome (MS)) with SS was evaluated.*
Inclusion criteria		Yes Partial No Not reported	*Not reported*
Exclusion criteria		Yes Partial No Not reported	*Yes* *PCOS and CON women were excluded if they had severe psychiatric disorders (schizophrenia, bipolar disorder ,severe depression), diabetes, severe liver or kidney disease, the use of oral contraceptive or anti-androgen therapy in the last 3 months or current pregnancy or diagnosed and/or treated infertility.*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Partial*
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Not relevant for the included studies*
Was matching performed?		Yes Partial No Not reported	*Yes* *Age matched*
Summary Result/s		*Patients with PCOS and MS had lower SS vs non-MS-PCOS. There w ere no significant differences in the level of SS, presence of depressiv e symptoms, or HRQoL between PCOS and CON (P > 0.05). Negative correlations were found between the SS level and BMI, waist circumference, and waist-to-height ratio i n PCOS women. However, overweight or obese PCOS women did not differ in SS levels vs no rmal-weight PCOS patients. The social dimension of WHOQOL-BREF was the only sign ificant predictor of SS in PCOS patients.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Not reported*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*

	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*Partial* *Only in a part of the control group*
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Partial* *Questionnaire was only once validated in Poland and not otherwise tested or used elsewhere.*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant for the included studies*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*Not reported*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Partial* *Significant difference in BMI, WC, WHtR between PCO and CON group. But is analysed in correlation analysis.*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*

	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS		*SS Questionnaire only validated in Poland.*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Mantzou et al. 2021*	
Study Citation	*Mantzou, D, Stamou, MI, Armeni, AK, Roupas, ND, Assimakopoulos, K, Adonakis, G, Georgopoulos, NA & Markantes, GK. (2021). Impaired sexual function in young women with PCOS: the detrimental effect of anovulation. J Sexual Medicine, 2021;18:1872-1879. doi.org/10.1016/j.jsxm.2021.09.004*	
Study Country	*Greece*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*PCOS 20-30 years* *Patients with PCOS were recruited* *from the Division of Endocrinology of the University Hospital* *of Patras;*	
Control population	*Healthy controls* *Recruited among attendees of 2 workshops of female sexuality* *conducted in the universities of Athens and Patras*	
PCOS diagnostic criteria	*Androgen Excess Society*	
N per group	*PCOS 76* *Controsl 133*	
Setting	*University Hospital*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary: FSFI* *Not relevant: HADS* *Self-report*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* *The aim of this study was to examine for the first time the different aspects of female sexuality in young women of Greek origin with polycystic ovary syndrome (PCOS) who do not seek fertility and to attempt to associate hormonal changes and ovulatory status with their sexual function.*
Inclusion criteria	Yes Partial	*Partial*

		No Not reported	*Controls had normal ovulatory menstrual cycles (28−35 days) and no clinical/biochemical hyperandrogenemia.* *All women recruited were sexually active in the last 4 weeks, participated voluntarily in the study and did not seek fertility*
Exclusion criteria		Yes Partial No Not reported	*Yes* *for both the women with PCOS and the healthy controls: chronic diseases, psychiatric disorders, use of drugs that could affect the hypothalamus−pituitary−gonadal axis (eg. oral contraceptive pills, GnRH agonists, antipsychotics, antidepressants, chemotherapeutic agents). Women on such drugs were excluded due to their inhibited ovarian hormone secretion.*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Partial*
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Not relevant for the included studies*
Was matching performed?		Yes Partial No Not reported	*Not reported*
Summary Result/s		*Women with PCOS demonstrated lower scores than controls in arousal (5.04 ± 1.19 vs 4.48 ±1.44, P < .001), lubrication (5.29 ± 1.17 vs 4.69 ± 1.54, P < .001), orgasm (4.78 ± 1.40 vs 4.11 ± 1.61, P = .001), satisfaction (5.22 ± 1.10 vs 4.78 ± 1.31, P = .016), and total score of the FSFI (29.51 ± 5.83 vs 26.76 ± 6.81, P < .001), even after correction for BMI. When corrected for total testosterone, the domains of lubrication, satisfaction, and total score of FSFI remained significantly impaired in women with PCOS (P values .037, .024, &.044 respectively). In multivariate logistic regression analysis, after adjusting for the effect of BMI and hormonelevels, dysfunction in orgasm, satisfaction and the total FSFI score were still 3−4 times more common in PCOS (adjusted OR [95% CI]: 3.54, P = .020; 2.96, P = .050; 3.87, P = .027). Even though no statistically significant differences were observed between women with ovulatory PCOS and controls, we detected statistically significant differences in all domains of sexual function apart from pain between controls and PCOS women with anovulation (desire P value .04, arousal P value <.001, lubrication P value <.001, orgasm P value .001, satisfaction P value .001 and FSFI total score P value <.001).*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*No*
	Was the case definition adequate and established	Yes Partial No	*Yes*

	in a standard, valid and reliable way?	Not reported	
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*Not clearly reported*
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Not reported*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant for the included studies*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*Not reported*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*No* *Significant difference in Weight and BMI* *Different populations*
	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*

OTHER BIAS	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS		*Some selection bias here because they were attending a workshop about female sexuality, which might already impact on their sexual satisfaction/function.*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*Low*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Naumova et al. 2021*	
Study Citation	*Naumova, I, Castelo-Branco, C, & Casals, G. (2021). Psychological issues and sexual function in women with different infertility causes: focus on polycystic ovary syndrome. Reproductive Sciences. 2021;28:2830-2838. doi.org/10.1007/s43032-021-00546-x*	
Study Country	*Spain*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*46 PCOS patients aged 18 to 40 who met the Rotterdam criteria and did not receive oral contraceptive pills or medications over the past 6 months were included in the study* *Patients were recruited at the reproductive medicine unit of the Hospital Clinic Barcelona where women complained of infertility.*	
Control population	*Women with tubal factor infertility* *Healthy Women with male factor infertility*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	*PCOS 46* *Women with TFI 50* *Women with MFI 31 (we only used this group as a comparison)*	
Setting	*Hospital*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary: FSFI* *Not relevant: BDI-II, HAMA-A* *All self-report*	
Does the study have a clearly focused question and/or PICO?	Yes Partial	*Yes*

	No Not reported	*The purpose of this study was to assess the prevalence of depressive and anxiety symptoms and sexual dysfunction in infertile PCOS patients in comparison with women with other infertility causes (tubal and male infertility factors), and to identify factors predisposing PCOS subjects to emotional distress and impaired sexual function.*
Inclusion criteria	Yes Partial No Not reported	*Not reported*
Exclusion criteria	Yes Partial No Not reported	*Not reported* *None of the women of the three groups was undergoing medically assisted reproduction (MAR) while participating in the present study. None of the women had any extragenital pathology.*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Not reported*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Not relevant for the included studies*
Was matching performed?	Yes Partial No Not reported	*Not reported*
Summary Result/s	*Women with infertility due to PCOS showed a significantly higher prevalence of depressive (48.6 vs 19.4 and 12.9%, p < 0.01) and anxiety symptoms (21.6 vs 5.6 and 3.2%, p = 0.041) than respondents of reference groups. Sexual function in PCOS subjects was impaired in the areas orgasm and satisfaction (p < 0.01 for both) compared to patients of reference groups. Clinical, biochemical hyperandrogenism, and overweight were associated with a higher incidence of depressive and anxiety symptoms in the infertile PCOS group (p < 0.01 for all). Besides, the severity of anxiety symptoms was associated with the number of medically assisted reproduction attempts (p = 0.014). Weight gain and age (p = 0.04 and p = 0.047) were associated with impaired sexual functioning. The relation between reduced sexuality and depressive/anxiety symptoms was found (p = 0.038 and p = 0.012, respectively).*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Yes*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*Partial.* *The endogenous and exogenous infertility criteria were not clearly defined how they were assessed.*
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Not reported*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant for the included studies*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*PCOS 9/46* *TFI 14/50* *MFI 0*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Yes*

OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*No* *Power was calculated at 102 cases for two groups*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate* *(insufficient information?)*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Taghavi et al. 2021*
Study Citation	*Thagavi, SA, Aramesh, S, Azizi-Kutenaee, M, Allan, H, Safarzadeh, T, Taheri, M, Salari, S, Khashavi & Bazarganipour, F. (2021) The influence of infertility on sexual and marital satisfaction in Iranian women with polycystic ovary syndrome: a case-control study. Middel East Fertilty Society Journal. 2021;26(2). doi.org/10.1186/s43043-020-00047-y*
Study Country	*Iran*
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*women with PCOS referred to an infertility clinic in Omelila Hospital in Hormozgan province in Iran*
Control population	*The control group was also consistent with healthy married women within the age range of 18-45 who had no chronic disease, had a regular menstrual cycle, and they were selected from patients' companions by convenience sampling method.*
PCOS diagnostic criteria	*Rotterdam*
N per group	*PCOS 90* *Control 90*
Setting	*Infertility clinic*
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary: FSFI* *Not relevant: ENRICH, Larson questionnaire, IIEF-5* *All self-report*

Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* *the aim of this study is to evaluate sexual and marital satisfaction in couples with PCOS compared with a control group.*
Inclusion criteria	Yes Partial No Not reported	*Partial* *PCOS: desire to participate in the study, being 18–45 years of age, married, Iranian, having two of the following Rotterdam diagnostic criteria [10]: (1) polycystic ovaries visualized on ultrasound scan (presence of 12 follicles or more in one or both ovaries and/or increased ovarian volume, i.e., > 10 ml), (2) clinical signs of hyperandrogenism (hirsutism score based on hirsutism score greater than 7 or obvious acne) or chemical hyperandrogenism, (3) having an interval between menstrual periods > 35 days and/or amenorrhea, defined as the absence of vaginal bleeding for at least 6 months (i.e.,* *199 days). However, it should be noted we used only clinical signs for this study as our previous studies.*
Exclusion criteria	Yes Partial No Not reported	*Yes* *Our exclusion criteria were as follows: having nonclassic adrenal hyperplasia, thyroid dysfunction, hyperprolactinemia, smoking, problems in speaking or listening, taking any prescription medication (except allergy* *medications and occasional pain medications) for at least 3 months before entering the study, severe psychological stress at least 3 months before entering the study (loss of relatives, etc.), history of taking psychiatric medications at least 3 months before entering the study, having score* *< 12 according to International index of erectile function to both groups.*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Partial*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Not relevant for the included studies*
Was matching performed?	Yes Partial No Not reported	*Not reported*
Summary Result/s	*The results of this study show that the mean scores of sexual function, sexual satisfaction, and marital satisfaction were significantly lower in PCOS couples compared with the control group (P < 0.05). Infertility was reported as the strongest predictive factor for sexual function and marital satisfaction in couples with PCOS (P < 0.05). Compared to the control group, sexual and marital satisfaction was lower in patients with PCOS and their partners.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Partial*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Partial*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*Partial*
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Not reported*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant for the included studies*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*PCOS 9/99* *Control 14/104*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Partial* *Big difference in infertility status between the groups.. Was not defined precisely what the infertility criteria were.*

OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Yes*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 2

Question 2.3.

In women with PCOS what is the prevalence and severity of psychosexual dysfunction?

BACKGROUND:

Psychosexual function in PCOS may be influenced by the condition's complex interaction of endocrine, psychological, and metabolic factors. The first reports of psychosexual dysfunction in PCOS in the early 2000's suggest that PCOS may limit sexual self-worth, feminine identity, and sexual satisfaction (1-3). In 2018 a meta-analysis of 18 studies comparing sexual function as assessed by validated sexual function questionnaires and VAS (visual analogue scales) between PCOS and non-PCOS (4). While satisfaction with sex life was deemed equally important in both groups, sexual satisfaction, sexual attractiveness and sexual function were rated lower in those with PCOS. In terms of specific function subscales, the study showed lower scores for arousal, lubrication, and orgasm in PCOS.

Since then, a small meta-analysis, reported no difference in sexual function between PCOS and non-PCOS (5). However, this meta-analysis included a secondary analysis of a large infertility trial that required sexual intercourse three times a week, which may have increased sexual function scores for these participants (6). A subsequent, slightly larger meta-analysis from 2020, noted that individuals with PCOS tend to lack sexual satisfaction and report more dyspareunia (7).

Even though low sexual function scores are more common in PCOS, the prevalence of psychosexual function remains unknown, as most studies fail to report the percentage of low sexual function scores within their examined PCOS population. Furthermore, clinically relevant psychosexual dysfunction is defined through assessment of sexual distress in the context of low psychosexual function, which is not commonly reported. One study, that did report on psychosexual dysfunction in a PCOS treatment trial, found that lifestyle and combined oral contraceptive pills lead to an overall improvement of psychosexual dysfunction (8). However, the study lacked a non-PCOS comparison group. Therefore, the current GDG informing meta-analysis update is unable to report on the prevalence of psychosexual dysfunction in PCOS. In terms of psychosexual function alone, our meta-analysis notes a small but statistically significant reduction of sexual function in all assessed domains: desire, arousal, lubrication, orgasm and pain.

While subgroup analysis, separating impact by higher weight, infertility, presence of mood disorder (anxiety/depression), hormone levels and hirsutism would have been beneficial for GDG recommendations, the subgroup numbers of the current meta-analysis were still too small to result in clinically relevant data. Therefore, the relationship between PCOS and/or varying characteristics of PCOS and psychosexual dysfunction remains unclear.

GRADE EVIDENCE CERTAINTY	
Comparison	**GRADE for critical outcomes**
Comparison 1. Women with PCOS versus controls	⨁⨁◯◯ LOW

Evidence to Recommendations Framework

COMPARISONS (option versus other option)

PCOS vs non-PCOS

CONSENSUS RECOMMENDATION

- **CR:** Health professionals could consider the multiple factors that can influence psychosexual function in PCOS including higher weight, hirsutism, mood disorders, infertility and PCOS medications.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

- **CR:** Permission to discuss psychosexual function should be sought noting that the diagnosis of psychosexual dysfunction requires both low psychosexual function, combined with related distress

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

GRADE CONSIDERATIONS

Justifications:
Individuals with PCOS score statistically significantly lower on psychosexual function questionnaires than those that do not carry the diagnosis of PCOS but clinical relevance is unclear. We lack the corresponding distress scores which are required to meet the criteria for psychosexual dysfunction.
The impact of infertility, higher weight and other factors also cannot be ascertained on the current evidence and the independent impact of PCOS is unclear.

Subgroup considerations:
Not enough data is available to make subgroup recommendations in terms of risk for low sexual function including populations with infertility, different life stages, higher weight and mental health status.
The current tools are not inclusive of diversity.

Implementation considerations:
Health professionals may be reluctant to discuss psychosexual dysfunction [9].

Monitoring and evaluation considerations:
None

Research priorities:
Psychosexual function in combination with sexual distress (psychosexual dysfunction) should be assessed concurrently in research.
More inclusive research of diverse populations is needed.
Intervention studies in PCOS should consider including psychosexual dysfunction as an outcome where appropriate.
Examination of the effectiveness of treatment for psychosexual dysfunction in women with PCOS, including the impact this has on the process and outcome of PCOS treatment and management
Even though the evidence points to lower psychosexual function in PCOS, the relative effect of varying PCOS associated findings such as higher weight, hirsutism, mood disorder, sub- or infertility, sleep disorder, metabolic and endocrine disturbance needs exploration. Furthermore, the effect of lifestyle or pharmacological intervention on psychosexual dysfunction should be further explored by treatment type.

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Appendix:

BSSC-W

1. Are you satisfied with your sexual function? (mark one)

☐ Yes ☐ No

If NO, please continue to question 2

2. How long have you been dissatisfied with your sexual function?

.....

3. The problem(s) with your sexual function is (mark one or more)

☐ 1. Problems with little or no interest in sex

☐ 2. Problem with decreased sensation of clitoris or vagina

☐ 3. Problem with decreased vaginal lubrication (dryness)

☐ 4. Problem reaching orgasm

☐ 5. Problem with pain and/or cramping during sex

☐ 6. Other: .....

4. Which problem is most bothersome (circle)

Problem: 1 2 3 4 5 6

5. Would you like to talk about it with your GP?

☐ Yes ☐ No

If NO, please continue to question 6

6. Would you like to talk about it with another GP?

☐ Yes ☐ No

PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by ECR Lead: Punith Kempegowda

Other Members: Halimah Khalil, Kashish Malhotra, Eka Melson, Meri Davitadze

Supervised, edited and supported by the Evidence Team

GDG 2

Question 2.4.

In women with PCOS, what is the prevalence and severity of body image distress?

1. STUDY SELECTION

Table 1. PICO Criteria for Inclusion	
Question	**Q 2.4.1) In women with PCOS, what is the prevalence and severity of body image distress?** **Clinical Practice Points:** **- Should body image distress be screened as part of standard care?**
Clinical leads (key contacts)	**Elisabet Stener-Victorin, Leah Brennan**
Allocation ranking	**Level 1 – New systematic review**

	Participants (P)	**Intervention (I)**	**Comparison (C)**	**Outcomes (O)**	**Study type (S)**	**Limits** ***(language, year)***
Inclusion criteria	Females with PCOS (diagnosed by Rotterdam, NIH or AES) of any age, ethnicity and weight. Subgroups: • Adolescents • Ethnicity • Phenotype • Pregnancy If no evidence in PCOS, evidence related to obesity will be sought narratively by key contact (not searched by evidence team).	No restrictions (Any tools assessing body image distress) Note: tools to screen body image distress Body Image Scale, Rosenberg Self-Esteem Scale, Beck Depression, Body Image Concern Inventory (BICI), Stunkard Figure Rating Scale (FRS), Body Esteem Scale, Body Image Disturbance Body Image States Scale Situational Inventory of Body-Image Dysphoria (SIBID) (and short-form version) Body Image Acceptance and Action Questionnaire (BI-AAQ) Appearance Schemas Inventory (ASI, and revised versions) Body Esteem Scale for Adolescent and Adults Body Image Coping Strategies Inventory Body Satisfaction Scale (BSS) Body Image Ideals Questionnaire Assessment of Body-Image Cognitive Distortions Body Image Quality of Life Inventory Multidimensional Body self-relations questionnaire (MBSRQ) Body image avoidance questionnaire Body appreciation scale Body image scale Ben-Tovim Walker Body Attitudes Questionnaire Body shape questionnaire Body cathexis scale Figure rating scale Derriford Appearance Scale	People without PCOS	Outcomes relating to body image concerns dysmorphic in women with PCOS. Studies are likely to vary significantly in their methods for measurement of these outcomes and as such we will place no constraints on how outcomes are measured. Studies should use **validated questionnaires** to assess body image concerns.	Original research studies done after getting informed consent and ethics committee approval wherever applicable. Randomized controlled trials, non-randomized controlled trials, Observational studies including cohort, case-control, and cross-sectional studies will be included in the review.	No limits on publication date. English language only articles were included.
Exclusion criteria	Females with PCOS not fulfilling the criteria above.				Non-evidence based guidelines, non-systematic reviews, non-comparative cohort studies, case-control studies, case series, editorials, letters, commentaries.	

2. SEARCH STRATEGY

Table 2.1. Search details

Search strategy source: *[enter doi or 2018 technical report page number where search string was derived]*

Evidence source	Date of search
Medline (Ovid)	12/06/2022
PsychInfo (Ovid)	12/06/2022
EMBASE (Ovid)	12/06/2022
All EBM (Ovid)	N/A
CINAHL	N/A
PubMed	12/06/2022
Web of Science (Core Collection)	12/06/2022
CENTRAL	12/06/2022
Any subsequent updates - enter database and date:	

Table 2.2. Questions addressed by this search *(add more rows as needed)*:

GDG	Q1	What is the prevalence of body image dissatisfaction/distress among women with PCOS?
	Q2	Is there a higher degree of body image concerns among women with PCOS, compared to women without PCOS?
	Q3	What is the current evidence base evaluating body image concerns among women with PCOS?

Table 2.3. Search strings used in OVID or other database/s – *please save a screenshot of search results to submit alongside this template*

OVID Medline, EMBASE, PsychInfo

1. Exp Polycystic Ovary Syndrome/
2. ("pcos" or "pcod").mp.
3. (polycystic ovar* or "polycystic ovarian disease").mp.
4. *Hirsutism/ or *Hyperandrogenism/
5. **1 or 2 or 3 or 4**
6. *Depression/
7. *Anxiety/ or *Anxiety Disorders/
8. *Mental Health/ or *Mental Disorders/
9. *Body Image/ or *Body Weight/
10. ("body dysmorphic disorder" or "body image concerns" or exp Body Weight/).mp.
11. *Social Stigma/ or *"Quality of Life"/
12. exp Sexual Dysfunctions, Psychological/ or *Sexual Behaviour/
13. **6 or 7 or 8 or 9 or 10 or 11 or 12**
14. **5 and 13**

PubMed

1. "Polycystic Ovary Syndrome"[Mesh] OR "polycystic ovar*"[tw] OR pcos[tw] or pcod[tw] or "polycystic ovarian disease"[tw]
2. "Hirsutism"[Mesh] OR "Hyperandrogenism"[Mesh]
3. 1 or 2

4. "Depression"[Mesh] OR "Depressive Disorder"[Mesh:NoExp] OR depression[tw]
5. "Anxiety"[Mesh:NoExp] OR "Anxiety Disorders"[Mesh:NoExp] OR anxiety[tw]
6. "Mental Health"[Mesh] OR "Mental Disorders"[Mesh:NoExp]
7. "Body Image"[Mesh:NoExp] OR "Body Weight"[Mesh:NoExp] OR "Body Dysmorphic Disorders"[Mesh] OR “body image”[tw] OR "Feeding and Eating Disorders"[Mesh:NoExp]
8. "Social Stigma"[Mesh:NoExp] OR stigma[tw] OR "Quality of Life"[Mesh:NoExp] OR “quality of life”[tw]
9. "Sexual Dysfunctions, Psychological"[Mesh] OR “sexual dysfunction*”[tw] OR "Sexual Behavior"[Mesh:NoExp] OR “sexual behaviour*”[tw]
10. 4 or 5 or 6 or 7 or 8 or 9
11. 3 and 10

Web of Science (Core Collection)

1. ALL=("polycystic ovary syndrome" OR "polycystic ovarian syndrome" OR "polycystic ovary disease" OR "polycystic ovar*" OR "stein-leventhal syndrome" OR OR pcos OR pcod OR hirsutism OR hyperandrogenism)
2. ALL=(depression OR "depressive symptom*" OR "depressive disorder*" OR anxiety OR "anxiety disorder*" OR "mental health")
3. ALL=("body image" OR "body weight" OR "body dysmorphic disorder*" OR "eating disorder*")
4. ALL=("stigma")
5. ALL=("quality of life")
6. ALL=("sexual behaviour*" OR "sexual dysfunction*" OR "psychosexual dysfunction*" OR "psychological sexual dysfunction" OR "sexual disorder*")
7. 2 or 3 or 4 or 5 or 6
8. 1 and 7
9. (#1) AND (#7) and Science Citation Index Expanded (SCI-EXPANDED) or Social Sciences Citation Index (SSCI) (Web of Science Index)
10. (#1) AND (#7) and Science Citation Index Expanded (SCI-EXPANDED) or Social Sciences Citation Index (SSCI) (Web of Science Index) and Articles (Document Types)

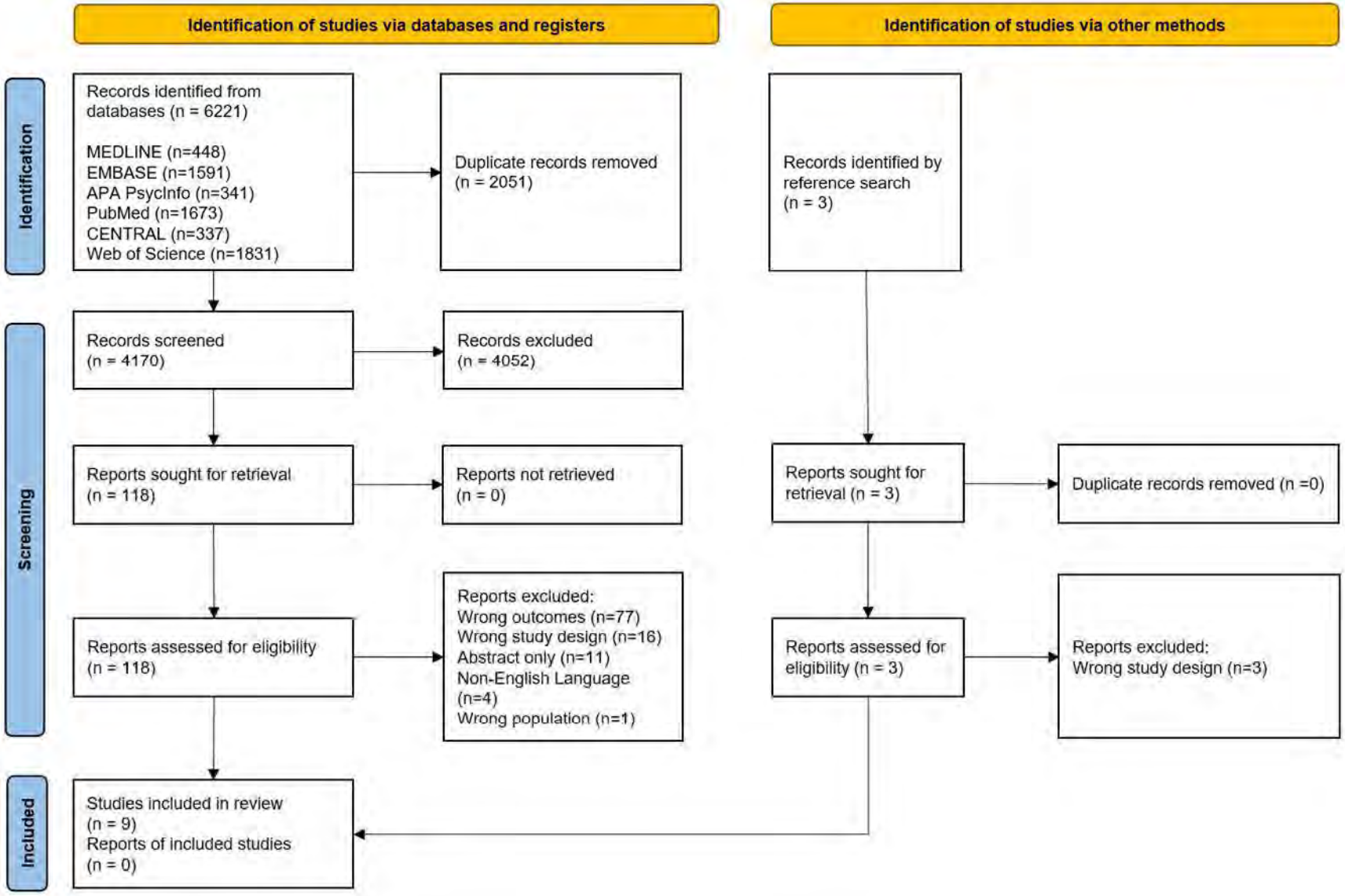
CENTRAL

1. MeSH descriptor: [Polycystic Ovary Syndrome] explode all trees
2. MeSH descriptor: [Hirsutism] explode all trees
3. MeSH descriptor: [Hyperandrogenism] explode all trees
4. pcos OR pcod OR "polycystic ovar*" OR "polycystic ovarian disease"
5. #1 OR #2 OR #3 OR #4
6. MeSH descriptor: [Depression] explode all trees
7. MeSH descriptor: [Anxiety] this term only

8. depression OR "depressive symptom*" OR "depressive disorder*" OR "anxiety" OR "anxiety disorder*" OR "mental health"
9. MeSH descriptor: [Body Image] explode all trees
10. MeSH descriptor: [Body Weight] this term only
11. MeSH descriptor: [Body Dysmorphic Disorders] explode all trees
12. MeSH descriptor: [Feeding and Eating Disorders] explode all trees
13. "body image" OR "body dysmorphic disorder"
14. MeSH descriptor: [Social Stigma] explode all trees
15. MeSH descriptor: [Quality of Life] explode all trees
16. stigma OR "quality of life"
17. MeSH descriptor: [Sexual Dysfunctions, Psychological] explode all trees
18. "sexual behaviour*" OR "sexual dysfunction*" OR "psychosexual dysfunction*" OR "psychological sexual dysfunction*" OR "sexual disorder*"
19. 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14
20. #5 AND #20 (Trials)

Evidence processing: Studies were selected and appraised by two reviewer/s in consultation with the evidence team/ key contact using study selection and appraisal criteria (PICO above) established a priori. The articles were reviewed by title and abstract by two reviewers. When a decision could not be made based on title and abstract alone, full text was retrieved. **A total of nine studies were included in this review.**

3. SEARCH RESULTS - PRISMA flowchart



4. STUDY INCLUSION

4.1 Included studies

1	Alur-Gupta, S., Chemerinski, A., Dokras, A., Liu, C., Lipson, J., Allison, K., & Sammel Mary D. AO - Dokras, A. O. http://orcid. org/0000-0002-1085-3969. (2019). Body-image distress is increased in women with polycystic ovary syndrome and mediates depression and anxiety. *Fertility and Sterility*, *112*(5), 930.
2	Annagür BB, Tazegül A, Akbaba N. Body Image, Self-Esteem and Depressive Symptomatology in Women with Polycystic Ovary Syndrome. Noro Psikiyatr Ars. 2014 Jun;51(2):129-132
3	Azizi Kutenaee, M., Amirjani, S., Taghavi, S.-A., Asemi, Z., Allan, H., Kamalnadian, S.-N., Khashavi, Z., & Bazarganipour, F. (2020). The impact of depression, self-esteem, and body image on sleep quality in patients with PCOS: a cross-sectional study. *Sleep and Breathing*, *24*(3), 1027–1034.
4	Deeks, A. A., Gibson-Helm, M. E., Paul, E., & Teede, H. J. (2011). Is having polycystic ovary syndrome a predictor of poor psychological function including anxiety and depression? *Human Reproduction*, *26*(6), 1399–1407.
5	Himelein, M. J., & Thatcher, S. S. (2006). Depression and body image among women with polycystic ovary syndrome. *Journal of Health Psychology*, *11*(4), 613–625.
6	Karacan, E., Caglar, G. S., Gursoy, A. Y., & Yilmaz, M. B. (2014). Body satisfaction and eating attitudes among girls and young women with and without polycystic ovary syndrome. *Journal of Pediatric and Adolescent Gynecology*, *27*(2), 72–77.
7	Morotti, E., Battaglia, B., Fabbri, R., Meriggiola, M. C., Venturoli, S., Battaglia, C., & Persico, N. (2013). Body imaging and sexual behavior in lean women with polycystic ovary syndrome. *Journal of Sexual Medicine*, *10*(11), 2752–2760.
8	Pastore, L. M., Dalal, P., Bray, M. J., Patrie, J. T., & Morris, W. L. (2011). Depression symptoms and body dissatisfaction association among polycystic ovary syndrome women. *Journal of Psychosomatic Research*, *71*(4), 270–276.
9	Scaruffi, E., Franzoi, I. G., Civilotti, C., Guglielmucci, F., la Marca, L., Tomelini, M., Veglia, F., & Granieri, A. (2019). Body image, personality profiles and alexithymia in patients with polycystic ovary syndrome (PCOS). *Journal of Psychosomatic Obstetrics and Gynaecology*, *40*(4), 294–303.

4.2 Excluded Studies (on full text assessment)

No.	Study details	Reason for exclusion
1	ACTRN12619000906156. (2019). The effect of weight stigma and the polycystic ovary syndrome (PCOS) disease label and causal explanations on intention to eat healthier and perceived personal control over weight: a randomised online study in reproductive aged women. *Http://Www.Who.Int/Trialsearch/Trial2.Aspx?TrialID=ACTRN12619000906156*. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01975150/full	Wrong outcomes
2	Akbari Sene, A., Tahmasbi, B., Keypour, F., Zamanian, H., Golbabaei, F., & Amini-Tehrani, M. (2021). Differences in and Correlates of Sexual Function in Infertile Women with and without Polycystic Ovary Syndrome. *International Journal of Fertility & Sterility*, *15*(1), 65–72. https://doi.org/10.22074/IJFS.2021.6206	Wrong outcomes
3	Aloulou, J., Halouani, N., Charfeddine, F., Mseddi, N., Charfi, N., Abid, M., & Amami, O. (2012). Marital sexual satisfaction in women with polycystic ovary syndrome. *European Psychiatry*, *27*.	Wrong design
4	Alur-Gupta, S., Chemerinski, A., Liu, C., Lipson, J., Allison, K., Sammel, M. D., & Dokras, A. (2019). Body image distress increased in women with PCOS and mediates depression and anxiety. *Fertility and Sterility*, *112*(5), 930. https://doi.org/10.1016/J.FERTNSTERT.2019.06.018	Wrong outcomes
5	Amini, L., Sadeghi-Avval-Shahr, H., Valian, K., & Montazeri, A. (2014). Body esteem components in women with polycystic ovary syndrome. *Journal of Mazandaran University of Medical Sciences*, *23*(2), 212–216. http://jmums.mazums.ac.ir/browse.php?a_id=2563&slc_lang=en&sid=1&ftxt=1	non-english
6	Ashrafi, M., Jahangiri, N., Jahanian Sadatmahalleh, S., Mirzaei, N., Gharagozloo Hesari, N., Rostami, F., Mousavi, S. S., & Zeinaloo, M. (2022). Does prevalence of sexual dysfunction differ among the most common causes of infertility? A cross-sectional study. *BMC Women's Health*, *22*(1), 140. https://doi.org/10.1186/s12905-022-01708-y	Wrong outcomes
7	Aydogan Kirmizi, D., Baser, E., Onat, T., Demir Caltekin, M., Yalvac, E. S., Kara, M., & Gocmen, A. Y. (2020). Sexual function and depression in polycystic ovary syndrome: Is it associated with inflammation and neuromodulators? *Neuropeptides*, *84*, 102099. http://www.elsevier-international.com/journals/npep/	Wrong outcomes
8	Baez, K. (2012). The influence of polycystic ovary syndrome on sexual satisfaction of heterosexual married women. *Dissertation Abstracts International: Section B: The Sciences and Engineering*, *72*(12), 7677.	Wrong design
9	Basirat, Z., Faramarzi, M., Esmaelzadeh, S., Firoozjai, S. A., Mahouti, T., & Geraili, Z. (2019). Stress, Depression, Sexual Function, and Alexithymia in Infertile Females with and without Polycystic Ovary Syndrome: A Case-Control Study. *International Journal of Fertility & Sterility*, *13*(3), 203–208. https://doi.org/10.22074/IJFS.2019.5703	Wrong outcomes
10	Battaglia, C., Mancini, F., Cianciosi, A., Persico, N., Busacchi, P., Sisti, G., Nappi, R. E., & Facchinetti, F. (2008). PCOS, sexuality, and clitoral vascularisation: A pilot study. *Journal of Sexual Medicine*, *5*(12), 2886–2894. http://www.journals.elsevier.com/the-journal-of-sexual-medicine	Wrong outcomes
11	Bazarganipour, F., Ziaei, S., Montazeri, A., Foroozanfard, F., Kazemnejad, A., & Faghihzadeh, S. (2014a). Health-related quality of life in patients with polycystic ovary syndrome (PCOS): A model-based study of predictive factors. *Journal of Sexual Medicine*, *11*(4), 1023–1032. https://doi.org/10.1111/jsm.12405	Wrong outcomes
12	Bazarganipour, F., Ziaei, S., Montazeri, A., Foroozanfard, F., Kazemnejad, A., & Faghihzadeh, S. (2014b). Sexual functioning among married Iranian women with polycystic ovary syndrome. *International Journal of Fertility and Sterility*, *8*(3), 273–280. http://www.ijfs.ir/library/upload/article/af_426233235263223323374674344533243446233 3Int-J-Fertil-Steril-8-273.pdf	Wrong outcomes
13	Benetti-Pinto, C. L., Ferreira, S. R., Antunes, A., & Yela, D. A. (2015). The influence of body weight on sexual function and quality of life in women with polycystic ovary syndrome. *Archives of Gynecology and Obstetrics*, *291*(2), 451–455. http://link.springer.de/link/service/journals/00404/index.htm	Wrong outcomes

14	Beyazit, F., Gencer, M., Sahin, B., & Ertekin, H. (2017). The effect of hirsutismus and body mass index on body image and anxiety in patients with polycystic ovarian syndrome. *Turkiye Klinikleri Jinekoloji Obstetrik*, *27*(3), 130–137. http://www.turkiyeklinikleri.com/pdf/?pdf=af846da0d4914b36b5840e2ac8aa6cfe	non-english
15	Brown, A. J., Amundsen, C. L., & Anger, J. T. (2007). Sexual dysfunction in women with polycystic ovary syndrome: The effects of testosterone, obesity, and depression. *Journal of Pelvic Medicine and Surgery*, *13*(3), 119–124.	Wrong outcomes
16	Chen, S.-F., Yang, Y.-C., Hsu, C.-Y., Shen, Y.-C., & Brutocao Carvalho, C. D. E. E.-M. J. K. M. N. P. R. S. T. V. (2020). Risk of bipolar disorder in patients with polycystic ovary syndrome: A nationwide population-based cohort study. *Journal of Affective Disorders*, *263*, 458–462.	Wrong outcomes
17	Czyzyk, A., Rojewska, P., Szeliga, A., Podfigurna, A., & Pal, L. (2017). Sexual function, dysfunction and effect of aging in women with PCOS. *Maturitas*, *100*, 128.	Abstract only
18	Dashti, S., Latiff, L. A., Hamid, H. A., Sani, S. M., Akhtari-Zavare, M., Abu Bakar, A. S., Binti Sabri, N. A. I., Ismail, M., & Esfehani, A. J. (2016). Sexual Dysfunction in Patients with Polycystic Ovary Syndrome in Malaysia. *Asian Pacific Journal of Cancer Prevention : APJCP*, *17*(8), 3747–3751.	Wrong outcomes
19	de Frène, V., Verhofstadt, L., Loeys, T., Stuyver, I., Buysse, A., & de Sutter, P. (2015). Sexual and relational satisfaction in couples where the woman has polycystic ovary syndrome: a dyadic analysis. *Human Reproduction (Oxford, England)*, *30*(3), 625–631. https://doi.org/10.1093/HUMREP/DEU342	Wrong outcomes
20	Deniz, A., & Kehribar, D. Y. (2020). Evaluation of sexual functions in infertile Women with Polycystic Ovary Syndrome. *Nigerian Journal of Clinical Practice*, *23*(11), 1548–1554.	Wrong outcomes
21	Dowdy, D. (2012). Emotional Needs of Teens With Polycystic Ovary Syndrome. *JOURNAL OF PEDIATRIC NURSING-NURSING CARE OF CHILDREN & FAMILIES*, *27*(1), 55–64.	Wrong design
22	Drosdzol, A., Skrzypulec, V., Mazur, B., & Pawlińska-Chmara, R. (2007). Quality of life and marital sexual satisfaction in women with polycystic ovary syndrome. *Folia Histochemica et Cytobiologica*, *45 Suppl 1*, S93-7.	Wrong outcomes
23	Eftekhar, T., Sohrabvand, F., Haghollahi, F., Zabandan, N., Ghahghaei-Nezamabadi, A., & Shariat, M. (2014). Sexual dysfunction in patients with polycystic ovary syndrome and its affected domains. *Iranian Journal of Reproductive Medicine*, *12*(8), 539–546. http://www.ssu.ac.ir/ijrm/index.php/ijrm/article/download/1146/735	Wrong outcomes
24	Elsenbruch, S., Benson, S., Hahn, S., Tan, S., Mann, K., Pleger, K., Kimmig, R., & Janssen, O. E. (2006). Determinants of emotional distress in women with polycystic ovary syndrome. *HUMAN REPRODUCTION*, *21*(4), 1092–1099.	Wrong outcomes
25	Elsenbruch, S., Schedlowski, M., Hahn, S., Kowalsky, D., Mann, K., Offner, A. H., & Janssen, O. E. (2003). Quality of Life, Psychosocial Well-Being, and Sexual Satisfaction in Women with Polycystic Ovary Syndrome. *Journal of Clinical Endocrinology and Metabolism*, *88*(12), 5801–5807.	Wrong outcomes
26	Ercan, C. M., Coksuer, H., Alanbay, I., Keskin, U., Karasahin, K. E., Baser, I., & Aydogan, U. (2013). Sexual dysfunction assessment and hormonal correlations in patients with polycystic ovary syndrome. *International Journal of Impotence Research*, *25*(4), 127–132.	Wrong outcomes
27	Esler, D. M., Travers, C. A., Guttikonda, K., Dixon, A., & Lewis, P. R. (2007). The psychosocial experience of women with PCOS - A case control study. *AUSTRALIAN FAMILY PHYSICIAN*, *36*(11), 965–967.	Wrong outcomes
28	Farahmand, M., Tehrani, F. R., Behboudi-Gandevani, S., Noroozzadeh, M., & Dovom, M. R. (2017). Polycystic ovary syndrome and sexual function among Iranian women. *Journal of Reproduction and Infertility*, *18*(2), 120. http://www.jri.ir/documents/supplement/71.pdf	Abstract only
29	Ferraresi, S. R., Lara, L. A. da S., Reis, R. M., & de Sa Rosa e Silva, A. C. J. (2013). Changes in Sexual Function among Women with Polycystic Ovary Syndrome: A Pilot Study. *Journal of Sexual Medicine*, *10*(2), 467–473. http://www.journals.elsevier.com/the-journal-of-sexual-medicine	Wrong outcomes
30	Fliegner, M., Richter-Appelt, H., Krupp, K., & Brunner, F. (2019). Sexual Function and Socio-Sexual Difficulties in Women with Polycystic Ovary Syndrome (PCOS). *Geburtshilfe Und Frauenheilkunde*, *79*(5), 498–509. https://doi.org/10.1055/A-0828-7901	Wrong outcomes
31	Forouhari, S., Doryanizadeh, L., Farzanehfarahi, Bahianamavarjahromi, & Nourimand, F. (2019). Sexual function in fertile and infertile women with polycystic ovary syndrome. *International Journal of Pharmaceutical Research*, *11*(3). http://www.ijpronline.com/DownloadFile.aspx?FilePath=36d4c2cd-0764-4d48-9e6a-78320e378ce0.pdf	Wrong outcomes
32	Francis, B., Wah, K. Y., Jawan, R. A., Sulaiman, A. H., & Gill, J. S. (2018). Depressive disorders and sexual functioning among Malaysian women with polycystic ovarian syndrome (PCOS): A cross-sectional study. *European Psychiatry*, *48*, S219.	Abstract only
33	Gateva, A., & Kamenov, Z. (2011). Sexual function in Bulgarian patients with pcos and/or obesity before and after metformin treatment. *Journal of Sexual Medicine*, *8*, 381.	Wrong outcomes
34	Glowinska, A., Siakowska, M., Pawelczyk, L., Banaszewska, B., Duleba, A. J., & Zielona-Jenek, M. (2020). Disparate Relationship of Sexual Satisfaction, Self-Esteem, Anxiety, and Depression with Endocrine Profiles of Women With or Without PCOS. *Reproductive Sciences*, *27*(1), 432–442. https://www.springer.com/journal/43032	Wrong outcomes
35	Gorzynski, G., & Katz, J. L. (1977). The polycystic ovary syndrome: Psychosexual correlates. *Archives of Sexual Behavior*, *6*(3), 215–222.	Wrong outcomes
36	H., D., & Caltekin M.D. AO - Dogan, H. O. http://orcid. org/0000-0002-2294-2483. (2021). Does polycystic ovary syndrome with phenotype d affect the cardiovascular endurance, core endurance, body awareness, and the quality of life? A prospective, controlled study. *Turkish Journal of Obstetrics and Gynecology*, *18*(3), 203–211. http://cms.galenos.com.tr/Uploads/Article_49006/TJOG-18-203-En.pdf	Wrong outcomes
37	Hamidi, R., Yasir, A., & Khaleel, M. (2021). Sexual Satisfaction Among Married Polycystic Ovarian SyndromeWomen - BiblioMed.org - Deposit for Medical Articles. *Journal of Cardiovascular Disease Research*, *12*(4). https://www.bibliomed.org/?mno=99125	Wrong outcomes
38	Hashemi, S., Ramezani Tehrani, F., Farahmand, M., & Bahri Khomami, M. (2014). Association of PCOS and its clinical signs with sexual function among Iranian women affected by PCOS. *The Journal of Sexual Medicine*, *11*(10), 2508–2514. https://doi.org/10.1111/JSM.12627	Wrong outcomes
39	Hashemi, S., Ramezani Tehrani, F., Noroozzadeh, M., Rostami Dovom, M., & Azizi, F. (2014). Infertility, the most adverse outcome among sexual function outcome affecting of Iranian women with polycystic ovarian syndrome. *Iranian Journal of Endocrinology and Metabolism*, *16*(3). http://ijem.sbmu.ac.ir/browse.php?a_id=1702&slc_lang=en&sid=1&ftxt=1	non-english
40	Hill, B., Tay, C. T., Teede, H. J., Joham, A. E., & Loxton Deborah AO - Tay, C. T. ; O. http://orcid. org/0000-0001-6228-2654. (2019). Increased prevalence of eating disorders, low self-esteem, and psychological distress in women with polycystic ovary syndrome: a community-based cohort study. *Fertility and Sterility*, *112*(2), 353–361. http://www.elsevier.com/locate/fertnstert	Wrong outcomes
41	Holton, S., Papanikolaou, V., Hammarberg, K., Rowe, H., Kirkman, M., Jordan, L., McNamee, K., Bayly, C., McBain, J., Sinnott, V., & Fisher, J. (2018). Fertility management experiences of women with polycystic ovary syndrome in Australia. *The European Journal of Contraception & Reproductive Health Care : The Official Journal of the European Society of Contraception*, *23*(4), 282–287. https://doi.org/10.1080/13625187.2018.1483020	Wrong outcomes

42	Huddleston, H. G. (2021). Sexual dysfunction in polycystic ovary syndrome: a complex entity that may find improvement with the simplest of solutions. *Fertility and Sterility*, *115*(2), 332–333. https://doi.org/10.1016/J.FERTNSTERT.2020.12.014	Wrong design
43	Javed, H., Niazi, S., Adil, A., Yousaf, A., Khan, A., & Ghayas, S. (2022). Body image concern as mediator between obesity and sexual satisfaction: a comparative study of married women with and without polycystic ovarian syndrome. *Rawal Medical Journal*, *47*(2), 400–402. http://www.rmj.org.pk/fulltext/27-1610892034.pdf?1653324718	Wrong outcomes
44	Kałużna, M., Nomejko, A., Słowińska, A., Wachowiak-Ochmańska, K., Pikosz, K., Ziemnicka, K., & Ruchała, M. (2021). Lower sexual satisfaction in women with polycystic ovary syndrome and metabolic syndrome. *Endocrine Connections*, *10*(9), 1035–1044. https://doi.org/10.1530/EC-21-0257	Wrong outcomes
45	Kanwal, S., Fatima, S. S., Abid, F., Jafri, A., Kazmi, F. H., & Fatima, N. (2021). Comparison of Body Image Perception and Depression in Polycystic Ovarian Syndrome (PCOS) and Non-PCOS Women. *World Family Medicine Journal /Middle East Journal of Family Medicine*, *20*(11). https://doi.org/10.5742/mewfm.2021.94163	Wrong outcomes
46	Karsten, M. D. A., Wekker, V., Groen, H., Painter, R. C., Mol, B. W. J., Laan, E. T. M., Roseboom, T. J., & Hoek, A. (2021). The role of PCOS in mental health and sexual function in women with obesity and a history of infertility. *Human Reproduction Open*, *2021*(4). https://doi.org/10.1093/hropen/hoab038	Wrong outcomes
47	Kepczynska-Nyk, A., Nowak, A., Bednarczuk, T., Ambroziak, U., & Kurylowicz, A. A. O.-K. A. ; O. http://orcid. org/0000-0001-8632-4927 A. O.-B. T. ; O. http://orcid. org/0000-0002-5752-8709 A. O.-A. U. ; O. http://orcid. org/0000-0002-8778-1959. (2021). Sexual function in women with androgen excess disorders: classic forms of congenital adrenal hyperplasia and polycystic ovary syndrome. *Journal of Endocrinological Investigation*, *44*(3), 505–513. http://link.springer.com/journal/40618	Wrong outcomes
48	Khafagy, G., Sayed, I. el, Abbas, S., & Soliman, S. (2020). Perceived Stress Scale Among Adolescents with Polycystic Ovary Syndrome. *International Journal of Women's Health*, *12*, 1253–1258. https://doi.org/10.2147/IJWH.S279245	Wrong outcomes
49	Kobilkova, J., Raboch, J., & Starka, L. (1985). Sexual life of women with the Stein-Leventhal Syndrome. *Archives of Sexual Behavior*, *14*(3), 263–270.	Wrong outcomes
50	Kowalczyk, R., Skrzypulec-Plinta, V., Nowosielski, K., & Lew-Starowicz, Z. (2015). Sexuality in women with polycystic ovary syndrome. *Ginekologia Polska*, *86*(2), 100–106.	Wrong outcomes
51	Krysiak, R., Drosdzol-Cop, A., Skrzypulec-Plinta, V., & Okopien, B. (2016). Sexual Function and Depressive Symptoms in Young Women With Nonclassic Congenital Adrenal Hyperplasia. *The Journal of Sexual Medicine*, *13*(1), 34–39.	Wrong population
52	Lara, L. A. S., Ramos, F. K. P., Kogure, G. S., Costa, R. S., Silva de Sá, M. F., Ferriani, R. A., & dos Reis, R. M. (2015). Impact of Physical Resistance Training on the Sexual Function of Women with Polycystic Ovary Syndrome. *The Journal of Sexual Medicine*, *12*(7), 1584–1590. https://doi.org/10.1111/JSM.12909	Wrong outcomes
53	Lara, L. A. S., Zueff, L. N., Vieira, C. S., & Ferriani, R. A. (2014). Body image variables that predict the sexual functioning of women with and without PCOS. *Journal of Sexual Medicine*, *11*, 245.	Wrong outcomes
54	Lara, L., Lopes, I. P., dos Reis, R. M., Ribeiro, V. B., de Souza, H. C. D., & Silva, R. C. (2018). Aerobic physical training improves sexual function and qol of pcos women: randomized conrrolled tria. *International Journal of Gynaecology and Obstetrics*, *143*, 357-358. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01654062/full	Abstract only
55	Lara, L., Romao, A., Gorayeb, R., Tiezzi, M., Reis, M., Pandochi, H., & Rosa-E-Silva, A. (2015). Prevalence of sexual complaints and epidemiological profile of women with polycycstic ovary syndrome. *Journal of Sexual Medicine*, *12*, 61.	Wrong design
56	Legro, R. S., Coutifaris, C., Barnhart, K., Alvero, R., Schlaff, W., Santoro, N., Robinson, R. D., Casson, P. A., Christman, G. M., Hansen, K. R., Baker, V., Usadi, R., Seungdamrong, A., Bates, G. W., Rosen, R. M., Haisenleder, D., Diamond, M. P., Krawetz, S. A., Trussell, J. C., … Zhang Heping AO - Alvero, R. O. http://orcid. org/0000-0001-6542-710X A. O.-S. A. O. http://orcid. org/0000-0002-0065-1845 A. O.-E. E. O. http://orcid. org/0000-0003-3033-6384. (2017). Sexual function in infertile women with polycystic ovary syndrome and unexplained infertility. *American Journal of Obstetrics and Gynecology*, *217*(2), e1-191. http://www.elsevier.com/inca/publications/store/6/2/3/2/7/7/index.htt	Wrong outcomes
57	Lopes, I. P., Ribeiro, V. B., Reis, R. M., Silva, R. C., de Souza, H. C., Kogure, G. S., Ferriani, R. A., & Silva Lara, L. A. da. (2018). Comparison of the Effect of Intermittent and Continuous Aerobic Physical Training on Sexual Function of Women With Polycystic Ovary Syndrome: Randomized Controlled Trial. *The Journal of Sexual Medicine*, *15*(11), 1609–1619.	Wrong outcomes
58	Maldonado-Carceles, A. B., Menarguez-Puche, J. F., Reina-Nicolas, I. M., Lillo-Garcia, M. I., Soler-Ferreria, D. C., Tudela-de-Gea, M. B., & Torres-Cantero, A. M. (2021). Sexual dysfunction and polycystic ovary syndrome among women attending a primary care center in Spain. *Paediatric and Perinatal Epidemiology*, *35*, 26.	Abstract only
59	Mànsson, M., Norström, K., Holte, J., Landin-Wilhelmsen, K., Dahlgren, E., & Landén, M. (2011). Sexuality and psychological wellbeing in women with polycystic ovary syndrome compared with healthy controls. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, *155*(2), 161–165. https://doi.org/10.1016/J.EJOGRB.2010.12.012	Wrong outcomes
60	Mantzou, D., Stamou, M. I., Armeni, A. K., Roupas, N. D., Assimakopoulos, K., Adonakis, G., Georgopoulos, N. A., & Markantes, G. K. (2021). Impaired Sexual Function in Young Women With PCOS: The Detrimental Effect of Anovulation. *The Journal of Sexual Medicine*, *18*(11), 1872–1879. https://doi.org/10.1016/J.JSXM.2021.09.004	Wrong outcomes
61	Maya, J., Siegel, J., Rousseau-Pierre, T., & Cheng Tina Q. AO - Maya, J. O. http://orcid. org/0000-0003-4522-4633. (2020). Prevalence and risk factors of polycystic ovarian syndrome among an ethnically diverse overweight/obese adolescent population. *International Journal of Adolescent Medicine and Health*, 20190109. http://www.degruyter.com/view/j/ijamh?rskey=qYlGDI&result=1&q=International%20Journal%20of%20Adolescent%20Medicine%20and%20Health	Wrong outcomes
62	Mccook, J. G. (2002). The influence of hyperandrogenism, obesity and infertility on the psychosocial health and well-being of women with polycystic ovary syndrome. *Dissertation Abstracts International: Section B: The Sciences and Engineering*, *63*(2), 740.	Wrong design
63	Micskei, O., Bugan, A., Deli, T., & Jakab, A. (2014). Body image and quality of life in women with polycystic ovary syndrome. *Orvosi Hetilap*, *155*(27), 1071–1077. http://www.akademiai.com/content/0030-6002	non-english
64	Mizgier, M., Jarzabek-Bielecka, G., Kedzia, W., Opydo-Szymaczek, J., Wendland, N., & Wieckowska, B. (2020). Risk factors of overweight and obesity related to diet and disordered eating attitudes in adolescent girls with clinical features of polycystic ovary syndrome. *Journal of Clinical Medicine*, *9*(9), 1–18. https://www.mdpi.com/2077-0383/9/9/3041/pdf	Wrong outcomes
65	Moran-Sanchez, I., Adoamnei, E., Sanchez-Ferrer, M. L., Prieto-Sanchez, M. T., Arense-Gonzalo, J. J., Carmona-Barnosi, A., Hernandez-Penalver, A. I., Mendiola, J., & Torres-Cantero, A. M. (2021). Assessment of Optimism in Women with Polycystic Ovary Syndrome: A Case Control-Study. *INTERNATIONAL JOURNAL OF ENVIRONMENTAL RESEARCH AND PUBLIC HEALTH*, *18*(5).	Wrong outcomes

66	Moreira, S. da N. T., de Sa, J. C. assia F., Costa, E. C. aldas, & de Azevedo, G. D. antas. (2013). [Quality of life and psychosocial aspects of polycystic ovary syndrome: a quali-quantitative approach]. *Revista brasileira de ginecologia e obstetricia : revista da Federacao Brasileira das Sociedades de Ginecologia e Obstetricia*, *35*(11), 503–510.	Wrong outcomes
67	Nasiri Amiri, F., Esmailzadeh, S., Basirat, Z., Ramezani Tehrani, F., Tohidi, M., & Azizi, F. (2018). Sexual function in women with polycystic ovary syndrome and their hormonal and clinical correlations. *International Journal of Impotence Research*, *30*(2), 54–61. http://www.nature.com/ijir/index.html	Abstract only
68	Nasiri Amiri, F., & Ramezani Tehrani, F. (2016). Sexual function in women with polycystic ovary syndrom: Clinical and hormonal parameters. *International Journal of Fertility and Sterility*, *10*, 95–96. http://ijfs.ir/journal/article/4487/download	Wrong outcomes
69	Naumova, I., Castelo-Branco, C., & Casals, G. (n.d.). Psychological Issues and Sexual Function in Women with Different Infertility Causes: Focus on Polycystic Ovary Syndrome. *REPRODUCTIVE SCIENCES*.	Wrong outcomes
70	Nesbitt, R. E., Hollender, M., Fisher, S., & Osofsky, H. J. (1968). Psychologic correlates of the polycystic ovary syndrome and organic infertility. *Fertility and Sterility*, *19*(5), 778–786. https://doi.org/10.1016/S0015-0282(16)36793-0	Wrong outcomes
71	Nohr, E. A., Hansen, A. S. B., Andersen, M. S., & Hjorth, S. (2022). Sexual health in parous women with a history of polycystic ovary syndrome: A national cross-sectional study in Denmark. *International Journal of Gynaecology and Obstetrics: The Official Organ of the International Federation of Gynaecology and Obstetrics*, *157*(3), 702–709. https://doi.org/10.1002/IJGO.13911	Wrong outcomes
72	Noroozzadeh, M., Ramezani Tehrani, F., Bahri Khomami, M., & Azizi, F. (2017). A Comparison of Sexual Function in Women with Polycystic Ovary Syndrome (PCOS) Whose Mothers Had PCOS During Their Pregnancy Period with Those Without PCOS. *Archives of Sexual Behavior*, *46*(7), 2033–2042. https://doi.org/10.1007/S10508-016-0919-8/TABLES/4	Wrong outcomes
73	Noroozzadeh, M., Tehrani, F. R., Mobarakabadi, S. S., Farahmand, M., & Dovom, M. R. (2017). Sexual function and hormonal profiles in women with and without polycystic ovary syndrome: a population-based study. *INTERNATIONAL JOURNAL OF IMPOTENCE RESEARCH*, *29*(1), 1–6.	Wrong outcomes
74	Pastoor, H., Both, S., Timman, R., Laan, E. T. M., & Laven, J. S. E. (2020). Sexual Function in Women With Polycystic Ovary Syndrome: Design of an Observational Prospective Multicenter Case Control Study. *Sexual Medicine*, *8*(4), 718–729. https://doi.org/10.1016/J.ESXM.2020.07.002	Wrong design
75	Redman, L. M., Elkind-Hirsch, K., & Ravussin, E. (2011). Aerobic exercise in women with polycystic ovary syndrome improves ovarian morphology independent of changes in body composition. *Fertility and Sterility*, *95*(8), 2696–2699. https://doi.org/10.1016/J.FERTNSTERT.2011.01.137	Wrong outcomes
76	Rellini, A. H., Stratton, N., Tonani, S., Santamaria, V., Brambilla, E., & Nappi, R. E. (2013). Differences in sexual desire between women with clinical versus biochemical signs of hyperandrogenism in polycystic ovarian syndrome. *Hormones and Behavior*, *63*(1), 65–71.	Wrong outcomes
77	Rich, M., Austin, S. B., Gordon, C. M., & Trent, M. E. (2003). Fertility concerns and sexual behavior in adolescent girls with polycystic ovary syndrome: Implications for quality of life. *Journal of Pediatric and Adolescent Gynecology*, *16*(1), 33–37.	Wrong outcomes
78	Robinson, S. L., Sundaram, R., Trinh, M.-H., Mendola, P., Yeung, E. H., Ghassabian, A., & Bell Erin M. AO - Robinson, S. L. ; O. http://orcid. org/0000-0002-7707-9728 A. O.-M. P. O. http://orcid. org/0000-0001-5330-2844 A. O.-Y. E. H. ; O. http://orcid. org/0000-0002-3851-2613. (2020). The associations of maternal polycystic ovary syndrome and hirsutism with behavioral problems in offspring. *Fertility and Sterility*, *113*(2), 435–443. http://www.elsevier.com/locate/fertnstert	Wrong outcomes
79	Rodrigues, C. E. G., Ferreira, L. de L., Jansen, K., Lopez, M. R. A., Drews Junior, C. R., & Souza, L. D. de M. (2012). Evaluation of common mental disorders in women with polycystic ovary syndrome and its relationship with body mass index. *Revista Brasileira de Ginecologia e Obstetricia*, *34*(10), 442–446. http://www.scielo.br/pdf/rbgo/v34n10/a02v34n10.pdf	Wrong outcomes
80	Romao, A. P. M. S., Lara, L. A. S., Junqueira, F. R. R., Romao, G. S., Rosa-E-Silva, A. C. J. D. S., & Gorayeb, R. (2014). Prevalence of sexual complaints of women with polycystic ovary syndrome in a teaching hospital in ribeirao preto. *Journal of Sexual Medicine*, *11*, 249–250.	Abstract only
81	Santoro, N., Eisenberg, E., Trussell, J. C., Craig, L. B., Gracia, C., Huang, H., Alvero, R., Casson, P., Christman, G., Coutifaris, C., Diamond, M., Jin, S. S., Legro, R. S., Robinson, R. D., Schlaff, W. D., Zhang, H. P., & Investigators, R. M. N. (2016). Fertility-related quality of life from two RCT cohorts with infertility: unexplained infertility and polycystic ovary syndrome. *HUMAN REPRODUCTION*, *31*(10), 2268–2279.	Wrong outcomes
82	Shafti, V., & Shahbazi, S. (2016). Comparing sexual function and quality of life in polycystic ovary syndrome and healthy women. *Journal of Family and Reproductive Health*, *10*(2), 92–98. http://jfrh.tums.ac.ir/index.php/jfrh/article/download/413/356	Wrong outcomes
83	Shakil, M., Ashraf, F., & Wajid, A. (2020). Sexual functioning as predictor of depressive symptoms and life satisfaction in females with polycystic ovary syndrome (Pcos). *Pakistan Journal of Medical Sciences*, *36*(7), 1500–1504. http://www.pjms.org.pk/index.php/pjms/article/download/2562/729	Wrong outcomes
84	Sheikh, J., Hebbar, M., Zia, N., Khalil, H., Wicks, S., Jayaprakash, S., Narendran, A., Melson, E., Tehrani, A. A., Manolopoulos, K. N., Gillett, C. D. T., Kempegowda, P., Busby, M., Hillman, S., Chapman, R., Gleeson, H., Arlt, W., Singh, R., Robinson, L., & Thangaratinam, S. (2021). Blue Morpho Survey: Increased anxiety, depression and body dysmorphia in PCOS. *BJOG: An International Journal of Obstetrics and Gynaecology*, *128*, 247.	Abstract only
85	Simon, S., Keitel, M., Bigony, C., & Park-Taylor, J. (2021). Psychological distress in women with polycystic ovary syndrome: the role of attachment and coping. *PSYCHOLOGY HEALTH & MEDICINE*, *26*(6), 735–744.	Wrong outcomes
86	Singh, S., & Joshi, R. (2020). PCOS: Understanding the depressive-anxiety states, body image concerns, self esteem and eating behaviors. *Indian Journal of Psychiatry*, *62*(7), S12.	Abstract only
87	Skrzypulec-Plinta, V., Kowalczyk, R., & Skrzypulec, A. (2011). Sex uality of women with polycystic ovary syndrome. *Journal of Sexual Medicine*, *8*, 390.	Abstract only
88	Soucie, K., Samardzic, T., Schramer, K., Salam, Z., & Ly, C. (2021b). Body- and symptom-related concerns in women diagnosed with polycystic ovary syndrome: A gap in symptom management. *Journal of Health Psychology*, *26*(5), 701–712. https://doi.org/10.1177/1359105319840696	Wrong outcomes
89	Stadnicka, G., Lepecka-Klusek, C., Kostrzewska, K., Baczek, G., & Pilewska-Kozak, A. (2014). The sexuality of women treated for infertility. *European Journal of Contraception and Reproductive Health Care*, *19*, S225–S226.	Abstract only
90	Stapinska-Syniec, A., Grabowska, K., Szpotanska-Sikorska, M., & Pietrzak Bronislawa AO - Szpotanska-Sikorska, M. O. http://orcid. org/0000-0001-9051-0319. (2018). Depression, sexual satisfaction, and other psychological issues in women with polycystic ovary syndrome. *Gynecological Endocrinology*, *34*(7), 597–600. http://www.tandfonline.com/loi/igye20	Wrong outcomes
91	Steinberg Weiss, M., Roe, A. H., Allison, K. C., Dodson, W. C., Kris-Etherton, P. M., Kunselman, A. R., Stetter, C. M., Williams, N. I., Gnatuk, C. L., Estes, S. J., & et al. (2020). Lifestyle modifications alone or combined with hormonal contraceptives improve sexual dysfunction in women with polycystic ovary syndrome. *Fertility and Sterility*. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02194773/full	Wrong outcomes
92	Stoian, D., Craina, M., Anastasiu, D., & Craciunescu, M. (2013). Life style changes versus combined oral contraceptives treatment impact on sexual life of young females with Polycystic Ovary syndrome. *European Journal of Contraception and Reproductive Health Care*, *18*, S155–S156.	Wrong outcomes

93	Stovall, D. W., Scriver, J. L., Williams, C. D., Pastore, L. M., & Clayton, A. H. (2012). Sexual function in women with polycystic ovary syndrome. *Journal of Sexual Medicine*, *9*(1), 224–230. http://www.journals.elsevier.com/the-journal-of-sexual-medicine	Wrong outcomes
94	Tian, X., Du, J., Wang, J., Yin, D., Cheng, J., Ju, R., Ruan, X., & Mueck Alfred O. AO - Ruan, X. O. http://orcid. org/0000-0001-7777-247X. (2021). Sexual Function in Chinese Women with Polycystic Ovary Syndrome and Correlation with Clinical and Biochemical Characteristics. *Reproductive Sciences*. https://www.springer.com/journal/43032	Wrong outcomes
95	Tzalazidis, R., & Oinonen, K. A. (2021). Continuum of Symptoms in Polycystic Ovary Syndrome (PCOS): Links with Sexual Behavior and Unrestricted Sociosexuality. *JOURNAL OF SEX RESEARCH*, *58*(4), 532–544.	Wrong outcomes
96	Urszula, S.-M., & Olszewska, M. (2021). Polycystic ovary syndrome and the perception of body image by women. *Ginekologia i Położnictwo Medical Project*, *16*(1). https://www.ginekologiaipoloznictwo.com/articles/polycystic-ovary-syndrome-and-the-perception-of-body-image-by-women-81618.html	Wrong outcomes
97	Varanasi, L. C., Subasinghe, A., Jayasinghe, Y. L., Callegari, E. T., Garland, S. M., Gorelik, A., & Wark, J. D. (2018). Polycystic ovarian syndrome: Prevalence and impacton the wellbeing of Australian women aged 16-29years. *AUSTRALIAN & NEW ZEALAND JOURNAL OF OBSTETRICS & GYNAECOLOGY*, *58*(2), 222–233.	Wrong outcomes
98	Veras, A. B., Bruno, R. v, de Avila, M. A. P., & Nardi, A. E. (2011). Sexual dysfunction in patients with polycystic ovary syndrome: Clinical and hormonal correlations. *Comprehensive Psychiatry*, *52*(5), 486–489.	Wrong outcomes
99	Zachurzok, A., Gawlik, A., Nowak, A., Drosdzol-Cop, A., & Malecka-Tendera, E. (2014). Social abilities and gender roles in adolescent girls with polycystic ovary syndrome - a pilot study. *ENDOKRYNOLOGIA POLSKA*, *65*(3), 189–194.	Wrong outcomes
100	Zueff, L. N., Lara, L. A. D. S., Vieira, C. S., Martins, W. D. P., & Ferriani, R. A. (2015). Body composition characteristics predict sexual functioning in obese women with or without PCOS. *Journal of Sex & Marital Therapy*, *41*(3), 227–237. https://doi.org/10.1080/0092623X.2013.864369	Wrong outcomes
101	Soucie, K., Samardzic, T., Schramer, K., Salam, Z., & Ly, C. (2021a). Body- and symptom-related concerns in women diagnosed with polycystic ovary syndrome: A gap in symptom management. *Journal of Health Psychology*, *26*(5), 701–712.	Wrong population
102	van Niekerk, L. M., Bromfield, H., & Matthewson, M. (2022). Physical and psychological correlates of self and body compassion in women with polycystic ovary syndrome. *Journal of Health Psychology*, *27*(11).	Wrong population
103	Yin, M. X. C., Leng, L. L., Liang, Z., Chen, X. Y., Chan, C. H. Y., & Chan, C. L. W. (2022). Objectification and ambiguity of body image in women with Polycystic Ovary Syndrome: A mixed-method study. *Journal of Affective Disorders*, *310*, 296–303.	Wrong study design
104	Kogure, G. S., Lopes, I. P., Mendes, M. C., de Sa, M. F., Ferriani, R. A., Lara, L. A. da S., Reis, R. M. dos, Ribeiro, V. B., Kodato, S., & Furtado, C. L. M. (2020). The effects of aerobic physical exercises on body image among women with polycystic ovary syndrome. *Journal of Affective Disorders*, *262*, 350–358.	Wrong study design
105	Kogure, G. S., Ribeiro, V. B., Lopes, I. P., Furtado, C. L. M., Kodato, S., Silva de Sá, M. F., Ferriani, R. A., Lara, L. A. da S., & Maria dos Reis, R. (2019). Body image and its relationships with sexual functioning, anxiety, and depression in women with polycystic ovary syndrome. *Journal of Affective Disorders*, *253*, 385–393.	Wrong study design
106	Liao, L. M., Chadwick, P. M., Nesic, J., Brooke-Wavell, K., & Prelevic, G. M. (2008). Exercise and body image distress in overweight and obese women with polycystic ovary syndrome: A pilot investigation. *Gynecological Endocrinology*, *24*(10), 555–561.	Wrong study design
107	Joshi, R. D., Sawant, N., & Mayadeo Niranjan M. AO - Sawant, N. O. (2021). How Common are Depressive-Anxiety States, Body Image Concerns and Low Self-Esteem in Patients of PCOS? *Journal of Obstetrics and Gynecology of India*. http://medind.nic.in/jaq/jaqm.shtml	Wrong study design
108	Hasanpoor-Azghady, S. B., Amiri-Farahani, L., & Arbabi-Moghadam, R. (2022). Confirmatory factor analysis and psychometric properties of the Persian version of the Multidimensional Body-Self Relations Questionnaire-Appearance Scales (MBSRQ–AS) in women with polycystic ovary syndrome. *Eating and Weight Disorders*, *27*(2).	Wrong study design
109	de Niet, J. E., de Koning, C. M., Pastoor, H., Duivenvoorden, H. J., Valkenburg, O., Ramakers, M. J., Passchier, J., de Klerk, C., & Laven, J. S. E. (2010). Psychological well-being and sexarche in women with polycystic ovary syndrome. Human Reproduction, *25*(6), 1497–1503.	Wrong study design

5. STUDY CHARACTERISTICS TABLE FOR INCLUDED STUDIES

No.	Author, year, country	Population/ Setting	Study Design	Sample Size per group	Intervention/ exposure details	Comparison/ control details	Follow up Duration	Outcomes	Summary of findings
1	Alur-Gupta et al. 2019. USA	Women diagnosed with PCOS	Case Control	PCOS (n=189) Non-PCOS (n=225)	Multidimensional Body-Self Relations-Appearance Subscale (MBSRQ-AS) Stunkard Figure Rating Scale (FRS)	Healthy volunteers	None	Women with PCOS had worse BID scores on all five MBSRQ-AS subscales adjusted for age, body mass index, race, pregnancy history, income, and employment, and larger differences on the FRS compared with the control women. Most MBSRQ-AS subscale scores statistically significantly correlated with depression, anxiety, and quality of life scores.	Women with PCOS have increased body image distress and depressive and anxiety symptoms.
2	Annagur et al. 2014. Turkey	Women diagnosed with PCOS	Case Control	PCOS (n=83) Non-PCOS (n=64)	Body Image Scale	Healthy volunteers	None	The mean±S.D. BMI of PCOS and control groups were 23.85±4.67 kg/m2 and 22.00±2.43 kg/m2, respectively. Body mass index values of the PCOS group were significantly higher than the controls ($p<0.05$). There was no significant difference between the PCOS group and healthy controls for Body Image Scale (BIS) scores.	No significant difference in body image concerns between women with and without PCOS.
3	Deeks et al 2011. Australia	Women diagnosed with PCOS	Case Control	PCOS (n=177) Non-PCOS (n=109)	Multidimensional Body Self Relations-Appearance Subscale (MBSRQ-AS)	Healthy volunteers	None	women with PCOS had lower appearance evaluation, fitness orientation, health evaluation, health orientation, body areas satisfaction, higher overweight preoccupation and higher self-classified weight than women without PCOS.	In women with or without PCOS, body image and self-worth are predictors of both anxiety and depression, while QOL also predicts only depression.
4	Himelein et al. 2006. USA	Women diagnosed with PCOS	Case Control	PCOS (n=40) Non-PCOS (n=60)	Multidimensional Body Self Relations-Appearance Subscale (MBSRQ-AS) Body Features Satisfaction (BFS)	None	None	Women with PCOS reported higher depression scores and greater body dissatisfaction ($p < .001$) than comparison group women. Body image was strongly associated with depression overall, even after controlling body mass.	Among women with PCOS, body dissatisfaction measures and education explained 66 percent of the variance in depression, suggesting explanations of the PCOS-depression link should consider the role of potentially mediating psychosocial variables.
5	Karacan et al. 2014. Turkey	Women diagnosed with PCOS	Case Control	PCOS (n=42) Non-PCOS (n=52)	Stunkard Figure Rating Scale (FRS) body esteem scale	None	None	Women with PCOS viewed their actual body as significantly larger (M = 4.14, SD = 1.37) than their own ideal body. Similarly, participants in control group viewed also their actual body as	body esteem was important for predicting eating attitudes in both groups and sociocultural internalization of thinness ideal and body dissatisfaction were also significant factors in PCOS group.

								significantly larger (M = 3.59, SD = 1.49) than their own ideal body.	
6	Kutenaee et al. 2020. Iran	Women diagnosed with PCOS	Case Control	PCOS (n=201) Non-PCOS (n=199)	Body Image Concern Inventory (BICI)	Healthy volunteers	None	Mean BICI Score for PCOS Group; 39.17 (+/- 32.23) and Mean Body Image Score for Non-PCOS Group; 32.61 (+/-11.11). The strongest effect from a psychological variable on sleep quality was body image which had negative impact on sleep quality of patients with PCOS.	Our study showed that body image plays an important role in the sleep quality of women with PCOS.
7	Morotti et al. 2013. Italy	Women diagnosed with PCOS	Case Control	PCOS (n=33) Non-PCOS (n=22)	Stunkard Figure Rating Scale (FRS)	Healthy volunteers	None	two-factor Italian MFSQ, the FRS, and the BDI were similar in both groups.	moderate hirsutism and hyperandrogenism do not have any important influence on body image and self-esteem and, as a consequence, on sexual function.
8	Pastore et al. 2011. USA	Women diagnosed with PCOS	Case Control	PCOS (n=94) Non-PCOS (n=96)	Body Esteem Scale	Healthy volunteers	None	Body dissatisfaction (especially perception of physical conditioning) was strongly associated with more severe depression symptoms in non-obese PCOS women (BMI < 30, P < .04) before and after controlling for age, testosterone and free testosterone.	Among non-obese PCOS women, their subjective body image was strongly associated with the severity of their depression symptoms. Most of the obese PCOS cohort had low body satisfaction and depression symptoms, therefore individual differences in the body dissatisfaction scores were not helpful in identifying depression symptom severity.
9	Scaruffi et al 2019. Italy	Women diagnosed with PCOS	Case Control	PCOS (n=59) Non-PCOS (n=38)	Body Uneasiness Test (BUT)	Healthy volunteers	None	The PCOS group showed higher body uneasiness.	physical appearance and bodily function have a central place in the minds of women with PCOS, as well as in their relationships

5. FINDINGS

▪ EVIDENCE SUMMARY

Nine studies were included, all of case-control design, from various countries including Iran, Italy, USA, Turkey and Australia. All studies were ranked as moderate risk of bias due mainly to the lack of information on whether the cases and controls were taken from comparable populations and whether outcome assessors were blinded to case and control status. While some studies did not report whether the control status was established in a standard, valid and reliable way, a few others did not report whether the study was sufficiently powered to detect any differences between the groups.

▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS:

Studies showed that women with PCOS had higher body image concerns compared to healthy controls. However, certainty in the evidence was low across all outcomes, downgraded due to the moderate risk of bias in the included studies.

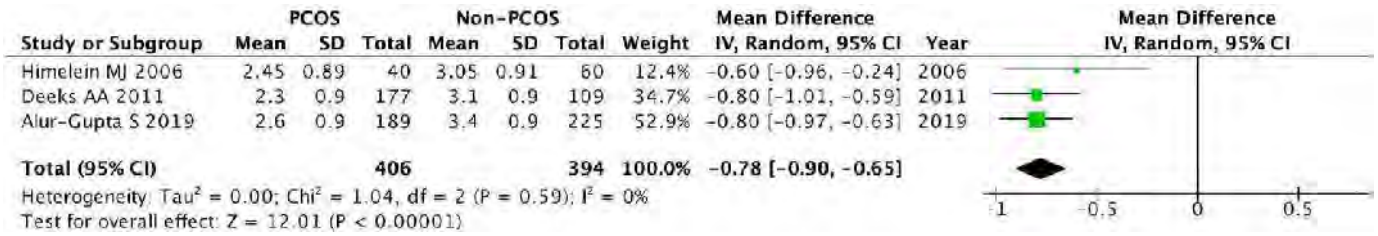
Outcome or subgroup	Studies	n	Effect, fixed [95% CI]	P	Favours	Certainty	Importance
Body image concerns- MBSRQ-AS Appearance Evaluation	3	800	MD -0.78 [-0.90, -0.65]	p=0.59 I^2=0%	Lower score in PCOS	⨁⨁◯◯ LOW	CRITICAL
Body image concerns- MBSRQ-AS Overweight Preoccupation	2	700	MD +0.60 [0.42, 0.78]	p=1.0 I^2=0%	Lower score in Non-PCOS	⨁⨁◯◯ LOW	CRITICAL
Body image concerns- MBSRQ-AS Appearance Orientation	3	800	MD +0.22 [0.07, 0.36]	p=0.11 I^2=54%	Lower score in Non-PCOS	⨁⨁◯◯ LOW	CRITICAL
Body image concerns- MBSRQ-AS Body Areas Satisfaction	2	700	MD -0.55 [-0.65, -0.45]	p=0.32 I^2=0%	Lower score in PCOS	⨁⨁◯◯ LOW	CRITICAL
Body image concerns- MBSRQ-AS Body Weight Classification	2	700	MD +0.54 [+0.25, +0.55]	p=0.02 I^2=83%	Lower score in Non-PCOS	⨁⨁◯◯ LOW	CRITICAL
Body image concerns- BESAA appearance	2	284	MD -0.29 [-1.92, +1.34]	p=0.99 I^2=0%	Lower score in None	⨁⨁◯◯ LOW	CRITICAL
Body image concerns- BESAA weight	2	284	MD -2.04 [-3.93, -0.15]	p=0.53 I^2=0%	Lower score in PCOS	⨁⨁◯◯ LOW	CRITICAL
Body image concerns- BESAA attribution	2	284	MD -0.75 [-2.34, +0.84]	p=0.06 I^2=72%	Lower score in None	⨁⨁◯◯ LOW	CRITICAL

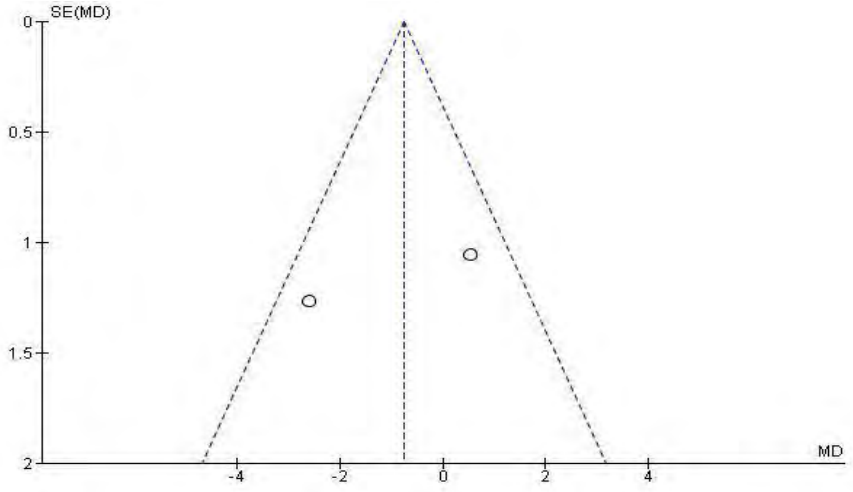
OUTCOME: MBSRQ-AS Appearance Evaluation						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable): eg. PCOS vs Non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size in PCOS group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size in non-PCOS group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Himelein MJ 2006	Score	**MBSRQ-AS**	2.45	0.89	40	3.05	0.91	60	Crude	
Alur-Gupta, S 2019	Score	**MBSRQ-AS**	2.6	0.9	189	3.4	0.9	225	Crude	
Deeks AA 2011	Score	**MBSRQ-AS**	2.3	0.9	177	3.1	0.9	109	Crude	

MBSRQ-AS: Multidimensional Body-Self Relations Questionnaire. Appearance subscale

Figure 1: *MBSRQ-AS appearance evaluation subdomain score in women with and without PCOS.*

(High score- satisfied; low score- **dis**satisfied)



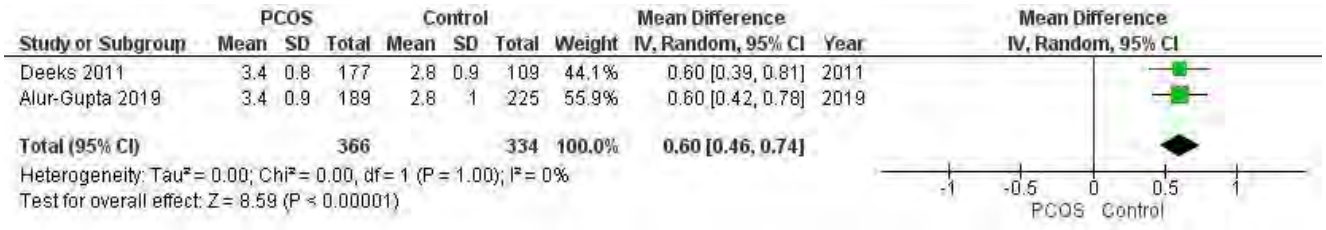


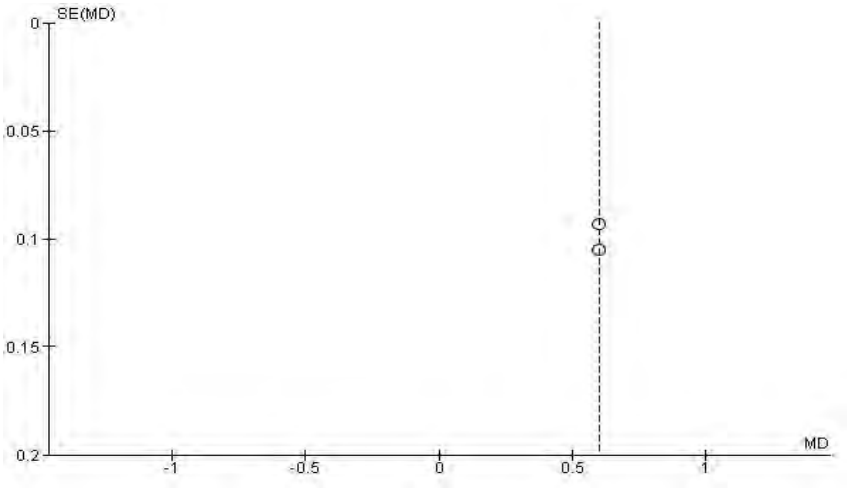
OUTCOME: MBSRQ-AS Overweight Preoccupation						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable): eg. PCOS vs Non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size in PCOS group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size in non-PCOS group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Deeks AA 2011	Score	**MBSRQ-AS**	3.4	0.8	189	2.8	0.9	225	Crude	
Alur-Gupta, S 2019	Score	**MBSRQ-AS**	3.4	0.9	177	2.8	1.0	109	Crude	

MBSRQ-AS: Multidimensional Body-Self Relations Questionnaire. Appearance subscale

Figure 2: *MBSRQ-AS Overweight Preoccupation subdomain score in women with and without PCOS.*

(High score- **dis**satisfied; low score- satisfied)



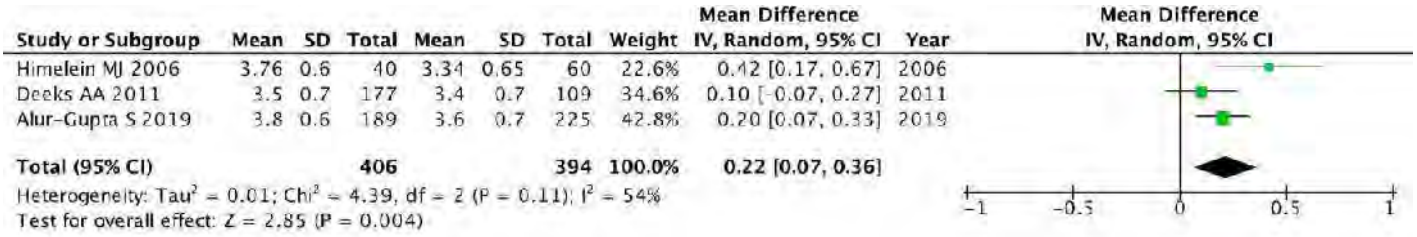


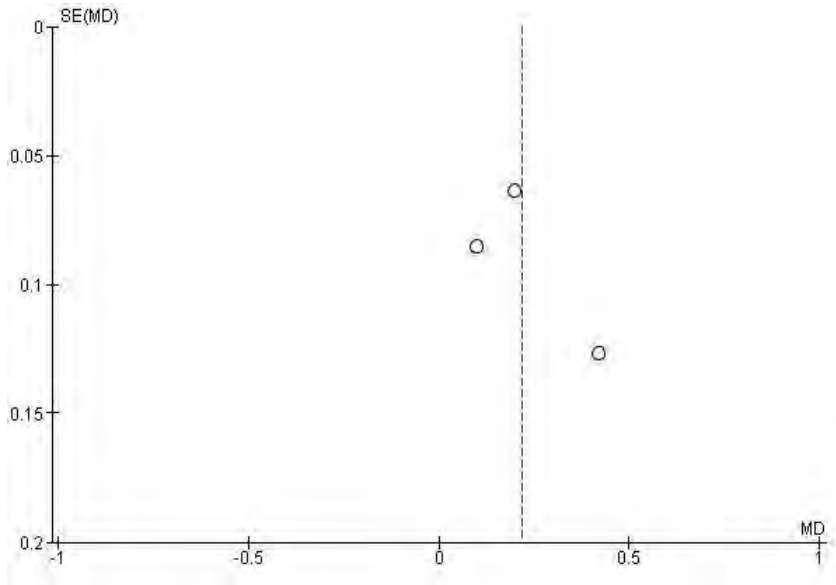
OUTCOME: MBSRQ-AS Appearance Orientation						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable): eg. PCOS vs Non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size in PCOS group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size in non-PCOS group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Himelein MJ 2006	Score	**MBSRQ-AS**	3.76	0.6	40	3.34	0.65	60	Crude	
Alur-Gupta, S 2019	Score	**MBSRQ-AS**	3.8	0.6	189	3.6	0.7	225	Crude	
Deeks AA 2011	Score	**MBSRQ-AS**	3.5	0.7	177	3.4	0.7	109	Crude	

MBSRQ-AS: Multidimensional Body-Self Relations Questionnaire. Appearance subscale

Figure 3: *MBSRQ-AS appearance orientation subdomain score in women with and without PCOS.*

(High score- **dis**satisfied; low score- satisfied)



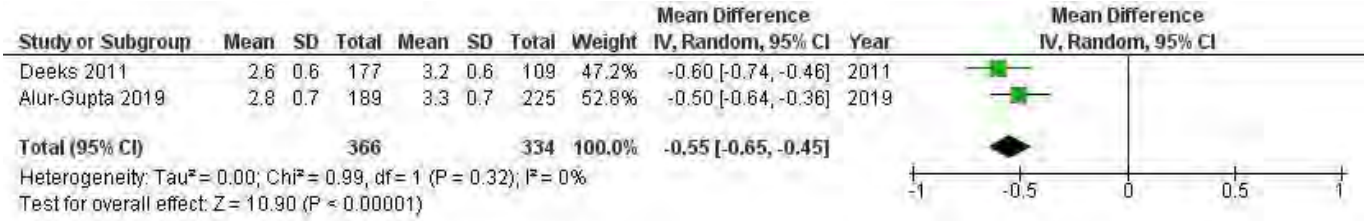


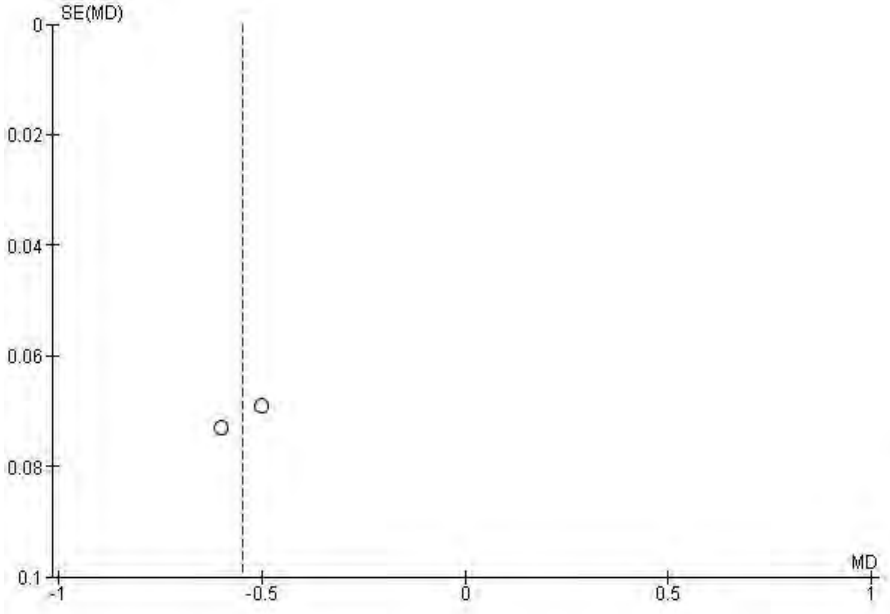
OUTCOME: MBSRQ-AS Body Areas Satisfaction						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable): eg. PCOS vs Non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size in PCOS group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size in non-PCOS group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Deeks AA 2011	Score	**MBSRQ-AS**	2.6	0.6	189	3.2	0.6	225	Crude	
Alur-Gupta, S 2019	Score	**MBSRQ-AS**	2.8	0.7	177	3.3	0.7	109	Crude	

MBSRQ-AS: Multidimensional Body-Self Relations Questionnaire. Appearance subscale

Figure 4: *MBSRQ-AS Body Areas Satisfaction subdomain score in women with and without PCOS.*

(High score- **dis**satisfied; low score- satisfied)



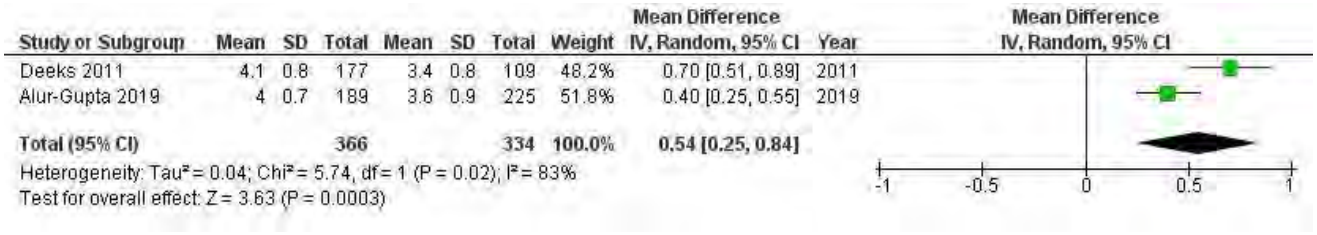


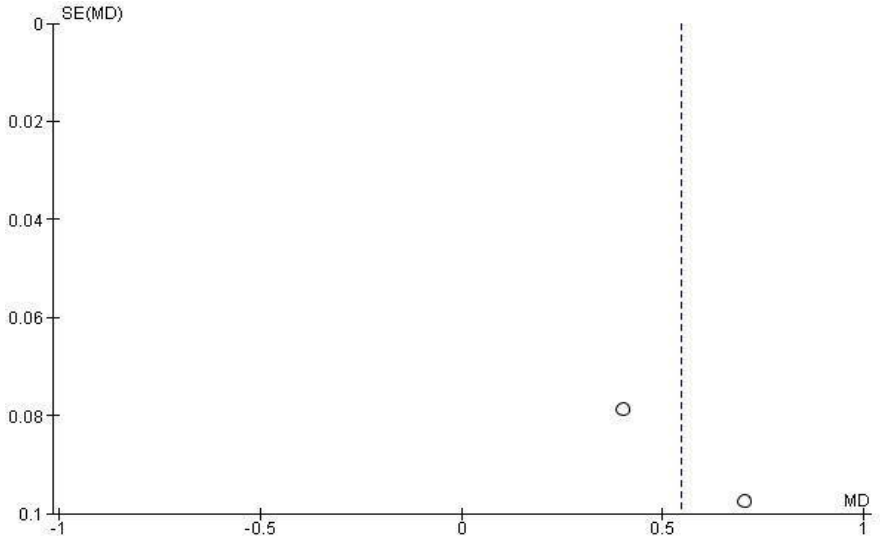
OUTCOME: MBSRQ-AS Weight Classification						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable): eg. PCOS vs Non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size in PCOS group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size in non-PCOS group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Alur-Gupta, S 2019	Score	**MBSRQ-AS**	4.1	0.8	189	3.4	0.8	225	Crude	
Deeks AA 2011	Score	**MBSRQ-AS**	4.0	0.7	177	3.6	0.9	109	Crude	

MBSRQ-AS: Multidimensional Body-Self Relations Questionnaire. Appearance subscale

Figure 5: *MBSRQ-AS Weight Classification subdomain score in women with and without PCOS.*

(High score- **dis**satisfied; low score- satisfied)

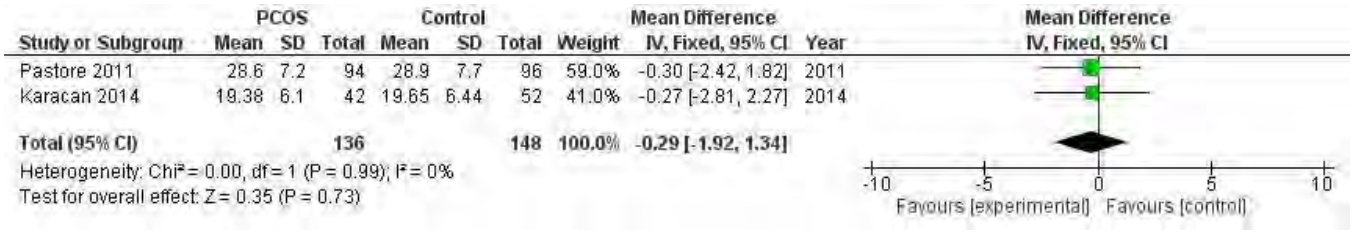


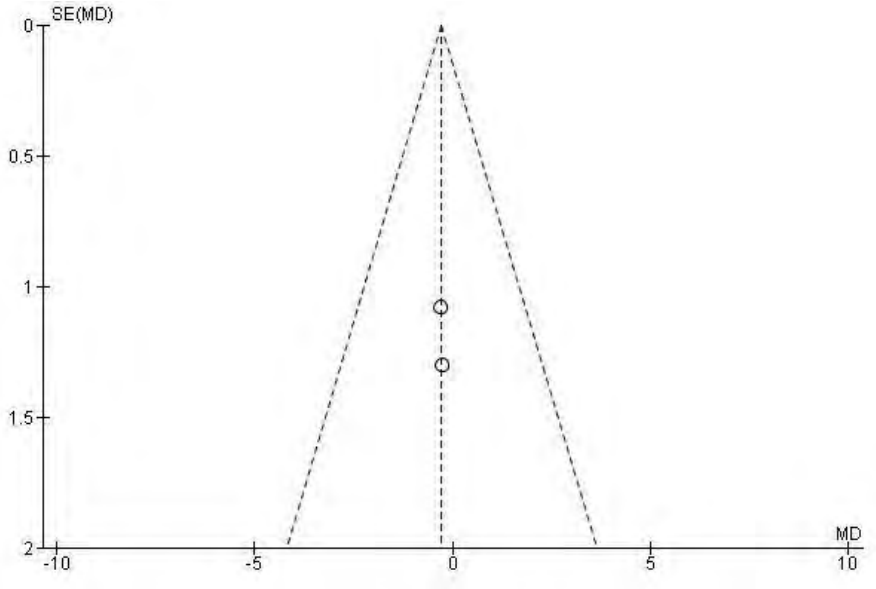


OUTCOME: BESAA appearance						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable): eg. PCOS vs Non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size in PCOS group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size in non-PCOS group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Pastore 2011	Score	**BESAA**	28.6	7.2	94	28.9	7.7	96	Crude	
Karacan 2014	Score	**BESAA**	19.38	6.1	42	19.65	6.44	52	Crude	

BESAA- Body Esteem Scale for Adolescents and Adults

Figure 6: *BESAA appearance subdomain score in women with and without PCOS.*

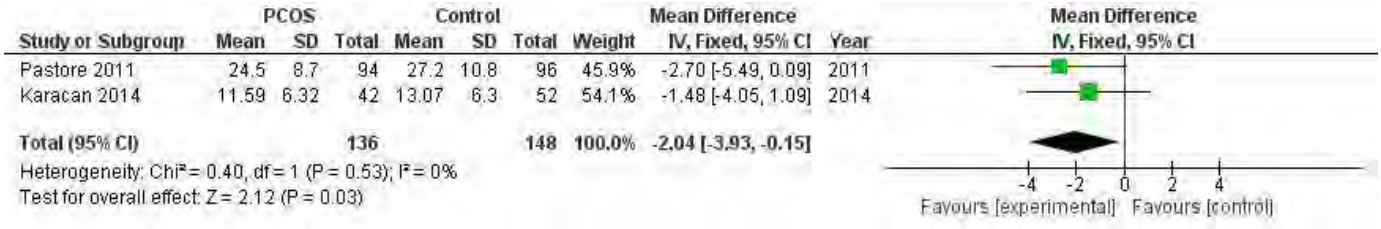


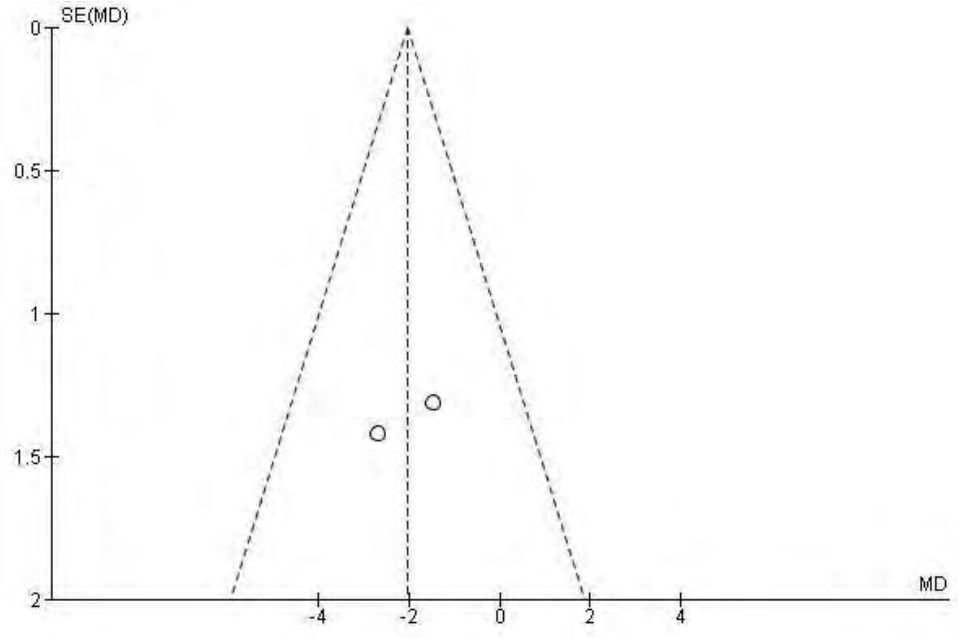


OUTCOME: BESAA weight						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable): eg. PCOS vs Non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size in PCOS group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size in non-PCOS group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Pastore 2011	Score	**BESAA**	24.5	8.7	94	27.2	10.8	96	Crude	
Karacan 2014	Score	**BESAA**	11.59	6.32	42	13.07	6.3	52	Crude	

BESAA- Body Esteem Scale for Adolescents and Adults

Figure 7: *BESAA Weight subdomain score in women with and without PCOS.*

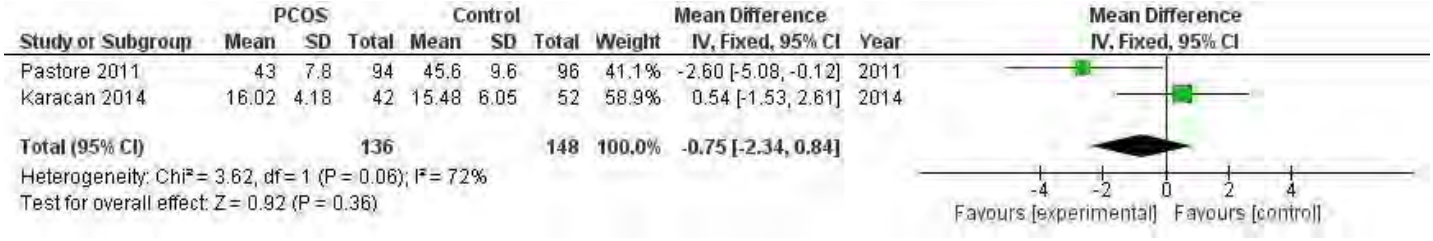


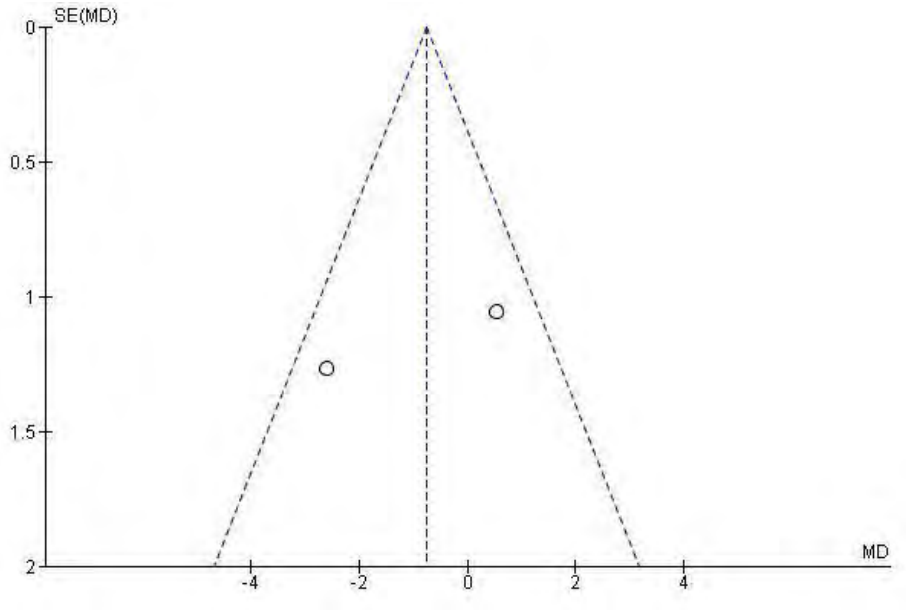


OUTCOME: BESAA attribution						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable): eg. PCOS vs Non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size in PCOS group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size in non-PCOS group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Pastore 2011	Score	**BESAA**	43	7.8	94	45.6	9.6	96	Crude	
Karacan 2014	Score	**BESAA**	16.02	4.18	42	15.48	6.05	52	Crude	

BESAA- Body Esteem Scale for Adolescents and Adults

Figure 8: BESAA *attribution subdomain score in women with and without PCOS.*





OUTCOME: Body Features Satisfaction							**OUTCOME TYPE:** Continuous	
COMPARISON (if applicable): eg. PCOS vs Non-PCOS								
Author, year	**Unit of outcome**	**Method of measurement**	**Mean in PCOS group**	**SD in PCOS group**	**Mean in non-PCOS group**	**SD in non-PCOS group**	**Values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Himelein et al. 2006	Score	**Body Features Satisfaction score**	4.1	1.1	5.2	1.2	Crude	

OUTCOME: Body Image						**OUTCOME TYPE:** Continuous		
COMPARISON (if applicable): eg. PCOS vs Non-PCOS								
Author, year	**Unit of outcome**	**Method of measurement**	**Mean in PCOS group**	**SD in PCOS group**	**Mean in non-PCOS group**	**SD in non-PCOS group**	**Values adjusted or crude?**	**If adjusted, what variables were in the model?**
Annagur et al. 2014	Score	**Body Image Scale (BIS)**	97.6	20.4	93.1	17.1	Crude	

Body Image Scale (BIS)

OUTCOME: Body Image							**OUTCOME TYPE:** Continuous	
COMPARISON (if applicable): eg. PCOS vs Non-PCOS								
Author, year	**Unit of outcome**	**Method of measurement**	**Mean in PCOS group**	**SD in PCOS group**	**Mean in non-PCOS group**	**SD in non-PCOS group**	**Values adjusted or crude?**	**If adjusted, what variables were in the model?**
Annagur et al. 2014	Score	**Body Image Scale (BIS)**	97.6	20.4	93.1	17.1	Crude	

Body Image Scale (BIS)

OUTCOME: Positive Total Symptom Index (PST)							**OUTCOME TYPE:** Continuous	
COMPARISON (if applicable): eg. PCOS vs Non-PCOS								
Author, year	**Unit of outcome**	**Method of measurement**	**Mean in PCOS group**	**SD in PCOS group**	**Mean in non-PCOS group**	**SD in non-PCOS group**	**Values adjusted or crude?**	**If adjusted, what variables were in the model?**
Scaruffi et al. 2019	Score	**Body Uneasiness Test (BUT)**	19.6	10.0	14.7	8.8	Crude	

Body Uneasiness Test (BUT)

OUTCOME: Global Severity Index							**OUTCOME TYPE:** Continuous	
COMPARISON (if applicable): eg. PCOS vs Non-PCOS								
Author, year	**Unit of outcome**	**Method of measurement**	**Mean in PCOS group**	**SD in PCOS group**	**Mean in non-PCOS group**	**SD in non-PCOS group**	**Values adjusted or crude?**	**If adjusted, what variables were in the model?**
Scaruffi et al. 2019	Score	**Body Uneasiness Test (BUT)**	1.7	1.0	1.1	0.8	Crude	

Body Uneasiness Test (BUT)

OUTCOME: Body image								**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): eg. PCOS vs Non-PCOS								
Author, year	**Unit of outcome**	**Method of measurement**	**Mean in PCOS group**	**SD in PCOS group**	**Mean in non-PCOS group**	**SD in non-PCOS group**	**Values adjusted or crude?**	**If adjusted, what variables were in the model?**
Kutenaee et al. 2020	Score	Body image concern inventory	39.17	32.23	32.61	11.11	Crude	

OUTCOME: Ideal weight					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): eg. PCOS vs Non-PCOS								
Author, year	**Unit of outcome**	**Method of measurement**	**Mean in PCOS group**	**SD in PCOS group**	**Mean in non-PCOS group**	**SD in non-PCOS group**	**Values adjusted or crude?**	**If adjusted, what variables were in the model?**
Morotti et al. 2013	Kg	Stunkard Figure Rating Scale	54.5	5.4	52.8	4.8	Crude	

OUTCOME: Actual body silhouette					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): eg. PCOS vs Non-PCOS								
Author, year	**Unit of outcome**	**Method of measurement**	**Mean in PCOS group**	**SD in PCOS group**	**Mean in non-PCOS group**	**SD in non-PCOS group**	**Values adjusted or crude?**	**If adjusted, what variables were in the model?**
Morotti et al. 2013	Score	Stunkard Figure Rating Scale	3.6	1.1	3.7	1.0	Crude	

OUTCOME: Ideal silhouette					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): eg. PCOS vs Non-PCOS								
Author, year	**Unit of outcome**	**Method of measurement**	**Mean in PCOS group**	**SD in PCOS group**	**Mean in non-PCOS group**	**SD in non-PCOS group**	**Values adjusted or crude?**	**If adjusted, what variables were in the model?**
Morotti et al. 2013	Score	Stunkard Figure Rating Scale	3.1	0.8	2.9	0.6	Crude	

OUTCOME: Most attractive silhouette					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): eg. PCOS vs Non-PCOS								
Author, year	**Unit of outcome**	**Method of measurement**	**Mean in PCOS group**	**SD in PCOS group**	**Mean in non-PCOS group**	**SD in non-PCOS group**	**Values adjusted or crude?**	**If adjusted, what variables were in the model?**
Morotti et al. 2013	Score	Stunkard Figure Rating Scale	3.4	0.7	3.1	0.6	Crude	

OUTCOME: Most attractive silhouette for partner					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): eg. PCOS vs Non-PCOS								
Author, year	**Unit of outcome**	**Method of measurement**	**Mean in PCOS group**	**SD in PCOS group**	**Mean in non-PCOS group**	**SD in non-PCOS group**	**Values adjusted or crude?**	**If adjusted, what variables were in the model?**
Morotti et al. 2013	Score	Stunkard Figure Rating Scale	3.3	0.8	3.1	0.5	Crude	

OUTCOME: Satisfaction of their own body					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): eg. PCOS vs Non-PCOS								
Author, year	**Unit of outcome**	**Method of measurement**	**Mean in PCOS group**	**SD in PCOS group**	**Mean in non-PCOS group**	**SD in non-PCOS group**	**Values adjusted or crude?**	**If adjusted, what variables were in the model?**
Morotti et al. 2013	Score	Stunkard Figure Rating Scale	3.3	1.0	3.2	0.8	Crude	

OUTCOME: Feeling well with their own silhouette							**OUTCOME TYPE:** Continuous	
COMPARISON (if applicable): eg. PCOS vs Non-PCOS								
Author, year	**Unit of outcome**	**Method of measurement**	**Mean in PCOS group**	**SD in PCOS group**	**Mean in non-PCOS group**	**SD in non-PCOS group**	**Values adjusted or crude?**	**If adjusted, what variables were in the model?**
Morotti et al. 2013	Score	Stunkard Figure Rating Scale	3.2	0.9	3.1	0.7	Crude	

OUTCOME: Self-esteem							**OUTCOME TYPE:** Continuous	
COMPARISON (if applicable): eg. PCOS vs Non-PCOS								
Author, year	**Unit of outcome**	**Method of measurement**	**Mean in PCOS group**	**SD in PCOS group**	**Mean in non-PCOS group**	**SD in non-PCOS group**	**Values adjusted or crude?**	**If adjusted, what variables were in the model?**
Kutenaee 2020	Score	Rosenberg Self-Esteem Scale (RSES)	15.32	2.04	15.66	1.90	Crude	

Rosenberg Self-Esteem Scale (RSES

OUTCOME: Self-esteem							**OUTCOME TYPE:** Continuous	
COMPARISON (if applicable): eg. PCOS vs Non-PCOS								
Author, year	**Unit of outcome**	**Method of measurement**	**Mean in PCOS group**	**SD in PCOS group**	**Mean in non-PCOS group**	**SD in non-PCOS group**	**Values adjusted or crude?**	**If adjusted, what variables were in the model?**
Karacan 2014	Score	socio-cultural attitudes toward appearance questionnaire	15.32	2.04	15.66	1.90	Crude	

8. GRADE ASSESSMENTS AND EVIDENCE PROFILE

COMPARISON: PCOS vs non-PCOS												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	PCOS	Non-PCOS	Effect, fixed [95% CI]	Worse	Certainty	Importance
Outcome: **Body image concerns- MBSRQ-AS Appearance Evaluation**												
3	Case-control	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	406	394	MD -0.78 [-0.90, -0.65]	PCOS	⊕⊕◯◯ LOW	CRITICAL
Outcome: **Body image concerns- MBSRQ-AS Overweight Preoccupation**												
2	Case-control	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	366	334	MD +0.60 [0.42, 0.78]	PCOS	⊕⊕◯◯ LOW	CRITICAL
Outcome: **Body image concerns- MBSRQ-AS Appearance Orientation**												
3	Case-control	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	406	394	MD +0.22 [0.07, 0.36]	PCOS	⊕⊕◯◯ LOW	CRITICAL
Outcome: **Body image concerns- MBSRQ-AS Body Areas Satisfaction**												
2	Case-control	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	366	334	MD -0.55 [-0.65, -0.45]	PCOS	⊕⊕◯◯ LOW	CRITICAL
Outcome: **Body image concerns- MBSRQ-AS Body Weight Classification**												
2	Case-control	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	366	334	MD +0.54 [+0.25, +0.55]	PCOS	⊕⊕◯◯ LOW	CRITICAL
Outcome: **Body image concerns- BESAA appearance**												
2	Case-control	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	136	148	MD -0.29 [-1.92, +1.34]	None	⊕⊕◯◯ LOW	CRITICAL
Outcome: **Body image concerns- BESAA weight**												
2	Case-control	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	136	148	MD -2.04 [-3.93, -0.15]	PCOS	⊕⊕◯◯ LOW	CRITICAL
Outcome: **Body image concerns- BESAA attribution**												
2	Case-control	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	136	148	MD -0.75 [-2.34, +0.84]	None	⊕⊕◯◯ LOW	CRITICAL
Outcome: **Body Image Scale**												
1	Case-control	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	83	64	Not estimable	None	⊕⊕◯◯ LOW	CRITICAL

Due to the observational design of all included studies, the grading of evidence for all outcomes began at the moderate level (not high) as the starting point.
[1] Downgraded once due to the included studies having moderate risk of bias

Outcome: **Rosenberg Self-Esteem Scale**											
1	Case-control	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	366	334	Not estimable	PCOS	⊕⊕◯◯ LOW	CRITICAL
Outcome: **Body Features Satisfaction (BFS)**											
1	Case-control	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	136	148	Not estimable	PCOS	⊕⊕◯◯ LOW	CRITICAL
Outcome: **Stunkard Figure Rating Scale (FRS)**											
1	Case-control	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	189	225	Not estimable	PCOS	⊕⊕◯◯ LOW	CRITICAL
1	Case-control	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	33	22	Not estimable	None	⊕⊕◯◯ LOW	CRITICAL
1	Case-control	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	42	52	Not estimable	None	⊕⊕◯◯ LOW	CRITICAL
Outcome: **Body Image Concern Inventory (BICI)**											
1	Case-control	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	201	199	Not estimable	PCOS	⊕⊕◯◯ LOW	CRITICAL
Outcome: **Body Uneasiness Test (BUT)**											
1	Case-control	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	59	38	Not estimable	PCOS	⊕⊕◯◯ LOW	CRITICAL
Outcome: S**ocio-cultural attitudes toward appearance questionnaire (SATAQ)**											
1	Case-control	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	42	52	Not estimable	None	⊕⊕◯◯ LOW	CRITICAL

Due to the observational design of all included studies, the grading of evidence for all outcomes began at the moderate level (not high) as the starting point.
[1] Downgraded once due to the included studies having moderate risk of bias

APPENDIX. STUDY CHARACTERISTICS AND QUALITY APPRAISAL TEMPLATES CROSS-SECTIONAL or CASE-CONTROL STUDIES

Study ID	Annagur BB et al. 2014	
Study Citation	Annagür BB, Tazegül A, Akbaba N. Body Image, Self-Esteem and Depressive Symptomatology in Women with Polycystic Ovary Syndrome. Noro Psikiyatr Ars. 2014 Jun;51(2):129-132. doi: 10.4274/npa.y6778. Epub 2014 Jun 1. PMID: 28360612; PMCID: PMC5353087.	
Study Country	Turkey	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	83 patients diagnosed with PCOS according to Rotterdam Criteria. Ethnicity breakdown was 83.9% in Caucasian/White, 6.5% in Middle Eastern, 1.6% in South Asian, 1.6% in Jamaican and 6.5% in mixed descent.	
Control population	N=64 (Non-PCOS)	
PCOS diagnostic criteria	Rotterdam	
N per group	PCOS (n=83) Non-PCOS (n=64)	
Setting	Recruited from the patients with untreated PCOS who admitted to the Outpatient Clinic of Gynecology and Obstetrics of Faculty of Medicine of Selçuk University. Age matched healthy controls (n=64) were recruited from employees at Selçuk University Hospital.	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary outcomes: - Body Image Scale (BIS) Outcomes not relevant: - Rosenberg Self-Esteem Scale (RSES) - Beck Depression Inventory (BDI)	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes
Inclusion criteria	Yes Partial No Not reported	Yes. Patients with untreated PCOS diagnosed according to Rotterdam criteria.
Exclusion criteria	Yes Partial No Not reported	Yes. The exclusion criteria for the study were the following: a history or existence of bipolar disorder, schizophrenia or related disorders, a history of neurological disease and concomitant severe medical illnesses (e. g., cardiovascular or pulmonary diseases, severe renal or liver failure, any cancer) and those who were under hormone replacement or psychotropic medications within the last 4 weeks.
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes

Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	Yes, case-control
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	Not relevant to this systematic review
Was matching performed?	Yes Partial No Not reported	Yes, age matched healthy controls (n=64) were recruited.
Summary Result/s	The mean±S.D. BMI of PCOS and control groups were 23.85±4.67 kg/m2 and 22.00±2.43 kg/m2, respectively. Body mass index values of the PCOS group were significantly higher than the controls ($p<0.05$). There was no significant difference between the PCOS group and healthy controls for Body Image Scale (BIS) scores.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS – **Were the cases and controls taken from comparable populations?**	Yes Partial No Not reported	No
SELECTION BIAS – **Was the case definition adequate and established in a standard, valid and reliable way?**	Yes Partial No Not reported	Not reported
SELECTION BIAS – **Was the control status established in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes
PERFORMANCE BIAS – **Aside from the exposure/ intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes
DEDETECTION BIAS – **Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes
DEDETECTION BIAS – **Were outcome assessors blind to case and control status?**	Yes Partial No Not reported	Not reported
DEDETECTION BIAS – **Were all outcomes measured in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes

	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Not reported
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	X% treatment X% control/ comparison Not reported	Not relevant to case-control
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Not relevant to case-control
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported No protocol or PROSPERO
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?			

Study ID	Alur-Gupta S et al. 2019
Study Citation	Alur-Gupta, S., Chemerinski, A., Dokras, A., Liu, C., Lipson, J., Allison, K., & Sammel Mary D. AO - Dokras, A. O. http://orcid. org/0000-0002-1085-3969. (2019). Body-image distress is increased in women with polycystic ovary syndrome and mediates depression and anxiety. Fertility and Sterility, 112(5), 930.
Study Country	USA

CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	189 patients diagnosed with PCOS according to Rotterdam Criteria.	
Control population	Non-PCOS (n=225)	
PCOS diagnostic criteria	Rotterdam	
N per group	PCOS (n=189 Non-PCOS (n=225)	
Setting	Secondary. University of Pennsylvania's Penn PCOS center and gynecology clinics. From January-October 2018, non-pregnant women aged 18–50 years presenting to these clinics were approached for participation in the study.	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary outcomes: - Multidimensional Body Self Relations-Appearance Subscale (MBSRQ-AS) - Stunkurd Figure Rating Scale (FRS) Outcomes not relevant: - Hospital Anxiety and Depression Scale (HADS)	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes
Inclusion criteria	Yes Partial No Not reported	Yes. Women with PCOS met the Rotterdam criteria, defined as two out of three criteria: elevated clinical or biochemical androgens (identified in this study by chart review for Ferriman-Gallwey [FG] scores and/or serum testosterone levels), irregular menses, and polycystic-appearing ovaries (identified by chart review for ultrasound report) . No restrictions were placed based on the history of mood disorders, use of antidepressants, hormonal contraception, or presence of other medical comorbidities.
Exclusion criteria	Yes Partial No Not reported	Not reported
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	Yes, case-control
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	Not relevant to this systematic review
Was matching performed?	Yes Partial No Not reported	No

Summary Result/s	All assessed areas of the MBSRQ-AS showed statistically significant differences between PCOS and controls suggestive of BID. On the Stunkard FRS survey, women with PCOS had larger differences compared with controls for Stunkard Score 1 (P=.020) and Score 2 (P=.011) but not Score 3 (P=.276). For both Score 1 and Score 2, the values were noted to be 2 or greater, indicative of BID		

BID measure	PCOS (n = 189)	Controls (n = 225)	P value[a]
MBSRQ-AS			
Appearance evaluation[b]	2.6 ± 0.9	3.4 ± 0.9	<.001
Overweight preoccupation	3.4 ± 0.9	2.8 ± 1.0	<.001
Appearance orientation	3.8 ± 0.6	3.6 ± 0.7	.002
Body areas satisfaction	2.8 ±0.7	3.3 ± 0.7	<.001
Self-classified weight	4.0 ± 0.7	3.6 ± 0.9	.013

INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes Partial No Not reported	Yes
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Not reported
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Not relevant
PERFORMANCE BIAS	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes
DEDETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Not reported

ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	X% treatment X% control/ comparison Not reported	Not relevant to case-control
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Not relevant to case-control
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	No
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No risk of bias the same across all outcomes	

Study ID	Scaruffi E et al 2019
Study Citation	Scaruffi, E., Franzoi, I. G., Civilotti, C., Guglielmucci, F., la Marca, L., Tomelini, M., Veglia, F., & Granieri, A. (2019). Body image, personality profiles and alexithymia in patients with polycystic ovary syndrome (PCOS). Journal of Psychosomatic Obstetrics and Gynaecology, 40(4), 294–303.
Study Country	Italy
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	59 patients diagnosed with PCOS according to Rotterdam Criteria.
Control population	N=38 (Non-PCOS)

PCOS diagnostic criteria	Rotterdam	
N per group	PCOS (n=59) Non-PCOS (n=38)	
Setting	PCOS group recruited from outpatients at the two gynecological endocrinology services of the University Hospital Città della Scienza e della Salute in Turin. The control group of 38 healthy age-matched women was enrolled through local general practitioners	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary outcomes: - Body Uneasiness Test (BUT) Outcomes not relevant: - Toronto Alexithymia Scale (TAS-20) - (MMPI-2)	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes
Inclusion criteria	Yes Partial No Not reported	Yes. Inclusion criteria for PCOS patients were defined according to the revised criteria of the Rotterdam Consensus Workshop. These criteria require 2 out of 3 between oligo- and/or anovulation, clinical and/or biochemical signs of hyperandrogenism and polycystic ovaries.
Exclusion criteria	Yes Partial No Not reported	Yes. Exclusion criteria for both the PCOS and the control groups were (1) having a poor knowledge of the Italian language, (2) having a certified psychiatric diagnosis, (3) having a certified diagnosis of a neurogenerative disease (i.e. Alzheimer disease, Parkinson disease, etc.), (4) having a certified medical disease, (5) being pregnant and (6) having been in psychiatric or psychological therapy in the last 6 months.
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	Yes, case-control
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	Not relevant to this systematic review
Was matching performed?	Yes Partial No Not reported	Yes, age matched healthy controls (n=38) were recruited.
Summary Result/s	On the BUT, PCOS patients show higher values compared to the controls in both the Positive Symptom Total Index (p = .015) and the Global Severity Index (p = .002) scales.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes Partial No Not reported	No
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Not reported
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
PERFORM ANCE BIAS	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes
DEDETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Not reported
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	X% treatment X% control/ comparison Not reported	Not relevant to case-control
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Not relevant to case-control
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported No protocol or PROSPERO
CONFOUN DING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes

OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No risk of bias the same across all outcomes	

Study ID	Morotti E et al. 2013
Study Citation	Morotti, E., Battaglia, B., Fabbri, R., Meriggiola, M. C., Venturoli, S., Battaglia, C., & Persico, N. (2013). Body imaging and sexual behavior in lean women with polycystic ovary syndrome. Journal of Sexual Medicine, 10(11), 2752–2760.
Study Country	Italy
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	33 patients diagnosed with PCOS according to Rotterdam Criteria.
Control population	N=22 (Non-PCOS)
PCOS diagnostic criteria	Rotterdam
N per group	PCOS (n=33) Non-PCOS (n=22)
Setting	Not reported
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary outcomes: - Stunkard Figure Rating Scale (FRS) Outcomes not relevant - Ferriman-Gallwey score (FG) - Italian McCoy female questionnaire (MFSQ) - Beck Depression Inventory (BDI)

Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	Yes. The study aims to examine the differences in mood, perceived body image, sexual behavior, and clitoral vascularization between lean PCOS patients and healthy eumenorrheic controls.
Inclusion criteria		Yes Partial No Not reported	Yes.
Exclusion criteria		Yes Partial No Not reported	Yes.
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Yes, case-control
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Not relevant to this systematic review
Was matching performed?		Yes Partial No Not reported	No
Summary Result/s		The FG score and the androgens resulted, as expected, more elevated in PCOS patients than in controls. However, the US assessment of the clitoral body volume and the resistances registered at the level of the dorsal clitoral artery did not show any difference between Group I and Group II patients. Moreover, the two-factor Italian MFSQ, the FRS, and the BDI were similar in both groups.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes Partial No Not reported	Not reported
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Not reported
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes

PERFORMANCE BIAS	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes
DEDETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Not reported
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	X% treatment X% control/ comparison Not reported	Not relevant to case-control
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Not relevant to case-control
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported No protocol or PROSPERO
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes

COMMENTS		
What is the overall risk of bias?	Low Moderate High Insufficient information	Moderate
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?	No risk of bias the same for all outcomes	

Study ID	Pastore, LM et al. 2011	
Study Citation	Pastore, L. M., Dalal, P., Bray, M. J., Patrie, J. T., & Morris, W. L. (2011). Depression symptoms and body dissatisfaction association among polycystic ovary syndrome women. Journal of Psychosomatic Research, 71(4), 270–276.	
Study Country	USA	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	94 patients diagnosed with PCOS according to NICHD Criteria.	
Control population	N=96 (Non-PCOS)	
PCOS diagnostic criteria	NICHD criteria	
N per group	PCOS (n=94) Non-PCOS (n=96)	
Setting	Community. Anonymous waiting room surveys (BES and the QIDS-SR16) were implemented at three university OB/GYN and Family Medicine clinics(80% of the sample), and the university cafeterias (20% of the sample)in the fall 2009/winter 2010 (exempt IRB study).	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary outcomes: - Body Uneasiness Test (BUT) Outcomes not relevant: - Toronto Alexithymia Scale (TAS-20) - (MMPI-2)	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes
Inclusion criteria	Yes Partial No Not reported	Yes. Inclusion criteria were: a) a diagnosis of PCOS, as confirmed through the study using the NICHD criteria of oligomenorrheic and non-diabetic, with self-reported hirsutism and/or acne and/or elevated free testosterone (> 6.8 pg/mL), b) aged 18 to 43 years, c) weight of 250 lb (113 kg) or less, and d) at least one menses in the past six months but no more than eight periods in the most recent 12 months without hormonal intervention.

Exclusion criteria		Yes Partial No Not reported	Yes. Exclusion criteria were: a) use of metformin or hormonal contraceptives in the 60 days prior to enrollment, b) currently pregnant or breastfeeding during the prior 30 days, and c) bleeding/coagulation conditions that would contraindicate a blood draw.
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Yes, case-control
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Not relevant to this systematic review
Was matching performed?		Yes Partial No Not reported	No
Summary Result/s		Body dissatisfaction (especially perception of physical conditioning) was strongly associated with more severe depression symptoms in non-obese PCOS women (BMI < 30, P < .04) before and after controlling for age, testosterone and free testosterone.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes Partial No Not reported	No
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Not reported
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Not reported
PERFORMANCE BIAS	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes
DEDETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes

	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Not reported
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	X% treatment X% control/ comparison Not reported	Not relevant to case-control
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Not relevant to case-control
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported No protocol or PROSPERO
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?			

Study ID	Himelein MJ et al. 2006	
Study Citation	Himelein, M. J., & Thatcher, S. S. (2006). Depression and body image among women with polycystic ovary syndrome. Journal of Health Psychology, 11(4), 613–625.	
Study Country	USA	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	40 patients diagnosed with PCOS	
Control population	N=60 (Non-PCOS)	
PCOS diagnostic criteria	N/A	
N per group	PCOS (n=40) Non-PCOS (n=60)	
Setting	PCOS group recruited from two separate offices of a southeastern-US clinic specializing in the treatment of reproductive and endocrine disorders. A convenience control sample of women with neither PCOS nor infertility was recruited via advertisement at the first author's university and by direct solicitation at informal community events.	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary outcomes: - Multidimensional Body Self Relations-Appearance Subscale (MBSRQ-AS) - Body Features Satisfaction (BFS) Outcomes not relevant: - Beck Depression Inventroy (BDI)	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes
Inclusion criteria	Yes Partial No Not reported	Yes. Inclusion criteria for PCOS patients at the study was the presence of at least two of the following criteria: clinical symptoms (e.g. ovulatory dysfunction, hyperandrogenism); biochemical markers such as elevated androgen (all potential PCOS patients undergo laboratory screening consisting of endocrine, glucose and glucose tolerance testing); and ultrasound evidence (e.g. 10 or more follicle cysts).
Exclusion criteria	Yes Partial No Not reported	No
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	Yes, case-control

Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	Not relevant to this systematic review
Was matching performed?	Yes Partial No Not reported	No
Summary Result/s	Women with PCOS reported higher depression scores and greater body dissatisfaction ($p < .001$) than comparison group women. Body image was strongly associated with depression overall, even after controlling body mass. Among women with PCOS, body dissatisfaction measures and education explained 66 percent of the variance in depression, suggesting explanations of the PCOS-depression link should consider the role of potentially mediating psychosocial variables.	

Table 1. Group comparisons of depression and body dissatisfaction measures

	PCOS group (n = 40)		*Infertility control (n = 40)*		*Community control (n = 60)*		
Measure	*M*	*SD*	*M*	*SD*	*M*	*SD*	*ANOVA F (2, 137)*
Beck Depression Inventory	7.85_a	7.00	4.56_b	5.03	3.61_b	4.08	7.90**
MBSRQ–Appearance Evaluation	2.45_a	.89	3.30_b	.78	3.05_b	.91	10.30**
MBSRQ–Appearance Orientation	3.76_a	.60	3.67_a	.53	3.34_b	.65	6.71*
Body Features Satisfaction (BFS), total	4.14_a	1.12	5.61_b	.89	5.19_b	1.16	20.33**
BFS, facial features	5.30_a	1.29	5.98_b	1.19	5.67_a	1.49	2.50
BFS, skin complexion	4.33_a	1.67	5.40_b	1.43	5.15_b	1.65	5.11*
BFS, visible hair on face	3.34_a	2.00	6.15_b	1.31	5.58_b	1.68	32.08**
BFS, hair color, thickness, texture	4.90_a	1.69	6.30_b	1.14	5.92_b	1.41	10.48**
BFS, weight	2.85_a	1.82	4.45_b	1.75	3.90_b	1.87	8.01*
BFS, overall appearance	4.10_a	1.65	5.40_b	1.15	4.95_b	1.41	8.79**

Note: Means in a row with different subscripts differ significantly at $p < .05$ by the Tukey honestly significant difference test
*$p < .01$; **$p <$ or $= .001$

INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes Partial No Not reported	No
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Not reported
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes
DEDETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes

	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Not reported
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	X% treatment X% control/ comparison Not reported	Not relevant to case-control
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Not relevant to case-control
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported No protocol or PROSPERO
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

Study ID	Deeks AA et al 2011	
Study Citation	Deeks, A. A., Gibson-Helm, M. E., Paul, E., & Teede, H. J. (2011). Is having polycystic ovary syndrome a predictor of poor psychological function including anxiety and depression? Human Reproduction, 26(6), 1399–1407.	
Study Country	Australia	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	177 patients diagnosed with PCOS	
Control population	109 patients	
PCOS diagnostic criteria	PCOS status was based on a prior-established medical diagnosis, confirmation at phone screening and medical questions on PCOS features included in the survey. The in-depth phone screening was completed by an experienced researcher in PCOS (author M.G.H.) using diagnostic features based on the Rotterdam criteria.	
N per group	PCOS (n=177) Non-PCOS (n=109)	
Setting	Women were recruited throughout rural and metropolitan Austra-lia. Consistently worded advertisements stating 'We are very interested inwhat you think and feel about your health' were used across a range of community settings, including a general women's health website, a support group website for womenwith PCOS (women were not necessarily members of the support group,simply website visitors), medical clinics, newsletters, magazines and newspa-pers.	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary outcomes: - Multidimensional Body Self Relations-Appearance Subscale (MBSRQ-AS) Outcomes not relevant: - Quality of Life - Hospital Anxiety and Depression Scale (HADS) -	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes
Inclusion criteria	Yes Partial No Not reported	Yes. Women were required to reside in Australia, be aged 18–70 years, and be able to read and write in English. PCOS status was based on a prior-established medical diagnosis.
Exclusion criteria	Yes Partial No Not reported	Yes. Women were excluded whether pregnant or had been diagnosed with heart disease or a psychiatric illness other than depression or anxiety.
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No	Yes

		Not reported	
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Yes, case-control
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Not relevant to this systematic review
Was matching performed?		Yes Partial No Not reported	No
Summary Result/s		The average age for women with PCOS was 32.8 years (±7.8) and without PCOS was 41.9 years (±15.4) years [difference (95% confidence interval (CI): 9.1 (6.4–11.8); P < 0.001]. The average BMI for women with and without PCOS was 31.5 (±7.9) and 24.5 (±5.4), respectively [difference (95% CI): 7.1 (5.4–8.8); P < 0.001]. Results from the MBSRQ found that women with PCOS had lower appearance evaluation, fitness orientation, health evaluation, health orientation, body areas satisfaction, higher overweight preoccupation and higher self-classified weight than women without PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes Partial No Not reported	Yes
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Not reported
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Not reported
PERFORM ANCE BIAS	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes Partial No Not reported	YEs
DEDETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported

	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Not reported
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	X% treatment X% control/ comparison Not reported	Not relevant to case-control
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Not relevant to case-control
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported No protocol or PROSPERO
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No. Analysis of baseling demogrpahics showed significant differences with respect to age, BMI snf infertility.
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No - risk of bias was the same across all outcomes.	

Study ID	Kutenaee MA et al. 2020	
Study Citation	Azizi Kutenaee, M., Amirjani, S., Taghavi, S.-A., Asemi, Z., Allan, H., Kamalnadian, S.-N., Khashavi, Z., & Bazarganipour, F. (2020). The impact of depression, self-esteem, and body image on sleep quality in patients with PCOS: a cross-sectional study. Sleep and Breathing, 24(3), 1027–1034.	
Study Country	Iran	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	201 patients diagnosed with PCOS	
Control population	199 patients	
PCOS diagnostic criteria	Rotterdam Criteria	
N per group	PCOS (n=201) Non-PCOS (n=199)	
Setting	Women with referred to the infertility clinic of Omelila hospital in Hormozgan Province. The control group consisted of healthy women. The research team approached 453 women, and after explaining the purpose of the study, written informed consent was obtained from each participant who volunteered to participate and the questionnaires were distributed and completed.	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary outcomes: - Body Image Concern Inventory (BICI) Outcomes not relevant: - Hospital Anxiety and Depression Scale (HADS) - Rosenberg's Self Esteem Scale (RSES) - Pittsburgh Questionnaire (PSQI)	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes
Inclusion criteria	Yes Partial No Not reported	Yes. - Desire to participate in the study - Married - 15-40 years of age. - Absence of non-classic adrenal hyperplasia, thyroid dysfunction, hyperprolactinoma - Non-smoking - No problems in speaking or listening - Iranian - Not taking any prespecription medication - Rotterdam Criteria for PCOS
Exclusion criteria	Yes Partial No Not reported	Not reported
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes

Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	Yes, case-control
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Not relevant to this systematic review
Was matching performed?		Yes Partial No Not reported	No
Summary Result/s		Mean BICI Score for PCOS Group; 39.17 (+/- 32.23) and Mean Body Image Score for Non-PCOS Group; 32.61 (+/-11.11).	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes Partial No Not reported	Not reported
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Not reported
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes
DEDETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Not reported

ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	X% treatment X% control/ comparison Not reported	Not relevant to case-control
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Not relevant to case-control
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported No protocol or PROSPERO
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Partial. There was no significant difference between the two groups in the abovementioned characteristics except for acne score, hirsutism, and menstrual history (P > 0.05).
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No - risk of bias same for all outcomes.	

Study ID	Karacan 2014
Study Citation	Karacan, E., Caglar, G. S., Gursoy, A. Y., & Yilmaz, M. B. (2014). Body satisfaction and eating attitudes among girls and young women with and without polycystic ovary syndrome. Journal of Pediatric and Adolescent Gynecology, 27(2), 72–77.
Study Country	Turkey
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	Women with PCOS and Non-PCOS women (controls) Age= PCOS: 19.1±2.3 years, controls: 19.7±2.1 years BMI= PCOS: 22.4±3.8kg/m², controls: 21.4±3.82

Control population	Healthy volunteers	
PCOS diagnostic criteria	Rotterdam Criteria	
N per group	PCOS (n=42) Non-PCOS (n=52)	
Setting	Participants selected from Ufuk University Obstetrics and Gynecology Department in Ankara, Turkey	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Primary: Body Image Satisfaction measured using FRS, BESSA Secondary: • Eating Attitudes Test (EAT-26) • Sociocultural Attitudes towards Appearance Questionnaire (SATAQ) -	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes
Inclusion criteria	Yes Partial No Not reported	Yes. Diagnosis of PCOS according to Rotterdam criteria. All participants were lean (BMI < 25) in both groups.
Exclusion criteria	Yes Partial No Not reported	Not reported
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	Yes, case-control
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	Not relevant to this systematic review
Was matching performed?	Yes Partial No Not reported	No
Summary Result/s	On average, participants with PCOS viewed their actual body as significantly larger (M = 4.14, SD = 1.37) than their own ideal body. Similarly, participants in control group viewed also their actual body as significantly larger (M = 3.59, SD = 1.49) than their own ideal body.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes Partial No Not reported	Yes
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
PERFORM ANCE BIAS	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes
DEDETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Not reported
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	X% treatment X% control/ comparison Not reported	Not relevant
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Not relevant
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Yes
CONFOUN DING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes

OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No - risk of bias same for all outcomes.	

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 2

Question 2.4.

In women with PCOS, what is the prevalence and severity of body image distress?

BACKGROUND:

Body image is complex and is influenced by many factors. For this clinical question, body image is defined as the way a person may feel, think, and view their body including their appearance. Physical factors affecting appearance (e.g., excess weight and hirsutism), psychological factors (e.g., self-esteem) and sociocultural influences (e.g., thin ideal) all influence the way women think and feel about their bodies. Body image includes attitudes to physical appearance, understanding of health, physical fitness and body size, the mental picture that individuals form of their bodies, values, and self-esteem (1). Assessment of body image includes measures of body dissatisfaction, body size estimation, and weight perception (2).

Two third of women from the general population are dissatisfied with their bodies, yet negative body image has in some, but not all, studies been shown to be more prevalent in PCOS and impacts thoughts and feelings of health, appearance, quality of life (QoL), mood, and physical fitness. One recent study shows an increased prevalence of body image distress in a diverse population of women with PCOS (3).

Women with PCOS have a negative body image (4) and appear to feel less physically attractive, healthy or physically fit and are less satisfied with their body size and appearance than women without PCOS (5). Infertile women with PCOS have lower self-esteem and body satisfaction than non-infertile women with PCOS (6). Further, hirsute women experienced lower self-esteem than non-hirsute women, and women with menstrual irregularities and higher BMI had more body dissatisfaction (6). Thus, several PCOS features, in particular hirsutism and increased weight, appear to negatively impact body image and quality of life (QoL) (7, 8). Moreover, negative body image is strongly associated with depression (3, 9, 10), anxiety (3), and plays an important role in sleep quality (11) in women with PCOS, even after controlling for weight (9, 12).

Given that negative body image in women with PCOS is increased and associated with depression, anxiety, reduced health-related QoL (13), and likely impacts on a woman's likelihood of adhering to PCOS management strategies (14, 15), body image should be considered as part of a comprehensive assessment and management plan. Detection of negative body image provides the opportunity to address both psychological aspects such as self-esteem and self-acceptance as well as working on the physical aspects of the condition such as hirsutism, overweight and acne if appropriate. As it is not usual practice to screen and assess women with PCOS for negative body image, recommendations for screening and assessment that are easy to use and widely applicable are needed for women with PCOS. If identified, addressing negative body and associated mood disorders could assist to improve emotional well-being and QoL in PCOS, although more research in this area is needed.

Multiple methods of measuring body image were used in the literature but the psychometric analyses seem to generally tap into the same construct. Therefore, the broader body of knowledge informs recommendation over and above individual meta-analysis over single tools.

GRADE EVIDENCE CERTAINTY	
Comparison	**GRADE for critical outcomes**
Comparison 1. Women with PCOS versus controls	⊕⊕◯◯ LOW

Evidence to Recommendations Framework

COMPARISONS (option versus other option)

Negative body image in women with PCOS versus controls.

EVIDENCE-BASED RECOMMENDATION(S)

- **EBR:** Health professionals and women should be aware that features of PCOS can have a negative impact on body image.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

GRADE CONSIDERATIONS

Justifications:

Given that negative body image in women with PCOS is increased and associated with depression, anxiety, reduced health-related QoL (13), and likely impacts on a woman's likelihood of adhering to PCOS management strategies (14, 15), body image should be considered as part of a comprehensive assessment and management plan. Detection of negative body image provides the opportunity to address both psychological aspects such as self-esteem and self-acceptance as well as working on the physical aspects of the condition such as hirsutism, overweight and acne if appropriate. As it is not usual practice to screen and assess women with PCOS for negative body image, recommendations for screening and assessment that are easy to use and widely applicable are needed for women with PCOS. If identified, addressing negative body and associated mood disorders could assist to improve emotional well-being and QoL in PCOS, although more research in this area is needed.

Subgroup considerations:

Adult women with and without PCOS
There is no evidence to extend these recommendations to adolescent groups.
The evidence is consistent across ethnicities studied.

Implementation considerations:

Respectful and empathic communication is required when discussing these sensitive issues.
Screening may have resource implications in terms of impact on length of consultation and be burdensome to women and health professionals.
Implementation may require referral to other health practitioners.

Translation tools should note that:

- When considering body image issues, the following questions could be asked:

1) Do you worry a lot about the way you look and wish you could think about it less?
2) What specific concerns do you have about your appearance?
3) What effect does it have on your life?
4) Does it make it hard to do your work or be with your friends and family?

- If an issue is identified, the practitioner could consider:

a) Identifying any focus of concern of the patient (e.g. weight, hirsutism) and responding appropriately
b) Negative body image is a risk factor for disordered eating, anxiety and depression
c) Referral to appropriate patient resources including information, psycho-education, patient support groups or psychological consults as appropriate

Monitoring and evaluation considerations:
Body image assessment with any available body image scale should be considered in all PCOS health research as appropriate.

Research priorities:
Determine clinically meaningful differences in body image scores in PCOS.
More research of body image in the adolescent population should be conducted.
Validating existing body image measurement tools in PCOS.
Preferences of women with PCOS on treatment of body image issues, considering diversity.
Examine the impact of body image distress on the outcome of PCOS treatment and management, and the impact of PCOS treatment and management on body image.
Examination of the effectiveness of treatment for body image in women with PCOS, including the impact this has on the process and outcome of PCOS treatment and management

GRADE framework

GRADE DECIDE **Interactive Evidence to Decision Framework**

- **DESIRABLE EFFECTS**

How substantial are the desirable anticipated effects?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:
See Part 1- Evidence Summary and GRADE document.

Panel discussion:
EVIDENCE SUMMARY

- Nine studies were included, all of case-control design, from various countries including Iran, Italy, USA, Turkey and Australia.
- All studies were ranked as moderate risk of bias due mainly to the lack of information on whether the cases and controls were taken from comparable populations and whether outcome assessors were blinded to case and control status.
- Some studies did not report whether the control status was established in a standard, valid and reliable way, a few others did not report whether the study was sufficiently powered to detect any differences between the groups.

META-ANALYSIS/ DESCRIPTIVE ANALYSIS:

- Studies showed that women with PCOS had higher body image concerns compared to healthy controls.

- However, certainty in the evidence was low across all outcomes, downgraded due to the moderate risk of bias in the included studies.

● UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:
See Part 1- Evidence Summary and GRADE document.

Panel discussion:
Not screening for body image distress can potentially increase anxiety, depression, and management and impact adherence to treatment / management of body image distress.
Screening may be problematic if effective options for treatment/support are not available.

● CERTAINTY OF THE EVIDENCE

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☐ Very low	☒ Low	☐ Moderate	☐ High

Research evidence:
See Part 1- Evidence Summary and GRADE document.

Panel discussion:
The overall certainty of evidence is determined by the critical outcome with moderate certainty (quality) of evidence.
The broader body of evidence is not reflected in the meta-analysis due to the selected use of tools in literature and this can only be based on observational evidence which by definition in GRADE is always low certainty, however the significance of the studies was consistent. The GDG determines that certainty of the overall evidence is moderate.

● VALUES

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☐ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☐ Probably no important uncertainty or variability	☒ No important uncertainty or variability

Research evidence:
No research evidence was identified

Panel discussion:
There is no uncertainty about how much people value the main outcomes.

● BALANCE OF EFFECTS

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☒ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:
EVIDENCE SUMMARY

- Nine studies were included, all of case-control design, from various countries including Iran, Italy, USA, Turkey and Australia.
- All studies were ranked as moderate risk of bias due mainly to the lack of information on whether the cases and controls were taken from comparable populations and whether outcome assessors were blinded to case and control status.
- Some studies did not report whether the control status was established in a standard, valid and reliable way, a few others did not report whether the study was sufficiently powered to detect any differences
  between the groups.

META-ANALYSIS/ DESCRIPTIVE ANALYSIS:

- Studies showed that women with PCOS had higher body image concerns compared to healthy controls.
- However, certainty in the evidence was low across all outcomes, downgraded due to the moderate risk of bias in the included studies.

The balance of benefits of screening for negative body image, enables referral to appropriately trained and experienced health professionals with no increase in undesirable effects with screening of body image.

- **COSTS**

How large are the resource requirements (costs)?

Judgement:

☒ Don't know	☐ Varies	☐ Large costs	☐ Moderate costs	☐ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:
No research evidence was identified

Panel discussion:
- There was no evidence to inform this consideration.
- Screening may have resource implications in terms of impact on length of consultation.
- Intervention may require referral to other health practitioners.
- Where needed, access to appropriately trained and experienced health professionals is required.

- **CERTAINTY OF COST EVIDENCE**

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:
No research evidence was identified

Panel discussion:
There was no evidence to inform this consideration.

- **COST-EFFECTIVENESS**

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:
No research evidence was identified

Panel discussion:
- There was no evidence to inform this consideration.
- Screening may have resource implications in terms of impact on length of consultation.
- Intervention may require referral to other health practitioners.

● EQUITY

What would be the impact on health equity?

Judgement:

☐ Don't know	☒ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☐ Probably increased	☐ Increased

Research evidence:
No research evidence was identified

Panel discussion:
- Responses may vary depending on social and cultural background.
- Implementation and access to resources may vary depending on local circumstances.
- Access to appropriate evidence-based resources on body image may improve equity in PCOS.

● ACCEPTABILITY

Is the option acceptable to key stakeholders?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

Research evidence:
- No research evidence was identified

Panel discussion:
- Stronger focus on what is most relevant to the patient.
- A change in practice may be required

● **FEASIBILITY**

Is the option feasible to implement?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Fully feasible in clinical research but probably reduced feasibility in standard care.

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PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by ECR Lead: Laura Cooney

Other Members: Loyal Pattuwage, Kaley Gyorfi, Awa Sanneh, Leeann Bui

Supervised, edited and supported by the Evidence Team

GDG 2

Question 2.5.

In women with PCOS what is the prevalence and severity of disordered eating?

1. SELECTION CRITERIA

Table 1. PICO Criteria for Inclusion – Not to be adapted
To be used by evidence team to decide which studies will be included when screening search results.

Question	Q 2.5.1) In women with PCOS what is the prevalence and severity of disordered eating? CLINICAL PRACTICE POINT: - Should disordered eating be assessed as part of standard care?
Clinical leads (key contacts)	Prof Elisabet Stener-Victorin Endocrinologist Karolinska Institutet, Sweden elisabet.stener-victorin@ki.se A/Prof Leah Brennan Psychologist La Trobe University, Australia Leah.Brennan@latrobe.edu.au
Allocation ranking	Level 1- New systematic review

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(language, year)*
Inclusion	Females with PCOS (diagnosed by Rotterdam, NIH or AES) of any age, ethnicity and weight. Subgroups: • Adolescents • Ethnicity • Phenotype Self-report or medical/hospital records including ICD codes PCOS was acceptable	No restrictions (Any tools assessing disordered eating, self-reported, medical/hospital records - including ICD-9 or ICD-10) Note: tools to screen for disordered eating: Three-factor Eating Questionnaire (TFEQ-R21); Diagnostic Survey for Eating Disorders; Eating Disorder Examination Questionnaire (EDE-Q); Eating Attitudes Test (EAT-40); Anorectic Behaviour Observation Scale (ABOS); Questionnaire of Eating and Weight Patterns-Revised (QEWP-R); Dutch Eating Disorders Behaviours Questionnaire; Bulimia Cognitive Distortion Scale; Binge Eating Scale; Binge Scale; Eating Disorder Inventory; Eating Disorder Belief Questionnaire; Eating Disorder Core Belief Questionnaire; Eating Loss of Control Scale; Loss of Control over Eating Scale (LOCES); Disordered Eating Attitude Scale (DEAS); Eating Pathology Symptoms Inventory; Stirling Eating Disorders Scale; Binge Eating Disorder Test; Testable Assumption Questionnaire - Eating Disorders; Bulimia Test - Revised (BULIT-R); Bulimic Investigation Test-Edinburgh (BITE); Short Evaluation of Eating Disorders; Mizes Anorectic Scale	General Population. Women without PCOS.	Detection of and/or differences in disordered eating. Note the cut offs for each tool. Sensitivity and specificity of detecting disordered eating, PPV/NPV, AUC, ICC (if comparing two methods that use different scales), mean difference and limits of agreement (if comparing two methods that use the same scale and treating outcome as a continuous variable) Acceptability to users/ patients. Collect if reported tool development/validation process.	Evidence based guidelines, systematic reviews, comparative prospective cohort studies and comparative cross-sectional studies (include development/validation studies)	English, no year limits
Exclusion	Women without a diagnosis of PCOS					

2. SEARCH STRATEGY

Table 2.1. Search details

Search strategy source:
Although articles were identified for possible inclusion from prior to the 2019 publication (below), a new search was performed with expanded search criteria in Table 2.3 to allow for self-report of PCOS.

Lee, I., Cooney, L., Saini, S., Sammel, M. D., Allison, K. C., Dokras, A. (2019). Increased odds of disordered eating in polycystic ovary syndrome: a systematic review and meta-analysis. Eating and weight disorders: EWD, 24(5), 787-797.

Evidence source	Date of search
Medline (Ovid)	Aug 16, 2022
PsychInfo (Ovid)	Aug 16, 2022
EMBASE (Ovid)	Aug 16, 2022
All EBM (Ovid)	Aug 16, 2022
CINAHL	Not searched

Any subsequent updates - enter database and date: not applicable

Table 2.2. Questions addressed by this search *(add more rows as needed)*:

GDG	Q#	Question
2	2.5.	In women with PCOS what is the prevalence and severity of disordered eating?
		CLINICAL PRACTICE POINT: - Should disordered eating be assessed as part of standard care?

Table 2.3. Search strings used in OVID or other database/s – *please save a screenshot of search results to submit alongside this template*

OVID Medline, All EBM, PsychInfo, EMBASE

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to August 16, 2022>

1 exp "Feeding and Eating Disorders"/ 34876
2 eating disorder*.tw. 22866
3 anorexia nervosa.tw. 14559
4 anorex*.tw. 36368
5 bulimia nervosa.tw. 5803
6 bulim*.tw. 9011
7 "BN".tw. 12647
8 binge eating.tw. 6622
9 bing*.tw. 18674
10 (other Specified Feeding and Eating Disorder*).tw. 116
11 PICA.tw. 2682
12 rumination disorder.tw. 36
13 ((avoidant or restrictive) and food intake disorder*).tw. 294
14 avoidant food.tw. 0
15 restrict* food.tw. 1016
16 food intake.tw. 49460
17 (unspecified Feeding or Eating Disorder).tw. 12398
18 unspecified feed*.tw. 33
19 unspecified eating.tw. 26
20 UFED.tw. 14
21 muscle dysmorphia.tw. 194

22 orthorexia nervosa.tw. 277
23 overeat*.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 3242
24 night eating*.tw. 423
25 feeding.tw. 218914
26 hyperphagi*.tw. 4888
27 purg*.tw. 9349
28 compulsive exercise*.tw. 145
29 (eating disorder adj4 otherwise specified).tw. 439
30 ednos.tw. 364
31 food craving.tw. 554
32 food addiction*.tw. 774
33 or/1-32 352015
34 exp polycystic ovary syndrome/ 16980
35 polycystic ovar*.mp. 22535
36 poly-cystic ovar*.mp. 52
37 PCO*.mp. 36291
38 (stein-leventhal or leventhal).mp. 915
39 anovulation/ 2266
40 anovulat*.mp. 6774
41 oligo-ovulat*.mp. 108
42 oligoovulat*.mp. 61
43 (ovar* adj5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*)).mp. 23525
44 or/34-43 49889
45 33 and 44 770
46 limit 45 to (english language and humans) 377

Embase Classic+Embase <1947 to 2022 August 16>

1 exp "Feeding and Eating Disorders"/ 61439
2 eating disorder*.tw. 29559
3 anorexia nervosa.tw. 18545
4 anorex*.tw. 54441
5 bulimia nervosa.tw. 7270
6 bulim*.tw. 11688
7 "BN".tw. 15486
8 binge eating.tw. 8362
9 bing*.tw. 26140
10 (other Specified Feeding and Eating Disorder*).tw. 115
11 PICA.tw. 3704
12 rumination disorder.tw. 42
13 ((avoidant or restrictive) and food intake disorder*).tw. 432
14 avoidant food.tw. 1
15 restrict* food.tw. 1386
16 food intake.tw. 66519
17 (unspecified Feeding or Eating Disorder).tw. 15255
18 unspecified feed*.tw. 34
19 unspecified eating.tw. 35
20 UFED.tw. 18
21 muscle dysmorphia.tw. 215
22 orthorexia nervosa.tw. 313
23 overeat*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] 4401
24 night eating*.tw. 636
25 feeding.tw. 273538
26 hyperphagi*.tw. 6542
27 purg*.tw. 11788
28 compulsive exercise*.tw. 155
29 (eating disorder adj4 otherwise specified).tw. 525
30 ednos.tw. 477
31 food craving.tw. 718
32 food addiction*.tw. 1069

33 or/1-32 464088
34 exp polycystic ovary syndrome/ 33669
35 polycystic ovar*.mp. 28917
36 poly-cystic ovar*.mp. 204
37 PCO*.mp. 53787
38 (stein-leventhal or leventhal).mp. 1502
39 anovulation/ 6703
40 anovulat*.mp. 11178
41 oligo-ovulat*.mp. 155
42 oligoovulat*.mp. 123
43 (ovar* adj5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*)).mp. 38397
44 or/34-43 78733
45 33 and 44 1388
46 limit 45 to (english language and humans) 856

EBM Reviews - Cochrane Database of Systematic Reviews <2005 to August 10, 2022>
EBM Reviews - ACP Journal Club <1991 to July 2022>
EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016>
EBM Reviews - Cochrane Clinical Answers <July 2022>
EBM Reviews - Cochrane Central Register of Controlled Trials <July 2022>
EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012>
EBM Reviews - Health Technology Assessment <4th Quarter 2016>
EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>

1 exp "Feeding and Eating Disorders"/ 1886
2 eating disorder*.tw. 3051
3 anorexia nervosa.tw. 1304
4 anorex*.tw. 4286
5 bulimia nervosa.tw. 976
6 bulim*.tw. 1264
7 "BN".tw. 673
8 binge eating.tw. 1387
9 bing*.tw. 2661
10 (other Specified Feeding and Eating Disorder*).tw. 11
11 PICA.tw. 148
12 rumination disorder.tw. 4
13 ((avoidant or restrictive) and food intake disorder*).tw. 26
14 avoidant food.tw. 1
15 restrict* food.tw. 77
16 food intake.tw. 6057
17 (unspecified Feeding or Eating Disorder).tw. 2080
18 unspecified feed*.tw. 3
19 unspecified eating.tw. 5
20 UFED.tw. 1
21 muscle dysmorphia.tw. 19
22 orthorexia nervosa.tw. 8
23 overeat*.mp. [mp=ti, ab, tx, kw, ct, ot, fx, sh, hw] 467
24 night eating*.tw. 39
25 feeding.tw. 17831
26 hyperphagi*.tw. 238
27 purg*.tw. 852
28 compulsive exercise*.tw. 18
29 (eating disorder adj4 otherwise specified).tw. 66
30 ednos.tw. 52
31 food craving.tw. 215
32 food addiction*.tw. 104
33 or/1-32 33257
34 exp polycystic ovary syndrome/ 1712
35 polycystic ovar*.mp. 4675
36 poly-cystic ovar*.mp. 136
37 PCO*.mp. 6256
38 (stein-leventhal or leventhal).mp. 99
39 anovulation/ 154
40 anovulat*.mp. 1193
41 oligo-ovulat*.mp. 55

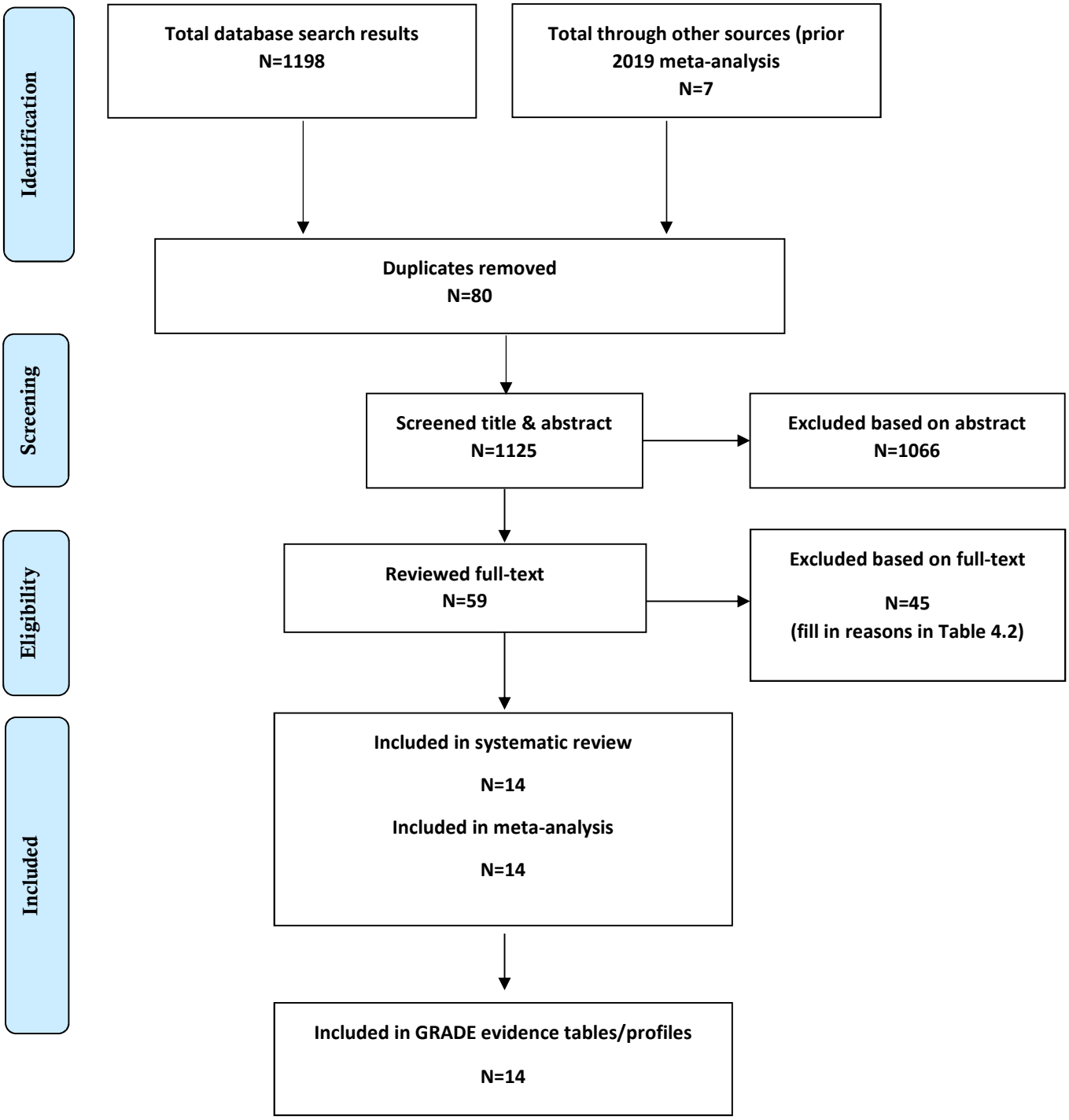
42	oligoovulat*.mp. 32
43	(ovar* adj5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*)).mp. 4868
44	or/34-43 8226
45	33 and 44 144
46	limit 45 to (english language and humans) 143

APA PsycInfo <1806 to August Week 2 2022>

1	exp Eating Disorders/ or exp Feeding Disorders/ 33805
2	eating disorder*.tw. 28807
3	anorexia nervosa.tw. 13411
4	anorex*.tw. 18456
5	bulimia nervosa.tw. 7338
6	bulim*.tw. 12442
7	"BN".tw. 2885
8	binge eating.tw. 6988
9	bing*.tw. 15868
10	(other Specified Feeding and Eating Disorder*).tw. 114
11	PICA.tw. 667
12	rumination disorder.tw. 71
13	((avoidant or restrictive) and food intake disorder*).tw. 308
14	avoidant food.tw. 0
15	restrict* food.tw. 587
16	food intake.tw. 12263
17	(unspecified Feeding or Eating Disorder).tw. 14755
18	unspecified feed*.tw. 27
19	unspecified eating.tw. 31
20	UFED.tw. 9
21	muscle dysmorphia.tw. 272
22	orthorexia nervosa.tw. 181
23	overeat*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] 2553
24	night eating*.tw. 337
25	feeding.tw. 28690
26	hyperphagi*.tw. 1619
27	purg*.tw. 2975
28	compulsive exercise*.tw. 178
29	(eating disorder adj4 otherwise specified).tw. 561
30	ednos.tw. 428
31	food craving.tw. 457
32	food addiction*.tw. 620
33	or/1-32 90309
34	exp Endocrine Sexual Disorders/ 1759
35	polycystic ovar*.mp. 523
36	poly-cystic ovar*.mp. 1
37	PCO*.mp. 1118
38	(stein-leventhal or leventhal).mp. 319
39	anovulation/ 0
40	anovulat*.mp. 161
41	oligo-ovulat*.mp. 0
42	oligoovulat*.mp. 0
43	(ovar* adj5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*)).mp. 542
44	or/34-43 3303
45	33 and 44 100
46	limit 45 to (english language and humans) 94

Evidence processing: Studies were selected and appraised by two reviewer/s in consultation with the evidence team/ key contact using study selection and appraisal criteria (PICO above) established a priori. The articles were reviewed by title and abstract by two reviewers. When a decision could not be made based on title and abstract alone, full text was retrieved. **A total of 14 studies met inclusion criteria for this review.**

3. SEARCH RESULTS - PRISMA flowchart



4. STUDY INCLUSION

Table 4.1. Included Studies
Original studies from prior search:
Hollinrake, E., Abrea, A., Maifield, M., Van Voorhis, B., Dokras, A. (2007). Increased risk of depressive disorders in women with polycystic ovary syndrome. Fertility and Sterility, 2007.
Mansson, M., Holte, J., Landin-Wilhelmsen, K., Dahlgren, E., Johansson, A., Landen, M. (2008). Women with polycystic ovary syndrome are often depressed or anxious—a case control study. Psychoneuroendocrinology, 2008.
Batcheller, A., Ressler, I., Sroga, J., Martinez, A., Thomas, M., Di Paola, K. (2013). Binge eating disorder in the infertile polycystic ovary syndrome patient. Fertility and Sterility, 2013.
Karacan, E., Caglar, G., Gursoy, A., Yilmaz, M. (2014). Body satisfaction and eating attitudes among girls and young women with and without polycystic ovary syndrome. Journal of Pediatric & Adolescent Gynecology, 2014.
Larsson, I., Hulthen, L., Landen, M., Palsson, E., Janson, P., Stener-Victorin, E. (2016). Dietary intake, resting energy expenditure, and eating behavior in women with and without polycystic ovary syndrome. Clinical Nutrition, 2016.
Lee, I., Cooney, L., Saini, S., Smith, M., Allison, K. Dokras, A. (2016). Increased risk of eating disorders in women with polycystic ovary syndrome. Fertility and Sterility, 2016.
Jeanes, Y., Reeves, S., Gibson, E., Piggot, C., May, V., Hart, K. (2017). Binge eating behaviors and food cravings in women with polycystic ovary syndrome. Appetite, 2017.
Original studies from 2022 search:
Sirmans, S., Parish, R., Blake, S., Wang, X. (2014). Epidemiology and comorbidities of polycystic ovary syndrome in an indigent population. Journal of Investigative medicine, 2014.
Cesta, C., Mansson, M., Palm, C., Lichtenstein, P., Iliadou, A., Landen, M. (2016). Polycystic ovary syndrome and psychiatric disorders: co-morbidity and heritability in a nationwide Swedish cohort. Psychoneuroendocrinology, 2016.
Maher, M., Sanders, A.(2018). Eating indicators in women with polycystic ovary syndrome and weight-matched controls. FASEB Journal, 2018.
Lidaka, L., Lazdane, G., Kivite-Urtane, A., Gailite, L., Dzivite-Krisane, I., Stokenberga, I. (2019). Health-related quality of life and binge eating among adolescent girls with PCOS. Clinical and Experimental Obstetrics and Gynecology, 2019.
Pirotta, S., Barillaro, M., Brennan, L., Grassi, A., Jeanes, Y., Joham, A., Kulkarni, J., Monahan Couch, L., Lim, S., Moran, L. (2019). Disordered eating behaviors and eating disorders in women in Australia with and without polycystic ovary syndrome: a cross-sectional study. Journal of Clinical Medicine, 2019.
Tay, C., Teede, H., Hill, B., Loxton, D., Joham, A. (2019). Increased prevalence of eating disorders, low self-esteem, and psychological distress in women with polycystic ovary syndrome: a community-based cohort study. Fertility and Sterility, 2019.
Asdaq, S., Jomah, S., Hasa, R., Al-Baroundi, D., Alharbi, M., Alsubaie, S., Buhamad, M., Alyahya, B., Al-Yamani, MM. (2020). Impact of polycystic ovary syndrome on eating behavior, depression, and health related quality of life: A cross-sectional study in Riyadh. Saudi J Biol Sci, 2020.

Table 4.2. Excluded Studies (on full text assessment)	
Reference	Reason
Chapdelaine 1991	Wrong study design
McCluskey et al. 1991	Wrong control group
McCluskey et al. 1992	PCOS not confirmed
Jahanfar et al. 1995	PCOS not confirmed
Morgan 1999	Wrong study design
Michelmore et al. 2001	PCOS not confirmed
Hirschberg et al. 2004	Wrong outcomes
Jahanfar et al. 2005	Wrong study design
Himelein et al. 2006	Wrong study design
Naessen et al. 2006	Wrong study design
Ghoreishi et al. 2010	Not English
Krepula et al. 2012	Wrong study design
Silva-de-Sa et al. Evaluation of hunger sensation, ad libitum food intake, and ghrelin postprandial response in obese women with and without polycystic ovary syndrome 2013	Wrong outcomes
Silva-de-Sa et al. Relationship between postprandial grelin and insulin blood levels in obese women with and without polycystic ovary syndrome 2013	Wrong outcomes
Farkas et al. 2014	Wrong study design
Scaruffi et al. 2014	Wrong outcomes
Shishehgar et al. 2014	Wrong study design
Brad et al. 2015	Wrong study design

Turner-McGrievy et al. 2015	Wrong study design
Rodino et al. 2015	Wrong study design/wrong control group
Rodino et al. 2016	Wrong outcomes
Bernadett et al. 2016	Not English
Blay et al. 2016	Wrong study design
Sam et al. 2016	Wrong outcomes
Azizi 2017	Wrong study design
Cleave et al. 2017	Wrong study design
Morosi et al. 2017	Wrong study design
Paganini et al. 2018	Wrong study design
Shahdadian et al. 2019	Wrong outcomes
Krug et al. 2019	Wrong study design
DeGiudeppe et al. 2019	Wrong outcomes
Yavarikia et al. 2019	Wrong study design
Cuhna et al. 2019	Wrong outcomes
Rodriguez-Paris et al. 2019	Wrong study design
Nayar et al. 2019	PCOS not confirmed, abstract only
Basar Goken, 2000	Wrong outcomes
Greenwood et al. 2020	Wrong control group
Mizgier et al. 2020	Wrong study design
Steegers-Thenissen et al. 2020	Wrong study design
Thannickal et al. 2020	Wrong study design
Yin et al. 2020	Wrong study design
Wang, 2021	Wrong outcomes
Yin et al. 2021	Wrong study design
Eyupoglu, 2022	Wrong outcomes
Cetik et al. 2022	Wrong outcomes

5. STUDY CHARACTERISTICS TABLE FOR INCLUDED STUDIES

Author, year (country)	ED screening tool	PCOS criteria/ recruitment location	N		Age (yrs) Mean ± SD	BMI (kg/m²) Mean ± SD	ED score Mean ± SD Prevalence of abnormal screening score n (%)		Prevalence of specific ED diagnoses n (%)	
			PCOS	Control			PCOS	Control		
Hollinrake et al, 2007 (USA)	PRIME-MD PHQ	Rotterdam P: university reproductive infertility clinic C: university gynecology clinic, seen for annual exam	103	103	P: 29.8 ± 6.2 C: 30.7± 8.5	P: 34.9 ± 8.5* C: 25.4 ± 4.7*	Not reported	Not reported	BED: 13 (12.6)**	BED: 2 (1.9)**
Mansson et al, 2008 (Sweden)	MINI	Rotterdam P: university outpatient clinic C: born on the same day from population registry	49	49	P: 35.9 ± 10.4 C: 35.9 ± 10.4	P: 29.1 ± 7.4** C: 23.5 ± 3.0**	Not reported	Not reported	Any ED[e]: 10 (21)* BN: 6 (12)	Any ED: 2 (4)* BN: 2 (4)
Batcheller et al, 2013 (USA)[a]	DSM V-based survey	Rotterdam P, C: university fertility center, undergoing IVF C: oocyte donors or male factor infertility	11	10	29.7 ± 3.0 (not separated by group)	28.0 ± 7.5 (not separated by group)	Not reported	Not reported	BED: 0 (0)	BED: 0 (0)
Karacan et al, 2014 (Turkey)[a]	EAT-26	Rotterdam P, C: University hospital, ob/gyn clinic	42	52	P: 19.1±2.3 C: 19.7±2.1	P: 22.4±3.8 C: 21.4±3.82	EAT-26: 46.6±17.0 Abnormal Score: 15 (35.7)	EAT-26: 48.2±17.6 Abnormal Score: 16 (30.8)	Not reported	Not reported
Sirmans et al, 2014 (USA)	Louisiana Medicaid claims data	Paid claim for PCOS or oligo/amenorrhea plus hirsutism P, C: Louisiana Medicaid claims data	1689	5067	P: 25.24 C: 25.23	Not available for analysis or report	Not reported	Not reported	All ED: 7 (0.4)	All ED: 15 (0.3)
Larsson et al, 2015 (Sweden)	TFEQ-R21; EAT-40 DSM -IV survey for BN	Rotterdam P, C: Recruited via community advertisements	72	30	P: 30.2 ± 4.4** C: 27.8 ± 3.6**	P: 28.5 ± 7.2** C: 24.6 ± 5.0**	TFEQ Cognitive restraint: 41±23 Uncontrolled eating: 42±20	TFEQ Cognitive restraint: 37±23 Uncontrolled eating: 39±15	BN: 0 (0)	BN: 0 (0)

							Emotional eating: 44±28 EAT-40: 16.4±10.1*** EAT-40 Abnormal Score: 6 (8.3)	Emotional eating: 37±19 EAT-40: 7.8±6.7*** EAT-40 Abnormal Score: 1 (3.3)		
Cesta et al, 2016 (Sweden)	ICD codes	Swedish National Patient Register (NPR)	24,385	243,850	Matched on age but mean not reported	Matched on BMI but mean not reported	Not reported	Not reported	Any ED: 598 (2.45)* AN:139 (0.57) BN: 179 (0.73)*	Any ED: 4,223 (1.73)* AN: 1,504 (0.62) BN:1,331 (0.55)*
Jeanes et al, 2016 (UK)	BITE	Self-report of PCOS diagnosis by a healthcare professional P, C: Recruited via community advertisements	45[c]	40	P: 31.3 ± 5.6 C: 28.3 ± 8.5	P: 22.5 ± 1.8 C: 21.8 ± 1.6	BITE Binge Eating Symptom Score: 10.9 ± 7.8* Abnormal Score: 16 (36)*	BITE Binge Eating Symptom Score: 7.4 ± 6.0* Abnormal Score: 5 (12)*	Not reported	Not reported
Lee et al, 2016 (USA)	EDE-Q NEQ, and DSM survey	Rotterdam P: PCOS center C: university gynecology clinic	148	106	P: 28.1 ± 5.2** C: 31.9 ± 8.1**	P: 33.9 ± 9.9** C: 26.8 ± 7.5**	EDE-Q Global: 2.38 ± 1.31** NEQ: 16.67 ± 6.18 Abnormal EDE-Q Score: 18 (12.2)* Abnormal NEQ Score: 19 (12.9)	EDE-Q Global: 1.29 ± 1.09** NEQ: 14.88 ± 5.43 Abnormal EDE-Q Score: 3 (2.8)* Abnormal NEQ Score: 7 (6.6)	Any ED: 42 (28.4) AN: 0 (0) BN: 9 (6.1) BED: 26 (17.6) NES: 19 (12.9)	Any ED: 20 (18.9) AN: 0 (0) BN: 6 (5.7) BED: 11 (10.4) NES: 13 (12.38)
Maher et al, 2018 (USA) [a]	EAT-26	Rotterdam P, C: Recruited through print advertisements	8	8	P: 32.9 ± 3.5 C: 35.0 ± 4.5	P: 30.8 ± 2.1 C: 30.8 ± 3.0	EAT-26 score: 6.38 ± 1.18 Abnormal EAT-26 score: 0 (0)	EAT-26 score: 3.88 ± 1.6 Abnormal EAT-26 score: 0 (0)	Not reported	Not reported

Pirotta et al, 2019 (Australia)	EDE-Q and DSM criteria	Self-report of prior PCOS diagnosis, PCOS status not evaluated in controls P, C: Recruited via online and community advertisements	501	398	P: 30.5 ± 5.9** C: 22.8 ± 5.5**	P:33.6 ± 9.3** C:24.3 ± .6.0**	Abnormal EDE-Q Score: 36 (7.2)**	Abnormal EDE-Q Score: 53 (13)**	Any ED: 310 (62) AN: 0 (0) BN: 26 (5.2) BED: 143 (29)	Any ED: 223 (56) AN: 5 (1.3) BN: 18 (4.5) BED: 92 (23)
Tay et al, 2019 (Australia)	Self-report on survey	Self-report on survey P, C: Australian Longitudinal Study on Women's Health (ALSWH)	875	7592	P: 24.8 ± 1.7* C: 24.6 ± 1.8*	P:29.2 ± 7.9** C:25.3± 5.8**	Not reported	Not reported	Any ED: 96 (11)** AN: 31 (3.5) BN: 30 (3.4) Other ED: 56 (6.4)**	Any ED: 575 (7.6)** AN: 258 (3.4) BN:195 (2.6) Other ED:257 (3.4)**
Asdaq et al, 2020 (Saudi Arabia)	Survey to assess binge eating	Rotterdam P, C: Tertiary care centers	116	378	Age ≥ 30 85.1% of overall group	BMI in Obese range: 89.1% of overall group	Not reported	Not reported	BED: 108 (93.1)**	BED: 312 (82.5)**
Lidaka et al, 2022 (Latvia)	BITE	ESHRE 2018 P, C: pediatric gynecology clinic, P: presenting with oligomenorrhea, C: presenting for contraception or routine care	63	66	P: 16 (IQR:2) C: 17 (IQR:1)	P: 89.9 (IQR: 46.7)** C:46.9 (IQR: 46.3)**	BES score: 12 (IQR: 14.5)	BES score: 12 (IQR: 17.0)	Any BED: 23 (37.7) Mild to moderate BED: 15 (24.6) Severe BED: 8 (13.1)	Any BED: 23 (35.9) Mild to moderate BED: 11 (17.2) Severe BED: 12 (18.8)

6. FINDINGS

Comparisons included:

- **Comparison 1:** PCOS versus controls

Outcomes included:

- **Outcome 1.** Any eating disorders
- **Outcome 2.** Disordered eating
- **Outcome 3.** Bulimia nervosa
- **Outcome 4.** Binge eating disorder
- **Outcome 5.** Anorexia nervosa

OUTCOME 1. Any eating disorders

- **EVIDENCE SUMMARY:**

Eleven cross-sectional studies reported the risk of at least one eating disorder including bulimia nervosa, binge eating disorder, anorexia nervosa, or night eating syndrome in adult women with PCOS compared to controls. One study had a low risk of bias (Lidaka 2022). Ten studies had a moderate risk of bias (Hollinrake 2007, Mansson 2008, Batcheller 2013, Sirmans 2014, Larsson 2016, Cesta 2016, Lee 2016, Pirotta 2019, Tay 2019, Asdaq 2020). Studies were conducted in Australia, Saudi Arabia, Sweden and the USA. Only study (Lidaka 2022) restricted inclusion to adolescents. No studies evaluated risk of any eating disorder based on ethnicity or phenotype.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

In the meta-analysis of all studies of adult women there was an increased odds of any eating disorder in women with PCOS. In the sub-analysis of only studies where PCOS diagnosis was confirmed by Rotterdam criteria, there was also an increased odds of any eating disorder in women with PCOS. Certainty in these results is moderate and was downgraded as the majority of studies were moderate quality. One study (Lidaka 2022) reported the odds of any eating disorder in adolescents with PCOS and did not find a higher odds in adolescents with PCOS.

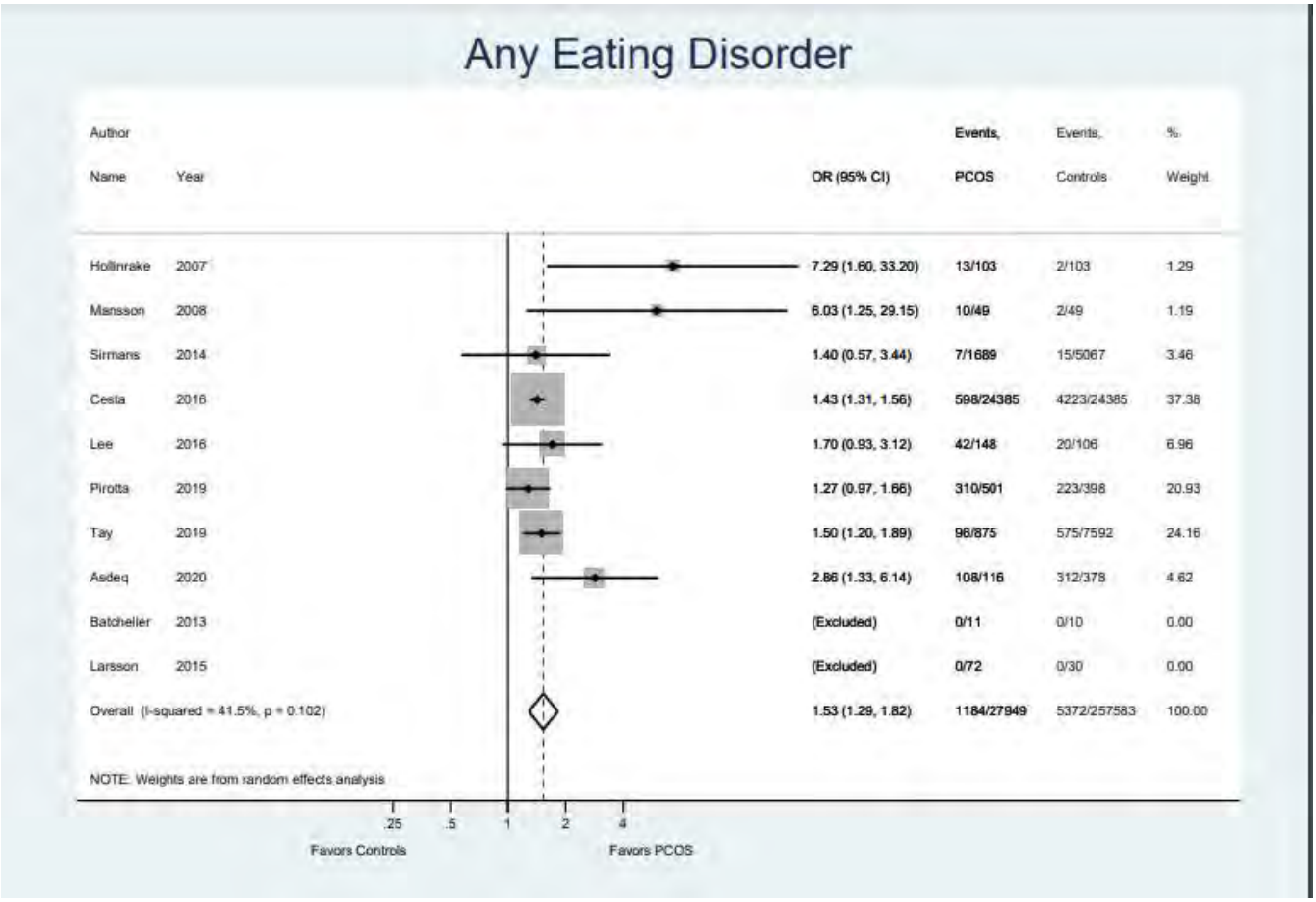
1.1. Individual Study Data Table for Any Eating Disorders

OUTCOME: Any eating disorder			OUTCOME TYPE: Dichotomous					
COMPARISON (if applicable): PCOS and control								
Author, year	Unit of outcome	Method of measurement	N events in intervention/ exposure group	N total in intervention/ exposure group	N events in control / comparison group	N total in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Hollinrake et al. 2007[a]	Count	PRIME-MG PHQ	13	103	2	103	Crude	NA
Mansson et al. 2008[a]	Count	MINI	10	49	2	49	Crude	NA
Batcheller et al. 2013[a]	Count	DSM-V based survey	0	11	0	10	Crude	NA
Sirmans et al. 2014	Count	Louisiana Medicaid claims data	7	1689	15	5067	Crude	NA
Larsson et al. 2016[a]	Count	DSM IV Survey	0	72	0	30	Crude	NA
Cesta et al. 2016	Count	ICD Codes	598	24,385	4,223	243,850	Crude	NA
Lee et al. 2016[a]	Count	DSM IV Survey	42	148	20	106	Crude	NA
Pirotta et al. 2019	Count	DSM Survey	310	501	223	398	Crude	NA
Tay et al. 2019	Count	Self-report	96	875	575	7592	Crude	NA
Asdaq et al. 2020[a]	Count	EAT-26	108	116	312	378	Crude	NA
Lidaka et al 2022[b]	Count	BITE	23	63	23	66	Crude	NA

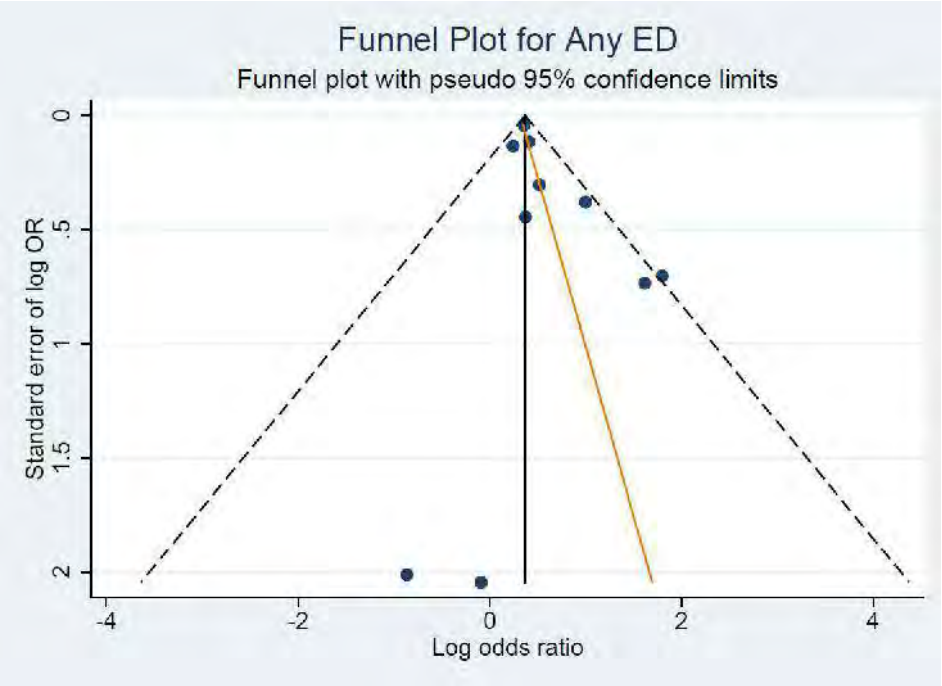
[a] Included in sensitivity analysis of studies that used confirmed Rotterdam criteria for PCOS diagnosis rather than self-report or hospital records

[b] Not included in meta-analysis as it was the only study in adolescents

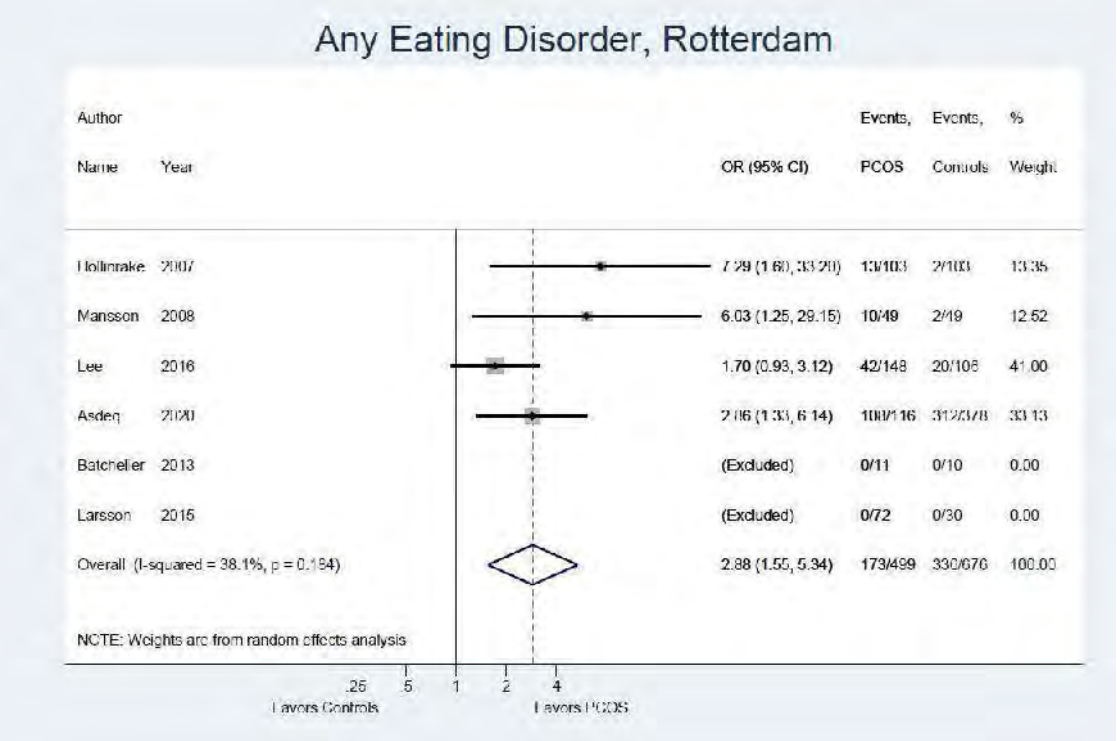
1.2 Forest plot for any eating disorder



1.3 Funnel plot for any eating disorder



1.4 Forest plot for any eating disorder, sensitivity analysis restricted to studies where PCOS diagnosis was confirmed by Rotterdam criteria



OUTCOME 2. Disordered eating

- **EVIDENCE SUMMARY:**

Six cross-sectional studies reported prevalence of disordered eating as defined as a score above the cutoff of a validated eating disorder questionnaire (Karacan 2004, Larsson 2016, Jeanes 2017, Lee 2016, Maher 2018, Pirotta 2019). All studies had a moderate risk of bias. Studies were conducted in Australia, Sweden, Turkey, the UK, and the USA. No studies evaluated risk of disordered eating in adolescents or based on ethnicity or phenotype.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

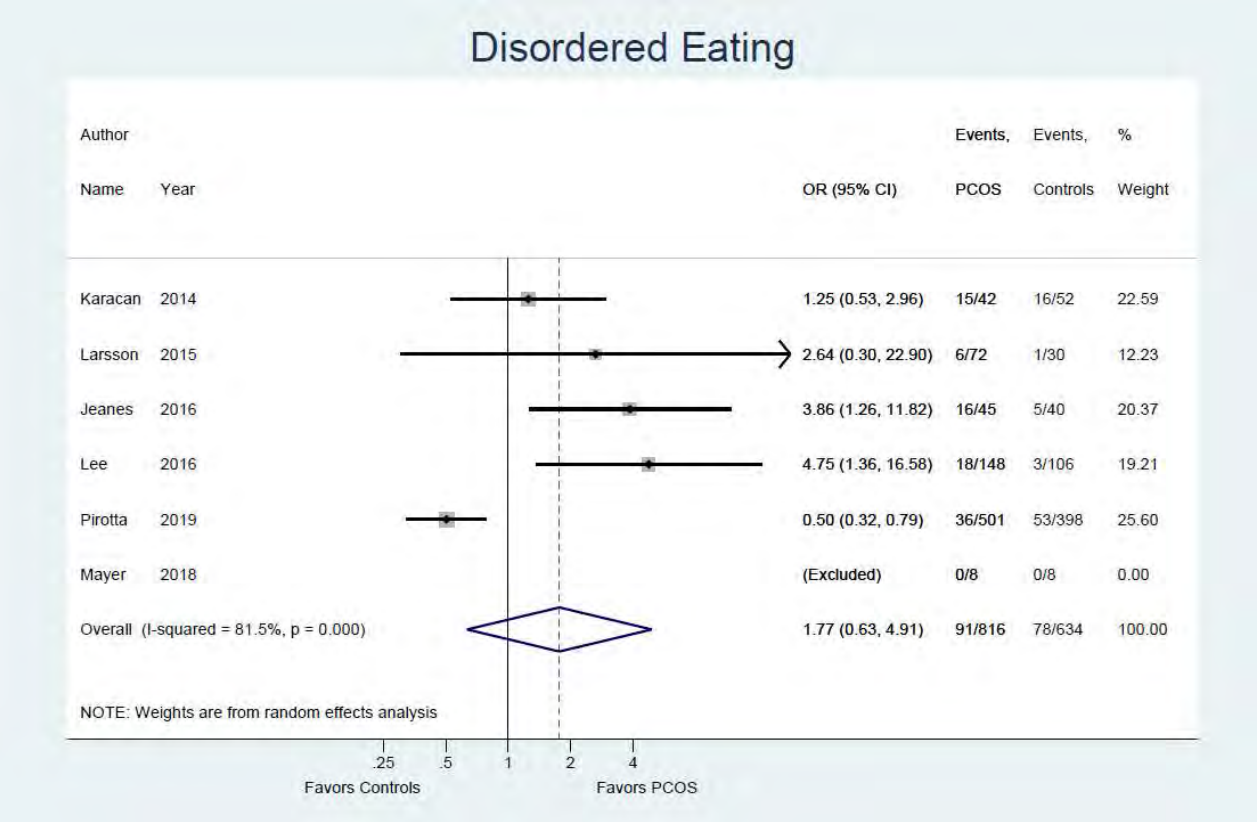
There was no increased odds of disordered eating in women with PCOS either in the meta-analysis of all adult women or the sub-analysis of only studies where PCOS diagnosis was confirmed by Rotterdam criteria. Certainty in these results is low and was downgraded once as the majority of studies were moderate quality and once because of imprecision as the confidence intervals were wide.

2.1. Individual Study Data Table for disordered eating

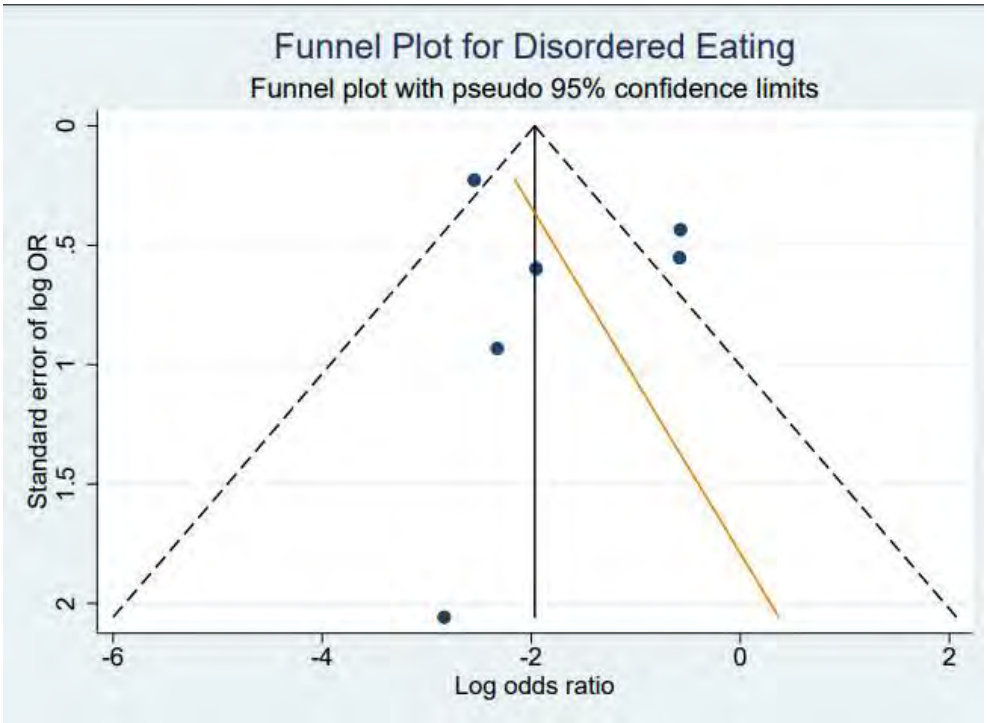
OUTCOME: Disordered eating defined as any abnormal eating disorder score				OUTCOME TYPE: Dichotomous				
COMPARISON (if applicable): PCOS and control								
Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	N events in intervention/ exposure group	N total in intervention/ exposure group	N events in control / comparison group	N total in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Karacan et al. 2014 [a]	Count	EAT-26	15	42	16	52	Crude	NA
Larsson et al. 2016 [a]	Count	EAT-40	6	72	1	30	Crude	NA
Jeanes et al. 2017	Count	BITE	16	45	5	40	Crude	NA
Lee et al. 2016[a]	Count	EDEQ	18	148	3	106	Crude	NA
Maher et al. 2018[a]	Count	EAT-26	0	8	0	8	Crude	NA
Pirotta et al. 2019	Count	EDEQ	36	501	53	398	Crude	NA

[a] Included in sensitivity analysis of studies that used confirmed Rotterdam criteria for PCOS diagnosis rather than self-report or hospital records

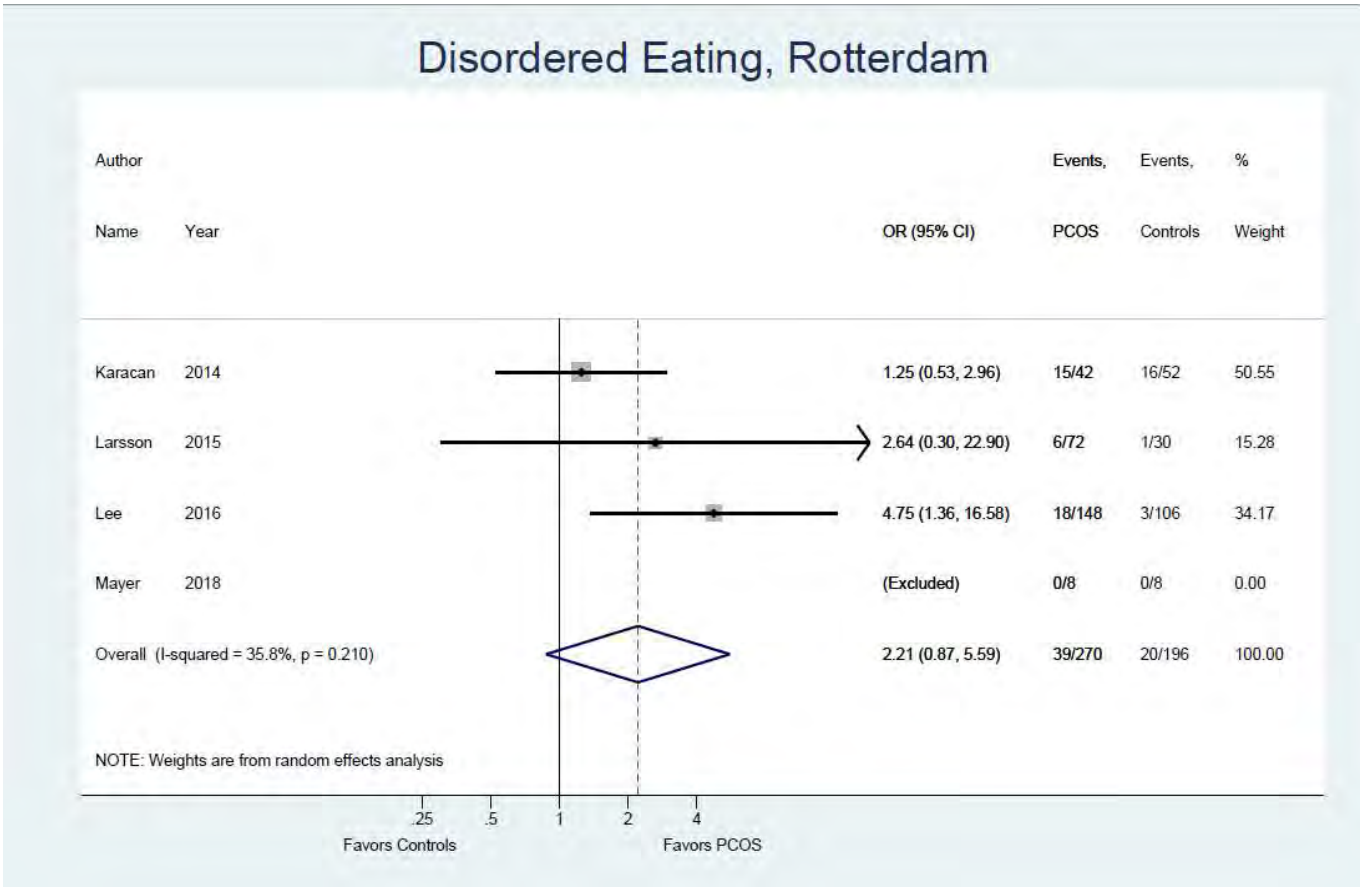
2.2. Forest plot for disordered eating



2.3. Funnel plot for disordered eating



2.4 Forest plot for disordered eating, sensitivity analysis restricted to studies where PCOS diagnosis was confirmed by Rotterdam criteria



OUTCOME 3. Bulimia Nervosa

- **EVIDENCE SUMMARY:**

Six cross-sectional studies reported prevalence of bulimia nervosa (Mansson 2008, Larsson 2016, Cesta 2016, Lee 2016, Pirotta 2019, Tay 2019). All studies had a moderate risk of bias. Studies were conducted in Australia, Sweden, and the USA. No studies evaluated risk of disordered eating in adolescents or based on ethnicity or phenotype.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

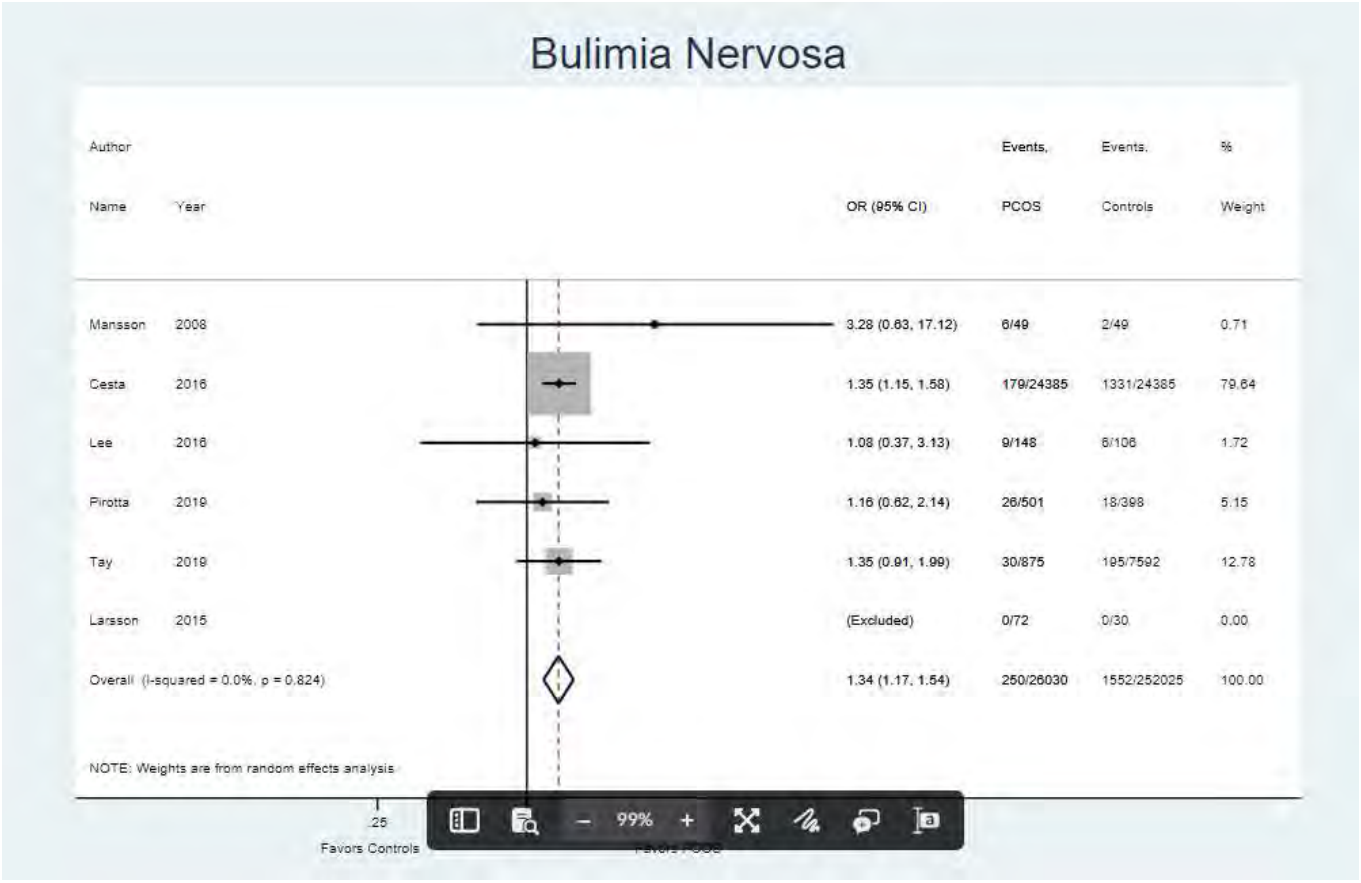
There was no increased odds of bulimia nervosa in women with PCOS in either in the meta-analysis of all adult women nor the sub-analysis of only studies where PCOS diagnosis was confirmed by Rotterdam criteria. Certainty in these results is very low and was downgraded once as the majority of studies were moderate quality, once because of imprecision as the confidence intervals were wide, and once due to risk of publication bias

3.1. Included studies for bulimia nervosa

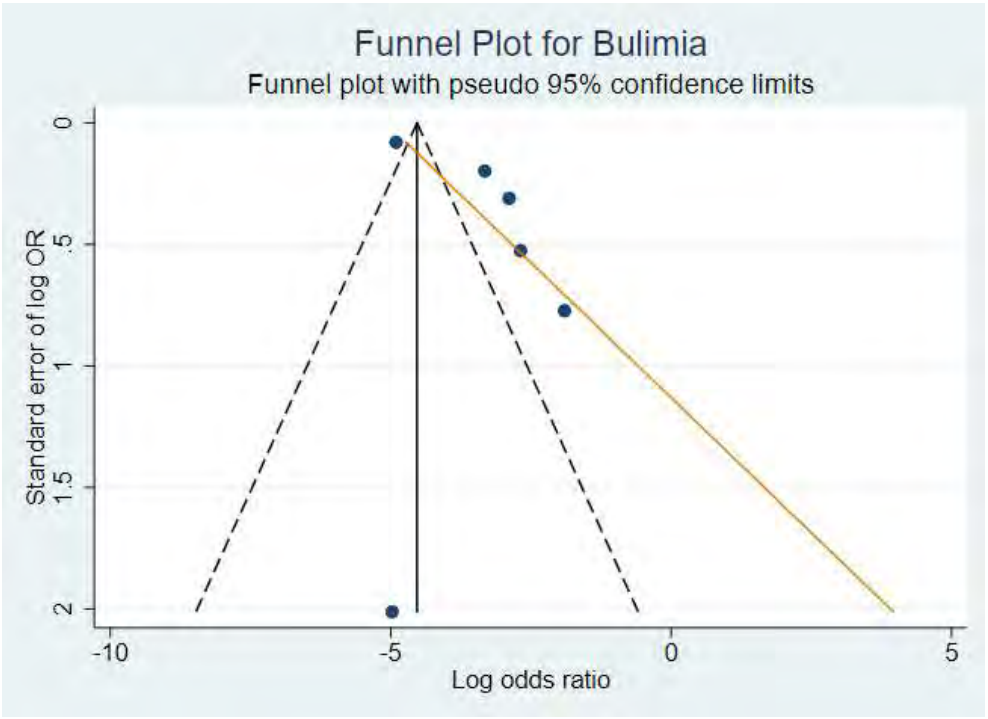
OUTCOME: Bulimia nervosa				OUTCOME TYPE: Dichotomous				
COMPARISON (if applicable): PCOS and control								
Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	N events in intervention/ exposure group	N total in intervention/ exposure group	N events in control / comparison group	N total in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Mansson et al. 2008[a]	Count	MINI	6	49	2	49	Crude	NA
Larsson et al. 2016[a]	Count	DSM IV Survey	0	72	0	30	Crude	NA
Cesta et al. 2016	Count	ICD Codes	179	24,385	1331	243,850	Crude	NA
Lee et al, 2016[a]	Count	DSM IV Survey	9	148	6	106	Crude	NA
Pirotta et al. 2019	Count	DSM Survey	26	501	18	398	Crude	NA
Tay et al. 2019	Count	Self-report	30	875	195	7592	Crude	NA

[a] Included in sensitivity analysis of studies that used confirmed Rotterdam criteria for PCOS diagnosis rather than self-report or hospital records

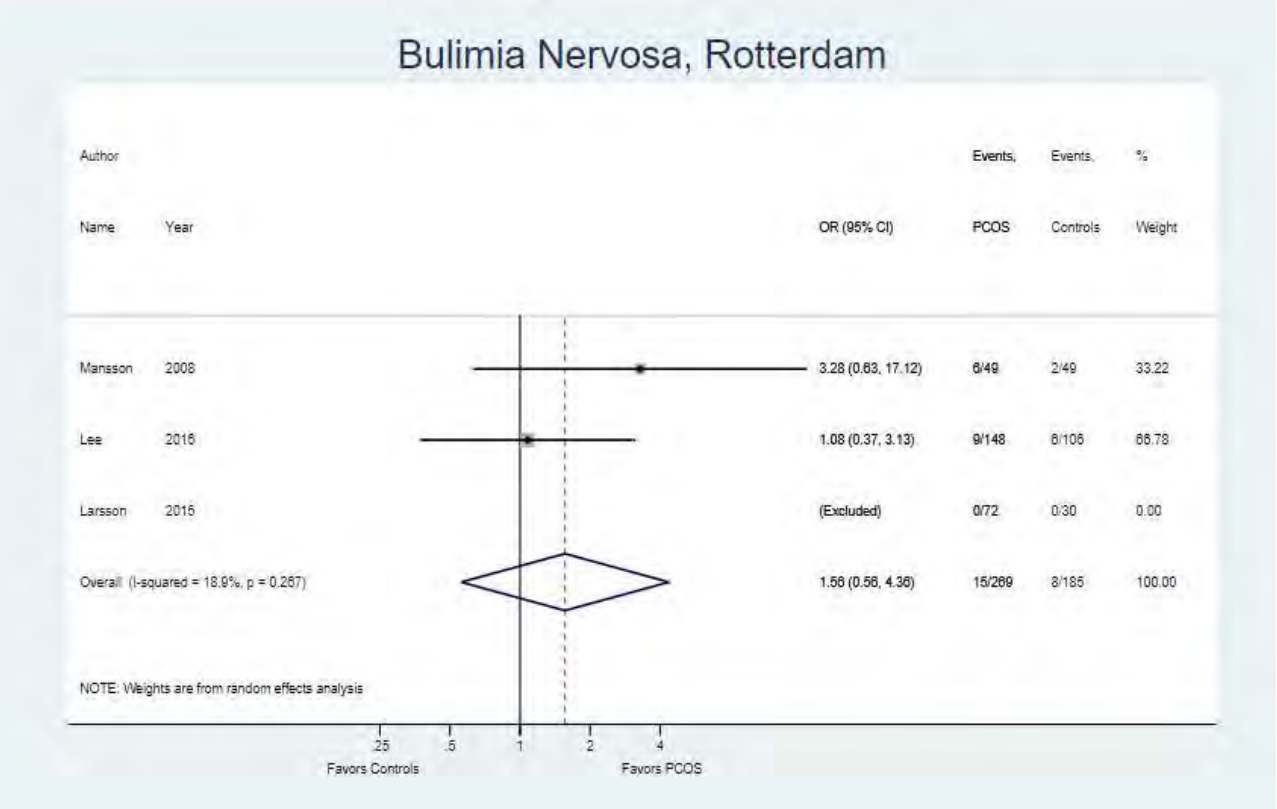
3.2. Forest plot for bulimia nervosa



3.3. Funnel plot for bulimia nervosa



3.4. Forest plot for bulimia nervosa, sensitivity analysis restricted to PCOS diagnosis with confirmed Rotterdam criteria only



OUTCOME 4. Binge eating disorder

- **EVIDENCE SUMMARY:**

Six cross-sectional studies reported prevalence of binge eating disorder. One (Lidaka 2022) had a low risk of bias and the other five had a moderate risk of bias (Hollinrake 2007, Batcheller 2013, Lee 2016, Pirotta 2019, Asdaq 2020, Lidaka 2022. Studies were conducted in Latvia, Saudi Arabia, and the USA. Only study (Lidaka 2022) restricted inclusion to adolescents. No studies evaluated risk of any eating disorder based on ethnicity or phenotype.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

There was an increased odds of binge eating disorder in women with PCOS in the meta-analysis of all adult women. Certainty in these results is low and was downgraded once as the majority of studies were moderate quality and once because of imprecision as the lower limit of the confidence interval included 1.25. There was an increased odds of binge eating disorder sub-analysis of only studies where PCOS diagnosis was confirmed by Rotterdam criteria. Certainty in these results is moderate and was downgraded once as the majority of studies were moderate quality. One study (Lidaka 2022) reported the odds of binge eating in adolescents with PCOS and did not find a higher odds in adolescents with PCOS.

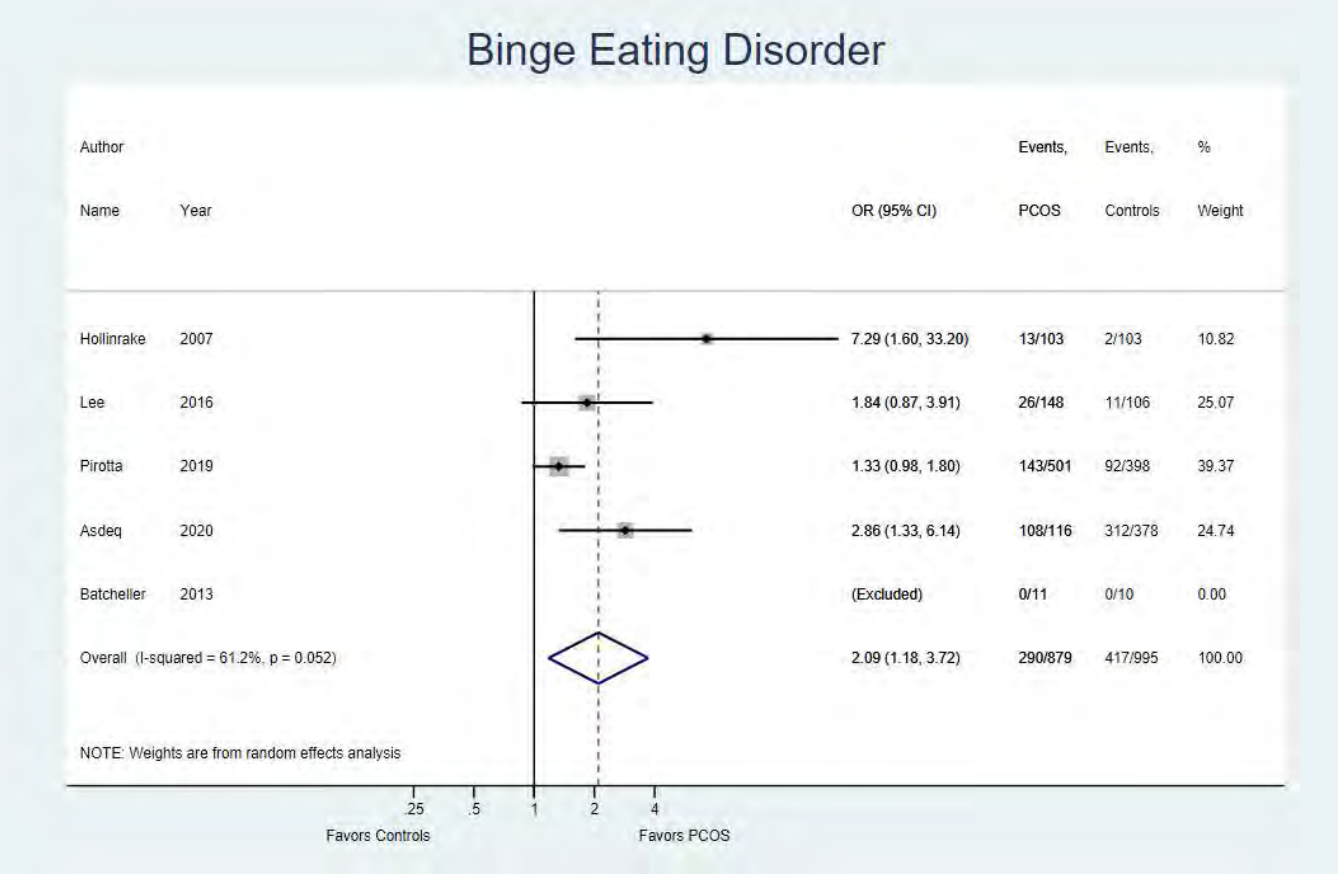
4.1. Included studies for binge eating disorder

OUTCOME: Binge Eating Disorder				OUTCOME TYPE: Dichotomous				
COMPARISON (if applicable): PCOS and control								
Author, year	Unit of outcome	Method of measurement	N events in intervention/ exposure group	N total in intervention/ exposure group	N events in control / comparison group	N total in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Hollinrake et al. 2007[a]	Count	PRIME MD PHQ	13	113	2	103	Crude	NA
Batcheller et al. 2013[a]	Count	DSM-V Based Survey	0	11	0	10	Crude	NA
Lee et al, 2016[a]	Count	DSM-IV Based Surgery	26	148	11	106	Crude	NA
Pirotta et al. 2019	Count	DSM Survey	143	501	92	398	Crude	NA
Asdaq et al. 2020[a]	Count	EAT-26	108	116	312	378	Crude	NA
Lidaka et al 2022[b]	Count	BITE	23	63	23	66	Crude	NA

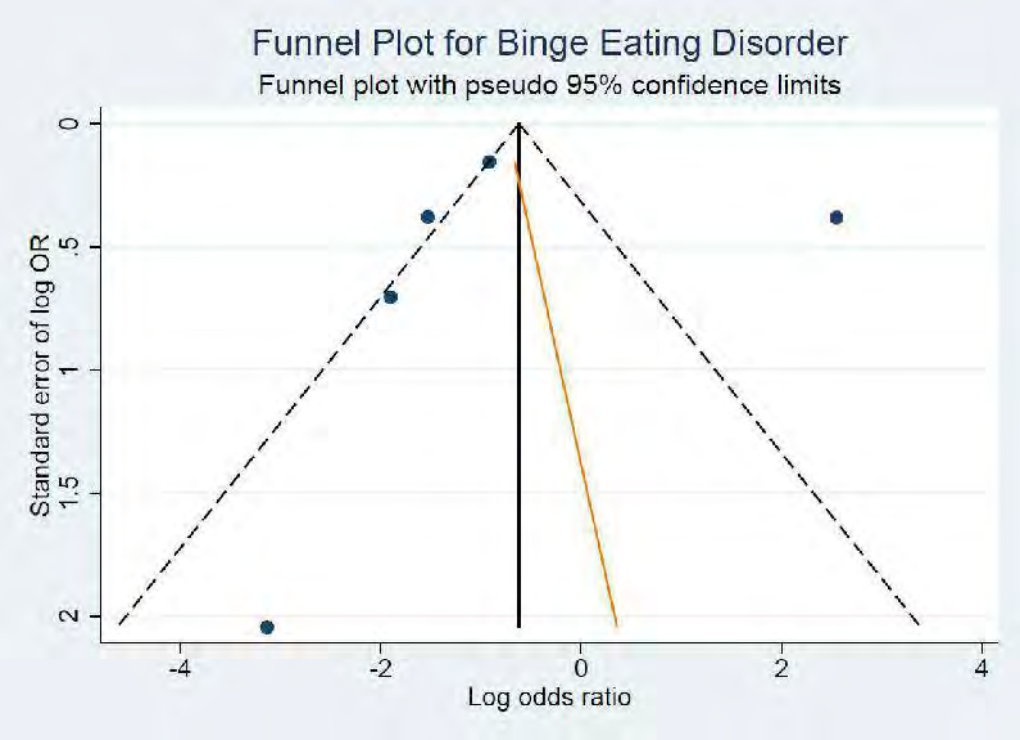
[a] Included in sensitivity analysis of studies that used confirmed Rotterdam criteria for PCOS diagnosis rather than self-report or hospital records

[b] Not included in meta-analysis as it was the only study in adolescents

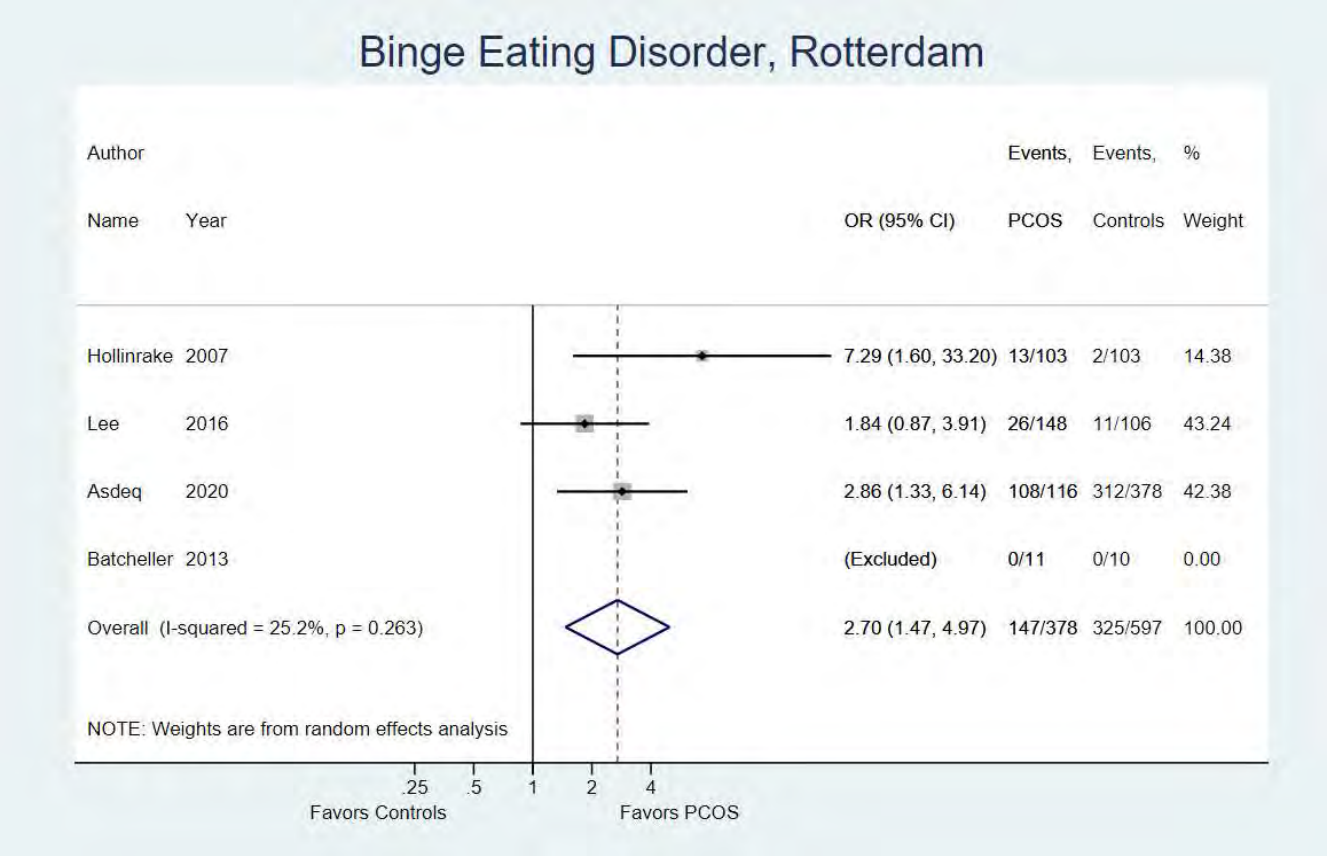
4.2 Forest plot for binge eating disorder



4.3 Funnel plot for binge eating disorder



4.4. Forest plot for binge eating disorder, sensitivity analysis restricted to PCOS diagnosis with confirmed Rotterdam criteria only



OUTCOME 5. Anorexia Nervosa

- **EVIDENCE SUMMARY:**

Four cross-sectional studies reported prevalence of anorexia nervosa (Cesta 2016, Lee 2016, Pirotta 2019 and Tay 2019). All studies had a moderate risk of bias. Studies were conducted in Australia, Sweden, and the USA. No studies evaluated risk of disordered eating in adolescents or based on ethnicity or phenotype. In none of the studies with non-zero events was PCOS diagnosis confirmed by Rotterdam criteria.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

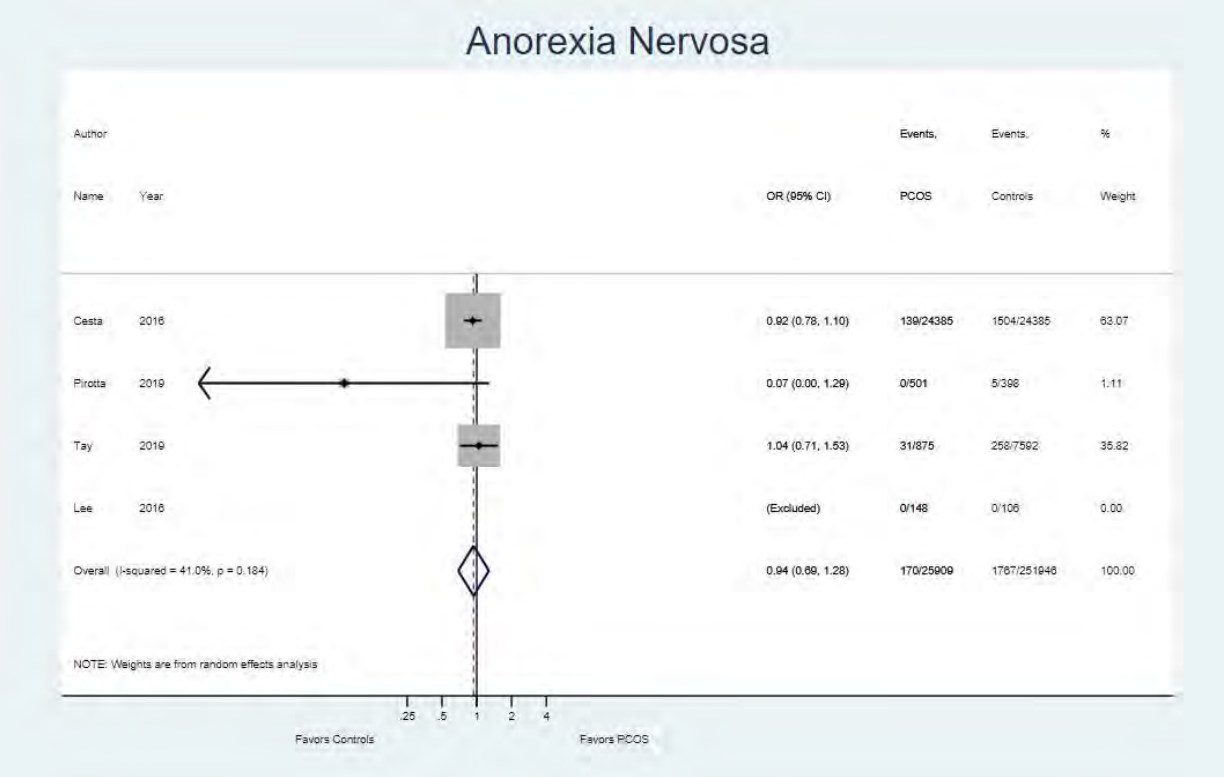
There was no increased odds of anorexia nervosa in women with PCOS in either the meta-analysis of all adult women. Certainty in these results is moderate and was downgraded once as the majority of studies were moderate quality and once because of imprecision as the confidence intervals were wide. No the sub-analysis of only studies where PCOS diagnosis was confirmed by Rotterdam criteria.

5.1. Individual Study Data Table for anorexia nervosa

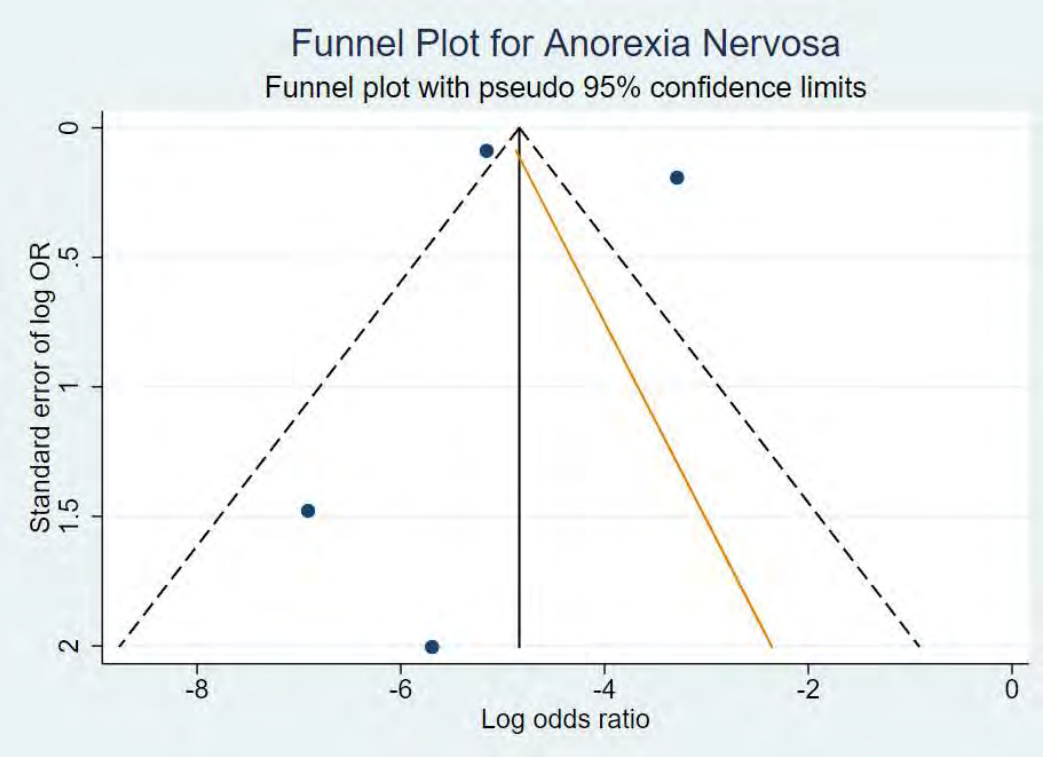
OUTCOME: Anorexia nervosa					**OUTCOME TYPE: Dichotomous**			
COMPARISON (if applicable): PCOS and control								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Cesta et al. 2016	**Count**	**ICD codes**	**139**	**24,385**	**1504**	**243,850**	**Crude**	**NA**
Lee et al. 2016[a]	**Count**	**DSM IV Survey**	**0**	**148**	**0**	**106**	**Crude**	**NA**
Pirotta et al. 2019	**Count**	**DSM Survey**	**0**	**501**	**5**	**398**	**Crude**	**NA**
Tay et al. 2019	**Count**	**Self-report**	**31**	**875**	**258**	**7592**	**Crude**	**NA**

[a] Included in sub-analysis of studies that used confirmed Rotterdam criteria for PCOS diagnosis rather than self-report or hospital records

5.2 Forrest plot for anorexia nervosa



5.3 Funnel plot for anorexia nervosa



5.4 Forrest plot for binge eating disorder, sensitivity analysis restricted to PCOS diagnosis with confirmed Rotterdam criteria only: Not performed as only one study (Lee et al, 2016) used Rotterdam criteria for PCOS diagnosis. This study had zero events.

7. GRADE ASSESSMENTS OF EVIDENCE CERTAINTY

COMPARISON: Any eating disorder												
	Quality assessment						No. participants					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**PCOS**	**Control**	**Effect estimate: OR [95% CI], M-H random**	**Favours**	**Certainty**	**Importance**
Outcome: All studies												
10	Cross-sectional	Serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	27,949	257,583	OR: 1.53 (1.29, 1.82)	PCOS	⊕⊕⊕◯ MODERATE	IMPORTANT
Outcome: PCOS diagnosis confirmed by Rotterdam criteria												
6	Cross-sectional	Serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	499	676	OR: 2.88 (1.55,5.34)	PCOS	⊕⊕⊕◯ MODERATE	IMPORTANT

[1] Downgraded once as the majority of evidence is at moderate risk of bias

COMPARISON: Disordered eating												
	Quality assessment						No. participants					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**PCOS**	**Control**	**Effect estimate: OR [95% CI], M-H random**	**Favours**	**Certainty**	**Importance**
Outcome: All studies												
6	Cross-sectional	Serious[1]	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	816	634	1.77 (0.63, 4.91)	None	⊕⊕◯◯ LOW	IMPORTANT
Outcome: PCOS diagnosis confirmed by Rotterdam criteria												
4	Cross-sectional	Serious[1]	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	270	196	2.21 (0.87, 5.59)	None	⊕⊕◯◯ LOW	IMPORTANT

[1] Downgraded once as the majority of evidence is at moderate risk of bias
[2] Downgraded once due to imprecision as confidence intervals (CIs) were wide

COMPARISON: Disordered eating												
	Quality assessment						No. participants					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**PCOS**	**Control**	**Effect estimate: OR [95% CI], M-H random**	**Favours**	**Certainty**	**Importance**
Outcome: Bulimia Nervosa												
6	Cross-sectional	Serious[1]	no serious inconsistency	no serious indirectness	serious imprecision[2]	serious risk for publication bias[3]	26,030	252,025	1.34 (1.17, 1.54)	None	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Bulimia Nervosa in PCOS diagnosis confirmed by Rotterdam criteria												
4	Cross-sectional	Serious[1]	no serious inconsistency	no serious indirectness	serious imprecision[2]	serious risk for publication bias[3]	269	185	1.56 (0.56, 4.36)	None	⊕◯◯◯ VERY LOW	IMPORTANT

[1] Downgraded once as the majority of evidence is at moderate risk of bias
[2] Downgraded once due to imprecision as confidence intervals (CIs) were wide
[3] Downgraded once due to serious risk of publication bias

COMPARISON: Binge eating disorder												
	Quality assessment						No. participants					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**PCOS**	**Control**	**Effect estimate: OR [95% CI], M-H random**	**Favours**	**Certainty**	**Importance**
Outcome: All studies												
5	Cross-sectional	Moderate[1]	no serious inconsistency	no serious indirectness	Serious imprecision[2]	none	879	998	OR: 2.09 (1.18, 3.75)	PCOS	⊕⊕◯◯ LOW	CRITICAL
Outcome: PCOS diagnosis confirmed by Rotterdam criteria												
4	Cross-sectional	Moderate[1]	no serious inconsistency	no serious indirectness	No serious imprecision	none	378	597	OR: 2.70 (1.47, 4.97)	PCOS	⊕⊕⊕◯ MODERATE	CRITICAL

[1] Downgraded once as the majority of evidence is at moderate risk of bias
[2] Downgraded once due to imprecision as confidence intervals (CIs) includes lower limit below 1.25.

COMPARISON: Anorexia nervosa												
	Quality assessment						No. participants					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**PCOS**	**Control**	**Effect estimate: OR [95% CI], M-H random**	**Favours**	**Certainty**	**Importance**
Outcome: All studies												
5	Cross-sectional	Moderate[1]	no serious inconsistency	no serious indirectness	No serious imprecision	none	25,909	251,946	OR: 0.94 (0.69, 1.28)	Neither	⨁⨁⨁◯ MODERATE	CRITICAL

[1] Downgraded once as the majority of evidence is at moderate or high risk of bias

APPENDIX. STUDY CHARACTERISTICS AND QUALITY APPRAISAL TEMPLATES

Study ID		Hollinrake et al, 2007	
Study Citation		Hollinrake E, Abrea A, Maifield M, Van Voorhis BJ, Dokras A. Increased risk of depressive disorders in women with polycystic ovary syndrome. Fertil Steril 2007;87:1369-76.	
Study Country		USA	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/ participants		*Cross-sectional study of women with PCOS seen at a university Reproductive Endocrinology and Infertility Clinic and women without PCOS seen at a university outpatient clinic for annual exams between* May 2004-August 2005.	
Control population		*Women without PCOS seen during the same time period for annual exams*	
PCOS diagnostic criteria		*Rotterdam criteria*	
N per group		*PCOS: N=103* *Controls: N=103*	
Setting		*University of Iowa Hospitals and Clinics between May 2004-August 2005*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)		*Primary outcomes:* *- Prevalence of depression (not relevant to this analysis)* *Secondary outcomes:* *-Prevalence of other DSM IV diagnoses including binge eating disorder* *- Scales used: the Primary Care Evaluation of Mental Disorders Patient Health Questionnaire (PRIME-MD PHQ) (15) and Beck Depression Inventory (BDI)*	
Does the study have a clearly focused question and/or PICO?		Yes	
Inclusion criteria		Yes	
Exclusion criteria		Yes	*Control subjects were randomly selected from women who had regular menses and absence of hirsutism*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes	
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes	
Was there sufficient duration of follow-up for outcomes to occur?		N/A	*Not relevant for cross-sectional study*
Was matching performed?		No	
Summary Result/s		*Binge eating disorder (BED) was more common in PCOS subjects than in control subjects (12.6% vs. 1.9%; P<.01).*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Partial	*PCOS subjects were from an REI clinic and thus had higher rates of trying to conceive than controls recruited from a gyn clinic.*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes	*Rotterdam 2003*
	Was the control status established in a standard, valid and reliable way?	Yes	
PERFORM	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes	
DE DE	**Were measurements (for exposures or outcomes)**	Yes	

	carried out and calculated in a standard, valid and reliable way?		
	Were outcome assessors blind to case and control status?	No	*Unlikely to cause bias as standardized questionnaires were used*
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	N/A	*In the methods, in both groups 90-94% of subjects approached agreed to participate in the study. No loss of follow-up given cross-sectional nature of the study.*
	What percentage of the individuals were not included in the analysis?	N/A	*All individuals were included*
REPORT	**Is the paper free of selective outcome reporting?**	Yes	
CONFOUN	**Are the cohorts comparable on the basis of design or analysis?**	Partial	*Because the PCOS came from an REI clinic, they might have had higher psychiatric comorbidities then controls recruited from general gyn clinics.*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	No	
	Was the study sufficiently powered to detect any differences between the groups?	Yes	*Power calculation was done for depression, but not eating disorders; however, significant difference was found in eating disorder outcome.*
	If statistical analysis was undertaken, was this appropriate?	Yes	*Yes*
COMMENTS		*BMI different in baseline characteristics; may confound rates of eating disorders in control vs exposure group*	
What is the overall risk of bias?		*Moderate*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	Mansson et al, 2008
Study Citation	Månsson M, Holte J, Landin-Wilhelmsen K, Dahlgren E, Johansson A, Landén M. Women with polycystic ovary syndrome are often depressed or anxious-A case control study. *Psychoneuroendocrinology*. 2008;33(8):1132-1138. doi:10.1016/j.psyneuen.2008.06.003
Study Country	*Sweden*
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Cross-sectional study of women with and without PCOS diagnosed at university outpatient units (Goteborg and Stockholm, Sweden) between 2002-2005.*

Control population		*49 age-matched controls born on the same day identified from the population registry who did not have known PCOS and did not report oligo- or amenorrhea*	
PCOS diagnostic criteria		*Rotterdam 2003*	
N per group		*PCOS: N=49* *Control: N=49*	
Setting		*University Hospital; clinical interviews*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)		*Primary outcomes:* *- Current and lifetime occurrence of Axis I DSM IV diagnoses using the semi structured MINI International Neuropsychiatric Interview* *- Eating disorder outcomes: prevalence of any eating disorder and bulimia nervosa*	
Does the study have a clearly focused question and/or PICO?		Yes	
Inclusion criteria		Yes	
Exclusion criteria		Yes	*Control group: excluded if known PCOS or if report oligo- or amenorrhea*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes	
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes	
Was there sufficient duration of follow-up for outcomes to occur?		N/A	*Not relevant for cross-sectional study*
Was matching performed?		Yes	*Controls were matched to PCOS group based on birthday*
Summary Result/s		*PCOS was associated with a higher odds of any eating disorder (21% vs. 4%; OR: 6.4; 95% CI: 1.3-31), but not bulimia nervosa (12 vs. 4%; OR: 3.5; 95% CI: 0.67-18).*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Partial	*- Intervention group recruited at hospital whereas control group using population-based registry.* *- Controls were age matched*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes	*Yes, used established Rotterdam criteria*
	Was the control status established in a standard, valid and reliable way?	Yes	
PERFO RMAN	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes	
DET ECT	**Were measurements (for exposures or outcomes)**	Yes	

	carried out and calculated in a standard, valid and reliable way?		
	Were outcome assessors blind to case and control status?	No	*Although given standardized use of MINI this should not introduce bias*
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	N/A	*Not relevant for cross-sectional study*
	What percentage of the individuals were not included in the analysis?	All were included	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes	
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Partial	*Because the PCOS came from hospital clinics, they might have had higher psychiatric comorbidities then controls recruited from a registry.*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	No	
	Was the study sufficiently powered to detect any differences between the groups?	Not reported	*Power calculations not reported, but they mentioned they were only powered to detect differences in psychiatric disorders that were relatively common*
	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS			
What is the overall risk of bias?		Moderate	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	Batchellar et al, 2013
Study Citation	Batchellar AE, Ressler IB, Sroga JM, Martinez AM, Thomas MA, DiPaola KB. Binge eating disorder in the infertile polycystic ovary syndrome patient. Fertil Steril 2013;100(Suppl 3):S413.

		This is an abstract only. Additional information was obtained from the authors.	
Study Country		USA	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/ participants		*Cross-sectional study of patients undergoing in vitro fertilization (IVF) at University of Cincinnati, Cincinnati. Patients were divided into three groups: obese PCOS (BMI >30 kg/m2), lean PCOS, (BMI<25 kg/m2), and controls (oocyte donors or male factor infertility.*	
Control population		*Oocyte donors or male factor infertility*	
PCOS diagnostic criteria		*Rotterdam 2003*	
N per group		*Obese PCOS: N=6* *Lean PCOS: N=5* *Controls: N=10*	
Setting		*University Reproductive Endocrinology and Infertility clinic*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)		*Primary outcome:* *Prevalence of binge eating disorder (BED) using DSM V criteria.*	
Does the study have a clearly focused question and/or PICO?		Yes	
Inclusion criteria		Not reported	
Exclusion criteria		Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?		Not reported	
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes	
Was there sufficient duration of follow-up for outcomes to occur?		N/A	*Not relevant for cross-sectional study*
Was matching performed?		No	
Summary Result/s		*No patients in either group were diagnosed with BED.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes	
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes	
	Was the control status established in a standard, valid and reliable way?	Yes	
PERFORMANCE BIAS	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes	
DETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes	
	Were outcome assessors blind to case and control status?	No	*Unlikely to cause bias as standardized questionnaires were used*
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	N/A	*Not relevant for cross-sectional study*
	What percentage of the individuals were not included in the analysis?	N/A	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Not reported	
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	No	
	Was the study sufficiently powered to detect any differences between the groups?	Not reported	*Given low numbers, unlikely to be powered to detect differences in this relatively rare outcome.*
	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS			
What is the overall risk of bias?		Moderate	
Did risk of bias differ by outcome		*No*	

Study ID	*Karacan et al, 2014*	
Study Citation	Karacan E, Caglar GS, Gürsoy AY, Yilmaz MB. Body satisfaction and eating attitudes among girls and young women with and without polycystic ovary syndrome. *J Pediatr Adolesc Gynecol*. 2014;27(2):72-77. doi:10.1016/j.jpag.2013.08.003	
Study Country	*Turkey*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Cross-sectional study of adolescent/young adult females with and without PCOS conducted at Ufuk University Obstetrics and Gynecology Department in Ankara, Turkey, between January 2009 and February 2010.*	
Control population	*Adolescent/young adult females without PCOS*	
PCOS diagnostic criteria	*Rotterdam 2003*	
N per group	*PCOS: N=42* *Control: N=52*	
Setting	*University hospital, OB-Gyn department, not reported how subjects were identified*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary Outcome:* *-Eating attitudes* *--Eating Attitudes Test (EAT-26)* *-- Figure Rating Scale (FRS)* *-- The Sociocultural Attitudes towards Appearance Questionnaire (SATAQ)* *-- Body Esteem Scale for Adolescents and Adults (BESAA)*	
Does the study have a clearly focused question and/or PICO?	Yes	

Inclusion criteria		Yes	*BMI <25, young/adolescent female (age range 15-24 years)*
Exclusion criteria		Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?		Partial	
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes	
Was there sufficient duration of follow-up for outcomes to occur?		N/A	*Not relevant for cross-sectional study*
Was matching performed?		No	
Summary Result/s		*There were no differences between PCOS and controls for prevalence of abnormal EAT=26 scores (35.7% vs. 30.6% NS) or mean EAT-26 scores (46.6±17 vs 48.2±17.6; p= ns)*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Partial	*Unclear recruitment procedures*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes	
	Was the control status established in a standard, valid and reliable way?	Not reported	*Not reported how PCOS was excluded in control group*
PERFORMANCE BIAS	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes	
DEDETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes	
	Were outcome assessors blind to case and control status?	Not reported	*Unlikely to impact results as standardized questionnaires used*
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	Not reported	
	What percentage of the individuals were not included in the analysis?	Not reported	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes	
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Partial	*Unclear recruitment procedures*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	No	
	Was the study sufficiently powered to detect any differences between the groups?	Not reported	*No power calculations reported*
	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS		*Prevalence of abnormal EAT-26 scores not reported in published manuscript, but authors provided this data for the meta-analysis.*	
What is the overall risk of bias?		Moderate	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Sirmans et al 2014*
Study Citation	*Sirmans, S., Parish, R., Blake, S., Wang, X. (2014). Epidemiology and comorbidities of polycystic ovary syndrome in an indigent population. Journal of Investigative medicine, 2014.*
Study Country	*USA*
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Cross-sectional study of women with and without PCOS using Louisiana, USA Medicaid claims database, queried to identify all women between the ages of 15 and 45 years who were Medicaid eligible on January 1, 2010.*
Control population	*Women without PCOS between the ages of 15 and 45 years, matched to PCOS subjects 3:1 based on age and race*
PCOS diagnostic criteria	*Diagnosed by at least 1 paid claim for a diagnosis of PCOS least 1 paid claim for oligomenorrhea or amenorrhea plus hyperandrogenism (hirsutism)*
N per group	*PCOS: N= 1689* *Control: N= 5067*
Setting	*Louisiana, USA Medicaid claims database*

Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)		*Primary outcomes:* *Association of PCOS with cardiovascular risk factors and comorbid conditions. Relevant outcomes for analysis:*	
Does the study have a clearly focused question and/or PICO?		Yes	
Inclusion criteria		Yes	
Exclusion criteria		Yes	*ICD codes for conditions that mimic PCOS, age <15 or >45. Pregnancy, receiving care at long-term care facility*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes	
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes	
Was there sufficient duration of follow-up for outcomes to occur?		N/A	*Not relevant for cross-sectional study*
Was matching performed?		Yes	*Age and race*
Summary Result/s		*There were no differences in prevalence of eating disorders between women with and without PCOS (0.4% vs. 0.3%; P=0.5)*	
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes	
	Was the case definition adequate and established in a standard, valid and reliable way?	Partial	*Claims data rather than Rotterdam*
	Was the control status established in a standard, valid and reliable way?	Partial	*Claims data*
PERFORMANCE BIAS	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes	
DEDETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes	
	Were outcome assessors blind to case and control status?	No	*Unlikely to cause bias as standardized questionnaires were used*

	Were all outcomes measured in a standard, valid and reliable way?	Partial	*Claims data*
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	N/A	*Cross-sectional study*
	What percentage of the individuals were not included in the analysis?	N/A	*All participants included in analysis*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes	
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	No	
	Was the study sufficiently powered to detect any differences between the groups?	Not reported	*Power calculations not reported, but large sample size*
	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS			
What is the overall risk of bias?		*Moderate*	
Did risk of bias differ by outcome		*No*	

Study ID	Larsson et al, 2016
Study Citation	Larsson I, Hulthén L, Landén M, Pålsson E, Janson PO, Stener-Victorin E. Dietary intake, resting energy expenditure, and eating behavior in women with and without polycystic ovary syndrome. Clin Nutr. 2016;35(1):213-218. doi:10.1016/j.clnu.2015.02.006
Study Country	Sweden
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Cross-sectional study of women with and without PCOS recruited between November 2005- September 2008 at the Sahlgrenska Academy University of Gothenburg, Sweden*

Control population		*Women without PCOS*	
PCOS diagnostic criteria		*Rotterdam 2003*	
N per group		*PCOS: N= 72* *Control: N= 30*	
Setting		*Participants recruited via newspapers and other community spaces*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)		*Primary outcome:* *- Determine if women with PCOS have altered eating behaviours compared to controls* *Scales used:* *- 21-item Three-Factor Eating Questionnaire (TFEQ-R21)* *- Eating Attitudes Test (EAT-40), clinical cut-off for eating disturbances was score ≥ 29* *- Psychiatric illness (self-reporting questionnaire using DSM-4 criteria)*	
Does the study have a clearly focused question and/or PICO?		Yes	
Inclusion criteria		Yes	
Exclusion criteria		Yes	*Women with congenital adrenal hyperplasia, hypothyroidism, hyperprolactinemia, Cushing syndrome, androgen secreting tumors and other related disorders, pharmacologic treatment within past 12 weeks, breastfeeding, HTN/DM, in treatment for psychiatric disease were excluded. Additionally, controls were excluded if they had menstrual irregularities, polycystic ovarian morphology on ultrasound (PCOM), or signs of hyperandrogenism.*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Partial	*Exclusion of participants with hypertension/diabetes and other comorbid conditions limits generalizability of study and those often co-exist with PCOS*
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes	
Was there sufficient duration of follow-up for outcomes to occur?		N/A	
Was matching performed?		No	
Summary Result/s		*There were no difference in eating behaviours (cognitive restraint, emotional eating and uncontrolled eating) between PCOS group vs controls. Women with PCOS did have higher total EAT-40 scores (PCOS 16.4 ± 10.1 vs Control 7.8 ± 6 (p= <0.001)). There were no differences in rates of abnormal EAT-40 scores or current bulimia.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes	
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes	
	Was the control status established in a standard, valid and reliable way?	Yes	

PERFORMANCE BIAS	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes	
DEDETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes	
	Were outcome assessors blind to case and control status?	Not reported	*Unlikely to cause bias as standardized questionnaires were used*
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	N/A	*Not relevant for cross-sectional study*
	What percentage of the individuals were not included in the analysis?	N/A	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes	
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	No	
	Was the study sufficiently powered to detect any differences between the groups?	Partial	*They conducted post hoc power analyses for noting differences in resting metabolic rate and respiratory exchange ratio. Power calculations not reported for eating attitudes and behaviors.*
	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS			
What is the overall risk of bias?		Moderate	*Moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Cesta et al, 2016*	
Study Citation	*Cesta, C., Mansson, M., Palm, C., Lichtenstein, P., Iliadou, A., Landen, M. (2016). Polycystic ovary syndrome and psychiatric disorders: co-morbidity and heritability in a nationwide Swedish cohort. Psychoneuroendocrinology, 2016.*	
Study Country	*Sweden*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Cross-sectional study of women identified from Swedish National Patient Register (NPR) between 1990 and 2013.*	
Control population	*Randomly selected individuals in general population of NPR*	
PCOS diagnostic criteria	*At least one PCOS ICD code in the NPR*	
N per group	*PCOS: N= 24,385* *Control: N= 243,850*	
Setting	*NPR*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcomes:* *Psychiatric disorders based on ICD codes in the NPR from 1973 to 2013*	
Does the study have a clearly focused question and/or PICO?	Yes	
Inclusion criteria	Yes	
Exclusion criteria	Yes	*PCOS group: PCOS excluded if they had a condition that may mimic PCOS and if a diagnosis was made before age 13 without additional diagnosis in adolescence or adulthood* *Immigration, emigration, death and diagnosis date conflicts*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Partial	*PCOS not excluded from controls*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes	
Was there sufficient duration of follow-up for outcomes to occur?	N/A	*Not relevant for cross-sectional study*
Was matching performed?	No	*A matched cohort design was used. Each PCOS patient was matched on sex, birth year, and county of residence within the decade of diagnosis to ten comparison individuals randomly selected from the general population.*
Summary Result/s	*Women with PCOS had a higher prevalence of any eating disorder (2.5% vs. 1.7%; P< 0.05) and bulimia (0.73% vs. 0.55%; P<0.05)*	

SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes	
	Was the case definition adequate and established in a standard, valid and reliable way?	Partial	*ICD codes used, not confirmed by Rotterdam*
	Was the control status established in a standard, valid and reliable way?	Partial	*PCOS not ruled out*
PERFORMANCE BIAS	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes	
DEDETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Partial	*ICD-9 codes used*
	Were outcome assessors blind to case and control status?	No	*Unlikely to cause bias ICD 9 codes used*
	Were all outcomes measured in a standard, valid and reliable way?	Partial	
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	N/A	*Cross-sectional study*
	What percentage of the individuals were not included in the analysis?	N/A	*All participants included in analysis*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes	
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	No	
	Was the study sufficiently powered to detect any differences between the groups?	Yes	*Yes, for primary outcome*

	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS			
What is the overall risk of bias?		*Moderate*	
Did risk of bias differ by outcome		*No*	

Study ID		*Jeanes 2017*	
Study Citation		Jeanes YM, Reeves S, Gibson EL, Piggot C, May VA, Hart KH. Binge eating behaviors and food cravings in women with Polycystic Ovary Syndrome. Appetite. 2017;109:24-32	
Study Country		England	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/ participants		*Cross-sectional study of women with PCOS and without PCOS. Healthy lean women were matched for* *weight, age and ethnicity to lean women with PCOS.* *All overweight/ obese women with PCOS were invited to participate and were not matched with controls, thus only lean women with PCOS and lean controls were included in analysis*	
Control population		*Women without PCOS*	
PCOS diagnostic criteria		*Self-report of PCOS diagnosis by a healthcare professional*	
N per group		*Controls (all lean): N=40* *PCOS (lean): 45*	
Setting		*England, social media sites and email advertisements at University of Surrey in Southern England*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)		*Primary outcome:* *- Prevalence of food cravings, binge eating behaviors, emotional eating, cognitive restraint, and uncontrolled eating scores* *Scores used:* *- Bulimia Investigatory Test, Edinburgh (BITE), Food Cravings-Trait Questionnaire ((FCQeT) and the Three Factor Eating Questionnaire revised-18 ((TFEQ-R18 version 2)*	
Does the study have a clearly focused question and/or PICO?		Yes	
Inclusion criteria		Partial	*At least 18 years of age, "healthy" – not defined*
Exclusion criteria		Yes	*Patients that were pregnant or breastfeeding*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Partial	
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes	
Was there sufficient duration of follow-up for outcomes to occur?		N/A	
Was matching performed?		Yes	*Weight, age and ethnicity*
Summary Result/s		*Lean women with PCOS had higher BITE scores and a higher prevalence of abnormal BITE scores than lean controls (36% vs. 12%; p=0.02)*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION	**Was the case definition adequate?**	Yes	
	Was ascertainment of exposure adequate?	Partial	*Self-report of physician diagnosis of PCOS*

	Was the control status established in a standard, valid and reliable way?	Yes	
PERFORMANCE BIAS	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes	
DETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes	
	Were outcome assessors blind to case and control status?	No	*Unlikely to cause bias as standardized questionnaires were used*
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	N/A	Cross-sectional survey
	What percentage of the individuals were not included in the analysis?	Not reported	*21.6% of patients with PCOS not included in analysis, but it was not reported if they were lean or obese*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes	
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	No	
	Was the study sufficiently powered to detect any differences between the groups?	No	*Not powered to report a difference in binge eating symptoms and depression.*
	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS			
What is the overall risk of bias?		Moderate	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Lee 2017*	
Study Citation	Lee I, Cooney LG, Saini S, et al. Increased risk of disordered eating in polycystic ovary syndrome. *Fertil Steril*. 2017;107(3):796-802. doi:10.1016/j.fertnstert.2016.12.014	
Study Country	*USA*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Cross-sectional study of women with and without PCOS ages 18-50 recruited Aug 2015 - Aug 2016 at the University of Pennsylvania, USA*	
Control population	*All women presenting for gyn routine care at a university hospital clinic were approached for participation and were excluded if they had menstrual irregularity or hirsutism.*	
PCOS diagnostic criteria	*Rotterdam criteria (2003)*	
N per group	*PCOS: N= 148* *Control: N= 106*	
Setting	*PCOS: Women seeking management of PCOS at Penn PCOS Center* *Controls: Women presenting to gyn care at the same university hospital*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcomes:* *- Determine the prevalence of disordered eating among women with PCOS as compared with controls* *-- Disordered eating defined as a score ≥ 4 on Eating Disorder Examination-Questionnaire (EDE-Q)),* *-- DSM-5 criteria for bulimia nervosa (BN), binge eating disorder (BED), anorexia nervosa (AN) based on responses to a survey* *-- Night eating syndrome (NES) defined by score ≥ 25 on the Night Eating Questionnaire (NEQ)*	
Does the study have a clearly focused question and/or PICO?	Yes	
Inclusion criteria	Yes	*All women presenting for care between age 15-50*
Exclusion criteria	Yes	*Pregnancy.* *Controls excluded for menstrual irregularities or hirsutism.*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes	
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes	
Was there sufficient duration of follow-up for outcomes to occur?	N/A	*Not relevant for cross-sectional study*
Was matching performed?	No	*PCOS group was younger, had higher BMI, and were more likely to be married/partnered than controls.*
Summary Result/s	*Women with PCOS had a higher prevalence of abnormal EDE-Q scores (12.2% vs. 2.8%; OR: 4.8; 95% CI: 1.4, 16.8).* *There were no differences between groups for prevalence of any ED diagnoses: (28.4% vs 18.9%); p= 0.8) or individual eating disorders (BN, BED, AN, or NES).*	

SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Partial	*Both recruited from university hospital though the cases were from a subspecialty PCOS clinic that may confer an unmeasured bias compared to those who present to routine Ob-gyn care.*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes	
	Was the control status established in a standard, valid and reliable way?	Yes	
PERFORMANCE BIAS	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes	
DETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes	
	Were outcome assessors blind to case and control status?	No	*Unlikely to cause bias as standardized questionnaires were used*
	Were all outcomes measured in a standard, valid and reliable way?	Partial	*Eating disorders diagnosed by using questionnaire and comparing to DSM-5 criteria. Questionnaire ask about symptoms over last 28 days whereas DSM criteria looks at symptoms over 3 months.*
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	N/A	
	What percentage of the individuals were not included in the analysis?	N/A	*All participants included in analysis*
REPORTING BIAS	**Is the paper free of selective outcome reporting?**	Yes	
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Partial	*Both groups were recruited from a University hospital; the cases from a subspecialty PCOS clinic vs controls from general gynecology clinic.*
	Were there any conflicts of interest in the writing or funding of this study?	No	

OTHER BIAS	**Was the study sufficiently powered to detect any differences between the groups?**	Yes	*Yes, for primary outcome*
	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS			
What is the overall risk of bias?		*Moderate*	
Did risk of bias differ by outcome		*No*	

Study ID	*Maher et al, 2016*	
Study Citation	*Maher, M., Sanders, A.(2018). Eating indicators in women with polycystic ovary syndrome and weight-matched controls. FASEB Journal, 2018.*	
Study Country	*USA*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Cross-sectional study of women with and without PCOS recruited University of Wisconsin-La Crosse, USA*	
Control population	*Women without PCOS matched by weight to women with PCOS*	
PCOS diagnostic criteria	*Rotterdam criteria (2003)*	
N per group	*PCOS: N= 8* *Control: N= 8*	
Setting	*Recruited by print advertisements, assessment at university clinic*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcomes:* *EAT-26 (Disordered eating diagnosed by score >20)* *Secondary outcomes (not relevant)* *-NIH Diet History Questionnaire and Diet interview* *-DEXA scan, lab draws*	
Does the study have a clearly focused question and/or PICO?	Yes	
Inclusion criteria	Yes	*Age 18-60, preferably overweight*
Exclusion criteria	Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes	

Is a cross sectional or case-control study the appropriate design to answer this question?		Yes	
Was there sufficient duration of follow-up for outcomes to occur?		N/A	*Not relevant for cross-sectional study*
Was matching performed?		Yes	*Weight*
Summary Result/s		*Women with PCOS had a higher mean EAT-26 score but no differences in the prevalence of disordered eating (0 in both groups).*	
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes	
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes	
	Was the control status established in a standard, valid and reliable way?	Yes	
PERFORMANCE	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes	
DETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes	
	Were outcome assessors blind to case and control status?	No	*Unlikely to cause bias as standardized questionnaires were used*
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	Not clearly reported	*Two participants withdrew due to scheduling conflicts and two relocated during the study. Not reported what group they were in.*
	What percentage of the individuals were not included in the analysis?	Not clearly reported	*See above*

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes	
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	No	
	Was the study sufficiently powered to detect any differences between the groups?	No	*Power not reported for prevalence of disordered eating, but unlikely to be powered*
	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS			
What is the overall risk of bias?		*Moderate*	
Did risk of bias differ by outcome		*No*	

Study ID	Pirotta et al, 2019
Study Citation	*Pirotta, S., Barillaro, M., Brennan, L., Grassi, A., Jeanes, Y., Joham, A., Kulkarni, J., Monahan Couch, L., Lim, S., Moran, L. (2019). Disordered eating behaviors and eating disorders in women in Australia with and without polycystic ovary syndrome: a cross-sectional study. Journal of Clinical Medicine, 2019.*
Study Country	*Australia*
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Cross-sectional study of women with and without PCOS via online survey collected between August 2017 and March 2018*
Control population	*Sampled from a cross-sectional online study that aimed to examine a range of eating-related psychosocial variables within an Australian sample. PCOS status not evaluated in controls*
PCOS diagnostic criteria	*Self-report of prior PCOS diagnosis*
N per group	*PCOS: N= 501* *Control: N= 398*
Setting	*PCOS recruited from PCOS-related Australian social media pages as well as Australian e-newsletter distribution servers.* *Controls recruited through social media and University intranet pages and groups*

Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)		*Primary outcomes:* *Prevalence of disordered eating and eating disorders* *Scales Used:* *-Eating Disorder Examination Questionnaire (EDE-Q)* *-The Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) criteria.*	
Does the study have a clearly focused question and/or PICO?		Yes	
Inclusion criteria		Yes	*Self-report as Australian, female, aged 18–45 years and had completed all of the EDE-Q, fluent in English language*
Exclusion criteria		Yes	*Pregnancy, breastfeeding, taking weight loss medication up to 6 months prior to questionnaires*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Partial	*PCOS status not evaluated in controls*
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes	
Was there sufficient duration of follow-up for outcomes to occur?		N/A	*Not relevant for cross-sectional study*
Was matching performed?		No	
Summary Result/s		*Women with PCOS had a lower prevalence of disordered eating based on elevated EDE-Q scores (cut-off ≥4) (7.2% vs. 13.0%; P=0.002). There were no differences in prevalence of all eating disorders (62% vs. 56%; P=0.076), bulimia nervosa or binge eating disorder. Controls had a higher prevalence of anorexia (1.3% vs. 0%; P=0.012).*	
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes	
	Was the case definition adequate and established in a standard, valid and reliable way?	Partial	*Self-report of PCOS status*
	Was the control status established in a standard, valid and reliable way?	Partial	*PCOS status not evaluated in controls*
PERFORMANCE BIAS	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes	
DETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes	

	Were outcome assessors blind to case and control status?	No	*Unlikely to cause bias as standardized questionnaires were used*
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	N/A	*Cross-sectional study*
	What percentage of the individuals were not included in the analysis?	N/A	*All participants included in analysis*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes	
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	No	
	Was the study sufficiently powered to detect any differences between the groups?	Yes	*Yes, for primary outcome*
	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS			
What is the overall risk of bias?		*Moderate*	
Did risk of bias differ by outcome		*No*	

Study ID	*Tay, 2019*
Study Citation	*Tay, C., Teede, H., Hill, B., Loxton, D., Joham, A. (2019). Increased prevalence of eating disorders, low self-esteem, and psychological distress in women with polycystic ovary syndrome: a community-based cohort study. Fertility and Sterility, 2019.*

Study Country		*Australia*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?			
Patient/population/ participants		*Cross-sectional analysis of women with and without PCOS in the Australian Longitudinal Study on Women's Health (ALSWH). Women born between 1989 and 1995 were included by using the data collected in survey 5 (2017)*	
Control population		*No self-report of PCOS*	
PCOS diagnostic criteria		*Self-report on questionnaire: "Have you ever been diagnosed with or treated for PCOS?"*	
N per group		*PCOS: N= 875* *Control: N= 7592*	
Setting		*Australian Longitudinal Study on Women's Health (ALSWH)*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)		*Primary outcomes:* *-Self-reported eating disorders including anorexia (AN) and bulimia (BN). All other EDs (including binge eating disorder) were grouped as "other ED' 'in the survey.* *Unrelated outcomes: Rosenberg Self-Esteem Scale, and Kessler psychological distress scale*	
Does the study have a clearly focused question and/or PICO?		Yes	
Inclusion criteria		Not reported	
Exclusion criteria		Yes	*Women with missing data regarding PCOS and EDs were excluded from our study.*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes	
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes	
Was there sufficient duration of follow-up for outcomes to occur?		N/A	*Not relevant for cross-sectional study*
Was matching performed?		No	
Summary Result/s		*Women with PCOS had a higher prevalence of all eating disorders (11% vs. 7.6%; P< 0.001) but not higher prevalence of AN or BN.*	
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes	
	Was the case definition adequate and established in a standard, valid and reliable way?	Partial	*Self-report*

	Was the control status established in a standard, valid and reliable way?	Partial	*Self-report*
PERFO RMAN	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes	
DETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	No	*Self-report*
	Were outcome assessors blind to case and control status?	No	*Unlikely to cause bias as standardized questionnaires were used*
	Were all outcomes measured in a standard, valid and reliable way?	Partial	*Self-report*
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	N/A	*Cross-sectional study*
	What percentage of the individuals were not included in the analysis?	N/A	*All participants included in analysis*
REP ORT	**Is the paper free of selective outcome reporting?**	Yes	
CO NFO	**Are the cohorts comparable on the basis of design or analysis?**	Yes	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	No	
	Was the study sufficiently powered to detect any differences between the groups?	Yes	*Yes, for primary outcome*
	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome		*No*	

Study ID	*Asdeq et al, 2020*

Study Citation	*Asdaq, S., Jomah, S., Hasa, R., Al-Baroundi, D., Alharbi, M., Alsubaie, S., Buhamad, M., Alyahya, B., Al-Yamani, MM. (2020). Impact of polycystic ovary syndrome on eating behavior, depression, and health related quality of life: A cross-sectional study in Riyadh. Saudi J Biol Sci, 2020.*	
Study Country	*Saudi Arabia*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Cross-sectional study of women with and without PCOS from government tertiary care centers in Riyadh, Saudi Arabia during January to March 2019*	
Control population	*Women presenting for general gynecologic care between 20-54 years*	
PCOS diagnostic criteria	*Rotterdam criteria (2003), selected from women presenting for management of PCOS, recruited by convenient sampling*	
N per group	*PCOS: N= 116* *Control: N= 378*	
Setting	*Tertiary care centers*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcomes:* *Prevalence of binge eating disorder (BED) and depression* *Self-developed questionnaire to assess questions on binge eating* *Depression scale: DASS 21*	
Does the study have a clearly focused question and/or PICO?	Yes	
Inclusion criteria	Yes	
Exclusion criteria	Yes	*Pregnant, postmenopausal, diagnosed with adrenal or pituitary disorders, any time of cancer, severe physical illness or mental handicap*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes	
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes	
Was there sufficient duration of follow-up for outcomes to occur?	N/A	*Not relevant for cross-sectional study*
Was matching performed?	No	
Summary Result/s	*Women with PCOS had a higher prevalence of binge eating disorder (93.1% vs. 82.5%; P=0.005)*	

SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes	
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes	
	Was the control status established in a standard, valid and reliable way?	Yes	
PERFORMANCE BIAS	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes	
DETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Partial	*Self-developed questionnaire that appears to be based on DSM criteria, but this is not specifically detailed*
	Were outcome assessors blind to case and control status?	No	*Unlikely to cause bias as standardized questionnaires were used*
	Were all outcomes measured in a standard, valid and reliable way?	Partial	
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	N/A	*Cross-sectional study*
	What percentage of the individuals were not included in the analysis?	N/A	*All participants included in analysis*
REPORTING BIAS	**Is the paper free of selective outcome reporting?**	Yes	
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	No	
	Was the study sufficiently powered to detect any differences between the groups?	Yes	

If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS		
What is the overall risk of bias?	*Moderate*	
Did risk of bias differ by outcome	*No*	

Study ID	*Lidaka et al, 2022*	
Study Citation	*Lidaka, L., Lazdane, G., Kivite-Urtane, A., Gailite, L., Dzivite-Krisane, I., Stokenberga, I. (2019). Health-related quality of life and binge eating among adolescent girls with PCOS. Clinical and Experimental Obstetrics and Gynecology, 2019.*	
Study Country	*Latvia*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Cross-sectional study of adolescent girls aged 13-18 with and without PCOS recruited from out-patient pediatric gynecology clinic at the Children's Clinical University Hospital, Riga, Latvia between January 1, 2017 and March 30, 2019*	
Control population	*Healthy adolescents who attended the same clinic for non-disease reasons, such as seeking contraception counselling or regular health control.*	
PCOS diagnostic criteria	*2018 ESHRE guidelines*	
N per group	*PCOS: N= 63* *Control: N= 66*	
Setting	*Out-patient pediatric gynecology clinic at the Children's Clinical University Hospital, Riga, Latvia*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcomes: The PCOS health-related quality of life questionnaire (PCOSQ) and Binge Eating Scale (BES) (no or minimal BE (score ≤≤17), mild to moderate BE (score 18–26) and severe BE (score ≥≥27)*	
Does the study have a clearly focused question and/or PICO?	Yes	
Inclusion criteria	Yes	
Exclusion criteria	Yes	*Serious comorbidities (including gynecological and endocrinological) and use of hormonal medication within the previous six months*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes	

Is a cross sectional or case-control study the appropriate design to answer this question?		Yes	
Was there sufficient duration of follow-up for outcomes to occur?		N/A	*Not relevant for cross-sectional study*
Was matching performed?		Yes	*Age*
Summary Result/s		*There were no differences in prevalence of binge eating between women with and without PCOS (37.7% vs. 35.9%; P=0.7)*	
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes	
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes	
	Was the control status established in a standard, valid and reliable way?	Yes	
PERFORMANCE BIAS	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes	
DETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes	
	Were outcome assessors blind to case and control status?	No	*Unlikely to cause bias as standardized questionnaires were used*
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	N/A	*Cross-sectional study*
	What percentage of the individuals were not included in the analysis?	N/A	*All participants included in analysis*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes	

CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	No	
	Was the study sufficiently powered to detect any differences between the groups?	Not reported	*Likely not powered*
	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS			
What is the overall risk of bias?		*Low*	
Did risk of bias differ by outcome		*No*	

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 2

Question 2.5.

In women with PCOS, what is the prevalence and severity of disordered eating?

BACKGROUND:

Diagnosable eating disorders include Anorexia Nervosa (AN); Bulimia Nervosa (BN), Binge-Eating Disorder (BED), Avoidant/Restrictive Food Intake Disorder (ARFID), Pica, Rumination Disorder, Other Specified Feeding or Eating Disorder (OSFED; atypical AN, BN of low frequency and/or duration, BED of low frequency and/or duration, purging disorder, and night eating syndrome), and Unspecified Feeding or Eating Disorders (USFED; symptoms consistent with eating disorders, including the severity of symptoms and distress and impairment, but do not meet the full criteria for any of the eating disorder diagnoses). Higher weight is not considered an eating disorder, but it is associated with increased risk of eating disorders and disordered eating (1, 2).

The 2000-2018 rate of lifetime eating disorders (EDs) worldwide was estimated to be 8.4% in women (3). The prevalence of weighted means (with ranges) for AN in women was 1.4% (0.1-3.6%), BN was 1.9% (0.3-4.6%), BED was 2.8% (0.6-5.8%), and EDNOS was 4.3% (0.6-14.6%) (3). Given the changes in DSM-5 criteria, data on OSFED is limited; however, a relatively recent study estimated OSFEDs had the highest prevalence of all EDs, above AN, BN, and BED, at ~7.4% (4).

Disordered eating refers to eating and weight related symptoms commonly associated with an eating disorder, this can include behavioural (e.g., bingeing, restriction), cognitive (e.g., dietary restraint, negative body image), and emotional (e.g., emotional eating) factors. The prevalence of disordered eating is far higher than the prevalence of eating disorders; many women who do not meet full criteria for an eating disorder experience disordered eating and associated distress. For example, Australian research (5) reports that 7.5% of women surveyed experienced binge eating, 2.1% purging, and 5.2% strict dieting or fasting. Rates are likely to be higher in women with metabolic/endocrine disorders. For example, recent Australian research (n = 2,977; Dias Santana et al., 2019 (6)), that separated participants by the absence versus presence of diabetes, found that 9.3 and 15.2% of women surveyed reported objective binge-eating, 2.5 and 7.1% subjective binge-eating, 6.1 and 6.4% strict dieting or fasting, and 0.8 and 1.7% purging, respectively.

Many women with eating disorders are undiagnosed and unaware that they have an eating disorder. Likewise, many women with disordered eating are unaware that their eating and weight related thoughts and behaviours are unusual, cause distress and/or are modifiable. Effective treatments are available for eating disorders and disordered eating. Therefore, screening, assessment and diagnosis are essential.

Eating disorders can only accurately be diagnosed via a clinical interview (e.g., the Eating Disorders Examination; Fairburn & Beglin, 1994 (7)). Unfortunately, there are no alternate standardized, widely implemented, and validated processes for screening and assessment. The variety of eating disorder diagnosis, and associated symptoms, makes it difficult to identify simple screening and assessment methods that cover all eating disorder diagnosis and symptoms (8). Additionally, the majority of available screening and assessment questionnaires were designed to assess anorexia nervosa and bulimia nervosa and do not adequately assess the full spectrum of eating disorders (e.g., atypical AN, BN of low frequency and/or duration, BED of low frequency and/or duration, purging disorder, and night eating syndrome). This is of concern given these other diagnoses are more common, and this may be particularly so in women with PCOS (because of their risk factors e.g., higher weight).

Women with PCOS are at increased risk of experiencing many of the identified risk factors for eating disorders (9). They are at increased risk of higher weight, depression, anxiety, self-esteem and poor body image. They are also more likely to be highly motivated for weight loss and to be prescribed dietary restriction. Available data suggests that, in women with PCOS, disordered eating is associated with a higher weight (9, 10), anxiety (9), depression (11, 12) and poorer quality of life (9). The presence of an eating disorder or disordered eating is likely to impact on the process and outcome of PCOS treatment and management.

There is a lack of good evidence regarding the prevalence of eating disorders and disordered eating in women with PCOS. In the only study to use a clinical interview (MINI for DSM-IV) to assess eating disorder prevalence in women with PCOS (n=49), Mansson and colleagues (13) reported increased prevalence of any eating disorder (21% vs. 4%) but not bulimia nervosa specifically (12% vs 4%) compared to controls. Of note, the MINI only assesses AN and BN, and this study uses the older DSM-IV diagnostic criteria which included fewer eating disorders and more stringent criteria. Therefore, DSM5 rates are likely to be higher.

A series of meta-analyses examined the prevalence of eating disorders and disordered eating in women with PCOS (determined either via self-report or clinical assessment) compared to controls across 14 studies. The majority of studies were conducted in the USA, Western Europe, and Australia. All but one study (14) examined adults (>18yrs). Of concern, all but one study (13) assessed eating disorders/disordered eating via self-report rather than clinical interview. Older studies reported based on DSM-IV criteria while newer studies used DSM5 criteria. Samples were recruited in a variety of ways including community advertising, large scale surveys, tertiary clinics, and national registries.

Results are summarized below

- Any eating disorder (including bulimia nervosa, binge eating disorder, anorexia nervosa, night eating syndrome) [NOTE: these are the disorders assessed across studies, not all studies examined the prevalence of all these eating disorders]: Increased odds in women with PCOS, for all studies (OR 1.53 (1.29, 1.82); K=10), and in the sub-group of studies with PCOS diagnosis confirmed by the Rotterdam criteria (2.88 (1.55, 5.34);K=6). Rates ranged from 0.5% to 62% for women with PCOS, and 0.3% to 56% for women without PCOS.
- Disordered eating (defined as a score above the cut-off of a validated eating disorder questionnaire): No increased odds of disordered eating in women with PCOS, for all studies (OR 1.77 (0.63, 4.91); K=6), or in the sub-group of studies with PCOS diagnosis confirmed by the Rotterdam criteria (2.21 (0.87, 5.59); K=4). Rates ranged from 0% to 36% for women with PCOS, and 0% to 31% for women without PCOS. Rates of disordered eating symptoms (e.g., binge eating, purging, fasting) in the absence of an eating disorder were not reported.
- Bulimia nervosa: No increased odds of bulimia nervosa in women with PCOS, for all studies (OR 1.34 (1.17, 1.54); K=6), or in the sub-group of studies with PCOS diagnosis confirmed by the Rotterdam criteria (1.56 (0.56, 4.36); K=3). Rates ranged from 0.7% to 12% in women with PCOS, and 0.6% to 6% in women without PCOS.
- Binge eating disorder: Increased odds in women with PCOS, for all studies (OR 2.09 (1.18, 3.72); K=5), and in the sub-group of studies with PCOS diagnosis confirmed by the Rotterdam criteria (2.70 (1.47, 5.97); K=3). Rates ranged from 0% to 93.1% in women with PCOS, and 0% to 83% in women without PCOS.
- Anorexia nervosa: No increased odds of anorexia nervosa in women with PCOS, for all studies (OR 0.94 (0.60, 1.28); K=4). Rates ranged from 0% to 93.1% in women with PCOS, and 0% to 83% in women without PCOS.
- Prevalence rates were not reported for other feeding and eating disorders.

The one study (14) assessing eating disorders and disordered eating in adolescents did not report higher odds of any eating disorder or of binge eating disorder (this study did not assess/report disordered eating, bulimia nervosa, or anorexia nervosa) in adolescents with PCOS. In women with PCOS it is not known whether: the prevalence of eating disorders or disordered eating changes over time; ethnic and cultural impacts on PCOS prevalence and severity; or PCOS treatments impact on the prevalence of eating disorders or disordered eating.

The importance of screening for eating disorders and disordered eating is noted in the previous International Evidence-based Guideline for the assessment and management of polycystic ovary syndrome (PCOS). Screening is also recommended for women with PCOS and/or PCOS symptoms in a number of eating disorder guidelines. For example, the Australian National Eating Disorders Collaboration list women with PCOS as one of the high-risk groups who may benefit from screening (https://nedc.com.au/eating-disorders/eating-disorders-explained/the-facts/eating-disorders-in-australia/). Likewise, the National Institute for Health and Care Excellence Guidelines for Eating Disorders: Recognition and Treatment (www.nice.org.uk/guidance/indevelopment/gid-cgwave0703/documents) suggest that clinicians think about the possibility of an eating disorder in individuals with a range of symptoms relevant to PCOS. The *Management of Eating Disorders for People with Higher Weight: Clinical Practice Guidelines* (15) provide guidance regarding assessment of eating disorders and disordered eating in people with higher weight.

GRADE EVIDENCE CERTAINTY		
Comparison	**GRADE for critical outcomes**	
Comparison 1. PCOS versus Controls	o Outcome 1. Any eating disorders	⊕⊕⊕◯ Moderate
	o Outcome 2. Disordered eating	⊕⊕◯◯ Low
	o Outcome 3. Bulimia nervosa	⊕◯◯◯ Very Low
	o Outcome 4. Binge eating disorder	⊕⊕◯◯ Low
	o Outcome 5. Anorexia nervosa	⊕⊕⊕◯ Moderate

Evidence to Recommendations Framework

COMPARISONS (option versus other option)

Eating disorders and disordered eating in women with PCOS vs control

EVIDENCE-BASED RECOMMENDATION(S)

EBR: Eating disorders and disordered eating should be considered in PCOS, regardless of BMI and especially in the context of weight management and lifestyle interventions. (see 2.4 and 3.6).

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

PRACTICE POINT(S)

- If disordered eating or eating disorders are suspected, appropriately qualified practitioners should further assess via a full diagnostic interview.
- If an eating disorder or disordered eating is detected, appropriate management and support should be offered.

GRADE CONSIDERATIONS

Justifications:

- Based on the meta-analyses conducted for this study, there were increased odds of women with PCOS experiencing any eating disorder (all studies (OR 1.53 (1.29, 1.82); K=10); confirmed by the Rotterdam criteria (2.88 (1.55, 5.34);K=6)) and binge eating disorder (all studies OR 2.09 (1.18, 3.72); K=5; confirmed by the Rotterdam criteria (2.70 (1.47, 5.97);K=3)), but not bulimia nervosa, anorexia nervosa or disordered eating.
- Ten studies had a moderate risk of bias. Studies were conducted in Australia, Saudi Arabia, Sweden and the USA. Only one study (14) restricted inclusion to adolescents. No studies evaluated risk of any eating disorder based on ethnicity or phenotype.
- Eating disorders can only be diagnosed via clinical interview. In the only study to use a clinical interview (MINI for DSM-IV) to assess eating disorder prevalence in women with PCOS (n=49), Mansson and colleagues (13) reported increased prevalence of any eating disorder (21% vs 4%) but not bulimia nervosa specifically (12% vs 4%) compared to controls. Of note, the MINI only assesses AN and BN, and this study uses the older DSM-IV diagnostic criteria.
- These studies did not assess all eating disorders (Avoidant/Restrictive Food Intake Disorder (ARFID), Pica, Rumination Disorder, Other Specified Feeding or Eating Disorder (OSFED; atypical AN, BN of low frequency and/or duration, BED of low frequency and/or duration, purging disorder, and night eating syndrome), and Unspecified Feeding or Eating Disorders (USFED; symptoms consistent with eating disorders, including the severity of symptoms and distress and impairment, but do not meet the full criteria for any of the eating disorder diagnoses)
- Women with PCOS are at increased risk of experiencing many of the identified risk factors for eating disorders (16, 17). They are at increased risk of higher weight, depression, anxiety, self-esteem and poor body image. They are also more likely to be highly motivated for weight loss and to be prescribed dietary restriction. Potential endocrine mechanisms have also been proposed (18). Available data suggests that, in women with PCOS, disordered eating is associated with a higher weight (9, 10), anxiety (9), depression (11, 12) and poorer quality of life (9).

Subgroup considerations:

The following subgroups needs to be considered (but are not considered in existing research)

- Adult/Adolescent (only one study considered adolescents)
- Cultural and ethnic subgroups

Implementation considerations:

Respectful and empathic communication is required when discussing these sensitive issues.
The cultural identity and preferred language of a woman are also important considerations. Be aware of possible variations in presentation of eating disorders and disordered eating and conduct screening in a culturally sensitive manner.
Screening may have resource implications such as an impact on length of consultation.
If eating disorders or disordered eating are detected, intervention may require referral to other health practitioners. Additional time with the patient may also be required to complete an appropriate care plan.
Access to appropriately trained and experienced health professionals will be required.

Translation tools should include:

- The following two questions may be helpful in screening
    - Does your weight affect the way you feel about yourself?
    - Are you satisfied with your eating patterns?
- The EDE-Q may be a helpful assessment tool

Monitoring and evaluation considerations:

Ongoing monitoring of eating disorders and disordered eating should be considered particularly in response to significant changes in weight, eating, exercise and/or body image or with lifestyle intervention.

Research priorities:
Prevalence of eating disorder/disordered eating in women with PCOS, including different subgroups (e.g., adolescents, ethnicity/culture), using a structured clinical interview (e.g., EDE, EDA5) and considering all types of eating disorders.
Validating existing screening and assessment tools in women with PCOS, including diverse groups, and adapting tools specifically for women with PCOS.
Examination of the impact of eating disorders/disordered eating on the process and outcome of PCOS treatment and management, and the impact of PCOS treatment and management on eating disorders/disordered eating.
Examination of the effectiveness of treatment for eating disorders/disordered eating in women with PCOS, including the impact this has on the process and outcome of PCOS treatment and management.

GRADE framework

GRADE DECIDE **Interactive Evidence to Decision Framework**

● DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:
See Part 1- Evidence Summary and GRADE document.

Panel discussion:

● CERTAINTY OF THE EVIDENCE

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☐ Very low	☒ Low	☐ Moderate	☐ High

Research evidence:
See Part 1- Evidence Summary and GRADE document.

Panel discussion:
Evidence is limited but clinical significance is important.

● UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:
See Part 1- Evidence Summary and GRADE document.

Panel discussion:
Screening, assessment and diagnosis of eating disorders, disordered treatment can temporarily elevate distress. This may be particularly problematic if treatment options are not available.

Screening, assessment and diagnosis is essential for identification, referral and treatment. Access and engagement to effective treatment is likely to result in improved outcomes in terms of eating disorders/disordered eating specifically and wellbeing more generally.
Failing to detect and treat eating disorders/disordered eating leaves the individual experiencing negative consequences. It may also negatively impact on the process and outcome of PCOS treatment and management.

● VALUES

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☐ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☐ Probably no important uncertainty or variability	☒ No important uncertainty or variability

Research evidence:
No research evidence was identified

Panel discussion:

● BALANCE OF EFFECTS

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☒ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:

● COSTS

How large are the resource requirements (costs)?

Judgement:

☐ Don't know	☐ Varies	☐ Large costs	☐ Moderate costs	☒ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:
No research evidence was identified

Panel discussion:
The costs of clinical interviews for diagnosis would be considerable given the time taken to conduct these interviews, and the clinical expertise required of the interviewer.
If eating disorders/disordered eating interventions are required costs for would be considerable, however there is evidence that eating disorders/disordered eating treatment is cost-effective in the general population. Treatment costs can be reduced via use of a stepped care approach.

● CERTAINTY OF COST EVIDENCE

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:
No research evidence was identified

Panel discussion:

● COST-EFFECTIVENESS

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:
No research evidence was identified

Panel discussion:
See above in cost.

● EQUITY

What would be the impact on health equity?

Judgement:

☐ Don't know	☒ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☐ Probably increased	☐ Increased

Research evidence:
No research evidence was identified

Panel discussion:
Some settings may not have the resources/capability to screen, assess, diagnose and/or treat eating disorders/disordered eating**.**

● ACCEPTABILITY

Is the option acceptable to key stakeholders?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

Research evidence:
No research evidence was identified

Panel discussion:
Respectful and empathic communication is required when discussing these sensitive issues.
Health professionals and women may have some sensitivity around screening, assessment, diagnosis and/or treatment of eating disorders/disordered eating.
Some of the recommendations for eating disorder/disordered eating treatment are inconsistent with restrictive dieting/weight loss commonly prescribed in women with PCOS.

● FEASIBILITY

Is the option feasible to implement?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

Research evidence:
No research evidence was identified

Panel discussion:

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PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by the Evidence Team (Jillian Tay, Aya Mousa)
Other Members: Tania Burgert, Loyal Pattuwage

GDG 2

Question 2.6.1.

What are the information, resource and education needs of women, adolescents, CALD groups and healthcare providers regarding PCOS?

1. STUDY SELECTION

Table 1. PICO Criteria for Inclusion	
Question	**2.6.1. What are the information, resource and education needs of women, adolescents, CALD groups and healthcare providers regarding PCOS?**
Clinical leads (key contacts)	**Tania Burgert, Jacky Boivin**
Allocation ranking	**Level 1 – New systematic review**

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(language, year)*
Inclusion	Women with PCOS (any definition) Subgroups: • Adolescents • Phenotypes • Ethnicity • Geographical and any healthcare provider who identify themselves as working with PCOS (e.g. Dietitians, physiotherapists, psychologists) etc.	Various sources of information Women with PCOS: (from family/peers health professions/internet/app/support groups/social media (FB, Instagram, tiktok/twitter), decision-support tools (e.g. question prompt lists) mainstream media (news, newspaper, magazine, TV, documentaries) Health professionals: (textbook, society, conferences, guidelines, care plans. algorithms, websites, apps, translation activities particularly associated with last guideline) medical education/training programmes	None, usual care, or others	Information or resource needs, knowledge gaps (by reproductive/metabolic/hormonal/psychologic/dermatological outcomes, by life stages, by gender identity, by cultural/ethnic background, by professional specialty) Include satisfaction, dissatisfaction, what they feel most important,	Quantitative observational studies, systematic reviews evidence based guidelines Qualitative studies.	English language
Exclusion	Females without diagnosed PCOS.		Not applicable	Not applicable	Non-evidence-based guidelines. Abstracts, protocol, clinical trial registration. Comparative intervention studies, clinical trials	

2. SEARCH STRATEGY

rch details	
Search strategy source: Not applicable	
Evidence source	**Date of search**
Medline (Ovid)	13/09/2022
PsychInfo (Ovid)	13/09/2022
EMBASE	13/09/2022
All EBM (Ovid)	13/09/2022
CINAHL	13/09/2022
Any subsequent updates - enter database and date: not applicable	

estions addressed by this search:		
GDG	Q#	Question
2	2.6.1	What are the information, resource and education needs of women, adolescents, CALD groups and healthcare providers regarding PCOS?
2	2.6.4	What are the key challenges for those with PCOS when interacting with healthcare professionals about polycystic ovary syndrome and related features?

OVID Medline, EMBASE		APA PsychInfo	
1	exp polycystic ovary syndrome/	1	exp Endocrine Sexual Disorders/
2	polycystic ovar*.mp.	2	polycystic ovar*.mp.
3	poly-cystic ovar*.mp.	3	poly-cystic ovar*.mp.
4	PCO*.mp.	4	PCO*.mp.
5	(stein-leventhal or leventhal).mp.	5	(stein-leventhal or leventhal).mp.
6	anovulation/	6	anovulation/
7	anovulat*.mp.	7	anovulat*.mp.
8	oligo-ovulat*.mp.	8	oligo-ovulat*.mp.
9	oligoovulat*.mp.	9	oligoovulat*.mp.
10	(ovar* adj5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*)).mp.	10	(ovar* adj5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*)).mp.
11	or/1-10	11	or/1-10
12	exp Allied Health Personnel/	12	exp Allied Health Personnel/
13	exp Physicians/	13	exp Physicians/
14	Doctor$2.tw.	14	Doctor$2.tw.
15	physician$2.tw.	15	physician$2.tw.
16	nurse$2.tw.	16	nurse$2.tw.
17	clinician$2.tw.	17	clinician$2.tw.
18	dietitian$2.tw.	18	dietitian$2.tw.
19	medical care provider$1.tw.	19	medical care provider$1.tw.
20	medical-care professional$1.tw.	20	medical-care professional$1.tw.
21	medical professional$1.tw.	21	medical professional$1.tw.
22	(medical adj1 worker$1).tw.	22	(medical adj1 worker$1).tw.
23	"health care provider$1".tw.	23	"health care provider$1".tw.
24	health-care provider$1.tw.	24	health-care provider$1.tw.
25	healthcare provider$1.tw.	25	healthcare provider$1.tw. 8106
26	"health care professional$2".tw.	26	"health care professional$2".tw.
27	healthcare professional$2.tw.	27	healthcare professional$2.tw.
28	health-care professional$2.tw.	28	health-care professional$2.tw.
29	exp Health Personnel/	29	exp Health Personnel/
30	(("health care" or health-care or healthcare) adj worker$1).tw.	30	(("health care" or health-care or healthcare) adj worker$1).tw.
31	health-worker$1.tw.	31	health-worker$1.tw.
32	healthworker$1.tw.	32	healthworker$1.tw.
33	"health worker$1".tw.	33	"health worker$1".tw.
34	"Obstetrician-Gynecologist$1".tw.	34	"Obstetrician-Gynecologist$1".tw.
35	gynaecologist$2.tw.	35	gynaecologist$2.tw.

36	(midwife or midwives).tw.
37	obstetrician$2.tw.
38	nutritionist$2.tw.
39	general practitioner$2.tw.
40	pharmacologist$1.tw.
41	GP$1.ab.
42	family physician$2.tw.
43	(primary care adj provider$2).tw.
44	(health care adj provider$2).tw.
45	psychologist$2.tw.
46	psychiatrist$2.tw.
47	obstetri* specialist$1.tw.
48	(gynecolog* specialist$1 or gyneacolog* specialist$1).tw.
49	medical specialist$1.tw.
50	endocrine specialist$1.tw.
51	endocrinologist$2.tw.
52	nurse practitioner$2.tw.
53	health personnel.tw.
54	(mental health adj (practitioner$1 or clini* or specialist$1)).tw.
55	or/12-54
56	exp Patients/
57	exp Inpatients/
58	exp Outpatients/
59	exp Female/
60	(consumer* or patient*).tw.
61	exp Adolescent/ or exp Culture/
62	"Ethnic and Racial Minorities"/
63	or/56-62
64	health literacy.tw.
65	health promotion.tw.
66	(Health seeking behaviour or Health seeking behavior).tw.
67	(Information seeking behaviour or Information seeking behavior or Information-seeking behaviour or Information-seeking behavior).tw.
68	Continuing education.tw.
69	Medical education.tw.
70	Professional education.tw.
71	Nursing education.tw.
72	Consumer health information.tw.
73	Information provision.tw.
74	exp Health Literacy/
75	exp Health Promotion/
76	exp Health Knowledge, Attitudes, Practice/ or exp "Patient Acceptance of Health Care"/
77	exp Information Seeking Behavior/
78	exp Consumer Health Information/ or exp Information Services/ or exp Patient Education as Topic/
79	(knowledge adj1 gap).tw.
80	(resource or resources).tw.
81	*Education, Medical/
82	exp Health Education/
83	exp Consumer Health Information/
84	exp Patient Education as Topic/
85	exp Sex Education/
86	*Needs Assessment/

36	(midwife or midwives).tw.
37	obstetrician$2.tw.
38	nutritionist$2.tw.
39	general practitioner$2.tw.
40	pharmacologist$1.tw.
41	GP$1.ab.
42	family physician$2.tw.
43	(primary care adj provider$2).tw.
44	(health care adj provider$2).tw.
45	psychologist$2.tw.
46	psychiatrist$2.tw.
47	obstetri* specialist$1.tw.
48	(gynecolog* specialist$1 or gyneacolog* specialist$1).tw.
49	medical specialist$1.tw.
50	endocrine specialist$1.tw.
51	endocrinologist$2.tw.
52	nurse practitioner$2.tw.
53	health personnel.tw.
54	(mental health adj (practitioner$1 or clini* or specialist$1)).tw.
55	or/12-54
56	exp Patients/
57	exp Hospitalized Patients/
58	exp Outpatients/
59	exp Human Females/
60	(consumer* or patient*).tw.
61	exp Adolescent Attitudes/ or exp Adolescent Health/
62	exp "Racial and Ethnic Differences"/ or exp Cultural Diversity/ or exp Multicultural Education/ or exp Cultural Sensitivity/ or exp "Racial and Ethnic Groups"/
63	or/56-62
64	health literacy.tw.
65	health promotion.tw.
66	(Health seeking behaviour or Health seeking behavior).tw.
67	(Information seeking behaviour or Information seeking behavior or Information-seeking behaviour or Information-seeking behavior).tw.
68	Continuing education.tw.
69	Medical education.tw.
70	Professional education.tw.
71	Nursing education.tw.
72	Consumer health information.tw.
73	Information provision.tw.
74	exp Health Literacy/
75	exp Health Promotion/
76	exp Consumer Health Information/ or exp Information Services/ or exp Patient Education as Topic/
77	(knowledge adj1 gap).tw.
78	(resource or resources).tw.
79	exp Medical Education/
80	exp Health Knowledge/ or exp Health Information/ or exp Information Seeking/ or

87 exp Attitude to Health/ 88 *Communication Barriers/ 89 *Informed Consent/ 90 *Truth Disclosure/ 91 *Health Communication/ 92 *Information Literacy/ 93 *Choice Behavior/ 94 *Decision Making/ or exp Decision Support Systems, Management/ or exp Decision Support Techniques/ or exp Decision Making/ 95 exp Professional-Patient Relations/ 147652 96 communications media/ or library materials/ or teaching materials/ or telecommunications/ or electronic mail/ or telemedicine/ or remote consultation/ or telephone/ or answering services/ or exp cellular phone/ or television/ 97 computers/ or exp Microcomputers/ or Minicomputers/ or exp Internet/ or electronic mail/ or video games/ 98 exp Social Media/ or exp Self-Help Groups/ or exp Decision Support Techniques/ or exp Algorithms/ or exp Decision Support Systems, Management/ or exp Decision Support Systems, Clinical/ or *Internet/ or *Mass Media/ or *Patient Care Planning/ or *Managed Care Programs/ or exp Practice Guideline/ or *Books/ or exp Textbooks as Topic/ or exp Internet/ 99 or/64-98 100 (perspective$1 or opinion$1 or perception or view$1 or viewpoint$1 or experience$1 or satisfaction or attitude$1 or preference$1 or expectation$1 or engagement or dissatisfaction or collaborat* or communicat* or cooperat* or relation* or interact* or challeng*).tw. 101 *Patient Satisfaction/ or *Patient Preference/ 102 100 or 101 103 55 or 63 14503199 104 11 and 99 and 103 105 11 and 55 and 102 106 104 or 105 107 limit 106 to (english language and humans and yr="1990 -Current")	exp Health Education/ or exp Communication/ 81 exp Sex Education/ 82 *Needs Assessment/ 83 *Communication Barriers/ 84 *Informed Consent/ 85 exp Professional Consultation/ 86 exp Health Promotion/ or exp Health Literacy/ or exp Health Information/ or exp Health Education/ 87 *Information Literacy/ 88 *Choice Behavior/ 89 *Decision Making/ or exp Decision Support Systems, Management/ or exp Decision Support Techniques/ or exp Decision Making/ 90 communications media/ or library materials/ or teaching materials/ or telecommunications/ or electronic mail/ or telemedicine/ or remote consultation/ or telephone/ or answering services/ or exp cellular phone/ or television/ 91 computers/ or exp Microcomputers/ or Minicomputers/ or exp Internet/ or electronic mail/ or video games/ 92 exp Social Media/ or exp Self-Help Groups/ or exp Decision Support Techniques/ or exp Algorithms/ or exp Decision Support Systems, Management/ or exp Decision Support Systems, Clinical/ or *Internet/ or *Mass Media/ or *Patient Care Planning/ or *Managed Care Programs/ or exp Practice Guideline/ or *Books/ or exp Textbooks as Topic/ or exp Internet/ 87706 93 (perspective$1 or opinion$1 or perception or view$1 or viewpoint$1 or experience$1 or satisfaction or attitude$1 or preference$1 or expectation$1 or engagement or dissatisfaction or collaborat* or communicat* or cooperat* or relation* or interact* or challeng*).tw. 94 *Patient Satisfaction/ or *Patient Preference/ 95 55 or 63 96 93 or 94 97 11 and 55 and 96 98 or/64-92 99 55 or 63 100 11 and 98 and 99 101 97 or 100 102 limit 101 to (human and english language and yr="1990 -Current")
All EBM	**CINAHL**
1 exp polycystic ovary syndrome/ 2 polycystic ovar*.mp. 3 poly-cystic ovar*.mp. 4 PCO*.mp. 5 (stein-leventhal or leventhal).mp. 6 anovulation/ 7 anovulat*.mp.	S1 (MM "Polycystic Ovary Syndrome") S2 TX polycystic ovar* S3 TX poly-cystic ovar* S4 TX PCO* S5 TX (stein-leventhal or leventhal) S6 (MM "Anovulation") S7 TX anovulat*

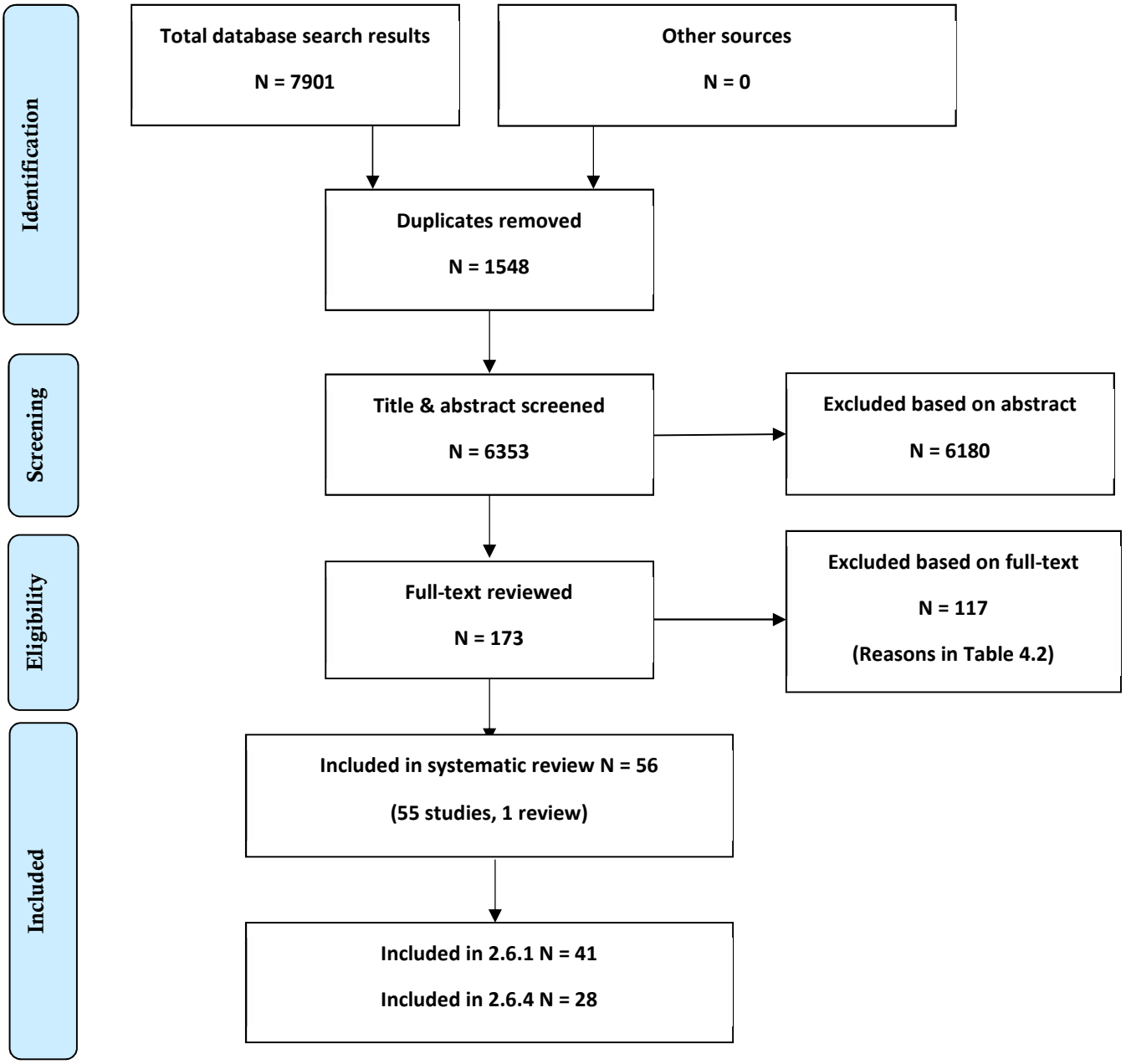
8	oligo-ovulat*.mp.	S8 TX oligo-ovulat*
9	oligoovulat*.mp.	S9 TX oligoovulat*
10	(ovar* adj5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*)).mp.	S10 TX (ovar* N5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*))
11	or/1-10	S11 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10
12	exp Allied Health Personnel/	S12 (MH "Allied Health Personnel+")
13	exp Physicians/	S13 (MH "Physicians+")
14	Doctor$2.tw.	S14 TI (doctor* OR physician* OR nurse* OR clinician* OR dietitian* OR medical care provider* OR medical-care professional* OR medical professional* OR health care provider* OR healthcare provider* OR healthcare professiona;* OT health care professional* OR health-worker* OR healthworker* OR health worker) OR AB (doctor* OR physician* OR nurse* OR clinician* OR dietitian* OR medical care provider* OR medical-care professional* OR medical professional* OR health care provider* OR healthcare provider* OR healthcare professiona;* OT health care professional* OR health-worker* OR healthworker* OR health worker)
15	physician$2.tw.	
16	nurse$2.tw.	
17	clinician$2.tw.	
18	dietitian$2.tw.	
19	medical care provider$1.tw.	
20	medical-care professional$1.tw.	
21	medical professional$1.tw.	
22	(medical adj1 worker$1).tw.	
23	"health care provider$1".tw.	
24	health-care provider$1.tw.	
25	healthcare provider$1.tw.	
26	"health care professional$2".tw.	
27	healthcare professional$2.tw.	
28	health-care professional$2.tw.	
29	exp Health Personnel/	S15 TI (Obstetrician-Gynecologist* OR gynaecologist* OR psychiatrist* midwife OR midwives OR obstetrician* OR nutritionist* OR general practitioner* OR pharmacologist* OR family physician* OR psychologist* OR psychiatrist*) OR AB (Obstetrician-Gynecologist* OR gynaecologist* OR psychiatrist* midwife OR midwives OR obstetrician* OR nutritionist* OR general practitioner* OR pharmacologist* OR family physician* OR psychologist* OR psychiatrist*)
30	(("health care" or health-care or healthcare) adj worker$1).tw. 2647	
31	health-worker$1.tw.	
32	healthworker$1.tw.	
33	"health worker$1".tw.	
34	"Obstetrician-Gynecologist$1".tw.	
35	gynaecologist$2.tw.	
36	(midwife or midwives).tw.	
37	obstetrician$2.tw.	
38	nutritionist$2.tw.	
39	general practitioner$2.tw.	
40	pharmacologist$1.tw.	
41	GP$1.ab.	S16 TI (medical specialist* OR endocrine specialist* OR endocrinologist* OR nurse practitioner* OR health personnel) OR AB (medical specialist* OR endocrine specialist* OR endocrinologist* OR nurse practitioner* OR health personnel)
42	family physician$2.tw.	
43	(primary care adj provider$2).tw.	
44	(health care adj provider$2).tw.	
45	psychologist$2.tw.	
46	psychiatrist$2.tw.	
47	obstetri* specialist$1.tw.	
48	(gynecolog* specialist$1 or gyneacolog* specialist$1).tw.	S17 TX ((("health care" or health-care or healthcare) N2 worker*)
49	medical specialist$1.tw.	S18 TI ((gynecolog* specialist* or gyneacolog* specialist*)) OR AB ((gynecolog* specialist* or gyneacolog* specialist*))
50	endocrine specialist$1.tw.	
51	endocrinologist$2.tw.	
52	nurse practitioner$2.tw.	
53	health personnel.tw.	S19 TX (mental health N2 (practitioner* or clini* or specialist*))
54	(mental health adj (practitioner$1 or clini* or specialist$1)).tw.	
55	or/12-54	S20 S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19
56	exp Patients/	S21 TI ((perspective* or opinion* or perception or view* or viewpoint* or experience* or satisfaction or attitude* or preference* or expectation* or engagement or dissatisfaction or collaborat* or communicat* or cooperat* or relation* or interact* or challeng*)) OR AB ((perspective* or opinion* or perception or view* or viewpoint* or experience* or satisfaction or attitude* or preference* or expectation* or engagement or dissatisfaction or collaborat* or communicat* or cooperat* or relation* or interact* or challeng*))
57	exp Inpatients/	
58	exp Outpatients/	
59	exp Female/	
60	(consumer* or patient*).tw.	S22 (MH "Patient Satisfaction+")
61	exp Adolescent/ or exp Culture/	S23 (MM "Patient Preference")

62	"Ethnic and Racial Minorities"/	S24 S21 OR S22 OR S23
63	or/56-62	S25 S11 AND S20 AND S24
64	health literacy.tw.	S26 (MH "Patients+")
65	health promotion.tw.	S27 (MM "Female")
66	(Health seeking behaviour or Health seeking behavior).tw.	S28 TI (consumer* or patient*) OR AB (consumer* or patient*)
67	(Information seeking behaviour or Information seeking behavior or Information-seeking behaviour or Information-seeking behavior).tw.	S29 TI (female or women or woman or females) OR AB (female or women or woman or females)
68	Continuing education.tw.	S30 (MH "Adolescence+")
69	Medical education.tw.	S31 (MM "Adolescent Health")
70	Professional education.tw.	S32 (MM "Minority Groups") OR (MH "Sexual and Gender Minorities+") OR (MH "Ethnic Groups+") OR "Ethnic and Racial Minorities"
71	Nursing education.tw.	S33 (MM "Cultural Diversity")
72	Consumer health information.tw.	S34 S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33
73	Information provision.tw.	S35 S20 OR S34
74	exp Health Literacy/	S36 TI health literacy OR AB health literacy OR TI health promotion OR AB health promotion OR TI ((Health seeking behaviour or Health seeking behavior)) OR AB ((Health seeking behaviour or Health seeking behavior))
75	exp Health Promotion/	S37 TI ((Information seeking behaviour or Information seeking behavior or Information-seeking behaviour or Information-seeking behavior)) OR AB ((Information seeking behaviour or Information seeking behavior or Information-seeking behaviour or Information-seeking behavior)) OR TI continuing education OR AB Continuing education OR TI Medical education OR AB Medical education OR TI Professional education OR AB Professional education OR TI Nursing education OR AB Nursing education OR TI Consumer health information OR AB Consumer health information
76	exp Health Knowledge, Attitudes, Practice/ or exp "Patient Acceptance of Health Care"/	
77	exp Information Seeking Behavior/	
78	exp Consumer Health Information/ or exp Information Services/ or exp Patient Education as Topic/	
79	(knowledge adj1 gap).tw.	
80	(resource or resources).tw.	
81	exp Health Education/	
82	exp Consumer Health Information/	
83	exp Patient Education as Topic/	
84	exp Sex Education/	
85	exp Attitude to Health/	
86	*Decision Making/ or exp Decision Support Systems, Management/ or exp Decision Support Techniques/ or exp Decision Making/	
87	exp Professional-Patient Relations/	
88	communications media/ or library materials/ or teaching materials/ or telecommunications/ or electronic mail/ or telemedicine/ or remote consultation/ or telephone/ or answering services/ or exp cellular phone/ or television/	
89	computers/ or exp Microcomputers/ or Minicomputers/ or exp Internet/ or electronic mail/ or video games/	
90	exp Social Media/ or exp Self-Help Groups/ or exp Decision Support Techniques/ or exp Algorithms/ or exp Decision Support Systems, Management/ or exp Decision Support Systems, Clinical/ or *Internet/ or *Mass Media/ or *Patient Care Planning/ or *Managed Care Programs/ or exp Practice Guideline/ or *Books/ or exp Textbooks as Topic/ or exp Internet/	S43 (MH "Patient Education+") OR (MM "Patient Discharge Education") OR (MH "Patient Education (Iowa NIC)+")
91	(perspective$1 or opinion$1 or perception or view$1 or viewpoint$1 or experience$1 or satisfaction or attitude$1 or preference$1 or expectation$1 or engagement or dissatisfaction or collaborat* or communicat* or cooperat* or relation* or interact* or challeng*).tw.	S44 TI knowledge N2 gap OR AB knowledge N2 gap
92	55 or 63	S45 (MH "Communication Barriers+")
93	11 and 55 and 91 43294 or/64-90	S46 (MH "Information Literacy+")
95	11 and 92 and 94	S47 (MH "Communications Media+")
		S48 (MH "Social Media+")
		S49 (MH "Internet+")
		S50 (MM "Decision Support Systems, Clinical") OR (MH "Decision Support Techniques+")
		S51 TI (communications media or library materials or teaching materials or telecommunications or electronic mail or telemedicine or remote consultation or telephone or answering services or television) OR AB (communications media or library materials or teaching materials or telecommunications or electronic mail or

96	93 or 95	telemedicine or remote consultation or telephone or answering services or television)
97	limit 96 to english language	S52 TI (Social Media or Self-Help Groups or Decision Support Techniques or Algorithms or Decision Support Systems or Internet or Mass Media or Patient Care Planning or Managed Care Programs or Practice Guideline* or Books or Textbooks) OR AB (Social Media or Self-Help Groups or Decision Support Techniques or Algorithms or Decision Support Systems or Internet or Mass Media or Patient Care Planning or Managed Care Programs or Practice Guideline* or Books or Textbooks)
98	limit 97 to yr="1990 -Current"	S53 S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52
99	limit 98 to humans	S54 S11 AND S35 AND S53
		S55 S25 OR S54
		S56 S25 OR S54 Limiters - Publication Year: 1990-2022; English Language; Human

Evidence processing: The search was performed for both topic 2.6.1 and 2.6.4. Studies were selected and appraised by two reviewers in consultation with the evidence team/ key contact using study selection and appraisal criteria (PICO above) established a priori. The articles were reviewed by title and abstract by two reviewers. When a decision could not be made based on title and abstract alone, full text was retrieved. In total, 54 studies met inclusion criteria for both 2.6.1 and 2.6.4. **41 studies met inclusion criteria for the review of 2.6.1.**

3. SEARCH RESULTS - PRISMA flowchart



4. STUDY INCLUSION

Included studies

Studies related to health professionals

1. Alzamil H, Aloraini K, AlAgeel R, Ghanim A, Alsaaran R, Alsomali N, Albahlal R, Alnuaim L. Disparity among Endocrinologists and Gynaecologists in the Diagnosis of Polycystic Ovarian Syndrome. Sultan Qaboos Univ Med J. 2020 Aug;20(3):e323-e329. doi: 10.18295/squmj.2020.20.03.012. Epub 2020 Oct 5. PMID: 33110648; PMCID: PMC7574802.
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Studies related to women with PCOS

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Table 4.2 Excluded studies (on full text assessment)

#	Title	Study	Journal	Vol	Issue	Pages	Notes
1	**Awareness of polycystic ovary disease among college students**	Sharwini 2019	Drug Invention Today		9	2063-2065	Wrong population
2	**An appraisal on the knowledge status of polycystic ovarian syndrome (PCOS)-Role and impact of clinical pharmacist to create awareness in their lifestyle by sophisticated patient counselling techniques - A community based study**	Muchukota 2020	International Journal of Pharmaceutical Research	12(2)		648-659	No full text
3	**The importance of collaboration in treating chronic disease: a focus on PCOS and group medical visits**	Moore 2011	Women's Health Care: A Practical Journal for Nurse Practitioners	10	9	10-18	No full text
4	**Knowledge, attitude and practices about poly-cystic ovary syndrome (Pcos) in Pakistan**	Qadir 2021	Endocrine Practice	27 (12 SUPPL)		S45	Abstract
5	**Women's perceptions of polycystic ovary syndrome following participation in a clinical research study: implications for knowledge, feelings, and daily health practices**	Colwell 2010	Journal of Obstetrics & Gynaecology Canada: JOGC	32	5	453-459	Wrong intervention
6	**Knowledge and attitudes towards polycystic ovary syndrome**	Jaber 2022	African Journal of Reproductive Health	26	1	92-102	Wrong population
7	**Attitudes Towards Transgender People Among Cisgender Women Who use Vaginismus and PCOS-related Online Forums**	Adams 2022	Journal of Sexual Medicine	19 (8 Supp 3)		S20-S21	Wrong outcomes
8	**Are patients with PCOS appropriately screened for associated CO morbidities?**	Dongerkery 2018	Endocrine Reviews. Conference: 100th Annual Meeting of the Endocrine Society, ENDO	39 (2 Supp 1)			Abstract
9	**Awareness and opinion about polycystic ovarian syndrome (PCOS) among young women: a developing country perspective**	Jena 2020	International Journal of Adolescent Medicine & Health	33	3	123-126	Wrong population
10	**Effect of structured awareness programme on polycystic ovarian syndrome (PCOS) among adolescent girls**	VeenaKirthika 2019	Research Journal of Pharmacy and Technology	12(12)		6097-6100	Wrong population
11	**It's not just physical: The adverse psychosocial effects of polycystic ovary syndrome in adolescents**	Lee 2015	Women's Healthcare: A Clinical Journal for NPs	3	1	20-27	Wrong study design

12	**Health-related knowledge, beliefs and self-efficacy in women with polycystic ovary syndrome**	Lin 2018	Human Reproduction	33	1	91-100	Wrong comparator
13	**Barriers and facilitators to the implementation of lifestyle management in polycystic ovary syndrome: Endocrinologists' and obstetricians and gynaecologists' perspectives**	Chhour 2022	Patient Education & Counseling	105	7	2292-2298	Wrong outcomes
14	**Preventive online and offline health management intervention in polycystic ovary syndrome**	Liu 2022	World Journal of Clinical Cases	10(10)		3060-3068	Wrong intervention
15	**Assessing self-efficacy and self-help methods in women with and without polycystic ovary syndrome**	Kozica 2013	Behavioral Medicine	39(3)		90-96	Wrong study design
16	**Health-related behaviors in women with lifestyle-related diseases**	Kozica 2012	Behavioral Medicine	38	3	65-73	Wrong study design
17	**199. Design of a Survey Instrument to Evaluate Primary Care Provider Behavior in the Diagnosis and Management of PCOS in Adolescents**	Conlon 2020	Journal of Adolescent Health	66 (2 Supp)		S100-S101	Abstract
18	**Dissecting individual experiences to reach a more comprehensive understanding of weight regulation in Polycystic Ovary Syndrome**	Cooper 2013	Obesity Facts	1)		217-218	Abstract
19	**Under-versus overdiagnosis: Exploring the benefits and harms of a pcos label and its impact on women's psychosocial wellbeing, lifestyle and behaviour**	Copp 2018	BMJ Evidence-Based Medicine	23 (Supp 2)		A44	Abstract
20	**Body- and symptom-related concerns in women diagnosed with polycystic ovary syndrome: A gap in symptom management**	Soucie 2021	Journal of Health Psychology	26	5	701-712	Wrong outcomes
21	**Nurse practitioner student perceptions and knowledge on polycystic ovarian syndrome: A quality improvement project**	Onwuzurumba 2020	Dissertation Abstracts International Section A: Humanities and Social Sciences	81	11-A	No Pagination Specified	Wrong study design
22	**Medical Journeyof Patientswithpcosand Obesity: A Cross-Sectional Survey of Patients and Pcps**	Sherif 2022	Journal of General Internal Medicine	37 (Supp 2)		S300	Wrong intervention
23	**Nurse-led peer support group: experiences of women with polycystic ovary syndrome**	Percy 2009	Journal of Advanced Nursing	65	10	2046-55	Wrong outcomes
24	**Addressing polycystic ovary syndrome in outpatient mental health practices: A brief intervention to increase awareness**	Shwarz 2016	Dissertation Abstracts International: Section B: The Sciences and Engineering	76	9-B(E)	No Pagination Specified	Wrong study design
25	**Evaluation of depression and anxiety in women with polycystic ovary syndrome by physician trainees**	Pakhdikian 2020	Journal of Investigative Medicine	68(1)		A168	Abstract
26	**Exploring how knowledge, attitudes, and practices affect health-related quality of life in women diagnosed with polycystic ovarian syndrome**	Nguyen 2018	Journal of the American Pharmacists Association	58(3)		e81-e82	Abstract

27	**PCOS T.A.C.T.: A program to assist psychologists in understanding and helping women diagnosed with polycystic ovary syndrome**	Niemi 2013	Dissertation Abstracts International: Section B: The Sciences and Engineering	73	7-B(E)	No Pagination Specified	Wrong study design
28	**Nutrition education intervention for the management of polycystic ovary syndrome (PCOS)**	Simha 2019	Medico-Legal Update	19(2)		21-27	Wrong intervention
29	**Physician knowledge of polycystic ovary syndrome diagnosis and comorbidities**	Stevenson 2020	Reproductive Sciences	27 (1 Supp)		360A-361A	Abstract
30	**Acupuncture for weight loss in Polycystic Ovary Syndrome: a qualitative study exploring feasibility and acceptability**	Ee 2019	Advances in Integrative Medicine	6 (Supp 1)		S102	Wrong intervention
31	**Screening for Polycystic Ovarian Syndrome and Effect of Health Education on its Awareness among Adolescents: A Pre-Post Study**	ElSayed 2020	International Journal of Nursing Education	12	4	227-236	Wrong population
32	**Practice patterns of diagnosis and management of polycystic ovary syndrome: A survey of physicians from the Middle East and Africa**	Beshyah 2021	Endocrine Practice	27 (12 SUPPL)		S29-S30	Abstract
33	**Acupuncture with manual and low frequency electrical stimulation as experienced by women with polycystic ovary syndrome: a qualitative study**		BMC Complementary & Alternative Medicine	12	1	32-37	Wrong intervention
34	**With Her: Women's Health Education for Internal Medicine Residents. Using the Jigsaw Teaching Method to Enhance Im Residents' Knowledge and Confidence in Cervical Health, Breast Health, and Pcos**	Gauvin 2022	Journal of General Internal Medicine	37 (Supp 2)		S661-S662	Abstract
35	**Understanding polycystic ovary syndrome from the patient perspective: a concept elicitation patient interview study**	Martin 2017	Health & Quality of Life Outcomes	15		1-10	Wrong outcomes
36	**Diagnosis and health implications of PCOS in symptomatic women presenting to four different clinics: Gynecology, infertility, dermatology and endocrinology**	Maruthini 2011	Human Fertility	1)		15	Abstract
37	**Remote assessment and reinforcement of patient awareness of role of lifestyle modification and treatment adherence in polycystic ovary syndrome using an online video based educational module**	Gour 2022	Journal of the Turkish German Gynecology Association	23(1)		1-7	Wrong intervention
38	**Effectiveness of Video-Assisted Teaching Module on Knowledge, Attitude and Body Mass Index (BMI) Scaling Down Among Over-Weight Women Diagnosed with PCOS in Selected Hospitals of Madhya Pradesh**	Massey 2021	Nursing Journal of India	112	5	203-207	Wrong intervention
39	**Effectiveness of video assisted teaching program regarding the knowledge of polycystic ovarian disease and its prevention among adolescent girls studying in selected higher secondary schools at Kollam, India**	Greeshma 2019	International Journal of Research in Ayurveda and Pharmacy	10(1)		67-70	Wrong population
40	**Assessing the impact of an educational intervention program based on the theory of planned behavior on the nutritional behaviors of adolescents and young adults with PCOS in Iran: a field trial study**	Hajivandi 2021	BMC Pediatrics	21	1	316	Wrong outcomes
41	**Healthcare providers' knowledge, diagnosis and management of polycystic ovary syndrome (PCOS) in**	Gibson-Helm 2017	Human Reproduction	32 (Supp 1)		i33-i34	Abstract

	Europe, North America and internationally						
42	**Polycystic ovaries: review of medical information on the internet for patients**	MallappaSaroja 2010	Archives of Gynecology & Obstetrics	281	5	839-43	Wrong population
43	**Sexuality and psychological wellbeing in women with polycystic ovary syndrome compared with healthy controls**	Mansson 2011	European Journal of Obstetrics, Gynecology, & Reproductive Biology	155	2	161-5	Wrong outcomes
44	**Polycystic Ovary Syndrome from Google to Bedside: Implications for Medical Education**	Hoyos 2018	Fertility and Sterility	110 (4 SUPPL)		e111-e112	Abstract
45	**Informing Translation: The Accuracy of Information on Websites for Lifestyle Management of Polycystic Ovary Syndrome**	Htet 2018	Seminars in Reproductive Medicine	36	1	80-85	Wrong population
46	**The accuracy of information for lifestyle management on websites for the management of PCOS**	Htet 2017	Clinical Endocrinology	86 (Supp 1)		47	Abstract
47	**Polycystic ovary syndrome: double click and right check. What do patients learn from the Internet about PCOS?**	Mousiolis 2012	European Journal of Obstetrics, Gynecology, & Reproductive Biology	163	1	43-6	Wrong population
48	**Provider experiences with lifestyle management in women with PCOS**	Huffman 2017	Fertility and Sterility	108 (3 Supp 1)		e247	Abstract
49	**Concerns of polycystic ovary syndrome women: A qualitative study**	NasiriAmiri 2013	Journal of Diabetes	1)		18	None English
50	**EFFECTIVENESS OF VIDEO ASSISTED TEACHING MODULE ON KNOWLEDGE OF ADOLESCENT GIRLS REGARDING POLYCYSTIC OVARIAN SYNDROME IN GAYATRI WOMEN'S +2 SCIENCE COLLEGE BERHAMPUR, GANJAM, ODISHA**	Nayak 2017	Journal on Nursing	7	2	27-31	Wrong population
51	**Assessment of Psychological Distress in Polycystic Ovarian Syndrome Infertile Patients at a Tertiary Level Infertility Care Centre in India**	Nayar 2019	Fertility and Sterility	112(3 SUPPL)		e394	Abstract
52	**Educational Program: Its Effect on Knowledge and Lifestyles among Paramedical Students with Polycystic Ovarian Syndrome (PCOS)**	AlKurdi 2021	Medico-Legal Update	21	3	58-69	Wrong study design
53	**Knowledge of Polycystic Ovarian Syndrome, Its Complications, and Management among Lebanese Women: A Cross-Sectional Survey**	AlSouheil 2022	Journal of Health & Allied Sciences NU	12	3	267-273	Wrong population
54	**Relationship between health literacy and body mass index among Arab women with polycystic ovary syndrome**	Al-Ruthia 2017	Saudi Pharmaceutical Journal	25(7)		1015-1018	Wrong outcomes
55	**PCOS symptom recognition and diagnosis: Time for better education and clinical resources**	Ali 2022	BJOG: An International Journal of Obstetrics and Gynaecology	129 (Supp 1)		221	Abstract
56	**Impact of limited reproductive health awareness on PCOS diagnosis timelines and the need for improved patient education**	Ali 2022	Human Reproduction	37 (Supp 1)		i536-i537	Abstract
57	**Assessing the effectiveness of a pharmaceutical care service on the quality of life of women with polycystic**	Alkoudsi 2020	Journal of Evaluation in Clinical Practice	26(5)		1467-1477	Wrong outcomes

	ovarian syndrome living in war and non-war countries						
58	**Effect of an educational program about polycystic ovarian syndrome on knowledge of adolescent female students**	Almukhtar 2019	Indian Journal of Public Health Research and Development	10(8)		1059-1063	Wrong outcomes
59	**Awareness of polycystic ovary syndrome: A university students' perspective**	Alshdaifat 2021	Annals of Medicine and Surgery	72			Wrong population
60	**The stigma of womanhood thiaf: Polycystic ovary syndrome**	Amini 2012	International Journal of Fertility and Sterility	1)		153	Abstract
61	**Evaluation of women knowledge and perception about polycystic ovary syndrome and its management in Jordan: A survey-based study**	Abu-Taha 2020	International Journal of Clinical Practice	74	10	e13552	Wrong population
62	**Diagnostic experiences and concerns in adolescents with polycystic ovary syndrome**	Pena 2018	Hormone Research in Paediatrics	90 (Supp 1)		567	Abstract
63	**Chasing Infertility - the Chat Bot-Way to Increase Fertility Awareness**	Schenk 2021	Fertility and Sterility	116 (3 SUPPL)		e269-e270	Abstract
64	**Polycystic Ovary Syndrome in American Indian Women: An Exploratory Study**	Carron 2018	Fertility and Sterility	110 (4 SUPPL)		e280-e281	Abstract
65	**Polycystic ovary syndrome in globalizing India: An ecosocial perspective on an emerging lifestyle disease**	Pathak 2015	Social Science & Medicine	146		21-8	Wrong outcomes
66	**Sexuality in women with polycystic ovary syndrome**	Kowalczyk 2015	Ginekologia Polska	86	2	100-6	Wrong intervention
67	**Diagnosis and lifestyle modification counseling for adolescents with pcos: An assessment of learning needs in OBGYN, pediatrics, and family medicine residents**	Dassow 2017	Obstetrics and Gynecology	130 (Supp 1)		55S-56S	Abstract
68	**Ask PCOS: Identifying Need to Inform Evidence-Based App Development for Polycystic Ovary Syndrome**	Boyle 2018	Seminars in Reproductive Medicine	36	1	59-65	Wrong population
69	**Analysis of the barriers and enablers to implementing lifestyle management practices for women with PCOS in Singapore**	Ko 2016	BMC Research Notes	9		311	Wrong outcomes
70	**The doctor will tweety ounow: Expanding accessto care through social media engagement**	Chen 2016	Fertility and Sterility	106 (Supp 3)		e111-e112	Abstract
71	**Resident Knowledge of Pcos: Identifying Gaps and Educational Opportunities**	Chemerinski 2018	Fertility and Sterility	110 (4 SUPPL)		e112	Abstract
72	**A comparison of polycystic ovary syndrome and related factors between lesbian and heterosexual women**	Smith 2011	Womens Health Issues	21	3	191-8	Wrong intervention
73	**Effectiveness of structured teaching programme on knowledge of**	Sowmya 2013	Nitte University Journal of Health Science	3(3)		54-58	Wrong population

	polycystic ovarian syndrome among adolescent girls						
74	**What Can You Find about Polycystic Ovary Syndrome (PCOS) Online? Assessing Online Information on PCOS: Quality, Content, and User-Friendliness**	Chiu 2018	Seminars in Reproductive Medicine	36	1	50-58	Wrong outcomes
75	**Challenges and uncertainties regarding polycystic ovary syndrome (PCOS) and the potential for overdiagnosis: Clinicians' views and experiences**	Copp 2018	BMJ Evidence-Based Medicine	23 (Supp 2)		A45	Abstract
76	**Barriers and facilitators to weight management in overweight and obese women living in Australia with PCOS: A qualitative study**	Lim 2019	BMC Endocrine Disorders	19(1)			Wrong outcomes
77	**The experiences of women with polycystic ovary syndrome on a very low-calorie diet**	Love 2016	International Journal of Women's Health	8		299-310	Wrong intervention
78	**Barriers and Facilitators to Weight and Lifestyle Management in Women with Polycystic Ovary Syndrome: General Practitioners' Perspectives**	Arasu 2019	Nutrients	11	5	7	Wrong outcomes
79	**Relationship between loci of control and health-promoting behaviors in Pakistani women with polycystic ovary syndrome: coping strategies as mediators**	Fatima 2021	BMC Women's Health	21(1)			Wrong outcomes
80	**Clinicians' Perceptions of Norwegian Women's Experiences of Infertility Diseases**	Fernandes 2020	International Journal of Environmental Research & Public Health [Electronic Resource]	17	3	5	Wrong outcomes
81	**Feasibility and acceptability of a proposed trial of acupuncture as an adjunct to lifestyle interventions for weight loss in Polycystic Ovary Syndrome: A qualitative study 11 Medical and Health Sciences 1117 Public Health and Health Services**	Ee 2018	BMC Complementary and Alternative Medicine	18(1)			Wrong outcomes
82	**Perceptions and experiences of lifestyle interventions in women with polycystic ovary syndrome (PCOS), as a management strategy for symptoms of PCOS**	Arentz 2021	BMC Women's Health	21(1)			Wrong outcomes
83	**Practice patterns in the diagnosis of PCOS: Low testing rates for other disorders with similar clinical presentations**	Willard 2014	Endocrine Reviews. Conference: 96th Annual Meeting and Expo of the Endocrine Society, ENDO	35	SUPPL. 3		Abstract
84	**Polycystic ovary syndrome (PCOS) in the adolescent patient: recommendations for practice**	Snyder 2005	Pediatric Nursing	31	5	416-21	Wrong study design
85	**The importance of screening for diabetes in women with polycystic ovary syndrome**	Shorakae 2015	Diabetes Management	5(1)		1-4	Wrong study design
86	**Patient requests for improved diagnosis and information in polycystic ovary syndrome**	Pugeat 2020	Annales d Endocrinologie	81	5	473-475	Wrong study design
87	**HER LIFESTYLE: a mneumonic for addressing polycystic ovary syndrome in adolescents**	Neal 2009	Nursing for Women's Health	13	6	472-478	Wrong study design
88	**Incorporating qualitative approaches is the path to adequate understanding of the psychosocial impact of polycystic ovary syndrome**	Moreira 2006	Human Reproduction	21	10	2723-4; author reply 2724-5	Wrong study design

89	**Recognizing and eliminating bias in those with elevated body mass index in women's health care**	Lindheim 2018	Fertility and Sterility	109(5)		775-776	Wrong study design
90	**Obesity, polycystic ovary syndrome, infertility treatment: asking obese women to lose weight before treatment increases stigmatisation**	Laredo 2006	BMJ	332	7541	609	Wrong study design
91	**Polycystic ovarian syndrome: what nurses need to know about this misunderstood disorder**	Jackson 2004	AWHONN Lifelines	8	6	511-8	Wrong study design
92	**A patient's guide: polycystic ovary syndrome (PCOS)**	Hoeger 2014	Journal of Clinical Endocrinology & Metabolism	99	1	35A-36A	Wrong study design
93	**Worldwide dissatisfaction with the diagnostic process and initial treatment of PCOS**	Cree-Green 2017	Journal of Clinical Endocrinology and Metabolism	102(2)		375-378	Wrong study design
94	**Are expanding disease definitions unnecessarily labelling women with polycystic ovary syndrome?**	Copp 2017	BMJ	358		j3694	Wrong study design
95	**Diagnostic features of polycystic ovary syndrome**	Barday-Karbanee 2006	South African Journal of Obstetrics and Gynaecology	12(1)		30-35	Wrong study design
96	**What You Need to Know about Pediatric and Adolescent Gynecology: Clinically Relevant Reviews Published in the Journal of Pediatric and Adolescent Gynecology**	AdamsHillard 2017	Journal of Pediatric and Adolescent Gynecology	30(5)		519	Wrong study design
97	**Testing for insulin resistance in polycystic ovary syndrome-a survey of american society for reproductive medicine (ASRM) physician members**	Asante 2013	Fertility and Sterility	1)		S82	Abstract
98	**Polycystic ovary syndrome support groups and their role in awareness, advocacy and peer support: A systematic search and narrative review**	Avery 2020	Current Opinion in Endocrine and Metabolic Research	12		98-104	Wrong population
99	**PCOS: perspectives from a pediatric endocrinologist and a pediatric gynecologist**	Kansra 2013	Current Problems in Pediatric & Adolescent Health Care	43	5	104-13	Wrong study design
100	**Study the Effectiveness of Structured-Teaching Programme on Knowledge Regarding Polycystic Ovarian Syndrome and Its Prevention among Higher Secondary Female Students in Selected School of Dehradun**	Karki 2018	International Journal of Nursing Education	10	3	96-101	Wrong population
101	**Is It Time to Update the Screening Recommendations for Patients with Polycystic Ovary Syndrome?**	Kaiser 2021	Fertility and Sterility	116 (3 SUPPL)		e122	Abstract
102	**Development and validation of a guideline on sexual and reproductive health services for polycystic ovary syndrome in Iran: a mixed-methods study protocol**	Kalhor 2021	Health Research Policy & Systems	19	1	144	Wrong outcomes
103	**Dietary management of women with polycystic ovary syndrome in the United Kingdom: the role of dietitians**	Jeanes 2009	Journal of Human Nutrition & Dietetics	22	6	551-8	Wrong outcomes
104	**Mental Health and PCOS Information-Sharing: Interviews with Health Care Providers in a Low-Income Urban Community**	Zamora 2022	Journal of racial and ethnic health disparities.	9			Wrong outcomes
105	**Transition to Self-Management among Adolescents with Polycystic Ovary Syndrome: Parent and Adolescent Perspectives**	Young 2019	Journal of Pediatric Nursing	47		85-91	Wrong outcomes

106	**Polycystic Ovarian Syndrome: Perception of Women with Pcos and Impact of Pharmacist's Intervention**	Ravi 2018	Value in Health	21 (Supp 2)		S59	Abstract
107	**Gaps in knowledge in diagnosis and management of polycystic ovary syndrome**	Saini 2016	Fertility and Sterility	106 (Supp 3)		e100	Abstract
108	**"Less Than A Wife": A Study of Polycystic Ovary Syndrome Content in Teen and Women's Digital Magazines**	Sanchez 2016	Journal of Medical Internet Research	18	6	e89	Wrong population
109	**Effectiveness of planned teaching program regarding polycystic ovarian disease in terms of knowledge and attitude among students of sgt university**	Umaisa 2021	Indian Journal of Forensic Medicine and Toxicology	15(3)		4332-4338	Wrong population
110	**Quality Improvement in the Evaluation and Diagnosis of Polycystic Ovary Syndrome in Adolescent Girls**	Torres 2021	Journal of Pediatric & Adolescent Gynecology	34	5	603-609	Wrong outcomes
111	**Effectiveness of self help strategies (SHS) for PCOS on biochemical parameters among young adult girls**	Tamilselvi 2020	International Journal of Research in Pharmaceutical Sciences	11(3)		3034-3041	Wrong outcomes
112	**Polycystic ovary syndrome: perceptions and attitudes of women and primary health care physicians on features of PCOS and renaming the syndrome**	Teede 2014	Journal of Clinical Endocrinology & Metabolism	99	1	E107-11	Wrong outcomes
113	**Diagnosis and management of polycystic ovary syndrome: Clinician perspectives in Singapore**	Teoh 2022	BJOG: An International Journal of Obstetrics and Gynaecology	129 (Supp 1)		13	Abstract
114	**Informing the design and delivery of a lifestyle program for women with polycystic ovary syndrome: A mixed-methods investigation on patients' perspectives**	Pirotta 2021	South African Journal of Clinical Nutrition	34(3)		157	Abstract
115	**A randomized pilot study of dietary treatments for polycystic ovary syndrome in adolescents**	Wong 2016	Pediatric Obesity	11	3	210-20	Wrong outcomes
116	**Transtheoretical model-based mobile health application for PCOS**	Wang 2022	Reproductive Health	19	1	117	Wrong outcomes
117	**The effect of polycystic ovary syndrome on daily activities, self-esteem and experiences in employment**	Washington 2005			Ph.D.	470 p-470 p	Wrong study design

5. STUDY QUALITY APPRAISAL

5.1 Studies assessing information needs of health professional:

		Selection bias			Performance bias	Detection bias				Attrition bias		Report Bias	Confounding	Other bias			
Study ID	Design	Comparable cases & controls	Established case definition	Established control definition	Groups treated the same	Standard measurements for exposure	Assessors blinded to case/control status	Standardised measurements for outcomes	Outcomes assessed objectively and independently	% lost to follow up	% included in analysis	Free of selective outcome reporting	Groups similar at baseline	Funding/ COI reported	Sufficient power	Adequate statistical analysis	Overall risk
Alzamil 2020	Cross-sectional	No	Partial	Partial	Yes	Yes	No	Yes	Yes	N/A	Yes	Not reported	No	Yes	Not reported	Partial	High
Arif 2020	Cross-sectional	N/A	Yes	N/A	N/A	Yes	N/A	Yes	Yes	N/A	Yes	Yes	N/A	No	Not reported	Yes	Moderate
Sasante 2015	Cross-sectional	N/A	Yes	N/A	N/A	Yes	N/A	Yes	Yes	N/A	Yes	Yes	N/A	Yes	Not reported	Yes	Low
Carron 2018	Pre-post study	N/A	Yes	N/A	N/A	Yes	N/A	Yes	Yes	N/A	Yes	Yes	N/A	Yes	Not reported	Yes	Low
Chemerinski 2020	Cross-sectional	N/A	No	N/A	N/A	Yes	N/A	Yes	Yes	N/A	Yes	Yes	N/A	Yes	Not reported	Yes	Low
Dokras 2017	Cross-sectional	No	Partial	Partial	Yes	Yes	No	Yes	Yes	N/A	Yes	Yes	No	Yes	Not reported	Yes	Moderate
Doll 2012	Cross-sectional	N/A	Yes	N/A	N/A	Yes	No	Yes	Yes	N/A	Yes	Not reported	N/A	Yes	Not reported	Yes	Low
Dutta 2020	Cross-sectional	No	Partial	Partial	Yes	Yes	No	Yes	Yes	N/A	Yes	Not reported	No	Yes	Not reported	Yes	Moderate
Gibson-Helm 2018	Cross-sectional	No	Partial	Partial	Yes	Yes	No	Yes	Yes	N/A	Yes	Not reported	No	No	Not reported	Yes	Moderate
Ma 2021	Cross-sectional	No	Partial	Partial	Yes	Yes	No	Yes	Yes	N/A	Yes	Not reported	No	Yes	Not reported	Yes	Moderate
Ning 2013	Cross-sectional	N/A	Yes	N/A	N/A	Yes	N/A	Yes	Yes	N/A	Yes	Not reported	N/A	Yes	Not reported	Yes	Low
Piltonen 2019	Cross-sectional	N/A	Partial	N/A	N/A	Yes	N/A	Yes	Yes	N/A	Yes	Not reported	N/A	Yes	Not reported	Yes	Low
Salman 2020	Cross-sectional	N/A	Yes	N/A	N/A	Yes	N/A	Yes	Yes	N/A	Yes	Not reported	N/A	Yes	Not reported	Yes	Low
Yan 2021	Cross-sectional	N/A	Yes	N/A	N/A	Yes	N/A	Yes	Yes	N/A	Yes	Not reported	N/A	Yes	Not reported	Yes	Low

5.2 Studies assessing information needs of women with PCOS:

		Selection bias			Performance bias	Detection bias				Attrition bias		Report Bias	Confounding	Other bias			
Study ID	Design	Comparable cases & controls	Established case definition	Established control definition	Groups treated the same	Standard measurements for exposure	Assessors blinded to	Standard measurements for outcomes	Outcomes assessed objectively	% lost to	% included	Free of selective	Groups similar at baseline	Funding/ COI reported	Sufficient power	Adequate statistical analysis	Overall risk

							case/control status		and independently	follow up	in analysis	outcome reporting					
Ching 2007	Cross sectional	N/A	Yes	N/A	N/A	Yes	No	Yes	Yes	N/A	Yes	Yes	N/A	Yes	Not reported	Yes	Low
Gibson-Helm 2014	Cross-sectional	N/A	Yes	N/A	N/A	Yes	No	Yes	Yes	N/A	Yes	Yes	N/A	Yes	Not reported	Yes	Low
Gibson-Helm 2017	Cross-sectional	N/A	No	N/A	N/A	Yes	No	Yes	Yes	N/A	Yes	Yes	N/A	Yes	Not reported	Yes	Low
Hoyos 2020	Cross-sectional	N/A	No	N/A	N/A	Yes	No	Yes	Yes	N/A	Yes	Not reported	N/A	Yes	Not reported	Yes	Moderate
Pena 2022	Cross-sectional	N/A	Yes	N/A	N/A	Yes	No	Yes	Yes	N/A	Yes	Yes	N/A	Yes	Not reported	Yes	Low
Sills 2001	Cross-sectional	N/A	No	N/A	N/A	Yes	No	Yes	Yes	N/A	Yes	Not reported	N/A	Yes	Not reported	Yes	Moderate

		A: Are the results valid?						B: What are the results?			C: Will the results help localy?	
Study ID	**Design**	**Clear research aims**	**Method appropriate for goals**	**Design appropriate for aims**	**Appropriate recruitement strategy**	**Appropriate data collection**	**Relationship considered between researcher and participant**	**Consideration of ethical issues**	**Rigorous data analysis**	**Clear statement of findings**	**Research value**	**Overall RoB**
Authier 2020	Qualitative	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Low
Avery 2007	Qualitative	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Low
Carron 2020	Qualitative	Can't tell	Can't tell	Can't tell	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Crete 2011	Qualitative	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes	Yes	Yes	Low
Ee 2020	Qualitative	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Hadjiconstantinou 2017	Qualitative	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Low
Hillman 2020	Mixed method	Yes	Yes	Yes	Yes	Can't tell	No	Yes	Yes	Yes	Yes	Low
Holbrey 2013	Qualitative	Yes	Yes	Yes	Yes	Yes	No	Yes	Can't tell	Yes	Yes	Low
Humphreys 2008	Mixed methods	Yes	Can't tell	Can't tell	Yes	Can't tell	Can't tell	Yes	Can't tell	Can't tell	Yes	High
Ismayilova 2022	Qualitative	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low

Ismayilova 2022b	Qualitative	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes	Yes	Low
Kaur 2021	Mixed method	Yes	Yes	Yes	Yes	Can't tell	No	Yes	Can't tell	Can't tell	Yes	Moderate
Khan 2018	Mixed method	Yes	Yes	Yes	Can't tell	Can't tell	No	Yes	Can't tell	Yes	Yes	High
Pirotta 2021	Qualitative	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Pirotta 2021	Mixed method	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes	Low
Tomlinson 2017	Qualitative	Yes	Yes	Yes	Yes	Yes	No	Yes	Can't tell	Yes	Yes	Low
Trent 2003	Mixed method	Yes	Yes	Yes	Yes	Can't tell	No	Yes	Can't tell	Yes	Yes	Moderate
Weiss 2011	Qualitative	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes	Low
Williams 2015	Qualitative	Yes	Can't tell	Can't tell	Can't tell	Can't tell	No	Yes	Can't tell	Yes	Can't tell	High

6. FINDINGS

See PART 2 for this question

7. GRADE ASSESSMENT AND EVIDENCE PROFILE

Due to the broad nature of the clinical question and the inclusion of studies of heterogeneous designs, populations and/or aims, it was not feasible to generate GRADE evidence profile tables for this question. Please see individual study risk of bias assessments to determine the quality of evidence.

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 2

Question 2.6.1.

What are the information, resource and education needs of women, adolescents, CALD groups and healthcare providers regarding PCOS?

BACKGROUND:

Prevalence and problem

PCOS is a chronic disease characterized by varied expression from adolescence to menopause. Therefore, informational needs are greatest at time of diagnosis. An international online questionnaire study found that one third of those affected consulted 3 or more healthcare professionals prior to establishment of the PCOS diagnosis and generally expressed dissatisfaction with health information received (1). In this study and in others, healthcare professional communication lacked recommendations for lifestyle modifications/weight management (2), discussion of long-term complications, extension of emotional support/counselling (3) and empathy (4). Comprehensive and supportive information furthermore may benefit quality of life in PCOS (5) and satisfy the desire for agency in the self-management of health issues related to PCOS (6).

Clinical practice gap

Understanding the needs of those affected by PCOS in terms of communication/recommendation from their health care professionals and discerning knowledge gaps among health care professionals that are contributing to unmet informational needs in PCOS care.

Individual's experiences of PCOS care

Due to the lack of comprehensive PCOS information at the time of diagnosis, those affected often search online to enhance understanding. In a Google Trends analysis, the frequency of PCOS related online searches was higher when compared to web interrogations for fibroids, another equally prevalent gynaecological condition (7). Overall, online searches as well as communication with online PCOS support groups enhance the effectiveness of health care visits as patients can ask more targeted questions (8, 9). A survey from Australia also found that a comprehensive question prompt list, if readily available (online or in an App), can further serve as a useful tool to enhance communication with healthcare professionals (10). Joining online discussion forums and sharing experiences also seem to reduce the psychological burden of PCOS (11). In a qualitative study that was conducted over a Skype platform video interview, participants remarked that PCOS impacted their sense of identity as a woman and challenged their perception of themselves (12). Over 50% of participants in this study discussed suicide-ideation and self-harm during their interview.

A recent, post-2018 International PCOS Guideline survey study from the United Kingdom noted that lag time to diagnosis of PCOS was only 6-12 months (13) as opposed to previous reports of > 2 years (1). However, patients continue to miss comprehensive discussion of comorbidities (13), healthy lifestyle and weight (11, 13) and enquiry about their mental health (11, 13). In a semi-structured interview study out of Canada, patients felt PCOS to be stigmatizing as weight gain, acne, and hirsutism were deemed undesirable by society (14). Furthermore, a lack of empathy and weight bias from health professionals seemed to enhance the feeling of stigmatization in patients from Canada (15). A recent study out of India looked at treatment seeking pathways in patients diagnosed with PCOS and observed that recurrent lack of clear treatment explanations led to 51 % of patients consulting 2-3 healthcare agencies for treatment (16). Even though similar treatment plans may have been provided by different clinicians, a lack of understanding treatment decisions in the context of PCOS, left patients dissatisfied.

While the 2018 International PCOS Guideline recommended lifestyle management as first-line treatment of PCOS, specific implementation models still need to be explored. A recent online PCOS survey study out of Australia reported that 95% of those surveyed would attend a lifestyle program if affordable, long-term and offer PCOS specific recommendations that addressed barriers to behaviour change (17). A subset of study participants who underwent structured interviews perceived PCOS comorbidities such as anxiety, depression, disordered eating, and poor body image as an impedance to successful lifestyle management (18).

Culturally and linguistically diverse groups

Information and resources should be framed and provided in a culturally appropriate way. An Australian study evaluating service for Aboriginal and Torres Strait Islanders with PCOS noted that group rather than individual consultations were sometimes preferred (19). Barriers to accessible and culturally appropriate information provision were identified, such as information not matched to health literacy, and unavailability of women physicians. Tribal attitude also shaped the impact of PCOS in American Indians in recent qualitative accounts (20). Menstrual dysfunction prevented American Indians from attending some tribal ceremonies, which led to social marginalization and stigmatization. PCOS furthermore affected status/identity within the tribe, where procreating was greatly valued. This sense of inadequacy was enhanced by a lack of access to fertility services in the rural contexts of tribal life. Attitudes of fatalistic acceptance additionally led to shame and unsought medical care. Like the Aboriginal and Torres Strait Islanders in Australia, American Indians often preferred to include friends and family when diagnostic and treatment information was provided (20).

Adolescents

In a quality-of-life cross-sectional examination, adolescents with PCOS were less sexually active and more worried about their ability to conceive later in life than their peers (21). In a qualitative study of young adults (age 18-23 years old) concerns about future fertility were “ever present” and on the mind of the participants (22).

Since the publication of the 2018 International PCOS Guideline, a recent cross-sectional analysis of the adolescent experience in Australia and the United Kingdom reported that time to diagnosis has shortened to < 1 year for most adolescents (23). While adolescents in this study were overall pleased with the diagnosis experience, there was dissatisfaction with information on lifestyle, psychological aspects and long term complications, although this varied by location/setting of care (23).

The 2018 International PCOS Guideline, while in support of Rotterdam criteria for diagnosis, recommends NIH criteria (menstrual dysregulation AND clinical or biochemical hyperandrogenism) for diagnosing adolescents. In a recent cross-sectional report of adolescents attending a comprehensive multi-specialty adolescent PCOS program, 247 teens who met NIH criteria for PCOS were compared to 243 teens who did not meet criteria at the time of assessment (24). During psycho-social assessment, teens that met diagnostic NIH criteria were more likely to report their gender identity as diverse (trans, fluid or non-binary). Among those diagnosed with PCOS, gender diversity was associated with higher hirsutism scores but not biochemical hyperandrogenism, suggesting that gender diverse teens might more likely embrace manifestations of hirsutism and choose to forgo common cosmetic treatments. Therefore, unawareness of a teen’s gender identity may inadvertently subject the adolescent to cis-normative treatments, potentially worsening psychological distress (24).

Healthcare providers' knowledge and practices

Aligning with patients' experience, surveys of health professionals in Europe/Asia and North America (25) and Nordic European countries (26) confirmed that clinician awareness of psycho-social morbidities associated with PCOS is low.

In terms of PCOS diagnostic criteria, a survey of physicians from North America found that only 68% of reproductive endocrinologists (REI-ObGyn) and less than half (41%) of general obstetrician-gynaecologists (ObGyn) knew to apply Rotterdam criteria for diagnosing PCOS (27). In this report REI-ObGyn specialists were more likely to prescribe lifestyle modification for both fertility and non-fertility related concerns than OBGyn physicians. In general, older physicians (age >46 years old) were less aware of Rotterdam criteria (27) and less frequently prescribed lifestyle modification (26). When ObGyn residents in training were surveyed, most residents (85%) knew that Rotterdam criteria are recommended to diagnose PCOS in adults (28). However, in this study, only 50% identified one component of each of the three diagnostic criteria. In another physician survey out of India clinical practice patterns of varying specialties were compared (29). Notably, in this study, laboratory examination to exclude a diagnosis of non-classical-congenital adrenal hyperplasia was rarely performed in any of the specialties and depression screening was most often performed by paediatricians when seeing adolescents with PCOS (29). Furthermore, hormone pills were more commonly prescribed by endocrinologists and gynaecologists, whereas metabolic complications were more likely screened for by endocrinologists and general physicians. In a small survey study in Saudi Arabia examining the practice patterns in application of the Rotterdam criteria, endocrinologists reported greater reliance on hyperandrogenism and gynaecologists more frequently used ultrasound to make the diagnosis (30). An examination of rural nurse practitioners in the United States observed that only about 40% of the practitioners recognized PCOS as a risk factor for type 2 diabetes mellitus (31). Given their customary clinical setting in family practice, women's health and internal medicine, nurse practitioners continuing education on the diagnosis and comorbidities of PCOS might greatly reduce diagnostic delays and prevent comorbidities of PCOS (31). In a qualitative study on clinician perspective in Australia, clinicians voiced concern about the diagnostic accuracy of the Rotterdam Criteria and felt that there was a risk for overdiagnosis PCOS (32). Most desired PCOS discussions with patients to be comprehensive while dispelling misconceptions about infertility (32). A recent qualitative study in allied health professionals (dietitians, physical therapists, and psychologists), explored their experience with the implementation of 2018 International PCOS Guideline lifestyle recommendations (33). Those interviewed wished to be more knowledgeable about the psychological issues associated with PCOS as these could affect body image, motivation and predisposition to disordered eating (33). Overall allied health professionals felt that the 2018 International PCOS Guideline lifestyle recommendations were too general and too weight focused. They also desired more communication with the treating clinicians in terms of hand-off and collaboration (33).

Evidence to Recommendations Framework

COMPARISONS (option versus other option)

Information resources vs none

EVIDENCE-BASED RECOMMENDATION(S)

- **EBR:** Tailored information, education and resources that are high-quality, culturally appropriate and inclusive should be provided to all with PCOS.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

- **EBR:** Information, education and resources are a high priority for women with PCOS and should be provided in a timely, respectful and empathic manner.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

CONSENSUS RECOMMENDATION

- Entities responsible for health professional education should ensure that information and education on PCOS is systemically embedded at all levels of health professional training to address knowledge gaps.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

PRACTICE POINT(S)

- The diversity of the population should be considered when adapting practice paradigms.
- Health professional education opportunities should be optimised at all stages of education, graduate and postgraduate training, continuing professional development and practice support resources.
- Women should be counselled on the risk of misinformation and guided to evidence-based resources.

GRADE CONSIDERATIONS

Justifications: Evidence shows knowledge gaps among health care professionals that are contributing to unmet informational needs in PCOS care. Adolescents and adults with PCOS highly prioritised information needs.
Subgroup considerations: It is important to ensure that PCOS resources are designed for those with a low health literacy level. It is also important that resources are culturally appropriate and available in languages other than English.
Implementation considerations: Continuing health professional education must be prioritised based on lack of healthcare professional knowledge and lack of patient satisfaction with education received by health professionals Use credible and high-quality resources that encompass best practice information delivery. Codesigned, accessible resources from these evidence-based guidelines should be widely disseminated and prioritised.
Monitoring and evaluation considerations: Monitoring of knowledge in healthcare professionals and those with PCOS.
Research priorities: Exploration of optimal delivery methods of health information for end users. Demonstration of satisfaction and impact of education strategies on practice and health outcomes. Avenues of integration into models of care.

GRADE framework

GRADE DECIDE **Interactive Evidence to Decision Framework**

- **DESIRABLE EFFECTS**

How substantial are the desirable anticipated effects?

Judgement:

☒ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:
See Part 1- Evidence Summary and GRADE document.

Panel discussion:

● UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

Judgement:

☒ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:
See Part 1- Evidence Summary and GRADE document.

Panel discussion:

● CERTAINTY OF THE EVIDENCE

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☐ Very low	☐ Low	☒ Moderate	☐ High

Research evidence:
See Part 1- Evidence Summary and GRADE document.

Panel discussion:
Evidence certainty is limited by observational data only, however these study designs are appropriate for this question and there are large numbers of studies showing consistent findings.

● VALUES

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☐ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☐ Probably no important uncertainty or variability	☒ No important uncertainty or variability

Research evidence:
No research evidence was identified

Panel discussion:

● BALANCE OF EFFECTS

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☒ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:

● COSTS

How large are the resource requirements (costs)?

Judgement:

☒ Don't know	☐ Varies	☐ Large costs	☐ Moderate costs	☐ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:
No research evidence was identified

Panel discussion:

● CERTAINTY OF COST EVIDENCE

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:
No research evidence was identified

Panel discussion:

● COST-EFFECTIVENESS

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:
No research evidence was identified

Panel discussion:
Unclear. Cost to implement but savings in prevention.

● EQUITY

What would be the impact on health equity?

Judgement:

☐ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☐ Probably increased	☒ Increased

Research evidence:
No research evidence was identified

Panel discussion:
Accessible, high quality information, education and resources increase equity.

● ACCEPTABILITY

Is the option acceptable to key stakeholders?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

Research evidence:
No research evidence was identified

Panel discussion:
System change may be challenging in PCOS being prioritised.

● **FEASIBILITY**

Is the option feasible to implement?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

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PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by ECR Lead: Eka Melson

Other Members: Meri Davitadze, Punith Kempegowda

Supervised, edited and supported by the Evidence Team (Jillian Tay, Aya Mousa)

GDG 2

Question 2.6.2.

What are the characteristics of available models of care implemented in PCOS clinic or service?

1. STUDY SELECTION

Table 1. PICO Criteria for Inclusion	
Question	2.6.2 What are the characteristics of available models of care implemented in PCOS clinic or service?
Clinical leads (key contacts)	Jacky Boivin, Chau Thien Tay, Mala Thondan
Allocation ranking	Level 1 – New systematic review

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(language, year)*
Inclusion	Females of any age, ethnicity or weight diagnosed with PCOS (by Rotterdam, NIH, or AES). Subgroups: • Adolescents • Phenotypes • Ethnicity • Geographical	Models of [health] care (collaboration between disciplines – bio- psychosocial approach to wellbeing) Note where defined. Include: interdisciplinary, integrated primary or specialist care; transition of care; individually tailored care plans; self-management, shared decision-making, patient-centred care, decision-support, community informed care, digital first.	None, usual care, or others	Delivery of a care Model, Cost Effectiveness (long-term), Patient-defined outcomes (e.g., satisfaction with care), Improved communication (between staff and between staff and patients), Patient health outcomes (e.g., improved physical functioning, improved mental functioning), Timely access to care and treatment (efficiency of care), Quality of Life, Self-rated emotional wellbeing, Optimal self-management indicators.	Evidence based guidelines, systematic reviews, any primary study.	English language
Exclusion	Females without diagnosed PCOS.	Clinical trials that evaluate specific interventions (lifestyle management, mobile app) that are not a component of a broader disease management framework (as defined above)	Not applicable	Not applicable	Non-evidence-based guidelines. Abstracts, protocol, clinical trial registration.	

2. SEARCH STRATEGY

Search details	
Search strategy source: 2018 PCOS Guideline Technical Report	
Evidence source	**Date of search**
Medline (Ovid)	**11/7/2022**
PsychInfo (Ovid)	**11/7/2022**
EMBASE	**11/7/2022**
All EBM (Ovid)	**11/7/2022**
CINAHL	**11/7/2022**
Any subsequent updates - enter database and date: not applicable	

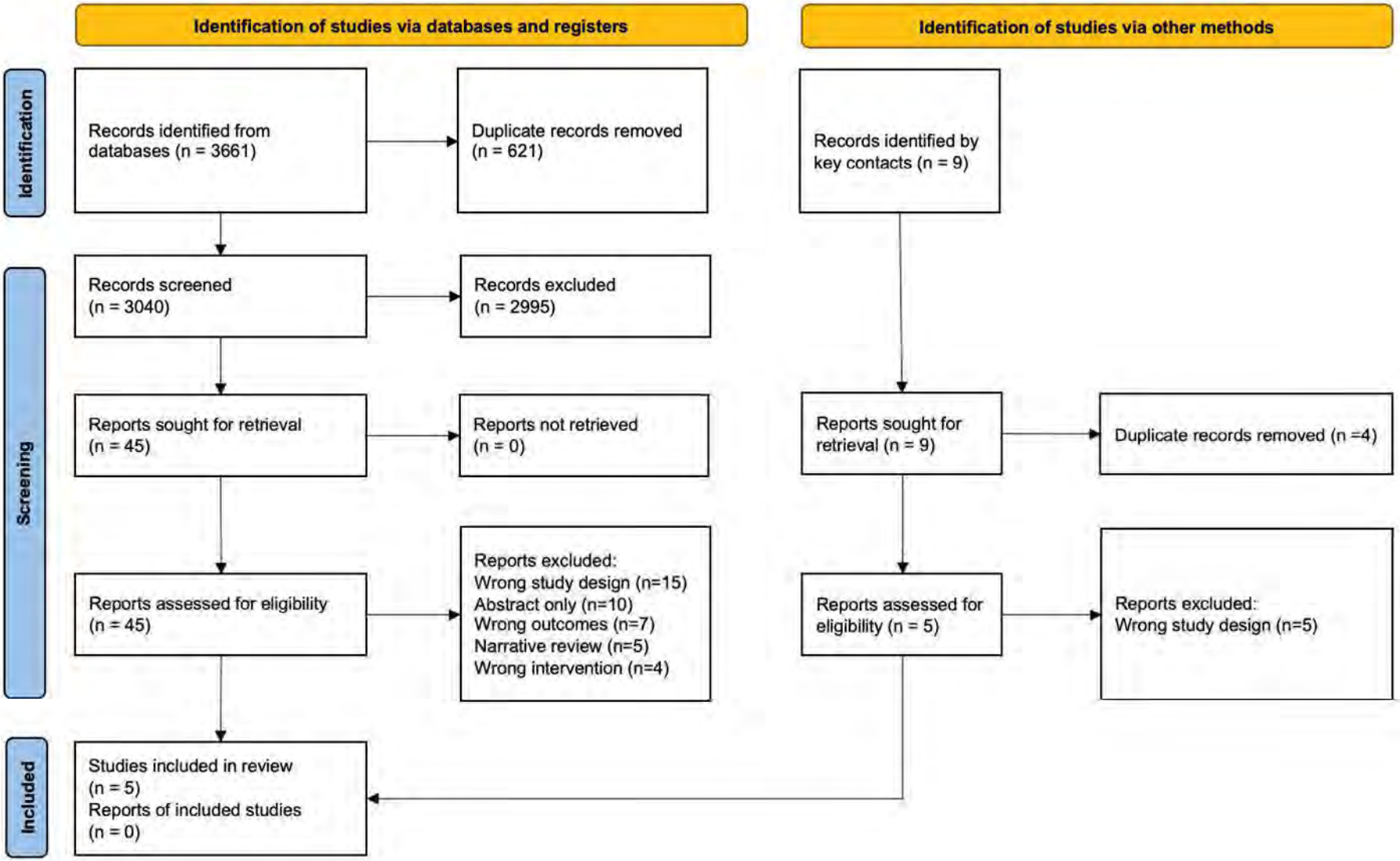
Questions addressed by this search:		
GDG	**Q#**	**Question**
2	**2.6.2**	**What are the characteristics of available models of care implemented in PCOS clinic or service?**

OVID Medline, All EBM, EMBASE	CINAHL
1. exp polycystic ovary syndrome/	1. SU polycystic ovary syndrome
2. polycystic ovar*.mp.	2. polycystic ovar*
3. poly-cystic ovar*.mp.	3. poly-cystic ovar*
4. PCO*.mp.	4. PCO*
5. (stein-leventhal or leventhal).mp.	5. Stein-leventhal or Leventhal
6. anovulation/	6. SU Ovarian cysts
7. anovulat*.mp.	7. SU anovulation
8. oligo-ovulat*.mp.	8. Oligo-ovulat*
9. oligoovulat*.mp.	9. Oligoovulat*
10. (ovar* adj5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*)).mp.	10. ovar* N5 sclerocystic or ovar* N5 polycystic or ovar* N5 poly-cystic or ovar* N5 degenerat* or ovar* N5 hyperandrogen*or ovar* N5 hyperandrogen*
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	11. S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10
12. exp Patient Care Team/	12. MH “Consumer Participation +”)
13. exp "Continuity of Patient Care"/	13. (MH "Self Care+")
14. exp Patient Care Planning/	14. (MH "Self Concept+"
15. exp Case Management/	15. ((self or self directed or self-directed or selfmonitor* or selfmonitor* or symptom*) N (care or help or manag* or efficacy or admin* or concept))
16. exp Patient Care Management/	16. Health communication
17. exp "Delivery of Health Care, Integrated"/	17. Interdisciplinary communication
18. exp Patient-Centered Care/	18. Patient Care Management
19. exp Interdisciplinary Communication/	19. Case-management Or care-coordination OR care-co-ordination Or care-planning
20. exp Managed Care Programs/	20. (MH "Continuity ofPatient Care+")
21. models, organizational/	21. (Multidisciplin* or multi-disciplin* or multiprofessional or multi-professional or interdisciplin* or interdisciplin* or (multi*and profession*))
22. (Case-management or care-coordination or care-co-ordination or care-planning).mp.	22. ((Interdiscipin* or step* or collaborat* or health or patient* or integrat* or parallel* or stratifi ed or matched or comanaged or comanaged or shared or primary or specialis* or transition* or tailored or biopsychosocial orcontin* or individual* ormodel*) N care)
23. (Multidisciplin* or multi-disciplin* or multiprofessional or multi-professional or interdisciplin* or inter-disciplin* or (multi* and profession*)).mp.	23. (MH "Patient CarePlans+") OR (MH"MultidisciplinaryCare Team+") OR
24. ((Interdiscipin* or step* or collaborat* or health or patient* or integrat* or parallel* or stratified or matched or co-managed or comanaged or shared or primary or specialis* or transition* or tailored or bio-psychosocial or contin*or individual* or model*) adj care).mp.	
25. ((team-oriented or team oriented) adj (healthcare or health-care or model or practice)).mp.	
26. ((inter-professional or interprofessional or integrat* or "home treatment") adj (team or health-care or healthcare or model or practice)).mp.	
27. exp Consumer Participation/	
28. exp Self Care/	

29. exp Self Concept/ 30. exp Decision Making, Shared/ 31. exp Decision Support Systems, Clinical/ or decision-support.mp. 32. community informed care.mp. 33. digital first.mp. 34. ((self or self directed or self-directed or self monitor* or self-monitor* or symptom*) adj (care or help or manag* or efficacy or admin* or concept)).mp. 35. or/12-34 36. 11 and 35 37. limit 36 to (english language and humans)	(MH"ComputerizedPatient Record") OR (MH"Patient CenteredCare") 24. (MH "CaseManagement") OR (MH"Decision SupportSystems, Management") 25. (MH "Health Care Delivery+") OR (MH"Health Care Delivery,Integrated") 26. (MH "Managed CarePrograms+") 27. ((team-oriented or team oriented) N (healthcare or healthcare or model or practice)) 28. ((inter-professional or interprofessional or integrat* or "home treatment") N (team or health-care or healthcare or model or practice)) 29. patient centered care or patient-centred care or person centred care or person-centred care 30. shared decision making 31. Decision support or decision-support 32. community informed care 33. digital first 34. S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 35. S11 AND S34

Evidence processing: Studies were selected and appraised by two reviewers in consultation with the evidence team/ key contact using study selection and appraisal criteria (PICO above) established a priori. The articles were reviewed by title and abstract by two reviewers. When a decision could not be made based on title and abstract alone, full text was retrieved. **In total, five studies met inclusion criteria for this review.**

3. SEARCH RESULTS - PRISMA flowchart



4. STUDY INCLUSION

4.1 Included studies

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4.2 Excluded Studies (on full text assessment)

1	Thomson, R. L., Buckley, J. D., Lim, S. S., Noakes, M., Clifton, P. M., Norman, R. J., & Brinkworth, G. D. (2010). Lifestyle management improves quality of life and depression in overweight and obese women with polycystic ovary syndrome. *Fertility and Sterility*, *94*(5), 1812–1816. https://doi.org/10.1016/J.FERTNSTERT.2009.11.001	Wrong study design
2	Colwell, K., Lujan, M. E., Lawson, K. L., Pierson, R. A., & Chizen, D. R. (2010). Women's perceptions of polycystic ovary syndrome following participation in a clinical research study: implications for knowledge, feelings, and daily health practices. *Journal of Obstetrics and Gynaecology Canada : JOGC = Journal d'obstetrique et Gynecologie Du Canada : JOGC*, *32*(5), 453–459. https://doi.org/10.1016/S1701-2163(16)34499-1	Wrong study design
3	Cooney, L. G., Milman, L. W., Hantsoo, L., Kornfield, S., Sammel, M. D., Allison, K. C., Epperson, C. N., & Dokras, A. (2018). Cognitive-behavioral therapy improves weight loss and quality of life in women with polycystic ovary syndrome: a pilot randomized clinical trial. *Fertility and Sterility*, *110*(1), 161-171.e1. https://doi.org/10.1016/J.FERTNSTERT.2018.03.028	Wrong study design
4	Jiskoot, G., Dietz de Loos, A., Beerthuizen, A., Timman, R., Busschbach, J., & Laven, J. (2020). Long-term effects of a three-component lifestyle intervention on emotional well-being in women with Polycystic Ovary Syndrome (PCOS): A secondary analysis of a randomized controlled trial. *PloS One*, *15*(6). https://doi.org/10.1371/JOURNAL.PONE.0233876	Wrong study design
5	Arentz, S., Smith, C. A., Abbott, J., Fahey, P., Cheema, B. S., & Bensoussan, A. (2017). Combined Lifestyle and Herbal Medicine in Overweight Women with Polycystic Ovary Syndrome (PCOS): A Randomized Controlled Trial. *Phytotherapy Research : PTR*, *31*(9), 1330–1340. https://doi.org/10.1002/PTR.5858	Wrong study design
6	Hephzibah Kirubamani, N., & Abraham, M. (2018). Effect of aerobic exercise (Self-help strategy) on the common endocrine problem (PCOS) in late adolescent & young women & impact on their quality of life. *International Journal of Research in Pharmaceutical Sciences*, *9*(4), 1238–1242. https://doi.org/10.26452/IJRPS.V9I4.1663	Wrong study design
7	Young, C. C. (2018). *An Integrated Self-Management Intervention for Adolescents With Polycystic Ovary Syndrome*. ClinicalTrials.Gov. https://www.clinicaltrials.gov/ct2/show/NCT03600337	Abstract only - abstract not found (clinicaltrial.gov)
8	al Khalifah, R. A., Flórez, I. D., Dennis, B., Neupane, B., Thabane, L., & Bassilious, E. (2015). The effectiveness and safety of treatments used for polycystic ovarian syndrome management in adolescents: a systematic review and network meta-analysis protocol. *Systematic Reviews*, *4*(1). https://doi.org/10.1186/S13643-015-0105-4	Wrong outcomes
9	Jiskoot G, Timman R, Beerthuizen A, de Loos AD, Busschbach J, & Laven J. (2019). The impact of a three-component lifestyle intervention on emotional well-being in	Wrong study design- RCT

	women with PCOS | Cochrane Library. *66th Annual Meeting of the Society for Reproductive Investigation*. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01912734/full	
10	Tamilselvi, S., Nalini, S. J., & Vijayaraghavan, R. (2018). Effectiveness of Self Help Strategies {SHS} for PCOS among Young Adult Girls at Selected Colleges at Chennai- Pilot study report. *Research Journal of Pharmacy and Technology*, *11*(7), 3145–3148. https://doi.org/10.5958/0974-360X.2018.00577.2	Wrong outcomes
11	Ansari, F., Hamzehgardeshi, Z., Elyasi, F., Moosazadeh, M., & Ahmadi, I. (2021). The effect of motivational interview based on WhatsApp on the psychological domains of quality of life in infertile women with pcos: A randomized clinical trial. *European Psychiatry*, *64*(S1), S789–S789. https://doi.org/10.1192/J.EURPSY.2021.2086	Abstract only and the data presented does not include description of the model.
12	Holbrey, S., & Coulson, N. S. (2013). A qualitative investigation of the impact of peer to peer online support for women living with Polycystic Ovary Syndrome. *BMC Women's Health*, *13*(1), 1–9. https://doi.org/10.1186/1472-6874-13-51/TABLES/1	looked only at peer to peer online support which is outside the scope of this review
13	Moore, A., & Caldwell, J. (n.d.). The importance of collaboration in treating chronic disease: a focus on PCOS and group medical visits. *Women's Health Care: A Practical Journal for Nurse Practitioners*, *10*(9), 10–18.	abstract only
14	Tamilselvi, S., & Nalini, S. J. (2020). Effectiveness of self help strategies (SHS) for PCOS on biochemical parameters among young adult girls. *International Journal of Research in Pharmaceutical Sciences*, *11*(3), 3034–3041. https://doi.org/10.26452/IJRPS.V11I3.2400	Wrong outcomes
15	Malik, S. (2016). Indian Fertility Society Good Clinical Practice PCOS Guidelines. *Women's Health*, *12*(1), 91. https://doi.org/10.2217/WHE.15.96	Narrative review
16	van der Spuy, Z. M. (2018). Guidelines for the assessment and management of polycystic ovary syndrome | Obstetrics and Gynaecology Forum. *Obstetrics and Gynaecology Forum*, *28*(4). https://journals.co.za/doi/10.10520/EJC-1221c30714	Wrong study design
17	Lathia, T., Joshi, A., Behl, A., Dhingra, A., Kalra, B., Dua, C., Bajaj, K., Verma, K., Malhotra, N., Galagali, P., Sahay, R., Mittal, S., Bajaj, S., Moorthy, S., Sharma, S., & Kalra, S. (2022). A Practitioner's Toolkit for Polycystic Ovary Syndrome Counselling. *Indian Journal of Endocrinology and Metabolism*, *26*(1), 17–25. https://doi.org/10.4103/IJEM.IJEM_411_21	Narrative review
18	Boyle, J. A., Xu, R., Gilbert, E., Kuczynska-Burggraf, M., Tan, B., Teede, H., Vincent, A., & Gibson-Helm, M. (2018). Ask PCOS: Identifying Need to Inform Evidence-Based App Development for Polycystic Ovary Syndrome. *Seminars in Reproductive Medicine*, *36*(1), 59–65. https://doi.org/10.1055/S-0038-1667187	Wrong study design – Explores the impact of Ask PCOS app rather than clinic service
19	Roessler, K. K., Glintborg, D., Ravn, P., Birkebaek, C., & Andersen, M. (2012). Supportive relationships--psychological effects of group counselling in women with polycystic ovary syndrome (PCOS). *Communication & Medicine*, *9*(2), 125–131. https://doi.org/10.1558/CAM.V9I2.125	examine the psychological impact of a group-oriented approach to disease management and health behaviour in PCOS
20	Young, C. C., Sagna, A. O., Monge, M., & Rew, L. (2020). A Theoretically Grounded Exploration of Individual and Family Self-Management of Polycystic Ovary Syndrome in Adolescents. *Comprehensive Child and Adolescent Nursing*, *43*(4), 348–362. https://doi.org/10.1080/24694193.2019.1679278	explored the context and processes of self-management among adolescents, and parents of adolescents, who have PCOS.
21	Alenzi, E. O. (2021). Cost-effectiveness analysis of polycystic ovary syndrome management and the risk of gestational diabetes in pregnant women: a decision-tree model. *Expert Review of Pharmacoeconomics & Outcomes Research*, *21*(5), 995–999. https://doi.org/10.1080/14737167.2020.1819796	estimated the cost-effectiveness of metformin to reduce the risk of gestational diabetes mellitus (GDM) in pregnant women with polycystic ovary syndrome (PCOS)
22	Harrison, E., & Lach, H. W. (2017). Group visits for management of patients with PCOS: A pilot study. *Women's Healthcare: A Clinical Journal for NPs* , *5*(4), 44–49. https://www.npwomenshealthcare.com/group-visits-patients-pcos/	aims were (1) to assess the feasibility of implementing group visits in a university setting, (2) to evaluate changes in patient confidence in their ability to self-manage PCOS (self-efficacy), and (3) to ascertain whether participants begin to engage in health-promoting diet and exercise behaviors.

23	Young, C. C., Rew, L., & Monge, M. (2019). Transition to Self-Management among Adolescents with Polycystic Ovary Syndrome: Parent and Adolescent Perspectives. *Journal of Pediatric Nursing*, *47*, 85. https://doi.org/10.1016/J.PEDN.2019.04.024	Wrong study design - explored parental and adolescent views of the transition to PCOS self-management
24	Newland, A. (2019). PCOS management: A multifaceted approach to care. *Nurse Practitioner*, *44*(7), 1–2. https://doi.org/10.1097/01.NPR.0000565124.92469.D2	Narrative review
25	Romanski, P., & Stanic, A. K. (2017). Practical Approach to the PCOS Patient. *Current Obstetrics and Gynecology Reports 2017 6:1*, *6*(1), 11–20. https://doi.org/10.1007/S13669-017-0190-6	Narrative review
26	Liu, R., Li, M., Wang, P., Yu, M., Wang, Z., & Zhang, G. Z. (2022). Preventive online and offline health management intervention in polycystic ovary syndrome. *World Journal of Clinical Cases*, *10*(10), 3060–3068. https://doi.org/10.12998/WJCC.V10.I10.3060	Wrong outcomes
27	Askue B, Buckworth J, Choi-Pearson R, Kiacz ML, Latanick M, & Warbel A. (2007). Encouraging lifestyle modification in the treatment of PCOS in college-age women: a multidisciplinary group approach. . *Women's Health Care: A Practical Journal for Nurse Practitioners* , *6*(11), 29–29.	Abstract only
28	Savage, K., Abudu, B., Porter, M., & Reynolds, R. (2019). Factors determining patient-reported improvement in hirsutism in a multidisciplinary PCOS clinic. *Journal of the American Academy of Dermatology*, *81*(4), AB211. https://doi.org/10.1016/j.jaad.2019.06.776	Wrong outcome
29	Tay, C. T., Moran, L. J., Wijeyaratne, C. N., Redman, L. M., Norman, R. J., Teede, H. J., & Joham, A. E. (2018). Integrated Model of Care for Polycystic Ovary Syndrome. *Seminars in Reproductive Medicine*, *36*(1), 86–94. https://doi.org/10.1055/S-0038-1667310	Narrative review
30	Auble, B., Elder, D., Gross, A., & Hillman, J. B. (2013). Differences in the management of adolescents with polycystic ovary syndrome across pediatric specialties. *Journal of Pediatric and Adolescent Gynecology*, *26*(4), 234–238. https://doi.org/10.1016/J.JPAG.2013.03.007	Wrong outcomes
31	Pirotta, S., Joham, A. E., Moran, L. J., Skouteris, H., & Lim, S. S. (2021). Implementation of the polycystic ovary syndrome guidelines: A mixed method study to inform the design and delivery of a lifestyle management program for women with polycystic ovary syndrome. *Nutrition & Dietetics: The Journal of the Dietitians Association of Australia*, *78*(5), 476–486. https://doi.org/10.1111/1747-0080.12670	Wrong intervention
32	Brooks, M. A. (2005). Online support services: General well-being in women with polycystic ovarian syndrome as a function of the amount of time and satisfaction with online support services. *Dissertation Abstracts International: Section B*, *66*(5-B), 2811.	Dissertation abstract. Not enough information to include in the review
33	Abudu, B., Golbari, N., Porter, M., & Reynolds, R. (2019). Patient characteristics and subjective improvement of acne in a multidisciplinary polycystic ovary syndrome clinic. *Journal of the American Academy of Dermatology*, *81*(4), AB99. https://doi.org/10.1016/j.jaad.2019.06.383	Abstract only. Wrong outcome
34	Liao, L. M., Nesic, J., Chadwick, P. M., Brooke-Wavell, K., & Prelevic, G. M. (2008). Exercise and body image distress in overweight and obese women with polycystic ovary syndrome: a pilot investigation. *Gynecological Endocrinology : The Official Journal of the International Society of Gynecological Endocrinology*, *24*(10), 555–561. https://doi.org/10.1080/09513590802288226	Wrong intervention - looked only at exercise intervention
35	R, R., JOSE, S. A., K, M., & KM, S. N. (2019). Quality of life in women with polycystic ovarian syndrome: Requisite of clinical pharmacist intervention. *Asian Journal of Pharmaceutical and Clinical Research*, *12*, 100–105. https://doi.org/10.22159/AJPCR.2019.V12I11.34426	Wrong study design - The study was designed to assess the impact of counseling on QOL in the above patients.not studying effectiveness
36	Eldridge, S., Murphy, C., & Elsheikh, M. (2007). Audit of the Polycystic Ovary Syndrome (PCOS) Nurse led weight management clinic. *Endocrine Abstracts*. https://www.endocrine-abstracts.org/ea/0013/ea0013p255	Conference abstract. Insufficient information to include in the review
37	Ghosh, D., Murphy, C., & Elsheikh, M. (2005). *A 2 year audit of the polycystic ovary syndrome (PCOS) clinic at the Royal Berkshire Hospital | BES2005 | 24th Joint Meeting of the British Endocrine Societies | Endocrine Abstracts*. Endocrine Abstracts. https://www.endocrine-abstracts.org/ea/0009/ea0009p79	Conference abstract. Insufficient information to include in the review

38	Gour, A., Dubey, P., Goel, A., & Halder, A. (2022). Remote assessment and reinforcement of patient awareness of role of lifestyle modification and treatment adherence in polycystic ovary syndrome using an online video based educational module. *Journal of the Turkish German Gynecological Association*, *23*(1), 1–7. https://doi.org/10.4274/JTGGA.GALENOS.2021.2021-9-29	Wrong study outcome - evaluated the role of an online, video-based, structured, educational module in increasing awareness in women with polycystic ovary syndrome (PCOS).
39	Hebbar, M., Shaikh, S., Zia, N., Sheikh, J., Wicks, S., Jayaprakash, S., Narendran, A., Khalil, H., Gleeson, H., Robinson, L., Ch, J. J., Lathia, T., Selvan, C., Arlt, W., & Kempegowda, P. (2022). PCOS SEVa: High prevalence anxiety and body dysmorphia in women with PCOS attending specialist care in the UK and India. *Endocrine Abstracts*, *81*. https://doi.org/10.1530/ENDOABS.81.EP898	Conference abstract. Insufficient information, did not study effectiveness
40	Kazemi, M., McBreairty, L. E., Zello, G. A., Pierson, R. A., Gordon, J. J., Serrao, S. B., Chilibeck, P. D., & Chizen, D. R. (2020). A pulse-based diet and the Therapeutic Lifestyle Changes diet in combination with health counseling and exercise improve health-related quality of life in women with polycystic ovary syndrome: secondary analysis of a randomized controlled trial. *Journal of Psychosomatic Obstetrics and Gynaecology*, *41*(2), 144–153. https://doi.org/10.1080/0167482X.2019.1666820	Not PCOS MoC
41	Percy, C. A., Gibbs, T., Potter, L., & Boardman, S. (2009). Nurse-led peer support group: experiences of women with polycystic ovary syndrome. *Journal of Advanced Nursing*, *65*(10), 2046–2055. https://doi.org/10.1111/J.1365-2648.2009.05061.X	Explore the experiences of women with polycystic ovary syndrome attending a nurse-led support group.
42	Schmidt, T. H., Khanijow, K., Cedars, M. I., Huddleston, H., Pasch, L., Wang, E. T., Lee, J., Zane, L. T., & Shinkai, K. (2016). Cutaneous Findings and Systemic Associations in Women With Polycystic Ovary Syndrome. *JAMA Dermatology*, *152*(4), 391–398. https://doi.org/10.1001/JAMADERMATOL.2015.4498	Wrong study design - To identify cutaneous and systemic features of PCOS that help distinguish women who do and do not meet the diagnostic criteria.
43	Moradi, F., Ghadiri-Anari, A., Dehghani, A., Vaziri, S. R., & Enjezab, B. (2020). The effectiveness of counseling based on acceptance and commitment therapy on body image and self-esteem in polycystic ovary syndrome: An RCT. *International Journal of Reproductive Biomedicine*, *18*(4), 243. https://doi.org/10.18502/IJRM.V13I4.6887	Wrong intervention - not multidisciplinary; determined the effectiveness of group counseling based on acceptance and commitment therapy (ACT) on body image and self-esteem in patients with PCOS
44	Wang, L. H., Liu, Y., Tan, H., & Huang, S. (2022). Transtheoretical model-based mobile health application for PCOS. *Reproductive Health*, *19*(1). https://doi.org/10.1186/S12978-022-01422-W	Wrong intervention - not multidisciplinary; examined the effect of transtheoretical model-based mobile health application intervention program for PCOS.
45	Young, C. C., Monge, M., Minami, H., Rew, L., Conroy, H., Peretz, C., & Tan, L. (2022). Outcomes of a Mindfulness-Based Healthy Lifestyle Intervention for Adolescents and Young Adults with Polycystic Ovary Syndrome. *Journal of Pediatric and Adolescent Gynecology*, *35*(3), 305–313. https://doi.org/10.1016/J.JPAG.2021.10.016	Wrong intervention - not multidisciplinary; examined the feasibility, acceptability, and preliminary efficacy of a mindfulness-based healthy lifestyle self-management intervention with adolescents and young adults diagnosed with polycystic ovary syndrome (PCOS).
46	Atijosan, A. B. (2020). Torturing the helpless: A review of PCOS induced infertility from a gender perspective. *Journal of Gender and Power*, *14*(2), 157–168. https://doi.org/10.2478/JGP-2020-0019	Wrong study design
47	Dapherede Otusanya, A. (n.d.). *"If You Never Came in and Saw Me, You Would Probably Be Dead": Exploring Intercultural Communication and Health Communication Issues Surrounding Pcos*.	Wrong study design- thesis on experiences rather than model of care
48	Gezer, E., Piro, B., Cantürk, Z., Çetinarslan, B., Sözen, M., Selek, A., Işik, A. P., & Seal, L. J. (2021). The Comparison of Gender Dysphoria, Body Image Satisfaction and Quality of Life Between Treatment-Naive Transgender Males With and Without Polycystic Ovary Syndrome. *Https://Home.Liebertpub.Com/Trgh*. https://doi.org/10.1089/TRGH.2021.0061	Wrong study design- evaluated the association of oligo-anovulation and/or features of hyperandrogenism with the scores on the Utrecht Gender Dysphoria Scale (UGDS), the Body Image Scale (BIS), and the Short Form-36 Health Survey

		(SF-36) in treatment-naive trans men with PCOS seeking help for gender transition
49	Guss, C. E., & Pitts, S. (2018). Remember to Ask About Gender: Management of Polycystic Ovary Syndrome in Transgender Male Adolescents. *Journal of Pediatric and Adolescent Gynecology*, *31*(2), 182–183. https://doi.org/10.1016/j.jpag.2018.02.060	Wrong study design- looked into experiences of transgender male adolescents in PCOS clinic

5. STUDY CHARACTERISTICS TABLE FOR INCLUDED STUDIES

Author, year, country	Population/ Setting	Study Design	Sample Size per group	Intervention details (Models of care (MoC) details)	Outcomes measured	Summary of findings	Risk of Bias (RoB)
Bekx et al. 2010	Adolescent girls with PCOS. American Family Children's Hospital in Madison, Wisconsin.	Retrospective chart review	70 adolescents	The team consists of 2 paediatric endocrinologists, a paediatric gynaecologist, a reproductive endocrinologist, a nutritionist, and a health psychologist.	Chart review of patients seen in the first 33 months for details of initial presentation, age, body mass index (BMI), menstrual pattern, clinical and laboratory features of androgen excess, insulin resistance, and dyslipidaemia.	Seventy patients (84% Caucasian) presented with an average age at referral of 16.2 years (range 11-22 y). Eighty four percent had a BMI O the 85th percentile and 70% had a BMI O 95th percentile. Menstrual pattern was quite varied, with some patients having primary amenorrhea, and over 50% experiencing hirsutism. There were 3 cases of type 2 diabetes, and over half of the patients had elevated fasting insulin levels and low HDL levels.	Mod
Geirer et al. 2012		Retrospective chart review	110 adolescents		Change in weight.	In this multidisciplinary clinic for adolescents with PCOS, nearly 70% of patients succeeded in short-term weight stabilization, with 57% demonstrating weight loss. Interactions with the health psychologist and dietitian appeared to play a key role in successful weight control, supporting the importance of psychology and nutrition expertise in the management of this disorder.	Mod
Boyle et al. 2017	Primary care clinic on Thursday Island	Mixed method comprising a medical record audit, semi-structured interviews and focus group discussions.	36 adult women with PCOS, 8 clinicians	Multidisciplinary clinic comprising a general practitioner, women's health nurse, dietitian and women's health worker	i) Fidelity to evidence-based guidelines, (ii) barriers and enablers to women using the service, (iii) the ability to meet the needs of women and the community.	The clinic was largely successful in providing evidence-based care with up to 78% of women receiving recommended cardiometabolic screening, 100% emotional screening and 89% lifestyle management despite the remoteness of the clinic and limited financial and human resources. Health care providers report sustainability of the clinic will be dependent on factors including staffing, administrative support and inclusion of Aboriginal and Torres Strait Islander health workers.	Mod
Tay et al. 2021	Public, tertiary hospital clinic	Semi structured interview and survey.	15 adults	The MoC comprises of endocrinologist clinic, dermal and laser therapy, mental health screening, lifestyle coaching and education	1) Evaluation of the service across the framework of appropriateness, effectiveness, efficiency and	Integrated, evidence-based PCOS service was well-received and women were generally satisfied with appropriateness, effectiveness, and reported	Low

				on evidence-based information.	impact. 2) Surveys on patient's satisfaction across services provided by the clinic.	positive health impact resulting from the service.	
Torres-Zegarra et al. 2021	Tertiary care hospital.	Retrospective chart review	92 adolescents	multidisciplinary clinic including endocrinology, gynaecology/adolescent medicine, dermatology, psychology, and nutrition to provide comprehensive care to adolescent girls with polycystic ovary syndrome (PCOS)	Medical history, physical examination findings, laboratory measurements and prescribed therapies.	In adolescents with PCOS and obesity, metabolic, dermatologic, and psychologic co-morbidities are common. The use of a multidisciplinary clinic model including dermatology in addition to endocrinology, gynaecology, psychology, and lifestyle experts provides care for most aspects of PCOS.	Low

6. FINDINGS

- **EVIDENCE SUMMARY:**

Five studies evaluated or examined outcomes on patients from four PCOS health services. Study designs included cross-sectional and mix-method evaluation. Two studies were rated low risk of bias (Tay 2021, Torres-Zegarra, 2021) and the rest were rated moderate risk of bias. Service evaluation was reported by two studies (Boyle 2016, Tay 2021), patient outcome evaluation was reported by four studies (Bekx 2010, Boyle 2016, Geier 2012, Tay 2021).

- **DESCRIPTIVE ANALYSIS SUMMARY:**

Of the four PCOS health services included in the review, two were adult services based in Australia and two were adolescent services based in the United States. Three of the services were within tertiary hospital settings and only one of the services was in a primary care clinic setting. All the services involved two or more disciplines. Some form of structural lifestyle management, cardiometabolic risk assessment or management, emotional well-being screening and reproductive health management were provided in all four services. Dermatological screening or management was described in three of the four services. Evaluation of the PCOS health services or patient outcomes were heterogeneous, precluding meta-analysis or GRADE assessment.

6.1 Outcome 1: PCOS models of care

Study	Bekx 2010 Geier, 2012	Boyle 2016	Tay 2021	Torres-Zegarra 2021
Service name	Adolescent polycystic ovarian syndrome (PCOS) clinic at the American Family Children's Hospital.	No specific name. Described as "pilot PCOS clinic on Thursday Island, total of 11 clinics involved.	Monash Health statewide integrated polycystic ovary syndrome (PCOS) service.	Multidisciplinary clinic for PCOS at (Children's Hospital Colorado) CHCO.
Location, country	Wisconsin, United States	Thursday Island, Queensland, Australia	Victoria, Australia	Colorado, United States
Year of establishment	2005	2012	2017	2012
Was this codesigned by clinician and patients?	Not described.	Not described.	Yes, not specified how it was codesigned.	Yes (They restructured the clinic taking into account of patients' feedback)

Setting	Tertiary. American Family Children's Hospital, Madison, Wisconsin.	Primary care clinic, private/public not described.	Public, tertiary hospital clinic	Tertiary hospital.
Patient group	Adolescent girls with PCOS (11.4-22yo) Beck 2010: In the first 33 months, among the new referrals, 84% of whom were Caucasian, 8.5% African American, 4% Hispanic, and 1.5% other.	Adult women with PCOS, women self-identified as Torres Strait Islander (75%)	Adult	Child and adolescents with PCOS, 11-24yo
Disciplines/ allied health involved	2 pediatric endocrinologists, a pediatric gynecologist, a reproductive endocrinologist, a nutritionist, and a health psychologist, reproductive endocrinologist, a nutritionist, and a heal: th psychologist	General practitioner, women's health nurse, dietitian and women's health worker.	Endocrinology, dermatology, health coach, dietician	Pediatric Endocrinologists, Gynecologists/Adolescent Medicine Specialists, Dermatologists (added 2 years later in 2014), Psychologists, Nutritionists, and Exercise Physiologists.
Description of model	Beck 2010: Thirty percent of the patients saw all 4 providers at the first visit (endocrinology, gynecology, health psychology, and nutrition). A breakdown of individual use demonstrated that 43% saw the health psychologist, 66% saw the nutritionist, 69% saw the gynecologist, and 100% saw the endocrinologist. Geier 2012: Forty-one percent (46/110) of the patients saw all 5 providers at the initial visit. A breakdown of the individual utilization demonstrated that 100% of the subjects saw an endocrinologist and endocrine nurse, 60.9% saw a health psychologist, 75.5% saw a dietitian, and 70.0% saw a gynecologist	The clinic is multidisciplinary comprising a general practitioner, women's health nurse, dietitian and women's health worker. The women's health nurse was unique in this clinic as she generated most of the PCOS clinic referrals from her work throughout the islands in the Torres Strait. Once a client was at the clinic her role was to take a detailed history and provide 30– 60 min of education on PCOS, which covered emotional health, bleeding problems, infertility, endometrial protection, lifestyle factors, etc. She arranged ultra- sounds if required. Most women (78%) saw all three (women's health nurse, GP and dietitian) on their first visit with 20% of patients missing the dietitian appointment when this was not available due to staff leave.	The MoC comprises of endocrinologist clinic, dermal and laser therapy, mental health screening, lifestyle coaching and education on evidence-based information. Endocrinologist provided comprehensive care including diagnosis confirmation, screening and management of long-term health complications. Dermal laser therapy uses medical grade laser to treat women with hirsutism at a heavily subsidised fee. Mental health screening uses modified PCOSQ and HADS on first appointment. lifestyle coaching involves 2 lifestyle group sessions facilitated by dietitian and/or health coach included discussion of healthy diet and physical activity, personal goal-setting activity and identifying techniques for potential barriers. Education on evidence-based information - education on clinical features, diagnosis, complications, and management of PCOS provided via a single group session or printed fact sheets on first appointment	8 patients per clinic. Each patient saw every specialty during the visit. Specialists and topics addressed in clinic were designed to follow the most recently published Endocrine Society PCOS guidelines. After clinic restructured, 6-7 patients and families presenting to clinic for a 90-minute group education session prior to their individual clinic visits. The first 45 minutes were taught by Endocrinology and Gynaecology and reviewed the pathophysiology of PCOS and medical treatment approaches. The remaining 45 minutes were taught by Nutrition and Exercise Physiology and reviewed lifestyle recommendations. Most updated structure: 75-minute group class for 6-7 new patients, who are then roomed for their individual appointments, and then 6-7 follow-up patients who have individual appointments with all specialists. For Spanish-speaking patients, a Spanish interpreter is present for the group class. With COVID restrictions in 2020 (initiated after data collection for this article), we had to stop providing the in-person class and recorded the content for patients to watch prior to their visit.

6.2 Outcome 2: Services or management provided

Study	Bekx 2010 Geier, 2012	Boyle 2016	Tay 2021	Torres-Zegarra 2021
Providing diagnosis	Unclear if any criteria is being used for patients attending the clinic	Unclear if any criteria is being used for patients attending the clinic. On medical audit, 89% women had confirmed diagnosis.	Not specified what criteria however endocrinologist clinic provided comprehensive care including diagnosis confirmation	All patients need clear diagnosis before attending the clinic
Education on long term risk	Not described	Not described	Via single group session or printed fact sheet on first appointment	Provided in powerpoint slides
Lifestyle management/referral	Techniques used by the health psychologist and nutritionist included motivational interviewing, with the health psychologist focusing on life-style changes that were small, but consistent, and likely to lead to more success. The health psychologist also worked with patients to identify barriers that may exist and possible solutions. The nutritionist focused on the role of insulin as an anabolic hormone and a meal plan benefiting those who are insulin resistant (3 meals with 1-2 snacks, and the avoidance of prolonged fasts, inclusion of high-fiber carbohydrates and protein and avoiding non-nutrient dense calories). The role of exercise was emphasized by all. Mentioned of prescription of metformin by endocrinologist for weight management.	Most women (83%) set their own lifestyle goals including reducing portion sizes and increasing daily walking (67%)	2 lifestyle group sessions facilitated by dietitian and/or health coach. included discussion of healthy diet and physical activity, personal goal-setting activity and identifying techniques for potential barriers	By dietitian: - Describe goals of exercise - Set activity and exercise goals at every appointment - Weight trend from baseline and follow up visits - Provide education regarding healthy eating habits
Cardiometabolic screening, management, referral	BMI centiles, lipid profile, insulin, OGTT taken for patients insulin resistance (by fasting glucose to fasting insulin ratio), OGTT, BMI, family hx of T2DM, presence of acanthosis nigricans, lipids	Cardiometabolic risk factors and biochemical variables were assessed after screening on the first visit. A diagnosis of dyslipidaemia, impaired glucose tolerance (IGT), impaired fasting glucose (IFG) and DM2 was made based on existing diagnoses or if abnormal after screening.	Endocrine clinic provided the management of long-term health complications	By endocrinologist: - Obesity: body mass index measurement. - Glucose intolerance / diabetes mellitus: glucose tolerance test, hemoglobin A1c - Dyslipidemia: lipid panel (ideally fasting) - Fatty liver: liver function test - Hypertension: measured blood pressure - Screen overweight/obese adolescents with PCOS for symptoms of obstructive sleep apnea
Emotional well being screening, management, referral	Has health psychologist focusing on life-style changes that were small, but consistent, and likely to lead to more success. However, nothing specific on emotional wellbeing screening/management or referral	Mental well-being screening was undertaken according to guideline recommendations with a Kessler Psychological Distress Scale performed by the GP if abnormal.	Mental health screening uses modified PCOSQ and HADS on first appointment.	By psychologist: - Mental health symptoms (e.g., anxiety, depression) - Appetite self-regulation - Emotional eating - Goal setting for lifestyle modification - Optimizing sleep health
Reproductive screening/family planning/infertility management or referral	Has paediatric gynaecologist however role were not clear	includes lifestyle management, metformin prescription or specialist referral	Family planning discussion provided by the endocrinologist	By gynaecologist/adolescent medicine: - Chronic anovulation:

				menstrual irregularities and diary - Clinical and/or biochemical signs of hyperandrogenism: total/free testosterone, dehydroepiandrosterone sulfate - Polycystic ovarian morphology: pelvic ultrasound - Endometrial hyperplasia: endometrial biopsy. Discussion regarding future infertility issues
Dermatological screening/management	Acne and hirsutisim evaluated	Not described	Dermal laser therapy uses medical grade laser to treat women with hirsutism at a heavily subsidised fee.	By dermatologist: - Hirsutism: Measure modified Ferriman-Gallwey (mFG score) - Presence or absence of acne by physical examination with score of severity - Presence or absence of acanthosis nigricans, androgenic alopecia, hidradenitis suppurativa by physical examination

6.3 Outcome 3: Services evaluation

Study	Bekx 2010 Geier, 2012	Boyle 2016	Tay 2021	Torres-Zegarra 2021
Patient health outcomes: Anthropometry Metabolic Reproductive Psychological Dermatological	Anthropometric: Nearly 70% of patients succeeded in short-term weight stabilization, with 57% demonstrating weight loss.	No evaluation	No evaluation	No evaluation
Patient reported outcomes	No evaluation	Semi-structured interviews: women were motivated to make positive changes to improve their health Focus groups: Women were positive about having access to the clinic and found staff were knowledgeable. collaboration with the dietitian to determine achievable lifestyle goal setting was perceived as valuable, women felt they needed more tailored information and supervised ongoing management.	Overall service 12/15 satisfied, 1/15 neutral and 2/15 unsatisfied. General education 10/15 satisfied, 1/15 neutral, 2/15 not satisfied and 2/15 N/A or DNA. Lifestyle coaching - 11/15 satisfied, 1/15 neutral, 2/15 unsatisfied, 1/15 N/A or DNA. Endocrine clinic 12/15 satisfied, 3/15 neutral. Laser hair reduction service 5/15 satisfied and 10/15 DNA or N/A. 14/15 participants would recommend the PCOS service and 1/15 maybe.	No evaluation
Health professional satisfaction	No evaluation	Semi-structured interviews: The lack of a psychologist was a particular problem. All staff described high levels of job satisfaction and professional investment. Staff perceived that women found the clinic useful, particularly the educational aspect.	No evaluation	No evaluation
Other outcomes	No evaluation	1) Fidelity check list on alignment to PCOS guideline: diagnosis 89&, cardiometabolic screening and test 78%, emotional screening 100%, lifestyle management 89%, infertility management 100% 2) semi-structured interviews: to explore barriers and enablers to clinic implementation, clinic sustainability, service delivery, health promotion and barriers to lifestyle change.	Semi-structured interview 1) Appropriateness: An integrated PCOS service is appropriate for women's multifaceted needs. 2) Effectiveness: The PCOS service was effective in providing care and communicating sensitively to women with PCOS, but more access to the service is required. 3) Impact: A specialized PCOS service had positive impacts on medical management of PCOS, PCOS symptom severity, women's understanding of PCOS, women's confidence in managing PCOS, and general emotional well-being. 4) Efficiency: The efficiency of the PCOS service requires improvement in patient communication, resource provision, infrastructure, and awareness of the service availability. 5) Future suggestions: Women desire more funding to increase and expand the existing PCOS service and be empowered with more resources that promote self management. Patient satisfaction with each clinic	No evaluation

7. GRADE ASSESSMENTS AND EVIDENCE PROFILE

Due to the broad nature of the clinical question and the inclusion of studies of heterogeneous designs, populations and/or aims, it was not feasible to generate GRADE evidence profile tables for this question.

Please see individual study risk of bias assessments to determine the quality of evidence.

APPENDIX. STUDY CHARACTERISTICS AND QUALITY APPRAISAL TEMPLATES

Study ID	Bekx, 2010	
Study Citation	Bekx MT, Connor EC, Allen DB. Characteristics of adolescents presenting to a multidisciplinary clinic for polycystic ovarian syndrome. J Pediatr Adolesc Gynecol. 2010 Feb;23(1):7-10. doi: 10.1016/j.jpag.2009.04.004. Epub 2009 Aug 3. PMID: 19648034.	
Study Country	*United States*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	Adolescent girls with PCOS. In the first 33 months, among the new referrals, 84% of whom were Caucasian, 8.5% African American, 4% Hispanic, and 1.5% other.	
Control population	*No controls*	
PCOS diagnostic criteria	*Not specified what criteria is used for diagnosis of PCOS*	
N per group	*70 patients with confirmed diagnosis of PCOS*	
Setting	*Tertiary. American Family Children's Hospital*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*To characterize patients referred to the adolescent polycystic ovarian syndrome (PCOS) clinic at the American Family Children's Hospital, University of Wisconsin, Madison, Wisconsin.*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* *"Medical records of patients seen as new referrals in the first 33 months were reviewed for details of initial presentation, age, body mass index (BMI), menstrual pattern, clinical and laboratory features of androgen excess as documented in the clinical chart, and insulin resistance. Only those testosterone levels drawn prior to oral contraceptive pill therapy were included in the analysis "*
Exclusion criteria	Yes Partial No Not reported	*Not reported*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*N/A*

Was matching performed?		Yes Partial No Not reported	*N/A*
Summary Result/s		70 patients (84% Caucasian) presented with an average age at referral of 16.2 years (range 11-22y). 84% had a BMI> 85th percentile and 70% had a BMI>95th percentile. Menstrual pattern was quite varied, with some patients having primary amenorrhea, and over 50% experiencing hirsutism. There were 3 cases of type 2 diabetes, and over half of the patients had elevated fasting insulin levels and low HDL levels.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*N/A*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*No* *Included adolescents with PCOS but not specified what criteria used*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*N/A*
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*N/A (only one group)*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*No* *"As many of the laboratory eval- uations were performed at various outside laboratory facilities, with significant differences in normal refer- ence rages, sensitive assays for free and total testos- terone, as well as fasting insulin, were noted as above reference level and not given as absolute values"*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*N/A (only one group)*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Partial. See above.*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*N/A (only one group)*

	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*Not reported*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*N/A (only one group)*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*N/A (only one group)*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes. Descriptive data were used*
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	Geirer, 2012
Study Citation	Geier LM, Bekx MT, Connor EL. Factors contributing to initial weight loss among adolescents with polycystic ovary syndrome. J Pediatr Adolesc Gynecol. 2012 Dec;25(6):367-70. doi: 10.1016/j.jpag.2012.06.008. Epub 2012 Oct 22. PMID: 23089571.
Study Country	*United States*
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	Adolescent girls with PCOS.
Control population	*No controls*
PCOS diagnostic criteria	*Rotterdam 2003*
N per group	*110 patients with confirmed diagnosis of PCOS*
Setting	*Tertiary. American Family Children's Hospital*

Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)		*Change in weight since joining clinic*	
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	*Yes*
Inclusion criteria		Yes Partial No Not reported	*Yes* *Patients seen at the multidisciplinary PCOS clinic…110 were given the diagnosis of PCOS based on the Rotterdam criteria.*
Exclusion criteria		Yes Partial No Not reported	*Not reported*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	*Partial*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Partial Seventy-one percent (78/110) of patients returned for a follow-up visit, with an average interval of 4.5 months (1.5-12 months) between visits.
Was matching performed?		Yes Partial No Not reported	N/A
Summary Result/s		The average age at first visit was 15.9 years. The average BMI was 34.7 kg/m2 (range 18.1-55.5). Seventy-six percent had an initial BMI above the 95th percentile. Interactions with providers at the initial visit included a paediatric endocrinologist (100%), health psychologist (60.9%), dietitian (75.5%) and gynaecologist (70.9%). Seventy one percent returned for a follow-up visit, (average time of 4.5 months between visits) with 57% achieving weight loss (average 3.5 kg) and an additional 12.6% demonstrating no significant weight gain (! 1.5 kg). Thus, 69.6% demonstrated weight loss/stabilization.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*N/A*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes* *Rotterdam criteria were used*
	Was the control status	Yes	*N/A*

	established in a standard, valid and reliable way?	Partial No Not reported	
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*N/A (only one group)*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*N/A (only one group)*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Not reported*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Not reported*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	29.1% lost to follow-up 71% (78/110) of patients returned for a follow-up visit, with an average interval of 4.5 months (1.5-12 months) between visits
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	None
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*N/A (only one group)*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*Not reported*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*N/A (only one group)*
	If statistical analysis was	Yes	*Yes*

	undertaken, was this appropriate?	Partial No Not reported	
COMMENTS		*Low risk of bias*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Boyle, 2017*	
Study Citation	Boyle J, Hollands G, Beck S, Hampel G, Wapau H, Arnot M, Browne L, Teede HJ, Moran LJ. Process evaluation of a pilot evidence-based Polycystic Ovary Syndrome clinic in the Torres Strait. Aust J Rural Health. 2017 Jun;25(3):175-181. doi: 10.1111/ajr.12288. Epub 2016 Apr 18. PMID: 27086940.	
Study Country	*Australia*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	GP, women's health nurse, dietitian involved with the clinic development or implementation, Torres Strait Islander health worker and n = 1 nurse working in sexual health who were not directly involved in the clinic) and focus group discussions with women with PCOS who attended the clinic	
Control population	*N/A*	
PCOS diagnostic criteria	*Rotterdam 2003*	
N per group	Total n = 6: n = 2 GP, n = 1 women's health nurse, n = 1 dietitian involved with the clinic development or implementation, n = 1 Torres Strait Islander health worker and n = 1 nurse working in sexual health who were not directly involved in the clinic) and focus group discussions with women with PCOS who attended the clinic (n = 8)	
Setting	Primary care clinic, private/public not described	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	Process evaluation to assess: (i) Fidelity to evidence-based guidelines, (ii) barriers and enablers to women using the service, (iii) the ability to meet the needs of women and the community.	
Was there a clear statement of the aims of the research?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	Partial. All women who attended the clinic for the first twelve months were eligible for the study but criteria for key informants were not stated.
Exclusion criteria	Yes Partial	No reported

		No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Insufficient information
Summary Result/s		The clinic was largely successful in providing evidence-based care with up to 78% of women receiving recommended cardiometabolic screening, 100% emotional screening and 89% lifestyle management despite the remoteness of the clinic and limited financial and human resources. Health care providers report sustainability of the clinic will be dependent on factors including staffing, administrative support and inclusion of Aboriginal and Torres Strait Islander health workers.	
VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
VALIDITY	Is a qualitative methodology appropriate?	Yes Partial No Not reported	*Yes*
	Was the research design appropriate to address the aims of the research?	Yes Partial No Not reported	*Yes*
	Was the recruitment strategy appropriate to the aims of the research?	Yes Partial No Not reported	Yes, all women (consumers) were included and appropriate staff were included in focus *group*
	Was the data collected in a way that addressed the issue?	Yes Partial No Not reported	Yes Quantitative data were collected to assess for the fidelity to evidence-based guidelines. Interviews and group discussion ranged from 25–45 min to 1–1.5 h respectively and were guided by themes emerging from quantitative data and literature review. This included community acceptance, clinic sustainability and barriers and enablers to the clinic.
	Has the relationship between researcher and participants been adequately considered?	Yes Partial No Not reported	Not reported.
RESULTS	Have ethical issues been taken into consideration?	Yes Partial No Not reported	Yes Ethics approval was received from Cairns and Hinterland, Cape York, Torres Strait and Northern Peninsula Hospital and Health Services Human Research Ethics Committee HREC/12/QCH/116-823 and Monash University Human Research Ethics Committee. Signed consent was obtained for qualitative interviews and focus groups.
	Was the data analysis sufficiently rigorous?	Yes Partial No Not reported	Yes Data were analysed in STATA version 12.1 with calculation of proportions and frequencies. Qualitative data were categorised manually into categories based on predetermined categories identified in the literature and topics covered in the interviews by one author for the semi–structured interviews (GH) and for the FGD (HW) (deductive analysis). Additional categories

			were then created based on new topics which arose in the interviews. GH and HW with JB then considered each category independently and identified major themes with relevant quotes summarised around each theme and how these related to the research questions.
	Is there a clear statement of findings?	Yes Partial No Not reported	Yes Data triangulation was used to capture complex issues surrounding developing culturally sensitive programmes. Findings were discussed in relation to the original research question
	Is there an indication of drop outs or non-respondents and was this appropriately dealt with?	Yes Partial No Not reported Not applicable	Not reported
VALUE	How valuable is the research?	Yes Partial No Not reported	Yes No other clinics for women with PCOS in Aboriginal and Torres Strait Islander communities. This study demonstrates it is feasible to implement an evidence-based clinic for PCOS in a geographically isolated context with limited human and financial resources. Some system barriers to service delivery and sustainability of the clinic exist, and whether the women's health needs are fully met is yet to be determined. These recommendations should be considered for future improvement of the clinic, and prior to upscaling this model to a national level.
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	Yes All outcomes were reported as per method section
OTHER	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	Not reported
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Tay, 2021*
Study Citation	Tay CT, Pirotta S, Teede HJ, Moran LJ, Robinson T, Skouteris H, Joham AE, Lim SS. Polycystic Ovary Syndrome Models of Care: A Review and Qualitative Evaluation of a Guideline-Recommended Integrated Care. Semin Reprod Med. 2021 Jul;39(3-04):133-142. doi: 10.1055/s-0041-1727191. Epub 2021 Jun 29. PMID: 34187051.
Study Country	*Australia*

CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*15 Adult women with PCOS, Women residing in Victoria can attend the integrated PCOS service for free with a medical referral from a doctor*	
Control population	*N/A*	
PCOS diagnostic criteria	*Not specified what criteria however endocrinologist clinic provided comprehensive care including diagnosis confirmation*	
N per group	*15 Adult women with PCOS*	
Setting	*Public, tertiary hospital clinic*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Semi structured interview* *1) Appropriateness: An integrated PCOS service is appropriate for women's multifaceted needs. 2) Effectiveness: The PCOS service was effective in providing care and communicating sensitively to women with PCOS, but more access to the service is required. 3) Impact: A specialized PCOS service had positive impacts on medical management of PCOS, PCOS symptom severity, women's understanding of PCOS, women's confidence in managing PCOS, and general emotional well-being. 4) Efficiency: The efficiency of the PCOS service requires improvement in patient communication, resource provision, infrastructure, and awareness of the service availability. 5) Future suggestions: Women desire more funding to increase and expand the existing PCOS service and be empowered with more resources that promote self-management. Patient satisfaction with each clinic*	
Was there a clear statement of the aims of the research?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes.* All women attending the integrated PCOS service were eligible to participate
Exclusion criteria	Yes Partial No Not reported	*No exclusion criteria*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Summary Result/s	Our study showed that a codesigned, integrated PCOS service which aligns with evidence-based practice and patients' priorities was reported by women as appropriate, beneficial, and effective to meet their needs. Integrated care and tailored treatments that combine general education on PCOS, lifestyle support, and laser therapy were highly valued. Clinic infrastructure, delays, and inconsistencies in service access and the tension between evidence-based treatment and patient preference for alternative therapies were among the negative experiences reported. Our study provides insights into key service elements that women value to guide the implementation of other much needed PCOS-dedicated services. The negative experiences that women encountered provide lessons to others regarding potential areas needing improvement to achieve optimal PCOS care. Publication and dissemination of evaluation incorporating both quantitative and qualitative	

		research methodologies, following a comprehensive framework, presents an important opportunity to guide the planning, implementation, and scale-up of evidence-based MoC to improve healthcare services, optimize patient experience, and ultimately deliver health benefits to the community.	
VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
VALIDITY	Is a qualitative methodology appropriate?	Yes Partial No Not reported	*Yes*
	Was the research design appropriate to address the aims of the research?	Yes Partial No Not reported	*Yes, mixed methods were used appropriately*
	Was the recruitment strategy appropriate to the aims of the research?	Yes Partial No Not reported	*Yes, all women were eligible for the study and data saturation was met for the qualitative interviews*
	Was the data collected in a way that addressed the issue?	Yes Partial No Not reported	*Yes, semi-structured interview were used, methods explained clearly*
	Has the relationship between researcher and participants been adequately considered?	Yes Partial No Not reported	*Yes, researchers have no relationship with recruited participants*
RESULTS	Have ethical issues been taken into consideration?	Yes Partial No Not reported	*Yes* *Ethics approval was obtained from the Monash Health Ethics Committee*
	Was the data analysis sufficiently rigorous?	Yes Partial No Not reported	*Yes.* *Coding and thematic analyses were used* Codes were organized into subthemes and mapped to the Markiewicz and Patrick's evaluation framework domains of appropriateness, effectiveness, efficiency, and impact, and an additional category of future suggestions. Coded all the interview transcripts, with 10% subset being double coded by S.P. Coding differences were discussed until consensus was reached. Codes were then discussed in depth between C.T.T., S.P., and S.S.L. (female dietitian) to synthesize subthemes and themes. Finally, research findings were cross-checked independently by T. R., H.S. (female psychologist), and H.J.T. (female endocrinologist and unit director) to explore alternative explanation of relationships between codes and to reduce researcher bias. Results of the qualitative component of the study were reported according to the Consolidated Criteria for Reporting Qualitative Research (COREQ) checklist.25 Quantitative data were analyzed using Excel for Mac version 15.4 (Microsoft Corporation) and presented asmean and standard deviations or frequencies and proportions

	Is there a clear statement of findings?	Yes Partial No Not reported	*Yes. All the research questions were answered in the manuscript with discussions around the comparisons with available evidence in the literature*
	Is there an indication of drop outs or non-respondents and was this appropriately dealt with?	Yes Partial No Not reported Not applicable	*No. No drop outs from this study*
VALUE	How valuable is the research?	Yes Partial No Not reported	Yes This study provides insights into key service elements that women value to guide the implementation of other much needed PCOS-dedicated services. The negative experiences that women encountered provide lessons to others regarding potential areas needing improvement to achieve optimal PCOS care. Publication and dissemination of evaluation incorporating both quantitative and qualitative research methodologies, following a comprehensive framework, presents an important opportunity to guide the planning, implementation, and scale-up of evidence-based MoC to improve healthcare services, optimize patient experience
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes* *Results sections were divided clearly to answer all the research questions*
OTHER	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*None declared*
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Low*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	Torres-Zegarra, 2021
Study Citation	Torres-Zegarra C, Sundararajan D, Benson J, Seagle H, Witten M, Walders-Abramson N, Simon SL, Huguelet P, Nokoff NJ, Cree-Green M. Care for Adolescents With Polycystic Ovary Syndrome: Development and Prescribing Patterns of a Multidisciplinary Clinic. J Pediatr Adolesc Gynecol. 2021 Oct;34(5):617-625. doi: 10.1016/j.jpag.2021.02.002. Epub 2021 Mar 29. PMID: 33794340; PMCID: PMC8808364.
Study Country	*United States*
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	

Patient/population/ participants	Child and adolescents with PCOS, 11-24yo	
Control population	*No controls*	
PCOS diagnostic criteria	*Not specified. Patients are required to have a confirmed diagnosis of PCOS*	
N per group	*92 patients with confirmed diagnosis of PCOS*	
Setting	*Tertiary care*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	The purpose of this study is to come up with description, to illustrate the need for such a clinic (MDT PCOS clinic), to provide details needed to create similar clinics at other sites, and to describe the type of medical treatment prescribed within 1 visit when a multi-disciplinary approach is used. Main outcomes: Medical history, physical examination findings, laboratory measurements and prescribed therapies.	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* *Patient with confirmed PCOS diagnosis who attended the clinic between 2014 and 2018*
Exclusion criteria	Yes Partial No Not reported	*None*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	Not relevant
Was matching performed?	Yes Partial No Not reported	Not relevant
Summary Result/s	A total of 92 patients seen from 2014 to 2018 are described (age 15.9 years, range 11-24 years, body mass index 35.6 kg/m^2, range 19.9-53.5). Metabolic syndrome features were common: 26% had a prediabetes haemoglobin A1c (>5.6%), 83% had a high-density lipoprotein (HDL) < 50 mg/dL, 40% had a systolic blood pressure > 120 mm Hg, and 43% had an alanine aminotransferase level of > 30 U/L. Dermatologic findings included acne 93%, hirsutism 38%, acanthosis nigricans 85%, hidradenitis suppurativa 16%, and androgenic alopecia 2%. Of the patients, 33% had a diagnosis of depression or anxiety, 16% of patients had a diagnosis of obstructive sleep apnoea, and an additional 59% had symptoms	

		warranting a sleep study The most commonly prescribed medications were topical acne preparations (62%), followed by estrogen-containing hormonal therapy (56%) and metformin (40%). In adolescents with PCOS and obesity, metabolic, dermatologic, and psychologic co-morbidities are common. The use of a multidisciplinary clinic model including dermatology in addition to endocrinology, gynaecology, psychology, and lifestyle experts provides care for most aspects of PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*N/A*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes* *Patients included any adolescents and young adults attending the clinic. Not definite diagnosis of PCOS needed*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*N/A*
PERFORMANC	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*N/A (only one group)*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*N/A (only one group)*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*N/A (only one group)*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*None.*

REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Yes*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*N/A (only one group)*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*Not reported*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*N/A (only one group)*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes. Descriptive data were used*
COMMENTS		*Low risk of bias*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*Low*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 2

Question 2.6.2.

What are the characteristics of available models of care implemented in PCOS clinic or service?

BACKGROUND:

Healthcare for women with PCOS is challenged by inconsistent diagnostic criteria, heterogeneous clinical phenotypes and evolving clinical features across the lifespan. Qualitative and quantitative research have consistently shown that women with PCOS were unsatisfied with their healthcare experiences (1-4). It is well acknowledged that PCOS affects a woman's biopsychosocial aspects of life and conventional siloed healthcare services based on a single medical specialty are failing to meet the multifaceted needs of women with PCOS (5, 6).

Part of the consumer engagement process of the International Evidence-based PCOS Guideline update includes an international consumer survey to determine the aspects of PCOS which were of most importance to women. Unpublished results from over 1500 women with PCOS showed that building a model of care for PCOS women is of utmost priority to support their care. There is no single definition of model of care, nor is there a standardised model of care as variation and adaptation needs to be based on local health systems, settings, resources and women's needs (6, 7). Most literature agreed that stakeholder engagement and evidence-based practice are the fundamental features of a model of care. Other important elements include improving patient selfcare, patient-centred care or shared-decision making, supporting integrated care, embedded evaluation with service refinement process and adaptability (5-9).

Several chronic disease models of care (e.g. diabetes, inflammatory bowel disease) have been described in the literature showing improvement in quality of care for patients (10-11). Patient self-care is crucial in all types of chronic disease management. Healthcare providers need to move from the traditional role of decision makers for patient disease management to the role of being a facilitator. Educating and providing information to the patient to improve the patient's disease or treatment knowledge, practising patient-centred care and encouraging shared-decision making, so that patients can take an active role in the management of their chronic condition. The nature of chronic diseases means community primary care providers play a central role in chronic disease model of care. However, smooth pathways to access specialist input for treatment escalation is essential for management of chronic diseases, and transparent interdisciplinary communication will support the continuity of care across different disciplines.

Extensive research for the 2018 International Evidence-based PCOS Guideline failed to identify any studies addressing the effectiveness of any type of model of care compared to standard care. A clinical consensus recommendation was made then to offer interdisciplinary care to women with PCOS, with an interdisciplinary care model defined as "the collaboration between a woman with PCOS and a care team who have shared goals for her total wellbeing". With careful consideration, the evidence research of the current International Evidence-based PCOS Guideline update on model of care of PCOS is focused on identifying the key elements of PCOS-dedicated healthcare services published in literature. Identifying these key elements will inform and assist with building a best practice framework for the PCOS model of care that is appropriate for women's needs and adaptable for any healthcare services that is feasible to implement. The International Osteoporosis Foundation Capture the Fracture Campaign is an excellent example that an internationally endorsed best practice framework can be very successful. Their best practice framework defines clearly both critical elements of service delivery, and aspirational elements of service delivery if resources allow 12-13). To date, more than 700 Fracture Liaison Services have been established globally in 50 countries (12-13).

To further facilitate implementation and upscaling of the model of care, it is also important to co-develop with stakeholders a set of implementation and evaluation toolkits, along with comprehensive benchmarking and key performance indicators. Healthcare benchmarking allows the continual assessment of key work processes, helps identifying gaps in care, promotes learning and can guide further refinement of the healthcare service (14).

Evidence to Recommendations Framework

COMPARISONS (option versus other option)

Not applicable. Information of key elements of any PCOS-dedicated healthcare services are drawn to make recommendations.

CONSENSUS RECOMMENDATION

- **CR:** Models of care should prioritise equitable access to evidence-based primary care with pathways for escalation to integrated specialist and multidisciplinary services as required.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

PRACTICE POINT

- Strategies to deliver optimal models of care could include health professional education, care pathways, virtual care, broader health professional engagement (e.g. nurse practitioners) and coordination tools.

GRADE CONSIDERATIONS

Justifications:
There is evidence of inadequate knowledge and dissatisfaction with care mandating new approaches to education and care. Whilst there is no direct evidence that any model of care is superior to make an evidence-based recommendation, clinical consensus recommendations are made based on indirect evidence showing that women were unsatisfied with conventional healthcare services and that published PCOS-dedicated healthcare services had reported improved women's satisfaction and health outcomes. Also, other models of care for chronic diseases have been shown to improve quality of care, patient health outcomes and satisfaction.

Subgroup considerations:
The PCOS-dedicated services identified were specific for either adolescents or adults. Transition from adolescent to adult care is still unclear.
Equitable access must consider the needs of underserved populations.

Implementation considerations:
Time and resource constraints are important implementation considerations. Also important are staffing issues, especially in areas with low health resources.
Regarding patient education or information provision, health professionals can refer women to free evidence-based resources published by the 2023 PCOS Guideline translation outputs.
Improvement in care coordination will be required.

Monitoring and evaluation considerations:
Internally, an evaluation plan should be embedded for any healthcare service implementation. Evaluation and monitoring indicators should be co-developed by stakeholders.

Research priorities:
- Developing a set of benchmarking and performance indicators that address all aspects of multidisciplinary service
- Developing and implement a best practice framework outlining critical and aspirational elements of a PCOS model of care

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PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by Maureen Busby
Edited by the Evidence team

GDG 2

Question 2.6.3.

How can we best support women to navigate the impact of PCOS on family and interpersonal relationships?

(Narrative Review)

1. STUDY SELECTION

Table 1. PICO Criteria for Inclusion	
Question	Is psychological therapy effective for management and support of depression and/or anxiety, disordered eating, body image distress, self-esteem, feminine identity or psychosexual dysfunction in women with PCOS?
Clinical leads (key contacts)	Leah Brennan
Allocation ranking	Level 4 Narrative Review

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(language, year)*
Inclusion	Females of any age, ethnicity or weight diagnosed with PCOS (by Rotterdam, NIH, or AES). Subgroups: • Adolescents • Phenotypes • Ethnicity • Geographical	Models of [health] care (collaboration between disciplines – bio- psychosocial approach to wellbeing) Note where defined. Include: interdisciplinary, integrated primary or specialist care; transition of care; individually tailored care plans; self-management, shared decision-making, patient-centred care, decision-support, community informed care, digital first.	None, usual care, or others	Delivery of a care Model, Cost Effectiveness (long-term), Patient- defined outcomes (e.g., satisfaction with care), Improved communication (between staff and between staff and patients), Patient health outcomes (e.g., improved physical functioning, improved mental functioning), Timely access to care and treatment (efficiency of care), Quality of Life, Self-rated emotional wellbeing, Optimal self-management indicators.	Evidence based guidelines, systematic reviews, any primary study.	English language
Exclusion	Females without diagnosed PCOS.	Clinical trials that evaluate specific interventions (lifestyle management, mobile app) that are not a component of a broader disease management framework (as defined above)	Not applicable	Not applicable	Non-evidence-based guidelines. Abstracts, protocol, clinical trial registration.	

2. SEARCH STRATEGY

Evidence processing: This question was allocated as a narrative review. Hence, no search or screening was undertaken and recommendations will be consensus based. Below is a narrative review in response to the clinical question.

3. FINDINGS

▪ CLINICAL NEED FOR THE QUESTION

Few well-controlled studies examine the effects of PCOS in the social domain or optimal choice of interventions for managing effects on family and interpersonal relationships.

PROBLEM CONTEXT

It is well established that PCOS has an impact on physical and psychological health. PCOS is associated with increased rates of anxiety, depression and a lower health related quality of life [1]. While PCOS does not appear to cause severe social phobias or panic disorders it can disrupt social, family and interpersonal relationships in the social domain [2]. PCOS can affect interactions and relationships with partners, family, friends, colleagues, and others with whom people with PCOS have social relations. These can create challenges in personal and social interaction which, in turn, can impact interpersonal relationships in a way that varies across the lifespan and cultures [3][4]. Currently, there is a paucity of reliable data on the impact of PCOS in the social domain. Some evidence suggests a positive effect of social and family support on healthy eating and participation in exercise. Family and peer support has also been found to reduce stress, increased confidence and provide a sense of security but results vary according to marital status with increased stress being experienced by married women experiencing pressure to have children. Immediate family tend to be more supportive in comparison to extended family members [5]. Better data could generate more understanding of the impact of PCOS on social, family, and interpersonal relationships including life-stage and cultural variations. Larger well-designed studies may also help clarify the nature of complex associations. This research could inform development and evaluation of support interventions to manage negative impacts on social domains [3].

▪ NARRATIVE SUMMARY

How can we best support women and people to navigate the impact of PCOS on family and interpersonal relationships?

Social & peer support

Awareness of PCOS in the social domain can have a positive impact on those living with PCOS, including a reduction of stigma and increased support. A multi-methods study (n=296) with 25 follow up interviews found that increased awareness of PCOS in the social domain was suggested to lead to help-seeking sooner due to recognition of symptoms among friends and peers [6]. Further qualitative investigation of PCOS experiences (n=25) found that understanding allows women with PCOS to be open about their condition and helps them cope with their feelings [7]. Community awareness and understanding was perceived to facilitate adherence to treatments but could also be a hindrance in lower literacy contexts if peers described treatment options as ineffective or painful [8].

Studies of social networking sites and face-to-face PCOS peer groups have shown some positive

effects concerning support for relationships and experiential knowledge sharing [9][10][11]. A thematic analysis of nine women with PCOS using social networking sites found positive perceptions of self and others and demonstrated support gained from

relationships with peers and an increase in support from relationships, improved navigation of the health system and knowledge about PCOS[9]. A qualitative study (n=13) of a nurse-led support group that provided socio-emotional and informational social support to women with PCOS found participants experienced a reduction in isolation and a gain in personally relevant information via social comparison within the group setting [10]. A qualitative analysis (n=211) of 7 online PCOS discussion forums found them to be beneficial in terms of social support and knowledge sharing [11]. Furthermore, studies examining psychological support and online forums have found it promotes psychological wellbeing. A quantitative study (n=331) found increased self-esteem and decreased risk of depression and benefits for social relationships [12]. Examination of online breast cancer communities have been found to enable more flexible access to support and knowledge exchange regardless of time or location [13].

In contrast, thematic analysis of a survey of people with PCOS (n=50) found both empowering and disempowering consequences of online peer support groups. Participants experienced both improvements in self-management and increased feelings of isolation due to reading the negative experiences of others, perhaps due to life-stage differences or the various phenotypes [14]. This concurs with more recent findings (n=20) that exposure to negative experiences of others with PCOS can instil fear and may inhibit help-seeking behaviours and treatment adherence [8]. In one study it was also found that attendance to peer support groups could be inhibiting if groups were not diverse or did not reflect cultural background of new members [30].

Despite those with PCOS being connected through social networks, online or face-to-face support,what works, for whom, under what circumstances and how is yet to be determined for effective support provision to be established [15].

Family & relationship satisfaction

Family impacts of PCOS include the impact on siblings and parent-child relationships. The family as a site of intervention and support has been proposed because PCOS is largely self-managed at home in the everyday setting. A qualitative investigation (17) studied the context and processes of self- management among adolescents (n=7) and their parents (n=8) using focus groups. Study findings showed improvements in self-management of PCOS, psychological health and well-being in a family setting with increased levels of engagement in optimal self-management of the condition. Larger studies of such interventions may help inform further development of this or similar interventions [17]. Family could be supportive through comforting, minimising [8], helping with managing medical appointments [29] and doing research on their behalf [9]. A multi-method study surveying women with PCOS (n=296) and follow up interviews (n=25) found that the lack of awareness of PCOS symptoms among parents was a barrier to diagnosis [8]. A qualitative analysis (n=62) highlighted too that lack of knowledge of family histories (e.g., of diabetes, heart disease) are an area of concern for those with PCOS due to potential exacerbation of PCOS symptomology[16]. Similarly, a mixed methods study, involving a survey (n=275) with 62 follow-up interviews found that in uninformed families symptoms and experiences were not taken seriously and affected adherence to treatment as people were discouraged to medicate [18]. In contrast, better family support led to increased adherence to treatments [8, 29].

Marital satisfaction and social support in people with PCOS and infertility has been specifically studied due to prevalence of infertility in PCOS groups. Systematic reviews suggest it is the infertility and the unfulfilled child wish that affects the marital relationship rather than PCOS per se[19][20]. Indeed, systematic review shows that infertility has negative impacts on sexual relationships and long-term wellbeing when the child-wish is unfulfilled [21]. However, the presence of this association should not be assumed for people with PCOS. A cross-sectional quantitative study of 31 women with PCOS and their partners found that lower parity and unfulfilled child-wish was associated with higher sexual and relationship satisfaction especially for the women in the relationships [19]. The findings were thought to be due to partners having increased time for each other compared to couples with children and in the case of unwanted childlessness, couples tend to have more stable relationships [22] [19]. It should note that despite women with PCOS having a higher ovarian reserve than women without PCOS, clinical pregnancy and live-birth rates in assisted reproductive technology were not higher in women with PCOS [34]. A large population-based study in Australia which followed up women across their reproductive lifespan also showed that significantly less women with PCOS achieved their ideal family size or child-wish than women without PCOS [35].

Marginalisation of people with PCOS

Women and people with PCOS have reported feelings of marginalization and stigmatization as a result of the symptoms that may be perceived as non-traditional social constructs of beauty, femininity and womanhood [23]. Qualitative analysis of women with PCOS (n=30) found them to feel less feminine describing themselves as “abnormal” and “not proper women”, which affected their ability to disclose their suffering to others due to shame and embarrassment [24]. In qualitative studies there are mixed views on discussing family menstruation [7, 29, 30] and some reported being told to be secretive about their PCOS because it could shame the family or affect future marital prospects (e.g., India) [9, 29]. People with PCOS often experience lack of culturally and gender-sensitive standards of care, underrepresentation in research and stigma because they do not conform to social constructs of beauty. Obesity and hirsutism appear to negatively impact self-esteem, sensitivity to social criticism, social activity and interpersonal relationships [25][26]. It has been suggested that people with PCOS may benefit from integrated behavioural health care that integrates management of the medical conditions and its related behavioural health effects that affect the health and wellbeing of those with PCOS. [27][28].

Primary socialisation instils perceptions of PCOS as taboo from an early age. Women and people with PCOS are socially constructed based on patriarchal social norms of women being defined by motherhood and femininity. Investigating the taboo of PCOS in Indian society, a qualitative study (n=35) found that PCOS was often not talked about even within close family members due to the social stigma associated with menstruation and reproduction [29]. Culture and socio-religious reasoning and teaching reinforced this stigma making PCOS a taboo illness from an early age. Second, the societal taboo then results in a general lack of awareness of PCOS that can mean people avoid help-seeking or treatment. This lost opportunity for prevention of long-term sequelae of PCOS is compounded by the fact that occurrence a regular period or birth leads to the mistaken belief there is no need to consider the condition further despite established long term

risks. For those without a birth, there is a negative socio-psychological impact of childlessness for example taunts by other family members for an inability to live up to stereotypical expectations.

Taboos surrounding PCOS are experienced differentially depending on culture. In a qualitative study (n=12) of a UK ethnically diverse sample marginalisation was experienced more in relation to childlessness than to hirsutism which is more widely accepted in some African cultures [30]. Additionally, a mixed methods study which surveyed 323 women with follow-up qualitative interviews (n=11) found that those of a British Asian background experienced more stigma related to the secrecy of discussing menstruation [31]. Similarly options offered could be perceived as taboo in some groups, for example Asian adolescents using contraceptive pills [30].

In addition, the lack of understanding of PCOS and its link to subfertility leads to some women not disclosing their condition with other family members for fear of judgement [29, 30]. Often internalised, stereotypical expectations lead to self-stigmatisation because peers often reinforce these ideas and it can lead to people with PCOS becoming socially aloof by minimising interaction to avoid confrontation. This further contributes to their marginalisation and feelings of isolation.

Further directions

In terms of the wider social domain, social competence with relation to PCOS tend to be less problematic during adolescence which may be explained by a lower level of symptom severity during adolescence [4] Further research is needed to examine the impact on wider family and interpersonal relationships across the lifespan and cultures [4]. In particular, there is a need for more research on the impact of social and peer support in PCOS [32].

Family relationships including siblings and parents may require further investigation with a view to informing future interventions [17]. Additionally, given the conflicting evidence surrounding the impact of infertility and unfulfilled child wish, more research on this could be beneficial in terms of guiding future intervention [19]. Available systematic review evidence suggests that patients with fertility problems could be helped with cognitive behaviour therapy (versus routine care) but whether this approach could help with challenges in the social domain is not known [33].

Examination of people with PCOS as a marginalised social group is greatly under-researched. Increasing societal awareness of PCOS through education could help to reduce social stigma and taboo. Tackling social stigma may reduce the socio-religious impact of the condition on those with PCOS but again more research is required [27].

<u>Summary of key information</u>

Support needs and experiences of family and interpersonal relationships of women and people with PCOS varies and needs more research. Social and cultural expectations may impact interpersonal relationships due to the physical symptoms of PCOS that may not meet socio-cultural constructs of attractiveness, motherhood or femininity. The family may provide a site of effective intervention in supporting better interpersonal relationships in adolescence.

Suggestions for how we can best support women and people to navigate the impact of PCOS on family and interpersonal relationships.

- Some but not everyone with PCOS experience problems in the social domain, often due to stigma related to features of their condition. Social support has been found to have both positive and negative effects for people living with PCOS. Increased societal awareness and education on PCOS is needed to help alleviate marginalisation of anyone with PCOS. Pathways to dissemination should be investigated as part of national public health agendas.

- Women and people with PCOS may have varying support needs at different times across the lifespan. Key moments could be adolescence (support needs related to self-management) and reproductive years (support needs for unfulfilled child-wish). Both family members and healthcare practitioners must be aware of these needs and signpost to appropriate support services. The value of a stepped approach from psychoeducation about individual effects to specialised psychological services should be examined as part of the PCOS pathway.

- Family interventions have shown promising results for self-management so further research and support of family initiatives is warranted.

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PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 2

Question 2.6.3.

How can we best support women to navigate the impact of PCOS on family and interpersonal relationships?

(Narrative Review)

BACKGROUND:

PROBLEM CONTEXT

It is well established that PCOS has an impact on physical and psychological health. PCOS is associated with increased rates of anxiety, depression and a lower health related quality of life (1) . While PCOS does not appear to cause severe social phobias or panic disorders it can disrupt social, family and interpersonal relationships in the social domain (2). PCOS can affect interactions and relationships with partners, family, friends, colleagues, and others with whom people with PCOS have social relations. These can create challenges in personal and social interaction which, in turn, can impact interpersonal relationships in a way that varies across the lifespan and cultures (3, 4) . Currently, there is a paucity of reliable data on the impact of PCOS in the social domain. Some evidence suggests a positive effect of social and family support on healthy eating and participation in exercise. Family and peer support has also been found to reduce stress, increase confidence and provide a sense of security but results vary according to marital status with increased stress being experienced by married women experiencing pressure to have children. Immediate family tend to be more supportive in comparison to extended family members (5). Better data could generate more understanding of the impact of PCOS on social, family, and interpersonal relationships including life-stage and cultural variations. Larger well-designed studies may also help clarify the nature of complex associations. This research could inform development and evaluation of support interventions to manage negative impacts on social domains (3). In some cultures, PCOS is constructed as a tabooed disease. This negatively impacts on the experiences of those with PCOS and their families. Often, PCOS is not discussed, even among people within the same family. Pressure to conform to social norms of womanhood are magnified by the internalisation of this idea of PCOS as a tabooed disease. It is important to recognise issues of cultural appropriateness including language, taboo and stigma in the delivery of PCOS care (6).

Recommendations Framework

CONSENSUS RECOMMENDATION

- **CR:** Public health actors should consider increase societal awareness and education on PCOS to reduce stigma and marginalisation.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

- **PP:** Culturally appropriate resources and education on PCOS across the life span for families of those with the condition, should be considered.

CONSIDERATIONS

Justifications:
Some but not everyone with PCOS experience problems in the social domain, often due to stigma related to features of their condition. Social support has been found to have both positive and negative effects for people living with PCOS.

Subgroup considerations:
Women and people with PCOS may have varying support needs at different times across the lifespan. Key moments could be adolescence (support needs related to self-management) and reproductive years (support needs for unfulfilled child-wish).

Implementation considerations:
Women and people with PCOS may have varying support needs at different times across the lifespan. Key moments could be adolescence (support needs related to self-management) and reproductive years (support needs for unfulfilled child-wish).
Family members and healthcare practitioners must be aware of these needs and signpost to appropriate support services.

Monitoring and evaluation considerations:
None

Research priorities:
Pathways to dissemination should be investigated as part of national public health agendas.
Need research on impact on wider family and interpersonal relationships.
Role of family in psychological support.
Impact of social and peer support.
Investigate stigma and explore strategies to reduce stigma in PCOS.

Equity: Likely will increase equity.
Acceptability Acceptability may vary depending on family beliefs. The diverse nature of families is an important consideration. Consider issues around cultural appropriateness such as preferred language, taboo and stigma to ensure best practice delivery.
FEASIBILITY Probably feasible but may require a change in practice.

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PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by the Evidence team (Jillian Tay, Aya Mousa)
Other Members: Loyal Pattuwage

GDG 2

Question 2.6.4.

What are the key challenges for those with PCOS when interacting with healthcare professionals about polycystic ovary syndrome and related features?

1. STUDY SELECTION

Table 1. PICO Criteria for Inclusion	
Question	2.6.4 What are the key challenges for those with PCOS when interacting with healthcare professionals about polycystic ovary syndrome and related features?
Clinical leads (key contacts)	Jacky Boivin, Maureen Busby
Allocation ranking	Level 1 – New systematic review

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(language, year)*
Inclusion	Females with PCOS (diagnosed by Rotterdam, NIH, AES or self reported) of any age, ethnicity and weight. Subgroups: • Adolescents • Ethnicity • Phenotype	Any healthcare interactions in any healthcare setting. Include interactions with specialist doctors, general practitioners, nurses and allied health professionals (dietitians, physiotherapists, psychologists, mental health, dermatologist etc.)	None	Patients' perspectives on interacting with health professionals. (adjacent to terms such as perspectives, views, perceptions, experience) Note: different types of topics discussed (reproductive, metabolic, dermatological, psychological concerns) Include challenges, barriers and enablers. Include positive and negative experiences. Include culture, satisfaction/dissatisfaction etc.	Qualitative studies (e.g. interviews, focused groups, ethnography) Mixed method studies Quantitative study - satisfaction survey on any type of PCOS/Sx/Mx discussion	English language
Exclusion	Females without diagnosed PCOS.	interactions with non-healthcare professionals. Doctors' perspectives of interacting with patients	None	experiences or feelings related to receiving the diagnosis for PCOS	Abstracts, letters to editors, clinical trials	None

2. SEARCH STRATEGY

Search details	
Search strategy source: Not applicable	
Evidence source	**Date of search**
Medline (Ovid)	**13/09/2022**
PsychInfo (Ovid)	**13/09/2022**
EMBASE	**13/09/2022**
All EBM (Ovid)	**13/09/2022**
CINAHL	**13/09/2022**
Any subsequent updates - enter database and date: not applicable	

Questions addressed by this search:		
GDG	**Q#**	**Question**
2	**2.6.1**	**What are the information, resource and education needs of women, adolescents, CALD groups and healthcare providers regarding PCOS?**
2	**2.6.4**	**What are the key challenges for those with PCOS when interacting with healthcare professionals about polycystic ovary syndrome and related features?**

OVID Medline, EMBASE	APA PsychInfo
1 exp polycystic ovary syndrome/	1 exp Endocrine Sexual Disorders/
2 polycystic ovar*.mp.	2 polycystic ovar*.mp.
3 poly-cystic ovar*.mp.	3 poly-cystic ovar*.mp.
4 PCO*.mp.	4 PCO*.mp.
5 (stein-leventhal or leventhal).mp.	5 (stein-leventhal or leventhal).mp.
6 anovulation/	6 anovulation/
7 anovulat*.mp.	7 anovulat*.mp.
8 oligo-ovulat*.mp.	8 oligo-ovulat*.mp.
9 oligoovulat*.mp.	9 oligoovulat*.mp.
10 (ovar* adj5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*)).mp.	10 (ovar* adj5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*)).mp.
11 or/1-10	11 or/1-10
12 exp Allied Health Personnel/	12 exp Allied Health Personnel/
13 exp Physicians/	13 exp Physicians/
14 Doctor$2.tw.	14 Doctor$2.tw.
15 physician$2.tw.	15 physician$2.tw.
16 nurse$2.tw.	16 nurse$2.tw.
17 clinician$2.tw.	17 clinician$2.tw.
18 dietitian$2.tw.	18 dietitian$2.tw.
19 medical care provider$1.tw.	19 medical care provider$1.tw.
20 medical-care professional$1.tw.	20 medical-care professional$1.tw.
21 medical professional$1.tw.	21 medical professional$1.tw.
22 (medical adj1 worker$1).tw.	22 (medical adj1 worker$1).tw.
23 "health care provider$1".tw.	23 "health care provider$1".tw.
24 health-care provider$1.tw.	24 health-care provider$1.tw.
25 healthcare provider$1.tw.	25 healthcare provider$1.tw. 8106
26 "health care professional$2".tw.	26 "health care professional$2".tw.
27 healthcare professional$2.tw.	27 healthcare professional$2.tw.
28 health-care professional$2.tw.	28 health-care professional$2.tw.
29 exp Health Personnel/	29 exp Health Personnel/
30 (("health care" or health-care or healthcare) adj worker$1).tw.	30 (("health care" or health-care or healthcare) adj worker$1).tw.
31 health-worker$1.tw.	31 health-worker$1.tw.
32 healthworker$1.tw.	32 healthworker$1.tw.
33 "health worker$1".tw.	33 "health worker$1".tw.
34 "Obstetrician-Gynecologist$1".tw.	34 "Obstetrician-Gynecologist$1".tw.
35 gynaecologist$2.tw.	35 gynaecologist$2.tw.
36 (midwife or midwives).tw.	36 (midwife or midwives).tw.
37 obstetrician$2.tw.	

38 nutritionist$2.tw. 39 general practitioner$2.tw. 40 pharmacologist$1.tw. 41 GP$1.ab. 42 family physician$2.tw. 43 (primary care adj provider$2).tw. 44 (health care adj provider$2).tw. 45 psychologist$2.tw. 46 psychiatrist$2.tw. 47 obstetri* specialist$1.tw. 48 (gynecolog* specialist$1 or gyneacolog* specialist$1).tw. 49 medical specialist$1.tw. 50 endocrine specialist$1.tw. 51 endocrinologist$2.tw. 52 nurse practitioner$2.tw. 53 health personnel.tw. 54 (mental health adj (practitioner$1 or clini* or specialist$1)).tw. 55 or/12-54 56 exp Patients/ 57 exp Inpatients/ 58 exp Outpatients/ 59 exp Female/ 60 (consumer* or patient*).tw. 61 exp Adolescent/ or exp Culture/ 62 "Ethnic and Racial Minorities"/ 63 or/56-62 64 health literacy.tw. 65 health promotion.tw. 66 (Health seeking behaviour or Health seeking behavior).tw. 67 (Information seeking behaviour or Information seeking behavior or Information-seeking behaviour or Information-seeking behavior).tw. 68 Continuing education.tw. 69 Medical education.tw. 70 Professional education.tw. 71 Nursing education.tw. 72 Consumer health information.tw. 73 Information provision.tw. 74 exp Health Literacy/ 75 exp Health Promotion/ 76 exp Health Knowledge, Attitudes, Practice/ or exp "Patient Acceptance of Health Care"/ 77 exp Information Seeking Behavior/ 78 exp Consumer Health Information/ or exp Information Services/ or exp Patient Education as Topic/ 79 (knowledge adj1 gap).tw. 80 (resource or resources).tw. 81 *Education, Medical/ 82 exp Health Education/ 83 exp Consumer Health Information/ 84 exp Patient Education as Topic/ 85 exp Sex Education/ 86 *Needs Assessment/ 87 exp Attitude to Health/ 88 *Communication Barriers/ 89 *Informed Consent/ 90 *Truth Disclosure/	37 obstetrician$2.tw. 38 nutritionist$2.tw. 39 general practitioner$2.tw. 40 pharmacologist$1.tw. 41 GP$1.ab. 42 family physician$2.tw. 43 (primary care adj provider$2).tw. 44 (health care adj provider$2).tw. 45 psychologist$2.tw. 46 psychiatrist$2.tw. 47 obstetri* specialist$1.tw. 48 (gynecolog* specialist$1 or gyneacolog* specialist$1).tw. 49 medical specialist$1.tw. 50 endocrine specialist$1.tw. 51 endocrinologist$2.tw. 52 nurse practitioner$2.tw. 53 health personnel.tw. 54 (mental health adj (practitioner$1 or clini* or specialist$1)).tw. 55 or/12-54 56 exp Patients/ 57 exp Hospitalized Patients/ 58 exp Outpatients/ 59 exp Human Females/ 60 (consumer* or patient*).tw. 61 exp Adolescent Attitudes/ or exp Adolescent Health/ 62 exp "Racial and Ethnic Differences"/ or exp Cultural Diversity/ or exp Multicultural Education/ or exp Cultural Sensitivity/ or exp "Racial and Ethnic Groups"/ 63 or/56-62 64 health literacy.tw. 65 health promotion.tw. 66 (Health seeking behaviour or Health seeking behavior).tw. 67 (Information seeking behaviour or Information seeking behavior or Information-seeking behaviour or Information-seeking behavior).tw. 68 Continuing education.tw. 69 Medical education.tw. 70 Professional education.tw. 71 Nursing education.tw. 72 Consumer health information.tw. 73 Information provision.tw. 74 exp Health Literacy/ 75 exp Health Promotion/ 76 exp Consumer Health Information/ or exp Information Services/ or exp Patient Education as Topic/ 77 (knowledge adj1 gap).tw. 78 (resource or resources).tw. 79 exp Medical Education/ 80 exp Health Knowledge/ or exp Health Information/ or exp Information Seeking/ or exp Health Education/ or exp Communication/ 81 exp Sex Education/ 82 *Needs Assessment/ 83 *Communication Barriers/ 84 *Informed Consent/ 85 exp Professional Consultation/

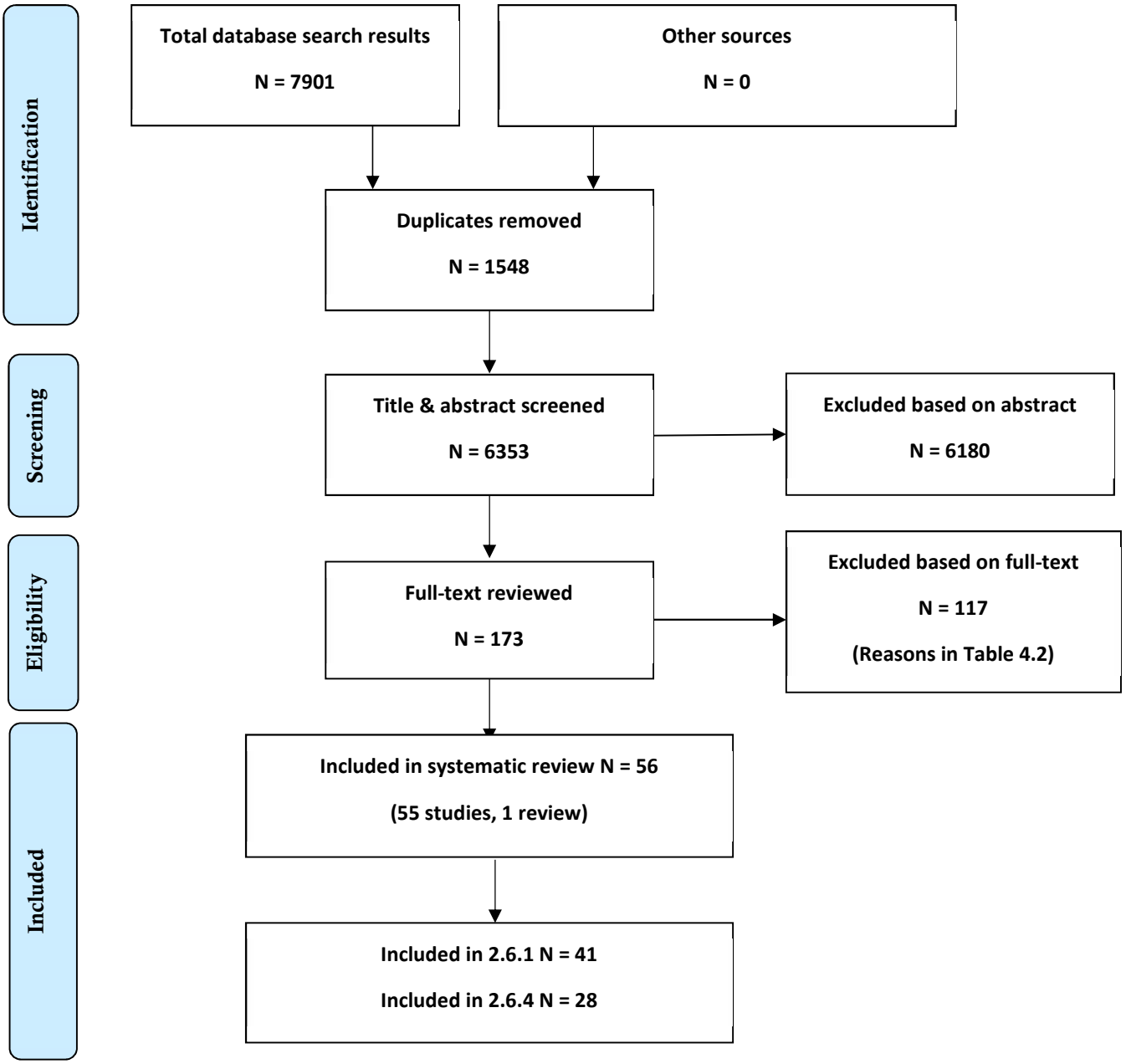
91 *Health Communication/ 92 *Information Literacy/ 93 *Choice Behavior/ 94 *Decision Making/ or exp Decision Support Systems, Management/ or exp Decision Support Techniques/ or exp Decision Making/ 95 exp Professional-Patient Relations/ 147652 96 communications media/ or library materials/ or teaching materials/ or telecommunications/ or electronic mail/ or telemedicine/ or remote consultation/ or telephone/ or answering services/ or exp cellular phone/ or television/ 97 computers/ or exp Microcomputers/ or Minicomputers/ or exp Internet/ or electronic mail/ or video games/ 98 exp Social Media/ or exp Self-Help Groups/ or exp Decision Support Techniques/ or exp Algorithms/ or exp Decision Support Systems, Management/ or exp Decision Support Systems, Clinical/ or *Internet/ or *Mass Media/ or *Patient Care Planning/ or *Managed Care Programs/ or exp Practice Guideline/ or *Books/ or exp Textbooks as Topic/ or exp Internet/ 99 or/64-98 100 (perspective$1 or opinion$1 or perception or view$1 or viewpoint$1 or experience$1 or satisfaction or attitude$1 or preference$1 or expectation$1 or engagement or dissatisfaction or collaborat* or communicat* or cooperat* or relation* or interact* or challeng*).tw. 101 *Patient Satisfaction/ or *Patient Preference/ 102 100 or 101 103 55 or 63 14503199 104 11 and 99 and 103 105 11 and 55 and 102 106 104 or 105 107 limit 106 to (english language and humans and yr="1990 -Current")	86 exp Health Promotion/ or exp Health Literacy/ or exp Health Information/ or exp Health Education/ 87 *Information Literacy/ 88 *Choice Behavior/ 89 *Decision Making/ or exp Decision Support Systems, Management/ or exp Decision Support Techniques/ or exp Decision Making/ 90 communications media/ or library materials/ or teaching materials/ or telecommunications/ or electronic mail/ or telemedicine/ or remote consultation/ or telephone/ or answering services/ or exp cellular phone/ or television/ 91 computers/ or exp Microcomputers/ or Minicomputers/ or exp Internet/ or electronic mail/ or video games/ 92 exp Social Media/ or exp Self-Help Groups/ or exp Decision Support Techniques/ or exp Algorithms/ or exp Decision Support Systems, Management/ or exp Decision Support Systems, Clinical/ or *Internet/ or *Mass Media/ or *Patient Care Planning/ or *Managed Care Programs/ or exp Practice Guideline/ or *Books/ or exp Textbooks as Topic/ or exp Internet/ 87706 93 (perspective$1 or opinion$1 or perception or view$1 or viewpoint$1 or experience$1 or satisfaction or attitude$1 or preference$1 or expectation$1 or engagement or dissatisfaction or collaborat* or communicat* or cooperat* or relation* or interact* or challeng*).tw. 94 *Patient Satisfaction/ or *Patient Preference/ 95 55 or 63 96 93 or 94 97 11 and 55 and 96 98 or/64-92 99 55 or 63 100 11 and 98 and 99 101 97 or 100 102 limit 101 to (human and english language and yr="1990 -Current")
All EBM	
1 exp polycystic ovary syndrome/ 2 polycystic ovar*.mp. 3 poly-cystic ovar*.mp. 4 PCO*.mp. 5 (stein-leventhal or leventhal).mp. 6 anovulation/ 7 anovulat*.mp. 8 oligo-ovulat*.mp. 9 oligoovulat*.mp. 10 (ovar* adj5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*)).mp. 11 or/1-10 12 exp Allied Health Personnel/ 13 exp Physicians/ 14 Doctor$2.tw. 15 physician$2.tw. 16 nurse$2.tw. 17 clinician$2.tw. 18 dietitian$2.tw. 19 medical care provider$1.tw. 20 medical-care professional$1.tw. 21 medical professional$1.tw. 22 (medical adj1 worker$1).tw.	S1 (MM "Polycystic Ovary Syndrome") S2 TX polycystic ovar* S3 TX poly-cystic ovar* S4 TX PCO* S5 TX (stein-leventhal or leventhal) S6 (MM "Anovulation") S7 TX anovulat* S8 TX oligo-ovulat* S9 TX oligoovulat* S10 TX (ovar* N5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*)) S11 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 S12 (MH "Allied Health Personnel+") S13 (MH "Physicians+") S14 TI (doctor* OR physician* OR nurse* OR clinician* OR dietitian* OR medical care provider* OR medical-care professional* OR medical professional* OR health care provider* OR healthcare provider* OR healthcare professiona;* OT health care professional* OR health-worker* OR healthworker* OR health worker) OR AB (doctor* OR physician* OR nurse* OR clinician* OR dietitian* OR medical care provider* OR medical-care professional*

23 "health care provider$1".tw. 24 health-care provider$1.tw. 25 healthcare provider$1.tw. 26 "health care professional$2".tw. 27 healthcare professional$2.tw. 28 health-care professional$2.tw. 29 exp Health Personnel/ 30 (("health care" or health-care or healthcare) adj worker$1).tw. 2647 31 health-worker$1.tw. 32 healthworker$1.tw. 33 "health worker$1".tw. 34 "Obstetrician-Gynecologist$1".tw. 35 gynaecologist$2.tw. 36 (midwife or midwives).tw. 37 obstetrician$2.tw. 38 nutritionist$2.tw. 39 general practitioner$2.tw. 40 pharmacologist$1.tw. 41 GP$1.ab. 42 family physician$2.tw. 43 (primary care adj provider$2).tw. 44 (health care adj provider$2).tw. 45 psychologist$2.tw. 46 psychiatrist$2.tw. 47 obstetri* specialist$1.tw. 48 (gynecolog* specialist$1 or gyneacolog* specialist$1).tw. 49 medical specialist$1.tw. 50 endocrine specialist$1.tw. 51 endocrinologist$2.tw. 52 nurse practitioner$2.tw. 53 health personnel.tw. 54 (mental health adj (practitioner$1 or clini* or specialist$1)).tw. 55 or/12-54 56 exp Patients/ 57 exp Inpatients/ 58 exp Outpatients/ 59 exp Female/ 60 (consumer* or patient*).tw. 61 exp Adolescent/ or exp Culture/ 62 "Ethnic and Racial Minorities"/ 63 or/56-62 64 health literacy.tw. 65 health promotion.tw. 66 (Health seeking behaviour or Health seeking behavior).tw. 67 (Information seeking behaviour or Information seeking behavior or Information-seeking behaviour or Information-seeking behavior).tw. 68 Continuing education.tw. 69 Medical education.tw. 70 Professional education.tw. 71 Nursing education.tw. 72 Consumer health information.tw. 73 Information provision.tw. 74 exp Health Literacy/ 75 exp Health Promotion/ 76 exp Health Knowledge, Attitudes, Practice/ or exp	OR medical professional* OR health care provider* OR healthcare provider* OR healthcare professiona;* OT health care professional* OR health-worker* OR healthworker* OR health worker) S15 TI (Obstetrician-Gynecologist* OR gynaecologist* OR psychiatrist* midwife OR midwives OR obstetrician* OR nutritionist* OR general practitioner* OR pharmacologist* OR family physician* OR psychologist* OR psychiatrist*) OR AB (Obstetrician-Gynecologist* OR gynaecologist* OR psychiatrist* midwife OR midwives OR obstetrician* OR nutritionist* OR general practitioner* OR pharmacologist* OR family physician* OR psychologist* OR psychiatrist*) S16 TI (medical specialist* OR endocrine specialist* OR endocrinologist* OR nurse practitioner* OR health personnel) OR AB (medical specialist* OR endocrine specialist* OR endocrinologist* OR nurse practitioner* OR health personnel) S17 TX (("health care" or health-care or healthcare) N2 worker*) S18 TI ((gynecolog* specialist* or gyneacolog* specialist*)) OR AB ((gynecolog* specialist* or gyneacolog* specialist*)) S19 TX (mental health N2 (practitioner* or clini* or specialist*)) S20 S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 S21 TI ((perspective* or opinion* or perception or view* or viewpoint* or experience* or satisfaction or attitude* or preference* or expectation* or engagement or dissatisfaction or collaborat* or communicat* or cooperat* or relation* or interact* or challeng*)) OR AB ((perspective* or opinion* or perception or view* or viewpoint* or experience* or satisfaction or attitude* or preference* or expectation* or engagement or dissatisfaction or collaborat* or communicat* or cooperat* or relation* or interact* or challeng*)) S22 (MH "Patient Satisfaction+") S23 (MM "Patient Preference") S24 S21 OR S22 OR S23 S25 S11 AND S20 AND S24 S26 (MH "Patients+") S27 (MM "Female") S28 TI (consumer* or patient*) OR AB (consumer* or patient*) S29 TI (female or women or woman or females) OR AB (female or women or woman or females) S30 (MH "Adolescence+") S31 (MM "Adolescent Health") S32 (MM "Minority Groups") OR (MH "Sexual and Gender Minorities+") OR (MH "Ethnic Groups+") OR "Ethnic and Racial Minorities" S33 (MM "Cultural Diversity") S34 S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 S35 S20 OR S34 S36 TI health literacy OR AB health literacy OR TI health promotion OR AB health promotion OR TI ((Health seeking behaviour or Health seeking behavior)) OR AB ((Health seeking behaviour or Health seeking behavior)) S37 TI ((Information seeking behaviour or Information seeking behavior or Information-seeking behaviour or Information-seeking behavior)) OR AB ((Information

"Patient Acceptance of Health Care"/ 77 exp Information Seeking Behavior/ 78 exp Consumer Health Information/ or exp Information Services/ or exp Patient Education as Topic/ 79 (knowledge adj1 gap).tw. 80 (resource or resources).tw. 81 exp Health Education/ 82 exp Consumer Health Information/ 83 exp Patient Education as Topic/ 84 exp Sex Education/ 85 exp Attitude to Health/ 86 *Decision Making/ or exp Decision Support Systems, Management/ or exp Decision Support Techniques/ or exp Decision Making/ 87 exp Professional-Patient Relations/ 88 communications media/ or library materials/ or teaching materials/ or telecommunications/ or electronic mail/ or telemedicine/ or remote consultation/ or telephone/ or answering services/ or exp cellular phone/ or television/ 89 computers/ or exp Microcomputers/ or Minicomputers/ or exp Internet/ or electronic mail/ or video games/ 90 exp Social Media/ or exp Self-Help Groups/ or exp Decision Support Techniques/ or exp Algorithms/ or exp Decision Support Systems, Management/ or exp Decision Support Systems, Clinical/ or *Internet/ or *Mass Media/ or *Patient Care Planning/ or *Managed Care Programs/ or exp Practice Guideline/ or *Books/ or exp Textbooks as Topic/ or exp Internet/ 91 (perspective$1 or opinion$1 or perception or view$1 or viewpoint$1 or experience$1 or satisfaction or attitude$1 or preference$1 or expectation$1 or engagement or dissatisfaction or collaborat* or communicat* or cooperat* or relation* or interact* or challeng*).tw. 92 55 or 63 93 11 and 55 and 91 43294 or/64-90 95 11 and 92 and 94 96 93 or 95 97 limit 96 to english language 98 limit 97 to yr="1990 -Current" 99 limit 98 to humans	seeking behaviour or Information seeking behavior or Information-seeking behaviour or Information-seeking behavior)) OR TI continuing education OR AB Continuing education OR TI Medical education OR AB Medical education OR TI Professional education OR AB Professional education OR TI Nursing education OR AB Nursing education OR TI Consumer health information OR AB Consumer health information S38 TI Information provision OR AB Information provision OR TI (knowledge N2 gap) OR AB (knowledge N2 gap) OR TI (resource or resources) OR AB (resource or resources) S39 (MM "Health Literacy") S40 (MH "Attitude of Health Personnel+") OR (MM "Health Knowledge") S41 (MM "Information Seeking Behavior") S42 (MH "Consumer Health Information+") S43 (MH "Patient Education+") OR (MM "Patient Discharge Education") OR (MH "Patient Education (Iowa NIC)+") S44 TI knowledge N2 gap OR AB knowledge N2 gap S45 (MH "Communication Barriers+") S46 (MH "Information Literacy+") S47 (MH "Communications Media+") S48 (MH "Social Media+") S49 (MH "Internet+") S50 (MM "Decision Support Systems, Clinical") OR (MH "Decision Support Techniques+") S51 TI (communications media or library materials or teaching materials or telecommunications or electronic mail or telemedicine or remote consultation or telephone or answering services or television) OR AB (communications media or library materials or teaching materials or telecommunications or electronic mail or telemedicine or remote consultation or telephone or answering services or television) S52 TI (Social Media or Self-Help Groups or Decision Support Techniques or Algorithms or Decision Support Systems or Internet or Mass Media or Patient Care Planning or Managed Care Programs or Practice Guideline* or Books or Textbooks) OR AB (Social Media or Self-Help Groups or Decision Support Techniques or Algorithms or Decision Support Systems or Internet or Mass Media or Patient Care Planning or Managed Care Programs or Practice Guideline* or Books or Textbooks) S53 S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 S54 S11 AND S35 AND S53 S55 S25 OR S54 S56 S25 OR S54 Limiters - Publication Year: 1990-2022; English Language; Human

Evidence processing: The search was performed for both topic 2.6.1 and 2.6.4. Studies were selected and appraised by two reviewers in consultation with the evidence team/ key contact using study selection and appraisal criteria (PICO above) established a priori. The articles were reviewed by title and abstract by two reviewers. When a decision could not be made based on title and abstract alone, full text was retrieved**. In total, 54 studies met inclusion criteria for both 2.6.1 and 2.6.4. Of these, 28 studies met inclusion criteria for the review of 2.6.4.**

3. SEARCH RESULTS - PRISMA flowchart



4. STUDY INCLUSION

4.1 Included studies

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Table 4.2 Excluded studies (on full text assessment)

#	Title	Study	Journal	Vol	Issue	Pages	Notes
1	Awareness of polycystic ovary disease among college students	Sharwini 2019	Drug Invention Today		9	2063-2065	Wrong population
2	An appraisal on the knowledge status of polycystic ovarian syndrome (PCOS)- Role and impact of clinical pharmacist to create awareness in their lifestyle by sophisticated patient counselling techniques - A community based study	Muchukota 2020	International Journal of Pharmaceutical Research	12(2)		648-659	No full text
3	The importance of collaboration in treating chronic disease: a focus on PCOS and group medical visits	Moore 2011	Women's Health Care: A Practical Journal for Nurse Practitioners	10	9	10-18	No full text
4	Knowledge, attitude and practices about poly-cystic ovary syndrome (Pcos) in Pakistan	Qadir 2021	Endocrine Practice	27 (12 SUPPL)		S45	Abstract
5	Women's perceptions of polycystic ovary syndrome following participation in a clinical research study: implications for knowledge, feelings, and daily health practices	Colwell 2010	Journal of Obstetrics & Gynaecology Canada: JOGC	32	5	453-459	Wrong intervention
6	Knowledge and attitudes towards polycystic ovary syndrome	Jaber 2022	African Journal of Reproductive Health	26	1	92-102	Wrong population
7	Attitudes Towards Transgender People Among Cisgender Women Who use Vaginismus and PCOS-related Online Forums	Adams 2022	Journal of Sexual Medicine	19 (8 Supp 3)		S20-S21	Wrong outcomes

8	Are patients with PCOS appropriately screened for associated CO morbidities?	Dongerkery 2018	Endocrine Reviews. Conference: 100th Annual Meeting of the Endocrine Society, ENDO	39 (2 Supp 1)			Abstract
9	Awareness and opinion about polycystic ovarian syndrome (PCOS) among young women: a developing country perspective	Jena 2020	International Journal of Adolescent Medicine & Health	33	3	123-126	Wrong population
10	Effect of structured awareness programme on polycystic ovarian syndrome (PCOS) among adolescent girls	VeenaKirthika 2019	Research Journal of Pharmacy and Technology	12(12)		6097-6100	Wrong population
11	It's not just physical: The adverse psychosocial effects of polycystic ovary syndrome in adolescents	Lee 2015	Women's Healthcare: A Clinical Journal for NPs	3	1	20-27	Wrong study design
12	Health-related knowledge, beliefs and self-efficacy in women with polycystic ovary syndrome	Lin 2018	Human Reproduction	33	1	91-100	Wrong comparator
13	Barriers and facilitators to the implementation of lifestyle management in polycystic ovary syndrome: Endocrinologists' and obstetricians and gynaecologists' perspectives	Chhour 2022	Patient Education & Counseling	105	7	2292-2298	Wrong outcomes
14	Preventive online and offline health management intervention in polycystic ovary syndrome	Liu 2022	World Journal of Clinical Cases	10(10)		3060-3068	Wrong intervention
15	Assessing self-efficacy and self-help methods in women with and without polycystic ovary syndrome	Kozica 2013	Behavioral Medicine	39(3)		90-96	Wrong study design
16	Health-related behaviors in women with lifestyle-related diseases	Kozica 2012	Behavioral Medicine	38	3	65-73	Wrong study design
17	199. Design of a Survey Instrument to Evaluate Primary Care Provider Behavior in the Diagnosis and Management of PCOS in Adolescents	Conlon 2020	Journal of Adolescent Health	66 (2 Supp)		S100-S101	Abstract
18	Dissecting individual experiences to reach a more comprehensive understanding of weight regulation in Polycystic Ovary Syndrome	Cooper 2013	Obesity Facts	1)		217-218	Abstract
19	Under-versus overdiagnosis: Exploring the benefits and harms of a pcos label and its impact on women's psychosocial wellbeing, lifestyle and behaviour	Copp 2018	BMJ Evidence-Based Medicine	23 (Supp 2)		A44	Abstract
20	Body- and symptom-related concerns in women diagnosed with polycystic ovary syndrome: A gap in symptom management	Soucie 2021	Journal of Health Psychology	26	5	701-712	Wrong outcomes
21	Nurse practitioner student perceptions and knowledge on polycystic ovarian syndrome: A quality improvement project	Onwuzurumba 2020	Dissertation Abstracts International Section A: Humanities and Social Sciences	81	11-A	No Pagination Specified	Wrong study design
22	Medical Journeyof Patientswithpcosand Obesity: A Cross-Sectional Survey of Patients	Sherif 2022	Journal of General Internal Medicine	37 (Supp 2)		S300	Wrong intervention

	and Pcps						
23	Nurse-led peer support group: experiences of women with polycystic ovary syndrome	Percy 2009	Journal of Advanced Nursing	65	10	2046-55	Wrong outcomes
24	Addressing polycystic ovary syndrome in outpatient mental health practices: A brief intervention to increase awareness	Shwarz 2016	Dissertation Abstracts International: Section B: The Sciences and Engineering	76	9-B(E)	No Pagination Specified	Wrong study design
25	Evaluation of depression and anxiety in women with polycystic ovary syndrome by physician trainees	Pakhdikian 2020	Journal of Investigative Medicine	68(1)		A168	Abstract
26	Exploring how knowledge, attitudes, and practices affect health-related quality of life in women diagnosed with polycystic ovarian syndrome	Nguyen 2018	Journal of the American Pharmacists Association	58(3)		e81-e82	Abstract
27	PCOS T.A.C.T.: A program to assist psychologists in understanding and helping women diagnosed with polycystic ovary syndrome	Niemi 2013	Dissertation Abstracts International: Section B: The Sciences and Engineering	73	7-B(E)	No Pagination Specified	Wrong study design
28	Nutrition education intervention for the management of polycystic ovary syndrome (PCOS)	Simha 2019	Medico-Legal Update	19(2)		21-27	Wrong intervention
29	Physician knowledge of polycystic ovary syndrome diagnosis and comorbidities	Stevenson 2020	Reproductive Sciences	27 (1 Supp)		360A-361A	Abstract
30	Acupuncture for weight loss in Polycystic Ovary Syndrome: a qualitative study exploring feasibility and acceptability	Ee 2019	Advances in Integrative Medicine	6 (Supp 1)		S102	Wrong intervention
31	Screening for Polycystic Ovarian Syndrome and Effect of Health Education on its Awareness among Adolescents: A Pre-Post Study	ElSayed 2020	International Journal of Nursing Education	12	4	227-236	Wrong population
32	Practice patterns of diagnosis and management of polycystic ovary syndrome: A survey of physicians from the Middle East and Africa	Beshyah 2021	Endocrine Practice	27 (12 SUPPL)		S29-S30	Abstract
33	Acupuncture with manual and low frequency electrical stimulation as experienced by women with polycystic ovary syndrome: a qualitative study		BMC Complementary & Alternative Medicine	12	1	32-37	Wrong intervention
34	With Her: Women's Health Education for Internal Medicine Residents. Using the Jigsaw Teaching Method to Enhance Im Residents' Knowledge and Confidence in Cervical Health, Breast Health, and Pcos	Gauvin 2022	Journal of General Internal Medicine	37 (Supp 2)		S661-S662	Abstract
35	Understanding polycystic ovary syndrome from the patient perspective: a concept elicitation patient interview study	Martin 2017	Health & Quality of Life Outcomes	15		1-10	Wrong outcomes

36	Diagnosis and health implications of PCOS in symptomatic women presenting to four different clinics: Gynecology, infertility, dermatology and endocrinology	Maruthini 2011	Human Fertility	1)		15	Abstract
37	Remote assessment and reinforcement of patient awareness of role of lifestyle modification and treatment adherence in polycystic ovary syndrome using an online video based educational module	Gour 2022	Journal of the Turkish German Gynecology Association	23(1)		1-7	Wrong intervention
38	Effectiveness of Video-Assisted Teaching Module on Knowledge, Attitude and Body Mass Index (BMI) Scaling Down Among Over-Weight Women Diagnosed with PCOS in Selected Hospitals of Madhya Pradesh	Massey 2021	Nursing Journal of India	112	5	203-207	Wrong intervention
39	Effectiveness of video assisted teaching program regarding the knowledge of polycystic ovarian disease and its prevention among adolescent girls studying in selected higher secondary schools at Kollam, India	Greeshma 2019	International Journal of Research in Ayurveda and Pharmacy	10(1)		67-70	Wrong population
40	Assessing the impact of an educational intervention program based on the theory of planned behavior on the nutritional behaviors of adolescents and young adults with PCOS in Iran: a field trial study	Hajivandi 2021	BMC Pediatrics	21	1	316	Wrong outcomes
41	Healthcare providers' knowledge, diagnosis and management of polycystic ovary syndrome (PCOS) in Europe, North America and internationally	Gibson-Helm 2017	Human Reproduction	32 (Supp 1)		i33-i34	Abstract
42	Polycystic ovaries: review of medical information on the internet for patients	MallappaSaroja 2010	Archives of Gynecology & Obstetrics	281	5	839-43	Wrong population
43	Sexuality and psychological wellbeing in women with polycystic ovary syndrome compared with healthy controls	Mansson 2011	European Journal of Obstetrics, Gynecology, & Reproductive Biology	155	2	161-5	Wrong outcomes
44	Polycystic Ovary Syndrome from Google to Bedside: Implications for Medical Education	Hoyos 2018	Fertility and Sterility	110 (4 SUPPL)		e111-e112	Abstract
45	Informing Translation: The Accuracy of Information on Websites for Lifestyle Management of Polycystic Ovary Syndrome	Htet 2018	Seminars in Reproductive Medicine	36	1	80-85	Wrong population
46	The accuracy of information for lifestyle management on websites for the management of PCOS	Htet 2017	Clinical Endocrinology	86 (Supp 1)		47	Abstract
47	Polycystic ovary syndrome: double click and right check. What do patients learn from the Internet about PCOS?	Mousiolis 2012	European Journal of Obstetrics, Gynecology, & Reproductive Biology	163	1	43-6	Wrong population

48	Provider experiences with lifestyle management in women with PCOS	Huffman 2017	Fertility and Sterility	108 (3 Supp 1)		e247	Abstract
49	Concerns of polycystic ovary syndrome women: A qualitative study	NasiriAmiri 2013	Journal of Diabetes	1)		18	None English
50	EFFECTIVENESS OF VIDEO ASSISTED TEACHING MODULE ON KNOWLEDGE OF ADOLESCENT GIRLS REGARDING POLYCYSTIC OVARIAN SYNDROME IN GAYATRI WOMEN'S +2 SCIENCE COLLEGE BERHAMPUR, GANJAM, ODISHA	Nayak 2017	Journal on Nursing	7	2	27-31	Wrong population
51	Assessment of Psychological Distress in Polycystic Ovarian Syndrome Infertile Patients at a Tertiary Level Infertility Care Centre in India	Nayar 2019	Fertility and Sterility	112(3 SUPPL)		e394	Abstract
52	Educational Program: Its Effect on Knowledge and Lifestyles among Paramedical Students with Polycystic Ovarian Syndrome (PCOS)	AlKurdi 2021	Medico-Legal Update	21	3	58-69	Wrong study design
53	Knowledge of Polycystic Ovarian Syndrome, Its Complications, and Management among Lebanese Women: A Cross-Sectional Survey	AlSouheil 2022	Journal of Health & Allied Sciences NU	12	3	267-273	Wrong population
54	Relationship between health literacy and body mass index among Arab women with polycystic ovary syndrome	Al-Ruthia 2017	Saudi Pharmaceutical Journal	25(7)		1015-1018	Wrong outcomes
55	PCOS symptom recognition and diagnosis: Time for better education and clinical resources	Ali 2022	BJOG: An International Journal of Obstetrics and Gynaecology	129 (Supp 1)		221	Abstract
56	Impact of limited reproductive health awareness on PCOS diagnosis timelines and the need for improved patient education	Ali 2022	Human Reproduction	37 (Supp 1)		i536-i537	Abstract
57	Assessing the effectiveness of a pharmaceutical care service on the quality of life of women with polycystic ovarian syndrome living in war and non-war countries	Alkoudsi 2020	Journal of Evaluation in Clinical Practice	26(5)		1467-1477	Wrong outcomes
58	Effect of an educational program about polycystic ovarian syndrome on knowledge of adolescent female students	Almukhtar 2019	Indian Journal of Public Health Research and Development	10(8)		1059-1063	Wrong outcomes
59	Awareness of polycystic ovary syndrome: A university students' perspective	Alshdaifat 2021	Annals of Medicine and Surgery	72			Wrong population
60	The stigma of womanhood thiaf: Polycystic ovary syndrome	Amini 2012	International Journal of Fertility and Sterility	1)		153	Abstract
61	Evaluation of women knowledge and perception about polycystic ovary syndrome and its management in Jordan: A survey-	Abu-Taha 2020	International Journal of Clinical Practice	74	10	e13552	Wrong population

	based study						
62	Diagnostic experiences and concerns in adolescents with polycystic ovary syndrome	Pena 2018	Hormone Research in Paediatrics	90 (Supp 1)		567	Abstract
63	Chasing Infertility - the Chat Bot-Way to Increase Fertility Awareness	Schenk 2021	Fertility and Sterility	116 (3 SUPPL)		e269-e270	Abstract
64	Polycystic Ovary Syndrome in American Indian Women: An Exploratory Study	Carron 2018	Fertility and Sterility	110 (4 SUPPL)		e280-e281	Abstract
65	Polycystic ovary syndrome in globalizing India: An ecosocial perspective on an emerging lifestyle disease	Pathak 2015	Social Science & Medicine	146		21-8	Wrong outcomes
66	Sexuality in women with polycystic ovary syndrome	Kowalczyk 2015	Ginekologia Polska	86	2	100-6	Wrong intervention
67	Diagnosis and lifestyle modification counseling for adolescents with pcos: An assessment of learning needs in OBGYN, pediatrics, and family medicine residents	Dassow 2017	Obstetrics and Gynecology	130 (Supp 1)		55S-56S	Abstract
68	Ask PCOS: Identifying Need to Inform Evidence-Based App Development for Polycystic Ovary Syndrome	Boyle 2018	Seminars in Reproductive Medicine	36	1	59-65	Wrong population
69	Analysis of the barriers and enablers to implementing lifestyle management practices for women with PCOS in Singapore	Ko 2016	BMC Research Notes	9		311	Wrong outcomes
70	The doctor will tweety ounow: Expanding accessto care through social media engagement	Chen 2016	Fertility and Sterility	106 (Supp 3)		e111-e112	Abstract
71	Resident Knowledge of Pcos: Identifying Gaps and Educational Opportunities	Chemerinski 2018	Fertility and Sterility	110 (4 SUPPL)		e112	Abstract
72	A comparison of polycystic ovary syndrome and related factors between lesbian and heterosexual women	Smith 2011	Womens Health Issues	21	3	191-8	Wrong intervention
73	Effectiveness of structured teaching programme on knowledge of polycystic ovarian syndrome among adolescent girls	Sowmya 2013	Nitte University Journal of Health Science	3(3)		54-58	Wrong population
74	What Can You Find about Polycystic Ovary Syndrome (PCOS) Online? Assessing Online Information on PCOS: Quality, Content, and User-Friendliness	Chiu 2018	Seminars in Reproductive Medicine	36	1	50-58	Wrong outcomes
75	Challenges and uncertainties regarding polycystic ovary syndrome (PCOS) and the potential for overdiagnosis: Clinicians' views and experiences	Copp 2018	BMJ Evidence-Based Medicine	23 (Supp 2)		A45	Abstract
76	Barriers and facilitators to weight management in overweight and obese women living in Australia with PCOS: A qualitative study	Lim 2019	BMC Endocrine Disorders	19(1)			Wrong outcomes
77	The experiences of women with polycystic ovary syndrome on a very low-calorie diet	Love 2016	International Journal of Women's Health	8		299-310	Wrong intervention

78	Barriers and Facilitators to Weight and Lifestyle Management in Women with Polycystic Ovary Syndrome: General Practitioners' Perspectives	Arasu 2019	Nutrients	11	5	7	Wrong outcomes
79	Relationship between loci of control and health-promoting behaviors in Pakistani women with polycystic ovary syndrome: coping strategies as mediators	Fatima 2021	BMC Women's Health	21(1)			Wrong outcomes
80	Clinicians' Perceptions of Norwegian Women's Experiences of Infertility Diseases	Fernandes 2020	International Journal of Environmental Research & Public Health [Electronic Resource]	17	3	5	Wrong outcomes
81	Feasibility and acceptability of a proposed trial of acupuncture as an adjunct to lifestyle interventions for weight loss in Polycystic Ovary Syndrome: A qualitative study 11 Medical and Health Sciences 1117 Public Health and Health Services	Ee 2018	BMC Complementary and Alternative Medicine	18(1)			Wrong outcomes
82	Perceptions and experiences of lifestyle interventions in women with polycystic ovary syndrome (PCOS), as a management strategy for symptoms of PCOS	Arentz 2021	BMC Women's Health	21(1)			Wrong outcomes
83	Practice patterns in the diagnosis of PCOS: Low testing rates for other disorders with similar clinical presentations	Willard 2014	Endocrine Reviews. Conference: 96th Annual Meeting and Expo of the Endocrine Society, ENDO	35	SUPPL. 3		Abstract
84	Polycystic ovary syndrome (PCOS) in the adolescent patient: recommendations for practice	Snyder 2005	Pediatric Nursing	31	5	416-21	Wrong study design
85	The importance of screening for diabetes in women with polycystic ovary syndrome	Shorakae 2015	Diabetes Management	5(1)		1-4	Wrong study design
86	Patient requests for improved diagnosis and information in polycystic ovary syndrome	Pugeat 2020	Annales d Endocrinologie	81	5	473-475	Wrong study design
87	HER LIFESTYLE: a mneumonic for addressing polycystic ovary syndrome in adolescents	Neal 2009	Nursing for Women's Health	13	6	472-478	Wrong study design
88	Incorporating qualitative approaches is the path to adequate understanding of the psychosocial impact of polycystic ovary syndrome	Moreira 2006	Human Reproduction	21	10	2723-4; author reply 2724-5	Wrong study design
89	Recognizing and eliminating bias in those with elevated body mass index in women's health care	Lindheim 2018	Fertility and Sterility	109(5)		775-776	Wrong study design
90	Obesity, polycystic ovary syndrome, infertility treatment: asking obese women to lose weight before treatment increases stigmatisation	Laredo 2006	BMJ	332	7541	609	Wrong study design
91	Polycystic ovarian syndrome: what nurses need to know about this	Jackson 2004	AWHONN Lifelines	8	6	511-8	Wrong study design

	misunderstood disorder						
92	A patient's guide: polycystic ovary syndrome (PCOS)	Hoeger 2014	Journal of Clinical Endocrinology & Metabolism	99	1	35A-36A	Wrong study design
93	Worldwide dissatisfaction with the diagnostic process and initial treatment of PCOS	Cree-Green 2017	Journal of Clinical Endocrinology and Metabolism	102(2)		375-378	Wrong study design
94	Are expanding disease definitions unnecessarily labelling women with polycystic ovary syndrome?	Copp 2017	BMJ	358		j3694	Wrong study design
95	Diagnostic features of polycystic ovary syndrome	Barday-Karbanee 2006	South African Journal of Obstetrics and Gynaecology	12(1)		30-35	Wrong study design
96	What You Need to Know about Pediatric and Adolescent Gynecology: Clinically Relevant Reviews Published in the Journal of Pediatric and Adolescent Gynecology	AdamsHillard 2017	Journal of Pediatric and Adolescent Gynecology	30(5)		519	Wrong study design
97	Testing for insulin resistance in polycystic ovary syndrome-a survey of american society for reproductive medicine (ASRM) physician members	Asante 2013	Fertility and Sterility	1)		S82	Abstract
98	Polycystic ovary syndrome support groups and their role in awareness, advocacy and peer support: A systematic search and narrative review	Avery 2020	Current Opinion in Endocrine and Metabolic Research	12		98-104	Wrong population
99	PCOS: perspectives from a pediatric endocrinologist and a pediatric gynecologist	Kansra 2013	Current Problems in Pediatric & Adolescent Health Care	43	5	104-13	Wrong study design
100	Study the Effectiveness of Structured-Teaching Programme on Knowledge Regarding Polycystic Ovarian Syndrome and Its Prevention among Higher Secondary Female Students in Selected School of Dehradun	Karki 2018	International Journal of Nursing Education	10	3	96-101	Wrong population
101	Is It Time to Update the Screening Recommendations for Patients with Polycystic Ovary Syndrome?	Kaiser 2021	Fertility and Sterility	116 (3 SUPPL)		e122	Abstract
102	Development and validation of a guideline on sexual and reproductive health services for polycystic ovary syndrome in Iran: a mixed-methods study protocol	Kalhor 2021	Health Research Policy & Systems	19	1	144	Wrong outcomes
103	Dietary management of women with polycystic ovary syndrome in the United Kingdom: the role of dietitians	Jeanes 2009	Journal of Human Nutrition & Dietetics	22	6	551-8	Wrong outcomes
104	Mental Health and PCOS Information-Sharing: Interviews with Health Care Providers in a Low-Income Urban Community	Zamora 2022	Journal of racial and ethnic health disparities.	9			Wrong outcomes
105	Transition to Self-Management among Adolescents with Polycystic Ovary Syndrome: Parent and Adolescent Perspectives	Young 2019	Journal of Pediatric Nursing	47		85-91	Wrong outcomes

106	Polycystic Ovarian Syndrome: Perception of Women with Pcos and Impact of Pharmacist's Intervention	Ravi 2018	Value in Health	21 (Supp 2)		S59	Abstract
107	Gaps in knowledge in diagnosis and management of polycystic ovary syndrome	Saini 2016	Fertility and Sterility	106 (Supp 3)		e100	Abstract
108	"Less Than A Wife": A Study of Polycystic Ovary Syndrome Content in Teen and Women's Digital Magazines	Sanchez 2016	Journal of Medical Internet Research	18	6	e89	Wrong population
109	Effectiveness of planned teaching program regarding polycystic ovarian disease in terms of knowledge and attitude among students of sgt university	Umaisa 2021	Indian Journal of Forensic Medicine and Toxicology	15(3)		4332-4338	Wrong population
110	Quality Improvement in the Evaluation and Diagnosis of Polycystic Ovary Syndrome in Adolescent Girls	Torres 2021	Journal of Pediatric & Adolescent Gynecology	34	5	603-609	Wrong outcomes
111	Effectiveness of self help strategies (SHS) for PCOS on biochemical parameters among young adult girls	Tamilselvi 2020	International Journal of Research in Pharmaceutical Sciences	11(3)		3034-3041	Wrong outcomes
112	Polycystic ovary syndrome: perceptions and attitudes of women and primary health care physicians on features of PCOS and renaming the syndrome	Teede 2014	Journal of Clinical Endocrinology & Metabolism	99	1	E107-11	Wrong outcomes
113	Diagnosis and management of polycystic ovary syndrome: Clinician perspectives in Singapore	Teoh 2022	BJOG: An International Journal of Obstetrics and Gynaecology	129 (Supp 1)		13	Abstract
114	Informing the design and delivery of a lifestyle program for women with polycystic ovary syndrome: A mixed-methods investigation on patients' perspectives	Pirotta 2021	South African Journal of Clinical Nutrition	34(3)		157	Abstract
115	A randomized pilot study of dietary treatments for polycystic ovary syndrome in adolescents	Wong 2016	Pediatric Obesity	11	3	210-20	Wrong outcomes
116	Transtheoretical model-based mobile health application for PCOS	Wang 2022	Reproductive Health	19	1	117	Wrong outcomes
117	The effect of polycystic ovary syndrome on daily activities, self-esteem and experiences in employment	Washington 2005			Ph.D.	470 p-470 p	Wrong study design

5. STUDY QUALITY APPRAISAL

		A: Are the results valid?						B: What are the results?			C: Will the results help localy?	
Study ID	**Design**	**Clear research aims**	**Method appropriate for goals**	**Design appropriate for aims**	**Appropriate recruitement strategy**	**Appropriate data collection**	**Relationship considered between researcher and participant**	**Consideration of ethical issues**	**Rigorous data analysis**	**Clear statement of findings**	**Research value**	**Overall RoB**
Atkinson 2021	Qualitative	Yes	Yes	Yes	Can't tell	Can't tell	No	Yes	No	Can't tell	Yes	High
Authier 2020	Qualitative	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Low
Avery 2007	Qualitative	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Low
Bazarganipour 2017	Qualitative	Yes	Yes	Yes	Can't tell	Yes	Can't tell	Yes	Yes	Yes	Yes	Low
Copp 2022	Qualitative	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Low
Crete 2011	Qualitative	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes	Yes	Yes	Low
Hadjiconstantinou 2017	Qualitative	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Low
Hillman 2020	Mixed method	Yes	Yes	Yes	Yes	Can't tell	No	Yes	Yes	Yes	Yes	Low
Holbrey 2013	Qualitative	Yes	Yes	Yes	Yes	Yes	No	Yes	Unclear	Yes	Yes	Low
Ismayilova 2022	Qualitative	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Ismayilova 2022b	Qualitative	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes	Yes	Low
Kaur 2021	Mixed method	Yes	Yes	Yes	Yes	Can't tell	No	Yes	Can't tell	Can't tell	Yes	Moderate
Kitzinger 2002	Qualitative	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes	Yes	Low
Lim 2019	Qualitative	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes	Yes	Yes	Low
Lim 2021	Qualitative	Yes	Yes	Yes	Can't tell	Can't tell	No	Yes	Can't tell	Yes	Yes	Moderate
Pirotta 2021	Mixed method	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes	Low
Sharma 2018	Qualitative	Yes	Yes	Yes	Can't tell	Can't tell	No	Yes	Can't tell	Yes	Yes	Moderate
Soucie 2021	Qualitative	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes	Low
Synder 2006	Qualitative	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Low
Tay 2021	Qualitative	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Tomlinson 2017	Qualitative	Yes	Yes	Yes	Yes	Yes	No	Yes	Can't tell	Yes	Yes	Low
Weiss 2011	Qualitative	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes	Low
Williams 2015	Qualitative	Yes	Can't tell	Can't tell	Can't tell	Can't tell	No	Yes	Can't tell	Yes	Can't tell	High
Williams 2016	Qualitative	Yes	Yes	Yes	Yes	Yes	No	Yes	Can't tell	Yes	Yes	Low
Wright 2020	Qualitative	Yes	Yes	Yes	Can't tell	Yes	No	Yes	Yes	Can't tell	Yes	Moderate

		Selection bias			Performance bias	Detection bias				Attrition bias		Report Bias	Confounding	Other bias			
Study ID	Design	Comparable cases & controls	Established case definition	Established control definition	Groups treated the same	Standard measurements for exposure	Assessors blinded to case/control status	Standard measurements for outcomes	Outcomes assessed objectively and independently	% lost to follow up	% included in analysis	Free of selective outcome reporting	Groups similar at baseline	Funding/ COI reported	Sufficient power	Adequate statistical analysis	Overall risk
Lin 2018	Cross-sectional	Yes	Partial	Yes	Yes	Yes	No	Yes	Yes	Not applicable	All	Yes	Yes	Yes	Not reported	Yes	Low

6. FINDINGS

Summary of findings 1. Summary of qualitative findings Table

Summary of review finding	GRADE-CERQual assessment of confidence in the evidence	Explanation of GRADE-CERQual	Studies contributing to the review finding[1]
Finding 1: Interactions were challenging when bad news was shared in a way that did not safeguard wellbeing	High confidence	No/very minor concerns methodological limitations No/very minor concerns regarding coherence No/very minor concerns adequacy No concerns regarding relevance	Studies [1,2,3,4,5, 6,8,10,11,14, 16, 17,20, 21, 22, 23, 24,25,26, 27,28].
Finding 2: Interactions were challenging when they did not provide opportunities to facilitate shared decision-making about outcomes that matter to people	High confidence	No/very minor concerns methodological limitations No/very minor concerns regarding coherence No/very minor concerns adequacy No concerns regarding relevance	Studies [1,2, 3,4,5,6, 8, 10,11, 12,14,16,17, 21, 23,24,25,26]
Finding 3: Interactions were challenging when healthcare professionals did not support patient agency (their ability to take independent actions to manage their health and care)	Moderate confidence	No/very minor concerns methodological limitations No/very minor concerns regarding coherence Very minor concerns adequacy No concerns regarding relevance	Studies [1,2,6,9,11, 12, 13, 15,16, 17,19, 21,23, 24,25,26,27]

- **EVIDENCE SUMMARY:**

A total of 28 studies were identified that provided data on key challenges for those with PCOS when interacting with healthcare professionals. Of these studies three were mixed methods designs, one a systematic review, and one a comparative design of people with and without PCOS. Only data describing patient perspectives on key challenges was sought and extracted which by design an almost exclusive focus on problematic areas of care.

Qualitative data synthesised comprised participant narrative and author interpretation which were used for the descriptive analysis summary. Most studies were carried out in the UK (8 studies), Australia (6 studies) or North America (USA 5 studies, Canada 5 studies). Four studies were from India or Iran. Most studies required participants to have received a medical diagnosis of PCOS. Age range was within 20 to 50 years of age (11 studies), only one study sampled adolescent girls but several studies with larger age ranges reported on the experiences of young women 18 to 20 years of age. The predominant data collection method was interview alone or in combination with other methods. Three studies acquired data through internet forums, citizen panels or photovoice. The most common analytic approach was unspecified or generic thematic analysis, with other approaches being framework analysis or phenomenological. Two studies were judged to have high quality, four moderate quality and the remaining low quality.

Summary of Findings:
Three main themes emerged from synthesis of qualitative and mixed-methods studies on challenges for patients interacting with healthcare professionals.

First, interactions were challenging when bad news (PCOS disease, its management, or long-term risks) was shared in a way that was not empathic and that did not safeguard patient wellbeing. PCOS bad news was shared in a suboptimal way due to lack of appropriate setting or preparation (by healthcare professional, of the patient) or by use of unhelpful strategies (normalising, minimising). Importantly interactions sharing bad news did not always provide necessary knowledge and resources, end with a well-formulated strategy for management or check that patients understood the bad news or the planned management strategy. The effect of sharing bad news poorly was that patients were alarmed, felt uninformed or poorly informed, and worried about their future. Healthcare professionals that owned up to lack of disease expertise and who took the time to research and support patients with a new diagnosis were perceived positively.

Second, interactions were challenging when they did not provide opportunities to facilitate shared decision-making about outcomes that matter to people. Interactions were often too abbreviated to meaningfully engage in shared decision-making because only a subset of information, options and attributes was presented (often due to bias), patient preferences were not elicited, and too little time was available for deliberating the options with a knowledgeable doctor. The main consequent effect of the suboptimal shared decision-making context was that patients felt excluded from the decision process and decision quality about disease management perceived to be poor (shared, uninformed, not value-based). Interactions that set-up shared decision-making were positively regarded though time consuming for healthcare professionals.

Third, interactions were challenging when healthcare professionals did not support patient agency that is, patient's ability to take independent actions to manage their health and care. Patients reported they were not valued as expert witnesses of their own health and their efforts for self-management (agency) not valued or supported. Lack of valuing meant patients felt dismissed and had to be very insistent to obtain resources or achieve outcomes that mattered to them which was challenging for many reasons. Healthcare professionals that were validating, supported patients in their

research and had consultations that were patient led and informed were viewed positively.

- **DESCRIPTIVE ANALYSIS SUMMARY:**

Studies identified THREE ways in which interactions between healthcare professionals (HCPs) and patients were challenging (see Table OF SUMMARY FINDINGS):

Finding 1: Interactions were challenging when bad news was shared in a way that did not safeguard wellbeing

Interactions were challenging when the setting for sharing bad news was not set-up to minimise distress or to receive dignified care, especially in lower middle income countries where other patients could be in examining room or could overhear [4] or where patients experienced waited many hours for potentially bad news [4].

Interactions of sharing bad news were challenging when perceptions and understanding of symptoms were not elicited prior to sharing bad news. These interactions were perceived to lead to rejection of healthcare professionals recommendations [4] or to patients receiving recommendations misaligned with their causal understanding (e.g., recommending pregnancy test to account for irregular periods [8]). Also challenging was healthcare professionals omitting to first seek the invitation to share bad news from patients to avoid giving bad news unexpectedly about the diagnosis [16] but especially about the risks for future fertility and disease [1,2].

Interactions involving sharing bad news were challenging when healthcare professionals were not prepared to share bad news with appropriate knowledge and information. Healthcare professionals did not always ascertain or justify the validity of a PCOS diagnosis [3, 4, 22]. Healthcare professionals were perceived as insufficiently prepared with the necessary PCOS disease knowledge to have informed discussions with patients [14,16,26], to avoid poor explanations (e.g., “ovaries filled with water” [14]) or incorrect explanations (e.g., “you’ll grow out of it” [26], due to poor diet [21], “probably puberty” [27], “you should not be concerned”[28]) that could lead to misunderstanding of disease or management. Explanations of disease were perceived to have important gaps (e.g., omission of risk factors [6]) and lacked checking of patients understanding of the explanations [6]. Missing important information about disease meant patients felt “left in the dark”[6]. If other healthcare professionals later diagnosed PCOS, trust in initial healthcare professionals (usually general practitioner) was reduced [6]. Healthcare professionals that owned up to lack of PCOS expertise and who took the time to research and support patients in understanding it were viewed positively [11, 17].

Interactions were challenging when sharing bad news was not done empathically (e.g., was impersonal[1], abrasive, rude insensitive[21], curt instructions[3]). Efforts to alleviate patient distress were not always appropriate or helpful for example normalising symptoms ([3], “nothing to worry about”[14]) or minimising symptoms

("have lots of sex"[10], "it's just one of those things" [24]) or could cause patients to feel brushed off. Normalising was especially common with young people[3, 21, 25,27]. Other efforts to minimise were perceived as insensitive and trivialising of the condition (e.g., facial hair: "you must have Spanish ancestry"[10]). Sharing bad news about risks of future disease (infertility, cancer, cardiovascular) often gave insufficient information for people to understand the risks[24] or was delivered in a way that was upsetting or alarming (["terrified"[1], "in tears" [2]) especially to young people[20]. Reassurance from healthcare professionals [5] or de-catastrophising [23] about disease or future risks was appreciated. Bad news was at times shared through non-medical staff (e.g., receptionist [25] which was perceived as inappropriate. Healthcare professionals that added good news to bad news were perceived favourably (e.g., have PCOS, but will accelerate fertility referral)[10].

Sharing bad news that did not end with a strategy for next steps in care was perceived as challenging. In particular, when consultation did not end with a treatment plan [6, 25], strategy of follow-up[5, 21] or know-how to access future care for high risk outcomes such as infertility [1]. Strategy was perceived to be especially important for those diagnosed at a young age [1, 5]. A lack of justification for follow-up testing was perceived to cause uncertainties[6] or patients to feel "passed-off"[6]. Insufficient support to implement treatment plans or planned strategy was challenging (e.g., connecting with specialists[17]. Participants perceived the lack of a well-formulated management/follow-up plan to be due to a lack of healthcare professional knowledge [6].

Finding 2: Interactions were challenging when they did not provide opportunities to facilitate shared decision-making about outcomes that matter to people.

Interactions with HCPs were perceived to offer some options (e.g., typically hormonal control or fertility referral) but not all options (e.g., lifestyle management, complementary alternatives) [1,4,5,14], or patients felt forced to choose which options informed about (e.g., endocrinology or fertility services [24,26]). Interactions were perceived to be too abbreviated to inform on options and attributes and often described as offered with "nothing more" [1,3,4,5,12,14,21,23]. The options offered were perceived to be constrained by HCP bias about patient age[12], patient knowledge[6], marital status [8,12], weight status[5, 12], patient ethnicity[10], or HCP causal understanding of PCOS, (e.g., genetics "nothing you can do about it" [5] or health system restrictions about referral[24,26]). Options offered were perceived to be misaligned to patient circumstances (e.g., cycle based testing when irregular[2], prior history of weight loss attempts[5], cultural beliefs about unmarried women using hormonal contraceptives [8,12], personal safety in neighbourhood[16], distance to services, instability of military life[26]). Healthcare professionals were often perceived not to have sufficient disease knowledge, to inform on the option set and attributes [3, 11,24,26]. The consequent effect of these interactions was that patients lacked confidence in the healthcare professional's knowledge of options and their attributes [18] or ability to understand patient's personal circumstances [17]. Interactions set-up to generate sufficient knowledge gain about options and attributes were positively regarded though could be time consuming for healthcare professionals (i.e., two hours, [25]).

Interactions were perceived not to be set-up to elicit preferences and therefore preferences for some options were perceived not to be addressed or integrated in care plans, for example, options that avoided long-term risks [5,6, 10] or specific risks affecting the patient (e.g., migraines)[6], about weight-management [5,16,25] or psychological outcomes such as mental health[23] or restoring personal agency [25]. Healthcare professionals were perceived to act on their own preferences especially in prioritising fertility [6,8,10,12,14,21,26]. Study participants perceived that preferences for information formats (e.g., written[6]) or content of information (e.g., baseline risks[3], practical information[17]) were not elicited. Interactions that aligned with patient preferences were positively viewed for example aligned to amount and type of information[3] or referral to fertility care for childwish[10]. Interactions that were validating, patient informed and led [21] or that elicited personal preferences due to integrated care in multidisciplinary care teams [17, 23] were positively regarded.

Interactions were perceived to have insufficient time or methods to help patients deliberate the options and attributes, and or reach decisions with their healthcare professionals [1,3,4,16, 21,23,24,25]. The consequent effect was that patients felt left out of decision-making process. None of the included studies referred to healthcare professionals evaluating decision-quality despite patients reporting they felt decisions about treatment were not shared, informed [1,3,4,5, 12,14,21,23] or value-based [5,6, 10,16, 23, 25].

Finding 3: Interactions were challenging when healthcare professionals did not support patient agency (their ability to take independent actions to manage their health and care).

Interactions were perceived to be challenging when healthcare professionals did not value patients as expert witnesses to their own health by not eliciting or listening to patient's story or explanations[1,2], especially about prior mis-diagnosis, repeated testing, or ineffective treatment [2,6], by dismissing or not taking seriously patient worries[1, 9, 15,17,24,25] or showing a "condescending "attitude [11]. Young people especially perceived their voice not to be valued [9, 21,24,25]. Lack of valuing was associated with patients feeling a lack of care (e.g., "waved on" [11], "brushed off"[12], "not giving a hoot"[13], "pushed me out the door"[24]) or feeling that the reproductive conditions of girls and women were not important[12].

Interactions were challenging when patients perceived healthcare professionals did not value or support patient efforts at agency. Lack of valuing was ascertained when patients needed to be very persistent to be heard or meet their needs ("super insistent", "finally they relented"[24], "right pain in the butt"[26], "had to push to get a diagnosis"[27]], when healthcare professionals were disinterested ("seemed bored"[9]), did not acknowledge or discuss patients' own PCOS research [13, 21], did not actively provide knowledge and resources for self-management [13, 17,27] or become sufficiently involved in their care (especially follow-up[13,17]). Also challenging and undermining of self-agency were interactions proposing burdensome or difficult to execute strategies, for example, to use a an inaccessible service[1, 17], to act without appropriate data exchange between primary and secondary care[3] or follow instructions that were insufficiently motivating on their own (e.g., "just lose

weight" [16, 19,23]). Lack of support for agency was perceived to cause a loss of trust in healthcare professionals[1], reduced willingness to follow recommendations[9], and the perception in patients that they needed to be their "own doctor"[13, 17]. Patients also reported these interactions made them think healthcare professionals thought ill of them (e.g., "healthcare professionals think I'm crazy"[6], "got fed up with me"[24]). In contrast, interactions that stimulated agency and provided encouragement and support to young people (from nutritionist, [9]), answered questions reassuringly (nurse, [8])] or where healthcare professionals discussed patient research positively [13] were viewed favourably.

7. GRADE ASSESSMENTS AND EVIDENCE PROFILE

Due to the broad nature of the clinical question and the inclusion of studies of heterogeneous designs, populations and/or aims, it was not feasible to generate GRADE evidence profile tables for this question.

Please see individual study risk of bias assessments to determine the quality of evidence.

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 2

Question 2.6.4.

What are the key challenges for those with PCOS when interacting with healthcare professionals about polycystic ovary syndrome and related features?

BACKGROUND:

Prevalence and problem

Interactions between patients, their doctors and the wider healthcare team about PCOS (hereafter "interactions") are important for patients to learn about their health, make decisions about their health, and be supported to achieve health outcomes that matter to them. Therefore, it is important to address challenges in interactions that could undermine positive outcomes that could be achieved from these interactions (e.g., acceptance and adjustment to bad news, decision quality, self-management).

Clinical practice gap: need for guidance

Challenges of interactions involving sharing news in PCOS care

A common definition of bad news in health is "any information that produces a negative alteration to a person's expectations about their present or future" (1). Receiving news about PCOS whether a diagnosis, treatment or care, or risk for future disease is likely to meet this definition, even if patients feel relief at receiving a diagnosis (2-4). Receiving information that produces a negative alteration to a person's expectations is typically understood as a process (versus single event) with the lead up, the news and the aftermath of disclosure all being important (5). Voluminous empirical research exists about best ways of sharing information that produces a negative alteration to a person's expectations and many frameworks have been developed to guide how to share this news.

SPIKES framework proposes six steps which proposes six steps in delivering bad news to patients: **S**etting up the interview, assessing the patient's **P**erception of the situation, obtaining the patient's **I**nvitation to deliver the news, giving **K**nowledge and information to the patient, addressing the patient's **E**motions empathically, and (6) providing a **S**ummary and discussing prognosis and treatment options. Survey research indicates that SPIKES is aligned to patient preferences for receiving bad news in many areas of health (7), which is corroborated in fertility care using a focus group design (8). Patients have preferences for how this news should be delivered (e.g., amount of detail, who should be present), and variation across ethnicity, religiosity, and country (5). Nevertheless, systematic review and meta-analysis (17 studies) have shown that use of SPIKES for training doctors out-performs other approaches in demonstrating significant improvements in observer-rated news delivery skills and doctor confidence in delivering such news in many countries (e.g., Belgium Germany, Israel, Japan, Hong Kong, UK, USA) (9).

According to the evidence reviewed in PCOS, interactions are challenging when PCOS information that produces a negative alteration to a person's expectations (PCOS disease, its management, or long-term risks) is shared in a way that does not safeguard patient wellbeing. PCOS news is often shared suboptimally due to lack of appropriate setting (10, 11) or advanced preparation of the patient for receiving it [e.g., being forewarned, (10-13)] especially when delivered to young people. Healthcare professionals can also be unprepared due to lack of knowledge relevant for informed and accurate discussions about PCOS not being acquired in advance of delivering PCOS news (10, 14-20). Interactions are sometimes not empathic (2, 17, 21) and efforts to alleviate patient distress at such news, based on unhelpful strategies (normalising, minimising) (13-15, 22) especially with young people (4, 14, 17, 19). Importantly, interactions sharing bad news do not always end with a well-formulated strategy for future management or include a check that patients understood the news or the planned management strategy (if any) (4, 17, 23, 24).

The effect of sharing such news sub-optimally was that patients were alarmed, felt uninformed or poorly informed, and worried about their future, especially young people (2, 21, 24, 25) . Three studies reported that patients felt relief at receiving a diagnosis because of having a name and recognition (and validation) of their symptoms after many years of searching (3, 14, 17) and because of now having a care team (3). Despite relief, women also reported the diagnosis made them feel "upset" (2) and "desolate" (3) and uncertain about their future because diagnosis was not shared optimally, leaving people feeling uncertain about the nature of their condition, and its future

risks and management strategy (3, 11, 17). Healthcare professionals that owned up to lack of disease expertise and who took the time to research and support patients with a new diagnosis were perceived positively (3, 26).

Challenges of shared decision-making in PCOS care

The complexity of PCOS as a disease, its features and correlates, and future risks (e.g., hirsutism, acne, higher weight, infertility, diabetes, cardiovascular disease) make it highly likely that people with PCOS will have to make decisions considered suitable for shared decision-making, namely decisions where more than one course of action is reasonable and where the consequences of actions are significant (26). An internationally adopted definition of shared decision-making: "... is an approach where clinicians and patients make decisions together using the best available evidence. Patients are encouraged to think about the available screening, treatment, or management options and the likely benefits and harms of each so that they can communicate their preferences and help select the best course of action for them. Shared decision-making respects patient autonomy and promotes patient engagement" (27, 28, 29). Shared decision-making is often supported using patient decision aids (supporting patients) and decision support tools (supporting healthcare professionals). There is a vast international corpus of shared decision-making research (including systematic review, meta-analysis), guidelines and training. In areas of relevance to PCOS results are positive. For example, in reproductive health when compared to usual care the use of shared decision making (decision aids) reduces decisional conflict, improves patient knowledge but has no effect on anxiety or satisfaction (30, 35 studies). The benefits are replicated in diabetes care, with additional benefits reported for higher decision quality and patient risk perception and understanding (31, 16 studies) reported internationally. Prospective systematic evaluation (exposed, unexposed cohorts) suggests that additional time for shared decision making could be much less, even in difficult clinical contexts (2 mins 11 s, and 3 mins 57s, for lung cancer and breast cancer, respectively) (32).

According to the evidence reviewed in PCOS, interactions are challenging when they do not provide opportunities to facilitate shared decision-making about outcomes that matter to people. Interactions in PCOS are often too abbreviated (10, 14, 15, 17, 21, 23, 33, 34) to meaningfully engage in shared decision-making. Only a subset of options available for management are offered to patients (10, 13, 15, 18, 21, 23) often due to bias related to characteristics of the patient (e.g., age, marital status, knowledge level) (11, 13, 18, 22-24, 33). According to patients, interactions often lack time for deliberating the options and their attributes with a knowledgeable doctor (3, 13, 14, 18). In these interactions, patient preferences are often not elicited (4, 22-24, 34) 20,21, 22,23, 34) or not aligned with options offered (2, 18, 23, 33, 35, 36) (11,17, 22,33, 35,36) or doctor preferences take precedence (e.g., prioritising fertility (15, 17, 18, 22, 24, 33, 35)). The main consequent effect of a suboptimal shared decision-making context is that patients feel excluded from the decision process and decision quality about disease management perceived to be poor (shared, uninformed, not value-based) (4, 10, 14, 15, 17, 21-24, 33, 34, 36). Interactions that set-up shared decision-making were positively regarded though time consuming for healthcare professionals (17, 26, 34). In the studies reviewed patients indicated that time was an issue in consultations. One patient described a consultation perceived to have had sufficient time as being 2 hours in duration (4), suggesting that most doctors could not meet time demands. Indeed, lack of time is a consistent barrier for adopting shared decision-making as proposed in many areas of health (37).

Challenges of interactions for patient agency in PCOS

PCOS requires patients to actively participate in their own care (self-management). Patient activation is about patients' confidence in achieving this goal (38) and includes modifiable knowledge, skills, ability, and willingness to manage one's own health and care (39). Although patient activation could be affected by disease characteristics (e.g., cognitive impairment, fatigue, anxiety) it is viewed as critical to overall health and health-related quality of life. According to the patient activation framework people work through different levels of activation from low (disengaged

and overwhelmed) to high (maintaining behaviours conducive to health and quality of life) as measured using the patient activation measure (38). A narrative review indicates that greater levels of patient activation is associated with uptake of preventive behaviours (e.g., check-ups, screening), healthy behaviours (healthy diet, regular exercise), health literacy (e.g., disease knowledge, use question prompts at consultation) whereas lower activations levels are associated with greater delay in medical care (40) and increased risk of hospitalisation and emergency care (41). In a recent innovative 20-week longitudinal study patients with diabetes mellitus targeted for low activation (in 10 primary care practices c in the Netherlands) walked with their healthcare team once per week for increasingly longer periods of time. Patient activation significantly increased over time and was associated with an increase in well-being, exercise behaviour, general diet behaviour, and a reduction in body mass index, weight, and HbA1c (42).

According to the evidence reviewed in PCOS, interactions were challenging when healthcare professionals did not support patient activation and agency, that is, patients' ability to take independent actions to manage their health and care. Patients reported that they are not valued as expert witnesses of their own health (2, 3, 21, 24) especially young people (4, 13, 17, 43). Lack of valuing means patients often feel their concerns and worries are dismissed (3, 4, 13, 21, 26, 33, 43-45) and they need to be very insistent to obtain resources or achieve outcomes that matter to them (13, 18, 19), which can be challenging. Interactions with healthcare professionals were not always supportive of patients' efforts for self-management for example doctors seemed disinterested (43), did not acknowledge or discuss patients own PCOS research (17, 44), did not actively provide resources for self-management or become sufficiently involved in management (19, 26, 44). Healthcare professionals that were validating, supported patients in their research and that had consultations that were patient led and informed were viewed positively (35, 43, 44).

System and organisational level issues

Many organisational and system level factors could undermine implementation of practices such as shared decision making, for example a scoping review identified culture of health care delivery (i.e., policies and guidelines, incentives, healthcare professional education and licensing) as well as organisational characteristics (i.e., culture, leadership, priorities, teamwork, resources, and workflows) [46]. These issues could impact healthcare professional choice with knock-on effects on patients.

According to the studies reviewed in PCOS, at least some of the challenges patients perceived with doctors could have been due to challenges related to the healthcare system or organisation. Patients reported having trouble navigating the health system, or finding or accessing the recommended services (2, 21, 26), disliked automated messaging (21), found frustrating the lack of (prompt) communication between levels of care [e.g., primary and secondary (10, 14)], found crowded facilities inappropriate (10) , were disappointed by restrictions on what topics could be discussed due to system imposed limited consultation time (24, 43) or on allowable referrals(3, 13, 22) . Doctors perceived to go beyond system restrictions "pushed for referral" (22) or with integrated care models [34] were perceived more favourably.

Summary of key information

A systematic search of peer-reviewed literature was conducted to identify articles investigating challenges for those with PCOS when interacting with healthcare professionals about polycystic ovary syndrome and related features.

Women with suspected or confirmed PCOS will receive news, must make decisions about PCOS and will need to self-manage their health condition over time. To facilitate sharing news, shared decision-making and patient self-management (agency), general practitioners, endocrinologists, gynaecologists, dermatologists, nurses and allied health practitioners should all become more knowledgeable of PCOS and shared decision-making, sharing news that has potential for profound impact for the patient and supporting patient agency.

Healthcare professionals should be prepared with knowledge relevant for informed and accurate discussions about PCOS when sharing news of this diagnosis (10, 14-20). Ineffective strategies aimed at alleviating distress (normalising, minimising) should not be used because they have the opposite effect on patients (13-15, 22) especially with young people (4, 14, 17, 19). Interactions of sharing news that has potential for profound impact for the patient, should end with a strategy for next steps in care (4, 17, 23, 24).

Systems and organisations should ensure sufficient time be allocated for interactions that involve decision-making (10, 14, 15, 17, 21, 23, 33, 34) and for time to have meaningful discussion and deliberation about relevant options without assumptions related to age, fertility, weight or other person characteristic affecting options presented (10, 13, 15, 18, 21-24, 33, 35). Patient preferences should be elicited to ensure decisions aligned with these (3, 12, 16, 17, 26, 33-36).

Patients should be supported in efforts for self-agency by eliciting their personal stories and causal understanding of their health condition (2, 3, 21, 24) especially in interactions with young people (4, 13, 17, 43). Worries and concerns should be heard and not automatically dismissed as irrelevant or unimportant (3, 4, 13, 21, 26, 33, 43-45). Healthcare professionals could support patient agency by acknowledging and discussing patient's own PCOS research (17, 44), and providing evidence-based resources (including follow-up) aligned to patient preferences for self-management (19, 26, 44).

Evidence to Recommendations Framework

COMPARISONS (option versus other option)

None

EVIDENCE-BASED RECOMMENDATION(S)

- **EBR:** Health professionals should employ shared decision-making and support patient agency or ability to take independent actions to manage their health and care.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

- **EBR:** The importance of being knowledgeable about PCOS, and applying evidence-based practices when sharing news on diagnosis, treatment and health implications, ascertaining and focusing on patient priorities should be recognised.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

CONSENSUS RECOMMENDATION

Health system actors should enable system wide changes to support health professional training, knowledge and practice in sharing news optimally, shared decision making and patient agency, including ensuring adequate consultation time and accessible resources.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

PRACTICE POINT(S)

Evidence-based strategies for shared decision making and for sharing news (such as the SPIKES framework) are readily available and should be used to inform PCOS care

All health professionals partnering with women with PCOS should be knowledgeable in sharing news, in shared decision-making and in supporting patient self-management.

Evidence-based care strategies can be used to support patient activation, which refers to modifiable knowledge, skills, ability, confidence and willingness to self-manage one's own health and care.

GRADE CONSIDERATIONS

Justifications:
(see Evidence summary)

Subgroup considerations:
Subgroups may include young people who may be particularly affected by news regarding PCOS, need additional decision-support and who may especially benefit from longer-term strategies for supporting self-management (.
Cultural, religious and resource issues and biases can impact on challenges that women with PCOS experience in care (10, 33, 35) .

Implementation considerations:
Most doctors have training in sharing news but variable training in shared decision-making and supporting patient agency.
Time for provision of information and deliberation for shared decision-making is not feasible (4) without shared decision-making tools that save time on presentation of options (e.g., option grids).
Common strategies like normalising and minimising (4, 13-15, 17, 19, 22) are intended to alleviate distress and may be difficult to avoid unless other strategies for managing patient distress are provided.
Cultural, religious and resource issues can impact on challenges that women with PCOS experiences of care (10, 33, 35).

General practitioners, endocrinologists, gynaecologists, dermatologists, nurses, and allied health practitioners should all become more knowledgeable of PCOS sharing news that has potential for profound impact for the patient, shared decision-making and supporting patient self-management.

The SPIKES model (6)] could be used to share news that have the potential to negatively alter expectations of the future. Resources from national health systems exist to facilitate using this model (e.g., UK, Australia (47, 48).

Trustworthy sources for learning about shared decision-making have been developed and are free to use for individual healthcare providers and organisations, individual healthcare providers (49) and organisations (50).

In patient activation, trustworthy sources to learn how to use and implement this strategy exist (51).

Monitoring and evaluation considerations:
Monitor quality of care.

Research priorities:
Examine whether and how to implement well-established and effective frameworks for sharing news and shared decision-making in PCOS care and evaluate their effectiveness for outcomes that matter to patients (e.g., decision quality, causal understanding, agency, good health).
Examine whether and how biases manifesting in interactions around sharing news and shared decision-making can be addressed.

GRADE framework

GRADE DECIDE **Interactive Evidence to Decision Framework**

● DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:
See Part 1- Evidence Summary and GRADE document.

Panel discussion:
Most doctors have training in sharing news, shared decision-making and supporting patient agency. As such recommendations should yield desirable effects that patients' value.

● UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

Judgement:

☒ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:
See Part 1- Evidence Summary and GRADE document.

Panel discussion:
Time for provision of information and deliberation for shared decision-making is not feasible in most primary care settings. This means that limited information and opportunity for deliberation would be provided to patients not referred to secondary care/specialist care/integrated care. How to approach shared decision-making to reduce undesirable effects.

● CERTAINTY OF THE EVIDENCE

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☐ Very low	☐ Low	☒ Moderate	☐ High

Research evidence:
See Part 1- Evidence Summary and GRADE document.

Panel discussion:
The certainty level was assigned based on lowest quality assessment (no or very minor considerations) for the evidence base. However, all research examined was qualitative, and many of the patients were sourced from patient support groups. Weighting of this should be discussed.
There is clear evidence of need, but there is lack of efficacy evidence specifically in PCOS.

● VALUES

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☐ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☒ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Research evidence:
No research evidence was identified

Panel discussion:
Research clearly shows that patients want news to be shared in an empathic way, that decisions be informed and value-based and that patients be seen as credible witnesses and agents in their own care.

● BALANCE OF EFFECTS

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:

● COSTS

How large are the resource requirements (costs)?

Judgement:

☐ Don't know	☐ Varies	☐ Large costs	☒ Moderate costs	☐ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:
No research evidence was identified

Panel discussion:
Costs to invest time and developing resources for patients.

● CERTAINTY OF COST EVIDENCE

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:
No research evidence was identified

Panel discussion:

● COST-EFFECTIVENESS

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:
No research evidence was identified

Panel discussion:
Implementation will cost but may generate savings in prevention.

● EQUITY

What would be the impact on health equity?

Judgement:

☒ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☐ Probably increased	☐ Increased

Research evidence:
No research evidence was identified

Panel discussion:
There seems to be unaccountable bias in the options provided to patients. Shared decision frameworks might be able to increase equity, but only if options are accessible.
It should increase equity if uniformly adopted.

● ACCEPTABILITY

Is the option acceptable to key stakeholders?

Judgement:

☐ Don't know	☒ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:
No research evidence was identified

Panel discussion:
Women and health professionals are likely to accept this but funders may be challenged.

● FEASIBILITY

Is the option feasible to implement?

Judgement:

☐ Don't know	☒ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:
No research evidence was identified

Panel discussion:
Most doctors have training in sharing news, but variable in shared decision-making and supporting patient agency. Feasibility is likely to be affected by lack of specific in-depth knowledge of the condition (10, 14-20). Time for provision of information and deliberation for shared decision-making is not feasible (4) (without shared decision-making tools that save time on presentation of options (e.g., option grids).

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PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by Leah Brennan
Edited by the Evidence team (Jillian Tay, Aya Mousa)

GDG 2

Question 2.7.

Is psychological therapy effective for management and support of depression and/or anxiety, disordered eating, body image distress, self-esteem, feminine identity or psychosexual dysfunction in women with PCOS?

(Narrative Review)

1. STUDY SELECTION

Table 1. PICO Criteria for Inclusion	
Question	Is psychological therapy effective for management and support of depression and/or anxiety, disordered eating, body image distress, self-esteem, feminine identity or psychosexual dysfunction in women with PCOS?
Clinical leads (key contacts)	Leah Brennan
Allocation ranking	Level 4 Narrative Review

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(language, year)*
Inclusion	Females of any age, ethnicity or weight diagnosed with PCOS (by Rotterdam, NIH or AES). Diagnosed depression and/or anxiety, disordered eating, body image distress and/or psychosexual dysfunction using any standardised assessment. Subgroups: • Adolescents • Ethnicity • Phenotype If no evidence in PCOS, relevant evidence will be sought narratively by key contact (not searched by evidence team).	Psychological therapy including: • Acceptance and commitment therapy • Compassionate mind training • Functional analytic psychotherapy • Behavioural activation • Metacognitive therapy • Mindfulness-based cognitive therapy (MBCT) • Dialectical behaviour therapy (DBT) • Psychodynamic therapies • Behavioural therapies • Humanistic therapies • Interpersonal, cognitive analytic and other integrative therapies • Cognitive-behavioural therapies	• Placebo • Wait list control • Usual care • Medication • Lifestyle intervention	Changes in depression and/or anxiety, disordered eating, body image distress, self-esteem, feminine identity and/or psychosexual dysfunction. Self-management indicators.	None	None
Exclusion	Females without diagnosed PCOS.				None	None

2. SEARCH STRATEGY

Evidence processing: This question was allocated as a narrative review. Hence, no search or screening was undertaken and recommendations will be consensus based. Below is a narrative review in response to the clinical question.

3. FINDINGS

See Part 2 for this question.

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 2

Question 2.7.

Is psychological therapy effective for management and support of depression and/or anxiety, disordered eating, body image distress, self-esteem, feminine identity or psychosexual dysfunction in women with PCOS?

(Narrative Review)

BACKGROUND:

Mental Health Disorders

Women with PCOS have a higher prevalence of clinically significant self-reported symptoms of depression, anxiety and eating disorders. Available research also suggests that women with PCOS have higher prevalence of depressive disorders, anxiety disorders and eating disorders as diagnosed by a psychiatrist using a structured clinical interview. Despite this, there is a lack of research examining the psychological treatment of clinical diagnosed anxiety, depression or eating disorders in women with PCOS.

Numerous empirically supported treatments (e.g., cognitive behaviour therapy, behaviour therapy, interpersonal therapy) are available for the treatment of depression, anxiety, eating disorders/disordered eating in the general population. These treatments result in clinically significant improvements in the condition and associated distress and impairment, as well as broader improvements including quality of life and psychosocial wellbeing. Of note, there is increasing evidence of the effectiveness of treatment delivered via telehealth (videoconference and telephone), as well as online programs (1), particularly if they are delivered with the assistance of a therapist or guide/coach (2). The choice of treatment is dependent on participant characteristics (e.g., age), diagnosis and symptoms severity, and available resources.

Regional general population guidelines typically provide guidance regarding identification, assessment and treatment for these disorders. They typically include information about treatment sequencing when multiple mental health disorders (or comorbid symptoms) are present, matching treatment intensity to symptoms severity including using stepped care treatment models, and consideration of physical health conditions when treating mental health disorders.

Links to some relevant general population guidelines are provided below.

- National Institute for Health and Care Excellence:
  https://www.nice.org.uk/guidance/published?type=csg,cg,mpg,ph,sg,sc
- National Institute of Mental Health:
  https://www.nimh.nih.gov/health/index.shtml
- American Psychiatric Association:
  https://www.psychiatry.org/psychiatrists/practice/clinical-practice-guidelines
- National Health and Medical Research Centre:
  https://www.clinicalguidelines.gov.au/

The *Management of Eating Disorders for People with Higher Weight: Clinical Practice Guidelines* (3) provide guidance regarding treatment of eating disorders and disordered eating in people with higher weight.

Mental Health Symptoms

Women with PCOS also have higher levels of body image distress, lower levels of self-esteem, loss of feminine identity and higher levels of psychosexual dysfunction. Of note, these symptoms are core features and/or common comorbidities of depressive, anxiety and eating disorders. Therefore, they may be expected to improve if depressive, anxiety or eating disorders are successfully treated.

There are no broadly accepted general population guidelines for the treatment of body image distress, self-esteem, feminine identity or psychosexual dysfunction. Therefore, psychological treatment of these mental health symptoms should be guided by the results of systematic reviews and meta-analyses where available, or where they are not available high quality randomised controlled trials.

Available research suggests that psychological treatment, particularly cognitive behaviour therapy, is effective in improving body image distress (4, 5, 6) and low self-esteem (7). These treatments have been shown to improve the condition and associated distress and impairment. A recent RCT demonstrated that women with PCOS who received Acceptance and Commitment Therapy (ACT)-based therapy, had significantly lower levels of self-esteem and body image concern at 1-month follow-up, compared to a control group (8). This suggests CBT-based interventions (such as ACT) may be effective in improving self-esteem and body image in women with PCOS.

We are not aware of any studies examining interventions targeting the impacts of loss of feminine identity. While there are no studies examining the treatment of psychosexual dysfunction in women with PCOS specifically, a number of studies have examined treatments for psychosexual dysfunction in women with related conditions such as higher weight, infertility, metabolic syndrome and pregnancy. Lifestyle interventions (9), yoga-based interventions (10), and cognitive behavioural interventions (11) have demonstrated improvements in psychosexual functioning compared to control groups.

Psychosocial Interventions in Women with PCOS

A recent systematic review assessed the efficacy of psychosocial interventions for women with PCOS in seven RCTs (12). This review included two types of psychosocial interventions: (1) two studies examined psychological interventions (ACT and Mindfulness-Based Stress Reduction (MBSR) primarily targeting mental health outcomes, and (2) five studies examined lifestyle interventions (i.e., diet, exercise) with behavioural/cognitive behavioural components, primarily targeting lifestyle change and including mental health measure as secondary outcomes, all evaluated in an RCT design. While significant pre-post intervention effects were evident across studies for most mental health outcomes, between group effects were inconsistent. Short-term (immediate to 8 weeks post-intervention) effects for depression, QOL, self-esteem, body image, stress and negative affect were found for some studies. Only two studies found long term effects for body image and stress. There were no significant effects for anxiety (at any time point), and no significant long-term effects for anxiety, depression or QoL. Of note, only one study (13) specifically included participants with mental health concerns (elevated depression scores), and most of the remaining studies excluded participants with mental health diagnoses and/or elevated scores on self-report measures of mental health. A second systematic review and meta-analyses examined the impact of psychological interventions on depression symptoms on women with PCOS (Jiskoot et.al., under review (14)). This review was not limited to RCTs so included some additional papers. All studies compared cognitive behaviour therapy, delivered in group or individual format, to control/comparison. The meta-analyses demonstrated a large effect in favour of CBT (Cohen's d = 1.16; 0.31-2.01). Again, most of these studies were not targeting women with mental health problems. Only one case study included a participant with diagnosed depression and anxiety (and disordered eating), and two randomised controlled trials (13, 15) specifically included participants with elevated depression scores. These reviews highlight the potential benefits of psychosocial interventions for women with PCOS, and the need for research examining more targeted interventions for those with mental health diagnoses or elevated mental health symptoms.

Recommendations Framework

CONSENSUS RECOMMENDATION(S)

- Women with PCOS diagnosed with depression, anxiety, and/or eating disorders should be offered psychological therapy guided by regional general population guidelines and the preference of the woman with PCOS.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

- Women with PCOS with disordered eating, body image distress, low self-esteem, problems with feminine identity, or psychosexual dysfunction should be offered evidence-based treatments (e.g., cognitive behaviour therapy) where appropriate.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

CONSIDERATIONS

Given the limited evidence, this question was allocated as a narrative review and therefore a systematic literature review was not conducted. A more general review revealed few studies typically of low quality. Given the insufficient evidence about effectiveness of psychological therapy in women with PCOS, the literature about psychological therapy in the general population has been used to inform this consensus recommendation.

Treatment of depression, anxiety, eating disorders/disordered eating should be guided by regional general population guidelines. These guidelines typically provide guidance regarding identification, assessment and treatment (including treatment sequencing) for these disorders.

Of note, negative body image, low self-esteem and psychosexual dysfunction are core features and/or common comorbidities of these disorders. Therefore, these symptoms are likely to improve if depression, anxiety or eating disorders are successfully treated.

There are no broadly accepted general population guidelines for the treatment of body image distress, self-esteem, feminine identity or psychosexual dysfunction. Limited available research suggests that cognitive behaviour therapy is effective in the treatment of body image distress, self-esteem, feminine identity or psychosexual dysfunction.

Subgroup considerations:

There is evidence that similar treatments are effective across adolescence and adulthood, however there are some minor differences in treatments.

There is evidence that evidence-based psychological interventions (e.g., cognitive behaviour therapy) are effective across cultures, however some adaptation may be required.

Implementation considerations:
Acceptability – Evidence-based psychological treatments tend to be well accepted
Availability – This has been improved with the availability of telehealth, as well as online interventions.
Cost – Costs are reduced by the use of stepped care interventions, online programs can be effective for some, particularly when used with a guide/coach.
Cost-effectiveness – Implementation of evidence-based programs, within a stepped care framework, improves cost-effectiveness.
Time consuming – Longer treatments tend to be more effective. Time demands can be reduced by the use of stepped-care approaches, and telehealth delivered interventions.
Feasibility – Evidence suggests that psychological services are poorly integrated into models of care of PCOS.

Monitoring and evaluation considerations:
Access to and use of different psychological treatment approaches would be valuable.

Research priorities:
Research is needed examining the role and efficacy of psychological intervention for depression and/or anxiety, disordered eating, body image distress, self-esteem, feminine identity or psychosexual dysfunction in adults and adolescents with PCOS.
Research examining stepped care models incorporating evidence-based interventions and delivery modes (e.g. telehealth, mobile health apps).

Equity:
Traditional, 1:1, face-to-face psychological interventions are expensive (albeit cost-effective) and often not covered by public health services. Consequently, they are more available to those of higher incomes.
The availability of telehealth (and the evidence indicating that it is similarly effective) improves access particularly for those in rural/remote areas.
The effectiveness of online materials, particularly when delivered with the assistance of a guide/coach, improves equity.
The use of stepped care models incorporating evidence-based interventions and technology solutions would improve equity.

Acceptability:
These treatments result in clinically significant improvements in the condition and associated distress and impairment, as well as broader improvements including quality of life and social functioning.
There is little evidence of negative effects of empirically supported psychosocial treatments for these conditions. Attrition from treatment can be high (up to 30%). Attrition rates are significantly higher for interventions delivered without in-person support (e.g., online interventions without a guide/coach). Therefore, there is a risk that women will not receive a full dose of treatment.
Other undesirable effects might include women with PCOS receiving non-empirically supported treatments which may be ineffective or harmful.

FEASIBILITY
Feasibility will be influenced by the availability of mental health care in the individual's local area.

REFERENCES:

1. Komariah, M., Amirah, S., Faisal, E. G., Prayogo, S. A., Maulana, S., Platini, H., ... & Arifin, H. (2022). Efficacy of internet-based cognitive behavioral therapy for depression and anxiety among global population during the covid-19 pandemic: a systematic review and meta-analysis of a randomized controlled trial study. Healthcare, 10(7), 1224). MDPI.

2. Al-Alawi, M., McCall, R. K., Sultan, A., Al Balushi, N., Al-Mahrouqi, T., Al Ghailani, A., ... & Al Sinawi, H. (2021). Efficacy of a six-week-long therapist-guided online therapy versus self-help internet-based therapy

for COVID-19–induced anxiety and depression: open-label, pragmatic, randomized controlled trial. JMIR mental health, 8(2), e26683.

3. Ralph, A.F. et al., *P395 Poster sessions: Management of Eating Disorders for People with Higher Weight: Clinical Practice Guidelines* Obesity Reviews, 2022. **23**(S2): p. e13503.

4. Alleva, J. M., Sheeran, P., Webb, T. L., Martijn, C., & Miles, E. (2015). A meta-analytic review of stand-alone interventions to improve body image. *PLoS One*, *10*(9), e0139177.

5. Guest, E., Costa, B., Williamson, H., Meyrick, J., Halliwell, E., & Harcourt, D. (2019). The effectiveness of interventions aiming to promote positive body image in adults: A systematic review. *Body Image*, *30*, 10-25.

6. Jarry, J. L., & Ip, K. (2005). The effectiveness of stand-alone cognitive-behavioural therapy for body image: A meta-analysis. *Body image*, *2*(4), 317-331.

7. Fennell, M. J. (2005). Low self-esteem. In *Encyclopedia of cognitive behavior therapy* (pp. 236-240). Springer, Boston, MA.

8. Moradi, F., Ghadiri-Anari, A., Dehghani, A., Vaziri, S. R., & Enjezab, B. (2020). The effectiveness of counseling based on acceptance and commitment therapy on body image and self-esteem in polycystic ovary syndrome: An RCT. International journal of reproductive biomedicine, 18(4), 243.

9. Wekker, V., Karsten, M. D., Painter, R. C., Van De Beek, C., Groen, H., Mol, B. W. J., ... & Roseboom, T. J. (2018). A lifestyle intervention improves sexual function of women with obesity and infertility: A 5 year follow-up of a RCT. PloS one, 13(10), e0205934.

10. Kim, H. N., Ryu, J., Kim, K. S., & Song, S. W. (2013). Effects of yoga on sexual function in women with metabolic syndrome: a randomized controlled trial. The journal of sexual medicine, 10(11), 2741-2751.

11. Babakhani, N., Taravati, M., Masoumi, Z., Garousian, M., Faradmal, J., & Shayan, A. (2018). The effect of cognitive-behavioral consultation on sexual function among women: a randomized clinical trial. Journal of caring sciences, 7(2), 83.

12. Phimphasone-Brady, P., Palmer, B., Vela, A., Johnson, R. L., Harnke, B., Hoffecker, L., ... & Epperson, C. N. (2021). Psychosocial interventions for women with polycystic ovarian syndrome: a systematic review of randomized controlled trials. F&S Reviews.

13. Cooney, L. G., Milman, L. W., Hantsoo, L., Kornfield, S., Sammel, M. D., Allison, K. C., ... & Dokras, A. (2018). Cognitive-behavioral therapy improves weight loss and quality of life in women with polycystic ovary syndrome: a pilot randomized clinical trial. *Fertility and sterility*, *110*(1), 161-171.

14. Jiskoot, G., van der Kooi, A. L., Busschbach, J., Laven, J., & Beerthuizen, A. (2022). Cognitive behavioural therapy for depression in women with Polycystic Ovary Syndrome (PCOS): systematic review and meta-analysis. *Reproductive BioMedicine Online*.

15. Ramazanzadeh, F., Nourbala, A. A., Tanha, F. D., & Mostaan, F. (2019). The Effect of Psychiatric Interventions on Depression and Fertility in Infertile Patients with Polycystic Ovarian Disease. *Journal of Research in Medical and Dental Science*, *7*(2), 187-191.

PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by ECR Lead: Snigdha Alur-Gupta

Other Members: Michelle Vu, Loyal Pattuwage

Supervised, edited and supported by the Evidence team (Aya Mousa, Jillian Tay)

GDG 2

Question 2.8.

Are anti-depressants and anxiolytics effective for management and support of depression and/or anxiety or disordered eating in women with PCOS?

1. STUDY SELECTION

Table 1. PICO Criteria for Inclusion	
Question	2.7 Are anti-depressants and anxiolytics effective for management and support of depression and/or anxiety or disordered eating in women with PCOS?
Clinical leads (key contacts)	Anuja Dokras, Leah Brennan
Allocation ranking	Level 2 - systematic review update

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(language, year)*
Inclusion	Females of any age, ethnicity or weight diagnosed with PCOS (by Rotterdam, NIH or AES). Diagnosed depression and/or anxiety, disordered eating, body image distress and/or psychosexual dysfunction using a different screening tool than that used for outcomes. Subgroups: Adolescents Ethnicity Phenotype	Anti-depressants and anxiolytics.	Placebo or psychological or other pharmacological interventions; lifestyle interventions; acupuncture.	Changes in depression and/or anxiety and/or disordered eating. Self-management indicators.	Evidence based guidelines, systematic reviews, health technology assessments, randomised controlled trials.	English language. Human studies
Exclusion	Females without diagnosed PCOS.	None	None	None	Non-evidence based guidelines, non-systematic reviews, any study lower than a RCT.	None

2. SEARCH STRATEGY

Search details	
Search strategy source: 2018 PCOS Guideline Technical Report	
Evidence source	Date of search (day/month/year)
Medline (Ovid)	1/8/2022
PsychInfo (Ovid)	1/8/2022
EMBASE	1/8/2022
All EBM (Ovid)	1/8/2022
CINAHL	1/8/2022
Any subsequent updates - enter database and date: not applicable	

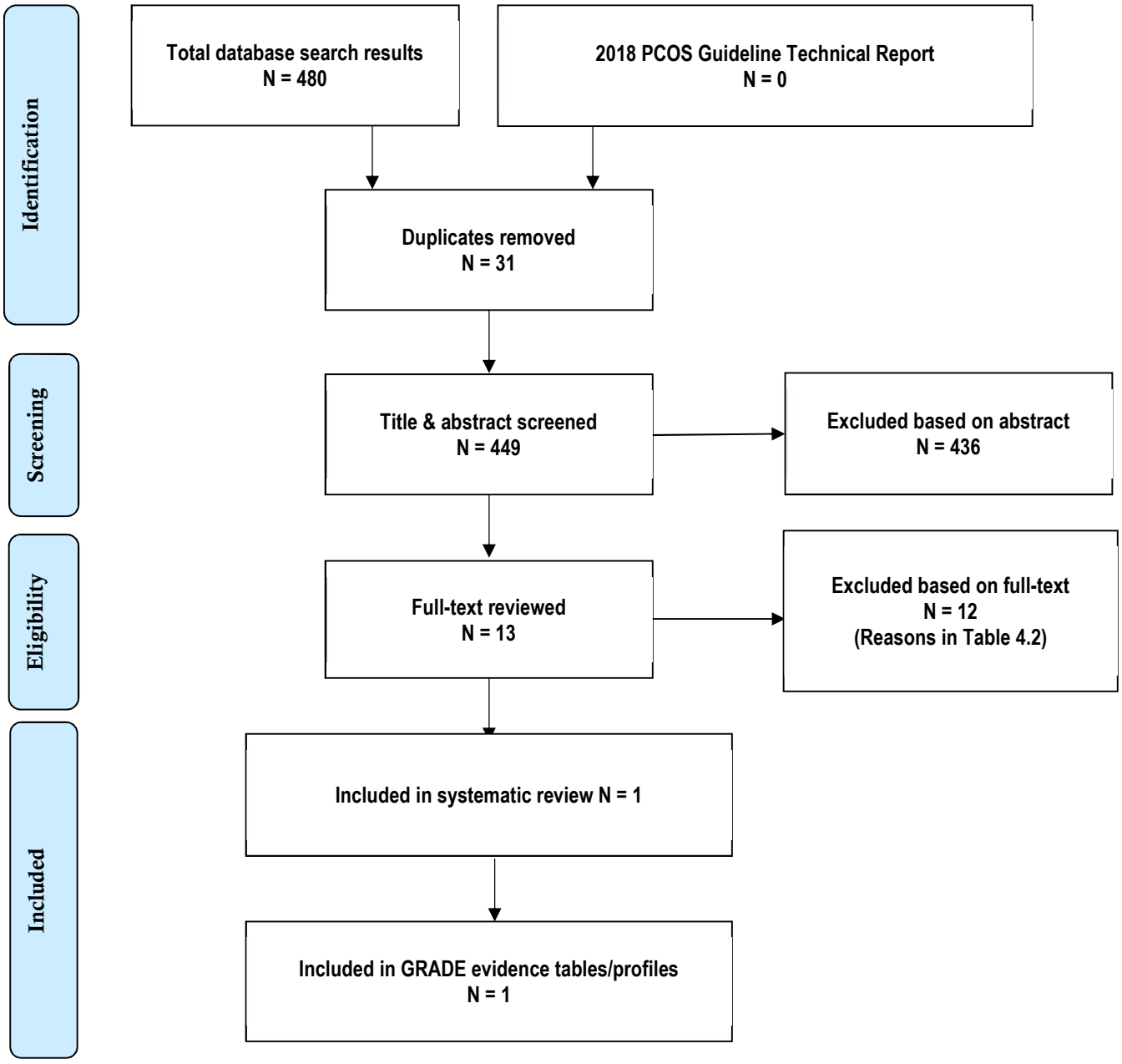
Questions addressed by this search:		
GDG	Q#	Question
2	2.7	Are anti-depressants and anxiolytics effective for management and support of depression and/or anxiety or disordered eating in women with PCOS?

OVID Medline, All EBM, EMBASE	CINAHL	PsychInfo
1 exp polycystic ovary syndrome/ 2 polycystic ovar*.mp. 3 poly-cystic ovar*.mp. 4 PCO*.mp. 5 (stein-leventhal or leventhal).mp. 6 anovulation/ 7 anovulat*.mp. 8 oligo-ovulat*.mp. 9 oligoovulat*.mp. 10 (ovar* adj5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*)).mp. 11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 12 exp Antidepressive Agents/ 13 exp Serotonin Uptake Inhibitors/ 14 exp Monoamine Oxidase Inhibitors/ 15 exp Adrenergic Uptake Inhibitors/ 16 exp Hypericum/ 17 exp Anti-Anxiety Agents/ 18 (anti-depress* or antidepress*).mp. 19 (selective serotonin reuptake inhibit* or SSRI* or serotonin	S1 SU polycystic ovary syndrome S2 polycystic ovar* S3 poly-cystic ovar* S4 PCO* S5 stein-leventhal or leventhal S6 SU ovarian cysts S7 SU anovulation S8 oligo-ovulat* S9 oligoovulat* S10 ovar* N5 sclerocystic or ovar* N5 polycystic or ovar* N5 poly-cystic or ovar* N5 degenerat* or ovar* N5 hyperandrogen* or ovar* N5 hyper- androgen* S11 S1ORS2ORS3OR S4ORS5ORS6OR S7ORS8ORS9OR S10 S12 (MH "Antidepressive Agents+") S13 (MH "Adrenergic Uptake Inhibitors+") OR (MH "Serotonin Uptake Inhibitors+") OR (MH "Monoamine Oxidase Inhibitors+") S14 (MH "Antianxiety Agents+") S15 anti-depress* or antidepress* S16 selective serotonin reuptake inhibit* or SSRI* or	1 exp Endocrine Sexual Disorders/ 2 polycystic ovar*.mp. 3 poly-cystic ovar*.mp. 4 PCO*.mp. 5 (stein-leventhal or leventhal).mp. 6 anovulation/ 7 anovulat*.mp. 8 oligo-ovulat*.mp. 9 oligoovulat*.mp. 10 (ovar* adj5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*)).mp. 11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 12 exp Antidepressant Drugs/ 13 exp Serotonin Reuptake Inhibitors/ or exp Antidepressant Drugs/ 14 exp Monoamine Oxidase Inhibitors/ 15 exp Hypericum/ 16 exp Tranquilizing Drugs/ 17 (anti-depress* or antidepress*).mp. 18 (selective serotonin reuptake inhibit* or SSRI* or serotonin norepinephrine reuptake inhibit* or SNRI*).mp.

norepinephrine reuptake inhibit* or SNRI*).mp. 20 ((serotonin or norepinephrine or noradrenaline or neurotransmitter* or dopamin*) adj (uptake or reuptake or re-uptake)).mp. 21 (tricyclic* or TCA* or tetracyclic* or TeCA* or heterocyclic*).mp. 22 (monoamine oxidase inhibit* or MAOI* or rMAO*).mp. 23 (('Noradrenergic and specific serotonergic') or NaSSA*).mp. 24 (RIMA* or SARI* or NDRI* or NARI*).mp. 25 (St John* wort or hypericum).mp. 26 (Anxiolytic* or antianxiety or anti-anxiety or antipanic or anti-panic).mp. 27 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 28 search$.tw. or meta-analysis.mp. or meta-analysis.pt. or review.pt. or di.xs. or associated.tw. 29 clinical trial.mp. or clinical trial.pt. or random.mp. or tu.xs. 30 28 or 29 31 11 and 27 and 30 32 limit 31 to (english language and humans) 33 limit 32 to yr="2017 -Current" 32	serotonin –norepinephrine reuptake inhibit* or SNRI* S17 ((serotonin or norepinephrine or noradrenaline or neurotransmitter* or dopamin*) N (uptake or reuptake or re-uptake)) S18 Tricyclic* or TCA* or tetracyclic* or TeCA* or heterocyclic* S19 monoamine oxidase inhibit* or MAOI* or rMAO-A* S20 “Noradrenergic and specific serotonergic” or NaSSA* S21 RIMA* or SARI* or NDRI* or NARI* S22 St John* wort or hypericum S23 Anxiolytic* or antianxiety or anti- anxiety or antipanic or anti-panic S24 S12 OR S13 OR S14 ORS15ORS16OR S17 OR S18 OR S19 ORS20ORS21OR S22 OR S23 S25 S11 AND S24 Limiters - English Language; Exclude MEDLINE records Search modes - Boolean/Phrase	19 ((serotonin or norepinephrine or noradrenaline or neurotransmitter* or dopamin*) adj (uptake or reuptake or re-uptake)).mp. 20 (tricyclic* or TCA* or tetracyclic* or TeCA* or heterocyclic*).mp. 21 (monoamine oxidase inhibit* or MAOI* or rMAO*).mp. 22 (('Noradrenergic and specific serotonergic') or NaSSA*).mp. 23 (RIMA* or SARI* or NDRI* or NARI*).mp. 24 (St John* wort or hypericum).mp. 25 (Anxiolytic* or antianxiety or anti-anxiety or antipanic or anti-panic).mp. 12409 26 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 27 search$.tw. or meta-analysis.mp. or meta-analysis.pt. or review.pt. or associated.tw. 28 clinical trial.mp. or clinical trial.pt. or random.mp. 29 27 or 28 30 11 and 26 and 29 31 limit 30 to (human and english language) 32 limit 31 to yr="2017 -Current"

Evidence processing: Studies were selected and appraised by two reviewers using study selection and appraisal criteria (PICO above) established a priori. The articles were reviewed by title and abstract by two reviewers. When a decision could not be made based on title and abstract alone, full text was retrieved. **One study met inclusion criteria for this review.**

3. SEARCH RESULTS - PRISMA flowchart



4. STUDY INCLUSION

4.1 Included studies

81. Masoudi M, Ansari S, Kashani L, Tavolinejad H, Hossein Rashidi B, Esalatmanesh S, Ghazizadeh-Hashemi M, Noorbala AA, Akhondzadeh S. Effect of sertraline on depression severity and prolactin levels in women with polycystic ovary syndrome: a placebo-controlled randomized trial. Int Clin Psychopharmacol. 2021 Sep 1;36(5):238-243. doi: 10.1097/YIC.0000000000000367. PMID: 34030169.

4.2 Excluded Studies (on full text assessment)

1	Wang Z, Dong H, Wang Q, et al. Effects of electroacupuncture on anxiety and depression in unmarried patients with polycystic ovarian syndrome: secondary analysis of a pilot randomised controlled trial. Acupuncture in Medicine. 2019;37(1):40-46. doi:10.1136/acupmed-2017-011615	Wrong intervention (not anti-depressive/anti-anxiety agent)
2	T. Cantelmi, E. Lambiase, VR. Unfer, R. Gambioli, V. Unfer *Inositol treatment for psychological symptoms in Polycystic Ovary Syndrome women.* Eur Rev Med Pharmacol Sci. 2021. 25 - N. 5: 2383-2389 DOI: 10.26355/eurrev_202103_25278	Wrong intervention (not anti-depressive/anti-anxiety agent)
3	AlHussain F, AlRuthia Y, Al-Mandeel H, Bellahwal A, Alharbi F, Almogbel Y, Awwad O, Dala'een R, Alharbi FA. Metformin Improves the Depression Symptoms of Women with Polycystic Ovary Syndrome in a Lifestyle Modification Program. Patient Prefer Adherence. 2020 Apr 15;14:737-746. doi: 10.2147/PPA.S244273. PMID: 32346286; PMCID: PMC7167265.	Wrong intervention (not anti-depressive/anti-anxiety agent)
4	S Arentz, C Smith, J Abbott, A Bensoussan. Herbal medicine plus lifestyle for overweight women with polycystic ovary syndrome: A randomised control trial. Australian Journal of Herbal and Naturopathic Medicine, 2019, 31(1), 38	Wrong intervention (not anti-depressive/anti-anxiety agent)
5	Glintborg, Dorte, Magda Lambaa Altinok, Pernille Ravn, Kurt Bjerregaard Stage, Kurt Højlund, and Marianne Andersen. "Adrenal activity and metabolic risk during randomized escitalopram or placebo treatment in PCOS". Endocrine Connections 7.3 (2018): 479-489. < https://doi.org/10.1530/EC-18-0077>. Web. 21 Sep. 2022.	Wrong patient population (excluded women with diagnosed depression)
6	Arentz, S., Smith, C. A., Abbott, J., Fahey, P., Cheema, B. S., and Bensoussan, A. (2017) Combined Lifestyle and Herbal Medicine in Overweight Women with Polycystic Ovary Syndrome (PCOS): A Randomized Controlled Trial. *Phytother. Res.*, 31: 1330– 1340. doi: 10.1002/ptr.5858.	Wrong intervention (not anti-depressive/anti-anxiety agent)
7	Nicolaides NC, Matheou A, Vlachou F, Neocleous V, Skordis N. Polycystic ovarian syndrome in adolescents: From diagnostic criteria to therapeutic management. Acta Biomed [Internet]. 2020 Sep. 7 [cited 2022 Sep. 21];91(3):e2020085.	Wrong outcomes (Review did not cover depression/anxiety agents)
8	S Arentz, C Smith, J Abbott, P Fahey, B Cheema, A Bensoussan. Randomized controlled trial of combined lifestyle and herbal medicine in women with polycystic ovary syndromeHuman reproduction 2017, 32 Suppl 1, i31-2	Conference abstract
9	Chung, Y. S. Comparative risk of poly-cystic ovary syndrome in young female patients newly initiating anti-psychotic medications. Pharmacoepidemiol Drug Saf August 2019;28(Supplement 2)():567. 2019 August. DOI: 10.1002/pds.4864	Wrong study design (retrospective cohort)
10	Cooney, L.G., Dokras, A. Depression and Anxiety in Polycystic Ovary Syndrome: Etiology and Treatment. *Curr Psychiatry Rep* 19, 83 (2017). https://doi.org/10.1007/s11920-017-0834-2	No studies assessing anti-anxiety/anti-depression agents
11	Tay, CT, Joham, AE, Hiam, DS, et al. Pharmacological and surgical treatment of nonreproductive outcomes in polycystic ovary syndrome: An overview of systematic reviews. *Clin Endocrinol (Oxf)*. 2018; 89: 535– 553. https://doi.org/10.1111/cen.13753	No studies assessing anti-anxiety/anti-depression agents
12	Glintborg D, Andersen MJ. Medical treatment and comorbidity in polycystic ovary syndrome: an updated review. *Curr Opin Endoc Metab Res* 2020; 12: 33–40.	No new studies assessing anti-anxiety/anti-depression agents (aside from the previously excluded study)

5. STUDY CHARACTERISTICS TABLE FOR INCLUDED STUDIES

Author, year, country	Population/ Setting	Study Design	Sample Size per group	Intervention/ exposure details	Comparison/ control details	Follow up Duration	Outcomes	Summary of findings	Pooled in MA?	RoB
Masoudi et al. 2021	Women with PCOS by Rotterdam attending outpatient gynecology clinics	RCT	Sertraline (prolactin< 25 mg/dL): 17 Sertraline (prolactin≥ 25 mg/dL): 15 Placebo (prolactin< 25 mg/dL): 17 Placebo (prolactin≥ 25 mg/dL): 15	Sertraline 25mg daily titrated up to 50mg daily the following week	Placebo	6 weeks	HDRS score and prolactin levels	Between both groups of patients with normal and high baseline prolactin levels, those who received sertraline had a significantly lower HDRS after treatment compared to the placebo group. Among patients who received sertraline in both normal and high prolactin groups, the effect of sertraline on HDRS was independent from the baseline prolactin level.	N/A	Mod

HRDS: Hamilton Depression Rating Scale

6. FINDINGS

Comparison included:

- **Comparison 1.** Sertraline versus placebo

COMPARISON 1: Sertraline versus Placebo

▪ EVIDENCE SUMMARY:

One study compared Sertraline versus placebo in women with PCOS (Masoudi et al., 2021). Relevant outcomes included depression scores using the Hamilton Depression Rating Scale. This study was judged as moderate risk of bias.

▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

Sertraline was more effective than placebo in reducing depression scores in women with PCOS. Evidence for this outcome was of low quality due to being derived from a single small study with a moderate risk of bias.

Outcome or Subgroup	Studies	n	Time*Treatment effects	P	Favours	Certainty
Hamilton Depression Rating Scale	1	64	F (2,124) = 171.12	<0.001	Sertraline	⊕⊕◯◯ LOW

Comparison 1.
1.1 Individual Study Data Tables

OUTCOME: HRDS: Hamilton Depression Rating Scale						OUTCOME TYPE: Continuous				
Comparison: Sertraline vs placebo										
Author, year	Unit	Method of measurement	Mean in intervention / exposure group	SD in intervention / exposure group	Sample size (n within this group)	Mean in control / comparison group	SD in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	What variables are adjusted for?
Masoudi et al. 2021	none	HDRS	Not reported	Not reported	prolactin <25 mg/dL) = 17 (prolactin> 25 mg/dL) = 15	Not reported	Not reported	prolactin <25 mg/dL) = 17 (prolactin> 25 mg/dL) = 15	NA	NA

7. GRADE ASSESSMENTS AND EVIDENCE PROFILE

COMPARISON 1: Sertraline versus placebo												
	Quality assessment						No. participants					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Sertraline**	**Control**	**Time*Treatment effects, p-value**	**Favours**	**Certainty**	**Importance**
Outcome: HRDS: Hamilton Depression Rating Scale												
1	RCT	serious[1]	not applicable	not applicable	serious imprecision[2]	none	32	32	F (2,124) = 171.12, p<0.001	Sertraline	⨁⨁◯◯ LOW	IMPORTANT

[1] Downgraded once as selective reporting, confounding and conflict of interest were not reported
[2] Downgraded once due to having a small number of studies/small sample sizes

Appendix: Quality Appraisal Tables

Study ID	Masoudi 2021	
Study Citation	Masoudi M, et al. Effect of sertraline on depression severity and prolactin levels in women with polycystic ovary syndrome: a placebo-controlled randomized trial. Int Clin Psychopharmacol. 2021 Sep 1;36(5):238-243.	
Study Country	Iran	
BRIEF CHARACTERISTICS OF RCT		
Patient/population/ participants	Women with PCOS (age 18-45)	
PCOS diagnostic criteria	Rotterdam	
Presence of infertility	*Not reported*	
Presence of other condition/s	*Excluded if BMI > 30 kg/m2, antidepressant use in prior 3months, pregnancy or breast-feeding, refusal or inability to provide written informed consent and presence of any comorbidity affecting the endocrine system (i.e. congenital adrenal hyperplasia, prolactinoma, pituitary adenoma or thyroid disease), anxiety disorders, and the use of any medications that increase the level of prolactin*	
Medication History	*See above*	
N per group	*Allocated/randomised:* *Sertraline (prolactin< 25 mg/dL): 19* *Sertraline (prolactin> 25 mg/dL): 18* *Placebo (prolactin< 25 mg/dL): 19* *Placebo (prolactin> 25 mg/dL): 18* *Assessed at end of study:* *Sertraline (prolactin< 25 mg/dL): 17* *Sertraline (prolactin> 25 mg/dL): 15* *Placebo (prolactin< 25 mg/dL): 17* *Placebo (prolactin> 25 mg/dL): 15*	
Setting	Outpatient gynecology clinics of Imam Khomeini and Arash hospitals [both affiliated with Tehran University of Medical Sciences]	
Intervention	*Sertraline 50mg daily*	
Comparison	*Placebo*	
Outcomes (primary and other) with definition (eg. self-reported, fasting)	Change in HDRS scores throughout the study and the safety outcome was the alteration in prolactin levels	
Follow up Duration	*6 weeks*	
Summary Result/s	*Between both groups of patients with normal and high baseline prolactin levels, those who received sertraline had a significantly lower HDRS after treatment compared to the placebo group. Among patients who received sertraline in both normal and high prolactin groups, the effect of sertraline on HDRS was independent from the baseline prolactin level.*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial	*Yes: The aim was to determine whether sertraline would significantly change HDRS scores throughout the study period and whether this*

		No Not reported	*was independent of initial prolactin level*
Does the study have specified inclusion/exclusion criteria?		Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Yes*
Inclusion criteria		Yes Partial No Not reported	PCOS diagnosis was based on the Rotterdam 2003 criteria (Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group, 2004) and exclusion of other gynecologic conditions.
Exclusion criteria		Yes Partial No Not reported	Key exclusion criteria were a BMI higher than 30 kg/m2 , antidepressant use in prior 3months, pregnancy or breast-feeding, refusal or inability to provide written informed consent and presence of any comorbidity affecting the endocrine system (i.e. congenital adrenal hyperplasia, prolactinoma, pituitary adenoma or thyroid disease). Moreover, clinical suspicion of other psychological disorders – especially anxiety disorders, which might alter prolactin levels (Labad, 2019) – and the use of any medications that increase the level of prolactin led to exclusion from the study.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Did the study have an adequate method of randomisation?	Yes Partial No Not reported	*Yes* Each group was randomly assigned with a 1:1 ratio to receive sertraline or placebo identical in appearance. The randomized sequence was generated centrally by computer in permuted blocks of four.
SELECTION BIAS	Was allocation to intervention group concealed?	Yes Partial No Not reported	Enrolling physicians, outcome assessors and study participants were all blinded to the treatment regimen.
PERFORMANCE BIAS	Were patients blind to intervention group?	Yes Partial No Not reported	*Yes*
PERFORMANCE BIAS	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*Yes*
PERFORMANCE BIAS	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	Were outcome assessors blind to intervention group?	Yes Partial No Not reported	*Yes*

	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study dropped out?	X% treatment X% control/ comparison Not reported	*Prolactin <25 mg/dL:* *Sertraline = 2/19 = 10.5%* *Placebo = 2/19 = 10.5%* *Prolactin> 25mg/dL:* *Sertraline = 3/18 = 16.7%* *Placebo = 3/18 = 16.7%*
ATTRITION BIAS	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Yes*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Not reported*
CONFOUNDING	Were the groups similar at baseline with regard to key prognostic variables?	Yes Partial No Not reported	*Yes*
CONFOUNDING	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Not reported*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*Not reported*
OTHER BIAS	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Yes for the prolactin <25 ng/dL group*
OTHER BIAS	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Partial, repeated measures analysis of variance conducted for HDRS*
COMMENTS		*Lack of randomisation and blinding key reason for high RoB*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate*

Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*No-but groups differed in that power calculations suggested sample size analysed was too low for prolactin≥25 ng/dL group*

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 2

Question 2.8.

Are anti-depressants and anxiolytics effective for management and support of depression and/or anxiety or disordered eating in women with PCOS?

BACKGROUND:

Depression and anxiety are exceptionally common throughout the world with a higher prevalence in women and represent a major public health problem. Psychoeducation, cognitive behavioural therapy, and combinations of psychotherapeutic approaches are considered to be the preferred treatment options for depression and anxiety (1, 2). Lifestyle and other therapies that target PCOS features have shown improvement in psychological symptoms in PCOS (3).

The Australian Clinical Practice Guidelines for Mood Disorders (4), advises that it is useful to construct a template to capture each patients' problems using the biopsychosocial and lifestyle model (BPSL Model) and to consider the predisposing, precipitating and perpetuating factors. Considering the PCOS patient's problems in this way is particularly useful, since the biological mechanisms related to mood disorder aetiology include altered reproductive and metabolic factors that are part of PCOS. In clinically managing depression in a woman with PCOS, any obvious precipitating environmental factors need to be addressed. Interpersonal violence, recent losses, physical ill health, financial and other social stresses are prominent factors that can trigger or perpetuate depression, in an acute or more persistent manner. It is important to take a careful history from the patient and her family and friends about any manic or hypomanic episodes to delineate bipolar from unipolar mood disorders. This delineation has very important implications for optimal management, prognosis, and avoiding iatrogenic worsening of affective instability.
Following physical examination and laboratory investigations aiming to eliminate other comorbid conditions, moderate to severe Major Depressive Disorder in women with PCOS, will need antidepressant pharmacotherapy. From clinical experience, antidepressants are useful in managing depression in women with PCOS, who have moderate to severe depression. The first line of antidepressant treatment is usually with one of the following – an SSRI, 'selective serotonin reuptake inhibitor', NARI 'noradrenergic reuptake inhibitor', a NaSSA 'noradrenergic and specific serotonergic antidepressants', a NDRI 'norepinephrine – dopamine reuptake inhibitor' or a melatonin agonist. Second line treatment includes SNRIs 'serotonin and noradrenaline reuptake inhibitors', TCAs 'tricyclic antidepressants' or serotonin modulators. Third line treatment includes MAOIs 'monoamine oxidase inhibitors' and reversible MAOIs (4).

Anxiolytics, Antidepressants and the Management of Anxiety Disorders in PCOS
Anxiety disorders are common in women with PCOS. Generalised Anxiety Disorder, Social Anxiety Disorder, Panic Disorder and the phobias as described in the DSM 5, can be present in PCOS but are often in a subsyndromal manner with many having anxiety symptoms without meeting DSM 5 criteria (5). In clinical practice, many women with PCOS present feeling anxious, with intermittent exacerbation of anxiety symptoms and even panic. Psychological therapy can be very helpful in this condition.
Where medical treatment is indicated, it is more common practice to prescribe an SSRI (particularly sertraline) to treat anxiety if the preferred first line psychotherapeutic treatment options have not succeeded. Consistent with general population guidelines, off-label use of very low dose antipsychotics is also used when anxiety symptoms are very severe – but some of these medications can cause weight gain and other metabolic issues which is not ideal in PCOS (6). Benzodiazepines are only used in very limited, short term fashion in severe anxiety/panic, but are not recommended for longer term use because of the addiction issues (1, 2). In particular, anxiolytics such as alprazolam are rapidly physiologically addictive as well as psychologically addictive, and can impair cognition.

Anxiolytics, Antidepressants and the Management of Eating Disorders in Women with PCOS
Cognitive behavioural therapy is the first-line treatment for eating disorders (7). In general antidepressants are used to treat superimposed depression in women with PCOS who have eating disorders. Antidepressants are not usually indicated as specific treatment for eating disorders. Similarly, anxiolytics are not used as standard treatments for eating disorders, but may be used to treat comorbid anxiety. Eating disorders generally do not respond well to antidepressants or anxiolytic medications (7).

GRADE EVIDENCE CERTAINTY	
Comparison	**GRADE for critical outcomes**
Comparison 1. Sertraline versus Placebo	⨁⨁◯◯ LOW

Evidence to Recommendations Framework

COMPARISONS (option versus other option)

Antidepressant medications versus none

CONSENSUS RECOMMENDATION

- **CR:** Psychological therapy could be considered first-line management, and antidepressant medications considered in adults where mental health disorders are clearly documented and persistent, or if suicidal symptoms are present, based on general population guidelines.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

PRACTICE POINT(S)

- Lifestyle intervention and other therapies (e.g. COCP, metformin, laser hair removal) that target PCOS features should be considered, given their potential to improve psychological symptoms.
- Where pharmacological treatment for anxiety and depression is offered in PCOS, health professionals should apply caution:
  - to avoid inappropriate treatment with antidepressants or anxiolytics.
  - to limit use of agents that exacerbate PCOS symptoms, including weight gain.
- Health professionals should be aware that not managing anxiety and depression may impact adherence to PCOS treatment / management.

GRADE CONSIDERATIONS

Justifications:
We only found one study that compared Sertraline versus placebo in women with PCOS (8). Relevant outcomes included depression scores using the Hamilton Depression Rating Scale and this study was judged as moderate risk of bias. The recommendation is based on general population guidelines for treatment of anxiety and depression.

Subgroup considerations:
We have no evidence in adolescents with PCOS.

Implementation considerations:

Health professionals need to be adequately trained in the management of common mental health disorders.

In many countries it is not usual practice to screen adolescents or adults with PCOS for depression and/or anxiety symptoms and doing so may identify affected patients who would otherwise be missed. Screening may have resource implications such as an impact on length of consultation, however this can be reduced by the use of the screening tools recommended here. If depression and/or anxiety symptoms are detected, intervention may require referral to other health practitioners. Additional time with the patient may also be required to complete an appropriate care plan. Access to appropriate information and appropriately trained and experienced health professionals is important but may be limited. It is the responsibility of all health professionals to understand the impact of PCOS on psychological health and to screen for and manage these disorders.

Feasibility - A pragmatic approach may be to screen all women and adolescents at the time of PCOS diagnosis and where appropriate, at the time of their regular physical health checks for PCOS. Use clinical judgment considering an individual woman's risk factors to inform if additional screening is warranted. Align timing and interval of screening during the antenatal and postnatal periods with regional general population guidelines.

Partner with mental health professionals to improve feasibility related to referral for further care

The life stage of a woman should also be considered when screening for mental health disorders as risk factors and life events may differ. Consider issues around culture and sexual orientation.

The cultural identity and preferred language of a woman are also important considerations. Be aware of possible variations in presentation of mental health disorders and conduct screening in a culturally sensitive manner.

Monitoring and evaluation considerations:

Follow general population guidelines for anxiety and depression for monitoring and evaluation, including tolerability to side effects (e.g. weight gain).

Research priorities:

The role of various therapies in mental health disorders in PCOS in adults and adolescents.

The etiology and pathophysiology of mental health disorders in PCOS which may inform more targeted therapy.

Examination of the impact of depression or anxiety on the process and outcome of PCOS treatment and management, and the impact of PCOS treatment and management on depression or anxiety.

Examination of the effectiveness of treatment for depression or anxiety in women with PCOS, including the impact this has on the process and outcome of PCOS treatment and management

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2. National Institute for Health and Care Excellence. Depression in adults: treatment and management. NICE Guideline. 2022; accessible at https://www.nice.org.uk/guidance/ng222/resources/depression-in-adults-treatment-and-management-pdf-66143832307909

3. Dokras A, Sarwer DB, Allison KC, Milman L, Kris-Etherton PM, Kunselman AR, Stetter CM, Williams NI, Gnatuk CL, Estes SJ, Fleming J, Coutifaris C, Legro RS. Weight Loss and Lowering Androgens Predict Improvements in Health-Related Quality of Life in Women With PCOS. J Clin Endocrinol Metab. 2016 Aug;101(8):2966-74. doi: 10.1210/jc.2016-1896. Epub 2016 Jun 2. PMID: 27253669; PMCID: PMC4971336.

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5. American Psychiatric Association. (2022). *Diagnostic and statistical manual of mental disorders* (5th ed., text rev.). https://doi.org/10.1176/appi.books.9780890425787

6. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders Martin A Katzman et al. BMC Psychiatry 2014, 14(Suppl 1):S1

7. (b) National Institute for Health and Care Excellence. Eating disorders: recognition and treatment. NICE Guideline. 2020; accessible at https://www.nice.org.uk/guidance/ng69/resources/eating-disorders-recognition-and-treatment-pdf-1837582159813

8. Masoudi M, Ansari S, Kashani L, Tavolinejad H, Hossein Rashidi B, Esalatmanesh S, Ghazizadeh-Hashemi M, Noorbala AA, Akhondzadeh S. Effect of sertraline on depression severity and prolactin levels in women with polycystic ovary syndrome: a placebo-controlled randomized trial. Int Clin Psychopharmacol. 2021 Sep 1;36(5):238-243. doi: 10.1097/YIC.0000000000000367. PMID: 34030169.

GUIDELINE DEVELOPMENT GROUP 3

Lifestyle Management

	Clinical Questions
3.1	In women with PCOS, are lifestyle interventions (compared to minimal or nothing) effective for improving anthropometric, metabolic, reproductive, fertility, quality of life and emotional wellbeing outcomes?
3.2	In women with PCOS, are behavioural interventions (compared to different types of behavioural interventions) effective for improving anthropometric, metabolic, reproductive, fertility, quality of life and emotional wellbeing outcomes?
3.3	In women with PCOS, are diet interventions (compared to different diets) effective for improving anthropometric, metabolic, fertility, and emotional wellbeing outcomes?
3.4	In women with PCOS, are exercise interventions (compared to different exercises) effective for improving anthropometric, metabolic, reproductive, fertility, quality of life and emotional wellbeing outcomes?
3.5	Why are women with PCOS at increased risk of weight gain?
3.6	What is the burden of weight stigma in PCOS? *CLINICAL PRACTICE POINT:* *How do we alleviate weight stigma in PCOS in and outside healthcare settings?*

PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by ECR Lead: Maryam Kazemi

Other team members: Stephanie Cowan, Kimberly Hopkins, Thais Rasia, Isabella Xavier, Julia Michalak

Supervised, edited and supported by the Evidence Team (Aya Mousa, Jillian Tay)

GDG 3

Question 3.1.

In women with PCOS, are lifestyle interventions (compared to minimal or nothing) effective for improving anthropometric, metabolic, reproductive, fertility, quality of life and emotional wellbeing outcomes?

1. SELECTION CRITERIA

Table 1. PICO Criteria for Inclusion	
Question	Q 3.1) In women with PCOS, are lifestyle interventions (compared to minimal or nothing) effective for improving anthropometric, metabolic, reproductive, fertility, quality of life, and emotional wellbeing outcomes?
Clinical leads (key contacts)	Dr. Kathleen Hoeger M.D., M.P.H. Obstetrics and Gynecology, Reproductive Endocrinology Kathy Hoeger: Kathy_Hoeger@URMC.Rochester.edu
Allocation ranking	Level 2- Update systematic review

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(Language, year)*
Inclusion	Females of reproductive age (postmenarchal and premenopausal) with PCOS (diagnosed by the NIH 1990 [1], Rotterdam 2003 [2], or AE-PCOS 2006 [3] criteria). Age ranges include (based on published Cochrane paper) Adolescents 13-18 years Young Adults 19-24 years Adults 19-44 years Middle Aged 45-64 years	Lifestyle intervention (defined as a dietary, exercise or behavioral intervention, or a combination) as further classified below: Dietary intervention versus minimal treatment. Exercise intervention (resistance or aerobic exercise) versus minimal treatment. Behavioral management techniques for modifying diet or exercise versus minimal treatment. A combination of dietary, exercise, or behavioral intervention versus minimal treatment. All study durations are over two weeks.	Usual Care	Primary outcomes *Fertility* Live birth and pregnancy, as defined by study authors Miscarriage, as defined by the study authors Secondary outcomes Reproductive Menstrual regularity (an initiation of menses or significant shortening of cycle length where possible), ovulation (number of ovulatory menstrual cycles where possible) Endocrine (total testosterone, sex hormone-binding globulin (SHBG), free androgen index (FAI), and clinical hyperandrogenism (hirsutism assessed clinically by Ferriman-Gallwey score) Anthropometric Weight, BMI, adiposity distribution (by measures including waist circumference, waist-to-hip ratio (WHR)) Metabolic Oral glucose tolerance test (OGTT), glucose Fasting glucose Fasting lipids (total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides) Fasting insulin Oral glucose tolerance test (OGTT), insulin	For the specified outcomes, systematic reviews and RCTs addressing the outcomes are sought.	English Limit to publications between March 5, 2018, to August 10, 2022 (the earlier date was a final search date of the previous guideline update as indicated in the Cochrane review 2019, Issue 3. Art. No.: CD007506
Exclusion	Women taking anti-obesity medications (e.g., orlistat). Women with PCOS who are not defined as diagnosed by the NIH 1990[38], Rotterdam 2003[39], or AE-PCOS 2006[40] criteria.			Quality of life and participant satisfaction	Any study lower than a RCT. Non-RCT studies are excluded.	

2. SEARCH STRATEGY

Table 2.1. Search details

Search strategy source: [Page 81, https://doi.org/10.1002%2F14651858.CD007506.pub4]

Evidence source	Date of search
Medline (Ovid) Search Strategy --- 1. exp Polycystic Ovary Syndrome/ 2. Polycystic Ovar$.tw. 3. (PCOS or PCOD).tw. 4. (sclerocystic adj3 ovar$).tw. 5. stein leventhal.tw. 6. or/1-5 7. exp Diet Therapy/ 8. diet$.tw. 9. exp Weight Loss/ 10. (weight adj2 lose).tw. 11. Weight Loss.tw. 12. (weight adj3 reduc$).tw. 13. ((body mass index adj2 loss) or reduc$ or decreas$).tw. 14. ((BMI adj2 loss) or (BMI adj2 reduc) or (BMI adj2 decreas$)).tw. 15. exp Exercise Therapy/ 16. (exercise$ or exercising).tw. 17. exp sports/ or exp bicycling/ or exp running/ or exp swimming/ or exp walking/ 18. (run$ or jog$).tw. 19. (sport$ or walk$).tw. 20. swim$.tw. 21. train$.tw. 22. fitness.tw. 23. yoga.tw. 24. exp cognitive therapy/ or exp relaxation techniques/ 25. (cognitive adj2 therap$).tw. 26. exp Psychotherapy/ 27. Psychotherapy.tw. 28. psychosocial.tw. 29. exp Behavior Therapy/	Database: Ovid MEDLINE(R) March 5, 2018, to August 10, 2022

30. (Behavio?r adj2 therap$).tw.
31. behavio?r modif$.tw.
32. (behavio?r adj2 manage$).tw.
33. CBT.tw.
34. exp life style/ or exp life change events/
35. ((life*style adj2 change$) or intervention$).tw.
36. counselling.tw.
37. social support/
38. (social adj2 support).tw.
39. relaxation.tw.
40. exp self elicacy/
41. self elicacy.tw.
42. exp Health Promotion/
43. (Health adj2 Promotion).tw.
44. exp Health Education/
45. (Health$ adj2 Education).tw.
46. (motivation$ adj2 therap$).tw.
47. or/7-46
48. randomised controlled trial.pt.
49. controlled clinical trial.pt.
50. randomized.ab.
51. placebo.tw.
52. clinical trials as topic.sh.
53. randomly.ab.
54. trial.ti.
55. (crossover or cross-over or cross over).tw.
56. or/48-55
57. 6 and 47 and 56
58. limit 57 to (English language, and Humans, and yr="2018 -Current")

Combined search run in Medline Ovid on August 10, 2022

1. exp Polycystic Ovary Syndrome/ OR Polycystic Ovar$.tw. OR (PCOS or PCOD).tw. OR (sclerocystic adj3 ovar$).tw. OR stein leventhal.tw.

2. exp Diet Therapy/ OR diet$.tw. OR exp Weight Loss/ OR (weight adj2 lose).tw. OR Weight Loss.tw. OR (weight adj3 reduc$).tw. OR ((body mass index adj2 loss) or reduc$ or decreas$).tw. OR ((BMI adj2 loss) or (BMI adj2 reduc) or (BMI adj2 decreas$)).tw. OR exp Exercise Therapy/ OR (exercise$ or exercising).tw. OR exp sports/ or exp bicycling/ or exp running/ or exp swimming/ or exp walking/ OR (run$ or jog$).tw. OR (sport$ or walk$).tw. OR swim$.tw. OR train$.tw. OR fitness.tw. OR yoga.tw. OR exp cognitive therapy/ or exp relaxation techniques/ OR (cognitive adj2 therap$).tw. OR exp Psychotherapy/ OR

Psychotherapy.tw. OR psychosocial.tw. OR exp Behavior Therapy/ OR (Behavio?r adj2 therap$).tw. OR behavio?r modif$.tw. OR (behavio?r adj2 manage$).tw. OR CBT.tw. OR exp life style/ or exp life change events/ OR ((life*style adj2 change$) or intervention$).tw. OR counselling.tw. OR social support/ OR (social adj2 support).tw. OR relaxation.tw. OR exp self elicacy/ OR self elicacy.tw. OR exp Health Promotion/ OR (Health adj2 Promotion).tw. OR exp Health Education/ OR (Health$ adj2 Education).tw. OR (motivation$ adj2 therap$).tw. 3. randomised controlled trial.pt. OR controlled clinical trial.pt. OR randomized.ab. OR placebo.tw. OR clinical trials as topic.sh. OR randomly.ab. OR trial.ti. OR (crossover or cross-over or cross over).tw. 4. 1 AND 2 AND 3 5. limit 4 to (English language, and humans AND yr="2018 -Current")	

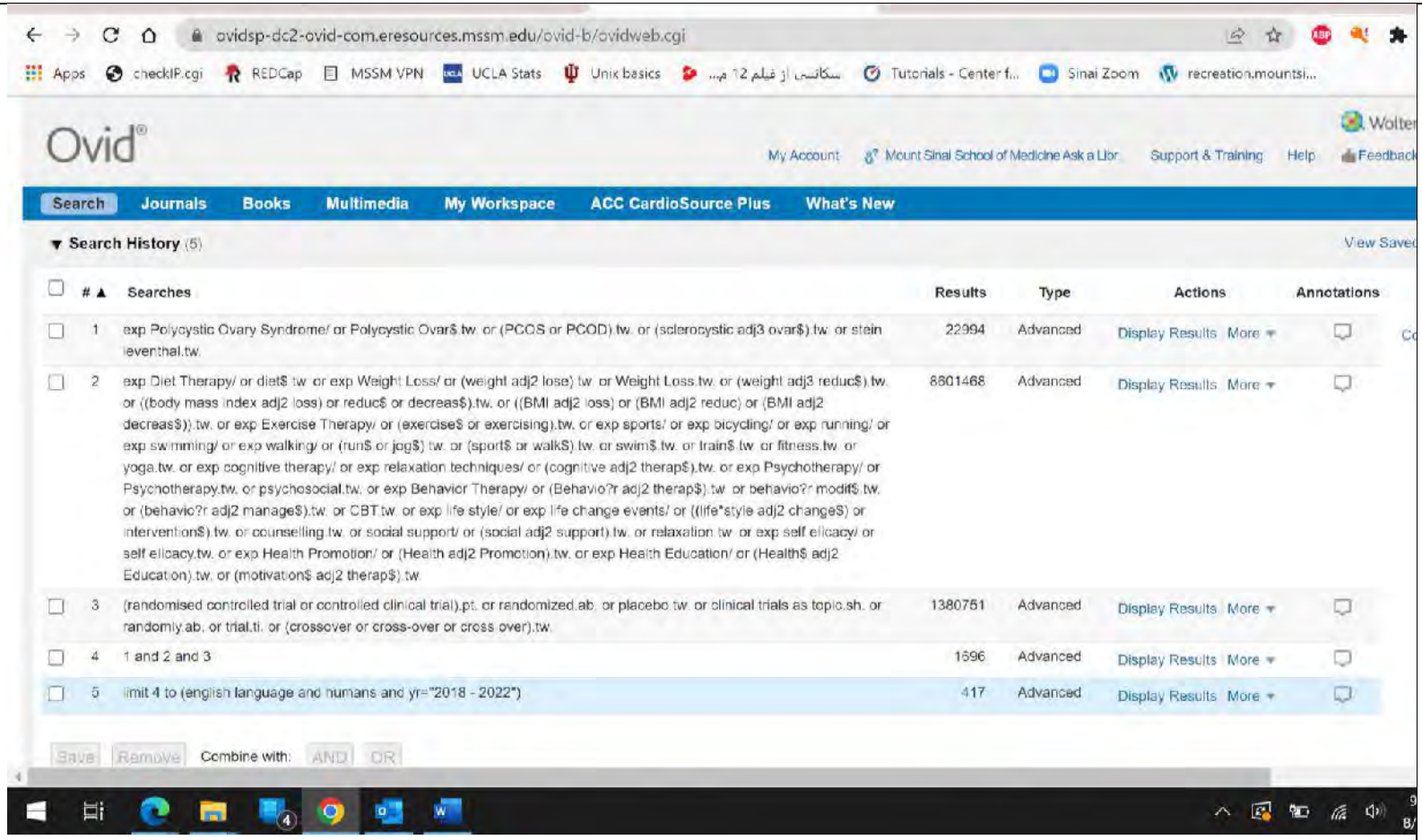


Figure 1. Ovid Search Query Screenshot (Date August 10, 2022)

Retrieved records from Ovid Medline: N=417

PsycInfo (Ovid) Combined search run in Medline Ovid on August 10, 2022	Database: Ovid MEDLINE(R) March 5,

1. exp Polycystic Ovary Syndrome/ OR Polycystic Ovar$.tw. OR (PCOS or PCOD).tw. OR (sclerocystic adj3 ovar$).tw. OR stein leventhal.tw. 2. exp Diet Therapy/ OR diet$.tw. OR exp Weight Loss/ OR (weight adj2 lose).tw. OR Weight Loss.tw. OR (weight adj3 reduc$).tw. OR ((body mass index adj2 loss) or reduc$ or decreas$).tw. OR ((BMI adj2 loss) or (BMI adj2 reduc) or (BMI adj2 decreas$)).tw. OR exp Exercise Therapy/ OR (exercise$ or exercising).tw. OR exp sports/ or exp bicycling/ or exp running/ or exp swimming/ or exp walking/ OR (run$ or jog$).tw. OR (sport$ or walk$).tw. OR swim$.tw. OR train$.tw. OR fitness.tw. OR yoga.tw. OR exp cognitive therapy/ or exp relaxation techniques/ OR (cognitive adj2 therap$).tw. OR exp Psychotherapy/ OR Psychotherapy.tw. OR psychosocial.tw. OR exp Behavior Therapy/ OR (Behavio?r adj2 therap$).tw. OR behavio?r modif$.tw. OR (behavio?r adj2 manage$).tw. OR CBT.tw. OR exp life style/ or exp life change events/ OR ((life*style adj2 change$) or intervention$).tw. OR counselling.tw. OR social support/ OR (social adj2 support).tw. OR relaxation.tw. OR exp self elicacy/ OR self elicacy.tw. OR exp Health Promotion/ OR (Health adj2 Promotion).tw. OR exp Health Education/ OR (Health$ adj2 Education).tw. OR (motivation$ adj2 therap$).tw. 3. randomised controlled trial.pt. OR controlled clinical trial.pt. OR randomized.ab. OR placebo.tw. OR clinical trials as topic.sh. OR randomly.ab. OR trial.ti. OR (crossover or cross-over or cross over).tw. 4. 1 AND 2 AND 3 5. limit 4 to (English language, and humans AND yr="2018 -Current")	2018, to August 10, 2022

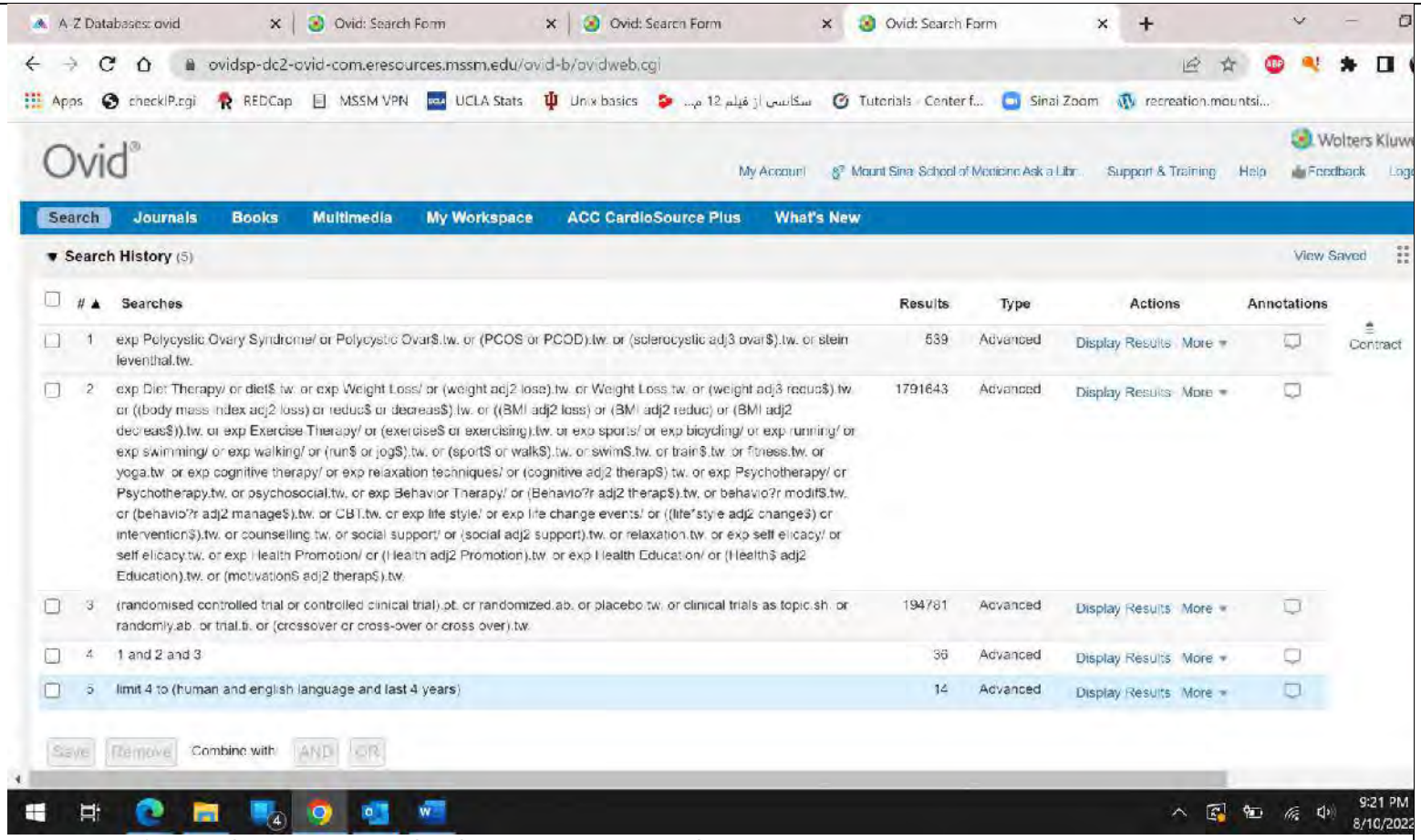


Figure 2. PsycInfo Search Query Screenshot (Date August 10, 2022)

Retrieved records from Ovid Medline: N=14

EMBASE (Ovid) Combined search run in Medline Ovid on August 10, 2022	Database: Ovid MEDLINE(R) March 5, 2018, to August 10, 2022

6. exp Polycystic Ovary Syndrome/ OR Polycystic Ovar$.tw. OR (PCOS or PCOD).tw. OR (sclerocystic adj3 ovar$).tw. OR stein leventhal.tw. 7. exp Diet Therapy/ OR diet$.tw. OR exp Weight Loss/ OR (weight adj2 lose).tw. OR Weight Loss.tw. OR (weight adj3 reduc$).tw. OR ((body mass index adj2 loss) or reduc$ or decreas$).tw. OR ((BMI adj2 loss) or (BMI adj2 reduc) or (BMI adj2 decreas$)).tw. OR exp Exercise Therapy/ OR (exercise$ or exercising).tw. OR exp sports/ or exp bicycling/ or exp running/ or exp swimming/ or exp walking/ OR (run$ or jog$).tw. OR (sport$ or walk$).tw. OR swim$.tw. OR train$.tw. OR fitness.tw. OR yoga.tw. OR exp cognitive therapy/ or exp relaxation techniques/ OR (cognitive adj2 therap$).tw. OR exp Psychotherapy/ OR Psychotherapy.tw. OR psychosocial.tw. OR exp Behavior Therapy/ OR (Behavio?r adj2 therap$).tw. OR behavio?r modif$.tw. OR (behavio?r adj2 manage$).tw. OR CBT.tw. OR exp life style/ or exp life change events/ OR ((life*style adj2 change$) or intervention$).tw. OR counselling.tw. OR social support/ OR (social adj2 support).tw. OR relaxation.tw. OR exp self elicacy/ OR self elicacy.tw. OR exp Health Promotion/ OR (Health adj2 Promotion).tw. OR exp Health Education/ OR (Health$ adj2 Education).tw. OR (motivation$ adj2 therap$).tw. 8. randomised controlled trial.pt. OR controlled clinical trial.pt. OR randomized.ab. OR placebo.tw. OR clinical trials as topic.sh. OR randomly.ab. OR trial.ti. OR (crossover or cross-over or cross over).tw. 9. 1 AND 2 AND 3 10. limit 4 to (English language, and humans AND yr="2018 -Current")	

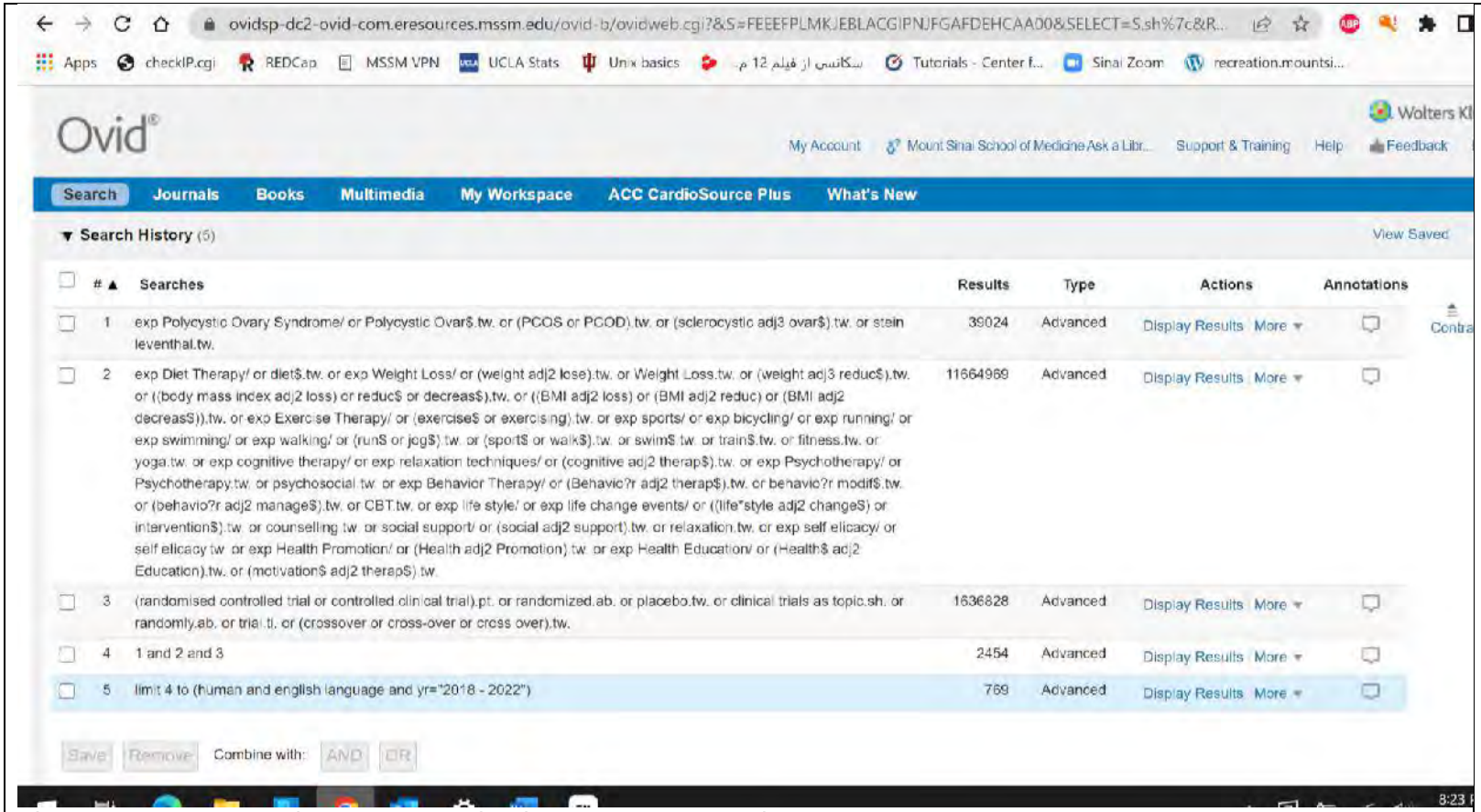


Figure 3. EMBASE Search Query Screenshot (Date August 10, 2022)

Retrieved records from Ovid Medline: N=769

All EBM (Ovid) Search in All EBM was conducted by loyal.pattuwage@monash.edu on on August 12, 2022 **EBM Reviews - Cochrane Central Register of Controlled Trials <July 2022>**	June 7, 2017, to August 12, 2022

1 exp polycystic ovary syndrome/ 1705 2 polycystic ovar*.mp. 4396 3 poly-cystic ovar*.mp. 136 4 PCO*.mp. 6012 5 (stein-leventhal or leventhal).mp. 58 6 anovulation/ 151 7 anovulat*.mp. 1092 8 oligo-ovulat*.mp. 38 9 oligoovulat*.mp. 28 10 (ovar* adj5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*)).mp. 4588 11 or/1-10 7749 12 exp Diet Therapy/ 6611 13 exp Weight Loss/ 7136 14 exp Exercise Therapy/ 16211 15 exp Sports/ 17296 16 exp Bicycling/ 1749 17 exp Running/ 2207 18 exp Jogging/ 52 19 exp Walking/ 6281 20 exp Cognitive Behavioral Therapy/ 10334 21 exp Relaxation Therapy/ 2064 22 exp Psychotherapy/ 26780 23 exp Behavior Therapy/ 18705 24 exp Life Style/ 6377 25 exp Life Change Events/ 461 26 exp Social Support/ 3545 27 exp Health Promotion/ 7165 28 exp Health Education/ 21239 29 (diet* or (weight adj2 lose) or Weight Loss or (weight adj3 reduc*) or (body mass index adj2 loss) or reduc* or decreas* or (BMI adj2 loss) or (BMI adj2 reduc) or (BMI adj2 decreas*) or (exercise* or exercising) or (run* or jog*) or (sport* or walk*) or swim* or train* or fitness or yoga or (cognitive adj2 therap*) or Psychotherapy or psychosocial or (Behavio?r adj2 therap*) or behavio?r modif* or (behavio?r adj2 manage*) or CBT or (life*style adj2 change*) or intervention* or counselling or (social adj2 support) or relaxation or self efficacy or (Health adj2 Promotion) or (Health* adj2 Education) or (motivation* adj2 therap*)).tw. 1044945 30 or/12-29 1052246 31 11 and 30 5069 32 limit 31 to (yr="2018 -Current" and english language) **1605** **Retrieved records from All EBM: N=1605**	

CINAHL EBSCO Search in All EBM was conducted by loyal.pattuwage@monash.edu on on August 12, 2022 Search yield are saved as a PDF file "Q 3.1_CINAHL_12 Aug 2022.pdf" in Kazemi PC – path: 2022. PCOS Guideline\Q3.1\RIS Inputs Covidence **Retrieved records from All EBM: N=315**	June 7, 2017, to August 12, 2022
Any subsequent updates - enter database and date: After March 5 2019 up to the present date: None	

Table 2.3. Search strings used in OVID or other database/s – *please save a screenshot of search results to submit alongside this template*		
OVID Medline, All EBM, PsycInfo, AMED, EMBASE (results= 2805)	CINAHL: Yes (results= 315)	Other: No
1. OVID MedLine: N=417 2. OVID PsychInfo: N=14 3. EMBASE: N=769 4. All EBM: N=1605 5. CINAHL: N=315 **Total (all 5 datasets): N=3120** **Total after deduplication using EndNote and Covidence: 1495**	Same or different search: Yes	Same or different search: N/A

Evidence processing: Studies were selected and appraised by a total of 5 reviewers (Steph Cowan, Kimberly Hopkins, Thais Rasia, Isabella Xavier, Julia Michalak) in consultation with the evidence team/ key contact (Kathy Hoeger, Lisa Moran) using study selection and appraisal criteria (PICO above) established a priori. The articles were reviewed by title and abstract by one reviewer. When a decision could not be made based on the title and abstract alone, the full text was retrieved. **Eighteen studies (7 RCTs retrieved in the current search, conducted after the previous guideline update in 2018) and 11 RCTs from the previous update guideline (published in the Cochrane review 2019) met the inclusion criteria for this review (see Table 4.1).**

*Note that four studies (Mani 2018, Mirfeizi 2013, Saremi 2016, Vizza 2016) out of a total of 15 RCTs initially identified in the Cochrane review were excluded from this review because their PCOS definition was unclear and therefore lacked compliance with the updated PICO of this GDG.

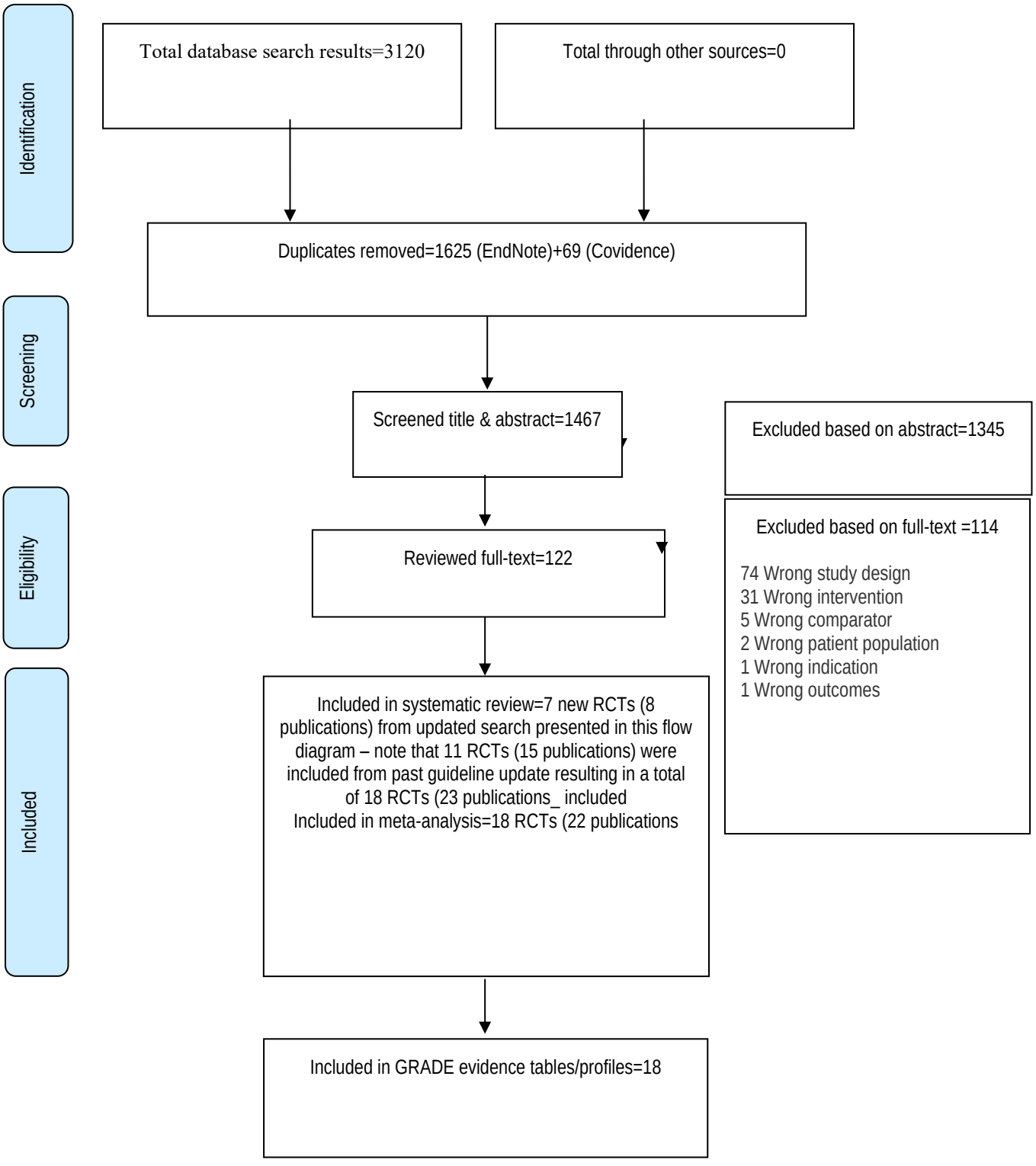
Statistical analyses (Description of meta-analysis)

Effect sizes for each outcome measure were expressed as the weighted mean difference (MD) and 95% confidence interval (CI) between the intervention and control (minimal treatment) groups, and the studies were weighted based on the inverse of the variance for the evaluated measure with a random-effects model.

Mean differences and standard deviations (SD) of lean tissue mass measures were collected to estimate pooled effects across evaluated measures except indicated explicitly for each outcome (e.g., for weight, BMI and waist circumference, mean change instead of post-intervention data were used for Moeller 2021, Oberg 2018, and Stener-Victorin 2009-2013. Consistent with the methodology used in the previous update of this GDG. [Cochrane review 2019, Issue 3. Art. No.: CD007506]). When medians and interquartile ranges were reported instead of means and SD, we used medians in place of means and the formula of SD=(third quartile-first quartile)/1.35 to calculate the SD.

The chi-square test was used to evaluate heterogeneity, and the Cochran Q and I^2 statistics were reported. The I^2 value describing the percentage variation between studies was calculated as 100%×([Q–df])/Q, Q being the χ2 value, and df corresponding to degrees of freedom. Low, moderate, and high heterogeneity were defined according to the cut-offs of 25%, 50%, and 75%, respectively, using the I^2 test values. Tau-square was estimated using the restricted maximum likelihood (REML) method to evaluate between-study variance. Maryam Kazemi performed all analyses using R version 3.6.1. (R Foundation for Statistical Computing, Vienna, Austria). Results were considered significant at $P<0.05$.

3. SEARCH RESULTS - PRISMA flowchart



4. STUDY INCLUSION

Table 4.1. Included Studies (full citation with doi)- *Sorted alphabetically* *N=7 studies or RCTs (8 publications) retrieved in the updated search (after 2018 Guideline: search date March 5, 2018, to August 10, 2022)* *(shown in the green rows below)* *N=11 studies or RCTs (15 publications) were included from the Cochrane review (4 studies that were included from the current list are enlisted in the excluded studies in table 4.2 with reasons; all included 11 studies from the Cochrane review are shown in grey rows below)*
1. Almenning I, Rieber-Mohn A, Lundgren KM, Shetelig Løvvik T, Garnæs KK, Moholdt T. Effects of high intensity interval training and strength training on metabolic, cardiovascular and hormonal outcomes in women with polycystic ovary syndrome: a pilot study. PloS One 2015;10(9):e0138793.
2. Brown AJ, Setji TL, Sanders LL, Lowry KP, Otvos JD, Kraus WE, et al. Effects of exercise on lipoprotein particles in women with polycystic ovary syndrome. Medicine and Sciences in Sports and Exercise 2009;41(3):497-504.
3. Costa, E. C., DE Sá, J., Stepto, N. K., Costa, I., Farias-Junior, L. F., Moreira, S., Soares, E., Lemos, T., Browne, R., & Azevedo, G. D. (2018). Aerobic Training Improves Quality of Life in Women with Polycystic Ovary Syndrome. Medicine and science in sports and exercise, 50(7), 1357–1366. https://doi.org/10.1249/MSS.0000000000001579
4. Dietz de Loos, A., Jiskoot, G., Beerthuizen, A., Busschbach, J., & Laven, J. (2021). Metabolic health during a randomized controlled lifestyle intervention in women with PCOS. European journal of endocrinology, 186(1), 53–64. https://doi.org/10.1530/EJE-21-0669
5. Guzick DS, Wing R, Smith D, Berga SL, Winters SJ. Endocrine consequences of weight loss in obese, hyperandrogenic, anovulatory women. Fertility and Sterility 1994;61(4):598-604.
6. Hoeger KM, Kochman L, Wixom N, Craig K, Miller RK, Guzick DS. A randomized, 48-week, placebo-controlled trial of intensive lifestyle modification and/or metformin therapy in overweight women with polycystic ovary syndrome: a pilot study. Fertility and Sterility 2004;82(2):421-9.
7. Hoeger K, Davidson K, Kochman L, Cherry T, Kopin L, Guzick DS. The impact of metformin, oral contraceptives, and lifestyle modification on polycystic ovary syndrome in obese adolescent women in two randomized, placebo-controlled clinical trials. Journal of Clinical Endocrinology and Metabolism 2008;93(11):4299-306.
8. Jedel E, Labrie F, Oden A, Holm G, Nilsson L, Janson PO, et al. Impact of electro-acupuncture and physical exercise on hyperandrogenism and oligo/amenorrhea in women with polycystic ovary syndrome: a randomised controlled trial. American Journal of Physiology-Endocrinology and Metabolism 2011;300(1):E37-45. Leonhardt H, Hellstrom M, Gull B, Lind AK, Nilsson L, Janson OP, et al. Serum anti-Mullerian hormone and ovarian morphology assessed by magnetic resonance imaging in response to acupuncture and exercise in women with polycystic ovary syndrome: secondary analyses of a randomized controlled trial. Acta Obstetricia et Gynecologica Scandinavica 2015;94:279-87. Stener-Victorin E, Baghaei F, Holm G, Janson PO, Olivecrona G, Lönn M, et al. Effects of acupuncture and exercise on insulin sensitivity, adipose tissue characteristics, and markers of coagulation and fibrinolysis in women with polycystic ovary syndrome: secondary analyses of a randomized controlled trial. Fertility and Sterility 2012;97(2):501-8. Stener-Victorin E, Holm G, Janson PO, Gustafson D, Waern M. Acupuncture and physical exercise for affective symptoms and health-related quality of life in polycystic ovary syndrome: secondary analysis from a randomized controlled trial. BMC Complementary and Alternative Medicine 2013;13:131. Stener-Victorin E, Jedel E, Janson PO, Sverrisdottir YB. Low-frequency electroacupuncture and physical exercise decrease high muscle sympathetic nerve activity in polycystic ovary syndrome. American Journal of Physiology - Regulatory, Integrative and Comparative Physiology 2009;297(2):R387-95.
9. Kiel, I. A., Lionett, S., Parr, E. B., Jones, H., Røset, M., Salvesen, Ø., Hawley, J. A., Vanky, E., & Moholdt, T. (2022). High-Intensity Interval Training in Polycystic Ovary Syndrome: A Two-Center, Three-Armed Randomized Controlled Trial. Medicine and science in sports and exercise, 54(5), 717–727. https://doi.org/10.1249/MSS.0000000000002849
10. Kogure, G. S., Lopes, I. P., Ribeiro, V. B., Mendes, M. C., Kodato, S., Furtado, C., Silva de Sá, M. F., Ferriani, R. A., Lara, L., & Reis, R. (2020). The effects of aerobic physical exercises on body image among women with polycystic ovary syndrome. Journal of affective disorders, 262, 350–358.
11. Moeller, L. V., Lindhardt, C. L., Andersen, M. S., Glintborg, D., & Ravn, P. (2019). Motivational interviewing in obese women with polycystic ovary syndrome - a pilot study. Gynecological endocrinology: the official journal of the International Society of Gynecological Endocrinology, 35(1), 76–80. https://doi.org/10.1080/09513590.2018.1498832
12. Nasrekani ZA, Fathi M. Efficacy of 12 weeks aerobic training on body composition, aerobic power and some women-hormones in polycystic ovary syndrome infertile women. Iranian Journal of Obstetrics, Gynecology and Infertility 2016;19(5):1-10.
13. Oberg, E., Gidlöf, S., Jakson, I., Mitsell, M., Tollet Egnell, P., & Hirschberg, A. L. (2019). Improved menstrual function in obese women with polycystic ovary syndrome after behavioural modification intervention-A randomized controlled trial. Clinical endocrinology, 90(3), 468–478. https://doi.org/10.1111/cen.13919
14. Ribeiro, V. B., Lopes, I. P., Dos Reis, R. M., Silva, R. C., Mendes, M. C., Melo, A. S., de Souza, H., Ferriani, R. A., Kogure, G. S., & Lara, L. (2021). Continuous versus intermittent aerobic exercise in the improvement of quality of life for women with polycystic ovary syndrome: A randomized controlled trial. Journal of health psychology, 26(9), 1307–1317. https://doi.org/10.1177/1359105319869806

Ribeiro, V. B., Pedroso, D., Kogure, G. S., Lopes, I. P., Santana, B. A., Dutra de Souza, H. C., Ferriani, R. A., Calado, R. T., Furtado, C., & Reis, R. (2021). Short-Term Aerobic Exercise Did Not Change Telomere Length While It Reduced Testosterone Levels and Obesity Indexes in PCOS: A Randomized Controlled Clinical Trial Study. International journal of environmental research and public health, 18(21), 11274. https://doi.org/10.3390/ijerph182111274
15. Saremi A, Nader, Karmali M, Kazemi M. Serum level of anti-mullerian hormone after exercise training in women with polycystic ovary syndrome: a randomised controlled trial. Iranian Journal of Obstetrics, Gynecology and Infertility 2013;16(64):10.
16. Stefanaki C, Bacopoulou F, Livadas S, Kandaraki A, Karacalios A, Chrousos G, et al. Impact of a mindfulness stress management program on stress, anxiety, depression and quality of life in women with polycystic ovary syndrome: a randomised controlled trial. Stress (Amsterdam, Netherlands) 2015;18(1):57-66.
17. Turan V, Mutlu EK, Solmaz U, Ekin A, Tosun O, Tosun G, et al. Benefits of short-term structured exercise in non-overweight women with polycystic ovary syndrome: a prospective randomised controlled study. Journal of Physical Therapy Science 2015;27(7):2293-7.
18. Vigorito C, Giallauria F, Palomba S, Cascella T, Manguso F, Lucci R, et al. Beneficial effects of a three-month structured exercise training program on cardiopulmonary functional capacity in young women with polycystic ovary syndrome. Journal of Clinical Endocrinology and Metabolism 2007;92(4):1379-84.

Table 4.2. Excluded Studies (on full-text assessment) - *Sorted alphabetically; for clarity, all studies excluded in the updated search after the publication of the Cochrane review in 2019 are shown in green rows, and others that were excluded in the Cochrane review are shown in grey rows below.*

Reference	Reason
Abbassy, A. (2022, December 1-). Role of the Ketogenic Diet in Women With PCOS. Identifer NCT04175964. https://clinicaltrials.gov/ct2/show/NCT04175964	Wrong study design
Ahmadi, A. (2020, March 20-). Comparison between the effect of counseling based on Rational-Emotive-Behaviour Theory (REBT) and Mindfulness-Based Art therapy (MBAT) on the body image of women with polycystic ovary syndrome (PCOS). Identifier IRCT20170611034452N9. https://en.irct.ir/trial/43617	Wrong study design
Ansari, F., & Hamzehgardesh, Z. (2020, May 12-2020, July 22).Effect of motivational interview on self-care and quality of life among infertile women with polycystic ovary syndrome. Identifier IRCT20160619028528N4. http://en.irct.ir/trial/48089	Wrong study design
Asemi Z., & Esmaillzadeh, A. (2015). DASH diet, insulin resistance, and serum hs-CRP in polycystic ovary syndrome: a randomized controlled clinical trial. *Hormone and Metabolic Research, 47* (3), 232-238.	No minimal intervention comparison group; caloric restriction and prescribed diet in both groups.
Atiomo, W., Read, A., Golding, M., Silcocks, P., Razali, N., Sarkar, S., Hardiman, P., & Thornton, J. (2009). Local recruitment experience in a study comparing the effectiveness of a low glycaemic index diet with a low calorie healthy eating approach at achieving weight loss and reducing the risk of endometrial cancer in women with polycystic ovary syndrome (PCOS). *Contemporary Clinical Trials, 30* (5), 451-456.	Control arm is not minimal treatment; low GI versus low-calorie diets.
Azadi-Yazdi, M., Karimi-Zarchi, M., Salehi-Abargouei, A., Fallahzadeh, H., & Nadjarzadeh, A. (2017). Effects of Dietary Approach to Stop Hypertension diet on androgens, antioxidant status and body composition in overweight and obese women with polycystic ovary syndrome: a randomised controlled trial. *Journal of Human Nutrition and Dietetics, 30*(3), 275-283.	No minimal comparison group; both intervention (low-calorie DASH) and control diets consist- ed of 50% to 55% carbohydrate, 15% to 20% protein and 25% to 30% total fat; both diets were equicaloric.
Beena, M.R., & Kochuthressiamma, T. (2016). Outcome of interventional programme on quality of life of infertile women with polycystic ovarian syndrome. *International Journal of Nursing Education, 8*(2), 27-33.	Not a randomized controlled trial: quasi-randomized, sampling technique; multi-stage random sampling.
Bruner, B., Chad, K., & Chizen, D. (2006). Effects of exercise and nutritional counseling in women with polycystic ovary syndrome. *Applied Physiology, Nutrition, and Metabolism, 31*(4), 384-391.	No minimal intervention comparison group; exercise and nutritional counselling versus nutritional counselling.

Chien, Y. J., Chang, C. Y., Wu, M. Y., Chen, C. H., Horng, Y. S., & Wu, H. C. (2021). Effects of Curcumin on glycemic control and lipid profile in Polycystic Ovary Syndrome: Systematic Review with Meta-Analysis and Trial Sequential Analysis. *Nutrients*, *13*(2), 684. https://doi.org/10.3390/nu13020684	Wrong intervention
Chilibeck, P. (2019, May 8-2021, October 21). Pulse-based Foods for Alleviation of Negative Consequences of Sedentary Behaviour. Identifer NCT03941704. https://www.clinicaltrials.gov/ct2/show/results/NCT03941704?view=results	Wrong patient population
Colonetti, L., Grande, A. J., Toreti, I. R., Ceretta, L. B., da Rosa, M. I., & Colonetti, T. (2022). Green tea promotes weight loss in women with Polycystic Ovary Syndrome: Systematic review and meta-analysis. *Nutrition Research*, *104*, 1–9. https://doi.org/10.1016/j.nutres.2022.03.009	Wrong intervention
Curi, D.D., Fonseca, A.M., Marcondes, J.A., Almeida, J.A., Bagnoli, V.R., Soares, J.M. Jr, (2012). Metformin versus lifestyle changes in treating women with polycystic ovary syndrome. *Gynecological Endocrinology, 28* (3), 182-185.	The control arm did not receive minimal treatment; the control arm received metformin.
De Loos, A. D., Timman, R., Jiskoot, G, Beerthuizen, A., Busschbach, J., & Laven, J. Favorable changes in phenotype expression and androgens in women with PCOS due to weight loss in a three-component lifestyle intervention program. (2019). *Reproductive Sciences, 26*, A62-A390. https://doi.org/10.1177/1933719119834079	Abstract only
Dilek O, Senay UA, Fatih C. (2022). Impact of the individual counseling program for polycystic ovary syndrome management among university students: A prospective randomized controlled trial. *Nigerian Journal of Clinical Practice, 25*(6), 809.	Wrong study design
Dos Santos, I. K., Ashe, M. C., Cobucci, R. N., Soares, G. M., de Oliveira Maranhão, T. M., & Dantas, P. (2020). The effect of exercise as an intervention for women with polycystic ovary syndrome: A systematic review and meta-analysis. *Medicine*, *99*(16), e19644. https://doi.org/10.1097/MD.0000000000019644	Wrong study design
Ebrahimi-Mamaghani, M., Saghafi-Asl, M., Pirouzpanah, S., & Asghari-Jafarabadi, M. (2014). Effects of raw red onion consumption on metabolic features in overweight or obese women with polycystic ovary syndrome: a randomized controlled clinical trial. *Journal of Obstetrics and Gynaecology Research, 40* (4), 1067-1076.	No minimal intervention comparison group; the control group received less onion from consuming compared to the intervention group.
Elbandrawy, A. M., Yousef, A. M., Morgan, E. N., Ewais, N. F., Eid, M. M., Elkholi, S. M., & Abdelbasset, W. K. (2022). Effect of aerobic exercise on inflammatory markers in polycystic ovary syndrome: a randomized controlled trial. European review for medical and pharmacological sciences, 26(10), 3506–3513. https://doi.org/10.26355/eurrev_202205_28845	Wrong outcomes
Federal State Budgetary Institution, V. A. Almazov Federal North-West Medical Research Centre, of the Ministry of Health. (2022, March 30). Low-Carb Versus Mediterranean Diet in PCOS. Identifier NCT05272657.https://clinicaltrials.gov/ct2/show/NCT05272657	Wrong study design
Floyd, R., & Tallaght University Hospital. (2021, May 5-). Time-restricted Eating to Improve Metabolic Abnormalities in Polycystic Ovarian Syndrome. Identifier NCT05126199. https://clinicaltrials.gov/ct2/show/NCT05126199	Wrong study design
Foroozanfard, F., Rafiei, H., Samimi, M., Gilasi, H.R., Gorjizadeh, R., Heidar, Z., & Asemi, Z. (2017). The effects of dietary approaches to stop hypertension diet on weight loss, anti-Müllerian hormone and metabolic profiles in women with polycystic ovary syndrome: a randomized clinical trial. *Clinical Endocrinology, 87* (1),51-58.	No minimal intervention comparison group; both intervention (low-calorie DASH) and control diets consisted of 52% to 55% carbohydrates, 16% to 18% proteins and 30% total fats; both diets were equicaloric.
Furtado, C. L., Ribeiro, V.B., Pedroso, D.C.C., Kogure, G.S., Ferriani, R. A., Calado, R. T., & dos Reis, R. M. (2020). Continous and intermittent aerobic training did not change telomere length, although it reduces hyperandrogenism and anthropometric indexes in PCOS. *ASRM Abstracts, 114 (3)*, 947. https://www.fertstert.org/article/S0015-0282(20)32245-7/pdf.	Abstract only
Fux Otta, C., Wior, M., Iraci, G.S., Kaplan, R., Torres, D., Gaido, M.I., & Wyse, E. P. (2010). Clinical, metabolic, and endocrine parameters in response to metformin and lifestyle intervention in women with polycystic ovary syndrome: a randomized, double-blind, and placebo control trial. *Gynecological Endocrinology, 26* (3), 173-178.	Control arm is not minimal treatment; randomization was to receive either oral metformin or placebo and all participants were given a nutrition plan.
Gambineri, A.(2021, March 16-).Ketogenic Diet in PCOS With Obesity and Insulin Resistance (VLCKD). Identifier NCT04801173. https://clinicaltrials.gov/ct2/show/NCT04801173	Wrong study design

Giallauria, F., Palomba, S., Maresca, L., Vuolo, L., Tafuri, D., Lombardi, G., Colao, A., Vigorito, C., & Francesco, O. (2008). Exercise training improves autonomic function and inflammatory pattern in women with polycystic ovary syndrome. *Clinical Endocrinology, 69* (5),792-798.	Not a randomized controlled trial; treatment allocated by participant choice.
Giudetti, A.M. (2022, January 19-). Effects of Fasting Mimicking Diet (FMD) in Women With Polycystic Ovary Syndrome (PCOS). Identifier NCT05196568. https://clinicaltrials.gov/ct2/show/NCT05196568	Wrong study design
Glueck, C.J., Aregawi, D., Winiarska, M., Agloria, M., Luo, G., Sieve, L., & Wang, P. (2006). Metformin-diet ameliorates coronary heart disease risk factors and facilitates resumption of regular menses in adolescents with polycystic ovary syndrome. *Journal of Pediatric Endocrinology and Metabolism, 19* (6), 831-842.	No minimal intervention comparison group; single group study (metformin and diet).
Goss, A.M, Chandler-Laney, P.C., Ovalle, F., Goree, L.L, Azziz, R., Desmond, R.A., Bates, G.W., & Gower, B.A. (2014). Effects of a eucaloric reduced-carbohydrate diet on body composition and fat distribution in women with PCOS. *Metabolism: Clinical & Experimental, 63* (10), 1257-1264. Gower, B.A., Chandler-Laney, P.C., Ovalle, F., Goree, L.L., Azziz, R., Desmond, R.A., Granger, W.M., Goss, A.M., & Bates, G.W. (2013). Favourable metabolic effects of a eucaloric lower-carbohydrate diet in women with PCOS. *Clinical Endocrinology, 79* (4):550-7. Gower, B.A., & Goss, A.M. (2015). A lower-carbohydrate, higher-fat diet reduces abdominal and intermuscular fat and increases insulin sensitivity in adults at risk of type 2 diabetes. *Journal of Nutrition, 145* (1), 177S-183S.	The control arm did not recieve minimal treatment; control group received a specific diet (55:18:27 CHO:protein:fat) for 8 weeks. Cross-over study.
Hamayeli Mehrabani, H., Tahbaz, F., Salehpour, S., Hedayati, M., Amiri, Z., & Ghassemi, A. (2010). Reproductive hormonal changes following two types of hypocaloric diets in overweight and obese polycystic ovary syndrome women. *Iranian Journal of Endocrinology and Metabolism,12* (2), 160-200.	Control arm is not minimal treatment; participants were assigned to either a weight loss diet (carbohydrates 55%, protein 15%, fat 30%) or a modified diet low glycaemic load (carbohydrates 40%, protein 30%, fat 30%)
Hewawasam, E., Brennan, L., Giles, L,, Hull, M.L., Short, A., Norman, R., & Peña, A.S. (2020). Assessing Whether Meditation Improves Quality of Life for Adolescent Girls With Polycystic Ovary Syndrome: Protocol for a Randomized Controlled Trial. JMIR Res Protoc, 9(1):e14542. doi: 10.2196/14542.	Wrong study design
Hussaini, S., & Mitra, S. (2020, October 10-Completed). Effect of Pilates exercise on fat reduction and improving quality of life in women with Polycystic Ovarian Syndrome (PCOS). Identifier CTRI/2020/10/028217. http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=47474	Wrong study design
Hutchison, S.K., Teede, H.J., Rachon, D., Harrison, C.L., Strauss, B.J., & Stepto, N.K. (2012). Effect of exercise training on insulin sensitivity, mitochondria and computed tomography muscle attenuation in overweight women with and without polycystic ovary syndrome. *Diabetologia, 55* (5), 1424-1434.	Not a randomized controlled trial.
Haudum, C., Lindheim, L., Ascani, A., Trummer, C., Horvath, A., Münzker, J., & Obermayer-Pietsch, B. (2020). Impact of Short-Term Isoflavone Intervention in Polycystic Ovary Syndrome (PCOS) Patients on Microbiota Composition and Metagenomics. *Nutrients*, *12*(6), 1622. https://doi.org/10.3390/nu12061622	Wrong intervention
Hoover, S. E., Gower, B. A., Cedillo, Y. E., Chandler-Laney, P. C., Deemer, S. E., & Goss, A. M. (2021). Changes in Ghrelin and Glucagon following a Low Glycemic Load Diet in Women with PCOS. *The Journal of clinical endocrinology and metabolism*, *106*(5), e2151–e2161. https://doi.org/10.1210/clinem/dgab028	Wrong comparator
Jakubowicz, D., Barnea, M., Wainstein, J., & Froy, O. (2013). Effects of caloric intake timing on insulin resistance and hyperandrogenism in lean women with polycystic ovary syndrome. *Clinical Science, 125* (9), 423-32.	No minimal intervention comparison group. 2 isocaloric diets prescribed with different meal timing distribution.
Javanbakht, M. (2020, April 19-). Effectiveness Comparison of Body-Mind Intervention in Virtual and Face to Face Method on Quality of Life in Polycystic Ovary Syndrome. Identifier IRCT20190916044783N1. https://en.irct.ir/trial/42858?revision=130238	Wrong study design
Jensterle, M., Kravos, N. A., Goričar, K., & Janez, A. (2017). Short-term effectiveness of low dose liraglutide in combination with metformin versus high dose liraglutide alone in treatment of obese PCOS: randomized trial. *BMC endocrine disorders*, *17*(1), 1-6.	Wrong study design
Jiskoot, G., Benneheij, S.H., Beerthuizen, A., de Niet, J.E., de Klerk, C., Timman, R., Busschbach, J.J, & Laven, J.S.E. (2017). A three-component cognitive behavioural lifestyle program for preconceptional weight-loss in women with polycystic ovary syndrome (PCOS): a protocol for a randomized controlled trial. *Reproductive Health, 14* (1), 34.	Control arm is not minimal treatment; control group had individual counselling about health risks associated with being

	overweight for both mother and child.
Jiskoot, G., Beerthuizen, A., Timman, R., Busschbach, J., & Laven, J. (2018). Effects on body weight of a 1-year three-component lifestyle RCT in obese PCOS women. *Gynecological Endrocrinology, 33* (1), i430-i431.	Abstract only
Jiskoot, G., Dietz de Loos, A., Beerthuizen, A., Timman, R., Busschbach, J., & Laven, J. (2020). Long-term effects of a three-component lifestyle intervention on emotional well-being in women with Polycystic Ovary Syndrome (PCOS): A secondary analysis of a randomized controlled trial. *PloS one*, *15*(6), e0233876. https://doi.org/10.1371/journal.pone.0233876	Wrong comparator
Jiskoot, G., Timman, R., Beerthuizen, A., de Loos, A.D., Busschbach, J., & Laven, J. (2019). The impact of a three-component lifestyle intervention on emotional well-being in women with PCOS. Reproductive Sciences, 26 (1), 283.	Wrong study design
Johnson, L.K., Holven, K.B., Nordstrand, N., Mellembakken, J.R., Tanbo, T., & Hjelmesæth, J. (2015). Fructose content of low calorie diets: effect on cardiometabolic risk factors in obese women with polycystic ovarian syndrome: a randomized controlled trial. *Endocrine Connections, 4*(3), 144-154.	No minimal intervention comparison group. Compared low-fructose to high-fructose diets.
Jugran, S. (2020, February 28-2021, May 30). To see the effect of Shatpushpa taila Nasya and Shatpushpa Taila Matrabasti with Tilamooladi churan in the management of Pushpaghni to Polycystic Ovarian Syndrome. ID CTRI/2020/03/024114. http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=41663	Wrong study design
Kaddam, L. (2020, January 25-).Effects of Gum Arabic Ingestion on Hormonal and Metabolic Changes in Patients With Polycystic Ovary Syndrome (GA&PCO). Identifier NCT04215380. https://clinicaltrials.gov/ct2/show/NCT04215380	Wrong intervention
Kamal, D., Salamt, N., Yusuf, A., Kashim, M., & Mokhtar, M. H. (2021). Potential Health Benefits of Curcumin on Female Reproductive Disorders: A Review. *Nutrients*, *13*(9), 3126. https://doi.org/10.3390/nu13093126	Wrong study design
Kamath, M.S. (2021, August 30-). Feasibility of diet and exercise as a treatment option for women with Polycystic ovarian syndrome who desire fertility: a preliminary study. Identifier CTRI/2021/12/038831. http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=61425	Wrong study design
Kazemi, M., McBreairty, L. E., Chizen, D. R., Pierson, R. A., Chilibeck, P. D., & Zello, G. A. (2018). A Comparison of a Pulse-Based Diet and the Therapeutic Lifestyle Changes Diet in Combination with Exercise and Health Counselling on the Cardio-Metabolic Risk Profile in Women with Polycystic Ovary Syndrome: A Randomized Controlled Trial. *Nutrients*, *10*(10), 1387. https://doi.org/10.3390/nu10101387	Wrong comparator
Khokta, S., & Bhardwaj, A. (2020, August 27-2021, February 16). Efficacy of Virechana and Shamana Yoga in Polycystic Ovarian Syndrome. Idenitifier CTRI/2020/08/027424. http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=45766	Wrong study design
Kumari, S., & Saini, R. (2021, September 12-). Clinical trial on polycystic ovarian syndrome. Identifier CTRI/2021/12/038533. http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=58629.	Wrong study design
Kiel, I.A., Jones, H., Lionett, S., Røsbjørgen, R., Lydersen, S., Vanky, E., & Moholdt, T. (2022). Cardiovascular Health Does Not Change Following High-Intensity Interval Training in Women with Polycystic Ovary Syndrome. *Journal of Clinical Medicine, 11*(6), 1626. https://doi.org/10.3390/jcm11061626	Wrong study design
Kim, C., Pi-Sunyer, X., Barrett-Connor, E., Stentz, F.B., Murphy, M.B., Kong, S., Nan, B., & Kitabchi, A.E. (2013). Sex hormone binding globulin and sex steroids among premenopausal women in the diabetes prevention program. *Journal of Clinical Endocrinology and Metabolism, 98* (7), 3049-3057.	Participants did not have PCOS.
Konopka, A.R., Asante, A., Lanza, I.R., Robinson, M.M., Johnson, M.L., Dalla Man, C., Cobelli, C., Amols, M.H., Irving, B.A., & Nair, K.S. (2015). Defects in mitochondrial efficiency and H2O2 emissions in obese women are restored to a lean phenotype with aerobic exercise training. *Diabetes, 64* (6), 2104-2105.	Control arm is not minimal treatment; all participants had a standardized, weight-maintaining diet provided for 3 days (50% carbohydrate, 30% fat, and 20% protein) prior to and during the study days.
Legro, R.S., Dodson, W.C., Kris-Etherton, P.M., Kunselman, A.R., Stetter, C.M., Williams, N.I., Gnatuk, C.L., Estes, S.J., Fleming, J., Allison, K.C., Sarwer, D.B., Coutifaris, C., & Dokras, A. (2015). Randomized controlled trial of preconception interventions in infertile women with polycystic ovary syndrome. *Journal of Clinical Endocrinology and Metabolism, 100* (11), 4048-4058.	No minimal intervention comparison group; compares oral contraceptive to lifestyle modification, to both

Legro, R. S., Hansen, K. R., Diamond, M. P., Steiner, A. Z., Coutifaris, C., Cedars, M. I., Hoeger, K. M., Usadi, R., Johnstone, E. B., Haisenleder, D. J., Wild, R. A., Barnhart, K. T., Mersereau, J., Trussell, J. C., Krawetz, S. A., Kris-Etherton, P. M., Sarwer, D. B., Santoro, N., Eisenberg, E., Huang, H., Zhang, H., & Reproductive Medicine Network (2022). Effects of preconception lifestyle intervention in infertile women with obesity: The FIT-PLESE randomized controlled trial. PLoS medicine, 19(1), e1003883. https://doi.org/10.1371/journal.pmed.1003883	Wrong study design
Li, C., Xing, C., Zhang, J., Zhao, H., Shi, W., & He, B. (2021). Eight-hour time-restricted feeding improves endocrine and metabolic profiles in women with anovulatory polycystic ovary syndrome. *Journal of translational medicine*, *19*(1), 148. https://doi.org/10.1186/s12967-021-02817-2	Wrong intervention
Li, G. (2016, October-2019, September 30). Lifestyle Intervention in Pregnant Women With PCOS. Identifier NCT04216485. https://www.clinicaltrials.gov/ct2/show/NCT04216485	Wrong study design
Li, J., Bai, W. P., Jiang, B., Bai, L. R., Gu, B., Yan, S. X., Li, F. Y., & Huang, B. (2021). Ketogenic diet in women with polycystic ovary syndrome and liver dysfunction who are obese: A randomized, open-label, parallel-group, controlled pilot trial. *The journal of obstetrics and gynaecology research*, *47*(3), 1145–1152. https://doi.org/10.1111/jog.14650	Wrong comparator
Lin, X. (2020, August 3-). A Randomized Controlled Trial of Lifestyle Intervention to Improve Endocrine and Metabolic Disorders in Adolescent PCOS. Identifier ChiCTR2000036436. http://www.chictr.org.cn/showproj.aspx?proj=58144	Wrong study design
Mani, H., Chudasama, Y., Hadjiconstantinou, M., Bodicoat, D. H., Edwardson, C., Levy, M. J., Gray, L. J., Barnett, J., Daly, H., Howlett, T. A., Khunti, K., & Davies, M. J. (2018). Structured education programme for women with polycystic ovary syndrome: a randomised controlled trial. *Endocrine Connections, 7*(1), 26–35. https://doi.org/10.1530/EC-17-0274	PCOS diagnostic criteria did not comply with the PICOS definition. Wrong study population.
Manteghi, G., Shahraki, Z., Moghadam, M.N., Ghanbarpour, M. H. (2021). Pregnancy outcome in PCOS patients: The effects of letrozol combined with exercise. *J. Klin. Endokrinol. Stoffw.,14* (3), 128–132. https://doi.org/10.1007/s41969-021-00142-z. https://doi.org/10.1007/s41969-021-00142-z	Wrong intervention
Marzouk, T.M., & Sayed Ahmed, W.A. (2015). Effect of dietary weight loss on menstrual regularity in obese young adult women with polycystic ovary syndrome. *Journal of Pediatric and Adolescent Gynecology, 28* (6), 457-461.	No minimal intervention comparison group; control group instructed to follow the same healthy food diet as the first group without restriction in calories
Mehrabani, H.H., Salehpour, S., Amiri, Z., Farahani, S.J., Meyer, B.J., & Tahbaz, F. (2012). Beneficial effects of a high-protein, low-glycemic- load hypocaloric diet in overweight and obese women with polycystic ovary syndrome: a randomized controlled intervention study. *Journal of the American College of Nutrition, 31* (2), 117-125.	Control arm is not minimal treatment; participants were assigned to either a weight loss diet (carbohydrates 55%, protein 15%, fat 30%) or a modified diet low glycaemic load (carbohydrates 40%, protein 30%, fat 30%).
Michalsen, A. (2021, June 28-). Efficacy of Fasting on Hormone Dosage in Fertility Treatment (KiWuA). Identifier NCT04942457. https://clinicaltrials.gov/ct2/show/NCT04942457	Wrong study design
Mirfeizi, M. (2013). Comparison of effects of diet and exercise program to improve clinical symptoms and laboratory tests in obese women with polycystic ovary syndrome (PCOS). *Medical Journal of Mashhad University of Medical Sciences, 56*(2), 77-84.	PCOS diagnostic criteria did not comply with the PICOS definition. Wrong study population.
Mohamed, M.S. (2021, March 1-2022, February 28). Effect Of Treadmill Based Aerobic Exercise Intervention On Menstruation And Quality Of Life In Women With Polycystic Ovarian Syndrome. Identifier NCT04744948. https://clinicaltrials.gov/ct2/show/NCT04744948.	Wrong study design
Moran, L.J., Noakes, M., Clifton, P., Buckley, J., Brinkworth, G., Thomson, R., Norman, R.J. (2019). Predictors of Lifestyle Intervention Attrition or Weight Loss Success in Women with Polycystic Ovary Syndrome Who Are Overweight or Obese. Nutrients, 11(3), 492. https://doi.org/10.3390/nu11030492	Wrong study design
Moran, L.J., Noakes, M., Clifton, P.M., & Norman, R.J. (2010). The effect of modifying dietary protein and carbohydrate in weight loss on arterial compliance and postprandial lipidemia in overweight women with polycystic ovary syndrome. *Fertility and Sterility, 94* (6), 2451-2454.	Control arm is not minimal treatment; participants were assigned to either low-protein or high-protein diets.

Moran, L.J., Noakes, M., Clifton, P.M., Wittert, G.A., Williams, G., & Norman, R.J. (2006). Short-term meal replacements followed by dietary macronutrient restriction enhance weight loss in polycystic ovary syndrome. *American Journal of Clinical Nutrition, 84* (1), 77-87.	No minimal intervention comparison group; comparison of 2 different dietary interventions.
Najafi, M.N., Kasaian, J., Kovatsi, L., Leon, G., Solout, E.K., Hashemzaei, M., Rezaee, R., Modiramani, P., & Ghazanfarpour, M. (2018). Phytoestrogens and the polycystic ovary syndrome: A systematic review of clinical evidence and laboratory findings. *Farmacia, 66* (2), 223-229.	Wrong study design
Nidhi, R., Padmalatha, V., Nagarathna, R., & Amritanshu, R. (2012). Effect of holistic yoga program on anxiety symptoms in adolescent girls with polycystic ovarian syndrome: a randomized control trial. *International Journal of Yoga, 5* (2), 112-117.	Control arm is not minimal treatment; the yoga group practiced a holistic yoga module while the control group practiced a matching set of physical exercises.
Nybacka, A., Carlstrom, K., Fabri, F., Hellstrom, P.M., & Hirschberg, A.L. (2013). Serum antimullerian hormone in response to dietary management and/or physical exercise in overweight/obese women with polycystic ovary syndrome: secondary analysis of a randomized controlled trial. *Fertility and Sterility, 100* (4), 1096-1102. Nybacka, A., Carlstrom, K., Stahle, A., Nyren, S., Hellstrom, P.M., & Hirschberg, A.L. (2011). Randomized comparison of the influence of dietary management and/or physical exercise on ovarian function and metabolic parameters in overweight women with polycystic ovary syndrome. *Fertility & Sterility, 96* (6), 1508-1513.T	Control arm is not minimal treatment; women were randomized to either dietary management, exercise or both.
Obermayer-Pietsch,B. (2020, November 3-). Probiotic Intervention in PCOS (ProPCO-RCT). Identifier NCT04593459. https://www.clinicaltrials.gov/ct2/show/NCT04593459	Wrong intervention
Orio, F., Giallauria, F., Palomba, S., Manguso, F., Orio, M., Tafuri, D., Lombardi, G., Carmina, E., Colao, A., & Vigorito, C. (2008). Metabolic and cardiopulmonary effects of detraining after a structured exercise training programme in young PCOS women. *Clinical Endocrinology, 68* (6), 976-981.	No minimal intervention comparison group; exercise training compared to exercise training and detraining.
Orio, F., Muscogiuri, G., Giallauria, F., Savastano, S., Bottiglieri, P., Tafuri, D., Predotti, P., Colarieti, G., Colao, A., & Palomba, S. (2016). Oral contraceptives versus physical exercise on cardiovascular and metabolic risk factors in women with polycystic ovary syndrome: a randomized controlled trial. *Clinical endocrinology, 85*(5), 764–771. https://doi.org/10.1111/cen.13112	No minimal intervention comparison group; poly-vitamin and caloric restriction in all groups.
Ornstein, R.M., Copperman, N.M., & Jacobson, M.S. (2011). Effect of weight loss on menstrual function in adolescents with polycystic ovary syndrome. *Journal of Pediatric & Adolescent Gynecology, 24* (3), 161-165.	Control arm is not minimal treatment; women were randomized to either: 1) low carbohydrate diet or 2) hypocaloric National Cholesterol Education Program II diet.
Padhi, S.R., & Pandey, M. (2022, March 1-). An Ayurvedic Approach With Life Style Modification In The Management Of Polycystic Ovarian Syndrome. Identifier CTRI/2022/01/039096.http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=63576	Wrong study design
Palomba, S., Giallauria, F., Falbo, A., Russo, T., Oppedisano, R., Tolino, A., Colao, A., Vigorito, C., Zullo, F., & Orio, F. (2008). Structured exercise training programme versus hypocaloric hyperproteic diet in obese polycystic ovary syndrome patients with anovulatory infertility: a 24-week pilot study. *Human reproduction, 23*(3), 642–650. https://doi.org/10.1093/humrep/dem391	No minimal intervention comparison group; exercise versus diet. Not a randomized controlled trial; treatment allocated by participant choice.
Palomba, S., Falbo, A., Giallauria, F., Russo, T., Rocca, M., Tolino, A., Zullo, F., & Orio, F. (2010). Six weeks of structured exercise training and hypocaloric diet increases the probability of ovulation after clomiphene citrate in overweight and obese patients with polycystic ovary syndrome: a randomized controlled trial. *Human reproduction, 25*(11), 2783–2791. https://doi.org/10.1093/humrep/deq254	Control arm is not minimal treatment; the 3 interventions were: SET plus hypocaloric diet for 6 weeks (group A); 2 weeks of observation followed by one cycle of clomiphene citrate (CC) therapy (group B); and SET plus hypocaloric diet for 6 weeks, with one cycle of

	CC after the first 2 weeks (group C)
Panico, A., Lupoli, G.A., Gelsy, A., Cioffi, I., Zacchia, G., Caldara, A., Lupoli, G., Contaldo, F., & Pasanisi, F. (2014). Effects of an isocaloric low-glycemic-load diet in polycystic ovary syndrome. *Nutritional Therapy & Metabolism, 32* (2), 85-92.	Control arm is not minimal treatment; cross-over protocol, with diet A (low glycaemic load) and di- et B (moderately high glycaemic load).
Papakonstantinou, E., Kechribari, I., Mitrou, P., Trakakis, E., Vassiliadi, D., Georgousopoulou, E., Zampelas, A., Kontogianni, M. D., & Dimitriadis, G. (2016). Effect of meal frequency on glucose and insulin levels in women with polycystic ovary syndrome: a randomised trial. *European Journal of Clinical Nutrition, 70*(5), 588–594. https://doi.org/10.1038/ejcn.2015.225	No minimal intervention comparison group; both groups on structured weight maintenance diet either on 3- or 6-meal pattern.
Pasquali, R., Fabbri, R., Venturoli, S., Paradisi, R., Antenucci, D., & Melchionda, N. (1986). Effect of weight loss and antiandrogenic therapy on sex hormone blood levels and insulin resistance in obese patients with polycystic ovaries. *American Journal of Obstetrics and Gynecology, 154* (1):139-144.	No minimal intervention comparison group; hypocaloric diet compared to hypocaloric diet and anti-androgen therapy.
Pasquali, R., Gambineri, A., Biscotti, D., Vicennati, V., Gagliardi, L., Colitta, D., Fiorini, S., Cognigni, G. E., Filicori, M., & Morselli-Labate, A. M. (2000). Effect of long-term treatment with metformin added to hypocaloric diet on body composition, fat distribution, and androgen and insulin levels in abdominally obese women with and without the polycystic ovary syndrome. The Journal of clinical endocrinology and metabolism, 85(8), 2767–2774. https://doi.org/10.1210/jcem.85.8.6738.	No minimal intervention comparison group; dietary treatment and placebo compared to dietary treatment and metformin.
Patel, V., Menezes, H., Menezes, C., Bouwer, S., Bostick-Smith, C. A., & Speelman, D. L. (2020). Regular Mindful Yoga Practice as a Method to Improve Androgen Levels in Women With Polycystic Ovary Syndrome: A Randomized, Controlled Trial. *The Journal of the American Osteopathic Association*, 10.7556/jaoa.2020.050. Advance online publication. https://doi.org/10.7556/jaoa.2020.050	Wrong intervention
Pekhlivanov, B., Mitkov, M., & Kavurdzhikova, S. (2006). Clinical, hormonal and biochemical changes after treatment with metformin and weight reduction in women with polycystic ovary syndrome. *Akusherstvo i Ginekologiia, 45* (6), 29-35.	No minimal intervention comparison group; metformin compared to diet.
Peking University Third Hospital. (2022, June 24). Effect of Dietary Fiber Intervention on Patients With Polycystic Ovary Syndrome. Identifier NCT05431816. https://clinicaltrials.gov/ct2/show/NCT05431816	Wrong study design
Raja-Khan, N., Agito, K., Shah, J., Stetter, C. M., Gustafson, T. S., Socolow, H., Kunselman, A. R., Reibel, D. K., & Legro, R. S. (2018). Mindfulness-based stress reduction decreases glucose and increases emotional quality of life in women with polycystic ovary syndrome. *Endrocrine Reviews, 39* (2 Supplement 1), 1349-1359.	Wrong intervention
Rao, M. (2021, June 28-). Effects of High-Intensity Interval Training and Strength Training On Levels of Testosterone and Physical Activity Among Women With Polycystic Ovary Syndrome. Identifier NCT04942366. https://clinicaltrials.gov/ct2/show/NCT04942366	Wrong study design
Roessler, K. K., Birkebaek, C., Ravn, P., Andersen, M. S., & Glintborg, D. (2013). Effects of exercise and group counselling on body composition and VO2max in overweight women with polycystic ovary syndrome. *Acta obstetricia et gynecologica Scandinavica, 92*(3), 272–277. https://doi.org/10.1111/aogs.12064.	Control arm is not minimal treatment; cross-over protocol comparing: a) high-intensity aerobic exercise with b) group counselling.
Sá, J. C., Costa, E. C., da Silva, E., Tamburús, N. Y., Porta, A., Medeiros, L. F., Lemos, T. M., Soares, E. M., & Azevedo, G. D. (2016). Aerobic exercise improves cardiac autonomic modulation in women with polycystic ovary syndrome. *International Journal of Cardiology 202*, 356–361. https://doi.org/10.1016/j.ijcard.2015.09.031	Did not report any relevant outcomes.
Sabag, A. (2022, July 4-). High-Intensity Functional Training for Polycystic Ovary Syndrome. Identifier ACTRN12622000639729. https://anzctr.org.au/ACTRN12622000639729.aspx	Wrong study design
Sahu, S. (2020, August 19-). A clinical trial on Ayurvedic therapies in Infertility. Identifier CTRI/2020/08/027240. https://trialsearch.who.int/Trial2.aspx?TrialID=CTRI/2020/08/027240	Wrong study design

Samarasinghe, S., & Miras, A. (2020, February 11-). BAMBINI: Bariatric surgery vs. Medical care for obesity and polycystic ovarian syndrome related infertility. Identifier ISRCTN16668711. https://doi.org/10.1186/ISRCTN16668711	Wrong intervention
Santos, I.S. (2018, January 19-Completed). Effect of exercise training on clinical markers ,quality of life and mental health in women with polycystic ovary syndrome. Identifier RBR-5db955. http://ensaiosclinicos.gov.br/rg/RBR-5db955	Wrong study design
Saremi, A., Shavandi, N., Karamali, M., & Kazemi, M. (2013). Serum level of anti-mullerian hormone after exercise training in women with polycystic ovary syndrome: a randomized controlled trial. *The Iranian Journal of Obstetrics, Gynecology and Infertility*, *16*(64), 10-18.	PCOS diagnostic criteria did not comply with the PICOS definition. Wrong study population.
Sargazi, F. (2020, May 21-). Investigate the effect of Marrubium Vulgare dry powder of extract on Hormonal parameters and clinical finding in polycystic ovarian syndrome. Identifier IRCT20200404046942N1. https://en.irct.ir/trial/46919	Wrong intervention
Saslow, L. (2022, August 15-). The Supporting Understanding of PCOS Education and Research (SUPER) Study (SUPER). Identifier NCT05452642. https://clinicaltrials.gov/ct2/show/NCT05452642	Wrong study design
Shanghai General Hospital. (2020, October 1-). Preventive effect of L-arginine supplementation on preeclampsia in middle and low-risk population: a randomized, double-blind, controlled clinical study. Identifier ChiCTR2000036626. http://www.chictr.org.cn/showproj.aspx?proj=59662	Wrong intervention
Shang, Y., Zhou, H., Hu, M., & Feng, H. (2020). Effect of Diet on Insulin Resistance in Polycystic Ovary Syndrome. *The Journal of clinical endocrinology and metabolism*, *105*(10), dgaa425. https://doi.org/10.1210/clinem/dgaa425	Wrong study design
Shehata, M.M.A. (2022, January 31-). Effect of Whole Body Vibration on Insulin Resistance in Females With Polycystic Ovarian Syndrome (WBV). Identifier NCT05215223. https://clinicaltrials.gov/ct2/show/NCT05215223 https://clinicaltrials.gov/ct2/show/NCT05215223	Wrong study design
Singh, A. (2020, November 27). Impact of online lifestyle therapy on PCOS related symptoms in adolescent girls. Identifier CTRI/2021/11/037844. http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=60007	Wrong study design
Singh, R. (Not started). Evaluate the dietetic modification and therapy in cases of polycystic ovary disease.Identifier CTRI/2021/12/038603. http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=63143	Wrong study design
Sordia-Hernández, L. H., Ancer Rodríguez, P., Saldivar Rodriguez, D., Trejo Guzman, S., Servín Zenteno, E. S., Guerrero González, G., & Ibarra Patiño, R. (2016). Effect of a low glycemic diet in patients with polycystic ovary syndrome and anovulation - a randomized controlled trial. *Clinical and Experimental Obstetrics & Gynecology, 43*(4), 555–559.	No minimal intervention comparison group; both intervention and control groups on calorie-restricted diets.
Sørensen, L.B., Søe, M., Halkier, K.H., Stigsby, B., & Astrup, A. (2012). Effects of increased dietary protein-to-carbohydrate ratios in women with polycystic ovary syndrome. *American Journal of Clinical Nutrition, 95* (1):39-48.	Control arm is not minimal treatment; a high-protein and a standard-protein diet were compared.
Sprung, V. S., Cuthbertson, D. J., Pugh, C. J., Aziz, N., Kemp, G. J., Daousi, C., Green, D. J., Cable, N. T., & Jones, H. (2013). Exercise training in polycystic ovarian syndrome enhances flow-mediated dilation in the absence of changes in fatness. *Medicine and Science in Sports and Exercise*, *45* (12), 2234–2242. https://doi.org/10.1249/MSS.0b013e31829ba9a1	Not a randomized controlled trial.
Simha, A., & Agarwal, S. (2019). Nutrition Education Intervention for the Management of Polycystic Ovary Syndrome (PCOS). *Medico-Legal Update, 19* (2), 21-27.https://doi.org/10.37506/mlu.v19i2.735	Wrong study design
Smith, C. A., Bensoussan, A., Arentz, S., & Abbott, J. (2019). Herbal medicine plus lifestyle for overweight women with Polycystic Ovary Syndrome: A randomised controlled trial. *Phytotherapy research*, *31*(1), 38. https://doi.org/10.1002/ptr.5858	Wrong intervention
Stepto, N. (2019, May 24-). Understanding the role of tissue Fibrosis in Insulin Resistance associated with Polycystic Ovary Syndrome (PCOS) and the impact of Exercise: The FIREx study using a cohort and randomized control trial in women with and without PCOS. Identifier U1111-1228-1587. https://anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12619000264189	Wrong study design
Talaat, B., & Ammar, I. M. M. (2018). The added value of cinnamon to metformin in controlling symptoms of polycystic ovary syndrome, a randomized controlled trial. Middle Eat Fertility Society Journal, 23 (4), 440-445. https://doi.org/10.1016/j.mefs.2018.03.005.	Wrong intervention
Talluto, C. (2002). The effects of a six-week aerobic and weight-resistance training program on infertility patients diagnosed with polycystic ovary syndrome. *Fertility and Sterility, 78* (3), 152.	Abstract only; attempted to contact the author but could not obtain full text and determine eligibility

Tamtaji, O. R., Milajerdi, A., Reiner, Ž., Dadgostar, E., Amirani, E., Asemi, Z., Mirsafaei, L., Mansournia, M. A., Dana, P. M., Sadoughi, F., & Hallajzadeh, J. (2020). Effects of flaxseed oil supplementation on biomarkers of inflammation and oxidative stress in patients with metabolic syndrome and related disorders: a systematic review and meta-analysis of randomized controlled trials. *Clinical Nutrition ESPEN*, *40*, 27–33. https://doi.org/10.1016/j.clnesp.2020.09.017	Wrong patient population
Tang, T., Glanville, J., Hayden, C.J., White, D., Barth, J.H., & Balen, A.H. (2006). Combined lifestyle modification and metformin in obese patients with polycystic ovary syndrome: a randomized, placebo-controlled, double-blind multicentre study. *Human Reproduction, 21* (1):80-89.	No minimal intervention comparison group; dietary treatment and placebo compared to dietary treatment and metformin.
Taylor, F. C., Dunstan, D. W., Fletcher, E., Townsend, M. K., Larsen, R. N., Rickards, K., Maniar, N., Buman, M., Dempsey, P. C., Joham, A. E., Cohen, N., Owen, N., Moran, L. J., & Green, D. J. (2021). Interrupting Prolonged Sitting and Endothelial Function in Polycystic Ovary Syndrome. *Medicine and science in sports and exercise*, *53*(3), 479–486. https://doi.org/10.1249/MSS.0000000000002513	Wrong intervention
The First Affiliated Hospital of Xiamen University. (2019, January 7-). Time-Restricted Feeding(TRF) on Overweight/Obese Women With Polycystic Ovarian Syndrome (PCOS). Identifier NCT03792282. https://clinicaltrials.gov/ct2/show/NCT03792282	Wrong study design
Thomson, R.L, Buckley, J.D., Noakes, M., Clifton, P.M., Norman, R.J., & Brinkworth, G.D. (2008). The effect of a hypocaloric diet with and without exercise training on body composition, cardiometabolic risk profile, and reproductive function in overweight and obese women with polycystic ovary syndrome. *Journal of Clinical Endocrinology and Metabolism,* (9):3373-3380.	No minimal intervention comparison group; diet compared to diet and aerobic exercise compared to diet and combined aerobic-resistance exercise.
Thomson, R.L., Buckley, J.D., & Brinkworth, G.D. (2016).Perceived exercise barriers are reduced and benefits are improved with lifestyle modification in overweight and obese women with polycystic ovary syndrome: a randomised controlled trial. *BMC Women's Health, 16,* 14.	Control arm is not minimal treatment; comparison was made between: 1) diet only, 2) diet and aerobic exercise and 3) diet + combined aerobic/resistance exercise.
Toscani, M.K., Mario, F.M., Radavelli-Bagatini, S., & Wiltgen, D., Matos, M.C., & Spritzer, P.M. (2011). Effect of high-protein or normal-protein diet on weight loss, body composition, hormone, and metabolic profile in southern Brazilian women with polycystic ovary syndrome: a randomized study. *Gynecological Endocrinology, 27* (11), 925-930.	Control arm is not minimal treatment; control group diet content was specified: "Normal Protein" group (15% protein, 55% carbohydrate, and 30% lipid).
Tucker, S., Gower, B., Piccinini, F., & Goss, A. (2020). Testosterone reduction is differently related to insulin sensitivity in low vs. high FAI in PCOS. *Obesity,* 28 (Supplement 2), 164. https://doi.org/10.1002/oby.23063	Wrong study design
Turner-McGrievy, G.M., Davidson, C.R., Wingard, E.E., & Billings, D.L. (2014). Low glycemic index vegan or low-calorie weight loss diets for women with polycystic ovary syndrome: a randomized controlled feasibility study. *Nutrition Research, 34* (6),552-558.	Control arm is not minimal treatment; women were randomized to vegan or low-calorie diet.
Universitair Ziekenhuis Brussel. (2021, September 10-). Optimising Preconceptual Health in Subfertile PCOS Patients Using a Lifestyle Modification Program. Identifier NCT05084274. https://clinicaltrials.gov/ct2/show/NCT05084274	Wrong study design
Veena Kirthika, S., Paul, J., Senthil Selvam, P., & Sathya Priya, V. (2019). Effect of progressive resisted exercises and aerobic exercises in the management of polycystic ovarian syndrome among young women-A pilot randomized controlled trial. *Indian Association of Biomedical Scientists, 39* (4), 608-612.	Wrong comparator
Vizza, L., Smith, C. A., Swaraj, S., Agho, K., & Cheema, B. S. (2016). The feasibility of progressive resistance training in women with polycystic ovary syndrome: a pilot randomized controlled trial. BMC sports science, medicine and rehabilitation, 8(1), 1-12.	PCOS diagnostic criteria did not comply with the PICOS definition. Wrong study population.
Wong, J. M., Gallagher, M., Gooding, H., Feldman, H. A., Gordon, C. M., Ludwig, D. S., & Ebbeling, C. B. (2016). A randomized pilot study of dietary treatments for polycystic ovary syndrome in adolescents. *Pediatric Obesity, 11*(3), 210–220. https://doi.org/10.1111/ijpo.12047	No minimal intervention comparison group; comparing low-fat or low glycemic load diet.

Wu, L., Zhang, H., Fan, M., & Yan, Y. (2022). Efficacy and Safety of Cangfu Daotan Decoction in Patients with Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis. Evidence-Based Complementary and Alternative Medicine, Evid Based Complement Alternat Med, 4395612. doi: 10.1155/2022/4395612.	Wrong intervention
Yazd University of Medical Sciences. (2021, September 23-). The effect of low calorie diets on anthropometric, glycemic, cardiovascular and hormonal factors in people with polycystic ovary syndrome. Identifier IRCT20170221032698N2. http://en.irct.ir/trial/58762	Wrong study design
Zarrinkoub, F., & Beigi, A. (2005). Insulin-sensitization versus lifestyle modification in the management of adolescent girls with polycystic ovary syndrome. *The 21st Annual Meeting of the European Society of Human Reproduction and Embryology*.	Abstract only; attempted to contact the author but could not obtain full text and determine eligibility
Zhang, J. (2020, July 26-Completed). Behavior therapy through mobile phone in improving reproductive function for polycystic ovary syndrome: a randomized controlled trial. Identifier ChiCTR2000034263. http://www.chictr.org.cn/showproj.aspx?proj=55840	Wrong study design
Zhang, M. (2022, May 23-). Treating PCOS with Digital CBT vs Metformin. Identifier NCT05386706. https://clinicaltrials.gov/ct2/show/NCT05386706.	Wrong study design
Zhang, X., Zheng, Y., Guo, Y., & Lai, Z. (2019). The Effect of Low Carbohydrate Diet on Polycystic Ovary Syndrome: A Meta-Analysis of Randomized Controlled Trials. *International Journal of Endocrinology*, https://doi.org/10.1155/2019/4386401	Wrong study design
Zilaee, M., Mansoori, A., Ahmad, H. S., Mohaghegh, S. M., Asadi, M., & Hormoznejad, R. (2020). The effects of soy isoflavones on total testosterone and follicle-stimulating hormone levels in women with polycystic ovary syndrome: a systematic review and meta-analysis. *The European Journal of Contraception & Reproductive Health Care: the Official Journal of the European Society of Contraception*, *25*(4), 305–310. https://doi.org/10.1080/13625187.2020.1761956	Wrong intervention

5. STUDY CHARACTERISTICS FOR INCLUDED STUDIES

Author, year, country	Population/ Setting	Study Design	Sample Size per group	Intervention/ exposure details	Comparison/ control details	Follow up Duration	Outcomes	Summary of findings	Other [add as needed]
Almenning et al. 2015 Norway	Women with PCOS; Medical Center	Parallel RCT	Intervention (high intensity interval training = 10 and strength training =11) Control = 10	3 weekly exercise sessions for 10 weeks with normal diet (high intensity interval training did high interval training, strength training did strength training)	Maintain normal diet and physical activity	10 weeks	testosterone, SHBG, FAI, total cholesterol, HDL-C, LDL-C, triglycerides, glucose, insulin, weight, BMI, waist circumference	High-intensity interval training for ten weeks improved insulin resistance, without weight loss, in women with polycystic ovary syndrome. Body composition improved significantly after both strength training and high-intensity interval training. This pilot study indicates that exercise training can improve the cardiometabolic profile in polycystic ovary syndrome without weight loss.	Not Applicable
Brown et al. 2009 USA	Women with PCOS aged 18 to 50; Medical Center	Parallel RCT	Intervention = 21 Control = 16	8-12 week ramp up followed by 12-week moderate intensity exercise	no change in lifestyle	12 weeks for control, 20-24 weeks for intervention	Bioavailable testosterone, Ferriman-Gallwey score, OGTT glucose, lipid profile, fasting glucose and insulin, OGTT insulin, weight, BMI, waist/hip ratio	Moderate-intensity exercise without significant weight loss improved several components of the lipoprotein profiles of women with PCOS.	Not Applicable
Costa et al. 2018, Brazil	Women with PCOS; Medical Center	Parallel RCT	Intervention =14 Control=13	16-weeklong supervised aerobic training three times per week	No exercise intervention	16 weeks	Health-related quality of life, cardiorespiratory fitness, cardiometabolic profile, and affective response	The exercise intervention was more effective in improving cardiometabolic profiles, anthropometry (body mass, waist circumference), cardiorespiratory fitness, and affective response versus the control.	Not Applicable
Dietz de Loos et al. 2022, Netherlands	Women with PCOS and BMI >25 kg/m^2; Outpatient clinic	Parallel RCT	Intervention (three-component lifestyle intervention with or without short message service [SMS]- = 27 SMS+) = 16	Lifestyle intervention (cognitive behavioral therapy, diet, exercise) with and without short message service	Care as usual (CAU)	1 year	Metabolic Syndrome prevalence, metabolic parameters, weight changes	Lifestyle intervention improved metabolic parameters and decreased weight and MetS prevalence vs control.	Not Applicable

Author, year, country	Population/ Setting	Study Design	Sample Size per group	Intervention/ exposure details	Comparison/ control details	Follow up Duration	Outcomes	Summary of findings	Other [add as needed]
			Control = 24						
Guzick et al. 1994 USA	Women with PCOS aged 20 to 40 years and Obese; Medical Center	Parallel RCT	Intervention = 6 Control = 6	12-week behavioral weight control program	No treatment	12 weeks	Total testosterone, SHBG, non-SHBG testosterone, height, weight, body fat distribution, fasting glucose, insulin	Weight loss in obese, hyperandrogenic, anovulatory women appears to reduce insulin and non-SHBG T concentrations despite the absence of a change in gonadotropin secretion and may lead to the resumption of ovulation.	Not Applicable
Hoeger et al. 2004 USA	Women with PCOS and BMI > 25 kg/m^2; Research Center	Parallel RCT	Intervention = 11 Control = 9	Lifestyle intervention with placebo (individualized meal plan and exercise plan)	No lifestyle intervention	48 weeks	Morning urinary pregnanediol glucuronide, menstrual diaries, testosterone, SHBG, FAI, F-G score, height, weight, BMI, waist/hip circumference, OGTT glucose, lipid profile, OGTT insulin	Key methodologic issues for a large-scale, randomized trial of lifestyle intervention in PCOS include minimizing early dropout from the lifestyle intervention and including a range of body mass index that is not skewed toward severe obesity. Weight reduction might play the most significant role in the restoration of ovulation in obese women with PCOS.	Not Applicable
Hoeger et al. 2008 USA	Women with PCOS ages 12 to 18 and obese; Research Center	Parallel RCT	Intervention: 11 Control = 11	Lifestyle intervention (training classes on diet, exercise, and behavior modification skills)	Standard office advice on nutrition and exercise	24 weeks	Urine pregnanediol, menstrual cycle average per 24 weeks, total and free testosterone, SHBG, FAI, hirsutism, OGTT glucose, lipid profile, OGTT insulin, BMI, waist circumference	Both lifestyle modification and oral contraceptives significantly reduce androgens and increase SHBG in obese adolescents with PCOS. Metformin, in combination with lifestyle modification and oral contraceptives, reduces central adiposity, reduces total testosterone, and increases HDL, but does not enhance overall weight reduction.	Not Applicable
Jedel et al. 2011 (Stener-Victorian 2009-2013) Sweden	Women with PCOS age 18 to 30; Academic Medical Center	Parallel RCT	Intervention = 34 Control = 17	Weight maintenance, moderate exercise	No exercise	16 weeks	Menstrual pattern, total testosterone, SHBG, free testosterone, FAI, F-G score, lipid profile, fasting glucose and insulin, height, weight, BMI, sagittal abdominal	Physical exercise lowered high sympathetic nerve activity, and menstrual frequency decreased the levels of several sex steroids and improved HRQoL in women with PCOS versus no intervention.	Not Applicable

Author, year, country	Population/ Setting	Study Design	Sample Size per group	Intervention/ exposure details	Comparison/ control details	Follow up Duration	Outcomes	Summary of findings	Other [add as needed]
							diameter, WHR, quality of life		
Kiel et al. 2021 Norway and Australia	Women with PCOS; Academic Medical Center	Parallel RCT	Interventions (low-intensity interval training [LV]-; high-intensity interval training [HIT] = 21 HV-HIT = 20) Control = 23	16-week low-volume HIT workout, or 16-week high-volume HIT workout followed by 36-week home-based HIT	Nonexercising	12 months	Menstrual frequency (primary), markers of cardiometabolic and reproductive health, quality of life, adherence to and enjoyment of HIT	A semi-supervised HIT intervention did not increase the menstrual frequency in women with PCOS. No between-group differences in menstrual frequency, but within-group change in each group was observed; HIT has the clinical benefit on both pregnancy rate and QoL in PCOS women	Not Applicable
Kogurea et al. 2020 Brazil	Women with PCOS; Academic Medical Center	Parallel RCT	Interventions (continuous aerobic training = 37 intermittent aerobic training = 35) Control = 38	16 weeks of continuous aerobic training or 16 weeks of intermittent aerobic training	Non-training	Not Applicable	testosterone, FAI, SHBG, height, weight, hip circumference, waist circumference, WHR, actual BMI, BSQ, FSFI, FRS, HADS	Only the continuous aerobic training group had improved the core for a cognitive-affective dimension of body image. However, both the continuous aerobic training and the intermittent aerobic training groups had lower depression, anxiety, and sexual function scores after the intervention.	Not Applicable
Moeller et al., 2018 Denmark	Women with PCOS; Academic Medical Center	Parallel RCT	Intervention (motivational interviews) = 19 Control = 18	Motivational interviews were conducted once every 2 weeks (12 total times)	Standard care (no extra appointments, patients seen initially and at follow up only)	6 months	Weight, hip and waist circumference, WHO-5, MDI, Sf-36, PCOS-Q, BMI	Motivational interviews had no effect on weight loss or QoL versus control.	Not Applicable
Nasrekani et al. 2016 Iran	Women with PCOS; Medical Center	Parallel RCT	Intervention = 10 Control = 10	3 days/week of aerobic training	No intervention	12 weeks	Weight, BMI	The intervention group had reduced weight and increased Vo2max compared to controls.	Not Applicable

Author, year, country	Population/ Setting	Study Design	Sample Size per group	Intervention/ exposure details	Comparison/ control details	Follow up Duration	Outcomes	Summary of findings	Other [add as needed]
Oberg et al., 2018, Sweden	Women with PCOS who were overweight/obese (BMI ≥ 27 kg/m^2)/ Teaching hospital	Parallel RCT	Intervention = 30 Control = 27	Group meetings 3 per month where they were counseled on weight control, personal leadership, mindfulness, physical activity and diet. Meetings incorporated goal setting, stimulus control, problem-solving and stress management techniques to aid in behavioral change. One-on-one coaching sessions 1 per month to discuss individual training regimens and diet changes	General healthy lifestyle rec-commendations given by a midwife and supported by a pamphlet with written advice about diet and exercise	Intervention and control groups occurred in parallel for 4 months; however, after 4 months, the control group undertook the intervention (again for 4 months) and the entire study sample was followed up at 12 months	Weight, BMI, fat mass, lean body mass, testosterone, SHBG, FAI, menstrual function	A significantly higher proportion of patients in the intervention the group improved their menstrual function compared to the control. Logistic regression analysis showed that receiving the 4-month intervention was the only significant predictor of improved menstrual function. The interventions significantly increased endometrial thickness and decreased levels of DHEA compared to the control.	Not Applicable
Ribeiro, 2019 and 2021 and 2021, Brazil (2 publications reporting on the same study)	Women with PCOS; Academic Medical Center	Parallel RCT	Interventions (Continuous aerobic training = 28 Intermittent aerobic training = 29) Control = 30	Both continuous and intermittent aerobic training on 3 days per week for 40-60 minutes with a 5-minute warm-up and 5 minutes cool down between 50%-60% of the maximum heart rate For specific protocols of continuous and intermittent training sessions (which varied	No training	4 months	WC, HC, WHR, fat mass, lean body mass, weight, BMI, testosterone, QoL, SHBG, fasting insulin, fasting glucose, HDL-C, TC, TG, LDL-C, FAI	Both exercises reduced obesity indices, hyperandrogenism, and quality of life in PCOS women without changes in telomere length or inflammatory biomarkers versus controls.	Not Applicable

Author, year, country	Population/ Setting	Study Design	Sample Size per group	Intervention/ exposure details	Comparison/ control details	Follow up Duration	Outcomes	Summary of findings	Other [add as needed]
				each week) see Table 1 of the published manuscript					
Saremi et al., 2013 Iran	Women with PCOS; Medical Center	Parallel RCT	Intervention = 11 Control = 11	Aerobic training 3 days/week for 40-60 min each	Asked not to do more physical activity then they used to	8 weeks	Total testosterone, HDL-C, LDL-C, triglycerides, fasting glucose, fasting insulin, weight, BMI, waist circumference, WHR	No summary report is available.	Not Applicable
Stefanaki et al., 2015 Greece	Women with PCOS aged 15 to 40; Academic Medical Center	Parallel RCT	Intervention = 23 Control = 23	8-week mindfulness stress management program	No intervention	8 weeks	BMI, QoL	Post-intervention, between-group results revealed statistically significant reductions in stress, depressive and anxiety symptoms, as well as in salivary cortisol concentrations, along with an increase in Life Satisfaction and Quality of Life scores in the intervention group only. There was no significant "placebo" effect on the outcome measures. Mindfulness techniques seem promising in ameliorating stress, anxiety, depression, and the quality of life in women with PCOS versus controls.	Not Applicable
Turan et al. 2015 Turkey	Women with PCOS and BMI < 25 kg/m^2; Academic Medical Center	Parallel RCT	Intervention = 16 Control = 16	Structured exercise programs 3 times/week (aerobic and resistance exercise)	General dietary and behavioral advice	8 weeks	Menstrual cycle, total testosterone, free testosterone, total cholesterol, HDL-C, LDL-C, triglycerides, fasting glucose, fasting insulin, BMI, waist circumference	Short-term regular exercise programs can improve the anthropometric, cardiovascular, and metabolic parameters of non-overweight women with PCOS versus controls.	Not Applicable
Vigorito et el. 2007 Italy	Women with PCOS and overweight;	Parallel RCT	Intervention = 45 Control = 45	Structured supervised training sessions 3 times/week	No training program	12 weeks	Menses diary, testosterone, SHBG, FAI, Ferriman-Gallwey	A 3-month structured exercise training program improves cardiopulmonary	Not Applicable

Author, year, country	Population/ Setting	Study Design	Sample Size per group	Intervention/ exposure details	Comparison/ control details	Follow up Duration	Outcomes	Summary of findings	Other [add as needed]
	Academic Medical Center						score, height, weight, BMI, waist circumference, WHR, OGTT glucose, lipid profile, fasting glucose and insulin, OGTT insulin	functional capacity in women with PCOS versus controls.	

Abbreviations: RCT: randomized control trial, CAU: care as usual, SMS+: with short message service, SMS-: without short message service, BMI: body mass index, PCOS: polycystic ovary syndrome, WHR: waist-to-hip ratio, WC: waist circumference, HC: hip circumference, mFG, F-G score: Ferriman-Galleway Score, LV-HIT: low volume-high intensity training, HV-HIT: high volume-high intensity training, HIT: high intensity training, QoL: quality of life, CAT: continuous aerobic training, IAT: intermittent aerobic training, FAI: free androgen index, SHBG: sex hormone binding globulin, BSQ: body shape questionnaire, FSFI: female sexual function index, FRS: Figure Rating Scale, HADS: hospital anxiety and depression scale, MI: motivational interview, WHO-5: world health organization 5 wellbeing index, MDI: major depression inventory, SF-36: short-form-36, PCOSQ: polycystic ovary syndrome questionnaire; 17-OHP, 17-Hydroxyprogesterone; AMH, anti-mullerian hormone; BMI, body mass index; CRP, c-reactive protein; DBP, diastolic blood pressure; DHEA, dehydroepiandrosterone; DHT, dihydrotestosterone; FAI, free androgen index; FSH, follicle stimulating hormone; HC, hip circumference; HOMA, homeostatic model assessment; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; LH, luteinizing hormone; PCOS, polycystic ovary syndrome; QoL, quality of life; RCT, randomised controlled trial; SBP, systolic blood pressure; SHBG, sex hormone-binding globulin; TC, total cholesterol; TG, triglycerides; TSH, thyroid stimulating hormone; WC, waist circumference; WHR, waist-hip-ratio.

6. FINDINGS

COMPARISON 1: LIFESTYLE vs MINIMAL/ NO TREATMENT

- **EVIDENCE SUMMARY:**

We included 18 RCTs (23 publications) with 634 participants. One study assessed fertility as the primary outcome of pregnancy rate. One study reported the secondary reproductive outcome of ovulation rate and two as menstrual regularity.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

Lifestyle treatment improved anthropometric outcomes, including WC (N=12 effect estimates; N=423 women; MD: -1.32; 95%CI [-2.46; -0.18] cm; P=0.0271; I^2=5%); WHR (N=6 effect estimates; N=288; MD: -0.03; 95%CI [-0.05; -0.01]; P=0.0257; I^2=0%), secondary endocrine and reproductive outcomes, including Ferriman-Gallwey score (N=6 effect estimates; N=230 women; MD: -0.97; 95%CI [-1.90; -0.03]; P=0.0448; I^2=0%); fasting insulin (N=14 effect estimates; N=467; MD: -1.87; 95%CI [-3.10; -0.65] pmol/L; P=0.0056; I^2=3%); total cholesterol (N=12 effect estimates; N=427; MD: -0.15; 95%CI [-0.26; -0.03] mmol/L; P=0.0161; I^2=0%) and LDL-C (N=12 effect estimates; N=387 women; MD: -0.15; 95%CI [-0.28; -0.02] mmol/L; P=0.0256; I^2=0) levels vs. minimal treatment. Groups exhibited comparable outcomes in other measures, including body weight, BMI, SHBG, total testosterone, FAI, glucose regulation (fasting and 2-hour postprandial glucose levels), HDL-C, and TG levels (all P≥0.05). Studies had a serious risk of bias across reported outcomes and were mainly of moderate (N=6 outcome: BMI, WC, HDL-C, LDL-C, TG), low (N=7 outcomes: weight, WHR, Ferriman-Gallwey score, SHBG, 2-hour area under the curve for OGTT, insulin, total cholesterol) while N=2 had a very low quality in reporting testosterone and FAI outcomes.

Lifestyle intervention may improve the WC, WHR, Ferriman-Gallwey score, fasting insulin, total cholesterol, and LDL-C levels in women with PCOS vs minimal treatment. We are uncertain of the effect of lifestyle intervention on other measures evaluated. Few studies looked at the impact of lifestyle intervention on pregnancy, ovulation rate, or menstrual cyclicity, and no study evaluated miscarriage to the best of our knowledge. Most studies in this review were of low quality, mainly due to a high risk of bias across most domains or high heterogeneity (>50%) for the testosterone and FAI outcomes.

7. GRADE ASSESSMENTS AND EVIDENCE PROFILE

COMPARISON: Lifestyle treatment v minimal treatment (control)												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Intervention	Control	Effect, random [95% CI]	Favours	Certainty	Importance
Outcome: Weight												
14*	RCT	serious	no serious inconsistency	serious indirectness	serious imprecision	none	324	230	MD: -1.02 9 [-2.08; 0.04]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: BMI												
19	RCT	serious	no serious inconsistency	serious indirectness	no serious imprecision	none	389	288	MD -0.30 [-0.60, 0.01]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: WC												
12	RCT	serious	no serious inconsistency	serious indirectness	no serious imprecision	none	245	178	MD -1.32 [-2.46; -0.18]	Lifestyle treatment	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: WHR												
6	RCT	serious	no serious inconsistency	serious indirectness	serious imprecision	none	167	121	MD: -0.03 [-0.05; -0.01]	Lifestyle treatment	⊕⊕◯◯ LOW	CRITICAL
Outcome: Ferriman-Gallwey score												
6	RCT	serious	no serious inconsistency	serious indirectness	serious imprecision	none	130	100	MD: -0.97 [-1.90; -0.03]	Lifestyle treatment	⊕⊕◯◯ LOW	CRITICAL
Outcome: SHBG												
13	RCT	serious	no serious inconsistency	serious indirectness	serious imprecision	none	302	209	MD 1.94 [-1.32; 5.21]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Testosterone												
14	RCT	serious	serious inconsistency	serious indirectness	serious imprecision	none	316	225	MD -0.06 [-0.21, 0.10]	No difference	⊕◯◯◯ Very LOW	CRITICAL
Outcome: FAI												
13	RCT	serious	serious inconsistency	serious indirectness	no serious imprecision	none	303	209	MD: 0.23 [-1.25; 0.78]	No difference	⊕◯◯◯ Very LOW	CRITICAL
Outcome: Glucose (fasting)												
15	RCT	serious	no serious inconsistency	no serious indirectness	serious imprecision	none	264	216	MD: -0.02 [-0.09, 0.05]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: 120 min AUC-OGTT, area under curve for OGTT												
4	RCT	serious	no serious inconsistency	serious indirectness	serious imprecision	none	73	75	MD -5.05 [-34.95, 24.85]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Insulin (fasting)												

14	RCT	serious	no serious inconsistency	serious indirectness	serious imprecision	none	257	210	MD: -1.87 [-3.10, -0.65]	Lifestyle treatment	⊕⊕◯◯ LOW	CRITICAL
Outcome: Total cholesterol												
12	RCT	serious	no serious inconsistency	serious indirectness	serious imprecision	none	217	170	MD: -1.15 [-0.26, -0.03]	Lifestyle treatment	⊕⊕◯◯ LOW	CRITICAL
Outcome: HDL-C												
12	RCT	serious	no serious inconsistency	serious indirectness	no serious imprecision	none	217	170	MD: 0.0 [-0.07; 0.07]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: LDL-C												
12	RCT	serious	no serious inconsistency	serious indirectness	no serious imprecision	none	217	170	MD: -0.15 [-0.28, -0.02]	Lifestyle treatment	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: TG												
11	RCT	serious	no serious inconsistency	serious indirectness	no serious imprecision	none	217	170	MD: 0.04 [-0.10, 0.19]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Abbreviations: BMI, body mass index, WC, waist circumference, WHR, waist to hip ratio, SHBG, sex hormone binding globulin, FAI, free androgen index; OGGT, oral glucose tolerance test; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride. *The number of outcomes reported correspond with the number of effect estimates (see Figures 2-16)												

8. FINDINGS: DATA EXTRACTION TABLES & FOREST PLOTS– DICHOTOMOUS OUTCOMES

OUTCOME: Pregnancy rate				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): LV-HIT vs HV-HIT vs non exercising group								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Kiel et al. 2021	Count	Self-report	Not Reported	LV-HIT: 5 HV-HIT: 3	Not Reported	0	Crude	Not Applicable
Abbreviations: LV-HIT: low volume-high intensity training, HV-HIT: high volume-high intensity training.								

Meta-analyses outcomes: Meta-analyses were not conducted due to insufficient (n<3) RCTs reporting this outcome.

OUTCOME: Ovulation rate				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Lifestyle versus minimum or no intervention								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Oberg et al., 2018	Count	Blood samples were collected on cycle days 21–23 for analysis of progesterone (electrochemiluminescence immunoassay (ECLIA)) to confirm ovulation	7	34	7	34	Crude	Not Applicable

Meta-analyses outcomes: Meta-analyses were not conducted due to insufficient (n<3) RCTs reporting this outcome.

5.2. DATA EXTRACTION TEMPLATE – CONTINUOUS OUTCOMES

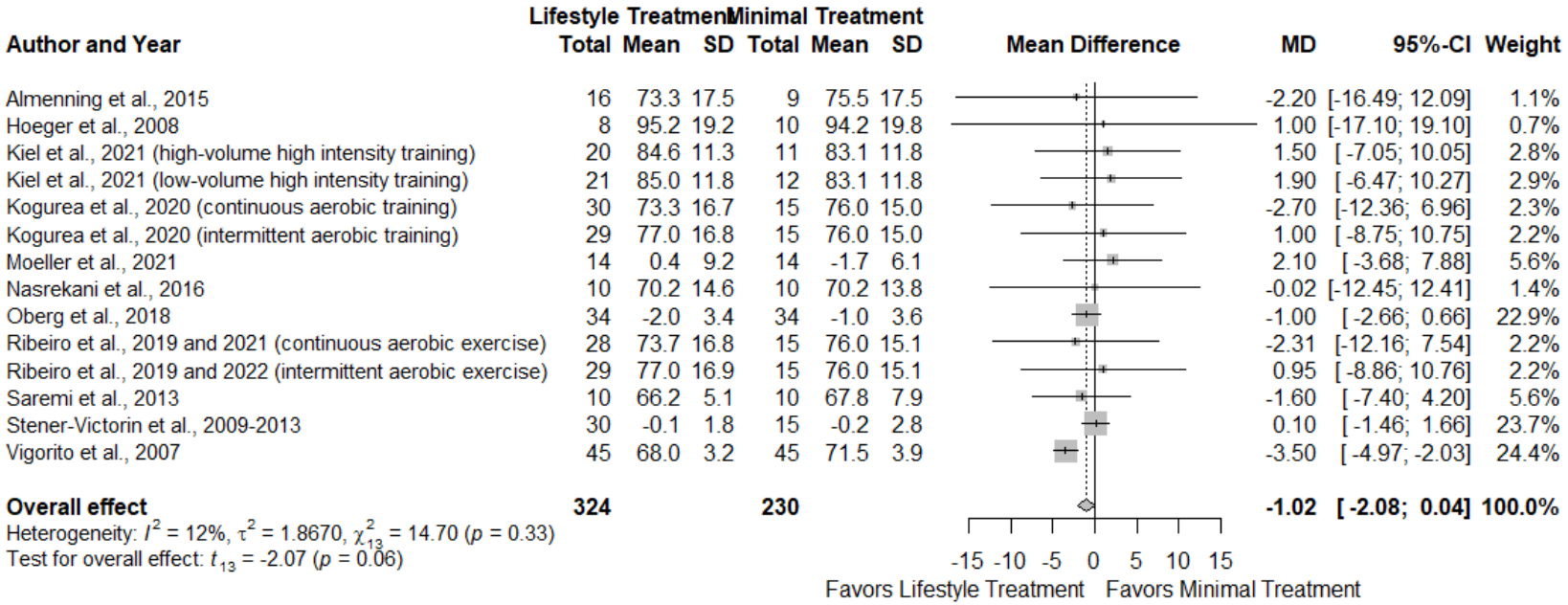
OUTCOME: Menstrual frequency										**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Kiel et al. 2021	Observed/expected	Self-reported (menstruation diary and questionnaire)	LV-HIT: 0.68 HV-HIT: 0.62	95% CI (0.52-0.90) 95 % CI (0.48-0.81)	LV-HIT: 18 HV-HIT: 20	0.67	95% CI (0.53-0.85)	20	Adjusted	Exposure time for participants who became pregnant or withdrew
Oberg et al., 2018	Count	Defined as shifting from amenorrhea to oligomenorrhea or regular cycles or from oligomenorrhea to regular cycles	Baseline: Not reported 4-month post-intervention: 20 out of 34	Not applicable	34	Baseline: Not reported 4-month post-intervention: 8 out of 34	Not applicable	34	Crude (count data)	Not Reported
Abbreviations: LV-HIT: low volume-high intensity training, HV-HIT: high volume-high intensity training.										

Meta-analyses outcomes: Meta-analyses were not conducted due to insufficient (n<3) RCTs reporting this outcome.

OUTCOME: Weight										**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Almenning et al., 2015	kg	Not Reported	Mean difference: 73.3	17.5 (SD)	16	Mean difference: 75.5	17.5 (SD)	9	Crude	Not Applicable
Hoeger et al., 2008	kg	Not Reported	Mean difference: 95.2	19.2 (SD)	8	Mean difference: 94.2	19.8 (SD)	10	Crude	Not Applicable
Kiel et al. 2021	kg	Not Reported	Baseline LV-HIT: 84 Baseline HV-HIT: 85.4 16-wk post-intervention LV-HIT: 85 16-wk post-intervention HV-HIT: 84.6	Baseline LV-HIT: 16.8 (SD) Baseline HV-HIT: 22.6 (SD) 16-wk post-intervention LV-HIT: (79.6-90.3 CI) 16-wk post-intervention HV-HIT: 7.2 (79.3-89.8 CI)	LV-HIT: 21 HV-HIT: 20	Baseline control: 86 16-wk post-intervention control: 83.1	Baseline control: 20.2 (SD) 16-wk post-intervention control: (77.9-88.2 CI)	23	Crude	Not Applicable
Kogurea et al., 2020	kg	Not Reported	Baseline CAT: 74.4 Baseline IAT: 77.3 Post-intervention CAT: 73.3 Post-intervention IAT: 77.0	Baseline CAT: 16.5 (SD) Baseline IAT: 17.0 (SD) Post-intervention CAT: 16.7 (SD)	CAT: 30 IAT: 29	Baseline control: 75.3 Post-intervention control: 76	Baseline control: 14.3 (SD) Post-intervention control: 15 (SD)	30	Crude	Not Applicable

				Post-intervention IAT: 16.8 (SD)						
Moeller et al. 2021	kg	Not Reported	Median difference: 0.4	IQR (-8.9;3.5)	14	Median difference: -1.7	IQR (-6.6;1.6)	14	Crude	Not Applicable
Nasrekani et al., 2016	kg	Not Reported	Mean difference: 70.16	14.56 (SD)	10	Mean difference: 70.18	13.78 (SD)	10	Crude	Not Applicable
Oberg et al., 2018	kg	Digital scale	Change from baseline = −2.0	95% CI = −3.2 to −0.8	34	Change from baseline = −1.0	95% CI = −2.3 to 0.3	34	Crude	Not Applicable
Ribeiro et al., 2019 and 2021	kg	As per standard procedures	Baseline continuous = 74.4 4 months continuous (aerobic exercise) = 73.74 Baseline intermittent (aerobic exercise) = 77.36 4 months intermittent = 77.00	Baseline continuous = 16.5 4 months continuous = 16.78 Baseline intermittent = 16.91 4 months intermittent = 16.81	continuous = 28 intermittent = 29	Baseline = 75.37 4 months = 76.05	Baseline = 14.33 4 months = 15.09	30	Adjusted	Age, BMI, testosterone and androstenedione for the 2021 paper
Saremi et al., 2013	kg	Not Reported	Mean difference: 66.2	5.06 (SD)	11	Mean difference: 67.8	SD: 7.88	10	Crude	Not Applicable
Stener-Victorin et al., 2009-2013	kg	Not Reported	Mean difference: -0.07	1.8 (SD)	15	Mean difference: -0.17	SD: 2.81	15	Crude	Not Applicable
Vigorito et al., 2007	kg	Not Reported	Mean difference: 68	3.2 (SD)	45	Mean difference: 71.5	SD: 3.9	45	Crude	Not Applicable
Abbreviations: LV-HIT: low volume-high intensity training, HV-HIT: high volume-high intensity training, CAT: continuous aerobic training; IAT, intermittent aerobic training.										

Figure 2. Forest plot of comparison: Lifestyle intervention versus minimal treatment: Outcome: Weight (kg). For weight mean changes instead of post-intervention data were used for Moeller 2021, Oberg 2018, and Stener-Victorin 2009-2013 (see Cochrane review 2019, Issue 3. Art. No.: CD007506). Meta-analyses of weight outcome: Groups exhibited comparable weight loss post-intervention (N=14 effect estimates; MD: -1.02; 95%CI [-2.08; 0.04]; P=0.0585; see forest plot below).

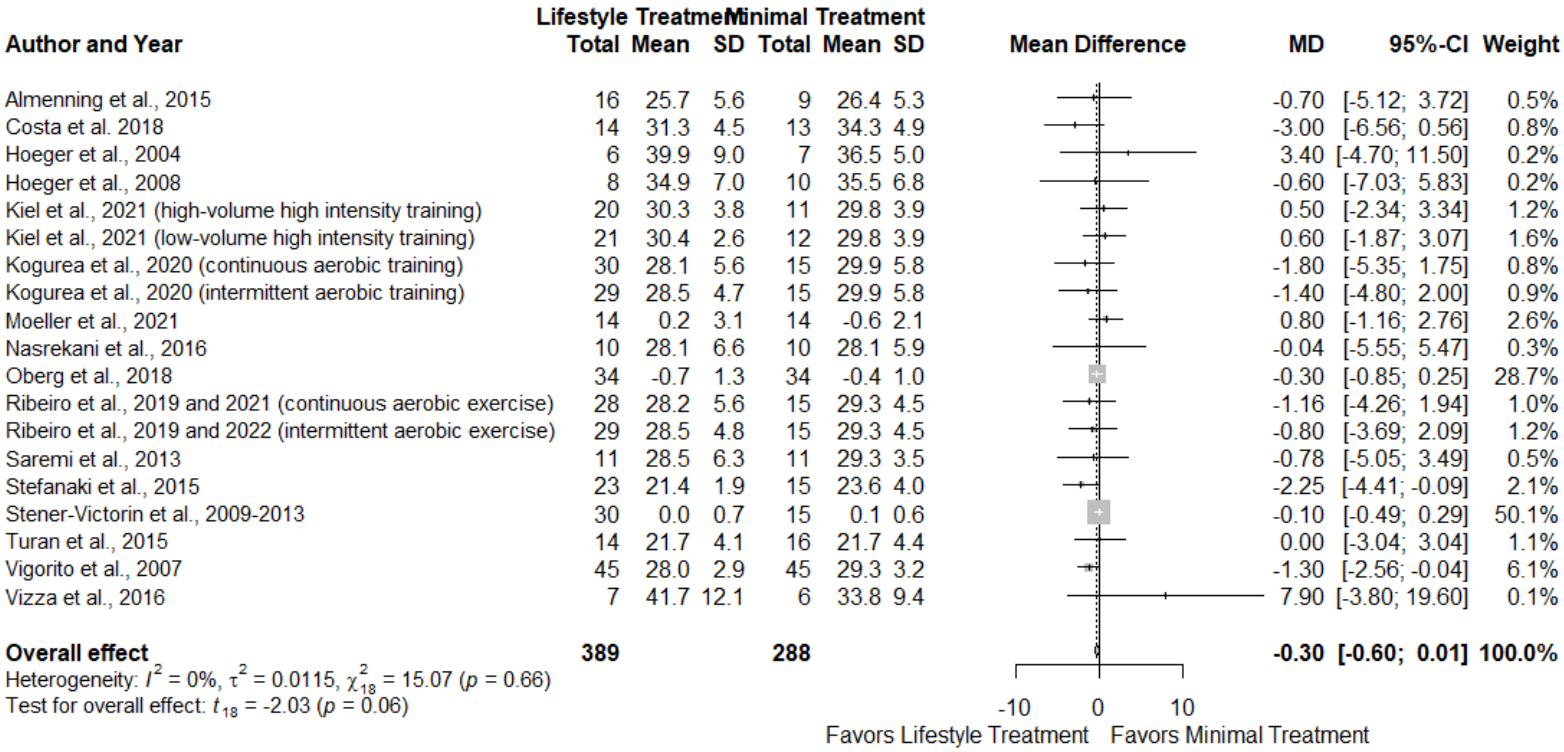


OUTCOME: BMI										**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Almenning et al., 2015	kg/m^2	Not Reported	Mean difference: 25.7	5.6 (SD)	16	Mean difference: 26.4	5.3 (SD)	9	Crude	Not Applicable
Costa et al. 2018	kg/m^2	Unspecified	Baseline exercise: 32 Post-intervention: 31.3	Baseline exercise: 4.2 (SD) Post-intervention: (SD) 4.5	14	Baseline control: 33.6 Post-intervention: 34.3	Baseline control: 5.1(SD) Post-intervention: 4.9 (SD)	13	Crude	Not Applicable
Hoeger et al., 2004	kg/m^2	Not Reported	Mean difference: 39.9	9 (SD)	6	Mean difference: 36.5	5 (SD)	7	Crude	Not Applicable
Hoeger et al., 2008	kg/m^2	Not Reported	Mean difference: 34.9	7 (SD)	8	Mean difference: 35.5	6.8 (SD)	10	Crude	Not Applicable
Kiel et al. 2021	kg/m^2	Not Reported	Baseline LV-HIT: 29.5 Baseline HV-HIT: 30.8 16-wk post-intervention LV-HIT: 30.4 16-wk post-intervention HV-HIT: 30.3	Baseline LV-HIT: 5.7 (SD) Baseline HV-HIT: 7.2 (SD) 16-wk post-intervention LV-HIT: (29.8-32.2 CI) 16-wk post-intervention HV-HIT: 7.2 (28.5-32.0 CI)	LV-HIT: 21 HV-HIT: 20	Baseline control 31.2 16-wk post-intervention control 29.8	Baseline control 6.7 (SD) 16-wk post-intervention control (28.1–31.5 CI)	23	Crude	Not Applicable
Kogurea et al. 2020	kg/m^2	Not Reported	Baseline CAT: 28.4 Baseline IAT: 28.6 Post-intervention CAT: 28.1	Baseline CAT: 5.6 (SD) Baseline IAT: 4.7 (SD)	CAT: 30 IAT: 29	Baseline control: 29.1	Baseline control: 5.2 (SD)	30	Crude	Not Applicable

			Post-intervention IAT: 28.5	Post-intervention CAT: 5.6 (SD) Post-intervention IAT: 4.8 (SD)		Post-intervention control: 29.9	Post-intervention control: 5.8 (SD)			
Moeller et al. 2018	kg/m^2	Not Reported	Median difference (0.2)	IQR (-3.1;1.2)	14	Median difference (-0.6)	IQR (-2.3;0.6)	14	Crude	Not Applicable
Nasrekani et al., 2016	kg/m^2	Not Reported	Mean difference: 28.07	6.65 (SD)	10	Mean difference: 28.11	5.9 (SD)	10	Crude	Not Applicable
Oberg et al. 2018	kg/m^2	As per standard procedures	Change from baseline = −0.7	95% CI = −1.2 to −0.3	34	Change from baseline = −0.4	95% CI (−0.8 -0.1)	34	Crude	Not Applicable
Ribeiro et al. 2019 and 2021	kg/m^2	As per standard procedures	Baseline continuous = 28.43 4 months continuous = 28.17 Baseline intermittent = 28.67 4 months intermittent = 28.53	Baseline continuous = 5.62 4 months continuous = 5.67 Baseline intermittent = 4.76 4 months intermittent = 4.82	continuous = 28 intermittent = 29	Baseline = 29.09 4 months = 29.33	Baseline = 5.25 4 months = 5.43	30	Adjusted	Age, BMI, testosterone, and androstenedione for the 2021 paper
Saremi et al., 2013	kg/m^2	Not Reported	Mean difference: 28.48	6.29 (SD)	11	Mean difference: 29.26	3.6 (SD)	11	Crude	Not Applicable
Stefanaki et al., 2015	kg/m^2	Not Reported	Mean difference: 21.37	1.89 (SD)	23	Mean difference: 23.62	4 (SD)	15	Crude	Not Applicable
Stener-Victorin et al., 2009-2013	kg/m^2	Not Reported	Mean difference: 0.01	0.7 (SD)	30	Mean difference: 0.11	0.6 (SD)	15	Crude	Not Applicable
Turan et al., 2015	kg/m^2	Not Reported	Mean difference: 21.7	4.1 (SD)	14	Mean difference: 21.7	4.4 (SD)	16	Crude	Not Applicable
Vigorito et al., 2007	kg/m^2	Not Reported	Mean difference: 28	2.9 (SD)	45	Mean difference: 29.3	3.2 (SD)	45	Crude	Not Applicable
Vizza et al., 2016	kg/m^2	Not Reported	Mean difference: 41.7	12.1 (SD)	7	Mean difference: 33.8	9.4 (SD)	6	Crude	Not Applicable

Abbreviations: BMI, body mass index; LV-HIT: low volume-high intensity training, HV-HIT: high volume-high intensity training, CAT: continuous aerobic training, IAT: intermittent aerobic training.

Figure 3. Forest plot of comparison: Lifestyle intervention versus minimal treatment: Outcome: BMI (kg/m^2). For BMI, mean changes instead of post-intervention data were used for Moeller 2021, Oberg 2018, and Stener-Victorin 2009-2013 (see Cochrane review 2019, Issue 3. Art. No.: CD007506). Meta-analyses of weight outcome: Groups exhibited comparable BMI post-intervention (N=19 effect estimates; MD: -0.30; 95%CI [-0.60; 0.01]; P=0.0571; see forest plot below).

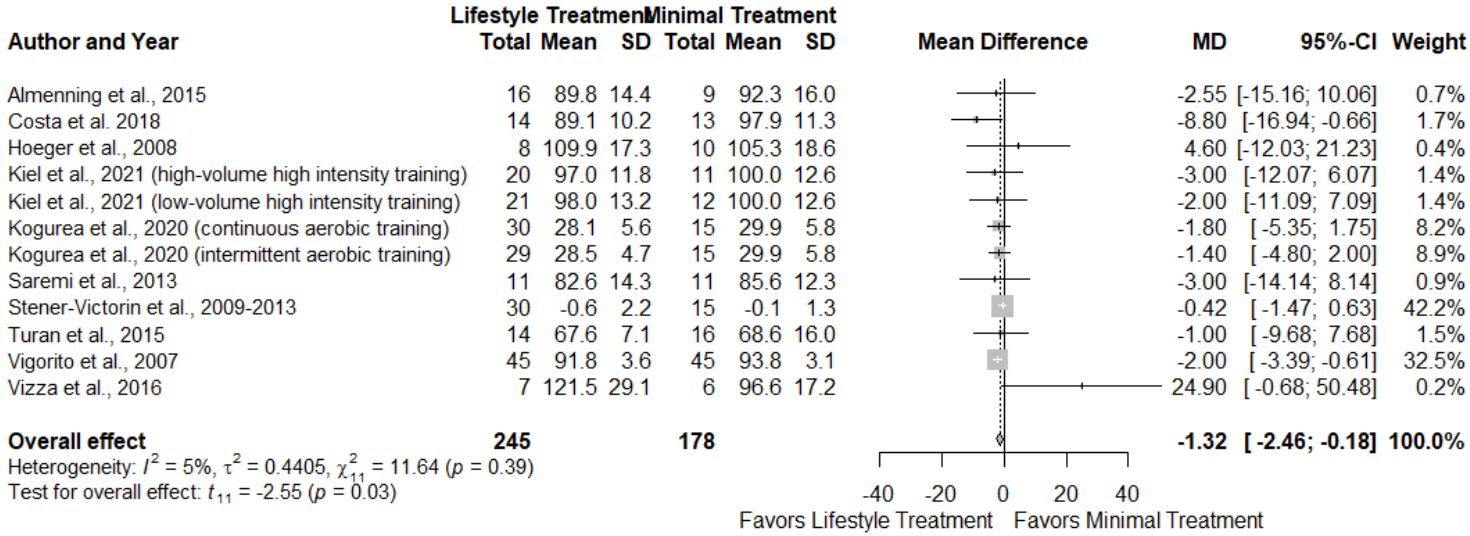


OUTCOME: Waist circumference						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/ L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Almenning et al., 2015	cm	Not Reported	Mean difference: 89.75	14.4 (SD)	16	Mean difference: 92.3	16 (SD)	9	Crude	Not Applicable
Costa et al., 2018	cm	Unspecified	Baseline exercise: 92.8 Post-intervention: 89.1	Baseline exercise: 10.3 (SD) Post-intervention: 10.2 (SD)	14	Baseline control: 94.1 Post-intervention: 97.9	Baseline control: 11.6 (SD) Post-intervention: (SD) 11.3	13	Crude	Not Applicable
Dietz de Loos et al., 2022	cm	Unspecified	Baseline only median SMS+: 101 SMS-: 96 Median Baseline SMS+: 102.9 Baseline SMS-: 100.1 Post-intervention SMS+: 94.5 Post-intervention SMS-: 96.3	Baseline only SMS+: (93-107 IQR) SMS-: (89-109 IQR) Post-intervention data not reported	Baseline SMS+: 60 SMS-: 63 Completed study SMS+: 16 SMS-: 27	Baseline only median CAU: 96 Median Baseline CAU: 100.3 Post-intervention CAU: 95.2	Baseline only: (89-109 IQR) Post-intervention data not reported	Baseline CAU: 60 Completed study 24	Crude	Not Applicable
Hoeger et al., 2008	cm	Not Reported	Mean difference: 109.9	17.3 (SD)	8	Mean difference: 105.3	18.6 (SD)	10	Crude	Not Applicable

Kiel et al. 2021	cm	Not Reported	Baseline LV-HIT: 99 Baseline HV-HIT: 103 16-wk post-intervention LV-HIT: 98 16-wk post-intervention HV-HIT: 97	Baseline LV-HIT: 15 (SD) Baseline HV-HIT: 20 (SD) 16-wk post-intervention LV-HIT: (92-104 CI) 16-wk post-intervention HV-HIT: (92-103 CI)	LV-HIT: 21 HV-HIT: 20	Baseline control: 100 16-wk post-intervention control: 100	Baseline control: 17 (SD) 16-wk post-intervention control: (94-105 CI)	23	Crude	Not Applicable
Kogurea et al. 2020	cm	Not Reported	Baseline CAT: 88.1 Baseline IAT: 90.5 Post-intervention CAT: 86.5 Post-intervention IAT: 88.6	Baseline CAT: 13.6 (SD) Baseline IAT: 11.3 (SD) Post-intervention CAT: 13.1 (SD) Post-intervention IAT: 12.4 (SD)	CAT: 30 IAT: 29	Baseline control: 89.5 Post-intervention control: 90.9	Baseline control: 12.6 (SD) Post-intervention control: (SD) 13.1	30	Crude	Not Applicable
Saremi et al., 2013	cm	Not Reported	Mean difference: 82.6	14.26 (SD)	11	Mean difference: 85.6	12.32 (SD)	11	Crude	Not Applicable
Stener-Victorin et al., 2009-2013	cm	Not Reported	Mean difference: -0.55	2.25 (SD)	30	Mean difference: -0.13	1.32 (SD)	15	Crude	Not Applicable
Turan et al., 2015	cm	Not Reported	Mean difference: 67.6	7.1 (SD)	14	Mean difference: 68.6	16 (SD)	16	Crude	Not Applicable
Vigorito et al., 2007	cm	Not Reported	Mean difference: 91.8	3.6 (SD)	45	Mean difference: 93.8	3.1 (SD)	45	Crude	Not Applicable
Vizza et al., 2016	cm	Not Reported	Mean difference: 121.5	29.1 (SD)	7	Mean difference: 96.6	17.2 (SD)	6	Crude	Not Applicable

Abbreviations: *LV-HIT: low volume-high intensity training, HV-HIT: high volume-high intensity training, CAT: continuous aerobic training, CAU: care as usual, IAT: intermittent aerobic training, SMS+: with short message service support, SMS-: without short message service support.

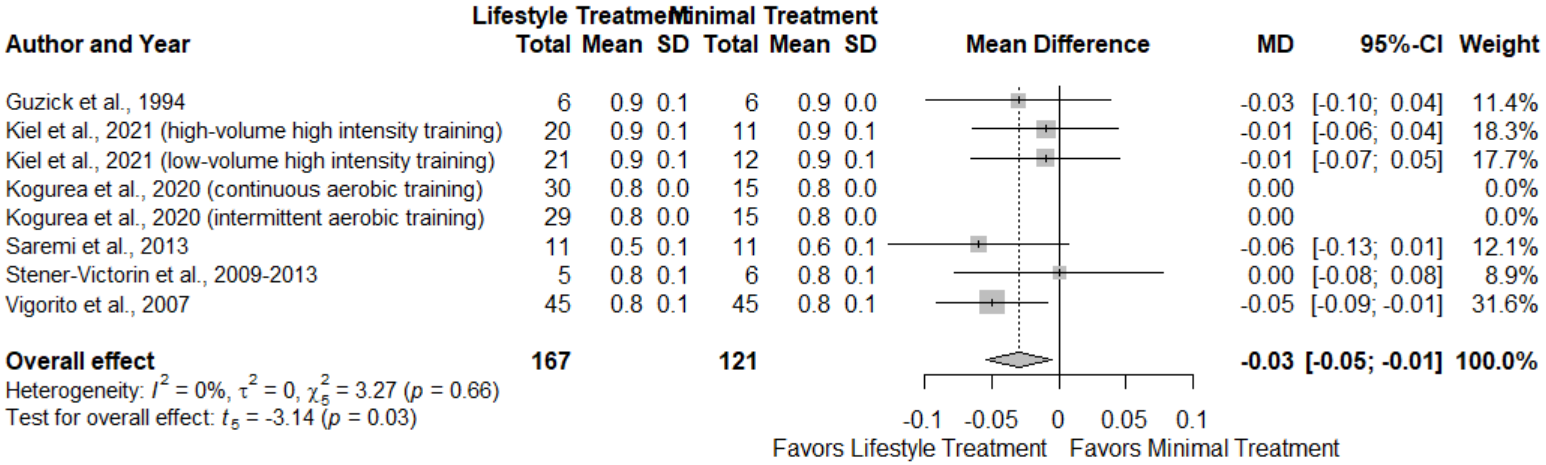
Figure 4. Forest plot of comparison: Lifestyle intervention versus minimal treatment: Outcome: Waist circumference (cm). For waist circumference mean changes instead of post-intervention data were used for Stener-Victorin 2009-2013 (Cochrane review 2019, Issue 3. Art. No.: CD007506). Meta-analyses of weight outcome: Lifestyle treatment groups exhibited higher reductions in waist circumference vs minimal treatment post-intervention (N=12 effect estimates; MD: -1.32; 95%CI [-2.46; -0.18]; P=0.0271; see forest plot below).



OUTCOME: Waist-hip ratio (WHR)							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Guzick et al., 1994	ratio	Not Reported	Mean difference: 0.92	0.07 (SD)	6	Mean difference: 0.05	0.05 (SD)	6	Crude	Not Applicable
Kiel et al. 2021	ratio	Not Reported	Baseline LV-HIT: 0.89 Baseline HV-HIT: 0.91 16-wk post-intervention LV-HIT: 0.87 16-wk post-intervention HV-HIT: 0.87	Baseline LV-HIT: 0.09 (SD) Baseline HV-HIT: 0.08 (SD) 16-wk post-intervention LV-HIT: (0.83-0.91 CI) 16-wk post-intervention HV-HIT: (0.84-0.91 CI)	LV-HIT: 21 HV-HIT: 20	Baseline control: 0.89 16-wk post-intervention control: 0.88	Baseline control: 0.09 (SD) 16-wk post-intervention control: (0.85-0.91 CI)	23	Crude	Not Applicable
Kogurea et al., 2020	ratio	Not Reported	Baseline CAT: 0.8 Baseline IAT: 0.8 Post-intervention CAT: 0.8 Post-intervention IAT: 0.8	Baseline CAT: 0 (SD) Baseline IAT: 0 (SD) Post-intervention CAT: 0 (SD) Post-intervention IAT: 0 (SD)	CAT: 30 IAT: 29	Baseline control: 0.8 Post-intervention control: 0.8	Baseline control: 0 (SD) Post-intervention control: 0 (SD)	30	Crude	Not Applicable

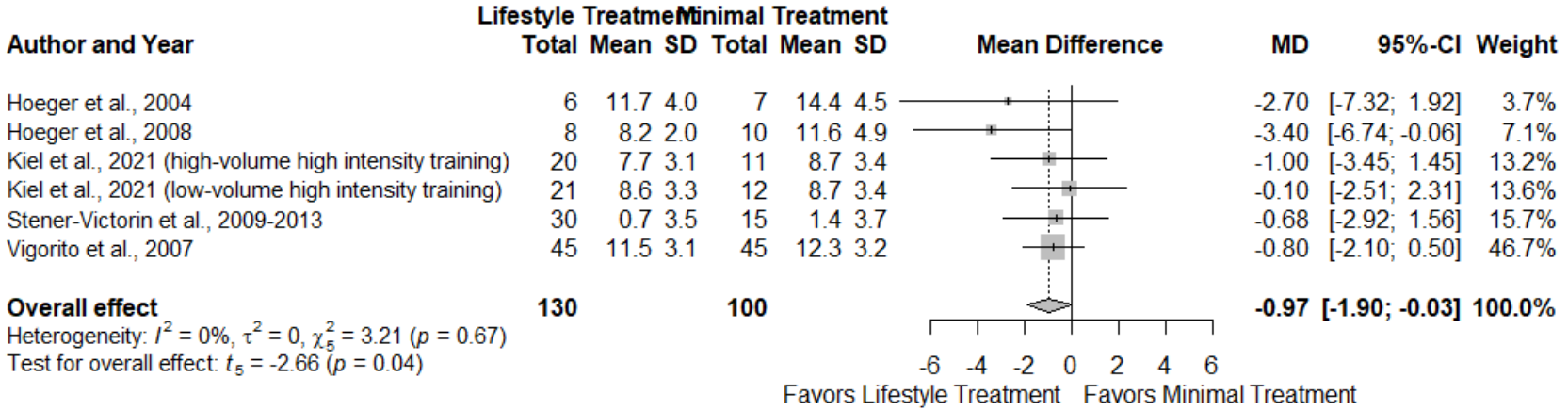
Saremi et al., 2013	Ratio	Not Reported	Mean difference: 0.51	0.09 (SD)	11	Mean difference: 0.57	0.068 (SD)	11	Crude	Not Applicable
Stener-Victorin et al., 2009-2013	Ratio	Not Reported	Mean difference: 0.8	0.07 (SD)	5	Mean difference: 0.8	0.06 (SD)	6	Crude	Not Applicable
Vigorito et al., 2007	Ratio	Not Reported	Mean difference: 0.8	0.1 (SD)	45	Mean difference: 0.85	0.1 (SD)	45	Crude	Not Applicable
Abbreviations: LV-HIT: low volume-high intensity training, HV-HIT: high volume-high intensity training, CAT: continuous aerobic training, IAT: intermittent aerobic training.										

Figure 5. Forest plot of comparison: Lifestyle intervention versus minimal treatment: Outcome: Waist-hip ratio. For waist-hip ratio, mean changes instead of post-intervention data were used for Stener-Victorin 2009-2013 (Cochrane review 2019, Issue 3. Art. No.: CD007506). Meta-analyses of weight outcome: Lifestyle treatment groups exhibited higher reductions in waist-hip ratio vs minimal treatment post-intervention (N=6 effect estimates; MD: -0.03; 95%CI [-0.05; -0.01]; P=0.0257; see forest plot below).



OUTCOME: Ferriman-Gallwey Score						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Hoeger et al., 2004	N/A	Not Reported	Mean difference: 11.7	4 (SD)	6	Mean difference: 14.4	4.5 (SD)	7	Crude	Not Applicable
Hoeger et al., 2008	N/A	Not Reported	Mean difference: 8.2	2 (SD)	8	Mean difference: 11.6	4.9 (SD)	10	Crude	Not Applicable
Kiel et al. 2021	N/A	Not Reported	Baseline LV-HIT: 8.1 Baseline HV-HIT: 8.0 16-wk post-intervention LV-HIT: 8.6 16-wk post-intervention HV-HIT: 7.7	Baseline LV-HIT: 4.6 (SD) Baseline HV-HIT: 5.8 (SD) 16-wk post-intervention LV-HIT:(7.1-10.1 CI) 16-wk post-intervention HV-HIT: (6.2-9.1 CI)	LV-HIT: 21 HV-HIT: 20	Baseline control: 8 16-wk post-intervention control: 8.7	Baseline control: 4.6 (SD) 16-wk post-intervention control: (7.2-10.2 CI)	23	Crude	Not Applicable
Stener-Victorin et al., 2009-2013	N/A	Not Reported	Mean difference: 0.72	3.54 (SD)	30	Mean difference: 1.4	3.66 (SD)	15	Crude	Not Applicable
Vigorito et al., 2007	N/A	Not Reported	Mean difference: 11.5	3.1 (SD)	45	Mean difference: 12.3	3.2 (SD)	45	Crude	Not Applicable
Abbreviations: LV-HIT: low volume-high intensity training, HV-HIT: high volume-high intensity training.										

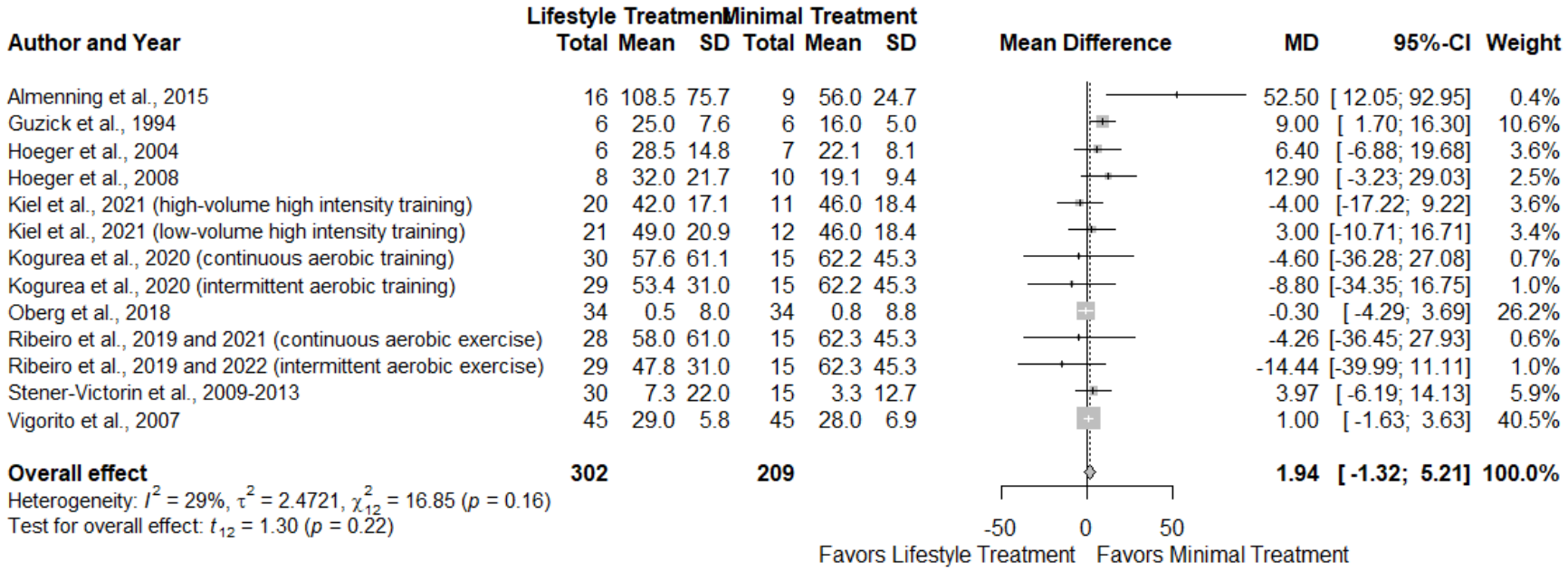
Figure 6. Forest plot of comparison: Lifestyle intervention versus minimal treatment: Outcome: Ferriman-Gallwey score. For Ferriman-Gallwey score mean changes were used except post-intervention data used for Kiel 2021 (consistent with the approach used in the Cochrane review 2019, Issue 3. Art. No.: CD007506). Meta-analyses of weight outcome: Lifestyle treatment groups exhibited higher reductions in Ferriman-Gallwey score vs minimal treatment post-intervention (N=6 effect estimates; MD: -0.97; 95%CI [-1.90; -0.03]; P=0.0448; see forest plot below).



OUTCOME: SHBG							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Almenning et al., 2015	nmol/L	Not reported	Mean difference: 108.5	75.7 (SD)	16	Mean difference: 56	24.7 (SD)	9	Crude	No applicable
Guzick et al., 1994	nmol/L	Not reported	Mean difference: 25	7.63 (SD)	6	Mean difference: 16	5 (SD)	6	Crude	No applicable
Hoeger et al., 2004	nmol/L	Not reported	Mean difference: 28.5	14.8 (SD)	6	Mean difference: 22.1	8.1 (SD)	7	Crude	No applicable
Hoeger et al., 2008	nmol/L	Not reported	Mean difference: 32	21.7 (SD)	8	Mean difference: 19.1	9.4 (SD)	10	Crude	No applicable
Kiel et al. 2021	nmol/L	Hormone assay	Baseline LV-HIT: 42 Baseline HV-HIT: 42 16-wk post-intervention LV-HIT: 49 16-wk post-intervention HV-HIT: 42	Baseline LV-HIT: 2 (SD) Baseline HV-HIT: 2 (SD) 16-wk post-intervention LV-HIT: (40-59 CI) 16-wk post-intervention HV-HIT: (35-51 CI)	LV-HIT: 21 HV-HIT: 20	Baseline control: 41 16-wk post-intervention control: 46	Baseline control: 18 (SD) 16-wk post-intervention control: (39-55 CI)	23	Crude	Not Applicable
Kogurea et al., 2020	nmol/L	Not Reported	Baseline CAT: 54.3 Baseline IAT: 47.8 Post-intervention CAT: 57.6	Baseline CAT: 40.9 (SD) Baseline IAT: 28.2 (SD) Post-intervention CAT: 61.1 (SD)	CAT: 30 IAT: 29	Baseline control: 50.5 Post-intervention control: 62.2	Baseline control: 34.2 (SD) Post-intervention control: (SD) 45.3	30	Crude	Not Applicable

			Post-intervention IAT: 53.4	Post-intervention IAT: 31.0 (SD)						
Oberg, 2018	nmol/L	Electro-chemiluminescence immunoassay	Change from baseline = 0.5	95% CI = −2.4 to 3.3	34	Change from baseline = 0.8	95% CI = −2.3 to 4.0	34	Crude	Not Applicable
Ribeiro, 2019 and 2021	nmol/L	Chemiluminescent method	Baseline continuous = 54.31 4 months continuous = 58 Baseline intermittent = 47.82 4 months intermittent = 53.49	Baseline continuous = 40.89 4 months continuous = 61 Baseline intermittent = 28.19 4 months intermittent = 31.00	continuous = 28 intermittent = 29	Baseline = 50.56 4 months = 62.26	Baseline = 34.21 4 months = 45.29	30	Adjusted	Age, BMI, testosterone and androstenedione for the 2021 paper
Stener-Victorin et al., 2009-2013	nmol/L	Not reported	Mean difference: 7.3	22 (SD)	30	Mean difference: 3.33	12.7 (SD)	15	Crude	Not applicable
Vigorito et al., 2007	nmol/L	Not reported	Mean difference: 29	5.8 (SD)	45	Mean difference: 28	6.9 (SD)	45	Crude	Not applicable
Abbreviations: SHBG: sex hormone binding globulin, LV-HIT: low volume-high intensity training, HV-HIT: high volume-high intensity training, CAT: continuous aerobic training, IAT: intermittent aerobic training.										

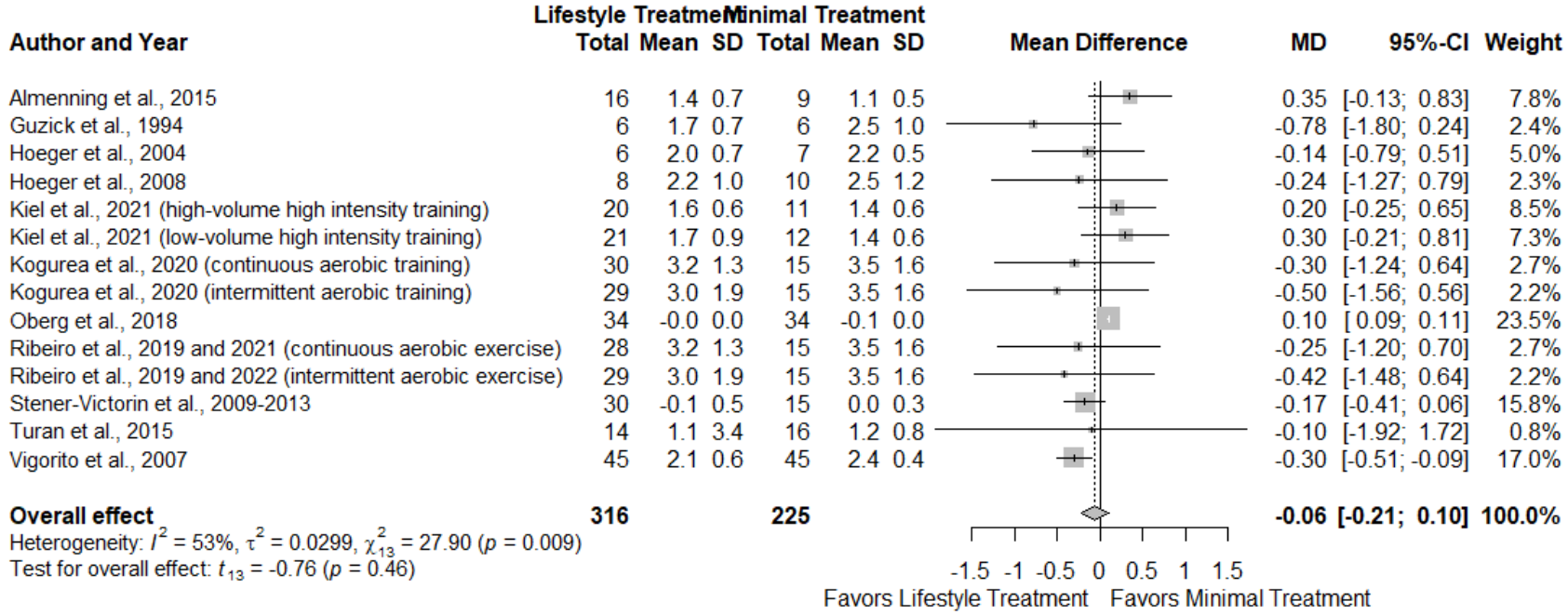
Figure 7. Forest plot of comparison: Lifestyle intervention versus minimal treatment: Outcome: SHBG (nmol/L). For SHBG mean changes instead of post-intervention data were used for Oberg 2018 and Stener-Victorin 2009-2013 (Cochrane review 2019, Issue 3. Art. No.: CD007506). Meta-analyses of weight outcome: Lifestyle treatment groups exhibited comparable SHBG levels vs minimal treatment post-intervention (N=13 effect estimates; MD: 1.94; 95%CI [-1.32; 5.21]; P=0.2192; see forest plot below).



OUTCOME: Testosterone						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Almenning et al., 2015	nmol/L	Not Reported	Mean difference: 1.45	0.72 (SD)	16	Mean difference: 1.1	0.5 (SD)	9	Crude	Not Applicable
Guzick et al., 1994	nmol/L	Not Reported	Mean difference: 1.7	0.73 (SD)	6	Mean difference: 2.48	1.04 (SD)	6	Crude	Not Applicable
Hoeger et al., 2004	nmol/L	Not Reported	Mean difference: 2.05	0.67 (SD)	6	Mean difference: 2.19	0.5 (SD)	7	Crude	Not Applicable
Hoeger et al., 2008	nmol/L	Not Reported	Mean difference: 2.24	1.05 (SD)	8	Mean difference: 2.48	1.17 (SD)	10	Crude	Not Applicable
Kiel et al. 2021	nmol/L	Not Reported	Baseline LV-HIT: 1.4 Baseline HV-HIT: 1.3 16-wk post-intervention LV-HIT: 1.7 16-wk post-intervention HV-HIT: 1.6	Baseline LV-HIT: 0.5 (SD) Baseline HV-HIT: 0.7 (SD) 16-wk post-intervention LV-HIT: (1.3-2.1 CI) 16-wk post-intervention HV-HIT: (1.3-1.9 CI)	LV-HIT: 21 HV-HIT: 20	Baseline control: 1.6 16-wk post-intervention control: 1.4 (SD)	Baseline control: 0.7 (SD) 16-wk post-intervention control: (1.2-1.7 CI)	23	Crude	Not Applicable
Kogurea et al., 2020	ng/dL	Not Reported	Baseline CAT: 116.7 Baseline IAT: 107.6 Post-intervention CAT: 92.7	Baseline CAT: 49.5 (SD) Baseline IAT: 51.5 (SD) Post-intervention CAT: 37.8 (SD)	CAT: 30 IAT: 29	Baseline control: 86.2 (SD)	Baseline control: 37.0 (SD)	30	Crude	Not Applicable

			Post-intervention IAT: 87.8	Post-intervention IAT: 54.2 (SD)		Post-intervention control: 99.6	Post-intervention control: 46.4 (SD)			
Oberg et al. 2018	pg/mL	Liquid chromatography-tandem-mass spectrometry	Change from baseline = −14.3	95% CI = −49.1 to 20.5 (SD)	34	Change from baseline = −43.7	95% CI = −81.7 to −5.7 (SD)	34	Crude	Not Applicable
Ribeiro et al. 2019 and 2021	ng/dL	Chemiluminescence method	Baseline continuous = 117 4 months continuous = 93 Difference baseline and 4 months continuous = 24.0 Baseline intermittent = 108 4 months intermittent = 88 Difference baseline and 4 months intermittent = 19.9	Baseline continuous = 50 4 months continuous = 38 Difference baseline and 4 months 95% CI continuous = 7.2 to 40.8 Baseline intermittent = 52 4 months intermittent = 54 Difference baseline and 4 months 95% CI intermittent = 3.30 to 36.4 (SD)	continuous = 28 intermittent = 29 (SD)	Baseline = 86 4 months = 100 Difference baseline and 4 months = −13.4 (SD)	Baseline = 37 4 months = 46 Difference baseline and 4 months 95% CI = −29.7 to 2.86 (SD)	30	Adjusted	Age, BMI, WHR, testosterone for 2019 paper
Stener-Victorin et al., 2009-2013	nmol/L	Not Reported	Mean difference: -0.13868	0.49 (SD)	30	Mean difference: 0.03467	0.31203 (SD)	15	Crude	Not Applicable
Turan et al., 2015	nmol/L	Not Reported	Mean difference: 1.1	3.4 (SD)	14	Mean difference:1.2	0.8 (SD)	16	Crude	Not Applicable
Vigorito et al., 2007	nmol/L	Not Reported	Mean difference: 2.1	0.6 (SD)	45	Mean difference: 2.4	0.4 (SD)	45	Crude	Not Applicable
Abbreviations: LV-HIT: low volume-high intensity training, HV-HIT: high volume-high intensity training, CAT: continuous aerobic training, IAT: intermittent aerobic training.										

Figure 8. Forest plot of comparison: Lifestyle intervention versus minimal treatment: Outcome: Total testosterone (nmol/L). For testosterone, mean changes instead of post-intervention data were used for Oberg 2018 and Stener-Victorin 2009-2013 (Cochrane review 2019, Issue 3. Art. No.: CD007506). Meta-analyses of weight outcome: Lifestyle treatment groups exhibited comparable total testosterone levels vs minimal treatment post-intervention (N=14 effect estimates; MD: -0.06; 95%CI [-0.21; 0.10]; P=0.4598; see forest plot below).

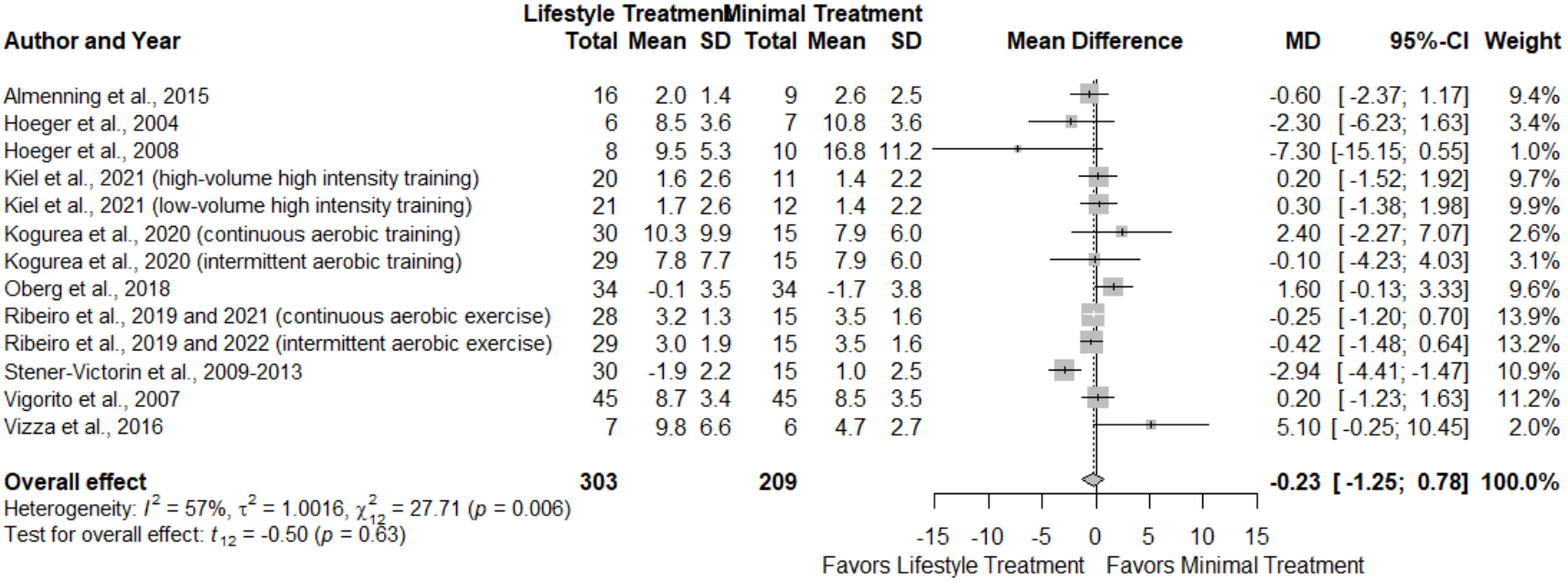


OUTCOME: FAI						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Almenning et al., 2015	percent	Not Reported	Mean difference: 2	1.4 (SD)	16	Mean difference: 2.6	2.5 (SD)	9	Crude	Not applicable
Hoeger et al., 2004	percent	Not Reported	Mean difference: 8.5	3.6 (SD)	6	Mean difference: 10.8	3.6 (SD)	7	Crude	Not applicable
Hoeger et al., 2008	percent	Not Reported	Mean difference: 9.5	5.3 (SD)	8	Mean difference: 16.8	11.2 (SD)	10	Crude	Not applicable
Kiel et al. 2021	percent	Not Reported	Baseline LV-HIT: 4.7 Baseline HV-HIT: 4.7 16-wk post-intervention LV-HIT: 4.4 16-wk post-intervention HV-HIT: 4.8	Baseline LV-HIT: 2.5 (SD) Baseline HV-HIT: 4.3 (SD) 16-wk post-intervention LV-HIT: (3.3-5.7 CI) 16-wk post-intervention HV-HIT: (3.7-6.1 CI)	LV-HIT: 21 HV-HIT: 20	Baseline control: 4.7 16-wk post-intervention control: 3.9	Baseline control: 2.5 (SD) 16-wk post-intervention control: (3.1-5.0 CI)	23	Crude	Not Applicable
Kogurea et al., 2020	percent	Not Reported	Baseline CAT: 11.3 Baseline IAT: 9.8 Post-intervention CAT: 10.3	Baseline CAT: 9.5 (SD) Baseline IAT: 7.2 (SD) Post-intervention CAT: 9.9 (SD)	CAT: 30 IAT: 29	Baseline control: 7.5 Post-intervention control: 7.9	Baseline control: 4.2 (SD) Post-intervention control: 6 (SD)	Baseline control: (SD) Post-intervention	Crude	Not Applicable

			Post-intervention IAT: 7.8	Post-intervention IAT: 7.7 (SD)				control: (SD) 30		
Oberg et al., 2018	percent	Testosterone nmol/L divided by SHBG nmol/L × 100 (see Testosterone and SHBG tables for specific analysis techniques)	Change from baseline = −0.1	95% CI = −1.4 to 1.1	34	Change from baseline = −1.7	95% CI = −3.0 to −0.3	34	Crude	Not Applicable
Ribeiro et al. 2019 and 2021	percent	Testosterone nmol/L divided by SHBG nmol/L × 100 (see Testosterone and SHBG tables for specific analysis techniques)	Baseline continuous = 11.33 4 months continuous = 10.3 Baseline intermittent = 9.87 4 months intermittent = 7.84	Baseline continuous = 9.58 4 months continuous = 10 Baseline intermittent = 7.2 4 months intermittent = 7.72	continuous = 28 intermittent = 29	Baseline = 7.52 4 months = 7.90	Baseline = 4.21 4 months = 5.98	30	Adjusted	Age, BMI, testosterone and androstenedione for the 2021 paper
Stener-Victorin et al., 2009-2013	percent	Not Reported	Mean difference: -1.89973	2.21 (SD)	30	Mean difference: 1.041141	2.456929 ((SD)	15	Crude	Not applicable
Vigorito et al., 2007	percent	Not Reported	Mean difference: 8.7	3.4 (SD)	45	Mean difference: 8.5	3.5 (SD)	45	Crude	Not applicable
Vizza et al., 2016	percent	Not Reported	Mean difference: 9.8	6.6 (SD)	7	Mean difference: 4.7	2.7 (SD)	6	Crude	Not applicable

Abbreviations: FAI: free androgen index, LV-HIT: low volume-high intensity training, HV-HIT: high volume-high intensity training, CAT: continuous aerobic training, IAT: intermittent aerobic training.

Figure 9. Forest plot of comparison: Lifestyle intervention versus minimal treatment: Outcome: FAI. For the FAI, mean changes instead of post-intervention data were used for Oberg 2018 and Stener-Victorin 2009-2013 (Cochrane review 2019, Issue 3. Art. No.: CD007506). Meta-analyses of weight outcome: Lifestyle treatment groups exhibited comparable total testosterone levels vs minimal treatment post-intervention (N=13 effect estimates; MD: 0.23; 95%CI [-1.25; 0.78]; P=0.6269; see forest plot below).

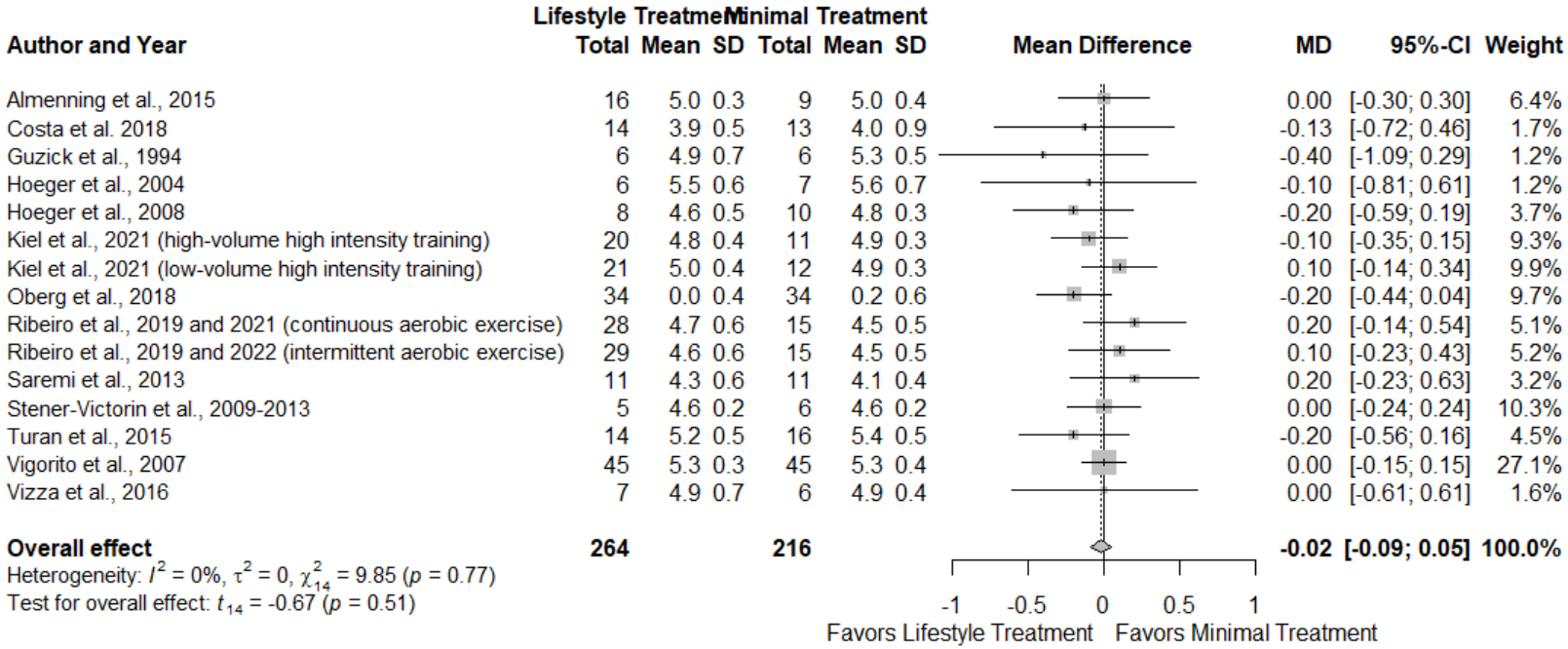


OUTCOME: Glucose						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Almenning et al., 2015	mmol/L	Not reported	Mean difference: 5	0.3 (SD)	16	Mean difference: 5	0.4 (SD)	9	Crude	Not Applicable
Costa et al. 2018	mmol/L	Colorimetric method/enzyme in equipment Bioplus, 2000 model	Baseline exercise: 3.66 Post-intervention: 3.89	Baseline exercise: 0.76 (SD) Post-intervention exercise: 0.53 (SD)	14	Baseline control: 4.09 Post-intervention: 4.02	Baseline control: 0.82 (SD) Post-intervention: 0.95 (SD)	13	Crude	Not Applicable
Dietz de Loos et al. 2022	mmol/L	Colorimetric method/enzyme in equipment Bioplus, 2000 model	Baseline only median SMS+: 5 SMS-: 5.2 Median Baseline SMS+: 5.1 Baseline SMS-: 5.2 Post-intervention SMS+: 5 Post-intervention SMS-: 5.1	Baseline only SMS+: (4.7-5.3 IQR) SMS-: (4.8-5.4 IQR) Post-intervention data not reported	Baseline SMS+: 60 SMS-: 63 Completed study SMS+: 16 SMS-: 27	Baseline only median CAU:5 Median Baseline CAU: 5.0 Post-intervention CAU: 5.2	Baseline only: (4.7-5.3 IQR) Post-intervention data not reported	Baseline CAU: 60 Completed study 24	Crude	Not Applicable
Guzick et al., 1994	mmol/L	Not reported	Mean difference: 4.9	0.7 (SD)	6	Mean difference: 5.3	0.5 (SD)	6	Crude	Not Applicable
Hoeger et al., 2004	mmol/L	Not reported	Mean difference: 5.5	0.6 (SD)	6	Mean difference: 5.6	0.7 (SD)	7	Crude	Not Applicable
Hoeger et al., 2008	mmol/L	Not reported	Mean difference: 4.6	0.5 (SD)	8	Mean difference: 4.8	0.3 (SD)	10	Crude	Not Applicable

Kiel et al. 2021	mmol/L	OGTT	Baseline LV-HIT: 4.9 Baseline HV-HIT: 4.9 16-wk post-intervention LV-HIT: 5.0 16-wk post-intervention HV-HIT: 4.8	Baseline LV-HIT: 0.5 (SD) Baseline HV-HIT: 0.6 (SD) 16-wk post-intervention LV-HIT: (4.8-5.2 CI) 16-wk post-intervention HV-HIT: (4.6-5.0 CI)	LV-HIT: 21 HV-HIT: 20	Baseline control: 5.0 16-wk post-intervention control: 4.9	Baseline control: 0.6 (SD) 16-wk post-intervention control: (4.7-5.0 CI)	23	Crude	Not Applicable
Oberg et al., 2018	mIE/L	Not specified (see supplementary materials)	Change from baseline = 0.0	95% CI = −0.1 to 0.2	34	Change from baseline = 0.2	95% CI = −0.02 to 0.4	34	Crude	NA
Ribeiro et al. 2019 and 2021	mg/dL	Oxidase method	Baseline continuous = 84.0 4 months continuous = 84.0 Baseline intermittent = 82.0 4 months intermittent = 82.0	Baseline continuous = 12.0 4 months continuous = 11.0 Baseline intermittent = 11.0 4 months intermittent = 11.0	continuous = 28 intermittent = 29	Baseline = 83.0 4 months = 81	Baseline = 7.0 4 months = 9.0	30	Adjusted	Age, BMI, testosterone and androstenedione for the 2021 paper
Saremi et al., 2013	mmol/L	Not reported	Mean difference: 4.3	0.6 (SD)	11	Mean difference: 4.1	0.4 (SD)	11	Crude	Not Applicable
Stener-Victorin et al., 2009-2013	mmol/L	Not reported	Mean difference: 4.6	0.2 (SD)	5	Mean difference: 4.6	0.2 (SD)	6	Crude	Not Applicable
Turan et al., 2015	mmol/L	Not reported	Mean difference: 5.2	0.5 (SD)	14	Mean difference: 5.4	0.5 (SD)	16	Crude	Not Applicable

Vigorito et al., 2007	mmol/L	Not reported	Mean difference: 5.3	0.3 (SD)	45	Mean difference: 5.3	0.4 (SD)	45	Crude	Not Applicable
Vizza et al., 2016	mmol/L	Not reported	Mean difference: 4.9	0.7 (SD)	7	Mean difference: 4.9	0.4 (SD)	6	Crude	Not Applicable
Abbreviations: CAU: care as usual, OGTT: oral glucose tolerance test, LV-HIT: low volume-high intensity training, HV-HIT: high volume-high intensity training, SMS+: with short message service support, SMS-: without short message service support.										

Figure 10. Forest plot of comparison: Lifestyle intervention versus minimal treatment: Outcome: Fasting glucose (mmol/L). For glucose, mean changes instead of post-intervention data were used for Oberg 2018 and Stener-Victorin 2009-2013 (Cochrane review 2019, Issue 3. Art. No.: CD007506). Meta-analyses of weight outcome: Lifestyle treatment groups exhibited comparable total testosterone levels vs minimal treatment post-intervention (N=15 effect estimates; MD: -0.02; 95%CI [-0.09; 0.05]; P=0.5138; see forest plot below).

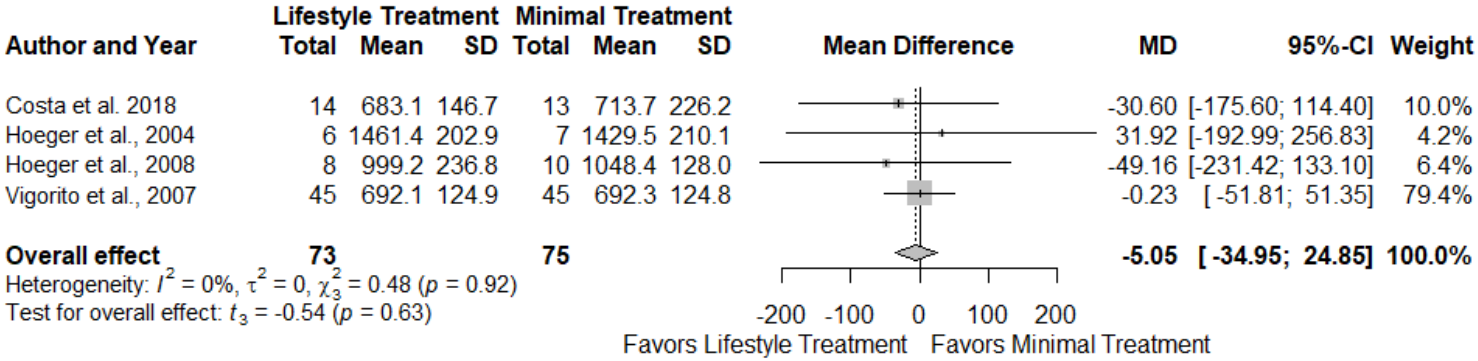


OUTCOME: 2-h Postprandial Glucose							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Costa et al. 2018	mmol/L	Colorimetric method/enzyme in equipment Bioplus, 2000 model	Baseline exercise: 6.17 Post-intervention: 5.46	Baseline exercise: 1.85 (SD) Post-intervention exercise: 1.17 (SD)	14	Baseline control: 6.96 Post-intervention control: 5.4	Baseline control: 2.25 (SD) Post-intervention control: (SD) 1.64	13	Crude	Not Applicable

Meta-analyses outcomes: Meta-analyses were not conducted due to insufficient (n<3) RCTs reporting this outcome.

OUTCOME: OGTT (120 min AUC-OGTT, area under curve for OGTT)						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Costa et al., 2018	mmol/L	OGTT assay	Baseline exercise: 754.0 Post-intervention: 683.1	Baseline exercise: 211.6 (SD) Post-intervention exercise: 146.7 (SD)	14	Baseline control: 771.7 Post-intervention control: 713.7	Baseline control: 198.8 (SD) Post-intervention control: (SD) 226.2	13	Crude	Not Applicable
Hoeger et al., 2004	mmol/L	Not reported	Mean difference: 1461.38	202.94 (SD)	6	Mean difference: 1429.46	210.06 (SD)	7	Crude	Not Applicable
Hoeger et al., 2008	mmol/L	Not reported	Mean difference: 999.21	236.82 (SD)	8	Mean difference: 1048.37	127.96 (SD)	10	Crude	Not Applicable
Vigorito et al., 2007	mmol/L	Not reported	Mean difference: 692.10	124.88 (SD)	45	Mean difference: 692.33	124.77 (SD)	45	Crude	Not Applicable
Abbreviations: OGTT, oral glucose tolerance test.										

Figure 11. Forest plot of comparison: Lifestyle intervention versus minimal treatment: Outcome: Oral glucose tolerance test (OGTT) glucose (mmol/L/minute). For OGTT, post-intervention data were used for Costa et al. 2018 (Cochrane review 2019, Issue 3. Art. No.: CD007506). Meta-analyses of weight outcome: Lifestyle treatment groups exhibited comparable total testosterone levels vs minimal treatment post-intervention (N=4 effect estimates; MD: -5.05; 95%CI [-34.95; 24.85]; P=0.6282; see forest plot below).

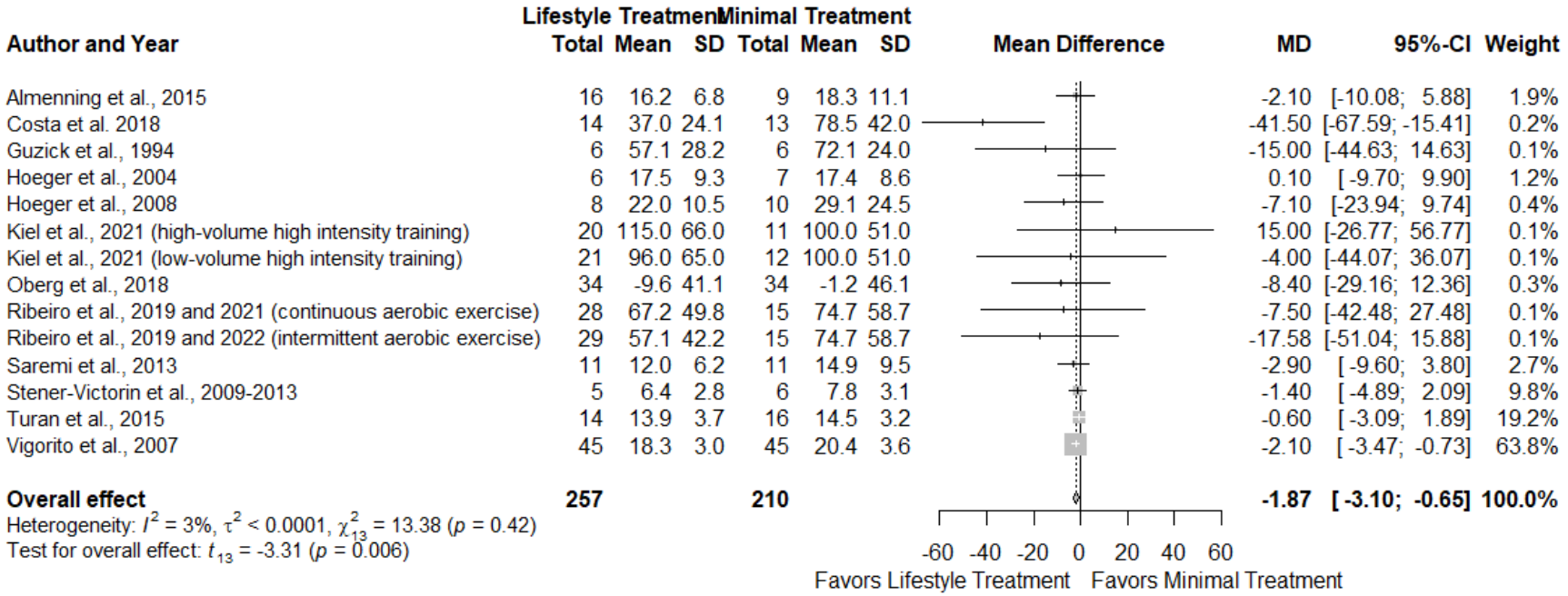


OUTCOME: Insulin						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Almenning et al., 2015	pmol/L	Not Reported	Mean difference: 16.2	6.8 (SD)	16	Mean difference: 18.3	11.1 (SD)	9	Crude	Not Applicable
Costa et al. 2018	pmol/L	Colorimetric method/enzyme in equipment Bioplus, 2000 model	Baseline exercise: 54.4 Post-intervention: 37.0	Baseline control: 28.9 (SD) Post-intervention control: 24.1 (SD)	14	Baseline control: 106.6 Post-intervention control: 78.5	Baseline control: 81.0 (SD) Post-intervention: 42.0 (SD)	13	Crude	Not Applicable
Dietz de Loos et al. 2022	pmol/L	Roche Modular E170 assay	Baseline only median SMS+: 87 SMS-: 103 Median Baseline SMS+: 100 Baseline SMS-: 111 Post-intervention SMS+: 89 Post-intervention SMS-: 110	Baseline only SMS+: (51-122 IQR) SMS-: (54-148 IQR) Post-intervention data not reported	Baseline SMS+: 60 SMS-: 63 Completed study SMS+: 16 SMS-: 27	Baseline only median CAU: 89 Median Baseline CAU: 118 Post-intervention CAU: 111	Baseline only: (62-123 IQR) Post-intervention data not reported	Baseline CAU: 60 Completed study 24	Crude	Not Applicable

Guzick et al., 1994	pmol/L	Not Reported	Mean difference: 57.1	28.2 (SD)	6	Mean difference: 72.1	24 (SD)	6	Crude	Not Applicable
Hoeger et al., 2004	pmol/L	Not Reported	Mean difference: 17.5	9.3 (SD)	6	Mean difference:17.4	8.6 (SD)	7	Crude	Not Applicable
Hoeger et al., 2008	pmol/L	Not Reported	Mean difference: 22	10.5 (SD)	8	Mean difference: 29.1	24.5 (SD)	10	Crude	Not Applicable
Kiel et al. 2021	pmol/L	Enzyme-linked immunosorbent assay	Baseline LV-HIT: 128 Baseline HV-HIT: 128 16-wk post-intervention LV-HIT: 96 16-wk post-intervention HV-HIT: 115	Baseline LV-HIT: 105 (SD) Baseline HV-HIT: 105 (SD) 16-wk post-intervention LV-HIT: (71-130 CI) 16-wk post-intervention HV-HIT: (88-150 CI)	LV-HIT: 21 HV-HIT: 20	Baseline control: 97 16-wk post-intervention control: 88	Baseline control: 48 (SD) 16-wk post-intervention control: (69-113 CI)	23	Crude	Not Applicable
Oberg et al., 2018	mIE/L	Not specified (see supplementary materials)	Change from baseline = −1.6	95% CI = −4.0 to 0.9	34	Change from baseline = −0.2	95% CI = −2.9 to 2.6	24	Crude	Not Applicable
Ribeiro et al. 2019 and 2021	µIU/mL	Chemiluminescent method	Baseline continuous = 11.31 4 months continuous = 11.2 Baseline intermittent = 9.52 4 months intermittent = 10.40	Baseline continuous = 8.09 4 months continuous = 8.3 Baseline intermittent = 7.18 4 months intermittent = 7.03	continuous = 28 intermittent = 29	Baseline = 12.83 4 months = 12.45	Baseline = 8.5 4 months = 9.79	30	Adjusted	Age, BMI, testosterone, and androstenedione for the 2021 paper

Saremi et al., 2013	pmol/L	Not Reported	Mean difference: 12	6.2 (SD)	11	Mean difference: 14.9	9.5 (SD)	11	Crude	Not Applicable
Stener-Victorin et al., 2009-2013	pmol/L	Not Reported	Mean difference: 6.4	2.8 (SD)	5	Mean difference: 7.8	3.1 (SD)	6	Crude	Not Applicable
Turan et al., 2015	pmol/L	Not Reported	Mean difference: 13.9	3.7 (SD)	14	Mean difference: 14.5	3.2 (SD)	16	Crude	Not Applicable
Vigorito et al., 2007	pmol/L	Not Reported	Mean difference: 18.3	3 (SD)	45	Mean difference: 20.4	3.6 (SD)	45	Crude	Not Applicable
Abbreviations: CAU: care as usual, LV-HIT: low volume-high intensity training, HV-HIT: high volume-high intensity training, SMS+: with short message service support, SMS-: without short message service support.										

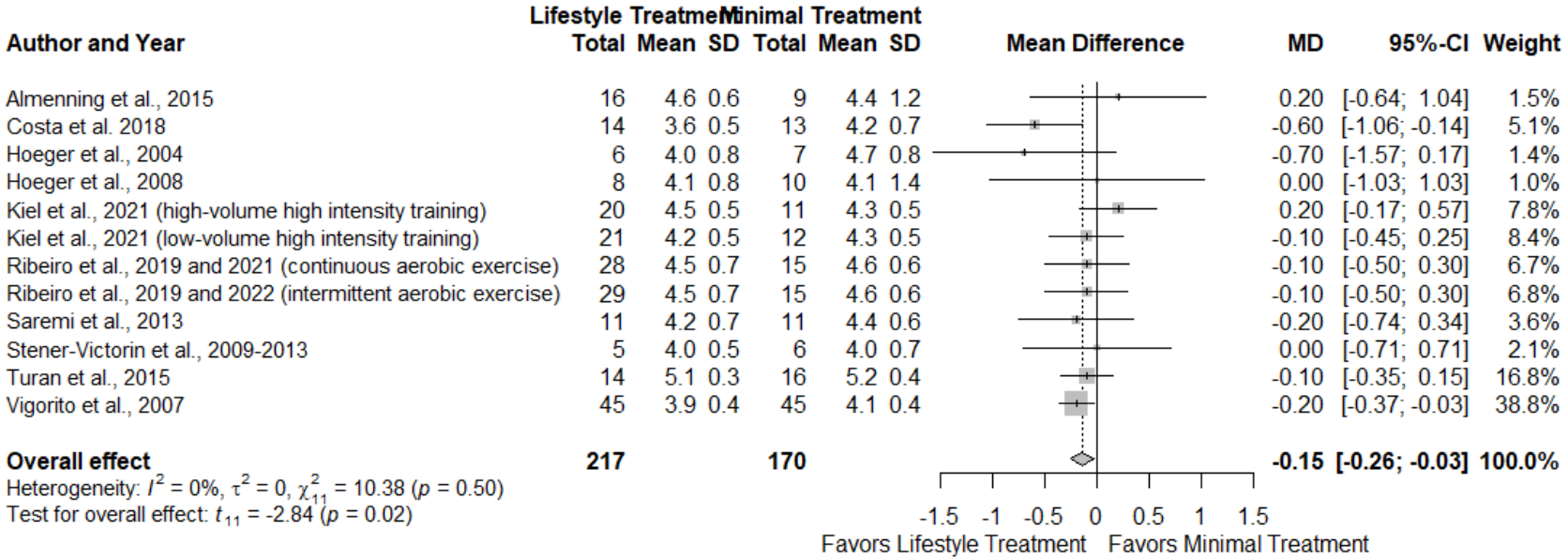
Figure 12. Forest plot of comparison: Lifestyle intervention versus minimal treatment: Outcome: Fasting insulin (pmol/L). For insulin, mean changes instead of post-intervention data were used for Oberg 2018 and Stener-Victorin 2009-2013 (Cochrane review 2019, Issue 3. Art. No.: CD007506). Meta-analyses of weight outcome: Lifestyle treatment groups exhibited decreased fasting levels vs minimal treatment post-intervention (N=14 effect estimates; MD: -1.87; 95%CI [-3.10; -0.65]; P=0.0056; see forest plot below).



OUTCOME: Total cholesterol						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Almenning et al., 2015	mmol/L	Not Reported	Mean difference: 4.6	0.6 (SD)	16	Mean difference: 4.4	1.2 (SD)	9	Crude	Not Applicable
Costa et al. 2018	mmol/L	Colorimetric method/enzyme in equipment Bioplus, 2000 model	Baseline exercise: 3.87 Post-intervention: 3.58	Baseline exercise: 0.5 (SD) Post-intervention: 0.54 (SD)	14	Baseline control: 3.8 Post-intervention: 4.18	Baseline control: 0.71 (SD) Post-intervention: 0.66 (SD)	13	Crude	Not Applicable
Dietz de Loos et al. 2022	mmol/L	COBAS 8000 Modular Analyser	Baseline only median SMS+: 4.8 SMS-: 4.7 Median Baseline SMS+: 4.7 Baseline SMS-: 4.8 Post-intervention SMS+: 4.3 Post-intervention SMS-: 4.6	Baseline only SMS+: (4.2-5.4 IQR) SMS-: (4.2-5.4 IQR) Post-intervention data not reported	Baseline SMS+: 60 SMS-: 63 Completed study SMS+: 16 SMS-: 27	Baseline only median CAU: 4.8 Median Baseline CAU: 4.7 Post-intervention CAU: 4.7	Baseline only: (4-5.2 IQR) Post-intervention data not reported	Baseline CAU: 60 Completed study 24	Crude	Not Applicable
Hoeger et al., 2004	mmol/L	Not Reported	Mean difference: 4	0.8 (SD)	6	Mean difference: 4.7	0.8 (SD)	7	Crude	Not Applicable
Hoeger et al., 2008	mmol/L	Not Reported	Mean difference: 4.1	0.8 (SD)	8	Mean difference: 4.1	1.4 (SD)	10	Crude	Not Applicable

Kiel et al. 2021	mmol/L	Not Reported	Baseline LV-HIT: 4.7 Baseline HV-HIT: 4.2 16-wk post-intervention LV-HIT: 4.2 16-wk post-intervention HV-HIT: 4.5	Baseline LV-HIT: 0.8 (SD) Baseline HV-HIT: 0.7 (SD) 16-wk post-intervention LV-HIT: (3.9-4.4 CI) 16-wk post-intervention HV-HIT: (4.2-4.7 CI)	LV-HIT: 21 HV-HIT: 20	Baseline control: 4.3 16-wk post-intervention control: 4.3	Baseline control: 0.7 (SD) 16-wk post-intervention control: (4.1-4.5 CI)	23	Crude	Not Applicable
Ribeiro et al. 2019 and 2021	mg/dL	Enzymatic method	Baseline continuous = 184.64 4 months continuous = 171.45 Baseline intermittent = 178.86 4 months intermittent = 174.17	Baseline continuous = 29.83 4 months continuous = 28.07 Baseline intermittent = 29.34 4 months intermittent = 26.86	continuous = 28 intermittent = 29	Baseline = 188.27 4 months = 177.53	Baseline = 34.13 4 months = 24.44	30	Adjusted	Age, BMI, testosterone and androstenedione for the 2021 paper
Saremi et al., 2013	mmol/L	Not Reported	Mean difference: 4.2	0.7 (SD)	11	Mean difference: 4.4	0.6 (SD)	11	Crude	Not Applicable
Stener-Victorin et al., 2009-2013	mmol/L	Not Reported	Mean difference: 4	0.5 (SD)	5	Mean difference: 4	0.7 (SD)	6	Crude	Not Applicable
Turan et al., 2015	mmol/L	Not Reported	Mean difference: 5.1	0.3 (SD)	14	Mean difference: 5.2	0.4 (SD)	16	Crude	Not Applicable
Vigorito et al., 2007	mmol/L	Not Reported	Mean difference: 3.9	0.4 (SD)	45	Mean difference: 4.1	0.4 (SD)	45	Crude	Not Applicable
Abbreviations: CAU: care, as usual, LV-HIT: low volume-high intensity training, HV-HIT: high volume-high intensity training, SMS+: with short message service support, SMS-: without short message service support.										

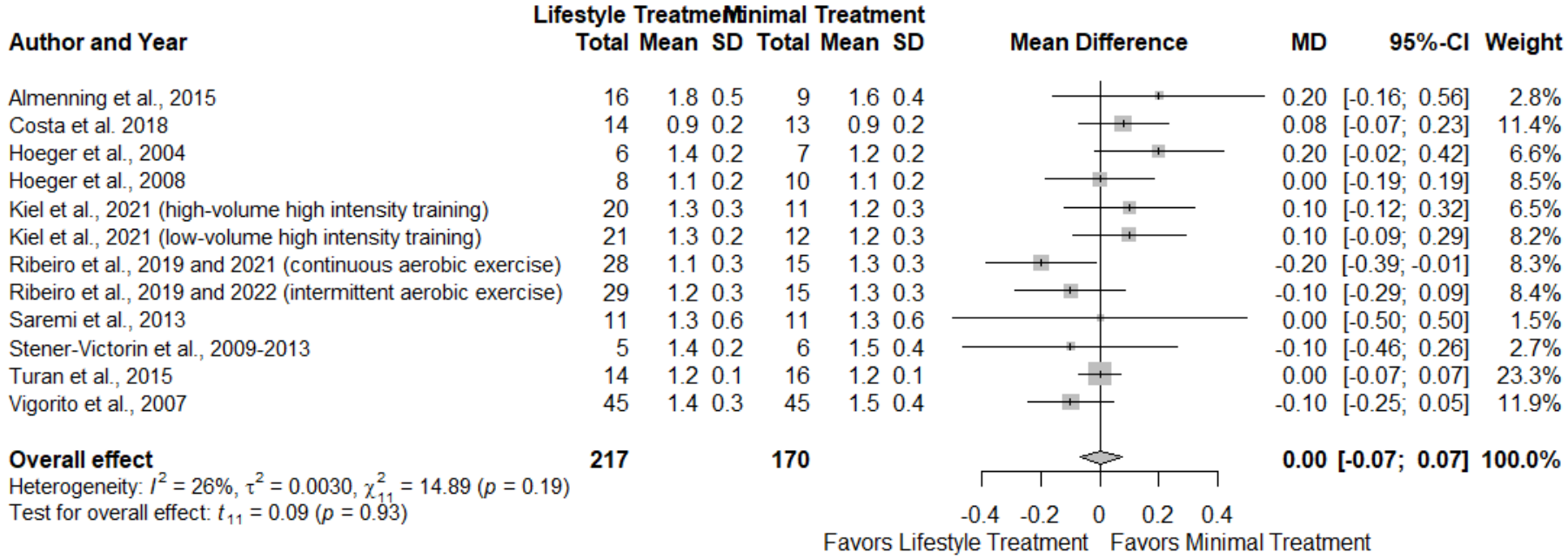
Figure 13. Forest plot of comparison: Lifestyle intervention versus minimal treatment: Outcome: Total cholesterol (mmol/L). For total cholesterol, post-intervention data were used for Costa et al. 2018, Kiel et al. 2021, and Riberio et al., 2019-2021. Meta-analyses of weight outcome: Lifestyle treatment groups exhibited decreased total testosterone levels vs minimal treatment post-intervention (N=12 effect estimates; MD: -1.15; 95%CI [-0.26; -0.03]; P=0.0056; see forest plot below).



OUTCOME: HDL-C						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Almenning et al., 2015	mmol/L	Not Reported	Mean difference: 1.8	0.5 (SD)	16	Mean difference: 1.6	0.4 (SD)	9	Crude	Not Applicable
Costa et al. 2018	mmol/L	Colorimetric method/enzyme in equipment Bioplus, 2000 model	Baseline exercise: 0.91 Post-intervention exercise: 0.95	Baseline exercise: 0.2 (SD) Post-intervention: 0.21 (SD)	14	Baseline control: 0.85 Post-intervention control: 0.87	Baseline control: 0.19 (SD) Post-intervention control: 0.19 (SD)	13	Crude	Not Applicable
Dietz de Loos et al. 2022	mmol/L	COBAS 8000 Modular Analyser	Baseline only median SMS+: 0.93 SMS-: 0.9 Median Baseline SMS+: 0.94 Baseline SMS-: 0.95 Post-intervention SMS+: 0.9 Post-intervention SMS-: 0.97	Baseline only SMS+: (0.79-1.05 IQR) SMS-: (0.76-1.1 IQR) Post-intervention data not reported	Baseline SMS+: 60 SMS-: 63 Completed study SMS+: 16 SMS-: 27	Baseline only median CAU: 0.85 Median Baseline CAU: 0.87 Post-intervention CAU: 0.93	Baseline only: (0.73-0.98 IQR) Post-intervention data not reported	Baseline CAU: 60 Completed study 24	Crude	Not Applicable
Hoeger et al., 2004	mmol/L	Not Reported	Mean difference: 1.4	0.2 (SD)	6	Mean difference: 1.2	0.2 (SD)	7	Crude	Not Applicable
Hoeger et al., 2008	mmol/L	Not Reported	Mean difference: 1.1	0.2 (SD)	8	Mean difference: 1.1	0.2 (SD)	10	Crude	Not Applicable
Kiel et al. 2021	mmol/L	Not Reported	Baseline LV-HIT: 1.4	Baseline LV-HIT: 0.4 (SD)	LV-HIT: 21 HV-HIT: 20	Baseline control: 1.3	Baseline control: 0.4 (SD)	23	Crude	Not Applicable

			Baseline HV-HIT: 1.3 16-wk post-intervention LV-HIT: 1.3 16-wk post-intervention HV-HIT: 1.3	Baseline HV-HIT: 0.3 (SD) 16-wk post-intervention LV-HIT: (1.2-1.4 CI) 16-wk post-intervention HV-HIT: (1.2-1.5 CI)		16-wk post-intervention control: 1.2	16-wk post-intervention control: (1.1-1.4 CI)			
Ribeiro et al. 2019 and 2021	mg/dL	Enzymatic method	Baseline continuous = 45.67 4 months continuous = 44.28 Baseline intermittent = 48.78 4 months intermittent = 47.08	Baseline continuous = 9.33 4 months continuous = 10.29 Baseline intermittent = 10.62 4 months intermittent = 10.27	continuous = 28 intermittent = 29	Baseline = 50.10 4 months = 48.47	Baseline = 13.09 4 months = 12.66	30	Adjusted	Age, BMI, testosterone, and androstenedione for the 2021 paper
Saremi et al., 2013	mmol/L	Not Reported	Mean difference: 1.3	0.6 (SD)	11	Mean difference: 1.3	0.6 (SD)	11	Crude	Not Applicable
Stener-Victorin et al., 2009-2013	mmol/L	Not Reported	Mean difference: 1.4	0.2 (SD)	5	Mean difference: 1.5	0.4 (SD)	6	Crude	Not Applicable
Turan et al., 2015	mmol/L	Not Reported	Mean difference: 1.2	0.1 (SD)	14	Mean difference: 1.2	0.1 (SD)	16	Crude	Not Applicable
Vigorito et al., 2007	mmol/L	Not Reported	Mean difference: 1.4	0.3 (SD)	45	Mean difference: 1.5	0.4 (SD)	45	Crude	Not Applicable
Abbreviations: CAU: care as usual, *HDL-C: high-density lipoprotein cholesterol, LV-HIT: low volume-high intensity training, HV-HIT: high volume-high intensity training, SMS+: with short message service support, SMS-: without short message service support.										

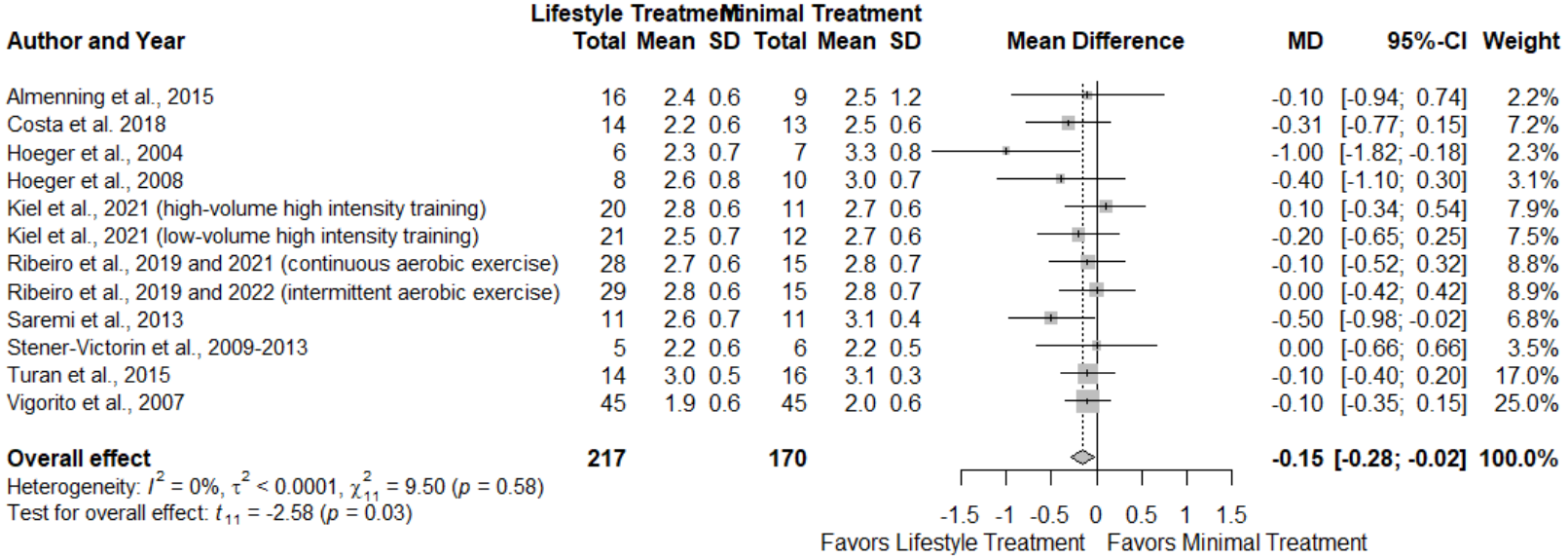
Figure 14. Forest plot of comparison: Lifestyle intervention versus minimal treatment: Outcome: HDL-C (mmol/L). For HDL-C, post-intervention data were used for Costa et al. 2018, Kiel et al. 2021, and Riberio et al., 2019-2021. Meta-analyses of weight outcome: Lifestyle treatment groups exhibited comparable HDL levels vs minimal treatment post-intervention (N=12 effect estimates; MD: 0.0; 95%CI [-0.07; 0.07]; P=0.9285; see forest plot below).



OUTCOME: LDL-C										**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Almenning et al., 2015	mmol/L	Not Reported	Mean difference: 2.4	0.6 (SD)	16	Mean difference: 2.5	1.2 (SD)	9	Crude	Not Applicable
Costa et al. 2018	mmol/L	Colorimetric method/enzyme in equipment Bioplus, 2000 model	Baseline exercise: 2.44 Post-intervention exercise: 2.18	Baseline exercise: 0.57 (SD) Post-intervention exercise: 0.58 (SD)	14	Baseline control: 2.09 Post-intervention control: 2.49	Baseline control: 0.75 (SD) Post-intervention: 0.64 (SD)	13	Crude	Not Applicable
Dietz de Loos et al. 2022	mmol/L	COBAS 8000 Modular Analyser	Baseline only median SMS+: 3.17 SMS-: 3.16 Median Baseline SMS+: 3.21 Baseline SMS-: 3.24 Post-intervention SMS+: 2.91 Post-intervention SMS-: 3.07	Baseline only SMS+: (2.67-3.83 IQR) SMS-: (2.65-3.85 IQR) Post-intervention data not reported	Baseline SMS+: 60 SMS-: 63 Completed study SMS+: 16 SMS-: 27	Baseline only median CAU: 3.17 Median Baseline CAU: 3.25 Post-intervention CAU: 3.14	Baseline only: (2.61-3.73 IQR) Post-intervention data not reported	Baseline CAU: 60 Completed study: 24	Crude	Not Applicable
Hoeger et al., 2004	mmol/L	Not Reported	Mean difference: 2.3	0.7 (SD)	6	Mean difference: 3.3	0.8 (SD)	7	Crude	Not Applicable
Hoeger et al., 2008	mmol/L	Not Reported	Mean difference: 2.6	0.8 (SD)	8	Mean difference: 3	0.7 (SD)	10	Crude	Not Applicable
Kiel et al. 2021	mmol/L	Not Reported	Baseline LV-HIT: 2.9	Baseline LV-HIT: 0.9 (SD)	LV-HIT: 21 HV-HIT: 20	Baseline control: 2.7	Baseline control: 0.7 (SD)	23	Crude	Not Applicable

			Baseline HV-HIT: 2.6 16-wk post-intervention LV-HIT: 2.5 16-wk post-intervention HV-HIT: 2.8	Baseline HV-HIT: 0.7 (SD) 16-wk post-intervention LV-HIT: (2.2-2.8 CI) 16-wk post-intervention HV-HIT: (2.5-3.1 CI)		16-wk post-intervention control: 2.7	16-wk post-intervention control: (2.5-3.0 CI)			
Ribeiro et al. 2019 and 2021	mg/dL	Fried Ewald formula: TC - HDL-C + TG/5 (see TC. HDL-C and TG tables for specific analysis techniques)	Baseline continuous = 111.71 4 months continuous = 102.46 Baseline intermittent = 112.31 4 months intermittent = 106.24	Baseline continuous = 23.55 4 months continuous = 23.14 Baseline intermittent = 23.49 4 months intermittent = 23.19	continuous = 28 intermittent = 29	Baseline = 115.73 4 months = 108.33	Baseline = 31.55 4 months = 26.80	30	Adjusted	Age, BMI, testosterone and androstenedione for the 2021 paper
Saremi et al., 2013	mmol/L	Not Reported	Mean difference: 2.6	0.7 (SD)	11	Mean difference: 3.1	0.4 (SD)	11	Crude	Not Applicable
Stener-Victorin et al., 2009-2013	mmol/L	Not Reported	Mean difference: 2.2	0.6 (SD)	5	Mean difference: 2.2	0.5 (SD)	6	Crude	Not Applicable
Turan et al., 2015	mmol/L	Not Reported	Mean difference: 3	0.5 (SD)	14	Mean difference: 3.1	0.3 (SD)	16	Crude	Not Applicable
Vigorito et al., 2007	mmol/L	Not Reported	Mean difference: 1.9	0.6 (SD)	45	Mean difference: 2	0.6 (SD)	45	Crude	Not Applicable

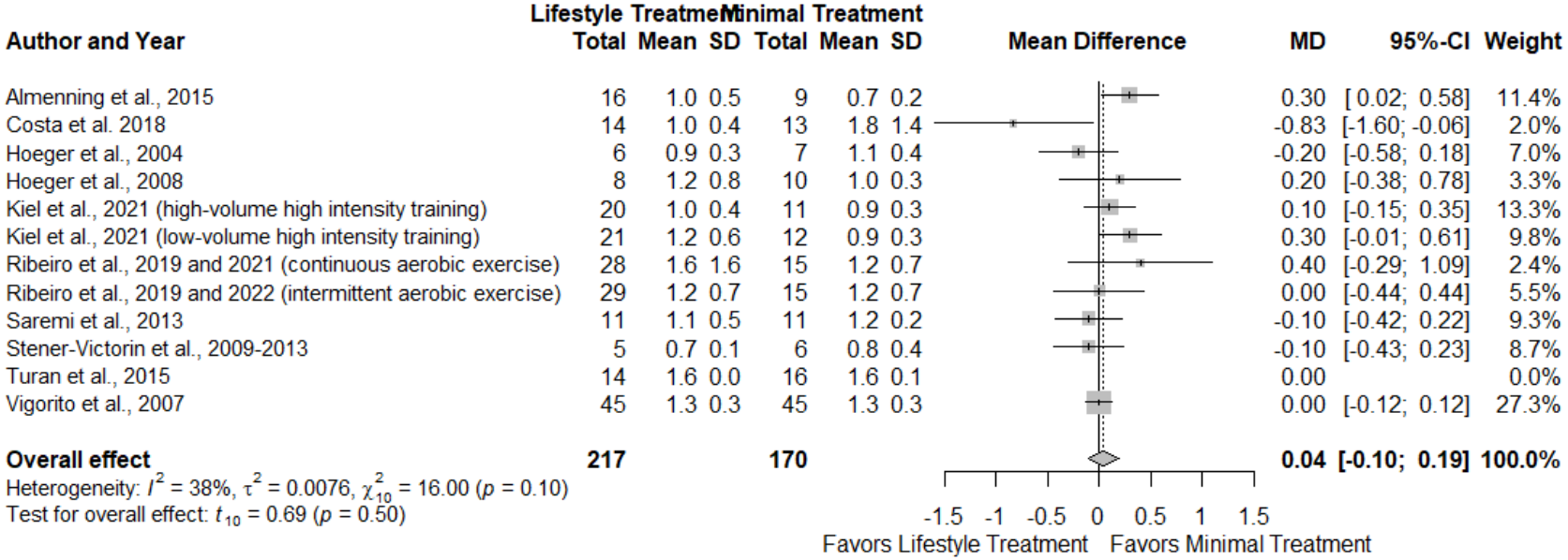
Figure 15. Forest plot of comparison: Lifestyle intervention versus minimal treatment: Outcome: LDL-C (mmol/L). For LDL-C, post-intervention data were used for Costa et al. 2018, Kiel et al. 2021, and Riberio et al., 2019-2021. Lifestyle treatment groups exhibited decreased LDL levels vs minimal treatment post-intervention (N=12 effect estimates; MD: -0.15; 95%CI [-0.28; -0.02]; P=0.0256; see forest plot below).



OUTCOME: Triglyceride										
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Almenning et al., 2015	mmol/L	Not Reported	Mean difference: 1	0.5 (SD)	16	Mean difference: 0.7	0.2 (SD)	9	Crude	Not Applicable
Costa et al. 2018	mmol/L	Colorimetric method/enzyme in equipment Bioplus, 2000 model	Baseline exercise: 1.13 Post-intervention exercise: 0.97	Baseline exercise: 0.51 (SD) Post-intervention exercise: 0.38 (SD)	14	Baseline control: 1.68 Post-intervention: 1.8	Baseline control: 0.7 (SD) Post-intervention: 1.36 (SD)	13	Crude	Not Applicable
Dietz de Loos et al. 2022	mmol/L	COBAS 8000 Modular Analyser	Baseline only median SMS+: 1.12 SMS-: 1.23 Median Baseline SMS+: 1.33 Baseline SMS-: 1.39 Post-intervention SMS+: 1.22 Post-intervention SMS-: 1.24	Baseline only SMS+: (0.83-1.69 IQR) SMS-: (0.91-1.7 IQR) Post-intervention data not reported	Baseline SMS+: 60 SMS-: 63 Completed study SMS+: 16 SMS-: 27	Baseline only median CAU: 1.27 Median Baseline CAU: 1.39 Post-intervention CAU: 1.45	Baseline only: (0.83-1.78 IQR) Post-intervention data not reported	Baseline CAU: 60 Completed study: 24	Crude	Not Applicable
Hoeger et al., 2004	mmol/L	Not Reported	Mean difference: 0.9	0.3 (SD)	6	Mean difference: 1.1	0.4 (SD)	7	Crude	Not Applicable
Hoeger et al., 2008	mmol/L	Not Reported	Mean difference: 1.2	0.8 (SD)	8	Mean difference: 1	0.3 (SD)	10	Crude	Not Applicable
Kiel et al. 2021	mmol/L	Not Reported	Baseline LV-HIT: 1.1	Baseline LV-HIT: 0.7 (SD)	LV-HIT: 21 HV-HIT: 20	Baseline control: 1.1	Baseline control: 0.6 (SD)	23	Crude	Not Applicable

			Baseline HV-HIT: 1.1 16-wk post-intervention LV-HIT: 1.2 16-wk post-intervention HV-HIT: 1.0	Baseline HV-HIT: 0.5 (SD) 16-wk post-intervention LV-HIT: (1.0-1.5 CI) 16-wk post-intervention HV-HIT: (0.9-1.3 CI)		16-wk post-intervention control: 0.9	16-wk post-intervention control: (0.8-1.1 CI)			
Ribeiro et al. 2019 and 2021	mg/dL	Enzymatic method	Baseline continuous = 151.43 4 months continuous = 144.35 Baseline intermittent = 98.62 4 months intermittent = 106.83	Baseline continuous = 172.63 4 months continuous = 139.16 Baseline intermittent = 54.49 4 months intermittent = 60.85	continuous = 28 intermittent = 29	Baseline = 111.77 4 months = 103.17	Baseline = 55.82 4 months = 58.87	30	Adjusted	Age, BMI, testosterone and androstenedione for the 2021 paper
Saremi et al., 2013	mmol/L	Not Reported	Mean difference: 1.1	0.5 (SD)	11	Mean difference: 1.2	0.2 (SD)	11	Crude	Not Applicable
Stener-Victorin et al., 2009-2013	mmol/L	Not Reported	Mean difference: 0.7	0.1 (SD)	5	Mean difference: 0.8	0.4 (SD)	6	Crude	Not Applicable
Turan et al., 2015	mmol/L	Not Reported	Mean difference: 1.6	0 (SD)	14	Mean difference: 1.6	0.1 (SD)	16	Crude	Not Applicable
Vigorito et al., 2007	mmol/L	Not Reported	Mean difference: 1.3	0.3 (SD)	45	Mean difference: 1.3	0.3 (SD)	45	Crude	Not Applicable
Abbreviations: CAU: care as usual, LV-HIT: low volume-high intensity training, HV-HIT: high volume-high intensity training, SMS+: with short message service support, SMS-: without short message service support.										

Figure 16. Forest plot of comparison: Lifestyle intervention versus minimal treatment: Outcome: Triglyceride (mmol/L). For triglyceride, post-intervention data were used for Costa et al. 2018 (Cochrane review 2019, Issue 3. Art. No.: CD007506). Meta-analyses of weight outcome: Groups exhibited comparable TG post intervention (N=11 effect estimates; MD: 0.04; 95%CI [-0.10; 0.19]; P=0.5036; see forest plot below).



OUTCOME: Quality of life										
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Kogurea et al., 2020	Perceived BMI (kg/m^2) Desired BMI (kg/m^2) Ideal BMI (kg/m^2) Decrease/increase score Perceptive accuracy score	Questionnaire (FRS)	Perceived BMI Baseline CAT: 32.0 Baseline IAT: 33.6 Post-intervention CAT: 31.2 Post-intervention IAT: 32.5 Desired BMI Baseline CAT: 23.4 Baseline IAT: 24.2 Post-intervention CAT: 22.6 Post-intervention IAT: 24.3 Ideal BMI Baseline CAT: 22.5 Baseline IAT: 23.5 Post-intervention CAT: 21.2 Post-intervention IAT: 23 Decrease/increase score Baseline CAT: -5.0 Baseline IAT: -4.4 Post-intervention CAT: -5.5 Post-intervention IAT: -4.2 Perceptive accuracy score Baseline CAT: 3.6 Baseline IAT: 33.6	Perceived BMI Baseline CAT: 7.4 (SD) Baseline IAT: 6.4 (SD) Post-intervention CAT: 9.1 (SD) Post-intervention IAT: 6.4 (SD) Desired BMI Baseline CAT: 5.9 (SD) Baseline IAT: 5.4 (SD) Post-intervention CAT: 6.0 (SD) Post-intervention IAT: 4.4 (SD) Ideal BMI Baseline CAT: 5.6 (SD) Baseline IAT: 6.8 (SD) Post-intervention CAT: 6.6 (SD)	CAT: 30 IAT: 29	Perceived BMI Baseline control: 32 Post-intervention control: 32.4 Desired BMI Baseline control: 23.6 Post-intervention control: 23.1 Ideal BMI Baseline control: 22.8 Post-intervention control: 22.4 Decrease/increase score Baseline control: -5.4	Perceived BMI Baseline control: 7.3 (SD) Post-intervention control: 6.2 (SD) Desired BMI Baseline control: 6.4 (SD) Post-intervention control: 5.6 (SD) Ideal BMI Baseline control: 5.3 (SD) Post-intervention control: 5.1 (SD)	30	Crude	Not Applicable

			Post-intervention CAT: 3 Post-intervention IAT: 3.9	Post-intervention IAT: 5.1 (SD) Decrease/increase score Baseline CAT: 4.8 (SD) Baseline IAT: 4.0 (SD) Post-intervention CAT: 4.3 (SD) Post-intervention IAT: 4.4(SD) Perceptive accuracy score Baseline CAT: 4.0 (SD) Baseline IAT: 6.4 (SD) Post-intervention CAT: 7.4 (SD) Post-intervention IAT: 4.2 (SD)		Post-intervention control: -6.8 Perceptive accuracy score Baseline control: 2.9 Post-intervention control: 2.3	Decrease/increase score Baseline control: 6.3 (SD) Post-intervention control: 6.5 (SD) Perceptive accuracy score Baseline control: 6.0 (SD) Post-intervention control: 6.1 (SD)			
Kogurea et al., 2020	Dissatisfaction grade	Questionnaire (BSQ)	Baseline CAT: 104.0 Baseline IAT: 111.1 Post-intervention CAT: 90.9 Post-intervention IAT: 98.8	Baseline CAT: 34.7 (SD) Baseline IAT: 30.7 (SD) Post-intervention CAT: 37.6 (SD) Post-intervention IAT: 30.5 (SD)	CAT: 30 IAT: 29	Baseline control: 110.9 Post-intervention control: 109.2	Baseline control: 40.8 (SD) Post-intervention control: (SD) 42.3	30	Crude	Not Applicable
Kogurea et al., 2020	Score	Questionnaire (FSFI)	Baseline CAT: 24.9 Baseline IAT: 25.0 Post-intervention CAT: 28 Post-intervention IAT: 29.9	Baseline CAT: 5.6 (SD) Baseline IAT: 6.5 (SD) Post-intervention CAT: 4.2 (SD)	CAT: 23 IAT: 22	Baseline control: 26.2 Post-intervention control: 25.3	Baseline control: 5.3 (SD) Post-intervention control: (SD)	24	Crude	Not Applicable

				Post-intervention IAT: 4.0 (SD)			5.6			
Kogurea et al. 2020	Anxiety Depression	Questionnaire (HADS)	Anxiety Baseline CAT: 8.9 Baseline IAT: 7.6 Post-intervention CAT: 6.7 Post-intervention IAT: 5.8 Depression Baseline CAT: 7.1 Baseline IAT: 5.6 Post-intervention CAT: 4.8 Post-intervention IAT: 4.0	Anxiety Baseline CAT: 3.8 (SD) Baseline IAT: 3.8 (SD) Post-intervention CAT: 3.6 (SD) Post-intervention IAT: 2.7 (SD) Depression Baseline CAT: 4.0 (SD) Baseline IAT: 3.6 (SD) Post-intervention CAT: 3.8 (SD) Post-intervention IAT: 3.2 (SD)	CAT: 30 IAT: 29	Anxiety Baseline control: 8.8 Post-intervention control: 8.4 Depression Baseline control: 6.9 Post-intervention control: 6.8	Anxiety Baseline control: 4.1 (SD) Post-intervention control: 4.7 (SD) Depression Baseline control: 3.9 (SD) Post-intervention control: 4.5 (SD)	30 30	Crude	Not Applicable
Moeller et al. 2018	Physical function score Physical health score Emotional health score Energy score Emotional score Social function score Pain score General health score	Questionnaire (SF-36)	Physical function score Baseline score: 90 Median difference: 5 Physical health score Baseline score: 75 Median difference: 0 Emotional health score Baseline score: 67 Median difference: 0 Energy score Baseline score: 45 Median difference: 5 Emotional well-being	Physical function score Baseline IQR: (54, 95) Post-intervention IQR: (0,9) Physical health score Baseline IQR: (56,100) Post-intervention IQR: (0, 31) Emotional health score	14	Physical function score Baseline score: 90 Median difference: 0 Physical health score Baseline score: 75 Median difference: 0 Emotional health score	Physical function score Baseline IQR: (65,100) Post-intervention IQR: (-5,8) Physical health score Baseline IQR: (25,100) Post-intervention IQR: (0, 25)	14	Crude	Not Applicable

			Baseline score: 60 Median difference: 12 Social function score Baseline score: 75 Median difference: 0 Pain score Baseline score: 74 Median difference: 0 General health score Baseline score: 60 Median difference: 10	Baseline IQR: (33, 100) Post-intervention IQR: (0, 67) Energy score Baseline IQR: (30, 69) Post-intervention IQR: (-5,36) Emotional well-being Baseline IQR: (54, 74) Post-intervention IQR: (-8, 25) Social function score Baseline IQR: (50, 100) Post-intervention IQR: (-16, 19) Pain score Baseline IQR: (43, 100) Post-intervention IQR: (-11,33) General health score Baseline IQR: (36, 80) Post-intervention IQR: (-5, 25)		Baseline score: 33 Median difference: 0 Energy score Baseline score: 25 Median difference: 15 Emotional well-being Baseline score: 40 Median difference: 13 Social function score Baseline score: 75 Median difference: 13 Pain score Baseline score: 68 Median difference: 0 General health score Baseline score: 40 Median difference: 15	Emotional health score Baseline IQR: (0, 67) Post-intervention IQR: (-17, 67) Energy score Baseline IQR: (18, 38) Post-intervention IQR: (-5,35) Emotional well-being Baseline IQR: (34, 56) Post-intervention IQR: (-4, 32) Social function score Baseline IQR: (38, 100) Post-intervention IQR: (-6, 38) Pain score Baseline IQR: (51, 84) Post-intervention IQR: (-18, 23) General health score			

							Baseline IQR: (25, 63) Post-intervention IQR: (-8, 25)			
Moeller et al. 2018	score	Questionnaire (MDI)	Baseline: 16 Median difference: -6	Baseline IQR (10, 29) IQR (-17;-1)	14	Baseline: 30 Median difference: -2	Baseline IQR (14, 35) IQR (-14, 6)	14	crude	Not Applicable
Moeller et al. 2018	score	Questionnaire (WHO-5)	Baseline: 46 Median difference: 8	Baseline IQR (35, 60) IQR (-5;25)	14	Baseline: 32 Median difference (24)	Baseline IQR (22, 52) IQR (-4;44)	14	crude	Not Applicable
Moeller et al. 2018	Weight score Emotion score Hair score Infertility score Menstruation score	Questionnaire (PCOS-Q)	Weight score Baseline: 6 Median difference:0 Emotion score Baseline: 4 Median difference:-1 Hair score Baseline: 4 Median difference:0 Infertility score Baseline: 3 Median difference:-1 Menstruation score Baseline: 4 Median difference:-1	Weight score Baseline IQR: (5,7) IQR: (-1, 0) Emotion score Baseline IQR: (2,4) IQR: (-1, 1) Hair score Baseline IQR: (3,5) IQR: (-1, 0) Infertility score Baseline IQR: (2,4) IQR: (-1, 0) Menstruation score Baseline IQR: (3,5) IQR: (-2, 0)	14	Weight score Baseline: 6 Median difference: -1 Emotion score Baseline: 4 Median difference: 0 Hair score Baseline: 5 Median difference: 0 Infertility score Baseline: 4 Median difference: 0 Menstruation score Baseline: 5 Median difference: 0	Weight score Baseline IQR: (5,7) IQR: (-2, 0) Emotion score Baseline IQR: (3,5) IQR: (-1, 1) Hair score Baseline IQR: (3,6) IQR: (-1, 0) Infertility score Baseline IQR: 3,6) IQR: (-1, 0) Menstruation score Baseline IQR: (3,6) IQR: (-1, 1)	14	crude	Not Applicable
Ribeiro, 2019 and 2021	score	Questionnaire	NB: Difference between baseline and 4 months is reported for all subscales	NB: 95% CI is reported for all subscales	continuous = 28	NB: Difference between baseline and 4	NB: 95% CI is reported for all subscales	30	Adjusted	Age, BMI, WHR,

		(Portuguese version of the self-reported MOS SF-36)	though baseline and 4 month data is also available Physical role functioning subscale continuous =−8.53 Physical role functioning subscale intermittent = −17.04 Physical functioning subscale continuous = −23.37 Physical functioning subscale intermittent = −15.66 Bodily pain subscale continuous = −5.35 Bodily pain subscale intermittent = −4.92 General health perception subscale continuous = −7.97 General health perception subscale intermittent = −13.26 Vitality subscale continuous = −13.24 Vitality subscale intermittent = −18.12 Social role functioning subscale continuous = −15.73 Social role functioning subscale intermittent = −11.97	Physical role functioning subscale continuous = −15.85 to −1.26 Physical role functioning subscale intermittent =−24.21 to −9.87 Physical functioning subscale continuous = −37.48 to −9.2 Physical functioning subscale intermittent = −29.53 to −1.79 Bodily pain subscale continuous = −13.82 to 3.12 Bodily pain subscale intermittent = −13.26 to 3.41 General health perception subscale continuous = −13.7 to −2.23 General health perception subscale intermittent = −18.91 to −7.62 Vitality subscale continuous = −20.54 to −5.95	intermittent = 29	months is reported for all subscales though baseline and 4 month data is also available Physical role functioning subscale = −4.63 Physical functioning subscale = 10.10 Bodily pain subscale = −0.54 General health perception subscale = 0.28 Vitality subscale = −5.38 Social role functioning subscale = −6.89 Emotional role functioning subscale = 1.23	Physical role functioning subscale = −11.60 to 2.32 Physical functioning subscale = −3.37 to 23.57 Bodily pain subscale = −8.60 to 7.53 General health perception subscale = −5.17 to 5.74 Vitality subscale = −12.32 to 1.55 Social role functioning subscale = −15.43 to 1.64 Emotional role functioning subscale = −14.03 to 16.49 Mental health subscale = −10.17 to 3.08			testosterone for the 2019 paper

			Emotional role functioning subscale continuous = −23.89 Emotional role functioning subscale intermittent = −20.54 Mental health subscale continuous = −13.96 Mental health subscale intermittent = −11.68	Vitality subscale intermittent = −25.30 to −10.94 Social role functioning subscale continuous = −24.71 to −6.75 Social role functioning subscale intermittent = −20.81 to −3.13 Emotional role functioning subscale continuous = −39.90 to −7.88 Emotional role functioning subscale intermittent = −36.28 to −4.79 Mental health subscale continuous = −20.93 to −6.9 Mental health subscale intermittent = −18.54 to −4.81		Mental health subscale = −3.54				
Abbreviations: CAT: continuous aerobic training, IAT: intermittent aerobic training, PCOSQ: polycystic ovary syndrome questionnaire, FRS: Figure Rating Scale, BSQ: body shape questionnaire, FSFI: female sexual function index, HADS: hospital anxiety and depression scale, WHO-5: world health organization 5 wellbeing index, MDI: major depression inventory, SF-36: short-form-36.										

Meta-analyses outcomes: Meta-analyses were not conducted due to insufficient (n<3) RCTs reporting this outcome.

APPENDIX. STUDY CHARACTERISTICS AND QUALITY APPRAISAL

For clarity: N=7 RCTs (8 publications) retrieved in the updated search (after 2018 Guideline: search date March 5, 2018, to August 10, 2022) are shown in the green highlights below) and N=11 RCTs (15 publications) included in the Cochrane review are highlighted in grey below. Studies are sorted alphabetically.

Study ID	Almenning 2015
Study Citation	Almenning I, Rieber-Mohn A, Lundgren KM, Shetelig Løvvik T, Garnæs KK, Moholdt T. EIects of high intensity interval training and strength training on metabolic, cardiovascular and hormonal outcomes in women with polycystic ovary syndrome: a pilot study. PloS One 2015;10(9):e0138793.
Study Country	Norway
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS (age not reported)
PCOS diagnostic criteria	ESHRE/ASRM
Presence of infertility	Not Reported
Presence of other condition/s	Not Reported
Medication History	No
N per group	HIT (high intensity interval training), n= 10; ST (strength training), n= 11; control, n= 10
Setting	Not Reported
Intervention	HIT: "two weekly sessions of four x 4 minute HIT at 90-95% of individual heart rate maximum separated by three minutes of moderate-intensity exercise at 70% of HR, and one weekly session of ten x 1 minute with maximal intensity HIT, separated by one minute of rest/ very low activity." ST: "eight dynamic strength drills with a resistance of 75% of one repetition maximum, with 10 reps and three sets separated by one-minute rest between sets. The load was progressively increased once the participant could successfully perform three sets of ten reps."
Comparison	Maintain a normal diet and physical activity
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Testosterone, SHBG, FAI, total cholesterol, HDL-C, LDL-C, triglycerides, glucose, insulin, weight, BMI, waist circumference
Follow up Duration	10 weeks
Summary Result/s	High-intensity interval training for ten weeks improved insulin resistance, without weight loss, in women with polycystic ovary syndrome. Body composition improved significantly after both strength training and high-intensity interval training. This pilot study indicates that exercise training can improve the cardiometabolic profile in polycystic ovary syndrome in the absence of weight loss.

Study ID	Almenning 2015	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Not Reported
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes
Inclusion criteria	Yes Partial No Not reported	PCOS was defined according to the ESHRE/ASRM criteria: A minimum of two of the following: PCO morphology (12 or more 2-9mm follicle or >10mL in volume, in at least one ovary)". Hyperandrogenism (either clinical signs of hirsutism (Ferriman Gallwey score ≥8) or acne or biochemical (testosterone >3.0nmol/L, calculated free testosterone >32nmmol/L, SHBG 5%). Oligomenorrhea (intermenstrual interval >35 days and androgenism. If they fulfilled only one of these criteria, a vaginal ultrasound was done to confirm the diagnosis before study entry
Exclusion criteria	Yes Partial No Not reported	Regular high-intensity endurance or strength training (defined as > 2 sessions of vigorous exercise per week), physical ailments/injuries that limited exercise performance, ongoing pregnancy, concurrent treatments (insulin sensitizers as metformin and pioglitazone) or drugs known to affect gonadotropin or ovulation, with a wash out period of one month prior to inclusion. The exception was regular use of oral contraceptives, and women were included if they did not change the type or dose > 1 month prior to the study or during the intervention period.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

Study ID		Almenning 2015	
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Yes Computer random number generator developed and administered at Unit for Applied Clinical Research at the University to randomise the subjects, Baseline testing was done before randomization.
	Was allocation to intervention group concealed?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	No
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	No
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	Yes
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	No
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	HIT 2/10 = 20% ST 3/11 = 27.27% Control 1/10 = 10%
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	Not reported

Study ID		Almenning 2015	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Yes
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	Yes
	If confounding was present, was it controlled for?	Yes Partial No Not reported	NR
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	Not Reported
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Yes (stated there was a power calculation)
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Not Reported
COMMENTS		Lack of randomization and a blinding key reason for high RoB	
What is the overall risk of bias?		Low Moderate High Insufficient information	High (no blinding for participant reported outcomes and clinician reported outcomes)
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

Study ID	Brown 2009	
Study Citation	Brown AJ, Setji TL, Sanders LL, Lowry KP, Otvos JD, Kraus WE, et al. EIects of exercise on lipoprotein particles in women with polycystic ovary syndrome. Medicine and Sciences in Sports and Exercise 2009;41(3):497-504.	
Study Country	USA	
BRIEF CHARACTERISTICS OF RCT		
Patient/population/ participants	Women with PCOS (age 18-50)	
PCOS diagnostic criteria	8 or fewer menses per year and clinical or biochemical hyperandrogenism (hirsutism: Ferriman-Gallwey < 8 or bioavailable testosterone > 8.4 ng/dL, 2 SD above laboratory mean)	
Presence of infertility	Not Reported	
Presence of other condition/s	No	
Medication History	No	
N per group	Intervention, n= 21; control, n= 16	
Setting	Duke University Medical Centre	
Intervention	active weight maintenance encouraged, 8- to 12-week ramp-up followed by a 12-week moderate-intensity exercise program (16 to 24 weeks total, average 228 minutes/week at 40% to 60% peak VO2)	
Comparison	no change in lifestyle	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	bioavailable testosterone (Mayo Lab), Ferriman-Gallwey score (clinician assessed), OGTT glucose, lipid profile (total cholesterol, HDL-C, LDL-C, triglycerides by conventional spectrophotometric assays), fasting glucose and insulin, OGTT insulin, weight, BMI, waist/hip circumference	
Follow up Duration	24 weeks for intervention, 12 weeks for control	
Summary Result/s	Not Reported	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Moderate-intensity exercise without significant weight loss improved several components of the lipoprotein profiles of women with PCOS.
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	Yes

Study ID		Brown 2009	
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Inclusion criteria		Yes Partial No Not reported	PCOS, age 18 to 50 years, sedentary lifestyle (no regular exercise during the usual week), ability to come to study exercise facility for monitored exercise, agreement to maintain current weight/dietary patterns for study
Exclusion criteria		Yes Partial No Not reported	menopause, current/planned pregnancy, recent breastfeeding, congenital adrenal hyperplasia, uncontrolled thyroid disease, hyperprolactinemia, or fasting hyperglycemia (> 6.9 mmol/L), unresolved medical conditions, history of malignancy other than non-melanoma skin cancer in the past 5 years, study participation in past 30 days
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Yes Randomization was accomplished by generating a random sequence of two variables (for instance, As and Bs, representing the two treatment groups)
	Was allocation to intervention group concealed?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	No
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	No
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	No

Study ID		Brown 2009	
DETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	Not Reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	No
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Not Reported
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	Intervention 13/21 = 61.9% Control 4/16 = 25%
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	Not Reported
REPORTBIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	No
CONFOUN	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	Partial (intervention group significantly older)

Study ID		Brown 2009	
D I N G	**If confounding was present, was it controlled for?**	Yes Partial No Not reported	Not Reported
O T H E R B I A S	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	Not Reported
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Yes (stated there was a power calculation)
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Not Reported
COMMENTS		Lack of randomisation and blinding key reason for high RoB	
What is the overall risk of bias?		Low Moderate High Insufficient information	Insufficient information (low participant reported outcome bias but the unclear risk for clinician-reported outcome bias)
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

Study ID	Costa 2018	
Study Citation	Costa et al., Med. Sci. Sports Exerc. 50: 1357-1366, 2018	
Study Country	Brazil	
BRIEF CHARACTERISTICS OF RCT		
Patient/population/ participants	Women with PCOS (age 18 to 34 yr)	
PCOS diagnostic criteria	Rotterdam	
Presence of infertility	Not reported	
Presence of other condition/s	Obese (39.9 kg/m^2≥BMI≥25 kg/m^2)	
Medication History	Excluded if the patient uses medications (including over-the-counter preparation)	
N per group	Randomized: 30 (15 exercise; 15 control) Assessed at the end of study: 27 (13 exercise; 14 control)	
Setting	University Hospital, Federal University of Rio Grande do Norte, Natal/RN, Brazil	
Intervention	Supervise aerobic exercise training three times per week for 16 weeks	
Comparison	No exercise intervention	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Changes in body mass, waist circumference, cardiometabolic profile (HDL, LDL, TG, FG, PG, OGTT, insulin, IR), inflammatory markers (Il-6, TFN-alpha, CRP), blood pressure (systolic, diastolic, mean), and cardiorespiratory fitness (VO2 peak).	
Follow up Duration	16 weeks	
Summary Result/s	In the exercise group, patients improved their cardiometabolic profiles, reduced BMI, WC, resting SBP, DBP, MBP and TC. Patients also increased their VO2peak values. There were no changes in the markers of inflammation in the exercise group. In the control group, there were an increase in TNF-alpha. Exercise intervention was more effective in improving cardiometabolic profiles, anthropometry (body mass, waist circumference) cardiorespiratory fitness, and affective response versus the control.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes	The aim was to determine whether a supervised 16-weeks long aerobic exercise intervention would have different effects on body weight, circulating hormones, markers of inflammation, lipid profiles, and cardiorespiratory fitness.
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	Yes

Study ID		Costa 2018	
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Inclusion criteria		Yes Partial No Not reported	Rotterdam criteria: The diagnosis of PCOS included at least two of the three features: i. oligo-ovulation or anovulation, ii. clinical (hirsutism and acne) or biochemical hyperandrogenism, iii. ovarian morphology on ultrasound, Overweight and obese: BMI between 25 and 39.9 kg/m^2
Exclusion criteria		Yes Partial No Not reported	Women who participated in an exercise training program in the last three months and performed 150min/week or more exercise were excluded. None of the women had renal or hepatic dysfunction, used medications (including over-the-counter) known to impact anxiety, depression, reproductive, cardiovascular, or metabolic function within 90 days of the study.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Randomization was computer generated (randomization.com)
	Was allocation to intervention group concealed?	Yes Partial No Not reported	Not reported
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	No
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	Not reported
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	Yes

Study ID		Costa 2018	
DETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	Women in aerobic training 1/15=6.67% Women without exercise intervention 2/15=13.33%
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	Yes
REPORTBIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Yes
CONFOUN	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	Yes

Study ID		Costa 2018	
DING	**If confounding was present, was it controlled for?**	Yes Partial No Not reported	Not reported
OTHERBIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Yes
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS		Five participants were considered sample of convenience who could not engage in aerobic training since located in remote location and allocated into control group	
What is the overall risk of bias?		Low Moderate High Insufficient information	High
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		Yes	

Study ID	Dietz de Loos 2022	
Study Citation	Dietz de Loos et al., European *Journal of Endocrinology* 186: 53–64 2022	
Study Country	Netherlands	
BRIEF CHARACTERISTICS OF RCT		
Patient/population/ participants	Women with PCOS (age: 18 to 38 years)	
PCOS diagnostic criteria	Rotterdam	
Presence of infertility	Not reported	
Presence of other condition/s	BMI (>25 kg/m2)	
Medication History	No	
N per group	Allocated/randomised: 183 (60 SMS+; 63 SMS-; 60 CAU) Assessed at the end of study: 67 (16 SMS+; 27 SMS-; 24 CAU)	
Setting	Outpatient clinic within the division of reproductive endocrinology and infertility at Erasmus MC, Netherlands	
Intervention	Three-component lifestyle intervention (LSI) with short message service support (SMS+ or SMS-)	
Comparison	Care as usual	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Changes in body weight (BMI), metabolic parameters (HOMA-IR, SBP, DBP, glucose, insulin, cholesterol, HDL, LDL, TG), and Metabolic Syndrome (prevalence, cMetS z-score)	
Follow up Duration	One year	
Summary Result/s	Lifestyle intervention improved metabolic parameters and decreased weight and MetS prevalence versus control.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	The aim was to determine whether a lifestyle intervention with and without SMS support would have different effects on MetS prevalence, metabolic parameters, and weight loss.
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes

Study ID		Dietz de Loos 2022	
Inclusion criteria		Yes Partial No Not reported	The diagnosis of PCOS was achieved if at least of the following features were present: ovulatory dysfunction (cycle interval length > 35 or < 21 days), clinical (modified Ferriman Gallwey score ≥ 5), and/or biochemical (testosterone measured with RIA: free androgen index (FAI) cut off > 4.5 and/or total testosterone > 3.0, testosterone measured with liquid chromatography-tandem mass spectrometry (LC-MS/MS): FAI cut off > 2.9 and/or total testosterone > 2.0 nmol/L) hyperandrogenism and polycystic ovarian morphology (PCOM; ≥12 follicles (measuring 2–9 mm in diameter) and/or ovarian volume > 10 cm^3 in at least one ovary using an ultrasound machine with a transvaginal probe of less than 8 MHz).
Exclusion criteria		Yes Partial No Not reported	Patients who lacked proficient use of Dutch language were excluded. Also, patients who have severe mental illness, adrenal diseases or ovarian tumours, other causes of androgen excess or malformations of internal genitalia were excluded. Using endocrine screening, women with secondary endocrine, drug-relate, and genetic causes of secondary obesity were also excluded. If the patient became pregnant during the study, they were excluded.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Yes, women were randomly assigned using a computer-generated random numbers table.
	Was allocation to intervention group concealed?	Yes Partial No Not reported	Not reported
PERFORMANCE	**Were patients blind to intervention group?**	Yes Partial No Not reported	No
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	Not reported

Study ID		Dietz de Loos 2022	
BIAS	**Aside from the experimental intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes
DETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	Treatment SMS+ = 44/60 = 73.3% SMS- = 36/63 = 57.1% CAU 36/60 = 60%
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	Yes
REPORTBIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported
CONFOUN	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	Yes

Study ID		Dietz de Loos 2022	
FUNDING	**If confounding was present, was it controlled for?**	Yes Partial No Not reported	Not reported
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	J. L.reports grants from Ansh Labs, Webster, Tx, USA, grants from Ferring, Hoofddorp, NL, grants from Dutch Heart Association, Utrecht, NL, grants from Zon MW, Amsterdam, NL, grants from Astellas, Tokyo, Japan, grants from Roche Diagnostics, Basel, Switzerland, personal fees from Ferring, Hoofddorp, NL, personal fees from Titus Healthcare, Hoofddorp, NL and is an unpaid board member and president-elect of the AE-PCOS Society, outside the submitted work.
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Insufficient information
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		Not Applicable	

Study ID	Guzick 1994	
Study Citation	Guzick DS, Wing R, Smith D, Berga SL, Winters SJ. Endocrine consequences of weight loss in obese, hyperandrogenic, anovulatory women. Fertility and Sterility 1994;61(4):598-604.	
Study Country	USA	
BRIEF CHARACTERISTICS OF RCT		
Patient/population/ participants	Women with PCOS (age 20-40)	
PCOS diagnostic criteria	Anovulation or oligo-ovulation (< 4 bleeding episodes in previous 12 months, anovulation confirmed by weekly progesterone levels and only anovulatory women used) and negative pregnancy test, hyperandrogenism (testosterone > 2.43 mmol/L)	
Presence of infertility	Not Reported	
Presence of other condition/s	No	
Medication History	Not Reported	
N per group	Intervention, n= 6; control, n= 6	
Setting	University Research Centre, University of Pittsburgh School of Medicine	
Intervention	weight loss, 12-week behavioral weight control program comprising 8 weeks of very low-calorie diet (Optifast, additional meals and multivitamin supplement), then reintroduction of foods and gradual increase in energy intake until 4200 to 5040 kJ/day reached. Behavior modification training around eating behaviors, increasing energy expenditure (1050 kJ/week extra to 4200 kJ/week extra, 2 miles, 5x week	
Comparison	no treatment or study visits, 12-week waiting interval	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Ovulation, total testosterone, SHBG, non-SHBG testosterone (based on separation of SHBG-bound titrated from unbound and albumin-bound testosterone by ammonium sulfate precipitation, height, weight, body fat distribution (WHR), fasting glucose, insulin	
Follow up Duration	12 weeks	
Summary Result/s	Weight loss in obese, hyperandrogenic, anovulatory women appears to reduce insulin and non-SHBG T concentrations despite the absence of a change in gonadotropin secretion and may lead to resumption of ovulation.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Not Reported

Study ID		Guzick 1994	
Does the study have specified inclusion/exclusion criteria?		Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Inclusion criteria		Yes Partial No Not reported	PCOS, age 20 to 40 years, obese (between 130% and 200% of ideal body weight according to 1983 Metropolitan Height and Weight Tables for women), negative pregnancy test
Exclusion criteria		Yes Partial No Not reported	medical conditions that would compromise the safety of a very low-calorie diet, including chronic renal failure, cardiovascular or cerebrovascular disease, liver disease, cancer or psychosis, exclusion of specific causes of hyperandrogenism (tumour of the adrenal gland, congenital adrenal hyperplasia, Cushing's syndrome, acromegaly, hyperprolactinemia, drug-induced hyperandrogenism)
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Not Reported
	Was allocation to intervention group concealed?	Yes Partial No Not reported	Not Reported
PERFORMANCE	**Were patients blind to intervention group?**	Yes Partial No Not reported	No
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	No

Study ID		Guzick 1994	
BIAS	**Aside from the experimental intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes
DETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	Not Reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Not Reported
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Not Reported
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	Intervention 0% Control 0%
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	Not Reported
REPORTBIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not Reported
CONFOUN	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	Yes

Study ID		Guzick 1994	
CONFOUNDING	**If confounding was present, was it controlled for?**	Yes Partial No Not reported	Not Reported
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	Not Reported
OTHER BIAS	**Was the study sufficiently powered to detect any differences between the groups?**	Yes Partial No Not reported	No (stated there was no power calculation)
OTHER BIAS	**If statistical analysis was undertaken, was this appropriate?**	Yes Partial No Not reported	Not Reported
COMMENTS		Lack of randomisation and blinding key reason for high RoB	
What is the overall risk of bias?		Low Moderate High Insufficient information	Insufficient information (low risk for participant-reported outcome bias but unclear risk for clinician-reported outcome bias and objective outcomes)
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

Study ID	Hoeger 2004	
Study Citation	Hoeger KM, Kochman L, Wixom N, Craig K, Miller RK, Guzick DS. A randomized, 48-week, placebo-controlled trial of intensive lifestyle modification and/or metformin therapy in overweight women with polycystic ovary syndrome: a pilot study. Fertility and Sterility 2004;82(2):421-9.	
Study Country	USA	
BRIEF CHARACTERISTICS OF RCT		
Patient/population/ participants	Women with PCOS (age not reported, BMI > 25 kg)	
PCOS diagnostic criteria	fewer than 6 menses/year, hyperandrogenism (serum total testosterone > 50 ng/dL, no hirsutism by Ferriman-Gallwey)	
Presence of infertility	Not Reported	
Presence of other condition/s	Not Reported	
Medication History	Not Reported	
N per group	Intervention, n=11; control, n= 9	
Setting	General Clinical Research Centre, University of Rochester	
Intervention	weight loss, lifestyle intervention with placebo defined as aim 7% to 10% weight loss, registered dietitian/exercise physiologists, individualized meal plan with 500 to 1000 calorie deficit/ day (50% carbohydrate, 25% protein, 25% fat, low GI foods, individualized exercise plan 150 minutes/week). Group meetings and progress monitoring weekly for 0 to 24 weeks, biweekly for 25 to 48 weeks	
Comparison	no lifestyle intervention and placebo (no dietary or exercise instruction)	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Weekly morning urinary pregnanediol glucuronide (if elevation in urinary pregnanediol glucuronide noted preceding menstrual flow counted as an ovulatory event, consecutive weekly elevated levels were counted as a single ovulatory event), menstrual diaries, testosterone, SHBG, FAI, F-G score (clinician assessed), height, weight (kg), BMI, waist/hip circumference, OGTT 0, 30, 60, 120, 180 minutes glucose (AUC calculated trapezoidally), lipid profile (total cholesterol, HDL-C, LDL-C, triglycerides), OGTT 0, 30, 60, 120, 180 minutes insulin (AUC calculated trapezoidally)	
Follow up Duration	48 weeks	
Summary Result/s	Key methodologic issues for a large-scale, randomized trial of lifestyle intervention in PCOS include minimizing early dropout from the lifestyle intervention and including a range of body mass index that is not skewed toward severe obesity. Weight reduction might play the most significant role in the restoration of ovulation in obese women with PCOS.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Not Reported

Study ID		Hoeger 2004	
Does the study have specified inclusion/exclusion criteria?		Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Inclusion criteria		Yes Partial No Not reported	overweight (BMI > 25 kg/m^2), PCOS
Exclusion criteria		Yes Partial No Not reported	pregnancy (hCG performed at each visit), DM2 (known or elevated fasting glucose), abnormal liver and kidney function, use of antihypertensives or statin therapy, exclusion of other reproductive disorders (Cushing's syndrome, hyperprolactinemia, thyroid disease, androgen-secreting tumors, adrenal disease
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Yes The randomization schedule was computer generated in blocks by an independent pharmacy representative.
	Was allocation to intervention group concealed?	Yes Partial No Not reported	Yes
PERFORMANCE	**Were patients blind to intervention group?**	Yes Partial No Not reported	No
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	No

Study ID		Hoeger 2004	
BIAS	**Aside from the experimental intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes
DETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	Yes
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Not Reported
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Not Reported
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	Intervention 5/11= 45.45% Control 2/9 = 22.2%
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	Not Reported
REPORTBIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not Reported
CONFOUN	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	Yes

Study ID		Hoeger 2004	
DING	**If confounding was present, was it controlled for?**	Yes Partial No Not reported	Not Reported
OTHERBIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	Not Reported
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	No (stated there was no power calculation)
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Not Reported
COMMENTS		Lack of randomisation and blinding key reason for high RoB	
What is the overall risk of bias?		Low Moderate High Insufficient information	Low
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

Study ID	Hoeger 2008
Study Citation	Hoeger K, Davidson K, Kochman L, Cherry T, Kopin L, Guzick DS. The impact of metformin, oral contraceptives, and lifestyle modification on polycystic ovary syndrome in obese adolescent women in two randomized, placebo-controlled clinical trials. Journal of Clinical Endocrinology and Metabolism 2008;93(11):4299-306.
Study Country	USA
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS (age 12-18, BMI > 95th percentile)
PCOS diagnostic criteria	irregular menses (> 45-day menstrual cycles/fewer than 8 menses in the preceding year), hyperandrogenism (acne, hirsutism Ferriman-Gallwey >7, elevated androgens)
Presence of infertility	Not Reported
Presence of other condition/s	Not Reported
Medication History	No
N per group	Intervention, n=11; control, n= 11
Setting	General Clinical Research Centre, University of Rochester
Intervention	weight loss, lifestyle intervention versus placebo. Closed group intervention format, 5 to 6 members per group, participants and one adult family member (parent or guardian) in structured training classes on diet, exercise, and behavior modification skills with frequent contact, flexible personal strategies, self-esteem, and social support. 16-session core curriculum group and individual appointments. Therapy goals of a 5% to 7% weight loss and a level of exercise of at least 150 minutes/week
Comparison	standard office advice on nutrition and exercise for healthy living (written information on best lifestyle choices at enrolment but no formal education) and seen monthly
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Weekly urine pregnanediol assessment for ovulation, menstrual cycle average per 24 weeks, total and free testosterone, SHBG, FAI, hirsutism (Ferriman-Gallwey), OGTT at 0, 30, 60, 120 minutes (AUC glucose), lipid profile (total cholesterol, HDL-C, LDL-C, triglycerides), OGTT at 0, 30, 60, 120 minutes (AUC insulin), BMI, waist circumference
Follow up Duration	24 weeks
Summary Result/s	Both lifestyle modification and oral contraceptives significantly reduce androgens and increase SHBG in obese adolescents with PCOS. Metformin, in combination with lifestyle modification and oral contraceptives, reduces central adiposity, reduces total testosterone, and increases HDL, but does not enhance overall weight reduction.
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT	

Study ID		Hoeger 2008	
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	Not Reported
Does the study have specified inclusion/exclusion criteria?		Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Inclusion criteria		Yes Partial No Not reported	PCOS, adolescent females, 1 year postmenarchal, ages 12 to 18 years, obese (BMI > 95th percentile)
Exclusion criteria		Yes Partial No Not reported	Cushing's syndrome, hyperprolactinemia, congenital adrenal hyperplasia, renal or hepatic impairment, exercise > 10 hours/week, smoking > 1 pack of cigarettes/week, significant ovarian surgery, current alcohol use or history of substance abuse, other causes of hyperandrogenism or menstrual irregularity
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Yes Use of computer-generated list of random numbers
	Was allocation to intervention group concealed?	Yes Partial No Not reported	Yes
PERFORMANCE	**Were patients blind to intervention group?**	Yes Partial No Not reported	No
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	No

Study ID		Hoeger 2008	
BIAS	**Aside from the experimental intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes
DETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	Yes
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Not Reported
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Not Reported
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	Intervention 2/11= 18.18% Control 1/11 = 9.09%
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	Not Reported
REPORTBIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not Reported
CONFOUN	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	Yes

Study ID		Hoeger 2008	
CONFOUNDING	**If confounding was present, was it controlled for?**	Yes Partial No Not reported	Not Reported
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	Not Reported
OTHER BIAS	**Was the study sufficiently powered to detect any differences between the groups?**	Yes Partial No Not reported	No (stated there was no power calculation)
OTHER BIAS	**If statistical analysis was undertaken, was this appropriate?**	Yes Partial No Not reported	Not Reported
COMMENTS		Lack of randomisation and blinding key reason for high RoB	
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate (low risk for allocation concealment, but high risk for participant/investigator blinding)
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

Study ID	Jedel 2011 (or Stener-Victorin 2009-2013)
Study Citation	Jedel et al., *American J of Phys-Endo and Metb* 300: E37-45, 2011. Leonhardt et al., *Acta Obs et Gyn Scandi* 94: 279-287, 2015. Stener-Victorin et al., *Fert and Ster* 97: 501-508, 2012. Stener-Victorin et al., *BMC Comp and Alterna Med* 13: 131, 2013. Stener-Victorin et al., *American J of Phys-Regulatory, Integra, and Comp Phys* 297: R387-R395, 2009. Jedel E, Labrie F, Oden A, Holm G, Nilsson L, Janson PO, et al. Impact of electro-acupuncture and physical exercise on hyperandrogenism and oligo/amenorrhea in women with polycystic ovary syndrome: a randomised controlled trial. *American Journal of Physiology-Endocrinology and Metabolism* 2011;**300**(1):E37-45. Leonhardt H, Hellstrom M, Gull B, Lind AK, Nilsson L, Janson OP, et al. Serum anti-Mullerian hormone and ovarian morphology assessed by magnetic resonance imaging in response to acupuncture and exercise in women with polycystic ovary syndrome: secondary analyses of a randomized controlled trial. *Acta Obstetricia et Gynecologica Scandinavica* 2015;**94**:279-87. Stener-Victorin E, Baghaei F, Holm G, Janson PO, Olivecrona G, Lönn M, et al. Effects of acupuncture and exercise on insulin sensitivity, adipose tissue characteristics, and markers of coagulation and fibrinolysis in women with polycystic ovary syndrome: secondary analyses of a randomized controlled trial. *Fertility and Sterility* 2012;**97**(2):501-8. Stener-Victorin E, Holm G, Janson PO, Gustafson D, Waern M. Acupuncture and physical exercise for affective symptoms and health-related quality of life in polycystic ovary syndrome: secondary analysis from a randomized controlled trial. *BMC Complementary and Alternative Medicine* 2013;**13**:131. Stener-Victorin E, Jedel E, Janson PO, Sverrisdottir YB. Low- frequency electroacupuncture and physical exercise decrease high muscle sympathetic nerve activity in polycystic ovary syndrome. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology* 2009;**297**(2):R387-95.
Study Country	Sweden
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS (age 18 to 37 years)
PCOS diagnostic criteria	PCO (at least 12 follicles, 2 mm to 9 mm and/or increased ovarian volume > 10 mL by 2D ultrasound on one or both ovaries) and one of following (oligomenorrhoea with an intermenstrual interval > 35 days and/or clinical and/or biochemical signs of hyperandrogenism (hirsutism or acne))
Presence of infertility	Not reported
Presence of other conditions	Not reported
Medication History	Women on medications < 3 months prior to study commencement excluded
N per group	Allocated/randomized: 84 (For intervention versus control N = 51 randomized (n = 34 intervention, n = 17 control), n = 45 completed and analyzed (n = 30 intervention, n = 15 control). For paper, n = 5 intervention and n = 6 control reported (subset))
Setting	University teaching hospital with patients from gynecology/ endocrinology clinics, Glasgow, UK

Study ID	Jedel 2011 (or Stener-Victorin 2009-2013)	
Intervention	Weight maintenance, exercise: instructed to do 30 to 45 minutes 3x per week moderate exercise beyond daily physical activity (brisk walking, cycling, aerobic) with pulse frequency above 120/minute and weekly follow-up and guidance	
Comparison	No exercise, given same information about importance of physical activity and diet as physical activity group in one session by a physiotherapist and given option to phone study coordinator at any point.	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Menstrual pattern by daily recordings of basal body temperature, 12-week documentation of menstrual pattern pre-study, menstrual bleeding patterns confirmed by daily recordings of basal body temperature throughout the entire study period and via interviews by gynecologists and gynecological assessment, total testosterone, SHBG, free testosterone (radioimmunoassay), FAI, F-G score (clinician assessed), lipid profile (total cholesterol, HDL-C, LDL-C, triglycerides), fasting glucose and insulin, height, weight, BMI, sagittal abdominal diameter, WHR, Quality of life: PCOSQ	
Follow up Duration	16 weeks	
Summary Result/s	Physical exercise lowered high sympathetic nerve activity and menstrual frequency, decreased the levels of several sex steroids, and improved HRQoL in women with PCOS versus no intervention.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	The aim was to determine whether weight maintenance exercise would have different effects on body weight, circulating hormones, menstrual patterns, and lipid profiles.
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes
Inclusion criteria	Yes Partial No Not reported	PCOS, age 18 to 37 years
Exclusion criteria	Yes Partial No Not reported	Breastfeeding < 6 months prior, known endocrine or neoplastic causes of hyperandrogenism, including adrenal secreting tumors, Cushing's syndrome, congenital adrenal hyperplasia and hyperprolactinaemia. Women on medications < 3 months prior to study commencement excluded
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SEL **Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Yes Randomization was performed by the study coordinator according to a computerized list with stratification for age and BMI using a randomized block model.

Study ID		Jedel 2011 (or Stener-Victorin 2009-2013)	
SELECTION BIAS	**Was allocation to intervention group concealed?**	Yes Partial No Not reported	Not reported
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	No Participant/treatment provider blinding not possible due to the interactive nature of the intervention. Potential for lack of participant blinding to introduce bias for the self-reported outcome of menstrual diaries.
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	Yes "Independent observers and with blind, independent analysis," outcome assessor and data analyst blinded and reduced risk of bias for clinician-reported outcomes of hirsutism (Ferriman-Gallwey), weight, body mass index, adiposity distribution.
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	Yes
DETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	Yes "Independent observers and with blind, independent analysis," outcome assessor and data analyst blinded and reduced risk of bias for clinician-reported outcomes of hirsutism (Ferriman-Gallwey), weight, body mass index, adiposity distribution.
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes
ATTRI	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	*Intervention women* *17/34= 50%* *Control women* *11/18=39%*

Study ID		Jedel 2011 (or Stener-Victorin 2009-2013)	
TIONBIAS	**Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?**	Yes Partial No Not reported	Yes
REPORTBIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Partial The study protocol is available and all of the studies prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way with the exception of: health-related quality of life, progsterone values mentioned in methods but not results and potential data for ovulation. On contacting authors these outcomes are to be included in future analysis.
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	Yes
	If confounding was present, was it controlled for?	Yes Partial No Not reported	Yes
OTHERBIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	Not reported
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported

Study ID	Jedel 2011 (or Stener-Victorin 2009-2013)	
If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Not reported
COMMENTS		
What is the overall risk of bias?	Low Moderate High Insufficient information	*High*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	No – all outcomes have a high risk of bias	

Study ID	Kiel 2021
Study Citation	Kiel IA, Lionett S, Parr EB, Jones H, Røset MAH, Salvesen Ø, Hawley JA, Vanky E, Moholdt T. High-Intensity Interval Training in Polycystic Ovary Syndrome: A Two-Center, Three-Armed Randomized Controlled Trial. Med Sci Sports Exerc. 2022 May 1;54(5):717-727. doi: 10.1249/MSS.0000000000002849. Epub 2022 January 12. PMID: 35019901.
Study Country	Norway and Australia
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS (age 18-45; BMI stratified for < or ≥ 27)
PCOS diagnostic criteria	Rotterdam
Presence of infertility	Measured in quality of life report
Presence of other condition/s	No
Medication History	No
N per group	Control = 23 (non-exercising) LV-HIT = 21 (low-volume HIT workout) HV-HIT = 20 (high-volume HIT workout)
Setting	Department of Circulation and Medical Imaging at the Norwegian University of Science and Technology in Trondheim, Norway, and at the Mary MacKillop Institute for Health Research at the Australian Catholic University in Melbourne, Victoria, Australia
Intervention	16-week low-volume HIT workout or 16-week high-volume HIT workout followed by 36-week home-based HIT
Comparison	Non-training
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Menstrual frequency (using menstruation diary and questionnaire), fertility (questionnaire), number of pregnancies, ovarian morphology (only Norway; multifrequency transvaginal ultrasound transducer), body composition (DXA in Australia, bioelectrical impedance analysis in Norway), waist and hip circumference, seated blood pressure, fasting blood samples, 2-h oral glucose tolerance test, insulin sensitivity (HOMA-IR), plasma glucose concentration (Roche Modular P), serum insulin concentrations (enzyme-linked immunosorbent assay), glucose and insulin AUC, HbA1c, total cholesterol, HDL, LDL, triglycerides,17OH-progesterone, prolactin, testosterone, albumin, AMH, SHBG, FAI, physical activity (questionnaire and activity monitor), dietary intake (diet recall), physical activity enjoyment (questionnaire), quality of life (polycystic ovary syndrome questionnaire), Ferriman Gallwey score; VO2 peak (indirect calorimetry)
Follow up Duration	12 months
Summary Result/s	A semi-supervised HIT intervention did not increase the menstrual frequency in women with PCOS. No between-group differences in menstrual frequency, but within-group change in each group was observed; HIT has clinical benefits on both pregnancy rate and QoL in women with PCOS.

Study ID		Kiel 2021	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT			
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	Yes, the aim was to determine whether 16 wks of LV-HIT or HV-HIT followed by 36 wk home based HIT would increase menstrual frequency during 12 months with PCOS women compared to no exercise control.
Does the study have specified inclusion/exclusion criteria?		Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Inclusion criteria		Yes Partial No Not reported	Eligible participants were aged between 18 and 45 yr and diagnosed with PCOS according to the Rotterdam criteria
Exclusion criteria		Yes Partial No Not reported	Already undertaking two or more weekly sessions of endurance exercise that induced heavy breathing, hormonal contraceptives, taking insulin sensitizers or drugs known to affect gonadotropin or ovulation (wash-out period of 3 months before inclusion), pregnancy, breastfeeding within 24 wk, known cardiovascular diseases, or other endocrine disorders (congenital adrenal hyperplasia, Cushing syndrome, or androgen-secreting tumors).
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Yes, a computer random number generator developed and administered at the Faculty of Medicine, Department of Public Health and General Practice, NTNU, Trondheim, Norway, was used at both study centers.
	Was allocation to intervention group concealed?	Yes Partial No Not reported	No Investigators were informed about the allocation results by email after registration of new participants. Participants and study personnel were not blinded to group allocation
PERF	**Were patients blind to intervention group?**	Yes Partial No Not reported	No Participants and study personnel were not blinded to group allocation

Study ID		Kiel 2021	
PERFORMANCE BIAS	**Were investigators and care providers blind to intervention group?**	Yes Partial No Not reported	No Investigators were informed about the allocation results by email after the registration of new participants
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	Not reported
DETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	HV-HIT 76.2% (only 8/20 analyzed for secondary outcomes, but 20/20 analyzed for primary outcomes) LV-HIT 60% (only 5/21 analyzed for secondary outcomes, but 18/21 analyzed for primary outcomes) Control 56.5% (only 10/23 were analysed for secondary outcomes, but 20/23 were analysed for primary outcomes)
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	Yes

Study ID		Kiel 2021	
REPORTBIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	Yes
	If confounding was present, was it controlled for?	Yes Partial No Not reported	No, no adjustments were made for multiple testing
OTHERBIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS		Not Applicable	

Study ID	Kiel 2021	
What is the overall risk of bias?	Low Moderate High Insufficient information	Low
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	No	

Study ID	Kogurea 2020	
Study Citation	Kogure GS, Lopes IP, Ribeiro VB, Mendes MC, Kodato S, Furtado CLM, Silva de Sá MF, Ferriani RA, Lara LADS, Reis RMD. The effects of aerobic physical exercises on body image among women with polycystic ovary syndrome. J Affect Disord. 2020 Feb 1;262:350-358. doi: 10.1016/j.jad.2019.11.025. Epub 2019 November 9. PMID: 31735408.	
Study Country	Brazil	
BRIEF CHARACTERISTICS OF RCT		
Patient/population/ participants	Women with PCOS (age 18-39)	
PCOS diagnostic criteria	Rotterdam	
Presence of infertility	No	
Presence of other condition/s	No	
Medication History	No	
N per group	Control = 38 (no training) CAT = 37 (aerobic training) IAT = 35 (aerobic training)	
Setting	Endocrine Gynecology and Infertility Outpatient Clinic of the Department of Gynecology and Obstetrics, University Hospital, Ribeirão Preto Medical School, University of São Paulo	
Intervention	16 weeks of continuous aerobic training or 16 weeks of intermittent aerobic training	
Comparison	Non-training	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Attitudinal component of body image (body shape questionnaire), perceptual dimension of body image (Figure Rating Scale), sexual dysfunction (female sexual function index questionnaire), anxiety and depression (HADS), testosterone, FAI, SHBG, height, weight, hip circumference, waist circumference, WHR, actual BMI	
Follow up Duration	Not Applicable	
Summary Result/s	Only the continuous aerobic training group had improved the core for the cognitive-affective dimension of body image. However, both the continuous aerobic training and the intermittent aerobic training groups had lower depression, anxiety, and sexual function scores after the intervention. Motivational interviews had no effect on weight loss or QoL versus control.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes, the aim was to evaluate the effects of two aerobic physical exercises, continuous and intermittent in different protocols on body dis(satisfaction) in women with PCOS, as well as the possible relation of the responses of anxiety, depression and sexual dysfunction to the exercise.

Study ID		Kogurea 2020	
Does the study have specified inclusion/exclusion criteria?		Yes Partial No Not reported	Partial
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Inclusion criteria		Yes Partial No Not reported	women aged 18–39 years with PCOS
Exclusion criteria		Yes Partial No Not reported	The exclusion criteria were: performance of regular physical exercise at least 3 times per week, smoking, pregnancy, diabetes, congenital adrenal hyperplasia, thyroid diseases, hyperprolactinemia, Cushing's syndrome or musculoskeletal disorders, and use of medications that interfere with the hypothalamic pituitary ovarian axis.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	***Did the study have an adequate method of randomisation?***	Yes Partial No Not reported	Yes The randomization was computer generated by an external source, in blocks of 15, with 5 women per group. Women were consecutively and separately collected, depending on the participant's BMI at the time of inclusion. A stratified randomization was performed according to BMI (<30 and ≥30 kg/m^2). The participants in the exercise were then further randomized into three groups: continuous aerobic physical training group (CAT), intermittent aerobic physical training group (IAT), and the control group with no aerobic exercise (CG).
	Was allocation to intervention group concealed?	Yes Partial No Not reported	Not Reported
PERFORMANCE	***Were patients blind to intervention group?***	Yes Partial No Not reported	Not Reported
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	Not Reported

Study ID		Kogurea 2020	
BIAS	***Aside from the experimental intervention, were the groups treated the same?***	Yes Partial No Not reported	Not reported
DEDETECTIONBIAS	***Were outcome assessors blind to intervention group?***	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes
ATTRITIONBIAS	***What percentage of the individuals recruited into each arm of the study dropped out?***	X% treatment X% control/ comparison Not reported	21.05% CG 18.91% CAT 17.14% IAT
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	Yes
REPORTBIAS	***Is the paper free of selective outcome reporting?***	Yes Partial No Not reported	Not reported

Study ID		Kogurea 2020	
CONFOUNDING	***Were the groups similar at baseline with regard to key prognostic variables?***	Yes Partial No Not reported	Yes
	If confounding was present, was it controlled for?	Yes Partial No Not reported	Yes (age, BMI, and testosterone)
OTHER BIAS	***Were there any conflicts of interest in the writing or funding of this study?***	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Low
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		No	

Study ID	Moeller 2018	
Study Citation	Moeller LV, Lindhardt CL, Andersen MS, Glintborg D, Ravn P. Motivational interviewing in obese women with polycystic ovary syndrome - a pilot study. Gynecol Endocrinol. 2019 Jan;35(1):76-80. doi: 10.1080/09513590.2018.1498832. Epub 2018 September 5. PMID: 30182773.	
Study Country	Denmark	
BRIEF CHARACTERISTICS OF RCT		
Patient/population/ participants	Women with PCOS (BMI ≥ 30)	
PCOS diagnostic criteria	Rotterdam	
Presence of infertility	No	
Presence of other condition/s	No	
Medication History	No	
N per group	Standard care = 18 Motivational interview with standard care = 19	
Setting	Department of Gynecology and Obstetrics, Odense University Hospital	
Intervention	MI was conducted using a mix of face-to-face or Skype video interviews. Field notes and mind mapping were used to keep track of the interviews. MI was planned once every 2 weeks, that is a total of 12 times for each participant in MI group. Cancellation of MI was handled by text messaging instead.	
Comparison	Standard care	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Weight, hip and waist circumference, QoL (WHO-5, MDI, SF-36, PCOS-Q)*, BMI *WHO-5: world health organization 5 wellbeing index *MDI: major depression inventory *SF-36: short-form-36	
Follow up Duration	6 months	
Summary Result/s	Intervention groups were comparable at baseline. Groups were comparable after 6 months in terms of weight, weight loss, BMI, QoL, serum testosterone, and serum lipids. Motivational interviews had no effect on weight loss or QoL versus control.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes, the aim was to investigate if MI as add on to standard advice (SA) improved weight loss and increased QoL in obese women with PCOS compared with SA alone
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	Yes

Study ID		Moeller 2018	
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Inclusion criteria		Yes Partial No Not reported	Inclusion criteria were PCOS diagnosed by the Rotterdam criteria and body mass index (BMI) ≥ 30 kg/m2. Participants accepted to use of barrier control as contraception during the study.
Exclusion criteria		Yes Partial No Not reported	Women were excluded if they used oral contraceptives or initiated metformin treatment within 3 months before study inclusion. Women with current pregnancy wishes were excluded.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Not Reported
	Was allocation to intervention group concealed?	Yes Partial No Not reported	Not Reported
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	Not Reported
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	Not Reported
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	Not reported
DED	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	Not reported

Study ID		Moeller 2018	
DETECTION BIAS	**Were all outcomes measured in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	22.2% control 26.3% motivational interview
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	Yes
REPORTBIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported
CONFOUN	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	Yes

Study ID		Moeller 2018	
D I N G	**If confounding was present, was it controlled for?**	Yes Partial No Not reported	Not Reported
O T H E R BI A S	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Low
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		No	

Study ID	Nasrekani 2016	
Study Citation	Nasrekani ZA, Fathi M. EIicacy of 12 weeks aerobic training on body composition, aerobic power and some women-hormones in polycystic ovary syndrome infertile women. Iranian Journal of Obstetrics, Gynecology and Infertility 2016;19(5):1-10.	
Study Country	Iran	
BRIEF CHARACTERISTICS OF RCT		
Patient/population/ participants	Women with PCOS (age not reported)	
PCOS diagnostic criteria	meeting 2 from 3 criteria as follows: 1) anovulation or low ovulation (having oligo-menorrhoea, amenorrhoea or poly-menorrhoea), 2) elevation of androgenic hormones in the body or having hirsutism and ratio of LH/FSH>2, 3) having polycystic ovaries in the ultra-sonography	
Presence of infertility	Not Reported	
Presence of other condition/s	Not Reported	
Medication History	Not Reported	
N per group	Intervention, n=10; control, n= 10	
Setting	Not Reported	
Intervention	12 weeks, 3 days/week aerobic training with the intensity of 40% to 65% maximum heart rate reserve	
Comparison	there was no intervention in the control group	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	weight, BMI	
Follow up Duration	12 weeks	
Summary Result/s	The intervention group had reduced weight and increased Vo2max compared to controls.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Not Reported
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	Partial (just inclusion)
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes

Study ID		Nasrekani 2016	
Inclusion criteria		Yes Partial No Not reported	Healthy women, according to the Health Questionnaire, not under medication, non-smokers, infertility, not participating in any exercise program and having PCOS according to 2 from the 3 criteria mentioned above
Exclusion criteria		Yes Partial No Not reported	Not Reported
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Yes Third-party randomization and allocation by the University's Unit for Applied Clinical Research
	Was allocation to intervention group concealed?	Yes Partial No Not reported	Not Reported
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	Not Reported
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	Not Reported
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	Yes
DETECT	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	Not Reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Not Reported

Study ID		Nasrekani 2016	
I O N B I A S	**Were outcomes assessed objectively and independently?**	Yes Partial No Not reported	Not Reported
A T T R I T I O N B I A S	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	Intervention 0% Control 0%
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	Not Reported
R E P O R T B I A S	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not Reported
C O N F O U N D I N G	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	Yes (but no test was done to confirm this)
	If confounding was present, was it controlled for?	Yes Partial No Not reported	Not Reported

Study ID		Nasrekani 2016	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	Not Reported
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Yes (stated there was a power calculation)
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Not Reported
COMMENTS		Lack of randomisation and blinding key reason for high RoB	
What is the overall risk of bias?		Low Moderate High Insufficient information	Insufficient Information
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

Study ID	Oberg 2018	
Study Citation	Oberg et al. Clin Endocrinol (Oxf). 2019 Mar;90(3):468-478.	
Study Country	Sweden	
BRIEF CHARACTERISTICS OF RCT		
Patient/population/ participants	Sixty-eight women, aged 18-40 years, BMI ≥ 27 kg/m^2	
PCOS diagnostic criteria	Rotterdam	
Presence of infertility	Not reported	
Presence of other condition/s	Not reported	
Medication History	Not reported. Indicated exclusion criteria were "taking regular medication."	
N per group	34	
Setting	Academic medical canter	
Intervention	Behavioral modification program (Intervention for 4 months consisted of a structured approach to achieve long-term weight control for improvement of reproductive and metabolic function, as well as the quality of life)	
Comparison	Minimal intervention	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Menstrual cyclicity (primary) Ovulation and pregnancy loss (secondary)	
Follow up Duration	4 months (intervention period) 12 months (post-intervention follow-up period)	
Summary Result/s	A significantly higher proportion of patients in the intervention group improved their menstrual function compared to the control. Logistic regression analysis showed that receiving the 4-month intervention was the only significant predictor of improved menstrual function. The interventions significantly increased endometrial thickness and decreased levels of DHEA compared to the control.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	Yes

Study ID		Oberg 2018	
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Inclusion criteria		Yes Partial No Not reported	Yes Women aged 18-40 years, with a body mass index (BMI) of at least 27 kg/m2 and fulfilling all three PCOS diagnostic criteria according to the Rotterdam Consensus21 of having oligomenorrhea or amenorrhea, displaying polycystic ovaries on a transvaginal ultrasound scan and having clinical or biochemical hyperandrogenism were eligible to enter the study.
Exclusion criteria		Yes Partial No Not reported	Yes Exclusion criteria were taking regular medication, another ongoing medical condition, smoking, pregnancy, or breastfeeding, having a history of an eating disorder or a substantial weight change during the past year. A wash-out period of 3 months was used if taking hormonal contraceptives. Several women had the desire to become pregnant, but all women accepted to use of nonhormonal contraception during the first 4 months of the study.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Yes Women were randomized in a ratio of 1:1 to either receive intervention (n = 34) or control treatment (n = 34). The randomization was performed with blocks of eight patients using the program SAS Systems 9.1 (SAS Institute Inc, Cary, NC, USA).
	Was allocation to intervention group concealed?	Yes Partial No Not reported	No Due to the apparent difference in the interventions, neither patients nor care providers were blinded to the allocation.
PERFOR MANCE	**Were patients blind to intervention group?**	Yes Partial No Not reported	No Due to the apparent difference in the interventions, neither patients nor care providers were blinded to the allocation.

Study ID		Oberg 2018	
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	No Due to the apparent difference in the interventions, neither patients nor care providers were blinded to the allocation.
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	Yes
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	Yes Partial No Not reported	11.8% (4/34) in the intervention arm 20.6% (7/34) in the control arm
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	Yes
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Yes

Study ID		Oberg 2018	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	Yes
	If confounding was present, was it controlled for?	Yes Partial No Not reported	Not reported (applicable)
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	No Although the a priori power calculation concluded that the sample size was adequate, one potential limitation of the study is the dropout rate (16% after 4 months and 31% after 1 year).
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Low to Moderate
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		Yes. Due to insufficient power to detect primary versus secondary outcomes, conclusions should be taken into account with caution.	

Study ID	Ribeiro 2019 (and 2021)	
Study Citation	Ribeiro et al. et al. J Health Psychol. 2021 Aug;26(9):1307-1317. Int J Environ Res Public Health. 2021 Oct 27;18(21):11274.	
Study Country	Brazil	
BRIEF CHARACTERISTICS OF RCT		
Patient/population/ participants	Eighty-seven women, aged 18-40 years, BMI 18-39.9 kg/m^2	
PCOS diagnostic criteria	Rotterdam	
Presence of infertility	Not reported	
Presence of other condition/s	Not reported	
Medication History	Not reported.	
N per group	37 (continuous aerobic training) 35 (intermittent aerobic training) 38 (control)	
Setting	Academic medical canter	
Intervention	The exercises were carried out on a treadmill, three times per week for 16 weeks. The participants' anthropometric characteristics and biochemical and hormonal concentrations were measured before and after aerobic training or observation period, as the telomere length that was evaluated using quantitative real-time PCR.	
Comparison	Minimal intervention	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Anthropometric metabolic, hormonal, and quality of life (by the validated Portuguese version of the self-reported MOS SF-36) without specification of primary or secondary outcomes	
Follow up Duration	4 months (intervention period)	
Summary Result/s	Both exercises reduced obesity indices, hyperandrogenism, and quality of life in women with women without changes in telomere length or inflammatory biomarkers versus controls.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	Yes

Study ID		Ribeiro 2019 (and 2021)	
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Inclusion criteria		Yes Partial No Not reported	Yes Women aged between 18 and 39 years, who did not practice regular physical exercise (at least three times per week) were included in this study. The participants were not using any pharmacological intervention for PCOS treatment and had no dietary energy restrictions. The subjects were recruited at the Gynecological Endocrinology Outpatient Clinic of the Human Reproduction Service of the Gynecology and Obstetrics Department of Ribeirao Preto Medical School, University of São Paulo.
Exclusion criteria		Yes Partial No Not reported	Yes Exclusion criteria were the presence of systemic diseases, use of drugs that interfere in the hypothalamic-pituitary-ovarian axis, congenital adrenal hyperplasia, diabetes, smoking, pregnancy, thyroid diseases, hyperprolactinemia, musculoskeletal disorders, or Cushing's disease.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Yes The allocation group was placed inside opaque, sealed envelopes, grouped in blocks of 15 and consecutively picked depending on the BMI of the participant at the time of study inclusion. After the run-in period, 110 volunteers were randomly assigned in a 1:1:1 fashion to one of three groups (continuous aerobic training (n=28), intermittent aerobic training (n=29), and control group (CG), without training (n=30). Random allocation was conducted by the principal investigator, and participants were enrolled and assigned to the intervention groups by research assistants.
	Was allocation to intervention group concealed?	Yes Partial No Not reported	Not reported
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	Not reported
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	Not reported

Study ID		Ribeiro 2019 (and 2021)	
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	Yes
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	Yes Partial No Not reported	24.3% (9/37) (continuous aerobic training) 17.1% (6/35) (intermittent aerobic training) 21.0% (8/38) (control)
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	Not reported
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported (cautions may be exercised due to not reporting whether analyses corroborated with the intention to treat analyses)
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	Yes

Study ID		Ribeiro 2019 (and 2021)	
	If confounding was present, was it controlled for?	Yes Partial No Not reported	Not reported (applicable)
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Yes According to Cohen's agreement, 24 patients are necessary to achieve a moderate difference between groups. The final sample was increased to cover the losses.
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Partial (cautions may be exercised due to not reporting whether analyses corroborated with the intention to treat analyses)
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Low to Moderate
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		Yes. Cautions may be exercised due to not reporting whether analyses corroborated with intention to treat analyses.	

Study ID	Saremi 2013	
Study Citation	Saremi et a. 2013, *Iranian J of Obs, Gyn, and Inf* 16: 10, 2013	
Study Country	Iran	
BRIEF CHARACTERISTICS OF RCT		
Patient/population/ participants	Women with PCOS (age not reported)	
PCOS diagnostic criteria	ESHRE/ASRM	
Presence of infertility	Not reported	
Presence of other condition/s	Not reported	
Medication History	OCP metformin excluded from study	
N per group	Allocated/randomized: 22 (11 intervention, 11 control) Assessed at the end of study: 22 (11 intervention, 11 control)	
Setting	Not specified	
Intervention	An 8-week aerobic training program consists of training 3 days per week for 8 weeks, for 40 to 60 minutes each. Each session involved 5 to 7 minutes of warm-up, 30 to 50 minutes of main exercises on the treadmill (starting at 40% to 45% of heart rate building up to 60% to 65% of heart rate by the end of the 8th week), finishing with cooling down exercises.	
Comparison	Patients asked not to do more physical activity than they used to and not to start any physical activity without informing the research group	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Changes in total testosterone, anthropometric features (weight, BMI, waist circumference, WHR), and lipid profiles (HDL-C, LDL-C, triglycerides, fasting glucose, fasting insulin)	
Follow up Duration	8 weeks	
Summary Result/s	No summary report is available.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	The aim was to determine whether an aerobic training program would have different effects on anthropometric features, circulating hormones, and lipid profiles
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes

Study ID		Saremi 2013	
Inclusion criteria		Yes Partial No Not reported	Irregular periods of less than 21 days or more than 31 days, polycystic ovaries on ultrasound, hyperandrogenism – hirsutism and acne
Exclusion criteria		Yes Partial No Not reported	Infection, metabolic diseases, cardiovascular, renal and adrenal, and extracranial, liver, and thyroid disease; oral contraceptive use and metformin, pregnancy, abnormal prolactin and participation in regular exercise
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Yes They were randomly divided into 2 11-person groups
	Was allocation to intervention group concealed?	Yes Partial No Not reported	Not reported
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	No Blinding of participants and study personnel would not have been possible due to the nature of the intervention, however, outcomes are biochemical assessments of hormones and triglycerides and are unlikely to be influenced by knowledge of group allocation.
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	No Not blinded, but biochemical outcomes are unlikely to be affected by blinding as they are objective measures.
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	Yes
DETECT	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	No
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes

Study ID		Saremi 2013	
I O N B I A S	**Were outcomes assessed objectively and independently?**	Yes Partial No Not reported	Yes
A T T R I T I O N B I A S	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	No dropouts
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	Yes
R E P O R T B I A S	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Partial No clinical trial reported but all prespecified outcomes reported.
C O N F O U N D I N G	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	Yes
	If confounding was present, was it controlled for?	Yes Partial No Not reported	Not reported

Study ID		Saremi 2013	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	Not reported
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Not reported
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	High
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		No – all outcomes have a high risk of bias	

Study ID	Stefanaki 2015	
Study Citation	Stefanaki et al., *Stress* 18: 57-66, 2015.	
Study Country	Greece	
BRIEF CHARACTERISTICS OF RCT		
Patient/population/ participants	Women with PCOS (intervention group n = 23, 23.4 ± 4.62; control group n = 15, 28.3 ± 7.20)	
PCOS diagnostic criteria	ESHRE/ASRM criteria	
Presence of infertility	Not reported	
Presence of other condition/s	Not reported	
Medication History	No psychotropic medication before or during study	
N per group	Allocated/randomized: 46 (23 intervention, 23 control) Assessed at the end of study: 28 (23 intervention, 15 control)	
Setting	Medical School of Athens University, and the First Department of Pediatrics of the National & Kapodistrian University of Athens, Greece.	
Intervention	An 8-week mindfulness stress management program, which consisted of a 30-minute audio CD of directed mindfulness and diaphragmatic breathing exercises that participants were required to undertake daily, preferably before bedtime. Participants were monitored by the principal investigator via a scheduled meeting or telephone call.	
Comparison	Control group with no intervention. Participants underwent salivary cortisol collection and questionnaires as per the intervention group but did not have the mindfulness stress management program.	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Changes in BMI and quality of life (PCOSQ)	
Follow up Duration	8 weeks	
Summary Result/s	Post-intervention, between-group results revealed statistically significant reductions in stress, depressive and anxiety symptoms, as well as in salivary cortisol concentrations, along with an increase in Life Satisfaction and Quality of Life scores in the intervention group only. There was no significant "placebo" effect on the outcome measures. Mindfulness techniques seem promising in ameliorating stress, anxiety, depression, and the quality of life in women with PCOS versus controls.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	The aim was to determine whether a stress management program would affect body weight and quality of life differently.

Study ID		Stefanaki 2015	
Does the study have specified inclusion/exclusion criteria?		Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Inclusion criteria		Yes Partial No Not reported	Pre-menopausal women age 15 to 40, diagnosed with PCOS by ESHRE/ASRM criteria (that is have at least 2 of the following: Quote: "(a) chronic anovulation, (b) clinical and/or biochemical hyperandrogenism and (c) polycystic ovaries on ultrasound after exclusion of related disorders). For adolescents, at least 2 years must have elapsed since menarche".
Exclusion criteria		Yes Partial No Not reported	Pregnancy, a genetic or endocrine disorder, neuropsychiatric disorders requiring psychotropic medication (eg antipsychotics, antidepressants, or anticonvulsants), practice of stress management techniques within 2 months of study enrolment, simultaneous participation in other trials, inability to read or write in Greek".
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Yes An online randomization internet site (www.random.org) was used to assign the participants to intervention and control groups
	Was allocation to intervention group concealed?	Yes Partial No Not reported	No Cannot blind participants; questionnaires are susceptible to bias, but salivary cortisol is an objective measure.
PERFORMANCE	**Were patients blind to intervention group?**	Yes Partial No Not reported	No No concealment was used within the groups.
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	Yes "The fellow researcher who administered the questionnaires and obtained the salivary cortisol devices at the end of the 8 weeks was blinded (unaware of the assigned group of the patients."

Study ID		Stefanaki 2015	
BIAS	**Aside from the experimental intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes
DEDETECTIONBIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes
ATTRITIONBIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	Not reported	Intervention women with PCOS 8/23 = 35% Control women with PCOS 0/23 = 0%
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	Yes
REPORTBIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	No Prespecified outcomes (from trial registration ANZCTS) were reported in the paper.

Study ID		Stefanaki 2015	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	Yes
	If confounding was present, was it controlled for?	Yes Partial No Not reported	Not reported
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	Not reported
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Not reported
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Low
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		No	

Study ID	Turan 2015	
Study Citation	Turan et al., *J of Physical Therapy Sci* 27: 2293-2297, 2015. Turan V, Mutlu EK, Solmaz U, Ekin A, Tosun O, Tosun G, et al. Benefits of short-term structured exercise in non-overweight women with polycystic ovary syndrome: a prospective randomised controlled study. *Journal of Physical Therapy Science* 2015;**27**(7):2293-7.	
Study Country	Turkey	
BRIEF CHARACTERISTICS OF RCT		
Patient/population/ participants	Women with PCOS (17 to 34 years)	
PCOS diagnostic criteria	ESHRE/ASRM	
Presence of infertility	Not reported	
Presence of other condition/s	Not reported	
Medication History	Not reported	
N per group	Allocated/randomized: 32 (16 training, 16 control) Assessed at the end of the study: 20 (14 training, 16 control)	
Setting	Physical Therapy and Rehabilitation Fitness Unit of Dokuz Eylul University, Turkey	
Intervention	Patients participated in a structured exercise program 3 times per week for 8 weeks. During each session (50 to 60 minutes), the patients performed aerobic and resistance exercises. Supervised by a physiotherapist.	
Comparison	At the beginning of the study, general dietary and behavioral advice, but not a structured calorie restriction program, was provided to all study participants. All patients were counseled regarding a healthy, balanced meal plan with regular food and nutritional composition in which 50% of the calories were from carbohydrates, 25% from protein and 25% from fat.	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Menstrual cycle, total testosterone, free testosterone, total cholesterol, HDL-C, LDL-C, triglycerides, fasting glucose, fasting insulin, BMI, and waist circumference.	
Follow up Duration	8 weeks	
Summary Result/s	Short-term regular exercise programs can lead to improvements in anthropometric, cardiovascular, and metabolic parameters of non-overweight in women with PCOS versus controls.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	The aim was to determine whether a structured exercise program would have different effects on body weight, circulating hormones, menstrual cycle, and lipid profiles

Study ID		Turan 2015	
Does the study have specified inclusion/exclusion criteria?		Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Inclusion criteria		Yes Partial No Not reported	Body mass index (BMI) was in the normal range (< 25 kg/m2); diagnosed on the ba- sis of ESHRE/ASRM criteria (2003), which requires the presence of 2 of the following: Quote: "(1) a poly- cystic ovary, defined as the presence of >10 cysts 2–8 mm in diameter, an ovarian volume >10 cm3, and an echodense stroma on transvaginal or pelvic ultrasonography; ... (2) clinical hyperandrogenism (Ferriman-Gallwey12) score >8) or biochemical hyperandrogenism (serum testosterone level >3.6 pg/mL in the absence of other causes of hyperandrogenism); and (3) oligomenorrhoea and/or anovulation".
Exclusion criteria		Yes Partial No Not reported	"Patients with endocrinological diseases, including diabetes, thyroid, adrenal, or pituitary gland dysfunction; cardiovascular, hepatic, or pulmonary disease; a history of orthopedic or other physical symptoms that would otherwise limit exercise performance; and those who had exercised regularly within the last 6 months".
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Yes Randomization was carried out using a computer-generated random number table and pre-labeled, sealed envelopes.
	Was allocation to intervention group concealed?	Yes Partial No Not reported	Yes Pre-labeled, sealed envelopes
PERFORMANCE	**Were patients blind to intervention group?**	Yes Partial No Not reported	No Unable to blind participants to intervention, but objective biochemical measures were used.
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	No Unable to blind participants to intervention, but objective biochemical measures were used.

Study ID		Turan 2015	
BIAS	**Aside from the experimental intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes
DETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	No
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	Women in an exercise program 2/16 = 12.5% Women not in an exercise program 0/16 = 0%
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	Yes
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported Not stated as registered; all prespecified outcomes reported. Data are presented as mean ± standard error rather than the standard deviation.

Study ID		Turan 2015	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	Partial Groups appear even at baseline, except for BP (the control group appears to have a lower mean BP of 110/70 compared to the intervention groups mean BP of 120/75, and the control group has a higher mean estradiol at 56.7 pmol/ L compared to the intervention groups mean estradiol of 36.0 pmol/L. The significance of this is unclear.
	If confounding was present, was it controlled for?	Yes Partial No Not reported	Not reported
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	Not reported
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Not reported
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	High
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		No – all outcomes have a high risk of bias	

Study ID	Vigorito 2016	
Study Citation	Vigorito C, Giallauria F, Palomba S, Cascella T, Manguso F, Lucci R, et al. Beneficial effects of a three-month structured exercise training program on cardiopulmonary functional capacity in young women with polycystic ovary syndrome. *Journal of Clinical Endocrinology and Metabolism* 2007;92(4):1379-84.	
Study Country	Italy	
BRIEF CHARACTERISTICS OF RCT		
Patient/population/ participants	Women with PCOS (age 21.7 ± 2.3-intervention versus 21.9 ± 1.9 year-control)	
PCOS diagnostic criteria	ESHRE/ASRM criteria, PCO identified by transvaginal ultrasound and hirsutism by Ferriman-Gallwey score > 8	
Presence of infertility	Not reported	
Presence of other condition/s	Overweight (not defined)	
Medication History	No use of oral contraceptives, glucocorticoids, anti-andro- gens, ovulation induction agents, anti-diabetic or anti-obesity drugs or other hormonal drugs within the previous 6 months and during 3 months of study duration	
N per group	Allocated/randomized: 90 (45 intervention,45 control)	
Setting	University Federico II of Naples, School of Medicine, Italy	
Intervention	Not specifically aimed to induce weight loss, structured, supervised training sessions 3 x/week, 5-minute warm up and cool down, 30-minute exercise with 60% to 70% VO2 max bicycle ergometer	
Comparison	No training program. Both intervention and control received general dietary and behavioral advice without a structured calorie restriction program, healthy balanced meal plan was encouraged (50% carbohydrate, 25% protein, 25% fat, low GI food intake)	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Menses regularity, testosterone, SHBG, FAI, clinical hyperandrogenism (clinician assessed Ferriman-Gallwey score), height, weight, BMI, waist circumference, waist/hip ratio, AUC OGTT glucose (0, 30, 60, 90, 120, 180 minutes), lipid profile (total cholesterol, HDL-C, LDL-C, triglycerides), fasting glucose and insulin, AUC OGTT insulin (0, 30, 60, 90, 120, 180 minutes)	
Follow up Duration	12 weeks	
Summary Result/s	A 3-month structured exercise training program improves cardiopulmonary functional capacity in women with PCOS versus controls.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	The aim was to determine whether a supervised, structured training session would have different effects on menstrual regularity, circulating hormones, anthropometric features, and metabolic profiles.

Study ID		Vigorito 2016	
Does the study have specified inclusion/exclusion criteria?		Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Inclusion criteria		Yes Partial No Not reported	PCOS, overweight (not defined)
Exclusion criteria		Yes Partial No Not reported	Pregnancy, glucose intolerance (2-hour OGTT), diabetes, hypothyroidism, hyper-prolactinoma, Cushing's syndrome, non-classical congenital adrenal hyperplasia, neoplastic, hepatic, respiratory, cardiovascular disorder, concurrent medical illness (i.e., heart failure, lung, renal disease), smoking
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Not reported Randomly assigned but not stated how; insufficient information about the process to permit a judgment. At study entry, PCOS women were randomly subdivided into two groups composed of 45 patients each.
	Was allocation to intervention group concealed?	Yes Partial No Not reported	Not reported Not stated, insufficient information about the process to permit a judgment.
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	No Participant/treatment provider blinding not possible due to the interactive nature of the intervention. Potential for lack of participant blinding to introduce bias for the self-reported outcome of menstrual diaries.
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	Yes All clinical assessments performed by a physician blinded to patient al- location into study protocol." Outcome assessor blinded and therefore reduced the risk of bias for the clinical reported outcomes of Ferriman-Gallwey score, weight, BMI, adiposity distribution. All clinical assessments performed by physician blinded to patient al- location into study protocol. Outcome assessors were blinded and therefore reduced the risk of bias for objective outcomes of biochemical data.

Study ID		Vigorito 2016	
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	Yes
DETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	No Insufficient information to permit a judgment, study not registered as a clinical trial. From the results section of the paper, all of the studies prespecified (primary and secondary) outcomes that are of interest in the review have been reported in a prespecified way with the exception of menstrual regularity data for controls.
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	No dropouts No intention to treat analysis but no dropouts were reported for intervention or control group and no missing outcome data.
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	Yes
REPORTBIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	No Insufficient information to permit a judgment, study not registered as a clinical trial. From results section of the paper, all of the studies prespecified (primary and secondary) outcomes that are of interest in the review have been reported in a prespecified way except menstrual regularity data for controls.

Study ID		Vigorito 2016	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	Yes
	If confounding was present, was it controlled for?	Yes Partial No Not reported	Not reported
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	Not reported
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	High
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		No – all outcomes have a high risk of bias	

6. **Study Characteristics Table-** ***please add columns/ column headers as relevant to your study design and question***
For clarity, all studies included in the updated search after the publication of the Cochrane review in 2019 (after the publication of PCOS guideline in 2018) are shown in green rows, and others that were excluded in the Cochrane review are shown in grey rows below.

Author, year, country	Population/ Setting	Study Design	Sample Size per group	Intervention/ exposure details	Comparison/ control details	Follow up Duration	Outcomes	Summary of findings	Other [add as needed]
Almenning et al. 2015 Norway	Women with PCOS; Medical Center	Parallel RCT	Intervention (high intensity interval training = 10 and strength training =11) Control = 10	3 weekly exercise sessions for 10 weeks with normal diet (high intensity interval training did high interval training, strength training did strength training)	Maintain normal diet and physical activity	10 weeks	testosterone, SHBG, FAI, total cholesterol, HDL-C, LDL-C, triglycerides, glucose, insulin, weight, BMI, waist circumference	High-intensity interval training for ten weeks improved insulin resistance, without weight loss, in women with polycystic ovary syndrome. Body composition improved significantly after both strength training and high-intensity interval training. This pilot study indicates that exercise training can improve the cardiometabolic profile in polycystic ovary syndrome without weight loss.	Not Applicable
Brown et al. 2009 USA	Women with PCOS aged 18 to 50; Medical Center	Parallel RCT	Intervention = 21 Control = 16	8-12 week ramp up followed by 12-week moderate intensity exercise	no change in lifestyle	12 weeks for control, 20-24 weeks for intervention	Bioavailable testosterone, Ferriman-Gallwey score, OGTT glucose, lipid profile, fasting glucose and insulin, OGTT insulin, weight, BMI, waist/hip ratio	Moderate-intensity exercise without significant weight loss improved several components of the lipoprotein profiles of women with PCOS.	Not Applicable
Costa et al. 2018, Brazil	Women with PCOS; Medical Center	Parallel RCT	Intervention =14 Control=13	16-weeklong supervised aerobic training three times per week	No exercise intervention	16 weeks	Health-related quality of life, cardiorespiratory fitness,	The exercise intervention was more effective in improving cardiometabolic profiles, anthropometry (body mass,	Not Applicable

Author, year, country	Population/ Setting	Study Design	Sample Size per group	Intervention/ exposure details	Comparison/ control details	Follow up Duration	Outcomes	Summary of findings	Other [add as needed]
							cardiometabolic profile, and affective response	waist circumference), cardiorespiratory fitness, and affective response versus the control.	
Dietz de Loos et al. 2022, Netherlands	Women with PCOS and BMI >25 kg/m^2; Outpatient clinic	Parallel RCT	Intervention (three-component lifestyle intervention with or without short message service [SMS]- = 27 SMS+) = 16 Control = 24	Lifestyle intervention (cognitive behavioral therapy, diet, exercise) with and without short message service	Care as usual (CAU)	1 year	Metabolic Syndrome prevalence, metabolic parameters, weight changes	Lifestyle intervention improved metabolic parameters and decreased weight and MetS prevalence vs control.	Not Applicable
Guzick et al. 1994 USA	Women with PCOS aged 20 to 40 years and Obese; Medical Center	Parallel RCT	Intervention = 6 Control = 6	12-week behavioral weight control program	No treatment	12 weeks	Total testosterone, SHBG, non-SHBG testosterone, height, weight, body fat distribution, fasting glucose, insulin	Weight loss in obese, hyperandrogenic, anovulatory women appears to reduce insulin and non-SHBG T concentrations despite the absence of a change in gonadotropin secretion and may lead to the resumption of ovulation.	Not Applicable
Hoeger et al. 2004 USA	Women with PCOS and BMI > 25 kg/m^2; Research Center	Parallel RCT	Intervention = 11 Control = 9	Lifestyle intervention with placebo (individualized meal plan and exercise plan)	No lifestyle intervention	48 weeks	Morning urinary pregnanediol glucuronide, menstrual diaries, testosterone, SHBG, FAI, F-G score, height, weight, BMI, waist/hip	Key methodologic issues for a large-scale, randomized trial of lifestyle intervention in PCOS include minimizing early dropout from the lifestyle intervention and including a range of body mass index that is not skewed toward severe	Not Applicable

Author, year, country	Population/ Setting	Study Design	Sample Size per group	Intervention/ exposure details	Comparison/ control details	Follow up Duration	Outcomes	Summary of findings	Other [add as needed]
							circumference, OGTT glucose, lipid profile, OGTT insulin	obesity. Weight reduction might play the most significant role in the restoration of ovulation in obese women with PCOS.	
Hoeger et al. 2008 USA	Women with PCOS ages 12 to 18 and obese; Research Center	Parallel RCT	Intervention: 11 Control = 11	Lifestyle intervention (training classes on diet, exercise, and behavior modification skills)	Standard office advice on nutrition and exercise	24 weeks	Urine pregnanediol, menstrual cycle average per 24 weeks, total and free testosterone, SHBG, FAI, hirsutism, OGTT glucose, lipid profile, OGTT insulin, BMI, waist circumference	Both lifestyle modification and oral contraceptives significantly reduce androgens and increase SHBG in obese adolescents with PCOS. Metformin, in combination with lifestyle modification and oral contraceptives, reduces central adiposity, reduces total testosterone, and increases HDL, but does not enhance overall weight reduction.	Not Applicable
Jedel et al. 2011 (Stener-Victorian 2009-2013) Sweden	Women with PCOS age 18 to 30; Academic Medical Center	Parallel RCT	Intervention = 34 Control = 17	Weight maintenance, moderate exercise	No exercise	16 weeks	Menstrual pattern, total testosterone, SHBG, free testosterone, FAI, F-G score, lipid profile, fasting glucose and insulin, height, weight, BMI, sagittal abdominal diameter, WHR, quality of life	Physical exercise lowered high sympathetic nerve activity, and menstrual frequency decreased the levels of several sex steroids and improved HRQoL in women with PCOS versus no intervention.	Not Applicable
Kiel et al. 2021 Norway and Australia	Women with PCOS; Academic Medical Center	Parallel RCT	Interventions (low-intensity interval training [LV]-; high-intensity interval	16-week low-volume HIT workout, or 16-week high-volume HIT workout followed by 36-week home-based HIT	Nonexercising	12 months	Menstrual frequency (primary), markers of cardiometabolic and reproductive health, quality of life,	A semi-supervised HIT intervention did not increase the menstrual frequency in women with PCOS. No between-group differences in menstrual frequency, but within-group	Not Applicable

Author, year, country	Population/ Setting	Study Design	Sample Size per group	Intervention/ exposure details	Comparison/ control details	Follow up Duration	Outcomes	Summary of findings	Other [add as needed]
			training [HIT] = 21 HV-HIT = 20) Control = 23				adherence to and enjoyment of HIT	change in each group was observed; HIT has the clinical benefit on both pregnancy rate and QoL in PCOS women	
Kogurea et al. 2020 Brazil	Women with PCOS; Academic Medical Center	Parallel RCT	Interventions (continuous aerobic training = 37 intermittent aerobic training = 35) Control = 38	16 weeks of continuous aerobic training or 16 weeks of intermittent aerobic training	Non-training	Not Applicable	testosterone, FAI, SHBG, height, weight, hip circumference, waist circumference, WHR, actual BMI, BSQ, FSFI, FRS, HADS	Only the continuous aerobic training group had improved the core for a cognitive-affective dimension of body image. However, both the continuous aerobic training and the intermittent aerobic training groups had lower depression, anxiety, and sexual function scores after the intervention.	Not Applicable
Moeller et al., 2018 Denmark	Women with PCOS; Academic Medical Center	Parallel RCT	Intervention (motivational interviews) = 19 Control = 18	Motivational interviews were conducted once every 2 weeks (12 total times)	Standard care (no extra appointments, patients seen initially and at follow up only)	6 months	Weight, hip and waist circumference, WHO-5, MDI, Sf-36, PCOS-Q, BMI	Motivational interviews had no effect on weight loss or QoL versus control.	Not Applicable
Nasrekani et al. 2016 Iran	Women with PCOS; Medical Center	Parallel RCT	Intervention = 10 Control = 10	3 days/week of aerobic training	No intervention	12 weeks	Weight, BMI	The intervention group had reduced weight and increased Vo2max compared to controls.	Not Applicable
Oberg et al., 2018, Sweden	Women with PCOS who were	Parallel RCT	Intervention = 30 Control = 27	Group meetings 3 per month where they were counseled on	General healthy lifestyle rec-	Intervention and control groups	Weight, BMI, fat mass, lean body mass, testosterone,	A significantly higher proportion of patients in the intervention	Not Applicable

Author, year, country	Population/ Setting	Study Design	Sample Size per group	Intervention/ exposure details	Comparison/ control details	Follow up Duration	Outcomes	Summary of findings	Other [add as needed]
	overweight/ obese (BMI ≥ 27 kg/m^2)/ Teaching hospital			weight control, personal leadership, mindfulness, physical activity and diet. Meetings incorporated goal setting, stimulus control, problem-solving and stress management techniques to aid in behavioral change. One-on-one coaching sessions 1 per month to discuss individual training regimens and diet changes	commendations given by a midwife and supported by a pamphlet with written advice about diet and exercise	occurred in parallel for 4 months; however, after 4 months, the control group undertook the intervention (again for 4 months) and the entire study sample was followed up at 12 months	SHBG, FAI, menstrual function	the group improved their menstrual function compared to the control. Logistic regression analysis showed that receiving the 4-month intervention was the only significant predictor of improved menstrual function. The interventions significantly increased endometrial thickness and decreased levels of DHEA compared to the control.	
Ribeiro, 2019 and 2021 and 2021, Brazil (2 publications reporting on the same study)	Women with PCOS; Academic Medical Center	Parallel RCT	Interventions (Continuous aerobic training = 28 Intermittent aerobic training = 29) Control = 30	Both continuous and intermittent aerobic training on 3 days per week for 40-60 minutes with a 5-minute warm-up and 5 minutes cool down between 50%- 60% of the maximum heart rate For specific protocols of continuous and intermittent training sessions (which varied each week) see Table 1	No training	4 months	WC, HC, WHR, fat mass, lean body mass, weight, BMI, testosterone, QoL, SHBG, fasting insulin, fasting glucose, HDL-C, TC, TG, LDL-C, FAI	**Both exercises reduced obesity indices, hyperandrogenism, and quality of life in PCOS women without changes in telomere length or inflammatory biomarkers versus controls.**	Not Applicable

Author, year, country	Population/ Setting	Study Design	Sample Size per group	Intervention/ exposure details	Comparison/ control details	Follow up Duration	Outcomes	Summary of findings	Other [add as needed]
				of the published manuscript					
Saremi et al., 2013 Iran	Women with PCOS; Medical Center	Parallel RCT	Intervention = 11 Control = 11	Aerobic training 3 days/week for 40-60 min each	Asked not to do more physical activity then they used to	8 weeks	Total testosterone, HDL-C, LDL-C, triglycerides, fasting glucose, fasting insulin, weight, BMI, waist circumference, WHR	No summary report is available.	Not Applicable
Stefanaki et al., 2015 Greece	Women with PCOS aged 15 to 40; Academic Medical Center	Parallel RCT	Intervention = 23 Control = 23	8-week mindfulness stress management program	No intervention	8 weeks	BMI, QoL	Post-intervention, between-group results revealed statistically significant reductions in stress, depressive and anxiety symptoms, as well as in salivary cortisol concentrations, along with an increase in Life Satisfaction and Quality of Life scores in the intervention group only. There was no significant "placebo" effect on the outcome measures. Mindfulness techniques seem promising in ameliorating stress, anxiety, depression, and the quality of life in women with PCOS versus controls.	Not Applicable
Turan et al. 2015 Turkey	Women with PCOS and BMI < 25 kg/m^2; Academic	Parallel RCT	Intervention = 16 Control = 16	Structured exercise programs 3 times/week (aerobic and resistance exercise)	General dietary and behavioral advice	8 weeks	Menstrual cycle, total testosterone, free testosterone, total cholesterol, HDL-C, LDL-C, triglycerides, fasting glucose,	Short-term regular exercise programs can improve the anthropometric, cardiovascular, and metabolic parameters of non-overweight women with PCOS versus controls.	Not Applicable

Author, year, country	Population/ Setting	Study Design	Sample Size per group	Intervention/ exposure details	Comparison/ control details	Follow up Duration	Outcomes	Summary of findings	Other [add as needed]
	Medical Center						fasting insulin, BMI, waist circumference		
Vigorito et el. 2007 Italy	Women with PCOS and overweight; Academic Medical Center	Parallel RCT	Intervention = 45 Control = 45	Structured supervised training sessions 3 times/week	No training program	12 weeks	Menses diary, testosterone, SHBG, FAI, Ferriman-Gallwey score, height, weight, BMI, waist circumference, WHR, OGTT glucose, lipid profile, fasting glucose and insulin, OGTT insulin	A 3-month structured exercise training program improves cardiopulmonary functional capacity in women with PCOS versus controls.	Not Applicable

Abbreviations: RCT: randomized control trial, CAU: care as usual, SMS+: with short message service, SMS-: without short message service, BMI: body mass index, PCOS: polycystic ovary syndrome, WHR: waist-to-hip ratio, WC: waist circumference, HC: hip circumference, mFG, F-G score: Ferriman-Galleway Score, LV-HIT: low volume-high intensity training, HV-HIT: high volume-high intensity training, HIT: high intensity training, QoL: quality of life, CAT: continuous aerobic training, IAT: intermittent aerobic training, FAI: free androgen index, SHBG: sex hormone binding globulin, BSQ: body shape questionnaire, FSFI: female sexual function index, FRS: Figure Rating Scale, HADS: hospital anxiety and depression scale, MI: motivational interview, WHO-5: world health organization 5 wellbeing index, MDI: major depression inventory, SF-36: short-form-36, PCOSQ: polycystic ovary syndrome questionnaire; 17-OHP, 17-Hydroxyprogesterone; AMH, anti-mullerian hormone; BMI, body mass index; CRP, c-reactive protein; DBP, diastolic blood pressure; DHEA, dehydroepiandrosterone; DHT, dihydrotestosterone; FAI, free androgen index; FSH, follicle stimulating hormone; HC, hip circumference; HOMA, homeostatic model assessment; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; LH, luteinizing hormone; PCOS, polycystic ovary syndrome; QoL, quality of life; RCT, randomised controlled trial; SBP, systolic blood pressure; SHBG, sex hormone-binding globulin; TC, total cholesterol; TG, triglycerides; TSH, thyroid stimulating hormone; WC, waist circumference; WHR, waist-hip-ratio.

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2. Rotterdam ESHRE/ASRM-sponsored PCOS Consensus Workshop Group, *Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS).* Hum Reprod, Rotterdam ESHRE/ASRM-sponsored PCOS Consensus Workshop Group 2004. **19**(1): p. 41-47.

3. Azziz, R., et al., *Androgen Excess Society. Positions statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline.* J Clin Endocrinol Metab, 2006. **91**(11): p. 4237-42

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 3

Question 3.1.

In women with PCOS, are lifestyle interventions (compared to minimal or nothing) effective for improving anthropometric, metabolic, reproductive, fertility, quality of life and emotional wellbeing outcomes?

BACKGROUND:

Lifestyle modification has been a cornerstone of management in PCOS and has been recommended as first line treatment by the first International Guidelines (1). There are many reasons for this recommendation including that women with PCOS have a greater prevalence of metabolic disorders such as type 2 diabetes and metabolic syndrome (2,3). Women with PCOS are also more likely to be overweight or obese (4) with subsequent exacerbation of metabolic and reproductive disorders, and have a predisposition to longitudinal weight gain that is greater than the general population, with women with PCOS gaining an excess of 2.6 kg over 10 years compared with women without PCOS (5). Weight gain in adulthood is an independent risk for metabolic disease (6) so prevention of weight gain or weight loss can be foundational to medical therapies to address the risks of PCOS.

Data from small studies of women with PCOS are generally supportive that women participating in lifestyle modification programs can reduce body weight in similar amount to women without PCOS (7). However there overall mixed results noted and with the majority of the studies reported considerable drop-out rates varying between 12% and 47%. The variable success of the interventions and the high drop-out rates make the implementation of such programs challenging in the clinical setting (8).

Additionally, the acceptance of lifestyle programs by women with PCOS is not well studied. Women with PCOS consume similar diets and engage in comparable levels of physical activity compared to women without PCOS, despite having a higher BMI (9). Notably no differences between minutes spent in moderate and vigorous physical activity (except in total activity) is seen between women with and without PCOS when studied previously and more detailed analysis is performed in Q 3.5 for diet and physical activity. The adoption and maintenance of lifestyle changes involve a complex set of behavioural changes. Support of these changes and implementation in general practices remains a challenge. (10)

Given the overall need identified therefore, the evaluation of RCTs of lifestyle modification trials in the setting of PCOS with respect to anticipated benefits or lack thereof in reproductive and metabolic health is important to inform the updated guidelines. This can be used to assist with translation of those areas found beneficial both to the women with PCOS and the practitioners assisting them.

Summary of Evidence

Included studies

Eighteen studies (7 RCTs conducted after the previous guideline update in 2018 and 11 RCTs from the previously update guideline and published in the Cochrane review 2019) were identified for this review for a total of 18 studies included. From the initial Cochrane review from 2019, 4 of the 15 studies were excluded as their definition of PCOS was unclear. There was a total of 23 publications reviewed with 634 participants. No study assessed fertility as the primary outcome, 1 reported pregnancy rate, 3 reported ovulation rates and 3 reported menstrual regularity as an outcome.

Methodological quality/risk of bias

Studies had a serious risk of bias across reported outcomes and were mainly of moderate (N=6 outcome: BMI, WC, HDL-C, LDL-C, TG), low (N=7 outcomes: weight, WHR, Ferriman -Gallwey score, SHBG, 2-hour area under the curve for OGTT, insulin, total cholesterol) while N=2 had a very low quality in reporting testosterone and FAI outcomes. Few studies looked at the impact of lifestyle intervention on pregnancy, ovulation rate, or menstrual cyclicity, and no study evaluated miscarriage. Most studies in this review were of low quality, mainly due to a high risk of bias across most domains or high heterogeneity (>50%) for the testosterone and FAI outcomes.

Certainty of the evidence

The body of evidence in the systematic review was of a low to moderate certainty with serious risk of bias, no serious risk of inconsistency, serious risk of indirectness, and serious risk of imprecision. There was no serious risk of publication bias.

Consistency of studies

The included studies were all parallel RCTs with variable interventions. Control groups were no intervention, care as usual or general healthy lifestyle advice. Eleven studies used an exercise intervention (1, 2, 3, 8, 9, 10, 12, 14a, 14b, 15,17, 18) , 5 used a combination lifestyle intervention with diet, exercise and behavioural treatment (4, 5, 6, 7, 13) , and 2 used behavioural intervention alone (11, 16) . Duration of the interventions were 8-48 weeks with the majority <16 weeks. Participant numbers ranges from 12-90.

Results

Fertility outcomes are described in Table 1. Lifestyle treatment improved anthropometric outcomes, including waist circumference (WC) (N=12 effect estimates; N=423 women; MD: -1.32; 95%CI [-2.46; -0.18] cm; P=0.0271; I2=5%); Waist: hip ratio (WHR) (N=6 effect estimates; N=288; MD: -0.03; 95%CI [-0.05; -0.01]; P=0.0257; I2=0%). With respect to secondary endocrine and reproductive outcomes, lifestyle treatment improved Ferriman-Gallwey score (N=6 effect estimates; N=230 women; MD: -0.97; 95%CI [-1.90; -0.03]; P=0.0448; I2=0%); fasting insulin (N=14 effect estimates; N=467; MD: -1.87; 95%CI [-3.10; -0.65] pmol/L; P=0.0056; I2=3%); total cholesterol (N=12 effect estimates; N=427; MD:-0.15; 95%CI [-0.26; -0.03] mmol/L; P=0.0161; I2=0%) and LDL-C (N=12 effect estimates; N=387 women; MD: -0.15; 95%CI [-0.28; -0.02] mmol/L; P=0.0256; I2=0) levels vs. minimal treatment. Lifestyle treatment and minimal treatment exhibited comparable outcomes in other measures, including body weight, BMI, SHBG, total testosterone, FAI, glucose regulation (fasting and 2-hour postprandial glucose levels), HDL-C, and TG levels (all P≥0.05). See Tables 1-4 below. There was insufficient reporting on impact of lifestyle intervention versus minimal treatment on quality of life as a secondary outcome for meta-analysis but these are summarized in Table 5.

Results for outcomes are presented in the tables below.

Table 1. Fertility outcomes

Pregnancy rates	No data were available for analysis on pregnancy outcomes, live birth or miscarriage. Kiel et al 2021 (9) demonstrated an increase in pregnancy rate with low volume High intensity Interval Training (LV-HIT) intervention versus control intervention; LV-HIT (n = 5/15; 33%) vs. control group (n = 0/16, P = 0.02). HV-HIT 3/16 became pregnant (NS).
Menstrual regularity	The studies reported data as mean±SD menstrual cycles for lifestyle versus minimal treatment (24 weeks 2.88±1.7 versus 2.85±1.6, MD 0.03 95% CI -1.64 to 1.70, p=0.97 and 48 weeks 5.4±3.6 versus 4.3±2.1 MD 1.10 95% CI -2.17 to 4.37, p=0.51) (6) , 27/45 (60%) of treatment group having normal menstrual cycles with no reported data for the control group (18) , an average of 2.3 versus 2.5 cycles per 24 weeks for lifestyle compared to controls (7) and Jedel et al. 2011 (8) reported a statistically significant difference in menstrual frequency between the exercise group and no intervention group after 16 (p<0.05) and 32 weeks (p<0.05). Kiel et al 2021 (9), found no differences with LV or HV HIT intervention compared with no intervention. Oberg et al 2018 demonstrated a higher proportion of patients in the intervention group (behavioural modification) improved menstrual regularity compared to the control group, mean difference 35% (95% CI: 16-60), P = 0.003.
Ovulation	The studies looking at ovulation reported data as mean±SD ovulations for lifestyle versus minimal treatment (24 weeks 2.25±1.7 versus 2.23±2.1, MD 0.02 95% CI -1.93 to 1.97, p=0.98, and 48 weeks 6.0±3.6 versus 2.8±2.9 MD 3.20 95% CI -1.02 to 7.42, p=0.14) (6) , 4/6 versus 1/6 people ovulatory in lifestyle versus control group (OR 6.59 95% CI 0.73 to 59.34, p=0.09) (5) and 60% versus 50% ovulatory cycles for lifestyle versus the controls (7) . Oberg et al 2018 (13), did not show a difference in ovulation rates between groups.

Table 2. Androgen outcomes

Biochemical hyperandrogenism	Lifestyle treatment groups demonstrated comparable total testosterone levels versus minimal treatment in 14 studies with 542 participants; MD: -0.06; 95%CI [-0.21; 0.10]; P=0.4598. For Free androgen index (FAI) lifestyle intervention was similar to minimal treatment post intervention in 13 studies and 512 participants; MD: 0.23; 95%CI [-1.25; 0.78]; P=0.6269. SHBG was measured in 13 studies and 512 participants and levels were comparable post intervention for lifestyle and minimal treatment groups; MD 1.94; 95%CI [-1.32; 5.21]; P=0.2192.
Clinical hyperandrogenism Ferriman Gallwey (FG) Score	Six papers reported FG scores with a total of 230 participants. There was a higher reduction in FG score with lifestyle intervention compared to minimal intervention, effect estimates; MD: -0.97; 95%CI [-1.90; -0.03]; P=0.0448; None of the trials reported on acne vulgaris.

Table 3. Anthropometric outcomes

Adiposity (BMI, weight)	There was comparable weight loss post-intervention in the lifestyle versus minimal treatment groups. There were 14 included studies with 554 participants with effect estimates of MD: -1.02; 95%CI [-2.08; 0.04]; P=0.0585. With respect to BMI, intervention groups lifestyle versus minimal treatment demonstrated comparable BMI post intervention, effect estimates: MD: -0.30; 95% CI [-0.60; 0.01] P=0.0571.
Adiposity distribution (WC, WHR)	Lifestyle intervention groups demonstrated greater reduction in waist Circumference (WC) than minimal treatment groups in 12 studies with 423 participants. Effect estimates; MD -1.32; 95% CI [-2.46; -0.18]; P=0.0271. In 6 studies with 288 participants, lifestyle intervention resulted in significant reduction in WHR compared to minimal treatment groups. Effect size MD: -0.03; 95%CI [-0.05; -0.01]; P=0.0257.

Table 4. Metabolic outcomes

Fasting insulin	Fasting insulin was measured in 14 trials with 467 participants. Lifestyle treatment groups demonstrated decreased fasting insulin levels compared to minimal treatment groups post intervention. Effect estimates MD: -1.87; 95% CI [-3.10; -0.65]; P=0.0056
Glucose tolerance	There was no evidence of effect for endpoint fasting glucose (nmol/L) (MD -0.02; 95% CI [-0.09; 0.05; 480 participants, 14 trials, p=0.5138) between lifestyle intervention and minimal treatment. For endpoint 2 hour OGTT glucose there was no evidence for effect for lifestyle compared to minimal treatment in 4 studies with 148 participants, effect estimate MD: -5.05; 95% CI [-34.95; 24.85]; P=0.6282.
Lipid profile	Twelve studies measured lipid profiles with 387 participants. Lifestyle treatment groups demonstrated decreased total cholesterol (mmol/L) with effect estimates MD: -0.15; 95% CI [-0.26; -0.03); P=0.0056 and LDL cholesterol (mmol/L) with effect estimates MD: -0.15 95% CI [-0.28; -0.02]; P=0.0256. There was no evidence for effect for HDL cholesterol (mmol/L) with effect estimate MD 0.0; 95% CI [p-0.07; 0.07]; P=0.9285 between the intervention groups.

Table 5. Quality of Life/Emotional Wellbeing summary

Body shape Questionnaire (BSQ), Female Sexual Function Index (FSFI) and Hospital	Kogurea et al 2020 (10) examined body image pre and post continuous (CAT) or intermittent aerobic training (IAT) versus a control group (CG). Exercise interventions did not impact body perceptual dimension. BSQ improved after CAT (P=<0.01) compared to CG and within the CAT and IAT intervention but this was confounded by BMI. FSFI and HADS improved after CAT and IAT compared to controls (P=0.02) and within the CAT and IAT groups.

Anxiety Depression Score (HADS), Short form-36 (SF-36)	Moeller et al 2018 (11) did not see significant changes in SF-36 with motivational interviewing intervention. Ribeiro et al 2019 (19) examined continuous (CAT) and intermittent aerobic (IAT) training compared to a control group with a 16 week intervention. There was a significant increase in Physical function in CAT (P=0.022), Physical Role Functioning (P<0.001), General Health Perception (P<0.001), Vitality (P<0.001), Social Role Functioning (P<0.001), Emotional Role Functioning (P<0.001), and Mental Health (P<0.001). For IAT significant increases were found in Physical Functioning (P<0.001), Physical Role Functioning (P=0.027), General Health Perception (P<0.001), Vitality (P<0.001), Social Role Functioning (P<0.001), Emotional Role Functioning (P=0.011) and Mental Health (P<0.001). These were not compared to CG however where there were no changed noted after 16 weeks.
PCOS-Q domains	Kiel et al 2021 (9) reported on 16 week and 12 month PCOS-Q after HIT or control group. There was no significant impact on any PCOS-Q domain at 16 weeks. At 12 months the body hair domain (P=0.007) and the infertility domain (P=0.003) improved after HV-HIT compared to control and in body hair domain in HV-HIT vs Lv-HIT9 (P=0.025). Moeller et al 2018 (11) demonstrated improvement in 3 domains of PCOS-Q with motivational interviewing, weight (P=0.004), Infertility (P=0.044) and menstruation (P=0.037).

GRADE EVIDENCE CERTAINTY	
Comparison	**GRADE for critical outcomes**
Comparison 1. Lifestyle intervention versus minimal/ no treatment	⊕◯◯◯ VERY LOW

Evidence to Recommendations Framework

COMPARISONS (option versus other option)

Lifestyle interventions versus minimal or no treatment

- Lifestyle interventions are included individually or in combination as detailed below:
    - Dietary intervention vs minimal treatment
    - Exercise intervention (resistance or aerobic) vs minimal treatment
    - Behavioural management techniques for modifying diet or exercise vs minimal treatment
    - Combination of dietary, exercise, or behavioural intervention vs minimal treatment
    - All with duration more than 2 weeks.

EVIDENCE-BASED RECOMMENDATION(S)

EBR: Lifestyle intervention (exercise alone or multicomponent diet combined with exercise and behavioural strategies) should be recommended for all women with PCOS, for improving metabolic health including central adiposity and lipid profile.

- **GRADE Direction and Strength of Recommendation**:

☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

- **CR:** Healthy lifestyle behaviours encompassing healthy eating and/or physical activity should be recommended in all those with PCOS to optimise general health, quality of life, body composition and weight management (maintaining weight, preventing weight gain and/or modest weight loss).

GRADE Direction and Strength of Recommendation:

☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

PRACTICE POINT(S)

- Health professionals should be aware that lifestyle management is a core focus in PCOS management.
- Lifestyle management goals and priorities should be co-developed in partnership with women with PCOS, and value women's individualised preferences.
- Health professionals should discuss barriers and facilitators to optimise engagement and adherence to lifestyle change, including psychological factors, physical limitations, socioeconomic factors, sociocultural factors, as well as personal motivators for change. The value of broader family engagement should be considered. Referral to suitably trained allied health professionals needs to be considered for lifestyle management in women with PCOS.
- Behavioural support in achieving lifestyle change could include: Goal setting, problem solving, self-monitoring and reviewing, e.g. use of SMART goals (Specific Measurable, Achievable, Realistic and Timely)
- There are benefits to a healthy lifestyle even in the absence of weight loss.
    - In those with higher weight, weight management can be associated with significant clinical improvements and the following key points need to be considered including: A lifelong focus on prevention of further

weight gain If the goal is to achieve weight loss, a tailored energy deficit could be prescribed for women, considering individual energy requirements, body weight and physical activity levels.
    - The value in improvement in central adiposity (e.g. waist circumference, waist-hip ratio) or metabolic health
    - The need for ongoing assessment and support

- Health providers should be aware of the higher prevalence of eating disorders and weight stigma when discussing lifestyle management with women with PCOS. [see 3.6]

- Healthy lifestyle and optimal weight management, in the context of structured, intensive and ongoing clinical support, appears equally effective in PCOS as in the general population.

- In those who are not overweight, in the adolescent and at key life points, the focus should be on healthy lifestyle and the prevention of excess weight gain.

- Insulin resistance is considered as a pathophysiological factor in PCOS. However, clinically available insulin assays are of limited clinical relevance and should not be used in routine care (refer to recommendation 1.9.12).

GRADE CONSIDERATIONS

Justifications:
Updated systematic review for this question identified more studies to be included than 2018 Guidelines. Recommendations from general population data are supportive of healthy lifestyle interventions. Few undesirable side effects noted although access, cost and equity are concerns.

Subgroup considerations:
Studies in this review were mainly from adult population with only 1 study including adolescent population. Predominantly these studies were in Caucasian populations with 3 from South America and one from the Middle East. Caution is noted in interpretation for other populations and ethnicities.
No studies included pregnant women or post-menopausal women.

Implementation considerations:
Substantial resources are likely needed to implement the comprehensive lifestyle modifications. The duration and type of intervention is not uniform across the studies therefore specific protocols cannot be recommended. Studies were predominantly in academic medical centers and not community based.

Monitoring and evaluation considerations:
Metrics around women's satisfaction of overall lifestyle management support.
Fidelity checks that health professionals' provision of lifestyle management is consistent with guideline recommendation.

Research priorities:
Additional adequately powered high quality randomised control trials and pragmatic implementation trials are needed to further clarify the efficacy of lifestyle interventions specifically:
Different delivery methods (app based for example)
Longer term follow up to interventions
Duration/sustainability
Co-designed lifestyle intervention

More well studied outcomes for:
Reproductive health – menstrual cycle, ovulation, pregnancy, live births
Emotional health

More diverse populations to be studied:
Diverse ethnicities in low resource environments
Across different life stages – adolescent, post-menopausal, pregnancy
Benefits in non-overweight population

The effects of lifestyle [including optimal amount and type of diet and physical activity] in the preconception period in women, reporting on live birth and obstetric outcomes.

Harmonisation of research outcomes for lifestyle interventions

GRADE framework

GRADE DECIDE **Interactive Evidence to Decision Framework**

● DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Summary of evidence shows benefit to lifestyle intervention in reduction in central adiposity, lipid profile and fasting insulin.

No significant benefit demonstrated to fertility although menstrual function may be improved. Improvement in endocrine function was not clearly demonstrated. There is too little data on emotional outcomes for clear recommendation although improvements were demonstrated in the majority of studies reporting this outcome.

● UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

High dropout rates are noted in many studies but no specific undesirable effects otherwise demonstrated or measured.

Undesirable effects can include women's loss of confidence due to difficulty maintaining sustainable lifestyle change.

● CERTAINTY OF THE EVIDENCE

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☒ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

The body of evidence is of a very low to moderate certainty depending on outcome.

Low certainty – WHR, FG score, fasting insulin, total cholesterol

Moderate certainty – waist circumference, LDL

Very low for other outcomes

● VALUES

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☐ Important uncertainty or variability	☒ Possibly important uncertainty or variability	☐ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Research evidence:

No research evidence was identified

Panel discussion:

No specific evidence available in the studies. Likely patient groups and health providers value improvements in health parameters but unclear regarding intervention.

Lack of evidence on quality metrics of lifestyle management with overall overemphasis on weight and BMI which are inadequate markers of metabolic health.

● BALANCE OF EFFECTS

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:

No significant undesirable effects demonstrated and evidence of some improvements likely favors the option.

● COSTS

How large are the resource requirements (costs)?

Judgement:

☐ Don't know	☐ Varies	☐ Large costs	☒ Moderate costs	☐ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:

No research evidence was identified

Panel discussion:

No identified cost assessments but the majority of interventions reported are intensive and would require substantial resources.

● CERTAINTY OF COST EVIDENCE

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

No research evidence was identified

Panel discussion:

No evidence.

● COST-EFFECTIVENESS

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

No research evidence was identified

Panel discussion:

There are no cost-effectiveness studies presented. As noted costs of studied interventions not reported but are resource intensive, but are balanced by health outcome improvements.

● EQUITY

What would be the impact on health equity?

Judgement:

☐ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☒ Probably increased	☐ Increased

Research evidence:

No research evidence was identified

Panel discussion:

The implementation may be variable due to availability of local resources but recommendation is likely to improve equity.

● ACCEPTABILITY

Is the option acceptable to key stakeholders?

Judgement:

☐ Don't know	☒ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Health care teams and patients are likely to find lifestyle intervention acceptable. Funders may not prioritise lifestyle management support.

● FEASIBILITY

Is the option feasible to implement?

Judgement:

☐ Don't know	☒ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Given the need for intervention teams in the lifestyle medication studies available, the feasibility of the implementation of the intervention would be highly variable.

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PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by ECR Lead: Geranne Jiskoot

Other team members: Vibhuti Rao, Anne-Lotte van der Kooi

Supervised, edited and supported by the Evidence Team (Aya Mousa, Jillian Tay)

GDG 3

Question 3.2.

In women with PCOS, are behavioural interventions (compared to different types of behavioural interventions) effective for improving anthropometric, metabolic, reproductive, fertility, quality of life and emotional wellbeing outcomes?

1. STUDY SELECTION

Table 1. PICO Criteria for Inclusion	
Question	In women with PCOS, are behavioural interventions in addition to diet and/or exercise (compared to diet and/or exercise alone) effective for improving anthropometric, metabolic, reproductive, fertility, quality of life and emotional wellbeing outcomes?
Clinical leads (key contacts)	Cheryce Harrison
Allocation ranking	Level 1 - new systematic review

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(language, year)*
Inclusion	Females of reproductive age (postmenarchal and premenopausal) with diagnosed PCOS (NIH, Rotterdam or AEPCOS criteria). Subgroup by age group: Adult 19-44 years Middle Aged 45-64 years Young Adult 19-24 years Adolescent 13-18 years	Behavioural intervention combined with a lifestyle intervention (the latter defined as a structured dietary or exercise intervention designed to induce weight loss through an energy deficit or not designed to induce weight loss through an energy deficit) Duration of lifestyle intervention ≥ 2 weeks.	Lifestyle intervention alone (as described in Intervention)	Primary: Fertility, live birth and pregnancy, Miscarriage, as defined by study authors Secondary: Menstrual regularity (an initiation of menses or significant shortening of cycle length where possible), ovulation (number of ovulatory menstrual cycles where possible) Endocrine: total testosterone, sex hormone-binding globulin (SHBG), free androgen index (FAI) and clinical hyperandrogenism (hirsutism assessed clinically by FerrimanGallwey score) Anthropometric: Weight, BMI, adiposity distribution (by measures including waist circumference, waist-to-hip ratio (WHR)) Metabolic: Oral glucose tolerance test (OGTT), glucose, Fasting glucose, Fasting lipids (total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides), Fasting insulin, Oral glucose tolerance test (OGTT), insulin, Quality of life and participant satisfaction	Evidence based guidelines, systematic reviews, health technology assessments, randomised controlled trials (RCTs).	English language New search - screen from beginning (no time limit/update).
Exclusion	Taking anti-obesity medications (other than metformin). Bariatric surgery. Conditions with reproductive symptoms similar to PCOS, including congenital adrenal hyperplasia, Cushing's syndrome, hyper-prolactinaemia, thyroid disease and androgen-secreting tumours. Participants are not excluded based on type 2 diabetes, co-morbidities or medication use for clinical or metabolic features of PCOS, as long as this medication use is not a primary component of the intervention or control arms.	Behavioural interventions that are not quantifiable or are delivered alone or with other interventions not classified as lifestyle interventions (diet/exercise), such as medications, supplements, etc. Behavioural interventions combined with anti-obesity medication or surgery	Other behavioural interventions/ minimum or usual care/ standard dietary or exercise advice Behavioural interventions that are not quantifiable or combined with anti-obesity medication or surgery	None	Any study lower than a randomized controlled trial study. Non-randomized controlled trials are excluded.	None

2. SEARCH STRATEGY

Search Date: 11 August 2022

Database searched	Platform	Years of coverage	Records	Records after duplicates removed
Embase	Embase.com	1971 - Present	834	825
Medline ALL	Ovid	1946 - Present	375	63
Web of Science Core Collection*	Web of Knowledge	1975 - Present	446	117
Cochrane Central Register of Controlled Trials	Wiley	1992 - Present	377	0
Additional Search Engines: Google Scholar			200	110
Total			2609	1281

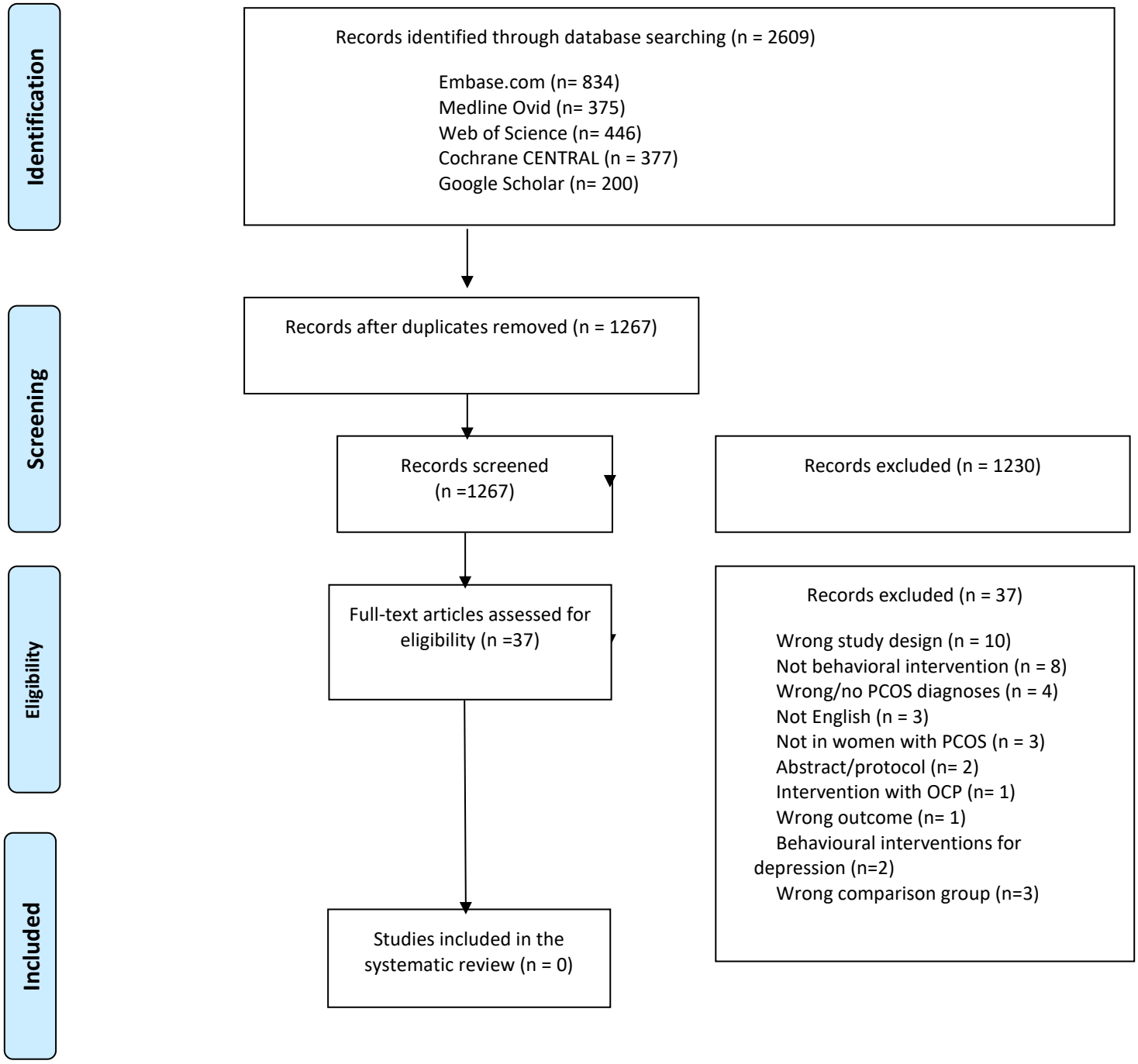
*Science Citation Index Expanded (1975-present) ; Social Sciences Citation Index (1975-present) ; Arts & Humanities Citation Index (1975-present) ; Conference Proceedings Citation Index- Science (1990-present) ; Conference Proceedings Citation Index- Social Science & Humanities (1990-present) ; Emerging Sources Citation Index (2005-present)

Embase – 834 refs
('ovary polycystic disease'/de OR 'anovulation'/de OR (PCOS OR PCO OR leventhal* OR ((polycyst* OR poly-cyst* OR scelerocystic* OR degenerat* OR hyperandrogen* OR hyper-androgen*) NEAR/6 (ovar*)) OR anovulat* OR oligo-ovulat* OR oligoovulat*):ab,ti,kw) AND ('cognitive behavioral therapy'/de OR 'cognitive therapy'/de OR 'lifestyle modification'/de OR 'lifestyle'/de OR 'behavior theory'/de OR 'Social Cognitive Theory'/de OR 'Theory of Planned Behavior'/de OR (lifestyle* OR ((behavior* OR behaviour* OR cognit* OR transtheoretical-stage* OR self-determination*) NEAR/3 (intervention* OR therap* OR modificat* OR advic* OR treatment* OR chang* OR theor*)) OR health-coach*):ab,ti,kw) AND ('randomization'/exp OR 'clinical trial'/exp OR 'systematic review'/exp OR 'meta analysis'/de OR (trial OR random* OR systematic-review* OR meta-analy* OR guideline*):ab,ti,kw) NOT ((animal/exp OR animal*:de OR nonhuman/de) NOT ('human'/exp))
Medline – 375 refs
(Polycystic Ovary Syndrome/ OR Anovulation/ OR (PCOS OR PCO OR leventhal* OR ((polycyst* OR poly-cyst* OR scelerocystic* OR degenerat* OR hyperandrogen* OR hyper-androgen*) ADJ6 (ovar*)) OR anovulat* OR oligo-ovulat* OR oligoovulat*).ab,ti,kf.) AND (Cognitive Behavioral Therapy/ OR Life Style/ OR Transtheoretical Model/ OR (lifestyle* OR ((behavior* OR behaviour* OR cognit* OR transtheoretical-stage* OR self-determination*) ADJ3 (intervention* OR therap* OR modificat* OR advic* OR treatment* OR chang* OR theor*)) OR health-coach*).ab,ti,kf.) AND (exp Clinical Trial/ OR Systematic Review/ OR Meta-Analysis/ OR (trial OR random* OR systematic-review* OR meta-analy* OR guideline*).ab,ti,kf.) NOT (exp animals/ NOT humans/)
Cochrane – 377 refs
((PCOS OR PCO OR leventhal* OR ((polycyst* OR poly-cyst* OR scelerocystic* OR degenerat* OR hyperandrogen* OR hyper-androgen*) NEAR/6 (ovar*)) OR anovulat* OR oligo-ovulat* OR oligoovulat*):ab,ti,kw) AND ((lifestyle* OR ((behavior* OR behaviour* OR cognit* OR transtheoretical-stage* OR self-determination*) NEAR/3 (intervention* OR therap* OR modificat* OR advic* OR treatment* OR chang* OR theor*)) OR health-coach*):ab,ti,kw)
Web of Science – 446 refs

TS=(((PCOS OR PCO OR leventhal* OR ((polycyst* OR poly-cyst* OR scelerocystic* OR degenerat* OR hyperandrogen* OR hyper-androgen*) NEAR/5 (ovar*)) OR anovulat* OR oligo-ovulat* OR oligoovulat*)) AND ((lifestyle* OR ((behavior* OR behaviour* OR cognit* OR transtheoretical-stage* OR self-determination*) NEAR/2 (intervention* OR therap* OR modificat* OR advic* OR treatment* OR chang* OR theor*)) OR health-coach*)) AND ((trial OR random* OR systematic-review* OR meta-analy* OR guideline*)) NOT ((animal* OR rat OR rats OR mouse OR mice OR murine OR dog OR dogs OR canine OR cat OR cats OR feline OR rabbit OR cow OR cows OR bovine OR rodent* OR sheep OR ovine OR pig OR swine OR porcine OR veterinar* OR chick* OR zebrafish* OR baboon* OR nonhuman* OR primate* OR cattle* OR goose OR geese OR duck OR macaque* OR avian* OR bird* OR fish*) NOT (human* OR patient* OR women OR woman OR men OR man)))
Google Scholar – 200 refs
“polycystic ovary syndrome|disease” lifestyle|”behavioral|behavioural|cognition|cognitive intervention|therapy|treatment”

Evidence processing: The literature search and screening were performed together in Covidence. Studies were selected and appraised by two reviewers using study selection and appraisal criteria (PICO above) established a priori. The articles were reviewed by title and abstract by two reviewers. When a decision could not be made based on title and abstract alone, full text was retrieved. No studies met inclusion criteria for this review.

3. SEARCH RESULTS - PRISMA flowchart



4. STUDY INCLUSION

Table 4.1. Included Studies (full citation with doi)- *add more rows as needed*

None.

Table 4.2. Excluded Studies (on full text assessment)	
Reference	Reason
Nikokavoura, E., Johnston, K. L., Broom, J., Wrieden, W., & Rolland, C. (2015). Weight loss for women with and without polycystic ovary syndrome following a very low-calorie diet in a community-based setting with trained facilitators for 12 weeks. In Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy (p. 495). Informa UK Limited. https://doi.org/10.2147/dmso.s85134	No NIH, Rotterdam or AEPCOS criteria for PCOS
Haqq, L., McFarlane, J., Dieberg, G., & Smart, N. (2014). Effect of lifestyle intervention on the reproductive endocrine profile in women with polycystic ovarian syndrome: a systematic review and meta-analysis. In Endocrine Connections (Vol. 3, Issue 1, pp. 36–46). Bioscientifica. https://doi.org/10.1530/ec-14-0010	No behavioural interventions included
Clark, A. M., Ledger, W., Galletly, C., Tomlinson, L., Blaney, F., Wang, X., & Norman, R. J. (1995). Weight loss results in significant improvement in pregnancy and ovulation rates in anovulatory obese women. Human Reproduction (Oxford, England), 10(10), 2705–2712. https://doi.org/10.1093/oxfordjournals.humrep.a135772	No NIH, Rotterdam or AEPCOS criteria for PCOS
Hoeger, K., Davidson, K., Kochman, L., Cherry, T., Kopin, L., & Guzick, D. S. (2008). The Impact of Metformin, Oral Contraceptives, and Lifestyle Modification on Polycystic Ovary Syndrome in Obese Adolescent Women in Two Randomized, Placebo-Controlled Clinical Trials. In The Journal of Clinical Endocrinology & Metabolism (Vol. 93, Issue 11, pp. 4299–4306). The Endocrine Society. https://doi.org/10.1210/jc.2008-0461	Wrong study design/ OCP
Forget-Renaud, A., Belan, M., Jean-Denis, F., & Baillargeon, J.-P. (2021). An Interdisciplinary Program Promoting the Adoption of a Healthy Lifestyle Increases Insulin Sensitivity in Women With Obesity and Infertility. In Canadian Journal of Diabetes (Vol. 45, Issue 7, pp. S17–S18). Elsevier BV. https://doi.org/10.1016/j.jcjd.2021.09.056	Abstract/study protocol
Jalilian, F., Kaboudi, M., TehraniZadeh, M., Naghizadeh Moghari, F., & Montazer, A. (2018). The effect of cognitive behavioral counseling on quality of life in women with polycystic ovarian syndrome. Payesh (Health Monitor), 17(6), 667–676. http://payeshjournal.ir/browse.php?a_id=948&sid=1&slc_lang=en	Not in English
Mahoney, D. (2014). Lifestyle modification intervention among infertile overweight and obese women with polycystic ovary syndrome. In Journal of the American Association of Nurse Practitioners (Vol. 26, Issue 6, pp. 301–308). Ovid Technologies (Wolters Kluwer Health). https://doi.org/10.1002/2327-6924.12073	No RCT/wrong study design
Rajagopal, G., Reddy, A. P., Venkata Harinarayan, C., Suresh, V., Bitla, A., P V L N Rao, S., & Sachan, A. (2012). Effect of lifestyle modification and metformin therapy on emerging cardiovascular risk factors in overweight Indian women with polycystic ovary syndrome. Metabolic Syndrome and Related Disorders, 10(4), 273–279. https://doi.org/10.1089/met.2011.0127	Not a behavioural/lifestyle intervention
Ladson, G., Dodson, W. C., Sweet, S. D., Archibong, A. E., Kunselman, A. R., Demers, L. M., Williams, N. I., Coney, P., & Legro, R. S. (2011). The effects of metformin with lifestyle therapy in polycystic ovary syndrome: a randomized double-blind study. In Fertility and Sterility (Vol. 95, Issue 3, pp. 1059-1066.e7). Elsevier BV. https://doi.org/10.1016/j.fertnstert.2010.12.002	Not a behavioural/lifestyle intervention
Ladson, G., Dodson, W. C., Sweet, S. D., Archibong, A. E., Kunselman, A. R., Demers, L. M., Lee, P. A., Williams, N. I., Coney, P., & Legro, R. S. (2011). Effects of metformin in adolescents with polycystic ovary syndrome undertaking lifestyle therapy: a pilot randomized double-blind study. In Fertility and Sterility (Vol. 95, Issue 8, pp. 2595-2598.e6). Elsevier BV. https://doi.org/10.1016/j.fertnstert.2011.05.048	Not a behavioural/lifestyle intervention
Nicholson, F. (2010). Effectiveness of long-term (twelve months) nonsurgical weight loss interventions for obese women with polycystic ovary syndrome: a systematic review. In International Journal of Women's Health (p. 393). Informa UK Limited. https://doi.org/10.2147/ijwh.s13456	Not a behavioural/lifestyle intervention
Kazemi, M., McBreairty, L., Chizen, D., Pierson, R., Chilibeck, P., & Zello, G. (2018). A Comparison of a Pulse-Based Diet and the Therapeutic Lifestyle Changes Diet in Combination with Exercise and Health Counselling on the Cardio-Metabolic Risk Profile in Women with Polycystic Ovary Syndrome: A Randomized Controlled Trial. In Nutrients (Vol. 10, Issue 10, p. 1387). MDPI AG. https://doi.org/10.3390/nu10101387	Not a behavioural/lifestyle intervention
Wang, Z., Groen, H., Cantineau, A. E. P., van Elten, T. M., Karsten, M. D. A., van Oers, A. M., Mol, B. W. J., Roseboom, T. J., & Hoek, A. (2021). Dietary Intake, Eating Behavior, Physical Activity, and	Control population included women without PCOS

Quality of Life in Infertile Women with PCOS and Obesity Compared with Non-PCOS Obese Controls. In Nutrients (Vol. 13, Issue 10, p. 3526). MDPI AG. https://doi.org/10.3390/nu13103526	
Harris-Glocker, M., Davidson, K., Kochman, L., Guzick, D., & Hoeger, K. (2010). Improvement in quality-of-life questionnaire measures in obese adolescent females with polycystic ovary syndrome treated with lifestyle changes and oral contraceptives, with or without metformin. In Fertility and Sterility (Vol. 93, Issue 3, pp. 1016–1019). Elsevier BV. https://doi.org/10.1016/j.fertnstert.2009.08.006	Wrong study design/ OCP
Lim, S. S., Norman, R. J., Clifton, P. M., & Noakes, M. (2011). The effect of comprehensive lifestyle intervention or metformin on obesity in young women. Nutrition, Metabolism, and Cardiovascular Diseases: NMCD, 21(4), 261–268. https://doi.org/10.1016/j.numecd.2009.10.006	Not in women with PCOS
Wang, Z., Groen, H., Cantineau, A. E. P., van Elten, T. M., Karsten, M. D. A., van Oers, A. M., Mol, B. W. J., Roseboom, T. J., & Hoek, A. (2021). Effectiveness of a 6-Month Lifestyle Intervention on Diet, Physical Activity, Quality of Life, and Markers of Cardiometabolic Health in Women with PCOS and Obesity and Non-PCOS Obese Controls: One Size Fits All? In Nutrients (Vol. 13, Issue 10, p. 3425). MDPI AG. https://doi.org/10.3390/nu13103425	Control population included women without PCOS
Abdulkhalikova, D., Sustarsic, A., Vrtačnik Bokal, E., Jancar, N., Jensterle, M., & Burnik Papler, T. (2022). The Lifestyle Modifications and Endometrial Proteome Changes of Women With Polycystic Ovary Syndrome and Obesity. In Frontiers in Endocrinology (Vol. 13). Frontiers Media SA. https://doi.org/10.3389/fendo.2022.888460	No RCT/wrong study design
Abdollahi, L., Mirghafourvand, M., Babapour, J. K., & Mohammadi, M. (2018). Effectiveness of cognitive-behavioral therapy (CBT) in improving the quality of life and psychological fatigue in women with polycystic ovarian syndrome: a randomized controlled clinical trial. In Journal of Psychosomatic Obstetrics & Gynecology (Vol. 40, Issue 4, pp. 283–293). Informa UK Limited. https://doi.org/10.1080/0167482x.2018.1502265	Not a behavioural/lifestyle intervention
Abdollahi, L., Mirghafourvand, M., Babapour Kheyradin, J., & Mohammadi, M. (2018). The Effect of Cognitive Behavioral Therapy on Depression and Obesity in Women with Polycystic Ovarian Syndrome: A Randomized Controlled Clinical Trial. In Iranian Red Crescent Medical Journal (Vol. 20, Issue 3). DoNotEdit. https://doi.org/10.5812/ircmj.62735	Not a behavioural/lifestyle intervention
Moran, L. J., Tassone, E. C., Boyle, J., Brennan, L., Harrison, C. L., Hirschberg, A. L., Lim, S., Marsh, K., Misso, M. L., Redman, L., Thondan, M., Wijeyaratne, C., Garad, R., Stepto, N. K., & Teede, H. J. (2020). Evidence summaries and recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome: Lifestyle management. In Obesity Reviews (Vol. 21, Issue 10). Wiley. https://doi.org/10.1111/obr.13046	Summary guideline
Lass, N., Kleber, M., Winkel, K., Wunsch, R., & Reinehr, T. (2011). Effect of Lifestyle Intervention on Features of Polycystic Ovarian Syndrome, Metabolic Syndrome, and Intima-Media Thickness in Obese Adolescent Girls. In The Journal of Clinical Endocrinology & Metabolism (Vol. 96, Issue 11, pp. 3533–3540). The Endocrine Society. https://doi.org/10.1210/jc.2011-1609	No RCT/wrong study design
Kazemi, M., McBreairty, L. E., Zello, G. A., Pierson, R. A., Gordon, J. J., Serrao, S. B., Chilibeck, P. D., & Chizen, D. R. (2019). A pulse-based diet and the Therapeutic Lifestyle Changes diet in combination with health counseling and exercise improve health-related quality of life in women with polycystic ovary syndrome: secondary analysis of a randomized controlled trial. In Journal of Psychosomatic Obstetrics & Gynecology (Vol. 41, Issue 2, pp. 144–153). Informa UK Limited. https://doi.org/10.1080/0167482x.2019.1666820	Not a behavioural/lifestyle intervention
De Frène, V., Verhofstadt, L., Lammertyn, J., Stuyver, I., Buysse, A., & De Sutter, P. (2015). Quality of life and body mass index in overweight adult women with polycystic ovary syndrome during a lifestyle modification program. Journal of Obstetric, Gynecologic, and Neonatal Nursing : JOGNN, 44(5), 587–599. https://doi.org/10.1111/1552-6909.12739	No RCT/wrong study design
Oberg, E., Lundell, C., Blomberg, L., Gidlöf, S. B., Egnell, P. T., & Hirschberg, A. L. (2020). Psychological well-being and personality in relation to weight loss following behavioral modification intervention in obese women with polycystic ovary syndrome: a randomized controlled trial. In European Journal of Endocrinology (Vol. 183, Issue 1, pp. 1–11). Bioscientifica. https://doi.org/10.1530/eje-20-0066	Wrong outcome
Domecq, J. P., Prutsky, G., Mullan, R. J., Hazem, A., Sundaresh, V., Elamin, M. B., Phung, O. J., Wang, A., Hoeger, K., Pasquali, R., Erwin, P., Bodde, A., Montori, V. M., & Murad, M. H. (2013). Lifestyle Modification Programs in Polycystic Ovary Syndrome: Systematic Review and Meta-Analysis. In The Journal of Clinical Endocrinology & Metabolism (Vol. 98, Issue 12, pp. 4655–4663). The Endocrine Society. https://doi.org/10.1210/jc.2013-2385	Meta-analysis, no new studies.
Amiri, M., Mirmiran, P., & Tehrani, F. R. (2017). Effect of interventions based on lifestyle modification on clinical, hormonal and metabolic findings in the patients with polycystic ovary syndrome: A systematic review. Amazonaws.com. https://regroup-	Not in English

production.s3.amazonaws.com/documents/ReviewReference/542034057/amiri%202016.pdf?response-content-type=application%2Fpdf&X-Amz-Algorithm=AWS4-HMAC-SHA256&X-Amz-Credential=AKIAYSFKCAWY23RWESRS%2F20221013%2Fus-east-1%2Fs3%2Faws4_request&X-Amz-Date=20221013T113247Z&X-Amz-Expires=604800&X-Amz-SignedHeaders=host&X-Amz-Signature=9a0ad57b1825c7304b8c82d97f439bdcf55cee70809c3869849c4f85b96195ee	
Abdolahian, S., Tehrani, F. R., Amiri, M., Ghodsi, D., Yarandi, R. B., Jafari, M., Majd, H. A., & Nahidi, F. (2020). Effect of lifestyle modifications on anthropometric, clinical, and biochemical parameters in adolescent girls with polycystic ovary syndrome: a systematic review and meta-analysis. In BMC Endocrine Disorders (Vol. 20, Issue 1). Springer Science and Business Media LLC. https://doi.org/10.1186/s12902-020-00552-1	Meta-analysis, no new studies.
Lim, S. S., Hutchison, S. K., Van Ryswyk, E., Norman, R. J., Teede, H. J., & Moran, L. J. (2019). Lifestyle changes in women with polycystic ovary syndrome. In Cochrane Database of Systematic Reviews (Vol. 2019, Issue 3). Wiley. https://doi.org/10.1002/14651858.cd007506.pub4	Meta-analysis, no new studies.
De Loos, A. D., Timman, R., Jiskoot, G., Beerthuizen, A., Van Busschbach, J., & Laven, J. (2019). Favorable changes in characteristics, phenotype and androgens as result of weight loss in a randomised controlled three-component lifestyle intervention in women with PCOS. In HUMAN REPRODUCTION (Vol. 34, pp. 144–144). OXFORD UNIV PRESS.	Abstract
Khatlani, K., Njike, V., & Costales, V. C. (2019). Effect of Lifestyle Intervention on Cardiometabolic Risk Factors in Overweight and Obese Women with Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis. In Metabolic Syndrome and Related Disorders (Vol. 17, Issue 10, pp. 473–485). Mary Ann Liebert Inc. https://doi.org/10.1089/met.2019.0049	Meta-analysis, no new studies.
Haqq, L., McFarlane, J., Dieberg, G., & Smart, N. (2015). The Effect of Lifestyle Intervention on Body Composition, Glycemic Control, and Cardiorespiratory Fitness in Polycystic Ovarian Syndrome: A Systematic Review and Meta-Analysis. In International Journal of Sport Nutrition and Exercise Metabolism (Vol. 25, Issue 6, pp. 533–540). Human Kinetics. https://doi.org/10.1123/ijsnem.2013-0232	Meta-analysis, no new studies.
H. Al Wattar, B., M. Hussain, N., & S. Khan, K. (2022). Lifestyle interventions in women with polycystic ovary syndrome: A scoping systematic review of randomised evidence. In Medicina de Familia. SEMERGEN (Vol. 48, Issue 3, pp. 186–194). Elsevier BV. https://doi.org/10.1016/j.semerg.2021.10.010	Meta-analysis, no new studies.
Cooney, L. G., Milman, L. W., Hantsoo, L., Kornfield, S., Sammel, M. D., Allison, K. C., Epperson, C. N., & Dokras, A. (2018). Cognitive-behavioral therapy improves weight loss and quality of life in women with polycystic ovary syndrome: a pilot randomized clinical trial. In Fertility and Sterility (Vol. 110, Issue 1, pp. 161-171.e1). Elsevier BV. https://doi.org/10.1016/j.fertnstert.2018.03.028	Behavioural intervention for depression
Jiskoot, G., Timman, R., Beerthuizen, A., Dietz de Loos, A., Busschbach, J., & Laven, J. (2020). Weight Reduction Through a Cognitive Behavioral Therapy Lifestyle Intervention in PCOS: The Primary Outcome of a Randomized Controlled Trial. In Obesity (Vol. 28, Issue 11, pp. 2134–2141). Wiley. https://doi.org/10.1002/oby.22980	Comparator not structured lifestyle management
Dietz de Loos, A. L. P., Jiskoot, G., Timman, R., Beerthuizen, A., Busschbach, J. J. V., & Laven, J. S. E. (2021). Improvements in PCOS characteristics and phenotype severity during a randomized controlled lifestyle intervention. In Reproductive BioMedicine Online (Vol. 43, Issue 2, pp. 298–309). Elsevier BV. https://doi.org/10.1016/j.rbmo.2021.05.008	Comparator not structured lifestyle management
Dietz de Loos, A., Jiskoot, G., Beerthuizen, A., Busschbach, J., & Laven, J. (2022). Metabolic health during a randomized controlled lifestyle intervention in women with PCOS. In European Journal of Endocrinology (Vol. 186, Issue 1, pp. 53–64). Bioscientifica. https://doi.org/10.1530/eje-21-0669	Comparator not structured lifestyle management
Oberg, E., Gidlöf, S., Jakson, I., Mitsell, M., Tollet Egnell, P., & Hirschberg, A. L. (2019). Improved menstrual function in obese women with polycystic ovary syndrome after behavioural modification intervention-A randomized controlled trial. In Clinical Endocrinology (Vol. 90, Issue 3, pp. 468–478). Wiley. https://doi.org/10.1111/cen.13919	Comparator not structured lifestyle management

4. FINDINGS

See PART 2 for this question

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 3

Question 3.2.

In women with PCOS, are behavioural interventions (compared to different types of behavioural interventions) effective for improving anthropometric, metabolic, reproductive, fertility, quality of life and emotional wellbeing outcomes?

BACKGROUND:

Clinical need for the question

Lifestyle intervention (diet, physical activity and behavioural interventions) is first line PCOS treatment. With weight gain increasing in women across the population, and prevention of weight gain a national and international priority, the need for preventive strategies also extends to PCOS [1]. Indeed, women with PCOS demonstrate a greater mean 10-year weight gain of 8.9kg (95% CI: 7.5-10.2) compared to women without PCOS [6.2kg (95% CI: 6.0-6.5)] [2] which translates to ~1kg average expected weight gain in PCOS per year compared to the mean of ~600 grams/year in young women without PCOS.

Previous lifestyle intervention studies in PCOS have focused on short-term dietary interventions with or without an exercise component. Numerous uncontrolled dietary intervention studies which have shown limited success, with an overall weight loss effect of between 5-15% of initial body weight in addition to improvement in complications exacerbated by weight gain including IR, menstrual dysfunction and psychological features [3], however retention and sustainability were suboptimal. With the majority of lifestyle intervention studies focused on dietary intervention there is an unmet need to explore other strategies in PCOS, including behaviour change interventions.

Behavioural and cognitive behavioural interventions are the most commonly used psychological approaches to weight management. Behaviour therapy results in significantly greater weight loss than placebo, and behaviour/cognitive behaviour therapy combined with diet and exercise is more effective than diet and exercise interventions alone. More intensive behavioural interventions are associated with greater weight loss [4]. Behavioural and cognitive behavioural intervention approaches target the behaviours (and their antecedents and consequences) and cognitions thought to be responsible for maintaining a positive energy balance [5]. Behavioural and cognitive behavioural interventions have the strongest empirical support in the treatment of overweight/obesity and are recommended by international practice guidelines for the treatment of overweight and obesity [e.g., 6, 7].

On systematic review, three randomised controlled trials (across five published papers (8-12) evaluating behavioural change therapy in conjunction with lifestyle (i.e. diet and/or physical activity) were identified. On evaluation all three trials were deemed ineligible for inclusion due to use of cognitive behavioural therapy (CBT) to address depression in women with PCOS (8) or lacked a structured lifestyle intervention comparator group (9, 10). Both RCTs (9, 10) contained a comparator group considered to be aligned to care as usual, with allocated participants provided unstructured, general healthy lifestyle recommendations with or without encouragement to lose weight through publicly available services.

Although not eligible to inform a GRADE recommendation the identified studies provide preliminary insight of the efficacy of behavioural therapy in conjunction with lifestyle (diet and/or physical activity) intervention in women with PCOS. Across the three RCTs, study design was highly heterogeneous, with sample sizes ranging 15 to 183 and intervention duration either 4 months (8, 10) or 12 months (9). Dropout rate was highly variable, ranging from 16.2% (10) to 63.3% (12-month trial (9)). Risk of bias was either moderate (n=2 studies) or high (n=1 study). All studies included overweight women.

The following outcomes were assessed:

<u>Outcome 1: Anovulation (assessed in 2 studies, moderate ROB)</u>

One study (10) reported a significantly higher proportion of participants with improved menstrual cyclicity following a 4-month intervention compared with care as usual (59% [n = 20/34] vs 24% [n = 8/34]) with a mean difference of 35% (95% CI: 16-60, P = 0.003).

<u>Outcome 2: Weight loss (assessed in 3 studies, moderate/high ROB)</u>

Two studies with small/moderate sample sizes of n=15 and n=68 reported no significant differences between groups in weight following intervention (8, 10).

One larger study (n=120) reported a significant difference in weight loss between groups at 12 months of 3.7 kg in favour of lifestyle with behavioural intervention compared with care as usual (d = −0.25; P < 0.001). However, the dropout rate was >50%, increasing uncertainty of reported results.

Outcome 3. Waist hip ratio (assessed in 2 studies, moderate/high ROB)

One study with small sample size (n=15) reported a significant difference in WHR between groups (p=0.04) in favour of intervention, however risk of bias was high. One study reported no change following intervention.

Outcome 4. Quality of life (assessed in 1 study, moderate ROB)

No significant difference between interventions

Outcome 5. HOMA-IR (assessed in 3 studies, moderate/high ROB)

No significant difference between interventions

Outcome 6. Lipids (cholesterol, triglycerides, HDL, LDL; assessed in 2 studies, moderate ROB)

No significant difference between intervention in any variables

Overall, results suggest intervention involving structured lifestyle (diet and/or exercise) with behavioural modification is not favourable to care as usual for the outcomes of WHR, QoL, HOMA-IR or lipids following intervention. There is some evidence to support lifestyle (diet and/or exercise) with behavioural modification for weight loss, however results need to be interpreted with caution due to a significant reported dropout rate (>50% at follow-up) and an overall moderate risk of bias.

There is some evidence to support lifestyle (diet and/or exercise) with behavioural modification for improving menstrual function from one study, deemed moderate risk of bias with relatively small sample size over 4-month period.

GRADE EVIDENCE CERTAINTY

Comparison	GRADE for critical outcomes
Comparison 1. Behavioural lifestyle versus control	No evidence

Evidence to Recommendations Framework

COMPARISONS (option versus other option)

Lifestyle (structured diet and/or exercise therapy) with behavioural intervention [L+B] versus Lifestyle (structured diet and/or exercise) intervention alone [L]

CONCENSUS RECOMMENDATION

CR: Lifestyle interventions could include behavioural strategies such as goal-setting, self-monitoring, , problem solving, assertiveness training, reinforcing changes and relapse prevention, to optimise weight management, healthy lifestyle and emotional wellbeing in women with PCOS.

GRADE Direction and Strength of Recommendation:

☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

PRACTICE POINT(S)

Behavioural support could include: goal setting, problem solving, self-monitoring and reviewing, or SMART goals (Specific, Measurable, Achievable, Realistic and Timely).

Comprehensive healthy behavioural or cognitive behavioural interventions could be considered to increase support, engagement, retention, adherence and maintenance of healthy lifestyle and improve health outcomes in women with PCOS.

GRADE CONSIDERATIONS

Justifications:
None of the identified studies met the eligible criteria for inclusion.

Subgroup considerations:
None

Implementation considerations:
Overall, there remains a paucity of evidence to definitively support implementation of the additional of behavioural therapy on top of lifestyle management in women with PCOS as an evidence base has not been established to guide what should be implemented, how, by whom, where and at what cost.

Cost effectiveness
High quality evidence to assess this criterion is not available. Regional circumstances should be considered when assessing cost and resources.

Equity
Lack of evidence to support equity in intervention design to diverse groups of women, using variable intervention delivery techniques to enhance reach, accessibility and engagement. Co-design not featured in intervention design broadly.

Acceptability
Health professional training, time, capability and confidence may limit acceptability for implementation of behavioural and cognitive behavioural interventions. Barriers could be related to the balance between consultation time available and efficacy to induce change.

Feasibility

Policy settings, health system enablers, education and engagement of health professionals and patient considerations (such as the cost of longer consultations and/or consultations with other health professionals) will affect feasibility.

Implementation
Barriers to implementation could include resources available to healthcare professionals, adequate training and clinical acceptability related to time, potentially increased engagement with additional health care providers and increased patient contact.

Monitoring and evaluation considerations:
Monitoring the access for behavioural therapy for lifestyle management.
Difficult to monitor due to lack of standardised training for delivering behavioural therapy.

Research priorities:
Clear and consistent definition of behavioural therapy, lifestyle interventions and outcomes in research.

There remains a paucity of high-quality evidence to inform this question. Further studies are required to definitely evaluate outcomes, alongside feasibility evaluation, include cost-effectiveness analysis to inform broader scale-up.

High-quality randomised controlled trials evaluating the efficacy of behavioural interventions to optimise health behaviour change and/or weight management are required to evaluate additional benefits of adding of behavioural strategies and/or behavioural/cognitive behavioural interventions to dietary and/or exercise prescription approaches in this population for improved anthropometric, metabolic, reproductive, fertility, quality of life and emotional wellbeing outcomes.

Longitudinal evaluation from PCOS specific research would address current gaps and provide insight across feasibility, acceptability, implementation and efficacy.

High-quality randomised controlled trials are important to address:

- The extent of the additional benefits of adding behavioural strategies and/or behavioural/cognitive behavioural interventions to stand-alone dietary and/or exercise prescription approaches in improving weight, metabolic, reproductive and psychosocial well-being;
- Provide evidence of the efficacy of differing types of lifestyle management;
- Provide evidence for the effect of behavioural strategies and/or behavioural/cognitive behavioural interventions across varying phenotypic profiles of women with polycystic ovary syndrome including variation by body mass index categories of healthy, overweight or obese;
- Provide evidence for the effect of behavioural strategies and/or behavioural/cognitive behavioural interventions in the prevention of weight gain compared to weight loss.
- Provide evidence for the effect of behavioural strategies and/or behavioural/cognitive behavioural interventions for improved metabolic (i.e. insulin resistance), reproductive (i.e. menstrual dysfunction, infertility) and psychosocial dysfunction (i.e. quality of life, depression, anxiety, disordered eating) in women with PCOS.
- Provide evidence to inform intervention acceptability to participants given high-dropout rates that are mainstay across lifestyle interventions, particularly those of longer duration.

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9. Jiskoot G, Timman R, Beerthuizen A, Dietz de Loos A, Busschbach J, Laven J. Weight Reduction Through a Cognitive Behavioral Therapy Lifestyle Intervention in PCOS: The Primary Outcome of a Randomized Controlled Trial. Obesity (Silver Spring). 2020 Nov;28(11):2134-2141. doi: 10.1002/oby.22980. Epub 2020 Sep 23. PMID: 32969197; PMCID: PMC7702123.
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11. Dietz de Loos A, Jiskoot G, Beerthuizen A, Busschbach J, Laven J. Metabolic health during a randomized controlled lifestyle intervention in women with PCOS. Eur J Endocrinol. 2021 Nov 30;186(1):53-64. doi: 10.1530/EJE-21-0669. PMID: 34714771; PMCID: PMC8679850.
12. Dietz de Loos ALP, Jiskoot G, Timman R, Beerthuizen A, Busschbach JJV, Laven JSE. Improvements in PCOS characteristics and phenotype severity during a randomized controlled lifestyle intervention. Reprod Biomed Online. 2021 Aug;43(2):298-309. doi: 10.1016/j.rbmo.2021.05.008. Epub 2021 May 19. PMID: 3423865.

PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by ECR Lead: Maryam Kazemi

Other team members: Stephanie Cowan, Kimberly Hopkins, Thais Rasia

Supervised, edited and supported by the Evidence Team (Aya Mousa, Jillian Tay)

GDG 3

Question 3.3.

In women with PCOS, are diet interventions (compared to different diets) effective for improving anthropometric, metabolic, fertility, and emotional wellbeing outcomes?

1. SELECTION CRITERIA

Table 1. PICO Criteria for Inclusion	
Question	Q 3.3) In women with PCOS, are diet interventions (compared to different diets) effective for improving anthropometric, metabolic, fertility, and emotional wellbeing outcomes?
Clinical leads (key contacts)	**Dr. Kate Marsh** PCOS Health and Nutrition Centre, Australia drkatemarsh@gmail.com
Allocation ranking	Level 2- Update systematic review

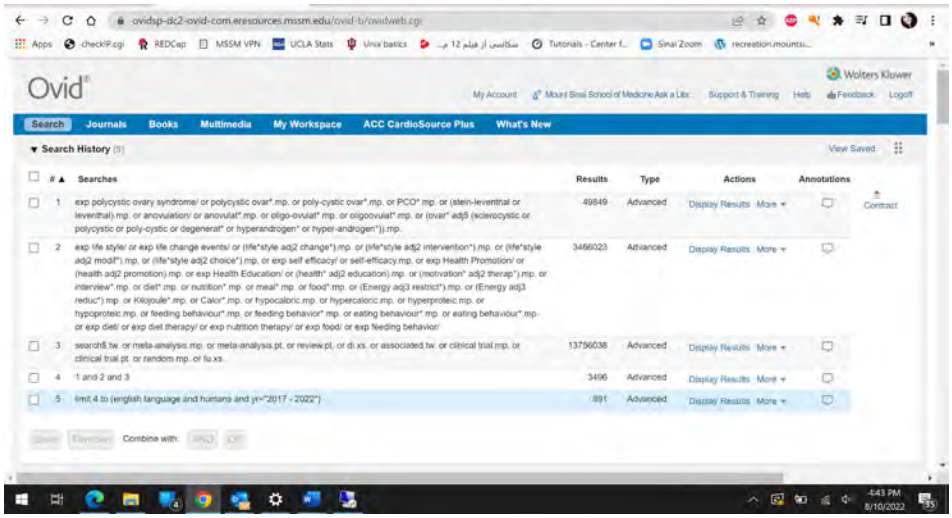
	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(Language, year)*
Inclusion	Women with Polycystic Ovary Syndrome. All ages (diagnosed by the NIH 1990 [1], Rotterdam 2003 [2], or AE-PCOS 2006 [3] criteria). Women of all weights. All medical conditions (co-morbidities). Document specific co-morbidities. Any lifestyle characteristics. Document all characteristics (e.g., smokers).	All types of dietary compositions. Interventions were included that both aimed to achieve weight loss and for which weight loss was not specifically aimed or weight maintenance was aimed for. Commonly prescribed dietary compositions include low carbohydrate, low GI, reduced calorie, very low calorie, and high protein diets. Diet intervention may include herbal or complementary medicines or ingredients, but the control diet must also use the same herbal or complementary medicine. Duration of dietary intervention ≥ 2 weeks.	All types of dietary compositions (different from the intervention diet).	**Anthropometric outcomes.** These include weight loss measures such as % and kg of original weight lost, % and kg weight loss over time (e.g., kg/week) if reported, reduction in BMI, reduction in WC and waist-to-hip ratio, % and kg fat mass (central/truncal and total) measured using BIA, DEXA, MRI or CT, % and kg lean mass. **Fertility outcomes** include the rate of pregnancy, rate of live birth, and rate of miscarriage. Menstrual regularity; Initiation of menses or significant shortening of cycle length or any other reporting formats. Ovulation measures such as the number of ovulatory menstrual cycles or any other reporting formats. **Non-fertility outcomes** such as reproductive hormonal parameters. These include total testosterone, sex hormone binding globulin (SHBG), measures of free androgens (e.g., free androgen index, free testosterone), and hirsutism (Ferriman-Gallwey score). **Metabolic outcomes.** These include insulin and glucose measures such as fasting blood glucose, oral glucose tolerance test (OGTT) glucose and insulin, fasting insulin, homeostasis assessment of insulin resistance (HOMA-IR), insulin sensitivity test – oral glucose tolerance test (ISI-OGTT), postprandial glucose, HbA1-C. Lipid profile measures such as total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), LDL: HDL ratios, triglycerides, apoproteins. Blood pressure, highly sensitive C-reactive protein (CRP), fibrinogen, and plasminogen activator inhibitor (PAI). **Quality of life outcomes, and emotional wellbeing outcomes.** **Surrogate measures of insulin resistance.**	Systematic reviews and RCTs addressing the outcomes are sought for the specified outcomes.	English Limit to publications between 7 June 2017 to 10 August 2022 (as an update of the previous draft of GDG 3.3. in the 2018 guideline)
Exclusion	Women taking anti-obesity medications (e.g., orlistat). Women with PCOS who are not defined as diagnosed by the NIH 1990[38], Rotterdam 2003[39], or AE-PCOS 2006[40] criteria.	Comparisons of different modes of delivery of the same or different dietary interventions. Use of other dietary supplements (e.g., meal replacements, diet pills).	Usual diet or original patient diet if it is has not defined its nutritional composition.	Fat mass measured using skin-fold tests.	Any study lower than an RCT. Non-RCT studies are excluded.	

2. SEARCH STRATEGY

Table 2.1. Search details

Search strategy source: [Page 730, TECHNICAL REPORT FOR International evidence-based guideline for the assessment and management of polycystic ovary syndrome 2018]

Evidence source	Date of search
Medline (Ovid) Search Strategy: ---------- 1. exp polycystic ovary syndrome/ 2. polycystic ovar*.mp. 3. poly-cystic ovar*.mp. 4. PCO*.mp. 5. (stein-leventhal or leventhal).mp. 6. anovulation/ 7. anovulat*.mp. 8. oligo-ovulat*.mp. 9. oligoovulat*.mp. 10. (ovar* adj5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*)).mp. 11. or/1-10 12. exp life style/ 13. exp life change events/ 14. (life*style adj2 change*).mp. 15. (life*style adj2 intervention*).mp. 16. (life*style adj2 modif*).mp. 17. (life*style adj2 choice*).mp. 18. exp self efficacy/ 19. self-efficacy.mp. 20. exp Health Promotion/ 21. (health adj2 promotion).mp. 22. exp Health Education/ 23. (health* adj2 education).mp. 24. (motivation* adj2 therap*).mp. 25. interview*.mp. 26. diet*.mp. 27. nutrition*.mp. 28. meal*.mp. 29. food*.mp. 30. (Energy adj3 restrict*).mp. 31. (Energy adj3 reduc*).mp. 32. Kilojoule*.mp. 33. Calor*.mp. 34. hypocaloric.mp. 35. hypercaloric.mp. 36. hyperproteic.mp. 37. hypoproteic.mp. 38. feeding behaviour*.mp. 39. feeding behavior*.mp. 40. eating behaviour*.mp. 41. eating behaviour*.mp. 42. exp diet/ 43. exp diet therapy/ 44. exp nutrition therapy/ 45. exp food/ 46. exp feeding behavior/ 47. or/12-46 48. search$.tw. or meta-analysis.mp. or meta-analysis.pt. or review.pt. or di.xs. or associated.tw. 49. clinical trial.mp. or clinical trial.pt. or random.mp. or tu.xs. 50. 48 or 49 51. 11 and 47 and 50 52. limit 51 to (english language and humans) 53. limit 52 to yr="2017 -Current" --- Combined search run in Medline Ovid on August 10, 2022	Database: Ovid MEDLINE(R) 7 June 2017 to 10 August 2022

1. exp polycystic ovary syndrome/ OR polycystic ovar*.mp. OR poly-cystic ovar*.mp. OR PCO*.mp. OR (stein-leventhal or leventhal).mp. OR anovulation/ OR anovulat*.mp. OR oligo-ovulat*.mp. OR oligoovulat*.mp. OR (ovar* adj5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*)).mp. 2. exp life style/ OR exp life change events/ OR (life*style adj2 change*).mp. OR (life*style adj2 intervention*).mp. OR (life*style adj2 modif*).mp. OR (life*style adj2 choice*).mp. OR exp self efficacy/ OR self-efficacy.mp. OR exp Health Promotion/ OR (health adj2 promotion).mp. OR exp Health Education/ OR (health* adj2 education).mp. OR (motivation* adj2 therap*).mp. OR interview*.mp. OR diet*.mp. OR nutrition*.mp. OR meal*.mp. OR food*.mp. OR (Energy adj3 restrict*).mp. OR (Energy adj3 reduc*).mp. OR Kilojoule*.mp. OR Calor*.mp. OR hypocaloric.mp. OR hypercaloric.mp. OR hyperproteic.mp. OR hypoproteic.mp. OR feeding behaviour*.mp. OR feeding behavior*.mp. OR eating behaviour*.mp. OR eating behaviour*.mp. OR exp diet/ OR exp diet therapy/ OR exp nutrition therapy/ OR exp food/ OR exp feeding behavior/ 3. search$.tw. or meta-analysis.mp. or meta-analysis.pt. or review.pt. or di.xs. or associated.tw. OR clinical trial.mp. or clinical trial.pt. or random.mp. or tu.xs. 4. 1 AND 2 AND 3 5. limit 4 to (English language and humans and yr="2017 -2022"  *Figure 1. Ovid Search Query Screenshot (Date Aug 10, 2022)* **Retrieved records from Ovid Medline: N=891**	
PsycInfo (Ovid) Combined search run in Medline Ovid on August 10, 2022 1. exp polycystic ovary syndrome/ OR polycystic ovar*.mp. OR poly-cystic ovar*.mp. OR PCO*.mp. OR (stein-leventhal or leventhal).mp. OR anovulation/ OR anovulat*.mp. OR oligo-ovulat*.mp. OR oligoovulat*.mp. OR (ovar* adj5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*)).mp. 2. exp life style/ OR exp life change events/ OR (life*style adj2 change*).mp. OR (life*style adj2 intervention*).mp. OR (life*style adj2 modif*).mp. OR (life*style adj2 choice*).mp. OR exp self efficacy/ OR self-efficacy.mp. OR exp Health Promotion/ OR (health adj2 promotion).mp. OR exp Health Education/ OR (health* adj2 education).mp. OR (motivation* adj2 therap*).mp. OR interview*.mp. OR diet*.mp. OR nutrition*.mp. OR meal*.mp. OR food*.mp. OR (Energy adj3 restrict*).mp. OR (Energy adj3 reduc*).mp. OR Kilojoule*.mp. OR Calor*.mp. OR hypocaloric.mp. OR hypercaloric.mp. OR hyperproteic.mp. OR hypoproteic.mp. OR feeding behaviour*.mp. OR feeding behavior*.mp. OR eating behaviour*.mp. OR eating behaviour*.mp. OR exp diet/ OR exp diet therapy/ OR exp nutrition therapy/ OR exp food/ OR exp feeding behavior/	Database: Ovid MEDLINE(R) 7 June 2017 to 10 August 2022

3. search$.tw. or meta-analysis.mp. or meta-analysis.pt. or review.pt. or associated.tw. OR clinical trial.mp. or clinical trial.pt. or random.mp.
4. 1 AND 2 AND 3
5. limit 4 to (english language and human and last 5 years)

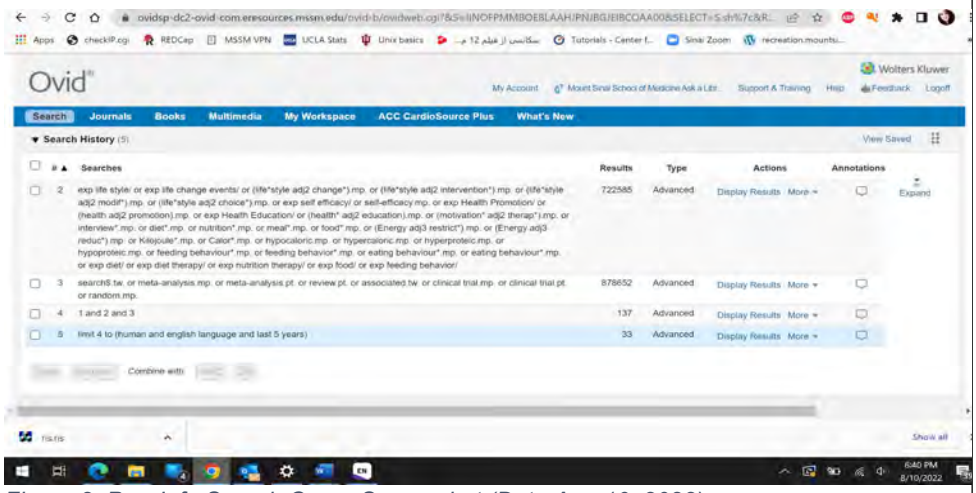


Figure 2. PsycInfo Search Query Screenshot (Date Aug 10, 2022)

Retrieved records from Ovid Medline: N=33

EMBASE (Ovid)

Combined search run in Medline Ovid on August 10, 2022

1. exp polycystic ovary syndrome/ OR polycystic ovar*.mp. OR poly-cystic ovar*.mp. OR PCO*.mp. OR (stein-leventhal or leventhal).mp. OR anovulation/ OR anovulat*.mp. OR oligo-ovulat*.mp. OR oligoovulat*.mp. OR (ovar* adj5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*)).mp.

2. exp life style/ OR exp life change events/ OR (life*style adj2 change*).mp. OR (life*style adj2 intervention*).mp. OR (life*style adj2 modif*).mp. OR (life*style adj2 choice*).mp. OR exp self efficacy/ OR self-efficacy.mp. OR exp Health Promotion/ OR (health adj2 promotion).mp. OR exp Health Education/ OR (health* adj2 education).mp. OR (motivation* adj2 therap*).mp. OR interview*.mp. OR diet*.mp. OR nutrition*.mp. OR meal*.mp. OR food*.mp. OR (Energy adj3 restrict*).mp. OR (Energy adj3 reduc*).mp. OR Kilojoule*.mp. OR Calor*.mp. OR hypocaloric.mp. OR hypercaloric.mp. OR hyperproteic.mp. OR hypoproteic.mp. OR feeding behaviour*.mp. OR feeding behavior*.mp. OR eating behaviour*.mp. OR eating behaviour*.mp. OR exp diet/ OR exp diet therapy/ OR exp nutrition therapy/ OR exp food/ OR exp feeding behavior/

3. search$.tw. or meta-analysis.mp. or meta-analysis.pt. or review.pt. or associated.tw. OR clinical trial.mp. or clinical trial.pt. or random.mp.
4. 1 AND 2 AND 3
5. limit 4 to (english language and human and current)

Database: Ovid MEDLINE(R) 7 June 2017 to 10 August 2022

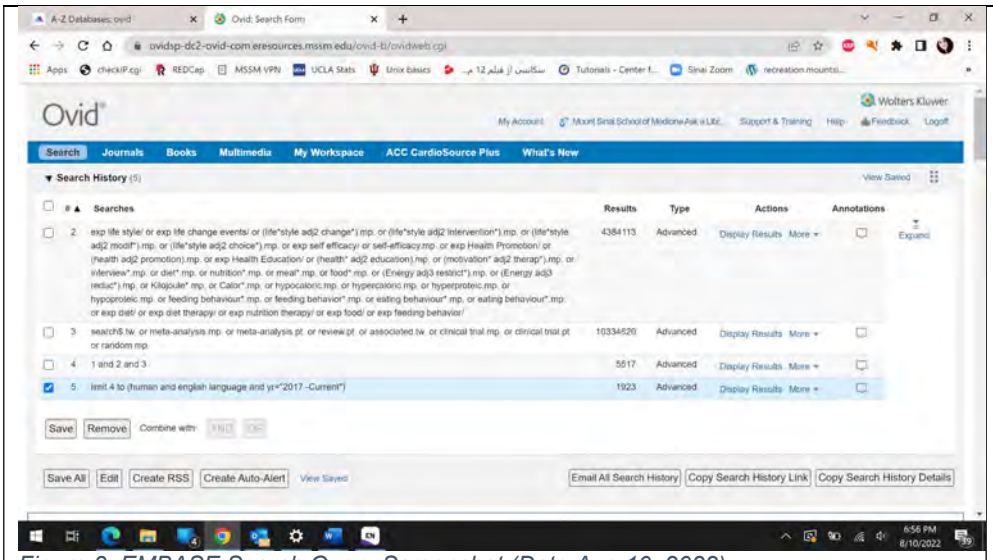


Figure 3. EMBASE Search Query Screenshot (Date Aug 10, 2022)

Retrieved records from Ovid Medline: N=1923

All EBM (Ovid) Search in All EBM was conducted by loyal.pattuwage@monash.edu on August 12, 2022 EBM Reviews - Cochrane Database of Systematic Reviews <2005 to August 10, 2022> EBM Reviews - ACP Journal Club <1991 to July 2022> EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016> EBM Reviews - Cochrane Clinical Answers <July 2022> EBM Reviews - Cochrane Central Register of Controlled Trials <July 2022> EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012> EBM Reviews - Health Technology Assessment <4th Quarter 2016> EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016> 1 exp polycystic ovary syndrome/ 1712 2 polycystic ovar*.mp. 4675 3 poly-cystic ovar*.mp. 136 4 PCO*.mp. 6256 5 (stein-leventhal or leventhal).mp. 99 6 anovulation/ 154 7 anovulat*.mp. 1193 8 oligo-ovulat*.mp. 55 9 oligoovulat*.mp. 32 10 (ovar* adj5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*)).mp. 4868 11 or/1-10 8226 12 exp life style/ 6496 13 exp life change events/ 464 14 (life*style adj2 change*).mp. 3486 15 (life*style adj2 intervention*).mp. 6764 16 (life*style adj2 modif*).mp. 5484 17 (life*style adj2 choice*).mp. 227 18 exp self efficacy/ 3497 19 self-efficacy.mp. 16564 20 exp Health Promotion/ 7449 21 (health adj2 promotion).mp. 12952 22 exp Health Education/ 21359 23 (health* adj2 education).mp. 15419 24 (motivation* adj2 therap*).mp. 937 25 interview*.mp. 48994 26 diet*.mp. 109821 27 nutrition*.mp. 52738 28 meal*.mp. 27171 29 food*.mp. 60291 30 (Energy adj3 restrict*).mp. 1479 31 (Energy adj3 reduc*).mp. 1813 32 Kilojoule*.mp. 97 33 Calor*.mp. 18008	7 June 2017 to 12 August 2022

34 hypocaloric.mp. 1217 35 hypocaloric.mp. 1217 36 hyperproteic.mp. 43 37 hypoproteic.mp. 10 38 feeding behaviour*.mp. 140 39 feeding behavior*.mp. 5567 40 eating behaviour*.mp. 837 41 eating behaviour*.mp. 837 42 exp diet/ 20558 43 exp diet therapy/ 6661 44 exp nutrition therapy/ 10481 45 exp food/ 54753 46 exp feeding behavior/ 9877 47 or/12-46 287108 48 11 and 47 1438 49 limit 48 to (english language and humans and yr="2017 -Current") 652 **Retrieved records from All EBM: N=652**	
CINAHL EBSCO Search in All EBM was conducted by loyal.pattuwage@monash.edu on August 12, 2022 Search yields are saved as a PDF file "Q 3.3_CINAHL_12 Aug 2022.pdf" in Kazemi PC – path: 2022. PCOS Guideline\Q3.3\RIS Inputs Covidence **Retrieved records from All EBM: N=545**	7 June 2017 to 12 August 2022
Any subsequent updates - enter database and date: After June 7 2017 up to August 10, 2022	

Table 2.2. Questions addressed by this search *(add more rows as needed)*:

GDG	Q#	Question
3	3.3.	In women with PCOS, are diet interventions (compared to different diets) effective for improving anthropometric, metabolic, fertility, and emotional wellbeing outcomes?

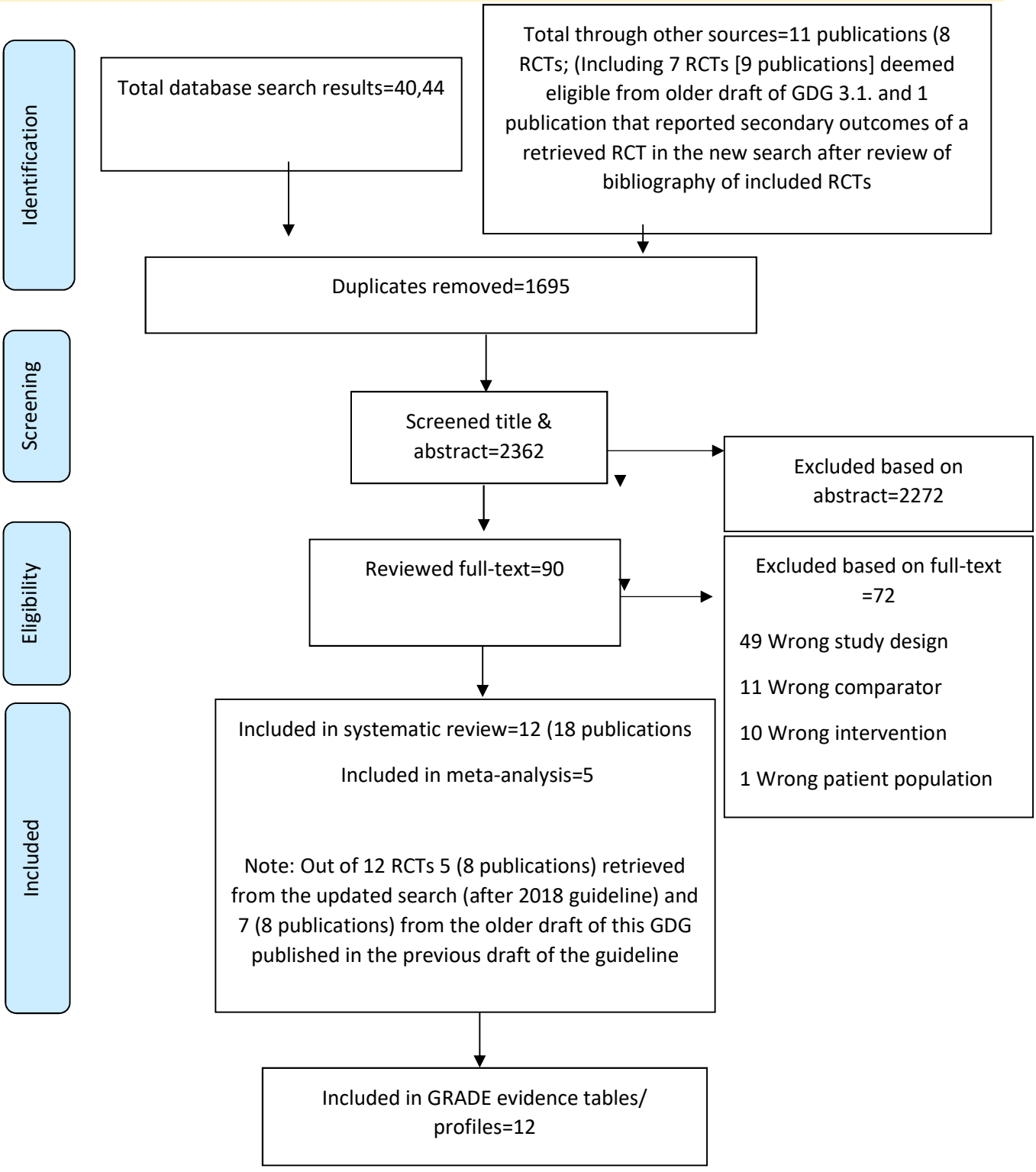
Table 2.3. Search strings used in OVID or other database/s

OVID Medline, All EBM, PsycInfo, EMBASE (results= 3499)	CINAHL: Yes (results= 545)	Other: No
1. OVID MedLine: N=891 2. OVID PsychInfo: N=33 3. EMBASE: N=1923 4. All EBM: N=652 5. CINAHL: N=545 **Total (all 5 datasets): 4044** After deduplication using EndNote and Covidence remaining records: 2351	Same or different search: Same for all; however, Maryam Kazemi modified line "search$.tw. or meta-analysis.mp. or meta-analysis.pt. or review.pt. or di.xs. or associated.tw. OR clinical trial.mp. or clinical trial.pt. or random.mp. or tu.xs." to remove terms with ".xs" suffice in PsychInfo and EMBASE (only). Reason: the ".xs"was not identified as a valid term resulting in the truncated line: "search$.tw. or meta-analysis.mp. or meta-analysis.pt. or review.pt. or associated.tw. OR clinical trial.mp. or clinical trial.pt. or random.mp."	Not Applicable

Evidence processing: Studies were selected and appraised by a total of 6 reviewers (Isabella Xavier, Julia Michalak, Steph Cowan, Kimberly Hopkins, Thais Rasia, Loyal Pattuwage) in consultation with the key contacts/ evidence team (Kate Marsh, Lisa Moran, Aya Mousa, Jillian Tay) using study selection and appraisal criteria (PICO above) established a priori. The articles were reviewed by title and abstract by one reviewer. When a decision could not be made based on the title and abstract alone, the full text was retrieved. Eighteen publications from 12 RCTs met the inclusion criteria for this review (see Table 4.1). Out of 12 RCTs, four (8 publications) were retrieved from the updated search (after the 2018 guideline); eight RCTs (10 publications) were retrieved from the previous version of the guideline.

*Note that five studies (Gower 2013/Hoover 2021, Mehrabani 2012, Panico 2014, Wong 2016, Moran 2003/7) that were initially excluded from the previous guideline met the revised PICO of the present update and were therefore included.

3. SEARCH RESULTS - PRISMA flowchart



4. STUDY INCLUSION

Table 4.1. Included Studies (full citation with doi)- *Sorted alphabetically. For clarity, all studies included in the updated search after the publication of previous guideline in 2018 are shown in grey rows, and others that were included in the updated search are shown in green rows.*

1. Asemi, Z. and A. Esmaillzadeh, DASH diet, insulin resistance, and serum hs-CRP in polycystic ovary syndrome: a randomized controlled clinical trial. Hormone & Metabolic Research, 2015. 47(3): p. 232-8. Asemi, Z., et al., Effects of DASH diet on lipid profiles and biomarkers of oxidative stress in overweight and obese women with polycystic ovary syndrome: a randomized clinical trial. Nutrition, 2014. 30(11-12): p. 1287-93.
2. Azadi-Yazdi, M., Karimi-Zarchi, M., Salehi-Abargouei, A., Fallahzadeh, H., & Nadjarzadeh, A. (2017). Effects of Dietary Approach to Stop Hypertension diet on androgens, antioxidant status and body composition in overweight and obese women with polycystic ovary syndrome: a randomised controlled trial. Journal of human nutrition and dietetics: the official journal of the British Dietetic Association, 30(3), 275–283. https://doi.org/10.1111/jhn.12433
3. Foroozanfard, F., Rafiei, H., Samimi, M., Gilasi, H. R., Gorjizadeh, R., Heidar, Z., & Asemi, Z. (2017). The effects of dietary approaches to stop hypertension diet on weight loss, anti-Müllerian hormone and metabolic profiles in women with polycystic ovary syndrome: A randomized clinical trial. Clinical endocrinology, 87(1), 51–58. https://doi.org/10.1111/cen.13333
4. Gower, B. A., Chandler-Laney, P. C., Ovalle, F., Goree, L. L., Azziz, R., Desmond, R. A., Granger, W. M., Goss, A. M., & Bates, G. W. (2013). Favourable metabolic effects of a eucaloric lower-carbohydrate diet in women with PCOS. Clinical endocrinology, 79(4), 550–557. https://doi.org/10.1111/cen.12175 Hoover, S. E., Gower, B. A., Cedillo, Y. E., Chandler-Laney, P. C., Deemer, S. E., & Goss, A. M. (2021). Changes in Ghrelin and Glucagon following a Low Glycemic Load Diet in Women with PCOS. The Journal of clinical endocrinology and metabolism, 106(5), e2151–e2161. https://doi.org/10.1210/clinem/dgab028
5. Hosseini Marnani E., Ghadiri-Anari A., Ramezani-Jolfaie N., Mohammadi M., Abdollahi, A., Namayandeh S. M., et al. Effect of fennel supplementation along with high-protein, low-carbohydrate weight-loss diet on insulin resistance and percentage of fat and muscle mass in overweight/obese women with polycystic ovary syndrome. Journal of Functional Foods 2020 Vol. 67 Pages 103848. https://doi.org/10.1016/j.jff.2020.103848
6. Kazemi, M., McBreairty, L. E., Chizen, D. R., Pierson, R. A., Chilibeck, P. D., & Zello, G. A. (2018). A Comparison of a Pulse-Based Diet and the Therapeutic Lifestyle Changes Diet in Combination with Exercise and Health Counselling on the Cardio-Metabolic Risk Profile in Women with Polycystic Ovary Syndrome: A Randomized Controlled Trial. Nutrients, 10(10), 1387. https://doi.org/10.3390/nu10101387 Kazemi, M., McBreairty, L. E., Zello, G. A., Pierson, R. A., Gordon, J. J., Serrao, S. B., Chilibeck, P. D., & Chizen, D. R. (2020). A pulse-based diet and the Therapeutic Lifestyle Changes diet in combination with health counseling and exercise improve health-related quality of life in women with polycystic ovary syndrome: secondary analysis of a randomized controlled trial. Journal of psychosomatic obstetrics and gynaecology, 41(2), 144–153. https://doi.org/10.1080/0167482X.2019.1666820 Kazemi, M., Pierson, R. A., McBreairty, L. E., Chilibeck, P. D., Zello, G. A., & Chizen, D. R. (2020). A randomized controlled trial of a lifestyle intervention with longitudinal follow-up on ovarian dysmorphology in women with polycystic ovary syndrome. Clinical endocrinology, 92(6), 525–535. https://doi.org/10.1111/cen.14179 McBreairty, L. E., Kazemi, M., Chilibeck, P. D., Gordon, J. J., Chizen, D. R., & Zello, G. A. (2020). Effect of a pulse-based diet and aerobic exercise on bone measures and body composition in women with polycystic ovary syndrome: A randomized controlled trial. Bone reports, 12, 100248. https://doi.org/10.1016/j.bonr.2020.100248
7. Mehrabani, H. H., Salehpour, S., Amiri, Z., Farahani, S. J., Meyer, B. J., & Tahbaz, F. (2012). Beneficial effects of a high-protein, low-glycemic-load hypocaloric diet in overweight and obese women with polycystic ovary syndrome: a randomized controlled intervention study. Journal of the American College of Nutrition, 31(2), 117–125. https://doi.org/10.1080/07315724.2012.10720017
8. Moran, LJ.J., Noakes, M., Clifton, P.M., Tomlinson L., Norman, R. J. (2003). Dietary Composition in Restoring Reproductive and Metabolic Physiology in Overweight Women with Polycystic Ovary Syndrome. The Journal of Clinical Endocrinology & Metabolism 88(2):812–819. Galletly C, Moran LJ, Noakes M, Clifton P, Tomlinson L, Norman RJ. (2007). Psychological benefits of a high-protein, low-carbohydrate diet in obese women with polycystic ovary syndrome—A pilot study. Appetite (49) 590-593. doi:10.1016/j.appet.2007.03.222
9. Panico A, Lupoli GA, Cioffi I, Zacchia G, Caldara A, Lupoli G, Contaldo F, Pasanisi F. Effects of an isocaloric low-glycemic-load diet in polycystic ovary syndrome. Nutr Ther Metab. 2014;32:85–92.
10. Stamets K, et al., A randomized trial of the effects of two types of short-term hypocaloric diets on weight loss in women with polycystic ovary syndrome. Fertility & Sterility, 2004. 81(3): p. 630-637.
11. Toscani, M. K., Mario, F. M., Radavelli-Bagatini, S., Wiltgen, D., Matos, M. C., & Spritzer, P. M. (2011). Effect of high-protein or normal-protein diet on weight loss, body composition, hormone, and metabolic profile in southern Brazilian women with polycystic ovary syndrome: a randomized study. Gynecological endocrinology: the official journal of the International Society of Gynecological Endocrinology, 27(11), 925–930. https://doi.org/10.3109/09513590.2011.564686
12. Wong, J. M., Gallagher, M., Gooding, H., Feldman, H. A., Gordon, C. M., Ludwig, D. S., & Ebbeling, C. B. (2016). A randomized pilot study of dietary treatments for polycystic ovary syndrome in adolescents. Pediatric obesity, 11(3), 210–220. https://doi.org/10.1111/ijpo.12047

Table 4.2. Excluded Studies (on full-text assessment)- *Sorted alphabetically; for clarity, all studies excluded in the updated search after the publication of the Cochrane review in 2019 are shown in green rows, and others that were excluded in the Cochrane review are shown in grey rows below.*

Reference	Reason
(2003). "ACOG practice bulletin: Polycystic ovary syndrome." International Journal of Gynecology and Obstetrics 80(3): 335-348.	Irrelevant setting. Unclear review processes.
(2004). "Position of the American Dietetic Association and Dietitians of Canada: nutrition and women's health." Journal of the American Dietetic Association 104(6): 984-1001.	Irrelevant setting. Unclear review processes.
(2009). "ACOG practice bulletin No. 108: Polycystic ovary syndrome." Obstetrics and Gynecology 114(4): 936-949.	Irrelevant setting. Unclear review processes.
Alieva E A, Fanchenko N D, Pshenichnikova T, Parshutin N P, Gasparov A S, Vetr M and Pshenichnikova T I (1990). "[The polycystic ovary syndrome and increased body mass]." Acta Universitatis Palackianae Olomucensis Facultatis Medicae 126: 233-240.	Irrelevant intervention. Not comparative for diet.
Atiomo W, Read A, Golding M, Silcocks P, Razali N, Sarkar S, Hardiman P and Thornton J (2009). "Local recruitment experience in a study comparing the effectiveness of a low glycaemic index diet with a low calorie healthy eating approach at achieving weight loss and reducing the risk of endometrial cancer in women with polycystic ovary syndrome (PCOS)." Contemporary Clinical Trials 30(5): 451-456.	Irrelevant intervention. Not enough information about diets.
Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale H F, Futterweit W, Janssen O E, Legro R S, Norman R J, Taylor A E and Witchel S F (2009). "The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report." Fertility and Sterility 91(2): 456-488.	Irrelevant setting. Not a systematic review.
Bahoosh et al. 2017: The effects of diet on the polycystic ovary syndrome: A review article (could not find article)	Wrong study design
Belan, M., Gélinas, M., Carranza-Mamane, B., Langlois, M. F., Morisset, A. S., Ruchat, S. M., Lavoie, K., Adamo, K., Poder, T., Gallagher, F., Pesant, M. H., Jean-Denis, F., Baillargeon, J. P., & Fit-For-Fertility Study Group (2022). Protocol of the Fit-For-Fertility study: a multicentre randomised controlled trial assessing a lifestyle programme targeting women with obesity and infertility. BMJ open, 12(4), e061554. https://doi.org/10.1136/bmjopen-2022-061554 (identified as an ongoing study on Covidence at the screening stage)	Wrong study design
Berra B, Montorfano G, Berselli P and Rizzo A M (2007). "Diet, exercise, long chain polyunsaturated omega-3 fatty acids and the metabolic syndrome." Progress in nutrition 9(2): 124-133.	Irrelevant setting. Not a systematic review. Not specifically in PCOS women.
Borges R, Temido P, Sousa L, Azinhais P, Conceicao P, Pereira B, Leao R, Retroz E, Brandao T, Cristo L and Sobral F (2009). "Metabolic syndrome and sexual (Dys)function." Journal of Sexual Medicine 6(11): 2958-2975.	Irrelevant setting. Not a systematic review. Not specifically in PCOS women.
Bruner B, Chad K and Chizen D (2006). "Effects of exercise and nutritional counseling in women with polycystic ovary syndrome." Applied Physiology, Nutrition, & Metabolism = Physiologie Appliquee, Nutrition et Metabolisme 31(4): 384-391.	Irrelevant intervention. Exercise vs exercise.
Buccola J M and Reynolds E E (2003). "Polycystic ovary syndrome: a review for primary providers." Primary Care 30(4): 697-710.	Irrelevant setting. Not a systematic review.
C Hmedeh, S El Iskandarni, I Tawfik, O-160 The effect of 6-month nutritional intervention on the anthropometric, biochemical, and reproductive profile of Lebanese women with Polycystic ovarian syndrome, Human Reproduction, Volume 36, Issue Supplement_1, July 2021, deab127.028, https://doi.org/10.1093/humrep/deab127.028	Wrong study design
Carolo, A. L., Mendes, M. C., Rosa E Silva, A., Vieira, C. S., Silva de Sá, M. F., Ferriani, R. A., & Reis, R. (2017). Nutritional Counseling Promotes Changes in the Dietary Habits of Overweight and Obese Adolescents with Polycystic Ovary Syndrome. O aconselhamento nutricional promove mudanças nos hábitos alimentares de adolescentes com excesso de peso e obesas e com síndrome dos ovários policísticos. Revista brasileira de ginecologia e obstetricia : revista da Federacao Brasileira das Sociedades de Ginecologia e Obstetricia, 39(12), 692–696. https://doi.org/10.1055/s-0037-1607458	Wrong study design
Chan C C, Koo M W, Ng E H, Tang O S, Yeung W S, Ho P C, Chan C C W, Koo M W L, Ng E H Y, Tang O-S, Yeung W S B and Ho P-C (2006). "Effects of Chinese green tea on weight, and hormonal and biochemical profiles in obese patients with polycystic ovary syndrome--a randomized placebo-controlled trial." Journal of the Society for Gynecologic Investigation 13(1): 63-68.	Irrelevant intervention. Not a macronutrient change.
Chavarro J E, Rich-Edwards J W, Rosner B A and Willett W C (2007). "Diet and lifestyle in the prevention of ovulatory disorder infertility." Obstetrics & Gynecology 110(5): 1050-1058.	Irrelevant setting. Not in PCOS women.
Chavarro J E, Rich-Edwards J W, Rosner B A and Willett W C (2007). "Dietary fatty acid intakes and the risk of ovulatory infertility." American Journal of Clinical Nutrition 85(1): 231-237.	Irrelevant setting. No analysis of PCOS population.
Chavarro J E, Rich-Edwards J W, Rosner B A and Willett W C (2008). "Use of multivitamins, intake of B vitamins, and risk of ovulatory infertility." Fertility & Sterility 89(3): 668-676.	Irrelevant setting. Not in PCOS women.

Chien, Y. J., Chang, C. Y., Wu, M. Y., Chen, C. H., Horng, Y. S., & Wu, H. C. (2021). Effects of Curcumin on Glycemic Control and Lipid Profile in Polycystic Ovary Syndrome: Systematic Review with Meta-Analysis and Trial Sequential Analysis. Nutrients, 13(2), 684. https://doi.org/10.3390/nu13020684	Wrong intervention
Cienfuegos, S., Corapi, S., Gabel, K., Ezpeleta, M., Kalam, F., Lin, S., Pavlou, V., & Varady, K. A. (2022). Effect of Intermittent Fasting on Reproductive Hormone Levels in Females and Males: A Review of Human Trials. Nutrients, 14(11), 2343. https://doi.org/10.3390/nu14112343	Wrong study design
Clark A and Roberts B (2000). "Maximizing weight loss in the overweight infertile patient: a prospective randomized controlled trial." Human Reproduction 15(Annual Meeting of ESHRE, 2000, Bologna, Italy, 2000. Abstract book 1): Abstract No.O-162, 165-166.	Irrelevant setting. Abstract only. Not locatable in the Human Reproduction journal.
Clark A M, Ledger W, Galletly C, Tomlinson L, Blaney F, Wang X and Norman R J (1995). "Weight loss results in significant improvement in pregnancy and ovulation rates in anovulatory obese women." Human Reproduction 10(10): 2705-2712.	Irrelevant control. No details of control treatment.
Clark A M, Thornley B, Tomlinson L, Galletley C and Norman R J (1998). "Weight loss in obese infertile women results in improvement in reproductive outcome for all forms of fertility treatment." Human Reproduction 13(6): 1502-1505.	Irrelevant control. Minimal details of control treatment. The "Drop out" group was used as control group.
Clarke J, Showell M G, Hart R J, Agarwal A and Gupta S (2009). "Antioxidants for female subfertility." Cochrane Database of Systematic Reviews.	Irrelevant setting. Protocol only.
Cussons A J, Watts G F, Mori T A and Stuckey B G A (2009). "Omega-3 fatty acid supplementation decreases liver fat content in polycystic ovary syndrome: a randomized controlled trial employing proton magnetic resonance spectroscopy." Journal of Clinical Endocrinology & Metabolism 94(10): 3842-3848.	Irrelevant intervention. Used omega-3 fatty acid supplementation.
Daniilidis A and Dinas K (2009). "Long term health consequences of polycystic ovarian syndrome: A review analysis." Hippokratia 13(2): 90-92.	Irrelevant setting. Not a systematic review.
de Azevedo G D, Costa E C, Micussi M T A B C and de Sa J C F (2008). "[Lifestyle modifications in the polycystic ovary syndrome: role of physical exercise and importance of multidisciplinary approach]." Revista Brasileira de Ginecologia e Obstetricia 30(5): 261-267.	Irrelevant setting. Not a systematic review. Portuguese language article.
Del Pup, L., & Cagnacci, A. (2021). IMPROVE lifestyle in polycystic ovary syndrome: a systematic strategy. Gynecological endocrinology: the official journal of the International Society of Gynecological Endocrinology, 37(10), 875–878. https://doi.org/10.1080/09513590.2021.1871892	Wrong study design
Diamanti-Kandarakis E and Panidis D (2006). "Update on polycystic ovary syndrome." Women's Health 2(4): 561-569.	Irrelevant setting. Not a systematic review.
Diamanti-Kandarakis, E., Papalou, O., Kandaraki, E. A., & Kassi, G. (2017). MECHANISMS IN ENDOCRINOLOGY: Nutrition as a mediator of oxidative stress in metabolic and reproductive disorders in women. European journal of endocrinology, 176(2), R79–R99. https://doi.org/10.1530/EJE-16-0616	Wrong study design
Dietz de Loos, A., Jiskoot, G., Beerthuizen, A., Busschbach, J., & Laven, J. (2021). Metabolic health during a randomized controlled lifestyle intervention in women with PCOS. European journal of endocrinology, 186(1), 53–64. https://doi.org/10.1530/EJE-21-0669	Wrong intervention
Dietz de Loos, A., Jiskoot, G., Timman, R., Beerthuizen, A., Busschbach, J., & Laven, J. (2021). Improvements in PCOS characteristics and phenotype severity during a randomized controlled lifestyle intervention. Reproductive biomedicine online, 43(2), 298–309. https://doi.org/10.1016/j.rbmo.2021.05.008	Wrong intervention
Domecq, J. P., Prutsky, G., Mullan, R. J., Hazem, A., Sundaresh, V., Elamin, M. B., Phung, O. J., Wang, A., Hoeger, K., Pasquali, R., Erwin, P., Bodde, A., Montori, V. M., & Murad, M. H. (2013). Lifestyle modification programs in polycystic ovary syndrome: systematic review and meta-analysis. The Journal of clinical endocrinology and metabolism, 98(12), 4655–4663. https://doi.org/10.1210/jc.2013-2385	Wrong comparator
Einarsson, S., Bergh, C., Friberg, B., Pinborg, A., Klajnbard, A., Karlström, P. O., Kluge, L., Larsson, I., Loft, A., Mikkelsen-Englund, A. L., Stenlöf, K., Wistrand, A., & Thurin-Kjellberg, A. (2017). Weight reduction intervention for obese infertile women prior to IVF: a randomized controlled trial. Human reproduction (Oxford, England), 32(8), 1621–1630. https://doi.org/10.1093/humrep/dex235	Wrong comparator
Erturk E, Kuru N, Savci V, Tuncel E, Ersoy C and Imamoglu S (2004). "Serum leptin levels correlate with obesity parameters but not with hyperinsulinism in women with polycystic ovary syndrome." Fertility & Sterility 82(5): 1364-1368.	Irrelevant intervention. No intervention was given.
Esfahanian F and Moeininia F (2006). "Comparison between the effects of metformin and hypocaloric diet on serum C-reactive protein and insulin resistance in obese women with polycystic ovary syndrome." XVIII FIGO World Congress of Gynecology and Obstetrics 3(165).	Irrelevant intervention. Metformin vs diet. Abstract only.
Esther López-Bayghen, Samantha García-Hernandez, M. Elba Gonzalez-Mejia, Leonardo M. Porchia, Women with polycystic ovarian syndrome and elevated levels of insulin resistance are more prone to benefit from diets to improve insulin sensitivity: a meta-analysis, Fertility and Sterility, Volume 112, Issue 3, Supplement, 2019, Page e388, ISSN 0015-0282, https://doi.org/10.1016/j.fertnstert.2019.07.1109.	Wrong study design

Florakis D, Diamanti-Kandarakis E, Katsikis I, Nassis G P, Karkanaki A, Georgopoulos N and Panidis D (2008). "Effect of hypocaloric diet plus sibutramine treatment on hormonal and metabolic features in overweight and obese women with polycystic ovary syndrome: a randomized, 24-week study." International Journal of Obesity 32(4): 692-699.	Irrelevant intervention. All women had sibutramine plus diet.
Frary JM, et al., 2016, The effect of dietary carbohydrates in women with polycystic ovary syndrome: a systematic review, Minerva Endocrinologica, 41(1): 57-69.	Did not do risk of bias assessment. Presented results as % change with no standard deviation. Diet vs diet.
Gambineri A, Patton L, De Iasio R, Cantelli B, Cognini G E, Filicori M, Barreca A, Diamanti-Kandarakis E, Pagotto U and Pasquali R (2005). "Efficacy of octreotide-LAR in dieting women with abdominal obesity and polycystic ovary syndrome." Journal of Clinical Endocrinology & Metabolism 90(7): 3854-3862.	Irrelevant intervention. Used octreotide-LAR plus diet.
Gambineri A, Patton L, Vaccina A, Cacciari M, Morselli-Labate A M, Cavazza C, Pagotto U and Pasquali R (2006). "Treatment with flutamide, metformin, and their combination added to a hypocaloric diet in overweight-obese women with polycystic ovary syndrome: a randomized, 12-month, placebo-controlled study." Journal of Clinical Endocrinology & Metabolism 91(10): 3970-3980.	Irrelevant intervention. Diet vs pharmaceutical.
Gambineri A, Patton L, Vaccina A, Pagotto U and Pasquali R (2005). "Effect of flutamide and metformin administered alone or in combination in dieting obese women with polycystic ovary syndrome (PCOS): A randomized, 12-months, placebo-controlled study." 3rd Annual Meeting of the Androgen Excess Society. 24p.	Irrelevant setting. Abstract only. Refer to the full text.
Gambineri A, Pelusi C, Genghini S, Morselli-Labate A M, Cacciari M, Pagotto U and Pasquali R (2004). "Effect of flutamide and metformin administered alone or in combination in dieting obese women with polycystic ovary syndrome." Clinical Endocrinology 60(2): 241-249.	Irrelevant intervention. Diet vs pharmaceutical.
Ganie, M. A., Sahar, T., Rashid, A., Wani, I. A., Nisar, S., Sathyapalan, T., Vishnubhatla, S., Ramakrishnan, L., Parvez, T., & Geer, I. (2019). Comparative Evaluation of Biomarkers of Inflammation Among Indian Women With Polycystic Ovary Syndrome (PCOS) Consuming Vegetarian vs. Non-vegetarian Diet. Frontiers in endocrinology, 10, 699. https://doi.org/10.3389/fendo.2019.00699	Wrong study design
González, F., Considine, R. V., Abdelhadi, O. A., Xue, J., & Acton, A. J. (2021). Saturated fat ingestion stimulates proatherogenic inflammation in polycystic ovary syndrome. American journal of physiology. Endocrinology and metabolism, 321(5), E689–E701. https://doi.org/10.1152/ajpendo.00213.2021	Wrong study design
Gower BA, and Goss AM, 2015, A lower-carbohydrate, higher-fat diet reduces abdominal and intermuscular fat and increases insulin sensitivity in adults at risk of type 2 diabetes, Journal of Nutrition, 145(1): 177S-183S.	Comparison between included study Gower 2013 and another study on non-PCOS women. Inadequate description of randomization. Diet vs diet.
Grant P (2009). "Spearmint herbal tea has significant anti-androgen effects in polycystic ovarian syndrome. A randomized controlled trial." Phytotherapy Research 24(2): 186-188.	Irrelevant intervention. Spearmint herbal tea.
Guzick D S, Wing R, Smith D, Berga S L and Winters S J (1994). "Endocrine consequences of weight loss in obese, hyperandrogenic, anovulatory women." Fertility & Sterility 61(4): 598-604.	Irrelevant intervention. Lifestyle vs nothing.
Haidari, F., Banaei-Jahromi, N., Zakerkish, M., & Ahmadi, K. (2020). The effects of flaxseed supplementation on metabolic status in women with polycystic ovary syndrome: a randomized open-labeled controlled clinical trial. Nutrition journal, 19(1), 8. https://doi.org/10.1186/s12937-020-0524-5	Wrong study design
Hamayeli Mehrabani H., Tahbaz F., Salehpour S., Hedayati M., Amiri Z. Ghassemi A. (2010), Reproductive hormonal changes following two types of hypocaloric diets in overweight and obese polycystic ovary syndrome women. Iran. J. Endocrinology Metab. 12:2 (160-168+200)	Irrelevant setting. Only abstract in English.
Hanjalic-Beck A., Gabriel B., Schaefer W., Zahradnik H.-P., Schories M. Tempfer C., Keck C., Denschlag D. (2010), Metformin versus acarbose therapy in patients with polycystic ovary syndrome (PCOS): A prospective randomised double-blind study. Gynecol. Endocrinol. 26:9 (690-697)	Irrelevant intervention. Pharmaceutical vs pharmaceutical.
Haqq, L., McFarlane, J., Dieberg, G., & Smart, N. (2015). The Effect of Lifestyle Intervention on Body Composition, Glycemic Control, and Cardiorespiratory Fitness in Polycystic Ovarian Syndrome: A Systematic Review and Meta-Analysis. International journal of sport nutrition and exercise metabolism, 25(6), 533–540. https://doi.org/10.1123/ijsnem.2013-0232	Wrong intervention
Hassink S G (2009). "Weighing risk: the Expert Committee's recommendations in practice." Seminars in Pediatric Surgery 18(3): 159-167.	Irrelevant setting. Not in PCOS women.
Hays J H, DiSabatino A, Gorman R T, Vincent S and Stillabower M E (2003). "Effect of a high saturated fat and no-starch diet on serum lipid subfractions in patients with documented atherosclerotic cardiovascular disease." Mayo Clinic Proceedings 78(11): 1331-1336.	Irrelevant setting. Not in PCOS women.

He H, Li S and Border C (2009). "Chinese medicinal herbs for female subfertility." Cochrane Database of Systematic Reviews.	Irrelevant intervention. Used Chinese herbal medicines.
Heymsfield S, van Mierlo C, van der Knaap H, Heo M and Frier H (2003). "Weight management using a meal replacement strategy: meta and pooling analysis from six studies." International Journal of Obesity and Related Metabolic Disorders 27: 537e549.	Irrelevant setting. In any obese population.
Hoeger K M, Kochman L, Wixom N, Craig K, Miller R K and Guzick D S (2004). "A randomized, 48-week, placebo-controlled trial of intensive lifestyle modification and/or metformin therapy in overweight women with polycystic ovary syndrome: A pilot study." Fertility and Sterility 82(2): 421-429.	Irrelevant intervention. Used metformin.
Hoeger K, Davidson K, Kochman L, Cherry T, Kopin L and Guzick D S (2008). "The impact of metformin, oral contraceptives, and lifestyle modification on polycystic ovary syndrome in obese adolescent women in two randomized, placebo-controlled clinical trials." Journal of Clinical Endocrinology and Metabolism 93(11): 4299-4306.	Irrelevant intervention. Lifestyle vs pharmaceutical
Jarrett, B. Y., & Lujan, M. E. (2016). Impact of hypocaloric dietary intervention on ovulation in obese women with PCOS. Reproduction (Cambridge, England), REP-16-0385. Advance online publication. https://doi.org/10.1530/REP-16-0385	Wrong study design
Jehi, T., Nguyen, K. and Dos Santos, H. (2021), Impact of Dietary Fiber Intake on Microbiota Diversity and Abundance in the Participants of the Full Plate Diet Trial. The FASEB Journal, 35:. https://doi.org/10.1096/fasebj.2021.35.S1.02750	Wrong patient population
Jiskoot, G., Benneheij, S. H., Beerthuizen, A., de Niet, J. E., de Klerk, C., Timman, R., Busschbach, J. J., & Laven, J. S. (2017). A three-component cognitive behavioural lifestyle program for preconceptional weight-loss in women with polycystic ovary syndrome (PCOS): a protocol for a randomized controlled trial. Reproductive health, 14(1), 34. https://doi.org/10.1186/s12978-017-0295-4	Wrong study design
Karimzadeh M.A. Javedani M (2010), An assessment of lifestyle modification versus medical treatment with clomiphene citrate, metformin, and clomiphene citrate-metformin in patients with polycystic ovary syndrome. Fertility and Sterility, 94:1 (216-220)	Irrelevant intervention. Lifestyle vs pharmaceutical.
Kasim-Karakas S E, Almario R U, Cunningham W, Kasim-Karakas S E, Almario R U and Cunningham W (2009). "Effects of protein versus simple sugar intake on weight loss in polycystic ovary syndrome (according to the National Institutes of Health criteria)." Fertility & Sterility 92(1): 262-270.	Irrelevant intervention. Only protein and sugar intake changes.
Kasim-Karakas S E, Almario R U, Gregory L, Wong R, Todd H and Lasley B L (2004). "Metabolic and endocrine effects of a polyunsaturated fatty acid-rich diet in polycystic ovary syndrome." Journal of Clinical Endocrinology & Metabolism 89(2): 615-620.	Irrelevant intervention. Fatty acid diet intervention.
Kasim-Karakas S E, Cunningham W M, Tsodikov A, Kasim-Karakas S E, Cunningham W M and Tsodikov A (2007). "Relation of nutrients and hormones in polycystic ovary syndrome." American Journal of Clinical Nutrition 85(3): 688-694.	Irrelevant intervention. Used a single meal only.
Katcher H I (2008). The metabolic and reproductive effects of whole grains and high fiber foods in metabolic syndrome and polycystic ovary syndrome, Katcher, Heather Ilene: The Pennsylvania State U , US.	Irrelevant intervention. High fiber diets only.
Katcher H I, Kunselman A R, Dmitrovic R, Demers L M, Gnatuk C L, Kris-Etherton P M, Legro R S, Katcher H I, Kunselman A R, Dmitrovic R, Demers L M, Gnatuk C L, Kris-Etherton P M and Legro R S (2009). "Comparison of hormonal and metabolic markers after a high-fat, Western meal versus a low-fat, high-fiber meal in women with polycystic ovary syndrome." Fertility & Sterility 91(4): 1175-1182.	Irrelevant intervention. Meals only given once.
Kazemi, M., Kim, J. Y., Wan, C., Xiong, J. D., Michalak, J., Xavier, I. B., Ganga, K., Tay, C. T., Grieger, J. A., Parry, S. A., Moran, L. J., & Lujan, M. E. (2022). Comparison of dietary and physical activity behaviors in women with and without polycystic ovary syndrome: a systematic review and meta-analysis of 39 471 women. Human reproduction update, dmac023. Advance online publication. https://doi.org/10.1093/humupd/dmac023	Wrong study design
Kilicdag E B, Bagis T, Tarim E, Aslan E, Erkanli S, Simsek E, Haydardedeoglu B and Kuscu E (2005). "Administration of B-group vitamins reduces circulating homocysteine in polycystic ovarian syndrome patients treated with metformin: A randomized trial." Human Reproduction 20(6): 1521-1528.	Irrelevant intervention. Used B-group vitamin supplementation.
Knowler W, Barratt-Connor E, Fowler S, Hamman R, Lachin J, Walker E and Diabetes Prevention Program Research Group (2002). "Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. Diabetes Prevention Program Research Group." New England Journal of Medicine 346(6): 393-403.	Irrelevant setting. Not in PCOS women
Koulouri O and Conway G S (2008). "A systematic review of commonly used medical treatments for hirsutism in women." Clinical Endocrinology 68(5): 800-805.	Irrelevant setting. Not in PCOS women
Łagowska, K., & Kapczuk, K. (2021). Effects of nutritional intervention with or without metformin on insulin resistance in adolescents with polycystic ovary syndrome: A preliminary study. Progress in Nutrition, 23(1), e2021015. https://doi.org/10.23751/pn.v23i1.9163	Wrong comparator

Levin, G., & Rottenstreich, A. (2019). Inositol for women with polycystic ovary syndrome-possibly just better than placebo. Acta obstetricia et gynecologica Scandinavica, 98(2), 262. https://doi.org/10.1111/aogs.13430	Wrong study design
Li, J., Bai, W. P., Jiang, B., Bai, L. R., Gu, B., Yan, S. X., Li, F. Y., & Huang, B. (2021). Ketogenic diet in women with polycystic ovary syndrome and liver dysfunction who are obese: A randomized, open-label, parallel-group, controlled pilot trial. The journal of obstetrics and gynaecology research, 47(3), 1145–1152. https://doi.org/10.1111/jog.14650	Wrong comparator
Liao L M, Nesic J, Chadwick P M, Brooke-Wavell K and Prelevic G M (2008). "Exercise and body image distress in overweight and obese women with polycystic ovary syndrome: a pilot investigation." Gynecological Endocrinology 24(10): 555-561.	Irrelevant intervention. Exercise vs no exercise (pre- and post-test).
Lie Fong, S., Douma, A., & Verhaeghe, J. (2021). Implementing the international evidence-based guideline of assessment and management of polycystic ovary syndrome (PCOS): how to achieve weight loss in overweight and obese women with PCOS?. Journal of gynecology obstetrics and human reproduction, 50(6), 101894. https://doi.org/10.1016/j.jogoh.2020.101894	Wrong comparator
Lorzadeh Nahid, Kazemirad Yasaman and Kazemirad Nastran , Advancements in Treatment Options of Women Infertility, Current Women`s Health Reviews 2021; 17(2) . https://dx.doi.org/10.2174/1573404816999200922144630	Wrong study design
Mallk et al., 2021 (full citation not available)	Wrong comparator
Marsh KA, et al. 2010, Effect of a low glycemic index compared with a Conventional healthy diet on polycystic ovary syndrome, American Journal of Clinical Nutrition, 92(1): 83-92.	The patients were assigned in alternate order, therefore not a RCT. Inadequate randomization method (consecutive assignment). Diet vs diet.
Mehrabani HH, et al., 2012, Beneficial effects of a high-protein, low-glycemic-load hypocaloric diet in overweight and obese women with polycystic ovary syndrome: a randomized controlled intervention study, Journal of the American College of Nutrition, 31(2): 117-125	Inadequate randomization method. Diet vs diet
Miao, C., Fang, X., & Zhang, Q. (2021). Letter to the Editor from Chenyun Miao, et al: "Effect of Diet on Insulin Resistance in Polycystic Ovary Syndrome". The Journal of clinical endocrinology and metabolism, 106(5), e2378–e2379. https://doi.org/10.1210/clinem/dgab021	Wrong study design
Moini Jazani, A., Hamdi, K., Tansaz, M., Nazemiyeh, H., Sadeghi Bazargani, H., Fazljou, S., & Nasimi Doost Azgomi, R. (2018). Herbal Medicine for Oligomenorrhea and Amenorrhea: A Systematic Review of Ancient and Conventional Medicine. BioMed research international, 2018, 3052768. https://doi.org/10.1155/2018/3052768	Wrong intervention
Moran L J, Hutchison S K, Norman R J and Teede H J (2008). "Lifestyle changes in overweight women with Polycystic Ovary Syndrome." Cochrane Database of Systematic Reviews (4).	Irrelevant intervention. Protocol only. Lifestyle vs nothing.
Moran L J, Noakes M, Clifton P M, Wittert G A, Tomlinson L, Galletly C, Luscombe N D and Norman R J (2004). "Ghrelin and measures of satiety are altered in polycystic ovary syndrome but not differentially affected by diet composition." Journal of Clinical Endocrinology & Metabolism 89(7): 3337-3344.	Irrelevant setting. Compared PCOS vs non-PCOS women.
Moran L J, Pasquali R, Teede H J, Hoeger K M, Norman R J, Moran L J, Pasquali R, Teede H J, Hoeger K M and Norman R J (2009). "Treatment of obesity in polycystic ovary syndrome: a position statement of the Androgen Excess and Polycystic Ovary Syndrome Society." Fertility & Sterility 92(6): 1966-1982.	Irrelevant setting. Not a systematic review.
Moran LJ, et al. 2013, Dietary composition in the treatment of polycystic ovary syndrome: a systematic review to inform evidence-based guidelines, Journal of the Academy of Nutrition & Dietetics, 113(4): 520-545.	The systematic review meets our PICO; however, it includes studies that don't meet the current PICO. Doesn't include any studies which haven't already been included. Diet vs diet.
Moran, L. J., Noakes, M., Clifton, P., Buckley, J., Brinkworth, G., Thomson, R., & Norman, R. J. (2019). Predictors of Lifestyle Intervention Attrition or Weight Loss Success in Women with Polycystic Ovary Syndrome Who Are Overweight or Obese. Nutrients, 11(3), 492. https://doi.org/10.3390/nu11030492	Wrong comparator
Morisset A, Blouin K and Tchernof A (2008). "Impact of diet and adiposity on circulating levels of sex hormone-binding globulin and androgens." Nutrition Reviews 66(9): 506-516.	Irrelevant setting. Not a systematic review. Not all in PCOS women.
Nadjarzadeh, A., Ghadiri-Anari, A., Ramezani-Jolfaie, N., Mohammadi, M., Salehi-Abargouei, A., Namayande, S. M., Mozaffari-Khosravi, H., & Hosseini-Marnani, E. (2021). Effect of hypocaloric high-protein, low-carbohydrate diet supplemented with fennel on androgenic and anthropometric indices in	Wrong study design

overweight and obese women with polycystic ovary syndrome: A randomized placebo-controlled trial. Complementary therapies in medicine, 56, 102633. https://doi.org/10.1016/j.ctim.2020.102633	
Nestler J E (2008). "The Androgen Excess Society guidelines on glucose intolerance in the polycystic ovary syndrome: What do they mean and what should we do?" Polskie Archiwum Medycyny Wewnetrznej 118(5): 264-266.	Irrelevant setting. Not a systematic review.
Norman R J, Homan G, Moran L and Noakes M (2006). "Lifestyle choices, diet, and insulin sensitizers in polycystic ovary syndrome." Endocrine 30(1): 35-43.	Irrelevant setting. Not a systematic review.
Nybacka, Å., Hellström, P. M., & Hirschberg, A. L. (2017). Increased fibre and reduced trans fatty acid intake are primary predictors of metabolic improvement in overweight polycystic ovary syndrome-Substudy of randomized trial between diet, exercise and diet plus exercise for weight control. Clinical endocrinology, 87(6), 680–688. https://doi.org/10.1111/cen.13427	Wrong comparator
Otta C F, Wior M, Iraci G S, Kaplan R, Torres D, Gaido M I and Wyse E P (2010). "Clinical, metabolic, and endocrine parameters in response to metformin and lifestyle intervention in women with polycystic ovary syndrome: A randomized, double-blind, and placebo control trial." Gynecological Endocrinology 26(3): 173-178.	Irrelevant intervention. Pharmaceutical vs lifestyle.
Oyesanya O A, van Wely M and Clarke M J (2009). "Life-style modification, non-pharmacological and pharmacological strategies for obese subfertile women." Cochrane Database of Systematic Reviews.	Irrelevant setting. Protocol only. No reply from authors.
Palomba S., Falbo A., Giallauria F., Russo T., Tolino A. Zullo F., Colao A., Orio F. (2010), Effects of metformin with or without supplementation with folate on homocysteine levels and vascular endothelium of women with polycystic ovary syndrome Diabetes Care, 33:2 (246-251)	Irrelevant intervention. Pharmaceutical vs pharmaceutical.
Papadakis, G., Kandaraki, E. A., Garidou, A., Koutsaki, M., Papalou, O., Diamanti-Kandarakis, E., & Peppa, M. (2021). Tailoring treatment for PCOS phenotypes. Expert review of endocrinology & metabolism, 16(1), 9–18. https://doi.org/10.1080/17446651.2021.1865152	Wrong study design
Pasquali R. (2018). Contemporary approaches to the management of polycystic ovary syndrome. Therapeutic advances in endocrinology and metabolism, 9(4), 123–134. https://doi.org/10.1177/2042018818756790	Wrong study design
Peter Chedraui, Lifestyle and PCOS: From the womb to the menopause, Maturitas, Volume 100, 2017, Page 94, ISSN 0378-5122, https://doi.org/10.1016/j.maturitas.2017.03.010.	Wrong study design
Pokale et al. 2021 (could not find text anywhere along with citation)	Wrong study design
Pourteymour Fard Tabrizi, F., Abbasalizad Farhangi, M., Vaezi, M., & Hemmati, S. (2020). Changes of body composition and circulating neopterin, omentin-1, and chemerin in response to thylakoid-rich spinach extract with a hypocaloric diet in obese women with polycystic ovary syndrome: A randomized controlled trial. Phytotherapy research : PTR, 10.1002/ptr.6999. Advance online publication. https://doi.org/10.1002/ptr.6999	Wrong intervention
Pourteymour Fard Tabrizi, F., Abbasalizad Farhangi, M., Vaezi, M., & Hemmati, S. (2020). Changes of body composition and circulating neopterin, omentin-1, and chemerin in response to thylakoid-rich spinach extract with a hypocaloric diet in obese women with polycystic ovary syndrome: A randomized controlled trial. Phytotherapy research : PTR, 10.1002/ptr.6999. Advance online publication. https://doi.org/10.1002/ptr.6999	Wrong intervention
Qublan H S, Yannakoula E K, Al-Qudah M A and El-Uri F I (2007). "Dietary intervention versus metformin to improve the reproductive outcome in women with polycystic ovary syndrome. A prospective comparative study." Saudi medical journal 28(11): 1694-1699.	Irrelevant intervention. Diet vs pharmaceutical
Ravn, P., Haugen, A. G., & Glintborg, D. (2013). Overweight in polycystic ovary syndrome. An update on evidence based advice on diet, exercise and metformin use for weight loss. Minerva endocrinologica, 38(1), 59–76.	Wrong setting
Roy K.K., Baruah J., Sharma A., Sharma J.B., Kumar S. Kachava G., Karmakar D. (2010), A prospective randomized trial comparing the clinical and endocrinological outcome with rosiglitazone versus laparoscopic ovarian drilling in patients with polycystic ovarian disease resistant to ovulation induction with clomiphene citrate, Arch. Gynecol. Obstet. 281:5 (939-944)	Irrelevant intervention. Pharmaceuticals vs surgery
Shah, A., Dodson, W. C., Kris-Etherton, P. M., Kunselman, A. R., Stetter, C. M., Gnatuk, C. L., Estes, S. J., Allison, K. C., Sarwer, D. B., Sluss, P. M., Coutifaris, C., Dokras, A., & Legro, R. S. (2021). Effects of Oral Contraception and Lifestyle Modification on Incretins and TGF-ß Superfamily Hormones in PCOS. The Journal of clinical endocrinology and metabolism, 106(1), 108–119. https://doi.org/10.1210/clinem/dgaa682	Wrong intervention
Shai I, Schwarzfuchs D, Henkin Y, Shahar D, Witkow S, Greenberg I and Dietary Intervention Randomized Controlled Trial (DIRECT) Group (2008). "Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. Dietary Intervention Randomized Controlled Trial (DIRECT) Group." New England Journal of Medicine 359(3): 229-241.	Irrelevant setting. Not in PCOS women

Shang, Y., Zhou, H., Hu, M., & Feng, H. (2020). Effect of Diet on Insulin Resistance in Polycystic Ovary Syndrome. The Journal of clinical endocrinology and metabolism, 105(10), dgaa425. https://doi.org/10.1210/clinem/dgaa425	Wrong comparator
Smyka, M., Grzechocinska, B., & Wielgos, M. (2018). The role of lifestyle changes in the treatment of polycystic ovary syndrome. Neuro endocrinology letters, 38(8), 521–527.	Wrong study design
Szczuko, M., Szydłowska, I., & Nawrocka-Rutkowska, J. (2021). A Properly Balanced Reduction Diet and/or Supplementation Solve the Problem with the Deficiency of These Vitamins Soluble in Water in Patients with PCOS. Nutrients, 13(3), 746. https://doi.org/10.3390/nu13030746	Wrong comparator
Szczuko, M., Zapałowska-Chwyć, M., Maciejewska, D., Drozd, A., Starczewski, A., & Stachowska, E. (2017). Significant Improvement Selected Mediators of Inflammation in Phenotypes of Women with PCOS after Reduction and Low GI Diet. Mediators of inflammation, 2017, 5489523. https://doi.org/10.1155/2017/5489523	Wrong study design
The Practice Committee of the American Society for Reproductive Medicine (2004). "The evaluation and treatment of androgen excess." Fertility and Sterility 82(SUPPL. 1): S173-S180.	Irrelevant setting. Not a systematic review
Thessaloniki E A-S P C W G (2008). "Consensus on infertility treatment related to polycystic ovary syndrome." Human Reproduction 23(3): 462-477.	Irrelevant setting. Not a systematic review
Thomson R L, Buckley J D, Noakes M, Clifton P M, Norman R J, Brinkworth G D, Thomson R L, Buckley J D, Noakes M, Clifton P M, Norman R J and Brinkworth G D (2008). "The effect of a hypocaloric diet with and without exercise training on body composition, cardiometabolic risk profile, and reproductive function in overweight and obese women with polycystic ovary syndrome." Journal of Clinical Endocrinology & Metabolism 93(9): 3373-3380.	Irrelevant intervention. Exercise vs exercise
Thomson R.L., Buckley J.D., Lim S.S., Noakes M., Clifton P.M. Norman R.J., Brinkworth G.D. (2010), Lifestyle management improves quality of life and depression in overweight and obese women with polycystic ovary syndrome, Fertil. Steril. 94:5 (1812-1816)	Irrelevant intervention. Exercise vs exercise vs diet
Toosy, S., Sodi, R., & Pappachan, J. M. (2018). Lean polycystic ovary syndrome (PCOS): an evidence-based practical approach. Journal of diabetes and metabolic disorders, 17(2), 277–285. https://doi.org/10.1007/s40200-018-0371-5	Wrong study design
Toulis K A, Goulis D G, Farmakiotis D, Georgopoulos N A, Katsikis I, Tarlatzis B C, Papadimas I and Panidis D (2009). "Adiponectin levels in women with polycystic ovary syndrome: A systematic review and a meta-analysis." Human Reproduction Update 15(3): 297-307.	Irrelevant intervention. Not about lifestyle interventions
Turner-McGrievy GM, 2014, Low glycemic index vegan or low-calorie weight loss diets for women with polycystic ovary syndrome: a randomized controlled feasibility study, Nutrition Research, 34(6): 552-558.	Some participants were taking Metformin. Diet vs diet
Valent, A. M., & Barbour, L. A. (2021). Management of Women with Polycystic Ovary Syndrome During Pregnancy. Endocrinology and metabolism clinics of North America, 50(1), 57–69. https://doi.org/10.1016/j.ecl.2020.10.005	Wrong study design
Wahrenberg H, Ek I, Reynisdottir S, Carlstrom K, Bergqvist A and Arner P (1999). "Divergent effects of weight reduction and oral anticonception treatment on adrenergic lipolysis regulation in obese women with the polycystic ovary syndrome." Journal of Clinical Endocrinology & Metabolism 84(6): 2182-2187.	Irrelevant intervention. Pharmaceutical vs diet
Yang, H., Xiao, Y. Q., Liu, J. J., Xu, G. X., Li, J., Xiao, Z. Y., Zhou, J., Zheng, X. Y., Liu, L. Y., Yu, Z., Yang, J., & Liang, F. R. (2022). Effect of non-pharmacological interventions for overweight/obese women with polycystic ovary syndrome on ovulation and pregnancy outcomes: a protocol for a systematic review and network meta-analysis. BMJ open, 12(6), e059090. https://doi.org/10.1136/bmjopen-2021-059090	Wrong study design
Yosri, M. M., Hamada, H. A., & Yousef, A. M. (2022). Effect of visceral manipulation on menstrual complaints in women with polycystic ovarian syndrome. Journal of osteopathic medicine, 122(8), 411–422. https://doi.org/10.1515/jom-2021-0255	Wrong study design
Zabaleta, María Eléxpuru. 'Mediterranean Diet: Woman Fertility and Pregnancy'. 1 Jan. 2020: 101 – 111.	Wrong study design
Zhang, X., Zheng, Y., Guo, Y., & Lai, Z. (2019). The Effect of Low Carbohydrate Diet on Polycystic Ovary Syndrome: A Meta-Analysis of Randomized Controlled Trials. International journal of endocrinology, 2019, 4386401. https://doi.org/10.1155/2019/4386401	Wrong study design
Zhang J, Zhou L, Tang L, Wu T, Lim D C E and Xu L (2009). "Chinese herbal medicine for subfertile women with polycystic ovarian syndrome." Cochrane Database of Systematic Reviews (1).	Irrelevant intervention. A systematic review on complementary medicines for PCOS
Zhang, J., Si, Q., & Li, J. (2017). Therapeutic effects of metformin and clomiphene in combination with lifestyle intervention on infertility in women with obese polycystic ovary syndrome. Pakistan journal of medical sciences, 33(1), 8–12. https://doi.org/10.12669/pjms.331.11764	Wrong comparator
# 4049: Micronutrient Supplementation in PCO-syndrome No paper available to cite (this record was identified as an ongoing study on Covidence without any further citations details at the time of literature screening)	Wrong study design

# 4105: New strategies to lose weight for women with polycystic ovary syndrome (this record was identified as an ongoing study on Covidence without any further citations details at the time of literature screening)	Wrong study design
# 4113: Time-Restricted Feeding (TRF) on Overweight/Obese Women With Polycystic Ovarian Syndrome (PCOS) (this record was identified as an ongoing study on Covidence without any further citations details at the time of literature screening)	Wrong study design
# 4120: Low Starch Dietary Education Program vs. Traditional Treatment for PCOS (this record was identified as an ongoing study on Covidence without any further citations details at the time of literature screening)	Wrong study design
# 4132: The Effect and Safety of the Low-Carbohydrate, Ketogenic Diet on the Polycystic Ovary Syndrome: A Randomized Controlled Study (this record was identified on Covidence without any further citations details at the time of literature screening)	Wrong study design
# 4139: Role of the Ketogenic Diet in Women With PCOS (this record was identified as an ongoing study on Covidence without any further citations details at the time of literature screening)	Wrong study design
# 4202: The effect of aerobic training and DASH diet on insulin resistance and sex hormones in women with polycystic ovary syndrome (this record was identified as an ongoing study on Covidence without any further citations details at the time of literature screening)	Wrong intervention
# 4235: The effectiveness of a Mediterranean diet on hormonal, metabolic and body composition in overweight and obese women with Polycystic Ovary Syndrome (this record was identified as an ongoing study on Covidence without any further citations details at the time of literature screening)	Wrong study design
#4046: Effect of Dietary Modification on Microbiota in Overweight and Obese Polycystic Ovary Syndrome Patients (this record was identified as an ongoing study on Covidence without any further citations details at the time of literature screening)	Wrong intervention
#4057: Effect of diet therapy in treatment of patients with polycystic ovary syndrome (this record was identified as an ongoing study on Covidence without any further citations details at the time of literature screening)	Wrong study design
#4071: A trial to compare the effect of weight loss diets on obese women with polycystic ovarian syndrome (PCOS) (this record was identified as an ongoing study on Covidence without any further citations details at the time of literature screening)	Wrong study design
#4104: Effect of oral thylakoid intake with low-calorie diet in the treatment of polycystic ovary syndrome (this record was identified as an ongoing study on Covidence without any further citations details at the time of literature screening)	Wrong study design
#4130: Fasting mimicking diet compared with low calorie diet among premenopausal obese women (this record was identified as an ongoing study on Covidence without any further citations details at the time of literature screening)	Wrong study design
#4150: Lifestyle Intervention in Pregnant Women With PCOS (this record was identified as an ongoing study on Covidence without any further citations details at the time of literature screening)	Wrong study design
#4184: Effect of diet therapy with and without Curcumin in treatment of Polycystic Ovary Syndrome (this record was identified as an ongoing study on Covidence without any further citations details at the time of literature screening)	Wrong study design
#4236: Application of Zury Innovation (digital therapeutics) in the management of Polycystic ovary syndrome (PCOS) in Indian women No paper available to cite (this record was identified as an ongoing study on Covidence without any further citations details at the time of literature screening)	Wrong study design
#4238: A Study To Compare The Effect of Ayurveda Nutritional Approach With Modern Nutritional Approach On The Biochemical Parameters Of Young Women With Polycystic Ovarian Syndrome (this record was identified as an ongoing study on Covidence without any further citations details at the time of literature screening)	Wrong study design
#4254: Effect of dietary fiber intervention on patients with polycystic ovary syndrome (this record was identified as an ongoing study on Covidence without any further citations details at the time of literature screening)	Wrong study design
#4258: Low-Carb Versus Mediterranean Diet in PCOS (this record was identified as an ongoing study on Covidence without any further citations details at the time of literature screening)	Wrong study design
#4274 In women with polycystic ovary syndrome, how do lifestyle changes affect outcomes? [Miscellaneous]. This record was identified on Covidence without any further citations details at the time of literature screening)	Wrong study design
#4754: Dietary composition in the treatment of polycystic ovary syndrome: a systematic review to inform evidence-based guidelines (Structured abstract). Database of Abstracts of Reviews of Effects 2015;(2): 2015	Wrong study design

5. Study Characteristics of Included Studies

Author, year, country	Population/ Setting	Study Design	Sample Size per group	Intervention/ exposure details	Comparison/ control details	Follow up Duration	Outcomes	Summary of findings	Other
Asemi et al. 2014-2015, Iran	Women with PCOS; AMC	Parallel RCT	Intervention, 24 Control, 24	DASH diet with target energy deficit 350–700 kcal/d	Iranian traditional dietary pattern and target energy deficit of 350–700 kcal/d	8 wks	Fasting insulin, fasting glucose, HOMA-IR, TC, LDL-C, HDL-C, TG, weight, WC	DASH eating pattern resulted in the improvement of insulin resistance, serum hs-CRP levels, and abdominal fat accumulation vs control diet.	Low risk
Azadi-Yazdi et al., 2016, Iran	Women with PCOS; AMC	Parallel RCT	Intervention, 28 Control, 27	DASH diet with target energy deficit 350–500 kcal/d	Control diet and target energy deficit of 350–500 kcal/d)	12 wk	Weight, BMI, WC, waist-to-hip ratio, lean mass, fat mass, FAI, total testosterone, SHBG	DASH diet had beneficial effects on weight, BMI, fat mass, androstenedione, SHBG, and antioxidant capacity vs control diet.	Moderate risk/Low certainty
Foroozanfard et al., 2017, Iran	Women with PCOS; AMC	Parallel RCT	Intervention, 30 Control, 30	DASH diet with target energy deficit 350–700 kcal/d	Iranian traditional dietary pattern with target energy deficit 350–700 kcal/d	12 wk	Weight, BMI, FAI, total testosterone, SHBG, fasting glucose, insulin sensitivity, insulin, HOMA-IR	DASH diet had beneficial effects on weight, BMI, AMH, markers of insulin metabolism, SHBG, FAI, NO, and MDA levels compared with the low-calorie control diet but did not affect other metabolic profiles vs control diet.	Low risk
Gower et al., 2013, USA	Women with PCOS; AMC	Cross-over RCT	Intervention, 27; Control, 23	Low carbohydrate diet without energy restriction	Standard diet without energy restriction	8 wks (20 wks post-intervention follow up)	β-cell responsiveness, Serum testosterone concentration, insulin sensitivity (primary); fasting glucose, fasting insulin, FSH, LH, SHBG, testosterone, free androgen index, serum cholesterol	Modest reduction in dietary CHO in the context of a weight-maintaining diet likely improves metabolic profile that may lead to a decrease in circulating testosterone vs control diet.	Moderate risk/Low certainty
Hoover et al., 2021, USA	Women with PCOS; AMC	Cross-over RCT	Intervention, 30 Control, 30	Low glycemic load diet	High glycemic load diet	Eight weeks (20 wks post-intervention follow-up)	Insulin, glucose	No significant differences between any outcomes between the groups of interest were observed.	High risk/Low certainty
Hosseini Marnani et al., 2021, Iran	Women with PCOS; AMC	Parallel RCT	Intervention, 15 Control, 15	High-protein, low-carbohydrate diet	Standard diet	12 wk	Fasting insulin, fasting glucose, HOMA-IR, fat%, muscle%	No significant differences between any outcomes between the groups of interest were observed.	High risk/Low certainty
Kazemi et al. 2018-2020, Canada	Women with PCOS; AMC	Parallel RCT	Intervention, 30 Control, 31	Low glycemic index pulse-based diet without energy restriction	TLC diet without energy restriction	16 wks (with 6 and 12 mos post-	Weight, BMI, WC, total body fat mass, trunk fat mass, total body fat, total body lean mass, SBP, DBP, FPG, Fasting insulin,	A low glycemic index diet rich in dietary pulses was more effective at reducing metabolic profile (insulin resistance, diastolic blood pressure,	Low risk

Author, year, country	Population/ Setting	Study Design	Sample Size per group	Intervention/ exposure details	Comparison/ control details	Follow up Duration	Outcomes	Summary of findings	Other
						intervention follow-up)	HbA1c, HOMA-IR, fasting insulin/glucose ratio, total cholesterol, HDL-C, LDL-C, TC/HDL-C, TG, hsCRP, FNPO, OV, FAI, menstrual cycle length, HRQol	LDL-C, TC/HDL-C and increasing HDL-C than the TLC group). Reproductive and HRQoL outcomes did not differ between groups post-intervention (similar improvements over time), despite a greater loss in femoral neck BMD in the pulse-based diet group.	
Mehrabani et al., 2012, Iran	Women with PCOS; AMC	Parallel RCT	Intervention, 23 Control, 26	Modified hypocaloric diet (MHCD) with a target energy deficit of 500-1000 kcal/d	Conventional hypocaloric diet (CHCD) with a target energy deficit of 500-1000 kcal/d	12 wks	Fasting insulin, fasting glucose, HOMA-IR, TC, LDL-C, HDL-C, TG, weight, WC, TT, FAI, body composition including total body fat and lean body mass, FSH, LH, estradiol, total testosterone, DHEAS, and androstenedione Fasting insulin and adiponectin Serum glucose, triglyceride, total cholesterol, HDL-C	Modified hypocaloric diet with high-protein and low-glycemic-load foods increased in insulin sensitivity and decreased in hsCRP level vs control diet.	Moderate risk/Low certainty
Moran et al. 2003, Australia	Caucasian women with PCOS and overweight BMI	RCT	Intervention, 14 Control, 14	High protein (HP; 40% carbohydrate and 30% protein)	low protein (LP; 55% carbohydrate and 15% protein) diet	12 wk restriction + 4 wk maintenance	Weight, BMI, body fat by DXA, SHBG, total testosterone (bound and unbound), LH, FSH, progesterone, estradiol, TSH, PRL, and 17α-hydroxyprogesterone; TC, LDL, HDL, TG, insulin, glucose (and AUC insulin + glucose); HOMA-IR, menstrual cyclicity, ovulation, hirsutism, dietary compliance.	Modest difference in HDL-C and TC/HLD-C ratio, glucose AUC and FAI between diets but all other outcomes NS, despite changes over time/ within-group in multiple outcomes.	High risk
Panico et al., 2014, Italy	PCOS women	Cross-over RCT	Intervention, 7 Control, 7	Isocaloric and isoenergetic moderately low-glycaemic-load diets	Moderately high-glycaemic-load diets	6 mos	Fasting insulin, fasting glucose, HOMA-IR, total cholesterol, TG, weight, TT, FSH, LH, DHEAS	An isocaloric and isoenergetic low-glycemic-load diet improved metabolic outcomes (insulin resistance and serum androgen levels) vs control diet.	High risk/Very low certainty
Stamets et al., 2004, USA	Women with PCOS; AMC	Parallel RCT	Intervention, 17 Control, 18	High protein (HP) diet (30% protein, 40% carbohydrate,	High carbohydrate (HC) diet (15% protein, 55% carbohydrate, and 30%	4 wks	Weight, BMI, WC, waist-hip girth ratio, OGTT, TC, serum TG, LDL-C, HDL-C, blood pressure,	No differences were reported between interventions.	Moderate risk/Low certainty

Author, year, country	Population/ Setting	Study Design	Sample Size per group	Intervention/ exposure details	Comparison/ control details	Follow up Duration	Outcomes	Summary of findings	Other
				and 30% fat) with 1000 kcal energy deficit/d	fat) with 1000 kcal energy deficit/d		ferriman-gallwey scores, fasting testosterone, free and weakly bound testosterone, FSH, prolactin, 17-OH P, DHEAS, LH		
Toscani et al., 2011, Brazil	Women with PCOS; AMC	Parallel RCT	Intervention, 9 Control, 9	High protein (HP) diet	Normal protein (NP) diet	8 wks	Weight, BMI, WC, OGTT, TG	No differences were reported between interventions.	High risk/Very low certainty
Wong et al., 2016, USA	Adolescents with PCOS; AMC	Parallel RCT	Intervention, 7 Control, 9	Low-glycaemic load diet	Low-fat diet	6 mos	Bioavailable testosterone, total testosterone, free testosterone SHBG, DHEAS, TC, LDL-C, HDL-C, TG, HbA1c, Self-reported HRQL	No differences were reported between interventions.	Moderate risk/Low certainty

Abbreviations: PCOS: polycystic ovary syndrome, RCT: randomized control trial, AMC: academic medical center, DASH: dietary approaches to stop hypertension, BMI: body mass index, FAI: free androgen index, SHBG: sex hormone binding globulin, HOMA-IR: homeostatic model assessment for insulin resistance, AMH: anti mullerian hormone, NO: nitric oxide, MDA: malondialdehyde, GL: glycaemic load, HPP: high-protein, low-carbohydrate diet + placebo capsule, SDP: standard diet + placebo capsule, PBD: pulse-based diet, TLC: therapeutic lifestyle changes, FNPO: follicle numbers per ovary, SHBG: sex hormone binding globulin, OV: ovarian volume, FAI: free androgen index, HA: hyperandrogenism, OD: ovarian dysmorphology, PI: postintervention, HRQoL: Health related quality of life, TC: total cholesterol, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, TG: triglycerides, WC: waist circumference, hsCRP: high-sensitivity C-reactive protein, FSH: follicle stimulating hormone, LH: luteinizing hormone, CHO: carbohydrate, BMD: bone mineral density, FPG: fasting plasma glucose, HbA1c: hemoglobin A1C, TT: total testosterone, DHEAS: dehydroepiandrosterone sulfate, HP: high protein, NP: normal protein, HC: high cholesterol, MHCD: modified hypocaloric diet, CHCD: conventional hypocaloric diet, 17-OH P: 17-hydroxyprogesterone, OGTT: oral glucose tolerance test.

6. FINDINGS:

COMPARISON 1: Diet interventions versus other diet interventions

Evidence Summary:

We included 12 RCTs (18 publications) with 496 participants. With the exception of the comparison of high protein/low carb diet versus standard diets, all other results are summarized descriptively for most comparisons since meta-analyses were not feasible due to: (1) heterogeneity in the dietary composition of intervention arms; (2) variability in the dietary composition of control arms (e.g., high glycaemic, standard diet, TLC diet, high fat diet); and (3) variability in energy restriction prescribed (e.g., with energy restriction to variable levels or without energy restriction). For the three trials that compared the DASH to variable control diet (Asemi 2014-2015, Azadi-Yazdi 2016, and Foroozanfard 2017, see rows 1-3 in Section 5 Table above), all were small (n=48-60) and from only a single country (Iran), making any pooled analyses or assumptions less representative/ generalizable across PCOS populations for the purposes of the present report. Note also that there are notices of concern published alongside studies from this group (including Asemi et al. 2015) regarding concerns around study integrity and unsatisfactory responses from the authors/ ethics committees. Hence, results should be interpreted with caution.

Overall, out of the 12 included RCTs, nine had a parallel design, and two had a cross-over design (Gower et al., 2013 & Hoover et al., 2021 [same study population] and Panico et al., 2014) and approximately half (50%) were conducted in Iran (n=6 RCTs) with 25% in the USA (n=3 RCTs).

Regarding the meta-analysis results of high protein/low carb diet versus standard diets, our pooled analyses revealed that HDL-C decreased following the consumption of the high protein diet (N=3 effect estimates; N=95 women; MD: -2.27; 95%CI [-4.29; -0.24] mg/dL; P=0.03; I^2=79%). In contrast, other evaluated outcomes did not differ between diet groups, including WC (N=1 effect estimate; N=18 women; MD: -4.03; 95%CI [-14.87; -6.81] cm; P=0.5), total testosterone (N=1 effect estimate; N=49 women; MD: 0.20; 95%CI [-0.24; 0.64] ng/mL; P=0.4), FAI (N=1 effect estimate; N=49 women; MD: 0.90; 95%CI [-0.95; 2.75] mg/dL; P=0.3), fasting insulin (N=3 effect estimates; N=106 women; SMD: 0.45; 95%CI [-0.56; -1.46] mg/dL; P=0.4; I^2=83%), glucose (N=4 effect estimates; N=125 women; MD: -1.68; 95%CI [-0.13; 3.50] mg/dL; P=0.07; I^2=0%), HOMA-IR (N=3 effect estimates; N=106 women; SMD: 0.39; 95%CI [-0.51; 1.29]; P=0.4; I^2=79%), LDL-C (N=3 effect estimates; N=95 women; MD: -7.62; 95%CI [-27.70; 12.45] mg/dL; P=0.5; I^2=80%), TG (N=2 effect estimates; N=77 women; MD: -6.58; 95%CI [-15.52; 2.36] mg/dL; P=0.03; I^2=79%). Further details are available in Table 1.1.1. Summary table of meta-analysis results. As clarified earlier, meta-analyses for comparing the impacts of other dietary patterns on PCOS health outcomes were not possible due to the paucity of data.

Overall, these observations highlight the need for more RCTs across geographically, racially, and ethnically diverse populations. Overall, mounting data point to the potential health benefits of modifying the glycaemic index or load of the diet with an emphasis on energy control for achieving and maintaining a healthy weight/ body composition and balancing the dietary composition of the diet with healthy eating habits. The dietary patterns may include plant-based diets rich in vegetables, pulse foods, complex carbohydrates, or the DASH eating plan. These dietary patterns may benefit metabolic regulation (e.g., insulin sensitivity) and androgen status (testosterone) levels in PCOS, albeit data are sparse on HRQoL and emotional well-being.

Conclusions: Together, there remains uncertainty around the effects of any specific diet interventions (compared to different diets) for improving anthropometric, metabolic, fertility, and emotional well-being outcomes in PCOS, due to significant heterogeneity across studies, small sample sizes of current RCTs and lack of harmonized assessment of health outcomes (including fertility and emotional well-being), making pooling of results challenging. However, descriptive evaluations indicate that modifying the glycaemic index may improve the metabolic (e.g., insulin resistance) and reproductive (hyperandrogenism) health outcomes of PCOS. Few studies looked at the impact of lifestyle intervention on menstrual cyclicity and HRQoL, and no study evaluated pregnancy, ovulation rate, or miscarriage to

the best of our knowledge. Most studies were heterogeneous and of moderate to high risk of bias and low quality/ certainty.

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2. Rotterdam ESHRE/ASRM-sponsored PCOS Consensus Workshop Group, *Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS).* Hum Reprod, Rotterdam ESHRE/ASRM-sponsored PCOS Consensus Workshop Group 2004. **19**(1): p. 41-47.
3. Azziz, R., et al., *Androgen Excess Society. Positions statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline.* J Clin Endocrinol Metab, 2006. **91**(11): p. 4237-4245.

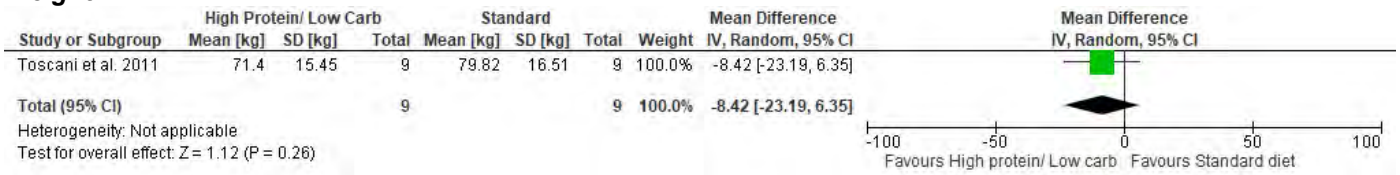
1.1. META-ANALYSIS of HIGH PROTEIN vs STANDARD DIET

1.1.1. Summary table of meta-analysis results

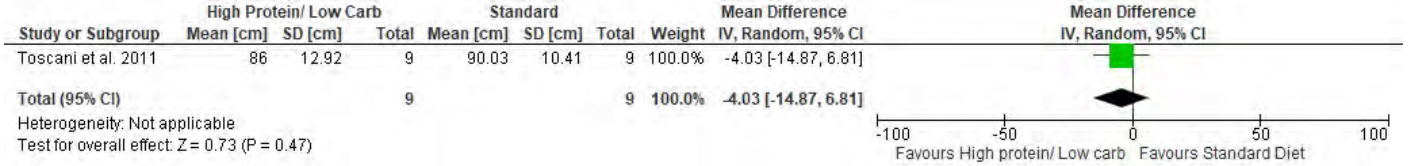
Outcome	Studies	n	Effect Estimate; MD [95% CI], random	P	I^2 (P_{het})	Favours	Certainty
Weight	1	18	-8.42 [-23.19, 6.35]	0.3	NA	No difference	⊕◯◯◯ VERY LOW
BMI [kg/m2]	2	46	NA (not pooled; data NR)	NA	NA	No difference (based on descriptive analysis of 2 studies; data NR)	⊕◯◯◯ VERY LOW
Waist circumference [cm]	1	18	-4.03 [-14.87, 6.81]	0.5	NA	No difference	⊕◯◯◯ VERY LOW
Total testosterone [ng/ml]	1	49	0.20 [-0.24, 0.64]	0.4	NA	No difference	⊕◯◯◯ VERY LOW
Free androgen index	1	49	0.90 [-0.95, 2.75]	0.3	NA	No difference	⊕◯◯◯ VERY LOW
Fasting insulin	3	106	SMD= 0.45 [-0.56, 1.46]	0.4	83% (p=0.003)	No difference	⊕◯◯◯ VERY LOW
Fasting blood glucose [mg/dl]	4	125	1.68 [-0.13, 3.50]	0.07	0% (p=0.9)	No difference	⊕◯◯◯ VERY LOW
HOMA-IR	3	106	SMD= 0.39 [-0.51, 1.29]	0.4	79% (p=0.008)	No difference	⊕◯◯◯ VERY LOW
HDL-C [mg/dl]	3	95	-2.27 [-4.29, -0.24]	**0.03**	0% (p=0.5)	**Lower in the high protein diet**	⊕◯◯◯ VERY LOW
LDL-C [mg/dl]	3	95	-7.62 [-27.70, 12.45]	0.5	80% (p=0.006)	No difference	⊕◯◯◯ VERY LOW
Triglycerides [mg/dl]	2	77	-6.58 [-15.52, 2.36]	0.2	0% (p=0.6)	No difference	⊕◯◯◯ VERY LOW
Change in Total testosterone [ng/ml]	2	75	-0.01 [-0.15, 0.13]	0.9	0% (p=0.7)	No difference	⊕◯◯◯ VERY LOW
Change in HDL-C [mg/dl]	2	75	1.33 [-3.26, 5.92]	0.6	11% (p=0.3)	No difference	⊕◯◯◯ VERY LOW
Change in LDL-C [mg/dl]	2	75	-1.87 [-10.77, 7.02]	0.7	0% (p=0.8)	No difference	⊕◯◯◯ VERY LOW
Change in Triglycerides [mg/dl]	2	75	1.51 [-13.83, 16.86]	0.9	0% (p=0.7)	No difference	⊕◯◯◯ VERY LOW

1.1.2. Forest plots/ funnel plots:

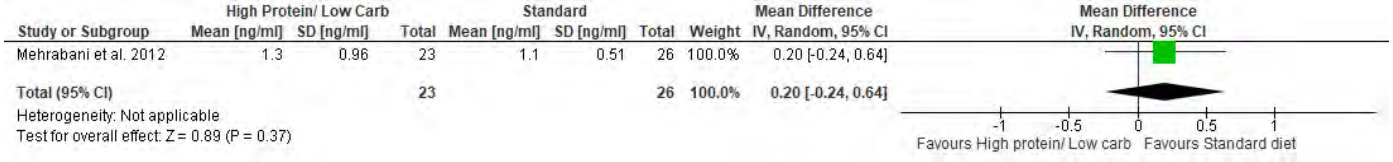
Weight



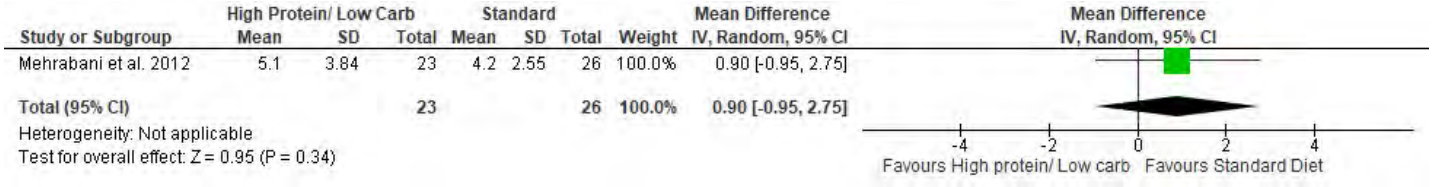
Waist circumference



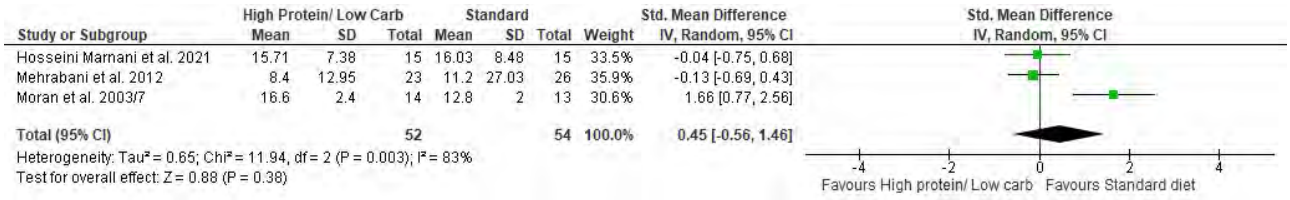
Total testosterone

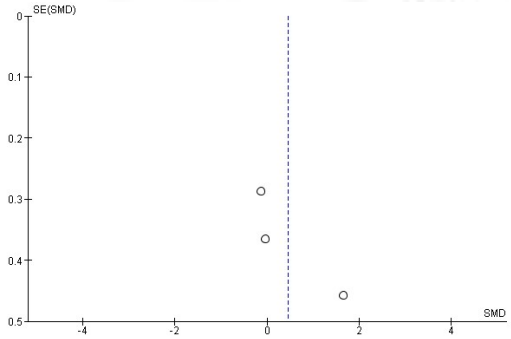


Free androgen index



Fasting insulin *(using SMD to account for variation in measures/ units)*

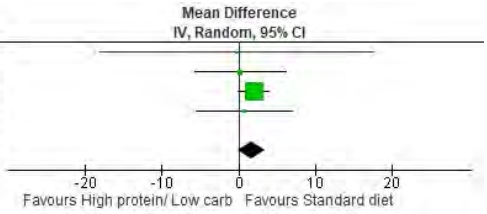


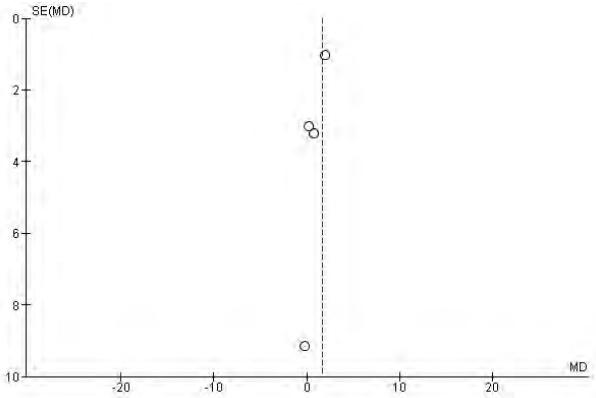


Fasting glucose

Study or Subgroup	High Protein/ Low Carb Mean [mg/dl]	SD [mg/dl]	Total	Standard Mean [mg/dl]	SD [mg/dl]	Total	Weight	Mean Difference IV, Random, 95% CI
Hosseini Marnani et al. 2021	104.35	31.72	15	104.6	15.79	15	1.0%	-0.25 [-18.18, 17.68]
Mehrabani et al. 2012	98.5	11.99	23	98.3	8.67	26	9.4%	0.20 [-5.73, 6.13]
Moran et al. 2003/7	97.56	2.34	14	95.58	3.06	14	81.2%	1.98 [-0.04, 4.00]
Toscani et al. 2011	90.5	7.23	9	89.78	6.38	9	8.3%	0.72 [-5.58, 7.02]
Total (95% CI)			**61**			**64**	**100.0%**	**1.68 [-0.13, 3.50]**

Heterogeneity: Tau² = 0.00; Chi² = 0.46, df = 3 (P = 0.93); I² = 0%
Test for overall effect: Z = 1.82 (P = 0.07)

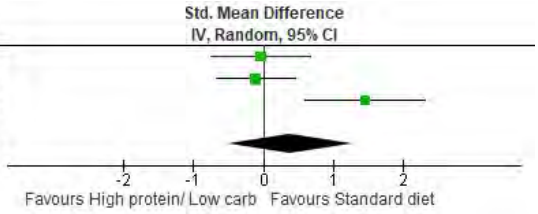


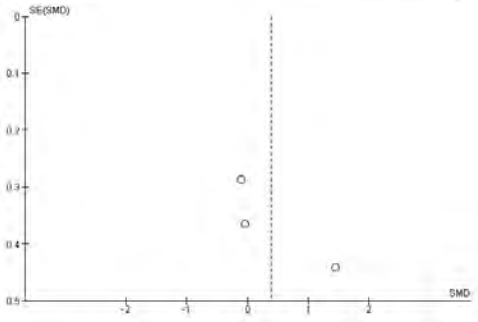


HOMA-IR *(using SMD to account for variation in measures/ units)*

Study or Subgroup	High Protein/ Low Carb Mean	SD	Total	Standard Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Hosseini Marnani et al. 2021	4.1	2.2	15	4.18	2.01	15	33.3%	-0.04 [-0.75, 0.68]
Mehrabani et al. 2012	2	4.32	23	2.7	7.65	26	36.3%	-0.11 [-0.67, 0.45]
Moran et al. 2003/7	0.28	0.02	14	0.25	0.02	13	30.4%	1.45 [0.59, 2.32]
Total (95% CI)			**52**			**54**	**100.0%**	**0.39 [-0.51, 1.29]**

Heterogeneity: Tau² = 0.49; Chi² = 9.65, df = 2 (P = 0.008); I² = 79%
Test for overall effect: Z = 0.85 (P = 0.39)

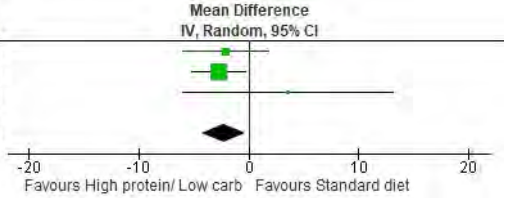


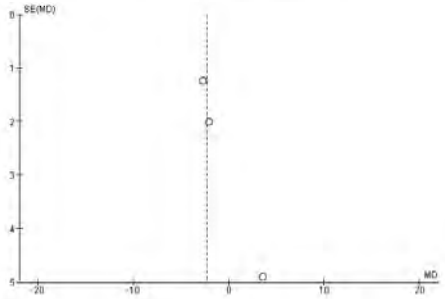


HDL-C

Study or Subgroup	High Protein/ Low Carb Mean [mg/dl]	SD [mg/dl]	Total	Standard Mean [mg/dl]	SD [mg/dl]	Total	Weight	Mean Difference IV, Random, 95% CI
Mehrabani et al. 2012	59.2	7.67	23	61.3	6.12	26	26.7%	-2.10 [-6.02, 1.82]
Moran et al. 2003/7	39.83	3.09	14	42.54	3.48	14	68.9%	-2.71 [-5.15, -0.27]
Toscani et al. 2011	49	7.89	9	45.44	12.38	9	4.5%	3.56 [-6.03, 13.15]
Total (95% CI)			**46**			**49**	**100.0%**	**-2.27 [-4.29, -0.24]**

Heterogeneity: Tau² = 0.00; Chi² = 1.55, df = 2 (P = 0.46); I² = 0%
Test for overall effect: Z = 2.20 (P = 0.03)

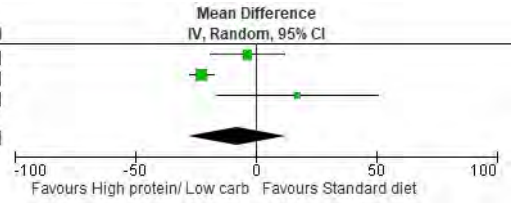


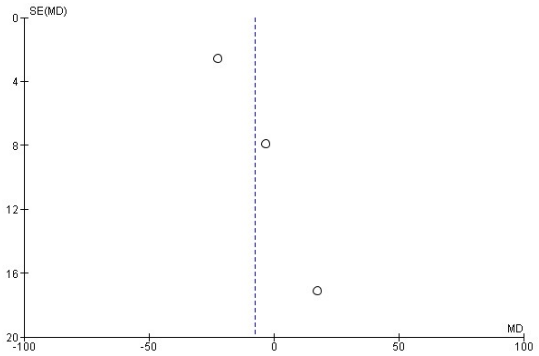


LDL-C

Study or Subgroup	High Protein/ Low Carb Mean [mg/dl]	SD [mg/dl]	Total	Standard Mean [mg/dl]	SD [mg/dl]	Total	Weight	Mean Difference IV, Random, 95% CI
Mehrabani et al. 2012	116.7	20.62	23	120	33.65	26	35.8%	-3.30 [-18.74, 12.14]
Moran et al. 2003/7	124.9	8.12	14	147.33	5.027	14	44.2%	-22.43 [-27.43, -17.43]
Toscani et al. 2011	145.8	42.32	9	128.49	29.05	9	20.0%	17.31 [-16.23, 50.85]
Total (95% CI)			**46**			**49**	**100.0%**	**-7.62 [-27.70, 12.45]**

Heterogeneity: Tau² = 231.01; Chi² = 10.15, df = 2 (P = 0.006); I² = 80%
Test for overall effect: Z = 0.74 (P = 0.46)

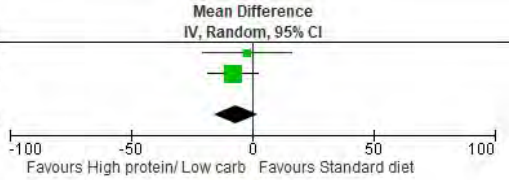


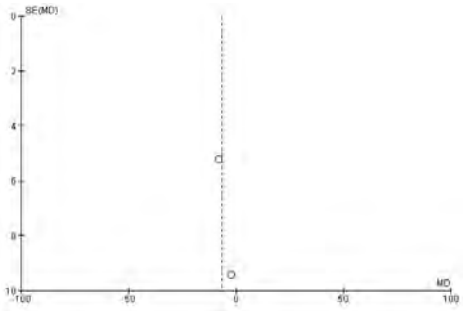


Triglycerides

Study or Subgroup	High Protein/ Low Carb Mean [mg/dl]	SD [mg/dl]	Total	Standard Mean [mg/dl]	SD [mg/dl]	Total	Weight	Mean Difference IV, Random, 95% CI
Mehrabani et al. 2012	122.4	27.34	23	124.4	38.24	26	23.4%	-2.00 [-20.46, 16.46]
Moran et al. 2003/7	117.8	15.058	14	125.78	12.4	14	76.6%	-7.98 [-18.20, 2.24]
Total (95% CI)			**37**			**40**	**100.0%**	**-6.58 [-15.52, 2.36]**

Heterogeneity: Tau² = 0.00; Chi² = 0.31, df = 1 (P = 0.58); I² = 0%
Test for overall effect: Z = 1.44 (P = 0.15)

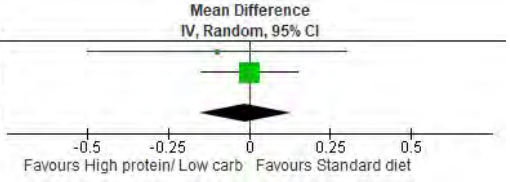


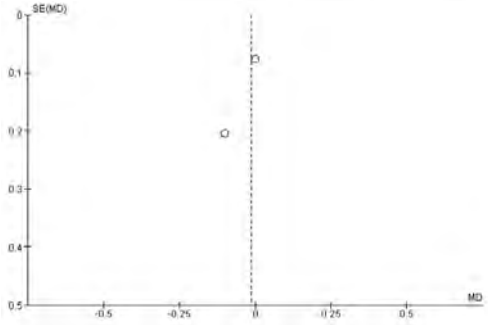


Change in total testosterone

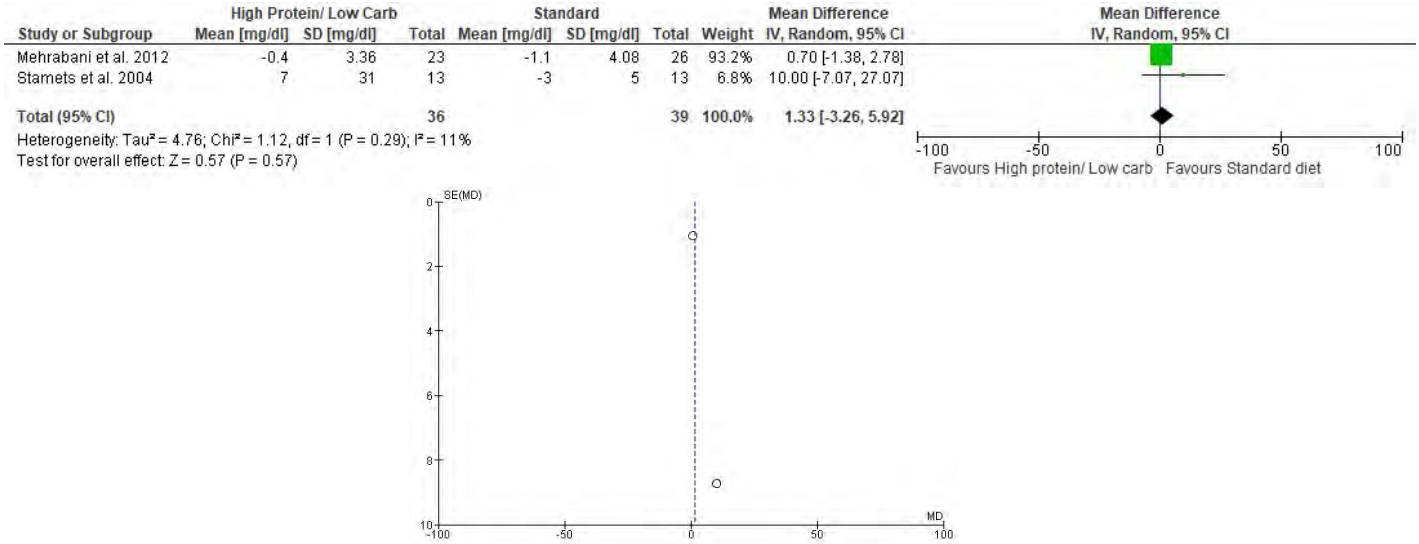
Study or Subgroup	High Protein/ Low Carb Mean [ng/ml]	SD [ng/ml]	Total	Standard Mean [ng/ml]	SD [ng/ml]	Total	Weight	Mean Difference IV, Random, 95% CI
Mehrabani et al. 2012	-0.5	0.96	23	-0.4	0.204	26	12.4%	-0.10 [-0.50, 0.30]
Stamets et al. 2004	-0.09	0.21	13	-0.09	0.18	13	87.6%	0.00 [-0.15, 0.15]
Total (95% CI)			**36**			**39**	**100.0%**	**-0.01 [-0.15, 0.13]**

Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 1 (P = 0.65); I² = 0%
Test for overall effect: Z = 0.17 (P = 0.86)

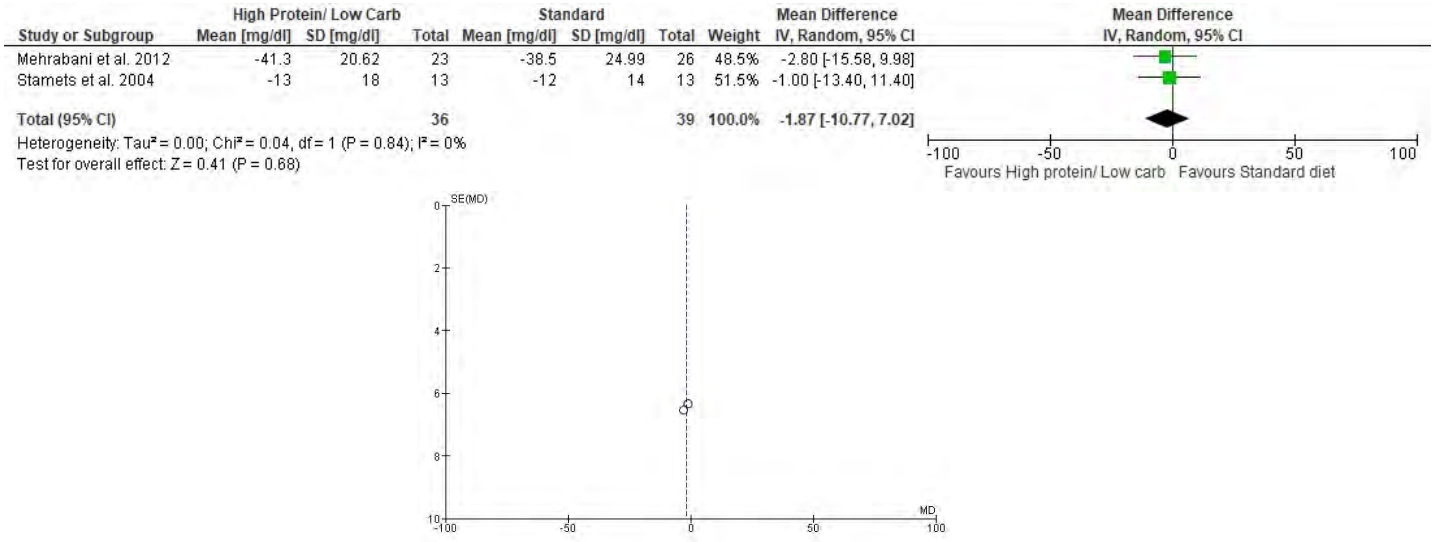




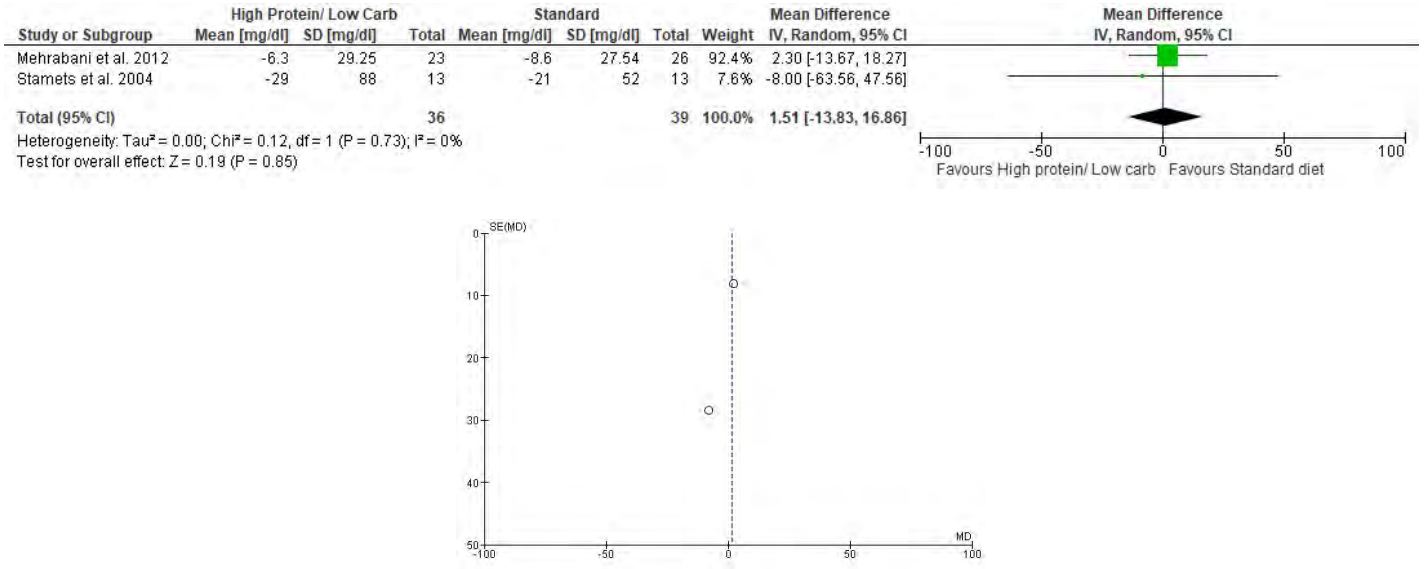
Change in HDL-C



Change in LDL-C



Change in Triglycerides



7. GRADE ASSESSMENTS AND EVIDENCE PROFILE

COMPARISON 1: DASH versus control/ traditional diets (350-500 or 700 kcal deficit)												
	Quality assessment						No. participants*					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	DASH	Control	Effect, narrative	Favours	Certainty	Importance
Outcome: Weight												
3	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	Low external validity[3]	82	81	2/3 studies showed benefit of DASH	**MIXED** (2/3 DASH; 1/3 NS)	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: BMI												
2	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	Low external validity[3]	58	57	2/2 studies showed benefit of DASH	**DASH**	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Waist circumference												
1	RCT	no serious risk of bias	not applicable	not applicable	very serious[4]	Low external validity[3]	24	24	1/1 study showed benefit of DASH	**DASH**	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Total testosterone												
2	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	Low external validity[3]	58	57	NS differences in both studies	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Free androgen index												
2	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	Low external validity[3]	58	57	1/2 studies showed benefit of DASH	**MIXED** (1/2 DASH; 1/2 NS)	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Fasting insulin												
2	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	Low external validity[3]	54	54	2/2 studies showed benefit of DASH	**DASH**	⊕⊕◯◯ LOW	CRITICAL
Outcome: Fasting glucose												
2	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	Low external validity[3]	54	54	NS differences in both studies	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: HOMA-IR												
2	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	Low external validity[3]	54	54	2/2 studies showed benefit of DASH	**DASH**	⊕⊕◯◯ LOW	CRITICAL
Outcome: HDL												
1	RCT	no serious risk of bias	not applicable	not applicable	very serious[4]	Low external validity[3]	24	24	NS differences	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: LDL												
1	RCT	no serious risk of bias	not applicable	not applicable	very serious[4]	Low external validity[3]	24	24	NS differences	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Triglycerides												
1	RCT	no serious risk of bias	not applicable	not applicable	very serious[4]	Low external validity[3]	24	24	NS differences	No difference	⊕◯◯◯ VERY LOW	CRITICAL

[1] Downgraded once for risk of bias due some/majority of the evidence being derived from moderate or high risk of bias studies
[2] Downgraded once for serious imprecision due to small sample sizes in the included studies
[3] Downgraded once due to all studies being conducted in Iran, two of which compared with DASH with a traditional Iranian diet, meaning the evidence has poor generalisability/ external validity
[4] Downgraded twice for very serious imprecision due to the evidence being derived from a single study with a small sample size

Note: Inconsistency was not downgraded for studies showing mixed results where some had an effect and the others did not; this was only downgraded where studies showed *significant* effects but in different directions. NS, non-significant. Please note: some studies by this group (including Asemi et al. 2015 included in this analysis) have been issued with Notices of Concern due to serious concerns raised about the integrity of the reported methods, results and analysis, where responses by the leading author and ethics committees were been unsatisfactory and inconclusive.

COMPARISON 2: Low glycaemic load (high fat/low carb) versus high glycaemic load												
	Quality assessment						No. participants*					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Low GL	High GL	Effect, narrative	Favours	Certainty	Importance
Outcome: Weight												
2	Cross-over RCTs	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	37	37	2/2 studies NS within-group (Gower; Panico); NR between-group	Cannot be determined (NR between-groups)	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: BMI												
1	Cross-over RCTs	very serious[1]	not applicable	not applicable	very serious[3]	none	7	7	NS within-group (Panico); NR between-group	Cannot be determined (NR between-groups)	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Total testosterone												
2	Cross-over RCTs	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	37	37	2/2 studies report within-group reduction for low GL diet (Gower; Panico); Not reported between-group	Cannot be determined (NR between-groups)	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Free androgen index												
1	Cross-over RCT	very serious[1]	not applicable	not applicable	very serious[3]	none	30	30	NS within-group (Gower); NR between-group	Cannot be determined (NR between-groups)	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Fasting insulin												
2	Cross-over RCTs	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	37	37	Mixed results: NS between-group (Hoover); Within-group reduction for low GL diet (Gower); NS within-group (Panico);	No difference between groups	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Fasting glucose												
2	Cross-over RCTs	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	37	37	Mixed results: NS between-group (Hoover); Within-group reduction for low GL diet (Gower); NS within-group (Panico);	No difference between groups	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: HOMA-IR												
2	Cross-over RCTs	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	37	37	2/2 studies report within-group reduction for low GL diet (Gower; Panico); NR between-group	Cannot be determined (NR between-groups)	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: HDL												
1	Cross-over RCT	very serious[1]	not applicable	not applicable	very serious[3]	none	30	30	Within-group reduction for both diets (Gower); NR between-group	Cannot be determined (NR between-groups)	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: LDL												
1	Cross-over RCT	very serious[1]	not applicable	not applicable	very serious[3]	none	30	30	Within-group reduction for low GL diet (Gower); NR between-group	Cannot be determined (NR between-groups)	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Triglycerides												

2	Cross-over RCTs	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	37	37	2/2 studies NS within-group (Gower; Panico); NR between-group	Cannot be determined (NR between-groups)	⊕◯◯◯ VERY LOW	CRITICAL

[1] Downgraded twice for risk of bias due all the evidence being derived from high/ moderate risk of bias studies
[2] Downgraded once for serious imprecision due to small sample sizes in the included studies
3 Downgraded twice for very serious imprecision due to the evidence being derived from a single study with a small sample size

***same participants in both groups as all studies were cross-over RCTs (i.e. Panico et al. included only 7 participants; Gower and Hoover included n=30 participants in total).**

Note: Studies by Gower et al. 2013 and Hoover et al. 2021 include the same population so have only been included as a single study here, with relevant outcomes collated from both studies. Inconsistency was not downgraded for studies showing mixed results where some had an effect and the others did not; this was only downgraded where studies showed *significant* effects but in different directions. NS, non-significant; NR, not reported. No studies reported on waist circumference.

COMPARISON 3: High protein / low carb versus Standard Diet (based on meta-analysis of reported data)												
	Quality assessment						No. participants*					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	High protein/ low carb	Standard Diet	Effect, random; MD (95%CI) and/or narrative	Favours	Certainty	Importance
Outcome: Weight												
1	RCT	very serious[1]	not applicable	not applicable	very serious[2]	none	9	9	-8.42 [-23.19, 6.35]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: BMI												
2	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	23	23	**Descriptive:** data NR/ not pooled; 2/2 studies reported no difference in BMI (Toscani, Moran)	No difference (descriptive)	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Waist circumference												
1	RCT	very serious[1]	not applicable	not applicable	very serious[2]	none	9	9	-4.03 [-14.87, 6.81]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Total testosterone												
1	RCT	very serious[1]	not applicable	not applicable	very serious[2]	none	23	26	0.20 [-0.24, 0.64]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Free androgen index												
1	RCT	very serious[1]	not applicable	not applicable	very serious[2]	none	23	26	0.90 [-0.95, 2.75]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Fasting insulin												
3	RCT	very serious[1]	very serious[5]	no serious indirectness	serious[3]	none	52	54	SMD= 0.45 [-0.56, 1.46]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Fasting glucose												
4	RCT	very serious[1]	serious[4]	no serious indirectness	serious[3]	none	61	64	1.68 [-0.13, 3.50]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: HOMA-IR												
3	RCT	very serious[1]	very serious[5]	no serious indirectness	serious[3]	none	52	54	SMD= 0.39 [-0.51, 1.29]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: HDL												
3	RCT	very serious[1]	serious[4]	no serious indirectness	serious[3]	none	46	49	-2.27 [-4.29, -0.24]	**Lower in High Protein Diet**	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: LDL												
3	RCT	very serious[1]	very serious[5]	no serious indirectness	serious[3]	none	46	49	-7.62 [-27.70, 12.45]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Triglycerides												
2	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	37	40	-6.58 [-15.52, 2.36]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Change in Testosterone												
2	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	36	39	-0.01 [-0.15, 0.13]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Change in HDL-C												
2	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	36	39	1.33 [-3.26, 5.92]	No difference	⊕◯◯◯ VERY LOW	CRITICAL

Outcome: Change in LDL-C											
2	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	36	39	-1.87 [-10.77, 7.02]	No difference	⨁◯◯◯ VERY LOW	CRITICAL
Outcome: Change in Triglycerides											
2	RCT	very serious[1]	serious[4]	no serious indirectness	serious[3]	none	36	39	1.51 [-13.83, 16.86]	No difference	⨁◯◯◯ VERY LOW	CRITICAL

[1] Downgraded twice for risk of bias due all the evidence being derived from high/ moderate risk of bias studies

[2] Downgraded twice for very serious imprecision due to the evidence being derived from a single study with a very sample size

[3] Downgraded once for serious imprecision due to small sample sizes in the included studies

[4] Downgraded once for inconsistency due to variation in the direction of the effect estimate and/or wide CI

[5] Downgraded twice for very serious inconsistency due to variation in the direction of the effect estimate and/or wide CI and significant heterogeneity by I^2 or CIs not overlapping

COMPARISON 4: Low glycaemic index versus therapeutic lifestyle change												
	Quality assessment						No. participants*					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Low GI**	**TLC**	**Effect, random [95% CI]**	**Favours**	**Certainty**	**Importance**
Outcome: Weight												
1	RCT	no serious risk of bias	not applicable	not applicable	very serious[1]	none	31	30	NS between groups	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: BMI												
1	RCT	no serious risk of bias	not applicable	not applicable	very serious[1]	none	31	30	NS between groups	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Waist circumference												
1	RCT	no serious risk of bias	not applicable	not applicable	very serious[1]	none	31	30	NS between groups	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Total testosterone												
1	RCT	no serious risk of bias	not applicable	not applicable	very serious[1]	none	31	30	NS between groups	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Free androgen index												
1	RCT	no serious risk of bias	not applicable	not applicable	very serious[1]	none	31	30	NS between groups	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Fasting insulin												
1	RCT	no serious risk of bias	not applicable	not applicable	very serious[1]	none	30	29	NS between groups	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Fasting glucose												
1	RCT	no serious risk of bias	not applicable	not applicable	very serious[1]	none	30	29	NS between groups	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: HOMA-IR												
1	RCT	no serious risk of bias	not applicable	not applicable	very serious[1]	none	30	29	NS between groups	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: HDL												
1	RCT	no serious risk of bias	not applicable	not applicable	very serious[1]	none	31	30	Increased in pulse-based low GI diet	**Low GI**	⊕⊕◯◯ LOW	CRITICAL
Outcome: LDL												
1	RCT	no serious risk of bias	not applicable	not applicable	very serious[1]	none	31	30	Reduced in pulse-based low GI diet	**Low GI**	⊕⊕◯◯ LOW	CRITICAL
Outcome: Triglycerides												
1	RCT	no serious risk of bias	not applicable	not applicable	very serious[1]	none	31	30	Reduced in pulse-based low GI diet	**Low GI**	⊕⊕◯◯ LOW	CRITICAL

[1] Downgraded twice for very serious imprecision due to the evidence being derived from a single study with a small sample size.
Note: single study by Kazemi et al. 2018 examined this comparison. Effects reported refer to differences between groups rather than differences from baseline within each group.

COMPARISON 5: Low glycaemic load (High fat/ low carb) versus low fat												
	Quality assessment						No. participants*					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Low GL (High fat/ low carb)	Low Fat	Effect, random [95% CI]	Favours	Certainty	Importance
Outcome: Weight												
1	RCT	serious[1]	not applicable	not applicable	very serious[2]	Low external validity[3]	7	9	NS between groups	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: BMI												
1	RCT	serious[1]	not applicable	not applicable	very serious[2]	Low external validity[3]	7	9	Greater decrease in BMI percentile in low fat group	**Low fat**	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Waist circumference												
1	RCT	serious[1]	not applicable	not applicable	very serious[2]	Low external validity[3]	7	9	NS between groups	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Total testosterone												
1	RCT	serious[1]	not applicable	not applicable	very serious[2]	Low external validity[3]	7	9	NS between groups	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Free androgen index												
1	RCT	serious[1]	not applicable	not applicable	very serious[2]	Low external validity[3]	7	9	NS between groups	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Fasting insulin												
1	RCT	serious[1]	not applicable	not applicable	very serious[2]	Low external validity[3]	7	9	NS between groups	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Fasting glucose												
1	RCT	serious[1]	not applicable	not applicable	very serious[2]	Low external validity[3]	7	9	NS between groups	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: HOMA-IR												
1	RCT	serious[1]	not applicable	not applicable	very serious[2]	Low external validity[3]	7	9	NS between groups	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: HDL												
1	RCT	serious[1]	not applicable	not applicable	very serious[2]	Low external validity[3]	7	9	NS between groups	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: LDL												
1	RCT	serious[1]	not applicable	not applicable	very serious[2]	Low external validity[3]	7	9	NS between groups	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Triglycerides												
1	RCT	serious[1]	not applicable	not applicable	very serious[2]	Low external validity[3]	7	9	NS between groups	No difference	⊕◯◯◯ VERY LOW	CRITICAL

[1] Downgraded once for serious risk of bias due to the evidence being derived from a single study with moderate risk of bias.
[2] Downgraded twice for very serious imprecision due to the evidence being derived from a single study with a very small sample size.
[3] Downgraded once due to low external validity since the single included study is limited to adolescents with overweight/obesity and results are not generalisable to wider populations of women with PCOS
Note: single study by Wong et al. 2015 examined this comparison. Effects reported refer to differences between groups rather than differences from baseline within each group.

7.1. DATA EXTRACTION TABLES – DICHOTOMOUS OUTCOMES

Not applicable.

7.2. DATA EXTRACTION TABLES – CONTINUOUS OUTCOMES

For clarity, all studies included in the updated search after the publication of the previous guideline in 2018 are shown in grey rows, and others that were included in the updated search are shown in green rows below.

OUTCOME: Weight										
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Asemi et al., 2014	kg	Not Reported	Post-intervention mean: 73.6	Post-intervention SD: 12.1	24	Post-intervention mean: 73.1	Post-intervention SD: 15.5	24	Crude	Not Applicable
Azadi-Yazdi et al., 2016	kg	Digital scale	Baseline intervention mean: 80.91 Post-intervention mean difference: -5.78	Baseline intervention SD: 11.53 Mean difference SD: 1.9	28	Baseline control mean: 77.68 Post-intervention mean difference: -4.34	Baseline control SD: 12.47 Post-intervention mean difference: 2.86	27	Crude	Not Applicable
Foroozanfard et al., 2017	kg	Not Reported	Baseline intervention mean: 87.4 Post-intervention mean: 83.1	Baseline intervention SD: 15.9 Post-intervention SD: 15.2	30	Baseline control mean: 84.7 Post-intervention control mean: 81.5	Baseline control SD: 12.4 Post-intervention control mean difference: 12.3	30	Adjusted	Baseline values of biochemical variables, age, and BMI
Kazemi et al., 2018	kg	Mechanical weight scale	Baseline pulse-diet mean: 89.9 Post-intervention pulse-diet mean: 84.4 Mean change pulse-diet: -5.5	Baseline pulse-diet SD: 27.0 Post-intervention pulse-diet SD: 26.8 Mean change pulse-diet SD: 4.5	31	Baseline TLC-diet mean: 93.3 Post-intervention TLC-diet mean: 88.4 Mean change TLC-diet: -4.9	Baseline TLC-diet SD: 25.4 Post-intervention TLC-diet SD: 23.0 Mean change TLC-diet SD: 15.8	30	Crude	Not Applicable
Mehrabani et al., 2013	kg %	Not Reported	CHCD Baseline: 78.9 (SE) Weight loss 3.3% No exact values reported	 Baseline: 5.2 (SE) Weight loss range (-2 to -10) 0.62%	26	MHCD Baseline: 83.0 (SE) Weight loss 4.1% No exact values reported	 Baseline: 11.7 (SE) Weight loss range (-1 to -9) 0.58%	23	Crude	Not Applicable

Panico et al., 2014	kg	Not Reported	Diet A Baseline: 71.7 Post intervention: 69.2	Baseline: 11.5 Post intervention: 10.7	Not Reported	Diet B Baseline: 71.7 Post intervention: 69.8	Baseline: 11.5 Post intervention: 10.7	Not Reported	Crude	Not Applicable
Stamets et al., 2014	kg	Not reported	Mean change high protein diet: -3.7	Mean change high protein diet SD: 1.9	13	Mean change high carbohydrate diet: -4.4	Mean change high carbohydrate diet SD:1.5	13	Crude	Not Applicable
Toscani et al., 2011	kg	Not reported	Post-intervention high protein diet mean: 71.4	Post-intervention high protein diet SD: 15.45	9	Post-intervention normal protein diet mean: 79.82	Post-intervention normal protein diet SD: 16.51	9	Crude	Not Applicable
Wong et al., 2015	kg	Not reported	Low-GL Baseline: 97.4 Post intervention: 96.2 Change from baseline: -1.2	Baseline: 8.8 Post intervention: 9.9 Change from baseline: 0.8 (SE)	10	Low-fat Baseline: 87.4 Post intervention: 82.6 Change from baseline: -4.8	Baseline: 11.3 Post intervention: 12.2 Change from baseline: 1.6 (SE)	9	Crude	Not Applicable
Abbreviations: BMI: body mass index, RIA: radioimmunoassay, TLC: therapeutic lifestyle changes, CHCD = Conventional hypocaloric diet, MHCD = modified hypocaloric diet.										

OUTCOME: BMI										**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Asemi et al., 2014	kg/m^2	Not Reported	Post-intervention mean: 28.6	Post-intervention SD: 4.4	24	Post-intervention mean: 28.0	Post-intervention SD: 5.7	24	Crude	Not Applicable
Azadi-Yazdi et al., 2016	kg/m^2	Not Reported	Baseline intervention mean: 31.92	Baseline intervention SD: 4.16	28	Baseline control mean: 30.20 Post-intervention	Baseline control SD: 3.25 Post-intervention control mean difference: 1.06	27	Crude	Not Applicable

			Post-intervention mean difference: -2.29	Mean difference SD: 0.78		control mean difference: -1.69				
Foroozanfard et al., 2017	kg/m^2	Not Reported	Baseline intervention mean: 32.3 Post-intervention mean: 30.8	Baseline intervention SD: 4.6 Post-intervention SD: 4.5	30	Baseline control mean: 32.2 Post-intervention control mean: 30.9	Baseline control SD: 3.9 Post-intervention control mean difference: 3.9	30	Adjusted	Baseline values of biochemical variables, age, and BMI
Kazemi et al., 2018	kg/m^2	Formula (bodyweight (kg)/(height squared)(m^2)	Baseline pulse-diet mean: 33.3 Post-intervention pulse-diet mean: 32.0 Mean change pulse-diet: -1.3	Baseline pulse-diet SD: 9.0 Post-intervention pulse-diet SD: 9.0 Mean change pulse-diet SD: 1.4	31	Baseline TLC-diet mean: 34.0 Post-intervention TLC-diet mean: 32.2 Mean change TLC-diet: -1.8	Baseline TLC-diet SD: 9.8 Post-intervention TLC-diet SD: 8.6 Mean change TLC-diet SD: 6.1	30	Crude	Not Applicable
Panico et al., 2014	kg/m^2	Not Reported	Diet A Baseline: 28.7 Post intervention: 27.6	 Baseline: 4.9 Post intervention: 4.6	Not Reported	Diet B Baseline: 28.7 Post intervention: 27.9	 Baseline: 4.9 Post intervention: 4.7	Not Reported	Crude	Not Applicable
Wong et al., 2015	kg/m^2	Not Reported	Low-GL Baseline: 36.5 Post intervention: 36.1 Change from baseline: -0.5	 4.3 4.7 0.3 (SE)	10	Low-fat Baseline: 32.8 Post intervention: 30.9 Change from baseline: -1.9	 3.2 3.7 0.7 0.6 (SE)	9	Crude	Not Applicable
Abbreviations: BMI: Body mass index, TLC: therapeutic lifestyle changes.										

OUTCOME: WC							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg,**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in**	**Sample size (n within this group)**	**Mean (specify if median) or median in**	**SD (or specify if other measure: SE, IQR or 95%**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were**

	mmol/L, etc.)			intervention / exposure group		control / comparison group	CI) in control/ comparison group			included in the model?
Azadi-Yazdi et al., 2016	cm	Plastic tape placed midway between iliac crest and lowest rib when participant in standing position	Baseline intervention mean: 100.95 Post-intervention mean difference: -4.97	Baseline intervention SD: 11.58 Mean difference SD: 3.77	28	Baseline control mean: 99.67 Post-intervention control mean difference: -3.77	Baseline control SD: 10.72 Post-intervention control mean difference: 3.09	27	Crude	Not Applicable
Kazemi et al., 2018	cm	World Health Organization WC Expert Consultation on WC protocol	Baseline pulse-diet mean: 103.9 Post-intervention pulse-diet mean: 99.5 Mean change pulse-diet: -4.4	Baseline pulse-diet SD: 19.8 Post-intervention pulse-diet SD: 18.0 Mean change pulse-diet SD: 11.2	31	Baseline TLC-diet mean: 103.5 Post-intervention TLC-diet mean: 101.8 Mean change TLC-diet: -1.7	Baseline TLC-diet SD: 20.2 Post-intervention TLC-diet SD: 19.3 Mean change TLC-diet SD: 7.6	30	Crude	Not Applicable
Toscani et al., 2011	cm	Not reported	Post-intervention high protein diet mean: 86	Post-intervention high protein diet SD: 12.92	9	Post-intervention normal protein diet mean: 90.3	Post-intervention normal protein diet SD: 10.41	9	Crude	Not Applicable
Stamets et al., 2014	cm	Not reported	Mean change high protein diet: -5	Mean change high protein diet SD: 5	13	Mean change high carbohydrate diet: -1	Mean change high carbohydrate diet SD: 6	13	Crude	Not Applicable
Abbreviations: WC, waist circumference, TLC: therapeutic lifestyle changes										

OUTCOME: Waist-to-hip ratio									**OUTCOME TYPE:** Continuous	
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

Azadi-Yazdi et al., 2016	Not Applicable	Non-stretch plastic tape	Baseline intervention mean: 0.89 Post-intervention mean difference: -0.0117	Baseline intervention SD: 0.065 Mean difference SD: 0.0138	28	Baseline control mean: 0.89 Post-intervention control mean difference: -0.0063	Baseline control SD: 0.073 Post-intervention control mean difference: 0.024	27	Crude	Not Applicable
Stamets et al., 2014	Not Applicable	Not reported	Mean change high protein diet: -0.01	Mean change high protein diet SD: 0.5	13	Mean change high carbohydrate diet: -0.01	Mean change high carbohydrate diet SD: 0.05	13	Crude	Not Applicable

OUTCOME: Menstrual cycle length						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Kazemi et al., 2020	Days	Self-Report	Baseline pulse mean: 102 Post-intervention 16 wk pulse mean: 81	Baseline pulse SD: 53 Post-intervention 16 wk pulse SD: 48	31	Baseline TLC mean: 109 Post-intervention 16 wk TLC mean: 67	Baseline TLC SD: 67 Post-intervention 16 wk TLC SD: 52	30	Crude	Not Applicable
Abbreviations: TLC: therapeutic life changes										

OUTCOME: SHBG						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/ L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

Azadi-Yazdi et al., 2016	nmol/L	ELISA	Baseline intervention mean: 28.93 Post-intervention mean difference: 28.80	Baseline intervention SD: 18.08 Mean difference SD: 21.71	28	Baseline control mean: 38.88 Post-intervention control mean difference: 11.66	Baseline control SD: 20.8 Post-intervention control mean difference: 18.82	27	Crude	Not Applicable
Foroozanfard et al., 2017	nmol/L	Commercial kit	Baseline intervention mean: 26.2 Post-intervention mean: 29.9 Change in mean intervention: 3.7	Baseline intervention SD: 16.8 Post-intervention SD: 17.1 Change in mean intervention SD: 8.5	30	Baseline control mean: 28.0 Post-intervention control mean: 26.5 Change in mean control: -1.5	Baseline control SD: 16.5 Post-intervention control mean difference: 16.0 Change in mean control SD: 7.2	30	Adjusted	Baseline values of biochemical variables, age and BMI
Gower et al., 2013	nm		Standard diet Baseline:50.1 Post intervention: 53.3	Baseline: 23.6 Post intervention: 23.9	23	Lower CHO diet Baseline: 50.5 Post intervention: 49.7	Baseline: 22.8 Post intervention: 25.6	27	Crude	Not Applicable
Kazemi et al., 2020	nmol/L	Solid-phase enzyme-labeled competitive chemiluminescent immunoassay	Baseline pulse mean: 28.3 Post-intervention 16 wk pulse mean: 41.2	Baseline pulse SD: 15.9 Post-intervention 16 wk pulse SD: 24.3	31	Baseline TLC mean: 31.2 Post-intervention 16 wk TLC mean: 38.5	Baseline TLC SD: 18.4 Post-intervention 16 wk TLC SD: 21.4	30	Crude	Not Applicable
Mehrabani 2013	nmol/l	Clinical laboratory assessment	CHCD Baseline: 26.9 Post intervention: 37.6 Change from baseline: 10.6	Baseline: 3.8 (SE) Post intervention: 4.6 (SE) Change from baseline: 4.1 (SE)	26	MHCD Baseline: 22.7 Post intervention: 31.4 Change from baseline: 8.8	Baseline: 4.0 (SE) Post intervention: 4.4 (SE) Change from baseline: 2.8 (SE)	23	Crude	NA
Wong et al., 2015	$nmol^{-l}$	Clinical laboratory assessment	Low-GL Baseline: 22.9 Post intervention: 21.4 Change from baseline: -1.5	Baseline: 9.4 Post intervention: 10.5 Change from baseline: -1.3 (SE)	10	Low-fat Baseline: 19.6 Post intervention: 22.0 Change from baseline: 2.4	Baseline: 11.9 Post intervention: 14.3 Change from baseline: -2.6	9	Crude	Not Applicable
Abbreviations: SHBG: sex hormone binding globulin, BMI: body mass index, ELISA: enzyme linked immunosorbent assay, TLC: therapeutic lifestyle changes, CHCD: Conventional hypocaloric diet, MHCD: modified hypocaloric diet.										

OUTCOME: Total testosterone	**OUTCOME TYPE:** Continuous

		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Azadi-Yazdi et al., 2016	**nmol/L**	**ELISA**	**Baseline intervention mean: 1.45 Post-intervention mean difference: -0.39**	**Baseline intervention SD: 0.77 Mean difference SD: 0.28**	**28**	**Baseline control mean: 1.02 Post-intervention control mean difference: -0.14**	**Baseline control SD: 0.20 Post-intervention control mean difference: 0.12**	**27**	**Crude**	**Not Applicable**
Foroozanfard et al., 2017	nmol/L	Commercial kit	Baseline intervention mean: 3.2 Post-intervention mean: 3.1 Change in mean intervention: -0.1	Baseline intervention SD: 1.8 Post-intervention SD: 1.5 Change in mean intervention SD: 0.5	30	Baseline control mean: 3.3 Post-intervention control mean: 3.4 Change in mean control: 0.1	Baseline control SD: 1.4 Post-intervention control mean SD: 1.3 Change in mean control SD: 0.4	30	Adjusted	Baseline values of biochemical variables, age and BMI
Gower et al., 2013	mM	Not Reported	Standard diet Baseline: 4.66 Post intervention:4.56	Baseline: 0.82 Post intervention: 0.78	23	Lower CHO diet Baseline: 4.75 Post intervention: 4.22	Baseline: 0.84 Post intervention: 0.65	27	Crude	Not Applicable
Kazemi et al., 2020	nmol/L	Solid-phase enzyme-labeled competitive chemiluminescent immunoassay	Baseline pulse mean: 1.8 Post-intervention 16 wk pulse mean: 1.4	Baseline pulse SD: 0.6 Post-intervention 16 wk pulse SD: 0.2	31	Baseline TLC mean: 1.7 Post-intervention 16 wk TLC mean: 1.2	Baseline TLC SD: 0.8 Post-intervention 16 wk TLC SD: 0.4	30	Crude	Not Applicable
Mehrabani et al., 2013	ng/mL	Not reported	CHCD Baseline:1.5 Post intervention: 1.1 Change from baseline: -0.4	Baseline: 0.2 (SE) Post intervention: 0.1 (SE) Change from baseline: 0.04 (SE)	26	MHCD Baseline: 1.8 Post intervention: 1.3 Change from baseline: -0.5	Baseline: 0.3 (SE) Post intervention: 0.2 (SE) Change from baseline: 0.2 (SE)	23	Crude	Not Applicable
Stamets et al., 2014	ng/dL	Not reported	Mean change high protein diet: -9	Mean change high protein diet SD: 20	13	Mean change high carbohydrate diet: -9	Mean change high carbohydrate diet SD: 18	13	Crude	Not Applicable

Wong et al., 2015	ng/dL	Clinical laboratory assessment (without further details)	Low-GL Baseline: 61.3 Post intervention: 60.0 Change from baseline: -1.3	Baseline: 30.1 Post intervention: 24.8 Change from baseline: 5.1	10	Low-fat Baseline: 55.2 Post intervention: 51.8 Change from baseline: -3.4	Baseline: 16.3 Post intervention: 19.7 Change from baseline: 4.6 (SE)	9	Crude	Not Applicable
Abbreviations: BMI: body mass index, ELISA: enzyme linked immunosorbent assay, TLC: therapeutic lifestyle changes, CHCD: conventional hypocaloric diet, MHCD: modified hypocaloric diet										

OUTCOME: FAI										**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Azadi-Yazdi et al., 2016	Not Applicable	Ratio of serum total testosterone divide by SHBG	Baseline intervention mean: 6.79 Post-intervention mean difference: -4.51	Baseline intervention SD: 4.83 Mean difference SD: 4.5	28	Baseline control mean: 3.45 Post-intervention control mean difference: -1.58	Baseline control SD: 2.17 Post-intervention control mean difference: 2.09	27	Crude	Not Applicable
Foroozanfard et al., 2017	Not Applicable	Ratio of total testosterone to SHBG	Baseline intervention mean: 0.20 Post-intervention mean: 0.16 Change in mean intervention: -0.03	Baseline intervention SD: 0.27 Post-intervention SD: 0.22 Change in mean intervention SD: 0.09	30	Baseline control mean: 0.20 Post-intervention control mean: 0.26 Change in mean control: 0.06	Baseline control SD: 0.28 Post-intervention control mean SD: 0.42 Change in mean control SD: 0.21	30	Adjusted	Baseline values of biochemical variables, age and BMI
Gower et al., 2013	Not Reported	Not Reported	Standard diet Baseline: 5.2	Baseline: 3.9	23	Lower CHO diet Baseline: 5.2	Baseline: 4.5	27	Crude	Not Applicable

			Post intervention: 4.8	Post intervention: 3.0		Post intervention: 4.3	Post intervention: 2.7			
Kazemi et al., 2020	Not Applicable	Formula (TT, nmol/L/ SHBG, nmol/L) × 100	Baseline pulse mean: 6 Post-intervention 16 wk pulse mean: 4	Baseline pulse SD: 4 Post-intervention 16 wk pulse SD: 1	31	Baseline TLC mean: 5 Post-intervention 16 wk TLC mean: 3	Baseline TLC SD: 4 Post-intervention 16 wk TLC SD: 2	30	Crude	Not Applicable
Mehrabani et al., 2013	Not Reported	Not Reported	CHCD Baseline: 6.6 Post intervention: 4.2 Change from baseline: -2.4	Baseline: 0.7 (SE) Post intervention: 0.5 (SE) Change from baseline: 0.5 (SE)	26	MHCD Baseline: 7.0 Post intervention: 5.1 Change from baseline: -1.9	Baseline: 0.9 (SE) Post intervention: 0.8 (SE) Change from baseline: 0.7 (SE)	23	Crude	Not Applicable
Abbreviations: FAI: free androgen index, BMI: body mass index, SHBG: sex hormone binding globulin, TLC: therapeutic lifestyle changes, TT: total testosterone, CHCD: Conventional hypocaloric diet, MHCD: modified hypocaloric diet										

OUTCOME: Bioavailable testosterone							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Stamets et al., 2014	ng/dL	Not reported	Mean change high protein diet: -3	Mean change high protein diet SD: 7	13	Mean change high carbohydrate diet: -3	Mean change high carbohydrate diet SD: 6	13	Crude	Not Applicable
Wong et al., 2015	ng/dL	Clinical laboratory assessment (without further details)	Low-GL Baseline: 13.6 Post intervention: 14.3 Change from baseline: 0.4	Baseline:4.8 Post intervention: 7.4 Change from baseline: 1.5 (SE)	10	Low-fat Baseline: 14.7 Post intervention: 12.9 Change from baseline: -1.8	Baseline: 8.5 Post intervention: 7.4 Change from baseline: 1.6 (SE)	9	Crude	Not Applicable

Abbreviations: BMI: body mass index, ELISA: enzyme linked immunosorbent assay, TLC: therapeutic lifestyle changes

OUTCOME: Free testosterone						**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable):										
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Wong et al., 2015	direct; pg ml^{-1})	Clinical laboratory assessment (without further details)	Low-GL Baseline: 1.8 Post intervention: 1.7 Change from baseline: -0.1	1.0 0.8 0.2 (SE)	10	Low-fat Baseline: 1.6 Post intervention: 1.2 Change from baseline: -0.4	Baseline:0.9 Post intervention: 0.4 Change from baseline: 0.3 (SE)	9	Crude	Not Applicable

OUTCOME: Ferriman-Gallwey score						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Stamets et al., 2014	Not Applicable	Not reported	Mean change high protein diet: 2	Mean change high protein diet SD: 3	13	Mean change high carbohydrate diet: -1	Mean change high carbohydrate diet SD: 4	13	Crude	Not Applicable

Abbreviations: BMI: body mass index, ELISA: enzyme linked immunosorbent assay, TLC: therapeutic lifestyle changes

OUTCOME: Dehydroepiandrosterone sulphate (DHEAS)						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg,**	**Method of measurement**	**Mean (specify if median) in intervention/**	**SD (or specify if other measure:**	**Sample size (n within this group)**	**Mean (specify if median) or median in control /**	**SD (or specify if other measure: SE,**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

	mmol/L, etc.)		**exposure group**	**IQR, SE or 95% CI) in intervention / exposure group**		**comparison group**	**IQR or 95% CI) in control/ comparison group**			
Mehrabani et al., 2013	ng/mL	Clinical laboratory assessment (without further details)	CHCD Baseline: 330.1 Post intervention: 298.1 Change from baseline: -32.0	30.6 (SE) 28.9 (SE) 8.9 (SE)	26	MHCD Baseline: 314.9 Post intervention: 272.8 Change from baseline: -42.1	31.9 (SE) 28.9 (SE) 16.1 (SE)	23	Crude	Not Applicable
Panico et al., 2014	µg/dL	Not reported	Diet A Baseline: 211.2 Post intervention: 184.4	35.8 20.8	Not reported	Diet B Baseline: 211.2 Post intervention: 201.1	35.8 76.2	NOT REPORTED	Crude	Not Applicable
Stamets et al., 2014	ng/mL	Not reported	Mean change high protein diet: 100	Mean change high protein diet SD: 390	13	Mean change high carbohydrate diet: 220	Mean change high carbohydrate diet SD: 185	13	Crude	Not Applicable
Wong et al., 2015	µg/dL	Clinical laboratory assessment (without further details)	Low-GL Baseline: 232.5 Post intervention: 161.4 Change from baseline: 28.9	129.3 147.4 19.7	10	Low-fat Baseline: 273.7 Post intervention: 268.4 Change from baseline: -5.3	135.7 126.4 22.8	9	Crude	Not Applicable
CHCD: Conventional hypocaloric diet, MHCD: modified hypocaloric diet										

OUTCOME: Androstenedione							OUTCOME TYPE: Continuous			
COMPARISON (if applicable):										
Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or Crude?	If adjusted, what variables were included in the model?

Panico et al., 2014	ng/mL		Diet A Baseline: 3.5 Post intervention: 3.8	Baseline: 0.9 Post intervention: 1.2	Not Reported	Diet B Baseline: 3.5 Post intervention: 3.3	Baseline: 0.9 Post intervention: 1.1	Not Reported	Crude	Not Applicable
Mehrabani et al., 2013	ng/dL	Clinical laboratory assessment (without further details)	CHCD Baseline: 1.9 Post intervention: 1.8 Change from baseline: -0.1	Baseline: 0.1 (SE) Post intervention: 0.2 (SE) Change from baseline: 0.1 (SE)	26	MHCD Baseline: 1.9 Post intervention: 1.8 Change from baseline: -0.1	Baseline: 0.1 (SE) Post intervention: 0.1 (SE) Change from baseline: 0.1 (SE)	23	Crude	Not Applicable

OUTCOME: FSH							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Foroozanfard et al., 2017	IU/L	ELISA	Baseline intervention mean: 5.5 Post-intervention mean: 5.6 Change in mean intervention: 0.1	Baseline intervention SD: 1.6 Post-intervention SD: 1.3 Change in mean intervention SD: 0.5	30	Baseline control mean: 5.3 Post-intervention control mean: 5.3 Change in mean control: 0.04	Baseline control SD: 1.4 Post-intervention control mean SD: 1.3 Change in mean control SD: 0.3	30	Adjusted	Baseline values of biochemical variables, age, and BMI
Gower et al., 2013	IU/L	Not Reported	Standard diet Baseline: 6.8 Post intervention: 6.9	Baseline: 3.5 Post intervention: 3.7	23	Lower CHO diet Baseline: 6.7 Post intervention: 6.6	Baseline: 2.5 Post intervention: 5.8	27	Crude	Not Applicable

Mehrabani et al., 2013	IU/L	Clinical laboratory assessment (without further details)	CHCD Baseline: 5.2 Post intervention: 4.5 Change from baseline: -0.7	Baseline: 0.6 (SE) Post intervention: 0.5 (SE) Change from baseline: 0.5 (SE)	26	MHCD Baseline: 5.6 Post intervention: 4.9 Change from baseline: -0.7	Baseline: 0.8 (SE) Post intervention: 0.6 (SE) Change from baseline: 0.9 (SE)	23	Crude	Not Applicable
Panico et al., 2014	mUI/mL	Not Reported	Diet A Baseline: 5.4 Post intervention: 5.5	Baseline: 2.8 1.1	Not Reported	Diet B Baseline: 5.4 Post intervention: 4.9	Baseline: 2.8 1.5	Not Reported	Crude	Not Applicable
Stamets et al., 2014	mIU/mL	Not reported	Mean change high protein diet: -1	Mean change high protein diet SD: 5	13	Mean change high carbohydrate diet: 2	Mean change high carbohydrate diet SD: 4	13	Crude	Not Applicable
Abbreviation: FSH: follicle stimulating hormone, ELISA: Enzyme-linked immunosorbent assay, CHCD: Conventional hypocaloric diet, MHCD: modified hypocaloric diet										

OUTCOME: LH									**OUTCOME TYPE:** Continuous	
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Foroozanfard et al., 2017	IU/L	ELISA	Baseline intervention mean: 6.0 Post-intervention mean: 5.7 Change in mean intervention: -0.3	Baseline intervention SD: 2.8 Post-intervention SD: 1.7 Change in mean intervention SD: 1.6	30	Baseline control mean: 6.9 Post-intervention control mean: 6.7 Change in mean control: -0.2	Baseline control SD: 3.4 Post-intervention control mean SD: 3.3 Change in mean control SD: 0.6	30	Adjusted	Baseline values of biochemical variables, age and BMI
Gower et al., 2013	IU/L	Not Reported	Standard diet Baseline: 9.0 Post intervention: 14.1	Baseline: 7.7	23	Lower CHO diet Baseline: 9.7 Post intervention: 8.4	Baseline: 7.7 Post intervention: 5.8	27	Crude	Not Applicable

				Post intervention: 17.2						
Mehrabani et al., 2013	IU/L	Clinical laboratory assessment (without further details)	CHCD Baseline: 2.9 Post intervention: 2.3 Change from baseline: -0.6	Baseline: 0.4 (SE) Post intervention: 0.4 (SE) Change from baseline: 0.4 (SE)	26	MHCD Baseline: 2.2 Post intervention: 2.6 Change from baseline: 0.4	Baseline: 0.2 (SE) Post intervention: 0.5 (SE) Change from baseline: 0.6 (SE)	23	Crude	Not Applicable
Panico et al., 2014	mUI/mL	Not Reported	Diet A Baseline: 11.9 Post intervention: 6.6	Baseline: 15.3 Post intervention: 3.9	Not Reported	Diet B Baseline: 11.9 Post intervention: 6.2	Baseline: 15.3 Post intervention: 2.7	Not Reported	Crude	Not Applicable
Stamets et al., 2014	mIU/mL	Not reported	Mean change high protein diet: 7	Mean change high protein diet SD: 30	13	Mean change high carbohydrate diet: 2	Mean change high carbohydrate diet SD: 11	13	Crude	Not Applicable
Abbreviation: LH: luteinizing hormone, ELISA: Enzyme-linked immunosorbent assay, CHCD: Conventional hypocaloric diet, MHCD: modified hypocaloric diet										

OUTCOME: Progesterone					**OUTCOME TYPE: Continuous**					
COMPARISON (if applicable):										
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or Crude?**	**If adjusted, what variables were included in the model?**
Panico et al., 2014	ng/mL	Not Reported	Diet A Baseline: 0.6 Post intervention: 0.5	Baseline: 0.4 Post intervention: 0.2	Not Reported	Diet B Baseline: 0.6 Post intervention: 0.5	Baseline: 0.4 Post intervention: 0.2	Not Reported	Crude	Not Applicable

OUTCOME: AMH						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable):								
Author, year	**Unit of outcome**	**Method of measurement**	**Mean (specify if**	**SD (or specify if other measure:**	**Sample size (n**	**Mean (specify if median) or**	**SD (or specify if other measure:**	**Sample size (n**	**Are these values**	**If adjusted, what**

	(e.g. g, mg, µg, mmol/L, etc.)		median) in intervention/ exposure group	IQR, SE or 95% CI) in intervention / exposure group	within this group)	median in control / comparison group	SE, IQR or 95% CI) in control/ comparison group	within this group)	adjusted or crude?	variables were included in the model?
Foroozanfard et al., 2017	ng/mL	ELISA	Baseline intervention mean: 8.5 Post-intervention mean: 7.4 Change in mean intervention: -1.1	Baseline intervention SD: 5.2 Post-intervention SD: 4.4 Change in mean intervention SD: 3.1	30	Baseline control mean: 7.6 Post-intervention control mean: 7.9 Change in mean control: -0.04	Baseline control SD: 4.6 Post-intervention control mean SD: 4.6 Change in mean control SD: 0.22	30	Adjusted	Baseline values of biochemical variables, age and BMI
Abbreviations: AMH: anti-müllerian hormone, ELISA: Enzyme-linked immunosorbent assay										

OUTCOME: Glucose (fasting)							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Foroozanfard et al., 2017	mmol/L	Commercial kit	Baseline intervention mean: 5.00 Post-intervention mean: 4.89 Change in mean intervention: -0.11	Baseline intervention SD: 0.36 Post-intervention SD: 0.36 Change in mean intervention SD: 0.41	30	Baseline control mean: 4.92 Post-intervention control mean: 4.88 Change in mean control: -0.04	Baseline control SD: 0.21 Post-intervention control mean SD: 0.30 Change in mean control SD: 0.22	30	Adjusted	Baseline values of biochemical variables, age, and BMI
Gower et al., 2013	mM	Not Reported	Standard diet Baseline: 5.18 Post intervention: 5.17	Baseline: 0.55 Post intervention: 0.59	23	Lower CHO diet Baseline: 5.30 Post intervention: 5.04	Baseline: 0.47 Post intervention: 0.47	27	Crude	Not Applicable
Hoover et al., 2021	mg/dL	Glucose oxidase method	Low GL Pre-intervention mean at 0 minutes: 94.08	Low GL Pre-intervention at 0 minutes SD: 8.54	Low GL: Not Reported	High GL Pre-intervention	High GL Pre-intervention at 0	High GL: Not Reported	Crude	Not Applicable

			Low GL Post-intervention mean at 240 minutes: 95.25	Low GL Post-intervention at 240 minutes SD: 9.41	Sample population: 30	mean at 0 minutes: 92.73 High GL Post-intervention mean at 240 minutes: 92.79	minutes SD: 9.40 High GL Post-intervention at 240 minutes SD: 11.78	Sample population: 30		
Hosseini Marnani et al., 2021	mg/dL	Enzymatic method	Baseline SDF mean: 94.81 Post-intervention SDF mean: 96.90 Baseline HPF mean: 99.40 Post-intervention HPF mean: 100.92 Baseline HPP mean: 108.26 Post-intervention HPP mean: 104.35	Baseline SDF SD: 7.89 Post-intervention SDF SD: 9.92 Baseline HPF SD: 9.41 Post-intervention HPF SD: 11.02 Baseline HPP SD: 34.37 Post-intervention HPP SD: 31.72	SDF: 11 HPF: 15 HPP: 15	Baseline SDP mean: 107.33 Post-intervention SDP mean: 104.60	Baseline SDP SD: 15.65 Post-intervention SDP SD: 15.79	SDP: 15	Crude	Not Applicable
Kazemi et al., 2018	mmol/L	Commercial kit	Baseline pulse-diet mean: 5.0 Post-intervention pulse-diet mean: 4.6 Mean change pulse-diet: -0.4	Baseline pulse-diet SD: 1.5 Post-intervention pulse-diet SD: 1.3 Mean change pulse-diet SD: 1.7	31	Baseline TLC-diet mean: 5.6 Post-intervention TLC-diet mean: 4.8 Mean change TLC-diet: -0.8	Baseline TLC-diet SD: 1.4 Post-intervention TLC-diet SD: 1.6 Mean change TLC-diet SD: 1.5	30	Crude	Not Applicable
Moran et al., 2003	mmol/L	Not Reported	Baseline HPLC diet mean: 5.52 12-wk post intervention HPLC diet mean: 5.42 16-wk post intervention HPLC diet mean: 5.57	Baseline HPLC diet mean: 0.12 12-wk post intervention HPLC diet mean: 0.13 16-wk post intervention HPLC diet mean: 0.13	14	Baseline LPHC diet mean: 5.66 12-wk post intervention LPHC diet mean: 5.31 16-wk post intervention LPHC diet mean: 5.53	Baseline LPHC diet mean: 0.27 12-wk post intervention LPHC diet mean: 0.17 16-wk post intervention LPHC diet mean: 0.21	14	Crude	Not Applicable
Panico et al., 2014	mg/dL		Diet A Baseline: 74.0 Post intervention: 78.0	Baseline: 3.3 Post intervention: 7.7	Not Reported	Diet B Baseline: 74.0 Post intervention: 75.4	Baseline: 3.3 Post intervention: 5.8	Not Reported	Crude	Not Applicable

Toscani et al., 2011	mg/dL	Not reported	Post-intervention high protein diet mean: 90.5	Post-intervention high protein diet SD: 7.23	9	Post-intervention normal protein diet mean: 89.78	Post-intervention normal protein diet SD: 6.38	9	Crude	Not Applicable
Wong et al., 2015	mg/dL	Clinical laboratory assessment (without further details)	Low-GL Baseline: 80.9 Post intervention: 81.0 Change from baseline: 0.1	Baseline:4.0 Post intervention: 4.0 Change from baseline: 2.2 (SE)	10	Low-fat Baseline: 80.3 Post intervention: 78.7 Change from baseline: -1.6	Baseline: 6.9 Post intervention: 7.4 Change from baseline:1.5 (SE)	9	Crude	Not Applicable
Abbreviations: BMI: body mass index, ELISA: enzyme linked immunosorbent assay, GL: glycemic load, HPF: high protein diet+fennel, HPP: high protein diet+placebo, SDF: standard diet+fennel, SDP: standard diet+placebom, TLC: therapeutic lifestyle changes; HPLC, high protein low-carbohydrate diet; LPHC, low-protein high-carbohydrate diet.										

OUTCOME: Glucose (120-min)						**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable):										
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or Crude?**	**If adjusted, what variables were included in the model?**
Panico et al., 2014	mg/dL	Not Reported	Diet A Baseline: 89.7 Post intervention: 78.6	Baseline: 9.0 Post intervention: 3.7	Not Reported	Diet B Baseline: 89.7 Post intervention: 96.3	Baseline: 9.0 Post intervention: 9.6	Not Reported	Crude	Not Applicable
Wong et al., 2015	mg/dL	Clinical laboratory assessment (without further details)	Low-GL Baseline: 129.3 Post intervention: 122.7 Change from baseline: -5.7	Baseline: 8.6 Post intervention: 11.9 Change from baseline: 3.8 (SE)	10* 6*	Low-fat Baseline: 124.7 Post intervention: 122.8 Change from baseline: -1.9	Baseline: 23.0 Post intervention: 28.9 Change from baseline: 6.3 (SE)	9	Crude	Not Applicable
*At baseline, data were available for 15 participants (9 in low-fat group, 6 in low-GL group)										

OUTCOME: Glucose area under the curve										**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Stamets et al., 2014	Not Reported	Area under the curve morning 3hr oral glucose tolerance test (OGTT) Area under the curve morning 3hr OGTT	Mean change high protein diet: -87 Mean change high protein diet: -2912	Mean change high protein diet SD: 2803 Mean change high protein diet SD: 13562	13	Mean change high carbohydrate diet: -93 Mean change high carbohydrate diet: -8734	Mean change high carbohydrate diet SD: 2049 Mean change high carbohydrate diet SD: 12218	13	Crude	Not Applicable
Toscani et al., 2011	mg/dL	2 hour OGTT glucose	Post-intervention high protein diet mean: 124.62	Post-intervention high protein diet SD: 35.98	9	Post-intervention normal protein diet mean: 119.68	Post-intervention normal protein diet SD: 39	9	Crude	Not Applicable
Wong et al., 2015	Not Applicable	2 hour OGTT glucose	Low-GL Baseline: 97.9 Post intervention: 109.5 Change from baseline: 11.6	 Baseline: 29.5 Post intervention: 20.3 Change from baseline: 11.5	10	Low-fat Baseline: 100.7 Post intervention: 90.5 Change from baseline: -10.2	 Baseline: 31.4 Post intervention: 22.0 Change from baseline: 8.5 (SE)	9	Crude	Not Applicable
Abbreviations: BMI: body mass index, ELISA: enzyme linked immunosorbent assay, GL: glycemic load, HPF: high protein diet+fennel, HPP: high protein diet+placebo, SDF: standard diet+fennel, SDP: standard diet+placebom, TLC: therapeutic lifestyle changes										

OUTCOME: Insulin (fasting)										**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg,**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjuste**	**If adjusted, what variables were**

	mmol/L, etc.)								d or crude?	included in the model?
Foroozanfard et al., 2017	pmol/L	ELISA	Baseline intervention mean: 81.0 Post-intervention mean: 55.8 Change in mean intervention: -25.2	Baseline intervention SD: 51.6 Post-intervention SD:27.0 Change in mean intervention SD: 51.0	30	Baseline control mean: 73.8 Post-intervention control mean: 72.6 Change in mean control: -1.2	Baseline control SD: 46.8 Post-intervention control mean SD: 25.2 Change in mean control SD: 28.8	30	Adjusted	Baseline values of biochemical variables, age, and BMI
Gower et al., 2013	pM	Not Reported	Standard diet Baseline: 48.0 Post intervention: 37.2	Baseline: 42.6 Post intervention: 23.4	23	Lower CHO diet Baseline: 58.8 Post intervention: 43.2	Baseline: 47.4 Post intervention: 32.4	27	Crude	Not Applicable
Hoover et al., 2021	µIU/mL	Immunofluorescence on a TOSOH AIA-II analyzer	Low GL Pre-intervention mean at 0 minutes: 9.24 Low GL Post-intervention mean at 240 minutes: 15.03	Low GL Pre-intervention at 0 minutes SD: 5.78 Low GL Post-intervention at 240 minutes SD: 14.52	Low GL: Not Reported Sample population: 30	High GL Pre-intervention mean at 0 minutes: 8.07 High GL Post-intervention mean at 240 minutes: 14.23	High GL Pre-intervention at 0 minutes SD: 6.40 High GL Post-intervention at 240 minutes SD: 13.60	High GL: Not Reported Sample population: 30	Crude	Not Applicable
Hosseini Marnani et al., 2021	micIU/mL	ELISA	Baseline SDF mean: 17.11 Post-intervention SDF mean: 11.76 Baseline HPF mean: 15.62 Post-intervention HPF mean: 11.51 Baseline HPP mean: 15.71 Post-intervention HPP mean: 13.57	Baseline SDF SD: 8.74 Post-intervention SDF SD: 6.42 Baseline HPF SD: 7.42 Post-intervention HPF SD: 4.28 Baseline HPP SD: 7.38 Post-intervention HPP SD: 7.87	SDF: 11 HPF: 15 HPP: 15	Baseline SDP mean: 16.03 Post-intervention SDP mean: 11.53	Baseline SDP SD: 8.48 Post-intervention SDP SD: 5.39	SDP: 15	Crude	Not Applicable
Kazemi et al., 2018	μIU/mL	ELISA	Baseline pulse-diet mean: 14.0 Post-intervention pulse-diet mean: 10.0 Mean change pulse-diet: -4.0	Baseline pulse-diet SD: 11.4 Post-intervention pulse-diet SD: 7.7 Mean change pulse-diet SD: 9.7	31	Baseline TLC-diet mean: 15.7 Post-intervention TLC-diet mean: 12.7 Mean change TLC-diet: -3.0	Baseline TLC-diet SD: 12.4 Post-intervention TLC-diet SD: 10.3 Mean change TLC-diet SD: 6.8	30	Crude	Not Applicable
Mehrabani et al., 2013	mu/mL	Clinical laborator	CHCD Baseline: 12.2	Baseline: 6.0 (SE)	26	MHCD Baseline: 12.1	Baseline: 3.3 (SE)	23	Crude	Not Applicable

		y assessment (without further details)	Post intervention: 11.2 Change from baseline: -1.0	Post intervention: 5.3 (SE) Change from baseline: 0.7 (SE)		Post intervention: 8.4 Change from baseline: -3.6	Post intervention: 3.7 (SE) Change from baseline: 0.7 (SE)			
Moran et al., 2003	mU/L	Not Reported	Baseline HPLC diet mean: 23 12-wk post intervention HPLC diet mean: 16.6 16-wk post intervention HPLC diet mean: 15.4	Baseline HPLC diet mean: 2.4 12-wk post intervention HPLC diet mean: 2.4 16-wk post intervention HPLC diet mean: 1.8	14	Baseline LPHC diet mean: 16.9 12-wk post intervention LPHC diet mean: 12.8 16-wk post intervention LPHC diet mean: 13.5	Baseline LPHC diet mean: 2.5 12-wk post intervention LPHC diet mean: 2.0 16-wk post intervention LPHC diet mean: 2.1	14	Crude	Not Applicable
Panico et al., 2014	µu/mL	Not Reported	Diet A Baseline: 14.4 Post intervention: 9.2	Baseline: 13.3 Post intervention: 6.4	NOT REPORTED	Diet B Baseline: 14.4 Post intervention: 5.9	Baseline: 13.3 Post intervention: 2.0	Not Reported	Crude	Not Applicable
Wong et al., 2015	µIu/mL	Clinical laboratory assessment (without further details)	Low-GL Baseline: 16.4 Post intervention: 18.8 Change from baseline: 2.4	Baseline: 7.5 Post intervention: 15.6 Change from baseline: 5.2 (SE)	10	Low-fat Baseline: 13.2 Post intervention: 10.3 Change from baseline: -2.9	Baseline: 5.7 Post intervention: 7.0 Change from baseline: 1.4 (SE)	9	Crude	Not Applicable

Abbreviations: BMI: body mass index, ELISA: enzyme linked immunosorbent assay, GL: glycemic load, HPF: high protein diet+fennel, HPP: high protein diet+placebo, SDF: standard diet+fennel, SDP: standard diet+placebo, TLC: therapeutic lifestyle changes, CHCD: Conventional hypocaloric diet, MHCD: modified hypocaloric diet; HPLC, high protein low-carbohydrate diet; LPHC, low-protein high-carbohydrate diet.

OUTCOME: Insulin (120-mins)							**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable):										
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or Crude?**	**If adjusted, what variables were included in the model?**

Panico et al., 2014	µu/mL	Not Reported	Diet A Baseline: 44.9 Post intervention: 18.4	Baseline: 24.0 Post intervention: 10.3	Not Reported	Diet B Baseline: 44.9 Post intervention: 30.4	Baseline: 24.0 Post intervention: 13.6	Not Reported	Crude	Not Applicable
Wong et al., 2015	µIu/mL	Clinical laboratory assessment (without further details)	Low-GL Baseline: 131.8 Post intervention: 115.7 Change from baseline: -21.7	Baseline: 98.4 Post intervention: 68.0 Change from baseline: 29.1	10* 7	Low-fat Baseline: 98.2 Baseline:96.9 Change from baseline: 5.5	Baseline: 72.2 Post intervention: 84.5 Change from baseline: 26.8	9* 8	Crude	Not Applicable
*At baseline, data were available for 15 participants (9 in low-fat group, 6 in low-GL group). At 6 months, data were available for 15 participants (8 in low-fat group, 7 in low-GL group).										

OUTCOME: Insulin iAUC (incremental area under the 2-h FS-OGTT curve)										**OUTCOME TYPE:** Continuous
COMPARISON (if applicable):										
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size**	**Are these values adjusted or Crude?**	**If adjusted, what variables were in the model?**
Wong et al., 2015	Not Applicable	Not Reported	Low-GL Baseline: 281.6 Post intervention: 230.0 Change from baseline: -51.6	Baseline: 242.8 Post intervention: 127.7 Change from baseline:53.8 (SE)	10	Low-fat Baseline: 175.5 Post intervention: 143.8 Change from baseline: -31.7	Baseline: 72.0 Post intervention: 82.3 Change from baseline: 17.7 (SE)	9	Crude	Not Applicable

OUTCOME: HbA1c										**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable):								
Author, year	**Unit of outcome**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**

Kazemi et al., 2018	%	ELISA	Baseline pulse-diet mean: 5.3 Post-intervention pulse-diet mean: 5.2 Mean change pulse-diet: -0.1	Baseline pulse-diet SD: 0.4 Post-intervention pulse-diet SD: 0.4 Mean change pulse-diet SD: 0.3	31	Baseline TLC-diet mean: 5.3 Post-intervention TLC-diet mean: 5.3 Mean change TLC-diet: 0.0	Baseline TLC-diet SD: 0.5 Post-intervention TLC-diet SD: 0.4 Mean change TLC-diet SD: 0.3	30	Crude	Not Applicable
Wong et al., 2015	%	Not Reported	Low-GL Baseline: 5.7 Post intervention: 5.7 Change from baseline: -0.0	Baseline: 0.3 Post intervention: 0.2 Change from baseline: 0.1 (SE)	10	Low-fat Baseline: 5.5 Post intervention: 5.3 Change from baseline: -0.1	Baseline: 0.3 Post intervention: 0.3 Change from baseline: 0.1 (SE)	9	Crude	Not Applicable
Abbreviations: ELISA: Enzyme-linked immunosorbent assay, TLC: therapeutic lifestyle changes										

OUTCOME: HOMA-IR									**OUTCOME TYPE:** Continuous	
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Foroozanfard et al., 2017	Not Applicable	Formula	Baseline intervention mean: 3.0 Post-intervention mean: 2.1 Change in mean intervention: -0.9	Baseline intervention SD: 2.0 Post-intervention SD: 1.0 Change in mean intervention SD: 2.0	30	Baseline control mean: 2.7 Post-intervention control mean: 2.6 Change in mean control: -0.1	Baseline control SD: 1.6 Post-intervention control mean SD: 0.9 Change in mean control SD: 1.0	30	Adjusted	Baseline values of biochemical variables, age and BMI
Gower et al., 2013	Not Reported	Not Reported	Standard diet Baseline: 1.9 Post intervention: 1.5	Baseline: 1.8 Post intervention: 1.1	23	Lower CHO diet Baseline: 2.4 Post intervention: 1.7	Baseline: 2.1 Post intervention: 1.4	27	Crude	Not Applicable
Hosseini Marnani et al., 2021	mg/dL	Enzymatic method (formula)	Baseline SDF mean: 4.01	Baseline SDF SD: 2.18	SDF: 11 HPF: 15 HPP: 15	Baseline SDP mean: 4.18	Baseline SDP SD: 2.01	SDP: 15	Crude	Not Applicable

			Post-intervention SDF mean: 2.85 Baseline HPF mean: 3.94 Post-intervention HPF mean: 2.84 Baseline HPP mean: 4.10 Post-intervention HPP mean: 3.43	Post-intervention SDF SD: 1.85 Baseline HPF SD: 2.10 Post-intervention HPF SD: 1.08 Baseline HPP SD: 2.20 Post-intervention HPP SD: 2.00		Post-intervention SDP mean: 2.92	Post-intervention SDP SD: 1.33			
Kazemi et al., 2018	Not Applicable	Index	Baseline pulse-diet mean: 3.1 Post-intervention pulse-diet mean: 2.1 Mean change pulse-diet: -1.0	Baseline pulse-diet SD: 2.5 Post-intervention pulse-diet SD: 1.9 Mean change pulse-diet SD: 2.1	31	Baseline TLC-diet mean: 4.2 Post-intervention TLC-diet mean: 2.9 Mean change TLC-diet: -1.3	Baseline TLC-diet SD: 4.4 Post-intervention TLC-diet SD: 3.6 Mean change TLC-diet SD: 2.1	30	Crude	Not Applicable
Mehrabani et al., 2013	mu/ml	Not Reported	CHCD Baseline: 2.9 Post intervention: 2.7 Change from baseline: -0.3	Baseline: 1.6 (SE) Post intervention: 1.5 (SE) Change from baseline: 0.2 (SE)	26	MHCD Baseline: 2.9 Post intervention: 2.0 Change from baseline: -0.8	Baseline: 1.4 (SE) Post intervention: 0.9 (SE) Change from baseline: 0.2 (SE)	23	Crude	Not Applicable
Moran et al., 2003	mU/L	Not Reported	Baseline HPLC diet mean: 0.33 12-wk post intervention HPLC diet mean: 0.28 16-wk post intervention HPLC diet mean: 0.29	Baseline HPLC diet mean: 0.02 12-wk post intervention HPLC diet mean: 0.02 16-wk post intervention HPLC diet mean: 0.02	14	Baseline LPHC diet mean: 0.29 12-wk post intervention LPHC diet mean: 0.25 16-wk post intervention LPHC diet mean: 0.27	Baseline LPHC diet mean: 0.03 12-wk post intervention LPHC diet mean: 0.02 16-wk post intervention LPHC diet mean: 0.02	14	Crude	Not Applicable
Panico et al., 2014	Not Reported	Not Reported	Diet A Baseline: 2.5	Baseline: 2.3	Not Reported	Diet B Baseline: 2.5	Baseline: 2.3	Not Reported	Crude	Not Applicable

			Post intervention: 1.7	Post intervention: 1.2		Post intervention: 1.1	Post intervention: 0.4			
Abbreviations: BMI: body mass index, HOMA-IR: homeostatic model assessment for insulin resistance, HPF: high protein diet+fennel, HPP: high protein diet+placebo, SDF: standard diet+fennel, SDP: standard diet+placebo, TLC: therapeutic lifestyle changes, CHCD: Conventional hypocaloric diet, MHCD: modified hypocaloric diet; HPLC, high protein low-carbohydrate diet; LPHC, low-protein high-carbohydrate diet.										

OUTCOME: Insulin sensitivity with QUICKI									**OUTCOME TYPE:** Continuous	
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Foroozanfard et al., 2017	Not Applicable	Formula	Baseline intervention mean: 0.33 Post-intervention mean: 0.35 Change in mean intervention:0.01	Baseline intervention SD: 0.03 Post-intervention SD: 0.02 Change in mean intervention SD: 0.03	30	Baseline control mean: 0.33 Post-intervention control mean: 0.33 Change in mean control: -0.004	Baseline control SD: 0.02 Post-intervention control mean SD: 0.01 Change in mean control SD: 0.01	30	Adjusted	Baseline values of biochemical variables, age, and BMI
Abbreviations: BMI: body mass index, QUICKI: quantitative insulin sensitivity check index										

OUTCOME: Fasting glucose to insulin ratio									**OUTCOME TYPE:** Continuous	
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Stamets et al., 2014	Not Applicable	Not Reported	Mean change high protein diet: 1	Mean change high protein diet SD: 2	13	Mean change high carbohydrate diet: 1	Mean change high carbohydrate diet SD: 2	13	Crude	Not Applicable

OUTCOME: Insulin sensitivity index*						**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable):										
Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or Crude?	If adjusted, what variables were included in the model?
Gower et al., 2013	Not Reported	Not Reported	Standard diet Baseline: 6.9 Post intervention: 7.6	Baseline: 4.4 Post intervention: 4.8	23	Lower CHO diet Baseline: 6.4 Post intervention: 7.6	Baseline: 4.2 Post intervention: 5.0	27	Crude	Not Applicable
* Insulin sensitivity index = 10 000/√[(mean fasting insulin 9 mean fasting glucose) X (mean post challenge insulin x mean post challenge glucose)].										

OUTCOME: SBP (systolic blood pressure)						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Kazemi et al., 2018	mmHg	Sphygmomanometer and a stethoscope	Baseline pulse-diet mean: 116 Post-intervention pulse-diet mean: 113 Mean change pulse-diet: -3	Baseline pulse-diet SD: 7 Post-intervention pulse-diet SD: 10 Mean change pulse-diet SD: 8	31	Baseline TLC-diet mean: 118 Post-intervention TLC-diet mean: 113 Mean change TLC-diet: -5	Baseline TLC-diet SD: 10 Post-intervention TLC-diet SD: 10 Mean change TLC-diet SD: 8	30	Crude	Not Applicable
Stamets et al., 2014	mmHg	Not Reported	Mean change high protein diet: -4	Mean change high protein diet SD: 13	13	Mean change high carbohydrate diet: -3	Mean change high carbohydrate diet SD: 13	13	Crude	Not Applicable
Wong et al., 2015	mmHg	Not Reported	Low-GL Baseline: 101.0	Baseline: 4.9	10	Low-fat Baseline: 101.6	Baseline: 6.9	9	Crude	Not Applicable

			Post intervention: 102.8 Change from baseline: 1.8	Post intervention: 5.9 Change from baseline: 2.5 (SE)		Post intervention: 102.8 Change from baseline: 1.1	Post intervention: 5.2 Change from baseline: 2.3 (SE)			
Abbreviations: TLC: therapeutic lifestyle changes										

OUTCOME: DBP (diastolic blood pressure)							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Kazemi et al., 2018	mmHg	Sphygmomanometer and a stethoscope	Baseline pulse-diet mean: 77 Post-intervention pulse-diet mean: 74 Mean change pulse-diet: -3	Baseline pulse-diet SD: 7 Post-intervention pulse-diet SD: 8 Mean change pulse-diet SD: 7	31	Baseline TLC-diet mean: 77 Post-intervention TLC-diet mean: 77 Mean change TLC-diet: 0	Baseline TLC-diet SD: 9 Post-intervention TLC-diet SD: 10 Mean change TLC-diet SD: 7	30	Crude	Not Applicable
Stamets et al., 2014	mmHg	Not reported	Mean change high protein diet: 0	Mean change high protein diet SD: 18	13	Mean change high carbohydrate diet: 0	Mean change high carbohydrate diet SD: 11	13	Crude	Not Applicable
Wong et al., 2015	mmHg	Not Reported	Low-GL Baseline: 64.8 Post intervention: 63.4 Change from baseline: -1.4	Baseline: 4.6 Post intervention: 3.5 Change from baseline: 1.3 (SE)	10	Low-fat Baseline: 62.6 Post intervention: 62.1 Change from baseline: -0.4	Baseline: 7.1 Post intervention: 5.6 Change from baseline: 2.4 (SE)	9	Crude	Not Applicable
Abbreviations: TLC: therapeutic lifestyle changes										

OUTCOME: Total body fat mass			**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable):	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Azadi-Yazdi et al., 2016	kg	Body composition analyser	Baseline intervention mean: 32.40 Post-intervention mean difference: -3.23	Baseline intervention SD: 9.32 Mean difference SD: 1.66	28	Baseline control mean: 30.35 Post-intervention control mean difference: -2.13	Baseline control SD: 8.28 Post-intervention control mean difference: 1.26	27	Crude	Not Applicable
Kazemi et al., 2018	kg	Whole-body scan by dual-energy X-ray absorptiometry	Baseline pulse-diet mean: 36.3 Post-intervention pulse-diet mean: 34.6 Mean change pulse-diet: -1.7	Baseline pulse-diet SD: 13.5 Post-intervention pulse-diet SD: 13.8 Mean change pulse-diet SD: 2.4	31	Baseline TLC-diet mean: 40.5 Post-intervention TLC-diet mean: 37.5 Mean change TLC-diet: -3.0	Baseline TLC-diet SD: 15.0 Post-intervention TLC-diet SD: 15.3 Mean change TLC-diet SD: 7.5	30	Crude	Not Applicable
Abbreviations: TLC: therapeutic lifestyle changes										

OUTCOME: Total body fat %									**OUTCOME TYPE:** Continuous	
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Hosseini Marnani et al., 2021	%	Omron digital scale	Baseline SDF mean: 42.79 Post-intervention SDF mean: 40.95 Baseline HPF mean: 44.71	Baseline SDF SD: 5.36 Post-intervention SDF SD: 4.91 Baseline HPF SD: 7.71 Post-intervention HPF SD: 10.98	SDF: 11 HPF: 15 HPP: 15	Baseline SDP mean: 23.95 Post-intervention SDP mean: 25.51	Baseline SDP SD: 2.53 Post-intervention SDP SD: 2.39	15	Crude	Not Applicable

			Post-intervention HPF mean: 42.11 Baseline HPP mean: 46.35 Post-intervention HPP mean: 44.67	Baseline HPP SD: 4.86 Post-intervention HPP SD: 5.46						
Kazemi et al., 2018	%	Whole-body scan by dual-energy X-ray absorptiometry	Baseline pulse-diet mean: 41.1 Post-intervention pulse-diet mean: 40.1 Mean change pulse-diet: -1.0	Baseline pulse-diet SD: 7.2 Post-intervention pulse-diet SD: 7.8 Mean change pulse-diet SD: 2.0	31	Baseline TLC-diet mean: 41.4 Post-intervention TLC-diet mean: 40.4 Mean change TLC-diet: -1.0	Baseline TLC-diet SD: 8.7 Post-intervention TLC-diet SD: 8.5 Mean change TLC-diet SD: 2.4	30	Crude	Not Applicable
Wong et al., 2015	%	Not Reported	Low-GL Baseline: 46.3 Post intervention: 45.1 Change from baseline: -1.2	Baseline: 4.2 Post intervention: 4.6 Change from baseline: 0.4 (SE)	10	Low-fat Baseline: 45.1 Post intervention: 40.9 Change from baseline: -2.2	Baseline: 4.6 Post intervention: 3.5 Change from baseline: 0.5 (SE)	9	Crude	Not Applicable
Abbreviations: HPF: high protein diet+fennel, HPP: high protein diet+placebo, SDF: standard diet+fennel, SDP: standard diet+placebo, TLC: therapeutic lifestyle changes										

OUTCOME: Trunk fat mass										**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Kazemi et al., 2018	kg	Whole-body scan by dual-energy X-ray absorptiometry	Baseline pulse-diet mean: 16.0 Post-intervention pulse-diet mean: 14.9 Mean change pulse-diet: -1.1	Baseline pulse-diet SD: 6.8 Post-intervention pulse-diet SD: 6.4 Mean change pulse-diet SD: 2.0	31	Baseline TLC-diet mean: 19.3 Post-intervention TLC-diet mean: 17.3 Mean change TLC-diet: -2	Baseline TLC-diet SD: 8.3 Post-intervention TLC-diet SD: 8.1 Mean change TLC-diet SD: 3.9	30	Crude	Not Applicable

Abbreviation: TLC: therapeutic lifestyle changes

OUTCOME: Lean body mass						**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable):										
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Azadi-Yazdi et al., 2016	kg	Body composition analyzer	Baseline intervention: 48.61 Post-intervention mean difference: -0.82	Baseline intervention SD: 5.61 Mean difference SD: 1.64	28	Baseline control mean: 46.79 Post-intervention control mean difference: -0.51	Baseline control SD: 5.57 Post-intervention control mean difference: 1.27	27	Crude	Not Applicable
Hosseini Marnani et al., 2021	%	Omron digital scale	Baseline SDF mean: 25.34 Post-intervention SDF mean: 25.67 Baseline HPF mean: 24.16 Post-intervention HPF mean: 25.45 Baseline HPP mean: 23.43 Post-intervention HPP mean: 24.31	Baseline SDF SD: 25.67 Post-intervention SDF SD: 1.89 Baseline HPF SD: 4.01 Post-intervention HPF SD: 5.51 Baseline HPP SD: 2.22 Post-intervention HPP SD: 2.37	SDF: 11 HPF: 15 HPP: 15	Baseline SDP mean: 23.95 Post-intervention SDP mean: 25.51	Baseline SDP SD: 2.53 Post-intervention SDP SD: 2.39	SDP: 15	Crude	Not Applicable
Kazemi et al., 2018	kg	Whole-body scan by dual-energy X-ray absorptiometry	Baseline pulse-diet mean: 47.5 Post-intervention	Baseline pulse-diet SD: 8.1	31	Baseline TLC-diet mean: 49.5	Baseline TLC-diet SD: 9.1	30	Crude	Not Applicable

			pulse-diet mean: 46.8 Mean change pulse-diet: -0.7	Post-intervention pulse-diet SD: 8.1 Mean change pulse-diet SD: 2.2		Post-intervention TLC-diet mean: 49.7 Mean change TLC-diet: 0.2	Post-intervention TLC-diet SD: 9.3 Mean change TLC-diet SD: 14.1			
Abbreviations: BMI: body mass index, HPF: high protein diet+fennel, HPP: high protein diet+placebo, RIA: radioimmunoassay, SDF: standard diet+fennel, SDP: standard diet+placebo, TLC: therapeutic lifestyle changes										

OUTCOME: hsCRP										**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Kazemi et al., 2018	mg/L	Electrochemiluminescence immunoassay	Baseline pulse-diet mean: 4.2 Post-intervention pulse-diet mean: 3.9 Mean change pulse-diet: -0.3	Baseline pulse-diet SD: 3.8 Post-intervention pulse-diet SD: 4.8 Mean change pulse-diet SD: 3.4	31	Baseline TLC-diet mean: 5.0 Post-intervention TLC-diet mean: 5.0 Mean change TLC-diet: 0.0	Baseline TLC-diet SD: 6.4 Post-intervention TLC-diet SD: 8.2 Mean change TLC-diet SD: 4.2	30	Crude	Not Applicable
Wong et al., 2015	mg/l^{-1}	Clinical laboratory assessment (without further details)	Low-GL Baseline: 4.0 Post intervention: 3.3 Change from baseline: -0.7	Baseline: 4.1 Post intervention: 3.7 Change from baseline: 1.4 (SE)	10	Low-fat Baseline: 1.6 Post intervention: 2.1 Change from baseline: 0.5	Baseline: 1.5 Post intervention: 2.2 Change from baseline: 0.6 (SE)	9	Crude	Not Applicable
Abbreviations: hsCRP: high sensitivity C-reactive protein, TLC: therapeutic lifestyle changes										

OUTCOME: LH/FSH ratio										**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable):								
Author, year	**Unit of outcome**	**Method of measurement**	**Mean (specify if median) in**	**SD (or specify if other measure:**	**Sample size (n**	**Mean (specify if**	**SD (or specify if other**	**Sample size (n**	**Are these values**	**If adjusted, what**

	(e.g. g, mg, µg, mmol/L, etc.)		intervention/ exposure group	IQR, SE or 95% CI) in intervention / exposure group	within this group)	median) or median in control / comparison group	measure: SE, IQR or 95% CI) in control/ comparison group	within this group)	adjusted or crude?	variables were included in the model?
Kazemi et al., 2020	Not Applicable	Electrochemiluminescence immunoassay	Baseline pulse mean: 2.8 Post-intervention 16 wk pulse mean: 1.2	Baseline pulse SD: 1.5 Post-intervention 16 wk pulse SD: 0.9	31	Baseline TLC mean: 2.4 Post-intervention 16 wk TLC mean: 2.4	Baseline TLC SD: 1.0 Post-intervention 16 wk TLC SD: 0.9	30	Crude	Not Applicable
Abbreviations: LH/FSH: Luteinizing hormone/follicle stimulating hormone, TLC: therapeutic lifestyle changes										

OUTCOME: Total cholesterol										**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Moran et al., 2003	mmol/L	Not Reported	Baseline HPLC diet mean: 5.25 12-wk post intervention HPLC diet mean: 4.87 16-wk post intervention HPLC diet mean: 4.81	Baseline HPLC diet mean: 0.23 12-wk post intervention HPLC diet mean: 0.24 16-wk post intervention HPLC diet mean: 0.21	14	Baseline LPHC diet mean: 6.1 12-wk post intervention LPHC diet mean: 5.56 16-wk post intervention LPHC diet mean: 5.49	Baseline LPHC diet mean: 0.19 12-wk post intervention LPHC diet mean: 0.16 16-wk post intervention LPHC diet mean: 0.16	14	Crude	Not Applicable
Kazemi et al., 2018	mmol/L	ELISA	Baseline pulse-diet mean: 5.0 Post-intervention pulse-diet mean: 4.6	Baseline pulse-diet SD: 1.0 Post-intervention pulse-diet SD: 0.8	31	Baseline TLC-diet mean: 4.4 Post-intervention	Baseline TLC-diet SD: 0.8 Post-intervention TLC-diet SD: 0.8	30	Crude	Not Applicable

			Mean change pulse-diet: -0.4	Mean change pulse-diet SD: 0.5		TLC-diet mean: 4.3 Mean change TLC-diet: 0	Mean change TLC-diet SD: 0.5			
Stamets et al., 2014	mg/dL	Not Reported	Mean change high protein diet: -27	Mean change high protein diet SD: 46	13	Mean change high carbohydrate diet: -18	Mean change high carbohydrate diet SD: 15	13	Crude	Not Applicable
Abbreviations: TLC: therapeutic lifestyle changes, ELISA: Enzyme-linked immunosorbent assay; HPLC, high protein low-carbohydrate diet; LPHC, low-protein high-carbohydrate diet.										

OUTCOME: HDL-C							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Gower et al., 2013	mM		Standard diet Baseline: 1.40 Post intervention: 1.27	Baseline:0.40 Post intervention: 0.39	23	Lower CHO diet Baseline: 1.38 Post intervention: 1.27	Baseline: 0.39 Post intervention: 0.39	27	Crude	Not Applicable
Kazemi et al., 2018	mmol/L	ELISA	Baseline pulse-diet mean: 1.3 Post-intervention pulse-diet mean: 1.4 Mean change pulse-diet: 0.1	Baseline pulse-diet SD: 0.3 Post-intervention pulse-diet SD: 0.3 Mean change pulse-diet SD: 0.2	31	Baseline TLC-diet mean: 1.3 Post-intervention TLC-diet mean: 1.2 Mean change TLC-diet: -0.1	Baseline TLC-diet SD: 0.4 Post-intervention TLC-diet SD: 0.3 Mean change TLC-diet SD: 0.2	30	Crude	Not Applicable
Mehrabani et al., 2013	mg/dl	Clinical laboratory assessment (without further details)	CHCD Baseline: 62.4 Post intervention: 61.3 Change from baseline: -1.1	Baseline: 1.6 (SE) Post intervention: 1.2 (SE) Change from baseline: 0.8 (SE)	26	MHCD Baseline: 59.6 Post intervention: 59.2 Change from baseline: -0.4	Baseline: 1.8 (SE) Post intervention: 1.6 (SE) Change from baseline: 0.7 (SE)	23	Crude	Not Applicable
Moran et al., 2003	mmol/L	Not Reported	Baseline HPLC diet mean: 0.97	Baseline HPLC diet mean: 0.08	14	Baseline LPHC diet mean: 1.21	Baseline LPHC diet mean: 0.09	14	Crude	Not Applicable

			12-wk post intervention HPLC diet mean: 1.03 16-wk post intervention HPLC diet mean: 1.07	12-wk post intervention HPLC diet mean: 0.08 16-wk post intervention HPLC diet mean: 0.09		12-wk post intervention LPHC diet mean: 1.10 16-wk post intervention LPHC diet mean: 1.15	12-wk post intervention LPHC diet mean: 0.09 16-wk post intervention LPHC diet mean: 0.09			
Stamets et al., 2014	mg/dL	Not Reported	Mean change high protein diet: 7	Mean change high protein diet SD: 31	13	Mean change high carbohydrate diet: -3	Mean change high carbohydrate diet SD: 5	13	Crude	Not Applicable
Wong et al., 2015	mg/dl	Clinical laboratory assessment (without further details)	Low-GL Baseline: 49.3 Post intervention: 52.6 Change from baseline: 3.3	Baseline: 13.3 Post intervention: 12.4 Change from baseline: 2.2 (SE)	10	Low-fat Baseline: 43.3 Post intervention: 42.1 Change from baseline: -1.2	Baseline: 8.3 Post intervention: 6.1 Change from baseline: 1.7 (SE)	9	Crude	Not Applicable

Abbreviations: HDL-C: high-density lipoprotein cholesterol, ELISA: Enzyme-linked immunosorbent assay, TLC: therapeutic lifestyle changes, CHCD: Conventional hypocaloric diet, MHCD: modified hypocaloric diet; HPLC, high protein low-carbohydrate diet; LPHC, low-protein high-carbohydrate diet.

OUTCOME: LDL-C										**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Kazemi et al., 2018	mmol/L	ELISA	Baseline pulse-diet mean: 2.9 Post-intervention pulse-diet mean: 2.7 Mean change pulse-diet: -0.2	Baseline pulse-diet SD: 0.4 Post-intervention pulse-diet SD: 0.8 Mean change pulse-diet SD: 0.4	31	Baseline TLC-diet mean: 2.6 Post-intervention TLC-diet mean: 2.5 Mean change TLC-diet: -0.1	Baseline TLC-diet SD: 0.7 Post-intervention TLC-diet SD: 0.6 Mean change TLC-diet SD: 0.4	30	Crude	Not Applicable
Moran et al., 2003	mmol/L	Not Reported	Baseline HPLC diet mean: 3.42 12-wk post intervention HPLC diet mean: 3.23 16-wk post intervention HPLC diet mean: 3.04	Baseline HPLC diet mean: 0.20 12-wk post intervention HPLC diet mean: 0.21 16-wk post intervention HPLC diet mean: 0.14	14	Baseline LPHC diet mean: 3.99 12-wk post intervention LPHC diet mean: 3.81 16-wk post intervention LPHC diet mean: 3.57	Baseline LPHC diet mean: 0.17 12-wk post intervention LPHC diet mean: 0.13 16-wk post intervention LPHC diet mean: 0.15	14	Crude	Not Applicable
Stamets et al., 2014	mg/dL	Not Reported	Mean change high protein diet: -13	Mean change high protein diet SD: 18	13	Mean change high carbohydrate diet: -12	Mean change high carbohydrate diet SD: 14	13	Crude	Not Applicable
Abbreviations: LDL-C: low-density lipoprotein cholesterol, ELISA: Enzyme-linked immunosorbent assay, TLC: therapeutic lifestyle changes; HPLC, high protein low-carbohydrate diet; LPHC, low-protein high-carbohydrate diet.										

OUTCOME: TC/HDL-C ratio										**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Gower et al., 2013	Not Reported	Not Reported	Standard diet Baseline: 3.54 Post intervention: 3.88	Baseline: 0.95 Post intervention: 1.16	23	Lower CHO diet Baseline: 3.68 Post intervention: 3.58	Baseline: 1.08 Post intervention: 0.97	27	Crude	Not Applicable
Kazemi et al., 2018	Not Applicable	Formula	Baseline pulse-diet mean: 4.0 Post-intervention pulse-diet mean: 3.6 Mean change pulse-diet: -0.4	Baseline pulse-diet SD: 1.2 Post-intervention pulse-diet SD: 1.1 Mean change pulse-diet SD: 0.4	31	Baseline TLC-diet mean: 3.7 Post-intervention TLC-diet mean: 3.8 Mean change TLC-diet: 0.1	Baseline TLC-diet SD: 1.3 Post-intervention TLC-diet SD: 1.3 Mean change TLC-diet SD: 0.4	30	Crude	Not Applicable
Moran et al., 2003	mmol/L	Not Reported	Baseline HPLC diet mean: 5.86 12-wk post intervention HPLC diet mean: 5.07 16-wk post intervention HPLC diet mean: 4.82	Baseline HPLC diet mean: 0.49 12-wk post intervention HPLC diet mean: 0.42 16-wk post intervention HPLC diet mean: 0.36	14	Baseline LPHC diet mean: 5.35 12-wk post intervention LPHC diet mean: 5.50 16-wk post intervention LPHC diet mean: 5.11	Baseline LPHC diet mean: 0.40 12-wk post intervention LPHC diet mean: 0.46 16-wk post intervention LPHC diet mean: 0.40	14	Crude	Not Applicable
Wong et al., 2015	Ratio	Not Reported	Low-GL Baseline: 3.8 Post intervention: 3.4 Change from baseline: -4.0	Baseline: 1.1 Post intervention: 0.9 Change from baseline: 0.1 (SE)	10	Low-fat Baseline: 4.0 Post intervention: 3.9 Change from baseline: -0.1	Baseline: 0.8 Post intervention: 0.6 Change from baseline: 0.1 (SE)	9	Crude	Not Applicable

Abbreviations: TC/HDL: Total cholesterol/high-density lipoprotein, TLC: therapeutic lifestyle changes; HPLC, high protein low-carbohydrate diet; LPHC, low-protein high-carbohydrate diet.

OUTCOME: Triglyceride							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Asemi et al., 2014	mg/dL	Not Reported	Post-intervention mean: 99.2	Post-intervention SD: 45.2	24	Post-intervention mean: 112.5	Post-intervention SD: 67.3	24	Crude	Not Applicable
Gower et al., 2013	mM	Not Reported	Standard diet Baseline: 0.90 Post intervention: 0.92	Baseline: 0.37 Post intervention: 0.36	23	Lower CHO diet Baseline: 0.87 Post intervention: 0.87	Baseline: 0.34 Post intervention: 0.37	27	Crude	Not Applicable
Kazemi et al., 2018	mmol/L	ELISA	Baseline pulse-diet mean: 1.5 Post-intervention pulse-diet mean: 1.3 Mean change pulse-diet: -0.2	Baseline pulse-diet SD: 0.8 Post-intervention pulse-diet SD: 0.7 Mean change pulse-diet SD: 0.6	31	Baseline TLC-diet mean: 1.3 Post-intervention TLC-diet mean: 1.3 Mean change TLC-diet: 0	Baseline TLC-diet SD: 0.7 Post-intervention TLC-diet SD: 0.8 Mean change TLC-diet SD: 0.5	30	Crude	Not Applicable
Mehrabani et al., 2013	mg/dl	Clinical laboratory assessment (without further details)	CHCD Baseline: 132.9 Post intervention: 124.4 Change from baseline: -8.6	Baseline: 7.8 (SE) Post intervention: 7.5 (SE) Change from baseline: 5.4 (SE)	26	MHCD Baseline: 128.7 Post intervention: 122.4 Change from baseline: -6.3	Baseline: 6.5 (SE) Post intervention: 5.7 (SE) Change from baseline: 6.1 (SE)	23	Crude	Not Applicable
Panico et al., 2014	mg/dl	Not Reported	Diet A Baseline: 67.6 Post intervention: 60.7	Baseline: 18.9 Post intervention: 26.4	Not Reported	Diet B Baseline: 67.6 Post intervention: 74.6	Baseline: 18.9 Post intervention: 23.2	Not Reported	Crude	Not Applicable
Stamets et al., 2014	mg/dL	Not Reported	Mean change high protein diet: -29	Mean change high protein diet SD: 88	13	Mean change high carbohydrate diet: -21	Mean change high carbohydrate diet SD: 52	13	Crude	Not Applicable

Wong et al., 2015	mg/dl	Clinical laboratory assessment (without further details)	Low-GL Baseline: 93.9 Post intervention: 77.0 Change from baseline: -16.9	Baseline: 44.0 Post intervention: 30.5 Change from baseline: 12.5 (SE)	10	Low-fat Baseline: 92.7 Post intervention: 88.7 Change from baseline: -4.0	Baseline: 33.1 Post intervention: 37.0 Change from baseline: 10.7 (SE)	9	Crude	Not Applicable
Abbreviations: ELISA: Enzyme-linked immunosorbent assay, TLC: therapeutic lifestyle changes, CHCD: Conventional hypocaloric diet, MHCD: modified hypocaloric diet										

OUTCOME: HRQoL										**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Kazemi et al., 2018	Not Applicable	Researcher-designed HRQoL questionnaire across five domains*	Not Applicable	Not Applicable**	28	Not Applicable	Not Applicable**	27	Crude	Not Applicable
Abbreviations: HRQoL, health-related quality of life, TLC: therapeutic lifestyle changes *Domains included: health concerns (12 items); (2) healthcare satisfaction (five items); (3) knowledge about PCOS (23 items); (4) healthy lifestyle behaviors (six and eight items in the subdomains of active living and healthy eating, respectively); and, (5) feelings and experiences about participating in the intervention (13 items). ** Baseline and post-intervention values across domains were reported on the Likert scale. Crude values not applicable for the purposes of current review and summarized below: Mean scores of the five domains of the HRQoL survey improved across both the pulse-based and TLC diet groups post-intervention without differences between groups. The largest mean increases in time-effects occurred in the domains of healthy eating ($p = 0.0001$, ES [partial eta squared as a result of the analyses of variance] = 0.68), knowledge about PCOS ($p < 0.001$, ES = 0.48), physical activity ($p = 0.0001$, ES = 0.37), healthcare satisfaction ($p < 0.0001$, ES = 0.35), feelings and experiences about participating in the lifestyle intervention ($p = 0.004$, ES = 0.14), and health concerns ($p = 0.02$, ES = 0.11). Together, both interventions improved HRQoL scores in women with PCOS without prescribed energy-restriction.										
OUTCOME: Emotional well-being										**OUTCOME TYPE:** Continuous

		COMPARISON (if applicable):								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Galletly et al., 2007	Score	The Hospital Anxiety and Depression Rating Scale (HAD) (Zigmond & Snaith, 1983) and the Rosenberg Self Esteem Rating Scale rating scale (SE) (Rosenberg, 1965)	Baseline HPLC for depression: 5.6 Baseline HPCL for anxiety: 9.1 Baseline HPLC for self-esteem: 27.2 16-week post-intervention HPLC for depression: 3.6 16-week post-intervention HPLC for anxiety: 7.8 16-week post-intervention HPLC for self-esteem: 31.1	Baseline HPLC for depression: 3.2 Baseline HPCL for anxiety: 3.3 Baseline HPLC for self-esteem: 6.3 16-week post-intervention HPLC for depression: 2.8 16-week post-intervention HPLC for anxiety: 3.9 16-week post-intervention HPLC for self-esteem: 5.6	12	Baseline LPHC for depression: 4.8 Baseline LPHC for anxiety: 8.6 Baseline LPHC for self-esteem: 27.4 16-week post-intervention LPHC for depression: 4.1 16-week post-intervention LPHC for anxiety: 9.1 16-week post-intervention LPHC for self-esteem: 29.0	Baseline LPHC for depression: 3.4 Baseline LPHC for anxiety: 3.9 Baseline LPHC for self-esteem: 7.5 16-week post-intervention LPHC for depression: 3.3 16-week post-intervention LPHC for anxiety: 3.1 16-week post-intervention LPHC for self-esteem: 5.3	13	Crude	Not Applicable
Abbreviations: HPLC, high protein low-carbohydrate diet; LPHC, low-protein high-carbohydrate diet.										

APPENDIX. STUDY CHARACTERISTICS AND QUALITY APPRAISAL

For clarity: N=5 RCTs retrieved in the updated search (after the 2018 Guideline) are shown in tables with heading rows highlighted in the green highlights below, and N=8 RCTs included from previous RCTs retrieved in the 2018 Guideline for this GDG are highlighted in tables with heading rows highlighted in the green highlights below. Studies are sorted alphabetically.

Study ID	Asemi 2014
Study citation	Asemi, Z., Samimi, M., Tabassi, Z., Shakeri, H., Sabihi, S. S., & Esmaillzadeh, A. (2014). Effects of DASH diet on lipid profiles and biomarkers of oxidative stress in overweight and obese women with polycystic ovary syndrome: a randomized clinical trial. *Nutrition, 30*(11-12), 1287-1293. Asemi, Z., & Esmaillzadeh, A. (2015). DASH diet, insulin resistance, and serum hs-CRP in polycystic ovary syndrome: a randomized controlled clinical trial. *Hormone & Metabolic Research, 47*(3), 232-238.
Study Country	Iran
BRIEF CHARACTERISTICS OF RCT	
Patient/population/participants	DASH diet group age= 22.1±3.2 years Control diet group age = 24.7±6.0 years
PCOS diagnostic criteria	Rotterdam
Presence of infertility	Not reported
Presence of other condition/s	DASH diet group BMI= 30.3±4.5 kg/m² Control diet group BMI = 28.6±5.8 kg/m²
Medication History	Women with "current or previous (within the last six mo) use of hormonal, antidiabetic, or ant obesity medications" were excluded
N per group	The number of participants that were: ● Allocated/randomised: DASH diet group= 27, control diet group= 27 ● Assessed at the end of study: DASH diet group= 24, control diet group= 24
Setting	Kashan, Iran. "women who attended gynecology clinics affiliated with Kashan University of Medical Sciences, Kashan, Iran, were screened for PCOS"
Intervention	Eight-week intervention. "As all study participants were overweight or obese, both diets were designed to be calorie-restricted (350–700 kcal less than the computed energy requirement for each participant; 350 kcal for women with BMI 25–27.5 kg/m2; 500 kcal for those with BMI 27.5–31 kg/m2; and 700 kcal for those with BMI >31 kg/m2) to avoid ethical problems. We used two dietary plans. The first was a DASH diet that consisted of 52% carbohydrates, 18% proteins, and 30% total fats. The DASH diet was designed to be rich in fruits, vegetables, whole grains, and low-fat dairy products and to be low in saturated fats, cholesterol, refined grains, and sweets. The prescribed sodium in the DASH diet was <2,400 mg/d…. This study was not a feeding trial; therefore, we did not prepare foods for the participants; they only received 7-d menu cycles. The diets were individually planned using a "calorie-count" system. To facilitate compliance with the diets, participants were given and instructed to use an exchange list. To control for the participants' dietary intakes throughout the study, the dietitian called the participants to resolve any problems. Furthermore, to examine compliance with the diets, we asked participants to record their dietary intakes every 2 wk. All participants spent about 45 min with a dietitian learning the basics of their diets"
Comparison	"As all study participants were overweight or obese, both diets were designed to be calorie-restricted (350–700 kcal less than the computed energy requirement for each participant; 350 kcal for women with BMI 25–27.5 kg/m2; 500 kcal for those with BMI 27.5–31 kg/m2; and 700 kcal for those with BMI >31 kg/m2) to avoid ethical problems. We used two dietary plans. The second plan, the control diet, also contained 52% carbohydrates, 18%

Study ID	Asemi 2014	
	protein, and 30% total fat; however, the two diets were different in terms of food groups contained. This study was not a feeding trial; therefore, we did not prepare foods for the participants; they only received 7-d menu cycles. The diets were individually planned using a "calorie-count" system. To facilitate compliance with the diets, participants were given and instructed to use an exchange list. To control for the participants' dietary intakes throughout the study, the dietitian called the participants to resolve any problems. Furthermore, to examine compliance with the diets, we asked participants to record their dietary intakes every 2 wk. All participants spent about 45 min with a dietitian learning the basics of their diets"	
Outcomes	Body weight, BMI, Dietary intake measurements (not relevant to systematic review), Total cholesterol (not relevant to systematic review), Triglycerides, VLDL (not relevant to systematic review), HDL (not relevant to systematic review), LDL (not relevant to systematic review), TC:HDL-C ratio (not relevant to systematic review), Total antioxidant capacity (not relevant to systematic review), Total glutathione (not relevant to systematic review), Fasting plasma glucose, Insulin, HOMA-IR (not relevant to systematic review), HOMA-B (not relevant to systematic review), High sensitivity CRP (not relevant to systematic review), WC, Hip circumference (not relevant to systematic review)	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Summary Result/s	DASH eating pattern resulted in the improvement of insulin resistance, serum hs-CRP levels, and abdominal fat accumulation vs controls.	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes
Inclusion Criteria	Yes Partial No Not reported	"Overweight or obese (body mass index [BMI]≥25 kg/m2) women ages 18 to 40 y diagnosed with PCOS based on the Rotterdam criteria were recruited in this study…Diagnosis of PCOS was determined according to the Rotterdam criteria. Women with two of the following criteria were considered as having PCOS: oligovulation, anovulation, or a combination of both; excess androgen activity (clinical or biochemical); and polycystic ovaries (by gynecologic ultrasound)."
Exclusion Criteria	Yes Partial No Not reported	"We did not include women ages <18 or >40 y; those with BMI < 25 kg/m2; women with neoplastic, hepatic, renal, cardiovascular or malabsorptive disorders; those with current or previous (within the last six mo) use of hormonal, antidiabetic, or antiobesity medications; and those

Study ID		Asemi 2014	
			intending to adopt a diet and/or a specific physical activity program."
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	"Random assignment was done by the use of computer-generated random numbers."
	Was allocation to intervention group concealed?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	Yes
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	No The study dietitian was aware of dietary assignment
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	Yes
DETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	Yes
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes
ATT	**What percentage of the individuals recruited into each**	X% treatment X% control/ comparison	DASH diet group= 11% (IVF treatment (n=1), health problems (n=1), use of medications (n=1)

Study ID		Asemi 2014	
RITIONBIAS	**arm of the study dropped out?**	Not reported	Control diet group= 11% (IVF treatment (n=1), became pregnant (n=1), use of medications (n=1))
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	Yes
REPORTBIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported No report of a registered protocol
CONFOUNDING	**Were the groups similar at baseline with regards to key prognostic variables?**	Yes Partial No Not reported	Yes
	If confounding was present, was it controlled for?	Yes Partial No Not reported	Yes "Participants were stratified according to BMI (<30 and ≥30 kg/m^2) and age (<30 and ≥30 y)"
OTHERINTERNALVALIDITY/BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes No Partial No Not reported	Not reported
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Yes
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
Comments			
What is the overall risk of bias?		Low Moderate High Insufficient information	Low - All of the criteria have been fulfilled or where criteria have not been fulfilled, it is very unlikely the conclusions of the study would be affected.

Study ID	Asemi 2014
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?	No

Study ID	Azadi-Yazdi 2016
Study Citation	Azadi-Yazdi M, Karimi-Zarchi M, Salehi-Abargouei A, Fallahzadeh H, Nadjarzadeh A. Effects of Dietary Approach to Stop Hypertension diet on androgens, antioxidant status and body composition in overweight and obese women with polycystic ovary syndrome: a randomised controlled trial. J Hum Nutr Diet. 2017 Jun;30(3):275-283. doi: 10.1111/jhn.12433. Epub 2016 Nov 7. PMID: 28466507.
Study Country	Iran
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS (BMI = 25-40; aged 20-40)
PCOS diagnostic criteria	Rotterdam
Presence of infertility	Not reported
Presence of other condition/s	Overweight and obese
Medication History	No
N per group	Control diet: 27 DASH diet: 28
Setting	Baghaeipoor Gynaecology clinic
Intervention	DASH diet: 50–55% carbohydrate, 15–20% protein and 25–30% total fat; rich in fruits, vegetables, whole grains and low-fat dairy products, as well as low in saturated fats, cholesterol, refined grains and sweets; 350-500kcal less than energy requirement
Comparison	Control diet: 50–55% carbohydrate, 15–20% protein and 25–30% total fat; 350-500kcal less than energy requirement
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Height (stadiometer), weight (digital scale), WC (nonstretch plastic tape), hip circumference circumference (nonstretch plastic tape), body composition (body composition analyzer), total testosterone (ELISA), SHBG (ELISA), androstenedione (ELISA), FAI, total antioxidant capacity (DPPH), energy intake, protein, carbohydrates, fat, cholesterol, MUFA, SFA, PUFA, dietary fibre, soluble fibre, vitamin C, magnesium, calcium, potassium, sodium, sucrose, grains, simple sugar, vegetables, fruits, diary, meats, nuts, fats and oils
Follow up Duration	12 weeks
Summary Result/s	DASH diet had beneficial effects on weight, BMI, fat mass, androstenedione, SHBG, and antioxidant capacity
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT	

Study ID		Azadi-Yazdi 2016	
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	Yes, the aim was to examine the effect of the DASH diet on the androgenic profile, total antioxidant capacity, body weight and composition in women with PCOS in the context of a randomised controlled clinical trial.
Does the study have specified inclusion/exclusion criteria?		Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Inclusion criteria		Yes Partial No Not reported	Overweight or obese (BMI = 25–40 kg m–2) women aged 20–40 years who were newly diagnosed with PCOS based on the Rotterdam criteria, did not use hormonal contraception or other medications that could alter the concentration of androgens, did not use hormones as medication for 3 months prior to the study, were without type 1 diabetes, and were not using anti-obesity medications or engaging in a specific physical activity program, were included in the trial.
Exclusion criteria		Yes Partial No Not reported	Participants were excluded from the study if hormonal therapy or other medications that could affect PCOS or weight were initiated for them during the study
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Yes, equally randomised into DASH diet and control diet groups using block randomisation. Random assignment was conducted using computer-generated random numbers
	Was allocation to intervention group concealed?	Yes Partial No Not reported	Yes
PERFORMANCE	**Were patients blind to intervention group?**	Yes Partial No Not reported	Yes
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	Not reported

Study ID		Azadi-Yazdi 2016	
BIAS	**Aside from the experimental intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes
DEDETECTIONBIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes
ATTRITIONBIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	Control diet 3/30 dropped = 10% DASH diet 2/30 dropped = 6.67%
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	Yes
REPORTBIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported

Study ID		Azadi-Yazdi 2016	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	Yes
	If confounding was present, was it controlled for?	Yes Partial No Not reported	Yes, adjusted for energy intake
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS		Lack of randomisation and blinding key reason for high RoB	
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

Study ID	Foroozanfard 2017	
Study Citation	Foroozanfard F, Rafiei H, Samimi M, Gilasi HR, Gorjizadeh R, Heidar Z, Asemi Z. The effects of dietary approaches to stop hypertension diet on weight loss, anti-Müllerian hormone and metabolic profiles in women with polycystic ovary syndrome: A randomized clinical trial. Clin Endocrinol (Oxf). 2017 Jul;87(1):51-58. doi: 10.1111/cen.13333. Epub 2017 Apr 11. PMID: 28316072.	
Study Country	Iran	
BRIEF CHARACTERISTICS OF RCT		
Patient/population/ participants	Women with PCOS (BMI > 25; aged 18-40)	
PCOS diagnostic criteria	Rotterdam	
Presence of infertility	Not reported	
Presence of other condition/s	Overweight and/or obese	
Medication History	No	
N per group	Control diet: 30 DASH diet: 30	
Setting	Naghavi Clinic in Kashan, Iran	
Intervention	DASH diet: consisted of 52%-55% carbohydrates, 16%-18% proteins and 30% total fats. The DASH diet was rich in fruits, vegetables, whole grains and low-fat dairy products and low in saturated fats, cholesterol, refined grains and sweets. Suggested sodium intake in the DASH diet was <2400 mg/d.	
Comparison	Control diet: also designed to contain 52%-55% carbohydrates, 16%-18% protein and 30% total fats; however, DASH and control diets were different in terms of food groups contained. Control diet was designed based on Iranian traditional dietary pattern.	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Height, weight, BMI, serum AMH (ELISA), fasting plasma glucose (commercial kits), serum insulin (ELISA), HOMA-IR, HOMA-B, QUICKI, total testosterone (commercial kits), SHBG (commercial kit), FAI, FSH (ELISA), LH (ELISA), 17-OH progesterone (ELISA), plasma NO (Griess method), MDA level (TBARs method), energy intake, fat, protein, carbohydrate, SFA, PUFA, cholesterol, total dietary fiber, sodium, potassium, magnesium, calcium, fruit, vegetable, nuts, fats and oils	
Follow up Duration	12 weeks	
Summary Result/s	Low-calorie DASH eating pattern for 12 weeks among overweight or obese subjects with PCOS had beneficial effects on weight, BMI, AMH, markers of insulin metabolism, SHBG, FAI, NO and MDA levels compared with low-calorie control diet, but did not affect other metabolic profiles.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes, they hypothesized that the DASH diet might benefit in patients with PCOS to improve their metabolic profiles.

Study ID		Foroozanfard 2017	
Does the study have specified inclusion/exclusion criteria?		Yes Partial No Not reported	Partial, no specified inclusion
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Inclusion criteria		Yes Partial No Not reported	Not reported
Exclusion criteria		Yes Partial No Not reported	We excluded women who were pregnant during the intervention, and adrenal hyperplasia, androgen-secreting tumours, hyperprolactinemia, thyroid dysfunction, diabetes or impaired glucose tolerance at enrollment.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Yes Prior to random assignment, patients were stratified based on BMI (25-29.9 and ≥30 kg/m2) and age (<40 and ≥40 years). Then, participants were randomly assigned to consume either the low-calorie DASH (N=30) or control diet (N=30) for 12 weeks. Randomization assignment was performed using computer-generated random numbers.
	Was allocation to intervention group concealed?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	Yes
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	Partial Only the study dietitian was not blinded
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	Yes

Study ID		Foroozanfard 2017	
DEDETECTIONBIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes
ATTRITIONBIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	Control diet 3/30 dropped = 10% (but still analysed all 30) DASH diet 4/30 dropped = 13.3% (but still analysed all 30)
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	Yes
REPORTBIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported
CONFOUN	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	Yes

Study ID		Foroozanfard 2017	
D I N G	**If confounding was present, was it controlled for?**	Yes Partial No Not reported	Yes We adjusted all analyses for baseline values of biochemical variables, age and BMI
O T H E R BI A S	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS		Lack of randomisation and blinding key reason for high RoB	
What is the overall risk of bias?		Low Moderate High Insufficient information	Low
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

Study ID	Gower 2013
Study Citation	Gower BA, et al., 2013, Favourable metabolic effects of a eucaloric lower-carbohydrate diet in women with PCOS, Clinical Endocrinology, 79(4): 550-557.
Study Country	USA
BRIEF CHARACTERISTICS OF RCT	

Study ID	Gower 2013
Patient/population/ participants	PCOS patients Age (years) 31.2 ± 5.8 BMI (kg/m2): 31.8 ± 5.7
PCOS diagnostic criteria	NIH "The criteria for diagnosis of PCOS were consistent with the NIH 1990 criteria and included (i) hyperandrogenism and/or hyperandrogenaemia, (ii) oligo-ovulation and (iii) the exclusion of any existing disorders such as Cushing's syndrome, hyperprolactinemia or congenital (nonclassic) adrenal hyperplasia."
Presence of infertility	Not reported
Presence of other condition/s	Not reported
Medication History	Not reported
N per group	N=30 Cross-over trial n=23 completed both arms n=27 completed the lower arm
Setting	All testing was conducted on an outpatient basis at the University of Alabama's Clinical Research Unit (CRU).
Intervention	Standard diet (55:18:27% energy from CHO/protein/fat) (8 weeks)
Comparison	Lower-CHO diet (41:19:40% energy from CHO/protein/fat) (8 weeks)
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Primary: β-cell responsiveness, serum testosterone concentration and insulin sensitivity. Secondary: other measures of the metabolic and reproductive endocrine profiles and the lipid profile β-cell response: using mathematical modeling techniques Insulin sensitivity: calculated using a formula based on insulin and glucose values throughout the meal test serum testosterone: immunofluorescence using the TOSOH Glucose, total cholesterol, HDL-cholesterol and triglycerides: SIRRUS analyser. Insulin was assayed by immunofluorescence on a TOSOH AIA-II analyzer FSH and LH: Immunofluorescence Sex hormone binding globulin (SHBG): immunoradiometric assay
Follow up Duration	Not reported (8 week intervention + 4 week washout + 8 week intervention)
Summary Result/s	Lower-CHO diet induced significant decreases in basal b-cell response (PhiB), fasting insulin, fasting glucose, HOMA-IR, total testosterone, and all cholesterol measures, and significant increases in insulin sensitivity and dynamic ('first-phase') b-cell response. The STD diet induced a decrease in HDL-C and an increase in the total cholesterol-to-HDL-C ratio. Across all data combined, the change in testosterone was positively associated with the changes in fasting insulin, PhiB and insulin AUC (P < 0_05).
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT	

Study ID		Gower 2013	
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	Yes "The objective of this study was to examine the effects of 8 weeks of controlled treatment with two eucaloric diets differing in CHO composition (41% vs 55%) on b-cell responsiveness, serum testosterone concentration and insulin sensitivity in women with PCOS."
Does the study have specified inclusion/exclusion criteria?		Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Inclusion criteria		Yes Partial No Not reported	Yes "Inclusion criteria were BMI _45 kg/m2, body weight <136 kg, age 21–50 years, nondiabetic and no weight change >2_3 kg over the past six months"
Exclusion criteria		Yes Partial No Not reported	Yes "Cushing's syndrome, hyperprolactinemia or congenital (nonclassic) adrenal hyperplasia." "Exclusion criteria included regular exercise >2 h per week, pregnancy, current breastfeeding, use of medication that could affect body composition or glucose metabolism (including oral contraceptives, cholesterol medications and blood pressure medications), current use of tobacco, use of illegal drugs in last six months, major food allergies or food dislikes, and a medical history that contraindicated inclusion in the study."
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Parital "….participants were assigned, using a randomization scheme, to one of two diets" Not clear how randomization was performed.
	Was allocation to intervention group concealed?	Yes Partial No Not reported	Not reported
PERF	**Were patients blind to intervention group?**	Yes Partial No Not reported	Not reported

Study ID		Gower 2013	
PERFORMANCE BIAS	**Were investigators and care providers blind to intervention group?**	Yes Partial No Not reported	Not reported
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	Yes
DETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	n=30 enrolled n=23 completed both arms (76.6%) n=27 completed the lower arm (Lower-CHO diet (41:19:40% energy from CHO/protein/fat) (90%)
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	Not reported
REPORTBIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Yes

Study ID		Gower 2013	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	Not reported Baseline characteristics for all 30 women have been reported in table 2.
	If confounding was present, was it controlled for?	Yes Partial No Not reported	Not reported
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	Yes "Nothing to declare"
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes **"**Descriptive statistics were calculated for all variables of interest. "Paired t-tests within each diet arm were used to examine changes in main outcomes of interest." "Spearman's correlation analysis was used to examine the association between changes in insulin outcome measures and changes in testosterone."
COMMENTS		Lack of randomization and the blinding key reason for high RoB	
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

Study ID	Hoover 2021	
Study Citation	Hoover SE, Gower BA, Cedillo YE, Chandler-Laney PC, Deemer SE, Goss AM. Changes in Ghrelin and Glucagon following a Low Glycemic Load Diet in Women with PCOS. J Clin Endocrinol Metab. 2021 Apr 23;106(5):e2151-e2161. doi: 10.1210/clinem/dgab028. PMID: 33491091; PMCID: PMC8063255.	
Study Country	USA	
BRIEF CHARACTERISTICS OF RCT		
Patient/population/ participants	Women with PCOS (BMI ≤ 45; aged 21-50)	
PCOS diagnostic criteria	NIH	
Presence of infertility	Not reported	
Presence of other condition/s	Not reported	
Medication History	Not reported	
N per group	High GL diet: 30 Low GL diet: 30	
Setting	Clinical Research Unit at the University of Alabama-Birmingham	
Intervention	Low GL: 41% energy from CHO, 19% energy from protein, and 40% energy from fat (GI = 50)	
Comparison	High GL diet: 55% energy from CHO, 18% energy from protein, and 27% energy from fat (GI = 60)	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Hunger, fullness, and desire to eat (VAS); GLP-1 (ELISA), ghrelin (ELISA), PYY (radioimmunoassay kits), cortisol (immunofluorescence), glucose (glucose oxidase method), Insulin (immunofluorescence), glucagon (RIA), HOMA-IR	
Follow up Duration	20 weeks	
Summary Result/s	Specifically, we found that greater glucagon was associated with lesser hunger during fasting following habituation to the low vs high GL diet. Additionally, greater postprandial glucagon was associated with lesser postprandial ghrelin following the low vs high GL meal. The high GL meal led to greater fullness in the early postprandial phase, while no significant differences were observed in the late postprandial phase. These findings suggest that a low GL diet may influence hunger/satiety through alterations in fasting and postprandial appetite-regulating hormones in women with PCOS with overweight or obesity.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes, the objective of this study was to test the hypothesis that following 4-week habituation to a low vs high GL diet, a low GL meal will increase glucagon and decrease ghrelin to reflect greater satiety and improve self-reported fullness compared with a high GL meal. Additionally, they explored the relationships among ghrelin, glucagon, and self-reported appetite in women with PCOS.

Study ID		Hoover 2021	
Does the study have specified inclusion/exclusion criteria?		Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Inclusion criteria		Yes Partial No Not reported	Yes Briefly, inclusion criteria were BMI ≤45 kg/m2, age 21-50 years, nondiabetic as determined by an oral glucose tolerance test at screening, and no weight change >2.3 kg over the previous six months.
Exclusion criteria		Yes Partial No Not reported	Yes Exclusion criteria included exercise >2 hours per week, pregnancy, current breastfeeding, medication affecting body composition or glucose metabolism (including oral contraceptives, cholesterol medication, and blood pressure medications), current tobacco use, use of illegal drugs in the past 6 months, major food allergies or food dislikes, and a medical history that contraindicated inclusion in the study.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Partial, after enrollment, participants were assigned to 1 of 2 eucaloric diet orders using a randomization scheme.
	Was allocation to intervention group concealed?	Yes Partial No Not reported	Not reported
PERFORMANCE	**Were patients blind to intervention group?**	Yes Partial No Not reported	Not reported
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	Not reported

Study ID		Hoover 2021	
BIAS	**Aside from the experimental intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes
DEDETECTIONBIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes
ATTRITIONBIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	Low GL diet 3/30 dropped = 10% High GL diet 3/30 dropped = 10%
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	Yes
REPORTBIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported

Study ID		Hoover 2021	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	Yes
	If confounding was present, was it controlled for?	Yes Partial No Not reported	Not reported
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS		Lack of randomisation and blinding key reason for high RoB	
What is the overall risk of bias?		Low Moderate High Insufficient information	High Did not detail randomization, and blinding was not reported
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

Study ID	Hosseini Marnani 2021	
Study Citation	Hosseini Marnani E., Ghadiri-Anari A., Ramezani-Jolfaie N., Mohammadi M., Abdollahi, A., Namayandeh S. M., et al., Effect of fennel supplementation along with high-protein, low-carbohydrate weight-loss diet on insulin resistance and percentage of fat and muscle mass in overweight/obese women with polycystic ovary syndrome, Journal of Functional Foods, Volume 67, 2020, 103848, ISSN 1756-4646, https://doi.org/10.1016/j.jff.2020.103848.	
Study Country	Iran	
BRIEF CHARACTERISTICS OF RCT		
Patient/population/ participants	Women with PCOS (BMI ≥ 25; aged 18-45)	
PCOS diagnostic criteria	Rotterdam	
Presence of infertility	Not reported	
Presence of other condition/s	No	
Medication History	No	
N per group	SDP: 15 HPP: 15	
Setting	Outpatient clinics of Imam Ali and Diabetes Research Center	
Intervention	HPP: high-protein, low-carbohydrate diet + placebo capsule (HPP); high-protein, low-carbohydrate diet consisted of 40% carbohydrate, 30% protein, and 30% fat	
Comparison	SDP: standard diet + placebo capsule (SDP); standard diet included 55% carbohydrate, 15% protein and 30% fat	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	fasting glucose (enzymatic method), fasting insulin (ELIZA), HOMA-IR, percentage of body fat and muscle mass (Omron digital scale), energy intake, carbohydrate, protein, fat	
Follow up Duration	12 weeks	
Summary Result/s	None of the outcomes were different between the groups of interest (SDP vs HPP) out of the 4 assessed arms in this trial. However, the percentage of body fat and muscle mass decreased in all groups compared with the baseline. Moreover, 12 weeks of intervention resulted in a decrease in fasting insulin levels and HOMA-IR in SDP group.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes, the aim of this trial was to investigate the combined effect of fennel supplementation and energy-restricted diets (high-protein, low-carbohydrate diet and standard diet) on the percentage of body fat and muscle mass and also insulin resistance in overweight/obese women with PCOS.
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	Yes

Study ID		Hosseini Marnani 2021	
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Inclusion criteria		Yes Partial No Not reported	Inclusion criteria followed were (a) the presence of at least two out of three Rotterdam criteria: 1) oligo or anovulation, 2) clinical or biochemical sign of hyperandrogenism and 3) polycystic ovaries based on ultrasound diagnosis (more than 12 follicles with 2–9 mm range in each ovary and/ or increase in the volume of ovarian greater than 11 cm3, (b) body mass index (BMI) ≥ 25 kg/m2 and (c) age range of 18–45 years.
Exclusion criteria		Yes Partial No Not reported	Participants were excluded if they were diagnosed with congenital adrenal hyperplasia, Cushing's syndrome, hyperprolactinemia, hypothyroidism, androgen tumors, severe hirsutism or acne, history of allergy to fennel or any of its compounds, allergic asthma, liver and renal diseases, cancer, pregnancy, and tendency to get pregnant, and also if the number of missing capsules was more than 10% of the total.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Yes, Random assignment was carried out by an independent researcher using computer random generation.
	Was allocation to intervention group concealed?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	Yes
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	Yes (double-blinded)
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	Yes

Study ID		Hosseini Marnani 2021	
DEDETECTIONBIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes
ATTRITIONBIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	SDP 1/16 dropped = 6.25% HPP 1/16 dropped = 6.25%
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	Yes
REPORTBIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported
CONFOUN	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	Yes

Study ID		Hosseini Marnani 2021	
D I N G	**If confounding was present, was it controlled for?**	Yes Partial No Not reported	Not reported
O T H E R BI A S	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS		Lack of randomisation and blinding key reason for high RoB	
What is the overall risk of bias?		Low Moderate High Insufficient information	High
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

Study ID	Kazemi, 2018-2020
Study Citation	Kazemi, M., McBreairty, L. E., Chizen, D. R., Pierson, R. A., Chilibeck, P. D., & Zello, G. A. (2018). A Comparison of a Pulse-Based Diet and the Therapeutic Lifestyle Changes Diet in Combination with Exercise and Health Counselling on the Cardio-Metabolic Risk Profile in Women with Polycystic Ovary Syndrome: A Randomized Controlled Trial. Nutrients, 10(10), 1387. https://doi.org/10.3390/nu10101387 Kazemi, M., Pierson, R. A., McBreairty, L. E., Chilibeck, P. D., Zello, G. A., & Chizen, D. R. (2020). A randomized controlled trial of a lifestyle intervention

Study ID	Kazemi, 2018-2020
	with longitudinal follow-up on ovarian dysmorphology in women with polycystic ovary syndrome. Clinical endocrinology, 92(6), 525–535. https://doi.org/10.1111/cen.14179 McBreairty, L. E., Kazemi, M., Chilibeck, P. D., Gordon, J. J., Chizen, D. R., & Zello, G. A. (2020). Effect of a pulse-based diet and aerobic exercise on bone measures and body composition in women with polycystic ovary syndrome: A randomized controlled trial. Bone reports, 12, 100248. https://doi.org/10.1016/j.bonr.2020.100248 Kazemi, M., McBreairty, L. E., Zello, G. A., Pierson, R. A., Gordon, J. J., Serrao, S. B., Chilibeck, P. D., & Chizen, D. R. (2020). A pulse-based diet and the Therapeutic Lifestyle Changes diet in combination with health counseling and exercise improve health-related quality of life in women with polycystic ovary syndrome: secondary analysis of a randomized controlled trial. Journal of psychosomatic obstetrics and gynaecology, 41(2), 144–153. https://doi.org/10.1080/0167482X.2019.1666820
Study Country	Canada
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS
PCOS diagnostic criteria	AE-PCOS
Presence of infertility	Reported-Part of inclusion criteria
Presence of other condition/s	None
Medication History	Family h/o DM, CVD, HTN. Women who took meds that are known or suspected to interfere with cardio metabolic and reproductive function, weight, and/or appetite were excluded, including hormonal and/or fertility meds w/I the past three months before recruitment; weight and appetite-affecting medications; cardiovascular disease medications, and anti-seizure or anti-psychotic medications use because of the potential to induce IR and polycystic appearing ovaries.
N per group	Randomized (computer-generated allocation schedule) Pulse-based group (PBG): 30 women Therapeutic Lifestyle Change (TLC): 31 women
Setting	Royal University Hospital in Saskatoon, Canada
Intervention	Pulse-based diet (soups, salads, and main course meals prepared with yellow split peas, green lentils, red split lentils, chickpeas, and pinto, black, and kidney beans. Two meals (i.e., lunch and dinner) were supplied daily. Each meal contained approximately 90 g of split peas or 225 g of chickpeas or beans or 150 g of lentils (cooked weight). No prescribed energy restriction.
Comparison	Standard Therapeutic Lifestyle Changes diet (TLC, including low-fat cuts of meat, poultry, and low-fat or skim dairy as the main sources of protein and limit their pulse consumption). No prescribed energy restriction.

Study ID	Kazemi, 2018-2020	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Changes in cardio-metabolic profile (Insulin, glucose, TC, HDL-C, TC/HDL-C ratio, TG, hsCRP, HbA1c), body composition and anthropometric measures (weight, BMI, WC, BMD, fat mass, lean mass), reproductive measures (ovarian morphology, female hormonal panel including testosterone, LH, FSH) FAI, hirsutism, SHBG, menstrual cyclicity and HRQoL	
Follow up Duration	16 week (intervention), 6 & 12 months (post-intervention follow up)	
Summary Result/s	Pulse-based diet was more effective at reducing insulin resistance, diastolic blood pressure, LDL-C, TC/HDL-C and increasing HDL-C than the TLC group. Both groups experienced comparable improvements in the reproductive, lumbar bone mineral density, and HRQoL outcomes, despite a greater loss in femoral neck BMD in the pulse-based diet group.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes Compare the effect of a pulse-based diet to the NCEP TLC diet on cardio-metabolic disease risk measures in reproductive-age women with PCOS for 16 weeks without energy restriction when the diets were combined with aerobic exercise and health counseling. Further, our study determined the long-term effects of the intervention on the cardio-metabolic profile of women with PCOS by follow-up of the participants 12 months after the intervention.
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes
Inclusion criteria	Yes Partial No Not reported	Yes Between 18 to 35 years of age, had irregular periods, unwanted male-pattern facial and/or body hair growth, and infertility. Women who used metformin were included and were stratified to be randomized separately than women who were not using metformin.
Exclusion criteria	Yes Partial No Not reported	Yes Women who took medications that are known or suspected to interfere with cardio-metabolic and reproductive function, weight, and/or appetite were excluded, including hormonal and/or fertility medications within the past three months before recruitment; weight and appetite-affecting medications; cardiovascular disease medications, and anti-seizure or anti-psychotic medications use because of the potential to induce IR and polycystic appearing ovaries. Women with untreated hyperprolactinemia or thyroid disease, or, excessive adrenal androgen production due to congenital adrenal hyperplasia, Cushing's syndrome, or an adrenal tumor were excluded. Further, women with medical (e.g., cardio-pulmonary) or

Study ID		Kazemi, 2018-2020	
			dietary conditions that limited physical activity or consumption of a pulse-based diet (allergies or intolerances) were excluded.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Yes Randomization was carried out using a computer-generated allocation schedule performed by an investigator who was not involved in obtaining, entering, or analyzing participant data. Randomization was stratified based on the current use of metformin, using a fixed block size of four and a permuted block design.
	Was allocation to intervention group concealed?	Yes Partial No Not reported	Partial Participants were notified of diet allocation via email and thus were not blinded. However, participants were blinded to the study hypothesis and investigators who collected and processed data analyses were blinded to allocation.
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	No (inherent to study design [nature of the dietary intervention)
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	Yes The allocation sequence was concealed from the dietitian who provided health counseling and those involved in assisting with exercise training and data entry. The investigators collecting and analyzing data were also blinded to group assignment
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	Yes
DETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	Yes
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes

Study ID		Kazemi, 2018-2020	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	PBG 16/47 = 34% TLC 18/48 = 37.5%
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	Yes
REPORTBIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Yes (all a-priori outcomes of the study previously published in the protocol of the study were reported irrespective of data and all analyses were conducted in compliance with the intention to treat statistics)
	Were the groups similar at baseline with regard to key prognostic variables?	Yes Partial No Not reported	Yes The baseline characteristics of women who did not complete the 16-week intervention were not different from those who completed the intervention
	If confounding was present, was it controlled for?	Yes Partial No Not reported	Yes For adaptation to a healthy diet, all women consumed a TLC diet for two weeks prior to the start of the intervention. As a standard of care, all women were enrolled in an aerobic training program and received health counseling about PCOS (i.e., the value of lifestyle modifications in the management of the condition).
OTHE	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No The authors declare no conflict of interest. The funders had no role in the study design, collection, analyses, interpretation of data, writing of the manuscript, and decision to publish.

Study ID		Kazemi, 2018-2020	
R BI A S	**Was the study sufficiently powered to detect any differences between the groups?**	Yes Partial No Not reported	Partial The inability to detect FPG differences between groups post-intervention may be due to the study being underpowered
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS		Randomisation, blinding and details of processes for reproducibility key reason for Low RoB	
What is the overall risk of bias?		Low Moderate High Insufficient information	Low
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No, all outcomes have a low risk of bias	

Study ID	Mehrabani 2012
Study Citation	Mehrabani HH, et al., 2012, Beneficial effects of a high-protein, low-glycemic-load hypocaloric diet in overweight and obese women with polycystic ovary syndrome: a randomized controlled intervention study, Journal of the American College of Nutrition, 31(2): 117-125.
Study Country	Iran
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Overweight and obese PCOS women CHCD Age (y) 28.5 ± 5.2 BMI (kg/m2) 31.1 ± 4.6 MHCD Age (y) 30.5 ± 6.4 BMI (kg/m2) 31.9 ± 4.0
PCOS diagnostic criteria	Diagnosis of PCOS by menstrual irregularity (cycle length, 21 days or .35 days), hirsutism, and biochemical hyperandrogenism.
Presence of infertility	Not reported

Study ID	Mehrabani 2012	
Presence of other condition/s	Not reported	
Medication History	Participants did not use insulin-sensitizing agents	
N per group	N=60 (randomized) n=49 (completed) CHCD n=26 MHCD n=23	
Setting	Taleghani infertility research center in Tehran, Iran	
Intervention	Conventional hypocaloric diet (CHCD) (15% of daily energy from protein)	
Comparison	modified hypocaloric diet (MHCD) with a high-protein, low-glycemic load (30% of daily energy from protein plus low-glycemic-load foods selected from a list)	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Body composition including total body fat and lean body mass: bioelectrical impedance, Skinfold thickness: supra iliac area using a skinfold caliper, WC: measured with a nonstretchable tape at the area demarcated by the umbilicus and hip circumference at the widest place over the buttocks, Weight, Follicle stimulating hormone (FSH), luteinizing hormone (LH): immunoenzymometric assay method, estradiol, total testosterone, dehydroepiandrosterone sulfate (DHEAS), and androstenedione: enzyme immunoassay using a commercially available kit, Fasting insulin and adiponectin: enzyme-linked immunosorbent assay, Serum glucose, triglyceride, total cholesterol, and high-density lipoprotein cholesterol (HDL-C) : a colorimetric enzymatic assay The homeostatic model assessment for insulin resistance (HOMA) was used as a surrogate measure of insulin sensitivity	
Follow up Duration	Intervention 12 weeks Followed up at weeks 0, 4, 8, and 12 Follow-up after 12 weeks not reported	
Summary Result/s	"Weight loss was significant and similar in the two groups. Mean of testosterone in the MHCD and CHCD groups decreased from 1.78 ± 0.32 to 1.31 ± 0.26 ng/ml and from 1.51 ± 0.12 to 1.15 ± 0.11 ng/ml, respectively ($p < 0.001$). Follicle sensitizing hormone (FSH), luteinizing hormone (LH), and blood lipids concentrations were not changed except low-density lipoprotein cholesterol (LDL-C) was reduced by 24.5% ± 12.3% ($p < 0.001$ for both) after 12 weeks of intervention. MHCD resulted in a significant reduction in insulin level, homeostatic model assessment for insulin resistance (HOMA), and high-sensitivity C- reactive protein (hsCRP) concentration ($p < 0.001$)."	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes	Yes "the aim of this controlled intervention study was to investigate and compare the effects of two kinds of diets, including a Conventional hypocaloric diet (CHCD) and a modified hypocaloric diet (MHCD) with low-GL and high protein content on reproductive hormones, lipid profile, inflammatory factors, glucose, and insulin levels in overweight and obese women with PCOS who had not started taking any medications or changed their exercise habits since the diagnosis of their disease."

Study ID		Mehrabani 2012	
Does the study have specified inclusion/exclusion criteria?		Yes	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes	Yes
Inclusion criteria		Yes	"Subjects were included if they were aged between 20 and 40 years, had a body mass index (BMI) greater than 25 and less than 38 kg/m2, and no history of using an insulin-sensitizing agent such as metformin or oral contraceptives. Inclusion criteria were diagnosis of PCOS by menstrual irregularity (cycle length, ,21 days or .35 days), hirsutism, and biochemical hyperandrogenism."
Exclusion criteria		Yes	Yes "Volunteers were excluded if they were smokers, exercised heavily, and/or had any history of cardiovascular, renal, gastrointestinal disorders, liver or metabolic diseases " "Women diagnosed with hyperprolactinemia, thyroid abnormalities, and/or nonclassic adrenal hyperplasia were also excluded from this study."
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Partial ".....randomized by an independent observer. " Unclear how randomization was carried out
	Was allocation to intervention group concealed?	Yes Partial No Not reported	Not reported
PERFORMANCE	**Were patients blind to intervention group?**	Yes Partial No Not reported	Yes "The investigator was not blinded as to the kind of dietary intervention, but subjects were."
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	No "The investigator was not blinded as to the kind of dietary intervention, but subjects were."

Study ID		Mehrabani 2012	
BIAS	**Aside from the experimental intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes
CTE CTIONBIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	No "The investigator was not blinded as to the kind of dietary intervention, but subjects were."
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes
ATTRITIONBIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	49/60 completed (81.6%) 18.4% drop out
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	No
REPORTBIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Yes
CONFOUN	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	Partial "No significant differences existed in subjects' characteristics at baseline for the two treatment groups, except for hip circumference"

Study ID		Mehrabani 2012	
D I N G	**If confounding was present, was it controlled for?**	Yes Partial No Not reported	Not reported
ER BI A S	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No "There are no conflicts of interest between the authors and the funding source. All coauthors accept responsibility for the content of the manuscript."
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Yes "It was calculated that 23 subjects per group would provide 80% power to detect a difference of 7.7 nmol/L in the sex hormone-binding globulin (SHBG) levels in serum. Therefore 30 subjects were recruited for each group to cover the assumed withdrawal. Subjects were stratified to ensure equality of distribution in 2 groups for known confounding factors like age and BMI and then were randomized by an independent observer."
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

Study ID	Moran 2003
Study Citation	Moran, LJ.J., Noakes, M., Clifton, P.M., Tomlinson L., Norman, R. J. (2003). Dietary Composition in Restoring Reproductive and Metabolic Physiology in Overweight Women with Polycystic Ovary Syndrome. The Journal of Clinical Endocrinology & Metabolism 88(2):812–819. Galletly C, Moran LJ, Noakes M, Clifton P, Tomlinson L, Norman RJ. (2007). Psychological benefits of a high-protein, low-carbohydrate diet in obese women with polycystic ovary syndrome—A pilot study. Appetite (49) 590-593. doi:10.1016/j.appet.2007.03.222
Study Country	Australia
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Caucasian women with PCOS and overweight BMI
PCOS diagnostic criteria	NIH definition: "Menstrual irregularity (cycle length, <21 d or >35 d or variation between consecutive cycles of >3 d) and clinical (hirsutism/acne) and/or biochemical hyperandrogenism"
Presence of infertility	Not reported
Presence of other condition/s	Not reported
Medication History	Less clear: "8 subjects were previously using hormonal medication"
N per group	Intervention: N=14 Control: N=14
Setting	North West Adelaide Health Service and CSIRO Division of Health Sciences and Nutrition, Australia
Intervention	High-protein low-carbohydrate (HPLC) diet with 40% carbohydrate and 30% protein
Comparison	Low-protein high-carbohydrate (LPHC) diet with 55% carbohydrate and 15% protein
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	TC, LDL-C, HDL-C, TG, Glucose, Insulin, HOMA-IR, Emotional well being
Follow up Duration	4 weeks
Summary Result/s	Modest difference in HDL-C and TC/HLD-C ratio, glucose AUC and FAI between diets but all other outcomes NS, despite changes over time/ within-group in multiple outcomes. "An HPLC diet may result in minor differential endocrine and metabolic improvements [vs. LPHC diet]. The HPLC diet was associated with significant

Study ID		Moran 2003	
		reduction in depression and improvement in self-esteem. There was no change in any psychological measures for the LPHC group. There was no difference in weight loss between the groups."	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT			
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	Yes
Does the study have specified inclusion/exclusion criteria?		Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Inclusion criteria		Yes Partial No Not reported	Yes "Inclusion criteria were diagnosis of PCOS by menstrual irregularity (cycle length, <21 d or >35 d or variation between consecutive cycles of >3 d) and clinical (hirsutism/acne) and/or biochemical hyperandrogenism. If a definition of menstrual irregularity as fewer than 9 menses/yr is used, 10 of 22 women fulfilled this criteria." "Subjects were eligible for the study if they had not been taking oral contraceptives for more than 4 wk or hormone treatment/insulin-sensitizing agents for more than 2 wk. Subjects with hyperprolactinemia, thyroid abnormalities, or nonclassic adrenal hyperplasia were excluded through appropriate hormone assessment."
Exclusion criteria		Yes Partial No Not reported	Yes "Exclusion criteria were inability to comply with study requirements, weight greater than 140 kg, smoking, and use of oral contraceptives/hormone treatment/insulin-sensitizing agents."
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTI	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Not reported "Subjects were stratified to ensure equal distribution for known confounding factors of weight, age, and desire to conceive and then randomized by an independent observer after obtaining informed written consent." This is not clear.

Study ID		Moran 2003	
ONBIAS	**Was allocation to intervention group concealed?**	Yes Partial No Not reported	Not reported
PERFORMANCEBIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	No "Subjects and investigators were not blinded as to the dietary intervention."
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	No "Subjects and investigators were not blinded as to the dietary intervention."
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	Yes
CTEDETECTIONBIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	No "Subjects and investigators were not blinded as to the dietary intervention."
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Not reported
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Not reported
ATTRITIONBIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	[8/22] 36.4% treatment [9/23] 39.1% control/ comparison Not reported	17/45 (37.8%) randomized dropped out from the trial by the end
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	Not reported

Study ID		Moran 2003	
REPORTBIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported No protocol available
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	Partial "The high drop-out rate, consequent reduced study power, and poor matching at baseline may have reduced the sensitivity of the results."
	If confounding was present, was it controlled for?	Yes Partial No Not reported	Not reported
ER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No "None declared"
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	No "The high drop-out rate, consequent reduced study power, and poor matching at baseline may have reduced the sensitivity of the results. Due to the small sample size, we cannot eliminate the possibility that no difference in diet composition was detected due to a type II error."
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			

Study ID	Moran 2003	
What is the overall risk of bias?	Low Moderate High Insufficient information	High Did not detail randomization, and blinding was not reported. Study had a small sample size.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?	No	

Study ID	Panico 2014
Study Citation	Panico A, et al., 2014, Effects of an isocaloric low glycemic-load diet in polycystic ovary syndrome, Nutritional Therapy & Metabolism, 32(2): 85-92.
Study Country	Italy
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	PCOS women with BMI (28.7 ± 4.9)
PCOS diagnostic criteria	Having two following manifestations 1. menstrual irregularity 2. clinical or biochemical hyperandrogenism 3. presence of polycystic ovaries on USS
Presence of infertility	Not reported
Presence of other condition/s	Not reported
Medication History	Not reported
N per group	N=7 completed protocol
Setting	Internal medicine surgery department, University Fedrico I Naples Italy
Intervention	Diet A: isocaloric and isoenergetic moderately low-glycaemic-load diets (diet A, glycaemic load = 79-105)
Comparison	Diet B: moderately high-glycaemic-load diets (diet B, glycaemic load = 123-134)
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Insulin sensitivity, FSH, LH, Testosterone, DHEAS, Cortisol, Serum glucose, Serum cholesterol
Follow up Duration	3 months period 1, subsequent 3 months period 2 (6-month study, no further follow up reported) No washup period reported

Study ID		Panico 2014	
Summary Result/s		"In conditions of stable body weight, a significant reduction of serum total testosterone (p < 0.026), dehydroepiandrosterone (p < 0.042), adrenocorticotropic hormone (ACTH; p < 0.009), glycemia (p < 0.011), and insulin 2 hours after breakfast (p < 0.019) was observed after the low-glycaemic-load diet."	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT			
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	Yes To compare the effects of isocaloric and isoenergetic moderately low glycaemic load diets (diet A, glycaemic load = 79-105) versus moderately high-glycaemic-load diets (diet B, glycaemic load = 123-134) on endocrine patterns of polycystic ovary syndrome
Does the study have specified inclusion/exclusion criteria?		Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Inclusion criteria		Yes Partial No Not reported	Yes Clinical (acne, alopecia, seborrhoea) and /or biochemical hyperandrogenism (testosterone >90 ng/dl, dehydro-epiandrosterone sulfate (DHEAS] >248 µg/dl Oligo-amenorrhoea (35-day menstrual cycles or total absence of menses) polycystic ovaries detected through USS: 10 or more follicles (having 2-8// diameter) in at least 1 of the two ovaries
Exclusion criteria		Yes Partial No Not reported	pregnancy, using OCP or insulin-sensitizing agents, endocrine disorder diabetes, nonclassic, 21-hydroxylase deficiency, ovarian or adrenal tumors, hypothalamic amenorrhoea, those planning to take part in regular physical activity
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Not reported "Following a crossover design, patients were randomly provided with an isocaloric and isoenergetic diet ….." This is not clear.
	Was allocation to intervention group concealed?	Yes Partial No Not reported	Not reported

Study ID		Panico 2014	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	Not reported
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	Not reported
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	Yes
TE DETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Not reported
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Not reported
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	76.6% dropped out from the crossover trials by the end
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	Not reported

Study ID		Panico 2014	
REPORTBIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported No protocol available
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	Not reported
	If confounding was present, was it controlled for?	Yes Partial No Not reported	Not reported
ER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No "None declared"
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			

Study ID	Panico 2014	
What is the overall risk of bias?	Low Moderate High Insufficient information	High
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?	No	

Study ID	Stamets 2004
Study Citation	Stamets K, Taylor DS, Kunselman A, Demers LM, Pelkman CL, and Legro RS, 2004, A randomized trial of the effects of two types of short-term hypocaloric diets on weight loss in women with polycystic ovary syndrome*, Fertility & Sterility*, 81(3): 630-637.
Study Country	USA
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS. Age = 21-37 years. BMI = 28-45 kg/m^2
PCOS diagnostic criteria	"A history of chronic anovulation (six spontaneous menstrual cycles per year) and unexplained elevated circulating T levels"
Presence of infertility	Not reported
Presence of other condition/s	Obese (BMI=>25 kg/m^2)
Medication History	Not reported
N per group	N = 35. High protein (HP) diet group = 17. High carbohydrate (HC) diet group = 18.
Setting	Participants were recruited from "a variety of sources" including private practices in Ohio and Pennsylvania, and at the M.S. Hershey Medical Center, Pennsylvania, and through advertisements (p631).
Intervention	High protein (HP) diet: The HP diet consisted of 30% protein, 40% carbohydrate, and 30% fat. "Energy needs of patients were calculated with the Harris-Benedict equation using an adjusted body weight for obesity and an activity factor of 1.5". Participants had a 1000kcal deficit per day [or equivalent to 4187kJ], which was 1000g/wk. Patients consumed a multivitamin/mineral supplement daily. Diet delivery regime: A dietitian guided the food choices for participants using "limited exchange lists from the American Diabetes Association Exchange Lists for Meal Planning" (p631). "Specific instructions were not given about types of carbohydrates or glycemic indices". The HP diet was given for four weeks.

Study ID	Stamets 2004	
	Other support: Patients maintained their current exercise levels throughout the four week study. Patients faxed weekly completed daily self-monitoring diet charts and their weight measurements. Patients "filled out satiety questionnaires and spoke with the dietitian weekly, reviewing their charts and answering questions related to" their prescribed diet plan.	
Comparison	High carbohydrate (HC) diet: The HC diet consisted of 15% protein, 55% carbohydrate, and 30% fat. "Energy needs of patients were calculated with the Harris-Benedict equation using an adjusted body weight for obesity and an activity factor of 1.5". Participants had a 1000kcal deficit per day [or equivalent to 4187kJ], which was 1000g/wk. Patients consumed a multivitamin/mineral supplement daily. Diet delivery regime: A dietitian guided the food choices for participants using "limited exchange lists from the American Diabetes Association Exchange Lists for Meal Planning" (p631). "Specific instructions were not given about types of carbohydrates or glycemic indices". The HC diet was given for four weeks. Other support: Patients maintained their current exercise levels throughout the four week study. Patients faxed weekly completed daily self-monitoring diet charts and their weight measurements. Patients "filled out satiety questionnaires and spoke with the dietitian weekly, reviewing their charts and answering questions related to" their prescribed diet plan.	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Anthropometric: Weight; BMI; WC; waist-hip girth ratio. Metabolic: Morning 3hr oral glucose tolerance test (OGTT), with a 75g oral glucose challenge done after 10hr overnight fast; total cholesterol; high-density lipoprotein (HDL); low-density lipoprotein (LDL); serum triglycerides; blood pressure. Non-fertility: Ferriman-Gallwey scores, fasting testosterone; free and weakly-bound testosterone; follicle-stimulating hormone (FSH); prolactin (PRL); 17-OH P; dehydroepiandrosterone sulphate (DHEAS); luteinizing hormone (LH).	
Follow up Duration	Four weeks	
Summary Result/s	"Both the HP and HC diets resulted in significant weight loss, with the HC diet demonstrating a slightly greater weight loss. However, there was no significant difference in mean weight loss between the two groups"	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes All elements of a PICO are clearly described.

Study ID		Stamets 2004	
Does the study have specified inclusion/exclusion criteria?		Yes Partial No Not reported	Yes Inclusion and exclusion criteria are clearly described (p631).
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes The authors have relevant criteria for detecting PCOS (p631).
Inclusion criteria		Yes Partial No Not reported	Yes PCOS women were selected based on a diagnosis of PCOS through "a history of chronic anovulation (≤ six spontaneous menstrual cycles per year) and unexplained elevated circulating T levels" (p631). Patients were not judged for inclusion or exclusion based on ultrasonography "because the presence or absence of polycystic ovaries has not been included in consensus criteria for the definition of the endocrine syndrome of PCOS". "None of the participants had been diagnosed previously with diabetes mellitus" (p631). "All patients were obese which was defined as a body mass index (BMI) ≥25 kg/m^2 ... were in good health and, for at least 1 month before the study, were not taking any medication (except for oral contraceptive agents which were stopped 3 months prior to the study) known to affect sex hormone levels, carbohydrate metabolism, or appetite. The participants were required to be non-smokers and to exercise no more than three times per week" (p631).
Exclusion criteria		Yes Partial No Not reported	Yes "Other causes of androgen excess (e.g. non-classical adrenal 21-hydroxylase deficiency, hyperprolactinemia, and androgen-secreting tumors)" (p631).
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Yes A random number table was used (p631).
	Was allocation to intervention group concealed?	Yes Partial No Not reported	Not reported
PERFO	**Were patients blind to intervention group?**	Yes Partial No Not reported	No Dietitians discussed the intervention or control diet plans with the respective intervention and control group patients. Patients also had to make conscious food choices to comply with either treatment group (p631-632).

Study ID		Stamets 2004	
RMANCEBIAS	**Were investigators and care providers blind to intervention group?**	Yes Partial No Not reported	No Dietitians knew the treatment groups (p631-632).
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	Yes
CTEDCTIONBIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Partial The laboratory biochemical tests are standard, valid and reliable tests. Measurements of weight-hip ratio measurements are standard, valid and reliable. The measurement of weight may be unreliable because it depended on participants' accurate self-reporting of weight. It is unclear if everyone performed weight measurements under the same conditions (e.g. same accuracy of weigh scales, same amount of clothing on) and were not subjectively recording weights or were reliably recording weights daily. The Ferriman-Gallwey scores is a standard and valid method of evaluating hirsutism. However, its reliability is varied due to the need for subjective decisions on the scoring by users.
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes The laboratory tests are independent. The weight and weight-hip outcomes are independent and are not always related to each other (depending on body phenotypes). The Ferriman-Gallwey scores may not be independent because each question within the tool may reinforce other answers. However, this outcome does not influence the other outcomes assessed. Laboratory tests are objective. Measurements of weight and weight-ratio measurements are mostly objective but may involve some observer judgment depending on the equipment being used for measuring. The Ferriman-Gallwey scores need subjective decisions on the scoring by users.
ATTR	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	For all the variables measured in Table 1, there were no significant differences (p633).

Study ID		Stamets 2004	
ITIONBIAS	**Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?**	Yes Partial No Not reported	Yes It appears that all participants were accounted for and analyzed to the group to which they were allocated to.
REPORTBIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported There is no published protocol available.
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	Yes For all the variables measured in Table 1, there were no significant differences (p633).
	If confounding was present, was it controlled for?	Yes Partial No Not reported	There was 24% (4/17) drop-out in the intervention group and 28% (5/18) drop-out in the control group.
IERBIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No Authors state their funding sources (p630)
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	No The study needed 17 participants per treatment arm to achieve 95% power to detect a weight loss difference of 1.5kg between the two arms, with a standard deviation of 1.2kg, in a two-sample t-test with a two-sided significance level of 5% (p632). However, the study only analyzed 13 participants per treatment arm.

Study ID		Stamets 2004	
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes It is unclear if the statistical tests were planned a priori because there is no published protocol to indicate this. The authors used two-sample t-tests to analyse outcomes that used continuous data. Point estimates and measures of variability were presented for outcomes. It is unclear if there was any missing data. Figures 2 and 3 shown graphs for "combined diets". It is unclear whether this analysis is necessary because the study is aimed at finding out which diet is more effective, so therefore combining the results of the two diets does not add any useful information.
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		Not reported	

Study ID	Toscani 2011
Study Citation	Toscani, M. K., Mario, F. M., Radavelli-Bagatini, S., Wiltgen, D., Matos, M. C., & Spritzer, P. M. (2011). Effect of high-protein or normal-protein diet on weight loss, body composition, hormone, and metabolic profile in southern Brazilian women with polycystic ovary syndrome: a randomized study. Gynecological Endocrinology, 27(11), 925-930.
Study Country	Brazil
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	All participants 22.72±5.68 years
PCOS diagnostic criteria	Not reported
Presence of infertility	Not reported
Presence of other condition/s	Overall, most study participants had BMI≥ 25 kg/m2 No diabetes
Medication History	"Women who had received any drugs known to interfere with hormone levels for at least 3 months before the study...were excluded"
N per group	The number of participants that were: Allocated/randomised: High protein diet= 9, normal protein diet= 9 Assessed at end of study: High protein diet= 9, normal protein diet= 9

Study ID	Toscani 2011	
Setting	Hospital de Clinicas de Porto, Brazil	
Intervention	"Energy needs were estimated by using 20–25 kcal/kg current weight/day for overweight/obese women and 25– 30 kcal/kg current weight/day for normoweight participants [19]. Patients were randomized to receive one of two diets: HP (30% protein, 40% carbohydrate, and 30% lipid)… Habitual physical activity was assessed by a digital pedometer (BP 148 Techline), which records the number of steps taken daily by each individual. Patients were not encouraged to walk more than usual". 8 week intervention	
Comparison	"Energy needs were estimated by using 20–25 kcal/kg current weight/day for overweight/obese women and 25– 30 kcal/kg current weight/day for normoweight participants [19]. Patients were randomized to receive one of two diets:… NP (15% protein, 55% carbohydrate, and 30% lipid). Habitual physical activity was assessed by a digital pedometer (BP 148 Techline), which records the number of steps taken daily by each individual. Patients were not encouraged to walk more than usual". 8 week intervention	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Body weight, WC, Physical activity (not relevant to systematic review), Blood pressure (not relevant to systematic review), Fasting glucose, 2 hour OGTT glucose, Fasting insulin, 2 hour insulin (not relevant to systematic review), HOMA (not relevant to systematic review), Total cholesterol (not relevant to systematic review), HDL (not relevant to systematic review), LDL (not relevant to systematic review), NHDL (not relevant to systematic review), Triglycerides, BMI (presented as a figure only) % body fat (not relevant to systematic review), Sum of trunk skinfolds (not relevant to systematic review), Total testosterone (not relevant to systematic review), SHBG (presented as a figure only), FAI (presented as a figure only)	
Follow up Duration	Eight weeks	
Summary Result/s	"There were no changes in lipid profile in either group. In contrast, body weight, body mass index (BMI), WC, percent of body fat, and sum of trunk skinfolds decreased significantly after both diets in both groups. Total testosterone also decreased in PCOS and controls regardless of diet."	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes

Study ID		Toscani 2011	
Inclusion criteria		Yes Partial No Not reported	Yes "The inclusion criteria were BMI ranging from 18.5 to 39.9 kg/m2 and age between 14 and 35 years…PCOS was considered in hirsute women presenting oligo/amenorrheic cycles (9 or less cycles/year), increased testosterone levels and/or free androgen index, and absence of other disorders causing hirsutism with or without polycystic ovaries at ultrasound."
Exclusion criteria		Yes Partial No Not reported	Yes "Women who had received any drugs known to interfere with hormone levels for at least three months before the study, with diabetes, liver or renal disease, or thyroid dysfunction were excluded from the study."
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Yes "The random allocation sequence to receive the HP or NP diets was performed in four blocks, according to BMI (525 or 25) and groups (control or PCOS)"
	Was allocation to intervention group concealed?	Yes Partial No Not reported	Not reported
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	Not reported Stated that the study was single-blinded, but no further detail as to who was blinded.
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	Not reported Stated that the study was single-blinded, but no further detail as to who was blinded.
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	Yes
CTECT	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	Not reported Stated that the study was single-blinded, but no further detail as to who was blinded.

Study ID		Toscani 2011	
I O N B I A S	**Were all outcomes measured in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes
A T T R I T I O N B I A S	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	No dropouts reported
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	Yes
R E P O R T B I A S	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported No report of a published study protocol
C O N F O U N D I N G	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	Not reported
	If confounding was present, was it controlled for?	Yes Partial No Not reported	No Habitual physical activity was monitored, however one group of participants may have been more physically active than the other and consequently this could have impacted their body weight

Study ID		Toscani 2011	
IER BI A S	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	High - Few or no criteria fulfilled or the conclusions of the study are likely or very likely to be affected.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		High	

Study ID	Wong 2016
Study Citation	Wong JMW, et al., 2016, A randomized pilot study of dietary treatments for polycystic ovary syndrome in adolescents, Pediatric Obesity, 11(3): 210-220.
Study Country	USA
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Overweight and obese adolescents with PCOS and not using hormonal contraceptives (HCs).
PCOS diagnostic criteria	AEPCOS "Each participant had a diagnosis of PCOS from her treating physician with confirmed biochemical hyperandrogenism (elevated serum-free testosterone within the last 6 months) and ovarian dysfunction (oligo-anovulation and/or polycystic ovaries on ultrasound), consistent with criteria established by the Androgen Excess Society".

Study ID	Wong 2016	
Presence of infertility	Not reported	
Presence of other condition/s	Not reported	
Medication History	not using hormonal contraceptives (HCs).	
N per group	N=19 LGL diet n=9 LF diet n= 10	
Setting	Adolescent and Young Adult Medicine Clinic at Boston Children's Hospital (BCH),	
Intervention	LGL (low-glycaemic load) Diet: Target macronutrient composition for the LGL diet was 45% of energy from carbohydrate, 35% from fat and 20% from protein	
Comparison	LF (low-fat) Diet: 55% energy from carbohydrates, 25% from fat and 20% from protein	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	The primary outcome was bioavailable testosterone. Other biochemical outcomes included blood levels of total testosterone, free testosterone, sex hormone binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEAS), total cholesterol, low-density lipoprotein cholesterol (direct determination by enzymatic spectrophotometric assay), high-density lipoprotein (HDL) cholesterol, triglycerides, high sensitivity C-reactive protein and haemoglobin (Hb) A1c. Self-reported HRQL Treatment fidelity	
Follow up Duration	6 months "Outcomes were assessed at baseline, prior to random assignment and at the end of a 6-month intervention period"	
Summary Result/s	Sixteen (LGL, n = 7; LF, n = 9) participants completed the study. Body fat percentage decreased ($P < 0.05$) in response to the interventions, with no difference between the LGL and LF groups (−1.2% vs. −2.2%; $P = 0.16$). Bioavailable testosterone did not change for either group (−0.4 vs. −1.8 ng dL^{-1}; $P = 0.35$).	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes To obtain preliminary data, comparing the impact of a low-glycaemic load (LGL) vs. low-fat (LF) diet on biochemical hyperandrogenism in overweight and obese adolescents with PCOS. To ascertain the feasibility of recruiting study participants in partnership with an adolescent clinic and implementing dietary interventions.

Study ID		Wong 2016	
Does the study have specified inclusion/exclusion criteria?		Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Inclusion criteria		Yes Partial No Not reported	Yes PCOS, age between 13 and 21 years, body mass index, (BMI) ≥ 85th percentile (14), and medical clearance from a treating physician.
Exclusion criteria		Yes Partial No Not reported	Yes "type 2 diabetes (fasting plasma glucose ≥126 mg dL−1), diagnosis of an eating disorder or any other major medical illness, abnormal screening laboratory measures indicating other causes of hyperandrogenism or obesity; and smoking (>1 cigarette per week). Use of medications (hormonal contraceptives [HCs] within the past 3 months, insulin-sensitizing agents within the past month) also was exclusionary."
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Yes "Participants were randomly assigned to receive either a LGL or LF dietary prescription"
	Was allocation to intervention group concealed?	Yes Partial No Not reported	Not reported
PERFORMANCE B	**Were patients blind to intervention group?**	Yes Partial No Not reported	No "The dietitian counselled participants to consume low-glycaemic index sources of carbohydrate (including non-starchy vegetables, legumes and fruits) and to limit intake of moderate or high glycaemic index sources (including refined grains, starchy vegetables and sweets)."
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	No Not explicitly reported but by above comment it can be judged that the patients and investigators knew what kind of die the women were going to have

Study ID		Wong 2016	
I A S	**Aside from the experimental intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes
ETE C T I O N B I A S	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	Yes "Outcome assessors were masked to random assignment"
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes
A T T R I T I O N B I A S	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	10% in LFD 28.6% in the LGD group dropped out
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	No
R E P O R T B I A S	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Yes
C O N F O U N	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	Yes

Study ID		Wong 2016	
D I N G	**If confounding was present, was it controlled for?**	Yes Partial No Not reported	No No confounding reported
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	Yes Funding sources were clearly reported and accompanied with the following statement "The funding organizations played no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication."
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Partial "According to a priori power calculations, a sample size of 40 participants would provide 80% power to detect a group differential approximating 20% when testing our primary hypothesis, and we proposed to recruit 50 participants to account for attrition. In light of recruitment challenges, we pooled available data from both dietary intervention groups to construct conditional power curves in July 2013. From these curves, we concluded that the enrolment of additional participants would not substantially enhance the power to detect a group effect for change in bioavailable testosterone. Thus, we stopped recruitment in July 2013, and this report is based on data from 16 of 19 (7/9 LGL, 9/10 LF) randomly assigned participants who completed the study."
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	Moderate
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 3

Question 3.3.

In women with PCOS, are diet interventions (compared to different diets) effective for improving anthropometric, metabolic, fertility, and emotional wellbeing outcomes?

BACKGROUND:

Lifestyle modification, including diet, exercise and weight management, are recommended as the first line of treatment for women with PCOS. While dietary interventions resulting in weight loss have shown benefits, long-term, well controlled studies investigating different dietary approaches in women with PCOS are lacking and the role of specific dietary composition remains controversial (1).

Given the general recommendations to reduce caloric (energy) intake, rather than modifying macronutrient composition, the widespread promotion of specific dietary composition in PCOS and the limited comparative research on efficacy of specific dietary approaches in PCOS, this clinical question was prioritised.

Evidence summary

Twelve RCTs were identified (from 18 publications) including 496 participants - ten with a parallel design and two a crossover design. The majority of studies were in adult women with PCOS but one was conducted in adolescents and the majority of participants were overweight or obese. Five studies were conducted in Iran, 3 in the USA and the remaining 4 in Canada, Italy, Australia and Brazil. Subject numbers range between 14 and 61; more than half (7) of the studies had between 50–60 participants and one quarter (3) had less than 20 in participants. Duration of the studies was 4 weeks to 6 months, with most between 8-12 weeks.

Dietary interventions included the DASH (Dietary Approaches to Stop Hypertension) diet (3 studies), higher protein/lower carbohydrate diets (5 studies), higher fat/lower carbohydrate diets (3 studies) and a pulse-based low glycaemic index diet (1 study). Where specified, the macronutrient composition of intervention diets ranged from 40-55% carbohydrate, 15-30% protein and 25-40% fat and control diets 50-55% carbohydrate, 15-20% protein and 25-30% fat.

A meta-analysis of five studies (2, 3, 4, 5, 6) comparing a hypocaloric high protein/low carbohydrate diet (40% carbohydrate, 30% protein, 30% fat) vs a control diet (55% carbohydrate, 15% protein, 30% fat) showed no significant differences in anthropometric or metabolic outcomes apart from HDL-cholesterol which favoured the control diet.

For the remaining studies, a meta-analysis was not conducted due to heterogeneity in the dietary composition of intervention and control arms and variability in energy restriction prescribed (with or without energy restriction). Results are therefore summarised descriptively below.

- Three studies (7, 8, 9, 10) compared a DASH diet to a control (traditional) diet- macronutrient composition was 50-55% carbohydrate, 15-20% protein and 25-30% fat and energy was restricted in both the intervention and control groups. Analysis showed greater improvements in BMI (2 of 2 studies), waist circumference (1 of 1 study), fasting insulin (2 of 2 studies) and HOMA-IR (2 of 2 studies) and mixed findings for weight (2 of 3 studies) and FAI (1 of 2 studies) with the DASH diet versus a control diet. No differences were seen for total testosterone, fasting glucose and blood lipids (HDL, LDL and TG). These findings were of low to very low certainty. Due to notices of concern and issues raised about integrity of the studies (both in the literature and across other GDGs), these studies were included, but not used to inform any recommendations.
- One study (11-14) showed greater improvements in blood lipids (reduction in LDL and TG and increase in HDL) with a low glycaemic index pulse-based diet (2 meals per day consisting of pulses) versus a control diet (protein from lean meat, poultry and low-fat dairy foods and limited intake of pulses). No differences between the diets were seen for anthropometric measures (weight, BMI and WC), fasting glucose, fasting insulin, HOMA-IR, total testosterone or FAI. Energy wasn't restricted and macronutrient composition changes were not significantly different between the two groups however there was a significantly

greater increase in dietary fibre and reduction in glycaemic index but not glycemic load with the pulse-based diet compared to the control diet.

- Two studies (15-17) compared a eucaloric higher/fat lower carbohydrate diet with a control diet (lower in fat and higher in carbohydrate) and found no differences between the groups for fasting insulin and glucose. For other outcomes, between group comparisons were not reported.
- One study (18) compared a hypocaloric low carbohydrate higher fat diet (45% carbohydrate, 20% protein, 35% fat) versus a low-fat diet (55% carbohydrate, 20% protein, 25% fat). A greater reduction in BMI was seen in the low-fat diet group but there were no significant differences in other outcomes (weight, waist circumference, fasting glucose, fasting insulin, HOMA-IR, HDL, LDL, TG, total testosterone or FAI) between the groups.

Together these findings suggest that diets with a range of macronutrient compositions could be recommended for women with PCOS. These findings are consistent with research in the general population. A systematic review and network meta-analysis of 121 randomised trials with almost 22 000 participants found that diets of varying macronutrient compositions result in modest weight loss and substantial improvements in cardiovascular risk factors over 6 months although these improvements are not maintained at 12 months (19). Compared to usual diets, low carbohydrate and low-fat diets had similar effects on weight loss at six months. Furthermore, evidence doesn't suggest a benefit of modifying the macronutrient composition of the diet based on insulin secretion (20).

Rather than restricting carbohydrate, research in other populations suggests that the quality of carbohydrates in the diet is important and diets containing carbohydrate foods which are high in fibre and have a lower glycemic index, including wholegrains, pulses/legumes and fruit, have been shown to reduce cardiometabolic risk factors and are associated with weight loss and a lower incidence of diabetes, cardiovascular disease and cardiovascular mortality (21).

Evidence to Recommendations Framework

COMPARISONS (option versus other option)

In women with PCOS, are diet interventions (compared to no diet or different diets) effective for improving weight loss, metabolic, fertility, and emotional wellbeing outcomes?

EVIDENCE-BASED RECOMMENDATION(S)

- **EBR:** Health professionals and women could consider that, there is a lack of evidence supporting any one type of diet composition over another for anthropometric, metabolic, hormonal, reproductive or psychological outcomes.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

- **CR:** Any diet composition consistent with population guidelines for healthy eating has health benefits, and within this, health professionals should advise sustainable healthy eating tailored to an individual's preferences and goals.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

PRACTICE POINT(S)

- Tailoring of dietary changes to food preferences, allowing for a flexible, individual and co-developed approach to achieving nutritional goals and avoiding unduly restrictive and nutritionally unbalanced diets, are important, as per general population recommendations.

- Barriers and facilitators to optimise engagement and adherence to dietary change should be discussed, including psychological factors, physical limitations, socioeconomic and sociocultural factors, as well as personal motivators for change. The value of broader family engagement should be considered. Referral to suitably trained allied healthcare professionals needs to be considered when women with PCOS need support with optimising their diet.

GRADE CONSIDERATIONS

Justifications:
Given that consumer targeted information about PCOS purport the benefit of specific macronutrient composition, this recommendation is important to ensure that women and health professionals are informed on the evidence on dietary composition and efficacy. Emphasis should be on individual preferences and cultural needs of each woman and on an overall balanced and healthy dietary composition to achieve individual nutritional goals. Education for both women and health professionals is needed in this area. Specific cost and resource implications were considered but recommendations were approved on balance, informed by recommendations in the general population and benefits in PCOS.

Subgroup considerations:
There was no population subgroup analysis presented. Caution should be exercised when generalising the findings to subgroups such as some ethnic populations. All but one study was performed in adults and the majority of participants were women with higher BMI. Caution should be exercised when generalising the findings to adolescents and women across the lifespan and lean women.

Implementation considerations:
Some consumer-targeted resources (including books, websites and online programs) claim benefits for specific macronutrient composition (particularly low carbohydrate diets) and other dietary restrictions (e.g. gluten and dairy free diets) for women with PCOS, so greater education for consumers and health professionals around evidence-based dietary approaches is important.
Providing evidence-based tailored dietary advice to women with PCOS may require referral to other health professionals (e.g. dietitians) and increase the length of consultations. This has both time and cost implications.

Monitoring and evaluation considerations:
Monitor that women's goals and preferences are being captured and needs are being met.
Monitor if health professionals are providing evidence-based approaches

Research priorities:
Well designed, long-term and adequately powered studies in women across the BMI range investigating the impact of different dietary interventions on a range of outcomes (including fertility and reproductive outcomes) in this population are needed.
Further research is needed to investigate the impact of a range of dietary interventions on anthropometric, metabolic, hormonal, reproductive or psychological outcomes in women with PCOS.

It is acknowledged that not all diets need to be trialled in women with PCOS and that adequately powered, general population studies will also be of relevance to this population.
There needs to be more monitoring of safety and harm of specific dietary interventions (including disordered eating and eating disorders) and long-term follow-up. There is also a need to address the high drop-out rate from dietary intervention studies.
Further research looking at appropriate strategies for dissemination of evidence-based dietary information is also needed.

GRADE framework

GRADE DECIDE **Interactive Evidence to Decision Framework**

● DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

Judgement:

☒ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

A range of healthy diets can assist with anthropometric, metabolic, hormonal, reproductive or psychological outcomes in women with PCOS. However, there is a lack of evidence to support one particular dietary intervention over another and for women across the BMI range particularly with respect to macronutrient composition.

● UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

No specific undesirable effects noted in most studies although dropout rates were high in some

In the Kazemi (pulse-based diet) study it was noted that 3 participants withdrew due to mild to moderate GI symptoms (bloating, flatulence, upset stomach) which were classified as 'possibly' related to the intervention.

● CERTAINTY OF THE EVIDENCE

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☒ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Macronutrient composition of the diet doesn't appear to impact anthropometric or metabolic outcomes.

● VALUES

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☐ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☒ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Research evidence:

No research evidence was identified

Panel discussion:

There is probably no important uncertainty or variability in how much women with PCOS and health professionals value the role of dietary intervention in improving PCOS outcomes.

Lifestyle changes have been identified as the first line of treatment of PCOS.

● BALANCE OF EFFECTS

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:

● COSTS

How large are the resource requirements (costs)?

Judgement:

☒ Don't know	☐ Varies	☐ Large costs	☐ Moderate costs	☐ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:

No research evidence was identified

Panel discussion:

Costs could include:

- development and distribution of educational resources for women with PCOS
- education of health professionals
- tailored dietary advice for women with PCOS by health professionals which could require longer consultation times

● CERTAINTY OF COST EVIDENCE

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

No research evidence was identified

Panel discussion:

There was no evidence to inform this consideration.

● COST-EFFECTIVENESS

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

No research evidence was identified

Panel discussion:

There is no evidence to compare the cost effectiveness of different dietary interventions for women with PCOS - these studies are needed.

The recommendations may increase healthcare costs through increased consultation times and referral to health professionals, however the long-term benefits of dietary and lifestyle modification may reduce the health and economic burden of PCOS

● EQUITY

What would be the impact on health equity?

Judgement:

☐ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☒ Probably increased	☐ Increased

Research evidence:

No research evidence was identified

Panel discussion:

No specific dietary intervention / composition

The implementation may be variable due to availability of local resources but recommendation is likely to improve equity.

● ACCEPTABILITY

Is the option acceptable to key stakeholders?

Judgement:

☐ Don't know	☒ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Findings suggest that healthy diets varying in macronutrient composition can be recommended, which allows for tailoring of dietary advice to suit the dietary preferences and resources of each woman with PCOS. This may increase acceptability among both women with PCOS and health professionals.

The recommendations are unlikely to significantly change usual care for most health practitioners although may necessitate longer consultation times and increased referral to health professionals.

Consumers (women with PCOS) may want more specific dietary advice to assist them in implementing the recommendations to lose weight and/or prevent weight gain.

Acceptability will be influenced by the expectations, cultural considerations and health literacy of the women and accessibility and affordability of the interventions.

● FEASIBILITY

Is the option feasible to implement?

Judgement:

☐ Don't know	☒ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Policy settings, health system enablers, education and engagement of health professionals and patient considerations (such as the cost of longer consultations and/or consultations with other health professionals) will affect feasibility.

The main requirement to implement the recommendation is education of health professionals and women with PCOS about evidence-based dietary recommendations, which is feasible.

There are significant expectations and misinformation that need to be combated.

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syndrome: a randomized controlled intervention study. J Am Coll Nutr. 2012 Apr;31(2):117-25. doi: 10.1080/07315724.2012.10720017. PMID: 22855917.

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PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by ECR Lead: Angelo Sabag

Other team members: Loyal Pattuwage, Rhiannon K. Patten, Giorgia E. Colombo, Xela Dafauce Bouzo

Supervised, edited and supported by the Evidence Team (Aya Mousa, Jillian Tay)

GDG 3

Question 3.4.

In women with PCOS, are exercise interventions (compared to different exercises) effective for improving anthropometric, metabolic, reproductive, fertility, quality of life and emotional wellbeing outcomes?

1. SELECTION CRITERIA

Table 1. PICO Criteria for Inclusion – Not to be adapted To be used by evidence team to decide which studies will be included when screening search results.		
Question	Q 3.4) In women with PCOS, are exercise interventions (compared to different exercises) effective for improving anthropometric, metabolic, reproductive, fertility, quality of life and emotional wellbeing outcomes?	
ECR Lead	Dr Angelo Sabag, Western Sydney University, Australia	
Clinical leads (key contacts)	Prof Leanne Redman Exercise physiologist Pennington Biomedical Research Centre, USA leanne.redman@pbrc.edu	Prof Anjelica Hirschberg Obstetrician-gynaecologist Karolinska Instututet, Sweden angelica.hirschberg.linden@ki.se
Allocation ranking	Level 2- Update systematic review	

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(language, year)*
Inclusion	Females with PCOS (diagnosed by Rotterdam, NIH or AES) of any age, ethnicity, weight and with any co-morbidity. Subgroup by: BMI, adolescents, adult, preconception, pregnancy, post-menopausal, PCOS phenotype, those using no other medication. Can be taking any medications to manage PCOS symptoms, DM2, co-morbidities, as long as this medication use is not a primary component of the intervention or control arms. Document diabetes status, smoking status.	All types of exercise regimes that can be quantifiable. Structure of exercise regime must be documented (eg. type, intensity, frequency, duration). Subgroup by aerobic/endurance and resistance. Short/medium/long term. "Free range exercises" or "physical activity" can be included as long as it can be quantified in terms of time, work, energy, and/or intensity. Duration of exercise intervention ≥ 2 weeks.	All types of other exercise regimes that can be quantifiable. Structure of exercise regime must be documented (eg. type, intensity, frequency, duration). Free range exercises can be included as long as it has tools for correlating to work, energy, and/or intensity. Duration of exercise intervention ≥ 2 weeks.	Anthropometric: Weight, BMI, WC Metabolic: HbA1c, Fasting insulin, fasting glucose, HOMA, OGTT insulin, OGTT glucose, lipids (total cholesterol, LDL, HDL, TG), Systolic BP Reproductive: Hirsutism (clinical HA) biochemical HA (total testosterone, SHBG, FAI, free testosterone), ovulation, menstrual regularity, Psychological: Anxiety, depression, quality of life *For pregnancy subgroups* Anthropometric: Weight, BMI, gestational weight gain Metabolic: Fasting insulin, fasting glucose, HOMA, OGTT insulin, OGTT glucose, lipids (total cholesterol, LDL, HDL, TG) Reproductive: Live birth, pregnancy, miscarriage, gestational diabetes, preeclampsia, birth weight Psychological: Anxiety, depression, quality of life	Evidence based guidelines, systematic reviews, health technology assessments, randomised controlled trials.	English language. Update original search for exercise versus other exercise and add RCT filter
Exclusion	Females without PCOS. Taking anti-obesity medications (metformin isn't an exclusion). Bariatric surgery. Patients using medications for DM2, co-morbidities or for clinical or metabolic features of PCOS, as the primary component of the intervention or control arms of a study.	Exercise interventions that cannot be quantifiable. Interventions taken with anti-obesity medications.	Treatment regime that cannot be quantifiable. Treatments used in conjunction with anti-obesity medications.		Non-evidence based guidelines, non-systematic reviews, any study lower than a RCT.	

2. SEARCH STRATEGY

Table 2.1. Search details	
Search strategy source: *2018 technical report page 774*	
Evidence source	Date of search
Medline (Ovid)	26th July 2022
PsychInfo (Ovid)	28th July 2022
EMBASE (Ovid)	26th July 2022
All EBM (Ovid)	26th July 2022
CINAHL	29th July 2022
Any subsequent updates - enter database and date:	

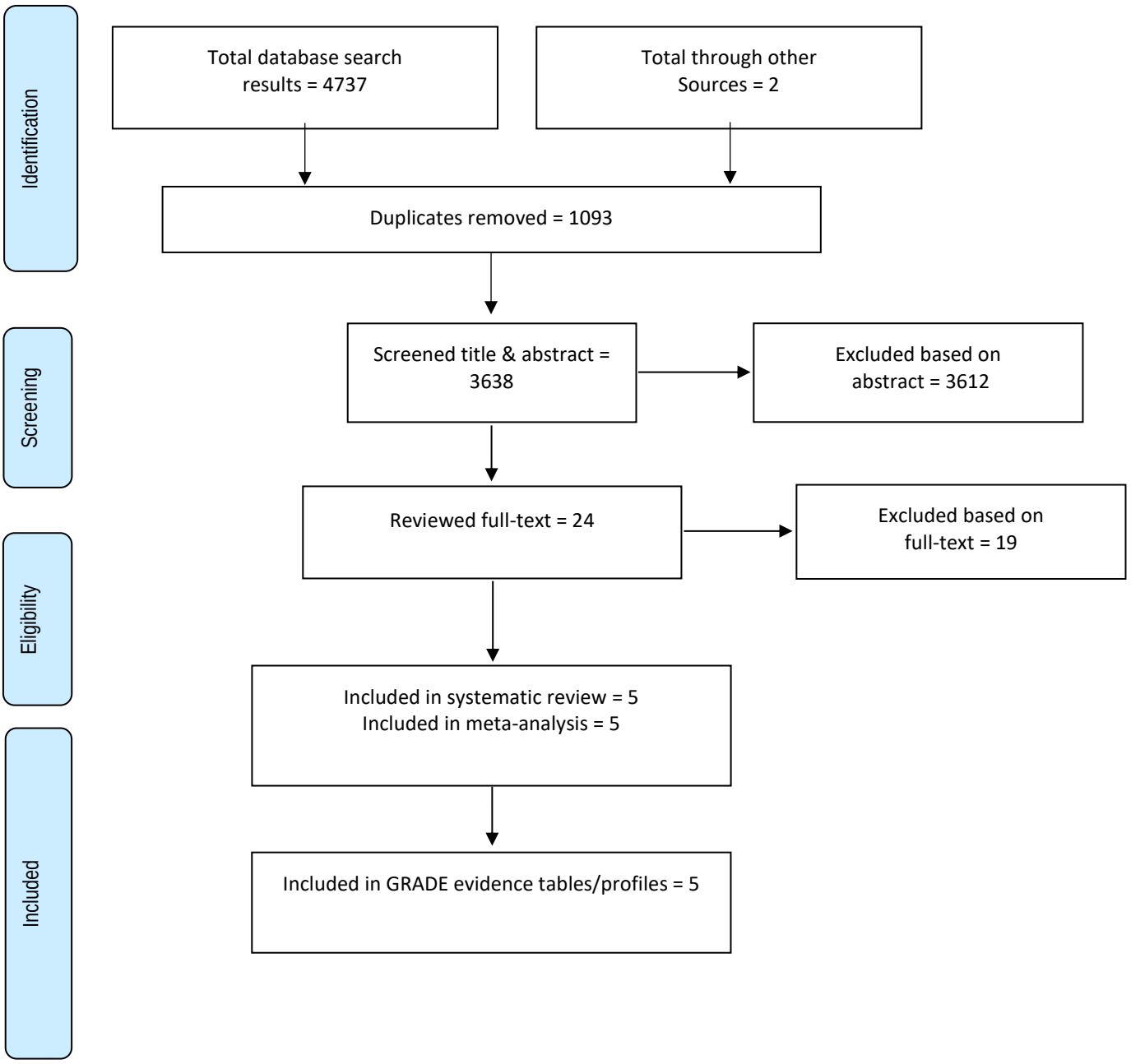
Table 2.2. Questions addressed by this search:		
GDG	Q3.4	In women with PCOS, are exercise interventions (compared to different exercises) effective for improving anthropometric, metabolic, reproductive, fertility, quality of life and emotional wellbeing outcomes?

Table 2.3. Search strings used in OVID or other database/s			
OVID Medline, All EBM, PsychInfo, EMBASE (results= 4618)		CINAHL (results= 119)	
1	exp polycystic ovary syndrome/	S1	SU polycystic ovary syndrome
2	polycystic ovar*.mp.	S2	polycystic ovar*
3	PCO*.mp.	S3	poly-cystic ovar*
4	(stein-leventhal or leventhal).mp.	S4	PCO*
5	anovulation/	S5	stein-leventhal or leventhal
6	anovulat*.mp.	S7	SU anovulation
7	oligo-ovulat*.mp.	S8	oligo-ovulat*
8	oligoovulat*.mp.	S9	oligoovulat*
9	(ovar* adj5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*)).mp.	S10	ovar* N5 sclerocystic or ovar* N5 polycystic or ovar* N5 poly-cystic or ovar* N5 degenerat* or ovar* N5 hyperandrogen* or ovar* N5 hyperandrogen*
10	poly-cystic ovar*.mp.	S11	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10
11	or/1-10	S12	exercise*
12	exercise*.mp.	S13	exercise therapy
13	exercise therapy.mp.	S14	physical activit*
14	exertion.mp.	S15	physical performance
15	physical fitness.mp.	S16	(strength N2 training)
16	physical activit*.mp.	S17	resistance training
17	physical performance.mp.	S18	(aerobic* N2 training)
18	sport*.mp.	S19	(endurance N training)
19	(strength adj2 training).mp.	S20	physical training
20	resistance training.mp.	S21	(strength* N2 exercise*)
21	(aerobic* adj2 training).mp.	S22	(weight-bearing N2 exercise*)
22	(endurance adj training).mp.	S23	(Resistance N2 exercise*)
23	physical training.mp.	S24	(Aerobic* N2 exercise*)
24	(strength* adj2 exercise*).mp.	S25	(Endurance N2 exercise*)
25	(weight-bearing adj2 exercise*).mp.	S26	(Physical N2 exercise*)
26	(Resistance adj2 exercise*).mp.	S27	(MH "Exercise+")
27	(Aerobic* adj2 exercise*).mp.	S28	(MH "Therapeutic Exercise+")
28	(Endurance adj2 exercise*).mp.	S29	(MH "Yoga+")
29	(Physical adj2 exercise*).mp.	S30	S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29

30	fit*.mp.	S31	S11 AND S30
31	bicycle*.mp.	S32	Limiters - Published Date: 20170101-20221231; English Language; Exclude MEDLINE records
32	cycl*.mp.		
33	run*.mp.		
34	swim*.mp.		
35	walk*.mp.		
36	jog*.mp.		
37	train*.mp.		
38	gym*.mp.		
39	aqua-aerobics.mp.		
40	pilates.mp.		
41	yoga.mp.		
42	danc*.mp.		
43	exp exercise/		
44	exp exercise therapy/		
45	physical exertion/		
46	exp sports/		
47	exp physical endurance/		
48	or/12-47		
49	search$.tw. or meta-analysis.mp. or meta-analysis.pt. or review.pt. or di.tw,kw. or associated.tw.		
50	clinical trial.mp. or clinical trial.pt. or random.mp. or tu.xs.		
51	49 or 50		
52	11 and 48 and 51		
53	limit 52 to (english language and humans and yr="2017 - Current")		

Evidence processing: Studies were selected and appraised by two reviewer/s in consultation with the evidence team/ key contact using study selection and appraisal criteria (PICO above) established a priori. The articles were reviewed by title and abstract by two reviewers. When a decision could not be made based on title and abstract alone, full text was retrieved. **A total of 5 unique studies met inclusion criteria for this review.**

3. SEARCH RESULTS - PRISMA flowchart



4. STUDY INCLUSION

Table 4.1. Included Studies
Almenning I, Rieber-Mohn A, Lundgren KM, Shetelig Løvvik T, Garnæs KK, Moholdt T. Effects of High Intensity Interval Training and Strength Training on Metabolic, Cardiovascular and Hormonal Outcomes in Women with Polycystic Ovary Syndrome: A Pilot Study. PLoS One. 2015 Sep 25;10(9):e0138793. doi: 10.1371/journal.pone.0138793.
Benham JL, Booth JE, Corenblum B, Doucette S, Friedenreich CM, Rabi DM, Sigal RJ. Exercise training and reproductive outcomes in women with polycystic ovary syndrome: A pilot randomized controlled trial. Clin Endocrinol (Oxf). 2021 Aug;95(2):332-343. doi: 10.1111/cen.14452.
Lopes IP, Ribeiro VB, Reis RM, Silva RC, Dutra de Souza HC, Kogure GS, Ferriani RA, Silva Lara LAD. Comparison of the Effect of Intermittent and Continuous Aerobic Physical Training on Sexual Function of Women With Polycystic Ovary Syndrome: Randomized Controlled Trial. J Sex Med. 2018 Nov;15(11):1609-1619. doi: 10.1016/j.jsxm.2018.09.002. Ribeiro VB, Kogure GS, Lopes IP, Silva RC, Pedroso DCC, de Melo AS, de Souza HCD, Ferriani RA, Miranda Furtado CL, Dos Reis RM. Effects of continuous and intermittent aerobic physical training on hormonal and metabolic profile, and body composition in women with polycystic ovary syndrome: A randomized controlled trial. Clin Endocrinol (Oxf). 2020 Aug;93(2):173-186. doi: 10.1111/cen.14194. Ribeiro VB, Lopes IP, Dos Reis RM, Silva RC, Mendes MC, Melo AS, de Souza HCD, Ferriani RA, Kogure GS, Lara LADS. Continuous versus intermittent aerobic exercise in the improvement of quality of life for women with polycystic ovary syndrome: A randomized controlled trial. J Health Psychol. 2021 Aug;26(9):1307-1317. doi: 10.1177/1359105319869806.
Patten RK, McIlvenna LC, Levinger I, Garnham AP, Shorakae S, Parker AG, McAinch AJ, Rodgers RJ, Hiam D, Moreno-Asso A, Stepto NK. High-intensity training elicits greater improvements in cardio-metabolic and reproductive outcomes than moderate-intensity training in women with polycystic ovary syndrome: a randomized clinical trial. Hum Reprod. 2022 May 3;37(5):1018-1029. doi: 10.1093/humrep/deac047.
Thomson RL, Buckley JD, Noakes M, Clifton PM, Norman RJ, Brinkworth GD. The effect of a hypocaloric diet with and without exercise training on body composition, cardiometabolic risk profile, and reproductive function in overweight and obese women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2008 Sep;93(9):3373-80. doi: 10.1210/jc.2008-0751.

Table 4.2. Excluded Studies (on full text assessment)	
Reference	Reason
Al-Eisa et al. 2017	Wrong comparator
Benham et al. 2020	Conference abstract
Elbandrawy et al. 2022	Wrong comparator
Furtado et al. 2020	Conference abstract
Hansen et al. 2020	Wrong patient population
Jerobin et al. 2021	Wrong comparator
Kazemi et al. 2018	Wrong comparator
Kiel et al. 2022	Wrong comparator
Kiel et al. 2022	Wrong comparator
Lara et al. 2018	Conference abstract
Li et al. 2019	Wrong intervention
Li et al. 2020	Wrong intervention
Lionett et al. 2020	Wrong comparator
Patel et al. 2018	Wrong intervention
Ramanjaneya et al. 2018	Wrong study design
Scott et al. 2017	Wrong study design
Shalini et al. 2020	Wrong intervention
Veena Kirthika el al 2019	Wrong comparator
Woodward et al. 2022	Wrong comparator

5. STUDY CHARACTERISTICS

Author, year, country	Population/ Setting	Study Design	Sample Size per group	Intervention/ exposure details	Comparison/ control details	Follow up Duration	Outcomes	Summary of findings
Almenning 2015 Norway	Women with PCOS	Parallel RCT	HIIT = 10 RT = 11	HIIT 3 days per week	RT 3 days per week	10 weeks	Metabolic, cardiovascular, and hormonal outcomes	HIIT improved insulin resistance, body composition. RT improved body composition
Benham 2021 Canada	Women with PCOS	Parallel RCT	HIIT = 16 MICT = 14	HIIT 3 days per week	MICT 3 days per week	6 months	Reproductive, anthropometric and cardiometabolic outcomes	MICT and HIIT were both effective at improving anthropometrics and some cardiometabolic health markers.
Patten 2022 Australia	Women with PCOS	Parallel RCT	HIIT = 15 MICT = 14	HIIT 3 days per week	MICT 3 days per week	12 weeks	Insulin sensitivity, hormonal profiles, menstrual cyclicity and body composition.	HIIT offers greater improvements in aerobic capacity, insulin sensitivity and menstrual cyclicity, and larger reductions in hyperandrogenism compared to MICT
Ribeiro 2020 Brazil	Women with PCOS	Parallel RCT	HIIT = 35 MICT = 37	HIIT 3 days per week	MICT 3 days per week	16 weeks	Hormonal, metabolic, anthropometric, quality of life, depression and anxiety.	MICT and HIIT training improved hormonal, anthropometric, anxiety and depression, and quality of life. Only HIIT training reduced the FAI. Only MICT training improved lipid profile.
Thomson 2008 Australia	Women with PCOS	Parallel RCT	MICT = 31 MICT+ RT = 33	MICT 5 days per week	MICT 3 days per week and RT 2 days per week	20 weeks	Weight, body composition, cardiometabolic risk factors, hormonal status, menstrual cyclicity, and ovulatory function.	The addition of aerobic or combined aerobic resistance exercise to an energy-restricted diet improved body composition but had no additional effect on improvements in cardiometabolic, hormonal, and reproductive outcomes relative to diet alone.

5.1. DATA EXTRACTION– CONTINUOUS OUTCOMES

Anthropometric outcomes

OUTCOME: Body weight				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): High-intensity interval training versus moderate-intensity continuous training								
Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD/SEM in intervention group	Mean in comparison group	SD/SEM in comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Benham et al. 2021	kg	Scale	Pre: 85.2 (n = 15) Post: 85.3 (n = 11)	Pre: 6.2 Post: 6.4 SEM	Pre: 84.5 (n = 12) Post: 83.3 (n = 12)	Pre: 6.9 Post: 7.1 SEM	Crude	NA
Patten et al. 2022	kg	Scale	Pre: 97.4 (n = 15) Post: 97.3 (n = 13)	Pre: 19.2 Post: 19.1 SD	Pre: 102.4 (n = 14) Post: 99.8 (n = 11)	Pre: 28.9 Post: 28.0 SD	Crude	NA
Ribeiro et al. 2020	kg	Scale	Pre: 77.4 (n = 29) Post: 77.0 (n = 29)	Pre: 16.9 Post: 16.8 SD	Pre: 74.4 (n = 28) Post: 73.3 (n = 28)	Pre: 17.0 Post: 17.0 SD	Crude	NA

OUTCOME: Body weight				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): High-intensity interval training versus resistance training								
Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD in intervention group	Mean in comparison group	SD in comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Almenning et al. 2015	kg	Scale	Pre: 73.5 (n = 10) Post: 68.5 (n = 8)	Pre: 16.7 Post: 14.2 SD	Pre: 76.5 (n = 11) Post: 78.1 (n = 8)	Pre: 20.2 Post: 20.0 SD	Crude	NA

OUTCOME: Body weight				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): Diet plus moderate-intensity continuous training versus diet plus moderate-intensity continuous training and resistance training								
Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD in intervention group	Mean in comparison group	SD in comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Thomson et al. 2008	kg	Scale	Pre: 97.6 (n = 18) Post: 87.5 (n = 18)	Pre: 18.4 Post: 18.4 SD	Pre: 102.1 (n = 20) Post: 93.5 (n = 20)	Pre: 18.4 Post: 18.4 SD	Crude	NA

OUTCOME: BMI				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): High-intensity interval training versus moderate-intensity continuous training								
Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD/SEM in intervention group	Mean in comparison group	SD/SEM in comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Benham et al. 2021	Kg/m^2	Scale and stadiometer	Pre: 31.8 (n = 15) Post: 31.9 (n = 11)	Pre: 2.3 Post: 2.3 SEM	Pre: 31.4 (n = 12) Post: 30.6 (n = 12)	Pre: 2.6 Post: 2.6 SEM	Crude	NA
Patten et al. 2022	Kg/m^2	Scale and stadiometer	Pre: 35.8 (n = 15) Post: 35.6 (n = 13)	Pre: 6.8 Post: 7.0 SD	Pre: 38.4 (n = 14) Post: 37.3 (n = 11)	Pre: 9.3 Post: 9.8 SD	Crude	NA
Ribeiro et al. 2020	Kg/m^2	Scale	Pre: 28.7 (n = 29) Post: 28.5 (n = 29)	Pre: 4.8 Post: 4.8 SD	Pre: 28.4 (n = 28) Post: 28.2 (n = 28)	Pre: 5.6 Post: 5.7 SD	Crude	NA

OUTCOME: BMI				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): High-intensity interval training versus resistance training								
Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD in intervention group	Mean in comparison group	SD in comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Almenning et al. 2021	Kg/m^2	Scale and stadiometer	Pre: 26.1 (n = 10) Post: 23.9 (n = 8)	Pre: 6.5 Post: 4.8 SD	Pre: 27.4 (n = 11) Post: 27.5 (n = 8)	Pre: 6.9 Post: 6.1 SD	Crude	NA

OUTCOME: Waist circumference				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): High-intensity interval training versus moderate-intensity continuous training								
Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD/SEM in intervention group	Mean in comparison group	SD/SEM in comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Benham et al. 2021	Cm	Measuring tape	Pre: 98.7 (n = 15) Post: 91.4 (n = 11)	Pre: 4.8 Post: 4.9 SEM	Pre: 98.5 (n = 12) Post: 91.6 (n = 12)	Pre: 5.4 Post: 5.4 SEM	Crude	NA
Patten et al. 2022	Cm	Measuring tape	Pre: 99.6 (n = 15) Post: 97.7 (n = 13)	Pre: 15.0 Post: 14.6 SD	Pre: 109.2 (n = 14) Post: 103.0 (n = 11)	Pre: 21.2 Post: 20.8 SD	Crude	NA
Ribeiro et al. 2020	Cm	Measuring tape	Pre: 90.5 (n = 29) Post: 88.7 (n = 29)	Pre: 11.3 Post: 12.4 SD	Pre: 88.1(n = 28) Post: 86.6 (n = 28)	Pre: 14.0 Post: 13.1 SD	Crude	NA

OUTCOME: Waist circumference				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): High-intensity interval training versus resistance training								
Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD in intervention group	Mean in comparison group	SD in comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Almenning et al. 2015	Cm	Measuring tape	Pre: 92.3 (n = 10) Post: 87.2 (n = 8)	Pre: 15.8 Post: 12.6 SD	Pre: 94.4 (n = 11) Post: 92.3 (n = 8)	Pre: 18.1 Post: 16.5 SD	Crude	NA

OUTCOME: Waist circumference				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): Diet plus moderate-intensity continuous training versus diet plus moderate-intensity continuous training and resistance training								
Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD in intervention group	Mean in comparison group	SD in comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Thomson et al. 2008	Cm	Measuring tape	Pre: 100.2 (n = 18) Post: 88.5 (n = 18)	Pre: 12.2 Post: 13.4 SD	Pre: 103.8 (n = 18) Post: 92.8 (n = 18)	Pre: 12.6 Post: 13.2 SD	Crude	NA

Metabolic Outcomes

OUTCOME: HbA1c				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): High-intensity interval training versus moderate-intensity continuous training								
Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD/SEM in intervention group	Mean in comparison group	SD/SEM in comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Benham et al. 2021	%	Tinaquant Hemoglobin A1cDx Gen.3 assay and a Cobas c513 analyser	Pre: 5.4 (n = 15) Post: 5.4 (n = 11)	Pre: 0.1 Post: 0.1 SEM	Pre: 5.3 (n = 12) Post: 5.4 (n = 12)	Pre: 0.1 Post: 0.1 SEM	Crude	NA
Patten et al. 2022	%	Commercial laboratory but otherwise not reported	Pre: 5.2 (n = 15) Post: 5.1 (n = 13)	Pre: 0.3 Post: 0.3 SD	Pre: 5.3 (n = 14) Post: 5.4 (n = 11)	Pre: 0.2 Post: 0.3 SD	Crude	NA

OUTCOME: Fasting glucose	OUTCOME TYPE: Continuous
COMPARISON (if applicable): High-intensity interval training versus moderate-intensity continuous training	

Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD/SEM in intervention group	Mean in comparison group	SD/SEM in comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Benham et al. 2021	mmol/L	Enzymatic methods on a Cobas c701 analyser	Pre: 5.0 (n = 15) Post: 5.3 (n = 11)	Pre: 0.1 Post: 0.1 SEM	Pre: 4.9 (n = 12) Post: 5.0 (n = 12)	Pre: 0.1 Post: 0.1 SEM	Crude	NA
Patten et al. 2022	mmol/L	Commercial laboratory but otherwise not reported	Pre: 5.0 (n = 15) Post: 4.6 (n = 13)	Pre: 0.4 Post: 0.3 SD	Pre: 5.0 (n = 14) Post: 4.7 (n = 11)	Pre: 0.6 Post: 0.3 SD	Crude	NA
Ribeiro et al. 2020	mg/dL	oxidase method (CMD 800X)	Pre: 82.0 (n = 29) Post: 82.0 (n = 29)	Pre: 11.0 Post: 11.0 SD	Pre: 84.0 (n = 28) Post: 84.0 (n = 28)	Pre: 12.0 Post: 11.0 SD	Crude	NA

OUTCOME: Fasting glucose				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): High-intensity interval training versus resistance training								
Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD in intervention group	Mean in comparison group	SD in comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Almenning et al. 2015	mmol/L	Roche Moduclar P	Pre: 5.1 (n = 10) Post: 4.9 (n = 8)	Pre: 0.3 Post: 0.2 SD	Pre: 5 (n = 11) Post: 5.1 (n = 8)	Pre: 0.2 Post: 0.4 SD	Crude	NA

OUTCOME: Fasting glucose				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): Diet plus moderate-intensity continuous training versus diet plus moderate-intensity continuous training and resistance training								
Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD in intervention group	Mean in comparison group	SD in comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Thomson et al. 2008	mmol/L	Commercial enzymatic kits on a Hitachi 902 autoanalyzer	Pre: 5.19 (n = 18) Post: 4.99 (n = 18)	Pre: 0.5 Post: 0.6 SD	Pre: 5.1 (n = 18) Post: 5.0 (n = 18)	Pre: 0.5 Post: 0.5 SD	Crude	NA

OUTCOME: Fasting insulin				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): High-intensity interval training versus moderate-intensity continuous training								
Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD/SEM in intervention group	Mean in comparison group	SD/SEM in comparison group	Are these values	If adjusted, what variables were included in the model?

							adjusted or crude?	
Benham et al. 2021	µIU/L	Immunoassay on an Architect i2000SR analyser (Abbott).	Pre: 90.1 (n = 15) Post: 88.8 (n = 11)	Pre: 15.9 Post: 20.2 SEM	Pre: 83.4 (n = 12) Post: 97.2 (n = 12)	Pre: 17.8 Post: 21.7 SEM	Crude	NA
Patten et al. 2022	µIU/L	RIA	Pre: 17.8 (n = 15) Post: 16.6 (n = 13)	Pre: 11.0 Post: 13.4 SD	Pre: 17.7 (n = 14) Post: 18.5 (n = 11)	Pre: 6.5 Post: 6.1 SD	Crude	NA
Ribeiro et al. 2020	µIU/L	chemiluminescence method (Immulite® 2000 Immunoassay System)	Pre: 9.5 (n = 29) Post: 10.4 (n = 29)	Pre: 7.2 Post: 7.0 SD	Pre: 11.3 (n = 28) Post: 11.2 (n = 28)	Pre: 8.1 Post: 8.2 SD	Crude	NA

OUTCOME: Fasting insulin				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): High-intensity interval training versus resistance training								
Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD in intervention group	Mean in comparison group	SD in comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Almenning et al. 2015	mU/L	ELISA	Pre: 21.8 (n = 10) Post: 18.8 (n = 8)	Pre: 7.1 Post: 6.7 SD	Pre: 14.9 (n = 11) Post: 13.6 (n = 8)	Pre: 6.2 Post: 6.3 SD	Crude	NA

OUTCOME: Fasting insulin				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): Diet plus moderate-intensity continuous training versus diet plus moderate-intensity continuous training and resistance training								
Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD in intervention group	Mean in comparison group	SD in comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Thomson et al. 2008	mmol/L	ELISA	Pre: 14.5 (n = 18) Post: 10.9 (n = 18)	Pre: 8.4 Post: 9.5 SD	Pre: 16.0 (n = 18) Post: 11.1 (n = 18)	Pre: 8.0 Post: 9.2 SD	Crude	NA

OUTCOME: HOMA	OUTCOME TYPE: Continuous
COMPARISON (if applicable): High-intensity interval training versus moderate-intensity continuous training	

Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD/SEM in intervention group	Mean in comparison group	SD/SEM in comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Benham et al. 2021		HOMA2-IR	Pre: 1.7 (n = 15) Post: 1.7 (n = 11)	Pre: 0.3 Post: 0.4 SEM	Pre: 1.5 (n = 12) Post: 1.8 (n = 12)	Pre: 0.4 Post: 0.3 SEM	Crude	NA
Ribeiro et al. 2020		HOMA-IR	Pre: 2.0 (n = 29) Post: 2.2 (n = 29)	Pre: 1.9 Post: 1.8 SD	Pre: 2.5 (n = 28) Post: 2.4 (n = 28)	Pre: 1.9 Post: 1.8 SD	Crude	NA

OUTCOME: HOMA				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): High-intensity interval training versus resistance training								
Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD in intervention group	Mean in comparison group	SD in comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Almenning et al. 2015		HOMA-IR	Pre: 4.9 (n = 10) Post: 4.1 (n = 8)	Pre: 1.7 Post: 1.4 SD	Pre: 3.3 (n = 11) Post: 3.1 (n = 8)	Pre: 1.3 Post: 1.5 SD	Crude	NA

OUTCOME: HOMA				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): Diet plus moderate-intensity continuous training versus diet plus moderate-intensity continuous training and resistance training								
Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD in intervention group	Mean in comparison group	SD in comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Thomson et al. 2008		HOMA-IR	Pre: 1.87 (n = 18) Post: 1.40 (n = 18)	Pre: 1.0 Post: 1.2 SD	Pre: 2.0 (n = 18) Post: 1.4 (n = 18)	Pre: 1.0 Post: 1.1 SD	Crude	NA

OUTCOME: LDL-C				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): High-intensity interval training versus moderate-intensity continuous training								
Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD/SEM in intervention group	Mean in comparison group	SD/SEM in comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Benham et al. 2021	mmol/L	Enzymatic methods on a Cobas c701 analyser	Pre: 2.6 (n = 15) Post: 2.5 (n = 11)	Pre: 0.2 Post: 0.2 SEM	Pre: 2.5 (n = 12) Post: 2.7 (n = 12)	Pre: 0.2 Post: 0.2 SEM	Crude	NA

Patten et al. 2022	mmol/L	Automated enzymatic methods (Architect C18000 analyzer)	Pre: 2.9 (n = 15) Post: 2.8 (n = 13)	Pre: 0.7 Post: 0.9 SD	Pre: 2.8 (n = 14) Post: 2.9 (n = 11)	Pre: 0.9 Post: 0.8 SD	Crude	NA
Ribeiro et al. 2020	mg/dL	enzymatic method (CMD 800X1)	Pre: 112.0 (n = 29) Post: 106.0 (n = 29)	Pre: 23.0 Post: 23.0 SD	Pre: 112.0 (n = 28) Post: 102.0 (n = 28)	Pre: 24.0 Post: 23.0 SD	Crude	NA

OUTCOME: LDL-C				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): High-intensity interval training versus resistance training								
Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD in intervention group	Mean in comparison group	SD in comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Almenning et al. 2015	mmol/L	Roche Moduclar P	Pre: 2.5 (n = 10) Post: 2.1 (n = 8)	Pre: 0.8 Post: 0.6 SD	Pre: 3.1 (n = 11) Post: 2.6 (n = 8)	Pre: 1.1 Post: 0.6 SD	Crude	NA

OUTCOME: LDL-C				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): Diet plus moderate-intensity continuous training versus diet plus moderate-intensity continuous training and resistance training								
Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD in intervention group	Mean in comparison group	SD in comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Thomson et al. 2008	mmol/L	Modified Friedewald equation	Pre: 3.22 (n = 18) Post: 2.76 (n = 18)	Pre: 0.8 Post: 1.0 SD	Pre: 3.5 (n = 18) Post: 3.0 (n = 18)	Pre: 0.9 Post: 0.9 SD	Crude	NA

OUTCOME: HDL-C				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): High-intensity interval training versus moderate-intensity continuous training								
Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD/SEM in intervention group	Mean in comparison group	SD/SEM in comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Benham et al. 2021	mmol/L	Enzymatic methods on a Cobas c701 analyser	Pre: 1.2 (n = 15) Post: 1.1 (n = 11)	Pre: 0.1 Post: 0.1 SEM	Pre: 1.2 (n = 12) Post: 1.1 (n = 12)	Pre: 0.2 Post: 0.2 SEM	Crude	NA
Patten et al. 2022	mmol/L	Automated enzymatic methods (Architect C18000 analyzer)	Pre: 1.5 (n = 15) Post: 1.5 (n = 13)	Pre: 0.3 Post: 0.4 SD	Pre: 1.4 (n = 14) Post: 1.4 (n = 11)	Pre: 0.3 Post: 0.3 SD	Crude	NA

Ribeiro et al. 2020	mg/dL	enzymatic method (CMD 800X1)	Pre: 49.0 (n = 29) Post: 47.0 (n = 29)	Pre: 11.0 Post: 10.0 SD	Pre: 46.0 (n = 28) Post: 44.0 (n = 28)	Pre: 9.0 Post: 10.0 SD	Crude	NA

OUTCOME: HDL-C				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): High-intensity interval training versus resistance training								
Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD/SEM in intervention group	Mean in comparison group	SD/SEM in comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Almenning et al. 2015	mmol/L	Roche Moduclar P	Pre: 1.5 (n = 10) Post: 2.0 (n = 8)	Pre: 0.4 Post: 0.5 SD	Pre: 1.5 (n = 11) Post: 1.6 (n = 8)	Pre: 0.5 Post: 0.4 SD	Crude	NA

OUTCOME: HDL-C				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): Diet plus moderate-intensity continuous training versus diet plus moderate-intensity continuous training and resistance training								
Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD in intervention group	Mean in comparison group	SD in comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Thomson et al. 2008	mmol/L	Commercial enzymatic kits on a Hitachi 902 autoanalyzer	Pre: 1.2 (n = 18) Post: 1.2 (n = 18)	Pre: 0.2 Post: 0.2 SD	Pre: 1.2 (n = 18) Post: 1.1 (n = 18)	Pre: 0.2 Post: 0.3 SD	Crude	NA

OUTCOME: Triglycerides				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): High-intensity interval training versus moderate-intensity continuous training								
Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD/SEM in intervention group	Mean in comparison group	SD/SEM in comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Benham et al. 2021	mmol/L	Enzymatic methods on a Cobas c701 analyser	Pre: 1.3 (n = 15) Post: 1.2 (n = 11)	Pre: 0.2 Post: 0.2 SEM	Pre: 1.1 (n = 12) Post: 1.1 (n = 12)	Pre: 0.2 Post: 0.2 SEM	Crude	NA
Patten et al. 2022	mmol/L	Automated enzymatic methods (Architect C18000 analyzer)	Pre: 1.0 (n = 15) Post: 1.0 (n = 13)	Pre: 0.4 Post: 0.4 SD	Pre: 1.4 (n = 14) Post: 1.5 (n = 11)	Pre: 0.7 Post: 0.6 SD	Crude	NA
Ribeiro et al. 2020	mg/dL	enzymatic method (CMD 800X1)	Pre: 99.0 (n = 29) Post: 107.0 (n = 29)	Pre: 54.0 Post: 61.0 SD	Pre: 151.0 (n = 28) Post: 144.0 (n = 28)	Pre: 172.0 Post: 139.0 SD	Crude	NA

OUTCOME: Triglycerides				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): High-intensity interval training versus resistance training								
Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD in intervention group	Mean in comparison group	SD in comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Almenning et al. 2015	mmol/L	Roche Moduclar P	Pre: 1.2 (n = 10) Post: 1.1 (n = 8)	Pre: 0.6 Post: 7.0 SD	Pre: 0.9 (n = 11) Post: 0.8 (n = 8)	Pre: 0.4 Post: 0.3 SD	Crude	NA

OUTCOME: Triglycerides				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): Diet plus moderate-intensity continuous training versus diet plus moderate-intensity continuous training and resistance training								
Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD in intervention group	Mean in comparison group	SD in comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Thomson et al. 2008	mmol/L	Commercial enzymatic kits on a Hitachi 902 autoanalyzer	Pre: 1.5 (n = 18) Post: 1.4 (n = 18)	Pre: 0.8 Post: 1.0 SD	Pre: 1.4 (n = 18) Post: 1.2 (n = 18)	Pre: 0.9 Post: 1.0 SD	Crude	NA

OUTCOME: Systolic blood pressure				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): High-intensity interval training versus moderate-intensity continuous training								
Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD/SEM in intervention group	Mean in comparison group	SD/SEM in comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Benham et al. 2021	mmHg	Automated device (Omron HEM-907)	Pre: 114.9 (n = 15) Post: 118.0 (n = 11)	Pre: 3.5 Post: 3.9 SEM	Pre: 113.8 (n = 12) Post: 114.0 (n = 12)	Pre: 3.9 Post: 4.0 SEM	Crude	NA

Reproductive Outcomes

OUTCOME: Total testosterone				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): High-intensity interval training versus moderate-intensity continuous training								
Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD in intervention group	Mean in comparison group	SD in comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?

Patten et al. 2022	nmol/L	Automated enzymatic methods (Architect C18000 analyzer)	Pre: 1.8 (n = 15) Post: 1.4 (n = 13)	Pre: 0.8 Post: 0.9 SD	Pre: 1.6 (n = 14) Post: 1.4 (n = 11)	Pre: 0.7 Post: 0.7 SD	Crude	NA
Ribeiro et al. 2020	ng/dL	Chemiluminescence method (Immulite 1000)	Pre: 108.0 (n = 29) Post: 88.0 (n = 29)	Pre: 52.0 Post: 54.0 SD	Pre: 117.0 (n = 28) Post: 93.0 (n = 28)	Pre: 50.0 Post: 38.0 SD	Crude	NA

OUTCOME: Total testosterone				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): High-intensity interval training versus resistance training								
Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD in intervention group	Mean in comparison group	SD in comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Almenning et al. 2015	nmol/L	Mass spectrometry	Pre: 1.5 (n = 10) Post: 1.6 (n = 8)	Pre: 1 Post: 0.9 SD	Pre: 1.4 (n = 11) Post: 1.3 (n = 8)	Pre: 0.6 Post: 0.5 SD	Crude	NA

OUTCOME: Total testosterone				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): Diet plus moderate-intensity continuous training versus diet plus moderate-intensity continuous training and resistance training								
Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD in intervention group	Mean in comparison group	SD in comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Thomson et al. 2008	nmol/L	Immunoradiometric assay	Pre: 2.6 (n = 18) Post: 2.0 (n = 18)	Pre: 0.7 Post: 0.9 SD	Pre: 2.5 (n = 18) Post: 2.2 (n = 18)	Pre: 0.7 Post: 0.8 SD	Crude	NA

OUTCOME: Free testosterone				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): High-intensity interval training versus moderate-intensity continuous training								
Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD in intervention group	Mean in comparison group	SD in comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Patten et al. 2022	pmol/L	Automated enzymatic methods (Architect C18000 analyzer)	Pre: 36.2 (n = 15) Post: 27.9 (n = 13)	Pre: 16.2 Post: 16.9 SD	Pre: 34.8 (n = 14) Post: 34.7 (n = 11)	Pre: 17.2 Post: 22.4 SD	Crude	NA

OUTCOME: Sex hormone-binding globulin				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): High-intensity interval training versus moderate-intensity continuous training								
Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD in intervention group	Mean in comparison group	SD in comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?

Patten et al. 2022	nmol/L	Automated enzymatic methods (Architect C18000 analyzer)	Pre: 32.6 (n = 15) Post: 39.3 (n = 13)	Pre: 17.1 Post: 24.5 SD	Pre: 31.1 (n = 14) Post: 29.2 (n = 11)	Pre: 13.7 Post: 12.0 SD	Crude	NA
Ribeiro et al. 2020	nmol/L	Chemiluminescence method (Immulite 1000)	Pre: 48.0 (n = 29) Post: 53.0 (n = 29)	Pre: 28.0 Post: 31.0 SD	Pre: 54.0 (n = 28) Post: 58.0 (n = 28)	Pre: 41.0 Post: 61.0 SD	Crude	NA

OUTCOME: Sex hormone-binding globulin				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): High-intensity interval training versus resistance training								
Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD in intervention group	Mean in comparison group	SD in comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Almenning et al. 2015	nmol/L	Immunologic method	Pre: 128.0 (n = 10) Post: 135.0 (n = 8)	Pre: 110.4 Post: 83.9 SD	Pre: 60.7 (n = 11) Post: 82.0 (n = 8)	Pre: 37.2 Post: 60.3 SD	Crude	NA

OUTCOME: Sex hormone-binding globulin				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): Diet plus moderate-intensity continuous training versus diet plus moderate-intensity continuous training and resistance training								
Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD in intervention group	Mean in comparison group	SD in comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Thomson et al. 2008	nmol/L	Immunoradiometric assay	Pre: 36.2 (n = 18) Post: 42.9 (n = 18)	Pre: 15.6 Post: 17.3 SD	Pre: 33.8 (n = 18) Post: 43.6 (n = 18)	Pre: 16.1 Post: 17.2 SD	Crude	NA

OUTCOME: Free androgen index				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): High-intensity interval training versus moderate-intensity continuous training								
Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD in intervention group	Mean in comparison group	SD in comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Patten et al. 2022	Arbitrary units	Automated enzymatic methods (Architect C18000 analyzer)	Pre: 6.9 (n = 15) Post: 4.5 (n = 13)	Pre: 3.5 Post: 2.8 SD	Pre: 6.2 (n = 14) Post: 5.7 (n = 11)	Pre: 3.7 Post: 3.9 SD	Crude	NA
Ribeiro et al. 2020	Arbitrary units	Chemiluminescence method (Immulite 1000)	Pre: 9.9 (n = 29) Post: 7.8 (n = 29)	Pre: 7.2 Post: 7.7 SD	Pre: 11.3 (n = 28) Post: 10.3 (n = 28)	Pre: 9.6 Post: 10.0 SD	Crude	NA

OUTCOME: Free androgen index	OUTCOME TYPE: Continuous
COMPARISON (if applicable): High-intensity interval training versus resistance training	

Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD in intervention group	Mean in comparison group	SD in comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Almenning et al. 2015	Arbitrary units	Calculated as100 x testosterone concentration (nmol/L)/SHBG concentration (nmol/L)	Pre: 1.9 (n = 10) Post: 1.9 (n = 8)	Pre: 1.3 Post: 1.8 SD	Pre: 2.8 (n = 11) Post: 2.1 (n = 8)	Pre: 1.7 Post: 1.1 SD	Crude	NA

OUTCOME: Free androgen index				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): Diet plus moderate-intensity continuous training versus diet plus moderate-intensity continuous training and resistance training								
Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD in intervention group	Mean in comparison group	SD in comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Thomson et al. 2008	nmol/L	Calculated as testosterone concentration (nmol/L)/SHBG concentration (nmol/L) x 100	Pre: 8.5 (n = 18) Post: 5.9 (n = 18)	Pre: 5.6 Post: 6.7 SD	Pre: 9.1 (n = 18) Post: 6.2 (n = 18)	Pre: 5.7 Post: 6.3 SD	Crude	NA

OUTCOME: Menstrual regularity				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): High-intensity interval training versus moderate-intensity continuous training								
Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD in intervention group	Mean in comparison group	SD in comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Benham et al. 2021		Unclear	% of participants with regular menses at baseline versus follow up (50% vs 53%) (n not reported)		% of participants with regular menses at baseline versus follow up (29% vs 42%) (n not reported)		Crude	NA
Patten et al. 2022		Self-report	Cycle improved: Yes (9 = 69%) No (4 = 31%)		Cycle improved: Yes (2 = 22%) No (7 = 78%)		Crude	NA

OUTCOME: Menstrual regularity				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): Diet plus moderate-intensity continuous training versus diet plus moderate-intensity continuous training and resistance training								
Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD in intervention group	Mean in comparison group	SD in comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?

Thomson et al. 2008		Self-report	Cycle improved: Yes (9 = 43%) No (12 = 57%)		Cycle improved: Yes (8 = 44%) No (10 = 64%)		Crude	NA

Psychological outcomes

OUTCOME: Anxiety				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): High-intensity interval training versus moderate-intensity continuous training								
Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD in intervention group	Mean in comparison group	SD in comparison group	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Lopes et al. 2018	Arbitrary units	Hospital Anxiety and Depression Scale	Pre: 8.3 (n = 22) Post: 6.0 (n = 22)	Pre: 3.8 Post: 2.7 SD	Pre: 9.3 (n = 23) Post: 7.3 (n = 23)	Pre: 3.9 Post: 3.5 SD	Crude	NA

OUTCOME: Depression				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): High-intensity interval training versus moderate-intensity continuous training								
Author, year	Unit of outcome	Author, year	Mean in intervention group	SD in intervention group	Mean in comparison group	SD in comparison group	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Lopes et al. 2018	Arbitrary units	Hospital Anxiety and Depression Scale	Pre: 6.2 (n = 22) Post: 4.5 (n = 22)	Pre: 3.8 Post: 3.4 SD	Pre: 7.8 (n = 23) Post: 5.43 (n = 23)	Pre: 3.9 Post: 3.6 SD	Crude	NA

OUTCOME: Quality of life (SF36)				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): High-intensity interval training versus moderate-intensity continuous training								
Author, year	Unit of outcome	Method of measurement	Mean in intervention group	SD in intervention group	Mean in comparison group	SD in comparison group	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Lopes et al. 2018	Arbitrary units	Physical role functioning	Pre: 76.0 (n = 29) Post: 93.5 (n = 29)	Pre: 21.1 Post: 7.1 SD	Pre: 81.6 (n = 28) Post: 91.3 (n = 28)	Pre: 15.3 Post: 13.0 SD	Crude	NA
Lopes et al. 2018	Arbitrary units	Physical functioning	Pre: 78.4 (n = 29) Post: 93.1 (n = 29)	Pre: 33.2 Post: 17.5 SD	Pre: 67.0 (n = 28) Post: 90.2 (n = 28)	Pre: 34.7 Post: 19.7 SD	Crude	NA
Lopes et al. 2018	Arbitrary units	Bodily pain	Pre: 66.9 (n = 29) Post: 71.0 (n = 29)	Pre: 21.4 Post: 22.8 SD	Pre: 64.4 (n = 28) Post: 68.4 (n = 28)	Pre: 21.2 Post: 21.8 SD	Crude	NA

Lopes et al. 2018	Arbitrary units	General health perception	Pre: 53.5 (n = 29) Post: 67.3 (n = 29)	Pre: 22.3 Post: 16.3 SD	Pre: 53.9 (n = 28) Post: 62.5 (n = 28)	Pre: 16.3 Post: 17.3 SD	Crude	NA
Lopes et al. 2018	Arbitrary units	Vitality	Pre: 47.8 (n = 29) Post: 66.4 (n = 29)	Pre: 21.3 Post: 17.4 SD	Pre: 51.4 (n = 28) Post: 65.2 (n = 28)	Pre: 17.9 Post: 16.7 SD	Crude	NA
Lopes et al. 2018	Arbitrary units	Social role functioning	Pre: 68.9 (n = 29) Post: 82.0 (n = 29)	Pre: 24.5 Post: 19.9 SD	Pre: 65.7 (n = 28) Post: 82.3 (n = 28)	Pre: 25.8 Post: 18.1 SD	Crude	NA
Lopes et al. 2018	Arbitrary units	Emotional role functioning	Pre: 55.2 (n = 29) Post: 79.4 (n = 29)	Pre: 36.0 Post: 32.6 SD	Pre: 54.8 (n = 28) Post: 82.8 (n = 28)	Pre: 41.8 Post: 28.0 SD	Crude	NA
Lopes et al. 2018	Arbitrary units	Mental Health	Pre: 60.4 (n = 29) Post: 73.0 (n = 29)	Pre: 18.2 Post: 15.4 SD	Pre: 55.1 (n = 28) Post: 70.1 (n = 28)	Pre: 15.6 Post: 16.7 SD	Crude	NA

6. FINDINGS

Comparisons Included:

- **Comparison 1. High-intensity interval training (HIIT) versus moderate-intensity continuous training (MICT)**
- **Comparison 2. HIIT versus resistance training (RT)**
- **Comparison 3. Diet + combined aerobic and resistance training (CT) versus diet + aerobic exercise (AEx)**

Outcomes Included:

- **Outcome 1. Body mass index**
- **Outcome 2. Body weight**
- **Outcome 3. Waist circumference**
- **Outcome 4. HbA1c**
- **Outcome 5. Fasting glucose**
- **Outcome 6. Fasting insulin**
- **Outcome 7. HOMA-IR**
- **Outcome 8. HDL-C**
- **Outcome 9. LDL-C**
- **Outcome 10. Triglycerides**
- **Outcome 11. Systolic blood pressure**
- **Outcome 12. Free androgen index**
- **Outcome 13. Testosterone**
- **Outcome 14. Menstrual regularity**
- **Outcome 15. Anxiety**
- **Outcome 16. Depression**
- **Outcome 17. Quality of Life**

COMPARISON 1. HIIT versus MICT

▪ EVIDENCE SUMMARY:

A total of three studies (Benham et al. 2021; Patten et al. 2022; Ribeiro et al. 2020) compared HIIT versus MICT for a range of anthropometric, metabolic and hormonal/ reproductive outcomes. These studies were conducted in Australia, Brazil, and Canada and ranged in size from 29 to 72 participants. They were deemed to have low or unclear risk of bias, for which the latter was mainly due to lack of blinding to participant group allocation by outcome assessors.

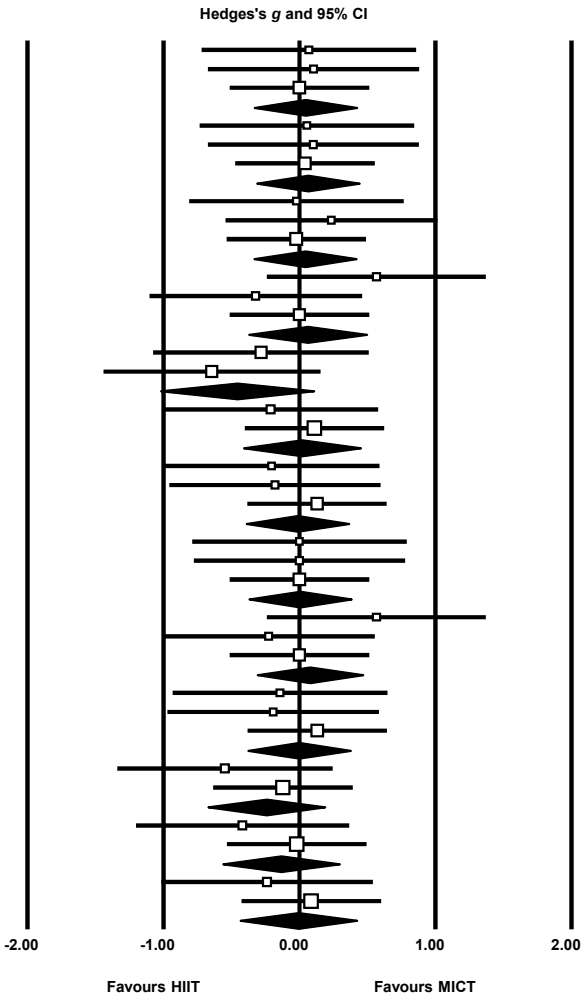
▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

In the meta-analyses of 2-3 pooled studies, there were no differences in any of the outcomes assessed, with most of the evidence being of low to very low certainty due primarily to imprecision (small sample sizes), in addition to unclear risk of bias and inconsistency of effect estimates and/or confidence intervals. In descriptive analysis (studies or outcomes not pooled in meta-analysis), HIIT was more effective than MICT for menstrual regularity (OR [95%CI] = 0.127 [0.017, 0.905]) with very low certainty due to imprecision (being derived from a single small study) as well as inconsistency and risk of bias. Benham et al. 2021 reported change in menstrual regularity as an absolute percentage, however, as no sample size was provided, these data could not be pooled in meta-analysis, nor could the OR be determined. In this study, HIIT improved menstrual regularity from 50% to 53% of participants, and MICT improved menstrual regularity from 29% to 42% of participants.

Meta-analyses for high-intensity interval training versus moderate-intensity continuous training											
Outcome	**MD**	**95% confidence interval**		**p value**	**Favours**	I^2	τ	**No. studies**	**HIIT (n)**	**MICT (n)**	**GRADE certainty**
BMI (kg/m^2)	0.186	-2.173	2.546	0.877	MICT	0	0	3	53	51	⊕⊕◯◯ Low
Body weight (kg)	1.058	-6.279	8.396	0.777	MICT	0	0	3	53	51	⊕⊕◯◯ Low
WC (cm)	0.378	-5.194	5.950	0.894	MICT	0	0	3	53	51	⊕⊕◯◯ Low
HbA1c (%)	-0.160	-0.336	0.017	0.076	HIIT	0	0	2	24	23	⊕⊕◯◯ Low
FBG (mmol/L)	0.053	-0.132	0.238	0.574	MICT	0	0	3	53	51	⊕◯◯◯ Very Low
Fasting Insulin (µIU/L)	0.352	-3.201	3.904	0.846	MICT	0	0	3	53	51	⊕◯◯◯ Very Low
HOMA-IR	-0.033	-0.742	0.675	0.926	HIIT	0	0	2	40	40	⊕◯◯◯ Very Low
HDL-C (mmol/L)	0.000	-0.111	0.111	1.000	No difference	0	0	3	53	51	⊕⊕◯◯ Low
LDL-C (mmol/L)	0.081	-0.125	0.288	0.441	MICT	0	0	3	53	51	⊕◯◯◯ Very Low
Triglycerides (mmol/L)	-0.049	-0.356	0.259	0.756	HIIT	0	0	3	53	51	⊕⊕◯◯ Low
SBP (mmHg)	-2.900	-6.042	0.242	0.070	MICT	0	0	1	11	12	⊕◯◯◯ Very Low
FAI	-1.677	-4.059	0.704	0.167	HIIT	0	0	2	42	39	⊕⊕◯◯ Low
SHBG (mmol/L)	6.324	-5.966	18.614	0.313	HIIT	0	0	2	42	39	⊕⊕◯◯ Low
Testosterone (nmol/L)	-0.086	-0.601	0.430	0.745	HIIT	0	0	2	42	39	⊕◯◯◯ Very Low
Menstrual regularity	OR 7.875	1.105	56.125	**0.039**	HIIT	0	0	1	13	11	⊕◯◯◯ Very Low
Anxiety	-0.300	-2.38	1.780	0.777	HIIT	0	0	1	22	23	⊕◯◯◯ Very Low
Depression	-0.700	-2.857	1.457	0.504	MICT	0	0	1	22	23	⊕◯◯◯ Very Low
Quality of life	SMD -0.278	-0.792	0.237	0.291	HIIT	0	0	1	29	28	⊕◯◯◯ Very Low

MD, mean difference; OR, odds ratio; SMD, standardised mean difference; HIIT, high-intensity interval training; MICT, moderate-intensity training; BMI, body mass index; WC, waist circumference; FBG, fasting blood glucose; HOMA-IR, homeostatic model assessment of insulin resistance; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; SBP, systolic blood pressure; FAI, free androgen index; SHBG, sex hormone-binding globulin.

1.1. Forest plot for High-intensity interval training versus moderate-intensity continuous training



Study name	Intervention	Comparator	Outcome	HIIT (*n*)	MICT (*n*)	*g*	Lower limit	Upper limit	*p* value	Relative weight
Benham 2021	HIIT	MICT	BMI	11	12	0.069	-0.720	0.858	0.864	22.70
Patten 2022	HIIT	MICT	BMI	13	11	0.104	-0.672	0.879	0.794	23.46
Ribeiro 2020	HIIT	MICT	BMI	29	28	0.000	-0.512	0.512	1.000	53.84
				53	**51**	**0.040**	**-0.336**	**0.416**	**0.835**	
Benham 2021	HIIT	MICT	Body weight	11	12	0.054	-0.734	0.843	0.892	22.70
Patten 2022	HIIT	MICT	Body weight	13	11	0.102	-0.673	0.878	0.796	23.47
Ribeiro 2020	HIIT	MICT	Body weight	29	28	0.041	-0.471	0.553	0.876	53.83
				53	**51**	**0.058**	**-0.317**	**0.434**	**0.761**	
Benham 2021	HIIT	MICT	Waist circumference	11	12	-0.022	-0.811	0.767	0.957	22.74
Patten 2022	HIIT	MICT	Waist circumference	13	11	0.235	-0.543	1.013	0.554	23.36
Ribeiro 2020	HIIT	MICT	Waist circumference	29	28	-0.023	-0.535	0.489	0.929	53.90
				53	**51**	**0.037**	**-0.339**	**0.413**	**0.846**	
Benham 2021	HIIT	MICT	FBG	11	12	0.566	-0.239	1.371	0.168	24.53
Patten 2022	HIIT	MICT	FBG	13	11	-0.322	-1.102	0.459	0.419	25.86
Ribeiro 2020	HIIT	MICT	FBG	29	28	0.000	-0.512	0.512	1.000	49.60
				53	**51**	**0.056**	**-0.377**	**0.489**	**0.801**	
Benham 2021	HIIT	MICT	HbA1c	11	12	-0.283	-1.076	0.510	0.484	50.22
Patten 2022	HIIT	MICT	HbA1c	13	11	-0.644	-1.440	0.153	0.113	49.78
				24	**23**	**-0.463**	**-1.024**	**0.099**	**0.107**	
Benham 2021	HIIT	MICT	HOMA-IR	11	12	-0.212	-1.003	0.579	0.599	29.58
Ribeiro 2020	HIIT	MICT	HOMA-IR	29	28	0.110	-0.402	0.623	0.674	70.42
				40	**40**	**0.015**	**-0.415**	**0.445**	**0.946**	
Benham 2021	HIIT	MICT	Insulin	11	12	-0.204	-0.995	0.587	0.613	22.65
Patten 2022	HIIT	MICT	Insulin	13	11	-0.180	-0.957	0.597	0.649	23.47
Ribeiro 2020	HIIT	MICT	Insulin	29	28	0.130	-0.383	0.642	0.620	53.88
				53	**51**	**-0.019**	**-0.395**	**0.358**	**0.923**	
Benham 2021	HIIT	MICT	HDL-C	11	12	0.000	-0.789	0.789	1.000	22.70
Patten 2022	HIIT	MICT	HDL-C	13	11	0.000	-0.775	0.775	1.000	23.49
Ribeiro 2020	HIIT	MICT	HDL-C	29	28	0.000	-0.512	0.512	1.000	53.81
				53	**51**	**0.000**	**-0.376**	**0.376**	**1.000**	
Benham 2021	HIIT	MICT	LDL-C	11	12	0.566	-0.239	1.371	0.168	22.53
Patten 2022	HIIT	MICT	LDL-C	13	11	-0.226	-1.003	0.552	0.570	24.10
Ribeiro 2020	HIIT	MICT	LDL-C	29	28	0.000	-0.512	0.512	1.000	53.38
				53	**51**	**0.073**	**-0.315**	**0.461**	**0.712**	
Benham 2021	HIIT	MICT	Triglycerides	11	12	-0.143	-0.932	0.647	0.723	22.71
Patten 2022	HIIT	MICT	Triglycerides	13	11	-0.193	-0.970	0.584	0.627	23.44
Ribeiro 2020	HIIT	MICT	Triglycerides	29	28	0.131	-0.382	0.644	0.617	53.85
				53	**51**	**-0.007**	**-0.383**	**0.369**	**0.971**	
Patten 2022	HIIT	MICT	FAI	13	11	-0.548	-1.339	0.242	0.174	29.60
Ribeiro 2020	HIIT	MICT	FAI	29	28	-0.122	-0.635	0.391	0.641	70.40
				42	**39**	**-0.248**	**-0.678**	**0.182**	**0.258**	
Patten 2022	HIIT	MICT	SHBG	13	11	-0.419	-1.203	0.365	0.295	29.90
Ribeiro 2020	HIIT	MICT	SHBG	29	28	-0.020	-0.533	0.492	0.937	70.10
				42	**39**	**-0.140**	**-0.568**	**0.289**	**0.523**	
Patten 2022	HIIT	MICT	Testosterone	13	11	-0.237	-1.015	0.541	0.551	30.25
Ribeiro 2020	HIIT	MICT	Testosterone	29	28	0.085	-0.427	0.597	0.745	69.75
				42	**39**	**-0.012**	**-0.440**	**0.416**	**0.955**	

Data presented as standardised mean difference (Hedge's g) with 95% confidence interval.
BMI, body mass index; WC, waist circumference; FBG, fasting blood glucose; HbA1c, glycated haemoglobin; HOMA-IR, homeostatic model assessment of insulin resistance; HDL, high-density lipoprotein cholesterol; LDL, Low-density lipoprotein cholesterol; TG, triglycerides; FAI, free androgen index; SHBG, sex hormone-binding globulin

COMPARISON 2. HIIT versus RT

▪ EVIDENCE SUMMARY:

One study compared HIIT with RT (Almenning, et al. 2015) on anthropometric, metabolic and hormonal/ reproductive outcomes. This study, by Almenning et al (2015) was conducted in Norway with 21 participants and had an unclear risk of bias due to lack of blinding to participant group allocation by outcome assessors and insufficient information around allocation concealment.

▪ DESCRIPTIVE ANALYSIS SUMMARY:

There were no differences between HIIT and RT for any of the outcomes. Certainty in these results is very low due to being derived from a single, relatively small study with an unclear risk of bias.

Meta-analyses for high-intensity interval training versus resistance training											
Outcome	**WMD**	**95% confidence interval**		**p value**	**Favours**	I^2	τ	**No. studies**	**HIIT (n)**	**RT (n)**	**GRADE certainty**
BMI (kg/m^2)	-0.300	-5.824	5.224	0.915	HIIT	0	0	1	8	8	⨁◯◯◯ Very Low
Body weight (kg)	-0.900	-18.141	16.341	0.919	HIIT	0	0	1	8	8	⨁◯◯◯ Very Low
WC (cm)	-1.800	-16.569	12.969	0.811	RT	0	0	1	8	8	⨁◯◯◯ Very Low
FBG (mmol/L)	-0.100	-0.402	0.202	0.516	HIIT	0	0	1	8	8	⨁◯◯◯ Very Low
Fasting Insulin (µIU/L)	-1.700	-8.156	4.756	0.606	HIIT	0	0	1	8	8	⨁◯◯◯ Very Low
HOMA-IR	-0.600	-2.063	0.863	0.422	HIIT	0	0	1	8	8	⨁◯◯◯ Very Low
HDL-C (mmol/L)	-0.300	-0.749	0.149	0.190	HIIT	0	0	1	8	8	⨁◯◯◯ Very Low
LDL-C (mmol/L)	-0.400	-1.165	-0.365	0.306	RT	0	0	1	8	8	⨁◯◯◯ Very Low
TG (mmol/L)	-1.000	-0.619	0.419	0.705	HIIT	0	0	1	8	8	⨁◯◯◯ Very Low
FAI	-1.100	-2.610	0.410	0.153	RT	0	0	1	8	8	⨁◯◯◯ Very Low
SHBG (mmol/L)	31.600	-46.981	110.181	0.431	RT	0	0	1	8	8	⨁◯◯◯ Very Low
Testosterone (nmol/L)	-0.200	-1.002	0.602	0.625	RT	0	0	1	8	8	⨁◯◯◯ Very Low

MD, mean difference; HIIT, high-intensity interval training; RT, resistance training; WC, waist circumference; FBG, fasting blood glucose; HOMA-IR, homeostatic model assessment of insulin resistance; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; FAI, free androgen index; SHBG, sex hormone-binding globulin

COMPARISON 3. Diet plus combined aerobic and resistance training versus diet plus aerobic exercise

- **EVIDENCE SUMMARY:**

One study compared diet plus combined aerobic and RT with diet and aerobic exercise (Thomson, et al. 2008) on anthropometric, metabolic and hormonal/ reproductive outcomes. This study, by Thomson et al (2008) was conducted in Australia with 64 participants and had a high risk of bias due to lack of blinding to participant group allocation by outcome assessors and insufficient information around allocation concealment.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

There were no differences between diet plus combined aerobic and resistance training and diet and aerobic exercise for any of the outcomes. Certainty in these results is very low due to being derived from a single, relatively small study with a high risk of bias due to lack of blinding of outcome assessors, concealment of allocation (opaque envelopes), high dropout rate, and unclear whether analyses were undertaken as per-protocol or as intention-to-treat.

Meta-analyses for diet plus combined aerobic and resistance training versus diet plus aerobic exercise											
Outcome	**MD**	**95% confidence interval**		**p value**	**Favours**	I^2	τ	**No. studies**	**HIIT (n)**	**RT (n)**	**GRADE certainty**
Body weight (kg)	-1.500	-13.217	10.217	0.802	D+AEx	0	0	1	20	18	⊕◯◯◯ Very Low
WC (cm)	-0.700	-8.901	7.501	0.867	D+CT	0	0	1	20	18	⊕◯◯◯ Very Low
FBG (mmol/L)	-0.100	-0.453	0.253	0.579	D+AEx	0	0	1	20	18	⊕◯◯◯ Very Low
Fasting Insulin (µIU/L)	-1.300	-6.919	4.319	0.650	D+CT	0	0	1	20	18	⊕◯◯◯ Very Low
HOMA-IR	-0.160	-0.846	0.526	0.648	D+CT	0	0	1	20	18	⊕◯◯◯ Very Low
HDL-C (mmol/L)	0.000	-0.166	0.166	1.000	No difference	0	0	1	20	18	⊕◯◯◯ Very Low
LDL-C (mmol/L)	-0.010	-0.580	0.560	0.973	D+AEx	0	0	1	20	18	⊕◯◯◯ Very Low
Triglycerides (mmol/L)	-0.180	-0.771	0.411	0.550	D+CT	0	0	1	20	18	⊕◯◯◯ Very Low
SBP (mmHg)	-3.100	-11.233	5.033	0.455	D+CT	0	0	1	20	18	⊕◯◯◯ Very Low
FAI	-0.300	-4.196	3.596	0.880	D+CT	0	0	1	20	18	⊕◯◯◯ Very Low
SHBG (mmol/L)	3.100	-7.471	13.671	0.565	D+CT	0	0	1	20	18	⊕◯◯◯ Very Low
Testosterone (nmol/L)	-0.250	-0.755	0.255	0.332	D+AEx	0	0	1	20	18	⊕◯◯◯ Very Low

MD, mean difference; D+AEx, diet plus aerobic exercise; D+CT, diet plus aerobic and resistance training; H HOMA-IR, homeostatic model assessment of insulin resistance; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; SBP, systolic blood pressure; FAI, free androgen index; SHBG, sex hormone-binding globulin.

8. GRADE ASSESSMENTS AND EVIDENCE PROFILE

COMPARISON: High-intensity interval training versus moderate-intensity continuous training												
	Quality assessment						No. participants					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**HIIT**	**MICT**	**Effect, fixed [95% CI]**	**Favours**	**Certainty**	**Importance**
Outcome: Body mass index (kg/m^2)												
3	RCT	Not serious	Not serious	Not serious	Very serious[1]	none	53	51	MD -0.19 [-2.546, 2.17]	MICT (No difference)	⨁⨁◯◯ Low	CRITICAL
Outcome: Body weight (kg)												
3	RCT	Not serious	Not serious	Not serious	Very serious[1]	none	53	51	MD -1.06 -8.40, 6.28]	MICT (No difference)	⨁⨁◯◯ Low	CRITICAL
Outcome: Waist circumference (cm)												
3	RCT	Not serious	Not serious	Not serious	Very serious[1]	none	53	51	MD -0.34 [-5.95, 5.19]	MICT (No difference)	⨁⨁◯◯ Low	CRITICAL
Outcome: HbA1c (%)												
2	RCT	Not serious	Not serious	Not serious	Very serious[1]	none	24	23	MD -0.16 [-0.34, 0.02]	HIIT (No difference)	⨁⨁◯◯ Low	CRITICAL
Outcome: Fasting blood glucose (mmol/L)												
3	RCT	Not serious	Serious[2]	Not serious	Very serious[1]	none	53	51	MD -0.05 [-0.24, 0.13]	MICT (No difference)	⨁◯◯◯ Very low	CRITICAL
Outcome: Fasting Insulin (µIU/L)												
3	RCT	Not serious	Serious[2]	Not serious	Very serious[1]	none	113	117	MD -0.35 [-3.90, 3.20]	MICT (Not significant)	⨁◯◯◯ Very low	CRITICAL
Outcome: HOMA-IR												
2	RCT	Serious[3]	Serious[2]	Not serious	Very serious[1]	none	40	40	MD -0.03 [-0.74, 0.68]	HIIT (No difference)	⨁◯◯◯ Very low	CRITICAL
Outcome: HDL-C (mmol/L)												
3	RCT	Not serious	Not serious	Not serious	Very serious[1]	none	53	51	MD 0.00 [-0.11, 0.11]	No difference	⨁⨁◯◯ Low	CRITICAL
Outcome: LDL-C (mmol/L)												
3	RCT	Not serious	Serious[2]	Not serious	Very serious[1]	none	53	51	MD 0.08 [-0.29, 0.13]	MICT (Not significant)	⨁◯◯◯ Very low	CRITICAL

[1] Downgraded twice as only few studies each with small samples.
[2] Downgraded once due to imprecision as results varied and confidence intervals (CIs) were wide.
[3] Downgraded once as one of two studies was deemed to have an unclear risk of bias.

Outcome: Triglycerides (mmol/L)												
3	RCT	Not serious	Not serious	Not serious	Very serious[1]	none	53	51	MD -2.90 [-6.04, 0.24]	HIIT (No difference)	⊕⊕◯◯ Low	CRITICAL
Outcome: Systolic blood pressure (mmHg)												
1	RCT	Not serious	Not applicable	Not serious	Very serious[4]	none	11	12	MD -2.90 [-6.04, 0.24]	MICT (Not significant)	⊕◯◯◯ Very low	CRITICAL
Outcome: Free androgen index												
2	RCT	Serious[3]	Not serious	Not serious	Very serious[1]	none	42	39	MD -1.68 [-4.06, 0.70]	HIIT (Not significant)	⊕⊕◯◯ Low	CRITICAL
Outcome: Sex hormone-binding globulin (mmol/L)												
2	RCT	Serious[3]	Not serious	Not serious	Very serious[1]	none	42	39	MD 6.32 [-5.97, 18.61]	HIIT (Not significant)	⊕⊕◯◯ Low	CRITICAL
Outcome: Testosterone (nmol/L)												
2	RCT	Serious[3]	Serious[2]	Not serious	Very serious[1]	none	42	39	MD -0.09 [-0.60, 0.43]	HIIT (Not significant)	⊕◯◯◯ Very low	CRITICAL
Outcome: Menstrual regularity												
1	RCT	Not serious	Not applicable	Serious[5]	Very serious[4]	none	13	11	OR 7.88 [1.11, 56.13]	HIIT (Significant)	⊕◯◯◯ Very low	CRITICAL
Outcome: Anxiety												
1	RCT	Very serious[6]	Not applicable	Serious[5]	Very serious[4]	none	22	23	MD -0.30 [-2.38,1.78]	HIIT (Not significant)	⊕◯◯◯ Very low	CRITICAL
Outcome: Depression												
1	RCT	Very serious [6]	Not applicable	Serious[5]	Very serious[4]	none	22	23	MD -0.70 [-2.86, 1.46]	MICT (Not significant)	⊕◯◯◯ Very low	CRITICAL
Outcome: Quality of life												
1	RCT	Very serious [6]	Not applicable	Serious[5]	Very serious[4]	none	29	28	SMD -0.28 [-0.79, 0.24]	HIIT (Not significant)	⊕◯◯◯ Very low	CRITICAL

MD, mean difference; OR, odds ratio; SMD, standardised mean difference; HbA1c, glycated haemoglobin; HOMA-IR, homeostatic model assessment of insulin resistance; HDL, high-density lipoprotein cholesterol; LDL, Low-density lipoprotein cholesterol.

[4] Downgraded twice as only one study with a small sample size.
[5] Downgraded once as the outcome was determined via self-report.
[6] Downgraded twice as the single study used was deemed to have an unclear risk of bias.

COMPARISON: High-intensity interval training versus resistance training												
	Quality assessment						No. participants					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**HIIT**	**RT**	**Effect [95% CI]**	**Favours**	**Certainty**	**Importance**
Outcome: Body mass index (kg/m^2)												
1	RCT	Serious[1]	Not applicable	Not serious	Very serious[2]	none	8	8	MD -0.30 [-5.82, 5.22]	HIIT (Not significant)	⨁◯◯◯ Very low	CRITICAL
Outcome: Body weight (kg)												
1	RCT	Serious[1]	Not applicable	Not serious	Very serious[2]	none	8	8	MD -0.90 -18.14, 16.34]	HIIT (Not significant)	⨁◯◯◯ Very low	CRITICAL
Outcome: Waist circumference (cm)												
1	RCT	Serious[1]	Not applicable	Not serious	Very serious[2]	none	8	8	MD -1.80 [-16.57,12.97]	RT (Not significant)	⨁◯◯◯ Very low	CRITICAL
Outcome: Fasting blood glucose (mmol/L)												
1	RCT	Serious[1]	Not applicable	Not serious	Very serious[2]	none	8	8	MD -0.10 [-0.40, 0.20]	HIIT (Not significant)	⨁◯◯◯ Very low	CRITICAL
Outcome: Fasting Insulin (µIU/L)												
1	RCT	Serious[1]	Not applicable	Not serious	Very serious[2]	none	8	8	MD -1.70 [-8.16, 4.76]	HIIT (Not significant)	⨁◯◯◯ Very low	CRITICAL
Outcome: HOMA-IR												
1	RCT	Serious[1]	Not applicable	Not serious	Very serious[2]	none	8	8	MD -0.03 [-0.74, 0.68]	HIIT (Not significant)	⨁◯◯◯ Very low	CRITICAL
Outcome: HDL-C (mmol/L)												
1	RCT	Serious[1]	Not applicable	Not serious	Very serious[2]	none	8	8	MD 0.30 [0.75, -0.15]	HIIT (Not significant)	⨁◯◯◯ Very low	CRITICAL
Outcome: LDL-C (mmol/L)												
1	RCT	Serious[1]	Not applicable	Not serious	Very serious[2]	none	8	8	MD -0.40 [-1.17, 0.37]	RT (Not significant)	⨁◯◯◯ Very low	CRITICAL
Outcome: Triglycerides (mmol/L)												
1	RCT	Serious[1]	Not applicable	Not serious	Very serious[2]	none	8	8	MD -1.00 [-0.62, 0.42]	HIIT (Not significant)	⨁◯◯◯ Very low	CRITICAL
Outcome: Free androgen index												
1	RCT	Serious[1]	Not applicable	Not serious	Very serious[2]	none	8	8	MD -1.10 [-2.61, 0.41]	RT (Not significant)	⨁◯◯◯ Very low	CRITICAL

[1] Downgraded once as the study was deemed to have an unclear risk of bias.
[2] Downgraded twice as only one study with a small sample size.

Outcome: Sex hormone-binding globulin (mmol/L)											
1	RCT	Serious[1]	Not applicable	Not serious	Very serious[2]	none	8	8	MD 31.60 [-110.18, 46.98]	RT (Not significant)	⨁◯◯◯ Very low	CRITICAL
Outcome: Testosterone (nmol/L)											
1	RCT	Serious[1]	Not applicable	Not serious	Very serious[2]	none	8	8	MD -0.02 [-1.00, 0.60]	RT (Not significant)	⨁◯◯◯ Very low	CRITICAL

MD, mean difference; HIIT, high-intensity interval training; RT, resistance training; HbA1c, glycated haemoglobin; HOMA-IR, homeostatic model assessment of insulin resistance; HDL, high-density lipoprotein cholesterol; LDL, Low-density lipoprotein cholesterol.

COMPARISON 3: Diet plus combined aerobic and resistance training versus diet plus aerobic exercise												
	Quality assessment						No. participants					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**D+CT**	**D+AEX**	**Effect [95% CI]**	**Favours**	**Certainty**	**Importance**
Outcome: Body weight (kg)												
1	RCT	Serious[1]	Not applicable	Not serious	Very serious[2]	none	20	18	MD -1.5 [-13.22,10.22]	D+AEx (Not significant)	⊕◯◯◯ Very low	CRITICAL
Outcome: Waist circumference (cm)												
1	RCT	Serious[1]	Not applicable	Not serious	Very serious[2]	none	20	18	MD -0.7 [-8.9, 7.5]	D+CT (Not significant)	⊕◯◯◯ Very low	CRITICAL
Outcome: Fasting blood glucose (mmol/L)												
1	RCT	Serious[1]	Not applicable	Not serious	Very serious[2]	none	20	18	MD -0.1 [-0.45, 0.25]	D+AEx (Not significant)	⊕◯◯◯ Very low	CRITICAL
Outcome: Fasting Insulin (µIU/L)												
1	RCT	Serious[1]	Not applicable	Not serious	Very serious[2]	none	20	18	MD -1.3 [-6.92, 4.32]	D+CT (Not significant)	⊕◯◯◯ Very low	CRITICAL
Outcome: HOMA-IR												
1	RCT	Serious[1]	Not applicable	Not serious	Very serious[2]	none	20	18	MD -0.16 [-0.85, 0.53]	D+CT (Not significant)	⊕◯◯◯ Very low	CRITICAL
Outcome: HDL-C (mmol/L)												
1	RCT	Serious[1]	Not applicable	Not serious	Very serious[2]	none	20	18	MD 0.00 [-0.17, 0.17]	No difference	⊕◯◯◯ Very low	CRITICAL
Outcome: LDL-C (mmol/L)												
1	RCT	Serious[1]	Not applicable	Not serious	Very serious[2]	none	20	18	MD -0.01 [-0.58, 0.56]	D+AEx (Not significant)	⊕◯◯◯ Very low	CRITICAL
Outcome: Triglycerides (mmol/L)												
1	RCT	Serious[1]	Not applicable	Not serious	Very serious[2]	none	20	18	MD -0.18 [-0.77, 0.41]	D+CT (Not significant)	⊕◯◯◯ Very low	CRITICAL
Outcome: Systolic blood pressure (mmHg)												
1	RCT	Serious[1]	Not applicable	Not serious	Very serious[2]	none	20	18	MD -3.10 [-11.23, 5.03]	D+CT (Not significant)	⊕◯◯◯ Very low	CRITICAL
Outcome: Free androgen index												
1	RCT	Serious[1]	Not applicable	Not serious	Very serious[2]	none	20	18	MD -0.30 [-4.2, 3.6]	D+CT (Not significant)	⊕◯◯◯ Very low	CRITICAL
Outcome: Sex hormone-binding globulin (mmol/L)												
1	RCT	Serious[1]	Not applicable	Not serious	Very serious[2]	none	20	18	MD 3.10 [13.67, -7.47]	D+CT (Not significant)	⊕◯◯◯ Very low	CRITICAL
Outcome: Testosterone (nmol/L)												
1	RCT	Serious[1]	Not applicable	Not serious	Very serious[2]	none	20	18	MD -0.25 [-0.76, 0.26]	D+AEx (Not significant)	⊕◯◯◯ Very low	CRITICAL

[1] Downgraded once as the study was deemed to have an unclear risk of bias.
[2] Downgraded twice as only one study with a small sample size.

MD, mean difference; AEx, Aerobic exercise; CT, Combined aerobic and resistance training, progressive resistance training; HbA1c, glycated haemoglobin; HOMA-IR, homeostatic model assessment of insulin resistance; HDL, high-density lipoprotein cholesterol; LDL, Low-density lipoprotein cholesterol.

APPENDIX. Quality Appraisal of RANDOMISED CONTROLLED TRIALS

Study ID	Almenning 2015	
Study Citation	Almenning I, Rieber-Mohn A, Lundgren KM, Shetelig Løvvik T, Garnæs KK, Moholdt T. Effects of High Intensity Interval Training and Strength Training on Metabolic, Cardiovascular and Hormonal Outcomes in Women with Polycystic Ovary Syndrome: A Pilot Study. PLoS One. 2015 Sep 25;10(9):e0138793. doi: 10.1371/journal.pone.0138793.	
Study Country	Norway	
BRIEF CHARACTERISTICS OF RCT		
Patient/population/ participants	Women with PCOS	
PCOS diagnostic criteria	Rotterdam	
Presence of infertility	Not reported	
Presence of other condition/s		
Medication History	Only menstrual regularity	
N per group	*Allocated/randomised:* 21 (10 HIIT, 11 RT) *Assessed at end of study:* 16 (8 HIIT, 8 RT)	
Setting	Location of assessments not reported. Interventions completed unsupervised at a gym.	
Intervention	HIIT: twice weekly sessions of 4x4-min t 90–95% HRmax, separated by three minutes of moderate intensity exercise at 70% of HRmax; and one weekly session of 10x1-min inteverals at maximal intensity (‘all out’), separated by 1-min rest/very low activity.	
Comparison	RT: eight dynamic exercises at 75% one repetition maximum, with three sets of ten repetitions separated by 1-min rest between sets.	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Preliminary efficacy outcomes included metabolic, cardiovascular, and hormonal outcomes.	
Follow up Duration	10 weeks	
Summary Result/s	High intensity interval training for ten weeks improved insulin resistance, without weight loss, in women with polycystic ovary syndrome. Body composition improved significantly after both strength training and high intensity interval training. This pilot study indicates that exercise training can improve the cardiometabolic profile in polycystic ovary syndrome in the absence of weight loss.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes	The primary objective was therefore to assess the effects of ten weeks of structured exercise training on insulin sensitivity, measured with homeostatic model assessment of insulin resistance (HOMA-IR) in women with PCOS.
Does the study have specified inclusion/exclusion criteria?	Yes	

If there were specified inclusion/ exclusion criteria, were these appropriate?		Partial	Didn't define age range.
Inclusion criteria		Partial	Didn't define age range.
Exclusion criteria		Yes	Exclusion criteria included regular high-intensity endurance or strength training (defined as 2 sessions of vigorous exercise per week), physical ailments/injuries that limited exercise performance, on-going pregnancy, concurrent treatments (insulin sensitizers as metformin and pioglitazone) or drugs known to affect gonadotropin or ovulation, with a wash out period of one month prior to inclusion. The exception was regular use of oral contraceptives, and women were included if they did not change the type or dose > 1 month prior to the study or during the intervention period.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Did the study have an adequate method of randomisation?	Yes	
	Was allocation to intervention group concealed?	Unclear	
PERFORMANCE BIAS	Were patients blind to intervention group?	No	Not applicable
	Were investigators and care providers blind to intervention group?	No	Not applicable
	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	Were outcome assessors blind to intervention group?	No	
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Yes	

ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study dropped out?	20% treatment 27% comparison	
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Partial	Per protocol analyses applied.
REPORT	Is the paper free of selective outcome reporting?	Yes	
CONFOUNDING	Were the groups similar at baseline with regard to key prognostic variables?	Yes	
	If confounding was present, was it controlled for?	Not applicable	
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	No	
	Was the study sufficiently powered to detect any differences between the groups?	Yes	
	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS		Lack of blinding of outcome assessors and concealment of allocation (opaque envelopes) primary reasons for moderate risk classification.	
What is the overall risk of bias?		Unclear	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		No	

Study ID	Benham 2021
Study Citation	Benham JL, Booth JE, Corenblum B, Doucette S, Friedenreich CM, Rabi DM, Sigal RJ. Exercise training and reproductive outcomes in women with polycystic ovary syndrome: A pilot randomized controlled trial. Clin Endocrinol (Oxf). 2021 Aug;95(2):332-343. doi: 10.1111/cen.14452.
Study Country	Canada

BRIEF CHARACTERISTICS OF RCT		
Patient/population/ participants	Previously inactive women aged 18-40 years with PCOS	
PCOS diagnostic criteria	Rotterdam	
Presence of infertility	Not reported	
Presence of other condition/s	Average BMI of participants 31.4 ± 8.4 (SD)	
Medication History	Yes	
N per group	*Allocated/randomised:* 30 (16 HIIT, 14 MICT) *Assessed at end of study:* 23 (11 HIIT, 12 MICT)*)*	
Setting	Location of assessments not reported. Interventions completed semi-supervised at a gym.	
Intervention	HIIT: participants completed 10 cycles of 30 s at high-intensity (90% of heart rate reserve (HRR), or 9/10 on a modified Borg scale1) alternating with 90 s of low-intensity aerobic exercise.	
Comparison	MICT: participants completed 40 min of moderate-intensity aerobic exercise (50%–60% HRR, or 4-6/10 on a modified Borg scale).	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Preliminary efficacy outcomes included reproductive, anthropometric and cardiometabolic health markers.	
Follow up Duration	6 months	
Summary Result/s	MICT and HIIT were both effective at improving anthropometrics and some cardiometabolic health markers.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes	The objective was to evaluate the effects of HIIT and MICT compared with no exercise on reproductive, anthropometric and cardiometabolic health markers in women with PCOS.
Does the study have specified inclusion/exclusion criteria?	Partial	Untrained women aged 18–40 years with PCOS defined by Rotterdam criteria.
If there were specified inclusion/ exclusion criteria, were these appropriate?	Partial	Should have described who determined PCOS diagnosis.
Inclusion criteria	Partial	Women with PCOS exercising < 40 min per week.
Exclusion criteria	Yes	Exclusion criteria included: medical conditions restricting exercise, participation in >40 min of exercise training weekly and medications potentially affecting ovulation (glucocorticoids, metformin, gonadotropins, clomiphene, letrozole, oestrogens, progestins).
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	Did the study have an adequate method of randomisation?	Yes	Block randomisation based on BMI using REDCap
	Was allocation to intervention group concealed?	Yes	
PERFORMANCE BIAS	Were patients blind to intervention group?	No	Not applicable
	Were investigators and care providers blind to intervention group?	No	Not applicable
	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	Were outcome assessors blind to intervention group?	Yes	
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study dropped out?	18.75% treatment 21.42% comparison	
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Partial	Per protocol analyses applied for primary outcomes except reproductive outcomes which was assessed as ITT.
REPORT	Is the paper free of selective outcome reporting?	Yes	
CONFOUNDING	Were the groups similar at baseline with regard to key prognostic variables?	Yes	
	If confounding was present, was it controlled for?	Not reported	

OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	No	
	Was the study sufficiently powered to detect any differences between the groups?	Yes	
	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS			
What is the overall risk of bias?		Low	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		No	

Study ID	Patten 2022
Study Citation	Patten RK, McIlvenna LC, Levinger I, Garnham AP, Shorakae S, Parker AG, McAinch AJ, Rodgers RJ, Hiam D, Moreno-Asso A, Stepto NK. High-intensity training elicits greater improvements in cardio-metabolic and reproductive outcomes than moderate-intensity training in women with polycystic ovary syndrome: a randomized clinical trial. Hum Reprod. 2022 May 3;37(5):1018-1029. doi: 10.1093/humrep/deac047.
Study Country	Australia
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Physically inactive caucasian premenopausal women (18-45 years) with PCOS and BMI> 25 kg/m^2.
PCOS diagnostic criteria	Rotterdam and confirmed by endocrinologist.
Presence of infertility	Not reported.
Presence of other condition/s	Average BMI of participants 31.4 ± 8.4 (SD)
Medication History	No but participants taking anti-hypertensive, insulin sensitizers, dietary supplements, weight loss medication or hormonal contraceptive medications in the 3 months prior to enrolment were excluded.
N per group	*Allocated/randomised:* 29 (15 HIIT, 14 MICT) *Assessed at end of study:* 24 (13 HIIT, 11 MICT)

Setting		Victoria University in Melbourne, Australia	
Intervention		HIIT: involved twice weekly sessions of 12, 1 min intervals at 90–100% peak heart rate (%HRpeak), separated by 1min of active recovery at a light load and one weekly session of eight, 4min intervals at 90–95% HRpeak, separated by a 2min light load, activity recovery.	
Comparison		MICT: involved three sessions per week of 45 min of continuous cycling at 60–75% HRpeak.	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)		The primary clinical outcomes were aerobic capacity (VO_{2peak}) and insulin sensitivity (euglycaemic–hyperinsulinaemic clamp). Secondary outcomes included hormonal profiles, menstrual cyclicity and body composition.	
Follow up Duration		12 weeks.	
Summary Result/s		HIIT offers greater improvements in aerobic capacity, insulin sensitivity and menstrual cyclicity, and larger reductions in hyperandrogenism compared to MICT.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT			
Does the study have a clearly focused question and/or PICO?		Yes	Does 12 weeks of high-intensity interval training (HIIT) result in greater improvements in cardio-metabolic and reproductive outcomes compared to standard moderate-intensity continuous training (MICT) in women with polycystic ovary syndrome (PCOS)?
Does the study have specified inclusion/exclusion criteria?		Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes	
Inclusion criteria		Yes	Inclusion criteria were Caucasian women aged 18–45 (pre-menopausal), with a BMI greater than 25 kg/m2, insufficiently active (do not meet the minimum physical activity recommendations of 150min of moderate to vigorous activity per week), and with diagnosed PCOS.
Exclusion criteria		Yes	Exclusion criteria included diabetes, pregnancy, smoking, illness or injury that prevented or limited exercise performance and existing participation in regular physical activity. Those taking anti-hypertensive, insulin sensitizers, dietary supplements, weight loss medication or hormonal contraceptive medications in the 3 months prior to enrolment were excluded.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Did the study have an adequate method of randomisation?	Yes	Simple randomization procedure through computerized sequence generation at an allocation ratio of 1:1 and stratified by BMI. Completed by independent statistician.
	Was allocation to intervention group concealed?	Unclear	Not reported

PERFORMANCE BIAS	Were patients blind to intervention group?	No	Not applicable
	Were investigators and care providers blind to intervention group?	No	Not applicable
	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	Were outcome assessors blind to intervention group?	No	
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study dropped out?	13.33% treatment 21.42% comparison	
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes	
REPORT	Is the paper free of selective outcome reporting?	Yes	
CONFOUNDING	Were the groups similar at baseline with regard to key prognostic variables?	Yes	
	If confounding was present, was it controlled for?	Yes	
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	No	
	Was the study sufficiently powered to detect any differences between the groups?	Yes	

	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS			
What is the overall risk of bias?		Low	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		No	

Study ID	Ribeiro 2020
Study Citation	Lopes IP, Ribeiro VB, Reis RM, Silva RC, Dutra de Souza HC, Kogure GS, Ferriani RA, Silva Lara LAD. Comparison of the Effect of Intermittent and Continuous Aerobic Physical Training on Sexual Function of Women With Polycystic Ovary Syndrome: Randomized Controlled Trial. J Sex Med. 2018 Nov;15(11):1609-1619. doi: 10.1016/j.jsxm.2018.09.002. Ribeiro VB, Kogure GS, Lopes IP, Silva RC, Pedroso DCC, de Melo AS, de Souza HCD, Ferriani RA, Miranda Furtado CL, Dos Reis RM. Effects of continuous and intermittent aerobic physical training on hormonal and metabolic profile, and body composition in women with polycystic ovary syndrome: A randomized controlled trial. Clin Endocrinol (Oxf). 2020 Aug;93(2):173-186. doi: 10.1111/cen.14194. Ribeiro VB, Lopes IP, Dos Reis RM, Silva RC, Mendes MC, Melo AS, de Souza HCD, Ferriani RA, Kogure GS, Lara LADS. Continuous versus intermittent aerobic exercise in the improvement of quality of life for women with polycystic ovary syndrome: A randomized controlled trial. J Health Psychol. 2021 Aug;26(9):1307-1317. doi: 10.1177/1359105319869806.
Study Country	Brazil
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Sendetary women (18-39 years) with PCOS and BMI between 18.0 to 39.9 kg/m^2.
PCOS diagnostic criteria	Rotterdam criteria
Presence of infertility	Not reported.
Presence of other condition/s	Not reported
Medication History	Not reported
N per group	*Allocated/randomised:* 72 (35 HIIT, 37 MICT) *Assessed at end of study:* 57 (29 HIIT, 28 MICT)
Setting	Ribeirão Preto Medical School, University of São Paulo, Brazil
Intervention	HIIT: involved twice weekly sessions of six to 10 2-min intervals at 70 to 90% maximal heart rate (HRmax) interspersed with 3-min recovery periods. Supervised exercise sessions.

Comparison		MICT: involved thrice weekly of 30 to 45-min of continuous cycling at 65–80% HRmax. Supervised exercise sessions. Work was matched between groups.	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)		The primary clinical outcomes were hormonal, metabolic and anthropometric outcomes. Secondary outcomes published in other manuscripts were quality of life, depression and anxiety, sexual function, and telomere length; Both protocols were effective to improve testosterone levels, anthropometric indices, and quality of life in polycystic ovary syndrome women.	
Follow up Duration		16 weeks.	
Summary Result/s		MICT and HIIT training reduced anthropometric indices and hyperandrogenism in PCOS, whereas only HIIT training reduced the FAI. Furthermore, only MICT training improved the lipid profile; Aerobic physical training protocols could be indicated to promote mental and sexual health in women with PCOS.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT			
Does the study have a clearly focused question and/or PICO?		Yes	
Does the study have specified inclusion/exclusion criteria?		No	
If there were specified inclusion/ exclusion criteria, were these appropriate?		Not applicable	
Inclusion criteria		Yes	Women diagnosed as having PCOS, aged between 18 and 39 years, with sedentary lifestyles, and with BMIs between 18 and 39.9kg/m^2 were considered eligible for this study.
Exclusion criteria		No	Exclusion criteria not reported
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Did the study have an adequate method of randomisation?	Yes	Simple randomization procedure through computerized sequence generation at an allocation ratio of 1:1 and stratified by BMI. Completed by independent statistician.
	Was allocation to intervention group concealed?	Yes	The allocation group was placed inside opaque, sealed envelopes, grouped in blocks of 15 and consecutively picked depending on the BMI of the participant at the time of study inclusion.
PERFORMANCE BIAS	Were patients blind to intervention group?	No	Not applicable
	Were investigators and care providers blind to intervention group?	No	Not applicable
	Aside from the experimental intervention, were the groups treated the same?	Yes	

DEDETECTION BIAS	Were outcome assessors blind to intervention group?	Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study dropped out?	17.14% treatment 24.32% comparison	
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	No	Per protocol analysis
REPORT	Is the paper free of selective outcome reporting?	Yes	Outcomes were published in separate manuscripts.
CONFOUNDING	Were the groups similar at baseline with regard to key prognostic variables?	Yes	
	If confounding was present, was it controlled for?	Yes	
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	No	
	Was the study sufficiently powered to detect any differences between the groups?	Yes	
	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS		Unclear whether assessors were blinded to participant group allocation.	
What is the overall risk of bias?		Unclear	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		No	

Study ID	Thomson 2008
Study Citation	Thomson RL, Buckley JD, Noakes M, Clifton PM, Norman RJ, Brinkworth GD. The effect of a hypocaloric diet with and without exercise training on body composition, cardiometabolic risk profile, and reproductive function in overweight and obese women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2008 Sep;93(9):3373-80. doi: 10.1210/jc.2008-0751.
Study Country	Australia
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS
PCOS diagnostic criteria	Rotterdam
Presence of infertility	Not reported
Presence of other condition/s	
Medication History	Not reported
N per group	*Allocated/randomised:* 64 (31 MICT, 33 MICT and RT) *Assessed at end of study:* 38 (18 MICT, 20 MICT and RT)
Setting	Metropolitan research clinic
Intervention	Diet: All subjects were prescribed the same energy-restricted, high-protein diet (5000–6000 kJ/d) for a planned weight loss of 8–12 kg over the study period. The diet provided 30% of energy as protein, 40% as carbohydrate, and 30% as fat (8% saturated fat). MICT: walking/jogging five times a week for 25-45 minutes at 60-80% HRmax.
Comparison	Diet: All subjects were prescribed the same energy-restricted, high-protein diet (5000–6000 kJ/d) for a planned weight loss of 8–12 kg over the study period. The diet provided 30% of energy as protein, 40% as carbohydrate, and 30% as fat (8% saturated fat). MICT: walking/jogging three times a week for 25-45 minutes at 60-80% HRmax. RT: two days of resistance training involving 5 exercises for three sets of 12 repetitions at 50-75% 1RM.
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Weight, body composition, cardiometabolic risk factors, hormonal status, menstrual cyclicity, and ovulatory function.
Follow up Duration	20 weeks
Summary Result/s	In overweight and obese women with PCOS, the addition of aerobic or combined aerobic resistance exercise to an energy-restricted diet improved body composition but had no additional effect on improvements in cardiometabolic, hormonal, and reproductive outcomes relative to diet alone.
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT	

Does the study have a clearly focused question and/or PICO?		Yes	The objective was to evaluate the effects of aerobic and aerobic-resistance exercise when combined with an energy-restricted high protein diet (5000 6000 kJ/d) on metabolic risk factors and reproductive function in women with PCOS.
Does the study have specified inclusion/exclusion criteria?		Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?		Partial	Didn't define age or BMI range.
Inclusion criteria		Partial	Didn't define age or BMI range.
Exclusion criteria		Yes	Potential participants were excluded if they were using fertility treatments or oral contraceptives; were smokers, pregnant, breastfeeding, or had history of cardiovascular, liver, kidney or respiratory disease, diabetes, uncontrolled hypertension, or malignancy; or were participating in regular physical activity. Subjects were also excluded if they had reproductive disorders unrelated to PCOS, thyroid abnormalities, or nonclassical adrenal hyperplasia.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Did the study have an adequate method of randomisation?	Unclear	They study was randomised but the authors didn't mention how they conducted the randomisation.
	Was allocation to intervention group concealed?	Unclear	Not reported
PERFORMANCE BIAS	Were patients blind to intervention group?	No	Not applicable
	Were investigators and care providers blind to intervention group?	No	Not applicable
	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	Were outcome assessors blind to intervention group?	Unclear	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Yes	

ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study dropped out?	42% treatment 39% comparison	
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Unclear	Not reported whether analyses were intention to treat or per protocol.
REPORT	Is the paper free of selective outcome reporting?	Yes	
CONFOUNDING	Were the groups similar at baseline with regard to key prognostic variables?	Yes	
	If confounding was present, was it controlled for?	Not applicable	
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	No	
	Was the study sufficiently powered to detect any differences between the groups?	Yes	
	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS		Lack of blinding of outcome assessors, concealment of allocation (opaque envelopes), high dropout rate, and unclear whether analyses were undertaken as per-protocol or as intention-to-treat are primary reasons for high risk classification.	
What is the overall risk of bias?		High	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		No	

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 3

Question 3.4.

In women with PCOS, are exercise interventions (compared to different exercises) effective for improving anthropometric, metabolic, reproductive, fertility, quality of life and emotional wellbeing outcomes?

BACKGROUND:

In general populations, physical activity (any bodily movement produced by skeletal muscles that requires energy expenditure) and structured exercise (an activity requiring physical effort, carried out to sustain or improve health and fitness) delivers metabolic, cardiovascular, and psychosocial benefits, whether alone or combined with diet changes (1-2). Both aerobic exercise (cardiorespiratory fitness training) and resistance exercise (muscle strengthening) are proven beneficial to reduce cardiometabolic risk factors but combined training seems to be most efficient (1-2).

Exercise can be classified as continuous aerobic exercises characterized by a constant submaximal power output throughout an entire session or intermittent aerobic exercises which consist of alternating periods of greater and lower intensity within an exercise period. High intensity interval training or HIIT is a newer form of exercise that is defined by repeated short bouts of high-intensity exercise. In populations with type 2 diabetes and healthy populations, compared to moderate intensity continuous aerobic physical training (MICT), HIIT has shown superior benefits to cardiometabolic parameters (3-5).

In women with PCOS, there is a range of evidence from small randomized controlled trials (RCTs) and high-quality mechanistic studies (cohort and case control studies) that physical activity, including formal exercise training in the form of aerobic and/or resistance training improves metabolic features, body composition, reproductive features and psychological wellbeing compared to minimal or no interventions (6-10). However, there is minimal high quality RCT evidence exploring what exercise best targets clinical features of PCOS and the benefits of exercise in combination with improvements to diet.

The key clinical question and knowledge gap relates to establishing which physical activity and/or formal exercise program or intervention is most effective for improving anthropometric, metabolic, reproductive, fertility, quality of life and emotional wellbeing outcomes in women with PCOS. The evidence summary of our meta-analysis and/or descriptive analysis for the three different comparisons is summarized below:

Comparison 1. High-intensity interval training versus moderate-intensity continuous training

In the meta-analysis of 2-3 pooled studies comparing HIIT to MICT three times per week and ranging from 10 weeks to 6 months (11-13), there were no differences in any of the anthropometric, metabolic, reproductive or hormonal outcomes assessed, with most of the evidence being of low to very low certainty due primarily to imprecision (small sample sizes), unclear risk of bias and inconsistency of effect estimates and/or confidence intervals. In descriptive analysis, HIIT was more effective than MICT for menstrual regularity (OR [95%CI] = 7.8 [1.1, 56.1]) with very low certainty due to imprecision (being derived from a single small study (12) as well as inconsistency and risk of bias.

Comparison 2. High-intensity interval training versus resistance training

Based on only one study in 21 women with PCOS where HIIT was compared to resistance training three times per week for 10 weeks (14), there were no observed differences between HIIT and resistance training for metabolic, cardiovascular and hormonal outcomes.

Comparison 3. Diet plus combined aerobic and resistance training versus diet plus aerobic exercise

The systematic review identified only one study that compared diet combined with aerobic exercise and resistance training with diet combined with aerobic exercise only (15). There were no significant differences in cardiometabolic, hormonal and reproductive outcomes.

GRADE EVIDENCE CERTAINTY	
Comparison	**GRADE for critical outcomes**
○ **Comparison 1. High-intensity interval training versus moderate-intensity continuous training**	⨁◯◯◯ VERY LOW
○ **Comparison 2. High-intensity interval training versus resistance training**	⨁◯◯◯ VERY LOW
○ **Comparison 3. Diet plus combined aerobic and resistance training versus diet plus aerobic exercise**	⨁◯◯◯ VERY LOW

Evidence to Recommendations Framework

COMPARISONS (option versus other option)

Comparison 1. High-intensity interval training (HIIT) versus moderate-intensity continuous training (MICT)

Comparison 2. HIIT versus resistance training (RT)

Comparison 3. Diet + combined aerobic and resistance training (CT) versus diet + aerobic exercise (AEx)

EVIDENCE-BASED RECOMMENDATION(S)

- **EBR:** Health professionals and women could consider that, there is no evidence to support any one type and intensity of exercise being better than another for anthropometric, metabolic, hormonal, reproductive or psychological outcomes.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

- **CR:** Any physical activity consistent with population guidelines will have health benefits and within this, health professionals should advise any sustainable physical activity based on individual preferences and goals.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

- **CR:** Health professionals should encourage and advise the following in concordance with general population physical activity guidelines:
    - All adults should undertake physical activity asdoing some physical activity is better than none.
    - Adults should limit the amount of time spent being sedentary (e.g. sitting, screen time) asreplacing sedentary time with physical activity of any intensity (including light intensity) provides health benefits.
- For the prevention of weight gain and maintenance of health, adults (18-64 years) should aim for a minimum of 150 to 300 minutes of moderate intensity activities or 75 to 150 minutes per week of vigorous intensity aerobic activity or an equivalent combination of both spread throughout the week, plus muscle strengthening activities (e.g. resistance/flexibility) on two non-consecutive days per week.
- For promotion of greater health benefits including modest weight-loss and prevention of weight-regain, adults (18-64 years) should aim for a minimum of 250 min/week of moderate intensity activities or 150 min/week of vigorous intensities or an equivalent combination of both, plus muscle strengthening activities (e.g. resistance/flexibility), ideally on two non-consecutive days per week.
- Adolescents should aim for at least 60 minutes of moderate- to vigorous-intensity physical activity per day including activities that strengthen muscle and bone, at least three times per week.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

PRACTICE POINT(S)

- Physical activity is any bodily movement produced by skeletal muscles that requires energy expenditure. It includes leisure time physical activity, transportation (e.g. walking or cycling), occupational (i.e. work), household chores, playing games, sports or planned exercise, or activities in the context of daily, family and community activities.
- Aerobic activity is best performed in bouts of at least 10 minutes duration, aiming to achieve at least 30 minutes daily on most days.
- Barriers and facilitators to optimise engagement and adherence to physical activity should be discussed, including psychological factors (e.g. body image concerns, fear of injury, fear of failure, mental health), personal safety concerns, environmental factors, physical limitations, socioeconomic factors, sociocultural factors, as well as personal motivators for change. The value of broader family engagement should be considered. Referral to suitably trained allied health professionals needs to be considered for optimising physical activity in women with PCOS.
- Self-monitoring including with fitness tracking devices and technologies for step count and exercise intensity, could be used as an adjunct to support and promote active lifestyles and minimise sedentary behaviours.

GRADE CONSIDERATIONS

Justifications:
With limited number and quality RCTs on optimal exercise programs for women with PCOS, we are referred to high quality mechanistic literature in PCOS and international exercise/physical activity recommendations for the general population.

COMPARISON 1. HIIT versus MICT
In the meta-analyses of 2-3 pooled studies (11-13), there were no differences in any of the outcomes assessed, with most of the evidence being of low to very low certainty due primarily to imprecision (small sample sizes), in addition to unclear risk of bias and inconsistency of effect estimates and/or confidence intervals. In descriptive analysis (studies

or outcomes not pooled in meta-analysis), HIIT was more effective than MICT for menstrual regularity (OR [95%CI] = 0.127 [0.017, 0.905]) with very low certainty due to imprecision (being derived from a single small study (12), as well as inconsistency and risk of bias.

COMPARISON 2. HIIT versus RT
One study compared HIIT with RT (14) on anthropometric, metabolic and hormonal/ reproductive outcomes. This study (14) was conducted in Norway with 21 participants and had an unclear risk of bias due to lack of blinding to participant group allocation by outcome assessors and insufficient information around allocation concealment. There were no differences between HIIT and RT for any of the outcomes. Certainty in these results is very low due to being derived from a single, relatively small study with an unclear risk of bias.

COMPARISON 3. Diet plus combined aerobic and resistance training versus diet plus aerobic exercise
One study compared diet plus combined aerobic and RT with diet and aerobic exercise (15) on anthropometric, metabolic and hormonal/ reproductive outcomes. This study (15) was conducted in Australia with 64 participants and had a high risk of bias due to lack of blinding to participant group allocation by outcome assessors and insufficient information around allocation concealment. There were no differences between diet plus combined aerobic and resistance training and diet and aerobic exercise for any of the outcomes. Certainty in these results is very low due to being derived from a single, relatively small study with a high risk of bias due to lack of blinding of outcome assessors, concealment of allocation (opaque envelopes), high dropout rate, and unclear whether analyses were undertaken as per-protocol or as intention-to-treat.

Subgroup considerations:
All studies were in adult populations.

Implementation considerations:
Recommendations may have cost implications especially in resource limited environment.

Monitoring and evaluation considerations:
As there is insufficient evidence for a specific type, mode or intensity of exercise being best for the management and treatment of PCOS, thus recommending gold-standard and expensive cardio-respiratory tests is unwarranted. Instead, simple easy to use tools would appropriate to monitor general fitness and exercise behaviours in women with PCOS.

Research priorities:
Clear clinical research gaps have been identified in this and prior extensive evidence syntheses (6-10), as well as stakeholder feedback including an international survey of 1592 women with PCOS and 1800 Health Professionals (2015–2017) (16). There is an urgent need to determine:

1) Exercise types, intensity, duration and duration of effect to optimise efficacy and efficiency.
2) Strategies to increase engagement and address barriers, cultural factors, acceptability, feasibility and sustainability of active lifestyles in PCOS management and treatment.
3) Medium to longer term exercise studies (6-12 months or greater)
4) Impact of improvements in cardiorespiratory fitness and/or strength on clinical features of clinical outcome of women with PCOS.
5) Assessing the impact of reducing sedentary behaviour on clinical outcomes.

Other priorities include:

- Across different life stages – adolescent, post-menopausal, pregnancy
- Cost effectiveness
- Sufficiently powered RCTs
- The contribution of social support

GRADE framework

GRADE DECIDE **Interactive Evidence to Decision Framework**

● DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

For comparison 1: Three trials of short duration (12 weeks to 6 months); HIIT vs MICT 3 times per week.

Menstrual regularity was reported in 2 studies of small sample size. A pilot study with feasibility as primary outcome and reproductive function as one of the preliminary efficacy outcomes showed no difference in menstrual regularity between the groups (11). Another study with menstrual cyclicity as one of the secondary outcomes showed benefits for HIIT in menstrual regularity (12).

_____

For comparison 2/3: meta-analysis was not possible. Only 1 study for each comparison.

Comparison 2 – 10 weeks long, 21 subjects

Comparison 3 – 20 weeks, lots of drop outs (64 enrolled, 38 completed/included in analysis)

● UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

For comparison 1: Three trials of short duration (12 weeks to 6 months); HIIT vs MICT 3 times per week.

Menstrual regularity was reported in 1 study, small sample size

_____

For comparison 2/3: meta-analysis was not possible. Only 1 study for each comparison.

Comparison 2 – 10 weeks long, 21 subjects

Comparison 3 – 20 weeks, lots of drop outs (64 enrolled, 38 completed/included in analysis)

● CERTAINTY OF THE EVIDENCE

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☒ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Small number of studies

Small numbers of subjects

High risk of bias

● VALUES

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☐ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☒ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Research evidence:

No research evidence was identified

Panel discussion:

Small number of studies

Small numbers of subjects

High risk of bias

Low quality evidence

● BALANCE OF EFFECTS

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☐ Favours this option	☐ Probably favours this option	X Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:

Women may prefer one type of exercise, intensity and duration over other types.

● COSTS

How large are the resource requirements (costs)?

Judgement:

☐ Don't know	☒ Varies	☐ Large costs	☐ Moderate costs	☐ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:

No research evidence was identified

Panel discussion:

It is important to consider the cost and resource requirements at a health systems level and for the individual woman with many low cost options available. Irrespective of the exercise programme or physical activity recommendation, implementation of exercise therapy/physical activity programs may result in increased referral to health professionals. This is likely to increase health professional time demands.

● CERTAINTY OF COST EVIDENCE

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

No research evidence was identified

Panel discussion:

No evidence available.

● COST-EFFECTIVENESS

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

No research evidence was identified

Panel discussion:

No cost effectiveness analysis has been conducted for comparing different exercise therapies in PCOS.

● EQUITY

What would be the impact on health equity?

Judgement:

☐ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☒ Probably increased	☐ Increased

Research evidence:

No research evidence was identified

Panel discussion:

The implementation may be variable due to availability of local resources but recommendation is likely to improve equity.

● ACCEPTABILITY

Is the option acceptable to key stakeholders?

Judgement:

☐ Don't know	☒ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Engagement of healthcare practitioners and healthcare funders, as well as the financial barriers for the woman may be an issue. Also, insufficient access to, as well as time constraint for, health professionals may be a barrier. Drop-out or non-adherence to physical activity recommendations may be a problem.

● FEASIBILITY

Is the option feasible to implement?

Judgement:

☐ Don't know	☒ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Likely feasible for health professionals to give general population physical activity advice but feasibility and sustainability for healthy physical activity in women may vary depending on socioeconomic, sociocultural, physical factors.

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PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by the Evidence Team (Jillian Tay, Aya Mousa)

Other team members: Maryam Kazemi, Yanan Hu, Joy Kim, Cynthia Wan, Julia Xiong, Adele Cave, Jessica Mills, Julia Michalak, Isabella Xavier, Kiran Ganga, Jessica Grieger, Mahnaz Bahri-Khomami, Margaret McGowan, Darren Rajit, Stephanie Cowan

GDG 3

Question 3.5.

Why are women with PCOS at increased risk of weight gain?

1. STUDY SELECTION

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(language, year)*
Inclusion	Women with PCOS (NIH 1990, Rotterdam 2003 or AE-PCOS 2006 criteria). No exclusion of age. Note age subgroups, phenotypes or pathological categories (HA or IR).	None	Females without PCOS	1) Extrinsic factors potentially related to challenges with weight management (ie lifestyle factors) a. Dietary intake (energy, glycemic index, glycemic load, protein, fat, carbohydrate) b. Physical activity (Total PA) 2) Intrinsic factors potentially related to challenges with weight management (ie energy homeostasis) a. Energy intake Include - Post meal/OGTT - Ghrelin, GLP1, GIP, PYY, Amylin, appetite/satiety/hunger (please only include AUC data) Exclude - fasting, post clamp or post weight loss measures of any above b. Energy expenditure Include – REE, MIT Exclude – RER, metabolic flexibility	Intervention (randomized, non-randomized controlled trials, single arm intervention trials) or observational (i.e., cross-sectional, case-control, cohort) studies	English language. Human studies
Exclusion	None	None	None	None	case reports, commentaries, letters to editor, abstracts.	None

Table 1. PICO Criteria for Inclusion	
Question	3.5 Why are women with PCOS at increased risk of weight gain?
Clinical leads (key contacts)	Lisa Moran
Allocation ranking	Level 1 – New systematic review

2. SEARCH STRATEGY

1.1 Search details	
Search strategy source: Kazemi, Maryam, Kim, Joy Y, Wan, Cynthia, Xiong, Julia D, Michalak, Julia, Xavier, Isabella B, Ganga, Kiran, Tay, Chau Thien, Grieger, Jessica A, Parry, Stephen A, Moran, Lisa J, & Lujan, Marla E. (2022). Comparison of dietary and physical activity behaviors in women with and without polycystic ovary syndrome: a systematic review and meta-analysis of 39 471 women. Human Reproduction Update. https://doi.org/10.1093/humupd/dmac023	
Evidence source	**Date of search (day/month/year)**
Medline (Ovid)	Inception until 15/2/22
Web of Science	Inception until 15/2/22
Scopus	Inception until 15/2/22
CINAHL	Inception until 15/2/22
Any subsequent updates - enter database and date: not applicable	

1.2 Questions addressed by this search:		
GDG	Q#	Question
3	3.5	Why are women with PCOS at increased risk of weight gain? Extrinsic factors

Search strategy for extrinsic weight gain factors

PCOS search terms:
polycystic ovary syndrome/
"polycystic ovar*".mp.
"poly-cystic ovar*".mp.
PCOS.mp.
PCO*.mp.
anovulation/
anovulat*.mp.
oligo-ovulat*.mp.
oligoovulat*.mp.
Stein-Leventhal.mp.
Leventhal.mp.
"sclerocystic ovary syndrome".mp.
OR/ 1-12

Diet search terms:
exp diet/
diet*.mp.
exp diet therapy/
nutrition*.mp.
nutrient*.mp.
exp food/
food.mp.
feeding behavior/
eat*.mp.
intake*.mp.
consum*.mp.
meat.mp.
poultry.mp.
chicken.mp.
fish.mp.
seafood.mp.
soy.mp.
legume*.mp.
bean*.mp.
nut*.mp.
seed*.mp.

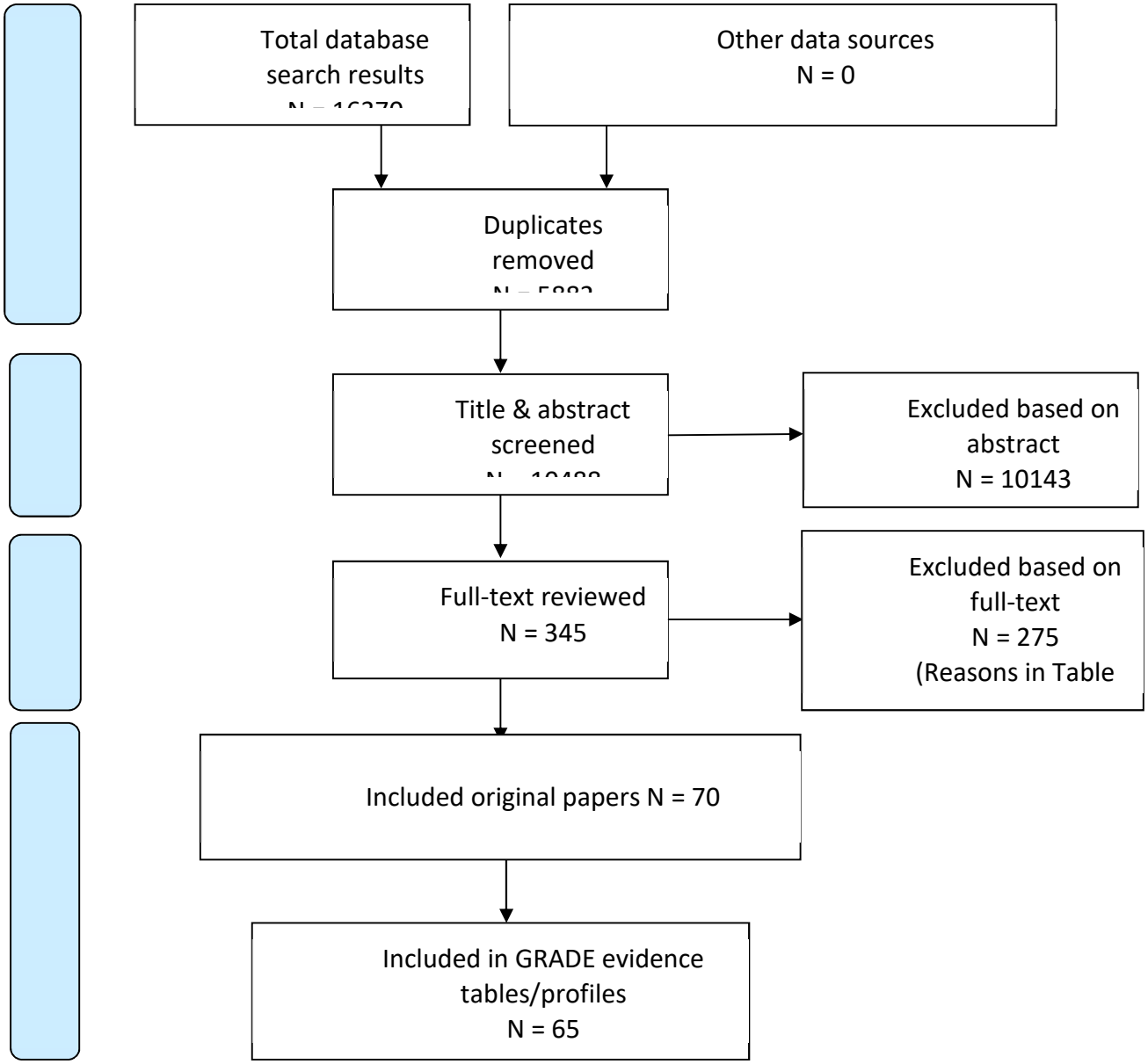
dairy.mp.
fruit.mp.
vegetable.mp.
cereal.mp.
grain*.mp.
"sugar-sweetened".mp.
"soft drink*".mp.
juice.mp.
"processed food*".mp.
exp Life Style/
lifestyle.mp.
"life style".mp.
OR/ 14-46

Physical activity search terms:
exp human activities/
"physical activity".mp.
exp exercise/
exercis*.mp.
exp leisure activities/
leisure.mp.
train*.mp.
fitness.mp.
sedentary behavior/
"sedentary behavior".mp.
"sedentary behaviour".mp.
OR/ 48-58

Limitations:
47 OR 59
13 AND 60
exp animals/ not humans/
#61 NOT #62

Evidence processing: Studies were selected and appraised by 2 reviewers using study selection and appraisal criteria (PICO above) established a priori. The articles were reviewed by title and abstract by 2 reviewers. When a decision could not be made based on title and abstract alone, full text was retrieved. **In total, 64 studies met inclusion criteria for this review.**

3. SEARCH RESULTS - PRISMA flowchart



4. STUDY INCLUSION

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4.2 Excluded studies (on full text assessment)

Title	Study	Journal	Volume	Issue	Pages	Notes
Diet and Nutrition in Gynecological Disorders: A Focus on Clinical Studies	Afrin 2021	Nutrients	13	6	1747-1747	Wrong design
The effects of high intensity-interval training on vaspin, adiponectin and leptin levels in women with polycystic ovary syndrome	Aktaş 2022	Arch Physiol Biochem	128	1	37-42	No control/reference group
Androgens and hirsutism score of overweight women with polycystic ovary syndrome improved after vitamin D treatment: A randomized placebo controlled clinical trial	Al-Bayyari 2021	Clinical Nutrition	40	3	870-878	No control/reference group
Effects of supervised aerobic training on the levels of anti-Mullerian hormone and adiposity measures in women with normo-ovulatory and polycystic ovary syndrome	Al-Eisa 2017	Journal of the Pakistan Medical Association	67	4	499-507	Wrong outcome
Nutritional Supplements and Complementary Therapies in Polycystic Ovary Syndrome	Alesi 2021	Adv Nutr				Wrong design
Educational Program: Its Effect on Knowledge and Lifestyles among Paramedical Students with Polycystic Ovarian Syndrome (PCOS)	AlKurdi 2021	Medico-Legal Update	21	3	58-69	No control/reference group
Polycystic ovary syndrome and a low glycemic index diet	Allen 2005	Canadian Journal of Dietetic Practice & Research	66	2	3-3	Wrong design (abstract)
Effects of High Intensity Interval Training and Strength Training on Metabolic, Cardiovascular and Hormonal Outcomes in Women with Polycystic Ovary Syndrome: A Pilot Study	Almenning 2015	Plos One	10	9		No control/reference group
Lifestyle Modifications in PCOS	Aly 2021	Clinical Obstetrics and Gynecology	64	1	83-89	Wrong design (book)
Lifestyle Modifications in PCOS	Aly 2021	Clinical Obstetrics and Gynecology	64	1	83-89	Wrong design (book)
Perceptions and experiences of lifestyle interventions in women with polycystic ovary syndrome (PCOS), as a management strategy for symptoms of PCOS	Arentz 2021	BMC Women's Health	21	1		self reported PCOS
Impact of polycystic ovary syndrome on eating behavior, depression and health related quality of life: A cross-sectional study in Riyadh	Asdaq 2020	Saudi Journal of Biological Sciences	27	12	3342-3347	Wrong outcome
Effects of DASH diet on lipid profiles and biomarkers of oxidative stress in overweight and obese women with polycystic ovary syndrome: A randomized clinical trial	Asemi 2014	Nutrition	30	11-12	1287-1293	No control/reference group
DASH diet, insulin resistance and inflammation in polycystic ovary syndrome: a randomized controlled clinical trial	Asemi 2014	Human Reproduction	29		316-316	Wrong design (abstract)
An intensive diet and exercise program improved anthropometric, nutritional, fitness, and reproductive outcomes in PCOS patients	Aubuchon 2006	Fertility and Sterility	86		S463-S464	Wrong design (abstract)

Longitudinal weight gain and lifestyle factors in women with and without polycystic ovary syndrome	Awoke 2021	INTERNATIONAL JOURNAL OF EPIDEMIOLOGY	50		20-20	Wrong design (abstract)
Weight gain and lifestyle factors in women with and without polycystic ovary syndrome	Awoke 2021	Human reproduction (Oxford, England)	37	1	129-141	Self-reported PCOS
Dynamic Change in Insulin Resistance Induced by Free Fatty Acids Is Unchanged Though Insulin Sensitivity Improves Following Endurance Exercise in PCOS	Aye 2018	Frontiers in Endocrinology	9			Wrong outcome
Ensuring Nutrition - Polycystic Ovary Syndrome, Management from Menarche to Menopause	Balen 2018	Australian & New Zealand Journal of Obstetrics & Gynaecology	58		12-12	Wrong design (abstract)
Dietary composition of UK women with Polycystic Ovary Syndrome	Barr 2007	Annals of Nutrition and Metabolism	51		345-346	Wrong design (abstract)
Dietary intake, body composition and physical activity levels in women with polycystic ovary syndrome compared with healthy controls...Selected abstracts from the British Dietetic Association Conference 2008	Barr 2008	Journal of Human Nutrition & Dietetics	21	4	377-377	Wrong design (abstract)
Efficacy of a low-glycaemic index diet in women with polycystic ovary syndrome	Barr 2010	Proceedings of the Nutrition Society	69	OCE6	E404-E404	Wrong design (abstract)
Dietary glycaemic index, glycaemic load and insulin resistance in lean and overweight women with polycystic ovary syndrome and controls	Barr 2010	Proceedings of the Nutrition Society	69	OCE1	E126-E126	Wrong design (abstract)
Habitual dietary intake, eating pattern and physical activity of women with polycystic ovary syndrome	Barr 2011	Eur J Clin Nutr	65	10	1126-32	Self-reported PCOS
An Isocaloric Low Glycemic Index Diet Improves Insulin Sensitivity in Women with Polycystic Ovary Syndrome	Barr 2013	Journal of the Academy of Nutrition and Dietetics	113	11	1523-1531	No control/reference group
Source and amount of carbohydrate in the diet and inflammation in women with polycystic ovary syndrome	Barrea 2018	Nutrition Research Reviews	31	2	291-301	Wrong design
Metabolically healthy obesity (Mho) vs. metabolically unhealthy obesity (muo) phenotypes in pcos: Association with endocrine-metabolic profile, adherence to the mediterranean diet, and body composition	Barrea 2021	Nutrients	13	11		No control/reference group
PCOS and nutritional approaches: Differences between lean and obese phenotype	Barrea 2021	Metabol Open	12		100123	Wrong design
Outcome of Interventional Programme on Quality of Life of Infertile Women with Polycystic Ovarian Syndrome	Beena 2016	International Journal of Nursing Education	8	2	27-33	Wrong outcome
Role of high-fat diet on letrozole-induced polycystic ovarian syndrome in rats	Begum 2022	Eur J Pharmacol	917		174746	Wrong population (Animal)
Exercise training and reproductive outcomes in women with polycystic ovary syndrome: A pilot randomized controlled trial	Benham 2021	Clinical Endocrinology	95	2	332-343	No control/reference group
Comparative success of recruitment strategies for an exercise intervention trial among women with polycystic ovary syndrome: Observational study	Benham 2021	Journal of Medical Internet Research	23	3		No control/reference group
A Low Insulinemic Diet Improves Binge Eating and Quality-of-Life in Women with PCOS	Berenson 2014	Journal of Womens Health	23	4	16-16	Wrong design (abstract)

Polycystic Ovary Syndrome, Fertility, Diet, and Lifestyle Modifications A Review of the Current Evidence	Boyd 2019	Topics in Clinical Nutrition	34	1	14-30	Wrong design
Dietary underreporting by women with Polycystic Ovary Syndrome (PCOS)	Braschi 2016	European Journal of Obstetrics & Gynecology & Reproductive Biology	206		e138-e139	Wrong design (abstract)
The Effect of Exercise on Cardiometabolic Risk Factors in Women with Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis	Breyley-Smith 2022	Int J Environ Res Public Health	19	3		Wrong design
Vitamin D levels among women with and without PCOS	Broughton 2013	17th World Congress on Controversies in Obstetrics, Gynecology & Infertility			129-132	No full text
THE EFFECT OF WEIGHT LOSS DIET AND OMEGA-3 FATTY ACIDS ON BODY WEIGHT AND SOME BIOCHEMICAL PARAMETERS IN PATIENTS WITH POLYCYSTIC OVARY SYNDROME	Cadyran 2013	Annals of Nutrition and Metabolism	63		567-567	Wrong design (abstract)
Polycystic ovary syndrome in insulin-resistant adolescents with obesity: The role of nutrition therapy and food supplements as a strategy to protect fertility	Calcaterra 2021	Nutrients	13	6		Wrong design
Nutritional status and food consumption of patients with polycystic ovary syndrome	Calixto 2012	Revista Mineira de Enfermagem	16	2	159-165	No control/reference group
Difference in body weight between American and Italian women with polycystic ovary syndrome: influence of the diet	Carmina 2003	Human Reproduction	18	11	2289-2293	No control/reference group
The impact of macro nutrients intake on insulin resistance in polycystic ovary syndrome...40th European Society for Clinical Nutrition and Metabolism Congress, September 1-4, 2018, Madrid, Spain	Celik 2018	Clinical Nutrition	37		S94-S94	Wrong design (abstract)
Investigation of taste function and eating behavior in women with polycystic ovary syndrome	Cetik 2022	Appetite	168			Wrong outcome
Dietary Interventions: A Promising Treatment for Polycystic Ovary Syndrome	Che 2021	Annals of Nutrition & Metabolism	77	6	313-323	Wrong design
Eating Behavior as Assessed by the Three-Factor Eating Questionnaire and Weight Loss Success in Obese Women with and without the Polycystic Ovary Syndrome	Cheang 2010	Endocrine Reviews	31	3		Wrong design (abstract)
Letter to the Editor from Chenyun Miao, et al: "Effect of Diet on Insulin Resistance in Polycystic Ovary Syndrome"	Chenyun 2021		106		e2378-e2379	Wrong design
Barriers and facilitators to the implementation of lifestyle management in polycystic ovary syndrome: Endocrinologists' and obstetricians and gynaecologists' perspectives	Chhour 2021	Patient Educ Couns				No PCOS group
STROKE VOLUME DURING EXERCISE IS ASSOCIATED WITH INSULIN SENSITIVITY AMONG WOMEN WITH POLYCYSTIC OVARIAN SYNDROME	Choi 2010	Journal of Investigative Medicine	58	2	384-384	Wrong design (abstract)
CARDIAC OUTPUT DURING EXERCISE IS INVERSELY ASSOCIATED WITH LEFT VENTRICULAR MASS IN WOMEN WITH POLYCYSTIC OVARIAN SYNDROME	Choi 2011	Journal of Investigative Medicine	59	2	409-409	Wrong design (abstract)

The effect of exercise and metformin treatment on circulating free DNA in pregnancy	Christiansen 2014	Placenta	35	12	989-993	Wrong population (Animal)
Effects of Synbiotic Supplementation and Lifestyle Modifications on Women with Polycystic Ovary Syndrome	Chudzicka-Strugała 2021	Journal of Clinical Endocrinology and Metabolism	106	9	2566-2573	No control/reference group
Effects of mixed of a ketogenic diet in overweight and obese women with polycystic ovary syndrome	Cincione 2021	International Journal of Environmental Research and Public Health	18	23		No control/reference group
Polycystic ovarian syndrome and infertility: overview and insights of the putative treatments	Collée 2021	Gynecological Endocrinology	37	10	869-874	Wrong design
Dietary intakes in infertile women a pilot study	Colombo 2009	Nutr J	10	8	53	PCOS not defined
Impact of a diagnosis of polycystic ovary syndrome on diet, physical activity and contraceptive use in young women: findings from the Australian Longitudinal Study of Women's Health	Copp 2020	Human Reproduction	35	2	394-403	Self-reported PCOS
Physical activity and Nutrition for the female athlete with polycystic ovary syndrome: An appraisal of scientific literature	Cortes 2019	Annals of Nutrition and Metabolism	75		74-75	Wrong design (abstract)
Resting metabolic rate and exercise capacity in women with polycystic ovary syndrome	Cosar 2008	International Journal of Gynecology & Obstetrics	101	1	31-34	Wrong outcome
Defining exercise prescription in lifestyle modification programs for overweight/obese polycystic ovary syndrome women...Fertil Steril. 2011 Dec;96(6):1508-13	Costa 2012	Fertility & Sterility	97	2	e5-e6	Wrong design
Higher circulating leukocytes in women with PCOS is reversed by aerobic exercise	Covington 2016	Biochimie	124		27-33	Wrong outcome
Insulin Resistance, Hyperinsulinemia, and Mitochondria Dysfunction in Nonobese Girls With Polycystic Ovarian Syndrome	Cree-Green 2017	Journal of the Endocrine Society	1	7	931-944	Wrong outcome
The food frequency intake and eating behaviours of metabolically obese and non obese polycystic ovary syndrome women	Czlapka-Matyasik 2020	Proceedings of the Nutrition Society	79	OCE2	E700-E700	Wrong design (abstract)
ANTHROPOMETRIC CHARACTERISTICS, DIET QUALITY AND DIFFERENCE IN FOOD INTAKE BETWEEN WOMEN WITH AND WITHOUT POLYCYSTIC OVARY SYNDROME	daCunha 2017	Annals of Nutrition and Metabolism	71		1116-1117	Wrong design (abstract)
A comparison of serum insulin and glucose responses to different hypocaloric diets in women with polycystic ovary syndrome (PCOS) and normal controls	Dahan 2007	Fertility and Sterility	88		S79-S79	Wrong design (abstract)
Polycystic Ovary Syndrome: Dietary Approaches to Counteract Insulin Resistance	Das 2020	University of Toronto Journal of Undergraduate Life Sciences	14	1		Wrong design
A study of the health-related quality of life in overweight and obese adult women with the polycystic ovary syndrome during a lifestyle modification program	DeFrene 2013	Human Reproduction	28		57-57	Wrong design (abstract)

Improvements in PCOS characteristics and phenotype severity during a randomized controlled lifestyle intervention	deLoos 2021	Reproductive BioMedicine Online	43	2	298-309	No control/reference group
Metabolic syndrome prevalence and severity during a randomized controlled three-component lifestyle intervention in women with PCOS	deLoos 2021	Human Reproduction	36		77-77	No control/reference group
Metabolic health during a randomized controlled lifestyle intervention in women with PCOS	deLoos 2022	European Journal of Endocrinology	186	1	53-64	No control/reference group
IMPROVE lifestyle in polycystic ovary syndrome: a systematic strategy	DelPup 2021	Gynecological Endocrinology	37	10	875-878	Wrong design
Metabolic health during a randomized controlled lifestyle intervention in women with PCOS	DietzdeLoos 2021	Eur J Endocrinol	186	1	53-64	No control/reference group
Effect of aerobic exercise on HDL function in women with polycystic ovary syndrome: a randomised controlled trial	Distelmaier 2014	Diabetologia	57		S513-S513	Wrong design (abstract)
Lifestyle management of polycystic ovary syndrome: a single-center study in Bosnia and Herzegovina	Djedjibegovic 2020	Aims Public Health	7	3	504-520	Wrong outcome
INCREASE IN PLASMA-CONCENTRATIONS OF SEX-HORMONE BINDING GLOBULIN (SHBG) AFTER SHORT-TERM DIETING IN WOMEN WITH POLYCYSTIC OVARIES (PCO)	Dobriansky 1987	Journal of Endocrinology	112		291-291	Wrong design (abstract)
Is cardiorespiratory fitness impaired in PCOS women? A review of the literature	Dona 2017	Journal of Endocrinological Investigation	40	5	463-469	Wrong design
Role of diet in the treatment of polycystic ovary syndrome (PCOS)	Douglas 2004	Obesity Research	12		A51-A51	Wrong design (abstract)
Effect of nutritional supplementation on oxidative stress and hormonal and lipid profiles in PCOS-affected females	Dubey 2021	Nutrients	13	9		Wrong design
Hormonal changes related to eating behavior in oligomenorrheic women	Dumoulin 1996	European Journal of Endocrinology	135	3	328-334	Wrong outcome
Improvement in Endocrine and Ovarian Function During Dietary Treatment of Obese Women With Polycystic Ovary Syndrome	Dunaif 1995	Diabetes Spectrum	8	2	107-108	Wrong design
Providing lifestyle advice to women with PCOS: an overview of practical issues affecting success	Ee 2021	BMC Endocrine Disorders	21	1	1-12	Wrong design
Diet and nutrition in polycystic ovary syndrome (PCOS): Pointers for nutritional management	Farshchi 2007	Journal of Obstetrics and Gynaecology	27	8	762-773	Wrong design
Relationship between loci of control and health-promoting behaviors in Pakistani women with polycystic ovary syndrome: coping strategies as mediators	Fatima 2021	BMC Women's Health	21	1		No control/reference group
Effect of a dietary and exercise intervention in women with overweight and obesity undergoing fertility treatments: protocol for a randomized controlled trial	Fawcett 2021	BMC NUTRITION	7	1		No control/reference group
Polycystic ovary syndrome: is a Western diet sabotaging our best efforts at management?	Foley 2019	Fertility and Sterility	112	4	653-654	Wrong design
Exercise training improves autonomic function and inflammatory pattern in women with polycystic ovary syndrome (PCOS)	Giallauria 2008	Clinical Endocrinology	69	5	792-798	No control/reference group

Abnormal heart rate recovery after maximal cardiopulmonary exercise stress testing in young overweight women with polycystic ovary syndrome	Giallauria 2008	Clinical Endocrinology	68	1	88-93	Wrong outcome
Incidence and treatment of metabolic syndrome in newly referred women with confirmed polycystic ovarian syndrome	Glueck 2003	Metabolism-Clinical and Experimental	52	7	908-915	Wrong outcome
Response to diet and metformin in women with idiopathic intracranial hypertension with and without concurrent polycystic ovary syndrome or hyperinsulinemia	Glueck 2005	MedGenMed	7	4	41	Wrong design
Effects of a eucaloric reduced-carbohydrate diet on body composition and fat distribution in women with PCOS	Goss 2014	Metabolism-Clinical and Experimental	63	10	1257-1264	No control/reference group
Elevated Glucagon Following Habitual Consumption of a Reduced Carbohydrate Diet May Reduce Perceived Hunger in Women with PCOS	Goss 2014	Endocrine Reviews	35	3		Wrong design (abstract)
Mechanism underlying beneficial effects of exercise in PCOS identified	Greenhill 2018	Nature Reviews Endocrinology	14	8	441-441	Wrong design
THE POWER OF SWEAT: VIGOROUS EXERCISE IS ASSOCIATED WITH IMPROVED OUTCOMES IN POLYCYSTIC OVARIAN SYNDROME (PCOS) INDEPENDENT OF TOTAL EXERCISE VOLUME	Greenwood 2014	Fertility and Sterility	102	3	E38-E38	Wrong design (abstract)
Vigorous exercise is associated with superior metabolic profiles in polycystic ovary syndrome independent of total exercise expenditure	Greenwood 2016	Fertility and Sterility	105	2	486-493	No control/reference group
ON YOUR FEET: IS SITTING TIME LINKED TO ADVERSE METABOLIC PROFILES IN POLYCYSTIC OVARY SYNDROME, INDEPENDENT OF EXERCISE?	Greenwood 2017	Fertility and Sterility	107	3	E40-E41	Wrong design (abstract)
Lifestyle interventions in women with polycystic ovary syndrome: A scoping systematic review of randomised evidence	H 2022	Semergen				Wrong design
Food habits in overweight and obese adolescent girls with Polycystic ovary syndrome (PCOS): a qualitative study in Iran	Hajivandi 2020	Bmc Pediatrics	20	1		Wrong comparison
Assessing the impact of an educational intervention program based on the theory of planned behavior on the nutritional behaviors of adolescents and young adults with PCOS in Iran: a field trial study	Hajivandi 2021	BMC Pediatrics	21	1		Unclear PCOS criteria
Metabolomics of Dynamic Changes in Insulin Resistance Before and After Exercise in PCOS	Halama 2019	Frontiers in Endocrinology	10			Wrong outcome
Exercise therapy in polycystic ovary syndrome: a systematic review	Harrison 2011	Human Reproduction Update	17	2	171-183	Wrong design
The impact of intensified exercise training on insulin resistance and fitness in overweight and obese women with and without polycystic ovary syndrome	Harrison 2012	Clinical Endocrinology	76	3	351-357	Wrong outcome
Suboptimal dietary intake is associated with cardiometabolic risk factors in women with polycystic ovary syndrome	Hart 2016	Nutrition & Dietetics	73	2	177-183	PCOS not defined
The effects of a reduced glycaemic load diet on women with polycystic ovary syndrome: An audit of patients attending a private health and hormone clinic	Herriot 2007	Annals of Nutrition and Metabolism	51		303-303	No control/reference group

The effect of 6-month nutritional intervention on the anthropometric, biochemical, and reproductive profile of Lebanese women with Polycystic ovarian syndrome	Hmedeh 2021	Human Reproduction	36		76-76	Wrong design (abstract)
Changes in Ghrelin and Glucagon following a Low Glycemic Load Diet in Women with PCOS	Hoover 2021	Journal of Clinical Endocrinology and Metabolism	106	5	E2151-E2161	No control/reference group
EXERCISE BEHAVIORS BY ETHNIC GROUP AMONG PATIENTS WITH POLYCYSTIC OVARY SYNDROME	Huang 2018	Fertility and Sterility	110	4	E112-E112	Wrong design (abstract)
PREVALENCE AND PREDICTORS OF ADEQUATE PHYSICAL ACTIVITY IN A MULTIETHNIC POLYCYSTIC OVARY SYNDROME PATIENT POPULATION	Huang 2019	Fertility and Sterility	112	3	E388-E388	Wrong design (abstract)
Predictors of adequate physical activity within a multiethnic polycystic ovary syndrome patient population: a cross-sectional assessment	Huang 2021	BMC Women's Health	21	1	1-7	No control/reference group
Habitual Diet Inadequacy Is Associated with Polycystic Ovary Syndrome and the Severity of the Phenotype	Huijgen 2014	Reproductive Sciences	21	3	325A-325A	Wrong design (abstract)
Dietary patterns and the phenotype of polycystic ovary syndrome: the chance of ongoing pregnancy	Huijgen 2017	Reproductive Biomedicine Online	34	6	668-676	No control/reference group
Effect of exercise training on insulin sensitivity, mitochondria and computed tomography muscle attenuation in overweight women with and without polycystic ovary syndrome	Hutchison 2012	Diabetologia	55	5	1424-1434	Wrong outcome
Natural molecules in the management of polycystic ovary syndrome (Pcos): An analytical review	Iervolino 2021	Nutrients	13	5		Wrong design
17α-Hydroxyprogesterone responses to leuprolide and serum androgens in obese women with and without polycystic ovary syndrome after dietary weight loss	Jakubowicz 1997	Journal of Clinical Endocrinology and Metabolism	82	2	556-560	Wrong outcome
Dietary management of women with polycystic ovary syndrome in the United Kingdom: the role of dietitians	Jeanes 2009	Journal of Human Nutrition and Dietetics	22	6	551-558	No control/reference group
Eating behaviours and BMI in women with polycystic ovary syndrome	Jeanes 2010	Proceedings of the Nutrition Society	69	OCE1	E57-E57	Wrong design (abstract)
Eating behaviours in obese and lean women with polycystic ovary syndrome	Jeanes 2012	Proceedings of the Nutrition Society	71	OCE3	E237-E237	Wrong design (abstract)
Regulation of circulating CTRP-2/CTRP-9 and GDF-8/GDF-15 by intralipids and insulin in healthy control and polycystic ovary syndrome women following chronic exercise training	Jerobin 2021	Lipids in Health and Disease	20	1		Wrong outcome
Losing Weight and Feeling Great: Changes in Depression and Eating Behavior of a Multidisciplinary Lifestyle Program for Obese PCOS women	Jiskoot 2015	Journal of Womens Health	24	4	21-22	Wrong design (abstract)
Prediction of weight loss and drop-out in a lifestyle intervention in women with pcos: A randomized controlled trial	Jiskoot 2021	Human Reproduction	36		75-76	No control/reference group
The effects of DASH diet on lipid profiles and biomarkers of oxidative stress in overweight and obese women with polycystic ovary syndrome: a randomised clinical trial	Karamali 2014	Human Reproduction	29		315-316	Wrong design (abstract)

A Comparison of a Pulse-Based Diet and the Therapeutic Lifestyle Changes Diet in Combination with Exercise and Health Counselling on the Cardio-Metabolic Risk Profile in Women with Polycystic Ovary Syndrome: A Randomized Controlled Trial	Kazemi 2018	Nutrients	10	10		No control/reference group
Randomized double blind clinical trial evaluating the Ellagic acid effects on insulin resistance, oxidative stress and sex hormones levels in women with polycystic ovarian syndrome	Kazemi 2021	Journal of Ovarian Research	14	1		No control/reference group
Effects of Dietary Glycemic Index and Glycemic Load on Cardiometabolic and Reproductive Profiles in Women with Polycystic Ovary Syndrome: A Systematic Review and Meta-analysis of Randomized Controlled Trials	Kazemi 2021	Adv Nutr	12	1	161-178	Wrong design
Effects of Dietary Glycemic Index and Glycemic Load on Cardiometabolic and Reproductive Profiles in Women with Polycystic Ovary Syndrome: A Systematic Review and Meta-analysis of Randomized Controlled Trials	Kazemi 2021	Advances in Nutrition	12	1	161-178	Wrong design
Lifestyle and pregnancy complications in polycystic ovary syndrome: The SCOPE cohort study	Khomami 2019	Clinical Endocrinology	90	6	814-821	Wrong population (Animal)
High-Intensity Interval Training in Polycystic Ovary Syndrome: A Two-Center, Three-Armed Randomized Controlled Trial	Kiel 2022	Medicine and science in sports and exercise				No control/reference group
[Polycystic ovary syndrome. Diet helps control hormone chaos]	Klein 2009	MMW Fortschr Med	151	37	16	Wrong design
Polycystic ovary syndrome: Diet helps against the hormonal chaos	Klein 2009	MMW-Fortschritte der Medizin	151	37	16	Wrong design
Resistance Exercise Impacts Lean Muscle Mass in Women with Polycystic Ovary Syndrome	Kogure 2016	Medicine and Science in Sports and Exercise	48	4	589-598	Wrong outcome
Aerobic Exercise Training Improves Insulin Sensitivity and Skeletal Muscle Mitochondrial Energetics in Women with Polycystic Ovary Syndrome	Konopka 2014	Diabetes	63		A60-A60	Wrong design (abstract)
Changes in diet composition with urbanization and its effect on the polycystic ovarian syndrome phenotype in a Western Indian population	Kulkarni 2019	Fertility and Sterility	112	4	758-763	Wrong outcome
Comparison of anthropometrical parameters and dietary habits of young women with and without menstrual disorders	Lagowska 2018	Nutrition & Dietetics	75	2	176-181	No PCOS group
Physical activity in women with polycystic ovary syndrome: prevalence, predictors, and positive health associations	Lamb 2011	American Journal of Obstetrics and Gynecology	204	4		No control/reference group
Impact of Physical Resistance Training on the Sexual Function of Women with Polycystic Ovary Syndrome	Lara 2015	Journal of Sexual Medicine	12	7	1584-1590	Wrong outcome
Eight-hour time-restricted feeding improves endocrine and metabolic profiles in women with anovulatory polycystic ovary syndrome	Li 2021	Journal of Translational Medicine	19	1		No control/reference group
Ketogenic diet in women with polycystic ovary syndrome and liver dysfunction who are obese: A randomized, open-label, parallel-group, controlled pilot trial	Li 2021	Journal of Obstetrics and Gynaecology Research	47	3	1145-1152	No control/reference group
Effects of Aerobic Exercise on Rats with Hyperandrogenic Polycystic Ovarian Syndrome	Li 2021	Int J Endocrinol	2021		5561980	Wrong population (Animal)

Implementing the international evidence-based guideline of assessment and management of polycystic ovary syndrome (PCOS): how to achieve weight loss in overweight and obese women with PCOS?	LieFong 2021	Journal of Gynecology Obstetrics and Human Reproduction	50	6		Wrong design
Sleep Duration, Exercise, Shift Work and Polycystic Ovarian Syndrome-Related Outcomes in a Healthy Population: A Cross-Sectional Study	Lim 2016	Plos One	11	11		No PCOS group
Health literacy needs in weight management of women with Polycystic Ovary Syndrome	Lim 2021	Health Promotion Journal of Australia	32	S1	41-48	No control/reference group
An Analysis on the Implementation of the Evidence-based PCOS Lifestyle Guideline: Recommendations from Women with PCOS	Lim 2021	Seminars in Reproductive Medicine	39	3-4	153-160	Wrong design
Comparison of Dietary Intake and Physical Activity between Women with and without Polycystic Ovary Syndrome: A Review	Lin 2014	Advances in Nutrition	5	5	486-496	Wrong design
Conservative possibilities influencing pcos syndrome the importance of nutrition	Líška 2021	Ceska Gynekologie	86	5	343-348	Wrong design
Androgen excess increases food intake in a rat polycystic ovary syndrome model by down-regulating hypothalamus insulin and leptin signaling pathways preceding weight gain	Liu 2021	Neuroendocrinology				Wrong population (Animal)
Lifestyle intervention for overweight/ obese pregnant women with polycystic ovarian syndrome: Lessons and challenges	Liu 2021	Obesity Facts	14	4	405-414	Wrong population (Animal)
IMPACT OF DIETARY ADVANCED GLYCATION END PRODUCTS (AGES) MODIFICATIONS ON METABOLIC AND HORMONAL PROFILE IN WOMEN WITH POLYCYSTIC OVARY SYNDROME	Livadas 2012	Wound Repair and Regeneration	20	5	A101-A101	Wrong design (abstract)
Diet, Nutritional Supplements, and Botanical Medicine in Polycystic Ovary Syndrome	Lucius 2021	Alternative & Complementary Therapies	27	6	289-297	Wrong design
Effectiveness of vitamin d supplementation on lipid profile in polycystic ovary syndrome women: A meta-analysis of randomized controlled trials	Luo 2021	Annals of Palliative Medicine	10	1	114-129	Wrong design
Eating Indicators In Women With Polycystic Ovary Syndrome And Weight-Matched Controls	Maher 2017	Faseb Journal	31			Wrong design (abstract)
Lifestyle modification intervention among infertile overweight and obese women with polycystic ovary syndrome	Mahoney 2014	Journal of the American Association of Nurse Practitioners	26	6	301-308	No control/reference group
Pregnancy outcome in PCOS patients: The effects of letrozol combined with exercise	Manteghi 2021	AUSTRIAN JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM	14	3	128-132	Wrong outcome
Impact of a Lifestyle Modification Program on Menstrual Irregularity among Overweight or Obese Women with Polycystic Ovarian Syndrome	Marzouk 2015	Korean Journal of Women Health Nursing	21	3	161-170	No control/reference group
Effectiveness of Video-Assisted Teaching Module on Knowledge, Attitude and Body Mass Index (BMI) Scaling Down Among Over-Weight Women Diagnosed with PCOS in Selected Hospitals of Madhya Pradesh	Massey 2021	Nursing Journal of India	112	5	203-207	Wrong outcome
RETRACTION: Serum Zinc and Adiponectin Levels in Patients with Polycystic Ovary Syndrome, Adjusted for Anthropometric, Biochemical, Dietary Intake, and Physical Activity Measures	Mazloomi 2018	Biological Trace Element Research	181	2	388-388	Wrong design

Diet and Polycystic Ovary Syndrome	McKittrick 2002	Nutr Today	37	2	63-69	Wrong design
Determination of relationship between dietary glycemic index, glycemic load and obesity in women with PCOS	Melekoglu 2015	Annals of Nutrition and Metabolism	67		209-209	Wrong design (abstract)
Mood and Ambulatory Monitoring of Physical Activity Patterns in Youth with Polycystic Ovary Syndrome	Michael 2015	Journal of Pediatric and Adolescent Gynecology	28	5	369-372	Wrong comparison
AEROBIC PHYSICAL TRAINING REDUCES ANTHROPOMETRIC INDEXES AND HYPERANDROGENISM IN POLYCYSTIC OVARY SYNDROME	Miranda-Furtado 2018	Fertility and Sterility	110	4	E9-E9	Wrong design (abstract)
Effect of estrogen and insulin sensitivity due to exercise training with dual intensities in female rats with estradiol valerate-induced PCOS	Miri 2021	MEDICINA BALEAR	36	3	88-92	Wrong population (Animal)
Evaluating exercise challenge to validate cardiac autonomic dysfunction in lean PCOS phenotype	Mishra 2019	J Basic Clin Physiol Pharmacol	30	4		Wrong outcome
Impact of an online multicomponent very-low-carbohydrate program in women with polycystic ovary syndrome: a pilot study	Missel 2021	F S Rep	2	4	386-395	No control/reference group
Risk Factors of Overweight and Obesity Related to Diet and Disordered Eating Attitudes in Adolescent Girls with Clinical Features of Polycystic Ovary Syndrome	Mizgier 2020	Journal of Clinical Medicine	9	9		Wrong comparison
Association of Macronutrients Composition, Physical Activity and Serum Androgen Concentration in Young Women with Polycystic Ovary Syndrome	Mizgier 2021	Nutrients	14	1		Duplication
Relation between inflammation, oxidative stress, and macronutrient intakes in normal and excessive body weight adolescent girls with clinical features of polycystic ovary syndrome	Mizgier 2021	Nutrients	13	3	1-16	No comparison
Yoga Effects on Anthropometric Indices and Polycystic Ovary Syndrome Symptoms in Women Undergoing Infertility Treatment: A Randomized Controlled Clinical Trial	Mohseni 2021	Evidence-based Complementary & Alternative Medicine (eCAM)			1-9	No control/reference group
Acute-phase glycoprotein profile responses to different oral macronutrient challenges: Influence of sex, functional hyperandrogenism and obesity	Moncayo 2021	Clinical Nutrition	40	3	1241-1246	Wrong outcome
Weight Management in Adolescents with Polycystic Ovary Syndrome	Moore 2021	Current Obesity Reports	10	3	311-321	Wrong design
Ghrelin and measures of satiety are altered in polycystic ovary syndrome but not differentially affected by diet composition	Moran 2004	Journal of Clinical Endocrinology & Metabolism	89	7	3337-3344	Wrong outcome
Exercise Decreases Anti-Mullerian Hormone in Anovulatory Overweight Women with Polycystic Ovary Syndrome - A Pilot Study	Moran 2011	Hormone and Metabolic Research	43	13	977-979	Wrong outcome
Lifestyle changes in women with polycystic ovary syndrome	Moran 2011	Cochrane Database of Systematic Reviews		7		Wrong design
Dietary composition in the treatment of polycystic ovary syndrome: a systematic review to inform evidence-based guidelines	Moran 2013	Human Reproduction Update	19	5	432-432	Wrong design (abstract)
THE CONTRIBUTION OF DIET, PHYSICAL ACTIVITY AND SEDENTARY BEHAVIOUR TO BODY MASS INDEX IN WOMEN WITH AND WITHOUT POLYCYSTIC OVARY SYNDROME	Moran 2013	Fertility and Sterility	100	3	S352-S352	Wrong design (abstract)

Dietary Composition in the Treatment of Polycystic Ovary Syndrome: A Systematic Review to Inform Evidence-Based Guidelines	Moran 2013	Journal of the Academy of Nutrition and Dietetics	113	4	520-545	Wrong design
The contribution of diet, physical activity and sedentary behaviour to body mass index in women with and without polycystic ovary syndrome	Moran 2013	Human reproduction (Oxford, England)	28	8	2276-83	Self-reported PCOS
Dietary composition in the treatment of polycystic ovary syndrome: a systematic review to inform evidence-based guidelines (vol 5, pg 432, 2013)	Moran 2014	Human Reproduction Update	20	1	152-152	Wrong design
The Association of a Mediterranean-Style Diet Pattern with Polycystic Ovary Syndrome Status in a Community Cohort Study.	Moran 2015	Nutrients	7	10	8553-64	Self-reported PCOS
Weight management practices associated with Polycystic Ovary Syndrome and their relationships with diet and physical activity	Moran 2017	Clinical Endocrinology	86		55-55	Wrong design (abstract)
Weight management practices associated with polycystic ovary syndrome and their relationships with diet and physical activity	Moran 2019	Obesity Research & Clinical Practice	13	1	49-50	Wrong design (abstract)
Effect of aerobic training on atrial natriuretic peptide and catecholamineinduced lipolysis in obese women with polycystic ovary syndrome	Moro 2008	International Journal of Obesity	32		S50-S50	Wrong design (abstract)
Aerobic Exercise Training Improves Atrial Natriuretic Peptide and Catecholamine-Mediated Lipolysis in Obese Women with Polycystic Ovary Syndrome	Moro 2009	Journal of Clinical Endocrinology & Metabolism	94	7	2579-2586	Wrong outcome
Food cravings, binge eating and emotional eating behaviours in overweight and obese women with polycystic ovary syndrome	Morosi 2017	Proceedings of the Nutrition Society	76	OCE1	E15-E15	Wrong design (abstract)
Exercise training in women with PCOS — finding clarity	Morris 2021	Nature Reviews Endocrinology	17	5	258	Wrong design
Food cravings in UK and South Asian women with polycystic ovary syndrome	Mulekar 2017	Proceedings of the Nutrition Society	76	OCE1	E11-E11	Wrong design (abstract)
Effect of hypocaloric high-protein, low-carbohydrate diet supplemented with fennel on androgenic and anthropometric indices in overweight and obese women with polycystic ovary syndrome: A randomized placebo-controlled trial	Nadjarzadeh 2021	Complementary Therapies in Medicine	56			No control/reference group
The effectiveness of lifestyle training program promoting adolescent health with polycystic ovarian syndrome: A study protocol for a randomized controlled study	Nahidi 2021	J Educ Health Promot	10		351	Wrong design (protocol)
Assessment of Associated Factors and Complications for Women with Poly Cystic Ovarian Syndrome in Baghdad City	Neamah 2021	Medico-Legal Update	21	2	140-145	No control/reference group
Nutritional and dietary aspects in polycystic ovary syndrome: insights into the biology of nutritional interventions	Neves 2020	Gynecological Endocrinology	36	12	1047-1050	Wrong design
The role of lifestyle modification in polycystic ovary syndrome	Norman 2002	Trends in Endocrinology and Metabolism	13	6	251-257	Wrong design
Lifestyle choices, diet, and insulin sensitizers in polycystic ovary syndrome	Norman 2006	Endocrine	30	1	35-43	Wrong design
Lifestyle factors in the etiology and management of polycystic ovary syndrome	Norman 2007	Polycystic Ovary Syndrome, 2nd Edition			121-139	Wrong design (book)

Lifestyle interventions and quality of life for women with polycystic ovary syndrome A systematic review and meta-analysis protocol	Nunes 2019	Medicine	98	50		Wrong design
SUN-LB017: Plasma Vitamin D in Response to Dietary Management and/ or Physical Exercise in Obese Women with Polycystic Ovary Syndrome	Nybacka 2015	Clinical Nutrition	34		S241-S241	Wrong design (abstract)
Could the Mediterranean diet be effective in women with polycystic ovary syndrome? A proof of concept	Orio 2015	European Journal of Clinical Nutrition	69	8	974-974	Wrong design
Weight management strategies for patients with PCOS: current perspectives	OzgenSaydam 2021	Expert Review of Endocrinology and Metabolism	16	2	49-62	Wrong design
Differences in percent body fat and plant protein intake between females with and without polycystic ovary syndrome in South Korea	Park 2010	Faseb Journal	24			Wrong design (abstract)
NUTRITIONAL ROLE OF POLYPHENOLS AS A COMPONENT OF A WHOLEFOOD DIET IN THE MANAGEMENT OF POLYCYSTIC OVARY SYNDROME	Parker 2021	Australasian College of Nutritional & Environmental Medicine Journal	40	2	6-12	Wrong design
Role of changes in dietary habits in polycystic ovary syndrome	Pasquali 2004	Reproductive Biomedicine Online	8	4	431-439	Wrong design
Effectiveness of exercise interventions on mental health and health-related quality of life in women with polycystic ovary syndrome: a systematic review	Patten 2021	BMC Public Health	21	1		Wrong design
Role Of Aerobic Exercise On Cardiac Autonomic Modulation And Adipokines In Polycystic Ovary Syndrome	Philbois 2019	Medicine and Science in Sports and Exercise	51	6	982-982	Wrong design (abstract)
Implementation of the polycystic ovary syndrome guidelines: A mixed method study to inform the design and delivery of a lifestyle management program for women with polycystic ovary syndrome	Pirotta 2021	Nutrition and Dietetics	78	5	476-486	No control/reference group
Informing a PCOS Lifestyle Program: Mapping Behavior Change Techniques to Barriers and Enablers to Behavior Change Using the Theoretical Domains Framework	Pirotta 2021	Seminars in Reproductive Medicine	39	3-4	143-152	No control/reference group
Relationships between self-management strategies and physical activity and diet quality in women with polycystic ovary syndrome	Pirotta 2022	Patient Education and Counseling	105	1	190-197	No control/reference group
Effect of a low-starch/low-dairy diet on fat oxidation in overweight and obese women with polycystic ovary syndrome	Pohlmeier 2014	Applied Physiology Nutrition and Metabolism	39	11	1237-1244	No control/reference group
Assessment of nutrients intake in polycystic ovary syndrome women compared to healthy subjects	Pourghassem Gargari 2011	The Iranian Journal of Obstetrics, Gynecology and Infertility	14	4	1-8	Non English
The Relationship between Intake of Dairy Products and Polycystic Ovary Syndrome in Women Who Referred to Isfahan University of Medical Science Clinics in 2013.	Rajaeieh 2014	Int J Prev Med	5	6	687-94	PCOS not defined
The association between amino acid intake and polycystic ovary syndrome in women who referred to Isfahan University of Medical Science Clinics.	Rajaeieh 2018	Nutrition and Food Sciences Research	5	2	11-17	PCOS not defined
Quality of Life in Women with Polycystic Ovary Syndrome after a Program of Resistance Exercise Training	Ramos 2016	Revista Brasileira De Ginecologia E Obstetricia	38	7	340-347	Wrong outcome

Overweight in polycystic ovary syndrome. An update on evidence based advice on diet, exercise and metformin use for weight loss	Ravn 2013	Minerva Endocrinologica	38	1	59-76	Wrong design
Continuous versus intermittent aerobic exercise in the improvement of quality of life for women with polycystic ovary syndrome: A randomized controlled trial	Ribeiro 2021	J Health Psychol	26	9	1307-1317	No control/reference group
HIIT'ing or MISS'ing the Optimal Management of Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis of High- Versus Moderate-Intensity Exercise Prescription	Richards 2021	FRONTIERS IN PHYSIOLOGY	12			Wrong design
Impact of restricted carbohydrate intake on women with Polycystic Ovarian Syndrome (PCOS)	Ripps 2003	Fertility and Sterility	80		S272-S272	Wrong design (abstract)
Altered cardiorespiratory response to exercise in overweight and obese women with polycystic ovary syndrome	Rissanen 2016	Physiological Reports	4	4		Wrong outcome
Poor quality diet is associated with overweight status and obesity in patients with polycystic ovary syndrome	Rodrigues 2015	Journal of Human Nutrition and Dietetics	28		94-101	No control/reference group
Poor quality diet is associated with overweight status and obesity in patients with polycystic ovary syndrome	Rodrigues 2015	J Hum Nutr Diet	28 Suppl 2		94-101	No control/reference group
Focus on metabolic and nutritional correlates of polycystic ovary syndrome and update on nutritional management of these critical phenomena	Rondanelli 2014	Archives of Gynecology and Obstetrics	290	6	1079-1092	Wrong design
The effect of low glycemic index diet on the reproductive and clinical profile in women with polycystic ovarian syndrome: A systematic review and meta-analysis	Saadati 2021	HELIYON	7	11		Wrong design
Effect of high-intensity interval training on metabolic parameters in women with polycystic ovary syndrome: A systematic review and meta-analysis of randomized controlled trials	Santos 2021	PLoS ONE	16	1 January		Wrong design
Associations of Vitamin D with Inter- and Intra-Muscular Adipose Tissue and Insulin Resistance in Women with and without Polycystic Ovary Syndrome	Scott 2016	Nutrients	8	12		Wrong outcome
Exploring factors related to changes in body composition, insulin sensitivity and aerobic capacity in response to a 12-week exercise intervention in overweight and obese women with and without polycystic ovary syndrome	Scott 2017	Plos One	12	8		Wrong outcome
Resting metabolic rate and postprandial thermogenesis in polycystic ovarian syndrome	Segal 1990	Int J Obes	14	7	559-67	Wrong outcome
Effects of Oral Contraception and Lifestyle Modification on Incretins and TGF-ß Superfamily Hormones in PCOS	Shah 2021	Journal of Clinical Endocrinology and Metabolism	106	1	108-119	No control/reference group
The association between dietary antioxidants, oxidative stress markers, abdominal obesity and poly-cystic ovary syndrome: A case control study.	Shahrokhi 2020	J Obstet Gynaecol	40	1	77-82	PCOS not defined
Dietary Modification for Reproductive Health in Women With Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis	Shang 2021	Front Endocrinol (Lausanne)	12		735954	Wrong design
A cross-sectional study on prevalence of menstrual problems, lifestyle, mental health, and PCOS awareness among rural and urban population of Punjab, India	Sharma 2022	JOURNAL OF PSYCHOSOMATIC				Wrong population

		OBSTETRICS & GYNECOLOGY				
Erratum: GLUT4 translocation is not impaired after acute exercise in skeletal muscle of women with obesity and polycystic ovary syndrome	SilvaDantas 2016	Obesity (Silver Spring)	24	9	2012	Wrong design
Female Fertility and the Nutritional Approach: The Most Essential Aspects	Skoracka 2021	Advances in Nutrition	12	6	2372-2386	Wrong design
Lifestyle modifications alone or combined with hormonal contraceptives improve sexual dysfunction in women with polycystic ovary syndrome	SteinbergWeiss 2021	Fertility and Sterility	115	2	474-482	No control/reference group
Exercise and insulin resistance in PCOS: muscle insulin signalling and fibrosis	Stepto 2020	Endocrine Connections	9	4	346-359	Wrong outcome
The burden of the probable polycystic ovarian syndrome and its associated factor among college going late adolescents and young adults: a cross sectional analytical study in urban Puducherry, South India	Suresh 2020	Int J Adolesc Med Health				No PCOS group
The Effect of Diet and Exercise in Women with Polycystic Ovary Syndrome	Sweatt 2015	Faseb Journal	29			Wrong design (abstract)
Quantitative assessment of nutrition in patients with polycystic ovary syndrome (PCOS)	Szczuko 2016	Rocz Panstw Zakl Hig	67	4	419-426	No control/reference group
High glycemic index diet in PCOS patients. The analysis of IGF I and TNF-alpha pathways in metabolic disorders	Szczuko 2016	Medical Hypotheses	96		42-47	Wrong outcome
Studies on the quality nutrition in women with polycystic ovary syndrome (PCOS)	Szczuko 2017	Rocz Panstw Zakl Hig	68	1	61-67	No control/reference group
Decrease in the level of nervonic acid and increased gamma linolenic acid in the plasma of women with polycystic ovary syndrome after a three-month low-glycaemic index and caloric reduction diet	Szczuko 2019	Open Life Sciences	14	1	224-236	Wrong outcome
Nutrition strategy and life style in polycystic ovary syndrome—narrative review	Szczuko 2021	Nutrients	13	7		Wrong design
Effect of aerobic training program on the obesity and insulin resistance in young girls with polycystic ovary syndrome	Taghavi 2009	Hormone Research	72		338-338	Wrong design (abstract)
The effects of a six-week aerobic and weight-resistance training program on infertility patients diagnosed with polycystic ovary syndrome	Talluto 2002	Fertility and Sterility	78	3	S152-S153	Wrong design (abstract)
Physical activity and sedentary behaviour in women with and without polycystic ovary syndrome: An Australian population-based cross-sectional study.	Tay 2020	Clinical Endocrinology	93	2	154-162	Self-reported PCOS
Interrupting Prolonged Sitting and Endothelial Function in Polycystic Ovary Syndrome	Taylor 2021	Medicine and science in sports and exercise	53	3	479-486	No control/reference group
Exercise for the treatment and management of overweight women with polycystic ovary syndrome: a review of the literature	Thomson 2011	Obesity Reviews	12	501	e202-e210	Wrong design
The impact of physical activity in a case of polycystic ovary syndrome	Trolle 2006	Acta Obstetricia Et Gynecologica Scandinavica	85	7	892-893	Wrong design
Dietary intake, glucose metabolism, and sex hormones in women with polycystic ovary syndrome (PCOS) compared with women with non-PCOS-related infertility (vol 109, pg 2190, 2013)	Tsai 2014	British Journal of Nutrition	111	11	2045-2045	Wrong design

Dietary intake, glucose metabolism, and sex hormones in women with polycystic ovary syndrome (PCOS) compared with women with non-PCOS-related infertility - CORRIGENDUM	Tsai 2014	Br J Nutr	111	11	2045	Wrong design
Low glycemic index vegan or low-calorie weight loss diets for women with polycystic ovary syndrome: a randomized controlled feasibility study	Turner-McGrievy 2014	Nutrition Research	34	6	552-558	No control/reference group
Dietary intake, eating behaviors, and quality of life in women with polycystic ovary syndrome who are trying to conceive	Turner-Mcgrievy 2015	Human Fertility	18	1	16-21	No control/reference group
Lifestyle intervention up-regulates gene and protein levels of molecules involved in insulin signaling in the endometrium of overweight/obese women with polycystic ovary syndrome	Ujvari 2014	Human Reproduction	29	7	1526-1535	Wrong outcome
A Pilot Trial: Fish Oil and Metformin Effects on ApoB-Remnants and Triglycerides in Women With Polycystic Ovary Syndrome	Vine 2021	JOURNAL OF THE ENDOCRINE SOCIETY	5	9		No control/reference group
EFFECTS OF DIETARY INTAKE ON GLUCOSE METABOLISM AND REPRODUCTIVE HORMONES IN WOMEN WITH POLYCYSTIC OVARY SYNDROME	Wang 2009	Annals of Nutrition and Metabolism	55		224-224	Wrong design (abstract)
Correlations between dietary intake or body mass index and serum androgen in women with polycystic ovary syndrome	Wang 2010	Faseb Journal	24			Wrong design (abstract)
Association between circadian rhythm disruption and polycystic ovary syndrome	Wang 2021	Fertility and Sterility	115	3	771-781	Wrong population (Animal)
A pilot study of a low carbohydrate ketogenic diet for obesity-related polycystic ovary syndrome	Westman 2004	Journal of General Internal Medicine	19		111-112	Wrong design (abstract)
Exercise and Polycystic Ovary Syndrome	Woodward 2020	Physical Exercise for Human Health	1228		123-136	Wrong design (book)
The impact of exercise perceptions and depressive symptoms on polycystic ovary syndrome-specific health-related quality of life	Wright 2021	WOMENS HEALTH	17			No control/reference group
Resistance Training as Therapeutic Management in Women with PCOS: What is the Evidence?	Wright 2021	Int J Exerc Sci	14	3	840-854	Wrong design
Improvement of anti-Müllerian hormone and oxidative stress through regular exercise in Chinese women with polycystic ovary syndrome	Wu 2021	Hormones	20	2	339-345	No control/reference group
Pentraxin 3 Levels in Young Women with and without Polycystic Ovary Syndrome (PCOS) in relation to the Nutritional Status and Systemic Inflammation	Wyskida 2020	International Journal of Endocrinology	2020			Wrong outcome
Dietary Patterns and Polycystic Ovary Syndrome: a Systematic Review	Xenou 2021	Maedica (Bucur)	16	3	516-521	Wrong design
The effects of canola and olive oils consumption compared to sunflower oil, on lipid profile and hepatic steatosis in women with polycystic ovarian syndrome: a randomized controlled trial	Yahay 2021	Lipids in Health and Disease	20	1		No control/reference group
Impacts of Metformin on Local Ovarian Cell Tissue of Rats with Polycystic Ovary Syndrome and Intestinal Flora Under Aerobic Exercise	Yan 2021	JOURNAL OF BIOMATERIALS AND TISSUE ENGINEERING	11	12	2381-2388	Wrong population (Animal)
Outcomes of a Mindfulness-Based Healthy Lifestyle Intervention for Adolescents and Young Adults with Polycystic Ovary Syndrome	Young 2021	J Pediatr Adolesc Gynecol				Wrong comparison

The effect of garlic (Allium sativum) supplementation on the lipid parameters and blood pressure levels in women with polycystic ovary syndrome: A randomized controlled trial	Zadhoush 2021	Phytotherapy Research	35	11	6335-6342	No control/reference group
Comparison of vitamin D dietary intake among four phenotypes of polycystic ovary syndrome and its association with serum androgenic components	Zaeemzadeh 2018	Razi Journal of Medical Sciences	25	167	87-96	No control/reference group
The study of dietary intake of macronutrients in four phenotypes of polycystic ovary syndrome based on Rotterdam criteria	Zaeemzadeh 2018	Razi Journal of Medical Sciences			46-56	Non English
Comparison of dietary micronutrient intake in PCOS patients with and without metabolic syndrome	Zaeemzadeh 2021	Journal of Ovarian Research	14	1		No control/reference group
Comparison of dietary micronutrient intake in PCOS patients with and without metabolic syndrome	Zaeemzadeh 2021	Journal of Ovarian Research	14	1		No control/reference group
The study of dietary intake of micronutrients in four phenotypes of polycystic ovary syndrome separately based on Rotterdam criteria	Zaimzadeh 2018	Razi Journal of Medical Sciences	25	3	59-68	Non English
Effects of exercise and dietary habits on the occurrence of polycystic ovary syndrome over 5 years of follow-up	Zhang 2018	International Journal of Gynecology & Obstetrics	142	3	329-337	Wrong population
Correlation Between Daily Energy Intake from Fat with Insulin Resistance in Patients with Polycystic Ovary Syndrome	Zheng 2021	Diabetes Metab Syndr Obes	14		295-303	No control/reference group
Effect of High-Fat Diet on the Intestinal Flora in Letrozole-Induced Polycystic Ovary Syndrome Rats	Zheng 2021	EVIDENCE-BASED COMPLEMENTARY AND ALTERNATIVE MEDICINE	2021			Wrong population (Animal)
Dietary proanthocyanidins alleviated ovarian fibrosis in letrozole-induced polycystic ovary syndrome in rats	Zhou 2021	Journal of Food Biochemistry	45	5		Wrong population (Animal)
Sleep disturbances may influence lifestyle behaviours in women with self-reported polycystic ovary syndrome		British Journal of Nutrition				Duplication
Environmental determinants and PCOS symptoms severity: a cross-sectional study		HEALTH CARE FOR WOMEN INTERNATIONAL				No control/reference group
Physical resistance training for women with PCOS may improve sexual function...PolyCystic Ovary Syndrome		Nursing Standard	29	40	15-15	Wrong design
Acupuncture for PCOS		Natural Solutions		140	13-13	Wrong design
A novel PCOS rat model and an evaluation of its reproductive, metabolic, and behavioral phenotypes	Int J Prev Med.	REPRODUCTIVE MEDICINE AND BIOLOGY				Wrong population (Animal)

5. STUDY CHARACTERISTICS TABLE FOR INCLUDED STUDIES

Author, year	Country	Study design	PCOS criteria	PCOS sample size Age and BMI mean	Control sample size Age and BMI mean	Dietary assessment tool	Physical activity assessment tool	RoB
Ahmadi 2013	Iran	Case-control	Rotterdam	65 Age = 25.11 BMI = 23.43	65 Age = 26.11 BMI = 23.14	three 24-hour dietary recall questionnaires (two weekdays and a weekend) by a trained dietition	NR	Low
Alipour *et al.,* 2019	Iran	Case-control	Rotterdam	45 Age = 26.64 BMI = 26.37	45 Age = 27.56 BMI = 25.29	3-day 24h food recall questionnaires (2 weekdays and 1 weekend day)	NR	Mod
Altieri *et al.,* 2013	Italy	Case-control	Rotterdam	100 Age = 27.7 BMI = 34.7	100 Age = 28.4 BMI = 34.8	7-day food diary (7 days of one week)	NR	Mod
Álvarez-Blasco *et al.*, 2011	Spain	Case-control	NIH	22 Age = 26.3 BMI = 35.2	59 Age = 32.2 BMI = 34.8	Modified (Spanish-population) semi-quantitative FFQ (Harvard Service FFQ)	Self-reported questionnaire (unspecified)	Mod
Amirjani 2019	Iran	Cross-sectional	Rotterdam	168	160 Age = 29.85 BMI = 33.32	FFQ	Lifestyle questionnaire	Low
Arusoglu 2020	Turkey	Case-control	Rotterdam	32 Age = 22.03 BMI = 22.64	31 Age = 21.71 BMI = 21.55	24 hours of food record	metabolic Holter equipment (SenseWear Armband, SWA)	Low
Badri-Fariman *et al.,* 2021	Iran	Case-control	Rotterdam	120 BMI = 29.55	120 BMI = 28.88	FFQ + 18-item USDA food security questionnaire	Metabolic equivalents (MET)-based questionnaire	Mod
Banting *et al.*, 2014	Australia	Cross-sectional	Self-reported	153 Age = 31.99 BMI = 31.32	64 Age = 31.5 BMI = 24.15	NR	Questionnaire (self-reported trans-theoretical model, developed based on NPAGA)	Mod
Barrea *et al.*, 2019	Italy	Cross-sectional	Rotterdam	112 Age = 24.21 BMI = 30.95	112 Age = 24.07 BMI = 30.76	14-item PREDIMED questionnaire used for Mediterranean diet assessment and 7-day food diary for dietary intake assessment (nutritionist-administered in the face to face interviews)	Questionnaire (self-reported habitual aerobic exercise engagement for a minimum of 30 min/day [yes/no])	Mod

Bialka-Kosiec 2019	Poland	Cross-sectional	Rotterdam	37 Age = 19.4 BMI = 23.3	48 Age = 20.0 BMI = 22.6	HBSC Questionnaire	HBSC Questionnaire	Low
Bykowska-Derda 2020 (included 17 yr olds)	Poland	Case-control	Rotterdam	122 Age = 27 BMI = 26.2	116 Age = 26 BMI = 22.8	the Dietary Habits and Nutrition Beliefs KomPAN Questionnaire	short version of the international physical activity questionnaire	Low
Cunha *et al.*, 2019	Brazil	Case-control	Rotterdam	39 Age = 25.17 BMI = 24.43	34 Age = 25.67 BMI = 23.95	7-day food report	NR	Mod
Cutillas-Tolin *et al.*, 2021	Spain	Case-control	Rotterdam	121	155	117-item FFQ (semiquantative, validated)	NR	Mod
Cutler *et al.,* 2019	Canada	Cross-sectional	Rotterdam	87 Age = 30.7 BMI = 29	50 Age = 35.7 BMI = 24.1	3-day 24h food recall questionnaires (2 weekdays and 1 weekend day)	3-day PA activity record (2 weekdays, 1 weekend), pedometer (SM-2000 Step Pedometer by Heart Rate Monitors USA) for daily steps	Mod
Dantas *et al.*, 2015	Brazil	NR	Rotterdam	15 Age = 24.8 BMI = 32.8	12 Age = 29.6 BMI = 30.3	NR	Actigraph GT3X accelerometer (freedson activity cut points were used to define the intensity of PA)	low
DeGiuseppe 2019 (lower age bound 16)	Italy	Case-control	Rotterdam	36 Age = 27.8 BMI = 31.5	37 Age = 28.3 BMI = 22.2	non-consecutive three-day dietary diary	BMR: basal metabolic rate	Mod
Douglas *et al.,* 2006	USA	Cohort	NIH	30 Age = 28.9 BMI = 29.7	27 Age = 28.9 BMI = 29.1	4-day food record (2 weekdays, 2 weekends), MC questionnaire	NR	Mod
Elefheridou et al, 2012	Greece	Cross-sectional	Rotterdam	35 Age = 15.1 BMI 23.8	46 Age = 14.6 BMI = 22.63	NR	Interview-administered lifestyle questionnaire	Mod
Elefheridou et al, 2012	Greece	Cross-sectional	Rotterdam	35 Age = 15.1 BMI 23.8	46 Age = 14.6 BMI = 22.63	Interview-administered lifestyle questionnaire	NR	High
Eslamian *et al.,* 2017	Iran	Case-control	Rotterdam	281 Age = 28.8 BMI = 31.2	472 Age = 29.4 BMI = 25.9	Validated semi-quantitative Food Frequency Questionnaire (consumption frequency asked on daily, weekly, or monthly basis)	Interviews using valid questionnaire (consisted of 9 different MET categories ranging from sleep to high intensity)	High

Forslund 2020	Sweden	Cohort	NIH	27 Age = 52.4 BMI = 30.7	94 Age = 52.4 BMI = 25.5	FFQ	Structured questionnaire not specified	Mod
Ganie *et al.*, 2019	India	Case-control	Rotterdam	144 Age = 26.06 BMI = 24.81	320 Age = 26.55 BMI = 23.97	FFQ, 72-hr dietary recall	NR	Low
Gargari 2015	Iran	Case-control	Rotterdam	30 Age = 25.83 BMI = 25	30 Age = 26.06 BMI = 23.68	3-day, 24-hour food recall and FFQ	NR	Mod
Gopalan et al. 2021	India	Case-control	Rotterdam	80 Age = 24.64 BMI = NR	80 Age = NR BMI = NR	detailed dietary history	NR	High
Graff 2013	Brazil	Cross-sectional	Rotterdam	61 Age = 22.7 BMI = 28.9	44 Age = 25 BMI = 27.1	FFQ	NR	Low
Graff 2017	Brazil	Cross-sectional	Rotterdam	84 Age = 23.5 BMI = 29.4	54 Age = 26.2 BMI = 27.2	FFQ	digital pedometer	Low
Hosseini *et al.* 2017	Iran	Case-control	AEPCOS	99 Age = 29 BMI = 26.6	198 Age = 29.2 BMI = 26	168-item semi-quantative FFQ	International interview-administered questionnaire	High
Huijgen *et al.* 2015	Netherlands	Case-cohort	Rotterdam	218 Age = 28.5 BMI = 25.6	799 Age = 33.1 BMI = 24.5	Questionnaire of 6 food groups to calculate Preconception Dietary Risk score (unspecified; self-reported)	NR	Mod
Jurewicz *et al.* 2021	Poland	Case-control	AEPCOS	199 Age = 26.6 BMI = 25.9	158 Age = 31.2 BMI = 25	Questionnaire for alcohol consumption	NR	Mod
Kazemi Jaliseh *et al.* 2017	Iran	Case-control	NIH	178 Age = 26.4 BMI = 26.1	1524 Age = 28.9 BMI = 25.4	NR	Lipid Research Clinic questionnaire	Low
Khademi *et al.* 2010	Iran	Case-control	Rotterdam	26 Age = 31 BMI = 23.8	268 Age = 33 BMI = 22.02	NR	Interviewer-administered questionnaire	Mod

Kulshreshtja et al., 2022	India	Cross sectional	Rotterdam	168 (lean 62, obese 106) Age = lean 23.1 Age = obese 24.23 BMI = lean = 20.44 BMI = obese 29.48	102 (lean 60, obese 42) Age = lean 23.22 Age = obese 28.2 BMI = lean 20.00 BMI = obese 27.6	2 day food recall	interview	Low
Larsson *et al.,* 2016	Sweden	Case-control	Rotterdam	72 Age = 30.2 BMI = 28.5	30 Age = 27.8 BMI = 24.6	FFQ (verified in Swedish youth)	NR	Mod
Lerchbaum *et al.,* 2021	Austria		Rotterdam	180 Age = 26 BMI = 27.6	150 Age = 35.8 BMI = 25.2	NR	NR	Mod
Liang *et al.,* 2021	China		Rotterdam	20	20	3-d 24-hr recall (interviewer-adminstrated)	NR	low
Lin *et al.,* 2019	USA	Case-control	Rotterdam	80 Age = 26.8 BMI = 31.5	44 Age = 29.5 BMI = 28	VioScreen (web based self-administered FFQ with ~1200 food images and branching questions)	Accelerometry (Actigraph triaxial accelerometer) and self-reported PA (Women's Health Initiative Physical Activity Questionnaire)	low
Lin *et al.*, 2021	USA	Cross-sectional	NIH	40 Age = 24.7 BMI = 25.5	529 Age = 25.4 BMI = 24.6	CARDIA diet history questionnaire (past 28 days; interviewer-administered)	CARDIA PA questionnaire (past year; self-reported)	Mod
Lu *et al*., 2021	China		Rotterdam	325 Age = 29.5 BMI = 21.8	325 Age = 30.2 BMI = 22.1	NR	NR	low
Mario-2012	Brazil	Case-control	Rotterdam	43	22 Age = 27.2 BMI = 27.6	FFQ	digital pedometer	Mod
Mario-2017 (exclusionary because of age 15)	Brazil	Cross-sectional	Rotterdam	84 Age = 24.6 BMI = 29.4	67 Age = 26.4 BMI = 28.4	NR	digital pedometer	Low
Melekoglu *et al*., 2020	Turkey	Cross-sectional	Rotterdam	65 Age = 26.45 BMI = 29.7	65 Age = 26.52 BMI = 22.6	3-day integrated food record (consecutive days)	3-day integrated PA record (consecutive days)	High
Misir *et al*., 2016	Croatia	Cross-sectional	Rotterdam	12 BMI = 27.4	16 BMI = 23.1	24-hr dietary recall	Survey on the Basic Data, Dietary Habits, and Physical Activity	Mod

Mizgier 2021 and Mizgier 2022	Poland	Cross-sectional	Rotterdam	61 Age = 16	35 Age = 15	3 day food record	NR	Low
Navarro-Lafuente *et al*., 2022	Spain		Rotterdam	121 Age = 27.3 BMI = 25.6	155 Age = 30.6 BMI = 23.3	NR	NR	High
Neubronner *et al*., 2021	Singapore	Cross-sectional	Rotterdam	134 Age = 29.84 BMI = 25.14	255 Age = 32.24 BMI = 23.08	NR	NR	Mod
Noormohammadi *et al*., 2021	Iran	Case-control	Rotterdam	303 Age = 29.1 BMI = 33.7	588 Age = 28.8 BMI = 24.2	Validated semi-quantitative FFQ (168 food items)	Validated self-reported physical activity scale	Mod
Orio *et al*., 2006	Italy	Case-control	Rotterdam	45 Age = 21.3 BMI = 29.4	45 Age = 21.6 BMI = 29	NR	Semiquantitative questionnaire, ergometer	High
Panjeshahin *et al*., 2020	Iran	Case-control	Rotterdam	108 Age = 28.95 BMI = 27.1	108 Age = 30.45 BMI = 26.63	178-item FFQ (Adjusted model of TLGS)	International Physical Activity Questionnaire -SH	Low
Pokorska-Niewiada *et al.,* 2021	Poland		Rotterdam	47 Age = 28.3 BMI = 29.95	16 Age = 29 BMI = 23.3	4-d dietary food record (2 weekdays and 2 weekend days)	NR	High
Sedighi *et al*., 2014	Iran	Case-control	Rotterdam	65 Age = 28.85 BMI = 24.02	65 Age = 29.57 BMI = 23.47	Diet questionnaire (28 items with 0 to 112 points, where higher score showed more appropriate diet)	International Physical Activity Questionnaire	High
Shahdadian *et al.,* 2019	Iran	Case-control	Rotterdam	225 Age = 29.51 BMI = 24.87	345 Age = 28.56 BMI = 24.35	168-item FFQ	International Physical Activity Questionnaire Short Form	Mod
Shishehgar 2016	Iran	Case-control	AEPCOS	142 Age = 28.56 BMI = 26.56	140 Age = 28.95 BMI = 26.04	FFQ	NR	Mod
Shishehgar 2016b	Iran	Case-control	AEPCOS	142 Age = 28.56 BMI = 26.56	140 Age = 28.95 BMI = 26.04	NR	International Physical Activity Questionnaire	Low

Shishehgar *et al.*, 2019	Iran	Cross-sectional	Rotterdam	33 Age = 29.7 BMI = 31	40 Age = 30.8 BMI = 30.9	3-day dietary food record (2 working days and one weekend day)	International Physical Activity Questionnaire-Short Form	Mod
Soodi *et al.,* 2021	Iran		Rotterdam	203 Age = 28.98 BMI = 25.74	291 Age = 30.15 BMI = 23.65	NR	NR	Low
Szczuko *et al.*, 2021	Poland	Case-control	Rotterdam	40 Age = 32.52 BMI = 29.65	15 Age = 30.23 BMI = 22.2	Food diary (referring to last 3-day)	NR	Mod
Thara *et al.*, 2017	India	Cross-sectional	Rotterdam	40 Age = 26-30	40 Age = 26-30	24-hr diet recall	NR	High
Thomson *et al.*, 2009	Australia	Cross-sectional	Rotterdam	10 Age = 33.6 BMI = 34.1	16 Age = 36.8 BMI = 35.5	NR	IPAQ-SF, doubly labelled water validation, and exercise (treadmill test)	High
Toscani 2011a	Brazil	RCT	HA+OA	18 Age = 22.72	22 Age = 29.35	validated 24 h dietary recall (24hR)	digital pedometer (BP 148 Techline)	Mod
Toscani 2011b	Brazil	Case-control	HA+OA	43 Age = 22.67 BMI = 30.92	37 Age = 29.7 BMI = 29.66	validated 24 h dietary recall (24hR)	NR	Mod
Tsai *et al.*, 2013	Taiwan ROC	NR	Rotterdam	45 Age = 32.7 BMI = 23	161 Age = 34.7 BMI = 21.3	3-d dietary record	NR	Mod
Wang et al. 2022	China		Rotterdam	202 Age = 30.15	325 Age = 31.77	NR	NR	Low
Wang Oct 2021a	Netherlands	Cross-sectional analysis of a RCT study	Rotterdam	170 Age = 28 BMI = 36	321 Age = 30.8 BMI = 36	FFQ	Short QUestionnaire to ASsess Health-enhancing physical activity (SQUASH)	Mod
Wang Sept 2021b	Netherlands	Prospective Cohort analysis of a RCT study	Rotterdam	87 Age = 27.9 BMI = 35.9	172 Age = 30.8 BMI = 36.1	FFQ	pedometer	Mod
Wright *et al.*, 2004	USA	Case-control	NIH	84 Age = 46.7 BMI = 32.1	79 Age = 48.2 BMI = 29	109-item self-administered Block FFQ	Paffenbarger Physical Activity Questionnaire	Mod

Zhang 2015 (exclusionary becuase of age 12)	China	Case-control	Rotterdam	169 Age = 22.07 BMI = 20.56	338 Age = 22.08 BMI = 20.07	FFQ	NR	Mod
Zhang 2018	China	Case-control	Rotterdam	Case-control: 169 Age = median 20 BMI = meidan 20.17 Nested case-control: 52 Age = median 18 BMI = median 20.82	Case-control: 1685 Age = median 28 BMI = median 20.08 Nested case-control: 1097 Age = median 28 BMI = median 24.15	FFQ	International Physical Activity Questionnaire	Low
Zhang *et al.*, 2020	China	Cross-sectional analysis	Rotterdam	2217 Age = with OA: 31.11; no OA: 31.56 BMI = with OA: 24.9 no OA: 25.31	279 Age = 29.81 BMI = 22.93	Interview-administered lifestyle questionnaire	Interview-administered lifestyle questionnaire	Mod
Zirak Sharkesh *et al.*, 2021	Iran		Rotterdam	203 Age = 28.98 BMI = 25.74	291 Age = 30.15 BMI = 23.65	NR	NR	Low

FFQ, food frequency questionnaire.; USDA, United States Dept of Agriculture; NR, not reported.

6. FINDINGS

Comparisons included:

- **Comparison 1.** PCOS versus controls

Outcomes included:

- **Outcome 1.** Total energy intake
- **Outcome 2.** Total carbohydrate intake
- **Outcome 3.** Total protein intake
- **Outcome 4.** Total fat intake
- **Outcome 5.** Dietary glycemic index
- **Outcome 6.** Dietary glycemic load
- **Outcome 7.** Total physical activity level

▪ EVIDENCE SUMMARY:

Total energy intake: Forty studies examined total energy intake of women with and without PCOS and thirty-two studies were suitable to be included in the meta-analysis. Four studies were judged as high risk of bias (Eslamian et al. 2017, Hosseini et al. 2017, Melekoglu et al. 2020, Navarro-Lafuente et al. 2022) while the rest were of low to moderate risk of bias. Very low evidence shows that women with and without PCOS had similar dietary total energy intake.

Total carbohydrate intake: Thirty-seven studies examined total carbohydrate intake of women with and without PCOS and thirty studies were suitable to be included in the meta-analysis. Twenty-three studies were included in meta-analysis for total gram/day of carbohydrate intake while thirteen studies were included in the meta-analysis for percentage of carbohydrate intake over total energy intake. Only three studies were judged as high risk of bias (Eslamian et al. 2017, Melekoglu et al. 2020, Navarro-Lafuente et al. 2022) while the rest were of low to moderate risk of bias. Very low evidence shows that women with and without PCOS had similar dietary total carbohydrate intake.

Total protein intake: Thirty-seven studies examined total protein intake of women with and without PCOS and thirty studies were suitable to be included in the meta-analysis. Twenty-five studies were included in meta-analysis for total gram/day of protein intake while thirteen studies were included in the meta-analysis for percentage of protein intake over total energy intake. Only three studies were judged as high risk of bias (Eslamian et al. 2017, Melekoglu et al. 2020, Navarro-Lafuente et al. 2022) while the rest were of low to moderate risk of bias. Very low evidence shows that women with and without PCOS had similar dietary total protein intake.

Total fat intake: Thirty-six studies examined total fat intake of women with and without PCOS and twenty-eight studies were suitable to be included in the meta-analysis. Twenty-two studies were included in meta-analysis for total gram/day of fat intake while thirteen studies were included in the meta-analysis for percentage of fat intake over total energy intake. Only three studies were judged as high risk of bias (Eslamian et al. 2017, Melekoglu et al. 2020, Navarro-Lafuente et al. 2022) while the rest were of low to moderate risk of bias. Very low evidence suggests that women with PCOS had higher total fat intake than women without PCOS (MD 6.22 g/day (95% CI 3.71-8.73)).

Dietary glycemic index: Nine studies examined dietary glycemic index of women with and without PCOS and seven were included in the meta-analysis (Alipour et al. 2019, Eslamian et al. 2017, Melekoglu et al. 2020, Shishehgar et al. 2016, Shishehgar et al. 2019, Graff et al. 2013, Graff et al. 2017). Two studies were judged as high risk of bias (Eslamian et al. 2017, Melekoglu et al. 2020)

and the rest were of low to moderate risk of bias. Very low evidence shows that women with and without PCOS had similar dietary glycemic index food.

Diatary glycemic load: Eight studies examined dietary glycemic load of women with and without PCOS and four were included in the meta-analysis (Alipour et al. 2019, Eslamian et al. 2017, Melekoglu et al. 2020, Shishehgar et al. 2019). Two studies were judged as high risk of bias (Eslamian et al. 2017, Melekoglu et al. 2020), the other two studies were of moderate risk of bias. Very low evidence shows that women with and without PCOS had similar dietary glycemic load food.

Total physical activity: Forty-nine studies examined physical activity of women with and without PCOS and nine were included in the meta-analysis (Eslamian et al. 2017, Hosseini et al. 2017, Noormohammadi et al., 2021, Panjeshahin et al., 2020, Sedighi et al., 2014, Shahdadian et al., 2019, Shishehgar et al., 2019). Three studies were judged as high risk of bias (Eslamian et al. 2017, Hosseini et al. 2017, Sedighi et al., 2014), five were of moderate risk of bias and only one study had low risk of bias. Very low evidence suggest women with PCOS had lower total physical activity than women without PCOS.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

Outcome	Studies	PCOS n	Control n	Effect Estimate; mean difference [95% CI], random	I^2	P-value	Favours	Certainty
Total energy intake	32	3309	4992	MD 65.36 [95%CI -42.16, 172.87]	97.4%	0.233	None	⊕○○○ VERY LOW
NIH	4	176	694	MD -223.767 [95%CI -631.16, 183.63]	90.8%	0.282	None	
AEPCOS	2	241	338	MD -295.88 [95%CI -800.61, 208.85]	94.3%	0.251	None	
NIH+AEPCOS (HA)	6	417	1032	MD -247.31 [95%CI -516.80, 22.19]	90.1%	0.072	None	
Rotterdam	26	2892	3960	MD 132.36 [95%CI 17.37, 247.35]	97.6%	0.024	None	
Total carbohydrate intake ***g/day***	23	2381	3907	MD -3.18 [95%CI -40.19, 33.83]	99.5%	0.866	None	⊕○○○ VERY LOW
NIH	4	176	694	MD -6.48 [95%CI -21.73, 8.77]	0.0%	0.405	None	
AEPCOS	1	142	140	MD -11.00 [95%CI -30.49, 8.49]	.%	0.269	None	
NIH+AEPCOS (HA)	5	318	834	MD -8.20 [95%CI -20.20, 3.81]	0.0%	0.181	None	
Rotterdam	18	2063	3073	MD -2.52 [95%CI -44.89, 39.85]	99.6%	0.907	None	
Total carbohydrate intake ***% of total energy intake***	13	1039	1403	MD -0.09 [95%CI -1.55, 1.37]	79.1%	0.901	None	⊕○○○ VERY LOW
NIH	1	22	59	MD 1.00 [95%CI -2.23, 4.23]	.%	0.544	None	
AEPCOS	1	142	140	MD -0.74 [95%CI -2.29, 0.81]	.%	0.350	None	
NIH+AEPCOS (HA)	2	164	199	MD -0.41 [95%CI -1.81, 0.98]	0.0%	0.562	None	
Rotterdam	11	875	1204	MD -0.09 [95%CI -1.90, 1.72]	82.2%	0.925	None	
Total protein intake ***g/day***	25	2633	4145	MD -0.94 [95%CI -4.62, 2.74]	93.4%	0.617	None	⊕○○○ VERY LOW
NIH	3	136	165	MD 1.84 [95%CI -3.65, 7.32]	0.0%	0.512	None	
AEPCOS	1	142	140	MD -4.53 [95%CI -12.45, 3.39]	.%	0.262	None	
NIH+AEPCOS (HA)	4	278	305	MD -0.23 [95%CI -4.74 , 4.28]	0.0%	0.921	None	

Rotterdam	21	2355	3840	MD -1.14 [95%CI -5.20, 2.92]	94.4%	0.583	None	
Total protein intake ***% of total energy intake***	13	1067	1462	MD -0.25 [95%CI -1.45, 0.95]	94.8%	0.681	None	⊕○○○ VERY LOW
NIH	1	22	59	MD 0.00 [95%CI -1.62, 1.62]	.%	1.000	None	
AEPCOS	1	142	140	MD -0.47 [95%CI -1.36, 0.42]	.%	0.301	None	
NIH+AEPCOS (HA)	2	164	199	MD -0.36 [95%CI -1.14, 0.42]	0.0%	0.365	None	
Rotterdam	10	903	1263	MD -0.25 [95%CI -1.62, 1.12]	95.2%	0.722	None	
Total fat intake ***g/day***	22	2348	3743	MD 6.22 [95%CI 3.71, 8.73]	98.1%	<0.001	PCOS	⊕○○○ VERY LOW
NIH	4	146	667	MD 1.64 [95%CI -4.50, 7.78]	0.0%	0.601	None	
AEPCOS	1	142	140	MD 1.94 [95%CI -4.83, 8.71]	.%	0.574	None	
NIH+AEPCOS (HA)	5	288	807	MD 1.77 [95%CI -2.77, 6.32]	0.0%	0.445	None	
Rotterdam	17	2202	2936	MD 7.02 [95%CI 4.29, 9.75]	98.5%	<0.001	None	
Total fat intake ***% of total energy intake***	13	1067	1462	MD 0.58 [95%CI -0.20, 1.36]	61.5%	0.143	None	⊕○○○ VERY LOW
NIH	1	84	79	MD 0.00 [95%CI -2.59, 2.59]	.%	1.000	None	
AEPCOS	1	142	140	MD 1.21 [95%CI -0.38, 2.80]	.%	0.135	None	
NIH+AEPCOS (HA)	2	226	219	0.879 -0.474 2.233	0.0%	0.203	None	
Rotterdam	11	841	1243	MD 0.54 [95%CI -0.37, 1.44]	66.8%	0.246	None	
Dietary glycaemic index	7	706	854	MD 1.98 [95%CI -0.69, 4.64]	95.2%	0.146	None	⊕○○○ VERY LOW
NIH	0	-	-	-	-	-	-	
AEPCOS	1	142	140	MD 0.68 [95%CI -0.70, 2.06]	.%	0.333	None	
NIH+AEPCOS (HA)	1	142	140	MD 0.68 [95%CI -0.70, 2.06]	.%	0.333	None	
Rotterdam	6	564	714	MD 2.15 [95%CI -0.79, 5.09]	95.1%	0.153	None	
Dietary glycaemic load	4	419	616	MD 1.00 [95%CI -19.56, 21.56]	89.9%	0.924	None	⊕○○○ VERY LOW
NIH	0	-	-	-	-	-	-	
AEPCOS	0	-	-	-	-	-	-	
NIH+AEPCOS (HA)	0	-	-	-	-	-	-	
Rotterdam	4	419	616	MD 1.00 [95%CI -19.56, 21.56]	89.9%	0.924	None	
Total physical activity level ***MET/h/day***	3	683	1258	SMD -1.07 [95%CI -2.02, -0.12]	98.7%	0.027	PCOS	⊕○○○ VERY LOW
NIH	0	-	-	-	-	-	-	
AEPCOS	1	99	198	SMD 0.08 [95%CI -0.17, 0.32]	.	0.536	None	
NIH+AEPCOS (HA)	1	99	198	SMD 0.08 [95%CI -0.17, 0.32]	.	0.536	None	
Rotterdam	2	584	1060	SMD -1.64 [95%CI -1.75, -1.52]	0.0%	<0.001	PCOS	
MET/min/week	4	568	692	SMD -0.59 [95%CI -0.91, -0.28]	76.8%	<0.001	PCOS	⊕○○○ VERY LOW
NIH	0	-	-	-	-	-	-	
AEPCOS	0	-	-	-	-	-	-	
NIH+AEPCOS (HA)	0	-	-	-	-	-	-	

Rotterdam	4	568	692	SMD -0.59 [95%CI -0.91, -0.28]	76.8%	<0.001	PCOS	

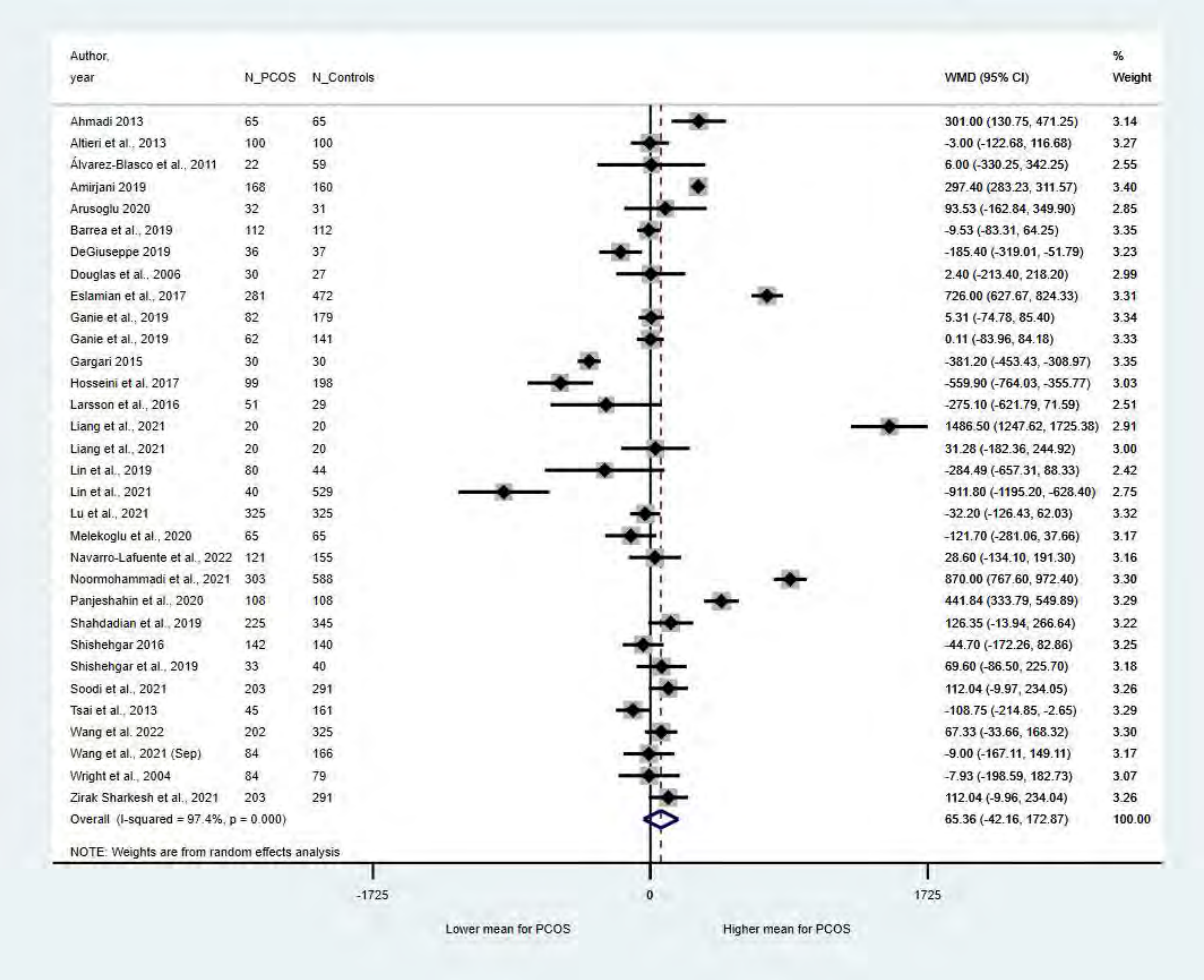
OUTCOME 1. Total energy intake

1.1 Individual Study Data Table

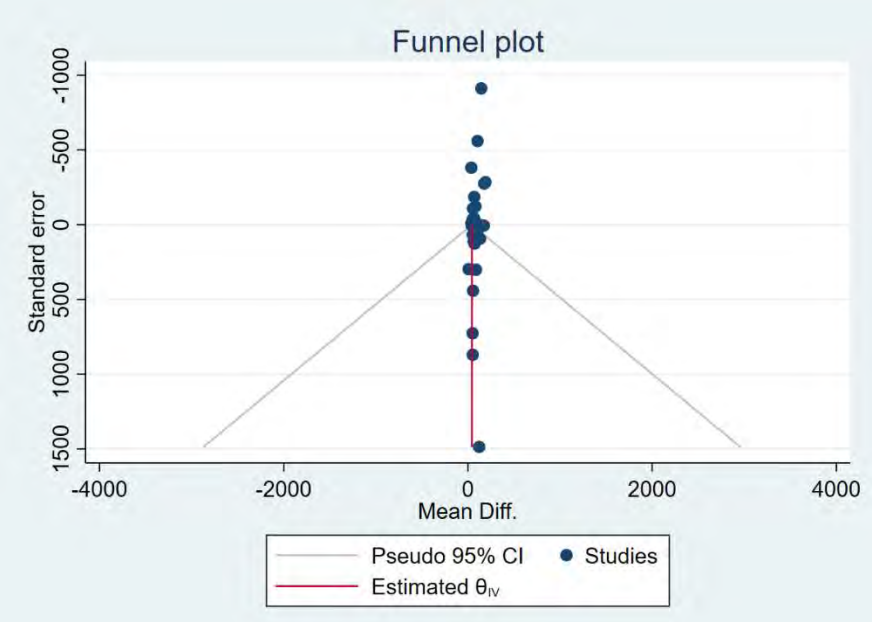
OUTCOME: Total energy intake					**OUTCOME TYPE:** continuous			
COMPARISON (if applicable): PCOS and control								
Author, year	**Measurement unit**	**Statistical unit**	**PCOS sample size**	**Control sample size**	**PCOS mean/median**	**PCOS variation**	**Control mean/median**	**Control variation**
Pooled in meta-analysis								
Ahmadi 2013	kcal/d	Mean, SD	65	65	1508	581	1207	391
Altieri *et al.*, 2013	kcal/d	Mean, SD	100	100	2220	457	2223	405
Álvarez-Blasco *et al.*, 2011	kcal/d	Mean, SD	22	59	2374	681	2368	702
Amirjani 2019	kcal/d	Mean, SD	168	160	2500.2	78.7	2202.8	49.6
Arusoglu 2020	kcal/d	Mean, SD	32	31	1907.78	559.71	1814.25	476.36
Barrea *et al.*, 2019	kcal/d	Mean, SD	112	112	2245.31	290.75	2254.84	272.37
DeGiuseppe 2019	kcal/d	Mean, SD	36	37	1790.1	365.5	1975.5	186.1
Douglas *et al.*, 2006	kcal/d	Mean, SD	30	27	1783.9	379.3	1781.5	444.8
Eslamian *et al.*, 2017	kJ/day kcal/day	Mean, SD Mean, SD	281	472	13451 3215	3016 721	10413 2489	2347 561
Ganie *et al.*, 2019	kcal/d (vegetarian) kcal/d (non-vegetarian)	Mean, SD Mean, SD	82 62	179 141	1862.78 1895.51	262.33 308.28	1857.47 1895.40	385.59 208.11
Gargari 2015	kcal/d	Mean, SD	30	30	1334.9	143.4	1716.1	142.07
Hosseini *et al.* 2017	kcal/day	Mean, SD	99	198	2600	892	2350	746
Larsson *et al.*, 2016	kcal/d	Mean, SD	51	29	2019	727	2059	779
Lin *et al.*, 2021	kcal/d	Mean, SD	40	529	2229.3	879.4	2246.7	912.3
Liang *et al.*, 2021	kcal/d (lean) kcal/d (overweight)	Mean, SD Mean, SD	20	20	1568.8 1588.7	351.01 336.84	1728.5 1831.5	417 352.37
Lu *et al.*, 2021	kcal/d	Mean, SD	325	325	1712.9	625.7	1745.1	599.8
Melekoglu *et al.*, 2020	kcal/d	Mean, SD	65	65	1732.7	474	1854.4	452.8
Navarro-Lafuente *et al.*, 2022	kcal/d	Mean, SD	121	155	1962.3	691.4	1933.7	675.1
Noormohammadi *et al.*, 2021	kcal/d	Mean, SD	303	588	3009	799	2139	605
Panjeshahin *et al.*, 2020	kcal/d	Mean, SD	108	108	2323.84	83.28	1882	566.84
Shahdadian *et al.*, 2019	kcal/d	Mean, SD	225	345	2501.63	902.83	2375.28	719.48
Shishehgar 2016 (2 papers)	kcal/d	Mean, SD	142	140	2457.8	572.7	2502.5	519.3
Shishehgar *et al.*, 2019	kcal/d	Mean, SD	33	40	2266.9	378.1	2197.3	283.6
Soodi *et al.*, 2021	kcal/d	Mean, SD	203	291	2500.07	696.19	2388.03	657.88
Wang *et al.* 2022	kcal/d	Mean, SD	202	325	1163.088	656.287	1095.757	412.218
Wright *et al.*, 2004	kcal/d	Mean, SD	84	79	1754.38	695.45	1762.31	541
Zirak Sharkesh *et al.*, 2021	kcal/d	Mean, SD	203	291	2500.07	696.16	2388.03	657.88
Wang *et al.*, 2021 (Sep)	kcal/d	Estimated marginal mean, SE	84	166	1874	70	1883	40.1
Lin *et al.*, 2019	kcal/d	Mean, 95% CI	80	44	2218	2017-2419	2180	1866-2494
Tsai *et al.*, 2013	kJ/d	Mean, SD	45	161	6311	1408	6766	1080
Not pooled in meta-analysis								
Alipour *et al.*, 2019	kcal/d	Median, IQR	45	45	1919	1655.5-2140	1880	1621.15-2076.50

Cutler *et al.*, 2019	kcal/d	Median, IQR	87	50	1783	1516-1966	1815	1578-2083
Eleftheridou et al. 2015	kcal/d	Mean	35	46	2324.8	NR	2217	NR
Graff 2013	kcal/d	Median, IQR	61	44	2250	1710-3786	1984	1620-2335
Graff 2017	kcal/d	Median, IQR	84 SFA <8.5%: 42 SFA ≥8.5%: 42	54 SFA <8.5%: 33 SFA ≥8.5%: 21	SFA <8.5%: 2295 SFA ≥8.5%: 2232	SFA <8.5%: 1522-2981 SFA ≥8.5%: 1674-3492	SFA <8.5%: 2056 SFA ≥8.5%: 1951	SFA <8.5%:1582-2489 SFA ≥8.5%: 1624-2773
Cunha *et al.*, 2019	kcal/d kcal/kg	Median, IQR Median, IQR	39	34	1651.42 23.56	1184.19-1949.22 17.34-31.96	1487.88 22.56	1240.79-1903.91 17.88-33.82
Kulshreshtha 2022	kcal	Non specified	Lean 62 Obese 106	Lean 60 Obese 42	Lean 1708.74 Obese 1675.39	Lean 414.20 Obese 441.40	Lean 1763.71 Obese 1544.22	Lean 371.39 Obese 368.60
Mario-2012	kcal/d	Median, IQR	Classic PCOS: 30 Ovulatory PCOS: 13	22	Classic PCOS: 3413 Ovulatory PCOS: 2630	Classic PCOS: 1819–4810 Ovulatory PCOS: 1594–3520	1891	1729–2638
Mizgier 2021	kcal	Median, IQR	61	35	1663.5	1444.7-1788.4	1474.01	1189.44-1746.39
Thara et al., 2017	kcal/d	Mean	40	40	2417.62	NR	2073.5	NR
Toscani 2011b	kJ	Median, IQR	43	37	7135	5409-9748	8368	5921-10039
Zhang 2015	kJ	Median, IQR	169	338	10837.2	9854.3-11833.8	7173.1	5894.8-8033.9
Zhang 2018	kJ/d	Median, IQR	Case-control phase: 169 Nested case-control phase: 52	Case-control phase: 1685 Nested case-control phase: 1097	Case-control phase: 7772.2 Nested case-control phase: 7058	Case-control phase: 5310.3-10297.3 Nested case-control phase: 5151.3-9447.7	Case-control phase: 7193.9 Nested case-control phase: 7215.5	Case-control phase: 5262.9-9855.8 Nested case-control phase: 5211.7-9808.9

- **1.2 Forest plot for total energy intake**



1.3 Funnel plot for total energy intake



OUTCOME 2. Total carbohydrate intake

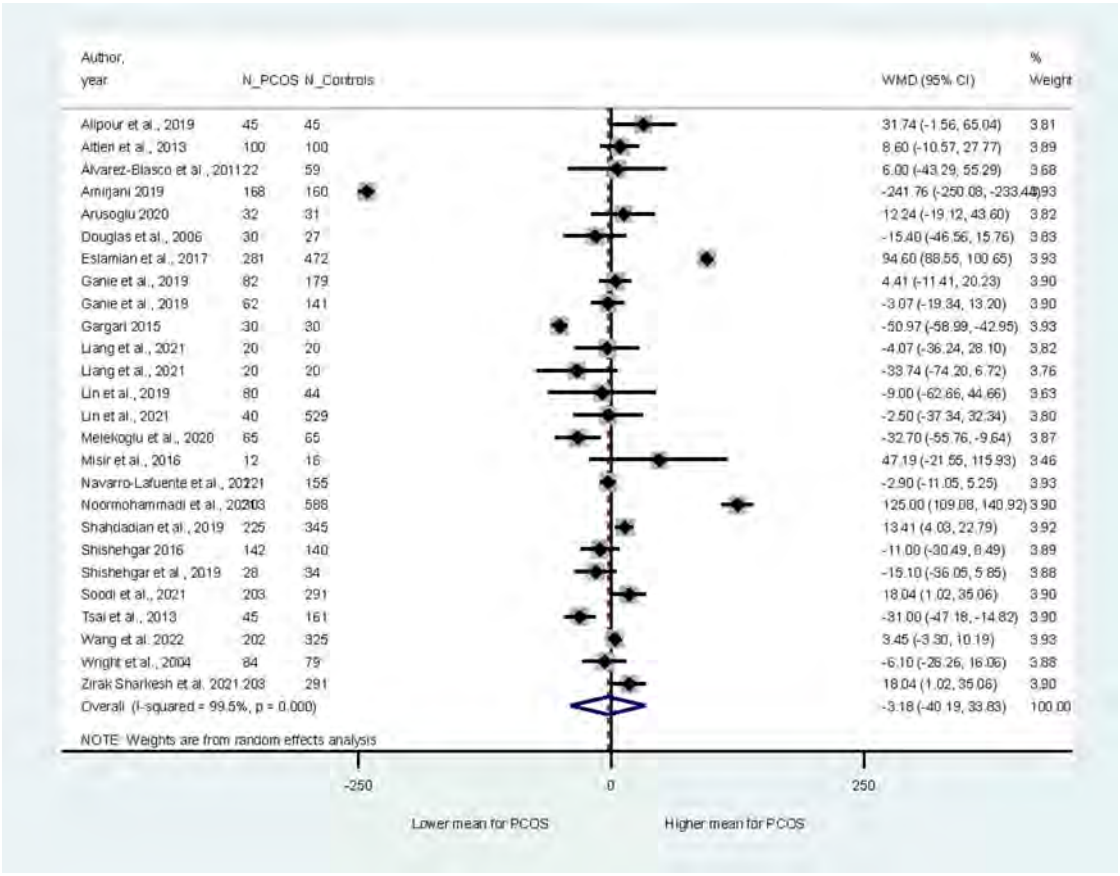
2.1 Individual Study Data Table

OUTCOME: Total carbohydrate intake					**OUTCOME TYPE:** continuous			
COMPARISON (if applicable): PCOS and control								
Author, year	**Measurement unit**	**Statistical unit**	**PCOS sample size**	**Control sample size**	**PCOS mean/median**	**PCOS variation**	**Control mean/median**	**Control variation**
Pooled in meta-analysis								
Alipour *et al.*, 2019	g/d	Mean, SD	45	45	301.36	98.25	269.62	57.75
Amirjani 2019	g/d	Mean, SD	168	160	380.26	54.02	622.02	10.13
Arusoglu 2020	g/d	Mean, SD	32	31	225.43	61.07	213.19	65.74
Eslamian *et al.*, 2017	g/d	Mean, SD	281	472	418.1	39.5	323.5	43.4
Ganie *et al.*, 2019	g/day (vegetarian) g/day (non-vegetarian)	Mean, SD	82 62	179 141	318.24 301.86	53.94 58.45	313.83 304.93	72.87 44.16
Gargari 2015	g/d	Mean, SD	30	30	171.6	9.3	222.57	20.4
Liang *et al.*, 2021	g/d (lean) g/d (overweight)	Mean, SD Mean, SD	20	20	184.47 188.72	49.6 49.32	188.54 222.46	54.12 78.03
Lin *et al.*, 2019	g/d	Mean, 95% CI	80	44	264	240-288	273	225-321
Lin *et al.*, 2021	g/d	Mean, SD	40	529	260	108.2	262.5	111
Misir *et al.*, 2016	g/d	Mean, SD	12	16	209.27	100.23	162.08	79.3
Navarro-Lafuente *et al.*, 2022	g/d	Mean, SD	121	155	173.4	31.9	176.3	37.1
Shahdadian *et al.*, 2019	g/d	Mean, SD	225	345	353.18	55.8	339.77	55.89
Soodi *et al.*, 2021	g/d	Mean, SD	203	291	344.1	95.78	326.06	93.83
Wang *et al.* 2022	g/d	Mean, SD	202	325	110.06	37.953	106.614	39.101
Wright *et al.*, 2004	g/d	Mean, SD	84	79	205.07	78.02	211.17	66.17
Zirak Sharkesh *et al.* 2021	g/d	Mean, SD	203	291	344.1	95.78	326.06	93.83
Álvarez-Blasco *et al.*, 2011	g/day % of total energy intake	Mean, SD Mean, SD	22	59	281 47	102 6	275 46	97 8
Douglas *et al.*, 2006	g/d % of total energy intake	Mean, SD Mean	30	27	220.3 49.5	50.5 NR	235.7 52.9	67.3 NR
Melekoglu *et al.*, 2020	g/day % of total energy intake	Mean, SD	65	65	216.7 51.4	69.0 7.7	249.4 55.5	65.1 5.2
Noormohammadi *et al.*, 2021	g/day % of total energy intake	Mean, SD Mean, SD	303	588	402 53.5	121 5.9	277 51.7	102 5.2
Shishehgar 2016	g/d % of total energy intake	Mean, SD	142	140	344.3 56.19	86.6 6.83	355.3 56.93	80.29 6.46
Shishehgar *et al.*, 2019	g/day % of total energy intake	Mean, SE Mean, SE	28	34	307.5 57.8	7.2 0.7	322.6 58.7	7.9 0.6
Tsai *et al.*, 2013	g/day % of total energy intake	Mean, SD	45	161	191 51.5	50 8.9	222 55.0	45 6.0
Ahmadi 2013	% of total energy intake	Mean, SD	65	65	56.09	6.5	57.21	8.1
Altieri *et al.*, 2013	g/d % of total energy intake	Mean, SD Mean, SD	100	100	270.8 48.1	71.1 6.3	262.2 46.2	67.2 6.6

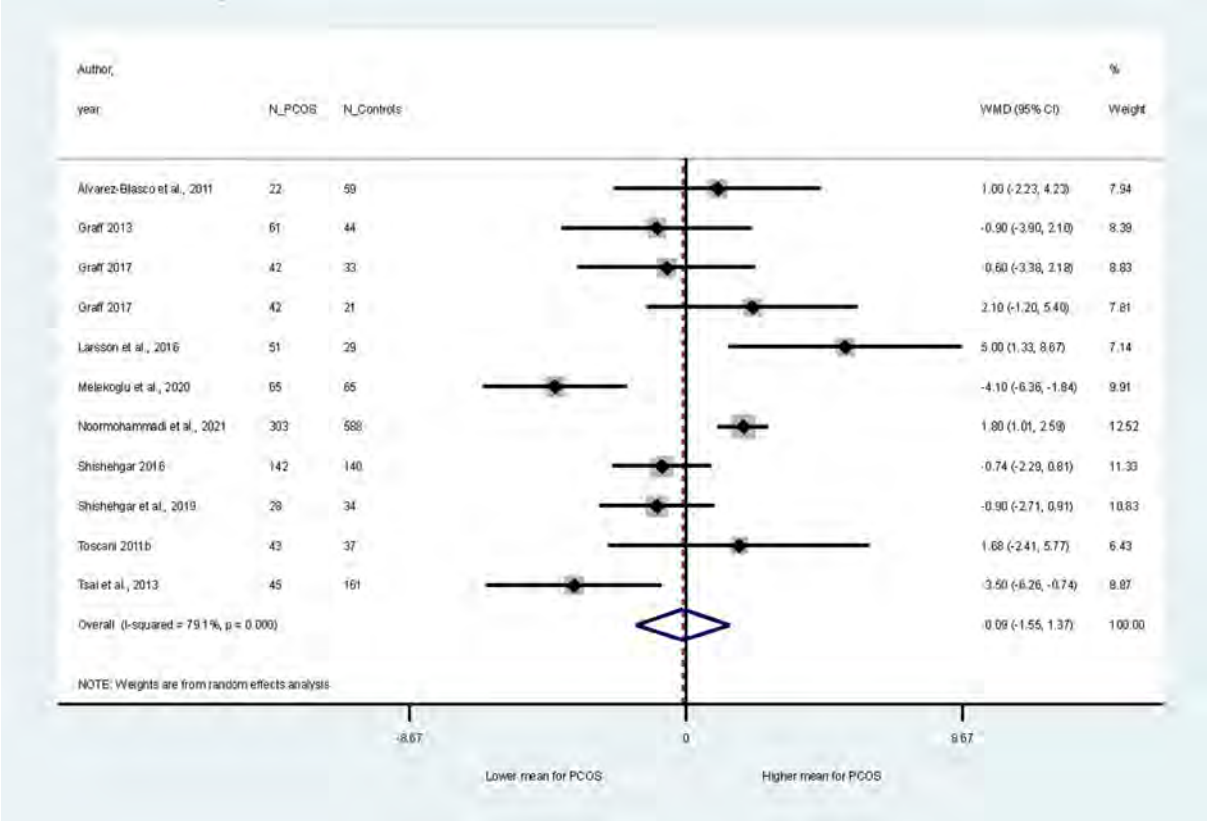
Graff 2013	% of total energy intake	Mean, SD	61	44	52.5	8.2	53.4	7.4
Graff 2017	% of total energy intake	Mean, SD	84	54	SFA <8.5%: 58.4 SFA ≥8.5%: 52.0	SFA <8.5%: 6.1 SFA ≥8.5%: 7.8	SFA <8.5%: 59.0 SFA ≥8.5%: 49.9	SFA <8.5%: 6.1 SFA ≥8.5%: 5.4
Larsson *et al.*, 2016	% of total energy intake	Mean, SD	51	29	49	6	44	9
Toscani 2011b	% of total energy intake	Mean, SD	43	37	53.51	8.36	51.83	10.06
Not pooled in meta-analysis								
Barrea *et al.*, 2019	g of total kcal	Mean, SD	112	112	307.98	42.03	310.47	37.42
Cunha *et al.*, 2019	g/d % of total energy intake g/kg	Median, IQR Median, IQR Median, IQR	39	34	203.47 49.22 2.85	122.24-241.27 41.53-55.50 2.05-4.40	182.90 46.83 2.87	134.62-235.86 38.75-50.79 1.81-3.83
Cutler *et al.*, 2019	% of total energy intake	Median, IQR	87	50	46.2	42.4-50.8	49	42.7-52.2
Kulshreshtha 2022	g	NR	lean 62 obese 106	lean 60 obese 42	lean 244.15 obese 241.24	lean 56.16 obese 69.9	lean 258.57 obese 229.46	Lean 51.77 obese 56.34
Mizgier 2021	g	Median, IQR	61	35	213.6	184.3-231	199.91	165.61-240.1
Thara *et al.*, 2017	g/d	Mean	40	40	439.17	NR	332.28	NR
Zhang 2015	g/d	Median, IQR	169	338	231.3	193.4-261.9	336.5	282.7-402.2
Zhang 2018	g/d	Median, IQR	Case-control phase: 169 Nested case-control phase: 52	Case-control phase: 1685 Nested case-control phase: 1097	Case-control phase: 330.2 Nested case-control phase: 377.4	Case-control phase: 224-443.5 Nested case-control phase: 252.6-448.8	Case-control phase: 319.6 Nested case-control phase: 318.8	Case-control phase: 229.6-435.4 Nested case-control phase: 223.9-436.4
DeGiuseppe 2019	Carbohydrates (45–60%)	Mean, SD	36	37	50.6	9.2	50.5	8

2.2 Forest plots for total carbohydrate intake

A) Total carbohydrate intake (g/day)

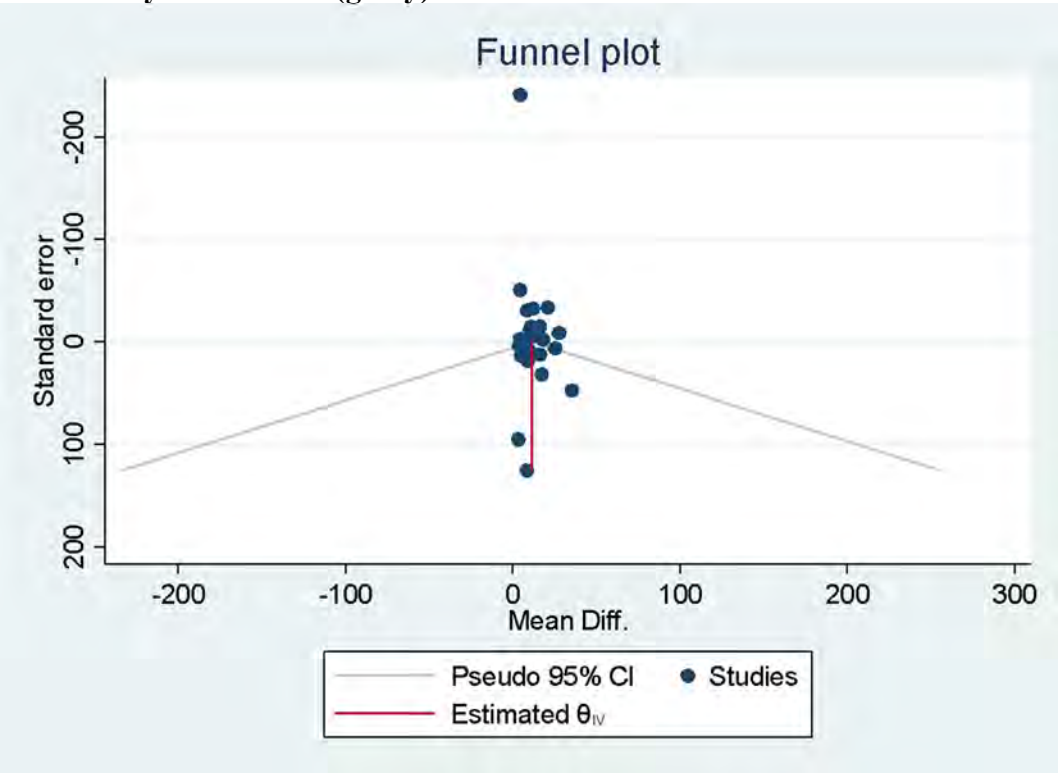


B) Total carbohydrate intake (%)

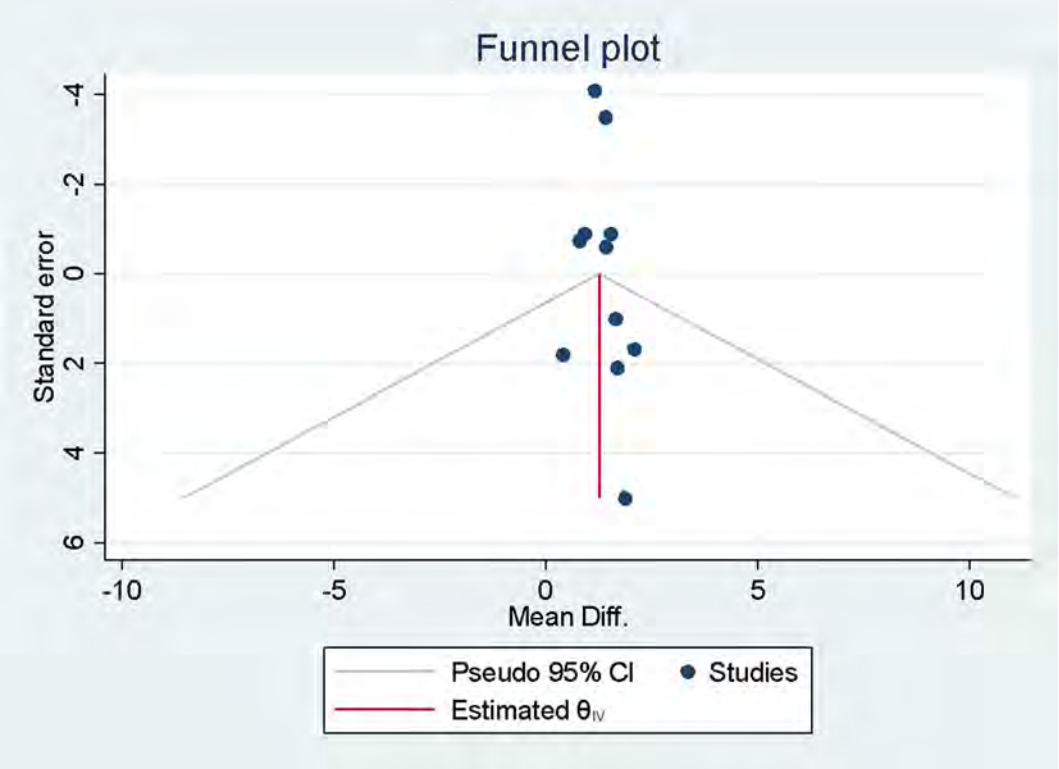


2.3 Funnel plots for total carbohydrate intake

A) Total carbohydrate intake (g/day)



B) Total carbohydrate intake (%)



OUTCOME 3. Total protein intake

3.1 Individual Study Data Table

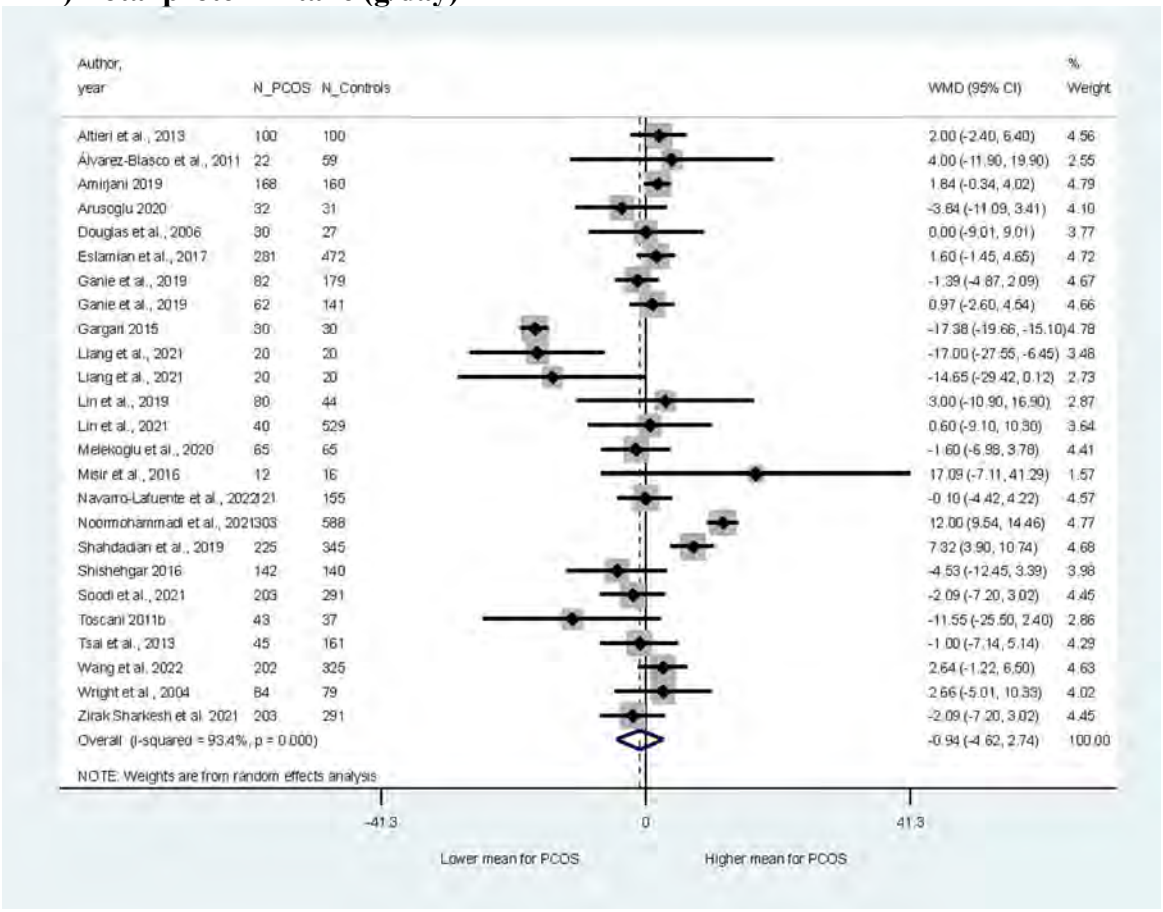
OUTCOME: Total protein intake					**OUTCOME TYPE:** continuous			
COMPARISON (if applicable): PCOS and control								
Author, year	**Measurement unit**	**Statistical unit**	**PCOS sample size**	**Control sample size**	**PCOS mean/median**	**PCOS variation**	**Control mean/median**	**Control variation**
Pooled in meta-analysis								

Amirjani 2019	g/day	Mean, SD	168	160	76.09	10.79	74.25	9.36
Arusoglu 2020	g/day	Mean, SD	32	31	58.45	15.38	62.29	13.96
Douglas *et al.*, 2006	g/day	Mean, SD	30	27	72.3	14.1	72.3	19.8
Eslamian *et al.*, 2017	g/day	Mean, SD	281	472	111.6	21.3	110	19.5
Ganie *et al.*, 2019	g/day (vegetarian) g/day (non-vegetarian)	Mean, SD	82 62	179 141	50.63 55.16	11.48 12.34	52.02 54.19	16.62 11.03
Gargari 2015	g/day	Mean, SD	30	30	49.9	2.43	67.28	5.89
Liang *et al.*, 2021	g/day (lean) g/day (overweight)	Mean, SD Mean, SD	20	20	60.21 64.39	13.6 17.32	77.21 79.04	19.86 28.9
Lin *et al.*, 2019	g/day	Mean, 95% CI	80	44	86	78-95	83	72-94
Lin *et al.*, 2021	g/day	Mean, SD	40	529	83.3	29.7	82.7	35.8
Misir *et al.*, 2016	g/day	Mean, SD	12	16	81.72	38.76	64.63	20.87
Navarro-Lafuente *et al.*, 2022	g/day	Mean, SD	121	155	91.8	18.4	91.9	17.9
Shahdadian *et al.*, 2019	g/day	Mean, SD	225	345	89.36	20.4	82.04	20.24
Soodi *et al.*, 2021	g/day	Mean, SD	203	291	86.17	28.89	88.26	27.96
Thara *et al.*, 2017	g/day	Mean	40	40	69.7	NR	59.18	NR
Wang *et al.* 2022	g/day	Mean, SD	202	325	51.195	23.593	48.555	19.129
Wright *et al.*, 2004	g/day	Mean, SD	84	79	65.7	28.12	63.04	21.59
Zirak Sharkesh *et al.* 2021	g/day	Mean, SD	203	291	86.17	28.89	88.26	27.96
Altieri *et al.*, 2013	g/day % of total energy intake	Mean, SD Mean, SD	100	100	81.1 14.9	16.7 2.6	79.1 14.6	15.0 2.7
Álvarez-Blasco *et al.*, 2011	g/day % of total energy intake	Mean, SD Mean, SD	22	59	106 18	33 3	102 18	31 4
Melekoglu *et al.*, 2020	g/day % of total energy intake	Mean, SD	65	65	52.9 12.7	15.9 3.1	54.5 12.2	15.4 1.9
Noormohammadi *et al.*, 2021	g/day % of total energy intake	Mean, SD Mean, SD	303	588	100 13.3	19 1.8	88 16.5	15 1.5
Shishehgar 2016	g/day % of total energy intake	Mean, SD	142	140	66.15 10.77	23.05 2.63	70.68 11.24	41.96 4.7
Shishehgar *et al.*, 2016	g/day % of total energy intake	Mean, SD Mean, SD	142	140	66.15 10.77	23.05 2.63	70.68 11.24	41.96 4.7
Toscani 2011b	g/day % of total energy intake	Mean, SD	43	37	69.22 17.12	30.7 10.08	80.77 16.78	32.62 4.15
Tsai *et al.*, 2013	% of total energy intake g/day	Mean, SD	45	161	17.6 67	4.2 19	17.3 68	7.3 17
Ahmadi 2013	% of total energy intake	Mean, SD	65	65	16.38	3.7	16.09	3.3
Graff 2013	% of total energy intake	Mean, SD	61	44	15.5	4.1	15.9	3.7
Graff 2017	% of total energy intake	Mean, SD	84 SFA <8.5%:	54 SFA <8.5%:	SFA <8.5%: 16.2 SFA ≥8.5%: 17.2	SFA <8.5%: 3.0	SFA <8.5%: 15.8	SFA <8.5%: 3.5

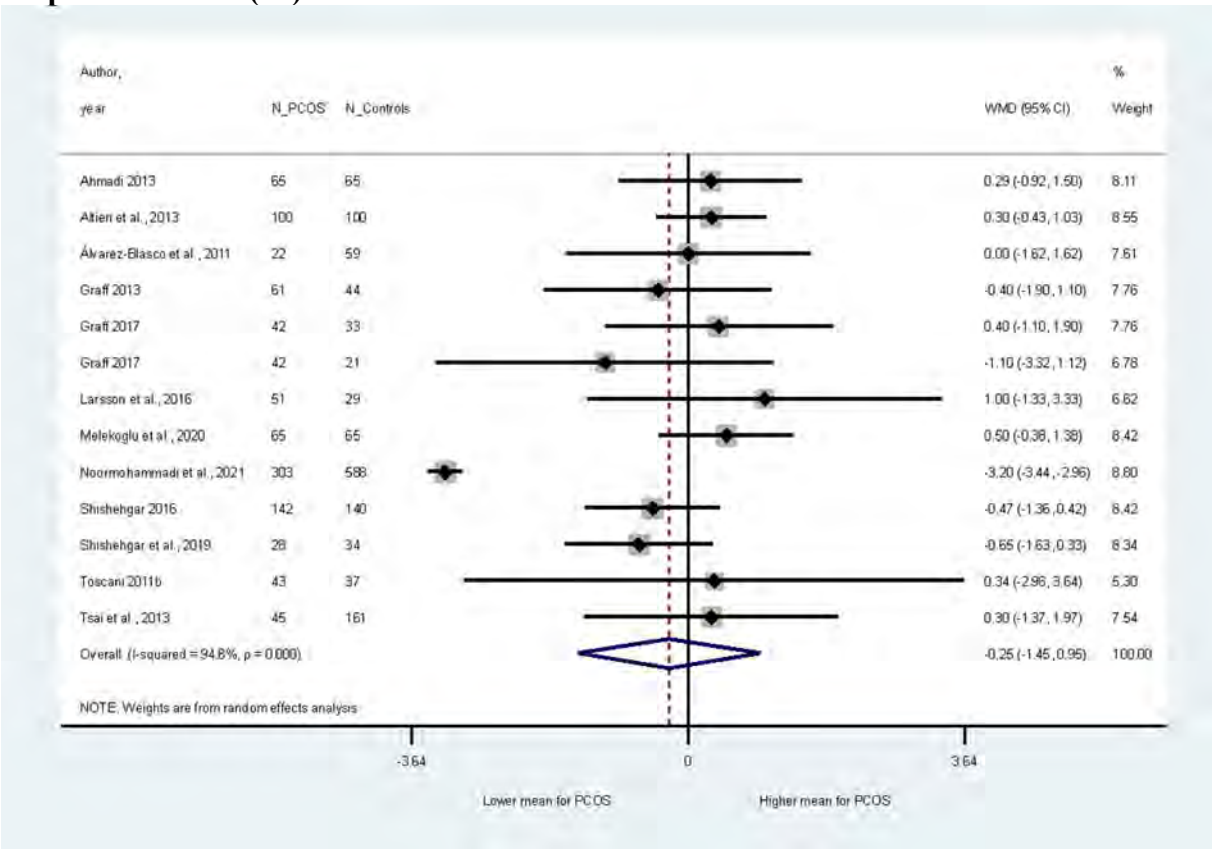
			42 SFA ≥8.5%: 42	33 SFA ≥8.5%: 21		SFA ≥8.5%: 5.0	SFA ≥8.5%: 18.3	SFA ≥8.5%: 3.8
Larsson *et al.*, 2016	% of total energy intake	Mean, SD	51	29	18	3	17	6
Shishehgar *et al.*, 2019	% of total energy intake	Mean, SE	28	34	10.55	0.4	11.2	0.3
Not pooled in meta-analysis								
Alipour *et al.*, 2019	g/day	Median, IQR	45	45	65.52	55.16-78.73	63.19	54.64-77.15
Barrea *et al.*, 2019	g of total kcal	Mean, SD	112	112	86.98	10.15	88.43	9.96
Cunha *et al.*, 2019	g/day % of total energy intake g/kg	Median, IQR Median, IQR Median, IQR	39	34	75.35 18.43 1.08	60.46-99.74 14.74-24.47 0.75-1.78	69.61 17.33 0.97	54.08-87.83 14.90-22.88 0.77-1.39
Cutler *et al.*, 2019	% of total energy intake	Median, IQR	87	50	16.8	14.2-19.8	16.4	14.4-18.8
DeGiuseppe 2019	Proteins (0.9 g/kg body weight)	Mean, SD	36	37	0.8	0.2	1.3	0.2
Kulshreshtha 2022	g	NR	lean 62 obese 106	lean 60 obese 42	lean 54.36 obese 53.51	lean 15.66 obese 17.13	lean 53.55 obese 48.08	Lean 10.82 obese 12.34
Mizgier 2021	g	Median, IQR	61	35	67.3	53.6-84.3	68.81	61.47-78.69
Zhang 2015	g/day	Median, IQR	169	338	66.3	58.9-74.4	67.4	58.7-79.7
Zhang 2018	g/day	Median, IQR	Case-control phase: 169 Nested case-control phase: 52	Case-control phase: 1685 Nested case-control phase: 1097	Case-control phase: 52.2 Nested case-control phase: 55.5	Case-control phase: 44.3-71.8 Nested case-control phase: 44.1-81.2	Case-control phase: 52 Nested case-control phase: 51.9	Case-control phase: 43.5-72.7 Nested case-control phase: 43.5-72.7

3.2 Forest plots for total protein intake

A) Total protein intake (g/day)

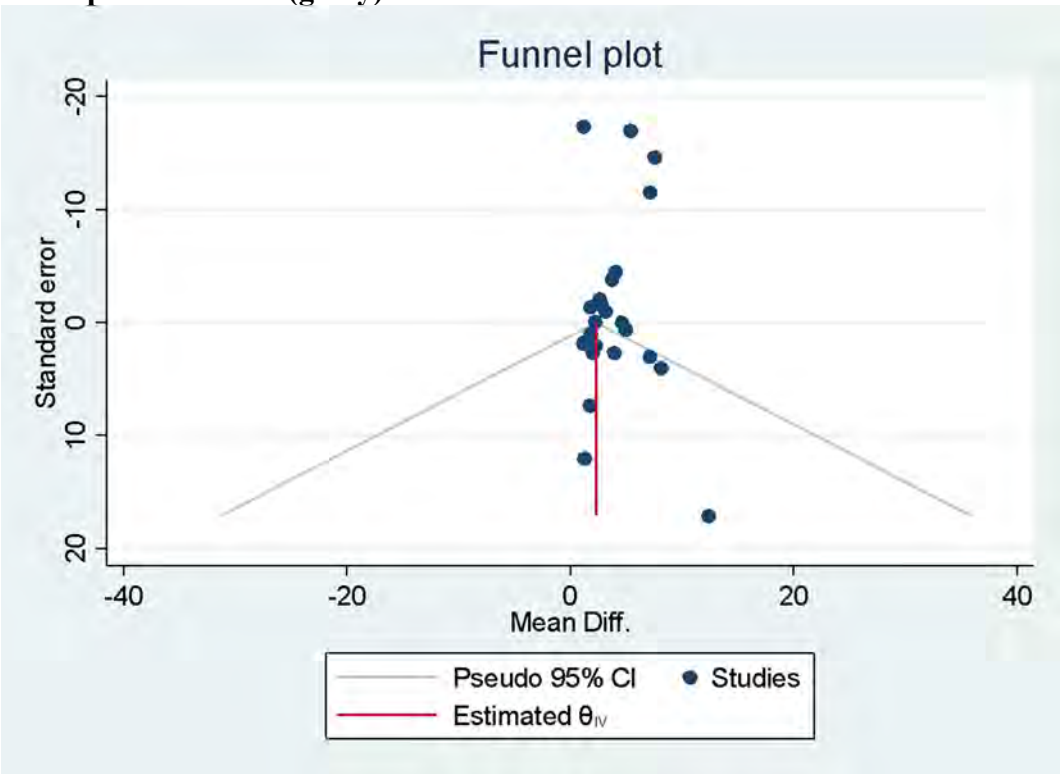


B) Total protein intake (%)

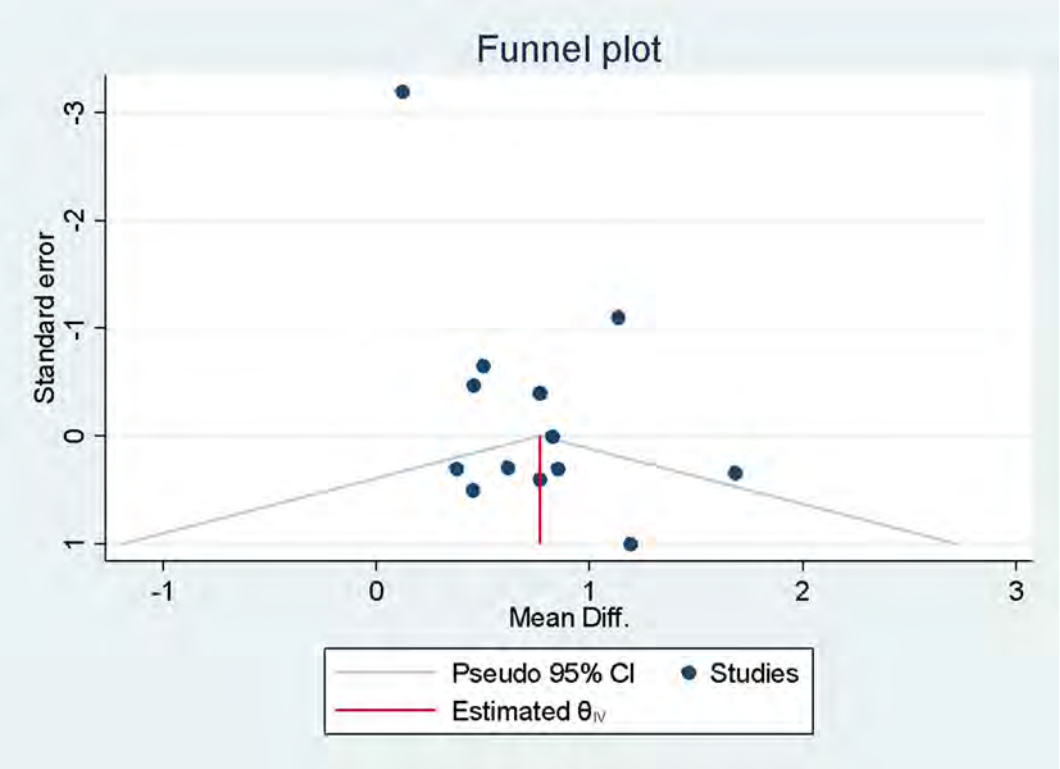


3.3 Funnel plots for total protein intake

A) Total protein intake (g/day)



B) Total protein intake (%)



OUTCOME 4. Total fat intake

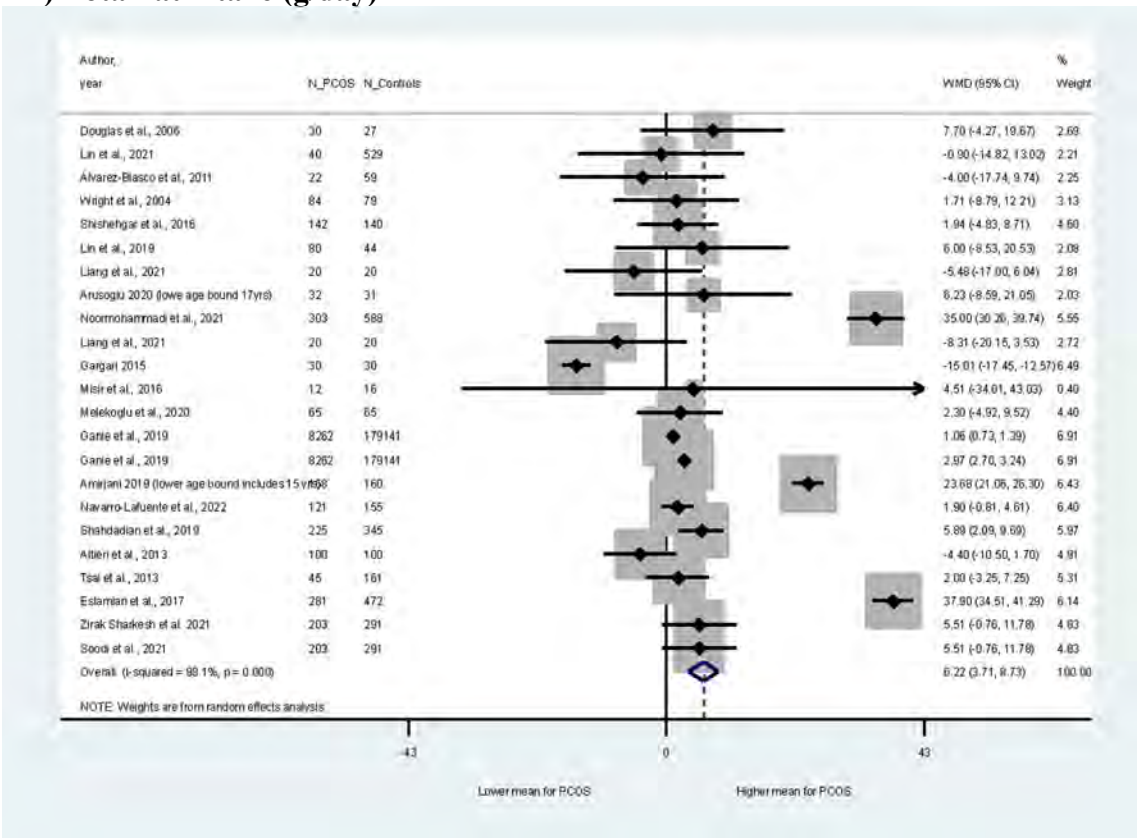
4.1 Individual Study Data Table

OUTCOME: Total fat intake					**OUTCOME TYPE:** continuous			
COMPARISON (if applicable): PCOS and control								
Author, year	**Measurement unit**	**Statistical unit**	**PCOS sample size**	**Control sample size**	**PCOS mean/median**	**PCOS variation**	**Control mean/median**	**Control variation**
Pooled in meta-analysis								
Amirjani 2019	g/day	Mean, SD	168	160	89.06	12.42	65.38	11.75
Arusoglu 2020	g/day	Mean, SD	32	31	83.51	34.74	77.28	24.58
Douglas *et al.*, 2006	g/day % of total energy intake	Mean, SD Mean	30	27	69.2 34.8%	25 NR	61.5 31.0%	21.1 NR
Eslamian *et al.*, 2017	g/day	Mean, SD	281	472	120.9	26.7	83	14.6
Ganie *et al.*, 2019	g/day (vegetarian) g/day (non-vegetarian)	Mean, SD	82 62	179 141	43.11 49.07	14.72 12.35	42.05 46.10	16.93 9.46
Gargari 2015	g/day	Mean, SD	30	30	50.72	2.72	65.73	6.24
Liang *et al.*, 2021	g/day (lean) g/day (overweight)	Mean, SD Mean, SD	20	20	65.58 63.99	20.33 18.32	73.89 69.47	17.79 18.85
Lin *et al.*, 2019	g/day	Mean, 95% CI	80	44	89	80-99	83	72-94
Lin *et al.*, 2021	g/day	Mean, SD	40	529	93.3	43.2	94.2	44.7
Misir *et al.*, 2016	g/day	Mean, SD	12	16	86.43	50.68	81.92	52.497
Mizgier 2021	g	Mean, SD	61	35	62.93	24.68	47.42	16.97
Navarro-Lafuente *et al.*, 2022	g/day	Mean, SD	121	155	72.1	10.4	70.2	12.6
Shahdadian *et al.*, 2019	g/day	Mean, SD	225	345	85.17	22.65	79.28	22.65
Soodi *et al.*, 2021	g/day	Mean, SD	203	291	92.49	36.18	86.98	33.15
Wright *et al.*, 2004	g/day	Mean, SD	84	79	75.53	38.47	73.82	29.56
Zirak Sharkesh *et al.* 2021	g/day	Mean, SD	203	291	92.49	36.18	86.98	33.15
Altieri *et al.*, 2013	g/day % of total energy intake	Mean, SD Mean, SD	100	100	89.7 37	22.6 6.5	94.1 38.4	21.4 5.5
Álvarez-Blasco *et al.*, 2011	g/day % of total energy intake	Mean, SD Mean, SD	22	59	95 37	25 5	99 37	35 6
Melekoglu *et al.*, 2020	g/day % of total energy intake	Mean, SD	65	65	69.6 36.0	22.2 6.4	67.3 32.4	19.7 4.7
Noormohammadi *et al.*, 2021	g/day % of total energy intake	Mean, SD	303	588	111 33.2	39 3.2	76 32.0	22 3.5
Shishehgar 2016	g/day % of total energy intake	Mean, SD	142	140	90.66 33.03	30.77 7.04	88.72 31.82	27.12 6.56
Shishehgar *et al.*, 2016	g/day % of total energy intake	Mean, SD Mean, SD	142	140	90.66 33.03	30.77 7.04	88.72 31.82	27.12 6.56
Tsai *et al.*, 2013	% of total energy intake g/day	Mean, SD	45	161	30.8 53	7.9 17	28.3 51	5.1 11
Ahmadi 2013	% of total energy intake	Mean, SD	65	65	22.04	5.1	20.15	3.7

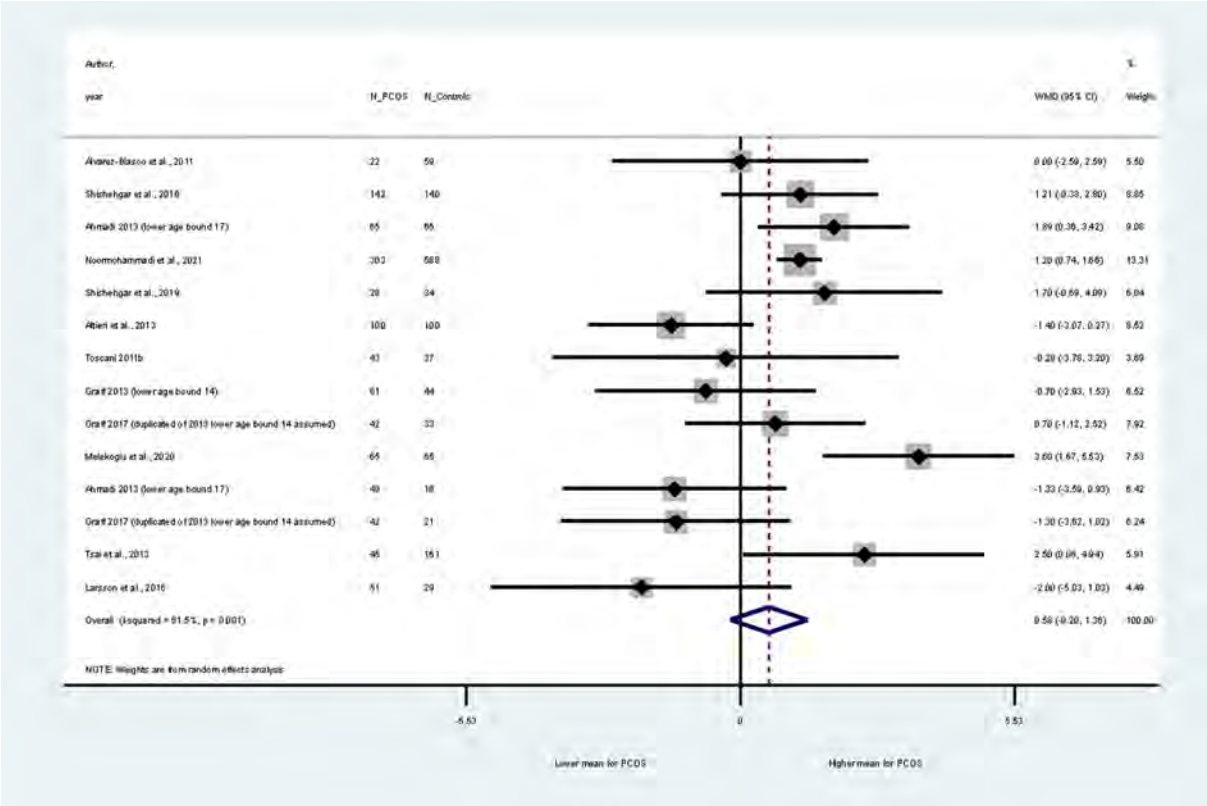
Graff 2013	% of total energy intake	Mean, SD	61	44	24.8	6.1	25.5	5.5
Graff 2017	% of total energy intake	Mean, SD	84 SFA <8.5%: 42 SFA ≥8.5%: 42	54 SFA <8.5%: 33 SFA ≥8.5%: 21	SFA <8.5%: 24.4 SFA ≥8.5%: 29.9	SFA <8.5%: 4.0 SFA ≥8.5%: 4.7	SFA <8.5%: 23.7 SFA ≥8.5%: 31.2	SFA <8.5%: 4.0 SFA ≥8.5%: 4.3
Larsson *et al.*, 2016	% of total energy intake	Mean, SD	51	29	31	6	33	7
Shishehgar *et al.*, 2019	% of total energy intake	Mean, SE	28	34	31.7	1	30	0.7
Toscani 2011b	% of total energy intake	Mean, SD	43	37	30.51	7.9	30.8	7.97
Not pooled in meta-analysis								
Alipour *et al.*, 2019	g/day	Median, IQR	45	45	58.18	45.95-70.87	57.33	48.74-65.41
Barrea *et al.*, 2019	g of total kcal	Mean, SD	112	112	73.94	13.59	70.07	10.73
Cunha *et al.*, 2019	g/day % of total energy intake g/kg	Median, IQR Median, IQR Median, IQR	39	34	57.08 31.61 0.85	36.18-70.32 24.83-36.15 0.51-1.12	55.54 34.29 0.86	44.28-84.45 28.80-35.98 0.61-1.38
Cutler *et al.*, 2019	% of total energy intake	Median, IQR	87	50	36	32.3-39.2	34	30.1-38.7
Kulshreshtha 2022	g	NR	lean 62 obese 106	lean 60 obese 42	lean 56.94 obese 56.55	lean 20.20 obese 18.17	lean 57.41 obese 48.34	Lean 18.90 obese 14.76
Thara *et al.*, 2017	g/day	Mean	40	40	40.61	NR	27.33	NR
Wang *et al.* 2022	g/day	Median, IQR	202	325	30.632	21.033-41.809	27.457	19.323-36.903
Zhang 2015	g/day	Median, IQR	169	338	95.8	88.1-99.7	90.58	74.8-97.8
Zhang 2018	g/day	Median, IQR	Case-control phase: 169 Nested case-control phase: 52	Case-control phase: 1685 Nested case-control phase: 1097	Case-control phase: 92.5 Nested case-control phase: 95.7	Case-control phase: 63.2-103.6 Nested case-control phase: 61.9-114.1	Case-control phase: 93.7 Nested case-control phase: 93.7	Case-control phase: 67.3-116.8 Nested case-control phase: 63.8-116.3

4.2 Forest plots for total fat intake

A) Total fat intake (g/day)

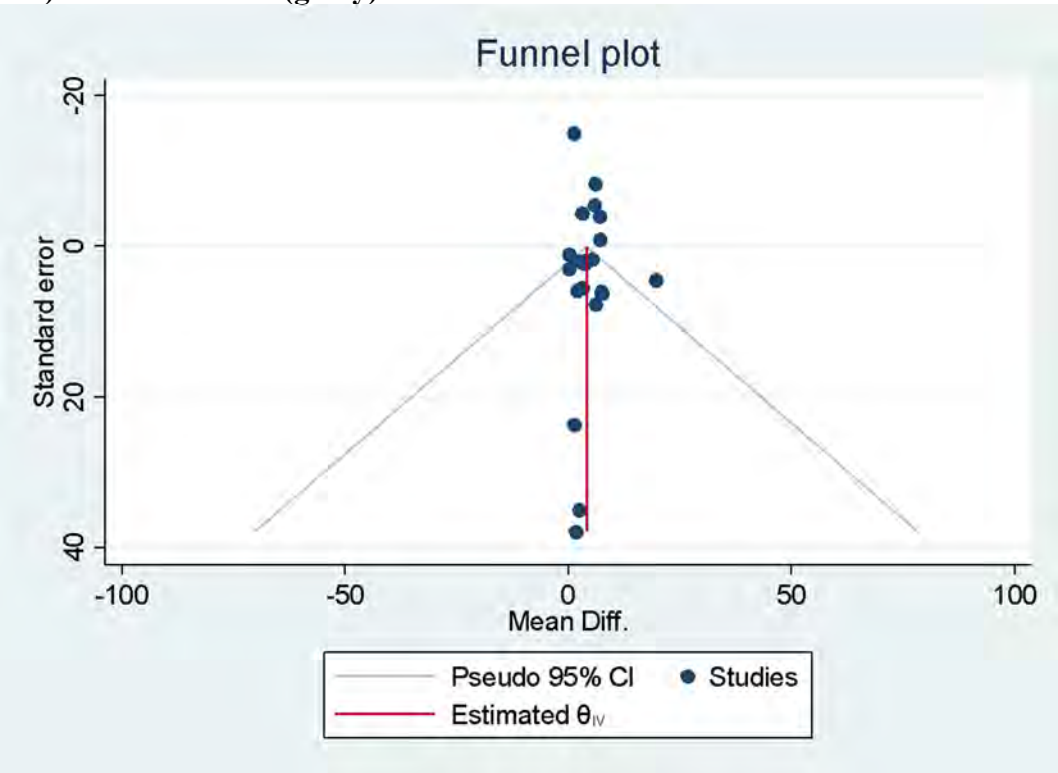


B) Total fat intake (%)

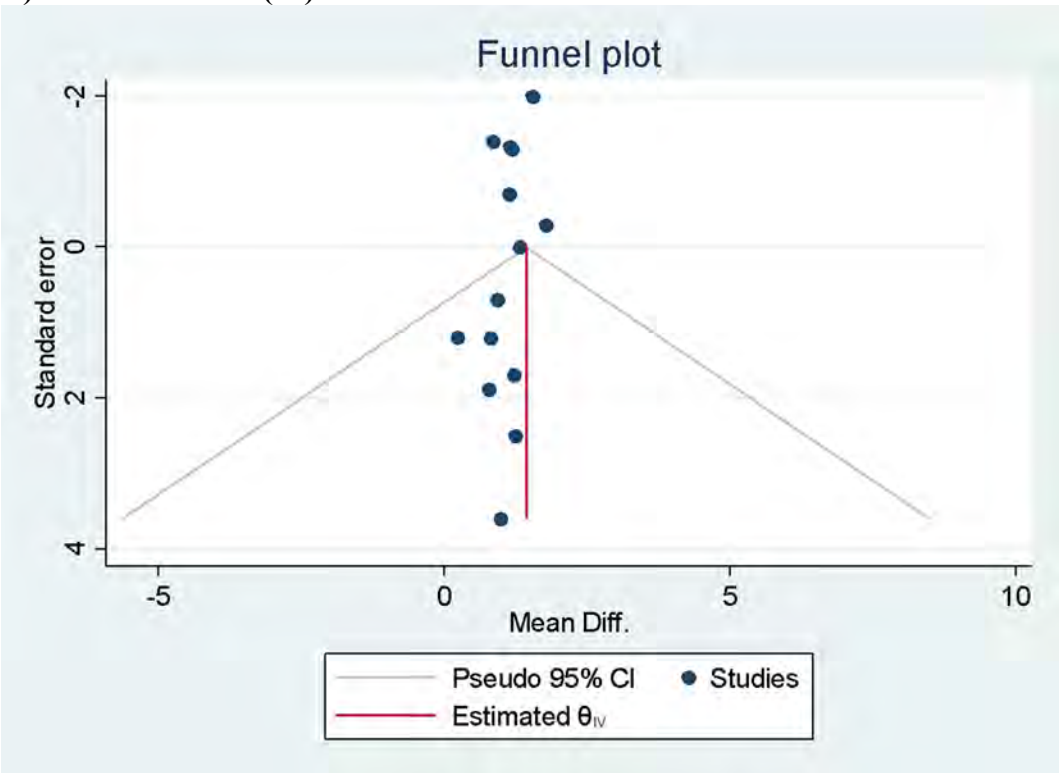


4.3 Funnel plots for total fat intake

A) Total fat intake (g/day)



B) Total fat intake (%)



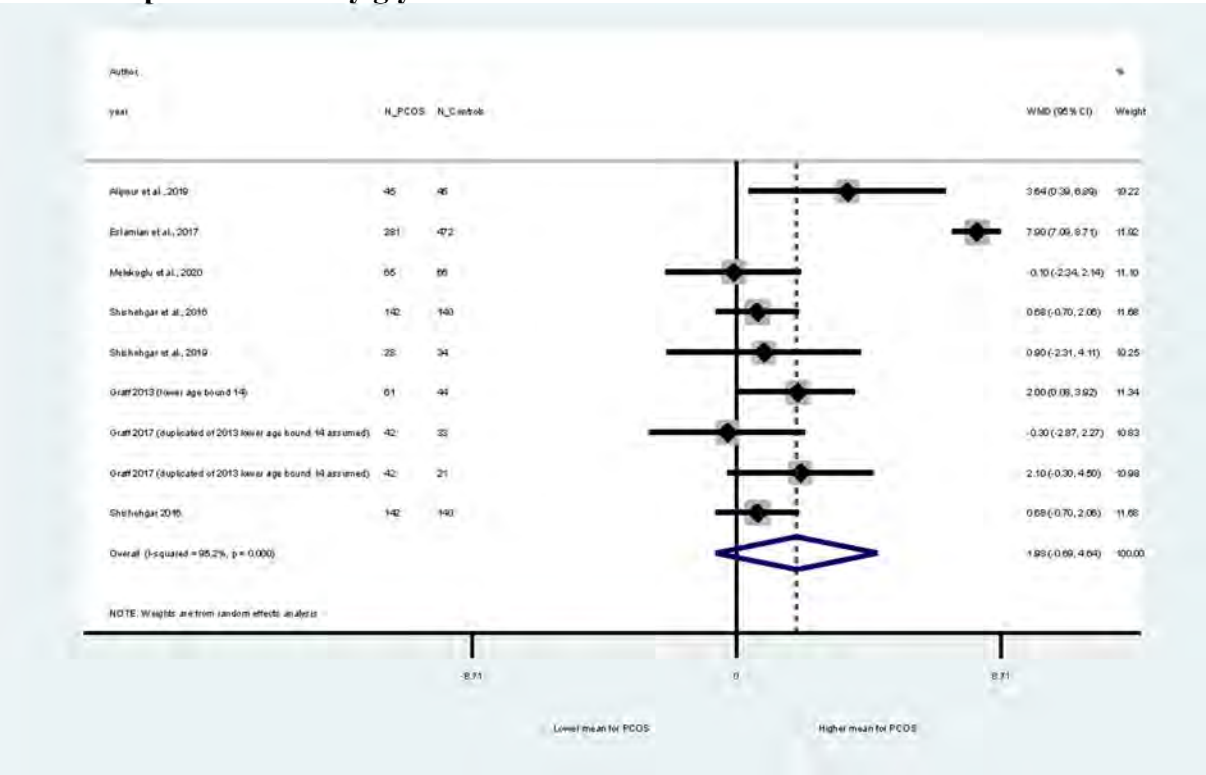
OUTCOME 5. Dietary glycaemic index

5.1 Individual Study Data Table

OUTCOME: Dietary glycemic index					**OUTCOME TYPE:** continuous			
COMPARISON (if applicable): PCOS and control								
Author, year	**Measurement unit**	**Statistical unit**	**PCOS sample size**	**Control sample size**	**PCOS mean/median**	**PCOS variation**	**Control mean/median**	**Control variation**
Pooled in meta-analysis								

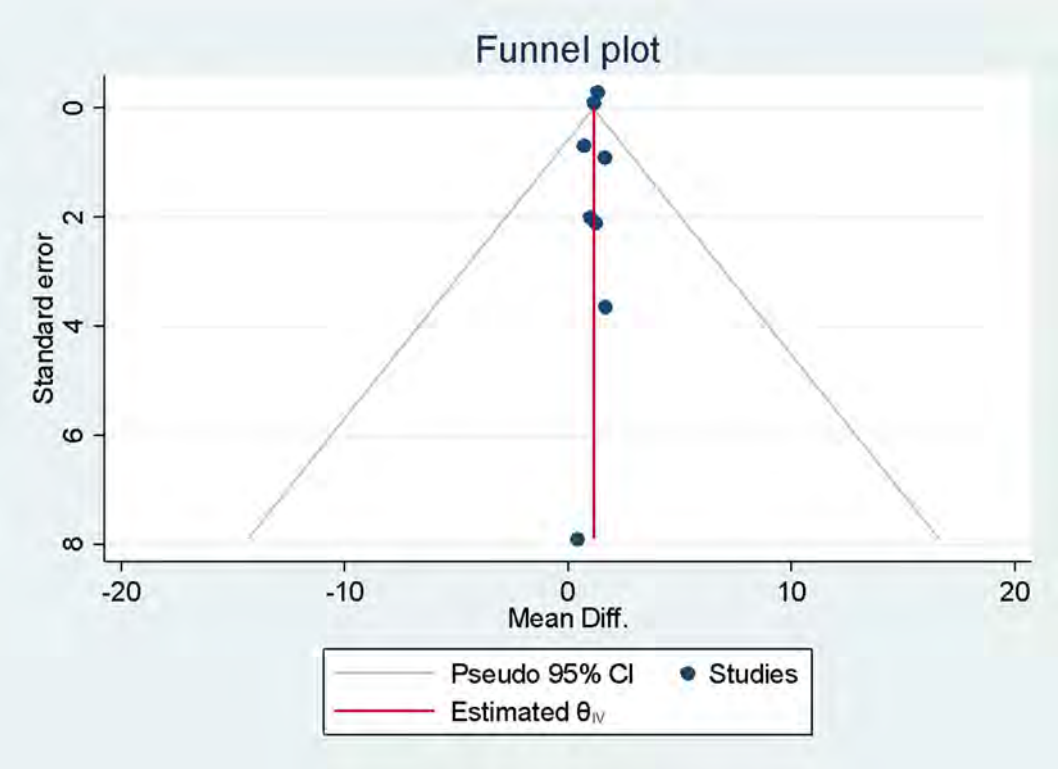
Alipour *et al.*, 2019	glycemic index	Mean, SD	45	45	66.23	8.34	62.59	7.38
Eslamian *et al.*, 2017	glycemic index	Mean, SD	281	472	59.7	5.9	51.8	4.7
Melekoglu *et al.*, 2020	glycemic index	Mean, SD	65	65	59.6	8	59.7	4.6
Shishehgar et al., 2016	glycemic index	Mean, SD	142	140	61.22	6.26	60.54	5.51
Shishehgar *et al.*, 2019	glycemic index	Mean, SE	28	34	59.9	1	59	1.3
Graff 2013	glycemic index	Mean, SD	61	44	57.7	5.3	55.7	4.7
Graff 2017	glycemic index	Mean, SD	84 SFA <8.5%: 42 SFA ≥8.5%: 42	54 SFA <8.5%: 33 SFA ≥8.5%: 21	SFA <8.5%: 57.0 SFA ≥8.5%: 58.5	SFA <8.5%: 5.0 SFA ≥8.5%: 5.7	SFA <8.5%: 57.3 SFA ≥8.5%: 56.4	SFA <8.5%: 6.1 SFA ≥8.5%: 3.9
Not pooled in meta-analysis								
Altieri *et al.*, 2013	g g	Mean, SD Mean, SD	100	100	246 67.9	79 40.3	232 57.8	86 30.1
Bykowska-Derda 2020	hGIDI-7, High-Glycemic-Diet-Index-7	Mean, SD	122	116	16.1	11.2	13.4	8.2
	GIDI-4, Low-Glycemic-Diet-Index-4	Mean, SD	122	116	27.5	13.1	30.5	12.7

5.2 Forest plots for dietary glycaemic index



5.3 Funnel plots for dietary glycaemic index

Note: Less than 10 studies



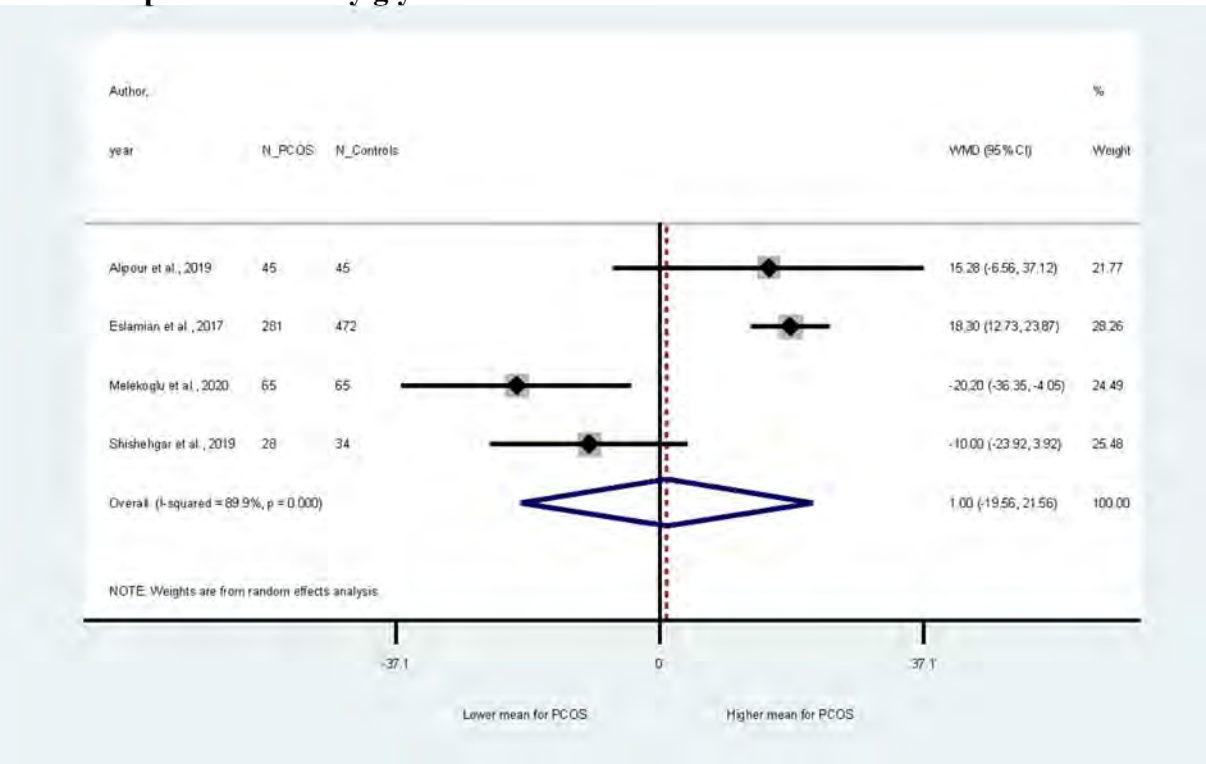
OUTCOME 6. Dietary glycaemic load

6.1 Individual Study Data Table

OUTCOME: Dietary glycemic load					**OUTCOME TYPE:** continuous			
COMPARISON (if applicable): PCOS and control								
Author, year	**Measurement unit**	**Statistical unit**	**PCOS sample size**	**Control sample size**	**PCOS mean/median**	**PCOS variation**	**Control mean/median**	**Control variation**
Pooled in meta-analysis								
Alipour *et al.*, 2019	glycemic load	Mean, SD	45	45	161.13	64.59	145.85	37.63
Eslamian *et al.*, 2017	glycemic load	Mean, SD	281	472	173.6	39.1	155.3	35.2
Melekoglu *et al.*, 2020	glycemic load	Mean, SD	65	65	136.2	52.9	156.4	40.2
Shishehgar *et al.*, 2019	glycemic load	Mean, SE	28	34	142.4	3.8	152.4	6
Not pooled in meta-analysis								
Cutler *et al.*, 2019	crude (Value) adjusted (Value)	Median, IQR	87	50	84.1 83.7	58.9-106.2 66.8-105.7	86.0 83.0	68.2-105.1 69.0-107.5
Shishehgar et al., 2016	glycemic load	Median, 25th-75th percentiles	142	140	166.61	132.52-194.15	155.01	130.07-185.69
Graff 2013	glycemic load	Median, IQR	61	44	176.3	111.4-269.8	143.8	111.1-186.3
Graff 2017	glycemic load	Median, IQR	84 SFA <8.5%: 42 SFA ≥8.5%: 42	54 SFA <8.5%: 33 SFA ≥8.5%: 21	SFA <8.5%: 197.5 SFA ≥8.5%: 191.3	SFA <8.5%: 121.1–253.8 SFA ≥8.5%: 117.4–250.5	SFA <8.5%: 160.2 SFA ≥8.5%: 134.5	SFA <8.5%: 135.3–202.1 SFA ≥8.5%:

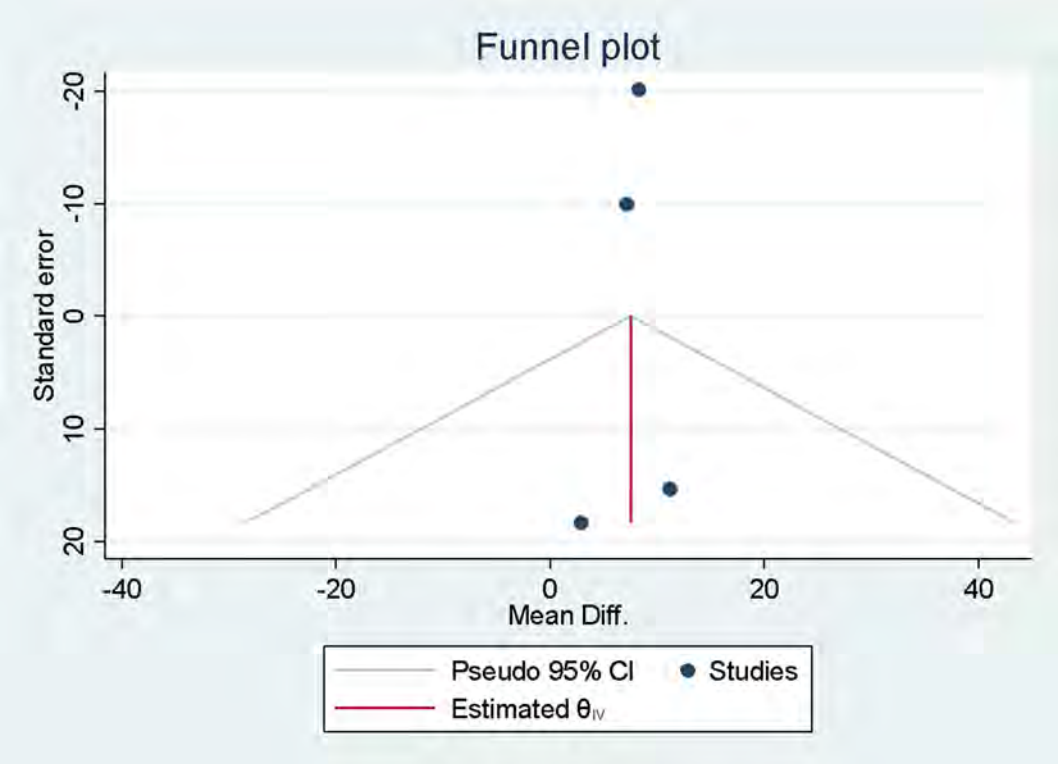
								99.0–174.9

6.2 Forest plots for dietary glycaemic load



6.3 Funnel plots for to dietary glycaemic load

Note: Less than 10 studies



OUTCOME 7. Total physical activity

7.1 Individual Study Data Table

OUTCOME: Physical activity					**OUTCOME TYPE:** continuous			
COMPARISON (if applicable): PCOS and control								
Author, year	**Measurement unit**	**Statistical unit**	**PCOS sample size**	**Control sample size**	**PCOS mean/median**	**PCOS variation**	**Control mean/median**	**Control variation**
Pooled in meta-analysis								
Alipour *et al.,* 2019	glycemic load	Mean, SD	45	45	161.13	64.59	145.85	37.63
Álvarez-Blasco et al., 2011	Hours of exercise per week	Mean, SD	22	59	0.39	1.02	0.63	1.87
Eslamian et al., 2017	MET/hr day	Mean, SD	281	472	48.6	5.1	59.8	7.5
Hosseini et al. 2017	MET-hr/day	Mean, SD	99	198	59	42	56	38
Noormohammadi et al., 2021	Physical activity (MET/h/d)	Mean, SD	303	588	47.3	5.9	58.1	7.1
Panjeshahin et al., 2020	MET-min/week	Mean, SD	108	108	987	201.22	1426	760.71
Sedighi et al., 2014	MET	Mean, SD	65	65	809.85	629.19	1916.8	1708.88
Shahdadian et al., 2019	MET-mins/wk	Mean, SD	225	345	787.07	797.37	1829.36	1870.12
Shishehgar et al., 2019	Met-min/week	Mean, SD	28	34	167.5	105.83	147.9	106.12
Not pooled in meta-analysis								
Álvarez-Blasco et al., 2011	% of women exercising regularly	Mean	22	59	11.9	NR	13.6	NR
arrea et al., 2019	n	NR	112	112	76	0.87	73	0.99
	%	NR	112	112	67.9	NR	65.2	NR
Cutler et al., 2019	Step Count	Median, IQR	87	50	6554	4918-9173	7234	5558-8663
Dantas et al., 2015	Step Count	Mean, SD	15	12	12224	5631	13721	4545
	Moderate to Vigorous PA	Mean, SD	15	12	25.5	22	31.1	21.9
Douglas et al., 2006	Frequency of exercise sessions per week	Mean, SD	30	27	0.8	1.2	1.3	1.2
Elefheridou et al, 2012	Participation in PA	N (%)	35	46	12 (34.3%)	NA	35 (76.1%)	NR
Kulshreshtha 2022	No exercise Exercise 2–3 days/week Exercise 4–7 days/week	N (%)	lean 62 obese 106	lean 60 obese 42	Lean: 49 (79.03%) 1 (1.6%) 12 (19.4%) Obese: 1 (76.41%) 0 (0%) 25 (23.6%)	NA	Lean: 41 (68.3%) 2 (3.3%) 17 (28.3%) Obese: 33 (78.6%) 0 (0%) 9 (21.4%)	NA
Huijgen et al. 2015	n (no PA)	NR	36	37	98	NR	366	NR
	% (no PA)	NR	218	799	51	NR	49.4	NR
Khademi et al. 2010	Hours (Duration of exercise)	Mean, min-max	26	268	31.5	8-108	26	12-90
	% (Walking)	NR	26	268	49.1	NR	44.5	NR
Lin et al., 2019	Self-reported, MET-h/week (Walking)	Mean, SD	48	34	2	NR	2	NR
	Self-reported, min/week (Walking)	Mean, SD	48	34	117	NR	114	NR
	Self-reported, min/week (Sitting/lying down)	Mean, SD	48	34	49	NR	49	NR

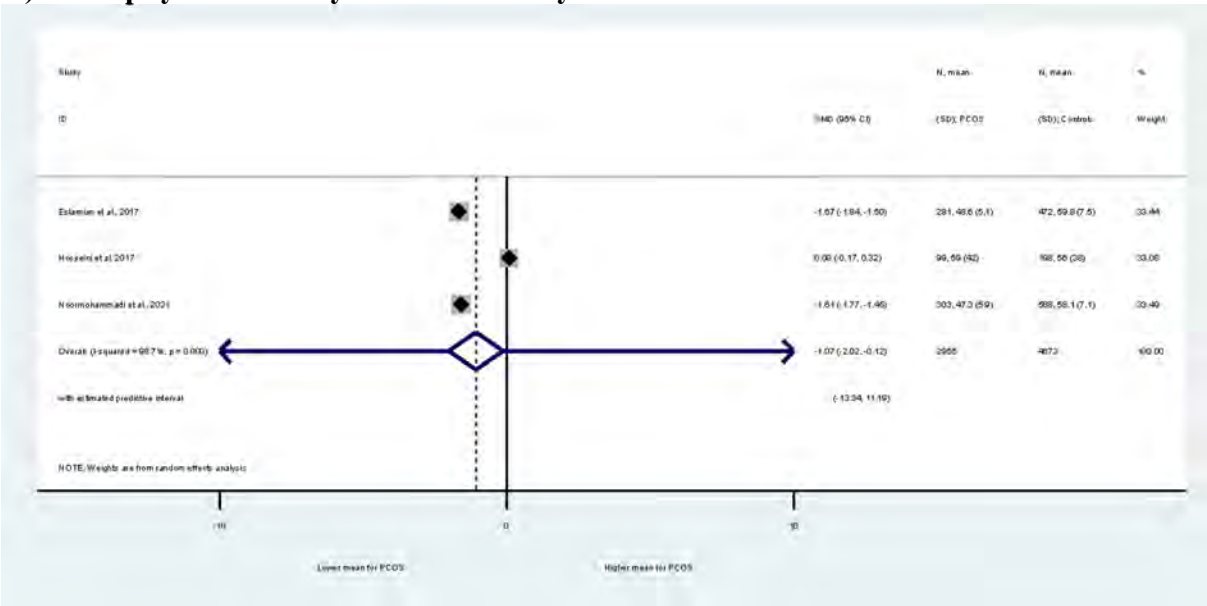
Lin et al., 2021	Total exercise units	Mean, SD	40	529	257	257	257	257
Lu et al., 2021	<1 time/week: n (%)	N (%)	325	325	185 (56.9)	NR	155 (47.7)	NR
	1-3 times/week: n (%)	N (%)	325	325	101 (31.1)	NR	112 (34.5)	NR
	>3 times/week: n (%)	N (%)	325	325	39 (12)	NR	58 (17.8)	NR
Melekoglu et al., 2020	Physical Activity Value (TEE/BMR)	Mean, SD	65	65	1.33	0.06	1.31	0.1
Misir et al., 2016	Work Activity	Mean	12	16	2.7	NR	2.5	NR
	Sports Activity	Mean	12	16	2.5	NR	3.7	NR
	Free time Activity	Mean	12	16	2.3	NR	3.2	NR
Navarro-Lafuente et al., 2022	hrs/week (of moderate-vigorous PA)	Mean, SD	121	155	10.3	13.4	9.9	13.0
Orio et al., 2006	Physical Activity Score 1-3 (1: low PA, 2: moderate PA, 3: high PA)	Mean, SD	45	45	2.1	0.5	2.3	0.6
Sedighi et al., 2014	MET	Mean, NR	65	65	809.85	629.19	1916.8	1708.88
Shahdadian et al., 2019	MET-mins/wk	Mean, SD	225	345	787.07	797.37	1829.36	1870.12
Shishehgar et al., 2016	Met/min/wek	Median, IQR	142	140	548	189-1044	539	261.25-1237.5
Shishehgar et al., 2019	Met-min/week	Mean, SE	28	34	167.5	20	147.9	18.2
Soodi et al., 2021	Met-min/d	Mean, SD	203	291	1638.97	572.95	1996.65	1258.03
Thomson et al., 2009	Physical activity score	Mean, SD	10	16	7.2	0.8	7.2	1.5
Wang et al. 2022	PALs	Median, IQR	202	325	8	3.00-18.13	9	3.00-18.00
Wang et al., 2021 (Oct)	Moderate to vigorous physical activity (<200 min/week)	n (% within group)	170	321	54 (32.1)	NR	108 (34.6)	NR
	Moderate to vigorous physical activity (200-700 min/week)	n (% within group)	170	321	59 (34.1)	NR	98 (31.4)	NR
	Moderate to vigorous physical activity (>700 min/week)	n (% within group)	170	321	55 (32.7)	NR	106 (34.0)	NR
Wang et al., 2021 (Sep)	Steps (steps/day)	Estimated marginal mean, SE	84	166	5962	393.6	6086	286.8
Zhang et al., 2020	% less than 10 hr	Mean	OA: 1274	181	64.9	NR	65.60	NR
			non OA: 133	181	57.10	NR	65.60	NR
	% 10-20 hr	Mean	OA: 468	68	23.8	NR	24.60	NR
			non OA: 62	68	26.60	NR	24.60	NR
	% more than 20 hr	Mean	OA: 221	27	11.3	NR	9.8	NR
			non OA: 38	27	16.30	NR	9.8	NR
Zirak Sharkesh et al. 2021	MET. min/d	Mean, SD	203	291	1638.97	572.95	1996.65	1258.03
Amirjani 2019 (lower age bound includes 15 yrs)	sports and fitness score	Mean, SD	168	160	12.05	3.52	15.42	4.82
Arusoglu 2020 (lowe age bound 17yrs)	physical activity durarion (hour)	Mean, SD	32	31	1.4	0.87	2.18	0.99
Arusoglu 2020 (lowe	total energy expenditure (kcal)	Mean, SD	32	31	2128.84	289.91	2124.66	314.66

age bound 17yrs)								
Bykowska-Derda 2020 (included 17 yr olds)	Insufficient physical activity (MET-minute/week)	Percentage	122	116	52	NR	49	NR
	Sufficient physical activity (MET-minute/week)	Percentage	122	116	18	NR	23	NR
	High physical activity (MET-minute/week)	Percentage	122	116	11	NR	9	NR
Bykowska-Derda 2020 (included 17 yr olds)	High-intensity physical activity(MET-minute/week)	Mean, SD	122	116	1892	9215	6855	21629
Bykowska-Derda 2020 (included 17 yr olds)	Medium-intensity physical activity(MET-minute/week)	Mean, SD	122	116	2168	6988	2995	9119
Bykowska-Derda 2020 (included 17 yr olds)	Walking(MET-minute/week)	Mean, SD	122	116	2637	7710	2990	7543
Bykowska-Derda 2020 (included 17 yr olds)	Sitting(MET-minute/week)	Mean, SD	122	116	2205	2863	1535	894
DeGiuseppe 2019 (lower age bound 16)	BMR: basal metabolic rate (kcal)	Mean, SD	36	37	1658.7	201.1	1359.2	103.7
Graff 2017 (duplicated of 2013 lower age bound 14 assumed)	resting metabolic rate (kcal/day)	Mean, SD	84	54	1463	248	1468	253
	Steps/day	Median, IQR	84	54	5821	3821–7664	6002	4375–7427
Mario-2012 (exclusionary because of age 14)	no. of steps/day	Mean, SD	Classic PCOS: 30 Ovulatory PCOS: 13	22	Classic PCOS: 6180 Ovulatory PCOS: 5452	Classic PCOS: 4132–8505 Ovulatory PCOS: 3919–6368	6496	4563–7431
Mario-2017 (exclusionary because of age 15)	Steps (steps/day)	Median, IQR	84	67	5931	3686–8887	5810	3884–7326
Mizgier 2021	Work/school PA low moderate high Leisure PA low moderate high	N(%)	61	35	work/school: 25 (41.67%); 29 (48.33%); 6 (10%) Leisure: 20 (32.79%), 27 (44.26%), 14 (22.95%)	NA	worl/school: 2 (6.06%), 20 (60.61%), 11 (33.33%) leisure: 2 (5.71%), 18 (51.43%), 15 (42.86%)	NA
Shishehgar 2016b	Met/min/week	Median, IQR	142	140	548	189-1044	539	261.25-1237.5
	Time spent sitting (hour)	Mean, SD	142	140	6.94	2.2	6.09	2.63
Toscani 2011a	no. of steps/day	Median, IQR	High protein: 9	High protein: 13	High protein: 7793	High protein: 3462-13111	High protein: 6363	High protein: 4057-9738
			Normal protein: 9	Normal protein: 9	Normal protein: 5528	Normal protein: 3906-8278	Normal protein: 4248	Normal protein: 1145-8683
Wang Oct 2021a	Total moderate-to-vigorous physical activity (<200 minute/week)	Mean	170	321	54	NR	108	NR
	Total moderate-to-vigorous physical activity (200–700 minute/week)	Mean	170	321	59	NR	98	NR

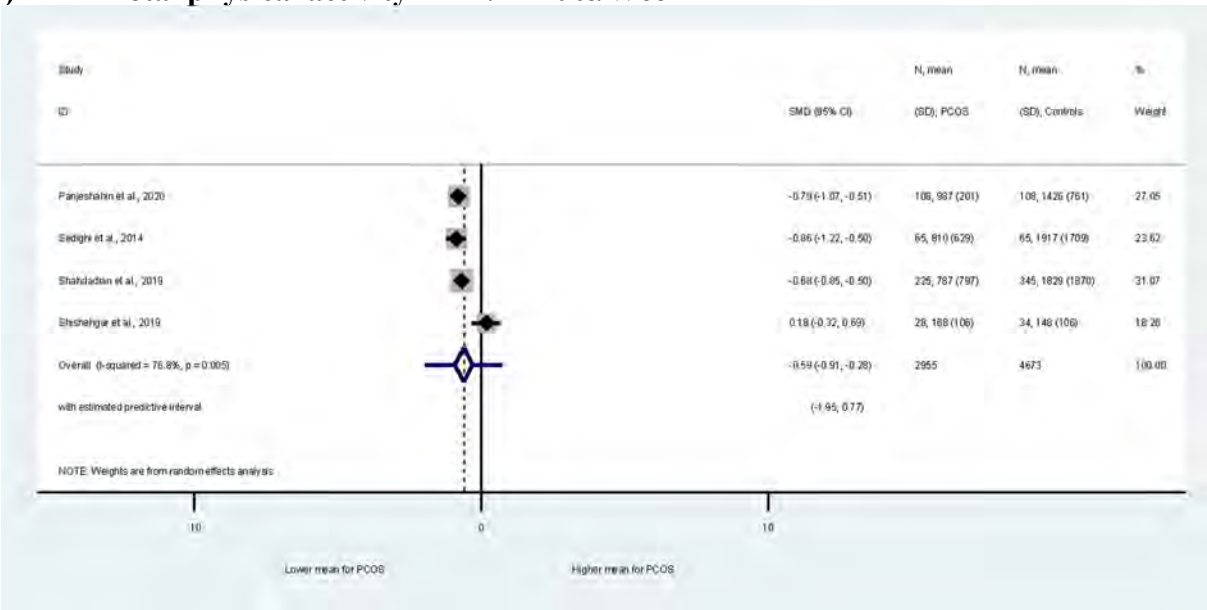
	Total moderate-to-vigorous physical activity (>700minute/week)	Mean	170	321	55	NR	106	NR
Zhang 2018	h/wk	Median, IQR	Case-control phase: 169 Nested case-control phase: 52	Case-control phase: 1685 Nested case-control phase: 1097	Case-control phase: 8.5 Nested case-control phase: 4.7	Case-control phase: 4.4-16.3 Nested case-control phase: 0-8.3	Case-control phase: 9.2 Nested case-control phase: 9.5	Case-control phase: 4.7-18 Nested case-control phase: 5-18.9

7.2 Forest plots for total physical activity

A) Total physical activity MET/Hour/Day



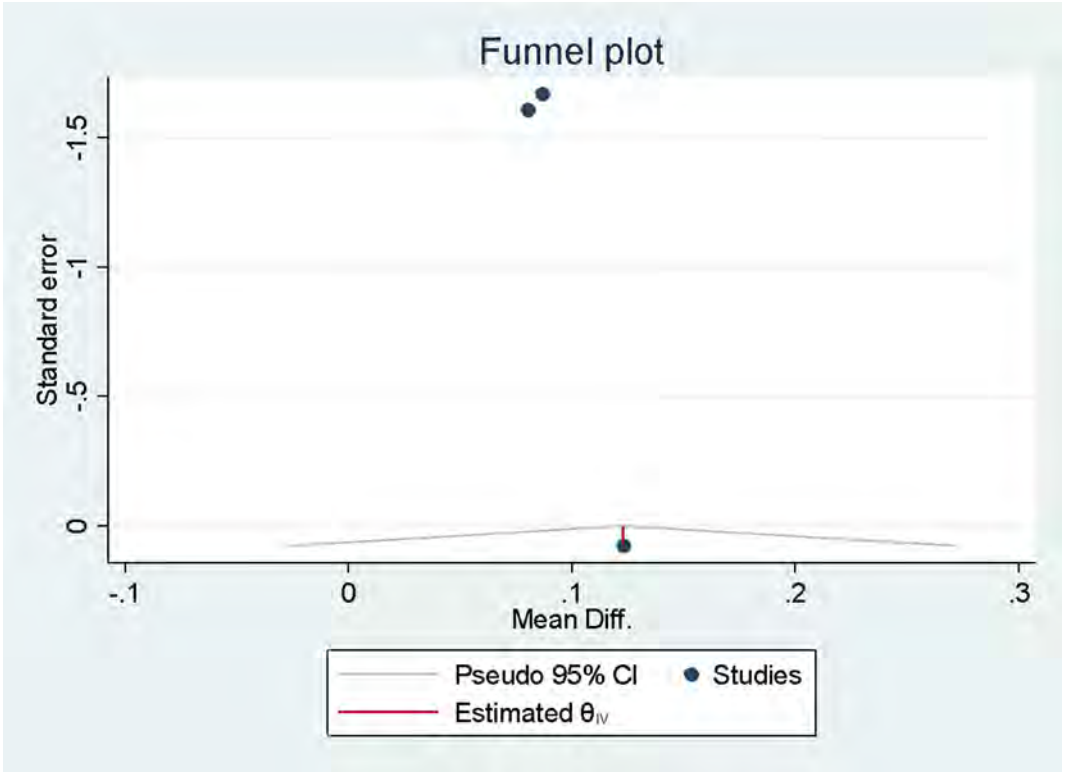
B) Total physical activity MET/Minute/Week



7.3 Funnel plots for total physical activity

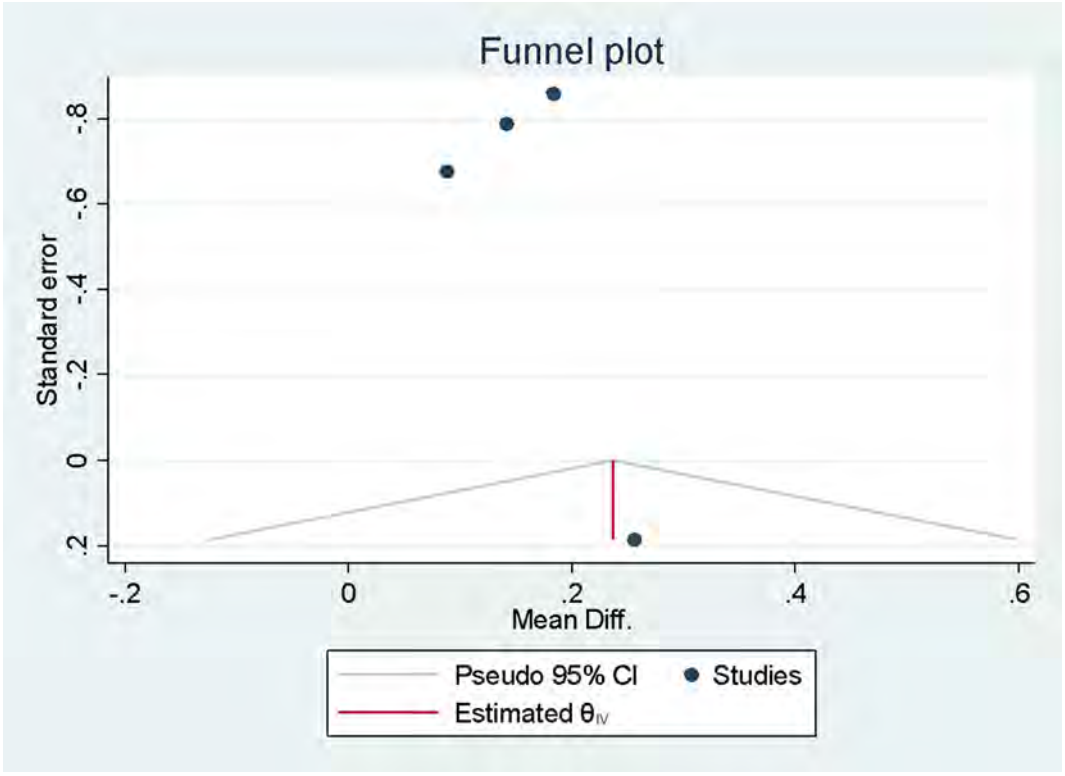
A) Total physical activity MET/Hour/Day

Note: Less than 10 studies



B) Total physical activity MET/Minute/Week

Note: Less than 10 studies



8. GRADE ASSESSMENTS AND EVIDENCE PROFILE

COMPARISON 1: PCOS vs control													
	Quality assessment						No. participants						
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Subgroup	PCOS	Controls	Effect estimate SMD (95% CI)	Favours	Certainty	Importance
Outcome: Total energy intake													
32	Observational	Serious[1]	very serious[2]	No serious indirectness	No serious imprecision	None	Overall	3309	4992	MD 65.36 [95%CI -42.16, 172.87]	None	⨁◯◯◯ Very Low	Critical
Outcome: Total carbohydrate intake													
23	Observational	Serious[1]	Very serious[2]	No serious indirectness	No serious imprecision	Publication bias	g/day	2381	3907	MD -3.18 [95%CI -40.19, 33.83]	None	⨁◯◯◯ Very Low	Critical
13	Observational	Serious[1]	Very serious[2]	No serious indirectness	No serious imprecision	None	% of energy	1039	1403	MD -0.09 [95%CI -1.55, 1.37]	None	⨁◯◯◯ Very Low	Critical
Outcome: Total protein intake													
25	Observational	Serious[1]	Very serious[2]	No serious indirectness	No serious imprecision	Publication bias	g/day	2633	4145	MD -0.94 [95%CI -4.62, 2.74]	None	⨁◯◯◯ Very Low	Critical
13	Observational	Serious[1]	Very serious[2]	No serious indirectness	No serious imprecision	Publication bias	% of energy	1067	1462	MD -0.25 [95%CI -1.45, 0.95]	None	⨁◯◯◯ Very Low	Critical
Outcome: Total fat intake													
22	Observational	Serious[1]	Very serious[2]	No serious indirectness	No serious imprecision	None	g/day	2348	3743	MD 6.22 [95%CI 3.71, 8.73]	PCOS	⨁◯◯◯ Very Low	Critical
13	Observational	Serious[1]	Serious[2]	No serious indirectness	No serious imprecision	None	% of energy	1067	1462	MD 0.58 [95%CI -0.20, 1.36]	None	⨁◯◯◯ Very Low	Critical
Outcome: Dietary glycaemic index													
7	Observational	Serious[1]	Very serious[2]	No serious indirectness	Serious[3]	None	Overall	706	854	MD 1.98 [95%CI -0.69, 4.64]	None	⨁◯◯◯ Very Low	Critical
Outcome: Dietary glycaemic load													
4	Observational	Very serious[1]	Very serious[2]	No serious indirectness	Very serious[3]	None	Overall	419	616	MD 1.00 [95%CI -19.56, 21.56]	None	⨁◯◯◯ Very Low	Critical
Outcome: Total physical activity													
3	Observational	Very serious[1]	Very serious[2]	No serious indirectness	Very serious[3]	None	MET/Hour/ Day	2955	4673	SMD -1.07 [95%CI -2.02, -0.12]	PCOS	⨁◯◯◯ Very Low	Critical
4	Observational	Serious[1]	Very serious[2]	No serious indirectness	Very serious[3]	None	MET/Minute/Week	2955	4673	SMD -0.59 [95%CI -0.91, -0.28]	PCOS	⨁◯◯◯ Very Low	Critical

[1] Downgraded once as the majority of evidence is at moderate or high risk of bias or downgraded twice as majority of evidence is at very high risk of bias

[2] Downgraded once as I^2 is 50-75% or downgraded twice as I^2 is >75%

[3] Downgraded once due to imprecision as number of studies 5-9 / confidence intervals (CIs) wide or downgraded twice due to imprecision as number of studies < 5 and confidence intervals (CIs) wide

▪ 7. QUALITY APPRAISAL OF INCLUDED STUDIES

			Selection bias			Performanc e bias	Detection bias				Attrition bias		Report Bias	Confoundin g	Other bias			
#	Study ID	Des ign	Compa rable cases & control s	Establi shed case definiti on	Establi shed control definiti on	Groups treated the same	Standard measure ments for exposure	Assess ors blinded to case/co ntrol status	Standard measure ments for outcomes	Outcome s assessed objectivel y + independ ently	% lost to follo w up	% inclu ded in anal ysis	Free of sele ctive outc ome repo rting	Groups similar at baseline	Fundin g/COI reporte d	Suffi cient pow er	Adeq uate stati stica l anal ysis	Ove rall risk
1	Alipour et al., 2019	Case-control	Yes	Partial	Partial	NA	yes	No	yes	Partial	NA	Yes	Yes	Yes	No	Partial	Partial	Mod
2	Ahmadi 2013	Case-control	Yes	Yes	Yes	NA	Yes	NR	Yes	Yes	NA	Yes	Yes	Yes	Yes	NR	Yes	Low
3	Altieri 2013	Case-control	Yes	Yes	Yes	Partial	Partial	No	yes	Yes	No	yes	Partial	yes	Yes	Yes	Yes	Mod
4	Álvarez-Blasco et al., 2011	Case-control	No	Yes	Partial	Yes	Partial	No	Partial	Partial	Yes	No	Yes	Partial	Yes	No	Partial	Mod
5	Amirjani 2019	Cross-sectiona l	Yes	Yes	Yes	NA	Yes	NR	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Low
6	Arusoglu 2020	Case-control	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	Yes	Yes	Yes	NR	Yes	Low
7	Badri-Fariman et al., 2021	Case-control	Yes	Yes	Yes	Partial	Yes	Partial	Yes	Yes	yes	no	yes	yes	Yes	Partial	Partial	Mod
8	Banting 2014	cross-sectiona l	Yes	Yes	Yes	Yes	Yes	Partial	Yes	Yes	no	No	Partial	Partial	Yes	yes	Yes	Mod
9	Barrea 2019	Cross-sectiona l	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	NA	Yes	Yes	NA	Yes	NR	Yes	Mod
10	Bykowska-Derda 2020	Case-control	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
11	Cunha 2019	case control	Yes	Yes	Yes	Partial	Yes	NA	Yes	Yes	NA	no	Partial	Yes	Yes	NR	Yes	Mod
12	Cutillas-Tolín 2021	case-control	Yes	Yes	Yes	Yes	Yes	Partial	Yes	Yes	no	no	Yes	Yes	Yes	No	No	Mod
13	Cutler 2019	cohort study	No	Yes	Yes	Yes	Yes	NA	Yes	Yes	no	no	Yes	Yes	Yes	Yes	Yes	Mod
14	Dantas 2015	Case-control	Yes	Yes	Yes	Yes	Partial	Partial	Yes	Yes	no	no	Yes	Yes	No	Yes	Yes	low
15	DeGiuseppe 2019	Case-control	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	NA	Yes	Yes	Yes	Yes	NR	Yes	Mod
16	Douglas et al., 2006	Cohort study	Yes	Yes	Yes	Partial	Yes	Partial	Yes	Yes	Partial	no	Yes	Yes	No	Partial	Yes	Mod
17	Eslamian et al., 2017	case-control	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	no	no	Partial	Partial	Yes	No	No	High
18	Forslund 2020	Cohort study	Partial	Yes	Yes	Yes	Yes	NR	Yes	Yes	NR	Yes	Yes	Partial	Yes	NR	Yes	Mod
19	Ganie et al., 2019	case-control	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	no	no	Yes	Yes	No	Yes	Yes	Low

20	Gargari 2015	Case-control	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	NA	Yes	Yes	Yes	Yes	NR	Yes	Mod
21	Gopalan et al. 2021	Case-control	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	NA	Yes	Yes	Yes	Yes	NR	No	High
22	Graff 2013	Cross-sectional	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Low
23	Graff 2017	Cross-sectional	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Low
24	Hosseini et al. 2017	case-control	No	Yes	Yes	Partial	yes	No	Partial	Partial	NR	No	Partial	Partial	Yes	Partial	Partial	High
25	Huijgen et al. 2015	Case-cohort	No	Yes	Yes	Partial	Partial	NA	Yes	Yes	no	No	Partial	Yes	Yes	Partial	yes	Mod
26	Jurewicz et al. 2021	case control	Yes	Yes	Yes	Yes	Partial	Partial	Yes	Yes	no	No	No	Yes	No	Yes	yes	Mod
27	Kazemi Jaliseh et al. 2017	case control	Yes	Yes	Yes	Yes	Yes	NA	Yes	Partial	NA	No	Yes	Yes	No	Yes	yes	Low
28	Khademi et al. 2010	case control	No	Yes	Yes	Partial	Partial	NA	No	Yes	no	No	Yes	Yes	Yes	No	Partial	Mod
29	Larsson et al., 2016	case control	No	Yes	Yes	Partial	Yes	No	Partial	Yes	NA	No	Yes	Yes	Yes	No	Partial	Mod
30	Lerchbaum et al., 2021	RCT	No	Yes	Yes	Yes	Yes	NA	No	Yes	no	No	Yes	Yes	Yes	No	Partial	Mod
31	Liang et al., 2021	case control	Yes	Yes	Yes	Yes	Partial	NA	No	Yes	no	No	Yes	Yes	Yes	No	Yes	low
32	Lin et al., 2019	case control	Yes	Yes	Yes	Yes	Yes	NA	No	Yes	no	Yes	No	Yes	Yes	No	Yes	low
33	Lin et al., 2021	Cross-sectional	NA	Yes	NA	NA	Yes	NA	No	Yes	NA	No	Yes	NA	Yes	NR	Yes	Mod
34	Lu et al., 2021	Case-control	Yes	Yes	Yes	yes	yes	NA	No	Yes	NA	NA	Partial	Yes	Yes	NR	Yes	low
35	Mario-2012	Case-control	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	NA	Yes	Yes	Yes	Yes	NR	Yes	Mod
36	Mario-2017	Cross-sectional	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Low
37	Melekoglu et al., 2020	Cross-sectional	No	Partial	Partial	Yes	Yes	No	No	Yes	NA	Yes	NR	No	Yes	NR	Partial	High
38	Misir et al., 2016	Cross-sectional	No	Yes	Yes	Partial	Partial	No	No	Yes	no	No	Yes	Yes	Yes	No	Partial	Mod
39	Navarro-Lafuente et al., 2022	Case-control	Yes	Yes	Yes	No	Yes	Partial	Yes	Yes	no	No	Partial	Yes	No	No	Partial	High
40	Neubronner et al., 2021	Cross-sectional	NA	Yes	NA	NA	Yes	Partial	Yes	Yes	NA	No	Yes	NA	No	NR	Yes	Mod
41	Noormohammadi et al., 2021	Case-control	No	Yes	Yes	Yes	Yes	Partial	Yes	Yes	NA	No	Yes	Yes	Yes	NR	Yes	Mod
42	Orio et al., 2006	Case-control	Yes	Yes	Yes	Yes	Yes	NA	No	No	no	No	No	Yes	No	No	no	High

43	Panjeshahin et al., 2020	Case-control	Yes	Yes	Yes	Yes	Yes	No	No	Yes	yes	Yes	Yes	Yes	No	Yes	yes	Low
44	Pokorska-Niewiada et al., 2021	No	Yes	Yes	Yes	No	No	No	No	Partial	no	No	Partial	Partial	Yes	No	Partial	High
45	Sedighi et al., 2014	Case-control	Yes	Yes	Yes	Partial	Partial	No	No	Partial	NA	No	Partial	Partial	No	Yes	Partial	High
46	Shahdadian et al., 2019	Case-control	Yes	Yes	Yes	Partial	Yes	No	No	Partial	no	No	Partial	Partial	Yes	Partial	Partial	Mod
47	Shishehgar 2016	Case-control	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	NA	Yes	Yes	Yes	Yes	NR	Yes	Mod
48	Shishehgar 2016b	Case-control	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Low
49	Shishehgar et al., 2019	Cross-sectional	Yes	Yes	Yes	Yes	Partial	NA	Yes	Partial	Yes	No	Partial	Partial	Yes	No	yes	Mod
50	Soodi et al., 2021	Case-control	Yes	Yes	Yes	Partial	Yes	NR	Yes	yes	no	No	Partial	Partial	Yes	Yes	yes	Low
51	Szczuko et al., 2021	Case-control	Yes	Yes	Yes	Yes	Partial	No	No	No	Yes	No	yes	Partial	Yes	No	Partial	Mod
52	Thara et al., 2017	Cross-sectional	Yes	No	No	Yes	No	No	No	No	No	No	No	Yes	No	No	no	High
53	Thomson et al., 2009	Cross-sectional	NA	Yes	NA	NA	Yes	NA	Yes	Yes	NA	No	No	NA	No	NR	no	High
54	Toscani 2011a	RCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	Mod
55	Toscani 2011b	Case-control	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	NA	Yes	Yes	Yes	Yes	NR	Yes	Mod
56	Tsai et al., 2013	Case control	No	No	No	Yes	Partial	No	No	Partial	No	No	Partial	Yes	Yes	NR	Partial	Mod
57	Wang et al. 2022	Case-control	No	Yes	Yes	Yes	Yes	NA	Yes	Yes	Yes	No	Partial	Yes	Yes	Yes	yes	Low
58	Wang Oct 2021a	Cross-sectional	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	Mod
59	Wang Sept 2021b	Cohort study	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	Mod
60	Wright et al., 2004	Case-control	Yes	Yes	Yes	Partial	Partial	NA	Yes	Yes	Yes	No	Yes	Partial	No	NR	yes	Mod
61	Zhang 2015	Case-control	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	NA	Yes	Yes	Yes	Yes	NR	Yes	Mod
62	Zhang 2018	Case-control	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	Low
63	Zhang et al., 2020	Cross-sectional	Yes	Yes	Yes	Yes	Yes	NA	No	No	Yes	No	Partial	Yes	Yes	No	Partial	Mod
64	Zirak Sharkesh et al., 2021	case-control	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Partial	Low
65	Eleftheridou et al. 2012	Cross-sectional	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	Partial	Yes	Yes	NR	No	Mod

66	Eleftheridou et al. 2015	Cross-sectional	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	No	Yes	Yes	NR	No	High
67	Kulshreshtha 2022	Cross-sectional	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	No	Low
68	Mizgier 2021	case control	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	Low
69	Mizgier 2022	case control	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	Low
70	Bialka-Koseic 2019	Cross-sectional	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	No	NR	Yes	Low

NR= not reported; NA= not applicable

1. STUDY SELECTION

Table 1. PICO Criteria for Inclusion	
Question	3.5 Why are women with PCOS at increased risk of weight gain? (Intrinsic factors)
Clinical leads (key contacts)	Lisa Moran
Allocation ranking	Level 1 – New systematic review

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(language, year)*
Inclusion	Women with PCOS (NIH 1990, Rotterdam 2003 or AE-PCOS 2006 criteria). No exclusion of age. Note age subgroups, phenotypes or pathological categories (HA or IR).	None	Females without PCOS	1) Extrinsic factors potentially related to challenges with weight management (ie lifestyle factors) a. Dietary intake (energy, glycemic index, glycemic load, protein, fat, carbohydrate) b. Physical activity (Total PA) 2) Intrinsic factors potentially related to challenges with weight management (ie energy homeostasis) a. Energy intake Include - Post meal/OGTT - Ghrelin, GLP1, PYY, Amylin, appetite/satiety/hunger (please only include AUC data) Exclude - fasting, post clamp or post weight loss measures of any above b. Energy expenditure Include – REE, MIT Exclude – RER, metabolic flexibility	Intervention (randomized, non-randomized controlled trials, single arm intervention trials) or observational (i.e., cross-sectional, case-control, cohort) studies	English language. Human studies
Exclusion	None	None	None	None	case reports, commentaries, letters to editor, abstracts.	None

2. SEARCH STRATEGY

Search details	
Search strategy source: Not applicable	
Evidence source	**Date of search (day/month/year)**
Medline (Ovid)	Inception until 22/6/22
Embase	Inception until 22/6/22
PsychInfo	Inception until 22/6/22
AMED	Inception until 22/6/22
CINAHL	Inception until 22/6/22
Any subsequent updates - enter database and date: not applicable	

Questions addressed by this search:		
GDG	Q#	Question
3	3.5	Why are women with PCOS at increased risk of weight gain? Intrinsic factors

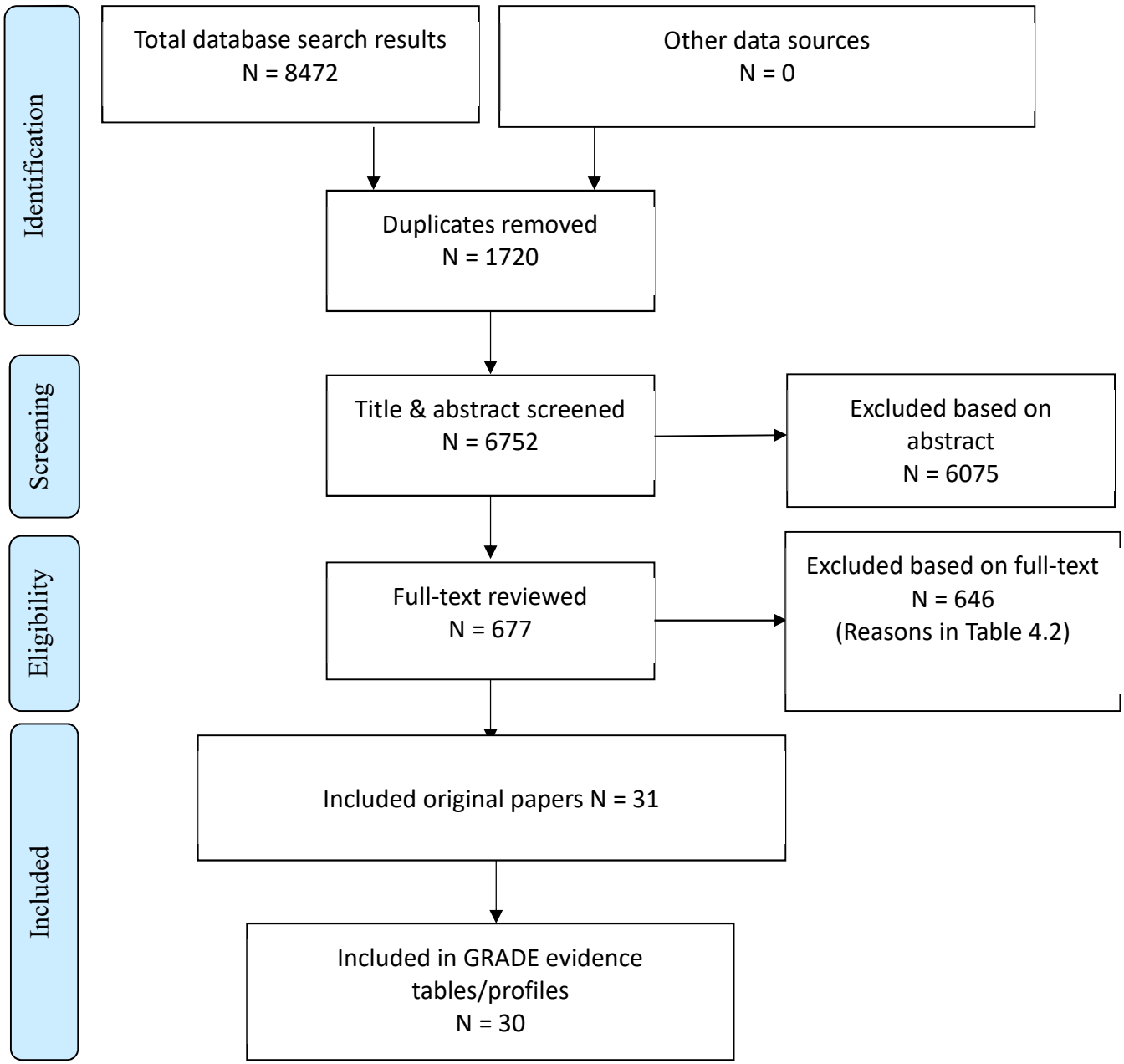
Population	Outcomes	Combined search
1. exp Polycystic Ovary Syndrome/ 2. Polycystic Ovar$.tw. 3. (PCOS or PCOD).tw. 4. (sclerocystic adj3 ovar$).tw. 5. stein leventhal.tw. 6. 5 or/1-4	**General terms for food intake regulation** 7. exp Appetite Regulation/ or exp Appetite/ 8. exp Gastrointestinal Hormones/ 9. appetite.tw. 10. gastrointestinal hormone$.tw. 11. gut peptide$.tw. 12. gut hormone$.tw. 13. gastrointestinal peptide$.tw. 14. GI hormone$.tw. 15. GI peptide$.tw. **General terms for energy expenditure** 16. exp Thermogenesis/ or exp Energy Metabolism/ 17. exp Basal Metabolism/ 18. exp Calorimetry, Indirect/ 19. exp Lipid Metabolism/ or exp Carbohydrate Metabolism/ 20. metab$ rate.tw. 21. (basal adj4 metab$).tw. 22. (resting adj4 metab$).tw. 23. BMR.tw. 24. (energy adj4 metab$).tw. 25. metab$ flexib$.tw. 26. metab$ inflexib$.tw. 27. (lipid adj3 oxidation).tw. 28. (fatty acid adj3 oxidation).tw. 29. (amino acid adj3 oxidation).tw. 30. (glucose adj3 oxidation).tw. 31. (fat adj3 oxidation).tw. 32. (protein adj3 oxidation).tw. 33. (carbohydrate adj3 oxidation).tw. 34. (postprandial adj3 oxidation).tw. 35. thermogenesis.tw. 36. respiratory quotient.tw. 37. respiratory coefficient.tw. 38. respiratory ratio.tw. 39. RQ.tw. 40. calorimet$.tw. 41. energy expend$.tw. 42. TEE.tw.	128. 6 and 127 129. exp animals/ not humans.sh. 130. 128 not 129

	43. TDEE.tw. 44. EE.tw. 45. doubl$ label$ water.tw. 46. DLW.tw. 47. (isotopic$ adj2 water).tw. **Orexigenic GI hormones with an established acute effect on appetite** 48. exp Ghrelin/ 49. ghrelin.tw. 50. (orexigenic adj4 hormone$).tw. 51. exp Cholecystokinin/ 52. exp Peptide YY/ 53. exp Pancreatic Polypeptide/ 54. exp Oxyntomodulin/ 55. exp Glucagon-Like Peptide 1/ 56. exp Gastric Inhibitory Polypeptide/ 57. exp Islet Amyloid Polypeptide/ **Anorexigenic GI hormones with an established acute effect on appetite** 58. cholecystokinin.tw. 59. CCK.tw. 60. pancreozymin.tw. 61. peptide YY.tw. 62. PYY.tw. 63. peptide tyrosine tyrosine.tw. 64. pancreatic peptide YY.tw. 65. pancreatic polypeptide.tw. 66. PP.tw. 67. oxyntomodulin.tw. 68. OXM.tw. 69. glucagon like peptide 1.tw. 70. GLP 1.tw. 71. gastric inhibitory polypeptide.tw. 72. gastric inhibitory peptide.tw. 73. GIP.tw. 74. glucose dependent insulinotropic polypeptide.tw. 75. amylin.tw. 76. islet amyloid polypeptide.tw. 77. IAPP.tw. 78. (anorexigenic adj4 hormone$).tw. 79. incretin$.tw. **Orexigenic neuropeptides with an established acute effect on appetite** 80. exp Orexins/ 81. exp Neuropeptide Y/ 82. exp Agouti-Related Protein/ 83. orexin$.tw. 84. hypocretin$.tw. 85. neuropeptide Y.tw. 86. NPY.tw. 87. agouti related p$.tw. 88. AgRP.tw. 89. melanin concentrating hormone.tw. 90. (orexigenic adj4 neuropeptide$).tw. **Anorexigenic neuropeptides with an established acute effect on appetite** 91. exp Pro-Opiomelanocortin/ 92. exp Melanocyte-Stimulating Hormones/ 93. pro-opiomelanocortin.tw. 94. proopiomelanocortin.tw. 95. POMC.tw. 96. melanocyte stimulating hormone$.tw.	

	97. MSH.tw. 98. melanotropin$.tw. 99. intermedin$.tw. 100. (cocaine adj2 amphetamine regulated transcript).tw. 101. CART.tw. 102. nesfatin 1.tw 103. (anorexigenic adj4 neuropeptide$).tw. **Adipokines with established links in long-term energy storage and emerging roles in the short term regulation of food (inhibits intake)** 104. exp Leptin/ 105. leptin.tw. **Adipokines with established links in long-term energy storage and emerging roles in the short term regulation of food (stimulates intake)** 106. exp Adiponectin/ 107. adiponectin.tw. **Central nervous system imaging techniques that can be used to understand the neuroendocrine actions/effects in PCOS** 108. exp Functional Neuroimaging/ 109. functional neuroimaging.tw. 110. functional magnetic resonance imaging.tw. 111. functional MRI.tw. 112. fMRI.tw. 113. functional brain imag$.tw. 114. BOLD.tw. 115. blood oxygen level dependen$.tw. 116. functional imag$.tw. 117. oxyhaemoglobin.tw. 118. oxyhemoglobin.tw. 119. deoxyhaemoglobin.tw. 120. deoxyhemoglobin.tw. **Subjective measures of appetite** 121. hunger.tw. 122. satiety.tw. 123. satiation.tw. 124. fullness.tw. 125. crav$.tw. 126. desire to eat.tw. 127. or/7-126	

Evidence processing: Studies were selected and appraised by two reviewers using study selection and appraisal criteria (PICO above) established a priori. The articles were reviewed by title and abstract by two reviewers. When a decision could not be made based on title and abstract alone, full text was retrieved. **In total, 30 studies met inclusion criteria for this review.**

3. SEARCH RESULTS - PRISMA flowchart



4. STUDY INCLUSION

4.1 Included studies

1. Arusoglu G, Koksal G, Cinar N, Tapan S, Aksoy DY, Yildiz BO. Basal and meal-stimulated ghrelin, PYY, CCK levels and satiety in lean women with polycystic ovary syndrome: effect of low-dose oral contraceptive. J Clin Endocrinol Metab. 2013 Nov;98(11):4475-82. doi: 10.1210/jc.2013-1526. Epub 2013 Sep 3. PMID: 24001751.
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3. Barber TM, Casanueva FF, Karpe F, Lage M, Franks S, McCarthy MI, Wass JA. Ghrelin levels are suppressed and show a blunted response to oral glucose in women with polycystic ovary syndrome. Eur J Endocrinol. 2008 Apr;158(4):511-6. doi: 10.1530/EJE-07-0683. PMID: 18362298.
4. Cosar E, Köken G, Sahin FK, Akgün L, Uçok K, Genç A, Yilmazer M. Resting metabolic rate and exercise capacity in women with polycystic ovary syndrome. Int J Gynaecol Obstet. 2008 Apr;101(1):31-4. doi: 10.1016/j.ijgo.2007.10.011. Epub 2008 Feb 20. PMID: 18082748.
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6. Doh E, Mbanya A, Kemfang-Ngowa JD, Dohbit S, Tchana-Sinou M, Foumane P, Donfack OT, Doh AS, Mbanya JC, Sobngwi E. The Relationship between Adiposity and Insulin Sensitivity in African Women Living with the Polycystic Ovarian Syndrome: A Clamp Study. Int J Endocrinol. 2016;2016:9201701. doi: 10.1155/2016/9201701. Epub 2016 Sep 8. PMID: 27672393; PMCID: PMC5031834.
7. Gama R, Norris F, Wright J, Morgan L, Hampton S, Watkins S, Marks V. The entero-insular axis in polycystic ovarian syndrome. Ann Clin Biochem. 1996 May;33 (Pt 3):190-5. doi: 10.1177/000456329603300303. PMID: 8791980.
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9. Glintborg D, Mumm H, Holst JJ, Andersen M. Effect of oral contraceptives and/or metformin on GLP-1 secretion and reactive hypoglycaemia in polycystic ovary syndrome. Endocr Connect. 2017 May;6(4):267-277. doi: 10.1530/EC-17-0034. Epub 2017 Apr 21. PMID: 28432082; PMCID: PMC5457494.
10. Graff SK, Mário FM, Alves BC, Spritzer PM. Dietary glycemic index is associated with less favorable anthropometric and metabolic profiles in polycystic ovary syndrome women with different phenotypes. Fertil Steril. 2013 Oct;100(4):1081-8. doi: 10.1016/j.fertnstert.2013.06.005. Epub 2013 Jul 2. PMID: 23830153.
11. Graff SK, Mario FM, Magalhães JA, Moraes RS, Spritzer PM. Saturated Fat Intake Is Related to Heart Rate Variability in Women with Polycystic Ovary Syndrome. Ann Nutr Metab. 2017;71(3-4):224-233. doi: 10.1159/000484325. Epub 2017 Nov 14. PMID: 29136632.
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15. Japur CC, Diez-Garcia RW, de Oliveira Penaforte FR, das Graças Pena G, de Araújo LB, de Sá MFS. Insulin, ghrelin and early return of hunger in women with obesity and polycystic ovary syndrome. Physiol Behav. 2019 Jul 1;206:252-258. doi: 10.1016/j.physbeh.2019.03.013. Epub 2019 Mar 17. PMID: 30894307.
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4.2 Excluded studies (after full text review)			
Title	**Authors**	**Year**	**Reasons**
The effect of bariatric surgery on inflammatory markers in women with polycystic ovarian syndrome	Abiad, F.; Khalife, D.; Safadi, B.; Alami, R.; Awwad, J.; Khalifeh, F.; Ghazeeri, G.	2018	Non energy homeostasis
Lipid Accumulation Product (LAP) and Visceral Adiposity Index (VAI) as Markers of Insulin Resistance and Metabolic Associated Disturbances in Young Argentine Women with Polycystic Ovary Syndrome	Abruzzese, G. A.; Cerrrone, G. E.; Gamez, J. M.; Graffigna, M. N.; Belli, S.; Lioy, G.; Mormandi, E.; Otero, P.; Levalle, O. A.; Motta, A. B.	2017	No outcomes of interest
Increased chemerin serum levels in hyperandrogenic and normoandrogenic women from Argentina with polycystic ovary syndrome	Abruzzese, G. A.; Gamez, J.; Belli, S. H.; Levalle, O. A.; Mormandi, E.; Otero, P.; Graffigna, M. N.; Cerrone, G. E.; Motta, A. B.	2020	No outcomes of interest
Normal metabolic flexibility despite insulin resistance women with polycystic ovary syndrome	Adamska, Agnieszka; Karczewska-Kupczewska, Monika; Nikolajuk, Agnieszka; Otziomek, Elzbieta; GÃ³rska, Maria; Kowalska, Irina; Straczkowski, Marek	2013	no outcome of interest
Plasma nesfatin-1 levels are increased in patients with polycystic ovary syndrome	Ademoglu, E. N.; Gorar, S.; Carlioglu, A.; Yazici, H.; Dellal, F. D.; Berberoglu, Z.; Akdeniz, D.; Uysal, S.; Karakurt, F.	2014	Non energy homeostasis
Metformin reduces arterial stiffness and improves endothelial function in young women with polycystic ovary syndrome: a randomized, placebo-controlled, crossover trial	Agarwal, N.; Rice, S. P.; Bolusani, H.; Luzio, S. D.; Dunseath, G.; Ludgate, M.; Rees, D. A.	2010	Non energy homeostasis
Hyperandrogenism, Insulin Resistance, and Acanthosis Nigricans (HAIR-AN) Syndrome Reflects Adipose Tissue Dysfunction ("Adiposopathy" or "Sick Fat") in Asian Indian Girls	Agrawal, K.; Mathur, R.; Purwar, N.; Mathur, S. K.; Mathur, D. K.	2021	Duplicate
Hyperandrogenism, Insulin Resistance, and Acanthosis Nigricans (HAIR-AN) Syndrome Reflects Adipose Tissue Dysfunction ("Adiposopathy" or "sick Fat") in Asian Indian Girls	Agrawal, K.; Mathur, R.; Purwar, N.; Mathur, S. K.; Mathur, D. K.	2021	Non energy homeostasis
Altered serum marker of adipokines profile in breast cancer women	Ahmed, S. E.; Sarhat, E. R.; Awni, N.; Sarhat, T.; Abass, K. S.	2021	Non energy homeostasis
Retinol-binding protein 4 in polycystic ovary syndrome-association with steroid hormones and response to pioglitazone treatment	Aigner, E.; Bachofner, N.; Klein, K.; De Geyter, C.; Hohla, F.; Patsch, W.; Datz, C.	2009	Non energy homeostasis
The effects of high intensity-interval training on vaspin, adiponectin and leptin levels in women with polycystic ovary syndrome	Aktas, H. S.; Uzun, Y. E.; Kutlu, O.; Pence, H. H.; Ozcelik, F.; Cil, E. O.; Irak, L.; Altun, O.; Ozcan, M.; Ozsoy, N.; Aydin Yoldemir, S.; Kalyon, S.; Arman, Y.; Tukek, T.	2019	Non energy homeostasis
The effects of high intensity-interval training on vaspin, adiponectin and leptin levels in women with polycystic ovary syndrome	Aktas, H. S.; Uzun, Y. E.; Kutlu, O.; Pence, H. H.; Ozcelik, F.; Cil, E. O.; Irak, L.; Altun, O.; Ozcan, M.; Ozsoy, N.; Aydin Yoldemir, S.; Kalyon, S.; Arman, Y.; Tukek, T.	2022	Non energy homeostasis

The high-molecular weight multimer form of adiponectin is a useful marker of polycystic ovary syndrome in Bahraini Arab women	Al-Awadi, A. M.; Sarray, S.; Arekat, M. R.; Saleh, L. R.; Mahmood, N.; Almawi, W. Y.	2016	Non energy homeostasis
Effects of supervised aerobic training on the levels of anti-Mullerian hormone and adiposity measures in women with normo-ovulatory and polycystic ovary syndrome	Al-Eisa, E.; Gabr, S. A.; Alghadir, A. H.	2017	Non energy homeostasis
Comparison of serum adiponectin and osteopontin levels along with metabolic risk factors between obese and lean women with and without PCOS	Alatas, Suleyman Erkan; Dogu, Sevilay Yavuz; Kilic, Derya; Guler, Tolga	2020	Non energy homeostasis
Is prolactin the missing link in adipose tissue dysfunction of polycystic ovary syndrome patients?	Albu, A.; Florea, S.; Fica, S.	2016	Non energy homeostasis
The association between serum nesfatin-1 level and bmi in iraqi patients with polycystic ovary syndrome (Pcos)	Ali, E. A.; Al-Jedda, W. A.; Al-Khateeb, S. M. J.; Al-Samarriae, A. Y.	2021	Non energy homeostasis
Serum irisin and leptin levels in obese and non-obese women with polycystic ovary syndrome with reference to glucose homeostasis	Ali, S. H.; Al-Nuaimi, A. M. A.; Al-Musawi, B. J.	2016	Non energy homeostasis
Roles of circulating WNT-signaling proteins and WNT-inhibitors in human adiposity, insulin resistance, insulin secretion, and inflammation	Almario, R. U.; Karakas, S. E.	2015	Non energy homeostasis
Effects of High Intensity Interval Training and Strength Training on Metabolic, Cardiovascular and Hormonal Outcomes in Women with Polycystic Ovary Syndrome: A Pilot Study	Almenning, I.; Rieber-Mohn, A.; Lundgren, K. M.; Shetelig Lovvik, T.; Garnaes, K. K.; Moholdt, T.	2015	Non energy homeostasis
Nesfatin-1 levels and metabolic markers in polycystic ovary syndrome	Alp, E.; Gormus, U.; Guducu, N.; Bozkurt, S.	2015	Non energy homeostasis
Nesfatin-1 levels in polycystic ovary syndrome	Alp, E.; Gormus, U.; Guducu, N.; Timirci Kahraman, O.; Bozkurt, S.	2014	Abstract
Serum leptin and body composition in polycystic ovarian syndrome	Alper, T.; Kahraman, H.; Cetinkaya, M. B.; Yanik, F.; Akcay, G.; Bedir, A.; Malatyalioglu, E.; Kokcu, A.	2004	Non energy homeostasis
Insulin sensitivity affects corticolimbic brain responses to visual food cues in polycystic ovary syndrome patients	Alsaadi, Hanin M.; Van Vugt, Dean A.	2015	no outcome of interest
Homocysteine and ghrelin link with polcystic ovary syndrome in relation to obesity	Altug Sen, T.; Koken, R.; Narci, A.; Yilmazer, M.	2011	Non energy homeostasis
Effects of oral contraceptives on serum concentrations of adipokines and adiposity indices of women with polycystic ovary syndrome: a randomized controlled trial	Amiri, M.; Rahmati, M.; Hedayati, M.; Nahidi, F.; Ramezani Tehrani, F.	2020	Non energy homeostasis
Effects of oral contraceptives on serum concentrations of adipokines and adiposity indices of women with polycystic ovary syndrome: a randomized controlled trial	Amiri, M.; Rahmati, M.; Hedayati, M.; Nahidi, F.; Ramezani Tehrani, F.	2021	Non energy homeostasis
Metformin treatment increases PYY levels in some women with PCOS	Anonymous,	2008	Wrong design
Plasma adiponectin and insulin resistance in women with polycystic ovary syndrome	Ardawi, M. S. M.; Rouzi, A. A.	2005	Non energy homeostasis
Serum resistin and adiponectin levels in young non-obese women with polycystic ovary syndrome	Arikan, S.; Bahceci, M.; Tuzcu, A.; Kale, E.; Gokalp, D.	2010	Non energy homeostasis
Metabolic and hormonal changes induced by pioglitazone in polycystic ovary syndrome: a randomized, placebo-controlled clinical trial	Aroda, V. R.; Ciaraldi, T. P.; Burke, P.; Mudaliar, S.; Clopton, P.; Phillips, S.; Chang, R. J.; Henry, R. R.	2009	Non energy homeostasis

Circulating and cellular adiponectin in polycystic ovary syndrome: relationship to glucose tolerance and insulin action	Aroda, V.; Ciaraldi, T. P.; Chang, S. A.; Dahan, M. H.; Chang, R. J.; Henry, R. R.	2008	Non energy homeostasis
Adiponectin gene expression in human granulosa cells of women with PCOS	Artimani, T.; Aflatoonian, R.; Saidijam, M.; Amiri, I.; Yavangi, M.; Shabab, N.; Ashrafi, M.; Mehdizadeh, M.	2013	Abstract
Downregulation of adiponectin system in granulosa cells and low levels of HMW adiponectin in PCOS	Artimani, T.; Saidijam, M.; Aflatoonian, R.; Ashrafi, M.; Amiri, I.; Yavangi, M.; SoleimaniAsl, S.; Shabab, N.; Karimi, J.; Mehdizadeh, M.	2016	Non energy homeostasis
Association between nuclear receptors of estrogen and progesterone with adiponectin receptors in granulosa cells of patients with poly cystic ovary syndrome	Artimani, T.; Saidijam, M.; Amiri, I.; Aflatoonian, R.; Ashrafi, M.; Shabab, N.; Soleimani Asl, S.; Mehdizadeh, M.	2015	Abstract
The Use of SenseWear Armband for Assessment of Daily Energy Expenditure and the Relation to Body Fat Distribution and Nutritional Intake in Lean Women with Polycystic Ovary Syndrome	Arusoglu, G.	2020	No outcomes of interest
Decreased levels of liver-expressed antimicrobial peptide-2 and ghrelin are related to insulin resistance in women with polycystic ovary syndrome	Aslanipour, B.; Alan, M.; Demir, I.	2020	Non energy homeostasis
Serum levels of leptin and homocysteine in women with polycystic ovary syndrome and its relationship to endocrine, clinical and metabolic parameters	Atamer, A.; Demir, B.; Bayhan, G.; Atamer, Y.; Ilhan, N.; Akkus, Z.	2008	Non energy homeostasis
Increase in subcutaneous adipose tissue and fat free mass in women with polycystic ovary syndrome is related to impaired insulin sensitivity	Aydogdu, A.; Tasci, I.; Kucukerdonmez, O.; Tapan, S.; Aydogdu, S.; Aydogan, U.; Sonmez, A.; Yazici, M.; Azal, O.	2013	Non energy homeostasis
Women with polycystic ovary syndrome have increased plasma chitotriosidase activity: a pathophysiological link between inflammation and impaired insulin sensitivity?	Aydogdu, A.; Tasci, I.; Tapan, S.; Sonmez, A.; Aydogan, U.; Akbulut, H.; Uckaya, G.; Aydogdu, S.; Basaran, Y.; Meric, C.; Taslipinar, A.; Kurt, I.; Azal, O.	2012	Non energy homeostasis
The relationship of epicardial adipose tissue thickness to clinical and biochemical features in women with polycystic ovary syndrome	Aydogdu, A.; Uckaya, G.; Tasci, I.; Baysan, O.; Tapan, S.; Bugan, B.; Serdar, M.; Akbulut, H.; Aydogan, U.; Sonmez, A.; Aydogdu, S.; Kutlu, M.	2012	Non energy homeostasis
Adverse metabolic phenotype of adolescent girls with non-alcoholic fatty liver disease plus polycystic ovary syndrome compared with other girls and boys	Ayonrinde, O. T.; Adams, L. A.; Doherty, D. A.; Mori, T. A.; Beilin, L. J.; Oddy, W. H.; Hickey, M.; Sloboda, D. M.; Olynyk, J. K.; Hart, R.	2016	Non energy homeostasis
Prevalence and significance of nonalcoholic fatty liver disease in adolescent girls with polycystic ovary syndrome	Ayonrinde, O. T.; Adams, L. A.; Doherty, D.; Olynyk, J. K.; Mori, T. A.; Beilin, L. J.; Oddy, W. H.; Hickey, M.; Sloboda, D.; Hart, R.	2011	Abstract
Cinnamon improves metabolic factors without detectable effects on adiponectin in women with polycystic ovary syndrome	Azam Borzoei; Maryam Rafraf; Mohammad Asghari-Jafarabadi	2018	No control group
Association between polycystic ovary syndrome and female-to-male transsexuality	Baba, T.; Endo, T.; Honnma, H.; Kitajima, Y.; Hayashi, T.; Ikeda, H.; Masumori, N.; Kamiya, H.; Moriwaka, O.; Saito, T.	2007	Non energy homeostasis
The contributions of resistin and adiponectin gene single nucleotide polymorphisms to the genetic risk for polycystic ovary syndrome in a Japanese population	Baba, T.; Endo, T.; Sata, F.; Nagasawa, K.; Honnma, H.; Kitajima, Y.; Hayashi, T.; Manase,	2009	Non energy homeostasis

	K.; Kanaya, M.; Moriwaka, O.; Kamiya, H.; Yamada, H.; Minakami, H.; Kishi, R.; Saito, T.		
Serum leptin levels in polycystic ovary syndrome and its relationship with metabolic and hormonal profile in Pakistani females	Baig, M.; Rehman, R.; Tariq, S.; Fatima, S. S.	2014	Non energy homeostasis
Type 2 diabetes and cardiovascular risks are present in adolescent girls with polycystic ovaries morphology	Bak, M. I.; Walewska-Wolf, M.; Szufladowicz-Wozniak, J.	2013	Abstract
Association of PPARG Pro12Ala polymorphism with insulin sensitivity and body mass index in patients with polycystic ovary syndrome	Baldani, D. P.; Skrgatic, L.; Cerne, J. Z.; Ferk, P.; Simunic, V.; Gersak, K.	2014	Non energy homeostasis
Altered leptin, adiponectin, resistin and ghrelin secretion may represent an intrinsic polycystic ovary syndrome abnormality	Baldani, D. P.; Skrgatic, L.; Kasum, M.; Zlopasa, G.; Kralik Oguic, S.; Herman, M.	2019	Non energy homeostasis
Serum visfatin and adiponectin - markers in women with polycystic ovarian syndrome	Bannigida, D. M.; Nayak, S. B.; R, V.	2020	Non energy homeostasis
Neuropeptide Y, leptin, galanin and insulin in women with polycystic ovary syndrome	Baranowska, B.; Radzikowska, M.; Wasilewska-Dziubinska, E.; Kaplinski, A.; Roguski, K.; Plonowski, A.	1999	Non energy homeostasis
Serum levels of retinol-binding protein 4 and adiponectin in women with polycystic ovary syndrome: associations with visceral fat but no evidence for fat mass-independent effects on pathogenesis in this condition	Barber, T. M.; Hazell, M.; Christodoulides, C.; Golding, S. J.; Alvey, C.; Burling, K.; Vidal-Puig, A.; Groome, N. P.; Wass, J. A.; Franks, S.; McCarthy, M. I.	2008	Non energy homeostasis
The impact of metformin treatment on adiponectin and resistin levels in women with polycystic ovary syndrome: a prospective clinical study	Basios, G.; Trakakis, E.; Chrelias, Ch; Panagopoulos, P.; Vaggopoulos, V.; Skarpas, P.; Kassanos, D.; Dimitriadis, G.; Hatziagelaki, E.	2015	Non energy homeostasis
The effect of combined oral contraceptives on adiponectin and resistin plasma levels in women with polycystic ovary syndrome	Basios, G.; Ytrakakis, E.; Panagopoulos, P.; Vaggopoulos, V.; Hatziagelaki, E.; Chrelias, C.; Dimitriadis, G.; Kassanos, D.	2014	Abstract
Il-6 serum levels and production is related to an altered immune response in polycystic ovary syndrome girls with insulin resistance	Batetta, B.; Fulghesu, A. M.; Sanna, F.; Uda, S.; Magnini, R.; Portoghese, E.	2011	Non energy homeostasis
Endothelial function varies according to insulin resistance disease type	Beckman, J. A.; Goldfine, A. B.; Dunaif, A.; Gerhard-Herman, M.; Creager, M. A.	2007	Non energy homeostasis
The associations between serum concentrations of irisin and glucose-dependent insulinotropic polypeptide with body mass index among women with and without polycystic ovary syndrome	Behboudi-Gandevani, S.; Hedayati, M.; Mansournia, M. A.; Nazemipour, M.; Rahmati, M.; Tehrani, F. R.	2021	Non energy homeostasis
The association between polycystic ovary syndrome, obesity, and the serum concentration of adipokines	Behboudi-Gandevani, S.; Ramezani Tehrani, F.; Bidhendi Yarandi, R.; Noroozzadeh, M.; Hedayati, M.; Azizi, F.	2017	Non energy homeostasis
Effect of rosiglitazone on insulin resistance, growth factors, and reproductive disturbances in women with polycystic ovary syndrome	Belli, S. H.; Graffigna, M. N.; Oneto, A.; Otero, P.; Schurman, L.; Levalle, O. A.	2004	Non energy homeostasis
Serum spexin, adiponectin and leptin levels in polycystic ovarian syndrome in association with FTO gene polymorphism	Beyazit, F.; Hiz, M. M.; Turkon, H.; Unsal, M. A.	2021	Non energy homeostasis
Circulating insulin-like peptide 5 levels and its association with metabolic and hormonal parameters in women with polycystic ovary syndrome	Bicer, M.; Alan, M.; Alarslan, P.; Guler, A.; Kocabas, G. U.; Imamoglu, C.; Aksit, M.;	2019	No outcomes of interest

	Bozkaya, G.; Isil, A. M.; Baloglu, A.; Aslanipoiur, B.; Calan, M.		
Elevated circulating levels of secreted frizzled-related protein 4 in relation to insulin resistance and androgens in women with polycystic ovary syndrome	Bicer, M.; Alarslan, P.; Guler, A.; Demir, I.; Aslanipour, B.; Calan, M.	2020	No outcomes of interest
Serum ghrelin, leptin and resistin levels in adolescent girls with polycystic ovary syndrome	Bideci, A.; Camurdan, M. O.; Yesilkaya, E.; Demirel, F.; Cinaz, P.	2008	Non energy homeostasis
Pro12Ala PPAR gamma2 gene polymorphism in PCOS women: the role of compounds regulating satiety	Bidzinska-Speichert, B.; Lenarcik, A.; Tworowska-Bardzinska, U.; Slezak, R.; Bednarek-Tupikowska, G.; Milewicz, A.	2012	Non energy homeostasis
The relationship between metabolic status and levels of adiponectin and ghrelin in lean women with polycystic ovary syndrome	Bik, W.; Baranowska-Bik, A.; Wolinska-Witort, E.; Chmielowska, M.; Martynska, L.; Baranowska, B.	2007	Non energy homeostasis
Plasma levels of Nesfatin-1 in patients with polycystic ovary sydrome	Binnetoglu, E.; Erbag, G.; Gencer, M.; Turkon, H.; Asik, M.; Gunes, F.; Sen, H.; Vural, A.; Ukinc, K.	2014	Non energy homeostasis
The effects of different therapeutic modalities on cardiovascular risk factors in women with polycyst[latin dotless i]c ovary syndrome: a random[latin dotless i]zed controlled study	Bodur, S.; Dundar, O.; Kanat-Pektas, M.; Kinci, M. F.; Tutuncu, L.	2018	Non energy homeostasis
Ovarian Expression of Adipokines in Polycystic Ovary Syndrome: A Role for Chemerin, Omentin, and Apelin in Follicular Growth Arrest and Ovulatory Dysfunction?	Bongrani, A.; Mellouk, N.; Rame, C.; Cornuau, M.; Guerif, F.; Froment, P.; Dupont, J.	2019	Non energy homeostasis
High androgen concentrations in follicular fluid of polycystic ovary syndrome women	Bongrani, A.; Plotton, I.; Mellouk, N.; Rame, C.; Guerif, F.; Froment, P.; Dupont, J.	2022	Non energy homeostasis
HPA axis function in obese women with PCOS	Bozic, I.; Macut, D.; Popovic, B.; Isailovic, T.; Bogavac, T.; Petakov, M.; Ognjanovic, S.; Damjanovic, S.	2010	Abstract
Metabolic and hormonal consequencies of the "obesity risk" MC4R variant (rs12970134) in Czech women	Bradnova, O.; Vejrazkova, D.; Vankova, M.; Lukasova, P.; Vcelak, J.; Stanicka, S.; Dvorakova, K.; Bendlova, B.	2015	Non energy homeostasis
Assessing Energy Requirements in Women With Polycystic Ovary Syndrome: A Comparison Against Doubly Labeled Water	Broskey, Nicholas T.; Klempel, Monica C.; Gilmore, L. Anne; Sutton, Elizabeth F.; Altazan, Abby D.; Burton, Jeffrey H.; Ravussin, Eric; Redman, Leanne M.	2017	no outcome of interest
Metabolic inflexibility in women with PCOS is similar to women with type 2 diabetes	Broskey, Nicholas T.; Tam, Charmaine S.; Sutton, Elizabeth F.; Altazan, Abby D.; Burton, Jeffrey H.; Ravussin, Eric; Redman, Leanne M	2018	no outcome of interest
Bidirectional Mendelian randomization to explore the causal relationships between body mass index and polycystic ovary syndrome	Brower, M. A.; Hai, Y.; Jones, M. R.; Guo, X.; Chen, Y. D. I.; Rotter, J. I.; Krauss, R. M.; Legro, R. S.; Azziz, R.; Goodarzi, M. O.	2019	No outcomes of interest
Effects of exercise and nutritional counseling in women with polycystic ovary syndrome	Bruner, Brenda; Chad, Karen; Chizen, Donna	2006	No control group

Serum immunoreactive leptin concentrations in women with polycystic ovary syndrome	Brzechffa, P. R.; Jakimiuk, A. J.; Agarwal, S. K.; Weitsman, S. R.; Buyalos, R. P.; Magoffin, D. A.	1996	Non energy homeostasis
The effects of drospirenone-ethinyl estradiol and drospirenone-ethinyl estradiol + metformin on ovarian ultrasonographic markers, body fat mass index, leptin, and ghrelin	Cakiroglu, Y.; Vural, B.; Isgoren, S.	2013	Non energy homeostasis
Association of decreased c1q/tumor necrosis factor-related protein-5 levels with metabolic and hormonal disturbance in polycystic ovary syndrome	Calan, M.; Alan, M.; Alarslan, P.; Kocabas, G. U.; Bozkaya, G.; Acara, A. C.; Aslanipour, B.; Fenercioglu, O.; Isil, A. M.; Guler, A.	2019	No outcomes of interest
Dlk1 and nesfatin-1 levels and the relationship with metabolic parameters in polycystic ovary syndrome: Prospective, controlled study	Caltekin, M. D.; Caniklioglu, A.; Yalcin, S. E.; Kirmizi, D. A.; Baser, E.; Yalvac, E. S.	2021	Non energy homeostasis
[Leptin in patients with polycystic ovary syndrome. Direct correlation with insulin resistance]	Calvar, C. E.; Intebi, A. D.; Bengolea, S. V.; Hermes, R.; Spinedi, E.	2003	Non English
M30 does not predict the severity of hepatosteatosis, whereas adiponectin level declined with increase of ALT and the severity of hepatic steatosis	Caner, S.; Altinbas, A.; Sayki, M.; Buyukcam, F.; Yilmaz, B.; Cakal, E.; Coban, S.; Delibasi, T.	2014	Non energy homeostasis
Insulin resistance and its relationship with high molecular weight adiponectin in adolescents with polycystic ovary syndrome and a maternal history of polycystic ovary syndrome	Cankaya, S.; Demir, B.; Aksakal, S. E.; Dilbaz, B.; Demirtas, C.; Goktolga, U.	2014	Non energy homeostasis
Polycystic ovary syndrome associated with increased adiposity interferes with serum levels of TNF-alpha and IL-6 differently from leptin and adiponectin	Cardoso, N. S.; Ribeiro, V. B.; Dutra, S. G. V.; Ferriani, R. A.; Gastaldi, A. C.; Araujo, J. E.; Souza, H. C. D.	2020	Non energy homeostasis
Circulating levels of adipose products and differences in fat distribution in the ovulatory and anovulatory phenotypes of polycystic ovary syndrome	Carmina, E.; Bucchieri, S.; Mansueto, P.; Rini, G.; Ferin, M.; Lobo, R. A.	2009	Non energy homeostasis
Subcutaneous and omental fat expression of adiponectin and leptin in women with polycystic ovary syndrome	Carmina, E.; Chu, M. C.; Moran, C.; Tortoriello, D.; Vardhana, P.; Tena, G.; Preciado, R.; Lobo, R.	2008	Non energy homeostasis
Evidence that insulin and androgens may participate in the regulation of serum leptin levels in women	Carmina, E.; Ferin, M.; Gonzalez, F.; Lobo, R. A.	1999	Non energy homeostasis
Evidence for altered adipocyte function in polycystic ovary syndrome	Carmina, E.; Orio, F.; Palomba, S.; Cascella, T.; Longo, R. A.; Colao, A. M.; Lombardi, G.; Lobo, R. A.	2005	Non energy homeostasis
Endothelial dysfunction in PCOS: role of obesity and adipose hormones	Carmina, E.; Orio, F.; Palomba, S.; Longo, R. A.; Cascella, T.; Colao, A.; Lombardi, G.; Rini, G. B.; Lobo, R. A.	2006	Non energy homeostasis
Biomarkers and insulin sensitivity in women with Polycystic Ovary Syndrome: Characteristics and predictive capacity	Cassar, S.; Teede, H. J.; Harrison, C. L.; Joham, A. E.; Moran, L. J.; Stepto, N. K.	2015	Non energy homeostasis
NUCB2/nesfatin-1 in the blood and follicular fluid in patients with polycystic ovary syndrome and poor ovarian response	Catak, Z.; Yavuzkir, S.; Kocdemir, E.; Ugur, K.; Yardim, M.; Sahin, I.; Agirbas, E. P.; Aydin, S.	2019	Non energy homeostasis
Serum FSH level is lower in dysovulating than in ovulating non-PCOS obese women, independently of body mass index	Catteau-Jonard, S.; Brunel, A.; Dumont, A.; Robin, G.; Pigny, P.; Dewailly, D.	2019	Wrong population
Evaluation of new adipocytokines and insulin resistance in adolescents with polycystic ovary syndrome	Cekmez, F.; Cekmez, Y.; Pirgon, O.; Canpolat, F. E.; Aydinoz, S.; Ipcioglu, O. M.; Karademir, F.	2011	Non energy homeostasis

Patatin-like phospholipase domain containing 3-gene (adiponutrin), preptin, kisspeptin and amylin regulates oocyte developmental capacity in PCOS	Celik, N.; Aydin, S.; Ugur, K.; Yardim, M.; Acet, M.; Yavuzkir, S.; Sahin, I.; Celik, O.	2018	Non energy homeostasis
Investigation of taste function and eating behavior in women with polycystic ovary syndrome.	Cetik S, Acikgoz A, Yildiz BO.		Non energy homeostasis
Investigation of taste function and eating behavior in women with polycystic ovary syndrome	Cetik, Sila; Acikgoz, Aylin; Yildiz, Bulent Okan	2022	No outcomes of interest
The prevalence of polycystic ovaries in Chinese women with a history of gestational diabetes mellitus	Chan, C. C.; Ng, E. H.; Tang, O. S.; Lee, C. P.; Ho, P. C.	2006	Wrong population
Polycystic ovarian syndrome and subclinical atherosclerosis among women of reproductive age in the Dallas heart study	Chang, A. Y.; Ayers, C.; Minhajuddin, A.; Jain, T.; Nurenberg, P.; de Lemos, J. A.; Wild, R. A.; Auchus, R. J.	2011	Non energy homeostasis
Circulating irisin underscores the development of polycystic ovary syndrome	Chang, C. L.; Huang, S. Y.; Soong, Y. K.; Cheng, P. J.; Wang, C. J.; Liang, I. T.	2014	Abstract
Circulating irisin and glucose-dependent insulinotropic peptide are associated with the development of polycystic ovary syndrome	Chang, C. L.; Huang, S. Y.; Soong, Y. K.; Cheng, P. J.; Wang, C. J.; Liang, I. T.	2014	Non energy homeostasis
Hypoadiponectinemia: a useful marker of dyslipidemia in women with polycystic ovary syndrome	Chang, C. Y.; Chen, M. J.; Yang, W. S.; Yeh, C. Y.; Ho, H. N.; Chen, S. U.; Yang, Y. S.	2012	Non energy homeostasis
Circulating leptin concentrations in polycystic ovary syndrome: relation to anthropometric and metabolic parameters	Chapman, I. M.; Wittert, G. A.; Norman, R. J.	1997	Non energy homeostasis
Regulation of adiponectin secretion by adipocytes in the polycystic ovary syndrome: role of tumor necrosis factor-{alpha}	Chazenbalk, G.; Trivax, B. S.; Yildiz, B. O.; Bertolotto, C.; Mathur, R.; Heneidi, S.; Azziz, R.	2010	Non energy homeostasis
Adiponectin and leptin in overweight/obese and lean women with polycystic ovary syndrome	Chen, C. I.; Hsu, M. I.; Lin, S. H.; Chang, Y. C.; Hsu, C. S.; Tzeng, C. R.	2015	Non energy homeostasis
[Effects of resolving method of Chinese medicine on the lipid metabolism in polycystic ovary syndrome accompanied with non-alcoholic fatty liver disease]	Chen, Y.; Wang, X. J.; Jin, H. L.; Jin, L.	2013	Non English
Association between levels of serum leptin and insulin resistance in patients with polycystic ovary syndrome. [Chinese]	Cheng, X.; Guo, J.; Xie, J.	2014	Non English
N-Acetylcysteine improves oocyte and embryo quality in polycystic ovary syndrome patients undergoing intracytoplasmic sperm injection: an alternative to metformin	Cheraghi, E.; Mehranjani, M. S.; Shariatzadeh, M. A.; Esfahani, M. H.; Ebrahimi, Z.	2016	Non energy homeostasis
Co-administration of metformin and N-acetyl cysteine fails to improve clinical manifestations in PCOS individual undergoing ICSI	Cheraghi, E.; Soleimani Mehranjani, M.; Shariatzadeh, M. A.; Nasr Esfahani, M. H.; Ebrahimi, Z.	2014	Non energy homeostasis
Effects of the administration of high-dose aspirin in the polysystic ovary syndrome patients	Chi, Ctr Trc	2014	Wrong design
Circulating irisin and GIP, but not asprosin, underscore the manifestation of polycystic ovary syndrome	Chin, T. H.; Huang, S. Y.; Hsu, Y. C.; Soong, Y. K.; Chang, C. L.	2017	Abstract
Plasma omentin-1 levels are reduced in non-obese women with normal glucose tolerance and polycystic ovary syndrome	Choi, J. H.; Rhee, E. J.; Kim, K. H.; Woo, H. Y.; Lee, W. Y.; Sung, K. C.	2011	Non energy homeostasis
Inflammatory cytokines and chemokines, skeletal muscle and polycystic ovary syndrome: effects of pioglitazone and metformin treatment	Ciaraldi, T. P.; Aroda, V.; Mudaliar, S. R.; Henry, R. R.	2013	Non energy homeostasis

Adiponectin and its receptors in the ovary: further evidence for a link between obesity and hyperandrogenism in polycystic ovary syndrome	Comim, F. V.; Hardy, K.; Franks, S.	2013	Non energy homeostasis
Localisation of adiponectin receptors in normal and polycystic ovaries	Comim, F.; Stubbs, S.; Hardy, K.; Franks, S.	2010	Abstract
Obesity and serum luteinizing hormone level have an independent and opposite effect on the serum inhibin B level in patients with polycystic ovary syndrome	Cortet-Rudelli, C.; Pigny, P.; Decanter, C.; Leroy, M.; Maunoury-Lefebvre, C.; Thomas-Desrousseaux, P.; Dewailly, D.	2002	Non energy homeostasis
Serum adiponectin levels in adolescents with polycystic ovary syndrome and its relation to clinical, metabolic and hormonal parameters. [Turkish]	Coskun, A. D. E.; Keven, M. C.; Idil, N. S.; Yasar, L.	2013	Non English
Polikistik over sendromlu adolesanlarda serum adiponektin duzeyleri ile klinik, metabolik ve hormonal belirteclerin iliskisi	Coşkun, Ayşe Deniz Ertürk; Keven, Mehmet Can; İdil, Nadire Sevda; Yaşar, Levent	2013	Non English
Early Predictors of Gestational Diabetes Mellitus in IVF-Conceived Pregnancies	Coussa, A.; Hasan, H. A.; Barber, T. M.	2021	Non energy homeostasis
Metabolic profiling of polycystic ovary syndrome reveals interactions with abdominal obesity	Couto Alves, A.; Valcarcel, B.; Makinen, V. P.; Morin-Papunen, L.; Sebert, S.; Kangas, A. J.; Soininen, P.; Das, S.; De Iorio, M.; Coin, L.; Ala-Korpela, M.; Jarvelin, M. R.; Franks, S.	2017	No outcomes of interest
Higher circulating leukocytes in women with PCOS is reversed by aerobic exercise	Covington, J. D.; Tam, C. S.; Pasarica, M.; Redman, L. M.	2016	Non energy homeostasis
Hepatic Steatosis is Common in Adolescents with Obesity and PCOS and Relates to De Novo Lipogenesis but not Insulin Resistance: Hepatic Steatosis in Girls with PCOS	Cree-Green, Melanie; Bergman, Bryan C.; Coe, Gregory V.; Newnes, Lindsey; Baumgartner, Amy D.; Bacon, Samantha; Sherzinger, Ann; Pyle, Laura; Nadeau, Kristen J.	2016	no outcome of interest
The preliminary association study of ADIPOQ, RBP4, and BCMO1 variants with polycystic ovary syndrome and with biochemical characteristics in a cohort of Polish women	Czeczuga-Semeniuk, E.; Galar, M.; Jarzabek, K.; Kozlowski, P.; Sarosiek, N. A.; Wolczynski, S.	2018	Non energy homeostasis
Can polyunsaturated fatty acids regulate Polycystic Ovary Syndrome via TGF-beta signalling?	D. Prabhu Y; Valsala Gopalakrishnan, A.	2021	Wrong design
Biomarker Profiles in Women with PCOS and PCOS Offspring; A Pilot Study	Daan, N. M.; Koster, M. P.; de Wilde, M. A.; Dalmeijer, G. W.; Evelein, A. M.; Fauser, B. C.; de Jager, W.	2016	Non energy homeostasis
Rs1799817 in INSR associates with susceptibility to polycystic ovary syndrome	Daghestani, M. H.	2019	Non energy homeostasis
Evaluation of biochemical, endocrine, and metabolic biomarkers for the early diagnosis of polycystic ovary syndrome among non-obese Saudi women	Daghestani, M. H.	2018	Non energy homeostasis
The influence of the rs1137101 genotypes of leptin receptor gene on the demographic and metabolic profile of normal Saudi females and those suffering from polycystic ovarian syndrome	Daghestani, M. H.; Daghestani, M. H.; Daghistani, M. H.; Bjorklund, G.; Chirumbolo, S.; Warsy, A.	2019	Non energy homeostasis
A study of ghrelin and leptin levels and their relationship to metabolic profiles in obese and lean Saudi women with polycystic ovary syndrome (PCOS)	Daghestani, M. H.; Daghestani, M.; Daghistani, M.; El-Mazny, A.; Bjorklund, G.; Chirumbolo, S.; Al Saggaf, S. H.; Warsy, A.	2018	Non energy homeostasis

Influence of b2 adrenergic receptor polymorphism (rs1042713 and rs1042714) on anthropometric, hormonal and lipid profiles in polycystic ovarian syndrome	Daghestani, M. H.; Omair, M.; Daghestani, M.; Abdel-Razeq, S. S.; Kaya, N.; Warsy, A.	2021	Non energy homeostasis
Adverse Effects of Selected Markers on the Metabolic and Endocrine Profiles of Obese Women With and Without PCOS	Daghestani, M. H.; Warsy, A.; El-Ansary, A.; Omair, M. A.; Hassen, L. M.; Alhumaidhi, E. M. H.; Al Qahtani, B.;Harrath, A. H.	2021	Non energy homeostasis
Contrasting association of Leptin receptor polymorphisms and haplotypes with polycystic ovary syndrome in Bahraini and Tunisian women: A case-control study	Dallel, M.; Douma, Z.; Finan, R. R.; Hachani, F.; Letaifa, D. B.; Mahjoub, T.; Almawi, W. Y.	2021	Non energy homeostasis
Contrasting association of Leptin receptor polymorphisms and haplotypes with polycystic ovary syndrome in Bahraini and Tunisian women: a case-control study	Dallel, M.; Douma, Z.; Finan, R. R.; Hachani, F.; Letaifa, D. B.; Mahjoub, T.; Almawi, W. Y.	2021	Non energy homeostasis
Circulating leptin concentration, LEP gene variants and haplotypes, and polycystic ovary syndrome in Bahraini and Tunisian Arab women	Dallel, M.; Sghaier, I.; Finan, R. R.; Douma, Z.; Hachani, F.; Letaifa, D. B.; Mahjoub, T.; Almawi, W. Y.	2019	Non energy homeostasis
Sitagliptin/metformin improves the fertilization rate and embryo quality in polycystic ovary syndrome patients through increasing the expression of GDF9 and BMP15: A new alternative to metformin (a randomized trial)	Daneshjou, D.; Mehranjani, M. S.; Zadehmodarres, S.; Shariatzadeh, S. M. A.; Mofarahe, Z. S.	2022	Non energy homeostasis
Circulating levels of Vitamin D<inf>3</inf> and leptin in lean infertile women with polycystic ovary syndrome	Dawood, A. S.; Elgergawy, A.; Elhalwagy, A.	2018	Non energy homeostasis
Dietary underreporting in women affected by polycystic ovary syndrome: A pilot study	De Giuseppe, R.; Braschi, V.; Bosoni, D.; Biino, G.; Stanford, F. C.; Nappi, R. E.; Cena, H.	2019	No outcomes of interest
Serum leptin levels in premature pubarche and prepubertal girls with and without obesity	de Jesus Teixeira, R.; Ginzbarg, D.; Rodrigues Freitas, J.; Fucks, G.; Silva, C. M.; Bordallo, M. A. N.	2004	Wrong population
Evidence for decreased expression of APPL1 associated with reduced insulin and adiponectin receptors expression in PCOS patients	Dehghan, R.; Saidijam, M.; Mehdizade, M.; Shabab, N.; Yavangi, M.; Artimani, T.	2016	Non energy homeostasis
Frequency of adiponectin gene polymorphisms in polycystic ovary syndrome and the association with serum adiponectin, androgen levels, insulin resistance and clinical parameters	Demirci, H.; Yilmaz, M.; Ergun, M. A.; Yurtcu, E.; Bukan, N.; Ayvaz, G.	2010	Non energy homeostasis
Serum leptin, oxidized low density lipoprotein and plasma asymmetric dimethylarginine levels and their relationship with dyslipidaemia in adolescent girls with polycystic ovary syndrome	Demirel, F.; Bideci, A.; Cinaz, P.; Camurdan, M. O.; Biberoglu, G.; Yesilkaya, E.; Hasanoglu, A.	2007	Non energy homeostasis
Nesfatin-1 and other hormone alterations in polycystic ovary syndrome	Deniz, R.; Gurates, B.; Aydin, S.; Celik, H.; Sahin, I.; Baykus, Y.; Catak, Z.; Aksoy, A.; Citil, C.; Gungor, S.	2012	Non energy homeostasis
Subfatin and asprosin, two new metabolic players of polycystic ovary syndrome	Deniz, R.; Yavuzkir, S.; Ugur, K.; Ustebay, D. U.; Baykus, Y.; Ustebay, S.; Aydin, S.	2020	No outcomes of interest
Sitagliptin Decreases Visceral Fat and Blood Glucose in Women With Polycystic Ovarian Syndrome	Devin, J. K.; Nian, H.; Celedonio, J. E.; Wright, P.; Brown, N. J.	2020	Non energy homeostasis
Metabolic Inflexibility Is a Feature of Women With Polycystic Ovary Syndrome and Is Associated With Both Insulin Resistance and Hyperandrogenism	Di Sarra, Daniela; Tosi, Flavia; Bonin, Cecilia; Fiers, Tom; Kaufman, Jean-Marc; Signori, Chiara; Zambotti, Francesca; Dall'Alda, Marlene; Caruso, Beatrice; Zanolin, Maria Elisabetta; Bonora, Enzo; Moghetti, Paolo	2013	No control group

Activating transcriptional factor 4 correlated with obesity and insulin resistance in polycystic ovary syndrome	Di, F.; Liu, J.; Li, S.; Hong, Y.; Chen, Z. J.; Du, Y.	2019	No outcomes of interest
Effect of testosterone on lipolysis in human pre-adipocytes from different fat depots	Dicker, A.; Ryden, M.; Naslund, E.; Muehlen, I. E.; Wiren, M.; Lafontan, M.; Arner, P.	2004	Wrong population
Plasma adiponectin and resistin levels in women with polycystic ovary syndrome: Relation to body mass index and insulin resistance	Dikmen, E.; Tarkun, I.; Ozturk, F.; Arslan, B.; Canturk, Z.	2011	Non energy homeostasis
The ameliorating effect of gut microbiota-targeted clinical intervention on metabolic disorders of impaired glucose tolerance women with PCOS	Ding, X.; Liu, R.; Shen, J.; Wang, X.; Yan, Q.; Greenberg, A. S.; Zhao, L.; Peng, Y.	2016	Abstract
Impact of Low Frequency Electro-acupuncture on Glucose and Lipid Metabolism in Unmarried PCOS Women: A Randomized Controlled Trial	Dong, Hao-xu; Wang, Qing; Wang, Zhi; Wu, Xiao-ke; Cheng, Ling; Zhou, Zhong-ming; Yang, Li; Yi, Ping; Huang, Dong-mei	2020	Non energy homeostasis
[Retrospective analysis on pregnancy outcomes and fat-related factors of treatment of endomorph PCOS infertility patients by acupuncture of 8 acupoints around umbilicus]	Dou, Z.; Ma, S. H.; Song, J. Y.; Xia, T.	2021	Non English
Difference in dietary intake between women with polycystic ovary syndrome and healthy controls	Douglas, C. C.; Norris, L. E.; Oster, R. A.; Darnell, B. E.; Azziz, R.; Gower, B. A.	2006	No outcomes of interest
Glucose-to-insulin ratio rather than sex hormone-binding globulin and adiponectin levels is the best predictor of insulin resistance in nonobese women with polycystic ovary syndrome	Ducluzeau, P. H.; Cousin, P.; Malvoisin, E.; Bornet, H.; Vidal, H.; Laville, M.; Pugeat, M.	2003	Non energy homeostasis
Adipose Insulin Resistance in Normal-Weight Women With Polycystic Ovary Syndrome	Dumesic, D. A.; Phan, J. D.; Leung, K. L.; Grogan, T. R.; Ding, X.; Li, X.; Hoyos, L. R.; Abbott, D. H.; Chazenbalk, G. D.	2019	Non energy homeostasis
Role of insulin and leptin in the pathogenesis of PCOS	E. L-Gharib M.N	2012	Non energy homeostasis
DNA methylation in promoter regions of genes involved in the reproductive and metabolic function of children born to women with PCOS	Echiburu, B.; Milagro, F.; Crisosto, N.; Perez-Bravo, F.; Flores, C.; Arpon, A.; Salas-Perez, F.; Recabarren, S. E.; Sir-Petermann, T.; Maliqueo, M.	2020	Wrong population
Enlarged adipocytes in subcutaneous adipose tissue associated to hyperandrogenism and visceral adipose tissue volume in women with polycystic ovary syndrome	Echiburu, B.; Perez-Bravo, F.; Galgani, J. E.; Sandoval, D.; Saldias, C.; Crisosto, N.; Maliqueo, M.; Sir-Petermann, T.	2018	Non energy homeostasis
Serum leptin as an additional possible pathogenic factor in polycystic ovary syndrome	El Orabi, H.; Abou Ghalia, A.; Khalifa, A.; Mahfouz, H.; El Shalkani, A.; Shoieb, N.	1999	Non energy homeostasis
Subclinical inflammation in obese women with polycystic ovary syndrome	Elkholi, D. G. E. Y.; Hammoudah, S. F.	2012	Non energy homeostasis
The effects of adipocytokines on the endocrino-metabolic features and obstetric outcome in pregnant obese women with polycystic ovary syndrome	Elkholi, D. G. E. Y.; Nagy, H. M.	2014	Non energy homeostasis
Comparison of single and combined treatment with exenatide and metformin on menstrual cyclicity in overweight women with polycystic ovary syndrome	Elkind-Hirsch, K.; Marrioneaux, O.; Bhushan, M.; Vernor, D.; Bhushan, R.	2008	Non energy homeostasis
Serum adiponectin levels and its association with insulin resistance and obesity in women with poly cystic ovarian syndrome	Emadi, Maryam; Tehrani, Fahimeh Ramezani; Yaghmaei, Parichehre; Sheikholeslami, Sara; Hedayati, Mehdi	2012	Non English

Role of kisspeptin in polycystic ovary syndrome (PCOS)	Emekci Ozay, O.; Ozay, A. C.; Acar, B.; Cagliyan, E.; Secil, M.; Kume, T.	2016	Non energy homeostasis
Leptin receptor variant in women with polycystic ovary syndrome	Erel, C. T.; Cine, N.; Elter, K.; Kaleli, S.; Senturk, L. M.; Baysal, B.	2002	Non energy homeostasis
Is serum leptin level regulated by thyroid functions, lipid metabolism and insulin resistance in polycystic ovary syndrome?	Erel, C. T.; Senturk, L. M.; Kaleli, S.; Gezer, A.; Baysal, B.; Tasan, E.	2003	Non energy homeostasis
Role of osteocalcin, tumor necrosis factor-alpha and adiponectin in polycystic ovary syndrome patients with insulin resistance	Erkan, GÃ¶nÃ¼l; Tayyar, Ahter Tanay; AÃ§maz, GÃ¶khan; MÃ¼derris, Ã°ptisam Ã°pek; BaÅŸkol, GÃ¼lden; Bayram, Fahri	2017	Non energy homeostasis
Decreased serum profile of the interleukin-36alpha in polycystic ovary syndrome	Eroglu, S.; Cakmakliogullari, E. K.	2021	Non energy homeostasis
Prediction of metabolic syndrome in women with polycystic ovary syndrome	Ersan, F.; Arslan, E.; Esmer, A. C.; Aydin, S.; Gedikbasi, A.; Alkis, I.; Ark, C.	2012	Non energy homeostasis
Serum leptin levels correlate with obesity parameters but not with hyperinsulinism in women with polycystic ovary syndrome	Erturk, Erdinc; Kuru, Nesrin; SavcÄ±, Vahide; Tuncel, Ercan; Ersoy, Canan; Imamoglu, Sazi	2004	No control group
Adiponectin and resistin in PCOS: a clinical, biochemical and molecular genetic study	Escobar-Morreale, H. F.; Villuendas, G.; Botella-Carretero, J. I.; Alvarez-Blasco, F.; Sanchon, R.; Luque-Ramirez, M.; San Millan, J. L.	2006	Non energy homeostasis
Effects on Endocrine-Metabolic Parameters and Body Composition of the Addition of Low-Dose Pioglitazone to Flutamide-Metformin Therapy in Young Women with Hyperinsulinemic Ovarian Hyperandrogenism and Cardiovascular Risk - Pioglitazone in PCOS	Euctr, E. S.	2005	Trial register
Alterations in plasma non-esterified fatty acid (NEFA) kinetics and relationship with insulin resistance in polycystic ovary syndrome	Ezeh, U.; Arzumanyan, Z.; Lizneva, D.; Mathur, R.; Chen, Y. H.; Boston, R. C.; Chen, Y. I.; Azziz, R.	2019	No outcomes of interest
Adiponectin (ADIPOQ) gene variants and haplotypes in Saudi Arabian women with polycystic ovary syndrome (PCOS): a case-control study	Ezzidi, I.; Mtiraoui, N.; Mohmmed Ali, M. E.; Al Masoudi, A.; Abu Duhier, F.	2020	Non energy homeostasis
Decreased serum levels of CTRP12/adipolin in patients with coronary artery disease in relation to inflammatory cytokines and insulin resistance	Fadaei, R.; Moradi, N.; Kazemi, T.; Chamani, E.; Azdaki, N.; Moezibady, S. A.; Shahmohamadnejad, S.; Fallah, S.	2019	Wrong population
Effect of Laparoscopic Sleeve Gastrectomy on Fasting Gastrointestinal, Pancreatic, and Adipose-Derived Hormones and on Non-Esterified Fatty Acids	Farey, J. E.; Preda, T. C.; Fisher, O. M.; Levert-Mignon, A. J.; Stewart, R. L.; Karsten, E.; Herbert, B. R.; Swarbrick, M. M.; Lord, R. V.	2017	Wrong population
Leptin and leptin binding activity in the preovulatory follicle of polycystic ovary syndrome patients	Fedorcsak, P.; Storeng, R.; Dale, P. O.; Tanbo, T.; Torjesen, P.; Urbancsek, J.; Abyholm, T.	2000	Non energy homeostasis
Antimullerian hormone levels and cardiometabolic risk in young women with polycystic ovary syndrome	Feldman, R. A.; O'Neill, K.; Butts, S. F.; Dokras, A.	2017	No outcomes of interest
Serum total L-carnitine levels in non-obese women with polycystic ovary syndrome	Fenkci, S. M.; Fenkci, V.; Oztekin, O.; Rota, S.; Karagenc, N.	2008	No outcomes of interest
Dpp4 Inhibitor Sitagliptin As A Potential Treatment Option In Metformin-Intolerant Obese Women With Polycystic Ovary Syndrome: A Pilot Randomized Study	Ferjan, Simona; Janez, Andrej; Jensterle, Mojca	2018	No control group

An impaired glucagon-like peptide-1 response is associated with prediabetes in polycystic ovary syndrome with obesity	Ferjan, Simona; Jensterle, Mojca; Oblak, Tjasa; Zitnik, Irena Prodan; Marc, Janja; Goricar, Katja; Dolzan, Vita; Janez, Andrej	2019	No control group
ORAL CONTRACEPTIVE USE in ADOLESCENTS with POLYCYSTIC OVARY SYNDROME and OBESITY IS ASSOCIATED with ALTERED FAT METABOLISM	Finn, E.; Severn, C.; Garcia-Reyes, Y.; Ware, M. A.; Rahat, H.; Cree-Green, M.	2021	Abstract
Ovarian function and metabolic factors in women with oligomenorrhea treated with metformin in a randomized double blind placebo-controlled trial	Fleming, R.; Hopkinson, Z. E.; Wallace, A. M.; Greer, I. A.; Sattar, N.	2002	Non energy homeostasis
Association between visceral adiposity index, hirsutism and cardiometabolic risk factors in women with polycystic ovarian syndrome: A cross-sectional study	Fonseka, S.; Subhani, B.; Wijeyaratne, C. N.; Gawarammana, I. B.; Kalupahana, N. S.; Ratnatunga, N.; Rosairo, S.; Vithane, K. P.	2019	Non energy homeostasis
Circulating levels of Meteorin-like protein in polycystic ovary syndrome: A case-control study	Fouani, F. Z.; Fadaei, R.; Moradi, N.; Zandieh, Z.; Ansaripour, S.; Yekaninejad, M. S.; Vatannejad, A.; Mahmoudi, M.	2020	Non energy homeostasis
Circulating vaspin levels and nutritional status and insulin resistance in polycystic ovary syndrome	Franik, G.; Plinta, R.; Madej, P.; Owczarek, A.; Bozentowicz-Wikarek, M.; Chudek, J.; Skrzypulec-Plinta, V.; Olszanecka-Glinianowicz, M.	2020	No outcomes of interest
Effect of liraglutide on ectopic fat in polycystic ovary syndrome: A randomized clinical trial	Frossing, S.; Nylander, M.; Chabanova, E.; Frystyk, J.; Holst, J. J.; Kistorp, C.; Skouby, S. O.; Faber, J.	2018	Non energy homeostasis
IL-6 serum levels and production is related to an altered immune response in polycystic ovary syndrome girls with insulin resistance	Fulghesu, A. M.; Sanna, F.; Uda, S.; Magnini, R.; Portoghese, E.; Batetta, B.	2011	Non energy homeostasis
Effects of ghrelin administration on endocrine and metabolic parameters in obese women with polycystic ovary syndrome	Fusco, A.; Bianchi, A.; Mancini, A.; Milardi, D.; Giampietro, A.; Cimino, V.; Porcelli, T.; Romualdi, D.; Guido, M.; Lanzone, A.; Pontecorvi, A.; De Marinis, L.	2007	Non energy homeostasis
Anti-androgen treatment increases circulating ghrelin levels in obese women with polycystic ovary syndrome	Gambineri, A.; Pagotto, U.; Tschop, M.; Vicennati, V.; Manicardi, E.; Carcello, A.; Cacciari, M.; De Iasio, R.; Pasquali, R.	2003	Non energy homeostasis
Comparative Evaluation of Biomarkers of Inflammation Among Indian Women With Polycystic Ovary Syndrome (PCOS) Consuming Vegetarian vs. Non-vegetarian Diet	Ganie, M. A.; Sahar, T.; Rashid, A.; Wani, I. A.; Nisar, S.; Sathyapalan, T.; Vishnubhatla, S.; Ramakrishnan, L.; Parvez, T.; Geer, I.	2019	Non energy homeostasis
The relationships of irisin with bone mineral density and body composition in PCOS patients	Gao, S.; Cheng, Y.; Zhao, L.; Chen, Y.; Liu, Y.	2016	Non energy homeostasis
Cardiovascular risk factors in non-obese PCOS patients	Garcia-Gamon, M.; Romeu, M.; Monzo, A.; Montanana, V.; Perez-Calvo, A.; Tresguerres, J.; Romeu, A.	2010	Abstract
Endometria from Obese PCOS Women with Hyperinsulinemia Exhibit Altered Adiponectin Signaling	Garcia, V.; Orostica, L.; Poblete, C.; Rosas, C.; Astorga, I.; Romero, C.; Vega, M.	2015	Non energy homeostasis
Relationship of serum leptin and ghrelin between insulin resistance and anthropometric indices in women with polycystic ovary syndrome. [Persian]	Gargari, B. P.; Houjeghani, S.; Mahboob, S.; Farzadi, L.; Safaeian, A.; Behzad, M. H.	2012	Non English

Relationship between Serum Leptin, Ghrelin and Dietary Macronutrients in Women with Polycystic Ovary Syndrome	Gargari, Bahram Pourghassem; Houjeghani, Shiva; Farzadi, Laya; Houjeghani, Sheyda; Safaeiyan, Abdolrasoul	2015	Non energy homeostasis
Ghrelin is independently associated with anti-mullerian hormone levels in obese but not non-obese women with polycystic ovary syndrome	Garin, M. C.; Butts, S. F.; Sarwer, D. B.; Allison, K. C.; Senapati, S.; Dokras, A.	2017	Non energy homeostasis
Association between follicular fluid leptin and serum insulin levels in nonoverweight women with polycystic ovary syndrome	Garruti, G.; de Palo, R.; Rotelli, M. T.; Nocera, S.; Totaro, I.; Nardelli, C.; Panzarino, M. A.; Vacca, M.; Selvaggi, L. E.; Giorgino, F.	2014	Non energy homeostasis
Follicular fluid leptin content correlates with insulinemia in normalweight women with polycystic ovary syndrome undergoing in vitro fertilization/embryo transfer	Garruti, G.; Vacca, M.; Rotelli, M. T.; Panzarino, M. A.; Nocera, S.; Cantatore, C.; Selvaggi, L. E.; Giorgino, F.; DePalo, R.	2011	Abstract
The counterregulatory response to hypoglycaemia in women with the polycystic ovary syndrome	Gennarelli, G.; Holte, J.; Stridsberg, M.; Niklasson, F.; Berne, C.; Backstrom, T.	1997	Non energy homeostasis
Is there a role for leptin in the endocrine and metabolic aberrations of polycystic ovary syndrome?	Gennarelli, G.; Holte, J.; Wide, L.; Berne, C.; Lithell, H.	1998	Non energy homeostasis
Adipocytokines, insulinresistance and androgen excess in women	Georgescu, C. E.; Goia-Socol, M.; Marian, I.; Ilie, I. R.	2015	Abstract
Effects of inositol on ovarian function and metabolic factors in women with PCOS: a randomized double blind placebo-controlled trial	Gerli, S.; Mignosa, M.; Di Renzo, G. C.	2003	Non energy homeostasis
Randomized, double blind placebo-controlled trial: effects of myo-inositol on ovarian function and metabolic factors in women with PCOS	Gerli, S.; Papaleo, E.; Ferrari, A.; Di Renzo, G. C.	2007	Non energy homeostasis
Association of -604G/A and -501A/C Ghrelin and Obestatin Prepropeptide Gene Polymorphisms with Polycystic Ovary Syndrome	Ghaleh, T. D.; Skandari, S. S.; Najafipour, R.; Rashvand, Z.; Darabi, M.; Sahmani, M.	2018	Non energy homeostasis
Evaluation of metabolic risk markers in polycystic ovary syndrome (PCOS). Adiponectin, ghrelin, leptin and body composition in hirsute PCOS patients and controls	Glintborg, D.; Andersen, M.; Hagen, C.; Frystyk, J.; Hulstrom, V.; Flyvbjerg, A.; Hermann, A. P.	2006	Non energy homeostasis
Evaluation of metabolic risk markers in polycystic ovary syndrome (PCOS). Adiponectin, ghrelin, leptin and body composition in hirsute PCOS patients and controls	Glintborg, D.; Andersen, M.; Hagen, C.; Frystyk, J.; Hulstrøm, V.; Flyvbjerg, A.; Hermann, A. P.	2006	Non energy homeostasis
Total and high molecular weight (HMW) adiponectin levels and measures of glucose and lipid metabolism following pioglitazone treatment in a randomized placebo-controlled study in polycystic ovary syndrome	Glintborg, D.; Frystyk, J.; Hojlund, K.; Andersen, K. K.; Henriksen, J. E.; Hermann, A. P.; Hagen, C.; Flyvbjerg, A.; Andersen, M.	2008	Non energy homeostasis
A randomized placebo-controlled study on the effects of pioglitazone on cortisol metabolism in polycystic ovary syndrome	Glintborg, D.; Hermann, A. P.; Hagen, C.; Jensen, L. T.; Frystyk, J.; Bennett, P.; Flyvbjerg, A.; Andersen, M.	2009	Non energy homeostasis
Adiponectin, interleukin-6, monocyte chemoattractant protein-1, and regional fat mass during 12-month randomized treatment with metformin and/or oral contraceptives in polycystic ovary syndrome	Glintborg, D.; Mumm, H.; Altinok, M. L.; Richelsen, B.; Bruun, J. M.; Andersen, M.	2014	Non energy homeostasis
Peritoneal fluid leptin concentration in infertile patients	Gogacz, M.; Polak, G.; Jakowicki, J.; Kotarski, J.	2001	Non energy homeostasis

Leptin-to-adiponectin, adiponectin-to-leptin ratios, and insulin are specific and sensitive markers associated with polycystic ovary syndrome: a case-control study from Bahrain	Golbahar, J.; Das, N. M.; Al-Ayadhi, M. A.; Gumaa, K.	2012	Non energy homeostasis
Lipoprotein Particles in Adolescents and Young Women With PCOS Provide Insights Into Their Cardiovascular Risk	Gourgari, E.; Lodish, M.; Shamburek, R.; Keil, M.; Wesley, R.; Walter, M.; Sampson, M.; Bernstein, S.; Khurana, D.; Lyssikatos, C.; Ten, S.; Dobs, A.; Remaley, A. T.; Stratakis, C. A.	2015	Non energy homeostasis
Adiponectin and leptin levels in normal weight women with polycystic ovary syndrome	Gozukucuk, M.; Yarcl Gursoy, A.; Destegul, E.; Taskln, S.; Satlroglu, H.	2020	Non energy homeostasis
Administration of exogenous ghrelin in obese patients with polycystic ovary syndrome: effects on plasma levels of growth hormone, glucose, and insulin	Guido, M.; Romualdi, D.; De Marinis, L.; Porcelli, T.; Giuliani, M.; Costantini, B.; Lanzone, A.	2007	Non energy homeostasis
Adiponectin is an independent determinant of insulin resistance in women with polycystic ovary syndrome	Gulcelik, N. E.; Aral, Y.; Serter, R.; Demir, Y.; Culha, C.	2006	Non energy homeostasis
Association of hypoadiponectinemia with metabolic syndrome in patients with polycystic ovary syndrome	Gulcelik, N. E.; Aral, Y.; Serter, R.; Koc, G.; Gulcelik, Nese Ersoz; Aral, Yalcin; Serter, Rustu; Koc, Gonul	2008	Non energy homeostasis
Decreased levels of spexin are associated with hormonal and metabolic disturbance in subjects with polycystic ovary syndrome	Guler, A.; Demir, I.	2020	No outcomes of interest
Examination of angiopoietin-like protein 4, neuropeptide Y, omentin-1 levels of obese and non-obese patients with polycystic ovary syndrome	Gunes, M.; Bukan, N.	2015	Non energy homeostasis
Endotrophin as a novel marker in PCOS and its relation with other adipokines and metabolic parameters: a pilot study	Guney, G.; Taskin, M. I.; Baykan, O.; Adali, E.l Gul Tezcan, S.; Sarikaya, S.; Kaya, C.; Tolu, E.	2021	Non energy homeostasis
Peritoneal fluid and serum leptin concentrations in women with primary infertility	Gungor, T.; Kanat-Pektas, M.; Karayalcin, R.; Mollamahmutoglu, L.	2009	Non energy homeostasis
L:A ratio, Insulin resistance and metabolic risk in women with polycystic ovarian syndrome	Gupta, V.; Mishra, S.; Mishra, S.; Gupta, V.	2017	Non energy homeostasis
Genetic determinants of insulin action in polycystic ovary syndrome	Haap, M.; Machicao, F.; Stefan, N.; Thamer, C.; Tschritter, O.; Schnuck, F.; Wallwiener, D.; Stumvoll, M.; Haring, H. U.; Fritsche, A.	2005	Non energy homeostasis
The peroxisome proliferator activated receptor gamma Pro12Ala polymorphism is associated with a lower hirsutism score and increased insulin sensitivity in women with polycystic ovary syndrome	Hahn, S.; Fingerhut, A.; Khomtsiv, U.; Khomtsiv, L.; Tan, S.; Quadbeck, B.; Herrmann, B. L.; Knebel, B.; Muller-Wieland, D.; Mann, K.; Janssen, O. E.	2005	Non energy homeostasis
The CC genotype of the GNAS T393C polymorphism is associated with obesity and insulin resistance in women with polycystic ovary syndrome	Hahn, S.; Frey, U. H.; Siffert, W.; Tan, S.; Mann, K.; Janssen, O. E.	2006	Non energy homeostasis
Decreased soluble leptin receptor levels in women with polycystic ovary syndrome	Hahn, S.; Haselhorst, U.; Quadbeck, B.; Tan, S.; Kimmig, R.; Mann, K.; Janssen, O. E.	2006	Non energy homeostasis
Low serum 25-hydroxyvitamin D concentrations are associated with insulin resistance and obesity in women with polycystic ovary syndrome	Hahn, S.; Haselhorst, U.; Tan, S.; Quadbeck, B.; Schmidt, M.; Roesler, S.; Kimmig, R.; Mann, K.; Janssen, O. E.	2006	Non energy homeostasis
The effects of flaxseed supplementation on metabolic status in women with polycystic ovary syndrome: a randomized open-labeled controlled clinical trial	Haidari, Fatemeh; Banaei-Jahromi, Nasrin; Zakerkish, Mehrnoosh; Ahmadi, Kambiz	2020	No control group

Role of adiponectin and its receptor in prediction of reproductive outcome of metformin treatment in patients with polycystic ovarian syndrome	Hamed, H. O.	2013	Non energy homeostasis
Association of Anti Mullerian Hormone with Biochemical markers in womens with and without Polycystic Ovarian disease	Hamid, S.; Qamar, I.; Malik, H.; Khan, S. R.; Jamil, H.; Iqbal, S.	2022	Non energy homeostasis
Molecular Mechanisms in Skeletal Muscle Underlying Insulin Resistance in Women Who Are Lean With Polycystic Ovary Syndrome	Hansen, S. L.; Svendsen, P. F.; Jeppesen, J. F.; Hoeg, L. D.; Andersen, N. R.; Kristensen, J. M.; Nilas, L.; Lundsgaard, A. M.; Wojtaszewski, J. F. P.; Madsbad, S.; Kiens, B.	2019	Non energy homeostasis
Molecular Mechanisms in Skeletal Muscle Underlying Insulin Resistance in Women Who Are Lean With Polycystic Ovary Syndrome	Hansen, Solvejg L.; Svendsen, Pernille F.; Jeppesen, Jacob F.; Hoeg, Louise D.; Andersen, Nicoline R.; Kristensen, Jonas M.; Nilas, Lisbeth; Lundsgaard, Anne-Marie; Wojtaszewski, Jørgen F. P.; Madsbad, Sten; Kiens, Bente	2018	Duplication
Association of serum adipsin levels with polycystic ovarian syndrome	Hashemi, Fatemeh; Yaghmaei, Parichehre; Saadati, Naghmeh; Haghighi Poodeh, Sepideh; Ramezani Tehrani, Fahimeh; Hedayati, Mehdi	2012	Non English
Association between insulin receptor gene and adiponectin gene polymorphism with polycystic ovary syndrome in Iranian population	Hashemi, S.; Ramezani Tehrani, F.; Daneshpour, M.; Zarkesh, M.; Azizi, F.	2012	Non English
Estimation of serum adiponectinirisin and apelin in iraqi obese women patients with polycystic ovary syndrome	Hashoosh, S. I.; Hussien, A. A.; Chalabi, S. A.	2020	Non energy homeostasis
Associations between TNF-alpha and interleukin-18 and ADIPOQ gene polymorphisms in iraqi obese women patients with polycystic ovary syndrome	Hashoosh, S. I.; Hussien, A. A.; Chalabi, S. A.	2020	Non energy homeostasis
Associations between two single nucleotide polymorphisms in the adiponectin gene and polycystic ovary syndrome	Heinonen, S.; Korhonen, S.; Helisalmi, S.; Koivunen, R.; Tapanainen, J.; Hippelainen, M.; Laakso, M.	2005	Non energy homeostasis
The relationship between NUCB2/Nesfatin-1 in the follicular fluid and the blood in iraqi women with polycystic ovary syndrome compared to poor ovarian response undergoing intracytoplasmic sperm injection	Helmi, Z.; Hussein, A. H.; Bad, A. H.; Alizzi, F. J.	2020	Non energy homeostasis
An retrospective audit of patients with polycystic ovary syndrome: the effects of a reduced glycaemic load diet	Herriot, A. M.; Whitcroft, S.; Jeanes, Y.	2008	No control group
The association between cord blood cardiometabolic and inflammatory markers and maternal PCOS status	Hodyl, N. A.; Stark, M. J.; Hague, W.; Rowan, J. A.; Coat, S.; Teede, H.; Moran, L. J.	2017	Abstract
Changes in Ghrelin and Glucagon following a Low Glycemic Load Diet in Women with PCOS	Hoover, Sarah E; Gower, Barbara A; Cedillo, Yenni E; Chandler-Laney, Paula C; Deemer, Sarah E; Goss, Amy M	2021	No control group
Changes in Ghrelin and Glucagon following a Low Glycemic Load Diet in Women with PCOS	Hoover, Sarah E.; Gower, Barbara A.; Cedillo, Yenni E.; Chandler-Laney, Paula C.; Deemer, Sarah E.; Goss, Amy M.; Cedillo, Yenni; Deemer, Sarah	2021	Non energy homeostasis
Serum leptin and ghrelin levels in women with polycystic ovary syndrome: Correlation with anthropometric, metabolic, and endocrine parameters	Houjeghani, S.; Gargari, B. P.; Farzadi, L.	2012	Non energy homeostasis

PCOS is associated with increased CD11c expression and crown-like structures in adipose tissue and increased central abdominal fat depots independent of obesity	Huang, Z. H.; Manickam, B.; Ryvkin, V.; Zhou, X. J.; Fantuzzi, G.; Mazzone, T.; Sam, S.	2013	Non energy homeostasis
Ethinylestradiol-drospirenone, flutamide-metformin, or both for adolescents and women with hyperinsulinemic hyperandrogenism: opposite effects on adipocytokines and body adiposity	Ibanez, L.; de Zegher, F.	2004	Non energy homeostasis
Flutamide-metformin plus ethinylestradiol-drospirenone for lipolysis and antiatherogenesis in young women with ovarian hyperandrogenism: the key role of metformin at the start and after more than one year of therapy	Ibanez, L.; de Zegher, F.	2005	Non energy homeostasis
Flutamide-metformin plus ethinylestradiol-drospirenone for lipolysis and antiatherogenesis in young women with ovarian hyperandrogenism: the key role of early, low-dose flutamide	Ibanez, L.; Valls, C.; Cabre, S.; De Zegher, F.	2004	Non energy homeostasis
Toward a Treatment Normalizing Ovulation Rate in Adolescent Girls With Polycystic Ovary Syndrome	Ibáñez, Lourdes; DÃaz, Marta; GarcÃa-BeltrÃ¡n, Cristina; Malpique, Rita; Garde, Edurne; LÃ³pez-Bermejo, Abel; Zegher, Francis de	2020	Non energy homeostasis
Evaluation of the Role of Ghrelin and Leptin as Biochemical Markers in Female with Polycystic Ovarian Syndrome	Ibrahim, M. K.; Alobaidi, A. H. A.	2021	Non energy homeostasis
The impact of follicular fluid adiponectin and ghrelin levels based on BMI on IVF outcomes in PCOS	Inal, H. A.; Yilmaz, N.; Gorkem, U.; Oruc, A. S.; Timur, H.	2016	Non energy homeostasis
Effect of metformin hydrochloride in correcting hyperinsulinemia and high leptin levels in treatment of infertile polycystic patients	Irfan, A.; Mughal, I. A.; Jalali, S.	2013	Non energy homeostasis
The role of serum adiponectin levels in women with polycystic ovarian syndrome	Itoh, H.; Kawano, Y.; Furukawa, Y.; Matsumoto, H.; Yuge, A.; Narahara, H.	2013	Non energy homeostasis
Leptin secretory burst mass correlates with body mass index and insulin in normal women but not in women with polycystic ovary syndrome	Iuorno, M. J.; Islam, L. Z.; Veldhuis, P. P.; Boyd, D. G.; Farhy, L. S.; Johnson, M. L.; Nestler, J. E.; Evans, W. S.	2007	Non energy homeostasis
Leptin and its association with polycystic ovary syndrome: a twin study	Jahanfar, S.; Maleki, H.; Mosavi, A. R.; Jahanfar, M.	2004	Non energy homeostasis
Subclinical eating disorder, polycystic ovary syndrome- is there any connection between these two conditions through leptin- a twin study	Jahanfar, Sh; Maleki, H.; Mosavi, A. R.	2005	Non energy homeostasis
Association of leptin and insulin resistance in PCOS: A case-controlled study	Jahromi, B. N.; Dabaghmanesh, M. H.; Parsanezhad, M. E.; Fatehpoor, F.	2017	Non energy homeostasis
[The effect of rosiglitazone on plasma adiponectin and resistin levels in obese PCO woman--preliminary report]	Jakubowska, J.; Bohdanowicz-Pawlak, A.; Milewicz, A.	2007	Non English
Plasma cytokines in obese women with polycystic ovary syndrome, before and after metformin treatment	Jakubowska, J.; Bohdanowicz-Pawlak, A.; Milewicz, A.; Szymczak, J.; Bednarek-Tupikowska, G.; Demissie, M.	2008	Non energy homeostasis
Genetic polymorphisms associated with polycystic ovary syndrome among Iranian women	Jamshidi, M.; Mohammadi Pour, S.; Bahadoram, M.; Mahmoudian-Sani, M. R.; Saeedi Boroujeni, A.	2021	Wrong design
Effects of empagliflozin on metabolic parameters in polycystic ovary syndrome: A randomized controlled study	Javed, Z.; Papageorgiou, M.; Deshmukh, H.; Rigby, A. S.; Qamar, U.; Abbas, J.; Khan, A. Y.; Kilpatrick, E. S.; Atkin, S. L.; Sathyapalan, T.	2019	No outcomes of interest

Short-term intervention with liraglutide improved eating behavior in obese women with polycystic ovary syndrome	Jensterle, M.; Kocjan, T.; Kravos, N. A.; Pfeifer, M.; Janez, A.	2015	No outcomes of interest
Genetic variability in GLP-1 receptor is associated with inter-individual differences in weight lowering potential of liraglutide in obese women with PCOS: a pilot study	Jensterle, M.; Pirs, B.; Goricar, K.; Dolzan, V.; Janez, A.	2015	Non energy homeostasis
Assessment of insulin resistance in young women with polycystic ovary syndrome	Jensterle, M.; Weber, M.; Pfeifer, M.; Prezelj, J.; Pfutzner, A.; Janez, A.	2008	Non energy homeostasis
Kisspeptin, leptin, and retinol-binding protein 4 in women with polycystic ovary syndrome	Jeon, Y. E.; Lee, K. E.; Jung, J. A.; Yim, S. Y.; Kim, H.; Seo, S. K.; Cho, S.; Choi, Y. S.; Lee, B. S.	2013	Non energy homeostasis
Accumulation of advanced glycation endproducts (AGE) are novel markers to detect women with poor IVF/ICSI outcomes independently of age and day-3-FSH levels: Possible novel therapy for poor responders by decreasing AGE	Jinno, M.; Takeuchi, M.; Watanabe, A.; Hirohama, J.; Eguchi, N.; Hatakeyama, N.	2010	Non energy homeostasis
Serum Anti-Mullerian hormone in polycystic ovary syndrome and its relationship with insulin resistance, lipid profile and adiponectin	Jun, T. J.; Jelani, A. M.; Omar, J.; Rahim, R. A.; Yaacob, N. M.	2020	Non energy homeostasis
Serum ghrelin, LH and FSH concentrations during menstrual cycle in non-obese PCOS women compared to healthy women	Kadhim, M. S.	2017	Non energy homeostasis
Clinical efficacy of metformin combined with clomiphene in patients with polycystic ovary syndrome and their effect on serum sex hormones	Kaiyun, X., Meiyan, Z., & Xiaolan, M	2018	Non energy homeostasis
Adiponectin, leptin and ghrelin levels in obese adolescent girls with polycystic ovary syndrome	Kale-Gurbuz, T.; Akhan, S. E.; Bastu, E.; Telci, A.; Iyibozkurt, A. C.; Topuz, S.	2013	Non energy homeostasis
Differential effects of walnuts vs almonds on improving metabolic and endocrine parameters in PCOS	Kalgaonkar, S; Almario, R U; Gurusinghe, D; Garamendi, E M; Buchan, W; Kim, K; Karakas, S E	2011	Kalgaonkar
Fasting plasma ghrelin in women with and without PCOS	Kamal, M.; Mohi, A.; Fawzy, M.; El-Sawah, H.	2010	Non energy homeostasis
Treatment effect of sibutramine compared to fluoxetine on leptin levels in polycystic ovary disease	Karabacak, I. Y.; Karabacak, O.; Toruner, F. B.; Akdemir, O.; Arslan, M.	2004	Non energy homeostasis
Determinants of impaired fasting glucose versus glucose intolerance in polycystic ovary syndrome	Karakas, S. E.; Kim, K.; Duleba, A. J.; Karakas, Sidika E.; Kim, Kyoungmi; Duleba, Antoni J.	2010	Non energy homeostasis
Association of leptin G2548A and leptin receptor Q223R polymorphisms and their serum levels with infertility and recurrent pregnancy loss in Iranian women with polycystic ovary syndrome	Kargasheh, F. B.; Ansaripour, S.; Borumandnia, N.; Moradi, N.; Zandieh, Z.; Maleki, M.; Mokhtar, S.; Karimi, A.; Fatemi, F.; Kheirollahi, A.; Vatannejad, A.	2021	Non energy homeostasis
Adiponectin levels reflect the different phenotypes of polycystic ovary syndrome: study in normal weight, normoinsulinemic patients	Karkanaki, A.; Piouka, A.; Katsikis, I.; Farmakiotis, D.; Macut, D.; Panidis, D.	2009	Non energy homeostasis
Relation of nutrients and hormones in polycystic ovary syndrome	Kasim-Karakas, Sidika E; Cunningham, Wendy M; Tsodikov, Alex	2007	Kalgaonkar
Leptin levels and adipose tissue percentage in adolescents with polycystic ovary syndrome	Kedikova, S. E.; Sirakov, M. M.; Boyadzhieva, M. V.	2013	Non energy homeostasis
Prevalence of hypovitaminosis D, and its association with hypoadiponectinemia and hyperfollistatinemia, in Saudi women with naive polycystic ovary syndrome	Kensara, O. A.	2018	Non energy homeostasis
Leptin levels in relation to marital status and neuroendocrine function in Iraqi females with polycystic ovary syndrome	Khalaf, B. H.	2010	Non energy homeostasis

The relevant hormonal levels and diagnostic features of polycystic ovary syndrome in adolescents	Khashchenko, E.; Uvarova, E.; Vysokikh, M.; Ivanets, T.; Krechetova, L.; Tarasova, N.; Sukhanova, I.; Mamedova, F.; Borovikov, P.; Balashov, I.; Sukhikh, G.	2020	Non energy homeostasis
Activation of systemic inflammation and oxidative stress in adolescent girls with polycystic ovary syndrome in combination with metabolic disorders and excessive body weight	Khashchenko, E.; Vysokikh, M.; Uvarova, E.; Krechetova, L.; Vtorushina, V.; Ivanets, T.; Volodina, M.; Tarasova, N.; Sukhanova, I.; Sukhikh, G.	2020	Non energy homeostasis
Impaired Lipolysis, Diminished Fat Oxidation, and Metabolic Inflexibility in Obese Girls With Polycystic Ovary Syndrome	Kim, Joon Young; Tfayli, Hala; Michaliszyn, Sara F; Arslanian, Silva	2018	no outcome of interest
Serum adiponectin is independently associated with the metabolic syndrome in Hong Kong, Chinese women with polycystic ovary syndrome	Ko, J. K.; Li, H. W.; Lam, K. S.; Tam, S.; Lee, V. C.; Yeung, T. W.; Ho, P. C.; Ng, E. H.	2016	Non energy homeostasis
Relationship between serum levels of anti-mullerian hormone, adiponectin and oxidative stress markers in patients with polycystic ovary syndrome	Kohzadi, M.; Khazaei, M. R.; Choobsaz, F.; Khazaei, M.	2020	Non energy homeostasis
Adipokine levels and carbohydrate metabolism in patients diagnosed de novo with polycystic ovary syndrome	Kolanska-Dams, E.; Boinska, J.; Socha, M. W.	2021	Non energy homeostasis
Adipokines, metabolic and atherogenic parameters in insulin resistant and non-insulin resistant women with polycystic ovary syndrome	Koleva, D. I. V.; Orbetzova, M. M.; Nyagolova, P. V.; Mitkov, M. D.	2016	Non energy homeostasis
Adipokines and soluble cell adhesion molecules in insulin resistant and non-insulin resistant women with polycystic ovary syndrome	Koleva, D. I.; Orbetzova, M. M.; Nikolova, J. G.; Tyutyundzhiev, S. B.	2016	Non energy homeostasis
Differences in the psychological and hormonal presentation of lean and obese patients with polycystic ovary syndrome	Komarowska, H.; Stangierski, A.; Warmuz-Stangierska, I.; Lodyga, M.; Ochmanska, K.; Wasko, R.; Wanic-Kossowska, M.; Ruchala, M.	2013	Non energy homeostasis
Ghrelin ovarian cell expression in patients with polycystic ovary syndrome: an immunohistochemical evaluation	Komarowska, H.; Wasko, R.; Iwanik, K.; Majewski, P.; Rafinska, L.; Warenik-Szymankiewicz, A.; Sowinski, J.	2006	Non energy homeostasis
Chemerin as a marker of body fat and insulin resistance in women with polycystic ovary syndrome	Kort, D. H.; Kostolias, A.; Sullivan, C.; Lobo, R. A.	2015	Non energy homeostasis
Plasma ghrelin concentrations in patients with polycystic ovary syndrome before and after 6months therapy: correlation with androgen levels	Kos-Kudla, B.; Malecka-Mikosz, O.; Foltyn, W.; Ostrowska, Z.; Kudla, M.; Mazur, B.	2006	Non energy homeostasis
Investigation of the relationship between insulin resistance and neuropeptide Y levels in polycystic ovary syndrome	Koseci, T.; Kaya, O.; Haksoyler, V.; Derici Yildirim, D.; Sezer, K.	2019	Non energy homeostasis
Insulin resistance Is associated with decreased circulating mannan-binding lectin concentrations in women with polycystic ovary syndrome	Kowalska, I.; Fernandez-Real, J. M.; Straczkowski, M.; Kozlowska, A.; Adamska, A.; Ortega, F.; Nikolajuk, A.; Karczewska-Kupczewska, M.; Wolczynski, S.; Gorska, M.	2008	Letter
Insulin, leptin, IGF-I and insulin-dependent protein concentrations after insulin-sensitizing therapy in obese women with polycystic ovary syndrome	Kowalska, I.; Kinalski, M.; Straczkowski, M.; Wolczynski, S.; Kinalska, I.	2001	Non energy homeostasis
[The influence of obesity on ovarian function. II. Plasma leptin concentration in women with polycystic ovary syndrome]	Kowalska, I.; Kinalski, M.; Wolczynski, S.; Straczkowski, M.; Kinalska, I.; Szamatowicz, M.	1999	Non English
Impact of the FTO gene variation on fat oxidation and its potential influence on body weight in women with polycystic ovary syndrome	Kowalska, Irina; Adamska, Agnieszka; T. Malecki, Maciej; Karczewska-Kupczewska, Monika;	2012	no outcome of interest

	Nikolajuk, Agnieszka; Szopa, Magdalena; Gorska, Maria; Straczkowski, Marek		
Leptin levels in patients with polycystic ovary syndrome in response to two different oral contraceptive treatments	Koyuncu, F. M.; Kuscu, N. K.; Var, A.; Onur, E.	2003	Non energy homeostasis
Fetuin-A levels in lean and obese women with polycystic ovary syndrome	Kozakowski, J.; Jeske, W.; Zgliczynski, W.	2014	Non energy homeostasis
Associations of vitamin D concentration with metabolic and hormonal indices in women with polycystic ovary syndrome presenting abdominal and gynoidal type of obesity	Kozakowski, J.; Kapuscinska, R.; Zgliczynski, W.	2014	Non energy homeostasis
Body composition, glucose metabolism markers and serum androgens - association in women with polycystic ovary syndrome	Kozakowski, J.; Zgliczynski, W.	2013	Non energy homeostasis
Leptin levels in women with polycystic ovary syndrome before and after treatment with diazoxide	Krassas, G. E.; Kaltsas, T. T.; Pontikides, N.; Jacobs, H.; Blum, W.; Messinis, I.	1998	Non energy homeostasis
Reduced serum ghrelin in a putative postmenopausal polycystic ovary syndrome phenotype	Krentz, A. J.; Barrett-Connor, E.	2009	Non energy homeostasis
Adipocytokine profiles in a putative novel postmenopausal polycystic ovary syndrome (PCOS) phenotype parallel those in premenopausal PCOS: the Rancho Bernardo Study	Krentz, A. J.; von Muhlen, D.; Barrett-Connor, E.	2012	Non energy homeostasis
The Î±2B and Î²3 Adrenergic Receptor Genes Polymorphisms in Women with Polycystic Ovarian Syndrome (PCOS) and their Association with Insulin Resistance and Basal Metabolic Rate (BMR)	Kritikou, Sosanna; Saltamavros, Alexandros D; Adonakis, George; Koufogiannis, Kleanthis; Spyropoulos, Kostas; Kourounis, George; Kyriazopoulou, Venetsana; Georgopoulos, Neoklis A; Flor, Christodoulos		no outcome of interest
Effect of two modes of antiandrogen treatment on insulin sensitivity and serum leptin in women with PCOS	Krotkiewski, M.; Landin, K.; Dahlgren, E.; Janson, P. O.; Holm, G.	2003	Non energy homeostasis
Proinsulin, adiponectin and hsCRP in reproductive age women with polycystic ovary syndrome (PCOS) - The effect of metformin treatment	Kruszynska, A.; Slowinska-Srzednicka, J.; Jeske, W.; Zgliczynski, W.	2014	Non energy homeostasis
Follicular fluid levels of anti-Mullerian hormone, insulin-like growth factor 1 and leptin in women with fertility disorders	Kucera, R.; Babuska, V.; Ulcova-Gallova, Z.; Kulda, V.; Topolcan, O.	2018	Wrong population
Effect of metformin-sustained release therapy on low-density lipoprotein size and adiponectin in the South Indian women with polycystic ovary syndrome	Kumar, D.; Seshadri, K.; Pandurangi, M.	2017	Non energy homeostasis
Association of serum leptin with anthropometric indices of obesity, blood lipids, steroidal hormones, and insulin resistance in polycystic ovarian syndrome	Kumawat, M.; Choudhary, P.; Aggarwal, S.	2021	Non energy homeostasis
Association between circulating neuregulin 4 levels and metabolic, aterogenic, and AMH profile of polycystic ovary syndrome	Kurek Eken, M.; Sahin Ersoy, G.; Yayla Abide, C.; Sanverdi, I.; Devranoglu, B.; Kutlu, T.; Cevik, O.	2019	No outcomes of interest
Plasma luteinizing hormone level affects the brain activity of patients with polycystic ovary syndrome	Lai, W.; Li, X.; Zhu, H.; Zhu, X.; Tan, H.; Feng, P.; Chen, L.; Luo, C.	2020	No outcomes of interest
Full-length visfatin levels are associated with inflammation in women with polycystic ovary syndrome	Lajunen, T. K.; Purhonen, A. K.; Haapea, M.; Ruokonen, A.; Puukka, K.; Hartikainen, A. L.; Savolainen, M. J.; Morin-Papunen, L.; Tapanainen, J. S.; Franks, S.; Jarvelin, M. R.; Herzig, K. H.		No outcomes of interest

Regional Cerebral Activation Accompanies Sympathoexcitation in Women With Polycystic Ovary Syndrome	Lansdown, A. J.; Warnert, E. A. H.; Sverrisdottir, Y.; Wise, R. G.; Rees, D. A.	2019	Non energy homeostasis
Serum leptin levels in women with polycystic ovary syndrome: the role of insulin resistance/hyperinsulinemia	Laughlin, G. A.; Morales, A. J.; Yen, S. S.	1997	Non energy homeostasis
Low plasma atrial natriuretic peptide: a new piece in the puzzle of polycystic ovary syndrome	Lauria, P. B.; Del Puerto, H. L.; Reis, A. M.; Candido, A. L.; Reis, F. M.	2013	Non energy homeostasis
Influence of adiposity on leptin, LH and androgen levels in lean, overweight and obese PCOS patients	LaZovic, G.; Radivojevic, U.; Milicevic, S.; Spremovic, S.	2007	Non energy homeostasis
Abdominal subcutaneous fat gene expression and circulating levels of leptin and adiponectin in polycystic ovary syndrome	Lecke, S. B.; Mattei, F.; Morsch, D. M.; Spritzer, P. M.	2011	Non energy homeostasis
Association between adipose tissue expression and serum levels of leptin and adiponectin in women with polycystic ovary syndrome	Lecke, S. B.; Morsch, D. M.; Spritzer, P. M.	2013	Wrong design
Adipokines, insulin-like growth factor binding protein-3 levels, and insulin sensitivity in women with polycystic ovary syndrome	Lee, H.; Oh, J. Y.; Sung, Y. A.	2013	Non energy homeostasis
Pericardial Fat Relates to Disturbances of Glucose Metabolism in Women with the Polycystic Ovary Syndrome, but Not in Healthy Control Subjects	Leutner, M.; Gobl, C.; Wolf, P.; Maruszczak, K.; Bozkurt, L.; Steinbrecher, H.; Just-Kukurova, I.; Ott, J.; Egarter, C.; Trattnig, S.; Kautzky-Willer, A.	2018	Non energy homeostasis
Adiponectin and resistin serum levels in women with polycystic ovary syndrome during oral glucose tolerance test: A significant reciprocal correlation between adiponectin and resistin independent of insulin resistance indices	Lewandowski, Krzysztof C.; Szosland, Konrad; Oâ€™Callaghan, Chris; Tan, Bee K.; Randeva, Harpal S.; Lewinski, Andrzej	2005	No control group
Changes in Resting-State Cerebral Activity in Women With Polycystic Ovary Syndrome: A Functional MR Imaging Study	Li, G.; Hu, J.; Zhang, S.; Fan, W.; Wen, L.; Wang, G.; Zhang, D.	2020	Non energy homeostasis
[A case-control study of correlation between serum adiponectin levels and polycystic ovary syndrome]	Li, H.; Chen, Y.; Li, Y.; Huang, J.; Zhao, X.; Chen, X.; Yang, D.	2015	Non English
Exploring the functional connectome in white matter. [References]	Li, Jiao; Biswal, Bharat B.; Wang, Pan; Duan, Xujun; Cui, Qian; Chen, Huafu; Liao, Wei	2019	Wrong population
Association study of +45G15G(T/G) and +276(G/T) polymorphisms in the adiponectin gene in patients with polycystic ovary syndrome	Li, L.; Yun, J. H.; Lee, J. H.; Song, S.; Choi, B. C.; Baek, K. H.	2011	Non energy homeostasis
Association of betatrophin with metabolic characteristics in overweight/obese and lean women with PCOS	Li, L.; Zhang, F.; Cui, J.; Shi, Y.; Xiang, J.; Wang, X.; Zhao, N.; Yan, Q.; Greenberg, A. S.; Peng, Y.; Ding, X.	2017	Non energy homeostasis
Association of serum and follicular fluid leptin concentrations with granulosa cell phosphorylated signal transducer and activator of transcription 3 expression in fertile patients with polycystic ovarian syndrome	Li, M. G.; Ding, G. L.; Chen, X. J.; Lu, X. P.; Dong, L. J.; Dong, M. Y.; Yang, X. F.; Lu, X. E.; Huang, H. F.	2007	Non energy homeostasis
[Correlations between adipocytokines and insulin resistance in women with polycystic ovary syndrome]	Li, X.; Li, X.; Huang, H. Y.; Ma, D.; Zhu, M. W.; Lin, J. F.	2009	Non English
Leptin down-regulates gamma-ENaC expression: a novel mechanism involved in low endometrial receptivity	Lin, X. H.; Liu, M. E.; Xu, H. Y.; Chen, X. J.; Wang, H.; Tian, S.; Sheng, J. Z.; Huang, H. F.	2015	Non energy homeostasis
Effects of Metformin Treatment on Soluble Leptin Receptor Levels in Women with Polycystic Ovary Syndrome	Liu, R. B.; Liu, Y.; Lv, L. Q.; Xiao, W.; Gong, C.; Yue, J. X.	2019	Non energy homeostasis

Dysbiosis of gut microbiota associated with clinical parameters in polycystic ovary syndrome	Liu, R.; Zhang, C.; Shi, Y.; Zhang, F.; Li, L.; Wang, X.; Ling, Y.; Fu, H.; Dong, W.; Shen, J.; Reeves, A.; Greenberg, A. S.; Zhao, L.; Peng, Y.; Ding, X.	2017	Non energy homeostasis
[On the relationship between serum total adiponectin and insulin resistance in polycystic ovary syndrome]	Liu, X.; Zhang, J.; Li, Y.; Xu, L.; Wei, D.; Qiu, D.; Han, D.	2010	Non English
Evidence of leptin expression in normal and polycystic human ovaries	Loffler, S.; Aust, G.; Kohler, U.; Spanel-Borowski, K.	2001	Non energy homeostasis
Predictive value of ovarian stroma measurement for cardiovascular risk in polycyctic ovary syndrome: A case control study	Loverro, G.; De Pergola, G.; Di Naro, E.; Tartagni, M.; Lavopa, C.; Caringella, A. M.	2010	Non energy homeostasis
Assessment of serum leptin levels in women with PCOS	Lovie, B. T.; Niveditha, P.; Padma, K.; Viji, D.; Umayal, C. C.; Anbuselvi, M. K. S.; Sumathi, V.	2016	Non energy homeostasis
[Expression of leptin mRNA in luteinized granulosa cells and leptin levels in serum and follicular fluid of non-obese infertile patients with polycystic ovary syndrome]	Lu, X. P.; Wang, B.; Huang, H. F.	2005	Non English
Influence of hypo- and hyperglycaemia on plasma leptin concentrations in healthy women and in women with polycystic ovary syndrome	Ludwig, A.K.; Weiss, J.M.; Tauchert, S.; Dietze, T.; Rudolf, S.; Diedrich, K.; Peters, A.; Oltmanns, K.M.	2007	no outcome of interest
Insulin resistance is a sufficient basis for hyperandrogenism in lipodystrophic women with polycystic ovarian syndrome	Lungu, A. O.; Zadeh, E. S.; Goodling, A.; Cochran, E.; Gorden, P.	2012	Wrong population
IGF-1 and IGFBP-1 in peripheral blood and decidua of early miscarriages with euploid embryos: comparison between women with and without PCOS	Luo, L.; Wang, Q.; Chen, M.; Yuan, G.; Wang, Z.; Zhou, C.	2016	Non energy homeostasis
Antiandrogenic contraceptives increase serum adiponectin in obese polycystic ovary syndrome patients	Luque-Ramirez, M.; Alvarez-Blasco, F.; Escobar-Morreale, H. F.	2009	Non energy homeostasis
Glucagon-like peptide-1 response to glucose challenge is not different in obese adolescents with PCOS, but girls with PCOS respond to acute glucagon-like peptide-1 agonist therapy	Lutchi, K.; Carreau, A.; Garcia-Reyes, Y.; Rahat, H.; Reusch, J. E.; Nadeau, K. J.; Cree-Green, M.	2019	Abstract
Nonobese women with polycystic ovary syndrome respond better than obese women to treatment with metformin	Maciel, G. A.; Soares Junior, J. M.; Alves da Motta, E. L.; Abi Haidar, M.; de Lima, G. R.; Baracat, E. C.	2004	Non energy homeostasis
The association of t45g polymorphism in the adiponectin gene with some hormonal parameters in iraqi women with polycystic ovary syndrome	Majeed, R. A.; Shihab, A. F.; Al-Assei, A. H.	2020	Non energy homeostasis
Rosiglitazone treatment increases plasma levels of adiponectin and decreases levels of resistin in overweight women with PCOS: A randomized placebo-controlled study	Majuri, A.; Santaniemi, M.; Kunnari, A.; Ruokonen, A.; Tapanainen, J. S.; Ukkola, O.; Morin-Papunen, L.	2007	Non energy homeostasis
Peritoneal fluid leptin level in women with unexplained infertility	Malhotra, N.; Tripathi, V.; Kumar, S.; Bahadur, A.; Mittal, S.	2010	Non English
Metabolic parameters in cord blood of newborns of women with polycystic ovary syndrome	Maliqueo, M.; Echiburu, B.; Crisosto, N.; Amigo, P.; Aranda, P.; Sanchez, F.; Sir-Petermann, T.	2009	Wrong population
Relationship of serum adipocyte-derived proteins with insulin sensitivity and reproductive features in pre-pubertal and pubertal daughters of polycystic ovary syndrome women	Maliqueo, M.; Galgani, J. E.; Perez-Bravo, F.; Echiburu, B.; de Guevara, A. L.; Crisosto, N.; Sir-Petermann, T.	2012	Wrong population
[Relationship between leptin and insulin sensitivity in patients with polycystic ovary syndrome]	Maliqueo, M.; Perez-Bravo, F.; Calvillan, M.; Piwonka, V.; Castillo, T.; Sir-Petermann, T.	1999	Non English

[Evaluation of acute effect of GnRH administration on leptin secretion in normal and hyperandrogenic women]	Maliqueo, M.; Piwonka, V.; Perez-Bravo, F.; Candia, M.; Contreras, B.; Contreras, J. M.; Sir-Petermann, T.	2000	Non English
Endothelial function and its relationship to leptin, homocysteine, and insulin resistance in lean and overweight eumenorrheic women and PCOS patients: a pilot study	Mancini, F.; Cianciosi, A.; Marchesini Reggiani, G.; Facchinetti, F.; Battaglia, C.; de Aloysio, D.	2009	Non energy homeostasis
Drospirenone and cardiovascular risk in lean and obese polycystic ovary syndrome patients: a pilot study	Mancini, F.; Cianciosi, A.; Persico, N.; Facchinetti, F.; Busacchi, P.; Battaglia, C.	2010	Non energy homeostasis
Gene expression in subcutaneous adipose tissue differs in women with polycystic ovary syndrome and controls matched pair-wise for age, body weight, and body mass index	Manneras-Holm, L.; Benrick, A.; Stener-Victorin, E.	2014	Non energy homeostasis
Adipose tissue has aberrant morphology and function in PCOS: enlarged adipocytes and low serum adiponectin, but not circulating sex steroids, are strongly associated with insulin resistance	Manneras-Holm, L.; Leonhardt, H.; Kullberg, J.; Jennische, E.; Oden, A.; Holm, G.; Hellstrom, M.; Lonn, L.; Olivecrona, G.; Stener-Victorin, E.; Lonn, M.	2011	Non energy homeostasis
Polycystic Ovary Syndrome and Insulin Physiology: An Observational Quantitative Serum Proteomics Study in Adolescent, Normal-Weight Females	Manousopoulou, A.; Al-Daghri, N. M.; Sabico, S.; Garay-Baquero, D. J.; Teng, J.; Alenad, A.; Alokail, M. S.; Athanasopoulos, N.; Deligeoroglou, E.; Chrousos, G. P.; Bacopoulou, F.; Garbis, S. D.	2019	No outcomes of interest
Predictive value of serum and follicular fluid leptin concentrations during assisted reproductive cycles in normal women and in women with the polycystic ovarian syndrome	Mantzoros, C. S.; Cramer, D. W.; Liberman, R. F.; Barbieri, R. L.	2000	Non energy homeostasis
Leptin concentrations in the polycystic ovary syndrome	Mantzoros, C. S.; Dunaif, A.; Flier, J. S.	1997	Non energy homeostasis
Oral contraceptive use increases risk of inflammatory and coagulatory disorders in women with Polycystic Ovarian Syndrome: An observational study	Manzoor, S.; Ganie, M. A.; Amin, S.; Shah, Z. A.; Bhat, I. A.; Yousuf, S. D.; Jeelani, H.; Kawa, I. A.; Fatima, Q.; Rashid, F.	2019	Non energy homeostasis
Changes and clinical significance of serum leptin levels in patients with polycystic ovarian syndrome. [Chinese]	Mao, X. Y.; Liu, W.; Tao, T.; Li, S. X.	2010	Non English
Correlation between serum adiponectin levels and hyperandrogenism in women with polycystic ovary syndrome	Maranhao, T. M. D. O.; Soares, E. M. M.; Silva, J.; Pontes, A.; Azevedo, G. D.; Lemos, T.; Micussi, M. T.; Pontes, A. G.	2011	Abstract
Relationship between adiponectin levels and measures of central obesity in women with PCOS	Maranhao, T. M.; Mafaldo, E.; Pontes, A.; Azevedo, G.; Lemos, T.; Silva, J.; Micussi, M.	2011	Abstract
Leptin concentrations in patients with polycystic ovary syndrome before and after metformin treatment depending on insulin resistance, body mass index and androgen concentrations - Introductory report	Marciniak, A.; Nawrocka-Rutkowska, J.; Brodowska, A.; Sienkiewicz, R.; Szydlowska, I.; Starczewski, A.	2009	Non energy homeostasis
Study of carbohydrate metabolism indices and adipocytokine profile and their relationship with androgens in polycystic ovary syndrome after menopause	Markopoulos, M. C.; Valsamakis, G.; Kouskouni, E.; Boutsiadis, A.; Papassotiriou, I.; Creatsas, G.; Mastorakos, G.	2013	Non energy homeostasis
Functional neuroimaging of emotional processing in women with polycystic ovary syndrome: a case-control pilot study	Marsh, C. A.; Berent-Spillson, A.; Love, T.; Persad, C. C.; Pop-Busui, R.; Zubieta, J. K.; Smith, Y. R.	2013	Non energy homeostasis

Association of Low Zinc Concentration and Hyperleptinemia with Overweight and Insulin Resistance in Polycystic Ovary Syndrome Women	Mazloomi, S.; Barartabar, Z.; Danesh, H.; Alizadeh, N.; Pilehvari, S.	2022	Non energy homeostasis
Association between Hypoadiponectinemia and Low Serum Concentrations of Calcium and Vitamin D in Women with Polycystic Ovary Syndrome	Mazloomi, Sahar; Sharifi, Faranak; Hajihosseini, Reza; Kalantari, Sadroddin; Mazloomzadeh, Saideh	2012	Non energy homeostasis
Hypoadiponectinemia and high TG/HDLc ratio as risk markers of insulin resistance in obese PCOS women	Meera, S.; Arul Senghor, K. A.; Vinodhini, V. M.; Samal, S.	2020	Non energy homeostasis
Plasma adiponectin in obese and non-obese women with polycystic ovary syndrome	Mejia-Montilla, J.; Alvarez-Mon, M.; Reyna-Villasmil, E.; Torres-Cepeda, D.; Reyna-Villasmil, N.; Fernandez-Ramirez, A.; Bravo-Henriquez, A.	2017	Non English
Supplementation with omega-3 fatty acids and plasma adiponectin in women with polycystic ovary syndrome	Mejia-Montilla, Jorly; Reyna-Villasmil, Eduardo; DomÃnguez-Brito, Lorena; Naranjo-RodrÃguez, Carmen; Noriega-Verdugo, Delia; Padilla-Samaniego, MarÃa; Vargas-Olalla, Vanessa	2018	No control group
Positive correlation of serum leptin with estradiol levels in patients with polycystic ovary syndrome	Mendonca, H. C.; Montenegro, R. M., Jr.; Foss, M. C.; Silva de Sa, M. F.; Ferriani, R. A.	2004	Non energy homeostasis
Polycystic ovary syndrome and nonalcoholic fatty liver in obese adolescents: association with metabolic risk profile	Michaliszyn, Sara F.; Lee, SoJung; Tfayli, Hala; Arslanian, Silva	2013	No control group
Clinical features in women with polycystic ovaries: Relationships to insulin sensitivity, insulin gene VNTR and birth weight	Michelmore, K.; Ken Ong, S. M.; Bennett, S.; Perry, L.; Vessey, M.; Balen, A.; Dunger, D.	2001	Non energy homeostasis
Leptin levels and insulin sensitivity in obese and non-obese patients with polycystic ovary syndrome	Micic, D.; Macut, D.; Popovic, V.; Sumarac-Dumanovic, M.; Kendereski, A.; Colic, M.; Dieguez, C.; Casanueva, F. F.	1997	Non energy homeostasis
Total ghrelin levels during acute insulin infusion in patients with polycystic ovary syndrome	Micic, D.; Sumarac-Dumanovic, M.; Kendereski, A.; Cvijovic, G.; Zoric, S.; Pejkovic, D.; Micic, J.; Milic, N.; Dieguez, C.; Casanueva, F. F.	2007	Non energy homeostasis
Growth-hormone response to combined stimulation with GHRH plus GH-releasing peptide-6 in obese patients with polycystic ovary syndrome before and after short-term fasting	Micic, D.; Sumarac-Dumanovic, M.; Macut, Dj; Kendereski, A.; Zoric, S.; Popovic, V.; Cvijovic, G.; Dieguez, C.; Casanueva, F. F.	2003	Non energy homeostasis
Basic and Meal Stimulated Plasma GIP Levels are Higher in Lean PCOS Women with FAI over 5	Milewicz, T.; Migacz, K.; KiaÅ‚ka, M.; Rogatko, I.; Kowalczuk, A.; Spalkowska, M.; MroziÅ„ska, S.; Czajkowska, Z.; Sztefko, K.	2016	No control group
Association between circulating adiponectin levels and polycystic ovarian syndrome	Mirza, S. S.; Shafique, K.; Shaikh, A. R.; Khan, N. A.; Anwar Qureshi, M.	2014	Non energy homeostasis
L:A ratio, Insulin resistance and metabolic risk in women with polycystic ovarian syndrome	Mishra, S.; Gupta, V.	2017	Non energy homeostasis
Serum markers off autoimmune thyroiditis in euthyroid women with polycystic ovary syndrome	Mitkov, M. D.; Nyagolova, P. V.; Orbetzova, M. M.	2015	Non energy homeostasis
Serum ghrelin level in women with polycystic ovary syndrome and its relationship with endocrine and metabolic parameters	Mitkov, M.; Pehlivanov, B.; Orbetzova, M.	2008	Non energy homeostasis

Expression of 11beta-hydroxysteroid dehydrogenase type 1 in visceral and subcutaneous adipose tissues of patients with polycystic ovary syndrome is associated with adiposity	Mlinar, B.; Marc, J.; Jensterle, M.; Bokal, E. V.; Jerin, A.; Pfeifer, M.	2011	No outcomes of interest
Decreased lipin 1 beta expression in visceral adipose tissue is associated with insulin resistance in polycystic ovary syndrome	Mlinar, B.; Pfeifer, M.; Vrtacnik-Bokal, E.; Jensterle, M.; Marc, J.	2008	Non energy homeostasis
The insulin resistance in women with hyperandrogenism is partially reversed by antiandrogen treatment: evidence that androgens impair insulin action in women	Moghetti, P.; Tosi, F.; Castello, R.; Magnani, C. M.; Negri, C.; Brun, E.; Furlani, L.; Caputo, M.; Muggeo, M.	1996	Non energy homeostasis
Serum levels of anti-mullerian hormone, leptin, T3, T4 and TSH in women with polycystic ovary syndrome in Iraq	Mohaisen, I. K.	2019	Non energy homeostasis
Effects of omegaâˆ’3 fatty acids supplementation on serum adiponectin levels and some metabolic risk factors in women with polycystic ovary syndrome	Mohammadi, Elahe; Rafraf, Maryam; Farzadi, Laya; Asghari-Jafarabadi, Mohammad; Sabour, Siamak		No control group
Relationships between free leptin and insulin resistance in women with polycystic ovary syndrome	Mohiti-Ardekani, J.; Tarof, N.; Aflatonian, A.	2009	Non energy homeostasis
Variations in alanine aminotransferase levels within the normal range predict metabolic and androgenic phenotypes in women of reproductive age	Mojiminiyi, O. A.; Safar, F. H.; Al Rumaih, H.; Diejomaoh, M.	2010	Non energy homeostasis
Gestational weight gain, appetite regulating hormones, and metformin treatment in polycystic ovary syndrome: A longitudinal, placebo-controlled study	Molin, J.; Vanky, E.; Lovvik, T. S.; Dehlin, E.; Bixo, M.	2022	Non energy homeostasis
Adiponectin levels and its relation with insulin secretion and insulin sensitivity in a group of sub-Saharan African women with polycystic ovary syndrome	Momo, A. S.; Ama Moor, V. J.; Tankeu, A. T.; Amazia, F.; Sadeu Wafeu, G.; Guewo-Fokeng, M.; Mbono Samba, E. A.; Nkeck, J. R.; Djieka, Y.; Chemaga Nkonpawa, C.; Djapa Tofeun, F.; Guifo, S.; Dohbit Sama, J.; Choukem, S. P.	2022	Non energy homeostasis
Novel inflammatory markers in overweight women with and without polycystic ovary syndrome and following pharmacological intervention	Moran, L. J.; Meyer, C.; Hutchison, S. K.; Zoungas, S.; Teede, H. J.	2010	Non energy homeostasis
The use of anti-mullerian hormone in predicting menstrual response after weight loss in overweight women with polycystic ovary syndrome	Moran, L. J.; Noakes, M.; Clifton, P. M.; Norman, R. J.	2007	Non energy homeostasis
Short-term meal replacements followed by dietary macronutrient restriction enhance weight loss in polycystic ovary syndrome	Moran, Lisa J; Noakes, Manny; Clifton, Peter M; Wittert, Gary A; Williams, Gemma; Norman, Robert J	2006	No control group
C-Reactive Protein before and after Weight Loss in Overweight Women with and without Polycystic Ovary Syndrome	Moran, Lisa J.; Noakes, Manny; Clifton, Peter M.; Wittert, Gary A.; Belobrajdic, Damien P.; Norman, Robert J.	2007	no outcome of interest
Decreased serum leptin concentrations during metformin therapy in obese women with polycystic ovary syndrome	Morin-Papunen, L. C.; Koivunen, R. M.; Tomas, C.; Ruokonen, A.; Martikainen, H. K.	1998	Non energy homeostasis
Metformin versus ethinyl estradiol-cyproterone acetate in the treatment of nonobese women with polycystic ovary syndrome: a randomized study	Morin-Papunen, L.; Vauhkonen, I.; Koivunen, R.; Ruokonen, A.; Martikainen, H.; Tapanainen, J. S.	2003	Non energy homeostasis
Peri-muscular adipose tissue may play a unique role in determining insulin sensitivity/resistance in women with polycystic ovary syndrome	Morrison, S. A.; Goss, A. M.; Azziz, R.; Raju, D. A.; Gower, B. A.	2017	Non energy homeostasis
Serum kisspeptin levels correlated with anti-mullerian hormone levels in women with and without polycystic ovarian syndrome	Mut, A.; Erel, C. T.; Inan, D.; Oner, Y. O.	2020	No outcomes of interest

Effect of Omega-3 Supplementation on Visfatin, Adiponectin, and Anthropometric Indices in Women with Polycystic Ovarian Syndrome	Nadjarzadeh, Azadeh; Dehghani-Firouzabadi, Razieh; Daneshbodi, Hoorieh; Lotfi, Mohammad Hassan; Vaziri, Niloofar; Mozaffari-Khosravi, Hassan	2015	No control group
Association of adiponectin and resistin gene polymorphisms in South Indian women with polycystic ovary syndrome	Nambiar, V.; Vijesh, V. V.; Lakshmanan, P.; Sukumaran, S.; Suganthi, R.	2016	Non energy homeostasis
The effect of leptin receptor gene polymorphisms (R223Q and P1019P) in susceptibility to polycystic ovarian syndrome in Kurdish women	Naseri, R.; Barzingarosi, E.; Sohrabi, M.; Alimoradi, Y.; Fard, M. C.; Jalili, C.	2021	Non energy homeostasis
Study of Association of Leptin and Insulin Resistance Markers in Patients of PCOS	Nasrat, H.; Patra, S. K.; Goswami, B.; Jain, A.; Raghunandan, C.	2016	Non energy homeostasis
Evaluating the Role of High Molecular Weight Adiponectin in Women with Polycystic Ovary Syndrome Treated with Omega-3 Fatty Acids	Nasser 2020	2020	No control group
Androgen Excess as a Cause for Adipogenic Dysfunction in PCOS Women	Nct,	2013	Trial register
Incretin Effect in PCOS Women	Nct,	2013	Trial register
Metformin for Ectopic Fat Deposition and Metabolic Markers in Polycystic Ovary Syndrome (PCOS)	Nct,	2015	Trial register
The Effect Of Vitamin D Replacement Therapy On Serum Leptin And Follicular Growth Pattern In Women With Resistant Polycystic Ovary	Nct,	2019	Trial register
The Effects of Semaglutide on Taste, Tongue Tissue Transcriptome, Gastric Emptying and Central Neural Response in Women With PCOS and Obesity	Nct,	2020	Trial register
Effects of metformin on ovulation rate, hormonal and metabolic profiles in women with clomiphene-resistant polycystic ovaries: a randomized, double-blinded placebo-controlled trial	Ng, E. H.; Wat, N. M.; Ho, P. C.	2001	Non energy homeostasis
Adiponectin as serum biomarker of insulin resistance in patients with polycystic ovarian syndrome	Niafar, M.; Nader, N. D.	2015	Non energy homeostasis
Changes of serum vitamin D levels in infertile patients with polycystic ovarian syndrome and its significance	Niu, Y.; Wang, X.; Wang, D.; Jiang, X.	2020	Non energy homeostasis
Adiponectin Gene Polymorphism (rs17300539) Has No Influence on the Occurrence of Metabolic Syndrome in Women with Polycystic Ovary Syndrome	Nowak, I.; Ciecwiez, S.; Loj, B.; Brodowski, J.; Brodowska, A.	2021	Non energy homeostasis
High-molecular-weight adiponectin is selectively reduced in women with polycystic ovary syndrome independent of body mass index and severity of insulin resistance	O'Connor, A.; Phelan, N.; Tun, T. K.; Boran, G.; Gibney, J.; Roche, H. M.	2010	Non energy homeostasis
Assessing the variability and predictability of adipokines (adiponectin, leptin, resistin and their ratios) in non-obese and obese women with anovulatory polycystic ovary syndrome	Obirikorang, C.; Owiredu, Wkba; Adu-Afram, S.; Acheampong, E.; Asamoah, E. A.; Antwi-Boasiakoh, E. K.; Owiredu, E. W.	2019	Non energy homeostasis
No evidence for mutations of the leptin or leptin receptor genes in women with polycystic ovary syndrome	Oksanen, L.; Tiitinen, A.; Kaprio, J.; Koistinen, H. A.; Karonen, S. L.; Kontula, K.	2000	Non energy homeostasis
Effects of short term metformin treatment on brown adipose tissue activity and plasma irisin levels in women with polycystic ovary syndrome: A randomized controlled trial	Oliveira, F. R.; Mamede, M.; Bizzi, M. F.; Rocha, A. L. L.; Ferreira, C. N.; Gomes, K. B.; Candido, A. L.; Reis, F. M.	2020	No outcomes of interest

Serum adiponectin and resistin in relation to insulin resistance and markers of hyperandrogenism in lean and obese women with polycystic ovary syndrome	Olszanecka-Glinianowicz, M.; Kuglin, D.; Dabkowska-Huc, A.; Skalba, P.	2011	Non energy homeostasis
Circulating apelin level in relation to nutritional status in polycystic ovary syndrome and its association with metabolic and hormonal disturbances	Olszanecka-Glinianowicz, M.; Madej, P.; Nylec, M.; Owczarek, A.; Szanecki, W.; Skalba, P.; Chudek, J.	2013	Non energy homeostasis
Circulating anti-Mullerian hormone levels in relation to nutritional status and selected adipokines levels in polycystic ovary syndrome	Olszanecka-Glinianowicz, M.; Madej, P.; Owczarek, A.; Chudek, J.; Skalba, P.	2015	Non energy homeostasis
Effect of short-term standard therapeutic regimens on neuropeptide Y and adipose tissue hormones in overweight insulin-resistant women with polycystic ovary syndrome	Orbetzova, M. M.; Pehlivanov, B. K.; Mitkov, M. M.; Atanassova, I. B.; Kamenov, Z. A.; Kolarov, G. B.; Genchev, G. D.	2011	Non energy homeostasis
Circulating ghrelin concentrations in the polycystic ovary syndrome	Orio, F., Jr.; Lucidi, P.; Palomba, S.; Tauchmanova, L.; Cascella, T.; Russo, T.; Zullo, F.; Colao, A.; Lombardi, G.; De Feo, P.	2003	Non energy homeostasis
Exon 6 and 2 peroxisome proliferator-activated receptor-gamma polymorphisms in polycystic ovary syndrome	Orio, F., Jr.; Matarese, G.; Di Biase, S.; Palomba, S.; Labella, D.; Sanna, V.; Savastano, S.; Zullo, F.; Colao, A.; Lombardi, G.	2003	Non energy homeostasis
Lack of an association between peroxisome proliferator-activated receptor-gamma gene Pro12Ala polymorphism and adiponectin levels in the polycystic ovary syndrome	Orio, F., Jr.; Palomba, S.; Cascella, T.; Di Biase, S.; Labella, D.; Russo, T.; Savastano, S.; Zullo, F.; Colao, A.; Vettor, R.; Lombardi, G.	2004	Non energy homeostasis
Adiponectin levels in women with polycystic ovary syndrome	Orio, F., Jr.; Palomba, S.; Cascella, T.; Milan, G.; Mioni, R.; Pagano, C.; Zullo, F.; Colao, A.; Lombardi, G.; Vettor, R.	2003	Non energy homeostasis
Plasma omentin and adiponectin levels as markers of adipose tissue dysfunction in normal weight and obese women with polycystic ovary syndrome	Orlik, B.; Madej, P.; Owczarek, A.; Skalba, P.; Chudek, J.; Olszanecka-Glinianowicz, M.	2014	Non energy homeostasis
Metformin Treatment Regulates the Expression of Molecules Involved in Adiponectin and Insulin Signaling Pathways in Endometria from Women with Obesity-Associated Insulin Resistance and PCOS	Orostica, M. L.; Astorga, I.; Plaza-Parrochia, F.; Poblete, C.; Carvajal, R.; Garcia, V.; Romero, C.; Vega, M.	2022	Non energy homeostasis
Relationship between adipocytokines and angiotensin converting enzyme gene insertion/deletion polymorphism in lean women with and without polycystic ovary syndrome	Ozegowska, K.; Bartkowiak-Wieczorek, J.; Bogacz, A.; Seremak-Mrozikiewicz, A.; Duleba, A. J.; Pawelczyk, L.	2020	Non energy homeostasis
C-Reactive Protein, Fibrinogen, Leptin, and Adiponectin Levels in Women with Polycystic Ovary Syndrome	Ozgokce, C.; Elci, E.; Yildizhan, R.	2020	Non energy homeostasis
Dipeptidyl peptidase-4 and adenosine deaminase enzyme levels in polycystic ovary syndrome	Ozturk, B.; Gurbuz, A. S.; Durak, Z. E.; Ozturk, H. S.	2019	No outcomes of interest
Plasma ghrelin, obesity, and the polycystic ovary syndrome: correlation with insulin resistance and androgen levels	Pagotto, U.; Gambineri, A.; Vicennati, V.; Heiman, M. L.; Tschop, M.; Pasquali, R.	2002	Non energy homeostasis
Correlates of food craving and quality of life in polycystic ovary syndrome	Painold, A.; Milz, P.; Kapfhammer, H. P.; Pieber, T.; Obermayer-Pietsch, B.; Lerchbaum, E.	2012	Abstract
Serum adiponectin and resistin in relation to insulin resistance and markers of hyperandrogenism in lean and obese women with polycystic ovary syndrome	Pangaribuan, B.; Yusuf, I.; Mansyur, M.; Wijaya, A.	2011	Non energy homeostasis
Study on the influence of adiponectin genetic variants and adiponectin levels among Indonesian women with polycystic ovary syndrome	Pangaribuan, B.; Yusuf, I.; Mansyur, M.; Wijaya, A.	2012	Non energy homeostasis

Decrease in adiponectin levels in women with polycystic ovary syndrome after an oral glucose tolerance test	Panidis, D; Farmakiotis, D; Rousso, D; Koliakos, G; Kaltsas, T; Krassas, G	2005	no outcome of interest
The influence of long-term administration of conjugated estrogens and antiandrogens to serum leptin levels in women with polycystic ovary syndrome	Panidis, D. K.; Rousso, D. H.; Matalliotakis, I. M.; Kourtis, A. I.; Stamatopoulos, P.; Koumantakis, E.	2000	Non energy homeostasis
Decreased active, total and altered active to total ghrelin ratio in normal weight women with the more severe form of polycystic ovary syndrome	Panidis, D.; Asteriadis, C.; Georgopoulos, N. A.; Katsikis, I.; Zournatzi, V.; Karkanaki, A.; Saltamavros, A. D.; Decavalas, G.; Diamanti-Kandarakis, E.	2010	Non energy homeostasis
Comparative study of plasma ghrelin levels in women with polycystic ovary syndrome, in hyperandrogenic women and in normal controls	Panidis, D.; Farmakiotis, D.; Koliakos, G.; Rousso, D.; Kourtis, A.; Katsikis, I.; Asteriadis, C.; Karayannis, V.; Diamanti-Kandarakis, E.	2005	Non energy homeostasis
Serum adiponectin levels in women with polycystic ovary syndrome	Panidis, D.; Kourtis, A.; Farmakiotis, D.; Mouselech, T.; Rousso, D.; Koliakos, G.	2003	Non energy homeostasis
Association of the T45G polymorphism in exon 2 of the adiponectin gene with polycystic ovary syndrome: role of Delta4-androstenedione	Panidis, D.; Kourtis, A.; Kukuvitis, A.; Farmakiotis, D.; Xita, N.; Georgiou, I.; Tsatsoulis, A.	2004	Non energy homeostasis
Serum leptin levels in normal-weight and overweight women with polycystic ovary syndrome	Panidis, D.; Rousso, D.; Kourtis, A.; Tsimas, V.; Papathanasiou, K.; Makedos, G.	2003	Non energy homeostasis
Effect of meal frequency on glucose and insulin levels in women with polycystic ovary syndrome: a randomised trial	Papakonstantinou, E; Kechribari, I; Mitrou, P; Trakakis, E; Vassiliadi, D; Georgousopoulou, E; Zampelas, A; Kontogianni, M D; Dimitriadis, G	2016	No control group
Effect of meal frequency on glucose levels in women with polycystic ovary syndrome: A randomized trial	Papakonstantinou, E.; Kechribari, I.; Mitrou, P.; Trakakis, E.; Vassiliadi, D.; Georgousopoulou, E.; Zampelas, A.; Kontogianni, M. D.; Dimitriadis, G.	2015	Abstract
Association of insulin resistance with anti-Mullerian hormone levels in women without polycystic ovary syndrome (PCOS)	Park, H. T.; Cho, G. J.; Ahn, K. H.; Shin, J. H.; Kim, Y. T.; Hur, J. Y.; Kim, S. H.; Lee, K. W.; Kim, T.	2010	Wrong population
Effect of long-term treatment with metformin added to hypocaloric diet on body composition, fat distribution, and androgen and insulin levels in abdominally obese women with and without the polycystic ovary syndrome	Pasquali, R.; Gambineri, A.; Biscotti, D.; Vicennati, V.; Gagliardi, L.; Colitta, D.; Fiorini, S.; Cognigni, G. E.; Filicori, M.; Morselli-Labate, A. M.	2000	Non energy homeostasis
Serum leptin levels correlate with clinical and biochemical indices of insulin resistance in women with polycystic ovary syndrome	Pehlivanov, B.; Mitkov, M.	2009	Non energy homeostasis
Elevated Serum Leptin Levels as a Predictive Marker for Polycystic Ovary Syndrome	Peng, Y.; Yang, H.; Song, J.; Feng, D.; Na, Z.; Jiang, H.; Meng, Y.; Shi, B.; Li, D.	2022	Non energy homeostasis
Evidence for visfatin as an independent predictor of endothelial dysfunction in polycystic ovary syndrome	Pepene, C. E.	2012	Non energy homeostasis
Are circulating leptin and luteinizing hormone synchronized in patients with polycystic ovary syndrome?	Petermann, T.; Piwonka, V.; Perez, F.; Maliqueo, M.; Recabarren, S. E.; Wildt, L.	1999	Non energy homeostasis
Adiponectin levels in adolescent girls with polycystic ovary syndrome (PCOS)	Pinhas-Hamiel, O.; Singer, S.; Pilpel, N.; Koren, I.; Boyko, V.; Hemi, R.; Pariente, C.; Kanety, H.	2009	Non energy homeostasis

Association of anti-mullerian hormone and adiponectin in normal weight and overweight plus obese women with polycystic ovary syndrome	Piouka, A.; Karkanaki, A.; Katsikis, I.; Delkos, D.; Mousatat, T.; Daskalopoulos, G.; Panidis, D.	2011	Abstract
Circulating leptin concentrations and ovarian function in polycystic ovary syndrome	Pirwany, I. R.; Fleming, R.; Sattar, N.; Greer, I. A.; Wallace, A. M.	2001	Non energy homeostasis
Visfatin and leptin levels in women with polycystic ovaries undergoing ovarian stimulation	Plati, E.; Kouskouni, E.; Malamitsi-Puchner, A.; Boutsikou, M.; Kaparos, G.; Baka, S.	2010	Non energy homeostasis
Effect of a low-starch/low-dairy diet on fat oxidation in overweight and obese women with polycystic ovary syndrome	Pohlmeier, Ali M.; Phy, Jennifer L.; Watkins, Phillip; Boylan, Mallory; Spallholz, Julian; Harris, Kitty S.; Cooper, Jamie A.	2014	No control group
The association of serum levels of leptin and ghrelin with the dietary fat content in non-obese women with polycystic ovary syndrome	Polak, A. M.; Krentowska, A.; Lebkowska, A.; Buczynska, A.; Adamski, M.; Adamska-Patruno, E.; Fiedorczuk, J.; Kretowski, A. J.; Kowalska, I.; Adamska, A.	2020	Non energy homeostasis
Changes of body composition and circulating neopterin, omentin-1, and chemerin in response to thylakoid-rich spinach extract with a hypocaloric diet in obese women with polycystic ovary syndrome: A randomized controlled trial	Pourteymour Fard Tabrizi, F.; Abbasalizad Farhangi, M.; Vaezi, M.; Hemmati, S.	2020	No outcomes of interest
Metformin induces lipid changes on sphingolipid species and oxidized lipids in polycystic ovary syndrome women	Pradas, I.; Rovira-Llopis, S.; Naudi, A.; Banuls, C.; Rocha, M.; Hernandez-Mijares, A.; Pamplona, R.; Victor, V. M.; Jove, M.	2019	No outcomes of interest
The effects of 8 months of metformin on circulating GGT and ALT levels in obese women with polycystic ovarian syndrome	Preiss, D.; Sattar, N.; Harborne, L.; Norman, J.; Fleming, R.	2008	Non energy homeostasis
Polycystic ovary syndrome: Dietary intervention needed while fertility treatment. [German]	Pruckler, J.; Leitner, G.; Klein, M.; Gruber, I.	2013	Non English
Circulating ANGPTL8 Is Associated with the Presence of Metabolic Syndrome and Insulin Resistance in Polycystic Ovary Syndrome Young Women	Pu, D.; Li, L.; Yin, J.; Liu, R.; Yang, G.; Liao, Y.; Wu, Q.	2019	Non energy homeostasis
Obesity and polycystic ovary syndrome: association with androgens, leptin and its genotypes	Pusalkar, M.; Meherji, P.; Gokral, J.; Savardekar, L.; Chinnaraj, S.; Maitra, A.	2010	Non energy homeostasis
The natural logarithm of zinc-alpha2-glycoprotein/HOMA-IR is a better predictor of insulin sensitivity than the product of triglycerides and glucose and the other lipid ratios	Qu, C.; Zhou, X.; Yang, G.; Li, L.; Liu, H.; Liang, Z.	2016	Non energy homeostasis
Effect of the use of L-Arginine, Caffeine or Creatine supplements associated with physical activity in women with Polycystic Ovary Syndrome with Metabolic Syndrome	R. B. R. jt	9832	Trial register
Haplotype TGTG from SNP 45T/G and 276G/T of the adiponectin gene contributes to risk of polycystic ovary syndrome	Radavelli-Bagatini, S.; de Oliveira, I. O.; Ramos, R. B.; Santos, B. R.; Wagner, M. S.; Lecke, S. B.; Gigante, D. P.; Horta, B. L.; Spritzer, P. M.	2013	Non energy homeostasis
Serum levels of angiopoietin-like protein 2 and obestatin in iranian women with polycystic ovary syndrome and normal body mass index	Rahmani, E.; Akbarzadeh, S.; Broomand, A.; Torabi, F.; Motamed, N.; Zohrabi, M.	2018	No outcomes of interest
Expression of leptin (Ob gene product) in reproductive system with special reference to polycystic ovary syndrome	Ram, M. R.; Shanthi, P.; Malathi, R.	2010	Non energy homeostasis
Body fat distribution and leptin correlation in women with polycystic ovary syndrome: Endocrine and biochemical evaluation in south Indian population	Ram, M. R.; Sundararaman, P. G.; Malathi, R.	2005	Non energy homeostasis

Influence of gene variants related to calcium homeostasis on biochemical parameters of women with polycystic ovary syndrome	Ranjzad, F.; Mahban, A.; Irani Shemirani, A.; Mahmoudi, T.; Vahedi, M.; Nikzamir, A.; Zali, M. R.	2011	Non energy homeostasis
A common variant in the adiponectin gene and polycystic ovary syndrome risk	Ranjzad, F.; Mahmoudi, T.; Irani Shemirani, A.; Mahban, A.; Nikzamir, A.; Vahedi, M.; Ashrafi, M.; Gourabi, H.	2012	Non energy homeostasis
Metabolic effects of short-term whey protein supplementation in polycystic ovary syndrome	Rao, M.; Zumbro, E.; Broughton, K. S.; LeMieux, M.	2019	Abstract
Differential Impact of Insulin Sensitizers vsAnti-Androgen on Serum Leptin Levels in Vitamin D Replete PCOS Women: A Six Month Open Labeled Randomized Study	Rashid, A.; Ganie, M. A.; Bhat, G. A.; Shaheen, F.; Wani, I. A.; Shrivastava, M.; Shah, Z. A.	2020	Non energy homeostasis
Endocrine and metabolic effects of rosiglitazone in overweight women with PCOS: a randomized placebo-controlled study	Rautio, K.; Tapanainen, J. S.; Ruokonen, A.; Morin-Papunen, L. C.	2006	Non energy homeostasis
Cytokines and leptin correlation in patients with polycystic ovary syndrome: Biochemical evaluation in south Indian population	Ravishankar Ram, M.; Sundararaman, P. G.; Mahadevan, S.; Malathi, R.	2005	Non energy homeostasis
Central arterial stiffness and diastolic dysfunction are associated with insulin resistance and abdominal obesity in young women but polycystic ovary syndrome does not confer additional risk	Rees, E.; Coulson, R.; Dunstan, F.; Evans, W. D.; Blundell, H. L.; Luzio, S. D.; Dunseath, G.; Halcox, J. P.; Fraser, A. G.; Rees, D. A.	2014	Non energy homeostasis
Does adiponectin protect against the cardiovascular dysfunction associated with central adiposity in young women with polycystic ovary syndrome?	Rees, E.; Hocking, R.; Dunstan, F.; Lewis, M.; Tunstall, K.; Halcox, J. P.; Fraser, A. G.; Rees, D. A.	2013	Abstract
Evidence for competing effects of body mass, hyperinsulinemia, insulin resistance, and androgens on leptin levels among lean, overweight, and obese women with polycystic ovary syndrome	Remsberg, K. E.; Talbott, E. O.; Zborowski, J. V.; Evans, R. W.; McHugh-Pemu, K.	2002	Non energy homeostasis
Oral quercetin supplementation enhances adiponectin receptor transcript expression in polycystic ovary syndrome patients: A randomized placebo-controlled double-blind clinical trial	Rezvan, N.; Moini, A.; Gorgani-Firuzjaee, S.; Hosseinzadeh-Attar, M. J.	2018	Non energy homeostasis
Effects of Quercetin on Adiponectin-Mediated Insulin Sensitivity in Polycystic Ovary Syndrome: A Randomized Placebo-Controlled Double-Blind Clinical Trial	Rezvan, N.; Moini, A.; Janani, L.; Mohammad, K.; Saedisomeolia, A.; Nourbakhsh, M.; Gorgani-Firuzjaee, S.; Mazaherioun, M.; Hosseinzadeh-Attar, M. J.	2017	Non energy homeostasis
Leptin as well as free leptin receptor is associated with polycystic ovary syndrome in young women	Rizk, N. M.; Sharif, E.	2015	Non energy homeostasis
Low validity of predictive equations for calculating resting energy expenditure in overweight and obese women with polycystic ovary syndrome	Rodrigues, A. M. dos S.; Costa, A. B. P.; Campos, D. L.; Silva, M. P. S.; CÃ¢ndido, A. L.; Santos, L. C. dos; Ferreira, A. V. M.	2018	No control group
Altered multihormone synchrony in obese patients with polycystic ovary syndrome	Roelfsema, Ferdinand; Kok, Petra; Veldhuis, Johannes D.; Pijl, Hanno	2011	no outcome of interest
Metformin treatment does not affect total leptin levels and free leptin index in obese patients with polycystic ovary syndrome	Romualdi, D.; Campagna, G.; Selvaggi Jr, L.; Cento, R.; Proto, C.; Lanzone, A.; Guido, M.	2008	Non energy homeostasis
Alteration of ghrelin-neuropeptide Y network in obese patients with polycystic ovary syndrome: role of hyperinsulinism	Romualdi, D.; De Marinis, L.; Campagna, G.; Proto, C.; Lanzone, A.; Guido, M.	2008	Non energy homeostasis

The resting metabolic rate in women with polycystic ovary syndrome and its relation to the hormonal milieu, insulin metabolism, and body fat distribution: a cohort study	Romualdi, D.; Versace, V.; Tagliaferri, V.; De Cicco, S.; Immediata, V.; Apa, R.; Guido, M.; Lanzone, A.	2019	No outcomes of interest
Serum leptin concentrations in women with polycystic ovary syndrome	Rouru, J.; Anttila, L.; Koskinen, P.; Penttila, T. A.; Irjala, K.; Huupponen, R.; Koulu, M.	1997	Non energy homeostasis
Serum metabolomics of Indian women with polycystic ovary syndrome using ¹H NMR coupled with a pattern recognition approach	RoyChoudhury, S.; Mishra, B. P.; Khan, T.; Chattopadhayay, R.; Lodh, I.; Datta Ray, C.; Bose, G.; Sarkar, H. S.; Srivastava, S.; Joshi, M. V.; Chakravarty, B.; Chaudhury, K.	2016	No outcomes of interest
Comparative studies of the role of hormone-sensitive lipase and adipose triglyceride lipase in human fat cell lipolysis	Ryden, M.; Jocken, J.; van Harmelen, V.; Dicker, A.; Hoffstedt, J.; Wiren, M.; Blomqvist, L.; Mairal, A.; Langin, D.; Blaak, E.; Arner, P.	2007	No outcomes of interest
The levels and ratios of adipokines in the follicular fluid as promising prognostic factors for in vitro fertilization outcomes	Ryzhov, J.; Shpakov, A.; Tkachenko, N.; Mahmadalieva, M.; Kogan, I.; Gzgzyan, A.	2021	Abstract
Association of SerumOmentin Levels in Women with PolyCystic Ovarian Syndrome	Saadati, N.; Yaghmaei, P.; Haghighi, S.; Hashemi, F.; Ramezani, Tehrani F.; Hedayati, M.	2012	Non English
Serum homocysteine is associated with polycystic ovarian syndrome in Jordan	Saadeh, N.; Alfaqih, M. A.; Mansour, H.; Khader, Y. S.; Saadeh, R.; Al-Dwairi, A.; Nusier, M.	2018	Non energy homeostasis
Serum homocysteine is associated with polycystic ovarian syndrome in Jordan	Saadeh, N.; Alfaqih, M. A.; Mansour, H.; Khader, Y. S.; Saadeh, R.; Al-Dwairi, A.; Nusier, M.	2018	Non energy homeostasis
Circulating levels of C1q/TNF-alpha-related protein 6 (CTRP6) in polycystic ovary syndrome	Sadeghi, A.; Fadaei, R.; Moradi, N.; Fouani, F. Z.; Roozbehkia, M.; Zandieh, Z.; Ansaripour, S.; Vatannejad, A.; Doustimotlagh, A. H.	2020	Non energy homeostasis
Computational methods are significant determinants of the associations and definitions of insulin resistance using the homeostasis model assessment in women of reproductive age	Safar, F. H.; Mojiminiyi, O. A.; Al-Rumaih, H. M.; Diejomaoh, M. F.	2011	Non energy homeostasis
The Effects of Raw Red Onion Consumption on Serum Levels of Adiponectin, Leptin, and hs-CRP in Overweight/Obese Females with Polycystic Ovarian Syndrome: A Randomized Controlled-Clinical Trial	Saghafi-Asl, Maryam; Ebrahimi-Mameghani, Mehranghiz	2017	No control group
The effects of oral contraceptives including low-dose estrogen and drospirenone on the concentration of leptin and ghrelin in polycystic ovary syndrome	Sagsoz, N.; Orbak, Z.; Noyan, V.; Yucel, A.; Ucar, B.; Yildiz, L.	2009	Non energy homeostasis
Nesfatin-1 and Vitamin D levels may be associated with systolic and diastolic blood pressure values and hearth rate in polycystic ovary syndrome	Sahin, F. K.; Sahin, S. B.; Ural, U. M.; Cure, M. C.; Senturk, S.; Tekin, Y. B.; Balik, G.; Cure, E.; Yuce, S.; Kirbas, A.	2015	Non energy homeostasis
Leptin levels increase during flutamide therapy in women with polycystic ovary syndrome	Sahin, I.; Serter, R.; Karakurt, F.; Demirbas, B.; Guler, S.; Culha, C.; Taskapan, C.; Aral, Y.	2003	Non energy homeostasis
Insulin levels, insulin resistance, and leptin levels are not associated with the development of ovarian hyperstimulation syndrome	Salamalekis, E.; Makrakis, E.; Vitoratos, N.; Chassiakos, D.; Baka, S.; Creatsas, G.	2004	Non energy homeostasis
Serum leptin elevation in obese women with PCOs: a continuing controversy	Saleh, H. A.; El-Nwaem, M. A.; El-Bordiny, M. M.; Maqlad, H. M.; El-Mohandes, A. A.; Eldaqaq, E. M.	2004	Non energy homeostasis

Evaluation of some physiological parameters for obese women suffering from pregnant disturbance in Basrah Governorate, Iraq-Case Study	Salman, S. A.; Yser, H. T.	2022	Non energy homeostasis
Assesment of relationships between the HMWAdiponectin and insulin resistance in normal weight adolescents with PCOS	Saltek, S.; Demir, B.; Dilbaz, B.; Demirtas, C.	2013	Abstract
Exaggerated glucagon responses to hypoglycemia in women with polycystic ovary syndrome	Sam, S.; Vellanki, P.; Yalamanchi, S. K.; Bergman, R. N.; Dunaif, A.	2017	No outcomes of interest
Association of the polycystic ovary syndrome with genomic variants related to insulin resistance, type 2 diabetes mellitus, and obesity	San Millan, J. L.; Corton, M.; Villuendas, G.; Sancho, J.; Peral, B.; Escobar-Morreale, H. F.	2004	Non energy homeostasis
Validity of adiponectin-to-leptin and adiponectin-to-resistin ratios as predictors of polycystic ovary syndrome	Sarray, S.; Madan, S.; Saleh, L. R.; Mahmoud, N.; Almawi, W. Y.	2015	Non energy homeostasis
Effect of rimonabant and metformin on glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 in obese women with polycystic ovary syndrome	Sathyapalan, T.; Cho, L.; Kilpatrick, E. S.; Le Roux, C. W.; Coady, A. M.; Atkin, S. L.	2010	Non energy homeostasis
Serum 25-Hydroxyvitamin D Levels, Phosphoprotein Enriched in Diabetes Gene Product (PED/PEA-15) and Leptin-to-Adiponectin Ratio in Women with PCOS	Savastano, S.; Valentino, R.; Di Somma, C.; Orio, F.; Pivonello, C.; Passeretti, F.; Brancato, V.; Formisano, P.; Colao, A.; Beguinot, F.; Tarantino, G.	2011	Non energy homeostasis
Circulating ghrelin levels in patients with polycystic ovary syndrome	Schofl, C.; Horn, R.; Schill, T.; Schlosser, H. W.; Muller, M. J.; Brabant, G.	2002	Non energy homeostasis
Does homocysteine and ghrelin link in polcystic ovary syndrome relate to obesity?	Sen, T. A.	2012	Non English
Effect of brisk walking on adiponectin levels in women with polycystic ovarian syndrome	Senghor, K. A. A.; Meera, S.; Vinodhini, V. M.; Anuradha, M.	2021	Abstract
Serum Preptin and Amylin Levels with Respect to Body Mass Index in Polycystic Ovary Syndrome Patients	Senturk, S.; Hatirnaz, S.; Kanat-Pektas, M.	2018	Non energy homeostasis
Expression levels of haem oxygenase-1 in the omental adipose tissue and peripheral blood mononuclear cells of women with polycystic ovary syndrome	Seow, K. M.; Hwang, J. L.; Wang, P. H.; Ho, L. T.; Lin, Y. H.; Juan, C. C.	2011	Non energy homeostasis
Omental fat expression of adiponectin and adiponectin receptors in non-obese women with PCOS: a preliminary study	Seow, K. M.; Tsai, Y. L.; Juan, C. C.; Lin, Y. H.; Hwang, J. L.; Ho, L. T.	2009	Non energy homeostasis
Adiponectin levels in women with polycystic ovary syndrome and severe insulin resistance	Sepilian, V.; Nagamani, M.	2005	Non energy homeostasis
Serum soluble leptin receptor levels and free leptin index in women with polycystic ovary syndrome: relationship to insulin resistance and androgens	Sepilian, Vicken P.; Crochet, John R.; Nagamani, Manubai	2006	no outcome of interest
The effect of vitamin D supplementation on insulin resistance, visceral fat and adiponectin in vitamin D deficient women with polycystic ovary syndrome: a randomized placebo-controlled trial	Seyyed Abootorabi, Maryam; Ayremlou, Parvin; Behroozi-Lak, Tahereh; Nourisaeidlou, Sakineh	2018	No control group
Effects of Oral Contraception and Lifestyle Modification on Incretins and TGF-s Superfamily Hormones in PCOS	Shah, A.; Dodson, W. C.; Kris-Etherton, P. M.; Kunselman, A. R.; Stetter, C. M.; Gnatuk, C. L.; Estes, S. J.; Allison, K. C.; Sarwer, D. B.; Sluss, P. M.; Coutifaris, C.; Dokras, A.; Legro, R. S.	2021	Duplicate
Effects of Oral Contraception and Lifestyle Modification on Incretins and TGF-ß Superfamily Hormones in PCOS	Shah, Aesha; Dodson, William C.; Kris-Etherton, Penny M.; Kunselman, Allen R.; Stetter, Christy M.; Gnatuk, Carol L.; Estes, Stephanie J.; Allison,	2021	Non energy homeostasis

	Kelly C.; Sarwer, David B.; Sluss, Patrick M.; Coutifaris, Christos; Dokras, Anuja; Legro, Richard S.		
Effect of treatment with metformin on omentin-1, ghrelin and other biochemical, clinical features in PCOS patients	Shaker, M.; Al-Mashhadani, Z. I.; Mehdi, A. A.	2010	Non energy homeostasis
Lower circulating levels of CTRP12 and CTRP13 in polycystic ovarian syndrome: Irrespective of obesity	Shanaki, M.; Moradi, N.; Fadaei, R.; Zandieh, Z.; Shabani, P.; Vatannejad, A.	2018	Non energy homeostasis
Decreased adiponectin levels in polycystic ovary syndrome, independent of body mass index	Sharifi, F.; Hajihosseini, R.; Mazloomi, S.; Amirmogaddami, H.; Nazem, H.	2010	Non energy homeostasis
Obesity and inflammatory biomarkers in women with polycystic ovary syndrome	Shen, S. H.; Shen, S. Y.; Liou, T. H.; Hsu, M. I.; Chang, Y. C.; Cheng, C. Y.; Hsu, C. S.; Tzeng, C. R.	2015	Non energy homeostasis
Insulin resistance and high molecular weight adiponectin in obese and non-obese patients with Polycystic Ovarian Syndrome (PCOS)	Shirazi, F. K. H.; Khodamoradi, Z.; Jeddi, M.	2022	Non energy homeostasis
High-molecular-weight adiponectin is inversely associated with sympathetic activity in polycystic ovary syndrome	Shorakae, S.; Abell, S. K.; Hiam, D. S.; Lambert, E. A.; Eikelis, N.; Jona, E.; Sari, C. I.; Stepto, N. K.; Lambert, G. W.; de Courten, B.; Teede, H. J.	2019	Non energy homeostasis
Brown adipose tissue thermogenesis in polycystic ovary syndrome	Shorakae, S.; Jona, E.; de Courten, B.; Lambert, G. W.; Lambert, E. A.; Phillips, S. E.; Clarke, I. J.; Teede, H. J.; Henry, B. A.	2019	No outcomes of interest
Inter-related effects of insulin resistance, hyperandrogenism, sympathetic dysfunction and chronic inflammation in PCOS	Shorakae, S.; Ranasinha, S.; Abell, S.; Lambert, G.; Lambert, E.; de Courten, B.; Teede, H.	2018	Non energy homeostasis
Young obese women with polycystic ovary syndrome have evidence of early coronary atherosclerosis	Shroff, R.; Kerchner, A.; Maifeld, M.; Van Beek, E. J.; Jagasia, D.; Dokras, A.	2007	Non energy homeostasis
Serum adiponectin in women with polycystic ovarian syndrome and its relation to clinical, metabolic and endocrine parameters	Sieminska, L.; Marek, B.; Kos-Kudla, B.; Niedziolka, D.; Kajdaniuk, D.; Nowak, M.; Glogowska-Szelag, J.	2004	Non energy homeostasis
Plasma adiponectin levels in women with polycystic ovary syndrome: impact of metformin treatment in a case-control study	Singh, S.; Akhtar, N.; Ahmad, J.	2012	Non energy homeostasis
Serum adiponectin and lipid concentrations in pregnant women with polycystic ovary syndrome	Sir-Petermann, T.; Echiburu, B.; Maliqueo, M. M.; Crisosto, N.; Sanchez, F.; Hitschfeld, C.; Carcamo, M.; Amigo, P.; Perez-Bravo, F.	2007	Non energy homeostasis
Secretory pattern of leptin and LH during lactational amenorrhoea in breastfeeding normal and polycystic ovarian syndrome women	Sir-Petermann, T.; Recabarren, S. E.; Lobos, A.; Maliqueo, M.; Wildt, L.	2001	Non energy homeostasis
The level of adiponectin in the obese women with menstruation disorders and insulin resistance. [Polish, English]	Skalba, P.; Kuglin, D.; Dabkowska-Huc, A.	2009	Non energy homeostasis
Analysis of leptin pulses in serum in women with polycystic ovary syndrome. [Polish]	Skalba, P.; Rudzki, K.; Mroczka, W.; Dabkowska-Huc, A.; Chelmicki, A.; Czech, E.	2006	Non English
Gherlin expression in women with polycystic ovary syndrome - A preliminary study	Skommer, J.; Katulski, K.; Poreba, E.; Meczekalski, B.; Slopien, R.; Plewa, R.; Gozdzicka-Jozefiak, A.; Warenik-Szymankiewicz, A.	2005	Non energy homeostasis

Pioglitazone enhances mitochondrial biogenesis and ribosomal protein biosynthesis in skeletal muscle in polycystic ovary syndrome	Skov, V.; Glintborg, D.; Knudsen, S.; Tan, Q.; Jensen, T.; Kruse, T. A.; Beck-Nielsen, H.; Hojlund, K.	2008	Non energy homeostasis
Assessment of leptin levels in the different genotypes and leptin receptor genes in the women with polycystic ovary syndrome and diabetes mellitus type 2 in Iraq population	Smaism, M. F.	2016	Non energy homeostasis
The effect of metformin and myoinositol on metabolic outcomes in women with polycystic ovary syndrome: role of body mass and adiponectin in a randomized controlled trial.	Soldat-Stanković V, Popović-Pejičić S, Stanković S, Prtina A, Malešević G, Bjekić-Macut J, Livadas S, Ognjanović S, Mastorakos G, Micić D, Macut D.	2022	Non energy homeostasis
Does polycystic ovary syndrome affect cognition? A functional magnetic resonance imaging study exploring working memory	Soleman, R. S.; Kreukels, B. P. C.; Veltman, D. J.; Cohen-Kettenis, P. T.; Hompes, P. G. A.; Drent, M. L.; Lambalk, C. B.	2016	Non energy homeostasis
Effects of pioglitazone on serum adipocytokines in polycystic ovary syndrome patients with insulin resistance. [Chinese]	Song, Q.; Gou, W. L.	2010	Non English
Effects of pioglitazone on serum leptin and adiponectin in polycystic ovary syndrome patients with insulin resistance	Song, Q.; Gou, W. L.; Ding, X. J.	2010	Non English
Adipokines, Insulin Resistance and Hyperandrogenemia in Obese Patients with Polycystic Ovary Syndrome: Cross-Sectional Correlations and the Effects of Weight Loss	Spanos, Nikolaos; Tziomalos, Konstantinos; Macut, Djuro; Koiou, Ekaterini; Kandaraki, Eleni A.; Delkos, Dimitrios; Tsourdi, Elena; Panidis, Dimitrios	2012	no outcome of interest
Adiponectin is independently associated with insulin sensitivity in women with polycystic ovary syndrome	Spranger, J.; Mohlig, M.; Wegewitz, U.; Ristow, M.; Pfeiffer, A. F.; Schill, T.; Schlosser, H. W.; Brabant, G.; Schofl, C.	2004	Non energy homeostasis
Influence of leptin, androgens and insulin sensitivity on increased GH response to clonidine in lean patients with polycystic ovary syndrome	Spritzer, P. M.; Comim, F. V.; Capp, E.; D'Avila, A.	2005	Non energy homeostasis
Leptin concentrations in hirsute women with polycystic ovary syndrome or idiopathic hirsutism: influence on LH and relationship with hormonal, metabolic, and anthropometric measurements	Spritzer, P. M.; Poy, M.; Wiltgen, D.; Mylius, L. S.; Capp, E.	2001	Non energy homeostasis
Effects of the insulin sensitizer pioglitazone on menstrual irregularity, insulin resistance and hyperandrogenism in young women with polycystic ovary syndrome	Stabile, G.; Borrielli, I.; Artenisio, A. C.; Bruno, L. M.; Benvenga, S.; Giunta, L.; La Marca, A.; Volpe, A.; Pizzo, A.	2014	Non energy homeostasis
A randomized trial of the effects of two types of short-term hypocaloric diets on weight loss in women with polycystic ovary syndrome	Stamets, Kelly; Taylor, Denise S; Kunselman, Allen; Demers, Laurence M; Pelkman, Christine L; Legro, Richard S	2004	No control group
Association between Circulating Adiponectin and Heart Rate Recovery in Women with Polycystic Ovarian Syndrome	Sun, W.; Liu, G.; Liu, B.	2022	Non energy homeostasis
Family-Based Association Study of rs17300539 and rs12495941 Polymorphism in Adiponectin Gene and Polycystic Ovary Syndrome in a Chinese Population	Sun, X.; Wu, X.; Duan, Y.; Liu, G.; Yu, X.; Zhang, W.	2017	Non energy homeostasis
Adipose expression of adipocytokines in women with polycystic ovary syndrome	Svendsen, P. F.; Christiansen, M.; Hedley, P. L.; Nilas, L.; Pedersen, S. B.; Madsbad, S.	2012	Non energy homeostasis
Incretin hormone secretion in women with polycystic ovary syndrome: roles of obesity, insulin sensitivity, and treatment with metformin	Svendsen, P. F.; Nilas, L.; Madsbad, S.; Holst, J. J.	2009	Non energy homeostasis

Obesity, body composition and metabolic disturbances in polycystic ovary syndrome	Svendsen, P. F.; Nilas, L.; Norgaard, K.; Jensen, J.-E. B.; Madsbad, S.	2008	no outcome of interest
Activity Of Dipeptidyl Peptidase-4 (Dpp-4) In Polycystic Ovary Syndrome And Its Association With Insulin Resistance	Syabakhash, R. A.; Alwasiti, E.; Adnan, E.	2020	No outcomes of interest
Basal leptin concentrations in women with normal and dysfunctional ovarian conditions	Takeuchi, T.; Tsutsumi, O.	2000	Non energy homeostasis
Assessment of the predictive value of follicular fluid insulin, leptin and adiponectin in assisted reproductive cycles	Takikawa, S.; Iwase, A.; Goto, M.; Harata, T.; Umezu, T.; Nakahara, T.; Kobayashi, H.; Suzuki, K.; Manabe, S.; Kikkawa, F.	2010	Non energy homeostasis
Correlation of serum amylin level to polycystic ovarian syndrome	Talaq, A. M.; Ahmed, S. S.	2019	Non energy homeostasis
Upregulation of adiponectin receptor 1 and 2 mRNA and protein in adipose tissue and adipocytes in insulin-resistant women with polycystic ovary syndrome	Tan, B. K.; Chen, J.; Digby, J. E.; Keay, S. D.; Kennedy, C. R.; Randeva, H. S.	2006	Non energy homeostasis
Expression of the CD11c gene in subcutaneous adipose tissue is associated with cytokine level and insulin resistance in women with polycystic ovary syndrome	Tao, T.; Li, S.; Zhao, A.; Zhang, Y.; Liu, W.	2012	Non energy homeostasis
Role of adiponectin/peroxisome proliferator-activated receptor alpha signaling in human chorionic gonadotropin-induced estradiol synthesis in human luteinized granulosa cells	Tao, T.; Wang, Y.; Xu, B.; Mao, X.; Sun, Y.; Liu, W.	2019	Non energy homeostasis
Distribution of adiponectin multimeric forms in Chinese women with polycystic ovary syndrome and their relation to insulin resistance	Tao, T.; Wickham, E. P., 3rd; Fan, W.; Yang, J.; Liu, W.	2010	Non energy homeostasis
Ovarian HMW adiponectin is associated with folliculogenesis in women with polycystic ovary syndrome	Tao, T.; Xu, B.; Liu, W.	2013	Non energy homeostasis
Impact of treatment with metformin on adipokines in patients with polycystic ovary syndrome	Tarkun, I.; Dikmen, E.; Cetinarslan, B.; Canturk, Z.	2010	Non energy homeostasis
Treatment of obstructive sleep apnea improves cardiometabolic function in young obese women with polycystic ovary syndrome	Tasali, E.; Chapotot, F.; Leproult, R.; Whitmore, H.; Ehrmann, D. A.	2011	Non energy homeostasis
NUCB2 gene polymorphism and its relationship with nesfatin-1 levels in polycystic ovary syndrome	Taskin, M. I.; Eser, B.; Adali, E.; Kara, H.; Cuce, C.; Hismiogullari, A. A.	2016	Non energy homeostasis
Acetyl-L-Carnitine Ameliorates Metabolic and Endocrine Alterations in Women with PCOS: A Double-Blind Randomized Clinical Trial	Tauqir, S.; Israr, M.; Rauf, B.; Malik, M. O.; Habib, S. H.; Shah, F. A.; Usman, M.; Raza, M. A.; Shah, I.; Badshah, H.; Ehtesham, E.; Shah, M.	2021	Non energy homeostasis
Post-prandial thermogenesis and insulin sensitivity in the polycystic ovary syndrome	Taylor, R.	1992	Wrong design
Relationship between polymorphism of insulin receptor gene, and adiponectin gene with PCOS	Tehrani, F. R.; Daneshpour, M.; Hashemi, S.; Zarkesh, M.; Azizi, F.	2013	Non energy homeostasis
Serum leptin levels in patients with polycystic ovary syndrome	Telli, M. H.; Yildirim, M.; Noyan, V.	2002	Non energy homeostasis
Serum nonesterified fatty acids, ghrelin, and homocysteine levels in women with polycystic ovary syndrome. [Turkish]	Temel, I.; Celik, O.; Hascalik, S.; Celik, N.; Sahin, I.; Aydin, S.	2010	Non energy homeostasis
Drospirenone/ethinyl estradiol versus rosiglitazone treatment in overweight adolescents with polycystic ovary syndrome: comparison of metabolic, hormonal, and cardiovascular risk factors	Tfayli, H.; Ulnach, J. W.; Lee, S.; Sutton-Tyrrell, K.; Arslanian, S.	2011	Non energy homeostasis

Differences in low-grade chronic inflammation and insulin resistance in women with previous gestational diabetes mellitus and women with polycystic ovary syndrome	Thomann, R.; Rossinelli, N.; Keller, U.; Tirri, B. F.; De Geyter, C.; Ruiz, J.; Kranzlin, M.; Puder, J. J.	2008	Non energy homeostasis
The predictive effect of inflammatory markers and lipid accumulation product index on clinical symptoms associated with polycystic ovary syndrome in nonobese adolescents and younger aged women	Tola, E. N.; Yalcin, S. E.; Dugan, N.	2017	No outcomes of interest
Adiponectin levels in women with polycystic ovary syndrome: impact of metformin treatment in a randomized controlled study	Trolle, B.; Lauszus, F. F.; Frystyk, J.; Flyvbjerg, A.	2010	Non energy homeostasis
Metformin increases fasting plasma peptide tyrosine tyrosine (PYY) in women with polycystic ovarian syndrome (PCOS)	Tsilchorozidou, T.; Batterham, R. L.; Conway, G. S.	2008	Non energy homeostasis
Lipid lipoprotein profile alterations in Greek infertile women with polycystic ovaries: influence of adipocytokines levels	Tsouma, I.; Kouskouni, E.; Demeridou, S.; Boutsikou, M.; Hassiakos, D.; Chasiakou, A.; Hassiakou, S.; Gennimata, V.; Baka, S.	2014	Non energy homeostasis
Leptin levels in women with polycystic ovaries undergoing ovarian stimulation: relation to lipoprotein profiles	Tsouma, I.; Kouskouni, E.; Gennimata, V.; Demeridou, S.; Boutsikou, M.; Grigoriou, V.; Chasiakou, A.; Hassiakou, S.; Baka, S.	2014	Non energy homeostasis
LEPR gene polymorphism and plasma soluble leptin receptor levels are associated with polycystic ovary syndrome in Han Chinese women	Tu, X.; Yu, C.; Gao, M.; Zhang, Y.; Zhang, Z.; He, Y.; Yao, L.; Du, J.; Sun, Y.; Sun, Z.	2017	Non energy homeostasis
Dietary intake, eating behaviors, and quality of life in women with polycystic ovary syndrome who are trying to conceive	Turner-McGrievy, G.; Davidson, C. R.; Billings, D. L.	2015	Non energy homeostasis
Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists in the Treatment of Obese Women with Polycystic Ovary Syndrome	Tzotzas, T.; Karras, S. N.; Katsiki, N.	2017	Wrong design
Phoenixin-14 concentrations are increased in association with luteinizing hormone and nesfatin-1 concentrations in women with polycystic ovary syndrome	Ullah, K.; Ur Rahman, T.; Wu, D. D.; Lin, X. H.; Liu, Y.; Guo, X. Y.; Leung, P. C. K.; Zhang, R. J.; Huang, H. F.; Sheng, J. Z.	2017	Non energy homeostasis
Serum leptin changes with metformin treatment in polycystic ovarian syndrome: Correlation with ovulation, insulin and testosterone levels	Upadhyaya, P.; Rehan, H. S.; Seth, V.	2011	Non energy homeostasis
Increase in daily LH secretion in response to short-term calorie restriction in obese women with PCOS	Van Dam, Eveline W. C. M.; Roelfsema, Ferdinand; Veldhuis, Johannes D.; Helmerhorst, Frans M.; FrÃ¶lich, Marijke; Meinders, A. Edo; Krans, H. Michiel J.; Pijl, Hanno	2002	no outcome of interest
Disorders of the glucose metabolism correlate with the phenotype and the severity in women with polycystic ovary syndrome	van Helden, J.; Evliyaoglu, O.; Kuberl, A.; Weiskirchen, R.	2020	Non energy homeostasis
Glucose-induced inhibition of the appetitive brain response to visual food cues in polycystic ovary syndrome patients	Van Vugt, Dean A.; Krzemien, Alicja; Alsaadi, Hanin; Frank, Tamar C.; Reid, Robert L.	2014	No control group
Effect of Insulin Sensitivity on Corticolimbic Responses to Food Picture in Women with Polycystic Ovary Syndrome: Insulin Sensitivity and Brain Activation	Van Vugt, Dean A.; Krzemien, Alicja; Alsaadi, Hanin; Palerme, Stephanie; Reid, Robert L.	2013	No control group
Metabolic and endocrine effects of long-chain versus essential omega-3 polyunsaturated fatty acids in polycystic ovary syndrome	Vargas, M. Luisa; Almario, Rogelio U.; Buchan, Wendy; Kim, Kyoungmi; Karakas, Sidika E.	2011	No control group
Plasma Complement C1q/tumor necrosis factor-related protein 15 concentration is associated with polycystic ovary syndrome	Vatannejad, A.; Fadaei, R.; Salimi, F.; Fouani, F. Z.; Habibi, B.; Shapourizadeh, S.; Eivazi, S.; Eivazi, S.; Sadeghi, A.; Moradi, N.	2022	Non energy homeostasis

Evaluation of angiopoietin-like protein 3 (ANGPTL3) levels in polycystic ovary syndrome	Vatannejad, A.; Salimi, F.; Moradi, N.; Fouani, F. Z.; Zandieh, Z.; Ansaripour, S.; Sadeghi, A.; Fadaei, R.	2020	Non energy homeostasis
Distinct response of fat and gastrointestinal tissue to glucose in gestational diabetes mellitus and polycystic ovary syndrome	Vejrazkova et al 2017		no outcome of interest
Disruption of the synchronous secretion of leptin, LH, and ovarian androgens in nonobese adolescents with the polycystic ovarian syndrome	Veldhuis, J. D.; Pincus, S. M.; Garcia-Rudaz, M. C.; Ropelato, M. G.; Escobar, M. E.; Barontini, M.	2001	Non energy homeostasis
Obesity and risk of female reproductive conditions: A mendelian randomisation study	Venkatesh, S. S.; Ferreira, T.; Benonisdottir, S.; Rahmioglu, N.; Becker, C. M.; Granne, I.; Zondervan, K. T.; Holmes, M. V.; Lindgren, C. M.; Wittemans, L. B. L.	2021	Abstract
Serum leptin in obese women with polycystic ovary syndrome is correlated with body weight and fat distribution but not with androgen and insulin levels	Vicennati, V.; Gambineri, A.; Calzoni, F.; Casimirri, F.; Macor, C.; Vettor, R.; Pasquali, R.	1998	no outcome of interest
Sam68 mediates leptin signaling and action in human granulosa cells: Possible role in leptin resistance in PCOS	Vilarino-Garcia, T.; Perez-Perez, A.; Santamaria-Lopez, E.; Prados, N.; Fernandez-Sanchez, M.; Sanchez-Margalet, V.	2020	Non energy homeostasis
Subtle metabolic alterations in adolescents with obesity and polycystic ovarian syndrome	Vital-Reyes, V. S.; Lopez-Alarcon, M. G.; Inda-Icaza, P.; Marquez-Maldonado, C.	2017	Non English
Determinants of circulating adiponectin in women with polycystic ovary syndrome	Vrbikova, J.; Dvorakova, K.; Hill, M.; Vcelak, J.; Stanicka, S.; Vankova, M.; Sramkova, D.; Vondra, K.; Bendlova, B.; Starka, L.	2005	Non energy homeostasis
Metabolic and endocrine effects of treatment with peroral or transdermal oestrogens in conjuction with peroral cyproterone acetate in women with polycystic ovary syndrome	Vrbikova, J.; Stanicka, S.; Dvorakova, K.; Hill, M.; Vondra, K.; Bendlova, B.; Starka, L.	2004	Non energy homeostasis
Association between serum adipocyte factor level and insulin resistance in polycystic ovarian syndrome	Wang Q.; Guo T.; Tao Y.; Wang Q.; Song Y.; Huang W.	2011	Non energy homeostasis
The clinical and biochemical characteristics associated with insulin resistance in non-obese young women	Wang, C. C.; Chang, C. J.; Hsu, M. I.	2016	Non energy homeostasis
Impact of metabolic disorders on endometrial receptivity in patients with polycystic ovary syndrome	Wang, C.; Wen, Y. X.; Mai, Q. Y.	2022	Non energy homeostasis
Serum concentrations of fibroblast growth factors 19 and 21 in women with gestational diabetes mellitus: association with insulin resistance, adiponectin, and polycystic ovary syndrome history	Wang, D.; Zhu, W.; Li, J.; An, C.; Wang, Z.	2013	Non energy homeostasis
Correlation between leptin and IFN-gamma involved in granulosa cell apoptosis in PCOS	Wang, J.; Gong, P.; Li, C.; Pan, M.; Ding, Z.; Ge, X.; Zhu, W.; Shi, B.	2020	Non energy homeostasis
Relationship between proinflammatory cytokines and clomiphene resistance in patients with polycystic ovary syndrome	Wang, J.; Teng, F.; Wu, Q.; Wu, Y.; Hu, L.	2021	Non energy homeostasis
No association of the Arg51Gln and Leu72Met polymorphisms of the ghrelin gene and polycystic ovary syndrome	Wang, K.; Wang, L.; Zhao, Y.; Shi, Y.; Wang, L.; Chen, Z. J.	2009	Non energy homeostasis
The expression of sex steroid synthesis and inactivation enzymes in subcutaneous adipose tissue of PCOS patients	Wang, L.; Li, S.; Zhao, A.; Tao, T.; Mao, X.; Zhang, P.; Liu, W.	2012	Non energy homeostasis
Effects of kisspeptin on pathogenesis and energy metabolism in polycystic ovarian syndrome (PCOS)	Wang, T.; Han, S.; Tian, W.; Zhao, M.; Zhang, H.	2019	No outcomes of interest

Variation analysis of Ghrelin gene in Chinese patients with obesity, having polycystic ovarian syndrome	Wang, X.; Qu, F.; Wang, C.; Wang, Y.; Wang, D.; Zhao, M.; Yun, X.; Zheng, Q.; Xu, L.	2020	Non energy homeostasis
High-Fiber Diet or Combined With Acarbose Alleviates Heterogeneous Phenotypes of Polycystic Ovary Syndrome by Regulating Gut Microbiota	Wang, Xuejiao; Xu, Ting; Liu, Rui; Wu, Guojun; Gu, Liping; Zhang, Yahui; Zhang, Feng; Fu, Huaqing; Ling, Yunxia; Wei, Xiaohui; Luo, Yunchen; Shen, Jian; Zhao, Liping; Peng, Yongde; Zhang, Chenhong; Ding, Xiaoying	2022	No control group
Evaluation of Adiponectin, Resistin, IL-6, TNF-alpha in Obese and Non-obese Women with Polycystic Ovary Syndrome	Wang, Y. X.; Zhu, W. J.	2012	Non energy homeostasis
Expression of Serum PSA, Nesfatin-1, and AMH in Patients with Polycystic Ovary Syndrome	Wang, Y.; Ma, X.; Luo, J.; Wang, X.; Han, L.	2021	Non energy homeostasis
Serum adiponectin and resistin levels in patients with polycystic ovarian syndrome and their clinical implications	Wang, Y.; Xie, X.; Zhu, W.	2010	Non energy homeostasis
[Clinical significance and changes of serum visfatin, adiponectin and leptin levels in patients with polycystic ovarian syndrome]	Wang, Y.; Yu, P.	2009	Non English
Elevated ghrelin plasma levels in patients with polycystic ovary syndrome	Wasko, R.; Komarowska, H.; Warenik-Szymankiewicz, A.; Sowinski, J.	2004	Non energy homeostasis
Prevalence of the metabolic syndrome in Asian women with polycystic ovary syndrome: using the International Diabetes Federation criteria	Weerakiet, S.; Bunnag, P.; Phakdeekitcharoen, B.; Wansumrith, S.; Chanprasertyothin, S.; Jultanmas, R.; Thakkinstian, A.	2007	Non energy homeostasis
Can adiponectin predict abnormal glucose tolerance in Thai women with polycystic ovary syndrome?	Weerakiet, S.; Tingthanatikul, Y.; Boonnag, P.; Wansumrith, S.; Rattanasiri, S.; Leelaphiwat, S.	2008	Non energy homeostasis
Women with polycystic ovary syndrome have modified resting metabolic rate relative to fat-free mass	Whigham, L. D.; Schoeller, D.; Lindheim, S. R.; Abbott, D. H.	2011	Abstract
Total and high-molecular weight adiponectin in women with the polycystic ovary syndrome	Wickham, E. P., 3rd; Cheang, K. I.; Clore, J. N.; Baillargeon, J. P.; Nestler, J. E.	2011	Non energy homeostasis
Differences of the association of anti-Mullerian hormone with clinical or biochemical characteristics between women with and without polycystic ovary syndrome	Woo, H. Y.; Kim, K. H.; Rhee, E. J.; Park, H.; Lee, M. K.	2012	Non energy homeostasis
Effects of laparoscopic ovarian drilling on young adult women with polycystic ovarian syndrome	Wu, M. H.; Huang, M. F.; Tsai, S. J.; Pan, H. A.; Cheng, Y. C.; Lin, Y. S.	2004	Non energy homeostasis
Alteration of ghrelin/obestatin ratio in adolescence with polycystic ovarian syndrome	Wu, W.; Fan, X.; Yu, Y.; Wang, Z.; Wang, Y.	2018	Non energy homeostasis
Peritoneal fluid leptin concentration and endocrine hormone in patients with polycystic ovarian syndrome. [Chinese]	Xiao, S. S.; Xue, M.; Deng, X. L.; Wan, Y. J.	2006	Non English
Effect of adiponectin gene polymorphisms on circulating adiponectin and insulin resistance indexes in women with polycystic ovary syndrome	Xita, N.; Georgiou, I.; Chatzikyriakidou, A.; Vounatsou, M.; Papassotiriou, G. P.; Papassotiriou, I.; Tsatsoulis, A.	2005	Non energy homeostasis
The adiponectin-to-leptin ratio in women with polycystic ovary syndrome: relation to insulin resistance and proinflammatory markers	Xita, N.; Papassotiriou, I.; Georgiou, I.; Vounatsou, M.; Margeli, A.; Tsatsoulis, A.	2007	Non energy homeostasis
Association between ghrelin gene variations, body mass index, and waist-to-hip ratio in patients with polycystic ovary syndrome	Xu, L.; Shi, Y.; Gu, J.; Wang, Y.; Wang, L.; You, L.; Qi, X.; Ye, Y.; Chen, Z.	2014	Non energy homeostasis

Untargeted metabolomics analysis of serum and follicular fluid samples from women with polycystic ovary syndrome	Xu, W. L.; Liu, G. Y.; Zhang, N.; Ren, J.; Li, X. Y.; Li, Y. Q.; Chen, Y.; Liu, J. Y.	2020	No outcomes of interest
Adiponectin/(FBGâ€šÃ—â€šFIns) as a predictor of insulin sensitivity and metabolic syndrome in patients with polycystic ovary syndrome	Xu, Xiaohui; Yerui, Lai; Gangyi, Yang; Mengliu, Yang; Ling, Li; Qin, Zhang; Hua, Liu; Hongting, Zheng; Danping, Zhu; Xu, Xiaohui; Lai, Yerui; Yang, Gangyi; Yang, Mengliu; Li, Ling; Zhang, Qin; Liu, Hua; Zheng, Hongting; Zhu, Danping	2016	Non energy homeostasis
Zinc-alpha2-glycoprotein is associated with insulin resistance in humans and is regulated by hyperglycemia, hyperinsulinemia, or liraglutide administration: cross-sectional and interventional studies in normal subjects, insulin-resistant subjects, and subjects with newly diagnosed diabetes	Yang, M.; Liu, R.; Li, S.; Luo, Y.; Zhang, Y.; Zhang, L.; Liu, D.; Wang, Y.; Xiong, Z.; Boden, G.; Chen, S.; Li, L.; Yang, G.	2013	Non energy homeostasis
Are serum chemerin levels different between obese and non-obese polycystic ovary syndrome women?	Yang, S.; Wang, Q.; Huang, W.; Song, Y.; Feng, G.; Zhou, L.; Tan, J.	2015	Non energy homeostasis
[Study on the relationship between serum adiponectin and insulin resistance in women with polycystic ovary syndrome]	Yang, X. F.; Ren, F. R.; Guo, S. P.	2006	Non English
Association between adiponectin receptor 1 gene polymorphism and insulin resistance in Chinese patients with polycystic ovary syndrome	Yang, Z.; Yang, X.; Xu, J.; Sun, Y.; Shi, Y.; Fang, S.	2013	Non energy homeostasis
Serum adiponectin levels in high school girls with polycystic ovary syndrome and hyperandrogenism	Yasar, L.; Ekin, M.; Gedikbasi, A.; Erturk, A. D.; Savan, K.; Ozdemir, A.; Temur, M.	2011	Non energy homeostasis
Quality of life specified for polycystic ovary syndrome and its relationship with nutritional attitude and behavior	Yavarikia, P.; Dousti, S.; Ostadrahimi, A.; Mobasseri, M.; Farshbaf-Khalili, A.	2019	No outcomes of interest
Serum adiponectin level and clinical, metabolic, and hormonal markers in patients with polycystic ovary syndrome	Yildiz, Y.; Ozaksit, G.; Serdar Unlu, B.; Ozgu, E.; Energin, H.; Kaba, M.; Ugur, M.	2014	Non energy homeostasis
Serum retinol-binding protein 4, leptin, and plasma asymmetric dimethylarginine levels in obese and nonobese young women with polycystic ovary syndrome	Yildizhan, R.; Ilhan, G. A.; Yildizhan, B.; Kolusari, A.; Adali, E.; Bugdayci, G.	2011	Non energy homeostasis
Serum resistin and adiponectin levels in women with polycystic ovary syndrome	Yilmaz, M.; Bukan, N.; Demirc, H.; Ozturk, C.; Kan, E.; Ayvaz, G.; Arslan, M.	2009	Non energy homeostasis
Glucose intolerance, insulin resistance and cardiovascular risk factors in first degree relatives of women with polycystic ovary syndrome	Yilmaz, M.; Bukan, N.; Ersoy, R.; Karakoc, A.; Yetkin, I.; Ayvaz, G.; Cakir, N.; Arslan, M.	2005	Wrong population
Expression of leptin long-form receptor mRNA in luteinized granulosa cells of obese women with polycystic ovary syndrome	Yin, J.; Liu, Y.; Lv, L.; Wang, D.; Gong, C.; Xiao, W.; Sheng, H.	2007	Non energy homeostasis
Association of single nucleotide polymorphisms in adiponectin and its receptor genes with polycystic ovary syndrome	Yoshihara, K.; Yahata, T.; Kashima, K.; Mikami, T.; Tanaka, K.	2009	Non energy homeostasis
Effects of electroacupuncture and Chinese kidney-nourishing medicine on polycystic ovary syndrome in obese patients	Yu, L.; Liao, Y.; Wu, H.; Zhao, J.; Wu, L.; Shi, Y.; Fang, J.	2013	Non energy homeostasis
Methylation of leptin promoter in ovarian granulosa cells of polycystic ovary syndrome-metabolic syndrome patients. [Chinese]	Yuan, H.; Niu, Z. H.	2018	Non English
A comparative study between serum leptin and follicular fluid leptin levels in women with polycystic ovary syndrome. [Japanese]	Yuki, H.; Murakami, T.; Watanabe, T.; Yokomizo, R.; Okamura, K.; Yajima, A.	2000	Non English
Metabolic abnormalities in young Egyptian women with polycystic ovary syndrome and their relation to ADIPOQ gene variants and body fat phenotype	Zaki, M.; Kholoussi, S.; Raouf, H. A.; Helwa, I.; Hassan, N.; Youness, E.; Mohamed, N. A.; Kamal,	2015	Non energy homeostasis

	S.; Yousef, W.; Shaker, M.; Ezzat, W.; Elhosary, Y. A.; Saleh, O. M.; El Gammal, M.; El-Bassyouni, H.; Ismail, S.; Bibars, M.; Azmy, O.		
A potential determinant role of adiponectin and receptors for the early embryo development in PCOS patients with obesity hinted by quantitative profiling	Zhang, N.; Hao, C.; Liu, X.; Zhang, S.; Zhang, F.; Zhuang, L.; Zhao, D.	2017	Non energy homeostasis
Association of +45G15G(T/G) and +276(G/T) polymorphisms in the ADIPOQ gene with polycystic ovary syndrome among Han Chinese women	Zhang, N.; Shi, Y. H.; Hao, C. F.; Gu, H. F.; Li, Y.; Zhao, Y. R.; Wang, L. C.; Chen, Z. J.	2008	Non energy homeostasis
[Effect of Qingre Yangyin Recipe on Endocrine and Metabolism of Polycystic Ovary Syndrome Patients]	Zhang, T.	2015	Non English
Family-based analysis of the adiponectin gene polymorphisms and polycystic ovary syndrome. [Chinese]	Zhang, W.; Sun, L.; Guo, J.; Yu, X.; Shi, Y.	2014	Non English
[Case-control based study between polymorphisms in the adiponectin gene and polycystic ovary syndrome]	Zhang, W.; Wu, X.; Ding, M.; Yu, X.; Liu, G.; Shi, Y.	2015	Non English
Family-based analysis of adiponectin gene polymorphisms in Chinese Han polycystic ovary syndrome	Zhang, Wenjuan; Wei, Daimin; Sun, Xianchang; Li, Jing; Yu, Xinyan; Shi, Yuhua; Chen, Zi-Jiang	2014	Non energy homeostasis
Decreased SFRP5 correlated with excessive metabolic inflammation in polycystic ovary syndrome could be reversed by metformin: implication of its role in dysregulated metabolism	Zhang, Y.; Ran, Y.; Kong, L.; Geng, L.; Huang, H.; Zhang, H.; Hu, J.; Qi, H.; Chen, Y.	2021	Non energy homeostasis
[Effects of metformin on gonadotropin-induced ovulation in patients with polycystic ovary syndrome]	Zhao, J. Z.; Ye, B. L.; Lin, J. J.; Lin, W. Q.; Chi, H. H.	2003	Non English
[Effect of rosiglitazone on insulin resistance and hyperandrogenism in polycystic ovary syndrome]	Zheng, Z.; Li, M.; Lin, Y.; Ma, Y.	2002	Non English
Effects of Combined Resveratrol and Myo-inositol on Altered Metabolic, Endocrine Parameters and Perceived Stress in Patients With Polycystic Ovarian Syndrome		2021	Trial register
The effect of metformin and myoinositol in women with polycystic ovary syndrome: role of body mass and adiponectin		2021	Duplicate

5. STUDY CHARACTERISTICS TABLE FOR INCLUDED STUDIES

Author, year	Country	Study design	PCOS criteria	Sample size	Age	BMI	Intervening factor	Description of intervening factor	Outcomes measured	RoB
Energy intake homeostasis										
Arusoglu, 2013	Turkey	Cross Sectional	Rotterdam	p: 18 c: 18 (BMI and age matched)	P = 22.1 (4.2) C = 21.7 (3.4) mean and sd	p = 22.2 (3.3) c = 21.9 (2.3) mean and sd	Meal tolerance test	meal tolerance test (Abbott standard oral enteral solution in 200ml package) as a complete balanced nutrition in a tetrapack 200 mL package. The nutritional energy content was 300 kcal, including 12.5 g protein (16% of energy), 9.84 g fat (29.2% of energy, polyun saturated/ saturated/ monounsaturated proportion fat), and 40.4 g carbohydrate (53.8% of energy).	Ghrelin, PYY, Satiety index	Low
Aydin 2014	Turkey	Cross Sectional	Rotterdam	P: 14 C: 11	P = 21.1 ±2.7 C = 21.1 ±2.0 not stated	P = 21.4 ± 3.0 C = 22.1 ± 2.4 not stated	Meal tolerance test	Oral enteral solution (Ensure plus), 300 kcal, 54% CHO, 30% fat, 16% protein; blood samples 0, 15, 30, 45, 60, 90, 120, 180 mins	GLP-1	Low
Barber 2008	UK	case control	Rotterdam	P: 50 C: 28	P = 29.1 ±5.8 C = 33.2 ±5.4	P = 35.3 ±2.7 C = 34.6 ±2.8	OGTT	OGTT 75g; blood samples 0, 30 mins	Ghrelin	Low
Daghestani 2011	Saudi Arabia	Cross Sectional	Rotterdam	P: 30 C: 30	P = 27.22(0.60) C = 26.05(1.11) mean and SEM	P = 29.35(7.25) C = 28.31(6.97) mean and SEM	Meal tolerance test	Standard mixed breakfast of about 527 kcal during 15 min- 50 g white bread, 33 g black bread, 18 g margarine,30 g cheese, 9 g jam and 200 ml of 0.5% fat milk (24.1% fat, 54.4% CHO, 21.5% protein); blood samples: 0, 60 mins	Ghrelin	Low
Gama 1996	UK	Cross Sectional	HA + OA	P: 7 C: 8	P = 28.5(1.4) C = 27.5(1.4) mean and SEM	P = 23.4(0.4) C = 22.7(0.5) mean and SEM	OGTT	OGTT 75 g; blood samples 0, 30, 60, 90, 120 mins	GLP-1	Low
Glintborg 2017	Denmark	RCT	Rotterdam	P1: 90 C1: 34	P = 28 (24,32) C = 26 (22,32) median and IQR	P = 26.8 (23.3,30.8) C = 25.1 (22.6,27.4) median and IQR	OGTT	OGTT (75g);blood samples 0, 30,60,90, 120, 180, 240,300 mins	GLP-1	Low
Hirschberg 2004	Sweden	Case-control	Rotterdam	P: 16 C: 16	P = 31.8 (1.5) C = 31.5 (1.5) mean and SEM	P = 25.0 (1.0) C = 25.0 (1.0) mean and SEM	Meal tolerance test	standardized breakfast consisting of 500 kcal (protein 18%, carbohydrates 54%, fat 28%), which was ingested within 15 min.	Hunger, Satiety	Low
James 2010	USA	cross-sectional	NIH	P: 20 C: 10 BMI matched	p: 27.5 (1.3) C: 35.6 (1.8) mean and SE	p: 36.3 (1.9) c: 35.7 (1.6) mean and SE	OGTT	After a high carbohydrate diet for 3 days, a 3-hour oral glu- cose tolerance test (OGTT) was performed in all PCOS and control subjects. Blood samples for glucose, insulin, and amylin were	Amylin	Low

								obtained while subjects were fasting and at 1, 2 and 3 hours after a 75-g oral glucose load.		
Japur 2014	Brazil	Cross Sectional	Rotterdam	P: 30 C: 23	P = 29.1 ±5.8 C = 33.2 ±5.4 mean and SD	P = 35.3 ±2.7 C = 34.6 ±2.8 mean and SD	Meal tolerance test	Meal 1600 g (2100 kcal), 58.8% CHO, 22.1% lipid, 17.8% protein; blood samples 0 15, 45, 75, 135 minutes from beginning of meal, 100 mm VAS to assess familiarity and palatability	Ghrelin	Low
Japur 2019	Brazil	Cross Sectional	Rotterdam	P: 30 C: 23	P = 29.1 ± 5.8 C = 33.2 ± 5.4 mean and SD	P = 35.3 ± 2.7 C = 34.6 ± 2.8 mean and SD	Meal tolerance test	Fixed breakfast 300 kcal and 73% CHO, ad libitum meal pasta with tomato sauce/ground beef (58.8% CHO, 22.1% fat, 17.8% P, 1.3 kcal/gram), blood samples at fasting and postprandial 15, 45, 75, 135 minutes, VAS 100 mm	Ghrelin, subjective hunger	Low
Lin 2015	China	Cross Sectional	Rotterdam	P: 30 C: 29	P = 26.6(1.10) C =28.9(0.96) mean and SE	P = 25.1(0.83) C = 23.3(0.71) mean and SE	OGTT	OGTT 75 g; blood samples 0, 30, 60,120, 180 mins	GLP-1, PYY	Mod
Martinez-Garcia 2021	Spain	Cross Sectional	HA+OA	P1:17 (8 OB) C1:17 (8 OB)	P1 = 24 ± 8; OB 30 ± 4 C1 = 26.5 ± 5; OB 27 ± 6 means and SD	P1 = 24 ± 2; OB 37 ± 5 C1 = 23 ± 2; OB 36 ± 4 means and SD	Meal tolerance test	Enteral nutrition supplement loads (300kcal): Isocaloric glucose (200 ml 37.5 g/dl glucose solution) lipid (66 ml 4.5 kcal/ml long-chain triglyceride; and protein (75 g containing caseinates); blood samples 0, 60, 120min (glucose/protein loads) or 0, 120, 240 min (lipid loads)	Ghrelin	Low
Moran, 2004	Australia	RCT	HA+OA	p: 20 c: 12 (weight, BMI matched)	Standard Protein (SP) diet p = 34.8 (1.2) c = 41.1 (3.1) High Protein (HP) diet p = 33.1 (1.7) c = 36.2 (3.2) mean and sd	Standard Protein (SP) diet p = 36.6 (2.2) c = 34.5 (1.6) High Protein (HP) diet p = 36.0 (1.6) c = 33.1 (1.5) mean and sd	Meal tolerance test	**180 min / 3h MTT** 3-h meal tolerance test (MTT) was performed with a 2700 kJ test meal using the allocated diet with equivalent energy densities (11% protein, 15% fat, and 76% carbohydrate for the SP and 31% protein, 14% fat, and 55% carbohydrate for the HP diet). Fasting venous blood was taken for measurement of insulin, glucose, and ghrelin (time 0). Subjects were then required to consume the meal within 20 min, and further blood samples were taken for assessment of insulin and glucose at 60, 120, and 180 min and ghrelin at 60 and 120 min. Subjective hunger, fullness, satiety, and desire to eat were assessed using a validated 10-cm linear scale visual analog scores (VAS) immediately before eating and at 60, 120, and 180 min (31). The change in ratings from baseline was quantified (32, 33).	Ghrelin, Satiety Index	Low
Moran, 2007b	Australia	prospective cohort	Rotterdam	p: 13 c: 13 (BMI, smoking status and age matched)	p = 32.3 (5.9) c = 36.2 (4.5) mean and sd	p = 35.3 (1.5) c = 35.3 (1.3) mean and sd	Meal tolerance test	**3 hour / 180 min MTT** All subjects consumed the same meal the evening before the test (3820 kJ; 20% of energy from protein, 17% from fat, and 62% from carbohydrate) and refrained from consuming alcohol for 24 h. A cannula was inserted into a forearm vein, and an overnight fasting venous blood sample was taken between 0800 and 1000.	Ghrelin, PYY, Satiety index	Low

								Subjects then completed a validated visual analogue scale (VAS) questionnaire to assess subjective hunger as previously described (25). Subjects consumed a liquid preload of Slimfast [325 mL, 936 kJ, 12 g protein (25% of energy from protein),2gfat (9% of energy from fat), and 35 g carbohydrate (67% of energy from carbohydrate)] within5min; additional blood sampleswere taken and VAS questionnaires were completed at 15, 30, 45, 60, 90, 120, and 180 min after meal consumption. At 180 min, subjects were given a mixed buffet-style lunch (12.1 MJ; 15% of energy from protein, 44%from fat, and41%from carbohydrate); each subject served his or her ownmeal from designated portions of the foods and ate until satisfied over a 30-min period.		
Ozgen, 2010	Turkey	case-control	AEPCOS	p: 26 c: 20 Subgroups p + obese : 13 p + non obese: 13 c + obese : 10 c + non obese : 10 Age, bmi matched (for subgroups)	p + obese = 14.90 (0.90) p + non obese = 15.45 (1.26) c + obese = 14.98 (1.55) c + non obese = 15.37 (0.96) mean and sd	p + obese = 32.6 (4.90) p + non obese = 20.4 (2.2) c + obese = 31.6 (4.7) c + non obese = 20.4 (1.5) mean and sd	OGTT	**3hr / 180 min OGTT** After overnight fasting, oral glucose tolerance test (OGTT) was performed for all adolescents within the same time interval (9:00e12:00 AM) on the third day of spontaneous or progesterone induced menstruation.	Ghrelin	Low
Ozgen, 2017	Turkey	cross-sectional	AEPCOS	p: 20 c: 20 Subgroups p + obese : 10 p + non obese: 10 c + obese : 10 c + non obese : 10 bmi matched	p + obese = 28.5 (18,34) p + non obese =20 (18,25) c + obese = 32 (20,39) c + non obese = 26.5 (25,40) median, IQR	p + obese =34.2 (30.8,44.3) p + non obese = 21.0 (18.6,24.9) c + obese = 38.2 (30.8,47.5) c + non obese = 20.5 (19.1,24.8) median, IQR	Meal tolerance test	**180min / 3hr MTT** Abbott standard oral enteral solution (Abbott Ensure plus; Abbott Laboratories, Columbus, OH). After an overnight fast, a standardized mixed meal was given as breakfast within 5 min. Blood samples were taken at 0, 15, 30, 45, 60, 90, 120 and 180 min to measure fasting levels of leptin and ghrelin and fasting and meal stimulated levels of GLP-1. Subjects completed a scale to assess subjective satiety before and during MTT before each venous sampling.	Ghrelin, GLP-1, Satiety index,	Mod
Pontikis, 2011	Greece	cross-sectional	Rotterdam	p: 20 c: 10 age matched	p + obese = 23.5 (3.37) p + non obese	p + obese = 31.23 (5.1) p + non obese =	OGTT	**180 min OGTT** All participants reported to our laboratory between 8.00 am and	GLP-1	Low

					= 22.2 (3.12) c = 25.3(4.99) mean and sd	21.1 (2.46) c = 25.03 (5.94)		8.30 am and underwent a 3-hour OGTT (75 grams). Blood samples were drawn at - 15, 0, 5, 10, 15, 20, 30, 60, 90, 120, 150, and 180 minutes. Participants were advised to avoid eating, drinking other than water, smoking, and walking in the course of the test. (Conducted after overnight fast)		
Rao, 2021	USA	case-control	Rotterdam	p : 14 c : 15 age-matched	p: 22.9 (5.8) c: 21.1 (3.2) mean and sd	p: 33.7 (9.5) c: 24.4 (4.0)	OGTT	**150 min OGTT** A 75g dextrose beverage was used for the OGTTs (Tru- Glu 100, Fisher Scientific, Pittsburg, PA). Venous blood samples were drawn at -30/ pre-preload, 0/ pre-dextrose, 15, 30, 60, 90, 120, and 150 minutes during all 3 OGTTs	GLP-1	Mod
Vejrazkova, 2017	Czech Republic	Case-control	Rotterdam	p: 19 c : 36 GDM: 22	p: 26.7, 95%CI : (24.8, 28.8) c: 30.4, 95% CI : (28.9, 32.0) GDM: 34,9, 95%CI: 32.8, 37.0) mean and 95%CI	p: 21.8, 95%CI : (21.2, 22.4) c: 21.6, 95% CI : (21.1, 22.0) GDM: 22.0, 95%CI: 21.5, 22.6)	OGTT	**3h / 180 min OGTT** 75g of glucose	GLP-1, Ghrelin, adiponectin	Low
Vrbikova, 2008	Czech Republic	Case-control	Rotterdam	p: 21 c: 13 age, bmi matched	p: 25.81 (3.98) c: 28.46 (6.90) mean and sd	p: 21.57 (1.68) c: 20.27 (2.37) mean and sd	OGTT	**3h / 180 min OGTT** OGTT was performed after overnight fasting by sampling blood before the 75 g glucose oral load and after 30, 60, 90, 120, 150, and 180 min	GLP-1	Low
Zwirska-Korczala, 2008	Poland	case-control	Rotterdam	p: 40 c: 20 age-matched	p + obese = 21 (2.9) p + lean = 22 (2.5) c = 21 (2.3)	p + obese : 32 (1.6) p + lean : 21 (0.9) c : 22 (1.3)	OGTT	**2h / 120 min OGTT** Subjects consumed a stadnard mixed meal of 527 kcal during 15 min. The meal consisted of 50g white bread, 33g black bread, 18g margarine, 30g cheese, 9 g jam and 200ml of 0.5% fat milk (24.1% fat, 54.4% carbohydrate, 21.5% protein). Blood samples were collected at 30, 60, 90 and 120 min after the meal ingestion. Blood samples were drawn in the follicular phase (cycle days 2-8) in all controls, but in patients on a random day	Ghrelin, PYY, adiponectin	Mod
Energy expenditure homeostasis										

Cosar, 2008	Turkey	Cross Sectional	Rotterdam	P=31 C=29 (age and BMI matched)	P=25.9 ± 5.3 C=27.1 ± 4.8	P=26.97 ± 5.12 C=26.03 ± 5.66	N/A	Indirect calorimetry (Quark b^2)	REE	Mod
Doh, 2016	Cameroon	Cross Sectional	Rotterdam	P1 (obese)=6 P2 (non-obese)=8 C (non-obese)=10 (BMI matched for P2 and C)	P1=26 (23-30) P2=27 (24-29) C=23 (23-24)	P1=34.1 (31.9-36.7) P2=26.4 (24.5-28.5) C=22.5 (19.7-24.6)	N/A	Indirect calorimetry (The Korr ReeVue) Adjusted for lean body mass	REE	High
Georgopoulos, 2008	Greece	Cross Sectional	Rotterdam	Total PCOS =91 P1 (PCOS with IR)=19 P2 (PCOS without IR)=43 C=23 (age and BMI matched results in Table 2)	P1=23.12 ± 1.07 P2=23.38 ± 0.67 C=25.17 ± 0.78	P1=27.10 ± 1.38 P2=24.54 ± 0.78 C=23.70 ± 1.02	N/A	Indirect calorimetry (Pulmolab EX505; Morgan Medical, Kent, U.K) Adjusted for fat mass, fat free mass, gender and age	REE	Mod
Graff, 2013	Brazil	Cross Sectional	Rotterdam	P=61 C=44	P=22.7 ± 6.3 C=25.0 ± 6.3	P=28.9 ± 5.6 C=27.1 ± 5.7	N/A	Indirect calorimetry (Fitmate Cosmed)	REE	Mod
Graff, 2017	Brazil	Cross Sectional	Rotterdam	P=84 C=54	P=29.4 ± 6.4 C=27.2 ± 5.8	P=29.4 ± 6.4 C=27.2 ± 5.8	N/A	Indirect calorimetry (Fitmate Cosmed)	REE	Mod
Koika, 2009	Greece	Cross Sectional	Rotterdam	P1 (Pro/pro variant)=136 P2 (X/Ala variant)=20 C=56	P1=22.81 ± 5.17 P2= 22.92 ± 3.12 C=22.91 ± 1.5	P1=25.76 ± 6.69 P2= 24.40 ± 3.49 C=21.191 ± 2.5	N/A	Indirect calorimetry (Pulmolab EX505; Morgan Medical, Kent, U.K)	REE	Mod
Larsson, 2016	Sweden	Cross Sectional	Rotterdam	P=72 C=30	P=30.2 ± 4.4 C=27.8 ± 3.6	P=28.5 ± 7.2 C=24.6 ± 5.0	N/A	Indirect calorimetry using a Deltatrack™ II Metabolic Monitor ventilated hood system (Datex, Helsinki, Finland)	REE	Mod
Robinson 1992	UK	Cross Sectional	NIH	P1 (healthy weight)=7 P2 (obese)=7 C1 (healthy	Not reported by subgroups P=27 (20-42) C=29 (23-40)	P1=21.3 (19.2-24.4) P2=32.8 (27.0-48.7) C1=22.6 (18.6-24.0) C2=33.1 (26.7-41.3)	N/A	REE: Continuous indirect calorimetry (Deltatrac) MIT:	REE MIT	Mod

				weight)=7 C2 (obese)=7 (age, weight, race, BMI, lean body mass and percentage fat mass matched)				Measured over 2 hours 42 kJ/kg meal body mass (10 kcal/kg), 32% fat, 22% P, 46% CHO The incremental area of metabolic rate above the REE was calculated and expressed in kilojoules. The area under the curve of the incremental rise in metabolic rate is the MIT		
Segal, 1990	USA	Cross Sectional	NIH	P (obese)=10 C1 (lean)=11 C2 (obese)=9 (P, C1 and C2 age matched and P and C2 fat free mass matched)	P=25 ± 2 C1=28 ± 1 C2=29 ± 2	NR	N/A	REE: Measured intermitently with use of a mouth piece and noseclip (e.g. a continuous ventilated hood was not used). Last 6 minutes of every half hour for 3 hours MIT: 3 hours 720 kcal (3014 kJ) liquid mixed meal (24% protein, 21% fat, 55% carbohydrate) consumed within 5 minutes Calculated as postprandial - fasting RMR (kcal/3 h)	REE MIT	Mod

6. FINDINGS

Comparison included:

- **Comparison 1:** PCOS versus controls

Outcomes included:

- **Outcome 1.** Energy intake homeostasis: Appetite stimulating gut hormones
- **Outcome 2.** Energy intake homeostasis: Appetite supressing gut hormones
- **Outcome 3.** Energy intake homeostasis: Subjective hunger
- **Outcome 4.** Energy intake homeostasis: Subjective satiety
- **Outcome 5.** Energy expenditure homeostasis: Meal induced thermogenesis
- **Outcome 6.** Energy expenditure homeostasis: Resting energy expenditure

▪ EVIDENCE SUMMARY:

A total of twenty studies compared energy intake homeostasis in women with and without PCOS. Outcomes examined included appetite stimulating gut hormones, appetite suppressing gut hormones, subjective hunger and subjective satisty post meal or glucose intake. Four studies were judged as being moderate risk of bias (Lin 2015, Ozgen 2017, Rao 2021 and Zwirska-Korczala 2008) while the rest were judged as being low risk of bias.

A total of nine studies examined energy expenditure homeostasis in women with and without PCOS. Outcomes examined included meal induced thermogenesis and resting energy expenditure, the latter of which was the only outcome amenable to meta-analysis (for five of the nine studies).

▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

Appetite stimulating gut hormones

Adiponectin and ghrelin were compared between women with and without PCOS post oral glucose tolerance test (OGTT) or mixed meal test (MMT). Meta-analysis was not possible due to heterogeneity between the studies and narrative evidence synthesis was conducted.

Two out of two studies which examined post stimulation adiponectin area under the curve (AUC) both reported significantly lower AUC in women with PCOS than controls (Verrazkova 2017 and Zwirska-Korvzala 2008).

Three out of seven studies reported lower ghrelin AUC post MMT in women with PCOS than controls (Arusoglu 2013, Moran 2007b, Zwirska-Korczala 2008). All three studies post OGTT reported lower ghrelin AUC in women with PCOS than controls (Barber 2008, Ozgen 2010, Vejrazkova 2017).

Overall, women with PCOS may have lower increase in appetite stimulating gut hormones (adiponectin and ghrelin) after meal or glucose intake than women without PCOS; however the evidence is of very low certainty due to the observational nature of the studies, as well a inconsistency and imprecision.

Appetite supressing gut hormones

GLP-1, PYY and amylin were compared between women with and without PCOS post oral glucose tolerance test (OGTT) or mixed meal test (MMT). Meta-analysis was not possible due to heterogeneity between the studies and narrative evidence synthesis was conducted.

Nine studies examined post OGTT or MMT GLP-1 AUC in women with and without PCOS. Three studies reported GLP-1 AUC was lower in women with than without PCOS (Aydin 2014, 2014, Vejrazkova 2017, Vrbikova 2008), one study reported GLP-1 AUC was higher in women with than without PCOS (Lin 2015) while the rest did not show any significant difference.

Four studies examined post OGTT or MTT PYY AUC in women with and without PCOS. Only one study reported that PYY AUC was lower in women with than without PCOS (Zwirska-Korczala 2008), the rest did not show any significant difference.

Only one study examined post OGTT or MMT amylin AUC in women with and without PCOS and it reported higher AUC in women with than without PCOS (James 2010).

Overall, results of studies comparing appetite supressing gut hormones (GLP-1, PYY and amylin) after meal or glucose intake in women with and without PCOS are conflicting, with very low certainty evidence supporting no difference between the groups.

Subjective hunger

One study examined subjective hunger post MMT in women with and without PCOS and found that women with PCOS had more hunger than women without PCOS. Overall quality for this evidence is very low due to being only one study and low sample size.

Subjective satiety

Four studies examined subjective satiety post MMT in women with and without PCOS and only one study reported that women with PCOS had lower satiety than women without PCOS (Moran 2004). The other three did not find any significant difference (Arusoglu 2013, Ozgen 2017, Moran 2007b). Overall, evidence suggest that women with and without PCOS do not have any difference in subjective satiety post meal intake. Certainty of evidence for this finding is very low due to conflicting results.

Meal induced thermogenesis (MIT)

Two studies examined MIT in women with and without PCOS (Robinson 1992, Segal 1990) and their results were conflicting. It is unclear if meal induced thermogenesis differs between women with and without PCOS.

Resting energy expenditure (REE)

Nine studies examined REE in women with and without PCOS, of which five were suitable for meta-analysis. The remaining studies either did not report results for REE, or they reported outcomes in median (IQR) or using inconsistent units. In meta-analysis, there was no difference in REE between women with PCOS and controls (WMD=-38.61 [95%CI= -301.48, 224.26]; p=0.8). Certainty in the evidence was very low due to high and statistically significant heterogeneity (I^2= 98%, p<0.0001), inconsistent direction of effect and variable effect sizes, and imprecision evidences by the wide CI. The observational nature of the data precludes causality and we cannot rule out residual confounding, further downgrading certainty in the evidence.

Outcome	Studies	PCOS sample	Control n	Intervening factor	Significance/ p-value	Favours	Certainty
Outcome 1: Appetite stimulating gut hormones							
Ghrelin	7	168	116	MMT	3/7 studies lower in PCOS	Uncertain	⊕◯◯◯ VERY LOW
	3	95	84	OGTT	3/3 studies lower in PCOS	Lower in PCOS	⊕◯◯◯ VERY LOW
Adiponectin	1	40	20	MMT	1 study lower in PCOS	Lower in PCOS	⊕◯◯◯ VERY LOW
	1	19	36	OGTT	1 study lower in PCOS	Lower in PCOS	⊕◯◯◯ VERY LOW
Outcome 2: Appetite supressing gut hormones							
GLP-1	2	34	31	MMT	1 study lower in PCOS	Uncertain	⊕◯◯◯ VERY LOW
	7	161	93	OGTT	1 study higher in PCOS 2 studies lower in PCOS	Uncertain	⊕◯◯◯ VERY LOW
PYY	3	71	51	MMT	1 study lower in PCOS	Uncertain	⊕◯◯◯ VERY LOW
	1	30	29	OGTT	No difference	No difference	⊕◯◯◯ VERY LOW
Amylin	1	29	10	OGTT	1/1 study higher in PCOS	Higher in PCOS	⊕◯◯◯ VERY LOW
Outcome 3: Subjective hunger							
Subjective hunger	1	30	23	MMT	1/1 study higher in PCOS	Higher in PCOS	⊕◯◯◯ VERY LOW
Outcome 4: Subjective satiety							
Subjective satiety	4	71	63	MMT	1/4 study significantly lower in PCOS	Uncertain	⊕◯◯◯ VERY LOW
Outcome 5: Meal induced thermogenesis							
Meal induced thermogenesis	2	24	34	NA	1/2 study lower in PCOS	Uncertain	⊕◯◯◯ VERY LOW
Outcome 6: Resting energy expenditure							
Resting energy expenditure	5 (pooled)	339	180	-38.61 [-301.48, 224.26]	P=0.8	No difference	⊕◯◯◯ VERY LOW

OUTCOME 1. Appetite stimulating gut hormones

1.1 Individual Study Data Table

Author, year	Country	Study design	Intervening factor	Outcome	Unit	Sample size	Descriptive statistics	PCOS mean/ median	PCOS variation	Control mean/ median	Control variation	Statistical significance	RoB
Arusoglu, 2013	Turkey	Cross Sectional	Meal tolerance test	Ghrelin	AUC, pg/ml *180min	p: 18 c: 18 (BMI and age matched)	not stated	118445	34883	159001	69660	Lower in PCOS	Low
Barber 2008	UK UK	Case Control Case Control	OGTT OGTT	Ghrelin	suppression: pg/ml*30min	P: 22 C: 22 BMI and fat mass matched	Median (IQR)	160	88-289	424	220-818	Lower in PCOS	Low
						P: 50 C: 28	Median (IQR)	154	64-371	398	186-854	Lower in PCOS	Low
Daghestani 2011	Saudi Arabia	Cross Sectional	Meal tolerance test	Ghrelin	postprandial: ng/ml (60min)	P: 30 C: 30	not stated	not stated	not stated	not stated	not stated	NS	Low
Japur 2014 (same study population as Japur 2019)	Brazil	Cross Sectional	Meal tolerance test	Ghrelin	AUC, pg/ml *135min	P: 30 C: 23	not stated	not stated	not stated	not stated	not stated	NS	Low
Martinez-Garcia 2021	Spain	Cross Sectional	Meal tolerance test	Ghrelin	AUC, pmol/l/min	P1:17 (8 OB) C1:17 (8 OB)	not stated	not stated	not stated	not stated	not stated	NS	Low
Moran, 2004	Australia	randomised control trial	Meal tolerance test	Ghrelin	pg / ml	p: 20 c: 12 (weight, BMI matched)	mean (SD)	not stated	not stated	not stated	not stated	NS	Low
Moran, 2007b	Australia	prospective cohort	Meal tolerance test	Ghrelin	AUC pmol/L*180 min	p: 13 c: 13 (BMI, smoking status and age matched)	mean (SD)	2118	480	3941	919	Lower in PCOS	Low
Ozgen, 2010	Turkey	case-control	OGTT	Ghrelin	pg/ml	p: 26 c: 20 Subgroups p + obese : 13	mean (SD)	obese: 888.7 non-obese: 1244.5	obese: 330.4 non-obese: 289.4	obese: 1020.4 non-obese: 1172.9	obese: 226.0 non-obese: 393.6	Lower in PCOS	Mod

						p + non obese: 13 c + obese : 10 c + non obese : 10 Age, bmi matched (for subgroups)							
Vejrazkova, 2017	Czech Republic	Case-control	OGTT	Ghrelin	pg/ml	p: 21 c: 13 age, bmi matched	not stated	not stated	not stated	not stated	not stated	Lower in PCOS	Low
Zwirska-Korczala, 2008	Poland	case-control	Meal tolerance test	Ghrelin (% change)	%	p: 40 obese + p : 21 lean + p : 19 c: 20 age-matched	mean (SEM)	p + obese = -12.8 p + lean : -18.2	p + obese = 1.66 p + lean : 1.64	-28.4	5.87	Lower in PCOS	Mod
Vejrazkova, 2017	Czech Republic	Case-control	OGTT	Adiponectin	pg/ml	p: 21 c: 13 age, bmi matched	not stated	not stated	not stated	not stated	not stated	Lower in PCOS, AUC values not provided	Low
Zwirska-Korczala, 2008	Poland	case-control	Meal tolerance test	Adiponectin	ng/L	p: 40 obese + p : 21 lean + p : 19 c: 20 age-matched	mean (SD)	p + obese = 9.87 p + lean = 15.23	p + obese : 2.07 p + lean = 2.39	23.41	4.25	Lower in PCOS (both obese and lean)	Mod

OUTCOME 2. Appetite suppressing gut hormones

2.1 Individual Study Data Table

Author, year	Country	Study design	Intervening factor	Outcome	Unit	Sample size	Descriptive statistics	PCOS mean/ median	PCOS variation	Control mean/ median	Control variation	Statistical significance	RoB
Aydin, 2014	Turkey	Cross Sectional	Meal tolerance test	GLP-1	AUC: ng/ml*180 min	P: 14 C: 11	mean (SD)	190.7	55.1	270.4	86.4	Lower in PCOS	Low
Gama 1996	UK	Cross Sectional	OGTT	GLP-1	integrated (pmol/L/h)* 120min	P: 7 C: 8	mean (SEM)	939	160	1539	542	NS	Low
Glintborg 2017	Denmark	RCT	OGTT OGTT	GLP-1 GLP-1	AUC, (10^2 mmol/L*h)* 2hr	P1: 90 C1: 34	Median (IQR)	18	15.4-22.7	18.1	16.1-23.7	NS	Low
					AUC, (10^2 mmol/L*h)* 5hr			38.6	31.7-44.4	37	34.5-46.6	NS	Low
Lin 2015	China	Cross Sectional	OGTT	GLP-1	AUC, pM*180min	P1: 90 C1: 34	not stated	not stated	not stated	not stated	not stated	Higher in PCOS	Mod
Ozgen, 2017	Turkey	case-control	Meal tolerance test	GLP-1	AUC (pM*180min)	p: 20 c: 20	median (min-max)	obese: 9739 non-obese: 6516	obese: (3104, 21620) non-obese: (3583, 10 380)	obese: 11145 non-obese: 7125	obese: (7728, 16070) non-obese: (4144, 9866)	NS	Low
Pontikis, 2011	Greece	case-control	OGTT	GLP-1	AUC: ng/ml*180 min	p: 20 c: 10 age matched	mean (SD)	obese: 7.18 non-obese: -1.6	obese: 3.2 non-obese: 7.96	18.95	11.57	NS	Low
Rao, 2021	USA	case-control	OGTT	GLP-1	AUC: pg/ml*150 min	p : 14 c : 15 age-matched	not stated	not stated	not stated	not stated	not stated	NS	Mod
Vejrazkova, 2017	Czech Republic	Case-control	OGTT	GLP-1	pg/ml	p: 19 c : 36 GDM: 22	not stated	not stated	not stated	not stated	not stated	Lower in PCOS, AUC values not provided	Low
Vrbikova, 2008	Czech Republic	Case-control	OGTT	GLP-1	pg/ml	p: 21 c: 13 age, bmi matched	not stated	not stated	not stated	not stated	not stated	Lower in PCOS, AUC values not provided	Low

Arusoglu, 2013	Turkey	prospective observational	Meal tolerance test	PPY	AUC, ng/ml*180 min	p: 18 c: 18 (BMI and age matched)	not stated	140	26	148	47	NS	Low
Lin 2015	China	Cross Sectional	OGTT	PYY	AUC, pg/ml*180 min	P1: 90 C1: 34	not stated	not stated	not stated	not stated	not stated	NS	Mod
Moran, 2007b	Australia	prospective cohort	Meal tolerance test	PYY	AUC (pmol / L*180 min)	p: 13 c: 13 (BMI, smoking status and age matched)	mean (SD)	3748	279	3295	194	NS	Low
Zwirska-Korczala, 2008	Poland	case-control	Meal tolerance test	PYY	% change	p: 40 obese + p : 21 lean + p : 19 c: 20 age-matched	mean (SEM)	p + obese = 33.6 p + lean : 17.4	p + obese = 3.76 p + lean : 2.07	43.8	5.48	Lower in PCOS (both obese and lean)	Mod
James 2010	USA	Cross Sectional	OGTT	Amylin	AUC pM/ml	P: 20 C: 10	mean (SE)	91.2	10.8	26.8	5.4	Higher in PCOS	Low

OUTCOME 3. Subjective hunger

3.1 Individual Study Data Table

Author, year	Country	Study design	Intervening factor	Outcome	Measurement unit	Sample size	Descriptive statistics	PCOS mean/median	PCOS variation	Control mean/median	Control variation	Statistical significance	RoB
Japur 2019	Brazil	Cross Sectional	Meal tolerance test	subjective hunger (visual analogue scale of 100mm)	mm*135min	P: 32 C: 23	Median (IQR)	517.5	45-5077.5	0	0-5865	Higher in PCOS	Low

OUTCOME 4. Subjective satiety

4.1 Individual Study Data Table

Author, year	Country	Study design	Intervening factor	Outcome	Measurement unit	Sample size	Descriptive statistics	PCOS mean/ median	PCOS variation	Control mean/ median	Control variation	Statistical significance	RoB
Arusoglu, 2013	Turkey	prospective observational	Meal tolerance test	Satiety index	AUC cm*180 min	p: 18 c: 18 (BMI and age matched)	not stated	394.6	161.0	512.1	201.3	NS	Low
Ozgen, 2017	Turkey	case-control	Meal tolerance test	Satiety index	AUC	p: 20 c: 20 Subgroups p + obese : 10 p + non obese: 10 c + obese : 10 c + non obese : 10 bmi matched	median (min-max)	obese: 851 non-obese: 735	obese: (353, 1230) non-obese: (315,1110)	obese: 619 non-obese: 750	obese: (293, 1118) non-obese: (210, 1005)	NS	Mod
Moran, 2004	Australia	randomised control trial	Meal tolerance test	Satiety index	AUC: mm	p: 20 c: 12 (weight, BMI matched)	mean (SD)	not stated	not stated	not stated	not stated	Lower in PCOS	Low
Moran, 2007b	Australia	prospective cohort	Meal tolerance test	Satiety index	AUC (mm/180 min	p: 13 c: 13 (BMI, smoking status and age matched)	mean (SD)	not stated	not stated	not stated	not stated	NS	Low

OUTCOME 5. Meal induced thermogenesis

5.1 Individual Study Data Table

Author, year	Country	Study design	Outcome	Details	Sample size	Measurement unit	Descriptive statistics	PCOS mean/ median	PCOS variation	Control mean/ median	Control variation	Statistical significance	RoB
Robinson 1992	UK	Cross Sectional	MIT	Measured over 2 hours 42 kJ/kg meal body mass (10 kcal/kg), 32% fat, 22% P, 46% CHO The incremental	P1 (healthy weight)=7 P2 (obese)=7 C1 (healthy weight)=7 C2 (obese)=7 (age, weight,	kJ	Median (IQR)	P1=79.4 P2=45.4	P1=73.5-108.4 P2=33.6-100.0	C1=89.9 C2=86.5	C1=76.0-109.2 C2=67.2-109.2	Lower in PCOS	Mod

				area of metabolic rate above the REE was calculated and expressed in kilojoules. The area under the curve of the incremental rise in metabolic rate is the MIT	race, BMI, lean body mass and percentage fat mass matched)								
Segal, 1990	USA	Cross Sectional	MIT	3 hours 720 kcal (3014 kJ) liquid mixed meal (24% protein, 21% fat, 55% carbohydrate) consumed within 5 minutes Calculated as postprandial - fasting RMR (kcal/3 h)	P (obese)=10 C1 (lean)=11 C2 (obese)=9 (P, C1 and C2 age matched and P and C2 fat free mass matched)	kcal/3 h	Mean ± SD	NR	NR	NR	NR	NS	Mod

OUTCOME 6. Resting energy expenditure

6.1 Individual Study Data Table

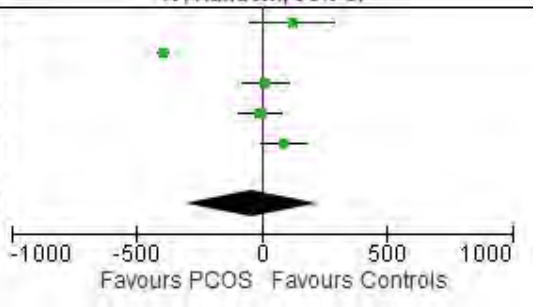
Author, year	Country	Study design	Outcome	Details	Sample size	Measurement unit	Descriptive statistics	PCOS mean/ median	PCOS variation	Control mean/ median	Control variation	Pooled in MA	RoB
Cosar, 2008	Turkey	Cross Sectional	REE	Indirect calorimetry (Quark b^2)	P=31 C=29 (age and BMI matched)	kcal/d	Mean ± SD	1167.87	370.98	1045.52	295.86	Yes	Mod
Doh, 2016	Cameroon	Cross Sectional	REE	Indirect calorimetry (The Korr ReeVue) Adjusted for lean body mass	P1 (obese)=6 P2 (non-obese)=8 C (non-obese)=10 (BMI matched for P2 and C)	Kcal/day	Median (IQR)	NR	NR	NR	NR	No	High
Georgopoulos, 2008	Greece	Cross Sectional	REE	Indirect calorimetry (Pulmolab EX505; Morgan Medical,	Total PCOS = 91 P1 (PCOS with IR)=19 P2 (PCOS without	Kcal/day	Mean ± SD	All P= 1445.57 P1=1087 P2=1562	All P=76 P1=106 P2=124	1841.05	44.0	Yes	Mod

				Kent, U.K) Adjusted for fat mass, fat free mass, gender and age	IR)=43 C=23 (age and BMI matched results in Table 2)								
Graff, 2013	Brazil	Cross Sectional	REE	Indirect calorimetry (Fitmate Cosmed)	P=61 C=44	Kcal/day	Mean ± SD	1469	227	1453	249	Yes	Mod
Graff, 2017	Brazil	Cross Sectional	REE	Indirect calorimetry (Fitmate Cosmed)	P=84 C=54	Kcal/day	Mean ± SD	1463	248	1468	253	Yes	Mod
Koika, 2009	Greece	Cross Sectional	REE	Indirect calorimetry (Pulmolab EX505; Morgan Medical, Kent, U.K)	P1 (Pro/pro variant)=136 P2 (X/Ala variant)=20 C=56	kcal/d	Mean ± SD	P1=1475.7 P2=893.2	P1=678.6 P2=312.4	NA	NA	Yes	Mod
Larsson, 2016	Sweden	Cross Sectional	REE	Indirect calorimetry using a Deltatrack™ II Metabolic Monitor ventilated hood system (Datex, Helsinki, Finland)	P=72 C=30	kcal/d	Mean ± SD	1411	229	1325	193	Yes	Mod
Robinson 1992	UK	Cross Sectional	REE	Continuous indirect calorimetry (Deltatrac)	P1 (healthy weight)=7 P2 (obese)=7 C1 (healthy weight)=7 C2 (obese)=7 (age, weight, race, BMI, lean body mass and percentage fat mass matched)	kJ/day	Median (IQR)	6796	5489-7774	6833	4893-8492	No	Mod
Segal, 1990	USA	Cross Sectional	REE	Measured intermittently with use of a mouth piece and nose clip (e.g. a continuous ventilated hood was not used) Last 6 minutes of every half hour for 3 hours	P (obese)=10 C1 (lean)=11 C2 (obese)=9 (P, C1 and C2 age matched and P and C2 fat free mass matched)	kcal/min	Mean ± SD	1.047	0.0037	C1=1.029 C2=1.082	C1=0.023 C2=0.0043	Yes	Mod

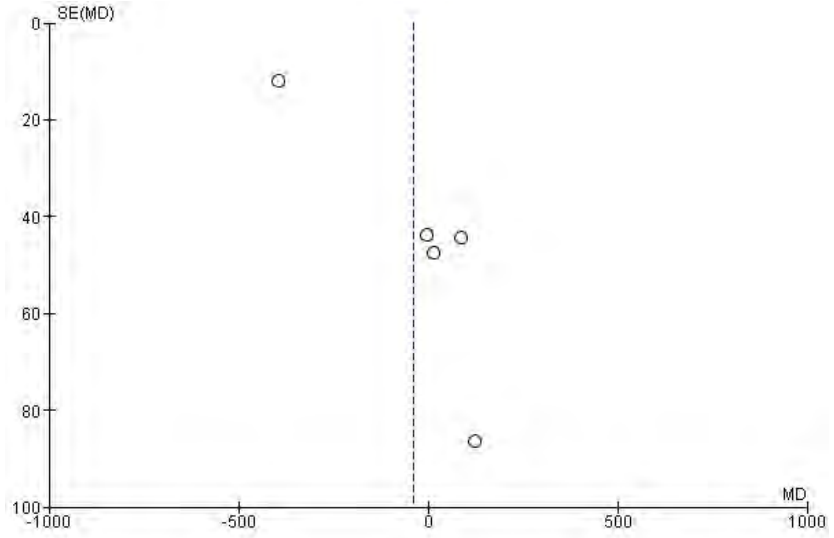
6.2. Forest plot for differences in resting energy expenditure between women with PCOS and controls

	PCOS			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean [kcal/day]	SD [kcal/day]	Total	Mean [kcal/day]	SD [kcal/day]	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Cosar et al. 2008	1,167.87	370.98	31	1,045.52	295.86	29	19.0%	122.35 [-46.91, 291.61]	
Georgopoulos et al. 2008	1,445.57	76	91	1,841.05	44	23	20.6%	-395.48 [-419.30, -371.66]	
Graff et al. 2013	1,469	227	61	1,453	249	44	20.1%	16.00 [-77.05, 109.05]	
Graff et al. 2017	1,463	248	84	1,468	253	54	20.2%	-5.00 [-90.83, 80.83]	
Larsson et al. 2016	1,411	229	72	1,325	193	30	20.2%	86.00 [-0.99, 172.99]	
Total (95% CI)			**339**			**180**	**100.0%**	**-38.61 [-301.48, 224.26]**	

Heterogeneity: Tau² = 87258.29; Chi² = 249.79, df = 4 (P < 0.00001); I² = 98%
Test for overall effect: Z = 0.29 (P = 0.77)



6.3. Funnel plot for assessment of publication bias



7. GRADE ASSESSMENTS AND EVIDENCE PROFILE

COMPARISON 1: PCOS vs control													
		Quality assessment						No. participants					
Subgroups	**No. studies**	**Design***	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**PCOS**	**Controls**	**Effect estimate WMD (95%CI); M-H, random**	**Favours**	**Certainty**	**Importance**
Outcome 1: Appetite stimulating gut hormones													
Ghrelin post MMT	7	Observational	No serious risk of bias	Serious[1]	No serious indirectness	Serious[2]	None	168	116	3/7 studies significant	Uncertain	⊕◯◯◯ Very low	Critical
Adiponectin post MMT	1	Observational	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[3]	None	40	20	1 study significant	Lower in PCOS	⊕◯◯◯ Very low	
Outcome 2: Appetite supressing gut hormones													
GLP-1	9	Observational	No serious risk of bias	Very serious[4]	No serious indirectness	No serious imprecision	None	235	173	Post MMT: 1/2 studies significantly lower in PCOS Post OGTT: 1/7 studies significantly higher in PCOS, 2/7 studies lower in PCOS	Uncertain	⊕◯◯◯ Very low	Critical
PYY	4	Observational	No serious risk of bias	Serious[1]	No serious indirectness	Serious[2]	None	101	80	Post MMT: 1/3 studies significantly lower in PCOS Post OGTT: 1 study no difference	No difference	⊕◯◯◯ Very low	
Amylin	1	Observational	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[3]	None	29	10	Post OGTT: 1/1 study higher in PCOS	Higher in PCOS	⊕◯◯◯ Very low	
Outcome 3: Subjective hunger													
Subjective hunger	1	Observational	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[3]	None	30	23	Post MMT: 1/1 study significant	Higher in PCOS	⊕◯◯◯ Very low	Critical
Outcome 4: Subjective satiety													
Subjective satiety	4	Observational	No serious risk of bias	Serious[1]	No serious indirectness	Serious[2]	None	71	63	Post MMT: 1/4 study significantly lower in PCOS	No difference	⊕◯◯◯ Very low	Critical
Outcome 5: Meal induced thermogenesis													
Meal induced thermogenesis	2	Observational	Serious[5]	Serious[1]	No serious indirectness	Serious[2]	None	24	34	1/2 study significantly lower in PCOS	Unclear	⊕◯◯◯ Very low	Critical
Outcome 6: Resting Energy Expenditure (REE)													

Resting energy expenditure	5	Observational	Serious[5]	Very serious[4]	No serious indirectness	No serious imprecision	None	339	180	-38.61 [-301.48, 224.26]	No difference	⨁◯◯◯ Very low	Critical

*due to the observational design of the studies, all GRADE assessments started at a lower level and were further downgraded or upgraded as applicable.
[1] Downgraded once due to inconsistent direction of findings
[2] Downgraded once due to small sample size
[3] Downgraded twice due to very small number of studies and small sample size
[4] Downgraded twice due to very inconsistent findings and/or high heterogeneity
[5] Downgraded once due to high or moderate risk of bias of included studies

8. QUALITY APPRAISAL OF INCLUDED STUDIES

		Selection bias			Performance bias	Detection bias				Attrition bias		Report Bias	Confounding	Other bias			
Study ID	Design	Comparable cases & controls	Established case definition	Established control definition	Groups treated the same	Standard measurements for exposure	Assessors blinded to case/control status	Standard measurements for outcomes	Outcomes assessed objectively and independently	% lost to follow up	% included in analysis	Free of selective outcome reporting	Groups similar at baseline	Funding/COI reported	Sufficient power	Adequate statistical analysis	Overall risk
Aydin 2014	Cross Sectional	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	Yes	Yes	No	NR	Yes	Low
Barber 2008	case control	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	Yes	Partial	no	yes	Yes	Low
Daghestani 2011	Cross Sectional	Yes	Yes	Yes	Yes	Yes	no	Yes	Yes	NA	Yes	Yes	Partial	No	yes	Yes	Low
Gama 1996	Cross Sectional	Yes	Yes	Yes	Yes	Yes	no	Yes	Yes	NA	Yes	Yes	Partial	No	NR	Yes	Low
Glintborg 2017	RCT	Yes	Yes	Yes	No	Yes	NR	Yes	Yes	72%	Yes	Yes	Yes	Yes	yes	Yes	Low
Hirschberg 2004	Case-control	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	Partial	Yes	Yes	NR	Yes	Low
Japur 2014	Cross Sectional	Yes	yes	yes	Yes	Yes	no	Yes	Yes	NA	Yes	Yes	Partial	Yes	NR	Yes	Low
Japur 2019	Cross Sectional	Yes	Yes	Yes	Yes	Yes	no	Yes	Yes	NA	Yes	Yes	Partial	Yes	yes	Yes	Low
Lin 2015	Cross Sectional	Yes	Yes	Yes	Yes	Yes	no	Yes	Yes	NA	Yes	Yes	no	yes	NR	Yes	Mod
Martinez-Garcia 2021	Cross Sectional	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	Yes	no	Yes	yes	Yes	Low
Moran, 2007b	Cohort	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NR	Yes (All)	Yes	Yes	Yes	NR	Yes	Low
Moran. 2004	RCT	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NR	Yes	Yes	Partial	Yes	NR	Yes	Low
Ozgen, 2010	case-control study	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes (All)	Yes	Yes	No	NR	Yes	Low
Ozgen, 2017	case-control study	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes (All)	Partial	Partial	Yes	NR	Yes	Mod

Pontikis, 2011	case-control study	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes (All)	Yes	No	Yes	NR	Yes	Low
Rao, 2021	prospective case-control study	Partial	Yes	Yes	Yes	Yes	No	Yes	Yes	case: 53.3% control: 67%	case: 46.7% control: 33%	Yes	Partial	Yes	NR	Yes	Mod
Vejrazkova, 2017	case-control study	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes (All)	Yes	Yes	Yes	NR	Yes	Low
Vrbikova, 2008	case-control study	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes (All)	Yes	Yes	Yes	NR	Yes	Low
Zwirska-Korczala, 2008	case-control study	Partial	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes (All)	Partial	Partial	Yes	NR	Yes	Mod
James 2010	case control	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	NA	Yes (All)	Yes	Partial	Yes	NR	Yes	Low
Arusoglu 2013	cross-sectional	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	NA	Yes (All)	Yes	Yes	Yes	NR	Yes	Low
Cosar 2008	Cross-sectional	Partial	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	Yes	No	No	NR	Yes	Mod
Doh 2016	Cross-sectional	Partial	Yes	Partial	Yes	Yes	No	Yes	Yes	NA	Yes	No	No	Yes	NR	Partial	High
Georgopoulos 2008	Cross-sectional	Partial	Yes	Partial	Yes	Yes	No	Yes	Yes	NA	Yes	Yes	NR	No	NR	Yes	Mod
Graff 2013	Cross-sectional	Partial	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	Yes	No	Yes	Yes	Yes	Mod
Graff 2017	Cross-sectional	No	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	Yes	No	Yes	Yes	Yes	Mod
Koika 2009	Cross-sectional	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	Yes	Yes	Yes	NR	Yes	Mod
Larsson 2016	Cross-sectional	No	Yes	Partial	Yes	Yes	No	Yes	Yes	NA	Yes	Yes	No	Yes	Yes	Yes	Mod
Robinson 1992	Cross-sectional	Partial	Partial	Partial	Yes	Yes	No	Yes	Yes	NA	Yes	Yes	No	Yes	No	Yes	Mod
Segal 1990	Cross-sectional	Partial	Partial	Partial	Yes	Yes	No	Yes	Yes	NA	Yes	Yes	No	Yes	No	Yes	Mod

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 3

Question 3.5.

Why are women with PCOS at increased risk of weight gain?

BACKGROUND:

Increased risk of weight gain in women with PCOS

In initial surveys conducted with women with PCOS for prioritising clinical questions for the 2023 PCOS guideline update, when asking which PCOS symptoms concerned them the most, 27% of responders ranked difficulty losing weight as the #1 symptom of concern and 16% ranked it as the second. When asking women to rank the top 5 areas they would like more research to focus on, 21% ranked difficulty losing weight as the top priority and 12% ranked it as the second.

Insulin resistance is a key aetiological feature of PCOS, which occurs in the majority of women in a form mechanistically distinct from obesity-associated insulin resistance [1]. Obesity then further worsens insulin resistance and exacerbates clinical features of PCOS [2]. Given the strong relationships between insulin resistance, obesity and PCOS, weight management through lifestyle interventions is the primary treatment strategy for PCOS, according to international evidence-based guidelines, and improves the presentation [3]. Of note, bidirectional relationship is hypothesised between PCOS and weight such that PCOS may result in greater weight gain which in turn increases the prevalence and severity of PCOS [4].

Excess weight is a common feature of PCOS and over half of women with PCOS are either overweight or obese [5]. This means women with PCOS commonly experience the additional burden of obesity-associated insulin resistance. In a comprehensive systematic review and meta-analysis of the prevalence of overweight, obesity and central obesity in women with and without PCOS in clinic-based women [6], women with PCOS had a significantly increased risk for adiposity when compared with controls with pooled estimated prevalence of overweight, obesity and central in PCOS being 61% (95% CI: 54–68%), 49% (95% CI: 42–55%) and 54% (95% CI: 43– 62%) respectively. The risk of overweight, obesity and central obesity were relative risk (RR) 1.95 (95% CI: 1.52-2.50), 2.77 (1.88, 4.10) and 1.73 (95% CI 1.31, 2.30) respectively. This increased risk was independent of the PCOS diagnostic criteria (NIH *versus*. Rotterdam), age and geographic region of the affected subjects. Caucasian women with PCOS had a greater prevalence of obesity than Asian women with PCOS, whether using the same criteria for overweight and obesity or ethnic specific criteria. The temporal trends of the prevalence of obesity among women with PCOS show an increase from 51% in the 90s to 74% in the following decades [5]. Weight gain is also a common presenting complaint of PCOS. The long-term weight gain over 10 years among women with PCOS is significantly greater than unaffected women in longitudinal community-based studies (mean difference 2.6kg 95% CI 1.2-4.0) [7] as is central obesity with a progressive increase in waist hip ratio between 20-25 years and 40-45 years [8]. This is consistent with reports from a prospective birth cohort of increased weight gain in early adulthood in women with symptoms of or a diagnosis of PCOS compared with controls [9]. Furthermore, a community-based longitudinal cohort study reported adverse lifestyle factors (higher energy intake, glycaemic index and sitting time and lower physical activity) had a greater impact on weight gain in women with PCOS compared to those without PCOS [10].

In keeping with this evidence, the 2018 International evidence-based guidelines for the assessment and management of polycystic ovary syndrome [11], the clinical consensus recommendations stated that ‘Health professionals and women should be aware that women with PCOS have a higher prevalence of weight gain and obesity, presenting significant concerns for women, impacting on health and emotional wellbeing, with a clear need for prevention’ and that ‘All those with PCOS should be offered regular monitoring for weight changes and excess weight.’ Following on from the 2018 guidelines, İnitial surveys were conducted with women with PCOS for prioritising clinical questions for the 2022 PCOS guideline update. When asking which PCOS symptoms concerned them the most, 27% of responders ranked difficulty losing weight as the #1 symptom of concern and 16% ranked it as the second. When asking women to rank the top 5 areas they would like more research to focus on, 21% ranked difficulty losing weight as the top priority and 12% ranked it as the second. As such, the focus of the clinical question in these guidelines was to examine why women with PCOS may have challenges with weight management.

Extrinsic factors potentially contributing to increased risk of weight gain in women with PCOS

Suboptimal diet and physical activity are modifiable environmental factors (extrinsic factors) that contribute to weight gain. Poorer dietary intake (including excess energy intake or poor diet quality including reduced core food group and increased discretionary food intake) and reduced physical activity have been proposed to contribute to increased weight in PCOS. However, this evidence is currently conflicting with worsened lifestyle behaviours [12-16], improved lifestyle behaviours [17] or no differences in lifestyle behaviours groups [18-21] reported between women with and without PCOS. It is crucial to understand differences in lifestyle behaviours (extrinsic factors) in women with and without PCOS that could be related to the observed increased weight gain and higher obesity prevalence in PCOS and therefore be targeted for lifestyle interventions to optimise weight management.

Intrinsic factors potentially contributing to increased risk of weight gain in women with PCOS

In addition to potential differences in extrinsic factors, potential mechanisms for excess weight gain in PCOS may be related to underlying hormonal abnormalities including insulin resistance and hyperandrogenism or specific barriers which are intrinsic to maintaining healthy weight, such as appetite dysregulation [22], altered metabolic rate [23], or postprandial thermogenesis [24]. However, the research to date is limited and inconsistent. It is crucial to understand the pathophysiological mechanisms that may be altered in PCOS and associated with impaired weight management to aid understanding and guiding of realistic weight management goals and to aid investigation of future pharmacological targets.

GRADE EVIDENCE CERTAINTY	
Comparison	**GRADE for critical outcomes**
○ Intrinsic factors in women with PCOS versus controls	⊕◯◯◯ VERY LOW
○ Extrinsic factors in women with PCOS versus controls	⊕◯◯◯ VERY LOW

Evidence to Recommendations Framework

COMPARISONS (option versus other option)

Women (any age) with PCOS versus women (any age) without PCOS

EVIDENCE-BASED RECOMMENDATION(S)

EBR: Health professionals and women with PCOS could consider that there is no clear evidence of physiological or behavioural lifestyle differences, related to weight, in women with PCOS compared to women without PCOS.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

PRACTICE POINT(S)

Whilst the specific mechanisms are unclear, it is recognised that many women with PCOS will have underlying mechanisms that drive greater longitudinal weight gain and higher BMI whichmay:

- Underpin greater challenges with weight management.
- Highlight the importance of lifelong healthy lifestyle strategies and prevention of excess weight gain.
- Assist women with PCOS and health professionals in forming realistic, tailored lifestyle goals.

GRADE CONSIDERATIONS

Justifications:

There is very low-quality evidence that women with PCOS may have some differences in lifestyle behaviours (higher total dietary fat intake and lower physical activity on self-report) and have may have some differences in appetite related hormones after a MMTT. There is no evidence of certainty for other outcomes including energy intake (on pooled analysis), other macronutrients (carbohydrate, protein), glycaemic index, glycaemic load, subjective hunger or satiety, meal induced thermogenesis or resting energy expenditure.

Most outcomes are self-reported and prone to recall bias and misreporting.

It is acknowledged that women with PCOS have higher rates of weight gain and obesity. A community-based longitudinal cohort study reported adverse lifestyle factors (higher energy intake, glycaemic index and sitting time and lower physical activity) had a greater impact on weight gain in women with PCOS compared to those without PCOS [10]; however, more research is needed.

Subgroup considerations: Evidence assessing differences across methodologies, age, BMI range, reproductive life stage and pathophysiological subgroups (eg hyperandrogenism or insulin resistance) is warranted in future research.
Implementation considerations: A focus on weight gain prevention will be important in implementation.
Monitoring and evaluation considerations: Audit of clinical practice and longitudinal population-based cohort studies
Research priorities: Examine more precise quantification of diet, physical activity, appetite hormone regulation, appetite, insulin and energy expenditure in women with and without PCOS and examine relationships with weight and weight change across the BMI spectrum. Specifically: Primary longitudinal studies assessing physiological, behavioural and psychosocial predictors of weight gain in PCOS, from early life and across different ethnic groups. Primary studies assessing food or nutrient intake on adipokines, gastrointestinal appetite hormones, functional MRI, meal induced thermogenesis, metabolic flexibility and neuropeptide responses in women with PCOS to better capture the accurate relationship with energy homeostasis. Primary studies characterising the total energy expenditure of women with PCOS using doubly labelled water, dietary intake using objective measures and physical activity using accelerometry.

GRADE framework

GRADE DECIDE **Interactive Evidence to Decision Framework**

● DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

May reduce personal blame women with PCOS feel if experiencing challenges with weight management and improve understanding of health professionals of these potential challenges

Allow provision of additional support for women for weight management and potential improved weight management.

● UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

There are no identified undesirable options related to favouring the option.

● CERTAINTY OF THE EVIDENCE

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☒ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Very low evidence for all outcomes

● VALUES

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☐ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☒ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Research evidence:

No research evidence was identified

Panel discussion:

A weight inclusive approach identifies lifestyle change rather than weight change as a primary treatment priority. For women and health professionals following this approach, these intrinsic and extrinsic outcomes would still likely be of importance as they relate to how women can achieve changes in lifestyle behaviour.

● BALANCE OF EFFECTS

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☒ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:

There are no identified undesirable options related to favouring the option.

● COSTS

How large are the resource requirements (costs)?

Judgement:

☐ Don't know	☒ Varies	☐ Large costs	☐ Moderate costs	☐ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:

No research evidence was identified

Panel discussion:

Clinical requirements for longer consultation times or increased referrals to allied health would confer additional time and resource requirements and costs. In some settings there may be subsidised costs for this and referral to community-based lifestyle management programs may be possible.

● CERTAINTY OF COST EVIDENCE

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

No research evidence was identified

Panel discussion:

● COST-EFFECTIVENESS

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

No research evidence was identified

Panel discussion:

● EQUITY

What would be the impact on health equity?

Judgement:

☒ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☐ Probably increased	☐ Increased

Research evidence:

No research evidence was identified

Panel discussion:

Dietary intake and physical activity can be different in women based on their socio-economic status. Access to appropriate health care services with sufficient time for assessment and consideration of barriers to weight management may vary depending on locality and women's socio-economic status.

Considering social determinants of health including support to maintain affordable healthy diet and exercise to assist weight management may have the potential for increased benefit to groups that experience increased socioeconomic disadvantage or discrimination.

● ACCEPTABILITY

Is the option acceptable to key stakeholders?

Judgement:

☐ Don't know	☒ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

In initial surveys conducted with women with PCOS for prioritising clinical questions for the 2022 PCOS guideline update, when asking which PCOS symptoms concerned them the most, 27% of responders ranked difficulty losing weight as the #1 symptom of concern and 16% ranked it as the second. When asking women to rank the top 5 areas they would like more research to focus on, 21% ranked difficulty losing weight as the top priority and 12% ranked it as the second.

● FEASIBILITY

Is the option feasible to implement?

Judgement:

☐ Don't know	☒ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Improving consultation times or referral to allied health professionals or community-based lifestyle management could be implemented in some settings. The cost and resource implications of this are acknowledged. It may also be important to address psychosocial issues that enable behaviour change.

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PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by ECR Lead: Hugh Bidstrup

Other team members: Loyal Pattuwage

Supervised, edited and supported by the Evidence Team (Aya Mousa, Jillian Tay)

GDG 3

Question 3.6.

What is the burden of weight stigma in PCOS?

2. SELECTION CRITERIA

Table 1. PICO Criteria for Inclusion – Not to be adapted To be used by evidence team to decide which studies will be included when screening search results.	
Question	Q 3.6) What is the burden of weight stigma in PCOS? CLINICAL PRACTICE POINT: How do we alleviate weight stigma in PCOS in and outside healthcare settings?
Clinical leads (key contacts)	**A/Prof Leah Brennan** Psychologist La Trobe University, Australia Leah.Brennan@latrobe.edu.au **Prof Chandrika Wijeyaratne** Endocrinologist University of Colombo, Sri Lanka chandrika@obg.cmb.ac.lk
Allocation ranking	Level 2- Update systematic review

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(language, year)*
Inclusion	Females with diagnosed PCOS (NIH, Rotterdam, AEPCOS criteria, clinician confirmed, self-reported, ICD-9/10). Health professionals working with women with polycystic ovary syndrome (clinically confirmed or self-reported).	None	None	Any form of weight stigma (experienced, perceived, internalised, or anticipated).	Any qualitative or quantitative	English language, no limits no year
Exclusion	Women without PCOS				Dissertations/ theses, reviews	

2. SEARCH STRATEGY

Table 2.1. Search details

Search strategy source: *created by current team*

Evidence source	Date of search
Medline (EBSCO)	August 12 2022
PsycINFO (EBSCO)	August 12 2022
EMBASE (EBSCO)	August 12 2022
All EBM (Ovid)	August 15 2022
CINAHL (EBSCO)	August 12 2022

Any subsequent updates - enter database and date: none

Table 2.2. Questions addressed by this search *(add more rows as needed)*:

GDG 3	Q 3.6	What is the burden of weight stigma in women with PCOS?

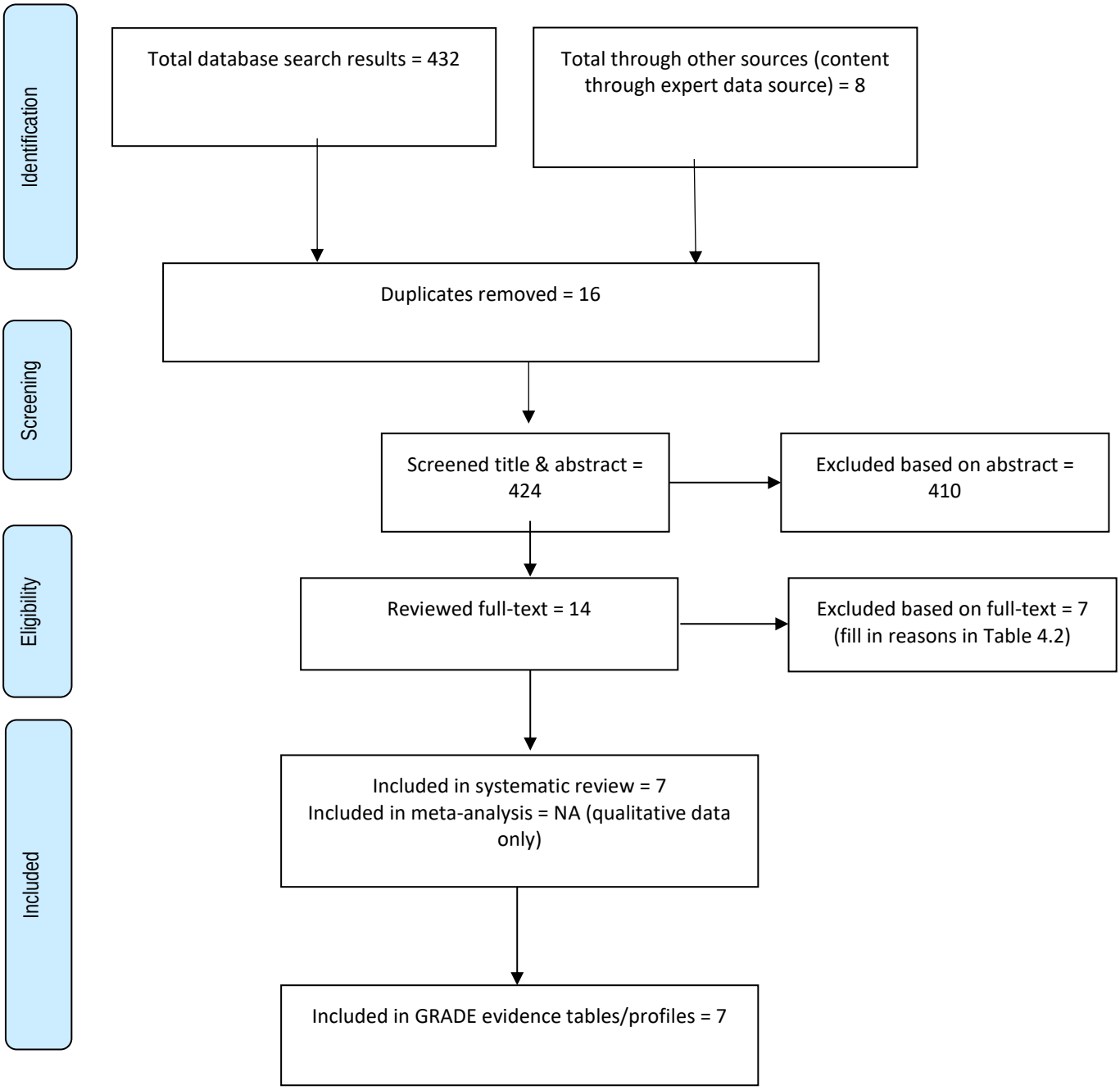
Table 2.3. Search strings used in OVID or other database/s

Medline, PsycINFO, EMBASE, and CINAHL (*n* = 421) via EBSCOhost	All EBM (conducted by LP; *n* = 11)
1. TI ((experienc* OR perceiv* OR perceptio* OR internal* OR "self direct*") N5 ("weight stigm*" OR "weight bias" OR "weight discrimination") OR ("weight" OR "self directed") N5 (bias OR stigm* OR stereotyp* OR discriminat* OR prejudic* OR attitude*) OR "Stigmati* weight experiences" OR "Weight self stigm*" OR WBIS OR SSI* OR WSSQ OR SSQ*) OR AB (experienc* OR perceiv* OR perceptio* OR internal* OR "self direct*") N5 ("weight stigm*" OR "weight bias" OR "weight discrimination") OR ("weight" OR "self directed") N5 (bias OR stigm* OR stereotyp* OR discriminat* OR prejudic* OR attitude*) OR "Stigmati* weight experiences" OR "Weight self stigm*" OR WBIS OR SSI* OR WSSQ OR SSQ*) 2. TX ("polycystic ovar*" OR "poly-cystic ovar*" OR PCO* OR (stein-leventhal OR leventhal) OR "exp polycystic ovary syndrome" OR anovulat* OR "oligo-ovulat*" oligoovulat* OR (ovar* N5 (sclerocystic OR polycystic OR "poly-cystic" OR degenerat* OR hyperandrogen* OR "hyper-androgen*")) OR (MM "Anovulation" OR "Polycystic Ovary Syndrome")) 3. S1 AND S2	1 exp polycystic ovary syndrome/ 1712 2 polycystic ovar*.mp. 4675 3 poly-cystic ovar*.mp. 136 4 PCO*.mp. 6256 5 (stein-leventhal or leventhal).mp. 99 6 anovulation/ 154 7 anovulat*.mp. 1193 8 oligo-ovulat*.mp. 55 9 oligoovulat*.mp. 32 10 (ovar* adj5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*)).mp. 4868 11 or/1-10 8226 12 ((experienc* or perceiv* or perceptio* or internal* or self-direct or "self direct") adj5 ("weight stigm*" or "weight-stigm*" or "weight-bias" or "weight bias" or "weight discrimination" or "weight-discrimination")).tw. 65 13 ((weight or "self directed" or "self-directed") adj5 (bias or stigm* or stereotyp* or discriminat* or prejudic* or attitude)).tw. 359 14 ("Stigmati* weight experiences" or "Weight self stigm*" or "WBIS" or "SSI*" or "WSSQ" or "ORSSQ*").tw. 2107 15 12 or 13 or 14 2448 16 11 and 15 11

Evidence processing: Studies were selected and appraised by one reviewer (HB) in consultation with the evidence team/ key contact using study selection and appraisal criteria (PICO above) established a priori. The articles were reviewed by title and abstract by one reviewer (HB). When a decision could not be made based on title and abstract alone, full text was retrieved. **Seven studies met inclusion criteria for this review.**

☐	S3	S1 AND S2	**Expanders** - Apply equivalent subjects **Search modes** - Find all my search terms	Rerun | View Details | Edit
☐	S2	TX ("polycystic ovar*" OR "poly-cystic ovar*" OR PCO* OR (stein-leventhal OR leventhal) OR "exp polycystic ovary syndrome" OR anovulat* OR "oligo-ovulat*" OR "oligoovulat* OR (ovar* N5 (sclerocystic OR polycystic OR "poly-cystic" OR degenerat* OR hyperandrogen* OR "hyper-androgen*")) OR (MM "Anovulation" OR "Polycystic Ovary Syndrome"))	**Expanders** - Apply equivalent subjects **Search modes** - Find all my search terms	Rerun | View Details | Edit
☐	S1	TI ((experienc* OR perceiv* OR perceptio* OR internal* OR "self direct*") N5 ("weight stigm*" OR "weight bias" OR "weight discrimination") OR ("weight" OR "self directed") N5 (bias OR stigm* OR stereotyp* OR discriminat* OR prejudic* OR attitude*) OR "Stigmati* weight experiences" OR "Weight self stigm*" OR WBIS OR SSI* OR WSSQ OR SSQ*) OR AB (experienc* OR perceiv* OR perceptio* OR internal* OR "self direct*") N5 ("weight stigm*" OR "weight bias" OR "weight discrimination") OR ("weight" OR "s...	**Expanders** - Apply equivalent subjects **Search modes** - Find all my search terms	Rerun | View Details | Edit

3. SEARCH RESULTS - PRISMA flowchart



4. STUDY INCLUSION

Table 4.1. Included Studies (full citation with doi)- *add more rows as needed*
Amiri, F. N., Tehrani, F. R., Simbar, M., Montazeri, A., & Thamtan, R. A. M. (2014). The experience of women affected by polycystic ovary syndrome: a qualitative study from Iran. International journal of endocrinology and metabolism, 12(2). https://doi.org/10.5812/ijem.13612
Chopra, S., Zehrung, R., Shanmugam, T. A., & Choe, E. K. (2021, May). Living with uncertainty and stigma: self-experimentation and support-seeking around polycystic ovary syndrome. In Proceedings of the 2021 CHI Conference on Human Factors in Computing Systems (pp. 1-18). https://doi.org/10.1145/3411764. 3445706
Ismayilova, M., & Yaya, S. (2022). 'I'm usually being my own doctor': women's experiences of managing polycystic ovary syndrome in Canada. International Health. https://doi.org/10.1093/inthealth/ihac028
Jones, G. L., Hall, J. M., Lashen, H. L., Balen, A. H., & Ledger, W. L. (2011). Health-related quality of life among adolescents with polycystic ovary syndrome. Journal of Obstetric, Gynecologic & Neonatal Nursing, 40(5), 577-588. https://doi.org/10.1111/j.1552-6909.2011.01279.x
Moran, L. J., Tan, Z. Q., Bayer, S., Boyle, J. A., Robinson, T., & Lim, S. S. (2022). Perspectives of allied health professionals on implementation of the lifestyle polycystic ovary syndrome guidelines: a qualitative study. Journal of the Academy of Nutrition and Dietetics, 122(7), 1305-1316. https://doi.org/10.1016/j.jand.2021.11.013
Tomlinson, J., Pinkney, J., Adams, L., Stenhouse, E., Bendall, A., Corrigan, O., & Letherby, G. (2017). The diagnosis and lived experience of polycystic ovary syndrome: A qualitative study. Journal of advanced nursing, 73(10), 2318-2326. https://doi.org/10.1111/jan.13300
Williams, S., Sheffield, D., & Knibb, R. C. (2016). A snapshot of the lives of women with polycystic ovary syndrome: A photovoice investigation. Journal of Health Psychology, 21(6), 1170-1182. https://doi.org/10.1177/1359105314547941

Table 4.2. Excluded Studies (on full text assessment)- *add more rows as needed*	
Arranz-Lara et al. (2010)	No outcomes of interest
Crino et al. (2019)	Did not assess target population
Dahl et al. (2014)	Did not assess target population
Dennet et al. (2018)	Not an empirical study
Gee et al. (2008)	Did not assess target population
Savas et al. (2019)	No outcomes of interest
Washington (2005)	Dissertation

5. STUDY CHARACTERISTICS TABLE

Author, year, country	Population/ Setting, Recruitment Techniques	Study Type	Age Range	Sample Age	Source of Weight Stigma	Summary of findings
Amiri et al., (2014), Iran	Clinical: women with PCOS attending the reproductive Endocrinology Research Centre	Qualitative (semi structured interviews)	18-40	18-24: 8 (34.8%) 25-34: 13 56.5%) 35-40: 2 (8.7%)	Unclear: could be a stranger, a healthcare administrator, or a doctor	A 25-year old participant reports an experience of weight stigma: *"… Last time I visited my doctor, a woman asked me, 'are you single?' After I answered, 'yes' she said, 'a single girl shouldn't have such a big belly', and I got so embarrassed. Although I put on the veil, she could see my big belly."*
Chopra et al., (2021), USA	Community: snowballing and purposive sampling using word of mouth and FB/listerv)	Qualitative (semi structured interviews)	22-55	Frequencies reported: 22 | 2 23 | 4 24 | 2 25 | 1 ... 55 | 1	Family Self (internalised societal ideals)	A participant describes experiences of weight stigma from family members: *"My family doesn't support me at all. I'm tired of receiving comments about how fat and hairy (which forces me to shave!) I am. I did not ask to have PCOS!... I just want to feel self-confident again but hearing their horrible comments doesn't let me feel so... Every time I try doing a diet, they say that I will give up."* A Reddit poster describes internalised weight stigma: *"I still find myself as unattractive, unworthy, not confident, and have serious body image issues. Some nights, I get anxious, feeling that I'm never going to lose weight and will remain fat forever. I'm TIRED of feeling like this, I'm TIRED"*
Ismayilova and Yaya (2022), Canada	Community: FB, Reddit, online forums, posts from PCOS Awareness Association	Qualitative (semi structured interviews)	18-63	Age rage: no (%) 18–24 | 5 (20) 25–30 | 10 (40) 31–36 | 4 (16) 37–40 | 2 (8) 41–50 | 2 (8) 51–66 | 1 (4)	Doctor Doctor Doctor	Zara, a 24-year old participant, describes her doctor assuming she was sedentary b/c of her weight: *"Totally negative. Kind of like without necessarily asking. Like I walk an hour and a half twice a day, every day. I'm not sedentary. But you just assuming is just very frustrating, especially when you're told that it's very hard for you to lose weight when you have PCOS. It's just like, oh my god, you need to talk about this better."* Lucy, a 47 year old participant, recalls an instance of perceived/experienced weight stigma: *"They just said 'Lose weight', which is really useless. You don't need to tell people to lose weight. None of my doctors have ever offered valuable advice. Not only with PCOS but with lifestyle or nutrition or anything, ever."* 11 of 25 (44%) of participants were told to lose weight by their doctors.

Jones et al. (2021), England	Clinical: out-patient gynaecology clinics by clinician	Qualitative (semi structured interviews)	17-21	20.1 (NR)	Self-Perceived judgement from general public	Reports of internalised weight stigma: "Participants reported feeling “upset,” “worried,” “horrible,” “depressed,” “unattractive,” and “not very feminine” because of their weight and/or body shape." Reports of anticipating weight-based stigma, summarised by the authors: Many felt self-conscious and lacked self-confidence, feelings that were enhanced in certain social situations due to the fear of being judged, such as shopping for clothes, going to pubs or nightclubs, lying on the beach, or swimming. (Unspecific participant): "*My friend asked me if I wanted to go swimming a couple of weeks ago, and I didn’t even let her finish the sentence. I just said no. I won’t let anybody see me in my swimming costume, well practically naked. I just don’t like it. If I don’t like it then nobody else is going to like it".*
Moran et al., (2021), Australia	Allied HCPs (dietetics, exercise physiology, psychology) / Purposive sampling via professional association newsletters and snowballing	Qualitative (semi structured interviews)	NR	Years of practice: <5 y | 5 5-10 y | 3 11-15 y | 3 16-20 y | 3 > 20 y | 1	HCPs	Psychologist talks about experiences of patients in the healthcare system with other health professionals that have a very weight-centric approach: *". . . many have experienced weight stigma associated with being overweight. Unfortunately that often comes from medical professionals. (participant 12, psychologist)*" Weight stigma identified by the authors as a barrier to care
Tomlinson et al., (2017), England	Clinical: various health settings in those with PCOS concerns By research nurse through various clinics	Qualitative (focus groups of 2-6 ps)	18-45	NR (NR)	Doctor Doctor	Participants report experienced/perceived weight stigma, as well as refusal of treatment, from doctors: *"I worked on a building site… a very active job … but all my weight it’s always around my middle. I just couldn’t lose it and he just basically told me I was fat so I just got up walked out. (Gemma)"* and *"My symptoms were never really taken seriously by my GP or I felt by the hospital… …I was more or less told that you're chubby, you're overweight, there's nothing we can do, we're not giving you any fertility treatment because you're overweight, that would be a danger to a baby, um and ‘bye bye’ and I was quite traumatised by that. (Jess)".*
Williams et al., (2016), UK	Community: online via PCOS charity website, Verity	Qualitative (daily diary)	20-45	NR (NR)	Self	A participant reports internalisation of weight stigma - not feeling feminine/like a woman because of her weight: *"makes me feel im not a woman… [carrying] fat around the middle like a man’s beer belly even though I go gym or swimming every week (Linda, 45)".*

HCP(s)= Health care professional(s)

6. SUMMARY OF FINDINGS AND GRADE ASSESSMENTS/ EVIDENCE PROFILE

▪ EVIDENCE SUMMARY

We systematically reviewed all published studies that assessed the burden of weight stigma in women with PCOS. We also reviewed studies that assessed healthcare professionals and weight stigma.

Seven studies met our inclusion criteria; all were qualitative. Three major sources of stigma were identified: healthcare professionals/doctors, family members, and societal. There were *five* central findings – women with PCOS reported: (1) experiencing weight stigma from doctors, (2) experiencing weight stigma from family members, (3) internalising weight stigma from a variety of societal sources, and (4) anticipating weight stigma from the general public. Finally, both women with PCOS *and* healthcare professionals report weight stigma in healthcare contexts from various sources.

Because all studies were qualitative, we used the GRADE CERQual (Lewin et al., 2015, 2018) to assess the quality of studies in this systematic review. This assessment estimated that we can have a high degree of confidence from findings 1 and 4, and moderate confidence in findings 2, 3, and 5.

▪ META-ANAYLSIS/DESCRIPTIVE SUMMARY ANALYSIS

Our review is limited in that there were few existing studies that report instances of weight stigma, and thus, these findings were descriptive and preliminary for this cohort (i.e., women with PCOS). However, the findings are consistent with those in other cohorts (e.g., community, clinical, and student; Emmer et al., 2020) – that is, weight stigma is (a) pervasive, (b) detrimental to mental health, (c) profoundly affected by societal attitudes toward weight, and (d) perpetrated in everyday settings – by family members in the home and doctors in healthcare settings.

Table 6.1. Table of Findings

Synthesis of Review Finding	Quality assessment					
	Methodological Limitations	**Coherence**	**Adequacy**	**Relevance**	**GRADE-CERQual Assessment of Confidence**	**Papers Supporting Finding**
Finding 1 Women with PCOS report experiences of weight stigma from doctors	no/very minor concerns	no/very minor concerns	no/very minor concerns	no/very minor concerns	⊕⊕⊕⊕ High confidence	Ismayilova and Yaya (2022) Tomlinson et al. (2017)
Finding 2 HCPs and women with PCOS report weight stigma in healthcare settings, from several sources	no/very minor concerns	no/very minor concerns	minor concerns	no/very minor concerns	⊕⊕⊕◯ Moderate confidence	Amiri et al. (2014) Moran et al. (2021)
Finding 3 Women with PCOS report experiences of weight stigma from family members	no/very minor concerns	no/very minor concerns	minor concerns	no/very minor concerns	⊕⊕⊕◯ Moderate confidence	Chopra et al. (2021)
Finding 4 Women with PCOS report internalisation of weight stigma (variety of societal sources)	no/very minor concerns	no/very minor concerns	no/very minor concerns	no/very minor concerns	⊕⊕⊕⊕ High confidence	Chopra et al. (2021) Jones et al. (2021) Williams et al. (2016)
Finding 5 Women with PCOS report anticipating weight stigma and changing their behaviour based on perceived, expected judgement	no/very minor concerns	no/very minor concerns	minor concerns	no/very minor concerns	⊕⊕⊕◯ Moderate confidence	Jones et al. (2021)

HCP= health care professional(s)

APPENDIX. QUALITY APPRAISAL TEMPLATES

Study ID	*Amiri et al. (2014)*	
Study Citation	*Amiri, F. N., Tehrani, F. R., Simbar, M., Montazeri, A., & Thamtan, R. A. M. (2014). The experience of women affected by polycystic ovary syndrome: a qualitative study from Iran. International journal of endocrinology and metabolism, 12(2). https://doi.org/10.5812/ijem.13612*	
Study Country	*Iran*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*25 individuals diagnosed with PCOS according to Rotterdam criteria*	
Control population	*NA*	
PCOS diagnostic criteria	*Rotterdam – 2003*	
N per group	*No subgroups*	
Setting	*Clinical – women attending RERC clinic*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Self-reported weight stigma*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes - "explore the experiences of QoL in Iranian women with PCOS."*
Inclusion criteria	Yes Partial No Not reported	*Yes, "18-40 years of age, met the Rotterdam criteria for diagnosis of PCOS (i.e., 2003), and [consented] to participate and share their experiences"*
Exclusion criteria	Yes Partial No Not reported	*Yes, coexisting illness, inability to read and speak Farsi, and having conditions similar to PCOS at presentation such as congenital adrenal hyperplasia.*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes, qualitative (cross-sectional) studies are appropriate as preliminary investigations to understand the burden of weight stigma in women with PCOS*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Not relevant*
Was matching performed?	Yes Partial No	*Not relevant*

		Not reported	
Summary Result/s		*Experience of weight stigma reported by 1 participant. Source of weight stigma were unclear based on quote (see Study Characteristics Table).*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Not relevant*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Not relevant*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*Not relevant*
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Not relevant*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Not relevant*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not relevant*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Not relevant*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes, interviews transcribed verbatim*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant to cross-sectional study*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*Not applicable*

REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Not applicable*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Not relevant*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not relevant*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Not relevant*
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Insufficient information*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Chopra et al. (2014)*
Study Citation	*Chopra, S., Zehrung, R., Shanmugam, T. A., & Choe, E. K. (2021, May). Living with uncertainty and stigma: self-experimentation and support-seeking around polycystic ovary syndrome. In Proceedings of the 2021 CHI Conference on Human Factors in Computing Systems (pp. 1-18). https://doi.org/10.1145/3411764. 3445706*
Study Country	*USA*
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*10 individuals with a self-reported PCOS diagnosis.*
Control population	*NA*
PCOS diagnostic criteria	*Self-reported*
N per group	*No subgroups*
Setting	*Community*

Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)		*Self-reported weight stigma*	
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	*Yes, to "inform the design of inclusive health technologies through an understanding of people's lived experiences and challenges with PCO"*
Inclusion criteria		Yes Partial No Not reported	*Yes, PCOS diagnosis*
Exclusion criteria		Yes Partial No Not reported	*Yes, those without PCOS*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	*Yes, qualitative (cross-sectional) studies are appropriate as preliminary investigations to understand the burden of weight stigma in women with PCOS*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*NR*
Was matching performed?		Yes Partial No Not reported	*Not relevant*
Summary Result/s		*Participant in semi-structured interviews reports experiences of weight stigma from family members. Reddit post describes internalised weight stigma. Please see Summary Table for quotes.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Not relevant*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Not relevant*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*Not relevant*

PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Not relevant*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Not relevant*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not relevant*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Not relevant*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes, interviews transcribed verbatim and Reddit posts assessed.*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant to cross-sectional study*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*Not applicable*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Not applicable*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Not relevant*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*Not reported*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not relevant*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Not relevant*

COMMENTS		
What is the overall risk of bias?	Low Moderate High Insufficient information	*Insufficient information*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*No*	

Study ID	*Ismayilova and Yaya (2022)*	
Study Citation	*Ismayilova, M., & Yaya, S. (2022). 'I'm usually being my own doctor': women's experiences of managing polycystic ovary syndrome in Canada. International Health. https://doi.org/10.1093/inthealth/ihac028*	
Study Country	*Canada*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*25 individuals self-reporting a PCOS diagnosis.*	
Control population	*47 heaNA*	
PCOS diagnostic criteria	*Self-reported*	
N per group	*No subgroups*	
Setting	*Community*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Self-reported weight stigma*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes, "explores the lived experiences of women with PCOS in Canada to better understand the meaning of that experience for them and identifies the barriers and facilitators in women's journeys to manage their condition"*
Inclusion criteria	Yes Partial No Not reported	*Yes: "age ≥18 y, reporting a medical diagnosis of PCOS, having lived in Canada since their diagnosis and able to speak and understand English. No upper age limit"*
Exclusion criteria	Yes Partial No Not reported	*Not reported, some implied from inclusion criteria.*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No	*Yes, qualitative (cross-sectional) studies are appropriate as preliminary investigations to understand the burden of weight stigma in women with PCOS*

		Not reported	
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*NR*
Was matching performed?		Yes Partial No Not reported	*Not relevant*
Summary Result/s		*Two participants report an instance of experienced/perceived weight stigma from doctors. 44% of participants have been told explicitly by doctors to lose weight. Please see Summary Table.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Not relevant*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Not relevant*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*Not relevant*
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Not relevant*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Not relevant*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not relevant*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Not relevant*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes, interviews transcribed verbatim*

ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant to cross-sectional study*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*Not applicable*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Not applicable*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Not relevant*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not relevant*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Not relevant*
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Insufficient information*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Jones et al. (2021)*
Study Citation	*Jones, G. L., Hall, J. M., Lashen, H. L., Balen, A. H., & Ledger, W. L. (2011). Health-related quality of life among adolescents with polycystic ovary syndrome. Journal of Obstetric, Gynecologic & Neonatal Nursing, 40(5), 577-588. https://doi.org/10.1111/j.1552-6909.2011.01279.x*
Study Country	*England*
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	

Patient/population/ participants		*15 individuals diagnosed with PCOS according to Rotterdam criteria.*	
Control population		*47 heaNA*	
PCOS diagnostic criteria		*Rotterdam 2003*	
N per group		*No subgroups*	
Setting		*Clinical*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)		*Self-reported weight stigma*	
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	*Yes, "explore the various effects PCOS has had on the physical, social, and psychological/ emotional aspects of the lives of Adolescents"*
Inclusion criteria		Yes Partial No Not reported	*Yes, PCOS diagnosis and adolescent (defined as 17-21 years)*
Exclusion criteria		Yes Partial No Not reported	*Yes,"the presence of a coexisting illness that may have a contributory effect on HRQoL; inability to read and speak English, because this study was conducted in English; and conditions similar in presentation to PCOS, such as congenital adrenal hyperplasia"*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	*Yes, qualitative (cross-sectional) studies are appropriate as preliminary investigations to understand the burden of weight stigma in women with PCOS*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*NR*
Was matching performed?		Yes Partial No Not reported	*Not relevant*
Summary Result/s		*Several participants reported self (internalised) weight stigma, and one additional participant reported anticipating weight stigma from the general public, and changing their behaviour as a consequence (please see Summary Table).*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Not relevant*

	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Not relevant*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*Not relevant*
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Not relevant*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Not relevant*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not relevant*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Not relevant*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes, interviews transcribed verbatim*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant to cross-sectional study*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*Not applicable*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Not applicable*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Not relevant*
	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*

OTHER BIAS	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not relevant*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Not relevant*
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Insufficient information*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Moran et al. (2021)*	
Study Citation	*Moran, L. J., Tan, Z. Q., Bayer, S., Boyle, J. A., Robinson, T., & Lim, S. S. (2022). Perspectives of allied health professionals on implementation of the lifestyle polycystic ovary syndrome guidelines: a qualitative study. Journal of the Academy of Nutrition and Dietetics, 122(7), 1305-1316. https://doi.org/10.1016/j.jand.2021.11.013*	
Study Country	*Australia*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*15 allied healthcare professionals involved in the management of PCOS.*	
Control population	*47 heaNA*	
PCOS diagnostic criteria	*NA*	
N per group	*Allied health professionals:* *1 | Psychologist* *5 | Exercise physiologists* *9 | Dietician*	
Setting	*Professional/Clinical*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Weight stigma in clients*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes, "explore the barriers and enablers to lifestyle and weight management for individuals with PCOS from the perspectives of allied health professionals."*
Inclusion criteria	Yes Partial	*Yes, allied HCPs who are involved in the management and treatment of women with PCOS*

		No Not reported	
Exclusion criteria		Yes Partial No Not reported	*Not reported*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	*Yes, qualitative (cross-sectional) studies are appropriate as preliminary investigations to understand the burden of weight stigma in women with PCOS as reported by allied HCPs*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Not relevant*
Was matching performed?		Yes Partial No Not reported	*Not relevant*
Summary Result/s		*One participant, a psychologist, reported that women with PCOS likely experience a very weight-centric (and thus stigmatising) environment with HCPs. Please see Summary Table.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Not relevant*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Not relevant*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*Not relevant*
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Not relevant*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Not relevant*

	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not relevant*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Not relevant*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes, interviews transcribed verbatim*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant to cross-sectional study*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*Not applicable*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Not applicable*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Not relevant*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not relevant*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Not relevant*
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Insufficient information*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Tomlinson et al. (2017)*	
Study Citation	*Tomlinson, J., Pinkney, J., Adams, L., Stenhouse, E., Bendall, A., Corrigan, O., & Letherby, G. (2017). The diagnosis and lived experience of polycystic ovary syndrome: A qualitative study. Journal of advanced nursing, 73(10), 2318-2326. https://doi.org/10.1111/jan.13300*	
Study Country	*England*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*32 individuals diagnosed with PCOS according to Rotterdam criteria.*	
Control population	*47 heaNA*	
PCOS diagnostic criteria	*Rotterdam 1992*	
N per group	*No subgroups*	
Setting	*Clinical*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Self-reported weight stigma*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes, "…impact of the diagnosis of polycystic ovary syndrome on health/ill health identity, how women experience this diagnosis and their health beliefs."*
Inclusion criteria	Yes Partial No Not reported	*Yes, PCOS diagnosis, adults 18-45 years*
Exclusion criteria	Yes Partial No Not reported	*Yes,"differential diagnoses (hypothyroidism, hyperprolactinaemia, congenital adrenal hyperplasia), peri or post-menopausal status, and a diagnosis of diabetes"*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes, qualitative (cross-sectional) studies are appropriate as preliminary investigations to understand the burden of weight stigma in women with PCOS*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*NR*
Was matching performed?	Yes Partial No Not reported	*Not relevant*

Summary Result/s		*Two participants reported experienced/perceived weight stigma from doctors. Please see Summary Table.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Not relevant*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Not relevant*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*Not relevant*
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Not relevant*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Not relevant*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not relevant*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Not relevant*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes, interviews transcribed verbatim*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant to cross-sectional study*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*Not applicable*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Not applicable*

CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Not relevant*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not relevant*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Not relevant*
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Insufficient information*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Williams et al., 2016*	
Study Citation	*Williams, S., Sheffield, D., & Knibb, R. C. (2016). A snapshot of the lives of women with polycystic ovary syndrome: A photovoice investigation. Journal of Health Psychology, 21(6), 1170-1182. https://doi.org/10.1177/1359105314547941*	
Study Country	*U.K.*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*9 women diagnosed with a self-reported PCOS symptoms*	
Control population	*47 he NA*	
PCOS diagnostic criteria	*Self-reported symptoms*	
N per group	*No subgroups*	
Setting	*Community*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Self-reported weight stigma*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No	*Yes, "explore the impact of PCOS using photovoice methodology*

		Not reported	
Inclusion criteria		Yes Partial No Not reported	*Yes, "participants aged 18 and over, living in the UK and suffering from symptoms of PCOS"*
Exclusion criteria		Yes Partial No Not reported	*Yes, "other chronic or mental illness that was not related to PCOS"*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	*Yes, qualitative (cross-sectional) studies are appropriate as preliminary investigations to understand the burden of weight stigma in women with PCOS*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*NR*
Was matching performed?		Yes Partial No Not reported	*Not relevant*
Summary Result/s		*One participant reports self (internalised) weight stigma. Please see Summary Table.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	Were the cases and controls taken from comparable populations?	Yes Partial No Not reported	*Not relevant*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Not relevant*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*Not relevant*
PERFORMANCE BIAS	Aside from the exposure/ intervention, were the groups treated the same?	Yes Partial No Not reported	*Not relevant*
DEDETECTION BIAS	Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?	Yes Partial No Not reported	*Not relevant*

	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not relevant*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Not relevant*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes, interviews transcribed verbatim*
ATTRITION BIAS	What percentage of the individuals recruited into each arm of the study were lost to follow up?	X% treatment X% control/ comparison Not reported	*Not relevant to cross-sectional study*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*Not applicable*
REPORT BIAS	Is the paper free of selective outcome reporting?	Yes Partial No Not reported	*Not applicable*
CONFOUNDING	Are the cohorts comparable on the basis of design or analysis?	Yes Partial No Not reported	*Not relevant*
OTHER BIAS	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No funding received (but no information reported on possible conflicts of interest)*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not relevant*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Not relevant*
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Insufficient information*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 3

Question 3.6.

What is the burden of weight stigma in PCOS?

BACKGROUND:

Weight stigma is the social devaluation of individuals because of their weight (1). Weight stigma is the combination of negative attitudes, stereotypes, and prejudice about high body weight. Weight stigma can be studied from the perspective of the perpetrator or the target. Research presented here will focus on the target's perspective and their weight stigma experiences/perceptions (e.g., being called names or being stared at in public), anticipation (e.g., expecting poor treatment at the doctors), and internalisation (i.e., applying negative stereotypes about weight to the self – e.g., believing you are not worthy of a job or love because of your weight). Weight stigma is particularly pervasive, in part because it is arguably the last form of acceptable stigma (2). Charlesworth and Banaji (3) found implicit weight-related attitudes are negative and have been worsening over time, a trend that runs contrary to other stigmatised groups (e.g., based on race or sexual orientation, which are trending to neutrality).

Weight stigma is common in many settings, including healthcare, the workplace, in education, and in the home (4). A systematic review on studies that estimated the prevalence of weight stigma found that between 19-41% of individuals with higher weight have experienced blatant weight discrimination, and that women more commonly experience this than men. Across the weight spectrum in a U.S. sample, weight-related mistreatment has been reported by ~40% of adults (5). Perpetration of weight stigma is common in healthcare professionals (and students), including those in nursing, clinical psychology, dietetics, and even those who specialise in obesity (1). Data collected by Puhl et al. (6) from a weight management program from the US, the UK, Australia, Canada, France, and Germany (*n* = 13,996) shows, of those participants who reported a history of weight stigma (over half the participants of all samples), 67% had experienced weight stigma from doctors. Similar results for healthcare professionals (i.e., doctors, nurses, healthcare providers) have been found in other, smaller studies (*n* = 85; 71% experienced weight stigma at least once in the last year; (7).

We systematically reviewed all published studies that assessed the burden of weight stigma in women with PCOS. We also reviewed studies that assessed healthcare professionals and weight stigma. Seven studies met our inclusion criteria; all were qualitative. Three major sources of stigma were identified: healthcare professionals/doctors, family members, and societal. There were four central findings – women with PCOS reported: (1) experiencing weight stigma from doctors, (2) experiencing weight stigma from family members, (3) internalising weight stigma from a variety of societal sources, and (4) anticipating weight stigma from the general public. Finally, both women with PCOS *and* healthcare professionals report weight stigma in healthcare contexts from various sources (see Table for a full list of findings). Our review is limited in that there were few existing studies that report instances of weight stigma, and thus, these findings were descriptive and preliminary for this cohort (i.e., women with PCOS). However, the findings are consistent with those in other cohorts (e.g., community, clinical, and student; (8)) – that is, weight stigma is (a) pervasive, (b) detrimental to mental health, (c) profoundly affected by societal attitudes toward weight, and (d) perpetrated in everyday settings – by family members in the home and health and medical professionals in healthcare settings.

Weight stigma is associated with negative biopsychosocial outcomes, including poorer health behaviours. Specifically, weight stigma is associated with exercise avoidance in undergraduate women (controlling for BMI; (9)), and experimental evidence shows that those exposed to weight stigmatising material had greater food consumption in higher weight individuals (compared to controls; (10). Further, weight stigma is associated with many of the negative biopsychosocial

outcomes associated with higher weight. Longitudinal evidence from the U.K. (*n* = 3,609) found that, from baseline to a 4-year follow up, weight stigma accounted for 27% of the prospective association between BMI and physiological dysregulation (i.e., biomarkers of health, e.g., inflammation, cardiovascular health, lipid/metabolic regulation; (11)). In other words, weight stigma explained nearly a quarter of the relationship between weight and physiological health. Experienced/perceived weight stigma is also moderately and significantly (*r* = -0.33; *k* = 241) associated with adverse mental health correlates (e.g., depression, anxiety, disordered eating, body image disturbance; (8)). There are proposed mechanisms that may explain the relationship between experienced weight stigma and adverse psychosocial correlates, such as the extent to which individuals *internalise* weight stigma (12, 13). A recent systematic review found that internalised weight stigma mediated the relationship between experienced/perceived weight stigma and biopsychosocial correlates, such as disordered eating, body shame, and exercise behaviour (14).

Whilst, it is acknowledged that weight is a risk factor for developing PCOS and exacerbates the features of PCOS, it is also important to recognise that higher weight is not a personal choice nor under the primary control of the individual. Indeed, weight stigma is thought to be perpetuated by the belief that body weight is controllable – that weight is a sum of poor choices (i.e., insufficient exercise and poor diet) and that sustainable weight loss can be achieved via behaviour change. Research has shown that the belief that weight is controllable is associated with negative attitudes toward individuals with higher weight (15). The popular narrative that weight is under personal control is not supported by research. Rubino et al. (4) summarised this body of evidence and provides a joint international consensus from a multidisciplinary research team. The review indicates that there are multiple factors outside an individual's control that affect weight, such as genetics, basal metabolic rate, and gut microbiota. It was also noted that diet and exercise account for a much smaller proportion of body weight compared to genetics, metabolic rate, and the food environment (4), and thus body weight is largely outside the individual's control. The consensus recommends healthcare professionals evaluate their role in the perpetuation of weight stigma.

In women with a significantly higher weight, where lifestyle intervention has failed, or is inappropriate (e.g. eating disorders), relying on lifestyle modification alone for sustainable weight loss is likely to be ineffective, and may induce weight stigma.

Hence, weight-neutral/weight-inclusive care has been proposed as an alternative to traditional weight-centric/weight-normative care. This approach promotes acceptance of and respect for body size diversity and improvement of health behaviours and health outcomes for people of all sizes, without promoting intentional weight loss. There is some evidence that engaging in health-promoting behaviours (i.e., sufficient fruit and vegetable intake, not smoking, regular exercise, and minimal to moderate alcohol consumption) are better predictors of morbidity and mortality than weight alone in the general population, and that improving health behaviours results in improved health outcomes even without weight loss (16, 17 18, 19, 20). A systematic review on the effectiveness of Health at Every Size (HAES) approaches, one example of weight-neutral/weight-inclusive care, on health-related outcomes (*n* = 14) found that compared to controls, those in HAES interventions had significantly improved physical activity and overall well-being, and reduced symptoms of disordered eating. Some studies showed improvements in body image and cardiovascular health, though some did not (21). Weight-neutral/weight-inclusive care targeting health behaviours and outcomes, rather than weight loss, is less likely to result in weight stigma.

Health care practices consistent with weight-neutral/weight-inclusive care include:

- Being aware of language in verbal and written communication. The terms “overweight” and “obese/obesity” are generally considered stigmatising and suggested alternatives include “higher body weight” and “person in a larger body”.
- Ensuring appropriate equipment (e.g., gown, blood pressure cuffs, needles, tables etc) are available for women of all sizes.
- Outlining weight-centric/weight-normative care and weight-neutral/weight-inclusive care including the short- and long-term outcomes of each, and providing the option of weight-neutral/weight-inclusive care for all women.
- Conducting comprehensive measures of biopsychosocial health for all women, rather than relying on weight/BMI as an indicator of health.
- If it is necessary to weigh a woman, the health professional should explain how weight information will be used to inform treatment decisions and how not knowing weight will impact on care. The health professional should then request the woman’s informed consent to weigh them and ask how this can be done in a way to minimise any discomfort.
- Not using weight/BMI to determine eligibility for care and/or requiring weight loss to be eligible for care. Offering all women best-practice assessment, treatment and support regardless of weight, unless there are treatments that have been found to be superior for women with higher weights.

Health professionals are encouraged to review the Rudd Centre Preventing Weight Bias: Helping Without Harming in Clinical Practice Toolkit http://biastoolkit.uconnruddcenter.org/index.html. The toolkit is designed to help clinicians improve delivery of care for patients.

GRADE EVIDENCE CERTAINTY	
Comparison	**GRADE for critical outcomes**
○ Not applicable - qualitative assessment(s)	⨁⨁◯◯ MODERATE

Synthesis of Review Finding	Quality assessment					
	Methodological Limitations	Coherence	Adequacy	Relevance	GRADE-CERQual Assessment of Confidence	Papers Supporting Finding
Finding 1 Women with PCOS report experiences of weight stigma from doctors	no/very minor concerns	no/very minor concerns	no/very minor concerns	no/very minor concerns	⊕⊕⊕⊕ High confidence	Ismayilova and Yaya (2022) Tomlinson et al. (2017)
Finding 2 HCPs and women with PCOS report weight stigma in healthcare settings, from several sources	no/very minor concerns	no/very minor concerns	minor concerns	no/very minor concerns	⊕⊕⊕◯ Moderate confidence	Amiri et al. (2014) Moran et al. (2021)
Finding 3 Women with PCOS report experiences of weight stigma from family members	no/very minor concerns	no/very minor concerns	minor concerns	no/very minor concerns	⊕⊕⊕◯ Moderate confidence	Chopra et al. (2021)
Finding 4 Women with PCOS report internalisation of weight stigma (variety of societal sources)	no/very minor concerns	no/very minor concerns	no/very minor concerns	no/very minor concerns	⊕⊕⊕⊕ High confidence	Chopra et al. (2021) Jones et al. (2021) Williams et al. (2016)
Finding 5 Women with PCOS report anticipating weight stigma and changing their behaviour based on perceived, expected judgement	no/very minor concerns	no/very minor concerns	minor concerns	no/very minor concerns	⊕⊕⊕◯ Moderate confidence	Jones et al. (2021)

HCP= health care professional(s)

Evidence to Recommendations Framework

COMPARISONS (option versus other option)

N/A

EVIDENCE-BASED RECOMMENDATION(S)

EBR: Many women with PCOS experience weight stigma in healthcare and other settings and the negative biopsychosocial impacts of this should be recognised.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

- **CR:** Health professionals should be aware of their weight biases and the impact this has on their professional practice and on women with PCOS.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

- **CR:** Health policy makers, managers and educators should promote awareness of weight stigma and invest in weight stigma education and minimisation strategies.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

PRACTICE POINT(S)

- Health professionals should be aware of weight-inclusive practices which promote acceptance of and respect for body size diversity and focus on improvement of health behaviours and health outcomes for people of all sizes In PCOS this includes:
    - Acknowledging that whilst higher weight is a risk factor for PCOS and its complications, it is only one indicator of health and broader factors should be assessed.Asking permission to discuss and measure weight and using strategies to minimise discomfort (e.g. blind weighing). Recognising that the terms “overweight” and “obese/obesity” can be stigmatising with suggested alternatives including “higher weight”..
    - If weighing, explaining how weight information will be used to inform risks, prevention and treatment and how not knowing may impact on recommendations.
    - Ensuring appropriate equipment are available for women of all sizes.
    - Offering options of weight-centric care (promoting intentional weight loss) or weight-inclusive care (promoting healthy lifestyle change without intentional weight loss) tailored to women’s goals and preferences.
    - Offering all women best-practice assessment, treatment and support regardless of weight, acknowledging that weight may be a non-modifiable risk factor when using lifestyle modification alone.
- Increasing awareness of weight stigma among family members of women and adolescents with PCOS should be considered.

GRADE CONSIDERATIONS

Justifications:
Available evidence indicates that women with PCOS experience

- weight stigma from health professionals and family members
- internalise weight stigma
- anticipate weight stigma

Weight stigma is associated with negative biopsychosocial outcomes, including poorer health behaviours (e.g., exercise avoidance, higher food consumption). Further, weight stigma is independently associated with many of the negative biopsychosocial outcomes associated with higher weight. Weight-neutral/weight-inclusive care targeting health behaviours and outcomes, rather than weight loss, and providing best-practice care regardless of weight, is less likely to result in weight stigma.

Subgroup considerations:
Most studies are conducted in Caucasian population.
The following subgroups needs to be considered (but are not considered in existing research)

- Cultural and ethnic subgroups
- Subgroups across the lifespan – including adolescents (only considered in one study), pre-pregnancy, pregnancy, post-partum, menopause

Implementation considerations:
Weight stigma is pervasive and entrenched. Weight-centric/weight-normative care is the norm in most health services. Many health professionals are unaware of their own weight-stigmatising beliefs and behaviours. Even health professionals who are aware of weight stigma and its impacts can find it difficult to provide weight-neutral/weight-inclusive care.

Monitoring and evaluation considerations:
Ongoing monitoring of weight bias by health professionals and experienced by women with PCOS.
Healthcare environment evaluation by using validated tools, for example: Rudd Centre Preventing Weight Bias: Helping Without Harming in Clinical Practice Toolkit Checklist for Assessing Office Environments
http://biastoolkit.uconnruddcenter.org/toolkit/Module-4/4-02-ChecklistForAssessing.pdf

Research priorities:
Extent of weight-stigma towards women with PCOS (across the weight spectrum) demonstrated by health professionals, family members, workplace and community.
Health professionals' awareness of their own weight-stigmatising beliefs and behaviours.
Health professional's implementation of weight-neutral/weight-inclusive care for women with PCOS.
The impacts of weight-neutral/weight-inclusive care on the biopsychosocial wellbeing of women with PCOS.
Consideration of other sources of stigma for women with PCOS (e.g. infertility, acanthosis nigricans, hirsutism, alopecia etc.)

GRADE framework

GRADE DECIDE Interactive Evidence to Decision Framework

● DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

Judgement:

☒ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

● UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

Judgement:

☒ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

● CERTAINTY OF THE EVIDENCE

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☐ Very low	☐ Low	☒ Moderate	☐ High

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

● VALUES

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☐ Important uncertainty or variability	☒ Possibly important uncertainty or variability	☐ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Research evidence:

No research evidence was identified

Panel discussion:

Weight stigma is pervasive and entrenched. Weight-centric/weight-normative care is the norm in most health services. Many health professionals are unaware of their own weight-stigmatising beliefs and behaviours. Even health professionals who are aware of weight stigma and its impacts can find it difficult to provide weight-neutral/weight-inclusive care.

● BALANCE OF EFFECTS

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☒ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:

● COSTS

How large are the resource requirements (costs)?

Judgement:

☐ Don't know	☒ Varies	☐ Large costs	☐ Moderate costs	☐ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:

No research evidence was identified

Panel discussion:

Weight stigma is pervasive and entrenched. Weight-centric/weight-normative care is the norm in most health services. Many health professionals are unaware of their own weight-stigmatising beliefs and behaviours. Even health professionals who are aware of weight stigma and its impacts can find it difficult to provide weight-neutral/weight-inclusive care.

Practicing weight-inclusive care will likely require increasing consultation time. Other potential causes for increased cost are training, education, equipment, resources, furniture. Increased allied health referral to assist with weight-inclusive interventions may also increase cost.

● CERTAINTY OF COST EVIDENCE

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

No research evidence was identified

Panel discussion:

● COST-EFFECTIVENESS

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

No research evidence was identified

Panel discussion:

Practicing weight-inclusive care will likely require increasing consultation time. Other potential causes for increased cost are training, education, equipment, resources, furniture. Increased allied health referral to assist with weight-inclusive interventions may also increase cost.

No evidence on cost effectiveness.

● EQUITY

What would be the impact on health equity?

Judgement:

☐ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☐ Probably increased	☒ Increased

Research evidence:

No research evidence was identified

Panel discussion:

● ACCEPTABILITY

Is the option acceptable to key stakeholders?

Judgement:

☐ Don't know	☒ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Women with PCOS are likely to find this acceptable.

Health professional used to working within a weight-centre/weight-normative paradigm are not likely to find this acceptable.

● FEASIBILITY

Is the option feasible to implement?

Judgement:

☐ Don't know	☒ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Will require paradigm shift to move the focus off weight-centric care.

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GUIDELINE DEVELOPMENT GROUP 4

Management of non-fertility features

	Clinical Questions
4.2	Is the oral contraceptive pill alone or in combination effective for management of hormonal and clinical PCOS features in adolescents and adults with PCOS?
4.3	Is metformin alone or in combination, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?
4.5	Are anti-obesity pharmacological agents alone or in combination, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?
4.6	Are anti-androgen pharmacological agents alone or in combination, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?
4.7	In adolescents and adults with PCOS, is inositol alone or in combination with other therapies, effective for management of hormonal and clinical PCOS features, weight and reproductive outcomes?
4.8	Is permanent hair reduction alone or in combination with other therapies, effective for management of hirsutism in adolescents and adults with PCOS?
4.9	In adults and adolescents with PCOS, is bariatric surgery effective for management of hormonal and clinical PCOS features and weight?
4.10	Are women with PCOS at increased risk of adverse pregnancy outcomes? *CLINICAL PRACTICE POINT:* *Should women with PCOS (preconception, early or late pregnancy) undergo screening or additional monitoring for adverse pregnancy outcomes and related risk factors?*
4.11	In women with PCOS in pregnancy, is metformin compared to placebo/standard care effective in reducing pregnancy complications and adverse neonatal outcomes?

PHARMACOLOGICAL TREATMENT PRINCIPLES IN PCOS

In reviewing the literature on pharmacological treatments, general principles emerged that apply across all pharmacological therapies. These have been extracted into a set of clinical practice points to inform women and guide health professionals when considering or recommending pharmacological therapy in PCOS. These practice points apply to all pharmacological treatments prioritised and addressed in the guideline.

Recommendations

4.1	**Pharmacology treatment principles in PCOS**
CPP	Shared decision-making between the patient (and parent/s or guardian/s, if the patient is a child) and the healthcare professional is required
CPP	An individual's characteristics, preferences and values must be considered when recommending any intervention alone or in combination.
CPP	Understanding how individual adults and adolescents value treatment outcomes is essential when prescribing medications.
CPP	Medical therapy is generally not approved for use specifically in PCOS and recommended use is therefore evidence-based, but off label. Health professionals need to inform adults, adolescents and their parents/s or guardian/s and discuss the evidence, possible concerns and side effects. Regulatory agencies should consider approval of evidence-based medications for use in PCOS.

'Off label' prescribing occurs when a drug is prescribed for an indication, a route of administration, or a patient group that is not included in the approved product information for that drug by the relevant regulatory body. Prescribing off label is often unavoidable and common and does not mean that the regulatory body has rejected the indication; more commonly there has not been a submission to request evaluation of a indication or patient group for any given drug.

PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by ECR Lead: Maria Forslund

Other team members: Johanna Melin, Simon Alesi

Supervised, edited and supported by the Evidence Team (Aya Mousa, Jillian Tay)

GDG 4
Question 4.2. & 4.3.

Is the oral contraceptive pill alone or in combination effective for management of hormonal and clinical PCOS features in adolescents and adults with PCOS?

1. SELECTION CRITERIA

Table 1. PICO Criteria for Inclusion	
Question	Q 4.2) Is the oral contraceptive pill alone or in combination effective for management of hormonal and clinical PCOS features in adolescents and adults with PCOS?
Clinical leads (key contacts)	**A/Prof Alexia Pena Vargas** Paediatric endocrinologist The Robinson Research Institute at the University of Adelaide, Australia alexia.pena@adelaide.edu.au **Prof Selma Witchel** Paediatric endocrinologist Children's Hospital of Pittsburgh of UPMC, University of Pittsburg, USA witchelsf@upmc.edu **Dr Daniela Romualdi** Obstetrician-gynaecologist Fondazione Policlinico Universitario Agostino Gemelli, Rome, Italy daniela.romualdi@policlinicogemelli.it
Allocation ranking	Level 1- New systematic review

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type	Limits
Inclusion criteria	Females with PCOS (diagnosed by Rotterdam, NIH or AES) of any ethnicity AND weight. Subgroups: adolescents (10-19y), adults, smokers. Collect: mean age of menarche (subgroup those that do and don't define age of menarche). If there are studies that include adolescents and young adults. Include all and revisit subgroups. No upper age limit.	Oral contraceptive pill alone or in combination with metformin, lifestyle, anti-androgens, anti-obesity agents. All types OCPs, low 20ug estrogens or less vs standard or high 30ug or more. Different generation progestins. Possible comparisons: OCP alone v combination 20ug and below v 30-35ug (Jas = 15ug estradiol in Europe); Progestins based on anti-androgenic activity; Estradiol and natural; For hirsutism, min 6 months At least 3 months for all other outcomes	Placebo or any other intervention (listed in intervention) or combinations of those listed in intervention.	Androgenicity: Hirsutism- FG score (ethnicities), FAI, testosterone and SHBG, DHEAS, androstenedione, Irregular cycles Metabolic: insulin resistance HOMA, Clamp, OGTT Chol LDL, HDL TG, CRP, Psychological: Qol, depression Adverse effects: Anthropometric: weight BMI, WHR Thromboembolic events, PAI-1 levels	Evidence based guidelines, systematic reviews, RCTs	English language. **New search.** Limit to last 20 years given change in doses and progestins over time.
Exclusion criteria	Females without PCOS. Less than 2 years post menarche. Women with DM2, co-morbidities or major depression.	Non oral formulation of contraceptives.	Agent or combination used in the intervention.		Non-evidence based GLs, non-SRs, any study lower than a RCT.	

2. SEARCH STRATEGY

Table 2.1. Search details	
Search strategy source: Technical report p 788-789	
Evidence source	**Date of search 2022-07-08** **Results:**
Medline (Ovid)	688
PsychInfo (Ovid)	3
EMBASE (Ovid)	370
All EBM (Ovid)	185
CINAHL	114
Any subsequent updates - enter database and date:	

Table 2.2. Questions addressed by this search *(add more rows as needed)*:		
GDG	Q#	Question
4	4.2	Is the oral contraceptive pill alone or in combination effective for management of hormonal and clinical PCOS features in adolescents and adults with PCOS?
4	4.3	Is metformin alone or in combination, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?
4	4.6	Are anti-androgen pharmacological agents alone or in combination, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?

Table 2.3. Search strings used in OVID or other database/s –
See page 3864-3865 under Q.4.6. on anti-androgens (the same search string was used for all three questions above)

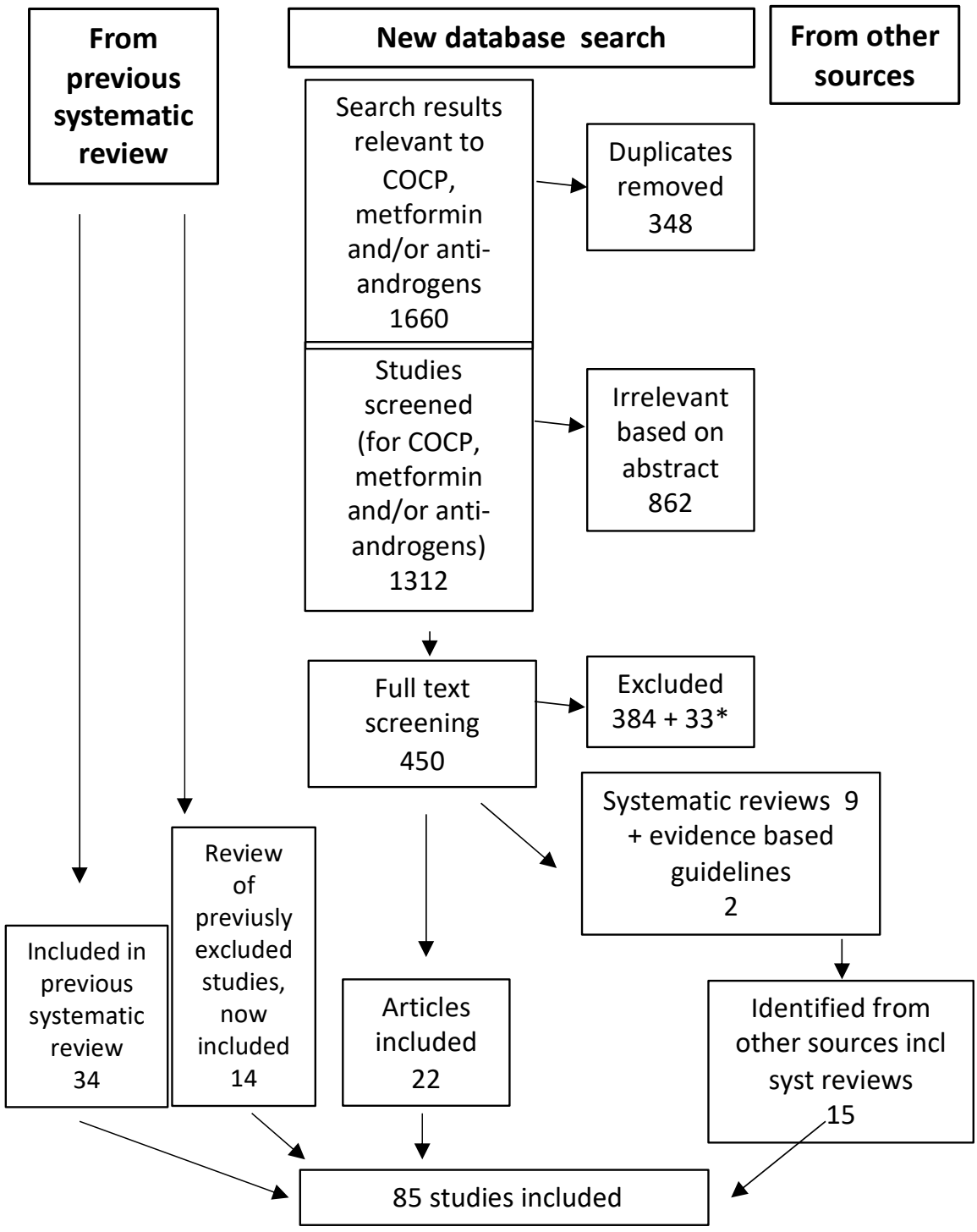
Evidence processing: Studies were selected and appraised by two reviewer/s using study selection and appraisal criteria (PICO above) established a priori. The articles were reviewed by title and abstract by two reviewers. When a decision could not be made based on title and abstract alone, full text was retrieved. Only studies that did not fit PICO for Q4.2, 4.3 or 4.6 were excluded. Full text screening was done by two reviewers. Conflicts were resolved by discussion and if needed, through contact with the evidence team/ key contacts. Included studies were double checked and approved by the clinical leads/ key contacts.

In addition to the studies included in previous guidelines, the excluded list from that search was reviewed, and studies were included if they met the current PICO.

Identified systematic reviews and evidence-based guidelines were screened manually for additional references.

In total, **84 RCTs met inclusion criteria for this review.**

3. SEARCH RESULTS - PRISMA flowchart



* Included for Q4.3 and/or Q4.6, excluded for Q4.2

4. STUDY INCLUSION

Table 4.1. Included Studies

RCT studies:

1. Aghamohammadzadeh N, Aliasgarzadeh A, Baglar L, Abdollahifard S, Bahrami A, Najafipour F, et al. Comparison of metformin and cyproteroneestrodiol compound effect on hs c-reactive protein and serum androgen levels in patients with poly cystic ovary syndrome. Pakistan journal of medical sciences. 2010;26(2):347-51.
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Systematic reviews (screened for additional references)

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Evidence based guidelines (for additional references)

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Table 4.2. Excluded studies (on full-text assessment)

Reference	Reason
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Sung, C.T.; Chao, T.; Lee, A.; Foulad, D.P.; Choi, F.; Juhasz, M.; Dobry, A.; Mesinkovska, N.A. Oral Metformin for Treating Dermatological Diseases: A Systematic Review. Journal of drugs in dermatology : JDD 2020, 19, 713-720, doi:https://dx.doi.org/10.36849/JDD.2020.4874.	**Wrong comparator**

Syed, S.Z.; Akram, F.; Aftab Hassan, S.M. Comparison of efficacy of metformin versus Pioglitazone on ovulation in patients of polycystic ovarian syndrome. Pakistan Journal of Medical and Health Sciences 2018, 12, 1240-1242.	**Wrong outcome**
Tagliaferri, V.; Romualdi, D.; Immediata, V.; De Cicco, S.; Di Florio, C.; Lanzone, A.; Guido, M. Metformin vs myoinositol: which is better in obese polycystic ovary syndrome patients? A randomized controlled crossover study. Clinical endocrinology 2017, 86, 725-730, doi:https://dx.doi.org/10.1111/cen.13304.	**Wrong comparator**
Talaat, B.; Ammar, I.M.M. The added value of cinnamon to metformin in controlling symptoms of polycystic ovary syndrome, a randomized controlled trial. Middle East Fertility Society Journal 2018, 23, 440-445, doi:http://dx.doi.org/10.1016/j.mefs.2018.03.005.	**Wrong comparator**
Tan, J.; Zhou, G.J.; Wang, Q.Y.; Liu, T.T.; Cao, Q.; Huang, W. [Effect of metformin and rosiglitazone in non-obese polycystic ovary syndrome women with insulin resistance]. Zhonghua fu chan ke za zhi 2021, 56, 467-473, doi:https://dx.doi.org/10.3760/cma.j.cn112141-20210424-00224.	**Wrong language**
Tang, L.; Ye, J.; Shi, Y.; Zhu, X. Association between CD16++ monocytes in peripheral blood and clinical features and short-term therapeutic effects of polycystic ovary syndrome. International Journal of Gynecology & Obstetrics 2019, 145, 12-17, doi:10.1002/ijgo.12779.	**Wrong study design**
Tao, T.; Wu, P.; Wang, Y.; Liu, W. Comparison of glycemic control and β-cell function in new onset T2DM patients with PCOS of metformin and saxagliptin monotherapy or combination treatment. BMC endocrine disorders 2018, 18, 1-1, doi:10.1186/s12902-018-0243-5.	**Wrong population**
Tauqir, S.; Israr, M.; Rauf, B.; Malik, M.O.; Habib, S.H.; Shah, F.A.; Usman, M.; Raza, M.A.; Shah, I.; Badshah, H., et al. Acetyl-L-Carnitine Ameliorates Metabolic and Endocrine Alterations in Women with PCOS: A Double-Blind Randomized Clinical Trial. Advances in therapy 2021, 38, 3842-3856, doi:https://dx.doi.org/10.1007/s12325-021-01789-5.	**Wrong comparator**
Tay, C.T.; Joham, A.E.; Hiam, D.S.; Gadalla, M.A.; Pundir, J.; Thangaratinam, S.; Teede, H.J.; Moran, L.J. Pharmacological and surgical treatment of nonreproductive outcomes in polycystic ovary syndrome: An overview of systematic reviews. Clinical endocrinology 2018, 89, 535-553, doi:https://dx.doi.org/10.1111/cen.13753.	**Wrong study design**
Tehrani, F.R.; Amiri, M. Polycystic ovary syndrome in adolescents: Challenges in diagnosis and treatment. International Journal of Endocrinology and Metabolism 2019, 17, e91554, doi:http://dx.doi.org/10.5812/ijem.91554.	**Wrong study design**
Tennilä, J.; Jääskeläinen, J.; Utriainen, P.; Voutilainen, R.; Häkkinen, M.; Auriola, S.; Morin-Papunen, L.; Liimatta, J. PCOS Features and Steroid Profiles Among Young Adult Women with a History of Premature Adrenarche. Journal of Clinical Endocrinology & Metabolism 2021, 106, e3335-e3345, doi:10.1210/clinem/dgab385.	**Wrong study design**
Toosy, S.; Sodi, R.; Pappachan, J.M. Lean polycystic ovary syndrome (PCOS): an evidence-based practical approach. Journal of Diabetes and Metabolic Disorders 2018, 17, 277-285, doi:http://dx.doi.org/10.1007/s40200-018-0371-5.	**Wrong study design**
Trouva, A.; Alvarsson, M.; Calissendorff, J.; Asvold, B.O.; Vanky, E.; Hirschberg, A.L. Thyroid Status During Pregnancy in Women With Polycystic Ovary Syndrome and the Effect of Metformin. Frontiers in endocrinology 2022, 13, 772801, doi:https://dx.doi.org/10.3389/fendo.2022.772801.	**Wrong outcome**
Tso, L.O.; Costello, M.F.; Albuquerque, L.E.T.; Andriolo, R.B.; Macedo, C.R. Metformin treatment before and during IVF or ICSI in women with polycystic ovary syndrome. The Cochrane database of systematic reviews 2020, 12, CD006105, doi:https://dx.doi.org/10.1002/14651858.CD006105.pub4.	**Wrong population**
Tzotzas, T.; Karras, S.N.; Katsiki, N. Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists in the Treatment of Obese Women with Polycystic Ovary Syndrome. Current vascular pharmacology 2017, 15, 218-229, doi:https://dx.doi.org/10.2174/1570161114666161221115324.	**Wrong study design**
Udesen, P.B.; Glintborg, D.; Sorensen, A.E.; Svendsen, R.; Nielsen, N.L.S.; Wissing, M.L.M.; Andersen, M.S.; Englund, A.L.M.; Dalgaard, L.T. Metformin decreases mir-122, mir-223 and mir-29a in women with polycystic ovary syndrome. Endocrine Connections 2020, 9, 1075, doi:https://doi.org/10.1530/EC-20-0195.	**Wrong outcome**
Underdal, M.O.; Salvesen, Ø.; Henriksen, A.H.; Andersen, M.; Vanky, E. Impaired Respiratory Function in Women With PCOS Compared With Matched Controls From a Population-Based Study. Journal of Clinical Endocrinology & Metabolism 2019, 10.1210/clinem/dgz053, N.PAG-N.PAG, doi:10.1210/clinem/dgz053.	**Wrong study design**
Underdal, M.O.; Stridsklev, S.; Andresen, M.S.; Vanky, E. Metabolic health in women with PCOS-5-11 years' followup after metformin or placebo in pregnancy. Endocrine reviews 2017, 38.	**Fulltext not obtainable**
Underdal, M.O.; Stridsklev, S.; Oppen, I.H.; Høgetveit, K.; Andersen, M.S.; Vanky, E. Does Metformin Treatment During Pregnancy Modify the Future Metabolic Profile in Women With PCOS? Journal of Clinical Endocrinology & Metabolism 2018, 10.1210/jc.2018-00485, N.PAG-N.PAG, doi:10.1210/jc.2018-00485.	**Wrong population**
Vatopoulou, A.; Tziomalos, K. Management of obesity in adolescents with polycystic ovary syndrome. Expert opinion on pharmacotherapy 2020, 21, 207-211, doi:https://dx.doi.org/10.1080/14656566.2019.1701655.	**Wrong study design**
Vedtofte, L.; Foghsgaard, S.; Zierau, L.; VilsbØLl, T.; Knop, F.K. 1186-P: Lean Women with Polycystic Ovary Syndrome and Insulin Resistance Have Normal Incretin Effect, which Is Unaffected by Metformin Therapy. Diabetes 2019, 68, N.PAG-N.PAG, doi:10.2337/db19-1186-P.	**Wrong publication type**
Venter, A. Obesity, Oligomenorrhoea and PCOS in Adolescence. Obstetrics and Gynaecology Forum 2018, 28, 27-30.	**Wrong study design**

Vine, D.; Proctor, E.; Weaver, O.; Ghosh, M.; Maximova, K.; Proctor, S. A Pilot Trial: fish Oil and Metformin Effects on ApoB-Remnants and Triglycerides in Women with Polycystic Ovary Syndrome. Journal of the Endocrine Society 2021, 5, doi:https://doi.org/10.1210/jendso/bvab114.	**Wrong comparator**
Walker, K.; Decherney, A.H.; Saunders, R. Menstrual Dysfunction in PCOS. Clinical Obstetrics & Gynecology 2021, 64, 119-125, doi:10.1097/GRF.0000000000000596.	**Wrong study design**
Wang, J.; Zhu, L.; Hu, K.; Tang, Y.; Zeng, X.; Liu, J.; Xu, J. Effects of metformin treatment on serum levels of C-reactive protein and interleukin-6 in women with polycystic ovary syndrome: a meta-analysis: A PRISMA-compliant article. Medicine 2017, 96, e8183-e8183, doi:10.1097/MD.0000000000008183.	**Wrong comparator**
Wang, L.; Liang, R.; Tang, Q.; Zhu, L. An Overview of Systematic Reviews of Using Chinese Medicine to Treat Polycystic Ovary Syndrome. Evidence-based Complementary and Alternative Medicine 2021, 2021, 9935536, doi:http://dx.doi.org/10.1155/2021/9935536	**Wrong intervention**
Wang, R.; Kim, B.V.; van Wely, M.; Johnson, N.P.; Costello, M.F.; Zhang, H.; Ng, E.H.Y.; Legro, R.S.; Bhattacharya, S.; Norman, R.J., et al. Treatment strategies for women with WHO group II anovulation: systematic review and network meta-analysis. BMJ (Clinical research ed.) 2017, 356, j138, doi:https://dx.doi.org/10.1136/bmj.j138.	**Wrong population**
Wang, R.; Li, W.; Bordewijk, E.M.; Legro, R.S.; Zhang, H.; Wu, X.; Gao, J.; Morin-Papunen, L.; Homburg, R.; Konig, T.E., et al. First-line ovulation induction for polycystic ovary syndrome: an individual participant data meta-analysis. Human reproduction update 2019, 25, 717-732, doi:https://dx.doi.org/10.1093/humupd/dmz029.	**Wrong outcome**
Wang, Y.-W.; He, S.-J.; Feng, X.; Cheng, J.; Luo, Y.-T.; Tian, L.; Huang, Q. Metformin: a review of its potential indications. Drug design, development and therapy 2017, 11, 2421-2429, doi:https://dx.doi.org/10.2147/DDDT.S141675.	**Wrong study design**
Wawrzkiewicz-Jalowiecka, A.; Kowalczyk, K.; Trybek, P.; Jarosz, T.; Radosz, P.; Setlak, M.; Madej, P. In Search of New Therapeutics-Molecular Aspects of the PCOS Pathophysiology: Genetics, Hormones, Metabolism and Beyond. International journal of molecular sciences 2020, 21, doi:https://dx.doi.org/10.3390/ijms21197054.	**Wrong study design**
Wen, Y.; Ma, H.L.; Wu, X.K. Acupuncture and clomiphene interventions in PCOS conversely affect the insulin resistance profiles in early pregnancy subjects: a secondary analysis of a randomized controlled trial. Journal of obstetrics and gynaecology research 2017, 43, 160, doi:https://doi.org/10.1111/jog.13394.	**Wrong publication type**
Wenjing, L.; Hongbo, H.; Guofang, Z.; Zhanzhong, M.; Jing, L.; Fanxiang, L.; Li, W.; Hu, H.; Zou, G.; Ma, Z., et al. Therapeutic effects of puerarin on polycystic ovary syndrome: A randomized trial in Chinese women. Medicine 2021, 100, 1-8, doi:10.1097/MD.0000000000026049.	**Wrong comparator**
Witchel, S.F.; Oberfield, S.E.; Peña, A.S. Polycystic Ovary Syndrome: Pathophysiology, Presentation, and Treatment With Emphasis on Adolescent Girls. Journal of the Endocrine Society 2019, 3, 1545-1573, doi:10.1210/js.2019-00078.	**Wrong study design**
Wiweko, B.; Susanto, C. The Effect of Metformin and Cinnamon on Serum Anti-Mullerian Hormone in Women Having PCOS: a Double-Blind, Randomized, Controlled Trial. Journal of Human Reproductive Sciences 2017, 10, 31, doi:https://doi.org/10.4103/jhrs.JHRS9016.	**Wrong comparator**
Wojciechowska, A.; Osowski, A.; Jozwik, M.; Gorecki, R.; Rynkiewicz, A.; Wojtkiewicz, J. Inositols' Importance in the Improvement of the Endocrine-Metabolic Profile in PCOS. International journal of molecular sciences 2019, 20, doi:https://dx.doi.org/10.3390/ijms20225787.	**Wrong study design**
Woodward, A.; Broom, D.; Harrop, D.; Lahart, I.; Carter, A.; Dalton, C.; Metwally, M.; Klonizakis, M. The effects of physical exercise on cardiometabolic outcomes in women with polycystic ovary syndrome not taking the oral contraceptive pill: a systematic review and meta-analysis. Journal of Diabetes and Metabolic Disorders 2019, 18, 597-612, doi:http://dx.doi.org/10.1007/s40200-019-00425-y.	**Wrong intervention**
Wu, Y.; Tu, M.; Huang, Y.; Liu, Y.; Zhang, D. Association of Metformin With Pregnancy Outcomes in Women With Polycystic Ovarian Syndrome Undergoing In Vitro Fertilization: A Systematic Review and Meta-analysis. JAMA network open 2020, 3, e2011995-e2011995, doi:10.1001/jamanetworkopen.2020.11995.	**Wrong outcome**
Xie, L.; Zhang, D.; Ma, H.; He, H.; Xia, Q.; Shen, W.; Chang, H.; Deng, Y.; Wu, Q.; Cong, J., et al. The Effect of Berberine on Reproduction and Metabolism in Women with Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis of Randomized Control Trials. Evidence-based Complementary & Alternative Medicine (eCAM) 2019, 10.1155/2019/7918631, 1-15, doi:10.1155/2019/7918631.	**Wrong intervention**
Xu, J.; Zuo, Y. [Efficacy of acupuncture as adjunctive treatment on infertility patients with polycystic ovary syndrome]. Zhongguo zhen jiu = Chinese acupuncture & moxibustion 2018, 38, 358-361, doi:https://dx.doi.org/10.13703/j.0255-2930.2018.04.004.	**Wrong language**
Xu, Q.; Xie, Q. Long-term effects of prenatal exposure to metformin on the health of children based on follow-up studies of randomized controlled trials: a systematic review and meta-analysis. Springer Nature: , <Blank>, 2019; Vol. 299, pp 1295-1303.	**Wrong outcome**
Xu, Z.; Meng, L.; Pan, C.; Chen, X.; Huang, X.; Yang, H. Does oral contraceptives pretreatment affect the pregnancy outcome in polycystic ovary syndrome women undergoing ART with GnRH agonist protocol?	**Wrong study design**

Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology 2019, 35, 124-127, doi:https://dx.doi.org/10.1080/09513590.2018.1500535.	
Yanbo, L.; Yupei, S.; Jiping, X.; Linlin, C.; Guang, Z.; Liu, Y.; Shao, Y.; Xie, J.; Chen, L.; Zhu, G. The efficacy and safety of metformin combined with simvastatin in the treatment of polycystic ovary syndrome: A meta-analysis and systematic review. Medicine 2021, 100, 1-8, doi:10.1097/MD.0000000000026622.	**Wrong intervention**
Yang, D.; Zhao, M.; Tan, J. [Effect of polycystic ovary syndrome treated with the periodic therapy of acupuncture]. Zhongguo zhen jiu = Chinese acupuncture & moxibustion 2017, 37, 825-829, doi:https://dx.doi.org/10.13703/j.0255-2930.2017.08.007.	**Wrong language**
Yang, J.; Liu, Y.; Huang, J.; Xu, J.; You, X.; Lin, Q.; Zhang, J.; Dun, J.; Huang, S. [Acupuncture and Chinese medicine of artificial cycle therapy for insulin resistance of polycystic ovary syndrome with phlegm damp type and its mechanism]. Zhongguo zhen jiu = Chinese acupuncture & moxibustion 2017, 37, 1163-1168, doi:https://dx.doi.org/10.13703/j.0255-2930.2017.11.007.	**Wrong language**
Yao, K.; Bian, C.; Zhao, X. Association of polycystic ovary syndrome with metabolic syndrome and gestational diabetes: Aggravated complication of pregnancy (Review). Experimental and Therapeutic Medicine 2017, 14, 1271-1276, doi:http://dx.doi.org/10.3892/etm.2017.4642.	**Wrong study design**
Yen, H.; Chang, Y.-T.; Yee, F.-J.; Huang, Y.-C. Metformin Therapy for Acne in Patients with Polycystic Ovary Syndrome: A Systematic Review and Meta-analysis. American journal of clinical dermatology 2021, 22, 11-23, doi:10.1007/s40257-020-00565-5.	**Wrong outcome**
Young, C.C.; Monge, M. Polycystic Ovary Syndrome in Primary Care: It Takes a Village. Journal for Nurse Practitioners 2019, 15, 694-695, doi:10.1016/j.nurpra.2019.05.008.	**Wrong study design**
Yousuf, S.D.; Ganie, M.A.; Jeelani, S.; Mudassar, S.; Shah, Z.A.; Zargar, M.A.; Amin, S.; Wani, I.A.; Rashid, F. Effect of six-month use of oral contraceptive pills on plasminogen activator inhibitor-1 & factor VIII among women with polycystic ovary syndrome: An observational pilot study. The Indian journal of medical research 2018, 148, S151-S155, doi:https://dx.doi.org/10.4103/ijmr.IJMR_1899_17.	**Wrong study design**
Zeng, L.; Yang, K. Effectiveness of myoinositol for polycystic ovary syndrome: a systematic review and meta-analysis. Endocrine 2018, 59, 30-38, doi:https://dx.doi.org/10.1007/s12020-017-1442-y.	**Wrong intervention**
Zhang, J.; Si, Q.; Li, J. Therapeutic effects of metformin and clomiphene in combination with lifestyle intervention on infertility in women with obese polycystic ovary syndrome. Pakistan journal of medical sciences 2017, 33, 8, doi:https://doi.org/10.12669/pjms.331.11764.	**Wrong intervention**
Zhang, J.; Su, M.; Xu, L.; Yang, Z.; Yin, W.; Nie, Y.; Qiao, X.; Cheng, R.; Ma, Y. [Efficacy and metabolic safety of long-term treatment with ethinyl oestradiol/cyproterone and desogestrel/ethinyl oestradiol tablets in women with polycystic ovary syndrome]. Nan fang yi ke da xue xue bao = Journal of Southern Medical University 2018, 38, 917-922, doi:https://dx.doi.org/10.3969/j.issn.1673-4254.2018.08.03.	**Wrong language**
Zhang, S.-W.; Zhou, J.; Gober, H.-J.; Leung, W.T.; Wang, L. Effect and mechanism of berberine against polycystic ovary syndrome. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 2021, 138, 111468, doi:https://dx.doi.org/10.1016/j.biopha.2021.111468.	**Wrong study design**
Zhang, Y.; Guo, X.; Ma, S.; Ma, H.; Li, H.; Wang, Y.; Qin, Z.; Wu, X.; Han, Y.; Han, Y. The Treatment with Complementary and Alternative Traditional Chinese Medicine for Menstrual Disorders with Polycystic Ovary Syndrome. Evidence-based Complementary & Alternative Medicine (eCAM) 2021, 10.1155/2021/6678398, 1-19, doi:10.1155/2021/6678398.	**Wrong study design**
Zhao, J.; Liu, X.; Zhang, W. The Effect of Metformin Therapy for Preventing Gestational Diabetes Mellitus in Women with Polycystic Ovary Syndrome: A Meta-Analysis. Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association 2020, 128, 199-205, doi:https://dx.doi.org/10.1055/a-0603-3394.	**Fulltext not obtainable**
Zhao, Y.X.; Wang, L.J.; Gong, F.Y.; Pan, H.; Miao, H.; Duan, L.; Yang, H.B.; Zhu, H.J. [Effects of orlistat and metformin on metabolism and gonadal function in overweight or obese patients with polycystic ovary syndrome]. Zhonghua nei ke za zhi 2021, 60, 1165-1168, doi:https://dx.doi.org/10.3760/cma.j.cn112138-20210302-00171.	**Wrong language**
Zhou, K.; Zhang, J.; Xu, L.; Lim, C.E.D. Chinese herbal medicine for subfertile women with polycystic ovarian syndrome. The Cochrane database of systematic reviews 2021, 6, CD007535, doi:https://dx.doi.org/10.1002/14651858.CD007535.pub4.	**Wrong intervention**
Zimmerman, L.D.; Setton, R.; Pereira, N.; Rosenwaks, Z. Contemporary Management of Polycystic Ovarian Syndrome. Clinical obstetrics and gynecology 2019, 62, 271-281, doi:https://dx.doi.org/10.1097/GRF.0000000000000449.	**Wrong study design**

5. FINDINGS

Comparisons included:

- **Comparison 1:** COCP with high vs. COCP with low levels of estrogen
- **Comparison 2:** COCP with 1st vs. COCP with 2nd generation progestin
- **Comparison 3:** COCP with 1st vs. COCP with 3rd generation progestin
- **Comparison 4:** COCP with 1st vs. COCP with 4th generation progestin
- **Comparison 5:** COCP with 2nd vs. COCP with 3rd generation progestins
- **Comparison 6:** COCP with 2nd vs. COCP with 4th generation progestins
- **Comparison 7:** COCP with 3rd vs. COCP with 4th generation progestins
- **Comparison 8:** COCP vs. EE/CPA
- **Comparison 9:** COCP vs. progestin
- **Comparison 10:** COCP vs. controls
- **Comparison 11:** COCP vs. placebo
- **Comparison 12:** COCP vs lifestyle
- **Comparison 13:** COCP vs. lifestyle ± anti-obesity treatment
- **Comparison 14:** COCP vs. combination of COCP and lifestyle with/without anti-obesity treatment
- **Comparison 15:** lifestyle ± anti-obesity treatment vs. combination of COCP and lifestyle ± anti-obesity treatment
- **Comparison 16:** COCP vs. anti-obesity
- **Comparison 17:** COCP vs. COCP + anti-obesity
- **Comparison 18:** COCP + metformin vs. COCP + anti-obesity
- **Comparison 19:** COCP vs. COCP + metformin + anti-obesity
- **Comparison 20:** COCP vs. metformin (also incl. in Q4.3)
- **Comparison 21:** COCP vs. COCP + metformin
- **Comparison 22:** COCP vs. anti-androgen (also in Q4.6, but their time limit 6 m treatment)
- **Comparison 23:** COCP vs. COCP + antiandrogen androgen (also in Q4.6, with time limit of 6m)
- **Comparison 24:** COCP vs. metformin + antiandrogen androgen (also in Q4.6, with time limit of 6m)
- **Comparison 25:** COCP + anti-androgen vs. metformin androgen (also in Q4.6, with time limit of 6m)
- **Comparison 26:** COCP + anti androgen vs. COCP + anti androgen + met androgen
- **Comparison 27:** COCP + anti-androgen vs. COCP + metformin androgen
- **Comparison 28:** COCP vs. COCP + metformin + anti-androgen androgen (also in Q4.6)
- **Comparison 29:** COCP vs. SPIOMET (=metformin + anti-androgen + glucose sensitizer) (also in Q4.6)
- **Comparison 30:** COCP + AA1 vs. COCP + AA2
- **Comparison 31:** Metformin vs COCP + metformin (reported in Q4.3)
- **Comparison 32:** COCP + met vs. EE/CPA + met

COCP: combined oral contraceptive pills

Abbrevations and classifications of progestins identified and included in the systematic review:

Generation of progestin	Progestin type	Abbrevation
1st generation	Chlormadinone acetate	CMA
2nd generation	Levonorgestrel	LNG
3rd generation	Desogestrel	DSG
	Gestodene	GSD
4th generation	Drospirenone	DRSP
	Dienogest	DNG
Other	Cyproterone acetate	CPA

Comparison 1: COCP with low vs. high EE

- **EVIDENCE SUMMARY:**

Two RCTs compared COCPs with high (30µg) vs. low (20µg) EE. Both studies had a low risk of bias and both had a duration of 12 m. Information about the included studies is shown in the table below.

- **META-ANALYSIS/DESCRIPTIVE ANALYSIS SUMMARY:**

A meta-analysis could not be performed. The only outcome reported by both studies was hirsutism (FG score), where no difference was seen between groups, with a moderate certainty of evidence. Other outcomes (BMI, WHR, FAI, total testosterone and SHBG), were only reported by Bhattacharya. High level EE COCP treatment resulted in a greater increase in SHBG levels, with a low certainty of evidence. No difference was seen between groups regarding other reported outcomes with a low certainty of evidence.

Included studies

Study ID	ROB	Interventions	Setting Duration	N	Mean age	Mean BMI	PCOS	Age at menarche	Smokers	Outcomes
Bhattacharya 2016 (1)	Low	1) 30µg EE + 3mg DRSP 21/7 2) 20µg EE + 3mg DRSP 24/4	ndia 12 months	1: 46 2: 48	1: 21.47±4.27 2: 22.28±3.91	1: 26.21±5.15 2: 26.38±5.70	Rott	21 (<18 years) >3y since menarche	Non-smokers	BMI, WHR, FG score, TT, SHBG, FAI,
Fonseka 2020 (2)	Low	1: 35µg EE + 2 mg CPA (Diane-35, 2: 20µg EE + 0.15 mg DSG (Fermion) 3: metformin + EE/CPA 4: metformin + EE/DSG	Sri Lanka 12 months	1:20 2:23 3: 26 6: 30	1: 23.35± 5.10 2: 22.39 ± 6.45 3: 24.81 ± 6.24 4. 27.90 ± 6.89	1: 28.27 ±6.94 2: 26.74 ±4.88 3: 27.93 ±4.89 4: 27.20 ± 4.28	Rott	NR	NR	mFG score

Results are presented descriptively in the table below as *change from baseline*, if not otherwise stated.

Outcome	Study ID	N	High EE	Low EE	P value	Favours	Certainty	Importance
BMI	Bhattacharya 2016	H 46 L 48	0.52±2.83	−0.01±4.11	0.42	No difference	⊕⊕◯◯ LOW[1]	CRITICAL
WHR	Bhattacharya 2016	H 46 L 48	0.01±0.06	−0.0004±0.05	0.32	No difference	⊕⊕◯◯ LOW[1]	IMPORTANT
Hirsutism (mFG score)	Bhattacharya 2016	H 46 L 48	2.12±3.50	1.54±4.73	0.46	No difference	⊕⊕⊕◯ MODERATE[2]	CRITICAL
	Fonseka 2020	H 20 L 23	Mean ± SD 14.25 ± 8.26	Mean ± SD 15.09 ± 5.26	NR			
SHBG (nmol/L)	Bhattacharya 2016	H 46 L 48	−167.38±89.0	−125.54±124.6	0.043	High EE	⊕⊕◯◯ LOW[1]	IMPORTANT
FAI	Bhattacharya 2016	H 46 L 48	5.23±5.79	4.99±5.86	0.82	No difference	⊕⊕◯◯ LOW[1]	IMPORTANT
Testosterone (nmol/L)	Bhattacharya 2016	H 46 L 48	0.00±0.01	0.00±0.01	NR	No difference	⊕⊕◯◯ LOW[1]	IMPORTANT

1. low certainty of evidence due to imprecision
2. moderate certainty of evidence due to indirectness (assessed differently)

Comparison 2: COCP with 1st vs. COCP with 2nd generation progestin

- **EVIDENCE SUMMARY:**

No studies were identified for this comparison.

Comparison 3: COCP with 1st vs. COCP with 3rd generation progestin

- **EVIDENCE SUMMARY:**

One study with a high risk of bias was identified. This study (DeLeo 2010) with a duration of 3 months had four arms. Relevant for this comparison, chlormadinone acetate (CMA), a 1st generation progestin was compared with two different 3rd generation progestins, desogestrel (DSG) and gestodene (GSD). Information about the included study is shown in the table below.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

A meta-analysis could not be performed. Results from the individual study showed a greater decrease in TT and androstenedione, and a greater increase in SHBG, after treatment with the 1st generation progestin, with a very low certainty of evidence. For the other reported outcomes, free testosterone and DHEAS, no difference was seen between the groups, with a very low certainty of evidence.

Included study:

Study ID	ROB	Interventions	Setting Duration	N	Mean age	Mean BMI	PCOS	Age at menarche	Smokers	Outcomes
De Leo 2010 (3)	High	1: 30 μg EE + DRSP 2: 30 μg EE + CMA 3: 30 μg EE + GSD 4: 30 μg EE +DSG	Italy 3 months	10/ group	age 16–35 years. Mean not reported	All lean, mean not reported	Rott	NR	NR	Free T, TT, A4, SHBG, DHEAS, adverse effects

Results shown in the table below. The "favours" are statements from the author, p values between groups were not reported. EE/CMA=1st gen.

Outcome	Unit	EE/CMA Mean	EE/CMA SD	EE/GSD Mean	EE/GSD SD	EE/DSG Mean	EE/DSG SD	Favours	Certainty[1]	Importance
TT	Pg/ml	380	85	420	110	560	120	1st gen (p value not reported)	⊕◯◯◯ VERY LOW	IMPORTANT
fT	Pg/ml	1.0	0.2	1.1	0.5	1.1	0.5	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
SHBG	Nmol/L	140	10	131	11	129	13	1st gen larger increase (p value not reported)	⊕◯◯◯ VERY LOW	IMPORTANT
A4	Pg/ml	975	235	1100	325	1400	330	1st gen (p value not reported)	⊕◯◯◯ VERY LOW	IMPORTANT
DHEAS	μg/ml	1.08	0.6	1.35	0.6	1.37	0.5	No difference	⊕◯◯◯ VERY LOW	IMPORTANT

[1] All outcomes were judged as of very low certainty of evidence due to very high risk of bias, and very serious imprecision.

Comparison 4: COCP with 1st vs. COCP with 4th generation progestins

- **EVIDENCE SUMMARY:**

  Four RCTs were identified, all with a high risk of bias. DeLeo had four arms. Relevant for this comparison, chlormadinone acetate (CMA), a 1st generation progestin was compared with the 4th generation progestins drospirenone(DRSP). Both Morgante, Podfigurna and Yildizhan used the same progestins in their RCTs. Study duration of included studies 3-24 months.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

Results from the meta-analysis showed a greater decrease in DHEAS (low certainty) and androstenedione (very low certainty) after treatment with the 4th generation progestin. There was no difference between treatments in SHBG and total testosterone levels. For the other reported outcomes, a meta-analysis could not be performed. With very low certainty of evidence, free testosterone,cholesterol and CRP levels were lower after treatment with the 4th generation progestin, compared with the 1st generation. There were no differences in other outcomes, with very low certainty of evidence.

Included studies, COCP with 1st vs 4th generation progestins:

Study ID	ROB	Interventions	Setting Duration	N	Mean age	Mean BMI	PCOS	Age at menarche	Smokers	Outcomes
De Leo 2010 (3)	High	1: 30 μg EE + DRSP 2: 30 μg EE + CMA 3: 30 μg EE + GSD 4: 30 μg EE +DSG	Italy 3 months	10/group	age 16–35 years. Mean not reported	All lean, mean not reported	Rott	NR	NR	Free T, TT, A4, SHBG, DHEAS, adverse effects
Morgante 2020 (4)	High	1: EE 30 mg/DRSP 3mg, 2: EE 30 mg/CMA 2mg, 3: EE 30 mg/DNG 2 mg	Italy 3 months	1:20 2:20 3:20	Mean age NR, aged 16-35	Mean BMI NR, stated to be < 25	Rott	NR	NR	DHEAS, TT, SHBG, androstendione
Podfigurna 2020 (5)	High	1: 3 mg DRSP/30 mcg EE 2: 2 mg CMA/30 mcg EE	Poland 6 months	1:60 2:60	26.92±4.72 for all	28.13±5.79 for all	Rott	NR	NR	FG score, BMI, T, DHEA-S, GLU, INS, HOMA
Yildizhan 2015 (6)	High	1: 3 mg DRSP/30 μg EE 2: 2 mg CMA/30 μg EE	Turkey 6, 12, 24 months	At 6 months: 1: 59 2: 58	1: 25.36±2.91 2: 24.82±3.20	1: 24.82±3.32 2: 23.56±3.32	Rott	NR	NR	BMI, WHR, HDL, LDL, TG, chol, HOMA, DHEAS, FG score, SHBG, CRP, TT, FAI

For some outcomes, meta-analysis could not be performed, these outcomes are presented narratively in the table below, as mean (SD) unless otherwise stated.

Outcome	Study	N	1st generation	4th generation	P-value	Favours	Certainty	Importance
BMI	Podfigurna 2020	1: 60 2: 60	27.21 (4.92)	26.34 (4.83)	P=0.33	No difference	⊕◯◯◯ VERY LOW [1,2]	CRITICAL
	Yildizhan 2015	1: 59 2: 58	Mean change -0.76 (0.6)	Mean change -0.97 (1.01)	P=0.688			
WHR	Yildizhan 2015	1: 59 2: 58	Mean change -0.017 (0.015)	Mean change 0.016 (0.011)	P=0.752	No difference	⊕◯◯◯ VERY LOW [1,3]	IMPORTANT
Hirsutism (FG score)	Podfigurna 2020	1: 60 2: 60	9.55 (5.45)	9.32 (1.36)	P=0.81	No difference	⊕◯◯◯ VERY LOW[1,2]	CRITICAL
	Yildizhan 2015	1: 59 2: 58	Mean change -0.88 (0.82)	Mean change -1.68 (1.36)	P=0.002			
FAI	Yildizhan 2015	1: 59 2: 58	Mean change -3.40 (2.15)	Mean change -4.65 (3.82)	P=0.055	No difference	⊕◯◯◯ VERY LOW [1,3]	IMPORTANT
Free testosterone (pmol/L)	DeLeo 2010	1: 10 2: 10	3.47 (0.69)	2.77 (0.69)	0.02	4th gen	⊕◯◯◯ VERY LOW [1,4]	IMPORTANT
Insulin (μU/mL)	Podfigurna 2020	1: 60 2: 60	11.53 (4.92)	10.32 (5.01)	P=0.18	No difference	⊕◯◯◯ VERY LOW[1,3]	IMPORTANT
Fasting glucose (mmol/L)	Podfigurna 2020	1: 60 2: 60	4.91 (0.28)	4.86 (0.28)	P=0.32	No difference	⊕◯◯◯ VERY LOW[1,3]	IMPORTANT
HOMA	Podfigurna 2020	1: 60 2: 60	2.5 (0.12)	2.2 (0.11)	P=0.21	No difference	⊕◯◯◯ VERY LOW[1,2]	IMPORTANT
	Yildizhan 2015	1: 59 2: 58	Mean change -0.26 (0.3)	Mean change -0.37 (0.26)	0.012			
Cholesterol (mmol/L)	Yildizhan 2015	1: 57 2: 55	Mean change 0.50 (0.14)	Mean change 0.38 (0.14)	P=0.001	4th gen	⊕◯◯◯ VERY LOW[1,3]	IMPORTANT
LDL (mmol/L)	Yildizhan 2015	1: 57 2: 55	Mean change 0.31 (0.14)	Mean change 0.33 (0.14)	P=0.274	No difference	⊕◯◯◯ VERY LOW[1,3]	IMPORTANT
HDL (mmol/L)	Yildizhan 2015	1: 57 2: 55	Mean change 0.21 (0.10)	Mean change 0.25 (0.11)	P=0.088	No difference	⊕◯◯◯ VERY LOW[1,3]	IMPORTANT
Triglycerids (mmol/L)	Yildizhan 2015	1: 57 2: 55	Mean change 0.16 (0.05)	Mean change 0.18 (0.05)	P=0.125	No difference	⊕◯◯◯ VERY LOW[1,3]	IMPORTANT
CRP mg/L	Yildizhan 2015	1: 59 2: 58	Mean change 0.72 (0.32)	Mean change 0.55 (0.23)	P=0.004	4th gen	⊕◯◯◯ VERY LOW[1,3]	IMPORTANT

1. Downgraded twice as all of evidence is at high risk of bias
2. Downgraded once for indirectness, since outcomes were reported in different ways
3. Downgraded once for imprecision, only one study
4. Downgraded twice for imprecision, very few participants

OUTCOME 4.1 BMI

4.1.1. Individual study data table

OUTCOME: BMI				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): **COCP with 1st vs. 4th generation progestins**								
Author, year	**Unit**	**Time point**	**N**	**EE/DRSP Mean**	**EE/DRSP SD**	**EE/CMA Mean**	**EE/CMA SD**	**Comments**
Podfigurna 2020	Kg/m2	6 m	EE/DRSP 60 EE/CMA 60	26.34	4.83	27.21	4.92	
Yildizhan 2015	Kg/m2	12 m	EE/DRSP 57 EE/CMA 55	Mean change -0.97	1.01	Mean change -0.76	0.6	

OUTCOME 4.2 WHR

4.2.1. Individual study data table

OUTCOME: WHR						**OUTCOME TYPE:** Continuous		
COMPARISON (if applicable): COCP with 1st vs. 4th generation progestins								
Author, year	**Unit**	**Time point**	**N**	**EE/DRSP Mean**	**EE/DRSP SD**	**EE/CMA Mean**	**EE/CMA SD**	**Comments**
Yildizhan 2015		12 m	1: 59 2: 58	Mean change 0.016 (0.011)		Mean change -0.017 (0.015)		

OUTCOME 4.3 HIRSUTISM

4.3.1. Individual study data table

OUTCOME: Hirsutism						**OUTCOME TYPE:** Continuous		
COMPARISON (if applicable): COCP with different sorts of gestagens								
Author, year	**Unit**	**Time point**	**N**	**EE/CMA Mean**	**EE/CMA SD**	**EE/DRSP Mean**	**EE/DRSP SD**	**Comments**
Podfigurna 2020	mFG score	6 m	EE/DRSP 60 EE/CMA 60	9.55	5.45	9.32	4.98	
Yildizhan 2015	FG score	12 m	EE/DRSP 57 EE/CMA 55	Mean change -0.88	0.82	Mean change -1.68	1.36	

OUTCOME 4.4 FAI

4.4.1. Individual study data table

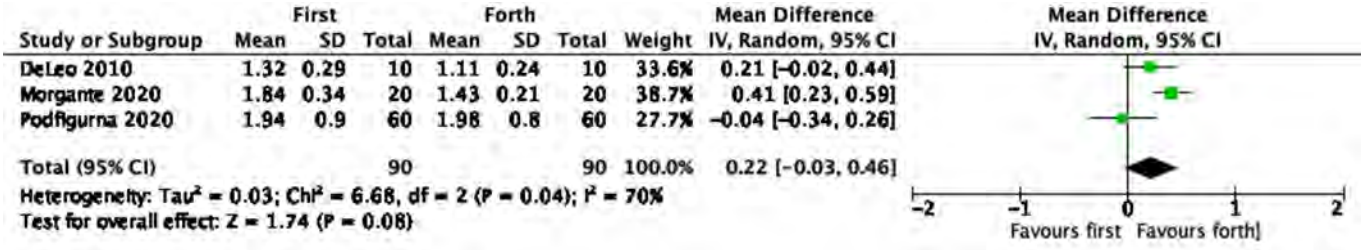
OUTCOME: FAI						**OUTCOME TYPE:** Continuous		
COMPARISON (if applicable): COCP with different sorts of gestagens								
Author, year	**Unit**	**Time point**	**N**	**EE/CMA Mean**	**EE/CMA SD**	**EE/DRSP Mean**	**EE/DRSP SD**	**Comments**
Yildizhan 2015	-	12 m	EE/DRSP 57 EE/CMA 55	Mean change -3.40	2.15	Mean change -4.65	3.82	

OUTCOME 4.5 TOTAL TESTOSTERONE

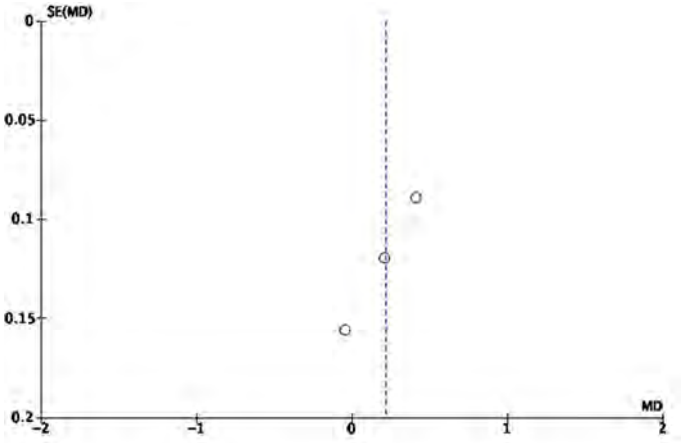
4.5.1. Individual study data table

OUTCOME: Total testosterone					**OUTCOME TYPE:** Continuous		
COMPARISON (if applicable): COCP with 1st vs. 4th generation progestin							
Author, year	**Unit**	**Time point**	**N**	**EE/DRSP Mean**	**EE/DRSP SD**	**EE/CMA Mean**	**EE/CMA SD**
DeLeo 2010	Nmol/L	3 m	EE/DRSP 10 EE/CMA 10	1.11	0.24	1.32	0.29
Morgante 2020	Nmol/L	3 m	EE/DRSP 20 EE/CMA 20	1.43	0.21	1.84	0.34
Podfigurna 2020	Nmol/L	6 m	EE/DRSP 60 EE/CMA 60	1.98	0.8	1.94	0.9
Yildizhan 2015	Nmol/L	12 m	EE/DRSP 57 EE/CMA 55	Mean change -0.36	0.15	Mean change -0.34	0.14

4.5.2. Forest Plot COCP with 1st vs. 4th generation progestin for total testosterone (nmol/L)



4.5.3. Funnel plot for assessment of publication bias



OUTCOME 4.6 Free testosterone

4.6.1. Individual study data table

OUTCOME: Free testosterone				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable):		**COCP with 1st vs. 4th generation progestins**						
Author, year	**Unit**	**Time point**	**N**	**EE/DRSP Mean**	**EE/DRSP SD**	**EE/CMA Mean**	**EE/CMA SD**	**Comments**
De Leo 2010	Pg/ml	3 m	1: 10 2: 10	0.8 (0.2)		1.0 (0.2)		

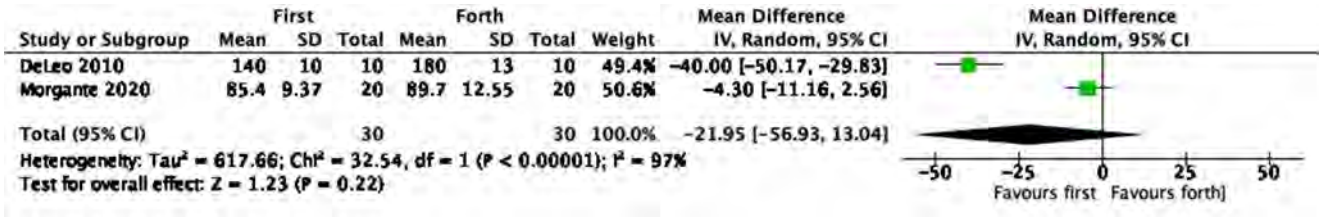
OUTCOME 4.7 SHBG

4.7.1. Individual study data table

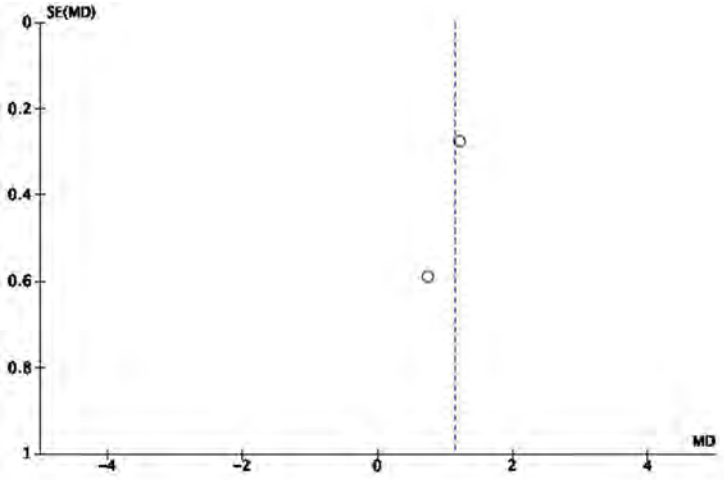
	OUTCOME: SHBG						
		COMPARISON (if applicable): COCP with different sorts of gestagens					
Author, year	**Unit**	**Time point**	**N**	**EE/DRSP Mean**	**EE/DRSP SD**	**EE/CMA Mean**	**EE/CMA SD**
DeLeo 2010	Nmol/L	3 m	EE/DRSP 10 EE/CMA 10	180	13	140	10
Morgante 2020	Nmol/L	3 m	EE/DRSP 20 EE/CMA 20	89.7	12.55	85.4	9.37

Yildizhan 2015	Nmol/L	12 m	EE/DRSP 57 EE/CMA 55	Mean change 13.29	4.7	Mean change 9.24	3.36

4.7.2. Forest Plot COCP with 1st vs. 4th generation progestin for SHBG (nmol/L)



4.7.3. Funnel plot for assessment of publication bias

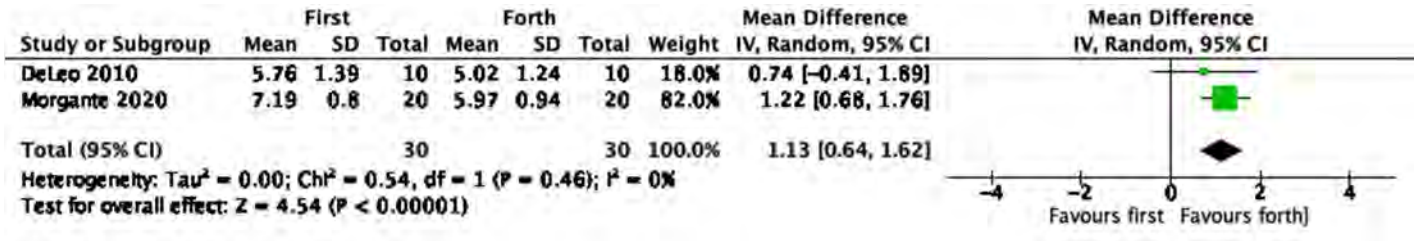


OUTCOME 4.8 ANDROSTENEDIONE

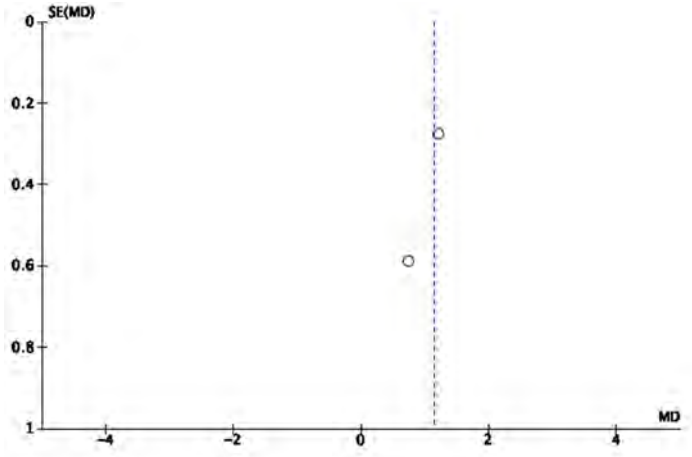
4.8.1. Individual study data table

OUTCOME: Androstendione							
COMPARISON (if applicable): COCP with different sorts of gestagens							
Author, year	**Unit**	**Time point**	**N**	**EE/DRSP Mean**	**EE/DRSP SD**	**EE/CMA Mean**	**EE/CMA SD**
DeLeo 2010	Nmol/L	3 m	EE/DRSP 10 EE/CMA 10	5.02	1.24	5.76	1.39
Morgante 2020	Nmol/L	3 m	EE/DRSP 20 EE/CMA 20	5.97	0.94	7.19	0.80

4.8.2. Forest Plot COCP with 1st vs. 4th generation progestin for androstenedione (nmol/L)



4.8.3. Funnel plot for assessment of publication bias

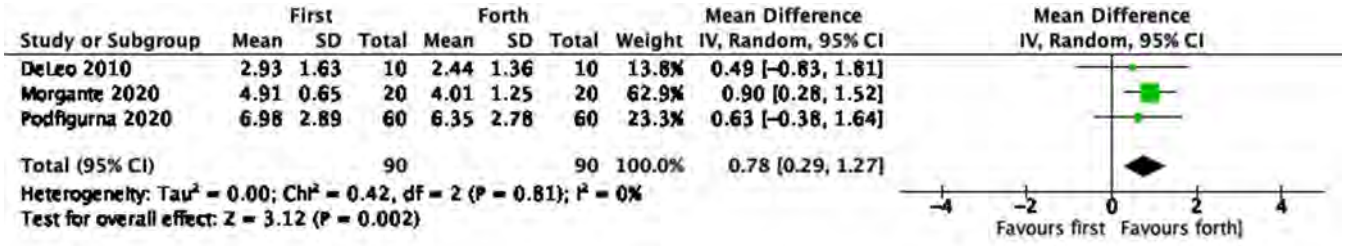


OUTCOME 4.9 DHEAS

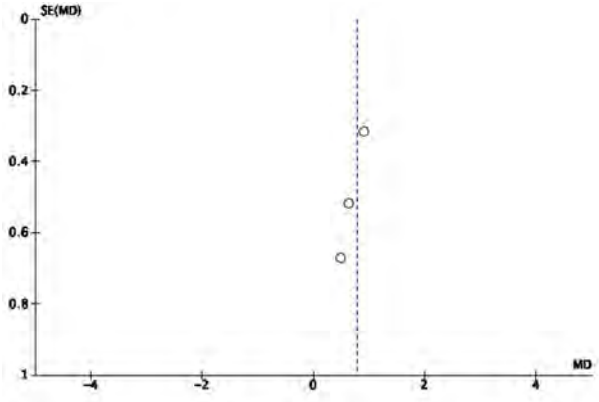
4.9.1. Individual study data table

OUTCOME: DHEAS							
COMPARISON (if applicable): COCP with 1st vs. 4th generation progestin							
Author, year	**Unit**	**Time point**	**N**	**EE/DRSP Mean**	**EE/DRSP SD**	**EE/CMA Mean**	**EE/CMA SD**
DeLeo 2010	μmol/L	3 m	EE/DRSP 10 EE/CMA 10	2.44	1.36	2.93	1.63
Morgante 2020	μmol/L	3 m	EE/DRSP 20 EE/CMA 20	4.01	1.25	4.91	0.65
Podfigurna 2020	μmol/L	6 m	EE/DRSP 60 EE/CMA 60	6.35	2.78	6.98	2.89
Yildizhan 2015	Microg/dl	12 m	EE/DRSP 57 EE/CMA 55	Mean change -21.43	21.57	Mean change -17.34	8.74

4.9.2. Forest Plot COCP with 1st vs. 4th generation progestin for DHEAS (μmol/L)



4.9.3. Funnel plot for assessment of publication bias



OUTCOME 4.10 INSULIN
4.10.1. Individual study data table

OUTCOME: Insulin							
COMPARISON (if applicable): COCP with 1st vs. 4th generation progestin							
Author, year	**Unit**	**Time point**	**N**	**EE/DRSP Mean**	**EE/DRSP SD**	**EE/CMA Mean**	**EE/CMA SD**
Podfigurna 2020	μU/mL	6 m	EE/DRSP 60 EE/CMA 60	10.32	5.01	11.53	4.92

OUTCOME 4.11 GLUCOSE
4.11.1. Individual study data table

OUTCOME: Glucose							
COMPARISON (if applicable): COCP with 1st vs. 4th generation progestin							
Author, year	**Unit**	**Time point**	**N**	**EE/DRSP Mean**	**EE/DRSP SD**	**EE/CMA Mean**	**EE/CMA SD**
Podfigurna 2020	g/dl	6 m	EE/DRSP 60 EE/CMA 60	87.54	4.98	88.45	5.03

OUTCOME 4.12 HOMA
4.12.1. Individual study data table

OUTCOME: HOMA							
COMPARISON (if applicable): COCP with 1st vs. 4th generation progestin							
Author, year	**Unit**	**Time point**	**N**	**EE/DRSP Mean**	**EE/DRSP SD**	**EE/CMA Mean**	**EE/CMA SD**
Podfigurna 2020	-	6 m	EE/DRSP 60 EE/CMA 60	2.2	0.11	2.5	0.12
Yildizhan 2015	-	12 m	EE/DRSP 57 EE/CMA 55	Mean change -0.37	0.26	Mean change -0.26	0.3

OUTCOME 4.13 TOTAL CHOLESTEROL
4.13.1. Individual study data table

OUTCOME: Cholesterol							
COMPARISON (if applicable): COCP with 1st vs. 4th generation progestin							
Author, year	**Unit**	**Time point**	**N**	**EE/DRSP Mean**	**EE/DRSP SD**	**EE/CMA Mean**	**EE/CMA SD**
Yildizhan 2015	Mg/dl	12 m	EE/DRSP 57 EE/CMA 55	Mean change 14.61 (5.41)		Mean change 19.30 (5.28)	

OUTCOME 4.14 LDL
4.14.1. Individual study data table

OUTCOME: LDL							
COMPARISON (if applicable): COCP with 1st vs. 4th generation progestin							
Author, year	**Unit**	**Time point**	**N**	**EE/DRSP Mean**	**EE/DRSP SD**	**EE/CMA Mean**	**EE/CMA SD**
Yildizhan 2015	Mg/dl	12 m	EE/DRSP 57 EE/CMA 55	Mean change 12.88 (5.43)		Mean change 11.82 (5.40)	

OUTCOME 4.15 HDL
4.15.1. Individual study data table

OUTCOME: HDL							
COMPARISON (if applicable): COCP with 1st vs. 4th generation progestin							
Author, year	**Unit**	**Time point**	**N**	**EE/DRSP Mean**	**EE/DRSP SD**	**EE/CMA Mean**	**EE/CMA SD**
Yildizhan 2015	Mg/dl	12 m	EE/DRSP 57 EE/CMA 55	Mean change 8.14 (3.85)		Mean change 9.55 (4.32)	

OUTCOME 4.16 TRIGLYCERIDES
4.16.1. Individual study data table

OUTCOME: TG							
COMPARISON (if applicable): COCP with 1st vs. 4th generation progestin							
Author, year	**Unit**	**Time point**	**N**	**EE/DRSP Mean**	**EE/DRSP SD**	**EE/CMA Mean**	**EE/CMA SD**
Yildizhan 2015	Mg/dl	12 m	EE/DRSP 57 EE/CMA 55	Mean change 15.57 (4.05)		Mean change 14.60 (4.38)	

OUTCOME 4.17 CRP
4.17.1. Individual study data table

OUTCOME: TG							
COMPARISON (if applicable): COCP with 1st vs. 4th generation progestin							
Author, year	**Unit**	**Time point**	**N**	**EE/DRSP Mean**	**EE/DRSP SD**	**EE/CMA Mean**	**EE/CMA SD**
Yildizhan 2015	Mg/L	12 m	EE/DRSP 57 EE/CMA 55	Mean change 0.55 (0.23)		Mean change 0.55 (0.23)	

Comparison 5: COCP with 2nd vs. COCP with 3rd generation progestins

- **EVIDENCE SUMMARY:**

Two RCTs were identified, both with a high risk of bias. Amiri 2020 was a crossover study, involving four arms. Treatment was ongoing for 6 months, then a 6-8 week washout period was allowed before change of treatment to a COCP with a different progestin. The results from this study are only presented as estimation of treatment, period, sequence and carry over effect using GEE models. Amiri 2021 was a 6 months four arm trial comparing COCPs with four different progestins regarding effects on lipid profiles and adiponectins. The progestins compared relevant for this comparison were the 2nd generation levonorgestrel (LNG) vs. 3rd generation desogestrel (DSG) in both studies

- **META-ANALYSIS/DESCRIPTIVE ANALYSIS SUMMARY:**

A meta-analysis could not be performed. Results from the crossover study showed a greater decrease in FAI, and a greater increase in SHBG, after treatment with the 3rd generation progestin, with a very low certainty of evidence. For the other reported outcomes, no difference was seen between the groups, with a very low certainty of evidence.

Included studies:

Study ID	ROB	Interventions	Setting Duration	N	Mean age	Mean BMI	PCOS	Age at menarche	Smokers	Comments	Outcomes
Amiri 2020 (7)	High	1: EE 30 µg +LNG 0.15 mg, then EE 30 µg +DSG 150 µg 2: EE 30 µg + LNG 0.15 mg, then EE 30 µg +CPA 2 mg 3: EE 30 µg + LNG 0.15 mg, then EE 30 µg +DRSP 3 mg 4: EE 30 µg +DSG 150 µg, then EE 30 µg +LNG 0.15 mg 5: EE 30 µg +CPA 2 mg, then EE 30 µg +LNG 0.15 mg 6: EE 30 µg +DRSP 3 mg, then EE 30 µg +LNG 0.15 mg	Iran 6 m	1.9 2. 9 3. 8 4. 26 5. 20 6. 16	NR, aged 18-45	NR	AES	NR	NR	Cross over	FAI, m-FG, weight, BMI, WHR, SHBG, DHEAS, glucose, insulin, HOMA, TG, chol, LDL, HDL,
Amiri 2021 (8)	High	1: OCs containing Ethinyl estradiol (EE) 30 µg + LNG 0.15 mg; 2: OCs containing EE 30 µg + DSG 150 µg; 3: OCs containing EE 35 µg + CPA 2 mg; and Group 4: OCs containing EE 30 µg + DRSP 3 mg.	Iran 6m	1=23 2=20 3=28 4=17	1. 28.5 ± 5.6 2. 27.6 ± 4.5 3. 30.7 ± 6.0 4. 30.0 ± 6.1	1. 25.5 ± 4.0 2. 25.7 ± 3.9 3. 26.0 ± 5.4 4. 25.8 ± 5.3	AES	NR	Excluded		BMI, WHR, TG, Chol, LDL, HDL

All individual results are shown in the table below. Results from Amiri 2020 are shown as mean difference adjusted for baseline values and are reported as β regression coefficients (95%CI), p value. Results from Amiri 2021 are unadjusted, shown as mean and SD.

COMPARISON: COCP with 2nd vs. COCP with 3rd generation progestins						**Certainty of evidence for all outcomes** ⊕◯◯◯ VERY LOW (very serious risk of bias, imprecision)	
Outcome	**Study ID**	**2nd generation**	**SD**	**3rd generation**	**SD**	**Favours**	**Importance**
Weight (kg)	Amiri 2020	Ref		-0.9 (-2.1; 0.3) 0.130		No difference	CRITICAL
	Amiri 2021	0.9	0.07	0.8	0.07		
BMI (kg/m2)	Amiri 2020	Ref		-0.3 (-0.7; 0.1) 0.163		No difference	CRITICAL
	Amiri 2021	25.2	4.0	25.8	4.4		
WHR	Amiri 2020	Ref		-0.08 (-0.02; 0.01) 0.397		No difference	IMPORTANT
Hirsutism (FG score)	Amiri 2020	Ref		0.3 (-1.2; 0.8) 0.677		No difference	CRITICAL
SHBG (nmol/L)	Amiri 2020	Ref		73 (37; 110) <0.001		higher with 3rd gen	IMPORTANT
DHEAS (μmol/L)	Amiri 2020	Ref		0.01 (-0.19; 0.22 0.884		No difference	IMPORTANT
FAI	Amiri 2020	Ref		-1.7 (-2.3; -1.0) <0.001		3rd gen	IMPORTANT
Total testosterone (nmol/L)	Amiri 2020	Ref		-0.02 (-0.03; 0.21) 0.917		No difference	IMPORTANT
Cholesterol (Mmol/L)	Amiri 2021	4.6	1.1	4.6	0.8	No difference	IMPORTANT
LDL (Mmol/L)	Amiri 2021	2.8	0.8	2.5	0.6	No difference	IMPORTANT
HDL (Mmol/L)	Amiri 2021	1.1	0.2	1.3	0.3	No difference	IMPORTANT
TG (Mmol/L)	Amiri 2021	Median 1.0	IQR 0.8-1.4	Median 1.3	IQR 0.8-1.4	No difference	IMPORTANT

Comparison 6: COCP with 2nd vs. COCP with 4th generation progestins

▪ EVIDENCE SUMMARY:

Two RCTs were identified, the same studies as in comparison 5. Both studies had a high risk of bias. The progestins compared relevant for this comparison were the 2nd generation levonorgestrel (LNG) vs. 4th generation drospirenone (DRSP) in both studies.

▪ META-ANALYSIS/DESCRIPTIVE ANALYSIS SUMMARY:

A meta-analysis could not be performed. Results from the crossover study showed a greater decrease in FAI, and a greater increase in SHBG, after treatment with the 4th generation progestin, with a very low certainty of evidence. For the other reported outcomes, free testosterone and DHEAS, no difference was seen between the groups, with a very low certainty of evidence.

Included studies:

Study ID	ROB	Interventions	Setting Duration	N	Mean age	Mean BMI	PCOS	Age at menarche	Smokers	Comments	Outcomes
Amiri 2020 (7)	High	1: EE 30 µg +LNG 0.15 mg, then EE 30 µg +DSG 150 µg 2: EE 30 µg + LNG 0.15 mg, then EE 30 µg +CPA 2 mg 3: EE 30 µg + LNG 0.15 mg, then EE 30 µg +DRSP 3 mg 4: EE 30 µg +DSG 150 µg, then EE 30 µg +LNG 0.15 mg 5: EE 30 µg +CPA 2 mg, then EE 30 µg +LNG 0.15 mg 6: EE 30 µg +DRSP 3 mg, then EE 30 µg +LNG 0.15 mg	Iran 6 m	1.9 2. 9 3. 8 4. 26 5. 20 6. 16	NR, aged 18-45	NR	AES	NR	NR	Cross over	FAI, m-FG, weight, BMI, WHR, SHBG, DHEAS, glucose, insulin, HOMA, TG, chol, LDL, HDL,
Amiri 2021 (8)	High	1: OCs containing Ethinyl estradiol (EE) 30 µg + LNG 0.15 mg; 2: OCs containing EE 30 µg + DSG 150 µg; 3: OCs containing EE 35 µg + CPA 2 mg; and Group 4: OCs containing EE 30 µg + DRSP 3 mg.	Iran 6m	1=23 2=20 3=28 4=17	1. 28.5 ± 5.6 2. 27.6 ± 4.5 3. 30.7 ± 6.0 4. 30.0 ± 6.1	1. 25.5 ± 4.0 2. 25.7 ± 3.9 3. 26.0 ± 5.4 4. 25.8 ± 5.3	AES	NR	Excluded		BMI, WHR, TG, Chol, LDL, HDL

All individual results are shown in the table below. Results from Amiri 2020 are shown as mean difference adjusted for baseline values and are reported as β regression coefficients (95%CI), p value. Results from Amiri 2021 are unadjusted, shown as mean and SD.

COMPARISON: COCP with 2nd vs. COCP with 4th generation progestins				**Certainty of evidence for all outcomes** ⊕◯◯◯ VERY LOW (very serious risk of bias, imprecision)			
Outcome	**Study ID**	**2nd generation**	**SD**	**4th generation**	**SD**	**Favours**	**Importance**
Weight (kg)	Amiri 2020	Ref		-0.9 (-1.7; -0.03) 0.044		4th	CRITICAL
BMI (kg/m2)	Amiri 2020	Ref		-0.3 (-0.6; -0.03) 0.032		No difference	CRITICAL
	Amiri 2021	25.2	4.0	26.1	5.7		
WHR	Amiri 2020	Ref		0.002 (-0.01; 0.1) 0.787		No difference	IMPORTANT
	Amiri 2021	0.9	0.07	0.8	0.09		
Hirsutism (FG score)	Amiri 2020	Ref		-0.2 (-1.3; 0.8) 0.784		No difference	CRITICAL
SHBG (nmol/L)	Amiri 2020	Ref		80 (51; 108) <0.001		2nd gen (higher SHBG with 4th)	IMPORTANT
DHEAS (μmol/L)	Amiri 2020	Ref		0.04 (-0.09; 0.17) 0.575		No difference	IMPORTANT
FAI	Amiri 2020	Ref		-2.0 (-2.6; -1.4) <0.001		4th gen	IMPORTANT
Total testosterone (nmol/L)	Amiri 2020	Ref		-0.03 (-0.03; 0.28) 0.810		No difference	IMPORTANT
Cholesterol (Mmol/L)	Amiri 2021	4.6	1.1	4.5	0.8	No difference	IMPORTANT
LDL (Mmol/L)	Amiri 2021	2.8	0.8	2.3	0.5	No difference	IMPORTANT
HDL (Mmol/L)	Amiri 2021	1.1	0.2	1.4	0.2	No difference	IMPORTANT
TG (Mmol/L)	Amiri 2021	Median 1.0	IQR 0.8-1.4	Median 1.1	IQR 0.8-1.3	No difference	IMPORTANT

Comparison 7: COCP with 3rd vs. COCP with 4th generation progestins

- **EVIDENCE SUMMARY:**

Five RCTs were identified. The progestins used in these studies were the 3rd generations desogestrel (DSG) and gestodene (GSD), and the 4th generations drospirenone (DRSP) and dienogest (DNG).
Amiri 2020 (7) included a 3rd and 4th generation progestin, but reported results as estimation of treatment, period, sequence and carry over effect using GEE models, and as the COCP with a second generation progestin was reference, the study is not reported here..
Amiri 2021 (8) was a 6 months four arm trial comparing COCPs with four different progestins regarding effects on lipid profiles and adiponectins. Relevant for this comparison was EE/DSG (n=20) and EE/DRSP (n=17). The study had a high risk of bias.
Bhattacharya 2012 (9) was a 12 months trial with three arms. Relevant for this comparison EE/DSG (n=49) and EE/DRSP (n=50). The study had a low risk of bias.
DeLeo 2010 (3) was a four-arm study with 3 months duration. The arms relevant to this comparison was EE/GSD (n=10); EE/DSG (n=10) and EE/DRSP (n=10. This study had thus two 3rd generation COCPs, and if possible to include in a meta-analysis, the EE/DSG group was chosen, since this combination was used in the other studies. The study had a high risk of bias. Kriplani 2010 (10) compared EE/DSG (n=29) with EE/DRSP (n=29), the treatments were used for 6 months. This study had a high risk of bias.
No studies were identified in adolesents.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

The meta-analysis showed a lower BMI after treatment with 4th compared with 3rd generation progestins with a low certainty of evidence. Total testosterone levels and LDL were lower, and HDL higher, after treatment with a 4th generation progestin, with a very low certainty of evidence. For other outcomes, no differences were seen between 3rd and 4th generations, with very low certainty of evidence.

Included studies:

Study ID	ROB	Interventions	Setting Duration	N	Mean age	Mean BMI	PCOS	Age at menarche	Smokers	Comments	Outcomes
Amiri 2020 (7)	High	1: EE 30 µg +LNG 0.15 mg, then EE 30 µg +DSG 150 µg 2: EE 30 µg + LNG 0.15 mg, then EE 30 µg +CPA 2 mg 3: EE 30 µg + LNG 0.15 mg, then EE 30 µg +DRSP 3 mg 4: EE 30 µg +DSG 150 µg, then EE 30 µg +LNG 0.15 mg 5: EE 30 µg +CPA 2 mg, then EE 30 µg +LNG 0.15 mg 6: EE 30 µg +DRSP 3 mg, then EE 30 µg +LNG 0.15 mg	Iran 6 m	1.9 2. 9 3. 8 4. 26 5. 20 6. 16	NR, aged 18-45	NR	AES	NR	NR	Cross over	FAI, m-FG, weight, BMI, WHR, SHBG, DHEAS, glucose, insulin, HOMA, TG, chol, LDL, HDL,
Amiri 2021 (8)	High	1: OCs containing Ethinyl estradiol (EE) 30 µg + LNG	Iran 6m	1=23 2=20 3=28 4=17	1. 28.5 ± 5.6	1. 25.5 ± 4.0 2. 25.7 ± 3.9	AES	NR	Excluded		BMI, WHR, TG, Chol, LDL, HDL

		0.15 mg; 2: OCs containing EE 30 µg + DSG 150 µg; 3: OCs containing EE 35 µg + CPA 2 mg; and Group 4: OCs containing EE 30 µg + DRSP 3 mg.			2. 27.6 ± 4.5 3. 30.7 ± 6.0 4. 30.0 ± 6.1	3. 26.0 ± 5.4 4. 25.8 ± 5.3					
Bhattacharya 2012 (9)	Low	1) 30ug EE + 150ug DSG 21/7 2) 35ug EE + 2000ug CPA 21/7 3) 30ug EE + 3000ug DRSP 21/7	India 12 months	1: 49 2: 51 3: 50	1: 22.24 ±4.47 2: 22.32 ±4.17 3: 22.33 ±4.76	1: 25.41±4.49 2: 26.41±3.81 3: 26.47±4.65	AES	NR	NR		BMI, WHR, FG score, TT, SHBG, FAI, glucose, insulin, HOMA
DeLeo 2010 (3)	High	1: 30 µg EE + DRSP 2: 30 µg EE + CMA 3: 30 µg EE + GSD 4: 30 µg EE +DSG	Italy 3 months	10/group	age 16–35 years.	All lean, mean not reported	Rott	NR	NR		Free T, TT, A4, SHBG, DHEAS, adverse effects
Kriplani 2010 (10)	High	1) 30mcg EE + 3mg DRSP 21/7 2) 30ug EE+ 150ug DSG 21/7	India 6 months	1: 29 2: 29	22.5± 4.7 (all participants)	1: 27.6±5.4 2: 26.1±3.6	Rott/ ESHRE/ ASRM criteria	NR	Excluded		TG, LDL, HDL, chol,glucose, insuilin, HOMA, TT, SHBG, FAI, bioavailable testo, side effects

Other outcomes, that could not be included in the meta-analysis, are reported narratively:

Outcome	Results	Favours
WHR	Bhattacharya 2012 reported mean change from baseline, 0.00 ± 0.08 for third generation vs. 0.02 ± 0.09 for 4th generation, p value not reported. Amiri 2021 reported mean 0.8 ± 0.07 vs. 0.8 ± 0.09.	No difference
Hirsutism	Bhattacharya 2012 reported mean change in FG score from baseline, -1.69 ± 5.69 for third generation vs. -2.12 ± 6.58 for 4th generation, p value not reported. Kriplani 2010 reports a reduction in FG score of 36.5% from baseline in the 4th generation treatment group, but no change in FG score in the 3rd generation group, figures or p values not reported.	No difference
FAI	Bhattacharya 2012 reported mean change in FAI from baseline, -5.58 ± 9.15 for third generation vs. -7.89 ± 9.13 for 4th generation, p value not reported. Kriplani 2010 reported means, 3.9 ± 1.9 vs. 2.8 ± 4.9, p=0.12.	No difference
Free testosterone	DeLeo reported means, 3.81 ± 1.73 pmol/L for 3rd generation EE/DSG; 4.16 ± 1.73 pmol/L for 3rd generation EE/GSD, and 2.77 ± 0.69 pmol/L for 4th generation EE/DRSP, p value not reported, but author reports significantly greater reduction after EE/DRSP.	4th
Androstenedione	DeLeo reported means, 8.27 ± 1.95 pmol/L for 3rd generation EE/DSG; 46.50 ± 1.92 pmol/L for 3rd generation EE/GSD, and 5.02 ± 1.24 pmol/L for 4th generation EE/DRSP, p value not reported, but author reports significantly greater reduction after EE/DRSP.	4th
DHEAS	.DeLeo reported means, 3.72 ± 1.36 µmol/L for 3rd generation EE/DSG; 3.66 ± 1.63 µmol/L for 3rd generation EE/GSD, and 2.44 ± 1.36 µmol/L for 4th generation EE/DRSP, p value not reported, but author reports no significant difference.	No difference
Insulin	Bhattacharya 2012 reported mean change in from baseline, -0.02 ± 17.35 for third generation vs. 2.78 ± 17.27 for 4th generation, p value not reported. Kriplani 2010 reported means, 11.7 ± 6.2 for 3rd generation vs. 8.7 ± 3.6 µU/ml for 4th generation, p=0.07.	No difference
Glucose	Bhattacharya 2012 reported mean change in from baseline, -4.28 ± 11.66 for third generation vs. -2.11 ± 14.02 for 4th generation, p value not reported. Kriplani 2010 reported means after treatment, 81.9 ± 6.1 mg/dl for 3rd generation vs. 80.6 ± 6.2 mg/dl for 4th generation, p=0.22.	No difference
HOMA	Bhattacharya 2012 reported mean change in from baseline, -0.28 ± 3.98 for third generation vs. 0.42 ± 3.82 for 4th generation, p value not reported.	No difference

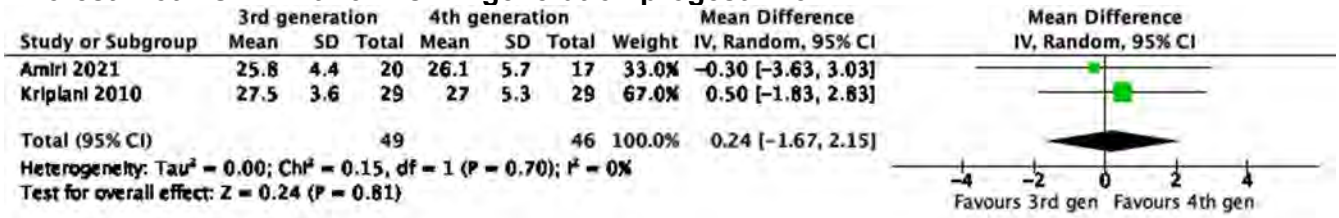
	Kriplani 2010 reported means after treatment, 1.8 ± 1.3 for 3rd generation vs. 1.7 ± 0.7 for 4th generation, p=0.1.	
OGTT	No studies	
Triglycerides	Amiri 2021 reported medians (IQR), 1.3 (0.8-1.4) for 3rd generation vs. 1.1 (0.8-1.3) mmol/L for 4th generation, p value not reported. Kriplani 2010 reported means, 1.17 ± 0.33 for 3rd generation vs. 1.33 ± 0.35 for 4th generation, p=0.07.	No difference
CRP	No studies	

OUTCOME 7.1 BMI

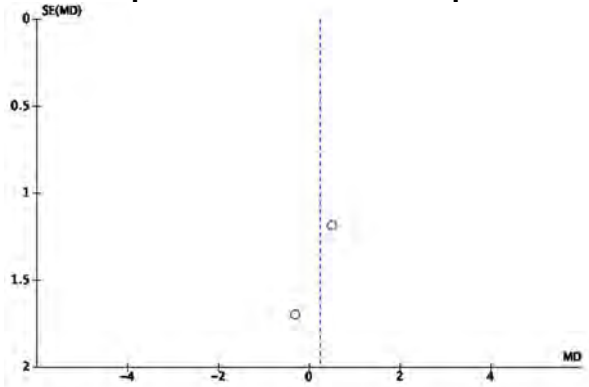
7.1.1. Individual study data table

OUTCOME: BMI							**OUTCOME TYPE:** Continuous	
COMPARISON (if applicable): COCP with different sorts of gestagens								
Author, year	**Unit**	**Time point**	**N**	**EE/DSG Mean**	**EE/DSG SD**	**EE/DRSP Mean**	**EE/DRSP SD**	**Comments**
Amiri 2020		6 m	*EE/LNG: 26* *EE/DSG: 26* *EE/CPA: 20* *EE/DRSP: 16*	Mean difference adjusted for baseline values, and are reported as β regression coefficients (95%CI), p value Ref= 2nd generation 3rd generation: -0.3 (-0.7; 0.1) 0.163 4th generation -0.3 (-0.6; -0.03) 0.032				
Amiri 2021		6m	*EE/LNG: 23* *EE/DSG: 20* *EE/CPA: 28* *EE/DRSP: 17*	25.8	4.4	26.1	5.7	
Bhattacharya 2012	Mean change from baseline	12 m	EE/DSG 49 EE/CPA 51 EE/DRSP 50	Mean change -0.45	6.75	Mean change 0.11	5.54	NS
Kriplani 2010		3 m	EE/DRSP 29 EE/DSG 29	27.5	3.6	27	5.3	

7.1.2. Forest Plot COCP with 3rd vs. 4th generation progestin for BMI



7.1.3. Funnel plot for assessment of publication bias



OUTCOME 7.2 Weight
7.2.1. Individual study data table

OUTCOME: weight							**OUTCOME TYPE:** Continuous	
COMPARISON (if applicable): COCP with different sorts of gestagens								
Author, year	**Unit**	**Time point**	**N**	**EE/DSG Mean**	**EE/DSG SD**	**EE/DRSP Mean**	**EE/DRSP SD**	**Comments**
Kriplani 2010	kg	6 m	EE/DRSP 29 EE/DSG 29	63.7	7.3	66.9	12.3	

OUTCOME 7.3 WHR
7.3.1. Individual study data table

OUTCOME: WHR						**OUTCOME TYPE:** Continuous		
COMPARISON (if applicable): COCP with different sorts of gestagens								
Author, year	**Unit**	**Time point**	**N**	**EE/DSG Mean**	**EE/DSG SD**	**EE/DRSP Mean**	**EE/DRSP SD**	**Comments**
Amiri 2021	-	6m	*EE/DSG: 20* *EE/DRSP: 17*	0.8	0.07	0.8	0.09	
Bhattacharya 2012	Mean change from baseline	12 m	EE/DSG 49 EE/CPA 51 EE/DRSP 50	Mean change 0.00	0.08	Mean change 0.02	0.09	

OUTCOME 7.4 HIRSUTISM
7.4.1. Individual study data table

OUTCOME: Hirsutism						**OUTCOME TYPE:** Continuous		
COMPARISON (if applicable): COCP with different sorts of gestagens								
Author, year	**Unit**	**Time point**	**N**	**EE/DSG Mean**	**EE/DSG SD**	**EE/DRSP Mean**	**EE/DRSP SD**	**Comments**
Bhattacharya 2012	Mean change from baseline FG score	12 m	EE/DSG 49 EE/CPA 51 EE/DRSP 50	-1.69	5.69	-2.12	6.58	
Kriplani 2010		6 m	EE/DRSP 29 EE/DSG 29	No significant change from baseline		-36% from baseline		P vale not reported

OUTCOME 7.5 FAI
7.5.1. Individual study data table

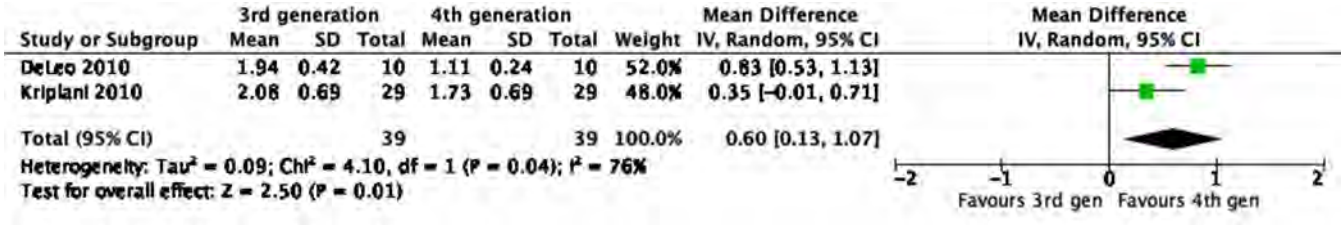
OUTCOME: FAI							**OUTCOME TYPE:** Continuous	
COMPARISON (if applicable): COCP with different sorts of gestagens								
Author, year	**Unit**	**Time point**	**N**	**EE/DSG Mean**	**EE/DSG SD**	**EE/DRSP Mean**	**EE/DRSP SD**	**Comments**
Bhattacharya 2012	Mean change from baseline	12 m	EE/DSG 49 EE/DRSP 50	-5.58	9.15	-7.89	9.13	
Kriplani 2010		6 m	EE/DRSP 29 EE/DSG 29	3.9	1.9	2.8	4.9	

OUTCOME 7.6 TOTAL TESTOSTERONE

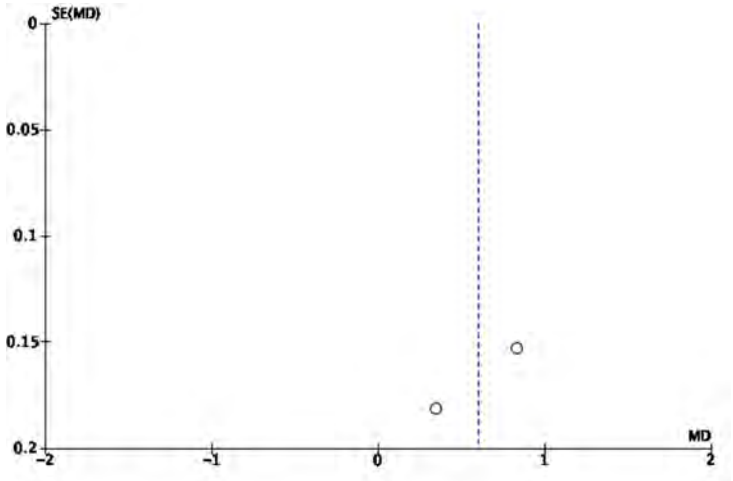
7.6.1. Individual study data table

OUTCOME: Total testosterone								
COMPARISON (if applicable): COCP with different sorts of gestagens								
Author, year	**Unit**	**Time point**	**N**	**EE/DSG Mean**	**EE/DSG SD**	**EE/DRSP Mean**	**EE/DRSP SD**	**Comments**
Bhattacharya 2012	Mean change from baseline	12 m	EE/DSG 49 EE/CPA 51 EE/DRSP 50	-0.10	0.39	-0.06	0.32	
DeLeo 2010	Nmol/L	3 m	EE/DRSP 10 EE/DSG 10	1.94	0.42	1.11	0.24	
Kriplani 2010	Nmol/L	6 m	EE/DRSP 29 EE/DSG 29	2.08	00.69	1.73	0.69	

7.6.2. Forest Plot COCP with 3rd vs. 4th generation progestin for total testosterone (nmol/L)



7.6.3. Funnel plot for assessment of publication bias



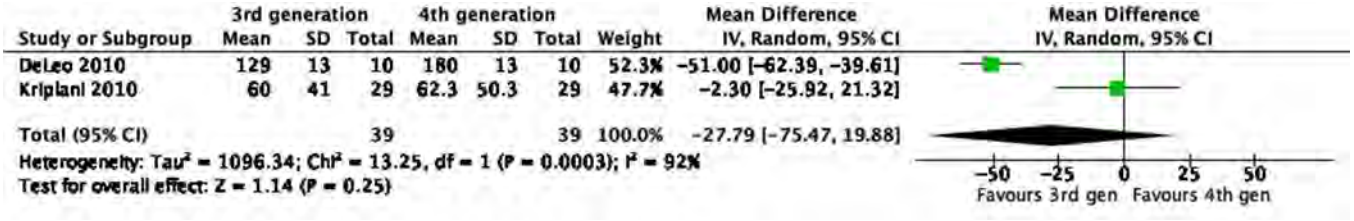
OUTCOME 7.7 FREE TESTOSTERONE
7.7.1. Individual study data table

OUTCOME: Free testosterone								
COMPARISON (if applicable): COCP with different sorts of gestagens								
Author, year	**Unit**	**Time point**	**N**	**EE/DSG Mean**	**EE/DSG SD**	**EE/DRSP Mean**	**EE/DRSP SD**	**Comments**
DeLeo 2010	Pg/ml	3 m	EE/DRSP 10 EE/DSG 10	1.1	0.5	0.8	0.2	

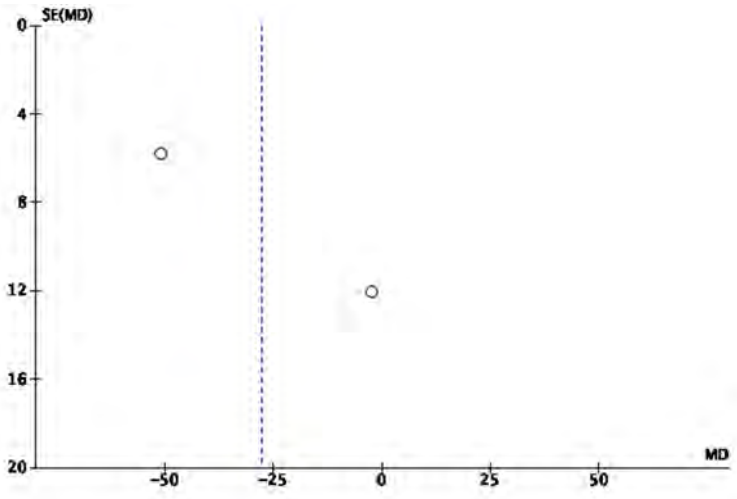
OUTCOME 7.8 SHBG
7.8.1. Individual study data table

OUTCOME: SHBG							
COMPARISON (if applicable): COCP with different sorts of gestagens							
Author, year	**Unit**	**Time point**	**N**	**EE/DSG Mean**	**EE/DSG SD**	**EE/DRSP Mean**	**EE/DRSP SD**
Bhattacharya 2012	Mean change from baseline	12 m	EE/DSG 49 EE/CPA 51 EE/DRSP 50	99.53	67.52	131.52	72.89
DeLeo 2010	Nmol/L	3 m	EE/DRSP 10 EE/DSG 10	129	13	180	13
Kriplani 2010	Nmol/L	6 m	EE/DRSP 29 EE/DSG 29	60	41.0	62.3	50.3

7.8.2. Forest Plot COCP with 3rd vs. 4th generation progestin for SHBG (nmol/L)



7.8.3. Funnel plot for assessment of publication bias



OUTCOME 7.9 ANDROSTENEDIONE
7.9.1. Individual study data table

OUTCOME: Androstenedione							
COMPARISON (if applicable): COCP with different sorts of gestagens							
Author, year	**Unit**	**Time point**	**N**	**EE/DSG Mean**	**EE/DSG SD**	**EE/DRSP Mean**	**EE/DRSP SD**
DeLeo 2010	Pg/ml	3 m	EE/DRSP 10 EE/DSG 10	1400	330	850	210

OUTCOME 7.10 DHEAS
7.10.1. Individual study data table

OUTCOME: DHEAS							
COMPARISON (if applicable): COCP with different sorts of gestagens							
Author, year	**Unit**	**Time point**	**N**	**EE/DSG Mean**	**EE/DSG SD**	**EE/DRSP Mean**	**EE/DRSP SD**
DeLeo 2010	μg/ml	3 m	EE/DRSP 10 EE/DSG 10	1.37	0.5	0.9	0.5

OUTCOME 7.11 INSULIN
7.11.1. Individual study data table

OUTCOME: Insulin							
COMPARISON (if applicable): COCP with different sorts of gestagens							
Author, year	**Unit**	**Time point**	**N**	**EE/DSG Mean**	**EE/DSG SD**	**EE/DRSP Mean**	**EE/DRSP SD**
Bhattacharya 2012	Mean change from baseline	12 m	EE/DSG 49 EE/CPA 51 EE/DRSP 50	-0.02	17.35	2.78	17.27
Kriplani 2010	μU/ml	6 m	EE/DRSP 29 EE/DSG 29	11.7	6.2	8.7	3.6

OUTCOME 7.12 GLUCOSE
7.12.1. Individual study data table

OUTCOME: Glucose							
COMPARISON (if applicable): COCP with different sorts of gestagens							
Author, year	**Unit**	**Time point**	**N**	**EE/DSG Mean**	**EE/DSG SD**	**EE/DRSP Mean**	**EE/DRSP SD**
Bhattacharya 2012	Mean change from baseline	12 m	EE/DSG 49 EE/DRSP 50	-4.28	11.66	-2.11	14.02
Kriplani 2010	Mg/dl	6 m	EE/DRSP 29 EE/DSG 29	81.9	6.1	80.6	6.2

OUTCOME 7.13 HOMA-IR
7.13.1. Individual study data table

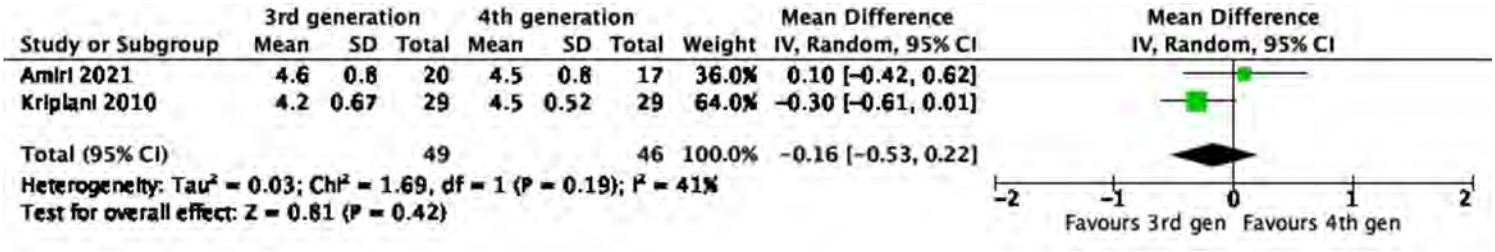
OUTCOME: HOMA-IR							
COMPARISON (if applicable): COCP with different sorts of gestagens							
Author, year	**Unit**	**Time point**	**N**	**EE/DSG Mean**	**EE/DSG SD**	**EE/DRSP Mean**	**EE/DRSP SD**
Bhattacharya 2012	Mean change from baseline	12 m	EE/DSG 49 EE/DRSP 50	-0.28	3.98	0.42	3.82
Kriplani 2010	-	6 m	EE/DRSP 29 EE/DSG 29	1.8	1.3	1.7	0.7

OUTCOME 7.14 TOTAL CHOLESTEROL

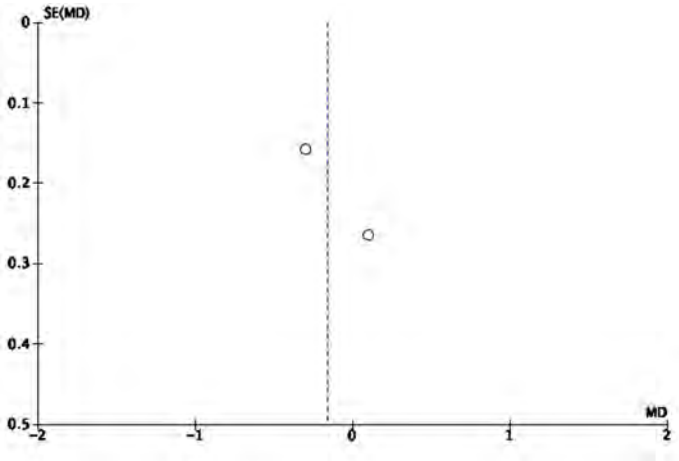
7.14.1. Individual study data table

OUTCOME: Cholesterol							
COMPARISON (if applicable): COCP with different sorts of gestagens							
Author, year	**Unit**	**Time point**	**N**	**EE/DSG Mean**	**EE/DSG SD**	**EE/DRSP Mean**	**EE/DRSP SD**
Amiri 2021	Mmol/L	6m	EE/DSG: 20 EE/DRSP: 17	4.6	0.8	4.5	0.8
Kriplani 2010	Mmol/L	6 m	EE/DRSP 29 EE/DSG 29	4.2	0.67	4.5	0.52

7.14.2. Forest Plot COCP with 3rd vs. 4th generation progestin for cholesterol (mmol/L)



7.14.3. Funnel plot for assessment of publication bias

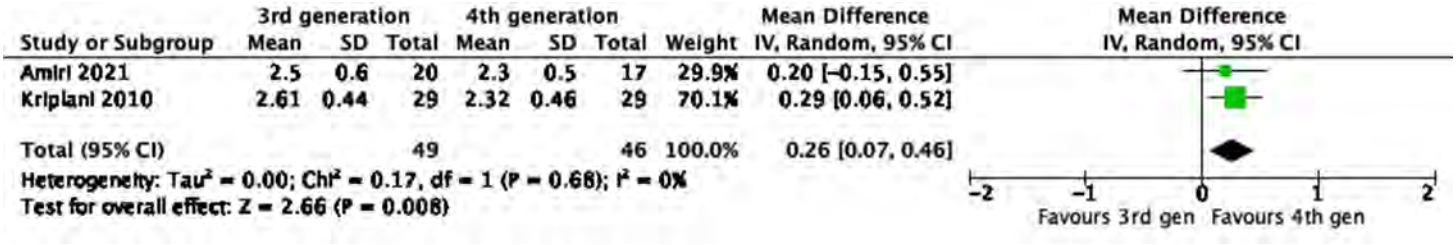


OUTCOME 7.15 LDL

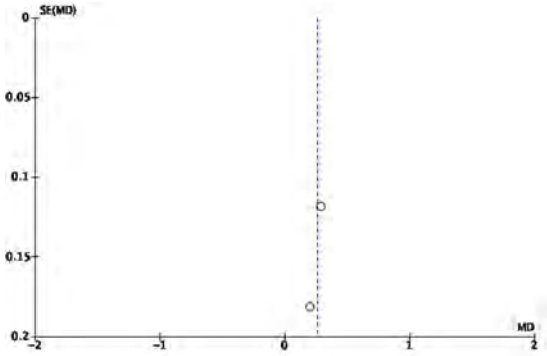
7.15.1. Individual study data table

OUTCOME: LDL							
COMPARISON (if applicable): COCP with different sorts of gestagens							
Author, year	**Unit**	**Time point**	**N**	**EE/DSG Mean**	**EE/DSG SD**	**EE/DRSP Mean**	**EE/DRSP SD**
Amiri 2021	Mmol/L	6m	EE/DSG: 20 EE/DRSP: 17	2.5	0.6	2.3	0.5
Kriplani 2010	Mmol/L	6 m	EE/DRSP 29 EE/DSG 29	2.61	0.44	2.32	0.46

7.15.2. Forest Plot COCP with 3rd vs. 4th generation progestin for LDL (mmol/L)



7.15.3. Funnel plot for assessment of publication bias

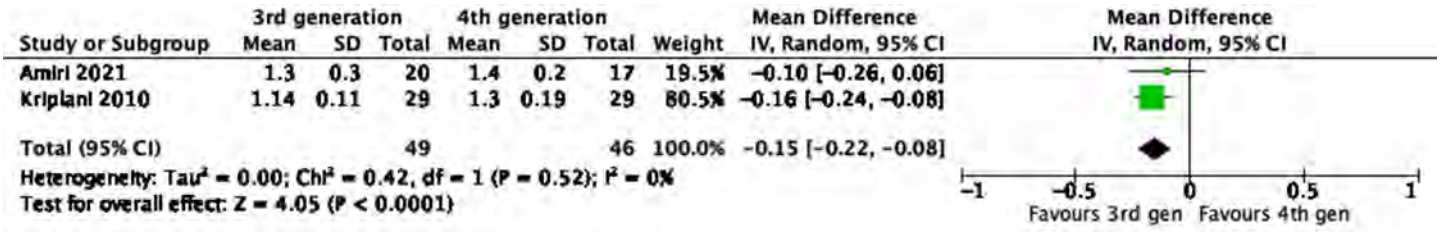


OUTCOME 7.16 HDL

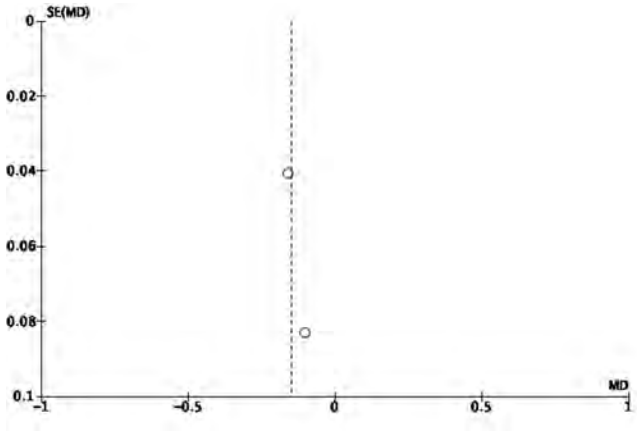
7.16.1. Individual study data table

OUTCOME: HDL							
COMPARISON (if applicable): COCP with different sorts of gestagens							
Author, year	**Unit**	**Time point**	**N**	**EE/DSG Mean**	**EE/DSG SD**	**EE/DRSP Mean**	**EE/DRSP SD**
Amiri 2021	Mmol/L	6m	EE/DSG: 20 EE/DRSP: 17	1.3	0.3	1.4	0.2
Kriplani 2010	Mmol/L	6 m	EE/DRSP 29 EE/DSG 29	1.14	0.11	1.3	0.19

7.16.2. Forest Plot COCP with 3rd vs. 4th generation progestin for HDL (mmol/L)



7.16.3. Funnel plot for assessment of publication bias



OUTCOME 7.17 ADVERSE EFFECTS

Summarized below. The one major adverse event reported, was a case of severe lower limb pain, where Doppler showed no sign of thrombosis, but the patient discontinued treatment.

	Study	3rd generation	4th generation
Spottings	DeLeo 2010	1/10 (GSD) 1/10 (DSG)	0/10
	Kriplani 2010 (at three months)	1/30	0/30
	Amiri 2020 (at sixth month	1/33	7 /33
Headache	DeLeo 2010	2/10 (GSD) 1/10 (DSG)	2/10
	Kriplani 2010	0/29	1/29
	Amiri 2020 (at sixth month)	2 /33	3 /33
Mastalgia	DeLeo 2010	1/10 /GSD) 2/10 (DSG)	1/10
	Kriplani 2010 (at one months)	2/29	2/29
	Amiri 2020 (at sixth month)	8 /33	3 /33
Nausea	Kriplani 2010	5/29	3/29
	Amiri 2020 (at sixth month)	2 /33	4/33
Nausea and headache	Bhattacharya 2012	1/54-58	1/55-57
Abdominal pain	Kriplani 2010	6/29	5/29
Bloating	Kriplani 2010	4/29	0/29
	Bhattacharya 2012	3/54-58	0/55-57
Rise of blood pressure	Bhattacharya 2012	1/54-58	0/55-57
Altered liver function tests	Bhattacharya 2012	0/54-58	1/55-57
Dizziness	Amiri 2020 (at sixth month)	1/33	3/33
Major adverse events	DeLeo 2010	0/10	0/10
	Kriplani 2010	1/29	0/29
	Bhattacharya 2012	0/58	0/57
	Amiri 2021	0/30	0/30

Comparison 8: COCP vs. EE/CPA

- **EVIDENCE SUMMARY:**

Ten studies were identified comparing convention COCPs and EE/CPA. Six had a high risk of bias, one moderate and three low risk of bias. Two of the studies involved adolescents, Mastorakos 2012 and Mastorakos 2016, the rest included adults. Study duration of the included studies were 3-12 months. The included studies are described in the table below.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

The meta-analysis showed that the combination EE/CPA, compared with convention COCPs, had a beneficial effect with lower BMI and lower total testosterone levels with a low certainty of evidence in the overall analysis. Regarding metabolic parameters, EE/CPA treatment resulted in higher cholesterol and LDL (very low certainty). The systematic review favoured EE/CPA in treatment of hirsutism, with low certainty of evidence.
In the subgroup analysis, total testosterone levels were lower after EE/CPA treatment in adults (low certainty) but not in adolescents (very low certainty). For androstenedione, EE/CPA resulted in lower levels compared with COCP in adults, but not in adolescents, with a very low certainty of evidence. Regarding adverse effects, the outcome was not assessed systematically, but no major adverse effects were reported.

Included studies:

Study ID	ROB	Interventions	Setting Duration	N	Mean age	Mean BMI	PCOS	Age at menarche	Smoker	Comments	Outcomes
Amiri 2020-1 (7)	High	1: EE 30 µg +LNG 0.15 mg, then EE 30 µg +DSG 150 µg 2: EE 30 µg + LNG 0.15 mg, then EE 30 µg +CPA 2 mg 3: EE 30 µg + LNG 0.15 mg, then EE 30 µg +DRSP 3 mg 4: EE 30 µg +DSG 150 µg, then EE 30 µg +LNG 0.15 mg 5: EE 30 µg +CPA 2 mg, then EE 30 µg +LNG 0.15 mg 6: EE 30 µg +DRSP 3 mg, then EE 30 µg +LNG 0.15 mg	Iran 6 months	*EE/LNG: 26* *EE/DSG: 26* *EE/CPA: 20* *EE/DRSP: 16*	NR, aged 18-45	NR in article, need to look at suppl tables	AES	NR	NR	Cross over,	FAI, m-FG, weight, BMI, WHR, SHBG, DHEAS, glucose, , HOMA, TG, chol, LDL, HDL,
Amiri 2021 (8)	High	1: OCs containing Ethinyl estradiol (EE) 30 µg + LNG 0.15 mg; 2: OCs containing EE 30 µg + DSG 150 µg; 3: OCs containing EE 35 µg + CPA 2 mg; and Group 4: OCs containing EE 30 µg + DRSP 3 mg.	Iran 6m	1=23 2=20 3=28 4=17	1. 28.5 ± 5.6 2. 27.6 ± 4.5 3. 30.7 ± 6.0 4. 30.0 ± 6.1	1. 25.5 ± 4.0 2. 25.7 ± 3.9 3. 26.0 ± 5.4 4. 25.8 ± 5.3	AES	NR	Excluded		BMI, WHR, TG, Chol, LDL, HDL
Bhattacharya 2012 (9)	Low[1]	1) 30ug EE + 150ug DSG 21/7 2) 35ug EE + 2000ug CPA 21/7 3) 30ug EE + 3000ug DRSP 21/7	India 12 months	1: 49 2: 51 3: 50	1: 22.24±4.47 2: 22.32±4.17 3: 22.33±4.76	1: 25.41±4.49 2: 26.41±3.81 3: 26.47±4.65	AES	NR	NR	MEAN DIFFERECES between before/after treatment	BMI, WHR, FG score, TT, SHBG, FAI, glucose, insulin, HOMA
Cagnacci 2006 (11)	High[1]	1) Biphasic - 40µg EE + 25µg DSG first 7 days, then 14 days 30µg EE+125µg DSG	NR	1:10 2: 10	1: 22.7±SE 0.7	1: 23.5±SE 1.9	Author determined	NR	NR		BMI, WHR, glucose, insulin,

		2) Monophasic - 35µg EE + 2 mg CPA	6 months		2: 21.8±SE 0.8	2: 22.6±SE 0.9	criteria (similar to Rotterdam)				
Christakou 2014 (12)	Mod	1: 35ug EE +2 mg CPA 2: 30 ug EE + 3 mg DRSP 3: met 1700 mg/day	Greece 6 months	1: 38 2: 36 3:35	1: 22±0.6 2: 23.2±0.6 3: 21.5±0.5	1: *21.80±0.35* *2: 22.37±0.48* *3: 23.03±0.67*	NIH	NR	All non-smokers		BMI, HOMA, TT, SHBG, FAI, CRP
Fonseka 2020 (2)	Low	1: EE/CPA (Diane-35, 2: EE/DES (Fermion) 3: metformin + EE/CPA 4: metformin + EE/DES	Sri Lanka 12 months	1:20 2:23 3: 26 6: 30	1: 23.35± 5.10 2: 22.39 ± 6.45 3: 24.81 ± 6.24 4. 27.90 ± 6.89	1: 28.27 ±6.94 2: 26.74 ±4.88 3: 27.93 ±4.89 4: 27.20 ± 4.28	Rott	NR	NR		mFG score
Mastorakos 2002 (13)	High	1: EE 30 µg + 0.15 mg DSG 2: EE 35 µg + 2 mg CPA	Greece 12 months	1:14 2: 14	*1: 17.5*±0.5 2: 17.5±0.4	*1:25.5*±1.8 2:24.8±1.1	NIH	NR	NR	Adolescents	TT, fT, A4, DHEAS, SHBG, chol, HDL, LDL
Mastorakos 2006 (14)	Low[1]	*1) 0.15mg DSG + 0.030 mg EE 21/7* *2) 2 mg CPA + 0.035mg EE 21/7*	Greece 12 months	*1: 18* *2: 18*	*1: 17.01±0.73* *2: 17.16± 0.63 (SE)*	*1: 25.8±1.81* *2: 0.73± 0.06 (SE)*	NIH	NR	NR	Adolescents	Glucose, insulin, HOMA, OGTT
Panidis 2011 (15)	High	1: 35 µg EE + 2 mg CPA 2: 3 mg DRSP/30 mcg EE 3: met 1700mg/day	Greece 6 months	1=15 2=15 3=15	1: 20.67 ± 4.13 2: 22.00 ± 2.07 3: 20.53 ±3.09	1: 21.04 + 1.97 2: 21.69 + 2.33 3: 21.83 + 1.73	NIH	NR	NR	Randomisation was non-blind and was based on patients' chronological presence at the outpatient endocrine infirmary	BMI, HOMA, glucose, insulin, TT, A4, DHEAS, SHBG, FAI
Taheripanah 2010 (16)	High	*1) OCP - no details* *2) EE + CPA (Diane) - no details*	Iran 3 months	*1: 30* *2: 30*	*1: 22.9±0.5* *2: 23.97±0.61*	*1: 21.17±2.06* *2: 21.73±2.76*	Rott	NR	NR	Exclude? Kind of OCP not reported	FG score, fT, DHEAS,

Outcomes where a meta-analysis could not be performed are reported narratively:

Outcome	Results	Favours	Certainty	Importance
Weight	No studies			CRITICAL

Hirsutism	Bhattacharya 2012 reported mean change in FG score, -1.69 ± 5.69 for a 3rd generation COCP vs. -5.29 ± 5.88 for EE/CPA, p=0.003. Kahraman 2014 reported median change in % from baseline, −18 (−72 to 30) for a 4th generation COCP vs −35 (−71 to 10)), p=0.04. Fonseka reported mean (SD) 15.09 (5.26) vs. 14.25 (8.26)	EE/CPA	⊕⊕◯◯ LOW [2,4]	CRITICAL
Free testosterone	Kahraman 2014 reported median % change, −50 (−77 to 85) for a 4th generation COCP vs −42 (−79 to 164 for EE/CPA, p=0.286. Mastorakos 2002 reported means after treatment, 5.79 ± 2.58 for COCP vs. 6.03 ± 1.12 pmol/L for EE/CPA, p value not reported.	Unable to make judgement	⊕◯◯◯ VERY LOW [1,2,3]	IMPORTANT
OGTT	Kahraman 2014 reported median % change (range) 5 (−42 to 66) vs. 17 (−23 to 76), p=0.339 at 2h glucose levels. Mastorakos 2006 reported ΔAUCI as mean ± SE for COCP 7,856.25 ± 1,083.34 vs. 10,567.27 ± 849.18, p not reported.	No difference	⊕◯◯◯ VERY LOW [1,2]	IMPORTANT
Triglycerids	Amiri 2021 reported median (IQR) for COCP 1.3 (0.8-1.4) vs. 1.6 (1.2-2.1) after EE/CPA, p value not reported. Kahraman reported median % change +43 (−60 to 180) after COCP and +53 (−49 to 502) after EE/CPA, p=0.361.	No difference	⊕◯◯◯ VERY LOW [1,2]	IMPORTANT
CRP	Christakou 2014 reported mean ± SD after COCP 1.93 ± 1.44 mg/l vs. 2.63 ± 0.73 after EE/CPA. Kahraman reported median % change +31 (−91 to 8,662) vs. +174 (−96 to 2,656), p=0.610.	Unable to make judgement	⊕◯◯◯ VERY LOW [1,2]	IMPORTANT

1. Downgraded twice due to high risk of bias
2. Downgraded once for indirectness since outcomes reported in different ways, not possible to combine
3. Downgraded once for imprecision, few study participants
4. Downgraded once for risk of bias

Adverse effects: No serious adverse effects were reported.

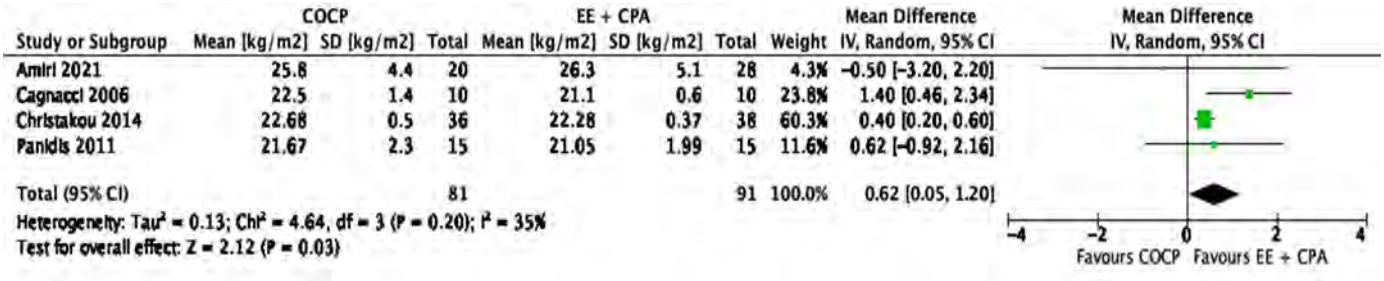
	Study	COCP	EE/CPA
Spottings	Amiri 2020 (at 6 months)	1/33	5/34
Absence of withdrawal bleeding	Bhattacharya 2012	0/58	1/53-56
Nausea and/or vomiting	Amiri 2020 (at 6 months)	2/33	5/34
	Fonseka 2020	0/25	1/25
Headache	Amiri 2020 (at 6 months)	2/33	5/34
	Fonseka 2020	0/25	1/25
Nausea and heandache	Bhattacharya 2012	1/54-58	0/56
Dizziness	Amiri 2020 (at 6 months)	1/33	3/34
	Fonseka 2020	0/25	1/25
Breast tenderness	8 Amiri 2020 (at 6 months)	8/33	4/34
	Bhattacharya 2012	0/58	1/53-56
	Fonseka 2020	0/25	1/25
Bloatedness	Bhattacharya 2012	3/54-58	0/56
Rise of blood pressure	Bhattacharya 2012	1/54-58	0/56
Joint stiffness	Fonseka 2020	0/25	1/25

OUTCOME 8.1 BMI

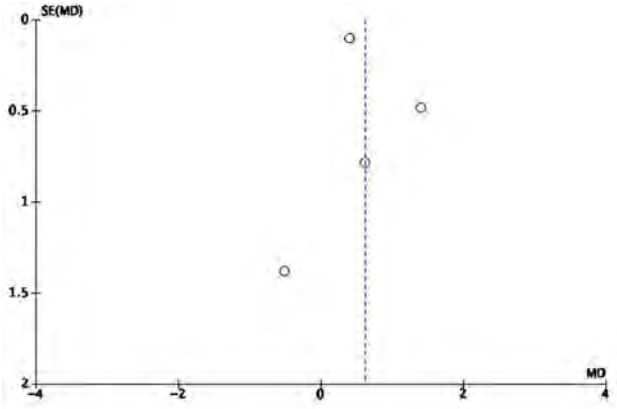
8.1.1 Individual study data table

OUTCOME: BMI										**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): COCP with different sorts of gestagens										
Author, year	**Time point**	**N**	**EE/LNG Mean**	**EE/LNG SD**	**EE/DSG Mean**	**EE/DSG SD**	**EE/CPA Mean**	**EE/CPA SD**	**EE/DRSP Mean**	**EE/DRSP SD**
Amiri 2020	6 m	*EE/LNG: 26* *EE/DSG: 26* *EE/CPA: 20* *EE/DRSP: 16*	EE/LNG: Ref data show mean difference adjusted for baseline values, and are reported as β regression coefficients (95%CI), p value EE/DSG: -0.3 (-0.7; 0.1) 0.163 EE/DRSP: -0.3 (-0.6; -0.03) 0.032 EE/CPA: -0.6 (-1.5: 0.2) 0.130							
Amiri 2021	6m	*EE/LNG: 23* *EE/DSG: 20* *EE/CPA: 28* *EE/DRSP: 17*	25.2	4.0	25.8	4.4	26.3	5.1	26.1	5.7
Bhattacharya 2012	12 m	EE/DSG 49 EE/CPA 51 EE/DRSP 50			-0.45	6.75	-0.59	4.76	0.11	5.54
Cagnacci 2006	6 m	EE/DSG 10 EE/CPA 10			22.5	1.4	21.1	0.6		
Christakou 2014	6 m	EE/CPA 38 EE/DRSP 36					22.28	0.37	22.68	0.50
Kahraman 2014	12 m	EE/CPA 19 EE/DRSP 20					Median change *−1 (−12 to 6)*		Median change *−1 (−9 to 17)*	
Panidis 2011	6 m	EE/CPA 15 EE/DRSP 15					21.05	1.99	21.67	2.30

8.1.2. Forest Plot COCP vs. EE/CPA for BMI



8.1.3. Funnel plot for assessment of publication bias



OUTCOME 8.2 WEIGHT

8.2.1 Individual study data table

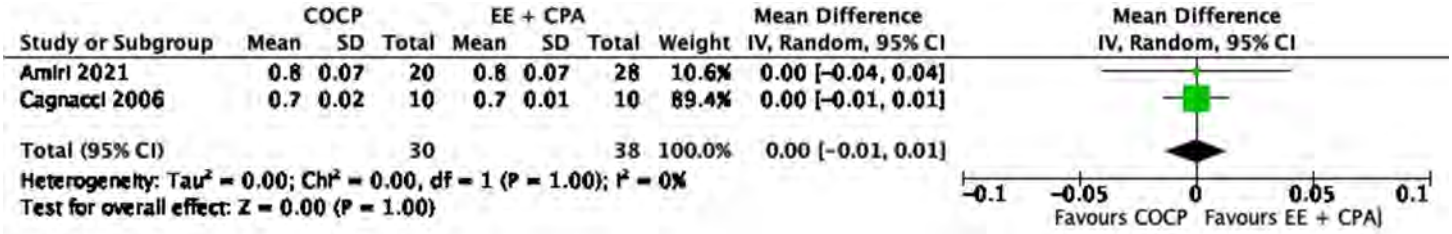
OUTCOME: BMI					
COMPARISON (if applicable): COCP with different sorts of gestagens					**Comments**
Study ID	EE+LNG (2nd generation)	EE+DSG (3rd generation)	EE+DRSP (4th generation)	EE+CPA	
Amiri 2020	Ref	-0.9 (-2.1; 0.3) 0.130	-0.9 (-1.7; -0.03) 0.044	1.7 (-4.5; 0.5) 0.114	GEE model: data show mean difference adjusted for baseline values, and are reported as β regression coefficients (95%CI), p value

OUTCOME 8.3 WHR

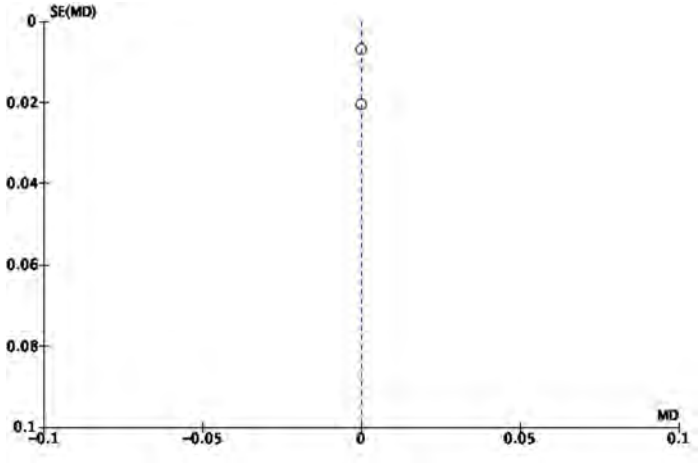
8.3.1 Individual study data table

OUTCOME: WHR											
OUTCOME TYPE: Continuous											
COMPARISON (if applicable): COCP with different sorts of gestagens											
Author, year	**Unit**	**Time point**	**N**	**EE/LNG Mean**	**EE/LNG SD**	**EE/DSG Mean**	**EE/DSG SD**	**EE/CPA Mean**	**EE/CPA SD**	**EE/DRSP Mean**	**EE/DRSP SD**
Amiri 2020	GEE model: data show mean difference adjusted for baseline values, and are reported as β regression coefficients (95%CI), p value			Ref		0.08 (-0.02; 0.01) 0.397		0.02 (-0.03; 0.0) 0.055		0.002 (-0.01; 0.1) 0.787	
Amiri 2021	-	6m	*EE/LNG: 23 EE/DSG: 20 EE/CPA: 28 EE/DRSP: 17*	0.9	0.07	0.8	0.07	0.8	0.07	0.8	0.09
Bhattacharya 2012	Mean change from baseline	12 m	EE/DSG 49 EE/CPA 51 EE/DRSP 50			0.00	0.08	-0.02	0.08	0.02	0.09
Cagnacci 2006		6 m	EE/DSG 10 EE/CPA 10			0.7	0.02	0.7	0.01		
Kahraman 2014		12 m	EE/CPA 19 EE/DRSP 20					Median change *0 (−11 to 14)*		Median change *−4 (−31 to 35)*	

8.3.2. Forest Plot COCP vs. EE/CPA for WHR



8.3.3. Funnel plot for assessment of publication bias



OUTCOME 8.4 HIRSUTISM

8.4.1 Individual study data table

OUTCOME: Hirsutism										**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): COCP with different sorts of gestagens										
Author, year	**Unit**	**Time point**	**N**	**EE/DSG Mean**	**EE/DSG SD**	**EE/CPA Mean**	**EE/CPA SD**	**EE/DRSP Mean**	**EE/DRSP SD**	**Comments**
Bhattacharya 2012	Mean change from baseline FG score	12 m	EE/DSG 49 EE/CPA 51 EE/DRSP 50	-1.69	5.69	-5.29	5.88	-2.12	6.58	CPA vs desogestrel significant (post hoc P..003). CPA vs drospirenone significant (post hoc P..02).
Fonseka 2020	FG score	12 m	EE/DSG 23 EE/CPA 20	15.09	5.26	14.25	8.26			
Fonseka 2020	VAS	12 m	EE/DSG 23 EE/CPA 20	48.3	21.9	45.0	24.4			
Kahraman 2014		12 m	EE/CPA 19 EE/DRSP 20			Median % change *−35 (−71 to 10))*		Median change *−18 (−72 to 30)*		P 0.04

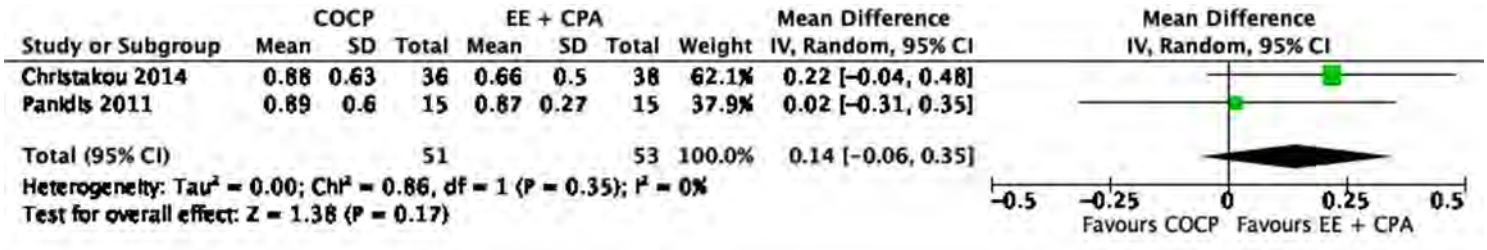
OUTCOME 8.5 FAI

8.5.1 Individual study data table

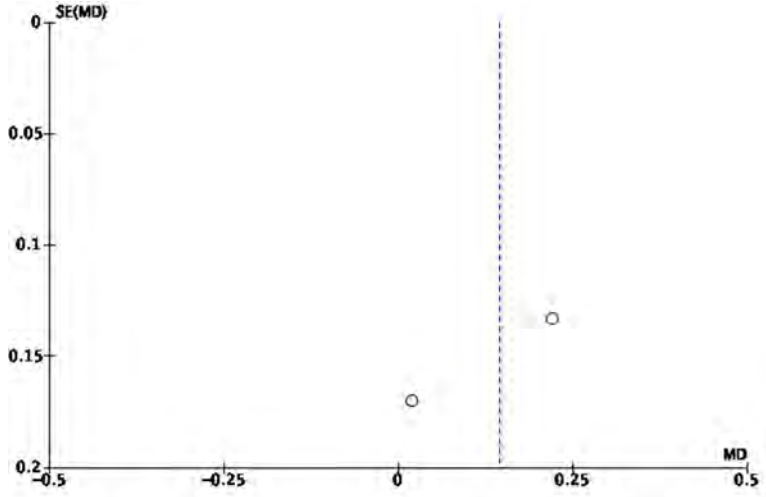
OUTCOME: FAI										**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): COCP with different sorts of gestagens										
Author, year	**Unit**	**Time point**	**N**	**EE/DSG Mean**	**EE/DSG SD**	**EE/CPA Mean**	**EE/CPA SD**	**EE/DRSP Mean**	**EE/DRSP SD**	**Comments**
Amiri 2020		6 m	*EE/LNG: 26* *EE/DSG: 26* *EE/CPA: 20* *EE/DRSP: 16*	EE/LNG: Ref data show mean difference adjusted for baseline values, and are reported as β regression coefficients (95%CI), p value EE/DSG -1.7 (-2.3; -1.0) <0.001 EE/DRSP: -2.0 (-2.6; -1.4) <0.001 EE/CPA: -1.8 (-2.4; -1.1) <0.001						GEE model:
Bhattacharya 2012	Mean change from baseline	12 m	EE/DSG 49 EE/CPA 51 EE/DRSP 50	-5.58	9.15	-10.57	7.93	-7.89	9.13	Cyproterone acetate vs desogestrel significant (post hoc P..001).

Christakou 2014		6 m	EE/CPA 38 EE/DRSP 36			0.66	0.50	0.88	0.63	
Kahraman 2014		12 m	EE/CPA 19 EE/DRSP 20							Median change −77 *(−97 to 510)* −79 *(−96 to 56) p=0.779*
Kriplani 2010		6 m	EE/DRSP 29 EE/DSG 29	3.9	1.9			2.8	4.9	
Panidis 2011		6 m	EE/CPA 15 EE/DRSP 15			0.87	0.27	0.89	0.60	

8.5.2. Forest Plot COCP vs EE/CPA for FAI



8.5.3. Funnel plot for assessment of publication bias



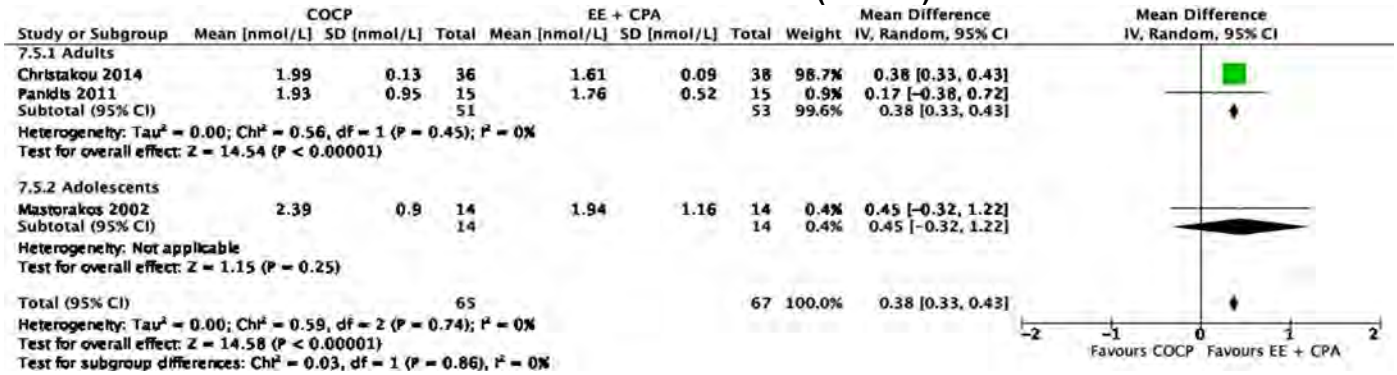
OUTCOME 8.6 TOTAL TESTOSTERONE

8.5.1 Individual study data table

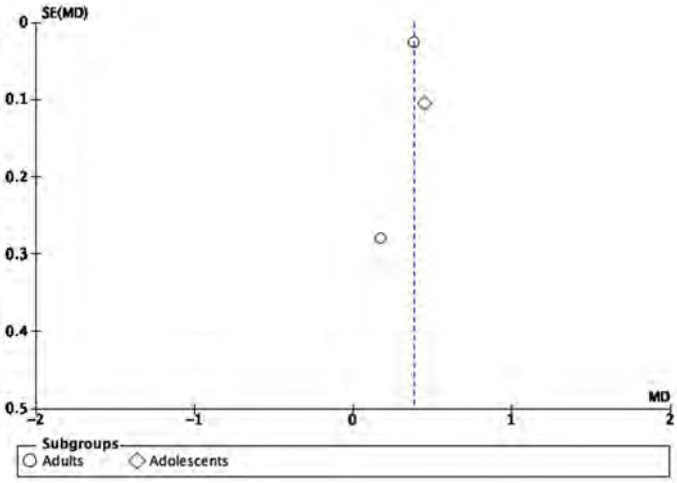
OUTCOME: Total testosterone									
COMPARISON (if applicable): COCP with different sorts of gestagens									
Author, year	**Unit**	**Time point**	**N**	**EE/DSG Mean**	**EE/DSG SD**	**EE/CPA Mean**	**EE/CPA SD**	**EE/DRSP Mean**	**EE/DRSP SD**
Amiri 2020	GEE model	6 m	*EE/LNG: 26* *EE/DSG: 26* *EE/CPA: 20* *EE/DRSP: 16*	EE/LNG: Ref data show mean difference adjusted for baseline values, and are reported as β regression coefficients (95%CI), p value EE/DSG: -0.02 (-0.03; 0.21) 0.917 EE/DRSP: -0.03 (-0.03; 0.28) 0.810 EE/CPA: -0.004 (-0.03 (0.35) 0.985					

Bhattacharya 2012	Mean change from baseline	12 m	EE/DSG 49 EE/CPA 51 EE/DRSP 50	-0.10	0.39	-0.03	0.42	-0.06	0.32
Christakou 2014	Nmol/L	6 m	EE/CPA 38 EE/DRSP 36			1.61	0.09	1.99	0.13
Kahraman 2014		12 m	EE/CPA 19 EE/DRSP 20			Median change *−16 (−78 to 125) −39 (−84 to 43) p=0.087*			
Mastorakos 2002 Adolescents	Nmol/L	12 m	1:14 2: 14	2.39	0.9	1.94	1.16		
Panidis 2011	Nmol/L	6 m	EE/CPA 15 EE/DRSP 15			1.76	0.52	1.93	0.95

8.5.2. Forest Plot COCP vs EE/CPA for total testosterone (nmol/L)



8.5.3. Funnel plot for assessment of publication bias



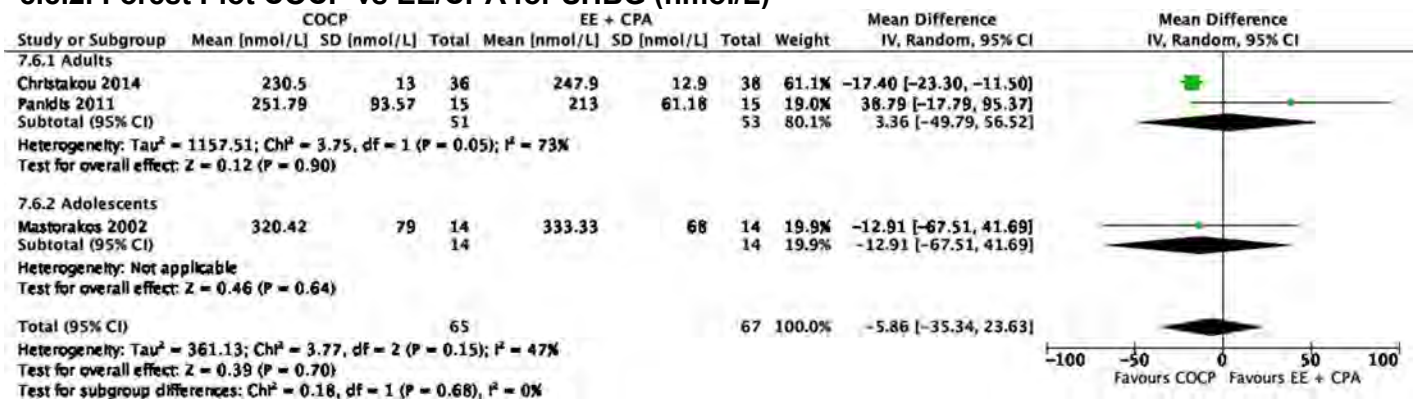
OUTCOME 8.7 FREE TESTOSTERONE
8.7.1 Individual study data table

OUTCOME: Free testosterone								
COMPARISON (if applicable): COCP with different sorts of gestagens								
Author, year	**Unit**	**Time point**	**N**	**EE/DSG Mean**	**EE/DSG SD**	**EE/CPA Mean**	**EE/CPA SD**	**Comments**
Kahraman 2014		12 m	EE/CPA 19 EE/DRSP 20	Median change (%) *−42 (−79 to 164) −50 (−77 to 85) p=0.286*				
Mastorakos 2002	pg/ml	12 m	1:14 2: 14	1.67	0.20	1.74	0.30	Adolescents

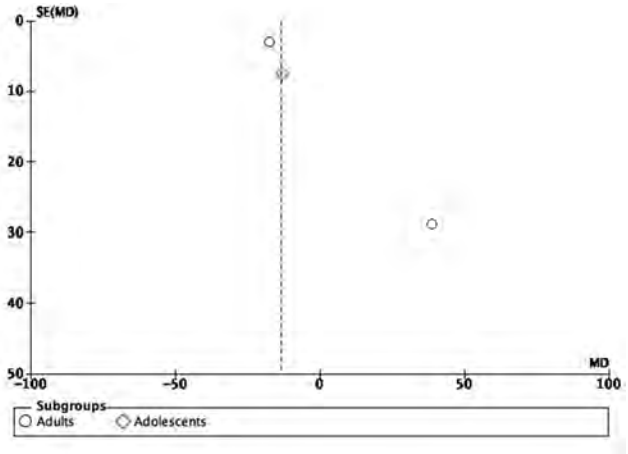
OUTCOME 8.8 SHBG
8.8.1 Individual study data table

OUTCOME: SHBG									
COMPARISON (if applicable): COCP with different sorts of gestagens									
Author, year	**Unit**	**Time point**	**N**	**EE/DSG Mean**	**EE/DSG SD**	**EE/CPA Mean**	**EE/CPA SD**	**EE/DRSP Mean**	**EE/DRSP SD**
Amiri 2020		6 m	*EE/LNG: 26* *EE/DSG: 26* *EE/CPA: 20* *EE/DRSP: 16*	EE/LNG: Ref data show mean difference adjusted for baseline values, and are reported as β regression coefficients (95%CI), p value EE/DSG: 73 (37; 110) <0.001 EE/DRSP: 80 (51; 108) <0.001 EE/CPA: 83 (47; 120) <0.001					
Bhattacharya 2012	Mean change from baseline	12 m	EE/DSG 49 EE/CPA 51 EE/DRSP 50	99.53	67.52	142.91	60.71	131.52	72.89
Christakou 2014	Nmol/L	6 m	EE/CPA 38 EE/DRSP 36			247.90	12.90	230.50	13.00
Kahraman 2014		12 m	EE/CPA 19 EE/DRSP 20			Median % change *+270 (31 to 1,062) +178 (−57 to 897) p=0.238*			
Mastorakos 2002 Adolescents	Nmol/L	12 m	1:14 2: 14	320.42	79	333.33	68		
Panidis 2011	Nmol/L	6 m	EE/CPA 15 EE/DRSP 15			213.00	61.18	251.79	93.57

8.8.2. Forest Plot COCP vs EE/CPA for SHBG (nmol/L)



8.8.3. Funnel plot for assessment of publication bias

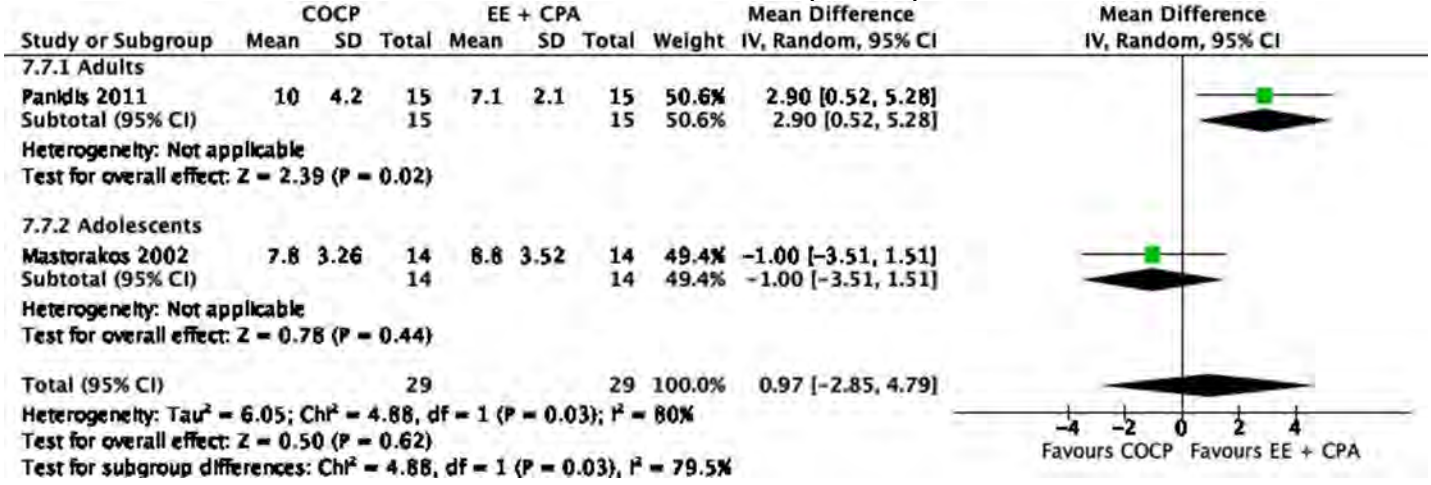


OUTCOME 8.9 ANDROSTENEDIONE

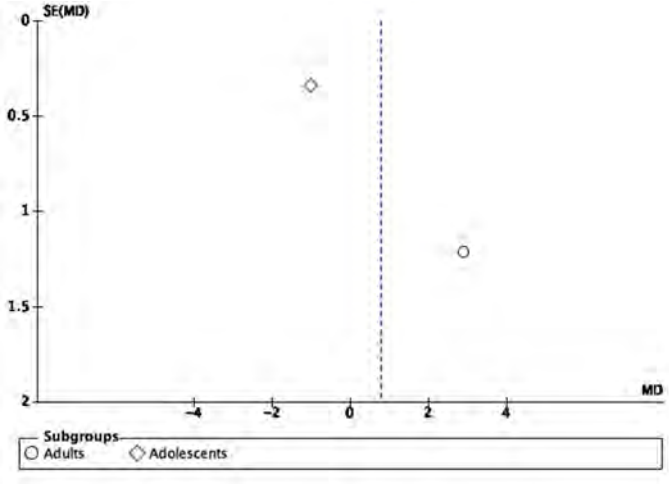
8.9.1 Individual study data table

OUTCOME: Androstendione									
COMPARISON (if applicable): COCP with different sorts of gestagens									
Author, year	**Unit**	**Time point**	**N**	**EE/DSG Mean**	**EE/DSG SD**	**EE/CPA Mean**	**EE/CPA SD**	**EE/DRSP Mean**	**EE/DRSP SD**
Kahraman 2014		12 m	EE/CPA 19 EE/DRSP 20			Median % change *−18 (−47 to 52)* *−29 (−100 to 25) p=0.052*			
Mastorakos 2002 Adolescents	Nmol&L	12 m	1:14 2: 14	7.8	3.26	8.8	3.52		
Panidis 2011	Nmol/L	6 m	EE/CPA 15 EE/DRSP 15			7.1	2.1	10	4.2

8.9.2. Forest Plot COCP vs EE/CPA for androstenedione (nmol/L)



8.9.3. Funnel plot for assessment of publication bias

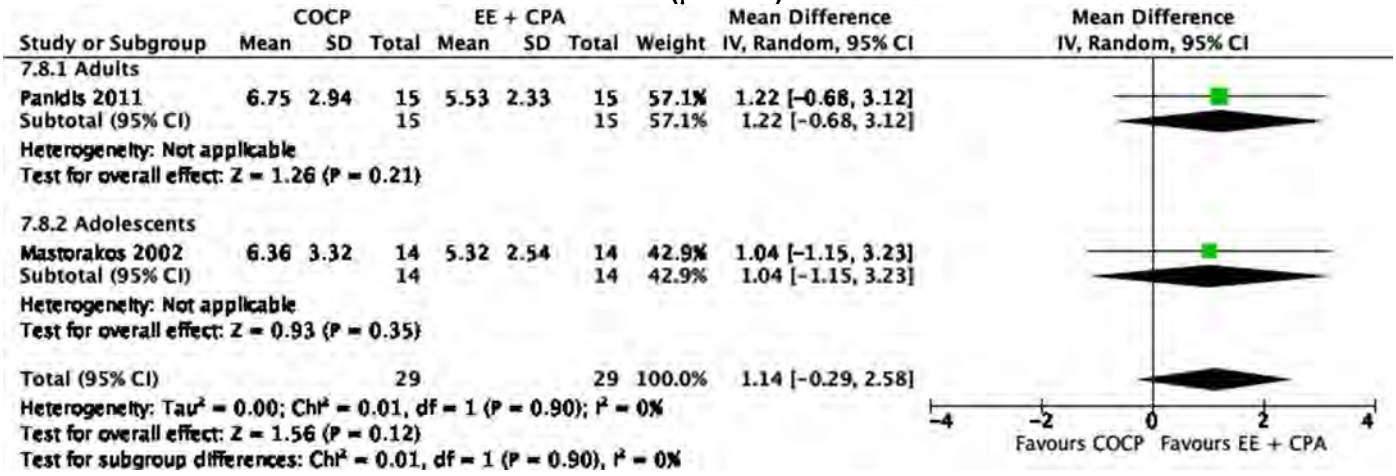


OUTCOME 8.10 DHEAS

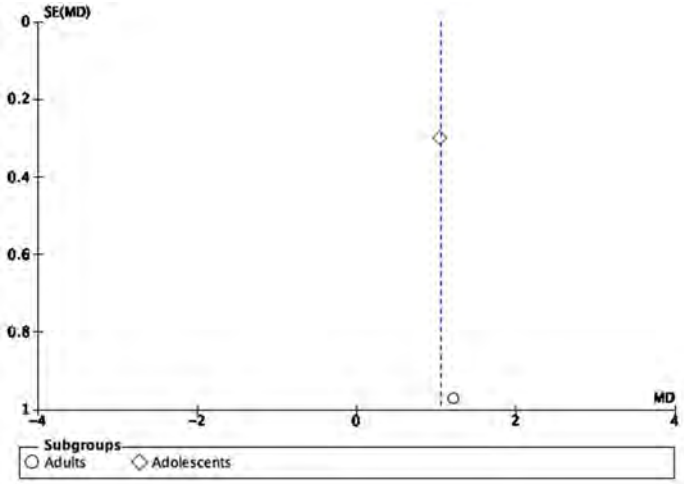
8.10.1 Individual study data table

OUTCOME: DHEAS									
COMPARISON (if applicable): COCP with different sorts of gestagens									
Author, year	**Unit**	**Time point**	**N**	**EE/DSG Mean**	**EE/DSG SD**	**EE/CPA Mean**	**EE/CPA SD**	**EE/DRSP Mean**	**EE/DRSP SD**
Amiri 2020	GEE model	6 m	*EE/LNG: 26* *EE/DSG: 26* *EE/CPA: 20* *EE/DRSP: 16*	EE/LNG: Ref data show mean difference adjusted for baseline values, and are reported as β regression coefficients (95%CI), p value EE/DSG: 0.01 (-0.19; 0.22 0.884 EE/DRSP: 0.04 (-0.09; 0.17) 0.575 EE/CPA: -0.03 (-0.23; 0.26) 0.747					
Kahraman 2014		12 m	EE/CPA 19 EE/DRSP 20			Median % change *−10 (−49 to 63) −32 (−53 to 15) p=0.046*			
Mastorakos 2002 Adolescents	Nmol/L	12 m	1:14 2: 14	6.36	3.32	5.32	2.54		
Panidis 2011	Nmol/L	6 m	EE/CPA 15 EE/DRSP 15			5.53	2.33	6.75	2.94

8.10.2. Forest Plot COCP vs EE/CPA for DHEAS (μmol/L)



8.11.3. Funnel plot for assessment of publication bias

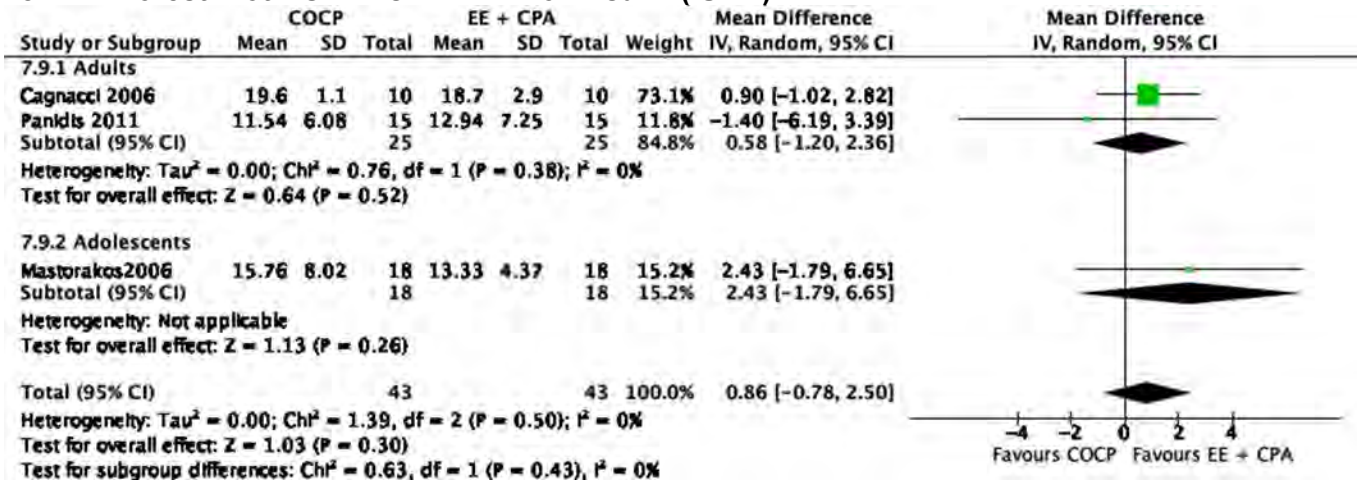


OUTCOME 8.11 INSULIN

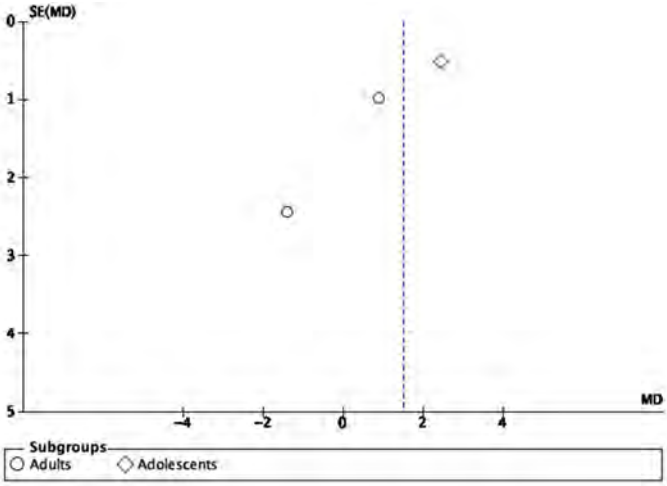
8.11.1 Individual study data table

OUTCOME: insulin							**OUTCOME TYPE:** Continuous		
	COMPARISON (if applicable): COCP with different sorts of gestagens								
Author, year	**Unit**	**Time point**	**N**	**EE/DSG Mean**	**EE/DSG SD**	**EE/CPA Mean**	**EE/CPA SD**	**EE/DRSP Mean**	**EE/DRSP SD**
Bhattacharya 2012	Mean change from baseline	12 m	EE/DSG 49 EE/CPA 51 EE/DRSP 50	-0.02	17.35	6.38	15.22	2.78	17.27
Cagnacci 2006	μU/ml	6 m	EE/DSG 10 EE/CPA 10	19.6	1.1	18.7	2.9		
Kahraman 2014		12 m	EE/CPA 19 EE/DRSP 20			% median change *−0 (−82 to 128) +7 (−85 to 223)* *P=0.603*			
Kriplani 2010	μU/ml	6 m	EE/DRSP 29 EE/DSG 29	11.7	6.2			8.7	3.6
Mastorakos 2006 Adolescents	μU/ml	12 m	1:18 2: 18	15.76	8.02	13.33	4.37		
Panidis 2011	μU/ml	6 m	EE/CPA 15 EE/DRSP 15			12.94	7.25	11.54	6.08

8.11.2. Forest Plot COCP vs EE/CPA for insulin (IU/ml)



8.11.3. Funnel plot for assessment of publication bias

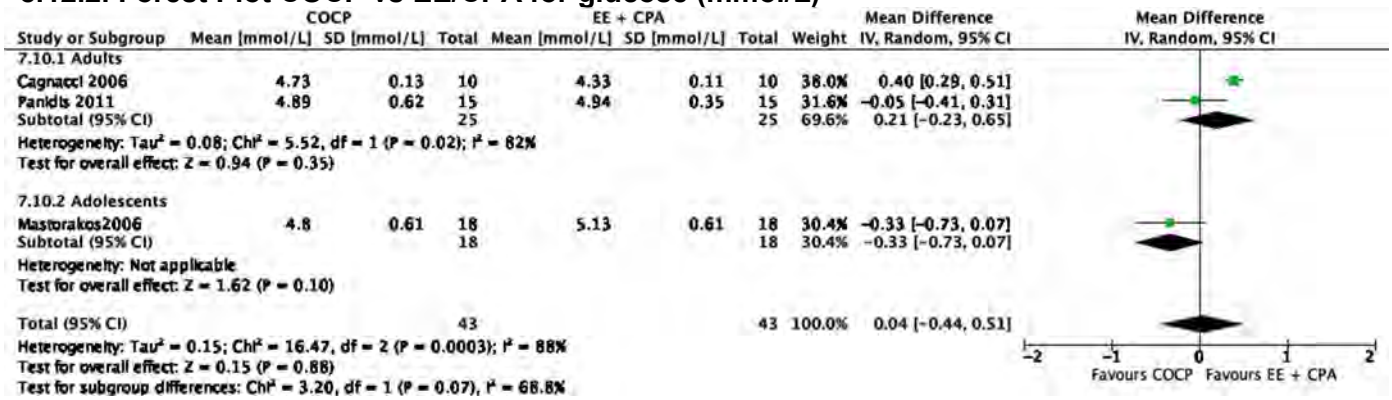


OUTCOME 8.12 GLUCOSE

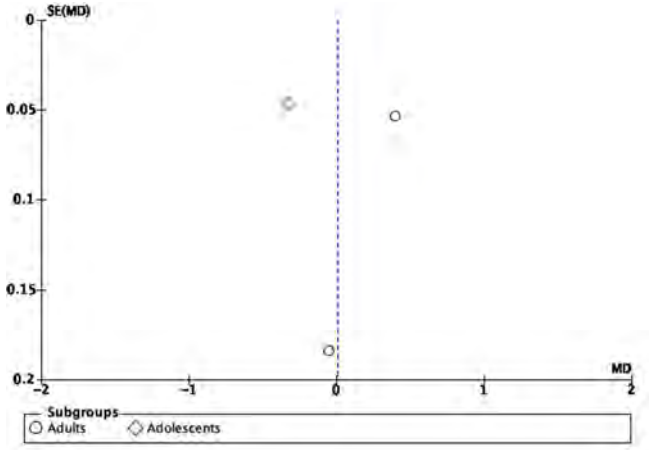
8.12.1 Individual study data table

OUTCOME: fasting glucose							**OUTCOME TYPE:** Continuous		
	COMPARISON (if applicable): COCP with different sorts of gestagens								
Author, year	**Unit**	**Time point**	**N**	**EE/DSG Mean**	**EE/DSG SD**	**EE/CPA Mean**	**EE/CPA SD**	**EE/DRSP Mean**	**EE/DRSP SD**
Bhattacharya 2012	Mean change from baseline	12 m	EE/DSG 49 EE/CPA 51 EE/DRSP 50	-4.28	11.66	-2.46	16.86	-2.11	14.02
Cagnacci 2006	Mmol/L	6 m	EE/DSG 10 EE/CPA 10	4.73	0.13	4.33	0.11		
Kahraman 2014		12 m	EE/CPA 19 EE/DRSP 20			% median change *+0 (−10 to 18) +0 (−15 to 6) p=0.397*			
Mastorakos 2006 Adolescents	Mmol/L	12 m	1:18 2: 18	4.8	0.61	5.13	0.61		
Panidis 2011	Mmol/L	6 m	EE/CPA 15 EE/DRSP 15			4.89	0.62	4.94	0.35

8.12.2. Forest Plot COCP vs EE/CPA for glucose (mmol/L)



8.12.3. Funnel plot for assessment of publication bias

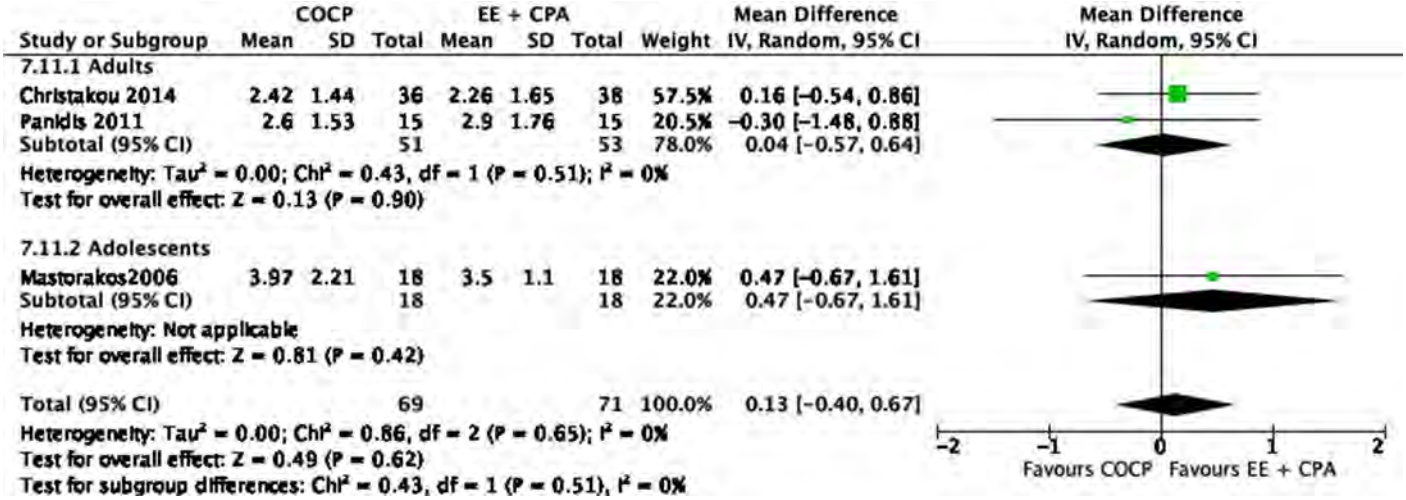


OUTCOME 8.13 HOMA-IR

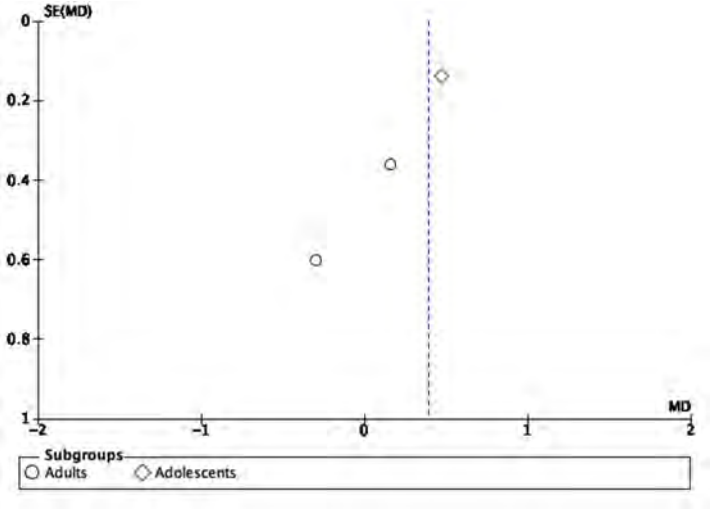
8.13.1 Individual study data table

	OUTCOME: HOMA							**OUTCOME TYPE:** Continuous	
	COMPARISON (if applicable): COCP with different sorts of gestagens								
Author, year	**Unit**	**Time point**	**N**	**EE/DSG Mean**	**EE/DSG SD**	**EE/CPA Mean**	**EE/CPA SD**	**EE/DRSP Mean**	**EE/DRSP SD**
Bhattacharya 2012	Mean change from baseline	12 m	EE/DSG 49 EE/CPA 51 EE/DRSP 50	-0.28	3.98	1.21	4.03	0.42	3.82
Christakou 2014		6 m	EE/CPA 38 EE/DRSP 36			2.26	1.65	2.42	1.44
Kahraman 2014		12 m	EE/CPA 19 EE/DRSP 20			% median change *−18 (−80 to 462) +2 (−71 to 216) p=0.227*			
Kriplani 2010		6 m	EE/DRSP 29 EE/DSG 29	1.8	1.3			1.7	0.7
Mastorakos 2006 Adolescents		12 m	1:18 2: 18	3.97	2.21	3.50	1.1		
Panidis 2011		6 m	EE/CPA 15 EE/DRSP 15			2.90	1.76	2.60	1.53

8.13.2. Forest Plot COCP vs EE/CPA for HOMA-IR



8.13.3. Funnel plot for assessment of publication bias



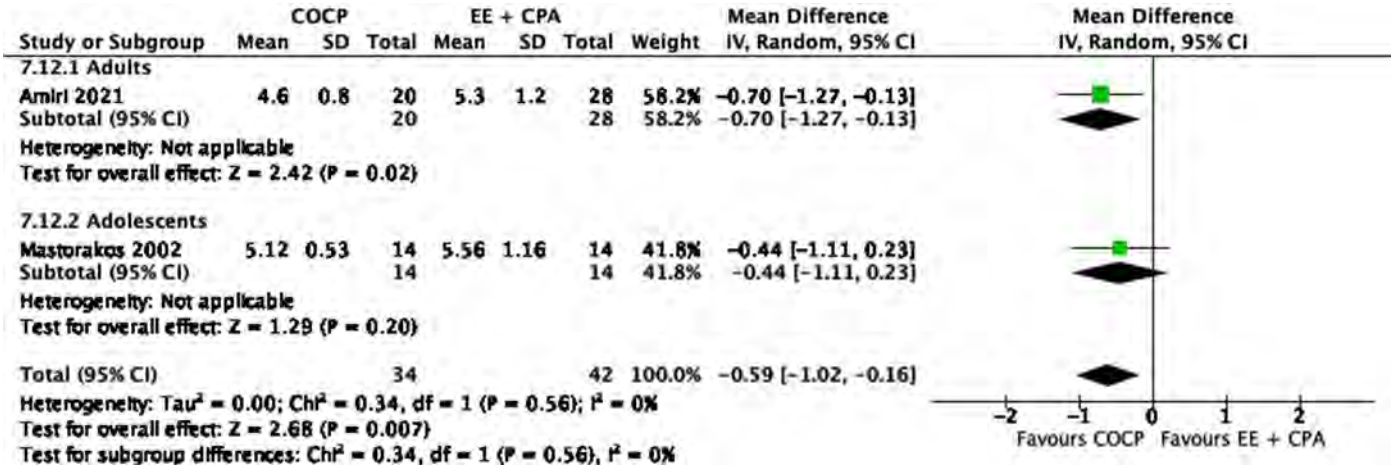
OUTCOME 8.14 OGTT
8.14.1 Individual study data table

OUTCOME: OGTT									**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): COCP with different sorts of gestagens									
Author, year	**Unit**	**Time point**	**N**	**EE/DSG Mean**	**EE/DSG SD**	**EE/CPA Mean**	**EE/CPA SD**	**EE/DRSP Mean**	**EE/DRSP SD**
Kahraman 2014		12 m	EE/CPA 19 EE/DRSP 20			% median change *+17 (−23 to 76) +5 (−42 to 66) p=0.339*			
Mastorakos 2006 Adolescents	ΔAUCI	12 m	1:18 2: 18	*7,856.25*	*SE: 1,083.34*	*10,567.27*	*SE: 849.18*		

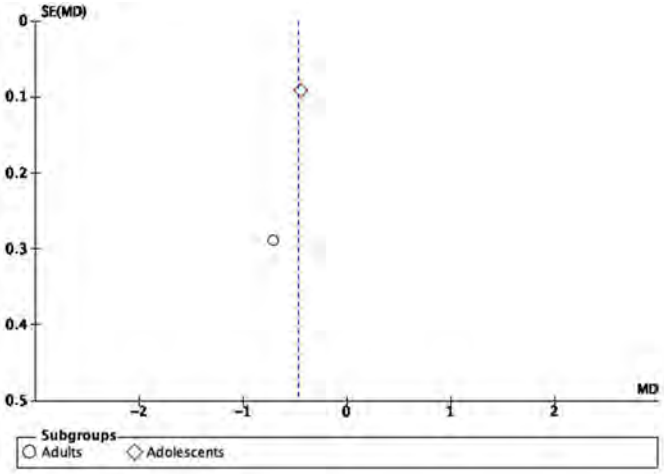
OUTCOME 8.15 CHOLESTEROL
8.15.1 Individual study data table

OUTCOME: Cholesterol											**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): COCP with different sorts of gestagens											
Author, year	**Unit**	**Time point**	**N**	**EE/LNG Mean**	**EE/LNG SD**	**EE/DSG Mean**	**EE/DSG SD**	**EE/CPA Mean**	**EE/CPA SD**	**EE/DRSP Mean**	**EE/DRSP SD**
Amiri 2021	Mmol/L	6m	*EE/LNG: 23 EE/DSG: 20 EE/CPA: 28 EE/DRSP: 17*	4.6	1.1	4.6	0.8	5.3	1.2	4.5	0.8
Kahraman 2014		12 m	EE/CPA 19 EE/DRSP 20					Median % change *+11 (−17 to 79) +7 (−13 to 59) 0.673*			
Mastorakos 2002 Adolescents	Mmol/L	12 m	1:14 2: 14			5.12	0.53	5.56	1.16		

8.15.2. Forest Plot COCP vs EE/CPA for cholesterol (mmol/L)



8.15.3. Funnel plot for assessment of publication bias

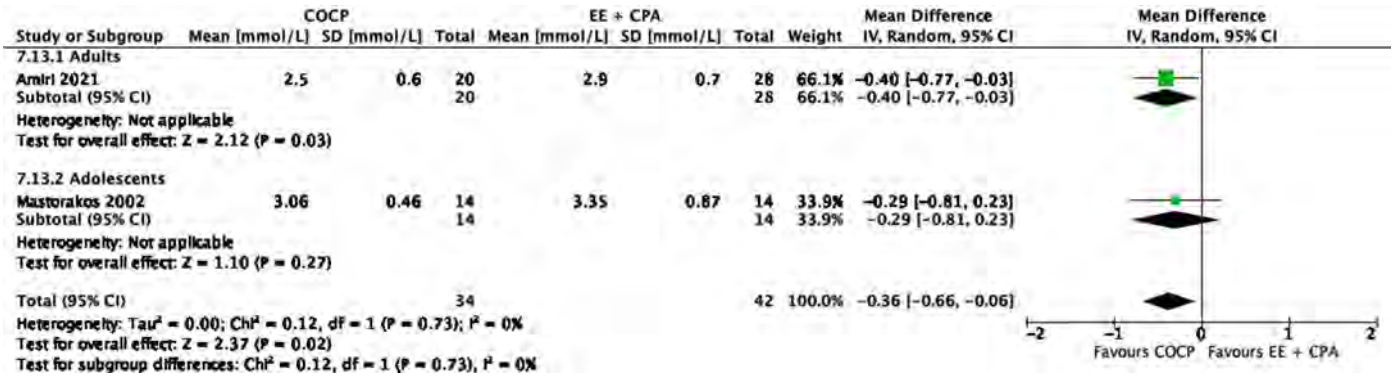


OUTCOME 8.16 LDL

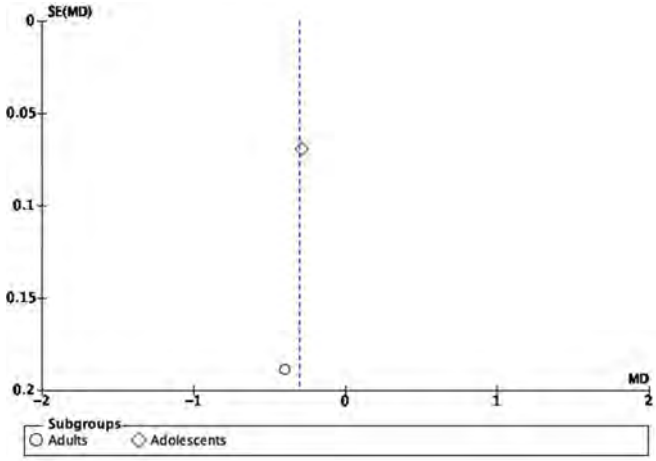
8.16.1 Individual study data table

OUTCOME: LDL								**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): COCP with different sorts of gestagens											
Author, year	**Unit**	**Time point**	**N**	**EE/LNG Mean**	**EE/LNG SD**	**EE/DSG Mean**	**EE/DSG SD**	**EE/CPA Mean**	**EE/CPA SD**	**EE/DRSP Mean**	**EE/DRSP SD**
Amiri 2021	Mmol/L	6m	*EE/LNG: 23 EE/DSG: 20 EE/CPA: 28 EE/DRSP: 17*	2.8	0.8	2.5	0.6	2.9	0.7	2.3	0.5
Kahraman 2014		12 m	EE/CPA 19 EE/DRSP 20					Median % change *+5 (−16 to 63) +2 (−30 to 68) 0.555*			
Mastorakos 2002 Adolescents	Mmol/L	12 m	1:14 2: 14			3.06	0.46	3.35	0.87		

8.16.2. Forest Plot COCP vs EE/CPA for LDL (mmol/L)



8.16.3. Funnel plot for assessment of publication bias

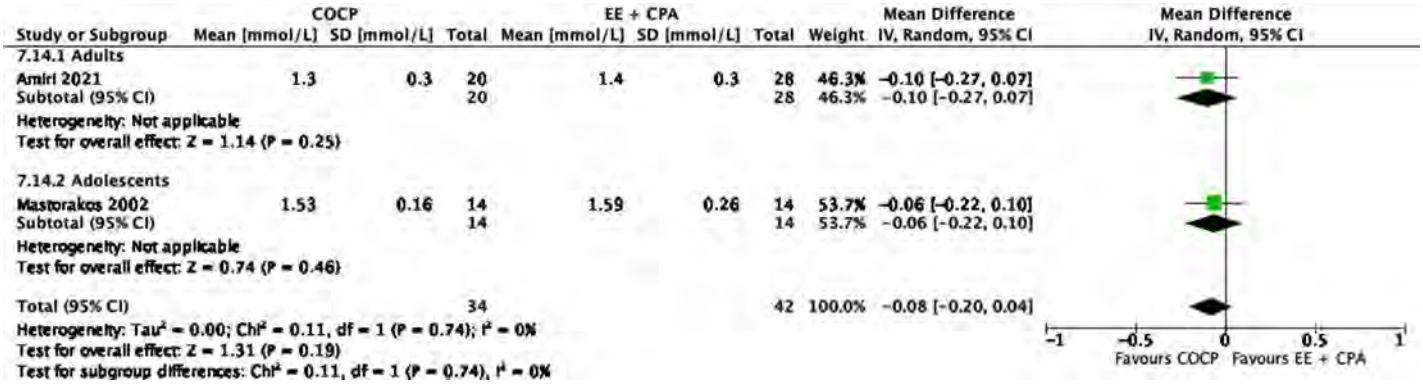


OUTCOME 8.17 HDL

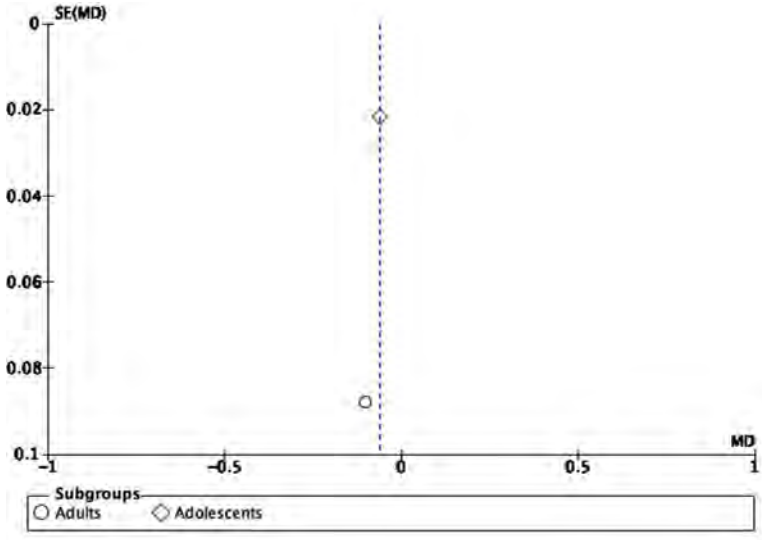
8.17.1 Individual study data table

OUTCOME: HDL						**OUTCOME TYPE:** Continuous					
COMPARISON (if applicable): COCP with different sorts of gestagens											
Author, year	**Unit**	**Time point**	**N**	**EE/LNG Mean**	**EE/LNG SD**	**EE/DSG Mean**	**EE/DSG SD**	**EE/CPA Mean**	**EE/CPA SD**	**EE/DRSP Mean**	**EE/DRSP SD**
Amiri 2021	Mmol/L	6m	*EE/LNG: 23 EE/DSG: 20 EE/CPA: 28 EE/DRSP: 17*	1.1	0.2	1.3	0.3	1.4	0.3	1.4	0.2
Kahraman 2014		12 m	EE/CPA 19 EE/DRSP 20					Median % change *+16 (−45 to 46) +5 (−42 to 45) 0.070*			
Mastorakos 2002 dolescents	Mmol/L	12 m	1:14 2: 14			1.52	0.16	1.59	0.26		

8.17.2. Forest Plot COCP vs EE/CPA for HDL (mmol/L)



8.17.3. Funnel plot for assessment of publication bias



OUTCOME 8.18 TRIGLYCERIDES

8.18.1 Individual study data table

OUTCOME: TG								**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): COCP with different sorts of gestagens											
Author, year	**Unit**	**Time point**	**N**	**EE/LNG Mean**	**EE/LNG SD**	**EE/DSG Mean**	**EE/DSG SD**	**EE/CPA Mean**	**EE/CPA SD**	**EE/DRSP Mean**	**EE/DRSP SD**
Amiri 2021	Mmol/L	6m	*EE/LNG: 23* *EE/DSG: 20* *EE/CPA: 28* *EE/DRSP: 17*	Median 1.0	IQR 0.8-1.4	Median 1.3	IQR 0.8-1.4	Median 1.6	IQR 1.2-2.1	Median 1.1	IQR 0.8-1.3
Kahraman 2014		12 m	EE/CPA 19 EE/DRSP 20					Median % change *+53 (−49 to 502)* *+43 (−60 to 180)* *0.361*			

OUTCOME 8.19 CRP
8.19.1 Individual study data table

OUTCOME: CRP									**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): COCP with different sorts of gestagens									
Author, year	**Unit**	**Time point**	**N**	**EE/CMA Mean**	**EE/CMA SD**	**EE/CPA Mean**	**EE/CPA SD**	**EE/DRSP Mean**	**EE/DRSP SD**
Christakou 2014	Mg/L	6 m	EE/CPA 38 EE/DRSP 36			2.63	0.73	1.93	1.44
Kahraman 2014		12 m	EE/CPA 19 EE/DRSP 20			Median % change *+174 (−96 to 2,656) +31 (−91 to 8,662) 0.610*			
Yildizhan 2015	Mg/l	12 m	EE/DRSP 57 EE/CMA 55	Mean change 0.55	0.23	Mean change 0.72	0.32		

Comparison 9: COCP vs. Progestin

- **EVIDENCE SUMMARY:**

Two studies were identified, one in adolescents (Chung 2014) with a moderate risk of bias, and one in adults (Ozdemir 2008) with a high risk of bias. The study duration was 4-6 months. The studies are shown in the table below.

- **META-ANALYSIS/DESCRIPTIVE ANALYSIS SUMMARY:**

In the meta-analysis, only the outcomes BMI, WHR and total testosterone could be included. There was no difference in any of these outcomes with low certainty of evidence. The other outcomes, with results only from one study, showed lower FAI and higher SGBG levels after COCP treatment and lower insulin and triglyceride levels, all with very low certainty of evidence. Regarding other outcomes, theses did differ between the treatments, with very low certainty of evidence.

Included studies COCP vs. progestin

Study ID	ROB	Interventions	Setting Duration	N	Mean age	Mean BMI	PCOS	Age at menarche	Smokers	Comments	Outcomes
Chung 2014 (crossover) (17)	Mod	1) 10mg MPA/d for 10d/m first 4m, then 4m washout, then 35µg EE + 2mg CPA/d 21/7 for 4m 2) As above in reverse	Hong Kong 4 m/ phase (12 m)	1: 38 2: 36	1: 16.7±1.6 2: 17.5±1.3	1: 23.7±5.3 2: 23.6±5.1	Rotterdam	*1: 12.1±1.4* *2: 12.1±1.3*	NR	Adolescents	Weight, BMI, WHR, hisutism score, TT, SF-36
Ozdemir 2008 (18)	High	*1) 10 mg MPA 10d/month* *2) 30 µg of EE + 3mg DRSP 21/7*	*Turkey 6 months*	*1: 31* *2: 32*	*1: 23.4±3.9* *2: 22.7±3.8*	*1: 23.6±4.4* *2: 24.3±4.8*	*Rott*	NR	Excluded		BMI, WHR, insulin, glucose, HOMA, chol LDL, HDL, TG, TT, SHBG, FAI, DHEAS, FG score

Outcomes reported narratively are outlined in the table below.

Outcome	Study ID	Time	N	COCP mean	COCP SD	Prog mean	Prog SD	P value	Favours	Importance
Weight /kg)	Chung 2014	4 m	C 36 CA 38	60.0	12.6	59.5	13.8	0.40	No difference	CRITICAL
FG score	Ozdemir 2018	6 m	C 32 CA 31	7.5	6.1	8.2	6.5	0.66	No difference	CRITICAL
FAI	Ozdemir 2018	6 m	C 32 CA 31	2.3	2.8	4.7	2.5	<0.001	COCP	IMPORTANT
SHBG (nmol/L)	Ozdemir 2018	6 m	C 32 CA 31	116.5	54.6	51.8	24.4	<0.001	COCP higher	IMPORTANT
DHEAS (µmol/L)	Ozdemir 2018	6 m	C 32 CA 31	4.76	2.46	4.76	2.56	1.00	No difference	IMPORTANT
Insulin (µIU/mL)	Ozdemir 2018	6 m	C 32 CA 31	12.4	5.7	7.9	3.4	<0.001	Progestin	IMPORTANT
Glucose (mmol/L)	Ozdemir 2018	6 m	C 32 CA 31	4.87	0.25	4.87	0.25	1.00	No difference	IMPORTANT

HOMA-IR	Ozdemir 2018	6 m	C 32 CA 31	1.8	1.3	1.7	0.8	0.71	No difference	IMPORTANT
Total cholesterol (mol/L)	Ozdemir 2018	6 m	C 32 CA 31	4.20	0.72	4.54	0.72	0.06	No difference	IMPORTANT
HDL (mmol/L)	Ozdemir 2018	6 m	C 32 CA 31	1.54	0.43	1.36	0.30	0.05	No difference	IMPORTANT
LDL (mmol/L)	Ozdemir 2018	6 m	C 32 CA 31	2.49	0.55	2.49	0.54	1.00	No difference	IMPORTANT
Triglycerides (mmol/L)	Ozdemir 2018	6 m	C 32 CA 31	1.06	0.45	0.83	0.45	0.04	Progestin	IMPORTANT
HRQoL										
Physical Functioning	Chung 2014	4 m	C 36 CA 38	94.5	11.3	95.5	8.5	0.67	No difference	CRITICAL
Physical role functioning	Chung 2014	4 m	C 36 CA 38	89.5	24.5	89.5	25.8	0.89	No difference	
Bodily pain	Chung 2014	4 m	C 36 CA 38	86.7	17.7	89.5	15.0	0.06	No difference	
General health	Chung 2014	4 m	C 36 CA 38	63.4	16.2	58.8	19.5	0.06	No difference	
Vitality	Chung 2014	4 m	C 36 CA 38	64.8	16.1	60.6	17.9	0.58	No difference	
Social role functioning	Chung 2014	4 m	C 36 CA 38	89.0	15.2	87.2	15.6	0.05	No difference	
Emotional role functioning	Chung 2014	4 m	C 36 CA 38	90.1	23.9	86.5	21.9	0.64	No difference	
Mental health	Chung 2014	4 m	C 36 CA 38	71.6	14.2	70.6	15.7	0.11	No difference	

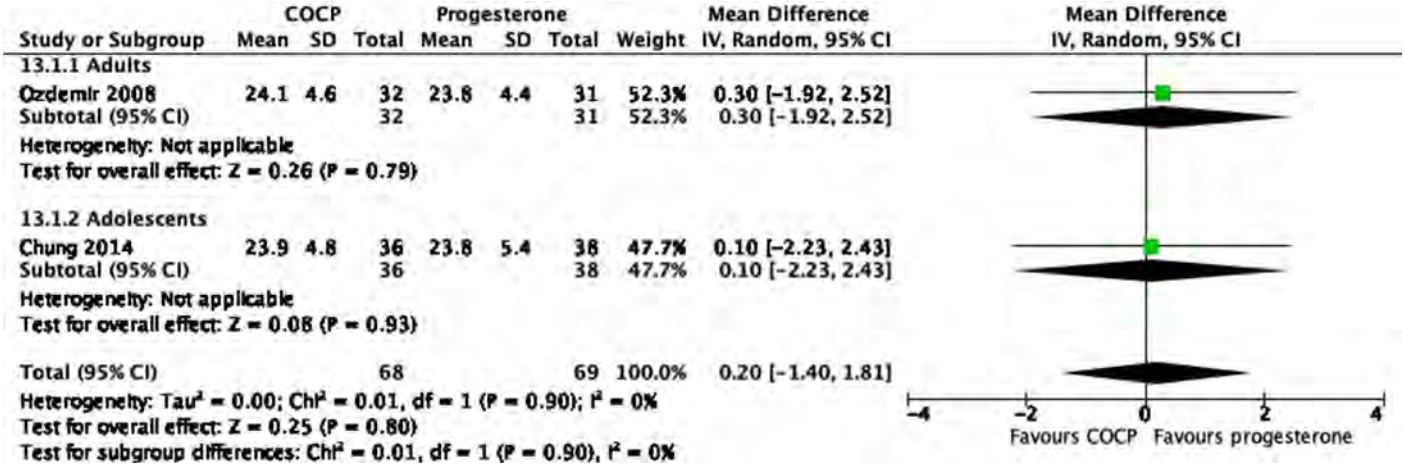
For the outcomes included in the meta-analysis, results are provided below:

OUTCOME 9.1. BMI

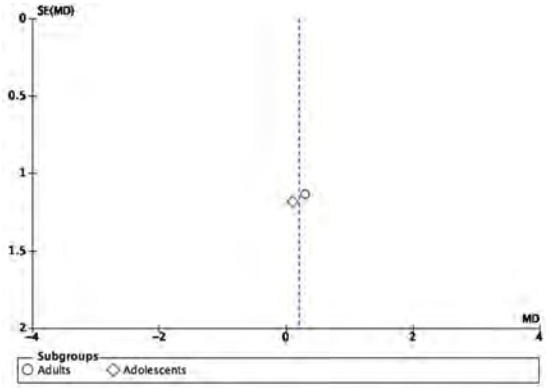
9.1.1 Individual Study Data Table

OUTCOME: BMI					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): COCP vs. progestin								
Author, year	**Unit**	**Time point**	**N**	**COCP Mean**	**COCP SD**	**Prog Mean**	**Prog SD**	**Comments**
Chung 2014		4 m	C 36 CA 38	23.9	4.8	23.8	5.4	
Ozdemir 2008		6m	C 32 CA 31	24.1	4.6	23.8	4.4	

9.1.2. Forest Plot COCP vs progestin for BMI (kg/m2)



9.1.3. Funnel plot for assessment of publication bias

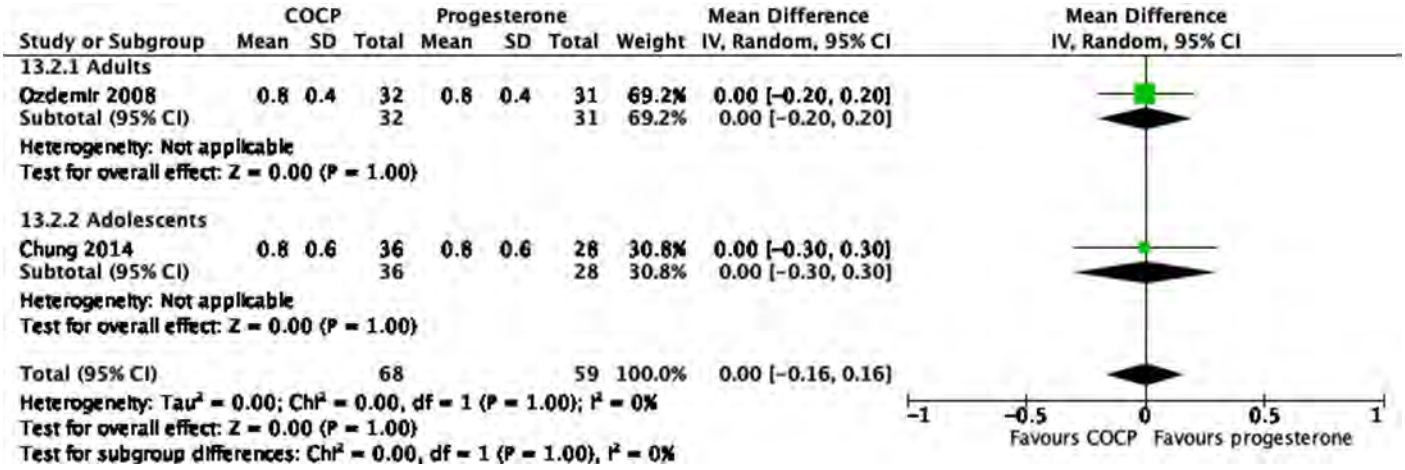


OUTCOME 9.2. WHR

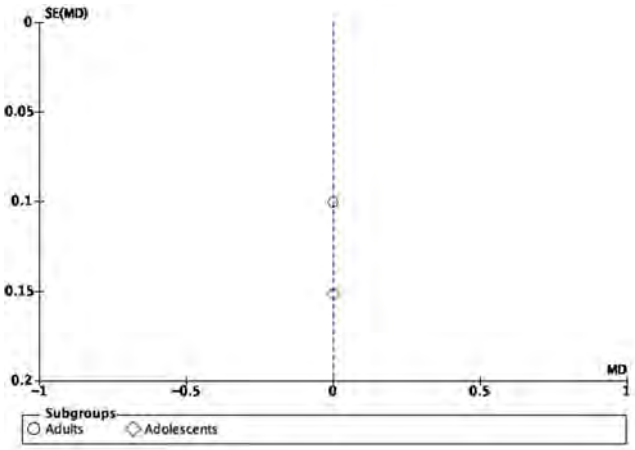
9.2.1 Individual Study Data Table

OUTCOME: WHR					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. progestin								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	Prog Mean	Prog SD	Comments
Chung 2014		4 m	C 36 CA 38	0.8	0.6	0.8	0.6	
Ozdemir 2008		6m	C 32 CA 31	0.8	0.4	0.8	0.4	

9.2.2. Forest Plot COCP vs progestin for WHR



9.9.3. Funnel plot for assessment of publication bias

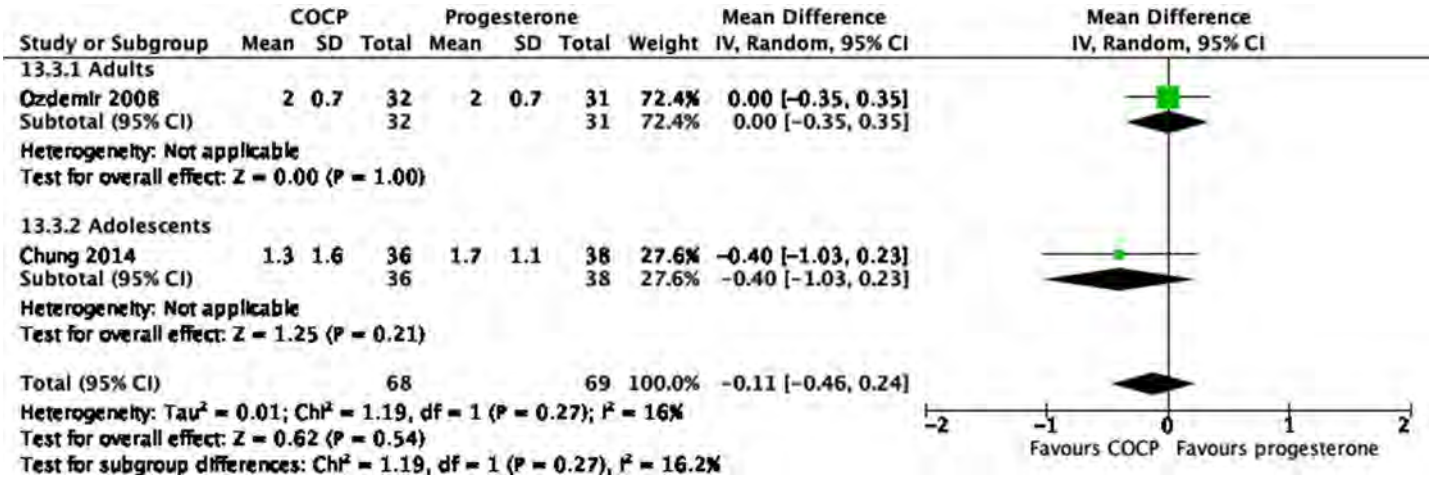


OUTCOME 9.3. TOTAL TESTOSTERONE

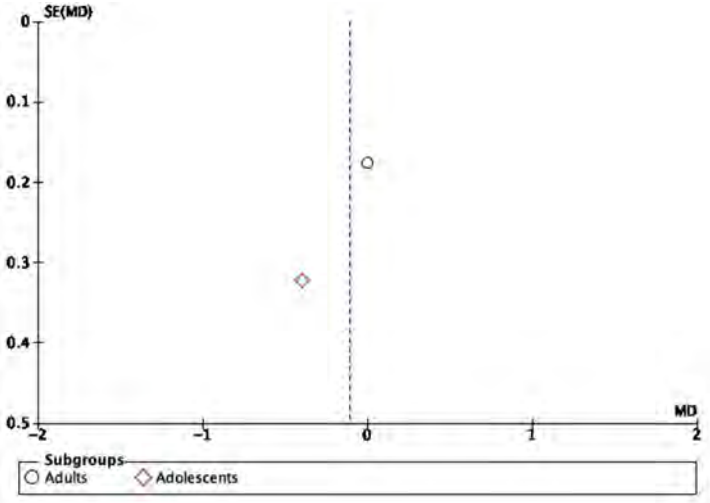
9.3.1 Individual Study Data Table

OUTCOME: Testosterone					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. progestin								
Author, year	**Unit**	**Time point**	**N**	**COCP Mean**	**COCP SD**	**Prog Mean**	**Prog SD**	**Comments**
Chung 2014	Nmol/L	4 m	C 36 CA 38	1.3	1.6	1.7	1.1	
Ozdemir 2008	Nmol/L	6m	C 32 CA 31	2.0	0.7	2.0	0.7	

9.3.2. Forest Plot COCP vs progestin for total testosterone (nmol/L)



9.3.3. Funnel plot for assessment of publication bias



Comparison 10: COCP vs. controls

▪ EVIDENCE SUMMARY:

Three RCTs compared COCPs with controls. All studies had a high risk of bias. In Dorgham 2021, all groups, including the control group received laser treatment, and in this study fascial hirsutism was an additional inclusion criterion. One study, El Maghraby 2015, involved adolescents. The study duration was 6-24 months. Information about the included studies is shown in the table below.

▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

A meta-analysis could not be performed. All outcomes were reported in only one study. COCP was superior to controls regarding improvement in cycle regularity with low certainty of evidence. HRQoL overall measured by VAS improved after COCP treatment, as well as in a dermatologic HRQoL questionnaire and a hirsutism HRQoL questionnaire, with very low certainty of evidence. Weight, testosterone, insulin levels were lower after COCP treatment, compared with controls, with very low certainty of evidence. The control group had lower after load insulin levels after an OGTT, and also had lower levels of CRP and PAI-1 compared with the group treated with COCP, with very low certainty of evidence. For all other outcomes, no difference was seen between groups with very low certainty of evidence. COCP treatment was associated with more minor adverse effects than controls.

Included studies:

Study ID	ROB	Comparisons	Country, duration	N	Mean age	Mean BMI	PCOS diagnosis	Menarche age	Smokers	Comments	Outcomes relevant to this review
Bodur 2018 (19)	High	1: 30 ug EE + 3 mg DRSP 2: 1700 g Met 3: 30 ug EE + 3 mg DRSP + 1700 g Met 4: controls, no mediciation	Turkey 6 months	1=17 2=17 3=12 4=15	1: 26.62 ± 4.92 2: 26.24 ± 3.96 3: 27.35 ± 5.65 4: 29.18 ± 5.20	1: 23.45 ± 3.40 2: 25.06 ± 3.08 3: 25.11 ± 3.75 4: 23.82 ± 2.80	Rott	NR	NR		CRP, PAI-1, glucose, HOMA
Dorgham 2021 (20)	High	1: only laser (controls) 2: laser + metformin 500 mg 3: laser 35 µg EE + 2 mg cyproterone acetate	Egypt 6 months (results available also for 3 months)	1:50 2:50 3:50	NR	NR	Rott	NR	NR	All received laser! Facial hirsutism required	HR-QoL (VAS, Dermatology Life Quality Index (DLQI) Hisutism Life Quality Index) (HLQI))
El Maghraby 2015 (21)	High	1: 30ug EE + 15mg progestin/ day 2: 1700mg MET/day 3: controls	Egypt (6, 12, 18, 24 m) 2 years	1: 33 2: 32 3: 25	1: 16.90 ± 1.60 2: 17.20 ± 2.00 3: 17.00 ±2.10	NR	Rott	NR	NR	adolescents	TT, ins, GIR, weight

Only results from one study per outcome was available, results are reported below.

Outcome	Author, year	Time point	N	COCP Mean	COCP SD	Controls Mean	Controls SD	P value	Favours	Certainty	Importance
Weight (kg)	El Maghraby 2015	24 m	COCP 33 controls 25	91.00	3.00	99.00	9.00	<0.0001	COCP	⊕◯◯◯ VERY LOW[2]	CRITICAL
Testosterone[1] (μg/ml)	El Maghraby 2015	24 m	COCP 33 controls 25	0.70	0.20	1.50	0.40	<0.0001	COCP	⊕◯◯◯ VERY LOW[2]	IMPORTANT
Insulin (μIU/ml)	El Maghraby 2015	24 m	COCP 33 controls 25	19.00	4.00	22.00	3.00	<0.01	COCP	⊕◯◯◯ VERY LOW[2]	IMPORTANT
Glucose (mg/dl)	Bodur 2018	6 m	COCP=17 controls=15	82.32	8.62	82.78	4.47	0.85	No difference	⊕◯◯◯ VERY LOW[2]	IMPORTANT
OGTT (after load insulin)	El Maghraby 2015	24 m	COCP 33 controls 25	187	22	111	12	<0.0001	Controls	⊕◯◯◯ VERY LOW[2]	IMPORTANT
HOMA	Bodur 2018	6 m	OCP=17 controls=15	3.10	2.01	2.20	0.59	0.11	No difference	⊕◯◯◯ VERY LOW[2]	IMPORTANT
CRP (mg/L)	Bodur 2018	6 m	COCP=17 controls=15	0.87	0.20	0.59	0.36	<0.01	Controls	⊕◯◯◯ VERY LOW[2]	IMPORTANT
PAI-1 (Ng/ml)	Bodur 2018	6 m	OCP=17 controls=15	19.19	2.97	14.59	2.50	<0.0001	Controls	⊕◯◯◯ VERY LOW[2]	IMPORTANT
HRQoL VAS (scale 0-10)	Dorgham 2021	6 m	COCP 50 controls 50	4.2	0.6	3.0	0.6	<0.0001	COCP	⊕◯◯◯ VERY LOW[3]	CRITICAL
HRQoL Dermatology Life Quality Index (DLQI)	Dorgham 2021	6 m	COCP 50 controls 50	1.0	0.6	5.5	2.5	0.002	COCP	⊕◯◯◯ VERY LOW[3]	CRITICAL
HRQoL Hisutism Life Quality Index (HLQI) 0-22, none to severe problems)	Dorgham 2021	6 m	COCP 50 controls 50	1.45	0.5	6.5	2.3	0.002	COCP	⊕◯◯◯ VERY LOW[3]	CRITICAL
Improvement in cycle regularity	El Maghraby 2015	24 m? NR		40/40 (100%)		0/40 (0%)		NA	COCP	⊕⊕◯◯ LOW[4]	CRITICAL

1. El Maghraby 2015 reports TT levels corresponding to extreme values.
2. Due to risk of bias (-2) and imprecision (-2, very few patients for each outcome).
3. Due to risk of bias (-2), and imprecision (-2, few patients for each outcome/one study).
4. Due to risk of bias (-2) and indirectness (-1, only one study involving one population), upgraded +1 for large effect

Adverse effects

The adverse effects reported are shown the table below:

	Study	COCP	Controls
Weight gain	El Maghraby 2015	7/40	0/39
Nausea	Bodur 2018	1/21	0/17
Dizziness	Bodur 2018	0/21	0/17
Sexual reluctance	Bodur 2018	1/21	0/17
Worsening of symptoms	El Maghraby 2015	0/40	7/39
Other	El Maghraby 2015	2/40	0/39
	Bodur 2018	Totally 4/21 dropouts, as above + Pregnancy, hirsutism	2/17 dropouts, unknown reason

Comparison 11: COCP vs. placebo

- **EVIDENCE SUMMARY:**

One RCT involving adolescents, Hoeger 2008, was included. No studies were identified involving adults. This study had a moderate risk of bias.

- **META-ANALYSIS/DESCRIPTIVE ANALYSIS SUMMARY:**

COCP treatment resulted in lower levels of testosterone, higher SHBG and lower FAI, with very low certainty of evidence. The placebo group had lower CRP levels compared with the COCP treated group, very low certainty of evidence.

Included studies:

Study ID	ROB	Comparisons	Country, duration	N	Mean age	Mean BMI	PCOS	Menarche age	Smokers	Comments	Outcomes relevant to this review
Hoeger 2008 (22)	Mod	1. 30 μg EE + 0.15 mg DSG 2. Placebo 3. Lifestyle addressing diet, exercise, behaviour 4: 1700 mg met/day	USA 6 mo	1 = 10 2 = 10 3 = 8 4 = 6	1: 15.4±1.4 2: 15.4±1.7 3: 15.4±1.2 4: 15.4±1.7	1: 37.8±5.1 2: 36.1±7.5 3: 37.8±8.2 4: 36.1±7.5	Rott	NR	All nonsmokers	Obese cohort Adolescents	BMI, FG score FAI, total T, SHBG, , chol, LDL, HDL, TG, CRP, BMI, PAI-1

Results are reported in the table below:

Hoeger 2008	Certainty of evidence for all outcomes: ⊕◯◯◯ VERY LOW (risk of bias, indirectness, imprecision)								
Outcome	**Time point**	**N**	**COCP Mean**	**COCP SD**	**Placebo Mean**	**Placebo SD**	**P value**	**Favours**	**Importance**
BMI (Kg/m^2)	6m	COCP 10 Pl 10	36.4	5.4	35.5	6.8	0.74	No difference	CRITICAL
Hirsutism (FG score)	6m	COCP 10 Pl 10	8.6	2.1	11.6	4.9	0.09	No difference	CRITICAL
FAI	6m	COCP 10 Pl 10	2.4	2.5	16.8	11.2	<0.001	COCP	IMPORTANT
Testosterone (nmol/L)	6m	COCP 10 Pl 10	1.20	0.99	2.48	1.17	0.02	COCP	IMPORTANT
SHBG (nmol/L)	6m	COCP 10 Pl 10	93.2	66.5	19.1	9.4	<0.01	Higher after COCP	IMPORTANT
Insulin (IU/mL)	6m	C10 P10	20.7	10.6	29.1	24.5	0.33	No difference	IMPORTANT
Glucose (Mg/dl)	6m	C10 P10	82.8	9.8	86.5	5.4	0.31	No difference	IMPORTANT
Cholesterol (mg/dl)	6m	COCP 10 Pl 10	188.6	20.7	157	53.2	0.10	No difference	IMPORTANT
LDL (mg/dl)	6m	COCP 10 Pl 10	128.6	37.5	114	27.1	0.33	No difference	IMPORTANT
HDL (mg/dl)	6m	COCP 10 Pl 10	47.6	9.9	43.6	8.9	0.35	No difference	IMPORTANT
TG (mg/dl)	6m	COCP 10 Pl 10	96.1	41.1	87.1	25.1	0.56	No difference	IMPORTANT
CRP (mg/L)	6m	C10 P10	9.5	7.4	4.2	2.8	<0.05	Placebo	IMPORTANT
PAI-1 (ng/ml)	6m	C10 P10	29.5	20.6	48.0	45.9	0.26	No difference	IMPORTANT

Adverse effects
The adverse effects are shown the table below:

	Study	COCP	Placebo/controls
Gastrointestinal problems	Hoeger 2008	0/11	1/11

Comparison 12: COCP vs lifestyle

- **EVIDENCE SUMMARY:**

One study was found, that addressed this comparison, Hoeger 2008, with no additional studies included since the last systematic review. This RCT included adolescents and had a moderate risk of bias.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

A meta-analysis could not be performed. LDL and triglycerides were lower after lifestyle treatment compared with COCP, with very low certainty of evidence. Total testosterone levels were lower after COCP treatment, compared with lifestyle, with very low certainty. For other outcomes, no difference was seen, with very low certainty of evidence.

Included studies:

Study ID	ROB	Comparisons	Country, duration	N	Mean age	Mean BMI	PCOS diagnosis	Menarche age	Smokers	Comments	Outcomes relevant to this review
Hoeger 2008 (22)	Mod	1. 30 μg EE + 0.15 mg DSG 2. Placebo 3. Lifestyle addressing diet, exercise, behaviour 4: 1700 mg met/day	USA 6 months	1 = 10 2 = 10 3 = 8 4 = 6	1: 15.4±1.4 2: 15.4±1.7 3: 15.4±1.2 4: 15.4±1.7	1: 37.8±5.1 2: 36.1±7.5 3: 37.8±8.2 4: 36.1±7.5	Rott	NR	All nonsmokers	Obese cohort Adolescents	BMI, FG score FAI, total T, SHBG, , chol, LDL, HDL, TG, CRP, BMI, PAI-1

Result from the individual study:

Hoeger 2008 (22)	Certainty[1] ⊕◯◯◯ VERY LOW						
Outcome (unit)	**COCP (n=10)**		**Lifestyle (n=8)**		**P value**	**Favours**	**Importance**
	Mean	SD	Mean	SD			
BMI (kg/m^2)	36.4	5.4	34.9	7.0	0.61	No difference	CRITICAL
Total testosterone (ng/dl)	34.5	28.6	64.5	30.2	<0.05	COCP	IMPORTANT
SHBG (nmol/liter)	93.2	66.5	32.0	21.7	ND	No difference	IMPORTANT
FAI	2.4	2.5	9.5	5.3	ND	No difference	IMPORTANT
Hirsutism (FG score)	8.6	2.1	8.2	2.0	ND	No difference	CRITICAL
Total cholesterol (mg/dl)	188.6	20.7	156.2	31	ND	No difference	IMPORTANT
HDL (mg/dl)	47.6	9.9	40.4	7.6	ND	No difference	IMPORTANT
LDL (mg/dl)	128.6	37.5	101.2	32.3	<0.05	Lifestyle	IMPORTANT
Triglycerides (mg/dl)	96.1	41.1	109.6	67.9	<0.05	Lifestyle	IMPORTANT
Fasting insulin (IU/ml)	20.7	10.6	22.0	10.5	0.80	No difference	IMPORTANT
Fasting blood sugar (mg/dl)	82.8	9.8	81.8	9.1	0.83	No difference	IMPORTANT
CRP (mg/liter)	9.5	7.4	3.8	3.6	0.06	No difference	IMPORTANT
PAI-1	29.5	20.6	45.0	25.6	0.17	No difference	IMPORTANT

All outcomes were judged as of very low certainty of evidence due to risk of bias (-1), indirectness (-1, only one study involving one population) and imprecision (-2, very few patients for each outcome).

Comparison 13: COCP vs. lifestyle ± anti-obesity treatment

Comparison 14: COCP vs. combination of COCP and lifestyle ± anti-obesity treatment

Comparison 15: Lifestyle ± anti-obesity treatment vs. combination of COCP and lifestyle ± anti-obesity treatment

- **EVIDENCE SUMMARY:**

One RCT with five publications (23-27) was identified addressing these comparisons. Legro 2015 (24) compared 20 µg EE+1mg NA (n=45) versus lifestyle intervention (n=44), and versus a combination of COCP and lifestyle (n=43). This was part of a larger study, and the interventions were part of a preconception treatment before infertility treatment. The lifestyle intervention included caloric restriction and exercise, and anti-obesity treatment if BMI>30 kg/m2. The medication used differed during the study period, initially sibutramine was used, but during the second part of the trial this was replaced with orlistat. The initial publication focused on reproductive outcomes and had a moderate risk of bias. Additional publications from this RCT, where additional outcomes could be extracted, focused on HRQoL (Dokras 2016 (27)), cholesterol efflux and lipoproteins (Dokras 2017 (23)), incretins and TNF-β (Shah 2021 (25)) and sexual dysfunction (Steinberg Weiss 2021 (26)). Steinberg Weiss reported sexual function measured with two different questionnaires. Female Sexual Function Index (FSFI) includes 19 questions grouped in six domains, the total score ranges from 2-36, and a higher score indicates a better sexual function. Female Sexual Distress Scale-Revised (FSDS-R) includes 13 questions, the total score ranges from 0-52, with a higher score corresponding to higher levels of sexual distress.

- **META-ANALYSIS/DESCRIPTIVE ANALYSIS SUMMARY:**

Lifestyle and combination of lifestyle + COCP resulted in lower weight compared with COCP alone with a very low certainty of evidence. COCP and the combined group had lower total testosterone and higher SHBG, compared with lifestyle alone, with a very low certainty of evidence. Triglycerides were higher after COCP treatment compared with lifestyle, but not compared with the combination COCP + lifestyle treatment, with a very low certainty of evidence. OGTT showed higher glucose levels after COCP compared with lifestyle and compared with the combined group, with a very low certainty of evidence.
There were no direct comparisons between the groups regarding sexual function scores, but in the combined treatment arm, patients improved in sexual desire, a tendency towards this was seen in the lifestyle arm, but no difference was seen in the COCP arm. Overall, there was no difference in HRQoL or prevalence of depression after treatments, with very low certainty of evidence.
Regarding adverse effects, lifestyle +/- anti-obesity treatment and the combined group had significantly more diarrhea compared with COCP treatment, and COCP and combination treatment was associated with more abnormal uterine bleeding than lifestyle +/- anti-obesity treatment alone.

Included studies:

Study ID	ROB	Comparisons	Country, duration	N	Mean age	Mean BMI	PCOS diagnosis	Menarche age	Smokers	Comments	Outcomes relevant to this review
Legro 2015 (24) Dokras 2016 (27) Dokras 2017 (23)	Mod	1. 20 µg EE+1mg NA 2: lifestyle and anti-obesity (first part of trial sibutramine, second part	USA 16 weeks	1:45 2:44 3:43	1: 29.8 (3.7) 2: 28.6 (3.4) 3: 28.7 (4.2)	1: 35.1 (4.2) 2: 35.1 (4.6) 3: 35.5 (4.4)	Rott	NR	NR	Nothing extracted from Shah	Weight, TT, SHBG, TG, OGTT, glucose, insulin, HRQoL, depression, BMI, Sexual function,

Shah 2021 (25) Steinberg Weiss 2021 (26)		orlistat) 3: combo									

Summary of findings (from Legro 2015 if not otherwise stated), differences in mean change (95%CI), outcomes were judged as of very low certainty of evidence ⊕◯◯◯ due to serious risk of bias (-1), indirectness (-1, only infertile women included) and imprecision (-2, few patients for each outcome and only one study).

Outcome	**Unit**	**Lifestyle ± AO (n=44) vs. COCP (n=45)**	**P value**	**COCP + Lifestyle ± AO (n=43) vs. COCP (n=45)**	**P value**	**Lifestyle ± AO (n=44) vs. COCP + Lifestyle ± AO (n=43)**	**P value**
Weight	kg	-5.0 (-6.3- -3.8)	<0.0001	-5.0 (-6.2– -3.7)	<0.0001	-0.1 (-1.3–1.2)	0.92
BMI (from Dokras 2017)	Kg/m^2	-2.3 (-2.7- -1.8) vs. -0.4 (-0.9- 0.0)	NR	-2.6 (-3.2- -2.1) vs. -0.4 (-0.9- 0.0)	NR	-2.3 (-2.7- -1.8) vs. -2.6 (-3.2- -2.1)	NR
Total testosterone	Ng/dl	2.24 (1.82–2.76)	<0.0001	0.99 (0.80 –1.22)	0.90	2.27 (1.83–2.81)	<0.0001
SHBG	Nmol/L	0.37 (0.28 –0.48)	<0.0001	0.95 (0.73–1.23)	0.69	0.39 (0.30 – 0.50)	<0.0001
Triglycerids	Mg/dl	0.81 (0.70 –0.94)	0.006	0.87 (0.75–1.01)	0.07	0.93 (0.80 –1.08)	0.32
OGTT, 2h glucose	Mg/dl	-27.8 (-40.9 – -14.8)	<0.0001	-17.4 (-30.5– -4.2)	0.01	-10.5 (-23.6 –2.7)	0.12
PCOS HRQoL	**Emotional**	-0.1 (-0.5–0.3)	0.58	0.2 (-0.1–0.6)	0.19	-0.3 (-0.7–0.0)	0.06
	Body hair	-0.6 (-1.0 – -0.3)	0.001	0.1 (-0.2–0.5)	0.48	-0.8 (-1.1–-0.4)	0.0001
	Weight	0.1 (-0.4 –0.6)	0.73	0.7 (0.2–1.2)	0.003	-0.6 (-1.1–-0.2)	0.10
	Infertility	0.0 (-0.4 –0.5)	0.83	0.5 (0.0 –0.9)	0.03	-0.4 (-0.9 –0.0)	0.05
	Menstural problems	-0.0 (-0.4 –0.4)	0.92	0.2 (-0.1–0.6)	0.21	-0.3 (-0.7–0.1)	0.18
	Overall physical wellbeing	0.4 (-0.2–0.9)	0.16	0.7 (0.2–1.3)	0.008	-0.4 (-0.9 –0.2)	0.20
	Overall emotional wellbeing	-0.1 (-0.7–0.5)	0.70	0.2 (-0.4 –0.8)	0.44	-0.3 (-0.9 –0.2)	0.25
	Overall general wellbeing	0.2 (-0.2–0.6)	0.31	0.3 (-0.1–0.7)	0.17	-0.1 (-0.5–0.3)	0.73
HRQoL (SF-36) from Dokras 2016	**Physical function**	1.70 (−0.31, 3.71) vs. 1.25 (−0.76, 3.26)	NR	0.44 (−1.59, 2.47) vs. 1.25 (−0.76, 3.26)	NR	1.70 (−0.31, 3.71) vs. 0.44 (−1.59, 2.47)	NR
	Role physical	−0.16 (−2.15, 1.83) vs. −0.16 (−2.15, 1.83)	NR	−0.38 (−2.40, 1.63) vs. −0.16 (−2.15, 1.83)	NR	−0.16 (−2.15, 1.83) vs. −0.38 (−2.40, 1.63)	NR

	Bodily pain	−0.37 (−2.57, 1.84) vs. 2.24 (0.06, 4.41)	NR	−0.75 (−2.97, 1.48) vs. 2.24 (0.06, 4.41)	NR	−0.37 (−2.57, 1.84) vs. −0.75 (−2.97, 1.48)	NR
	General health	2.11 (0.36, 3.87) vs. 3.14 (1.38, 4.90)	NR	2.34 (0.56, 4.12) vs. 3.14 (1.38, 4.90)	NR	2.11 (0.36, 3.87) vs. 2.34 (0.56, 4.12)	NR
	Vitality	5.20 (2.86, 7.54) vs. 2.42 (0.10, 4.73)	NR	1.89 (−0.48, 4.26) vs. 2.42 (0.10, 4.73)	NR	5.20 (2.86, 7.54) vs. 1.89 (−0.48, 4.26)	NR
	Social functioning	0.25 (−2.60, 3.09) vs. 1.57 (−1.24, 4.38)	NR	0.38 (−2.50, 3.26) vs. 1.57 (−1.24, 4.38)	NR	0.25 (−2.60, 3.09) vs. 0.38 (−2.50, 3.26)	NR
	Role emotional	1.32 (−1.32, 3.95) vs. 3.59 (0.96, 6.23)	NR	−0.98 (−3.65, 1.69) vs. 3.59 (0.96, 6.23)	NR	1.32 (−1.32, 3.95) vs. −0.98 (−3.65, 1.69)	NR
	Mental health	0.84 (−1.33, 3.02) vs. 0.98 (−1.18, 3.13)	NR	0.46 (−1.74, 2.67) vs. 0.98 (−1.18, 3.13)	NR	0.84 (−1.33, 3.02) vs. 0.46 (−1.74, 2.67)	NR
	Physical component summary	0.79 (−0.89, 2.46) vs. 1.20 (−0.48, 2.87)	NR	0.54 (−1.15, 2.23) vs. 1.20 (−0.48, 2.87)	NR	0.79 (−0.89, 2.46) vs. 0.54 (−1.15, 2.23)	NR
	Mental component summary	1.90 (−0.49, 4.29) vs. 1.20 (−0.48, 2.87)	NR	0.33 (−2.09, 2.75) vs. 1.20 (−0.48, 2.87)	NR	1.90 (−0.49, 4.29) vs. 0.33 (−2.09, 2.75)	NR
FSFI score (from Steinberg Weiss)	**Total**	2.79 (0.12, 5.47) vs 2.51 (–0.40, 5.42	NR	3.68 (0.46, 6.89) vs 2.51 (–0.40, 5.42	NR	2.79 (0.12, 5.47) vs 3.68 (0.46, 6.89)	NR
	Desire domain	0.51 (0.01, 1.00) vs. 0.44 (–0.10, 0.98)	NR	0.87 (0.27, 1.46) vs. 0.44 (–0.10, 0.98)	NR	0.51 (0.01, 1.00) vs. 0.87 (0.27, 1.46)	NR
	Arousal domain	0.72 (0.08, 1.35) vs. 0.33 (–0.36, 1.02)	NR	0.57 (–0.19, 1.33) vs. 0.33 (–0.36, 1.02)	NR	0.72 (0.08, 1.35) vs. 0.57 (–0.19, 1.33)	NR
	Lubrication domain	0.37 (–0.26, 1.00) vs.	NR	0.60 (–0.15, 1.35) vs.	NR	0.37 (–0.26, 1.00)	NR

		0.22 (–0.46, 0.90)		0.22 (–0.46, 0.90)		vs. 0.60 (–0.15, 1.35)	
	Orgasm domain	0.52 (–0.30, 1.34) vs. 0.40 (–0.49, 1.29)	NR	0.80 (–0.19, 1.79) vs. 0.40 (–0.49, 1.29)	NR	0.52 (–0.30, 1.34) vs. 0.80 (–0.19, 1.79)	NR
	Satisfaction domain	0.40 (–0.27, 1.07) vs. 1.02 (0.29, 1.74)	NR	0.98 (0.17, 1.78) vs. 1.02 (0.29, 1.74)	NR	0.40 (–0.27, 1.07) vs. 0.98 (0.17, 1.78)	NR
	Pain domain	0.28 (–0.25, 0.80) vs. 0.11 (–0.46, 0.68)	NR	0.28 (–0.25, 0.80) vs. 0.11 (–0.46, 0.68)	NR	0.28 (–0.25, 0.80) vs. 0.28 (–0.25, 0.80)	NR
FSDS-R score (from Steinberg Weiss)		–6.38 (–11.75, –1.02) vs. –4.09 (–9.92, 1.74)	NR	–6.89 (–13.34, –0.44) vs. –4.09 (–9.92, 1.74)	NR	–6.38 (–11.75, –1.02) vs. –6.89 (–13.34, –0.44)	NR
Depression	**% after treatment**	15.9% vs. 4.4%	0.09	11.9% vs. 4.4%	0.23	15.9% vs. 11.9%	0.56
Adverse effects	**Steatorrhea/diarrhea (%)**	12% vs. 0%	<0.05	24% vs. 0%	<0.05	12% vs. 24%	NS
	Breast pain (%)	2% vs. 20.4%	<0.05	12% vs. 20.4%	NS	2% vs. 12%	NS
	Abdominal pain (%)	10% vs. 2%	<0.05	20% vs. 2%	<0.05	10% vs. 20%	NS
	Dysmennorhea (%)	2% vs. 16.3%	<0.05	6% vs. 16.3%	NS	2% vs. 6%	NS
	Abnormal uterine bleeding (%)	0% vs. 8.2%	NS	12% vs. 8.2%	NS	0% vs. 12%	<0.05

Comparison 16: COCP vs. anti-obesity treatment

- **EVIDENCE SUMMARY:**

One study, with a high risk of bias, was found to address this comparison. Sabuncu 2003 (28) compared COCP with 35 µg EE + 2 mg CPA (n=14) vs. sibutramine 10 mg/day (n=12) for 6 months.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

A meta-analysis could not be performed. Anti-obesity medication resulted in lower BMI, lower triglycerides and lower insulin levels, compared with COCP treatment, with very low certainty. Regarding other outcomes, no difference was seen between the treatments, with very low certainty of evidence. Adverse effects were not reported.

Included study:

Study ID	ROB	Comparisons	Country, duration	N	Mean age	Mean BMI	PCOS	Menarche age	Smokers	Comments	Outcomes relevant to this review
Sabuncu 2003 (28)	High	1: 35 µg EE + 2 mg CPA 2: sibutramine 10 mg/day 3:combo	Turkey 6 months		1: 28.8±6.0, 2: 28.1±6.4 3: 28.9±6.8	1: 37.8 6.1 2: 37.5 5.0 3: 37.7 5.8	NIH	NR	All non-smokers	Obese cohort	Weight, BMI, WHR, FG scoe, chol, TG, LDL, HDL, TT, fT, SHBG, DHEAS, insulin, gluclose

Results from an individual study. All outcomes had a very low certainty of evidence due to risk of bias (-2), and imprecision (-2, very few patients for each outcome).

Outcome	Unit	COCP n=14 Mean	COCP SD	Anti obesity n=12 Mean	Anti obesity SD	P value	Favours	Importance
Weight	Kg	88.5	15.8	78.2	14.8	0.17	No difference	CRITICAL
BMI	Kg/m2	36.8	5.6	31.7	5.0	0.02	Anti-obesity	CRITICAL
WHR	-	0.84	0.07	0.81	0.07	0.29	No difference	IMPORTANT
Hirsutism	FG score	10.2	2.8	10.7	2.7	0.65	No difference	CRITICAL
Cholesterol	Mg/dl	203.9	45.9	189.9	42.5	0.43	No difference	IMPORTANT
HDL	Mg/dl	54.7	9.8	48.5	14.1	0.20	No difference	IMPORTANT
LDL	Mg/dl	110.3	41.2	120.0	38.1	0.54	No difference	IMPORTANT
TG	Mg/dl	195.3	55.6	107.1	30.7	<0.001	Anti-obesity	IMPORTANT
TT	Ng/dl	89.3	28.4	84.1	27.5	0.64	No difference	IMPORTANT
fT	Ng/dl	2.0	0.7	2.3	1.0	0.38	No difference	IMPORTANT
SHBG	Nmol/L	60.9	41.6	49.2	26.5	0.41	No difference	IMPORTANT
DHEAS	µg/dl	198.1	64.5	200.2	69.4	0.94	No difference	IMPORTANT
Insulin	AUC (µU/mL/h)	106.7	35.4	68.7	30.9	<0.01	Anti-obesity	IMPORTANT
Glucose	AUC *(mg/dL/h)*	240.1	41.0	211.4	34.8	0.07	No difference	IMPORTANT

Comparison 17: COCP vs. COCP + anti-obesity

- **EVIDENCE SUMMARY:**

Three RCTs with four publications were found for this comparison. Sabuncu 2003 (28) compared 35 µg EE + 2 mg CPA (n=14) vs. 35 µg EE + 2 mg CPA + sibutramine 10 mg/day (n= 14) for 6 months. In this cohort all women with PCOS were obese. This study had a high risk of bias. Song 2017 (29) compared 35 µg EE + 2 mg CPA (n=60) vs. 35 µg EE + 2 mg CPA + Orlistat 120 mgx3 (n=60), a secondary publication from this RCT came from Ruan 2018 (30) on androgens. The duration of the study was 3 months. Gu 2022 studied DRSP 3 mg/EE 20 µg (n=33) vs. DRSP 3 mg/EE 20 µg + Orlistat 120 mg x 3 (n=33) for 3 months. This study had a high risk of bias. Thus, all included studies had a high risk of bias, and they included only adults.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

The meta-analysis showed lower DHEAS levels after treatment with the combination COCP + anti-obesity drugs, with a low certainty of evidence. COCP + anti-obesity treated women had lower FAI after treatment, with a low certainty of evidence. For all other outcomes, there were no difference between treatments, with low or very low certainty of evidence.

Included studies

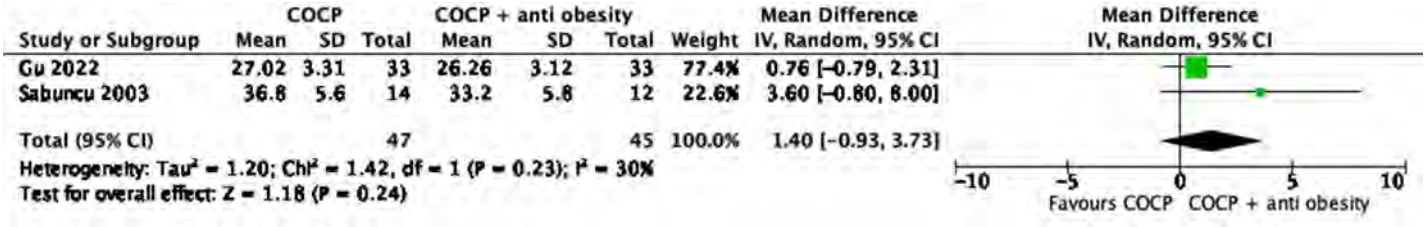
Study ID	ROB	Comparisons	Country, duration	N	Mean age	Mean BMI	PCOS diagnosis	Menarche age	Smokers	Comments	Outcomes relevant to this review
Gu 2022 (31)	High	1: DRSP 3 mg/EE 20 µg 24/4 plus Orlistat 2: EE/DRSP alone	China 3 months	1:33 2:33	1: 29.67 ± 2.53 2: 29.67 ± 2.36	1 28.23 ± 2.95 2: 28.01 ± 3.19	Rott	NR	NR		CRP, BMI, weight, TT, FT, SHBG, chol, LDL, HDL, TG, insulin, glucose
Sabuncu 2003 (28)	High	1: 35 µg EE + 2 mg CPA 2: sibutramine 10 mg/day 3:combo	Turkey 6 months	1:14 2:12 3:14	1: 28.8±6.0, 2: 28.1±6.4 3: 28.9±6.8	1: 37.8 6.1 2: 37.5 5.0 3: 37.7 5.8	NIH	NR	All non-smokers	Obese cohort	Weight, BMI, WHR, FG scoe, chol, TG, LDL, HDL, TT, fT, SHBG, DHEAS, OGTT
Song 2017 (29) Ruan 2018 (30)	High	1) 35 µg EE + 2 mg CPA (2) 35 µg EE + 2 mg CPA + Orlistat 120 mgx3 (3) 35 µg EE + 2 mg CPA + metformin 1500 mg/day (4) 35 µg EE + 2 mg CPA + Orlistat 120 mgx3 + metformin 1500 mg/day	China 3 months	1:60 2:60 3:60 4:60	1: 27.68 ± 4.99 2: 26.77 ± 4.12 3: 28.63 ± 5.12 4: 27.57 ± 4.58	1: 28.64 ± 4.89 2: 27.85 ± 4.10 3: 27.00 ± 3.47 4: 28.76 ± 3.43	Rott	NR	1: 22% 2: 20% 3: 25% 4: 18%		TT, chol, LDL, HDL, glucose, insulin, HOMA, From Ruan TT, DHEAS, androstendione, SHBG, FAI, adverse effects

Results from meta-analysis:

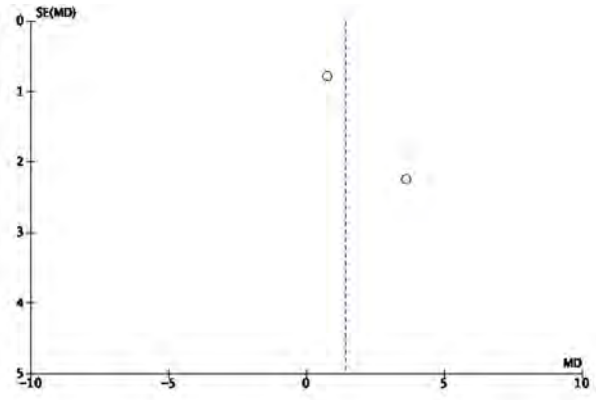
OUTCOME 17.1 BMI
17.1.1 Individual Study Data Table

OUTCOME: BMI						**OUTCOME TYPE:** Continuous		
COMPARISON (if applicable): COCP vs. COCP + anti obesity								
Author, year	**Unit**	**Time point**	**N**	**COCP Mean**	**COCP SD**	**COCP + AO Mean**	**COCP + AO SD**	**Comments**
Gu 2022		3 m	C 33 CO 33	27.02	3.31	26.26	3.12	
Sabuncu 2003		6 m	C:14 CO:12	36.8	5.6	33.2	5.8	

17.1.2. Forest Plot COCP vs COCP + anti-obesity for BMI (kg/m2)



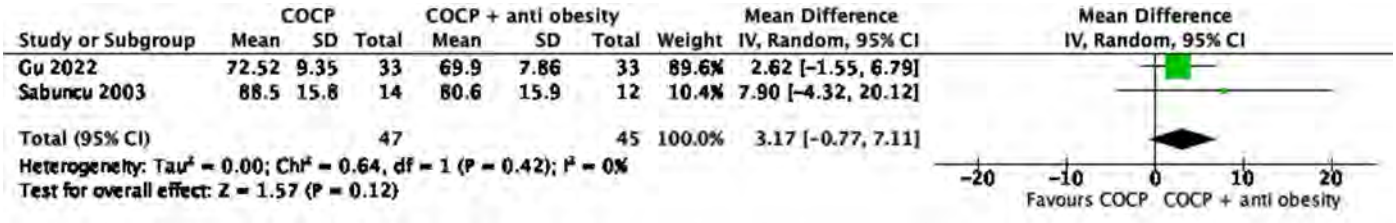
17.1.3. Funnel plot for assessment of publication bias



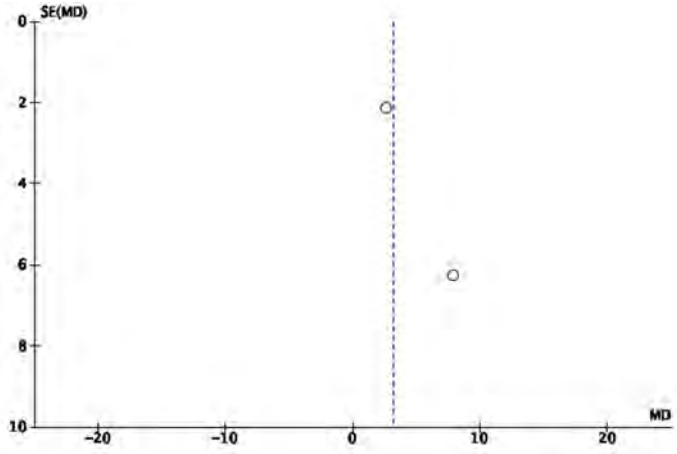
OUTCOME 17.2 WEIGHT
17.2.1 Individual Study Data Table

OUTCOME: weight						**OUTCOME TYPE:** Continuous		
COMPARISON (if applicable): COCP vs. COCP + anti obesity								
Author, year	**Unit**	**Time point**	**N**	**COCP Mean**	**COCP SD**	**COCP + AO Mean**	**COCP + AO SD**	**Comments**
Gu 2022	Kg	3 m	C 33 CO 33	72.52	9.35	69.90	7.86	
Sabuncu 2003	kg	6 m	C:14 CO:12	88.5	15.8	80.6	15.9	

17.2.2. Forest Plot COCP vs COCP + anti-obesity for weight (kg)



17.2.3. Funnel plot for assessment of publication bias



OUTCOME 17.3 WHR

17.3.1 Individual Study Data Table

OUTCOME: WHR					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): COCP vs. COCP + anti obesity								
Author, year	**Unit**	**Time point**	**N**	**COCP Mean**	**COCP SD**	**COCP + AO Mean**	**COCP + AO SD**	**Comments**
Sabuncu 2003		6 m	C:14 CO:12	0.84	0.07	0.82	0.06	

OUTCOME 17.4 HIRSUTISM

17.4.1 Individual Study Data Table

OUTCOME: Hirsutism					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): COCP vs. COCP + anti obesity								
Author, year	**Unit**	**Time point**	**N**	**COCP Mean**	**COCP SD**	**COCP + AO Mean**	**COCP + AO SD**	**Comments**
Sabuncu 2003	FG score	6 m	C:14 CO:12	10.2	2.8	8.78	2.6	

OUTCOME 17.5 FAI

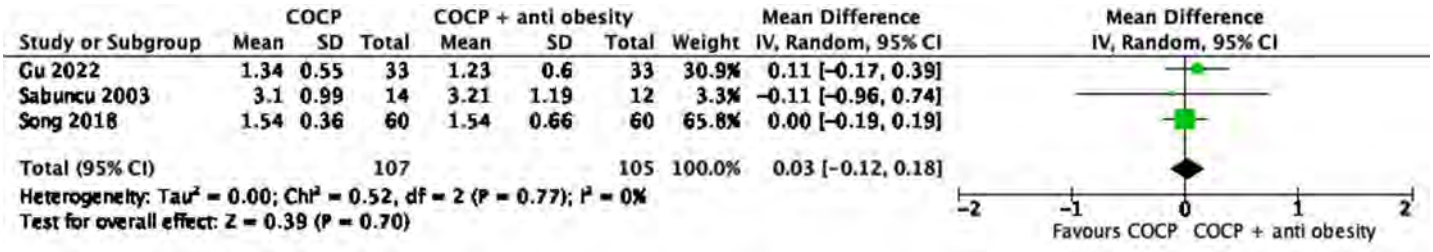
17.5.1 Individual Study Data Table

OUTCOME: FAI					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): COCP vs. COCP + anti obesity								
Author, year	**Unit**	**Time point**	**N**	**COCP Mean**	**COCP SD**	**COCP + AO Mean**	**COCP + AO SD**	**Comments**
Ruan 2018		3 m	C 60 CO 60	4.59	5.91	2.15	1.91	

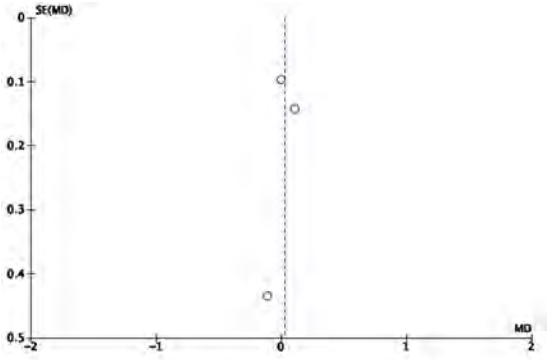
OUTCOME 17.6 TOTAL TESTOSTERONE
17.6.1 Individual Study Data Table

OUTCOME: Total testosterone						**OUTCOME TYPE:** Continuous		
COMPARISON (if applicable): COCP vs. COCP + anti-obesity								
Author, year	**Unit**	**Time point**	**N**	**COCP Mean**	**COCP SD**	**COCP + AO Mean**	**COCP + AO SD**	**Comments**
Gu 2022	Nmol/L	3 m	C 33 CO 33	1.34	0.55	1.23	0.6	
Song 2017	Nmol/L	3 m	C 60 CO 60	3.1	0.99	3.21	1.19	
Sabuncu 2003	Nmol/L	6 m	C:14 CO:12	1.54	0.36	1.54	0.66	

17.6.2. Forest Plot COCP vs COCP + anti-obesity for testosterone (nmol/L)



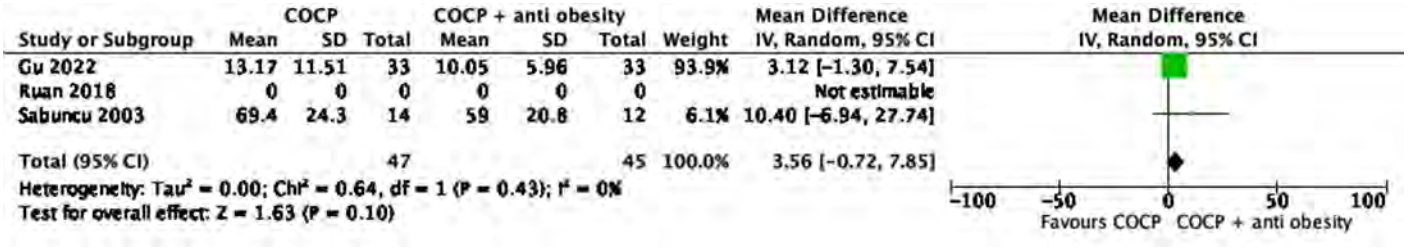
17.6.3. Funnel plot for assessment of publication bias



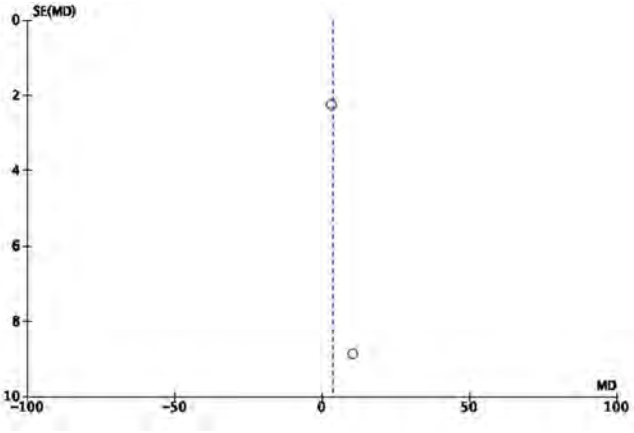
OUTCOME 17.7 FREE TESTOSTERONE
17.7.1 Individual Study Data Table

OUTCOME: Total testosterone						**OUTCOME TYPE:** Continuous		
COMPARISON (if applicable): COCP vs. COCP + anti-obesity								
Author, year	**Unit**	**Time point**	**N**	**COCP Mean**	**COCP SD**	**COCP + AO Mean**	**COCP + AO SD**	**Comments**
Gu 2022	pmol/L	3 m	C 33 CO 33	13.17	11.51	10.05	5.96	
Ruan 2018	Nmol/L	3 m	C 60 CO 60	1.47	0.54	1.41	0.97	Considered as reporting error, not included
Sabuncu 2003	pmol/L	6 m	C:14 CO:12	69.4	24.3	59	20.8	

17.7.2. Forest Plot COCP vs COCP + anti-obesity for free testosterone (pmol/L)



17.7.3. Funnel plot for assessment of publication bias

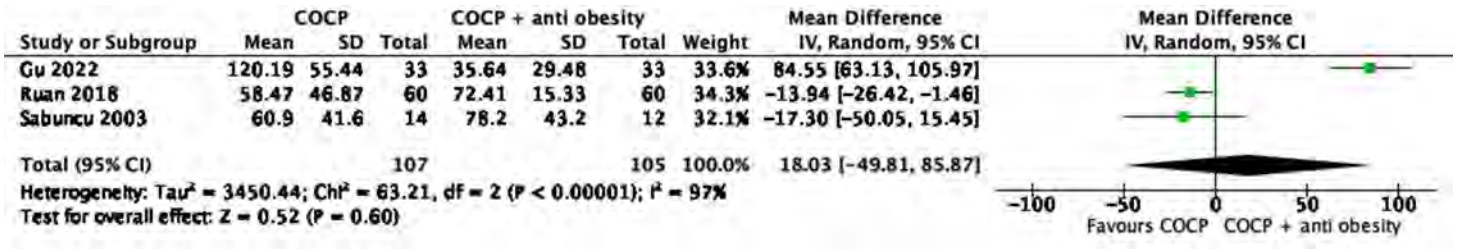


OUTCOME 17.8 SHBG

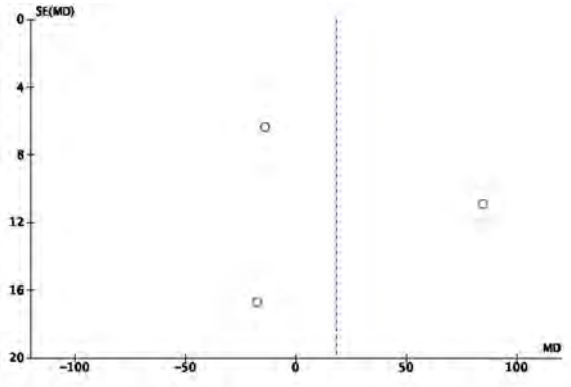
17.8.1 Individual Study Data Table

OUTCOME: SHBG					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): COCP vs. COCP + anti-obesity								
Author, year	**Unit**	**Time point**	**N**	**COCP Mean**	**COCP SD**	**COCP + AO Mean**	**COCP + AO SD**	**Comments**
Gu 2022	Nmol/L	3 m	C 33 CO 33	120.19	55.44	35.64	29.48	
Ruan 2018	Nmol/L	3 m	C 60 CO 60	58.47	46.87	72.41	15.33	Considered as reporting error, not included
Sabuncu 2003	Nmol/L	6 m	C:14 CO:12	60.9	41.6	78.2	43.2	

17.8.2. Forest Plot COCP vs COCP + anti-obesity for SHBG (nmol/L)



17.8.3. Funnel plot for assessment of publication bias



OUTCOME 17.9 ANDROSTENEDIONE

17.9.1 Individual Study Data Table

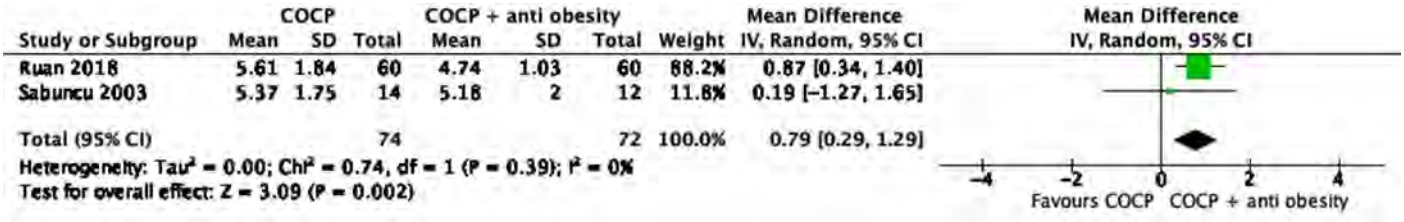
OUTCOME: Androstenedione					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. COCP + anti-obesity								
Author, year	**Unit**	**Time point**	**N**	**COCP Mean**	**COCP SD**	**COCP + AO Mean**	**COCP + AO SD**	**Comments**
Ruan 2018	Nmol/L	3 m	C 60 CO 60	7.89	2.86	*7.09*	3.99	

OUTCOME 17.10 DHEAS

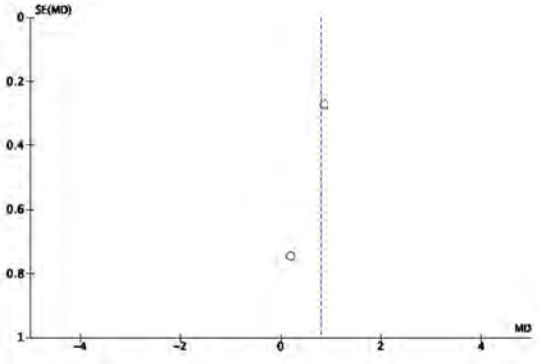
17.10.1 Individual Study Data Table

OUTCOME: DHEAS					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. COCP + anti-obesity								
Author, year	**Unit**	**Time point**	**N**	**COCP Mean**	**COCP SD**	**COCP + AO Mean**	**COCP + AO SD**	**Comments**
Ruan 2018	(μmol/L)	3 m	C 60 CMO 60	5.61	1.84	*1.03*	*60*	
Sabuncu 2003	(μmol/L)	6 m	C:14 CO:12	5.37	1.75	5.18	2	

17.10.2. Forest Plot COCP vs COCP + anti-obesity for DHEAS (μmol/L)



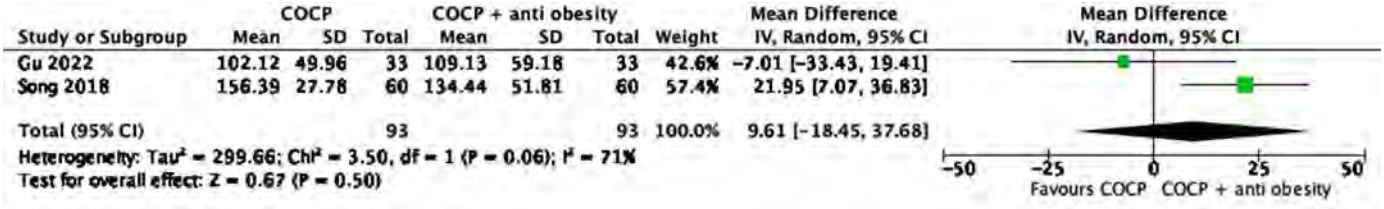
17.10.3. Funnel plot for assessment of publication bias



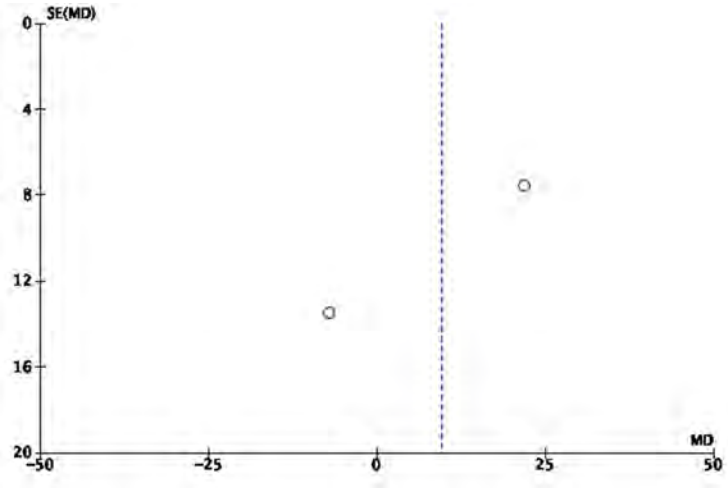
OUTCOME 17.11 INSULIN
17.11.1 Individual Study Data Table

	OUTCOME: insulin				OUTCOME TYPE: Continuous			
	COMPARISON (if applicable): COCP vs. COCP + anti-obesity							
Author, year	**Unit**	**Time point**	**N**	**COCP Mean**	**COCP SD**	**COCP + AO Mean**	**COCP + AO SD**	**Comments**
Gu 2022	Pmol/L	3 m	C 33 CO 33	102.12	49.96	109.13	59.18	
Song 2017	Pmol/L	3 m	C 60 CM 60	156.39	27.78	134.44	51.81	

17.11.2. Forest Plot COCP vs COCP + anti-obesity for insulin (IU/ml)



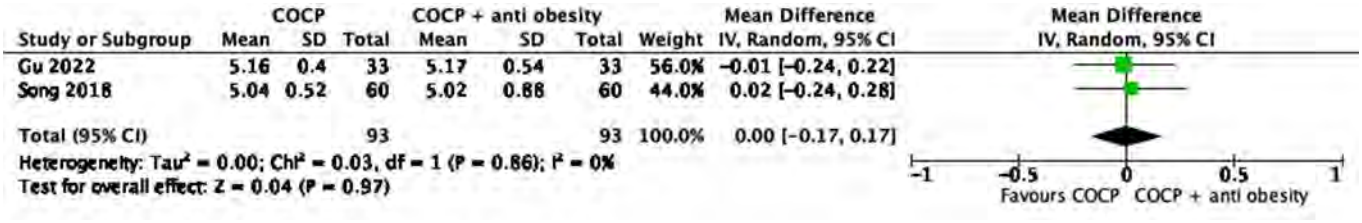
17.11.3. Funnel plot for assessment of publication bias



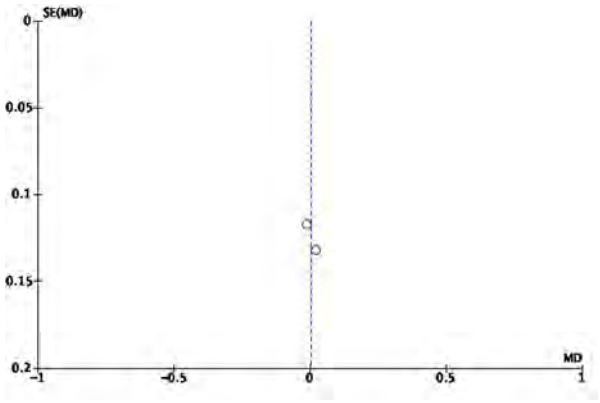
OUTCOME 17.12 GLUCOSE
17.12.1 Individual Study Data Table

OUTCOME: glucose					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. COCP + anti-obesity								
Author, year	**Unit**	**Time point**	**N**	**COCP Mean**	**COCP SD**	**COCP + AO Mean**	**COCP + AO SD**	**Comments**
Gu 2022	Mmol/L	3 m	C 33 CO 33	5.16	0.4	5.17	0.54	
Song 2017	Mmol/L	3 m	C 60 CM 60	5.04	0.52	5.02	0.88	

17.12.2. Forest Plot COCP vs COCP + anti-obesity for glucose (mmol/L)



17.12.3. Funnel plot for assessment of publication bias



OUTCOME 17.13 HOMA-IR

17.13.1 Individual Study Data Table

OUTCOME: HOMA-IR					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): COCP vs. COCP + anti-obesity								
Author, year	**Unit**	**Time point**	**N**	**COCP Mean**	**COCP SD**	**COCP + AO Mean**	**COCP + AO SD**	**Comments**
Song 2017	-	3 m	C 60 CAO 60	5.05	1.06	4.34	1.96	

OUTCOME 17.14 OGTT

17.14.1 Individual Study Data Table

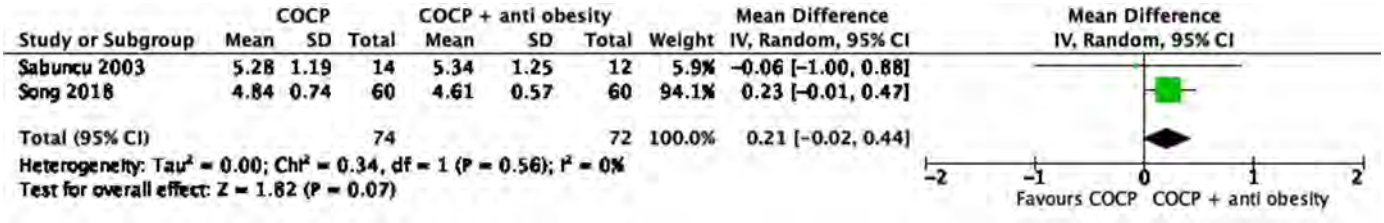
OUTCOME: OGTT					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): COCP vs. COCP + anti-obesity								
Author, year	**Unit**	**Time point**	**N**	**COCP Mean**	**COCP SD**	**COCP + AO Mean**	**COCP + AO SD**	**Comments**
Sabuncu 2003	AUC glucose *(mg/dL/h)*	6 m	C 14 C+AO 14	240.1	41.0	233.8	33.8	

OUTCOME 17.15 CHOLESTEROL

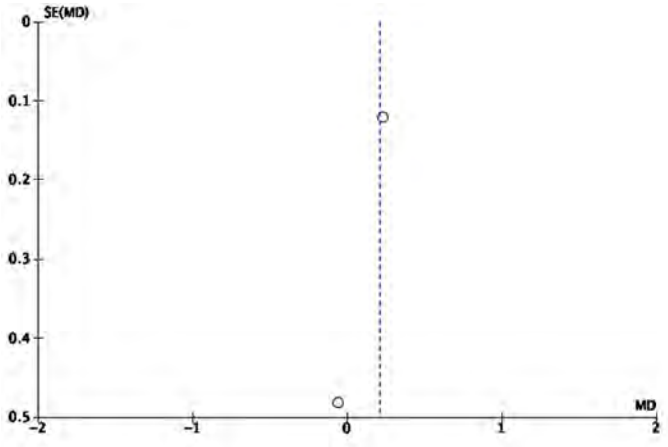
17.15.1 Individual Study Data Table

OUTCOME: cholesterol					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): COCP vs. COCP + anti-obesity								
Author, year	**Unit**	**Time point**	**N**	**COCP Mean**	**COCP SD**	**COCP + AO Mean**	**COCP + AO SD**	**Comments**
Gu 2022	Mmol/L	3 m	C 33 CO 33	Median 4.84		Median 4.81		NS
Song 2017	Mmol/L	3 m	C 60 CM 60	4.84	0.74	4.61	0.57	
Sabuncu 2003	Mmol/L	6 m	C:14 CO:12	5.28	1.19	5.34	1.25	

17.15.2. Forest Plot COCP vs COCP + anti-obesity for cholesterol (mmol/L)



17.15.3. Funnel plot for assessment of publication bias

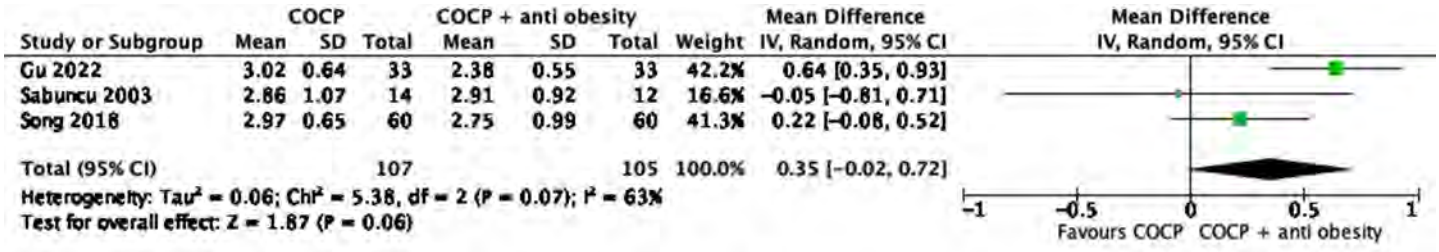


OUTCOME 17.16 LDL

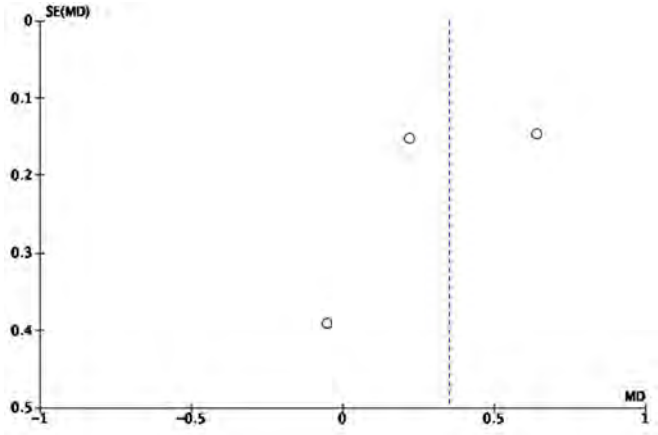
17.16.1 Individual Study Data Table

OUTCOME: LDL					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): COCP vs. COCP + anti-obesity								
Author, year	**Unit**	**Time point**	**N**	**COCP Mean**	**COCP SD**	**COCP + AO Mean**	**COCP + AO SD**	**Comments**
Gu 2022	Mmol/L	3 m	C 33 CO 33	3.02	0.64	2.38	0.55	NS
Song 2017	Mmol/L	3 m	C 60 CM 60	2.97	0.65	2.75	0.99	
Sabuncu 2003	Mmol/L	6 m	C:14 CO:12	2.86	0.65	2.91	0.92	

17.16.2. Forest Plot COCP vs COCP + anti-obesity for LDL (mmol/L)



17.16.3. Funnel plot for assessment of publication bias

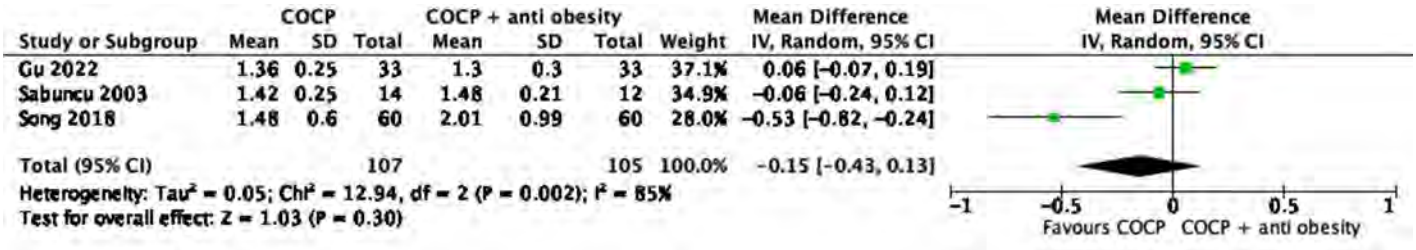


OUTCOME 17.17 HDL

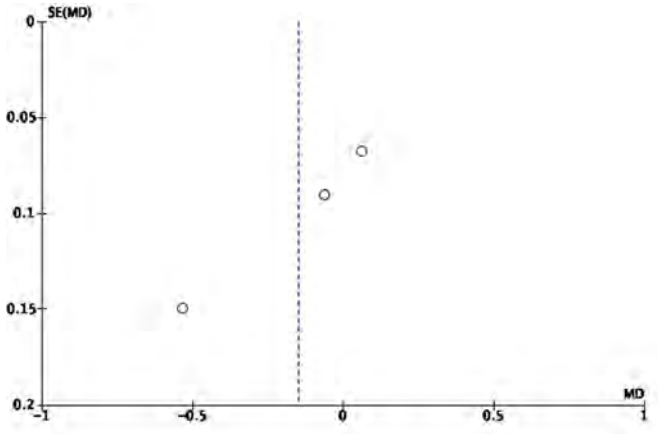
17.17.1 Individual Study Data Table

OUTCOME: HDL					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): COCP vs. COCP + anti-obesity								
Author, year	**Unit**	**Time point**	**N**	**COCP Mean**	**COCP SD**	**COCP + AO Mean**	**COCP + AO SD**	**Comments**
Gu 2022	Mmol/L	3 m	C 33 CO 33	1.36	0.25	1.30	0.30	
Song 2017	Mmol/L	3 m	C 60 CM 60	1.48	0.60	2.01	0.99	
Sabuncu 2003	Mmol/L	6 m	C:14 CO:12	1.42	0.6	1.48	0.21	

17.17.2. Forest Plot COCP vs COCP + anti-obesity for HDL (mmol/L)



17.17.3. Funnel plot for assessment of publication bias

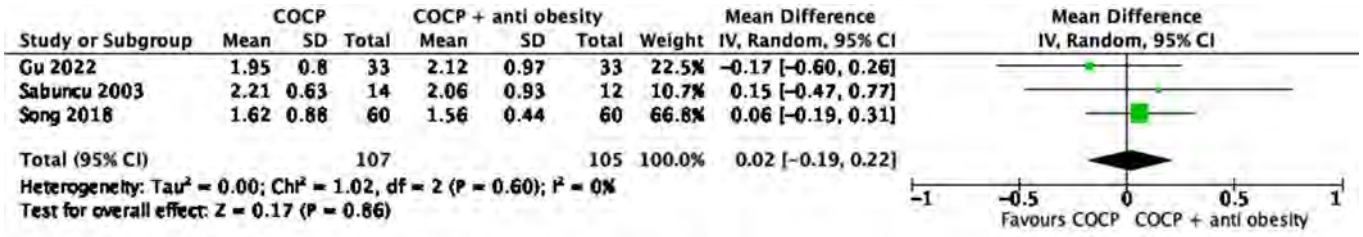


OUTCOME 17.18 TRIGLYCERIDES

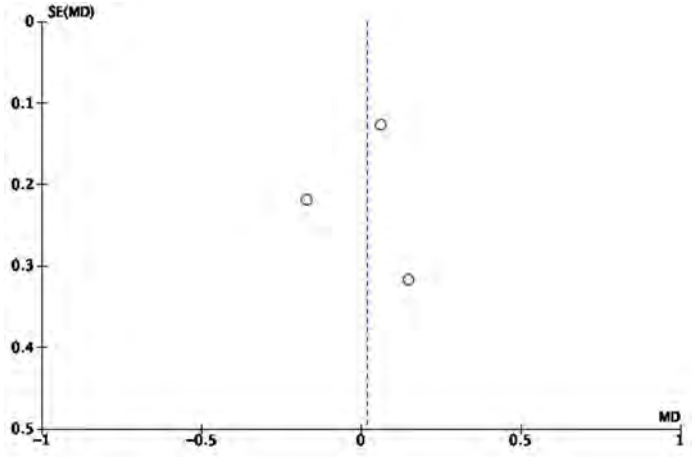
17.18.1 Individual Study Data Table

OUTCOME: TG						OUTCOME TYPE: Continuous		
COMPARISON (if applicable): COCP vs. COCP + anti-obesity								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	COCP + AO Mean	COCP + AO SD	Comments
Gu 2022	Mmol/L	3 m	C 33 CO 33	1.95	0.80	2.12	0.97	
Song 2017	Mmol/L	3 m	C 60 CM 60	1.62	0.88	1.56	0.44	
Sabuncu 2003	Mmol/L	6 m	C:14 CO:12	2.21	0.88	1.56	0.44	

17.18.2. Forest Plot COCP vs COCP + anti-obesity for triglycerids (mmol/L)



17.18.3. Funnel plot for assessment of publication bias



OUTCOME 17.19 CRP

17.19.1 Individual Study Data Table

OUTCOME: CRP						OUTCOME TYPE: Continuous		
COMPARISON (if applicable): COCP vs. COCP + anti-obesity								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	COCP + AO Mean	COCP + AO SD	Comments
Gu 2022	Mg/L	3 m	C 33 CO 33	4.69	3.84	4.43	3.69	
Song 2017	Mmol/L	3 m	C 60 CM 60	1.62	0.88	1.56	0.44	
Sabuncu 2003	Mmol/L	6 m	C:14 CO:12	2.21	0.88	1.56	0.44	

Adverse effects
Sabuncu 2003 did not report on adverse effects, neither did Gu 2022. Ruan/Song reported that 21 of the patients treated with COCP (as single treatment or in combination, total n=180)) experienced side effects including headaches, nausea, weight gain, breast tenderness, and loss of libido. There were no cases of venous thrombosis. Five patients who received anti obesity treatment (orlistat, together with COCP or a combination of COCP and metformin, total n=120) experienced gastrointestinal adverse effects (mainly flatulence and oily spotting) during the first 2 weeks of treatment, which decreased in frequency with ongoing treatment. No subject stopped treatment or required any dose reduction. Gu 2022 did not report adverse effects.

Comparison 18: COCP + metformin vs. COCP + anti-obesity

- **EVIDENCE SUMMARY:**

One RCT, with a high risk of bias, and with two publications, Song 2017 (29) and Ruan 2018 (30), were identified. COCP containing EE/CPA were given to both groups. One group had orlistat 120 mgx3, and one group had metformin 1500 mg/day, in addition to the COCP treatment, n=60 in both groups. The study had a duration for 3 months and had a high risk of bias.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

Results are reported narratively. Triglycerides and cholesterol levels were lower and HDL levels higher after treatment with COCP + anti-obesity, compared with COCP + metformin, with very low certainty of evidence. For other outcomes, there were no certain differences between the groups, with very low certainty of evidence.

Included studies:

Study ID	ROB	Comparisons	Country, duration	N	Mean age	Mean BMI	PCOS diagnosis	Menarche age	Smokers	Comments	Outcomes relevant to this review
Song 2017 (29) Ruan 2018 (30)	High	(1) 35 µg EE + 2 mg CPA (2) 35 µg EE + 2 mg CPA + Orlistat 120 mgx3 (3) 35 µg EE + 2 mg CPA + metformin 1500 mg/day (4) 35 µg EE + 2 mg CPA + Orlistat 120 mgx3 + metformin 1500 mg/day	China 12 weeks	1:60 2:60 3:60 4:60	1: 27.68 ± 4.99 2: 26.77 ± 4.12 3: 28.63 ± 5.12 4: 27.57 ± 4.58	1: 28.64 ± 4.89 2: 27.85 ± 4.10 3: 27.00 ± 3.47 4: 28.76 ± 3.43	Rott	NR	1: 22% 2: 20% 3: 25% 4: 18%		TT, chol, LDL, HDL, glucose, insulin, HOMA, From Ruan DHEAS, FAI, fT, androstendione, SHBG,, adverse effects

Result from the individual RCT. All outcomes had a a very low certainty of evidence due to risk of bias (-2), imprecision (-1, only one study involving one population).

Outcome	Unit	COCP + met Mean	COCP + met SD	COCP + anti obesity Mean	COCP + anti obesity SD	P value	Favours	Importance
TT	Ng/dl	44.92	20.26	44.28	18.92	0.86	No difference	IMPORTANT
DHEAS	µg/dl	172.29	48.83	175.02	38.10	0.73	No difference	IMPORTANT
A4	Nmol/L	6.39	3.05	7.09	3.99	0.28	No difference	IMPORTANT
SHBG	Nmol/L	73.33	48.01	72.41	15.33	0.89	No difference	IMPORTANT
fT	Nmol/L (?)	1.37	0.85	1.41	0.97	0.81	No difference	IMPORTANT
FAI	-	2.90	2.38	2.15	1.91	0.06	No difference	IMPORTANT
TG	Mmol/L	1.85	0.60	1.56	0.44	<0.01	COCP + anti-obesity	IMPORTANT
Cholesterol	Mmol/L	4.99	1.06	4.61	0.57	<0.05	COCP + anti-obesity	IMPORTANT
HDL	Mmol/L	1.70	0.66	2.01	0.99	<0.05	Higher after COCP + anti-obesity	IMPORTANT
LDL	Mmol/L	2.95	0.64	2.75	0.99	0.17	No difference	IMPORTANT
Glucose	Mmol/L	4.91	0.54	5.02	0.88	0.41	No difference	IMPORTANT
Insulin	mIU/L	21.37	4.10	19.36	7.46	0.07	No difference	IMPORTANT
HOMA	-	4.66	1.02	4.34	1.96	0.26	No difference	IMPORTANT

Regarding adverse effects, see comparison 19.

Comparison 19: COCP vs. COCP + metformin + anti-obesity

- **EVIDENCE SUMMARY:**

One RCT, with a high risk of bias, with two publications, Song 2017 (29) and Ruan 2018 (30), were identified. EE/CPA treatment alone was compared with the combination of EE/CPA + orlistat + metformin, n=60 in both groups. The study had a duration for 3 months.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

The combination of COCP + metformin + anti-obesity treatment resulted in higher SHBG, lower free testosterone, higher HDL and lower insulin and HOMA-IR compared with COCP alone, with very low certainty of evidence. However, triglycerides were lower after COCP alone, with very low certainty. No difference was seen for other outcomes, with very low certainty.

One RCT with two publications, Song 2017 (29) and Ruan 2018 (30), were identified.:

Study ID	ROB	Comparisons	Country, duration	N	Mean age	Mean BMI	PCOS diagnosis	Menarche age	Smokers	Comments	Outcomes relevant to this review
Song 2017 (29) Ruan 2018 (30)	High	(1) 35 µg EE + 2 mg CPA (2) 35 µg EE + 2 mg CPA + Orlistat 120 mgx3 (3) 35 µg EE + 2 mg CPA + metformin 1500 mg/day (4) 35 µg EE + 2 mg CPA + Orlistat 120 mgx3 + metformin 1500 mg/day	China 12 weeks	1:60 2:60 3:60 4:60	1: 27.68 ± 4.99 2: 26.77 ± 4.12 3: 28.63 ± 5.12 4: 27.57 ± 4.58	1: 28.64 ± 4.89 2: 27.85 ± 4.10 3: 27.00 ± 3.47 4: 28.76 ± 3.43	Rott	NR	1: 22% 2: 20% 3: 25% 4: 18%		TT, DHEAS, androstendione, SHBG, FAI, adverse effects From Song chol, LDL, HDL, glucose, insulin, HOMA,

Result from the individual RCT. All outcomes had a a **very low certainty of evidence** due to risk of bias (-2), imprecision (-1, only one study involving one population).

Outcome	Unit	COCP Mean	COCP SD	COCP + met + anti obesity Mean	COCP + met + anti obesity SD	P value	Favours	Importance
TT	Ng/dl	44.29	10.30	43.13	12.94	0.59	No difference	IMPORTANT
DHEAS	µg/dl	206.85	67.75	*177.72*	*94.93*	0.06	No difference	IMPORTANT
A4	Nmol/L	7.89	2.86	*7.51*	2.98	0.48	No difference	IMPORTANT
SHBG	Nmol/L	58.47	46.87	85.41	67.51	0.01	COCP + met + AO higher	IMPORTANT
fT	Nmol/L (?)	1.47	0.54	1.19	0.67	0.01	COCP + met + AO	IMPORTANT
FAI	-	4.59	5.91	3.01	3.24	0.07	No difference	IMPORTANT
TG	Mmol/L	1.48	0.60	1.94	1.20	<0.01	COCP	IMPORTANT
Cholesterol	Mmol/L	4.84	0.74	4.81	0.67	0.82	No difference	IMPORTANT
HDL	Mmol/L	1.48	0.60	1.85	0.43	<0.001	COCP + met + AO higher	IMPORTANT
LDL	Mmol/L	2.97	0.65	2.79	0.67	0.14	No difference	IMPORTANT
Glucose	Mmol/L	5.04	0.52	5.03	0.62	0.92	No difference	IMPORTANT
Insulin	mIU/L	22.52	4.00	20.61	4.48	<0.05	COCP + met + AO	IMPORTANT
HOMA	-	5.05	1.06	4.58	1.06	<0.05	COCP + met + AO	IMPORTANT

ADVERSE EFFECTS

The RCT described above (29, 30) had four arms, COCP vs. COCP + metformin vs. COCP + anti-obesity vs. COCP + metformin + anti-obesity, n=60 per arm. Adverse effects are described for the whole group:

Twenty-one patients who took **COCP** experienced side effects including headaches, nausea, weight gain, breast tenderness, and loss of libido. However, in general, COCP was well tolerated and no cases of venous thrombosis was observed.

Five patients who received **anti-obesity** treatment (orlistat) experienced gastrointestinal adverse effects (mainly flatulence and oily spotting) during the first 2 weeks of treatment, which decreased in frequency with ongoing treatment. No subject stopped treatment or required any dose reduction.

Nine patients taking **metformin** 1500 mg/day reported side-effects such as mild nausea and abdominal pain. Four patients tolerated the dose gradually, while in another five patients the tolerated dose was 1000 mg/day.

Comparison 20: COCP vs. metformin

- **EVIDENCE SUMMARY:**

In total 25 RCTs with 33 publications were included in this comparison, 21 RCTs (29 publications) involved adults and 4 RCTs studied adolescents.

Glintborg 2014a (32) was the first publication from an RCT comparing COCP (n=23), metformin (n=19) or a combination (not included in this comparison). Three further publications from the same RCT followed, Glintborg 2014b (33), Glintborg 2017 (34), Altinok 2018 (35).

Meyer 2007 (36) was the first publication from an Australian RCT comparing COCP (n=31) and metformin (n=36) (an arm with COCP + anti-androgens was also included in the RCT, not reported under this outcome). Later publications from the same RCT includes Hutchison 2008 (37), Moran 2010 (38) and Burchall 2017 (39). In some of the publications, only mean change is reported. When possible, publications reporting mean ± SD have been chosen to allow inclusion in meta-analyses.

Two of the included studies, Kilic 2011 (40) and Wu 2008 (41), are reported on subgroup level (thus reported as two), since the authors in the publications only report outcomes in that way.

Both Panidis 2011 (15) and Christakou 2014 (12) included two COCP groups and one metformin group. For both studies, the COCP containing EE/DRSP was used in the meta-analysis, not the group with EE/CPA, since CPA is not a progestin per se.

- **META-ANALYSIS/DESCRIPTIVE ANALYSIS SUMMARY:**

A meta-analysis, including subgroup analysis for adults and adolescents, was performed. In the overall analysis, there were no differences between treatments regarding BMI, weight or WHR, with very low certainty of evidence. No differences were seen in the subgroups. Menstrual cycle duration became shorter after COCP treatment compared with metformin, with moderate certainty of evidence.

Regarding hyperandrogenism, there was no difference in hirsutism (very low certainty of evidence), but COCP treatment resulted in lower FAI, total testosterone and higher SHBG levels, all with a low certainty of evidence, and in lower free testosterone with a very low certainty. Both androstenedione and DHEAS were lower after COCP treatment, with low and very low certainty, respectively.

In adolescents, similar results were seen regarding hyperandrogenism, but with very low certainty of evidence, except for total testosterone, which was lower after COCP treatment with moderate certainty of evidence. For free testosterone, no difference was seen in between treatments, with very low certainty of evidence. There were no studies in the adolescent cohort with androstenedione or DHEAS as outcomes for this comparison.

In adults, there was no difference in hirsutism with a very low certainty. FAI and total testosterone levels were lower after COCP treatment with low certainty and free testosterone lower with very low certainty. SHBG levels were higher (low certainty), androstenedione lower (moderate certainty) and DHEAS lower (very low certainty) after COCP treatment.

Regarding metabolic outcomes, insulin was lower overall (low certainty), and in adults (moderate certainty) after metformin. In adolescents there was no difference (very low certainty of evidence). Glucose levels did not differ, overall or in the subgroups. HOMA-IR was lower after metformin treatment bort overall and in adults, very low and low certainty of evidence, respectively. Cholesterol levels were lower after metformin both overall (very low certainty) and in subgroups (low certainty). There were no differences in LDL, HDL or triglyceride levels, except for adiolescents, where lower LDL levels were seen after metformin treatment (low certainty).

CRP levels were lower after metformin treatment, both overall (low certainty), in adults (low certainty), and in adolescents (very low certainty).

No difference was seen regarding PAI-1 levels.

Included studies:

Study ID	ROB	Comparisons	Country, duration	N	Mean age	Mean BMI	PCOS	Menarche age	Smokers	Comments	Outcomes relevant to this review
Aghamohammadzadeh 2010 (42)	High	1:EE 35µg + CPA 2mg 2: Metformin 1000 mg/d	Iran 3 + 6 months	1=30 2=30	All 23.4±8.1 years	All 25.57±5.4	NIH	NR	NR		TT, DHEAS, CRP, weight, BMI
Allen 2005 (43)	Low	C) 35ug EE + 0.25mg NOR/day M) 1000mg MET/day	USA 6 months	C: 15 M: 16	C: 15.3 (12.5-21) M: 15.4 (13.1-18.4)	C: 40.1 ± 2.1 M: 37.3 ± 1.3	Author defined			adolescents	BMI, weight, TT, fT, insulin, glucose/insration, QUICKI, chol, LDL, HDL, TG,
Al-Zubeidi 2015 (44)	High	C) 30ug EE + 1mg NORA/day M) 2000mg MET/day	USA 6 months	NIH	C: 10 M: 12	C: 16 (15-17) M: 16 (14-18)	C: 33.4 ± 9 M: 33.7 ± 6	>2 yrs post menarche	NR	adolescents	BMI, fT, TT, inslulin, HOMA, SHBG, HDL, TG, QOL,
Bodur 2018 (19)	High	1: 30 ug EE + 3 mg DRSP 2: 1700 g Met 3: 30 ug EE + 3 mg DRSP + 1700 g Met 4: controls, no mediciation	Turkey 6 months	1=17 2=17 3=12 4=15	1: 26.62 ± 4.92 2: 26.24 ± 3.96 3: 27.35 ± 5.65 4: 29.18 ± 5.20	1: 23.45 ± 3.40 2: 25.06 ± 3.08 3: 25.11 ± 3.75 4: 23.82 ± 2.80	Rott	NR	NR		CRP, PAI-1, fS-glucose, HOMA
Cetinkalp 2009 (45)	High	1: 35ug EE +2 mg CPA 2: metformin 2g/day	Turkey 4 months	1:33 2:47	Not reported	1: 24.72±4.1 2: 25.82±6.1	Rotterdam	NR	NR		BMI, weight, TG, Chol, LDL, HDL, insulin, glucose, HOMA, DHEAS, free T, TT, CRP, oligo-/amenorrhea, FG score
Christakou 2014 (12)	Mod	1: 35ug EE +2 mg CPA 2: 30 ug EE + 3 mg DRSP 3: met 1700 mg/day	Greece 3 + 6 months	1: 38 2: 36 3:3 5	1: 22±0.6 2: 23.2±0.6 3: 21.5±0.5	1: *21.80±0.35* *2: 22.37±0.48* *3: 23.03±0.67*	NIH	NR	All non-smokers	EE/DRSP used in meta-analysis	BMI, HOMA, TT, SHBG, FAI, CRP
Dardzinska 2014 (46)	Mod	C) 35µg EE + 2mg CPA M) 850mg MET BID (1700mg/d) 2 months washout	Poland 4 months	Phase 1 C: 21 M: 14 Phase 2 C: 14 M: 7	C 1st: 24.9 [23.5;26.4] M 1st: 24.6 [23.0;26.3]	C 1st: 24.9 ± 4.4 M 1st: 25.1 ± 9.8C 1st: 24.9 [23.5;26.4] M 1st: 24.6 [23.0;26.3]	Rotterdam	NR	20% of all	(Crossover)	BMI, weight, FG score, TT, A4, SHBG, FAI, chol, TG, LDL, HDL, HOMA, CRP
Dorgham 2021 (20)	High	1: only laser 2: laser + metformin 500 mg 3: laser 35 µg EE + 2 mg cyproterone acetate	Egypt 6 months (results available also for 3 months)	1:50 2:50 3:50	NR	NR	Rott	NR	NR	Facial hirsutism required	HR-QoL (VAS, Dermatology Life Quality Index (DLQI) Hisutism Life Quality Index) (HLQI))
El Maghraby 2015 (21)	High	1: 30ug EE + 15mg progestin/ day 2: 1700mg MET/day 3: controls	Egypt (6, 12, 18, 24 m) 2 years	1: 33 2: 32 3: 25	1: 16.90 ± 1.60 2: 17.20 ± 2.00 3: 17.00 ±2.10	NR	Rott	NR	NR	adolescents	TT, ins, GIR, weight

Glintborg 2014a (32) Glintborg 2014b (33) Altinok 2018 (35) Glintborg 2017 (34)	High	1: 30 μg EE + 150 mg DSG 2: met 2000 mg/day 3: combo	Denmark 12 months	1:23 2:19 3:23	Median, 25-75 percentile: 1: 28 (24; 32) 2: 31 (24; 33) 3: 30 (24; 31)	Median, 25-75 percentile: 1: 28.0 (22.9; 31.8) 2: 25.9 (24.1; 29.6) 3: 27.6 (24.3; 31.2)	Rott	NR	NR	Nothing extracted from Glintborg 2014b	Change in: Weight, BMI, FG, TT, SHBG, insulin, HOMA, In 2017: OGTT From Altinok: HR QoL: PCOS-specific visual analog scale (PCOS-VAS) with six items regarding discomforts with PCOS, PCOS-VAS1: Facial hair, PCOS-VAS2: Body hair, PCOS-VAS3: Acne, PCOS-VAS4: Menstrual irregularities, PCOS-VAS5: Weight and PCOS-VAS6: PCOS in general. SF-36
Harborne 2003 (47)	Mod	C) 35μg EE + 2mg CPA 21/7 M) 500mg MET TID (1500mg/d)	Scotland 12 months	C: 26 M: 26	C: 31.7 [26.8-36.5] M: 31.3 [27.9-34.7]	C: 31.8 [28.4-34.4] M: 31.7 [29.5-35.5]	Rotterdam	NR	NR		Hirsutism, insulin, glucose, HOMA, TT, SHBG, FAI, DHEAS, A4, BMI, WHR, chol, TG, LDL, HDL, side effects
Hoeger 2008 (22)	Mod	1. 30 μg EE + 0.15 mg DSG 2. Placebo 3. Lifestyle addressing diet, exercise, behaviour 4: 1700 mg met/day	USA 6 months	1 = 10 2 = 10 3 = 8 4 = 6	1: 15.4±1.4 2: 15.4±1.7 3: 15.4±1.2 4: 15.4±1.7	1: 37.8±5.1 2: 36.1±7.5 3: 37.8±8.2 4: 36.1±7.5	Rotterdam	NR	All nonsmokers	Obese cohort Adolescents	FG score FAI, total T, SHBG, , chol, LDL, HDL, TG, CRP, BMI, PAI-1
Kebapcilar 2010 (48)	High	1: 35 μg EE/2mg CPA 2: 35 μg EE/2mg CPA + met 1700 mg/day 3: metformin 1700 mg/day 4: met 1700 mg/day + spiro 100 mg/day	Turkey 3 months	12/group	24.0±5.4 years; for all	1: 28.7 ±6 2: 27.6 ± 3 3: 27.8 ± 4 4: 27.6 ± 4	Rott	NR	excluded		BMI, fT, DHEAS, insulin, HOMA, TG, LDL, HDL,
Kilic 2011 (40)	Low	C) 0.03mg EE + 0.15mg DSG M) 850mg MET 2/d (1700mg)	Turkey 6 months	Obese C: 25 M: 24 Non-Obese C: 24 M: 23	Obese C: 29.0 ± 3.5 M: 28.7 ± 3.7 Non-obese C: 26.7 ± 3.8	Obese C: 27.7±0.9 M: 31.5±2.2 Non-obese	Rotterdam	NR	excluded		BMI, CRP, HOMA

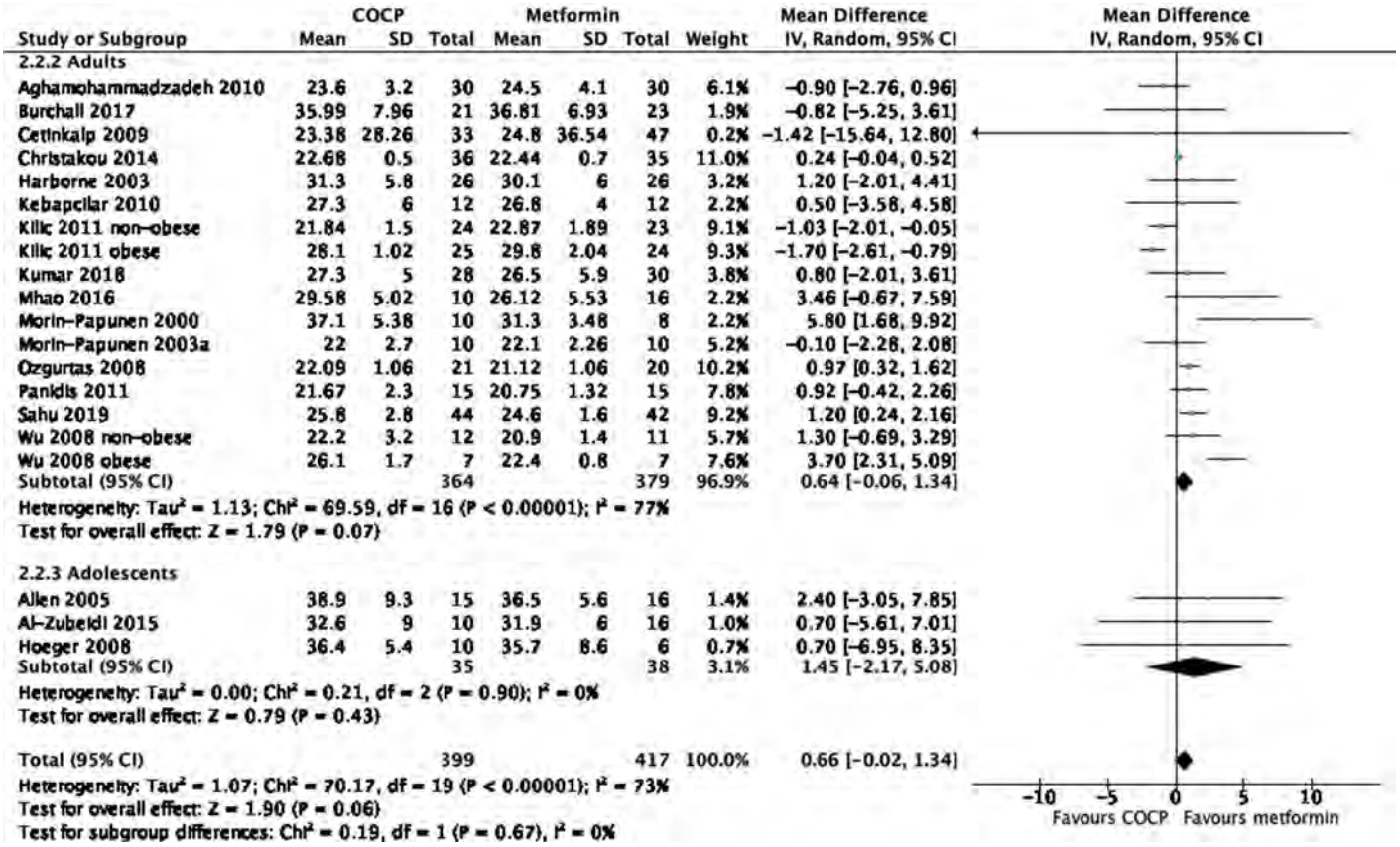
					M: 26.3 ± 3.0	C: 21.6±1.4 M: 23.3±1.6					
Kumar 2018 (49)	Mod	1: 35 µg EE/2mg CPA 2: metformin 2000 mg/day 3: 35 µg EE/2mg CPA + met 2000mg/day	India 6 months	1:28 2:30 3:29	1: 22.9 (5) 2: 22 (5.2) 3: 24.1 (5.9)	1: 26.15 (4.9) 2: 27.14 (6) 3: 30.10 (5.5)	Rott	NR	NR		BMI, weight, hirsutism score, TT, DHEAS, insulin, glucose, HOMA, TG, LDL, HDL, chol, CRP,
Luque-Ramírez 2009 (50)	Mod	1: 35 µg EE/2mg CPA 2: 1700 mg met/day	Spain 24 weeks	1: 15 2:19	1: *23.4 5.6* *2: 25.1 6.6*	1: *29.2 5.7* *2: 30.5 6.9*	NIH	NR	1:40% 2: 42%		Adverse effects
Meyer 2007 (36) Burchall 2017 (39) Hutchison 2008 (37) Moran 2010 (38)	Mod	HC) 35µg EE + 2mg CPA (high) LC) 20µg EE + 100µg LVG + 50mg SPL (low dose)*** M) 1g MET 2/d (2000mg/d)	Australia 6 months	HC: 31 LC: 33 M: 36	Average: 31 years	HC: 36.5 no SD LC: 35.5 no SD M: 36.3 no SD	NIH	NR	Excluded		Weight, BMI, glucose, insulin, HOMA, OGTT, chol, LDL, HDL, TG, CRP, TT, SHBG, FAI, PAI-1
Mhao 2016 (51)	High	1: EE 30 µg /CMA 2mg 2: met 1000 mg/day	Iraq 3 months	1:10 2:16	Age range 14-40 yrs	1: 30.5±5.3 2:27.2±5.4	NR	NR	NR		BMI, WHR, FG scorechol, HDL, LDL, TG, TT, OGTT
Morin-Papunen 2003a (52) Morin-Papunen 2000 (53) Morin-Papunen 2003b (54) Rautio 2005 (55)	Mod Mod	C) 35µg EE + 2mg CPA 21/7 M) 500mg bd 3 months (1000mg), then 1000mg bd next 3 months (2000mg)	Finland 6 months	Non-obese: C: 10 M: 10 Obese: C: 10 M: 8	C: 28.5±1.7 (SE) M: 28.2±1.4 Obese: C: 29.8±1.0 (SE) M: 29.9±1.5	C: 21.8±0.7 (SE) M 22.5±0.8 Obese: C: 37.2±1.8 (SE) M 32.5±1.1	Aligns with Rotterdam			Morin-Papunen 2003a (52) Non-obese cohort; Morin-Papunen 2000 (53) Obese cohort Morin-Papunen 2003b and Rautio 2005 combined cohort	BMI, WHR, Hirsutism score, period, glucose, insulin, clamp, TT, SHBG, FAI, A4, DHEAS, From Morin-Papunen 2003b CRP From Rautio chol, HDL, LDL, TG,
Moro 2013 (56)	Mod	1: 0.03mg EE + 3mg DRSP 2: 500mg MET 3/d (1500mg/d) 3: [0.03mg EE + 3mg DRSP] + 500mg MET 3/d (1500mg/d)	Italy 6 months	C: 25 M: 25 CM: 26	C: 26±3 M: 25±5 CM: 25±4	Median (range) C: 23.7 (20.8-28.6) M: 25.1 (21.9-28.3) CM:26.5(21.3-30)	Rotterdam	NR	1: 36% 2: 40% 3: 38%	*Described as hyperinsulinemic*	BMI, WHR, insulin, HOMA, chol LDL, HDL, TG, TT, SHBG, FAI, A4, DHEAS,
Ozgurtas 2008 (57)	High	1: 35 µg EE + 2 mg CPA	Turkey 3 months	1=21 2=20	NR (≥18 yrs)	1: 21.72 ±1.24	Rott	NR	All non-smokers	All non-obese	BMI, WHR, HOMA, chol, TG, HDL, LDL,

		2: met 1700mg/day				2: 21.81 ± 1.27					TT, fT, A4, DHEAS, SHBG
Panidis 2011 (15)	High	1: 35 µg EE + 2 mg CPA 2: 3 mg DRSP/30 mcg EE 3: met 1700mg/day	Greece 6 months	1=15 2=15 3=15	1: 20.67 ± 4.13 2: 22.00 ± 2.07 3: 20.53 ±3.09	1: 21.04 + 1.97 2: 21.69 + 2.33 3: 21.83 + 1.73	NIH	NR	NR	EE/DRSP used in meta-analysis	BMI, HOMA, glucose, insulin, TT, A4, DHEAS, SHBG, FAI
Sahu 2019 (58)	Mod	1: 35 ug EE + 2 mg CPA 21/7 2: metformin 500 mg x 2	India 6 months	C 44 M 42	1: 26.8 ±4.2 2: 27.0 ±5.2	1: 25.6 ±2.7 2: 25.7 ±2.6	Rott	NR	All non-smokers		BMI, cycle duration, hirsutism, TT, SHBG, DHEAS, chol, HDL, LDL, TG, glucose, insulin, HOMA
Wu 2008 (59)	Mod	C) 35µg EE + 2mg CPA M) 500mg MET 3/d (1500mg/d) CM: 35µg EE + 2mg CPA + 500mg MET 3/d (1500mg/d)	China 3 months	Obese C: 7 M: 7 CM:6 Non-Obese C: 12 M: 11 CM: 10	Obese C: 25.0±4.3 M: 25.6±3.6 CM: 24.5±2.4 Non-obese C: 26.1±4.6 M: 25.6±4.2 CM: 25.8±4.0	Obese C: 25.3±0.8 M: 25.6±0.6 CM: 25.2±1.0 Non-obese C: 21.4±1.6 M: 21.5±1.8 CM: 21.6±1.4	Rotterdam	NR	Excluded		BMI, FG score, WHR, insulin,

OUTCOME 20.1 BMI
20.1.1 Individual Study Data Table

OUTCOME: BMI						**OUTCOME TYPE:** Continuous		
COMPARISON (if applicable): COCP vs. met								
Author, year	**Unit**	**Time point**	**N**	**COCP Mean**	**COCP SD**	**met Mean**	**met SD**	**Comments**
Aghamohammadzadeh 2010	kg/m2	6 months	High dose COCP=30 met = 30	23.6	3.2	24.5	4.1	
Burchall 2017 (same as Meyer and Moran)	kg/m2	6 months	High dose COCP=21 met = 23	35.99	7.96	36.81	6.93	
Cetinkalp 2009	kg/m2	4 months	COCP=33 met=47	23.38	4.92 (SEM)	24.8	5.33 (SEM)	
Christakou 2014	kg/m2	6 m	EE/CPA=38 EE/DRSP=36 met=35	22.28 22.68	0.37 0.50	22.44	0.70	
Dardzinska 2014	kg/m2	4 m	COCP 21 met 14	Median (CI) 24.4 (23.2; 26.2)		25.1 (23.8; 27.1)		
Harborne 2003	kg/m2	12 m	COCP 26 met 26	31.3	5.8	30.1	6	
Glintborg 2014-1	kg/m2	12 m	COCP 23 met 19					Median change 0.38 (0.44; 1.17) - 1.0 (3.7; 0.2) p<0.05
Kebapcilar 2010	kg/m2	3 m	COCP 12 Met 12	27.3	6	26.8	4	
Kilic 2011-obese	kg/m2	6 m	C 25 M 24	28.10	1.02	29.8	2.04	
Kilic 2011-non obese	kg/m2	6 m	C 24 M 23	21.84	1.50	22.87	1.89	
Kumar 2018	kg/m2	6 m	C 28 M 30	27.3	5	26.5	5.9	
Mhao 2016	kg/m2	3 m	C 10 M 16	29.58	5.02	26.12	5.53	
Morin-Papunen 2000 (obese)	kg/m2	6 m	C10 M8	37.1	5.38	31.3	3.48	
Morin-Papunen 2003 (non-obese)	kg/m2	6 m	C10 M10	22	2.7	22.1	2.26	
Moro 2013	kg/m2	6 m	C 25 CM 26	Median, range 21.9 (20.4-27.8)		Median, range 23.5 (20.4-28.3)		
Ozgurtas 2008	kg/m2	3 m	C 21 M20	22.09	1.06	21.12	1.06	
Panidis 2011	kg/m2	6 m	COCP1: 15 COCP2: 15 Met: 15	21.05 21.67	1.99 2.30	20.75	1.32	
Sahu 2019	kg/m2	6 m	C 44 M 42	25.8	2.8	24.6	1.6	
Wu 2008 obese	kg/m2	3 m	C: 7 M: 7	26.1	1.7	22.4	0.8	
Wu 2008 Non obese	kg/m2	3 m	C: 12 M: 11	22.2	3.2	20.9	1.4	
Allen 2005	Kg/m^2	6 m	COCP 15 Met 16	38 9	9.3	36.5	5.6	

20.1.2. Forest Plot COCP vs metformin for BMI (kg/m2)



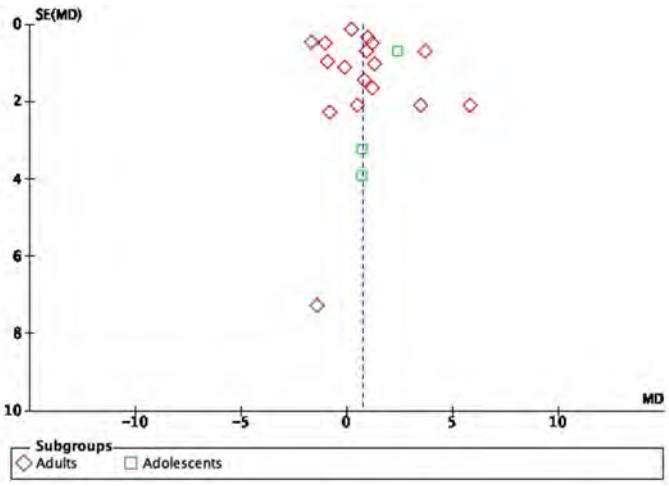
Study or Subgroup	COCP Mean	COCP SD	COCP Total	Metformin Mean	Metformin SD	Metformin Total	Weight	Mean Difference IV, Random, 95% CI
2.2.2 Adults								
Aghamohammadzadeh 2010	23.6	3.2	30	24.5	4.1	30	6.1%	−0.90 [−2.76, 0.96]
Burchall 2017	35.99	7.96	21	36.81	6.93	23	1.9%	−0.82 [−5.25, 3.61]
Cetinkaip 2009	23.38	28.26	33	24.8	36.54	47	0.2%	−1.42 [−15.64, 12.80]
Christakou 2014	22.68	0.5	36	22.44	0.7	35	11.0%	0.24 [−0.04, 0.52]
Harborne 2003	31.3	5.8	26	30.1	6	26	3.2%	1.20 [−2.01, 4.41]
Kebapcilar 2010	27.3	6	12	26.8	4	12	2.2%	0.50 [−3.58, 4.58]
Kilic 2011 non-obese	21.84	1.5	24	22.87	1.89	23	9.1%	−1.03 [−2.01, −0.05]
Kilic 2011 obese	28.1	1.02	25	29.8	2.04	24	9.3%	−1.70 [−2.61, −0.79]
Kumar 2018	27.3	5	28	26.5	5.9	30	3.8%	0.80 [−2.01, 3.61]
Mhao 2016	29.58	5.02	10	26.12	5.53	16	2.2%	3.46 [−0.67, 7.59]
Morin-Papunen 2000	37.1	5.38	10	31.3	3.48	8	2.2%	5.80 [1.68, 9.92]
Morin-Papunen 2003a	22	2.7	10	22.1	2.26	10	5.2%	−0.10 [−2.28, 2.08]
Ozgurtas 2008	22.09	1.06	21	21.12	1.06	20	10.2%	0.97 [0.32, 1.62]
Panidis 2011	21.67	2.3	15	20.75	1.32	15	7.8%	0.92 [−0.42, 2.26]
Sahu 2019	25.8	2.8	44	24.6	1.6	42	9.2%	1.20 [0.24, 2.16]
Wu 2008 non-obese	22.2	3.2	12	20.9	1.4	11	5.7%	1.30 [−0.69, 3.29]
Wu 2008 obese	26.1	1.7	7	22.4	0.8	7	7.6%	3.70 [2.31, 5.09]
Subtotal (95% CI)			364			379	96.9%	0.64 [−0.06, 1.34]
Heterogeneity: $Tau^2 = 1.13$; $Chi^2 = 69.59$, df = 16 ($P < 0.00001$); $I^2 = 77\%$								
Test for overall effect: Z = 1.79 (P = 0.07)								
2.2.3 Adolescents								
Allen 2005	38.9	9.3	15	36.5	5.6	16	1.4%	2.40 [−3.05, 7.85]
Al-Zubeidi 2015	32.6	9	10	31.9	6	16	1.0%	0.70 [−5.61, 7.01]
Hoeger 2008	36.4	5.4	10	35.7	8.6	6	0.7%	0.70 [−6.95, 8.35]
Subtotal (95% CI)			35			38	3.1%	1.45 [−2.17, 5.08]
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.21$, df = 2 ($P = 0.90$); $I^2 = 0\%$								
Test for overall effect: Z = 0.79 (P = 0.43)								
Total (95% CI)			399			417	100.0%	0.66 [−0.02, 1.34]
Heterogeneity: $Tau^2 = 1.07$; $Chi^2 = 70.17$, df = 19 ($P < 0.00001$); $I^2 = 73\%$								
Test for overall effect: Z = 1.90 (P = 0.06)								
Test for subgroup differences: $Chi^2 = 0.19$, df = 1 (P = 0.67), $I^2 = 0\%$								

Mean Difference IV, Random, 95% CI

−10 −5 0 5 10

Favours COCP Favours metformin

20.1.3. Funnel plot for assessment of publication bias

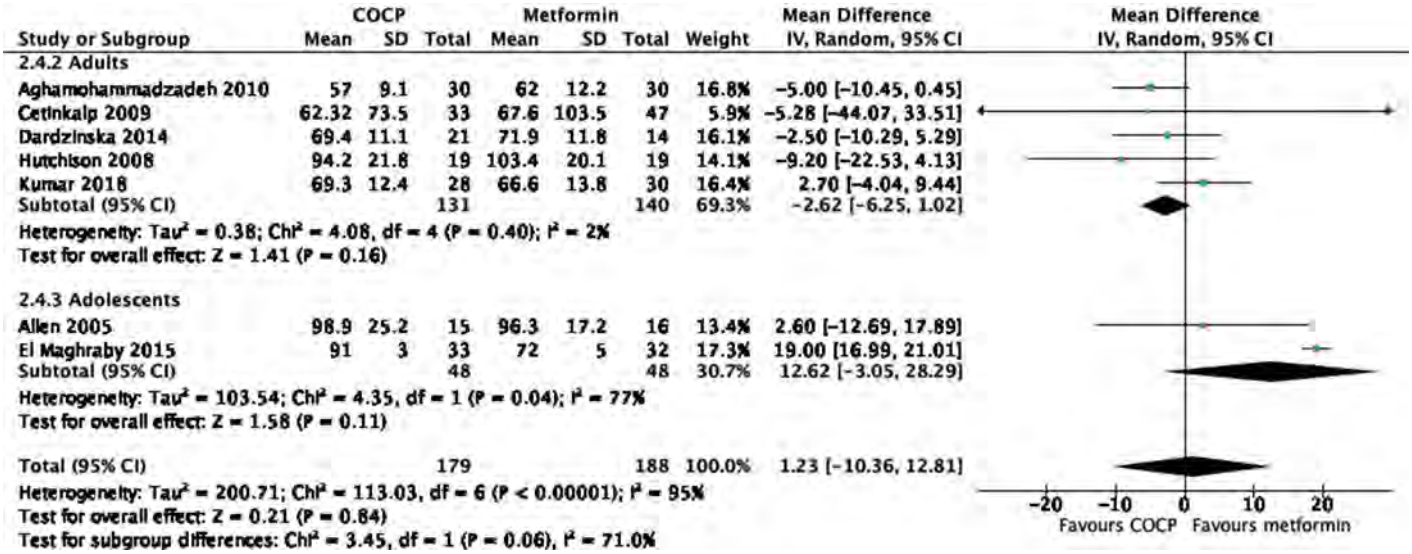


OUTCOME 20.2 WEIGHT

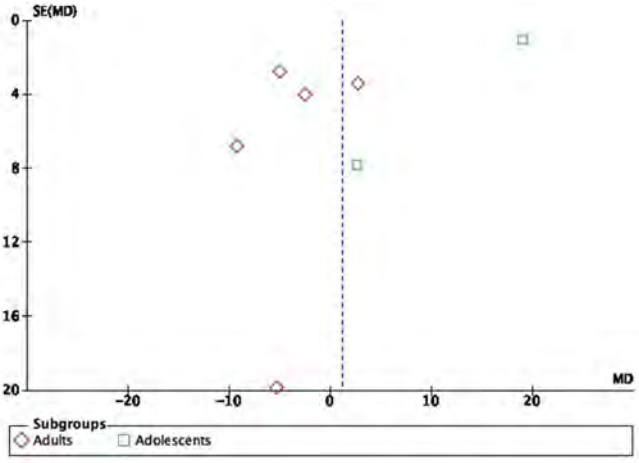
20.2.1 Individual Study Data Table

OUTCOME: weight					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): COCP vs. met								
Author, year	**Unit**	**Time point**	**N**	**COCP Mean**	**COCP SD**	**met Mean**	**met SD**	**Comments**
Aghamohammadzadeh 2010	kg	6 months	COCP=30 met = 30	57.0	9.1	62.0	12.2	
Cetinkalp 2009	kg	4 months	COCP=33 met=47	62.32	12.8	67.6	15.1	
Dardzinska 2014		4 m	COCP 21 met 14	69.4	11.1	71.9	11.8	
Glintborg 2014-1		12 m	COCP 23 met 19					Median change 1.2 (0.8; 3.0) -3.0 (10.3; 0.6, (p<0.05)
Hutchison 2008		6 m	C 19 M19	94.2	5.0	103.4	4.6	
Kumar 2018		6 m	C 28 M 30	69.3	12.4	66.6	13.8	
Allen 2005	Kg	6 m	COCP 15 Met 16	98.9	25.2	96.3	17.2	Adolescents
El Maghraby 2015	Kg		COCP 33 Met 32	91.0	3.0	72.0	5.0	Adolescents

20.2.2. Forest Plot COCP vs metformin for weight (kg)



20.2.3. Funnel plot for assessment of publication bias

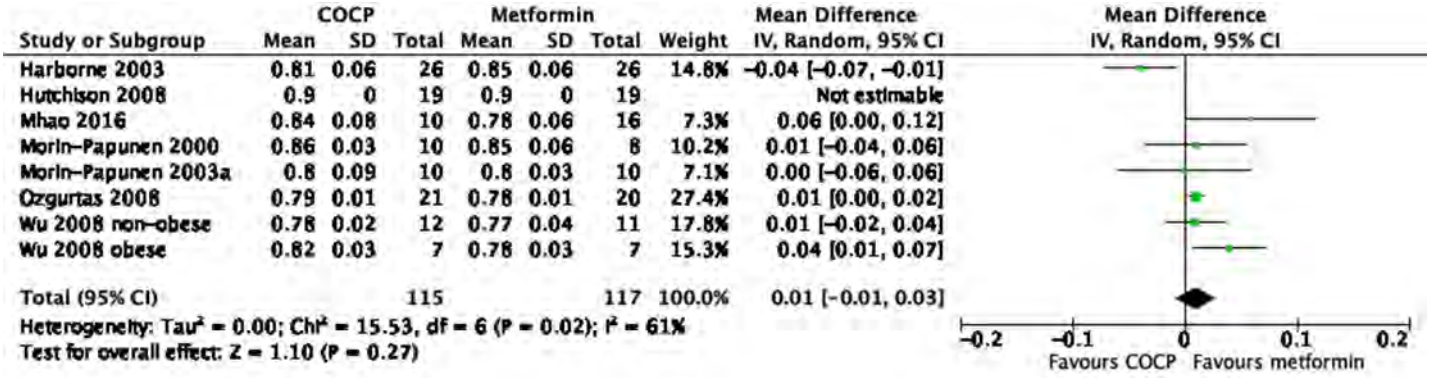


OUTCOME 20.3 WHR

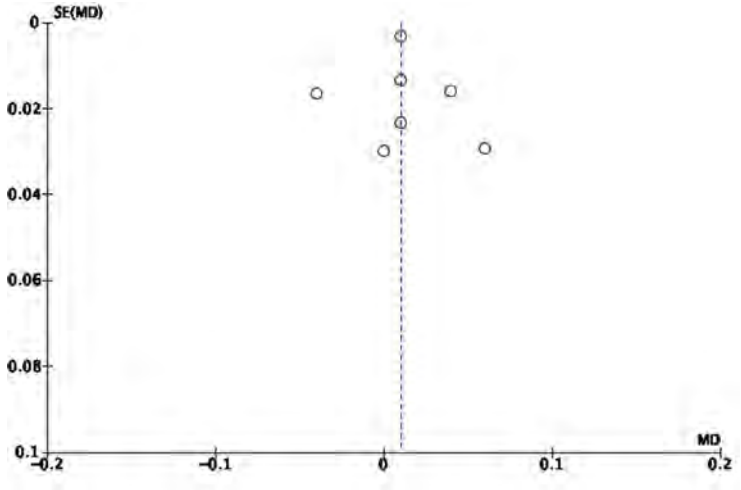
20.3.1 Individual Study Data Table

OUTCOME: WHR				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): COCP vs. metformin								
Author, year	**Unit**	**Time point**	**N**	**COCP Mean**	**COCP SD**	**Met Mean**	**Met SD**	**Comments**
Harborne 2003	-	12 m	COCP 26 met 26	0.81	0.06	0.85	0.06	
Hutchison 2008	-	6 m	C19 m19	0.9	0	0.9	0	
Mhao 2016	-	3 m	C 10 M 16	0.84	0.08	0.78	0.06	
Morin-Papunen 2000 (obese)	-	6 m	C10 M8	0.86	0.09	0.85	0.19	
Morin-Papunen 2003 (non-obese)	-	6 m	C10 M10	0.8	0.27	0.8	0.08	
Moro 2013	-	6 m	C 25 M25	Median, range 0.78 (0.76-0.88)		Median, range 0.84 (0.80-0.87)		
Ozgurtas 2008	-	3 m	C 21 M20	0.79	1.06	0.78	0.01	
Wu 2008 obese	-	3 m	C: 7 M: 7	0.82	0.03	0.78	0.03	
Wu 2008 Non obese	-	3 m	C: 12 M: 11	0.78	0.02	0.77	0.04	

20.3.2. Forest Plot COCP vs metformin for WHR



20.3.3. Funnel plot for assessment of publication bias

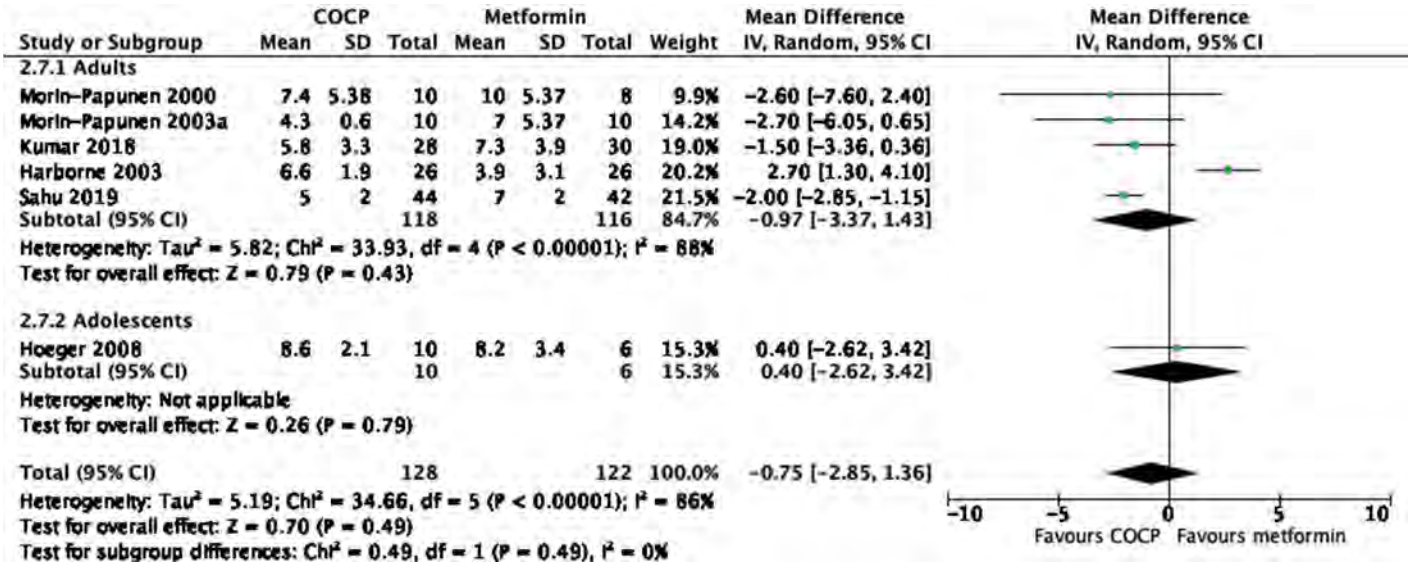


OUTCOME 20.4 HIRSUTISM
20.4.1 Individual Study Data Table

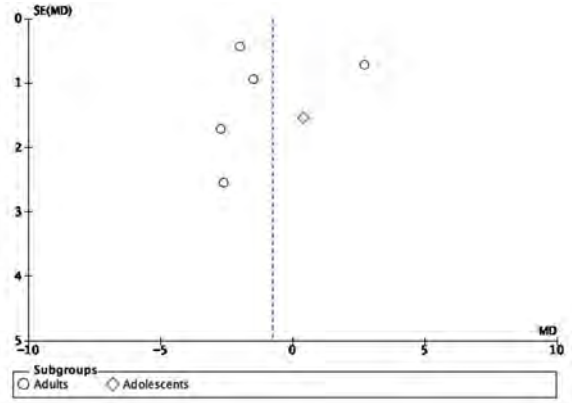
For this outcome, only studies with a duration more than six months were included.

OUTCOME: Hirsutism						**OUTCOME TYPE:** Continuous		
COMPARISON (if applicable): COCP vs. met								
Author, year	**Unit**	**Time point**	**N**	**COCP Mean**	**COCP SD**	**met Mean**	**met SD**	**Comments**
Harborne 2003	FG score Self assessment	12 m	COCP 26 met 26	6.6	1.9	3.9	3.1	
Glintborg 2014-1	FG score	12 m	COCP 23 met 19	Median change *0 (3; 0)* *0 (2; 1)* NS				
Kumar 2018	FG score	6 m	C 28 M 30	5.8	3.3	7.3	3.9	
Meyer 2007	FG score	6 m	C 31 M 36	Mean change -2.0	3.1	Mean change -2.7	3.5	
Morin-Papunen 2000 (obese)	FG score	6 m	C10 M8	7.4	5.38	10	5.37	
Morin-Papunen 2003 (non-obese)	FG score	6 m	C10 M10	4.3	0.6	7	5.37	
Sahu 2019	mFG score	6 m	C 44 M 42	5	2	7	2	
Hoeger 2008	FG score	6 m	C 10 M 6	*8.6*	*2.1*	*8.2*	*3.4*	

20.4.2. Forest Plot COCP vs metformin for hirsutism (FG score)



20.4.3. Funnel plot for assessment of publication bias

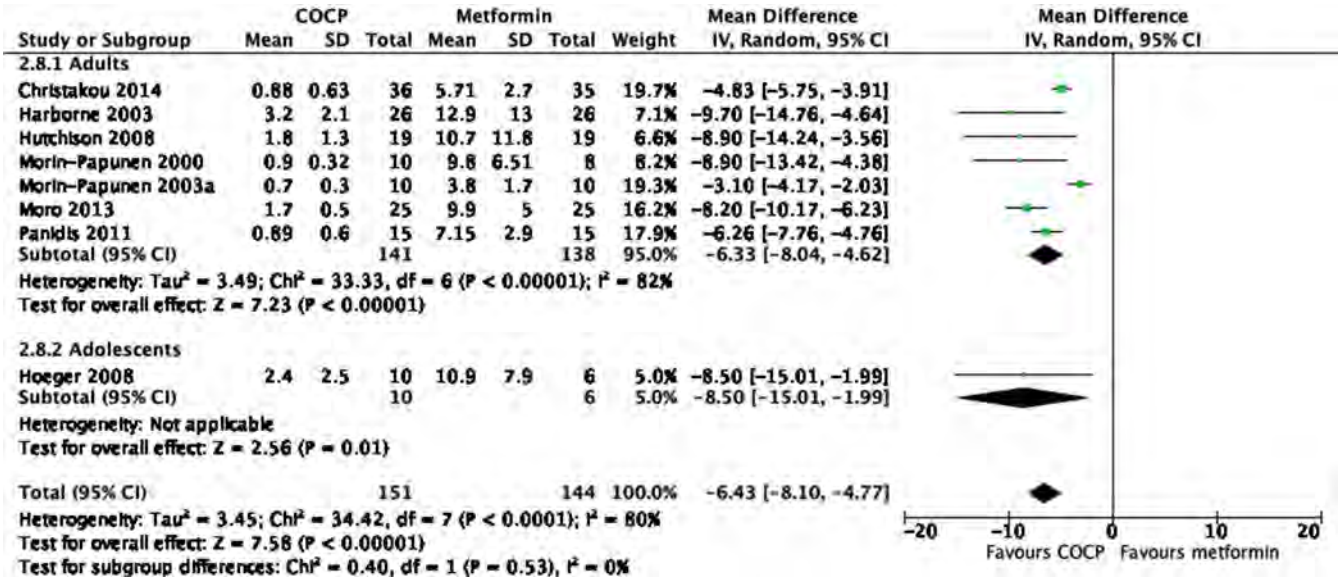


OUTCOME 20.5 FAI

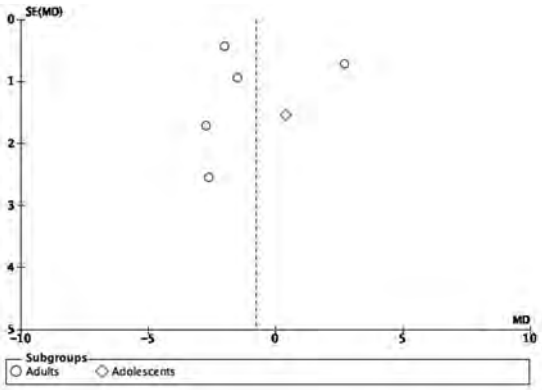
20.5.1 Individual Study Data Table

OUTCOME: FAI						OUTCOME TYPE: Continuous		
COMPARISON (if applicable): COCP vs. met								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	Met Mean	Met SD	Comments
Christakou 2014		6 m	COCP 1=38 COCP 2=36 met=35	0.66 0.88	0.50 0.63	5.71	2.70	
Dardzinska 2014		4 m	COCP 21 met 14	Mean, CI 2.0 (1.8; 3.2)		8.6 (7.9; 14.0)		
Harborne 2003		12 m	COCP 26 met 26	3.2	2.1	12.9	13	
Hutchison 2008	-	6 m	C19 m19	1.8	0.3	10.7	2.7	
Morin-Papunen 2000 (obese)		6 m	C10 M8	0.9	0.32	9.8	6.51	
Morin-Papunen 2003 (non-obese)		6 m	C10 M10	0.7	0.3	3.8	1.7	
Moro 2013		6 m	C 25 M25	1.7	0.5	9.9	5	
Panidis 2011		6 m	COCP1: 15 COCP2: 15 Met: 15	0.87 0.89	0.27 0.60	7.15	2.90	
Hoeger 2008		6m	C 10 M 6	*2.4*	*2.5*	*10.9*	*7.9*	

20.5.2. Forest Plot COCP vs metformin for FAI



20.5.3. Funnel plot for assessment of publication bias

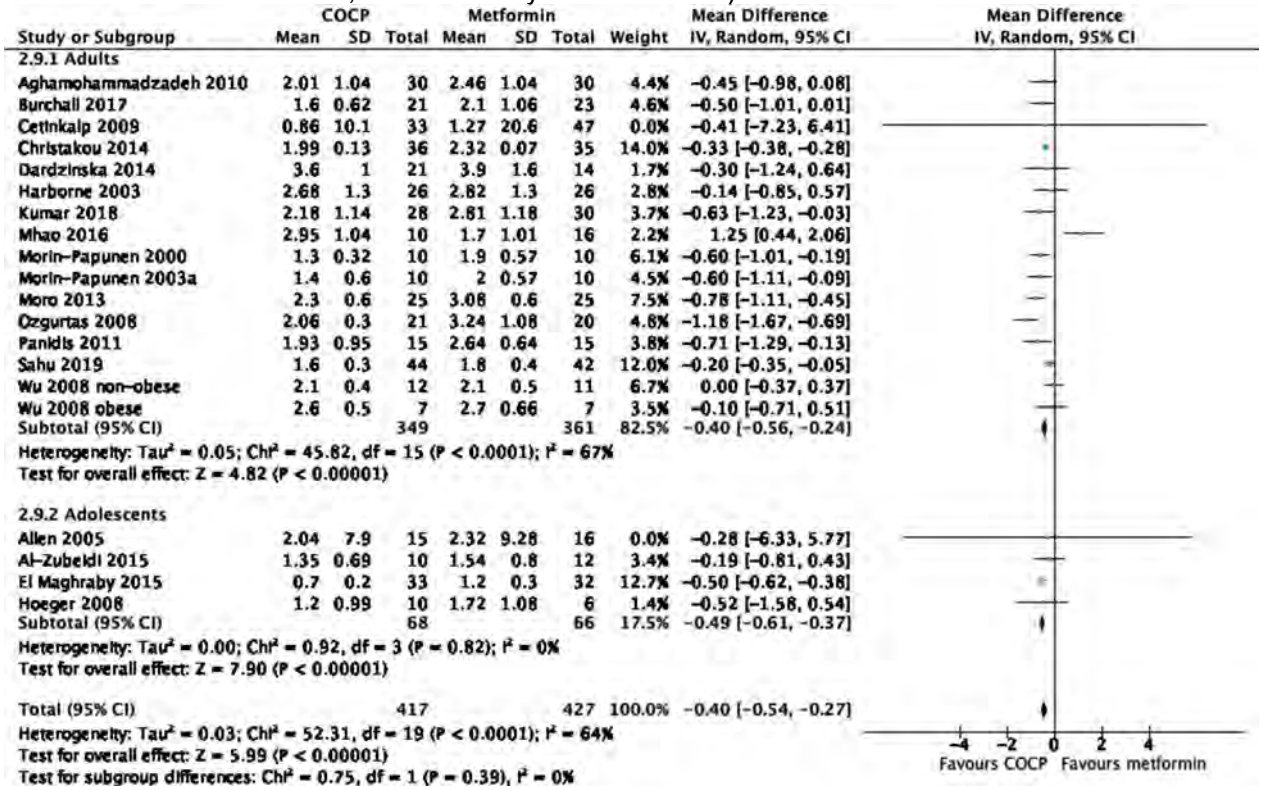


OUTCOME 20.6 TOTAL TESTOSTERONE
20.6.1 Individual Study Data Table

OUTCOME: Total testosterone						**OUTCOME TYPE:** Continuous		
COMPARISON (if applicable): COCP vs. met								
Author, year	**Unit**	**Time point**	**N**	**COCP Mean**	**COCP SD**	**met Mean**	**met SD**	**Comments**
Aghamohammadzadeh 2010	Nmol/l	6 months	High dose COCP=30 met = 30	2.01	1.04	2.46	1.04	
Burchall 2017 (same as Meyer/Moran	nM	6 months	COCP=21 met=23	1.60	0.62	2.10	1.06	
Cetinkalp 2009	Nmol/L	4 months	COCP=33 met=47	0.86	1.76	1.27	3.0	
Christakou 2014		6 m	EE/DRSP=36 met=35	1.99	0.13	2.32	0.07	
Dardzinska 2014	Nmol/L	4 m	COCP 21 met 14	3.6	1.0	3.9	1.6	
Essah 2011	nmol/L	3 m	C 10 CM 9	7.8	1.8	6.9	1.9	
Glintborg 2014-1	Nmol/L	12 m	COCP 23 met 19	Median change - 0.36 (- 1.17; - 0.04) - 0.35 (-0.97; - 0.06) NS				
Harborne 2003	nmol/L	12 m	COCP 26 met 26	2.68	1.3	2.82	1.3	
Kumar 2018	Nmol/L	6 m	C 28 M 30	2.18	1.14	2.81	1.18	
Mhao 2016	Mg/dl, assumed to mean ng/ml, converted to nmol/L	3 m	C 10 M 16	2.95	1.04	1.70	1.01	
Morin-Papunen 2000 (obese)	Nmol/L	6 m	C10 M8	1.3	0.32	1.9	0.57	
Morin-Papunen 2003 (non-obese)	Nmol/L	6 m	C10 M10	1.4	0.6	2	0.57	
Moro 2013	Nmol/L	6 m	C 25 M25	2.3	0.6	3.08	0.6	
Ozgurtas 2008	Nmol/L	3 m	C 21 M20	2.06	0.30	3.24	1.08	
Panidis 2011	Nmol/L	6 m	COCP2: 15 Met: 15	1.93	0.95	2.64	0.64	
Sahu 2019	Ng/dl assumed to mean nmol/L	6 m	C 44 M 42	1.6	0.3	1.8	0.4	
Wu 2008 obese	Nmol/L	3 m	C: 7 M: 7	2.6	0.5	2.7	0.66	
Wu 2008 Non obese	Nmol/L	3 m	C: 12 M: 11	2.1	0.4	2.1	0.5	
Allen 2005	Nmol/L	6 m	COCP 15 Met 16	2.04	1.20	2.32	0.92	
Al-Zubeidi 2015	Nmol/L	6 m	C: 10 M: 12	1.35	0.69	1.54	0.80	
El Maghraby 2015	μg/ml assumed to mean nmol/L	24 m	COCP 33 met 32	0.70	0.20	1.20	0.30	
Hoeger 2008	Nmol/L	6m	C 10 M6	1.20	0.99	1.72	1.08	

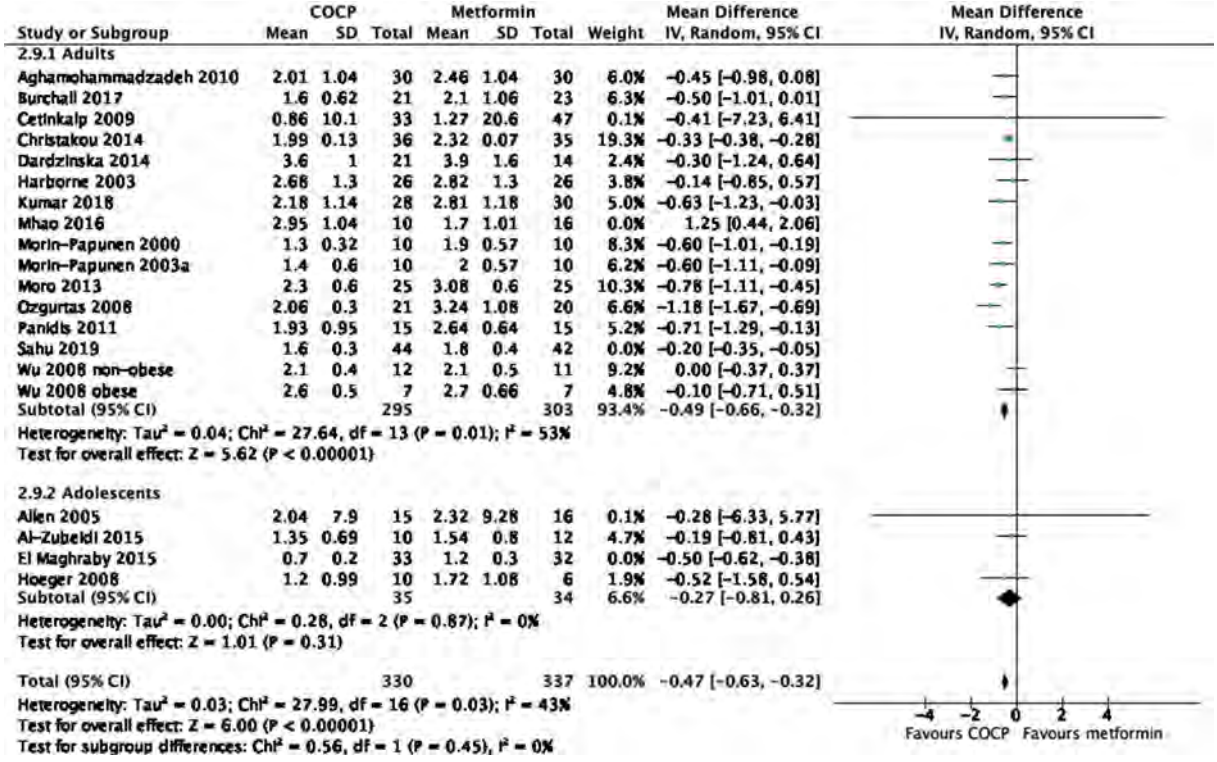
20.9.2.1. Forest Plot COCP vs metformin for total testosterone (nmol/L)

Version 1 – all studies included. (Mhao 2016 reported TT as mg/dl, this was considered a reporting error and that the unit reported should have been ng/ml, the study was included with this correction. Sahu 2019 reported TT as ng/dl, this too was considered a reporting error, the unit is presumed to be nmol/L, and the study was included with this assumption. El Maghraby reported TT as µg/ml, it was assumed that nmol/L was the unit meant, and the study was included.)

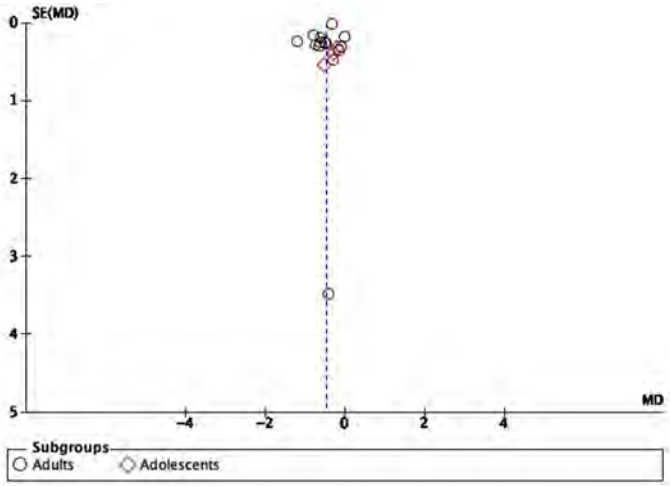


20.9.2.2. Forest Plot COCP vs metformin for total testosterone (nmol/L)

Version 2 - A sensitivity analysis was performed, without Mhao, Sahu and El Maghraby (due to unclear reporting). This did not change the results overall or for adults but became non-significant (no difference) for adolescents.



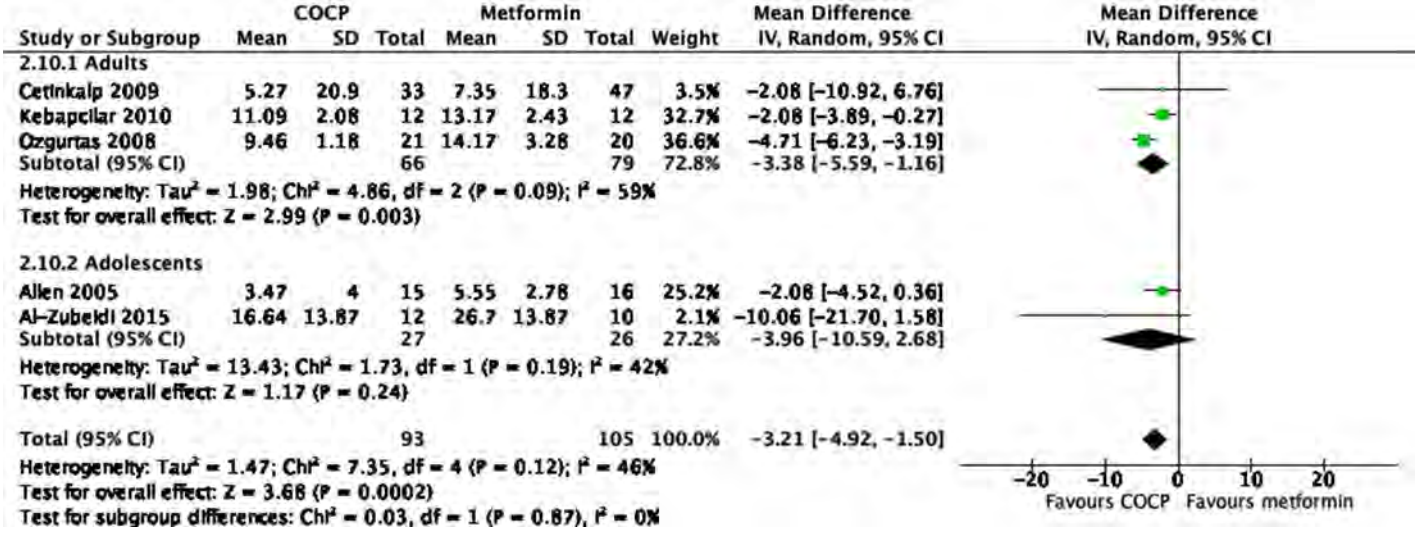
20.9.3. Funnel plot for assessment of publication bias
Version 1 , all studies included



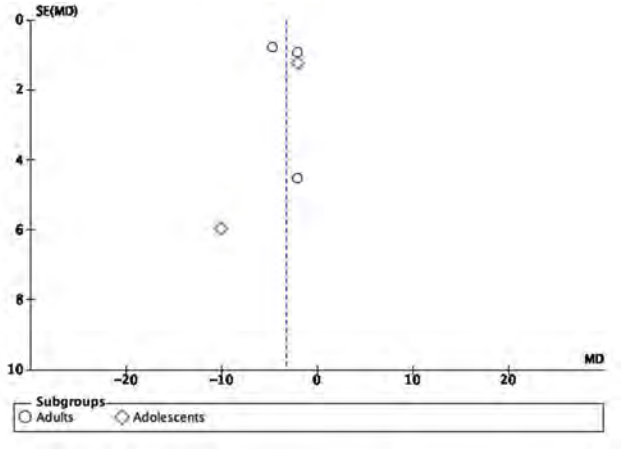
OUTCOME 20.10 FREE TESTOSTERONE
20.10.1 Individual Study Data Table

OUTCOME: Free testosterone					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. met								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	met Mean	met SD	Comment
Cetinkalp 2009	Pmol/L	4 months	COCP=33 met=47	5.27	3.64	7.35	2.67	
Kebapcilar 2010	Pmol/L	3 m	COCP 12 M 12	11.09	2.08	13.17	2.43	
Ozgurtas 2008	Pmol/L	3 m	C 21 M20	9.46	1.18	14.17	3.28	
Allen 2005	Pmol/L	6 m	COCP 15 Met 16	3.47	4.0	5.55	2.78	adolescents
Al Zubedi 2015	Pmol/L	6 m	C: 10 M: 12	16.64	13.87	26.7	13.87	adolescents

20.10.2. Forest Plot COCP vs metformin for free testosterone



20.10.3. Funnel plot for assessment of publication bias

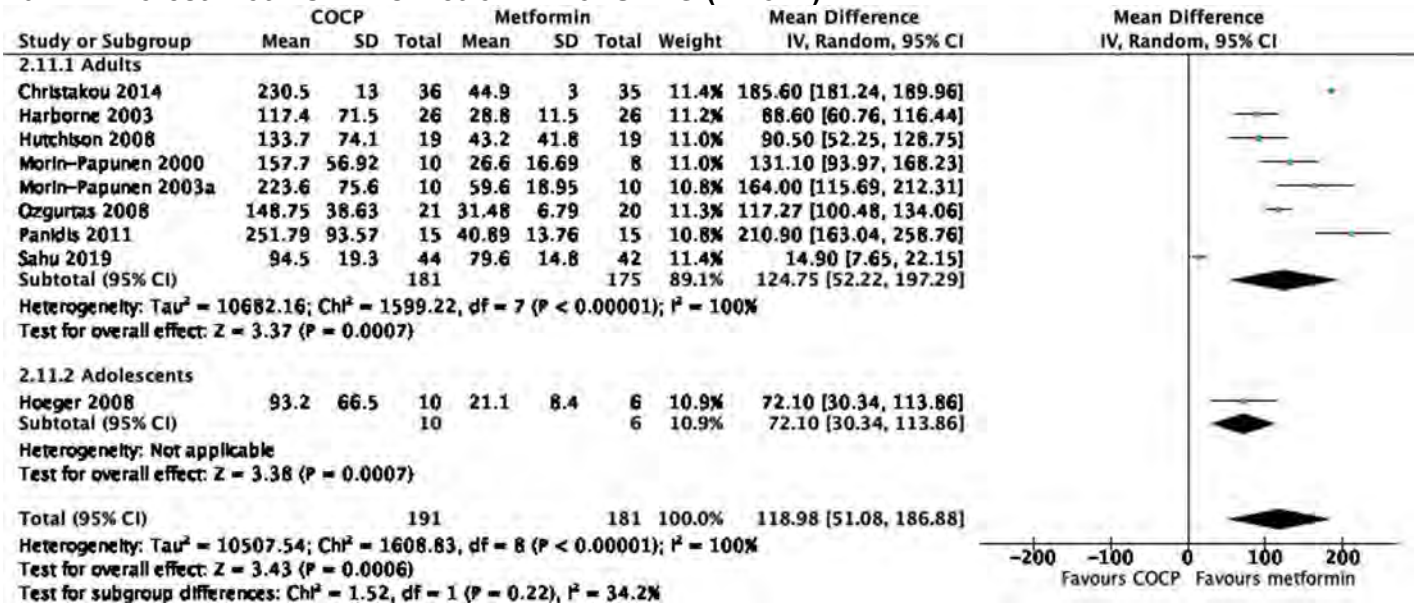


OUTCOME 20.11 SHBG

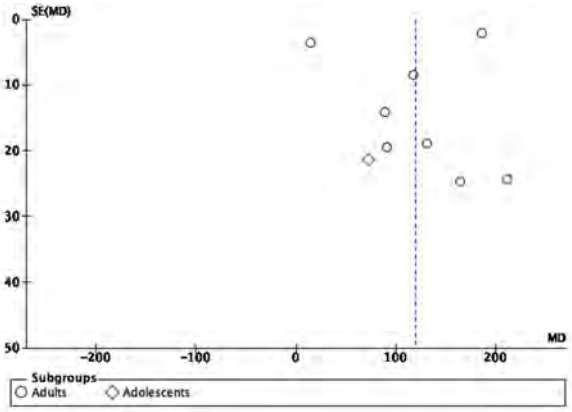
20.11.1 Individual Study Data Table

OUTCOME: SHBG					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. met								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	Met Mean	Met SD	Comments
Christakou 2014		6 m	COCP 2=36 met=35	230.50	13.00	44.90	3.00	
Dardzinska 2014	Nmol/L	4 m	COCP 21 met 14	Mean, CI 171(156-221)		44 (40;62)		
Glintborg 2014-1	Nmol/L	12 m	COCP 23 met 19					Median change *138 (89; 162)* *9 (- 2. 19* p<0.001
Harborne 2003	Nmol/L	12 m	COCP 26 met 26	117.4	71.5	28.8	11.5	
Hutchison	Nmol/l	6 m	C 19 M 19	133.7	17	43.2	9.6	
Morin-Papunen 2000 (obese)	Nmol/L	6 m	C10 M8	157.7	56.92	26.6	16.69	
Morin-Papunen 2003 (non-obese)	Nmol/L	6 m	C10 M10	223.6	75.6	59.6	18.95	
Moro 2013	Nmol/L	6 m	C 25 M25	Median *166.2 (83.7-242)*		*22.5 (15-56.5)*		
Ozgurtas 2008	Nmol/L	3 m	C 21 M20	148.75	38.63	31.48	6.79	
Panidis 2011	Nmol/L	6 m	COCP2: 15 Met: 15	251.79	93.57	40.89	13.76	
Sahu 2019	Nmol/L	6 m	C 44 M 42	94.5	19.3	79.6	14.8	
Al Zubeidi 2015	Nmol/L	6 m	COCP=12 MET=10	46	NR	18.8	NR	adolescents
Hoeger 2008	Nmol/L	6m	C 10 M6	*93.2*	*66.5*	21.1	8.4	adolescents

20.11.2. Forest Plot COCP vs metformin for SHBG (nmol/L)



20.11.3. Funnel plot for assessment of publication bias

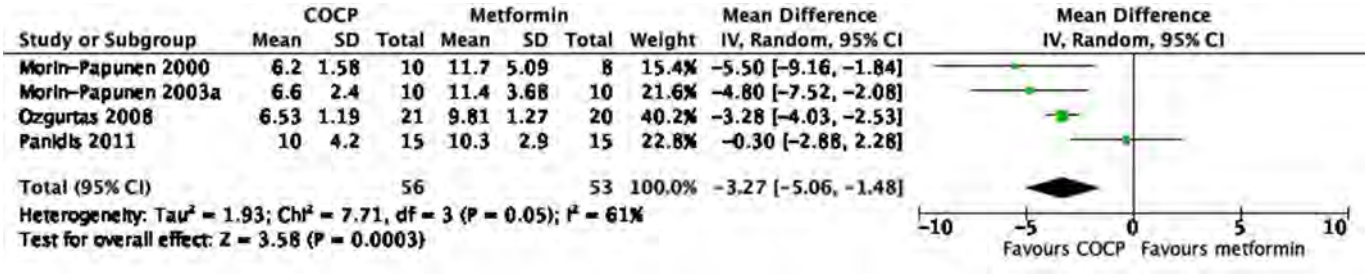


OUTCOME 20.12 ANDROSTENEDIONE

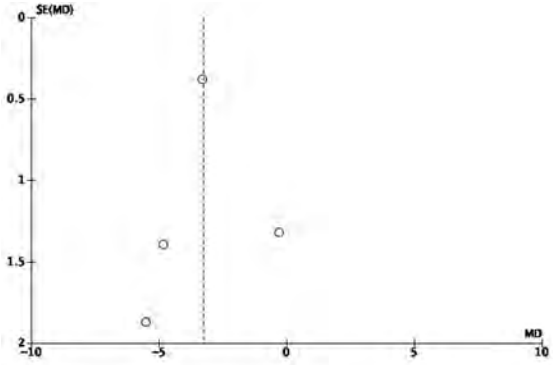
20.12.1 Individual Study Data Table

OUTCOME: androstendione					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. metformin								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	Met Mean	Met SD	Comments
Dardzinska 2014	Nmol/L	4 m	COCP 21 met 14	Mean, CI 10.1 (9.4; 12.2)		12.2 (11.2; 15.0)		
Harborne 2003	Ng/ml	12 m	COCP 26 met 26	8.2		10.4		
Morin-Papunen 2000 (obese)	nmol/L	6 m	C10 M8	6.2	1.58	11.7	5.09	
Morin-Papunen 2003 (non-obese)	nmol/L	6 m	C10 M10	6.6	2.4	11.4	3.68	
Moro 2013	Ng/ml	6 m	C 25 M25	Median *2.1 (1.3-3.4)*		*2.8 (2-5.8)*		
Ozgurtas 2008	Nmol/L	3 m	C 21 M20	6.53	1.19	9.81	1.27	
Panidis 2011	nmol/L	6 m	COCP2: 15 Met: 15	10.0	4.2	10.3	2.9	

20.12.2. Forest Plot COCP vs metformin for androstenedione (nmol/L)



20.12.3. Funnel plot for assessment of publication bias



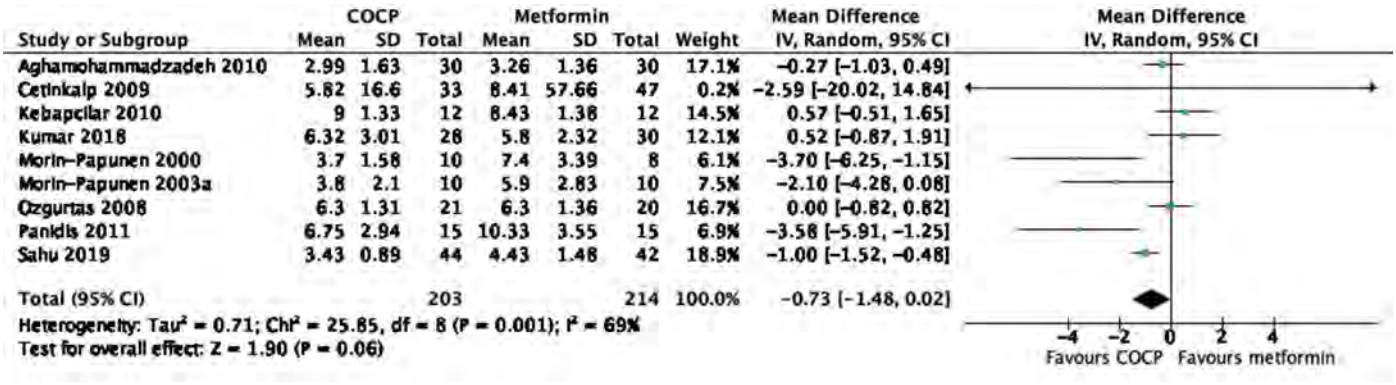
OUTCOME 20.13 DHEAS

20.13.1 Individual Study Data Table

OUTCOME: DHEAS								OUTCOME TYPE: Continuous
COMPARISON (if applicable): COCP vs. met								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	met Mean	met SD	Comments
Aghamohammadzadeh 2010	µg/dl; assumed as µg/ml before convertion to µmol/L	6 months	High dose COCP=30 met = 30	1.1 2.99	0.6 1.63	1.2 3.26	0.5 1.36	
Cetinkalp 2009	µmol/L	4 months	COCP=33 met=47	5.82	2.89	8.41	4.81	
Harborne 2003	µmol/L	12 m	COCP 26 met 26	4.4		7.4		
Kebapcilar 2010	Assumes mean µg/dl, converted to µmol/L	3 m	C 12 met 12	9.00	1.33	8.43	1.38	
Kumar 2018	µmol/L	6 m	C 28 M 30	6.32	3.01	5.80	2.32	
Meyer 2007	µmol/L	6 m	C 31 M 36	Mean change -1.4	1.9	Mean change -0.2	1.3	
Morin-Papunen 2000 (obese)	µmol/L	6 m	C10 M8	3.7	1.58	7.4	3.39	
Morin-Papunen 2003 (non-obese)	µmol/L	6 m	C10 M10	3.8	2.1	5.9	2.83	
Moro 2013	Ng/ml	6 m	C 25 M25	Median 2214 (1524-3573		2709 (2206-4307)		
Ozgurtas 2008	µmol/L	3 m	C 21 M 20	6.30	1.31	6.30	1.36	
Panidis 2011	µmol/L	6 m	COCP2: 15 Met: 15	6.75	2.94	10.33	3.55	
Sahu 2019	µmol/L	6 m	C 44 M 42	3.43	0.89	4.43	1.48	

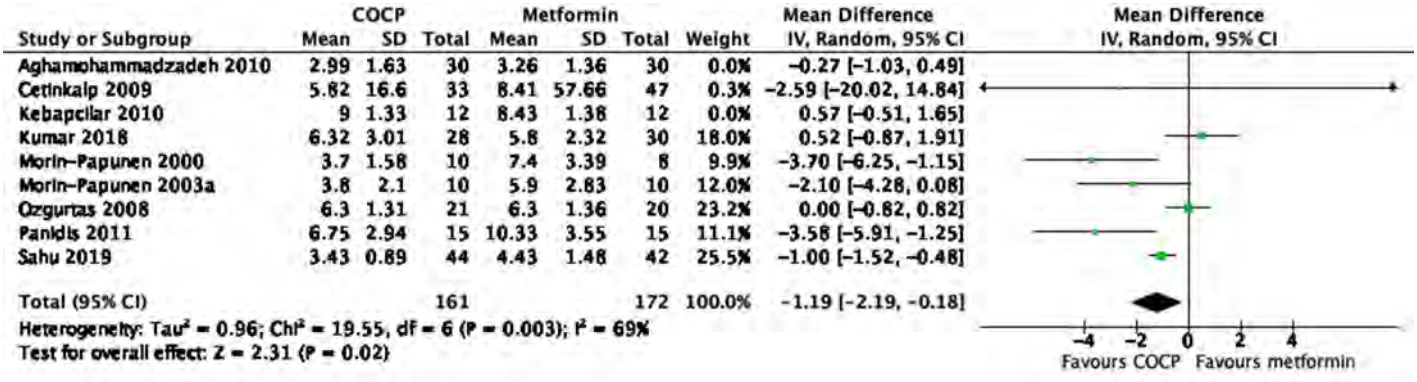
20.13.2.1 Forest Plot COCP vs metformin for DHEAS

Version 1 - Aghamohammadzadeh 2010 is reporting DHEAS as μg/dl, but this is assumed to be a reporting error, and are considered as μg/ml. Kebapcilar 2010 reports μg/ml but the unit is assumed to be μg/dl.

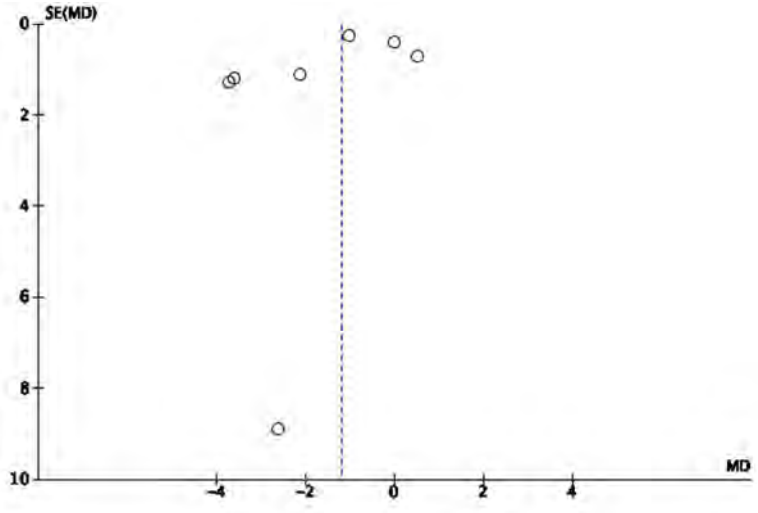


20.13.2.2 Forest Plot COCP vs metformin for DHEAS

Version 2 - If removing the two studies with reporting issues, the result became significant in favor of COCP. Since these studies affects results, this version is used.



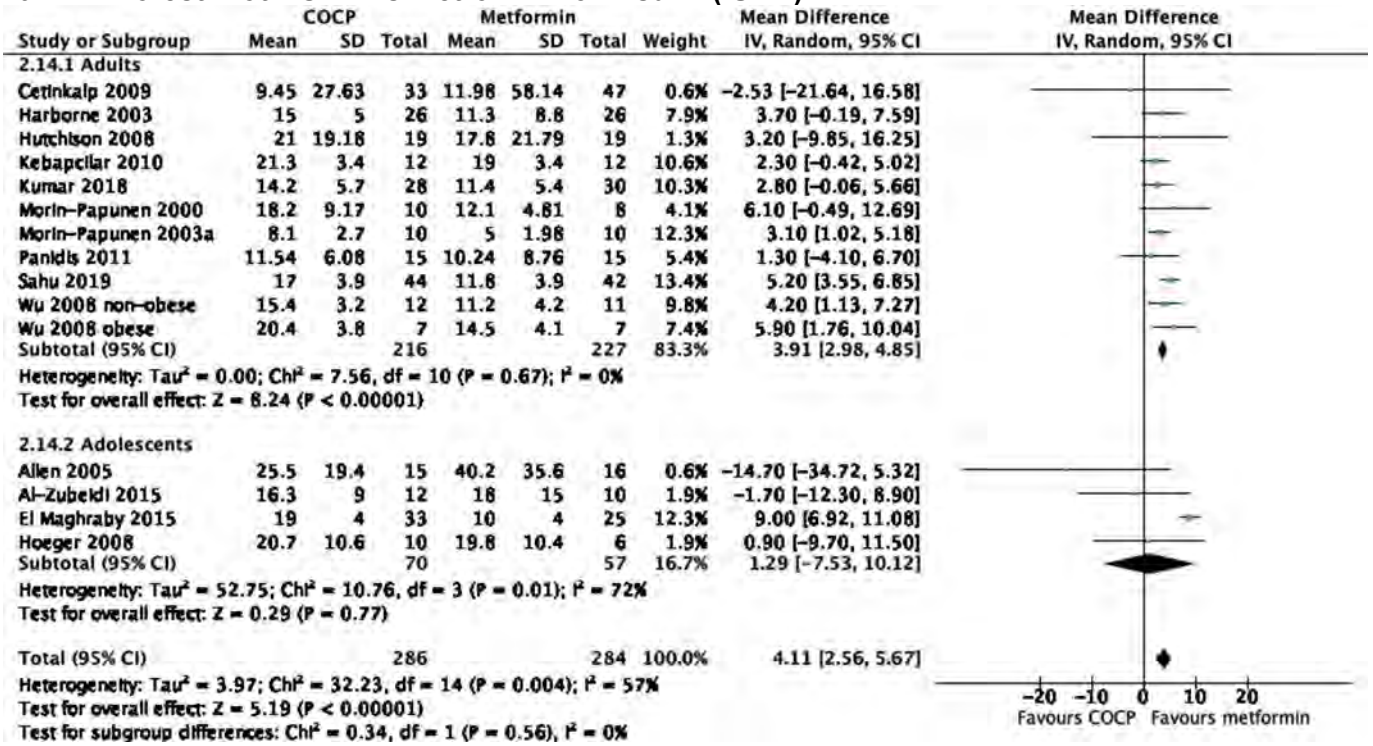
20.13.3. Funnel plot for assessment of publication bias (version 1 - all included studies)



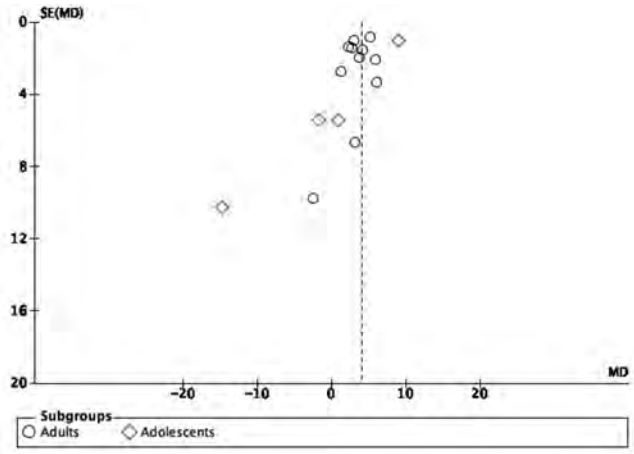
OUTCOME 20.14 INSULIN
20.14.1 Individual Study Data Table

OUTCOME: fasting insulin					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. met								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	met Mean	met SD	Comments
Hutchison 2008 Moran COCP 26; met 30, reporting mean (SD) difference	mU/L 6.0. 4.3	6 months	High dose COCP=19 met=19	21	4.4	17.8	5	
Cetinkalp 2009	mIU/ml	4 months	COCP=33 met=47	9.45	27.63	11.98	58.14	
Harborne 2003	mU/L	12 m	COCP 26 met 26	15.0	5	11.3	8.8	
Glintborg 2014-1	pmol/L	12 m	COCP 23 met 19					Median change 9 (-6; 46) - 8 (-18; 6) p<0.05
Kebapcilar 2010	μIU/ml	3 m	COCP 12 M 12	21.3	3.4	19.0	3.4	
Kumar 2018	μIU/ml	6 m	C 28 M 30	14.2	5.7	11.4	5.4	
Morin-Papunen 2000 (obese)	mIU/L	6 m	C10 M8	18.2	9.17	12.1	4.81	
Morin-Papunen 2003 (non-obese)	mIU/L	6 m	C10 M10	8.1	2.7	5	1.98	
Panidis 2011	mIU/ml	6 m	COCP1: 15 COCP2: 15 Met: 15	11.54	6.08	10.24	8.76	
Sahu 2019	IU/dl	6 m	C 44 M 42	17.0	3.9	11.8	3.9	
Wu 2008 obese	mIU/L	3 m	C: 7 M: 7	20.4	3.8	14.5	4.1	
Wu 2008 Non obese	mIU/L	3 m	C: 12 M: 11	15.4	3.2	11.2	4.2	
Allen 2005	uU/ml	6m	COCP 15 met 16	25.5	19.4	40.2	35.6	
Al Zubeidi 2015	uU/ml	6 m	COCP 12 met 10	16.3	9	18	15	
El Maghraby 2015	μIU/ml	24 m	COCP 33 controls 25	19.00	4.00	10.00	4.00	
Hoeger 2008	IU/ml	6m	C10 M6	*20.7*	*10.6*	19.8	10.4	

20.14.2. Forest Plot COCP vs metformin for insulin (IU/ml)



20.14.3. Funnel plot for assessment of publication bias



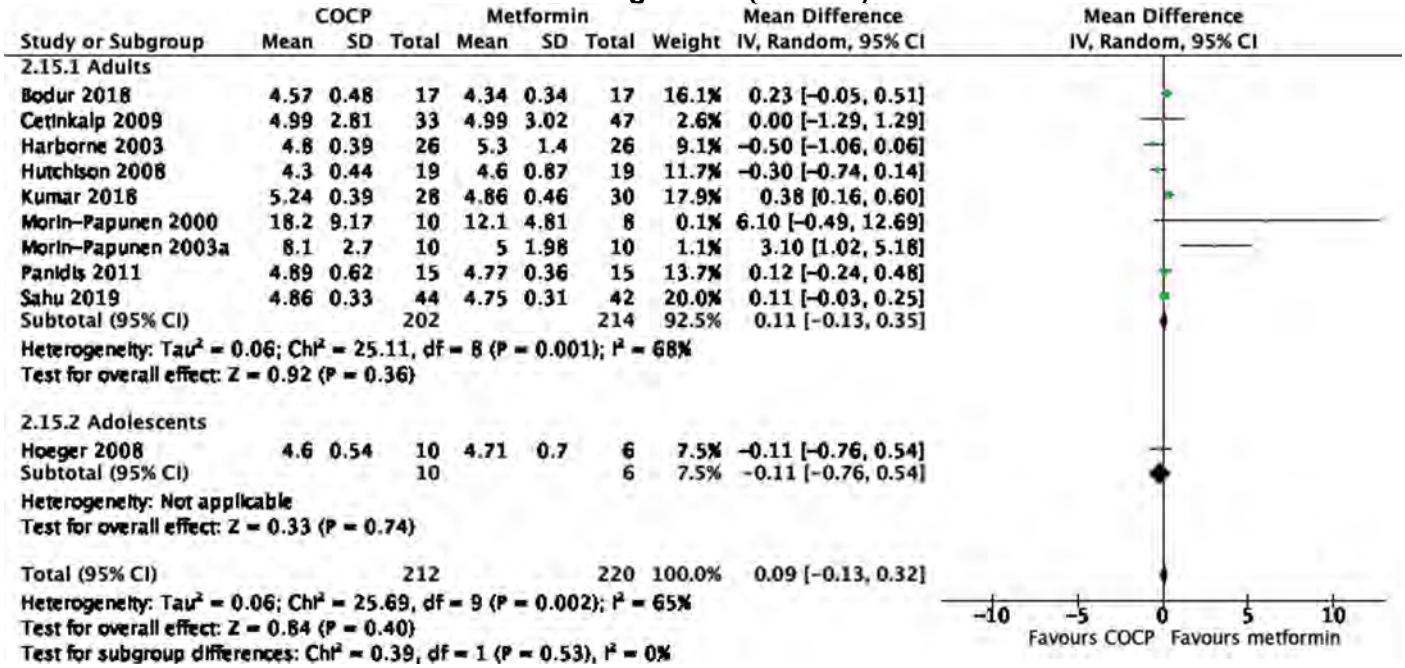
OUTCOME 20.15 GLUCOSE

20.15.1 Individual Study Data Table

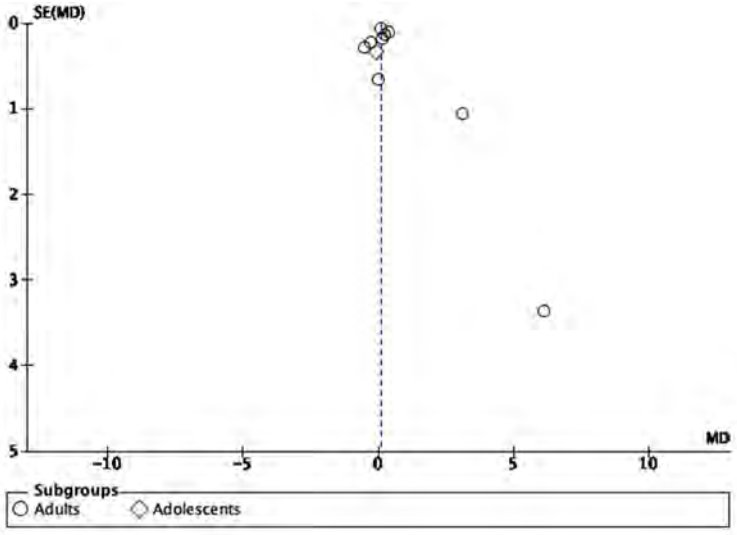
OUTCOME: fasting glucose					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. met								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	Met Mean	Met SD	Comments
Bodur 2018	Mmol/L	6 months	OCP=17 Met=17	4.57	0.48	4.34	0.34	
Cetinkalp 2009	Mmol/L	4 months	COCP=33 met=47	4.99	0.49	4.99	0.44	
Harborne 2003	Mmol/L	12 m	COCP 26 met 26	4.8	0.39	5.3	1.4	
Hutchison 2008	Mmol/l	6 m	COCP 19 Met 19	4.3	0.1	4.6	0.2	
Kumar 2018	Mmol/L	6 m	C 28 M 30	5.24	0.39	4.86	0.46	

Morin-Papunen 2000 (obese)	Mmol/L	6 m	C10 M8	18.2	9.17	12.1	4.81	
Morin-Papunen 2003 (non-obese)	Mmol/L	6 m	C10 M10	8.1	2.7	5	1.98	
Panidis 2011		6 m	COCP2: 15 Met: 15	4.89	0.62	4.77	0.36	
Sahu 2019	Mmol/L	6 m	C 44 M 42	4.86	0.33	4.75	0.31	
Hoeger 2008	Mmol/L	6m	C10 M6	4.60	0.54	4.71	0.70	adolescents

20.15.2. Forest Plot COCP vs metformin for glucose (mmol/L)



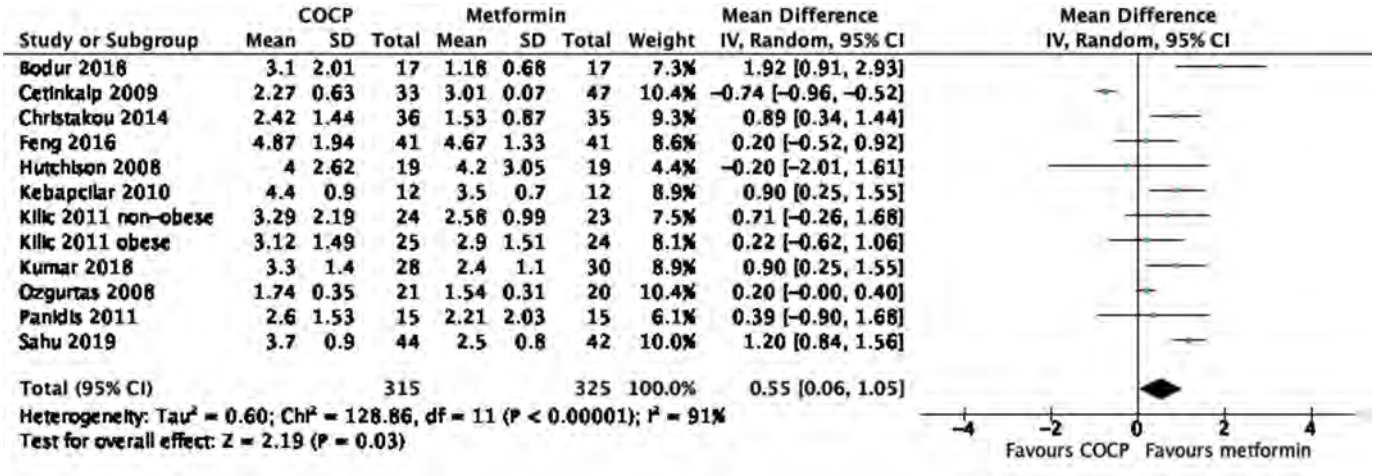
20.15.3. Funnel plot for assessment of publication bias



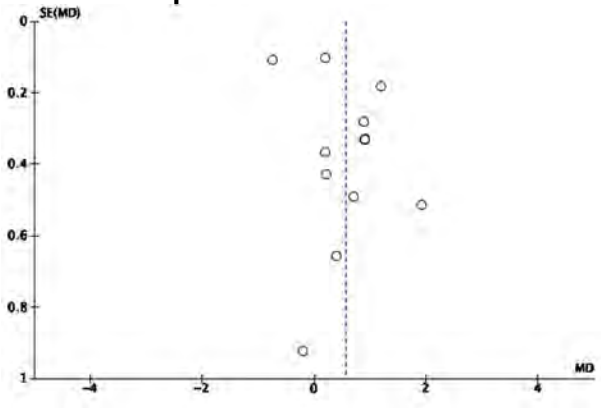
OUTCOME 20.16 HOMA-IR
20.16.1 Individual Study Data Table

OUTCOME: HOMA-IR					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs.met								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	Met Mean	Met SD	Commetns
Bodur 2018	-	6 months	OCP=17 met=17	3.10	2.01	1.18	0.68	
Hutchison 2008	-	6 months	COCP=19 met=19	4.0	0.6	4.2	1.7	
Cetinkalp 2009	-	4 months	COCP=33 met=47	2.27	0.11	3.01	0.07	
Christakou 2014		6 m	COCP 1=38 COCP 2=36 met=35	2.26 2.42	1.65 1.44	1.53	0.87	
Dardzinska 2014		4 m	COCP 21 met 14	Mean, CI 1.38 (1.30; 2.03)		1.34 (1.24; 1.94)		
Feng 2016		3 m	C: 41 CM: 41	4.87	1.94	4.67	1.33	
Glintborg 2014-1		12 m	COCP 23 met 19					Median change 1.7 (-1.1; 10.4) - 0.2 (-5.5; 4.1), NS
Harborne 2003	log	12 m	COCP 26 met 26	0.44		0.32		
Kebapcilar 2010		3 m	COCP 12 M 12	4.4	0.9	3.5	0.7	
Kilic 2011-obese		6 m	C 25 M 24	3.12	1.49	2.90	1.51	
Kilic 2011-non obese		6 m	C 24 M 23	3.29	2.19	2.58	0.99	
Kumar 2018		6 m	C 28 M 30	3.3	1.4	2.4	1.1	
Moro 2013		6 m	C 25 M25	Median 2.25 (1.25-2.5)		*1.4 (1-2.7)*		
Ozgurtas 2008		3 m	C 21 M20	1.74	0.35	1.54	0.31	
Panidis 2011		6 m	COCP1: 15 COCP2: 15 Met: 15	2.90 2.60	1.76 1.53	2.21	2.03	
Sahu 2019		6 m	C 44 M 42	3.7	0.9	2.5	0.8	
Al Zubeidi 2015		6 m	COCP 12 met 10	3.2	NR	3.7	NR	Adolescents

20.16.2. Forest Plot COCP vs metformin for HOMA-IR



20.16.3. Funnel plot for assessment of publication bias



OUTCOME 20.17 OGTT

20.17.1 Individual Study Data Table

OUTCOME: OGTT					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. met								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	met Mean	met SD	Comments
Burchall 2017	AUC	6 months	High dose COCP=21 met = 23	850.88	149.21	805.84	165.24	
Glintborg 2014-1	AUC 2 h insulin	12 m	COCP 23 met 19					Median change 6.5 (-5.3;23.0) 0.5)-13.0;7.2) NS
El Maghraby 2015	GIR	24 m	COCP 33 met 32	3.10	0.30	4.60	0.50	Adolescents

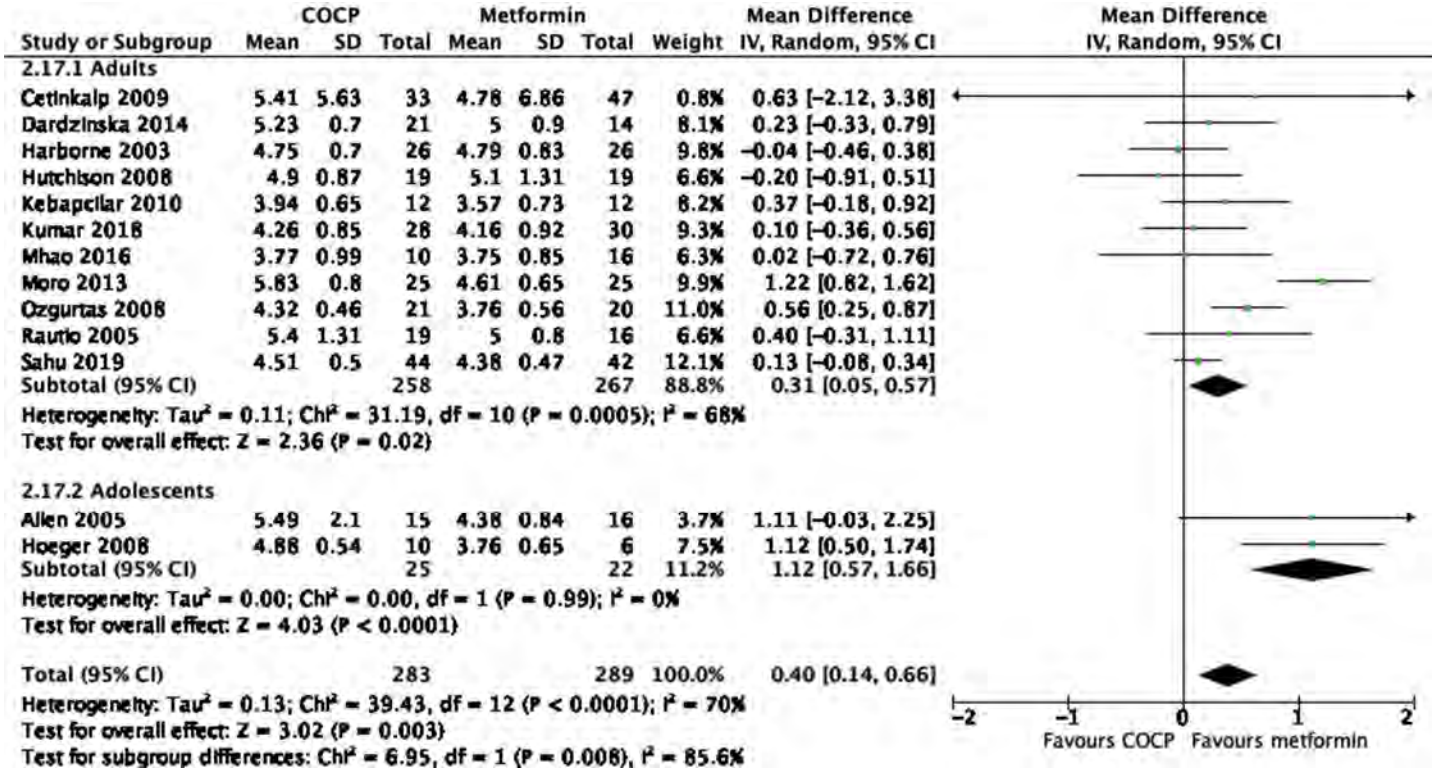
OUTCOME 20.18 CHOLESTEROL

20.18.1 Individual Study Data Table

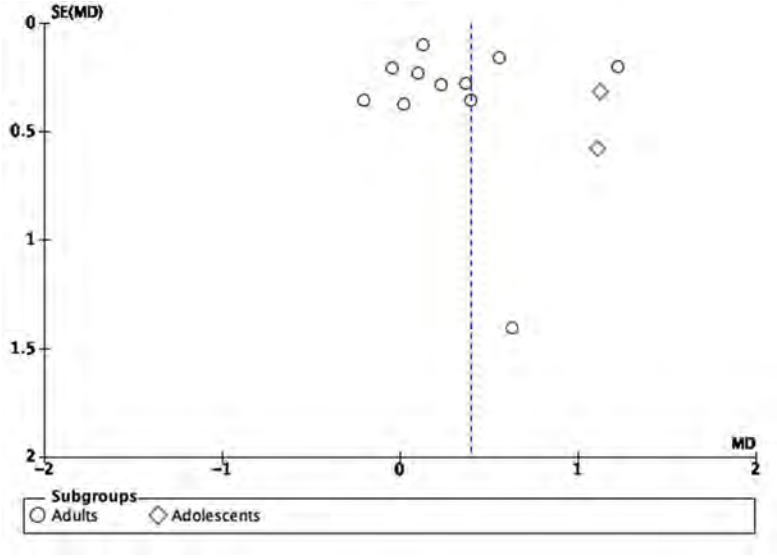
OUTCOME: cholesterol					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. met								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	met Mean	met SD	Comments
Cetinkalp 2009	Mmol/L	4 months	COCP=33 met=47	5.41	0.98	4.78	1.00	
Dardzinska	Mmol/L	4 m	COCP 21	5.23	0.70	5.0	0.90	

2014			met 14					
Harborne 2003	Mmol/L	12 m	COCP 26 met 26	4.75	0.7	4.79	0.83	
Hutchison 2008	Mmol/L	6 m	COCP 19 met 19	4.9	0.2	5.1	0.3	
Kebapcilar 2010	Mmol/L	3 m	COCP 12 M 12	3.94	0.65	3.57	0.73	
Kumar 2018	Mmol/L	6 m	C 28 M 30	4.26	0.85	4.16	0.92	
Mhao 2016	Mmol/L	3 m	C 10 M 16	3.77	0.99	3.75	0.85	
Moro 2013	Mmol/L	6 m	C 25 M25	5.83	0.80	4.61	0.65	
Ozgurtas 2008	mmol/L	3 m	C 21 M20	4.32	0.46	3.76	0.56	
Rautio 2005	Mmol/L	6 m	C19 M16	5.4	1.31	5.0	0.8	
Sahu 2019	Mmol/L	6 m	C 44 M 42	4.51	0.50	4.38	0.47	
Allen 2005	Mmol/L	6 m	COCP 15 Met 16	5.49	2.1	4.38	0.84	
Hoeger 2008	Mmol/L	6m	C 10 M6	4.88	0.54	3.76	0.65	

20.18.2. Forest Plot COCP vs metformin for cholesterol (mmol/L)



20.18.3. Funnel plot for assessment of publication bias

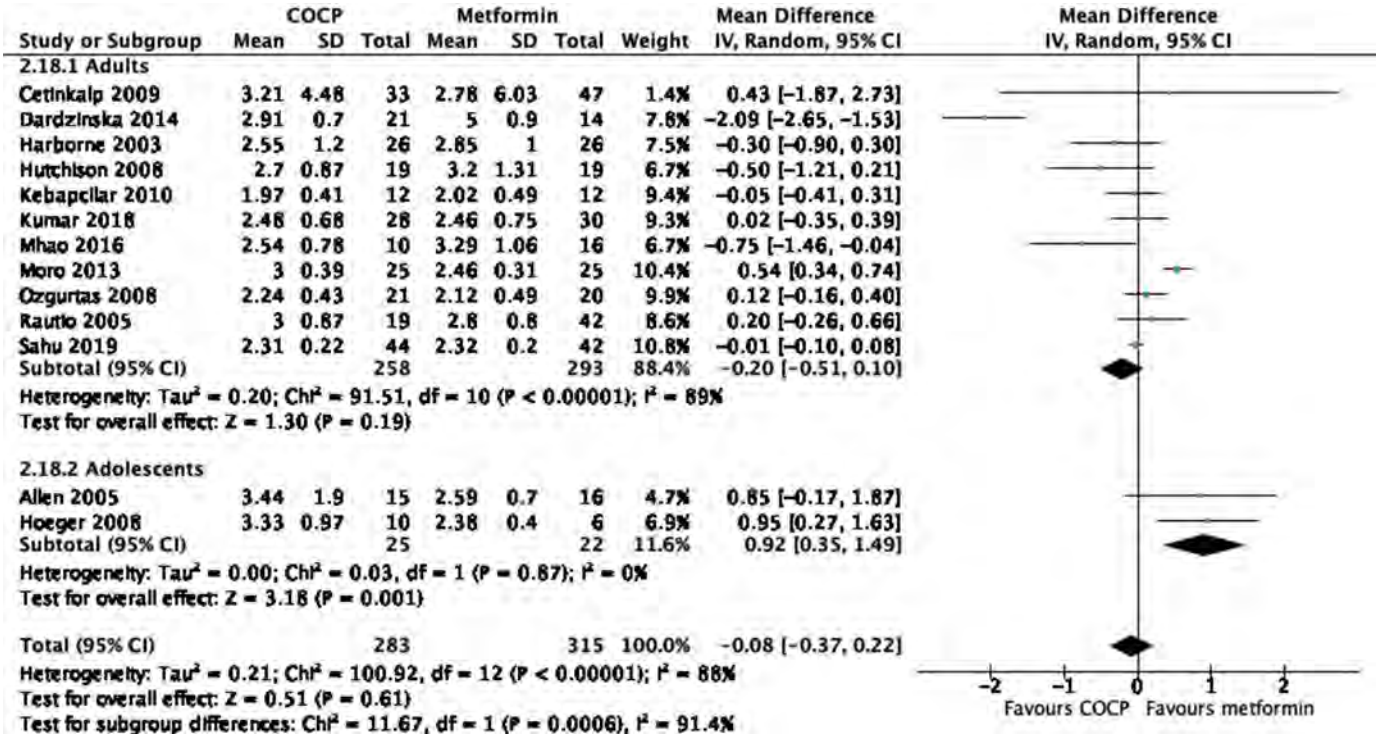


OUTCOME 20.19 LDL

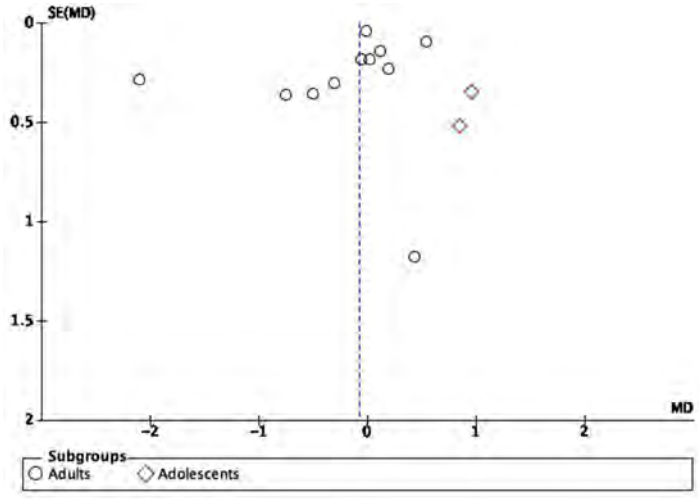
20.19.1 Individual Study Data Table

OUTCOME: LDL					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. met								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	met Mean	met SD	Comments
Cetinkalp 2009	Mmol/L	4 months	COCP=33 met=47	3.21	0.78	2.78	0.88	
Dardzinska 2014	Mmol/L	4 m	COCP 21 met 14	2.91	0.70	5.0	0.90	
Harborne 2003	Mmol/L	12 m	COCP 26 met 26	2.55	1.2	2.85	1	
Hutchison 2008	Mmol/L	6 m	COCP 19 met 19	2.7	0.2	3.2	0.3	
Kebapcilar 2010	Mmol/L	3 m	C 12 M 12	1.97	0.41	2.02	0.49	
Kumar 2018	Mmol/L	6 m	C 28 M 30	2.48	0.68	2.46	0.75	
Mhao 2016	Mmol/L	3 m	C 10 M 16	2.54	0.78	3.29	1.06	
Moro 2013	Mmol/L	6 m	C 25 M25	3.00	0.39	2.46	0.31	
Ozgurtas 2008	mmol/L	3 m	C 21 M20	2.24	0.43	2.12	0.49	
Rautio 2005	Mmol/L	6 m	C19 M16	3.0	0.87	2.8	0.8	
Sahu 2019	Mmol/L	6 m	C 44 M 42	2.31	0.22	2.32	0.20	
Allen 2005	Mmol/L	6 m	COCP 15 Met 16	3.44	1.9	2.59	0.7	Adolescents
Hoeger 2008	Mmol/L	6m	C 10 M6	3.33	0.97	2.38	0.40	Adolescents

20.19.2. Forest Plot COCP vs metformin for LDL (mmol/L)



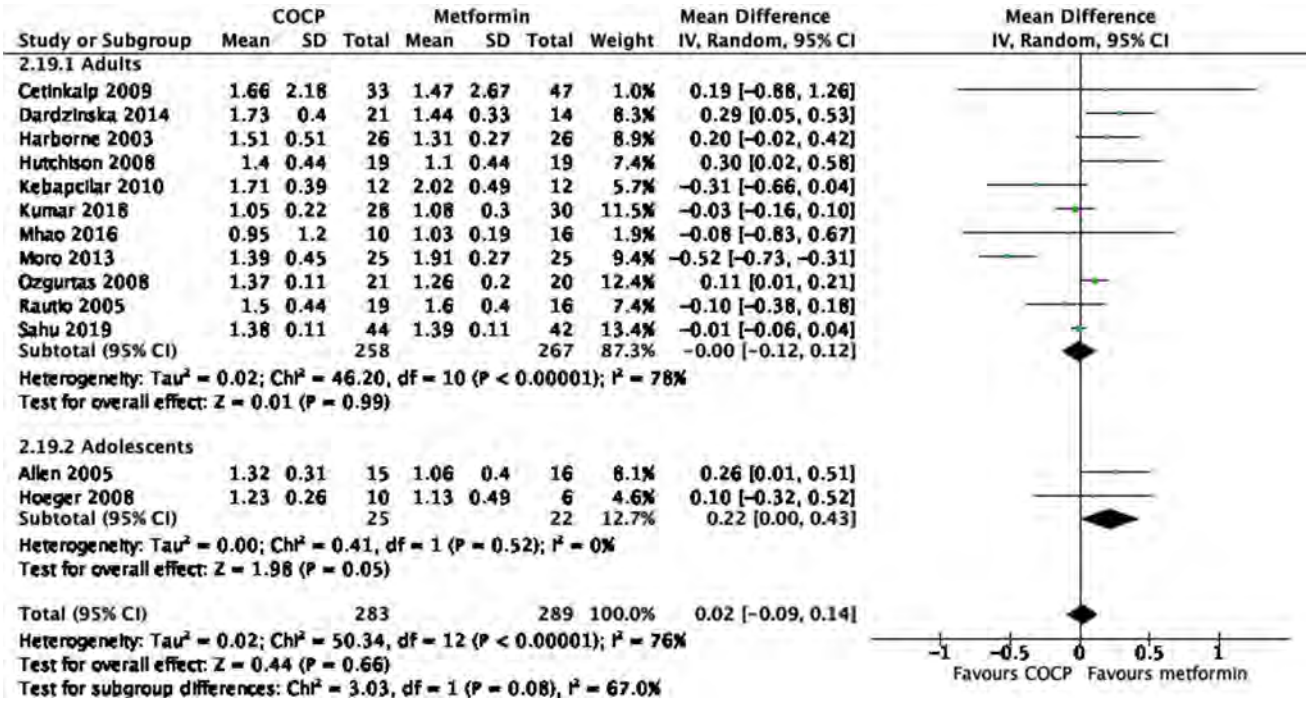
20.19.3. Funnel plot for assessment of publication bias



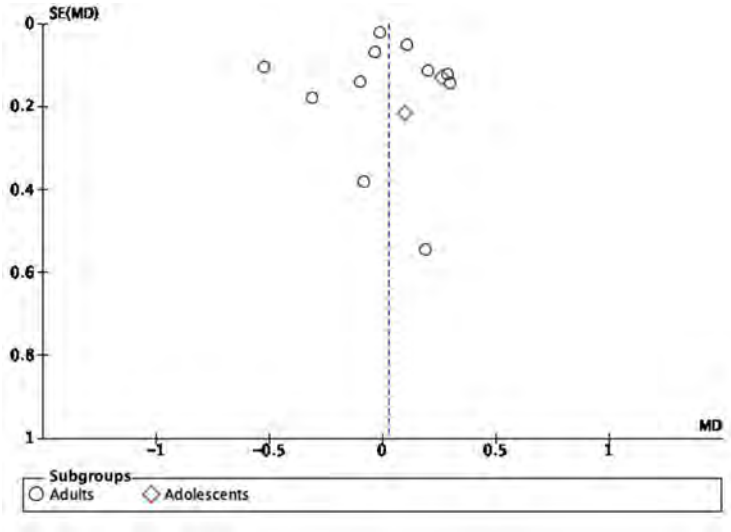
OUTCOME 20.20 HDL
20.20.1 Individual Study Data Table

OUTCOME: HDL					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. met								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	met Mean	met SD	Comments
Cetinkalp 2009	Mmol/L	4 months	COCP=33 met=47	1.66	0.38	1.47	0.39	
Dardzinska 2014	Mmol/L	4 m	COCP 21 met 14	1.73	0.40	1.44	0.33	
Harborne 2003	Mmol/L	12 m	COCP 26 met 26	1.51	0.51	1.31	0.27	
Hutchison 2008	Mmol/L	6 m	COCP 19 met 19	1.4	0.1	1.1	0.1	
Kebapcilar 2010	Mmol/L	3 m	C 12 M 12	1.71	0.39	2.02	0.49	
Kumar 2018	Mmol/L	6 m	C 28 M 30	1.05	0.22	1.08	0.30	
Mhao 2016	Mmol/L	3 m	C 10 M 16	0.95	1.20	1.03	0.19	
Moro 2013	Mmol/L	6 m	C 25 M25	1.39	0.45	1.91	0.27	
Ozgurtas 2008	mmol/L	3 m	C 21 M20	1.37	0.11	1.26	0.20	
Rautio 2005	Mmol/L	6 m	C19 M16	1.5	0.44	1.6	0.4	
Sahu 2019	Mmol/L	6 m	C 44 M 42	1.38	0.11	1.39	0.11	
Allen 2005	Mmol/L	6 m	COCP 15 Met 16	1.06	0.10	1.32	0.08	Adolescents
Al-Zubeidi 2015	Mmol/L	6 m	C: 12 M: 10	1.00	NR	1.30	0.26	Adolescents
Hoeger 2008	Mmol/L	6m	C 10 M6	1.23	0.26	1.13	0.49	Adolescents

20.20.2. Forest Plot COCP vs metformin for HDL (mmol/L)



20.20.3. Funnel plot for assessment of publication bias

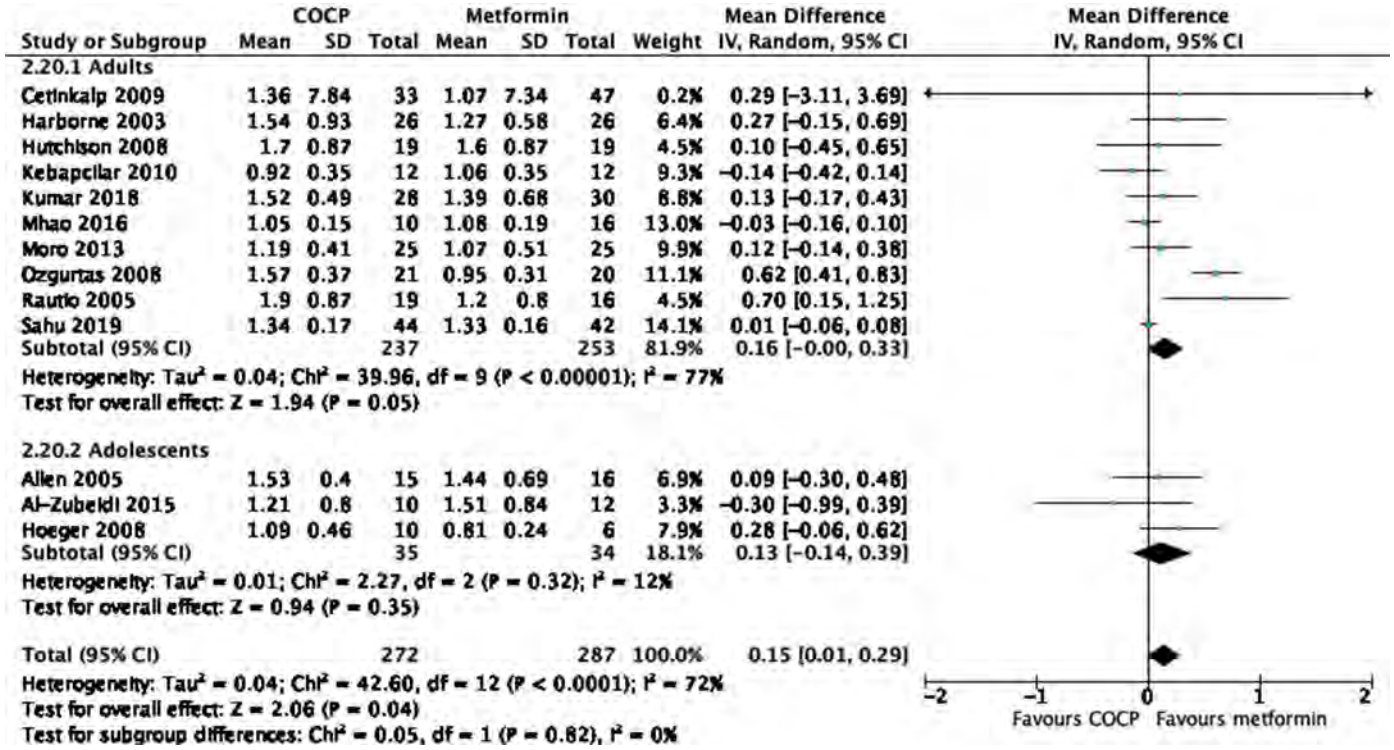


OUTCOME 20.21 TRIGLYCERIDES

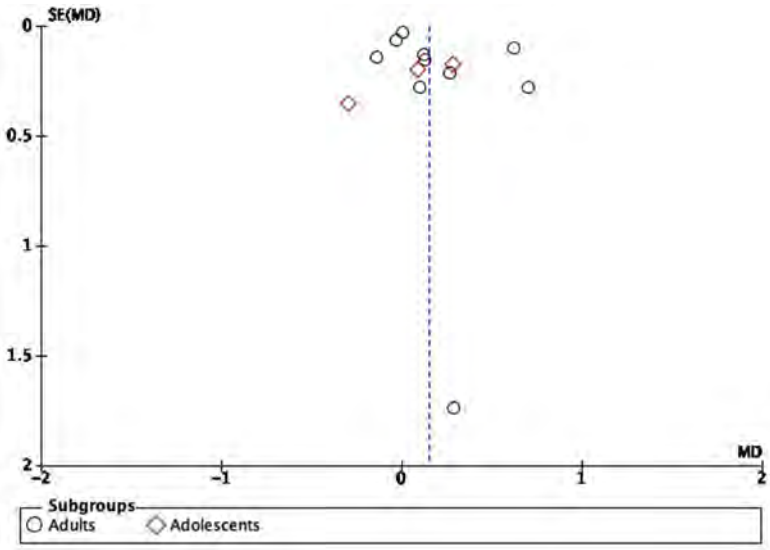
20.21.1 Individual Study Data Table

OUTCOME: TG						OUTCOME TYPE: Continuous		
COMPARISON (if applicable): COCP vs. met								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	met Mean	met SD	Comments
Cetinkalp 2009	Mmol/L	4 months	COCP=33 met=47	1.36	7.84	1.07	7.34	
Dardzinska 2014	Mmol/L	4 m	COCP 21 met 14	Mean, CI 1.14 * (1.02; 1.54)		0.90 (0.82; 1.15)		
Harborne 2003	Mmol/L	12 m	COCP 26 met 26	1.54	0.93	1.27	0.58	
Hutchison 2008	Mmol/L	6 m	COCP 19 met 19	1.7	0.2	1.6	0.2	
Kebapcilar 2010	Mmol/L	3 m	C 12 M 12	0.92	0.35	1.06	0.35	
Kumar 2018	Mmol/L	6 m	C 28 M 30	1.52	0.49	1.39	0.68	
Mhao 2016	Mmol/L	3 m	C 10 M 16	1.05	0.15	1.08	0.19	
Moro 2013	Mmol/L	6 m	C 25 M25	1.19	0.41	1.07	0.51	
Ozgurtas 2008	mmol/L	3 m	C 21 M20	1.57	0.37	0.95	0.31	
Rautio 2005	Mmol/L	6 m	C19 M16	1.9	0.87	1.2	0.8	
Sahu 2019	Mmol/L	6 m	C 44 M 42	1.34	0.17	1.33	0.16	
Allen 2005	Mmol/L	6 m	COCP 15 Met 16	1.53	0.4	1.44	0.69	Adolescents
Al-Zubeidi 2015	Mmol/L	6 m	C: 10 M: 12	1.21	0.80	1.51	0.84	Adolescents
Hoeger 2008	Mmol/L	6m	C 10 M6	1.09	0.46	0.81	0.24	Adolescents

20.21.2. Forest Plot COCP vs metformin for triglycerids (mmol/L)



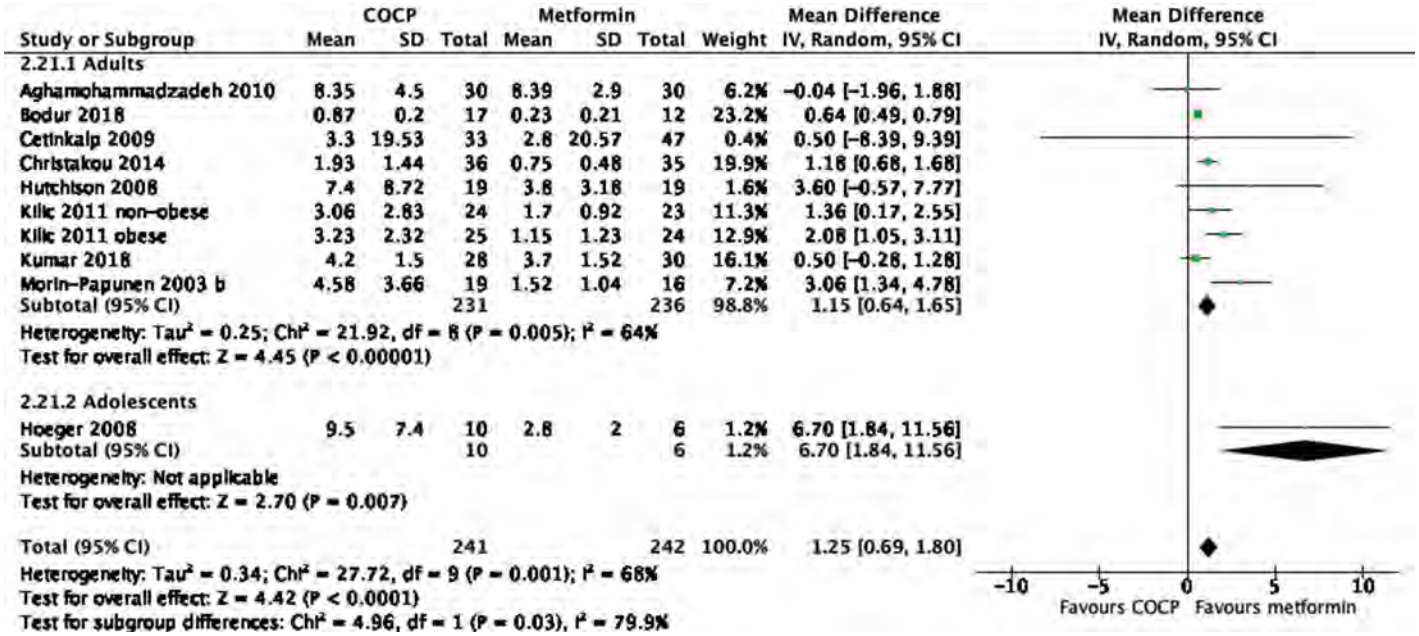
20.21.3. Funnel plot for assessment of publication bias



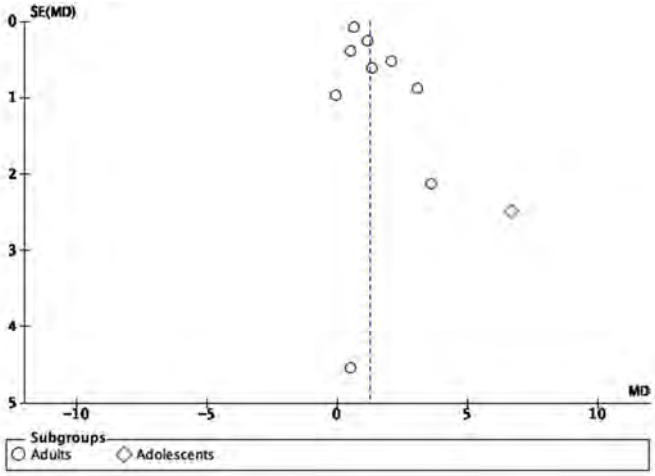
OUTCOME 20.22 CRP
20.22.1 Individual Study Data Table

OUTCOME: CRP					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. met								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	Met Mean	Met SD	Comments
Aghamohammadzadeh 2010	Mg/L	6 months	COCP=30 met = 30	8.35	4.5	8.39	2.9	
Bodur 2018	mg/L	6 months	OCP=17 met=12	0.87	0.20	0.23	0.21	
Cetinkalp 2009	mg/dl	4 months	COCP=33 met=47	0.33	0.34	0.28	0.3	
Christakou 2014	Mg/L	6 m	COCP =36 met=35	1.93	1.44	0.75	0.48	
Dardzinska 2014	Mg/L	4 m	COCP 21 met 14	Mean, CI 1.70 * (1.65; 3.69)		0.76 (0.62; 2.25)		
Hutchison 2008	Mg/l	6 m	COCP 19 met 19	7.4	2.0	3.8	0.73	
Kilic 2011-obese	Mg/L	6 m	C 25 M 24	3.23	2.32	1.15	1.23	
Kilic 2011-non obese	Mg/L	6 m	C 24 M 23	3.06	2.83	1.70	0.92	
Kumar 2018	Mg/L	6 m	C 28 M 30	4.2	1.5	3.7	1.52	
Morin-Papunen 2003b	Mg/L	6 m	C 19 M 16	4.58	3.66	1.52	1.04	
Hoeger 2008	Mg/L	6m	C10 M6	9.5	7.4	2.8	2.0	

20.22.2. Forest Plot COCP vs metformin for CRP (mg/L)



20.22.3. Funnel plot for assessment of publication bias

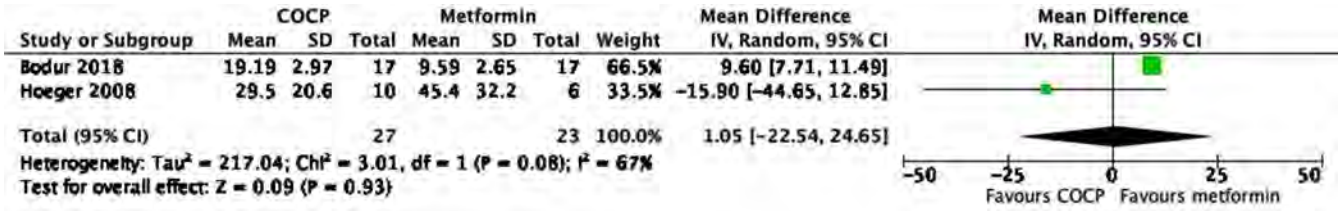


OUTCOME 20.23 PAI-1

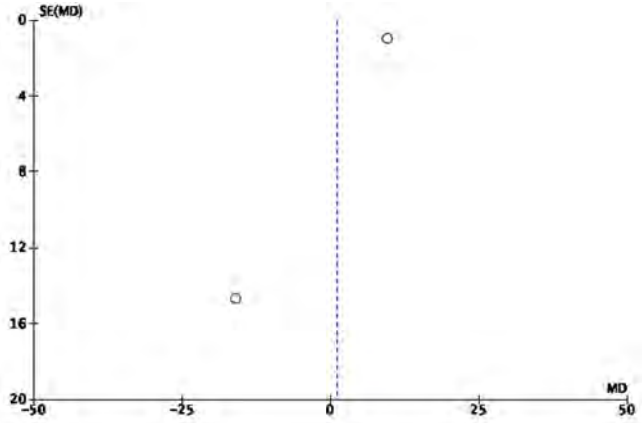
20.23.1 Individual Study Data Table

OUTCOME: PAI-1					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. met - adults								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	Met Mean	Met SD	Comments
Bodur 2018	Ng/ml	6 months	COCP=17 Met=17	19.19	2.97	9.59	2.65	
Burchall 2017	U/ml	6 months	COCP=21 Met=23	3.61		5.37		
Hoeger 2008	Ng/ml	6m	C10 M6	29.5	20.6	45.4	32.2	

20.23.2. Forest Plot COCP vs metformin for PAI-1 (ng/ml)



20.23.3. Funnel plot for assessment of publication bias



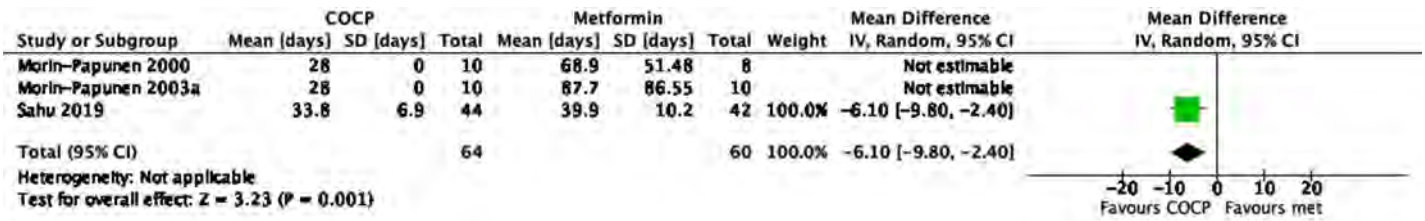
OUTCOME 20.24 HR-QoL
20.24.1 Individual Study Data Table

HRQoL	Favours: No difference	Certainty ⊕◯◯◯ VERY LOW (Due to risk of bias, indirectness, imprecision)					
Author, year	Measurement	N	COCP Mean	COCP SD	Met Mean	Met SD	P value
Al-Zubeidi 2015	%	C: 10 M: 12	69		76		NR
Dorgham 2021	VAS (scale 0-10)	C 50 M 50	4.2	0.6	3.2	0.4	<0.001
	Dermatology Life Quality Index	C 50 M 50	1.0	0.6	5.0	1.5	0.001
	Hisutism Life Quality Index 0-22, none to severe problems	C 50 M 50	1.45	0.5	4.45	1.2	0.001
Altinok 2018 (reports median (IQR) differences)	VAS 1: Facial hair growth VAS 2: Body hair growth VAS 3: Acne VAS 4: Menstrual disorder VAS 5: Overweight VAS 6: PCOS	C 23 M19	-1.2 (-2.9; -0.2) 0.7 (-2.3; 0.0) -1.8 (-4.0; 0.0) -1.4 (-3.4; 0.2) -0.2 (-2.0;0.7) -0.2 (-2.4;1.0)		0.0 (1.8; 0.2) -0.4 (-1.8; 0.0) -0.4 (-2.0; 0.1) -1 (-4; 0.7) -3.0 (-S.0;-0.2) -1.3 (-3.4;0.S)		<0.05 NR NR NR NR NR
	PF: Physical function RP: Role limitations physical BP: Bodily pain GH: General health VT: Vitality SF: Social function RE: Role limitations emotional MH: Mental health PCS: Summed physical scores MCS: Summed mental scores		0 (-4;6) 0 (0;0) 0 (-16;17) -3 (-6;9) -3 (-15;15) 0 (-16;13) 0 (-33;33) -6 (-16;6) 0 (-5;6) -2 (-11;9)		0 (0;5) 0 (-25;0) 0 (-11;1) 5 (-5;10) 5 (-20;10 0 (-13;13) 0 (-67;33) -2 (-12;8) -1 (-3;2) 1 (-11;5)		NR NR NR NR NR NR NR NR NR NR

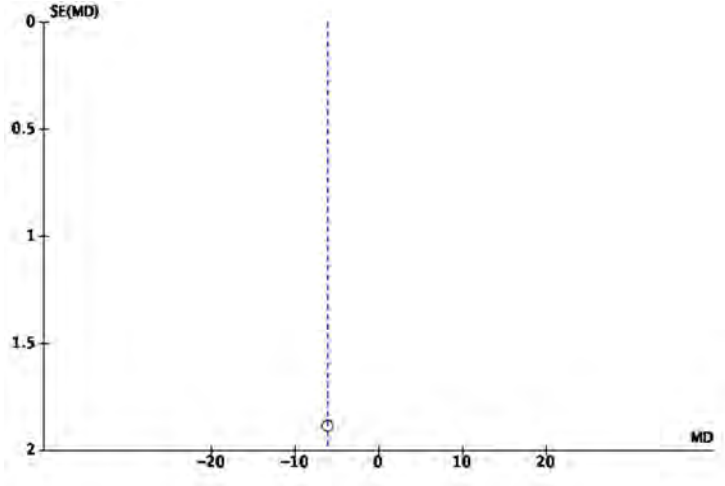
OUTCOME 20.25 MENSTRUAL CYCLES
20.25.1 Individual Study Data Table

OUTCOME: Menstrual cycle duration					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): COCP vs. met								
Author, year	**Unit**	**Time point**	**N**	**COCP Mean**	**COCP SD**	**Met Mean**	**Met SD**	**Comments**
Meyer	days	6 m	C31 M36	Mean change -44 ± 69.5		Mean change -47.1 ± 135.2		
Morin-Papunen 2000 (obese)	days	6 m	C10 M8	28	0	68.9	51.48	
Morin-Papunen 2003 (non-obese)	days	6 m	C10 M10	28	0	87.7	86.55	
Sahu	Days	6 m	C 44 M 42	33.8	6.9	39.9	10.2	

20.25.2. Forest Plot COCP vs metformin for menstrual cycles, days



20.25.3. Funnel plot for assessment of publication bias



OUTCOME 20.26 Adverse events

Due to the lack of systematic reporting, where many studies do not report adverse effects at all, and the ones that do, not report in a similar manner, it is difficult to draw strong conclusions, but the reports suggest more gastrointestinal side effects with metformin.

	Study	COCP	metformin
Gastrointestinal side effects	Christakou 2014	0/40	5/40
	Harborne	0/26	3/26
	Kilic 2011	0/49	5/48
	Luque-Ramírez 2009	0/15	2/19
	Morin-Papunen 2000 (obese)	0/16	1/16
	Morin-Papunen 2003[a] (non-obese)	0/10	1/10
	Moro 2013	0/31	2/31
	Wu 2018	0/19	2/19
Nausea	Glintborg 2014	0/30	1/30
	Bodur 2018	1/21	1/29
Dizziness	Bodur 2018	0/21	2/29
Depression	Glintborg 2014	0/30	1/30
	Harborne	1/26	0/26
Sexual reluctance	Bodur 2018	1/21	0/29
Weight gain	Harborne	5/26	0/26
	Wu 2018	1/19	0/19
Weight loss	Bodur 2018	0/21	1/29
Chest pain	Harborne	1/26	0/26
Other	Dardzinska 2014	10/35 (nausea, mastodynia, mood changes, abdominal discomfort, vomiting)	15/21 (nausea, abdominal discomfort, vomiting, diarrhoea)
	Glintborg 2014	3/30 (not reported which)	2/30 (as reported above)
	El Maghraby 2015	2/33	3/32
	Luque-Ramírez 2009	Hypertension at baseline 13%, after treatment 33%	Hypertension at baseline 18%, after treatment 0%
	Bodur 2018	Pregnancy 1/21, hirsutism 1.	Pregnancy 4/29 Feeling hunger 1, hypothyroididm 1, hirsutism 1

Comparison 21: COCP vs. COCP + metformin

- **EVIDENCE SUMMARY:**

A total of 18 RCTs with 22 publications were identified for this comparison. There were no studies involving adolescents. Wu 2008 is reported as two studies in the meta-analysis since the results are reported stratified for obese and non-obese women. Fonseka 2020 compared EE/DRSP ± metformin and EE/CPA ± metformin and are thus also reported in two separates in the meta-analysis. The studies are shown in the table below.

- **META-ANALYSIS/DESCRIPTIVE ANALYSIS SUMMARY**

Results are described for adults, since there were no studies in adolescents. COCP + metformin treatment resulted in lower FAI and higher SHBG levels, compared with COCP alone, with moderate and low certainty of evidence respectively. The combination COCP + metformin resulted in lower androstenedione and DHEAS levels, very low and low certainty. After treatment with the combination COCP + metformin, insulin and HOMA-IR were lower compared with after COCP, very low and low certainty.
With moderate certainty, the effect on total testosterone do not differ between treatments. There were no differences in blood lipids, CRP or anthropometry (low or very low certainty). There was no difference in HRQoL, very low certainty. Adverse effects are difficult to compare since this is an outcome assessed differently, but the combination COCP + metformin seems to be associated with more gastrointestinal side effects.

Included studies:

Study ID	ROB	Comparisons	Country, duration	N	Mean age	Mean BMI	PCOS diagnosis	Menarche age	Smokers	Comments	Outcomes relevant to this review
Bilgir 2009 (60)	High	1: 35ug EE + 2mg CPA 2: 35ug EE + 2mg CPA + met 1700 mg/day	Turkey 3 months	1:20 2:20	1: 24.3±5.7 2: 25.2±4.6	1: *28.2±6.0* *2: 28.2±4.3*	Rott	NR	Non smokers		BMI, TG, Chol, LDL, HDL, insulin, HOMA, DHEAS, free T
Bodur 2018 (19)	High	1: 30 ug EE + 3 mg DRSP 2: 1700 g Met 3: 30 ug EE + 3 mg DRSP + 1700 g Met 4: controls, no mediciation	Turkey 6 months	1=17 2=17 3=12 4=15	1: 26.62 ± 4.92 2: 26.24 ± 3.96 3: 27.35 ± 5.65 4: 29.18 ± 5.20	1: 23.45 ± 3.40 2: 25.06 ± 3.08 3: 25.11 ± 3.75 4: 23.82 ± 2.80	Rott	NR	NR		CRP, PAI-1, fS-glucose, HOMA
Cibula 2005 (61)	Mod	C) 35ug EE + 250ug NOR 21/7 CM) [35ug EE + 250ug NOR] + 500mg MET 3/d (1500mg/d)	Czech Republic 6 months	C: 15 CM: 13	C: 23.2±4.6 CM: 23.8±5.4	C: 22.1±3.1 CM: 24.7±4.9	Author defined				Weight, BMI, insulin, glucose, chol, TG, HDL, LDL, TT, FAI, A4, DHEAS, SHBG
Elter 2002 (62)	Mod	1: 35µg EE + 2mg CPA 21/7 2: 35µg EE + 2mg CPA + MET 1500mg/d	Turkey 4 months	1: 20 2: 20	1: 23.45±6.07 2: 24.90±6.62	1: 21.83±1.40 2: 22.74±2.66	Author defined	NR	NR		BMI, WHR, FG score, TT, fT, A4, DHEAS, SHBG, glucose, insulin, chol, TG, HDL, LDL
Essah 2011 (63)	Low	C) 35ug EE + 0.18/ 0.215/	USA	C: 10 CM: 9	NR (adults)	C: 32.6±2.3	Rotterdam	NR	All non-smokers		Glucose, insulin, CRP,

		0.25mg NOR (+ placebo) CM) [35ug EE + 0.18/ 0.215/ 0.25mg NOR] + 500mg MET 3/d (1500mg/d)	3 months			CM: 36.2±2.5					PAI-1, weight, BMI, WHR, TT, fT, SHBG, A4, chol, LDL, HDL, TG
Feng 2016 (64)	Mod	C) 35ug EE + 2mg CPA CM) [35ug EE + 2mg CPA] + 450mg-850mg MET 2/d	China 3 months	C: 41 CM: 41 Implied	C: 28.57±3.04 CM: 27.86±3.79	C: 27.77±4.23 CM: 29.46±4.43	Rotterdam	NR	NR		BMI, WHR, TT, hirsutism score, chol, TG, HDL, LDL, glucose, insulin, HOMA,
Fonseka 2020 (2)	Low	1: EE/CPA (Diane-35, 2: EE/DES (Fermion) 3: metformin + EE/CPA 4: metformin + EE/DES	Sri Lanka 12 months	1:20 2:23 3: 26 6: 30	1: 23.35± 5.10 2: 22.39 ± 6.45 3: 24.81 ± 6.24 4. 27.90 ± 6.89	1: 28.27 ±6.94 2: 26.74 ±4.88 3: 27.93 ±4.89 4: 27.20 ± 4.28	Rott	NR	NR		mFG score
Glintborg 2014a (32) Glintborg 2014b (33) Altinok 2018 (35) Glintborg 2017 (34)	High	1: 30 μg EE + 150 mg DSG 2: met 2000 mg/day 3: combo	Denmark 12 months	1:23 2:19 3:23	Median, 25-75 percentile: 1: 28 (24; 32) 2: 31 (24; 33) 3: 30 (24; 31)	Median, 25-75 percentile: 1: 28.0 (22.9; 31.8) 2: 25.9 (24.1; 29.6) 3: 27.6 (24.3; 31.2)	Rott	NR	NR	Nothing extracted from Glintborg 2014b	Change in: Weight, BMI, FG, TT, SHBG, insulin, HOMA, In 2017: OGTT From Altinok: HR QoL: PCOS-specific visual analog scale (PCOS-VAS) with six items regarding discomforts with PCOS, PCOS-VAS1: Facial hair, PCOS-VAS2: Body hair, PCOS-VAS3: Acne, PCOS-VAS4: Menstrual irregularities, PCOS-VAS5: Weight and PCOS-VAS6: PCOS in general. SF-36
Kaya 2012 (65)	High	30 µg EE/3mg DRSP 30 µg EE/3 mgDRSP + met	Turkey 6 months	1=19 2=18	1:23.2±5.4 2: 23.0±4.5	1:26.4±6.2 2:31.7±7.3	AES	NR	NR		BMI, weight, SHBG, TT, fT, FAI, androstendione, DHEAS, insulin, HOMA, TG, LDL, HDL, CRP,

Kaya 2015 (66)	High	30 µg EE/3mg DRSP 30 µg EE/3 mgDRSP + met 1700 mg/day	Turkey 6 months	1=25 2=25	1: 23±5 2: 24±4	1: 26.7±5.7 2: 29.8±6.9	AES	NR	excluded		BMI, weight, SHBG, TT, fT, FAI, androstendione, DHEAS, insulin, HOMA, TG, LDL, HDL, CRP,
Kebapcilar 2009 (67)	High	35 µg EE/2mg CPA 35 µg EE/2mg CPA + met 1700 mg/day	Turkey 3 months	1=22 2=21	1: 24.1±5.6 2: 25.1±4.4	1: 27.2±6.2 2: 28.7±4.4	Rott	NR	excluded		BMI, fT, DHEAS, insulin, HOMA, TG, LDL, HDL,
Kebapcilar 2010 (48)	High	1: 35 µg EE/2mg CPA 2: 35 µg EE/2mg CPA + met 1700 mg/day 3: metformin 1700 mg/day 4: met 1700 mg/day + spiro 100 mg/day	Turkey 3 months	12/group	24.0±5.4 years; for all	1: 28.7 ±6 2: 27.6 ± 3 3: 27.8 ± 4 4: 27.6 ± 4	Rott	NR	excluded		BMI, fT, DHEAS, insulin, HOMA, TG, LDL, HDL,
Kumar 2018 (49)	Mod	1: 35 µg EE/2mg CPA 2: metformin 2000 mg/day 3: 35 µg EE/2mg CPA + met 2000mg/day	India 6 months	1:28 2:30 3:29	1: 22.9 (5) 2: 22 (5.2) 3: 24.1 (5.9)	1: 26.15 (4.9) 2: 27.14 (6) 3: 30.10 (5.5)	Rott	NR	NR		BMI, weight, hirsutism score, TT, DHEAS, insulin, glucose, HOMA, TG, LDL, HDL, chol, CRP,
Lv 2005 (68)	High	1: 35 µg EE/2mg CPA 2: 35 µg EE/2mg CPA + met 500 mg/day	China 6 months	1=25 2=25	1: 24.4±5.1 2: 24.5±5.6	1: 21.8±1.4 2:22.1±20.2	Author defined	NR	NR		BMI, WHR, TT, A4, DHEAS, SHBG, glucose, insulin, chol, TG, LDL, HDL
Moro 2013 (56)	Mod	1: 0.03mg EE + 3mg DRSP 2: 500mg MET 3/d (1500mg/d) 3: [0.03mg EE + 3mg DRSP] + 500mg MET 3/d (1500mg/d)	Italy 6 months	C: 25 M: 25 CM: 26	C: 26±3 M: 25±5 CM: 25±4	Median (range) C: 23.7 (20.8-28.6) M: 25.1 (21.9-28.3) CM:26.5(21.3-30)	Rotterdam	NR	1: 36% 2: 40% 3: 38%	*Described as hyperinsulinemic*	BMI, WHR, insulin, HOMA, chol LDL, HDL, TG, TT, SHBG, FAI, A4, DHEAS,
Song 2017 (29) Ruan 2018 (30)	High	(1) 35 µg EE + 2 mg CPA (2) 35 µg EE + 2 mg CPA + Orlistat 120 mgx3 (3) 35 µg EE + 2 mg CPA + metformin 1500 mg/day (4) 35 µg EE + 2 mg CPA + Orlistat 120	China 12 weeks	1:60 2:60 3:60 4:60	1: 27.68 ± 4.99 2: 26.77 ± 4.12 3: 28.63 ± 5.12 4: 27.57 ± 4.58	1: 28.64 ± 4.89 2: 27.85 ± 4.10 3: 27.00 ± 3.47 4: 28.76 ± 3.43	Rott	NR	1: 22% 2: 20% 3: 25% 4: 18%		TT, chol, LDL, HDL, glucose, insulin, HOMA, From Ruan DHEAS, FAI, fT, androstendione, SHBG,, adverse effects

		mgx3 + metformin 1500 mg/day									
Wei 2012 (69)	Mod	1: 35 µg EE + 2 mg CPA + placebo 2: 35 µg EE + 2 mg CPA + met 1500 mg/day (the RCT also incl barbiturate, not incl here)	China 3 months	COCP =28 COCP + met=30	"All female were reproductive-aged"	1: 24.9± 1.7 2: 24.7±1.9	Rott	NR	All non-smokers	All insulin resistant	Weight, WHR, BMI, glucose, inslulin, OGTT, HOMA, chol, TG, LDL, HDL, TT, SHBG, FAI
Wu 2008 (59)	Mod	C) 35µg EE + 2mg CPA M) 500mg MET 3/d (1500mg/d) CM: 35µg EE + 2mg CPA + 500mg MET 3/d (1500mg/d)	China 3 months	Obese C: 7 M: 7 CM:6 Non-Obese C: 12 M: 11 CM: 10	Obese C: 25.0±4.3 M: 25.6±3.6 CM: 24.5±2.4 Non-obese C: 26.1±4.6 M: 25.6±4.2 CM: 25.8±4.0	Obese C: 25.3±0.8 M: 25.6±0.6 CM: 25.2±1.0 Non-obese C: 21.4±1.6 M: 21.5±1.8 CM: 21.6±1.4	Rotterdam	NR	Excluded		BMI, FG score, WHR, insulin,

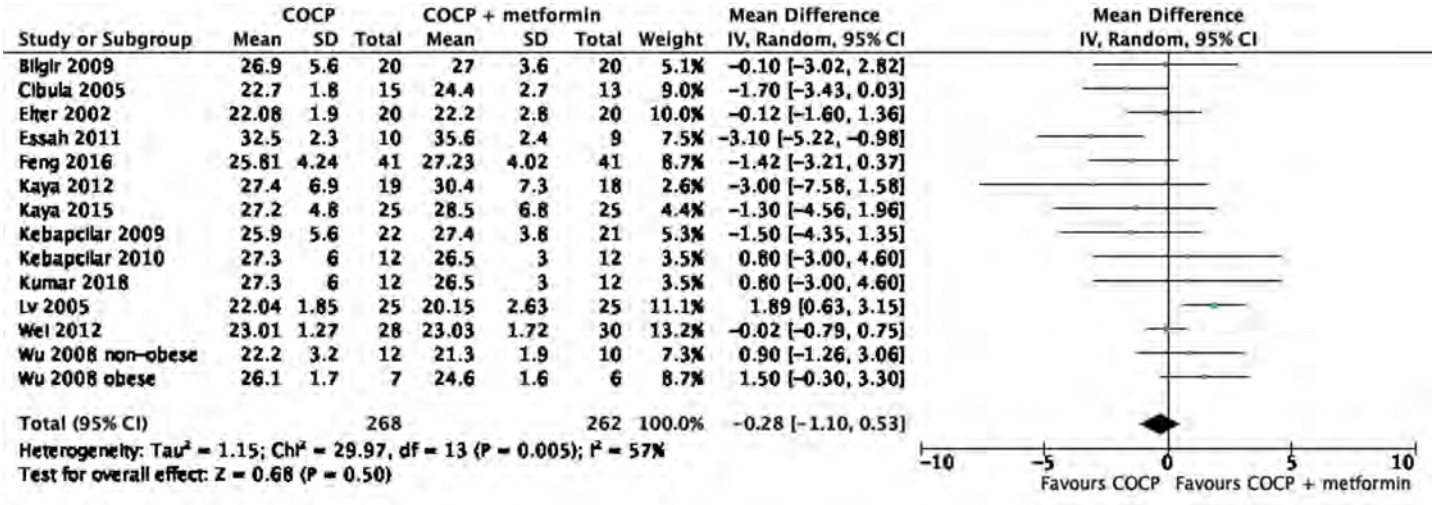
Results from the meta-analysis are shown below:

OUTCOME 21.1 BMI
21.1.1 Individual Study Data Table

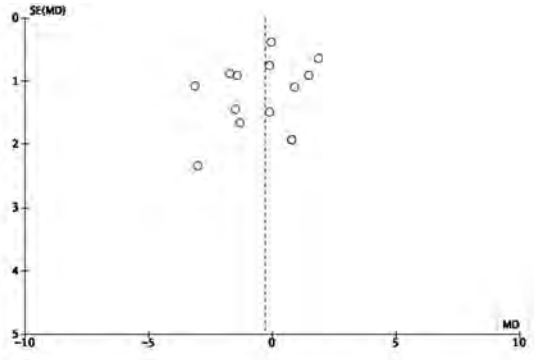
	OUTCOME: BMI				OUTCOME TYPE: Continuous			
	COMPARISON (if applicable): COCP vs. COCP+met							
Author, year	Unit	Time point	N	COCP Mean	COCP SD	COCP + met Mean	COCP + met SD	Comments
Bilgir 2009	kg/m2	3 months	COCP=20 COCP+met=20	26.9	5.6	27.0	3.6	
Cibula 2005		6 m	C 15 CM 13	22.7	1.8	24.4	2.7	
Elter 2002		4 m	C 20 CM 20	22.08	1.9	22.2	2.8	
Essah 2011		3 m	C 10 CM 9	32.5	2.3	35.6	2.4	
Feng 2016		3 m	C: 41 CM: 41	25.81	4.24	27.23	4.02	
Glintborg 2014-1		12 m	COCP 23 CM 23	Median change 0.38 (0.44; 1.17) -0.78 (1.76; 0.03. p<0.05				
Kaya 2012		6 m	C 19 CM 18	27.4	6.9	30.4	7.3	
Kaya 2015		6 m	C 25 CM 25	27.2	4.8	28.5	6.8	
Kebapcilar 2009		3 m	C 22 CM 21	25.9	5.6	27.4	3.8	
Kebapcilar 2010		3 m	COCP 12 CM 12	27.3	6	26.5	3	
Kumar 2018		6 m	C 28	27.3	5	29.5	5.5	

			CM 29					
Lv 2005		6 m	C 25 CM 25	22.04	1.85	20.15	2.63	
Moro 2013		6 m	C 25 CM 26	Median, range *21.9 (20.4-27.8)*		Median, range *24.5 (21.2-30)*		
Wei 2012		3 m	C 28 CM 30	23.01	1.27	23.03	1.72	
Wu 2008 obese		3 m	C: 7 CM: 6	26.1	1.7	24.6	1.6	
Wu 2008 Non obese		3 m	C: 12 CM: 10	22.2	3.2	21.3	1.9	

21.1.2. Forest Plot COCP vs COCP + metformin for BMI (kg/m2)



21.1.3. Funnel plot for assessment of publication bias



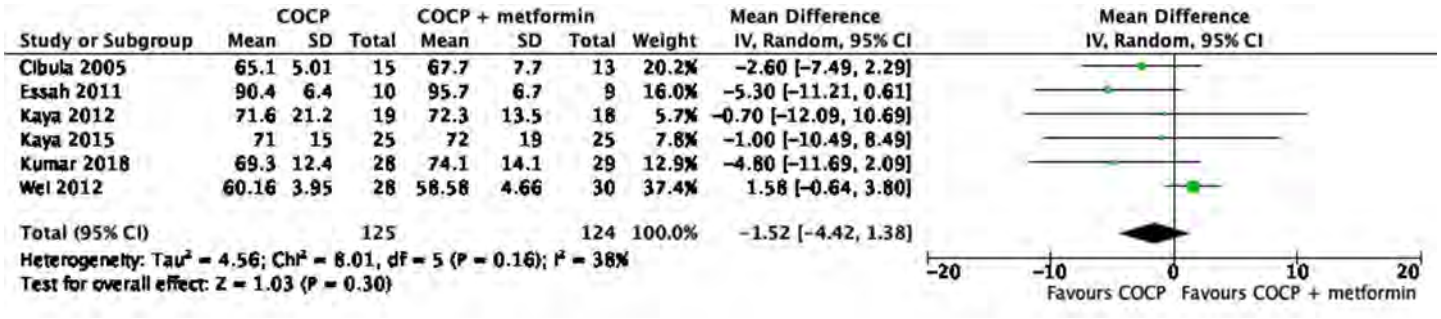
OUTCOME 21.2 WEIGHT

21.2.1 Individual Study Data Table

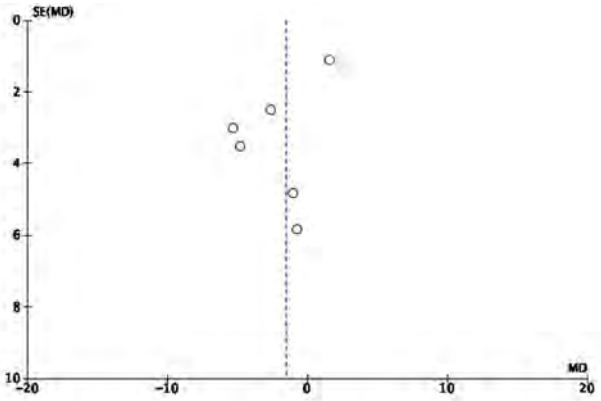
OUTCOME: weight					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. COCP + met								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	COCP + met Mean	COCP + met SD	Comments
Cibula 2005		6 m	C 15 CM 13	65.1	5.01	67.7	7.7	
Essah 2011		3 m	C 10 CM 9	90.4	6.4	95.7	6.7	
Glintborg 2014-1		12 m	COCP 23 CM 23	Median change 1.2 (0.8; 3.0) -1.9 (4.9; 0.1. p<0.05				
Kaya 2012		6 m	C 19	71.6	21.2	72.3	13.5	

			CM 18					
Kaya 2015		6 m	C 25 CM 25	71	15	72	19	
Kumar 2018		6 m	C 28 CM 29	27.3	5	74.1	14.1	
Wei 2012		3 m	C 28 CM 30	60.16	3.95	58.58	4.66	

21.2.2. Forest Plot COCP vs COCP + metformin for weight (kg)



21.2.3. Funnel plot for assessment of publication bias

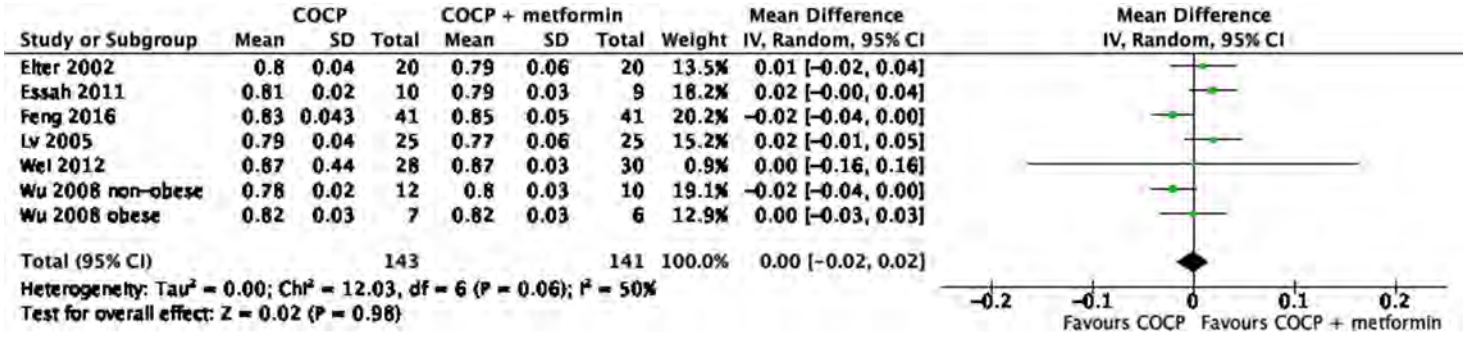


OUTCOME 21.3 WHR

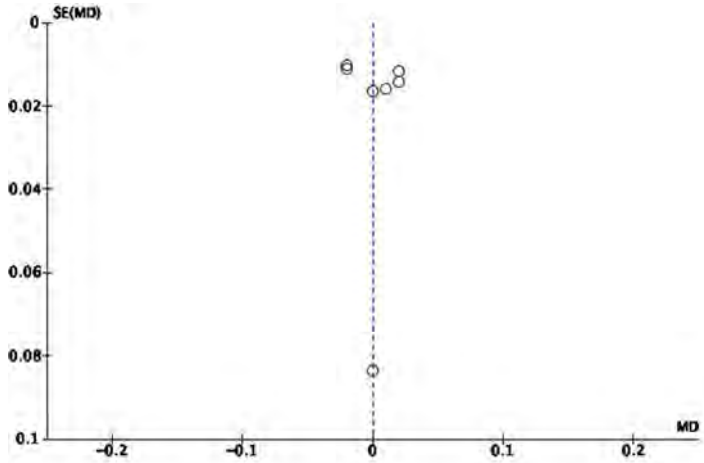
21.3.1 Individual Study Data Table

OUTCOME: WHR					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. COCP + metformin								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	COCP+met Mean	COCP+met SD	Comments
Elter 2002		4 m	C 20 CM 20	0.80	0.04	0.79	0.06	
Essah 2011		3 m	C 10 CM 9	0.81	0.02	0.79	0.03	
Feng 2016		3 m	C: 41 CM: 41	0.83	0.043	0.85	0.05	
Lv 2005		6 m	C 25 CM 25	0.79	0.04	0.77	0.06	
Moro 2013		6 m	C 25 CM26	Median, range *0.78 (0.76-0.88)*		Median, range *0.81 (0.77-0.85)*		
Wei 2012		3 m	C 28 CM 30	0.87	0.44	0.87	0.03	
Wu 2008 obese		3 m	C: 7 CM 6	0.82	0.03	0.82	0.03	
Wu 2008 Non obese		3 m	C: 12 CM 10	0.78	0.02	0.80	0.03	

21.3.2. Forest Plot COCP vs COCP + metformin for WHR



21.3.3. Funnel plot for assessment of publication bias



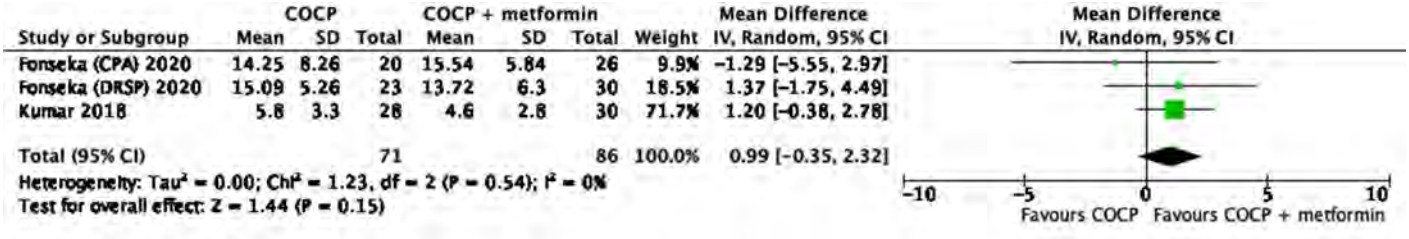
OUTCOME 21.4 HIRSUTISM

21.4.1 Individual Study Data Table

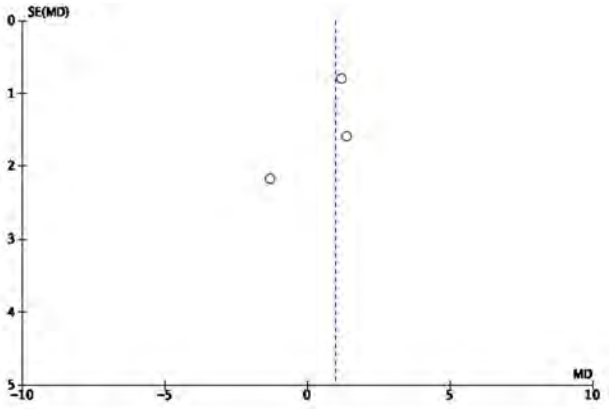
OUTCOME: Hirsutism					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. COCP + met								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	COCP + met Mean	COCP + met SD	Comments
Kumar 2018	FG score	6 m	C 28 M 30	5.8	3.3	4.6	2.8	
Fonseka 2020	FG score	6 months	EE/CPA = 20 COCP + met = 26	17.15	7.38	16.50	4.40	
Fonseka 2020	FG score	12 months	EE/CPA = 20 COCP + met = 26	14.25	8.26	15.54	5.84	
Fonseka 2020	VAS	6 months	EE/CPA = 20 COCP + met = 26	43.5	25.4	35.8	26.4	
Fonseka 2020	VAS	12 months	EE/CPA = 20 COCP + met = 26	45.0	24.4	40.8	23.3	
Fonseka 2020	FG score	6 months	EE/DSG = 23 1 = 30	17.35	4.76	15.03	5.66	
Fonseka 2020	FG score	12 months	EE/DSG = 23 1 = 30	15.09	5.26	13.72	6.30	
Fonseka 2020	VAS	6 months	EE/DSG = 23 1 = 30	38.3	27.4	38.4	23.4	
Fonseka	VAS	12 months	EE/DSG = 23	48.3	21.9	41.4	19.4	

2020			1 = 30					
Glintborg 2014-1	FG score	12 m	COCP 23 CM 23	Median change 0 (3; 0) -4 (7; 0) p<0.05				
Wu 2008 obese	FG score	3 m	C: 7 CM 6	6.8	1.3	6.4	0.8	
Wu 2008 Non obese	FG score	3 m	C: 12 CM: 10	6.9	1.1	6.7	1.2	

21.4.2. Forest Plot COCP vs COCP + metformin for hirsutism (FG score)



21.4.3. Funnel plot for assessment of publication bias

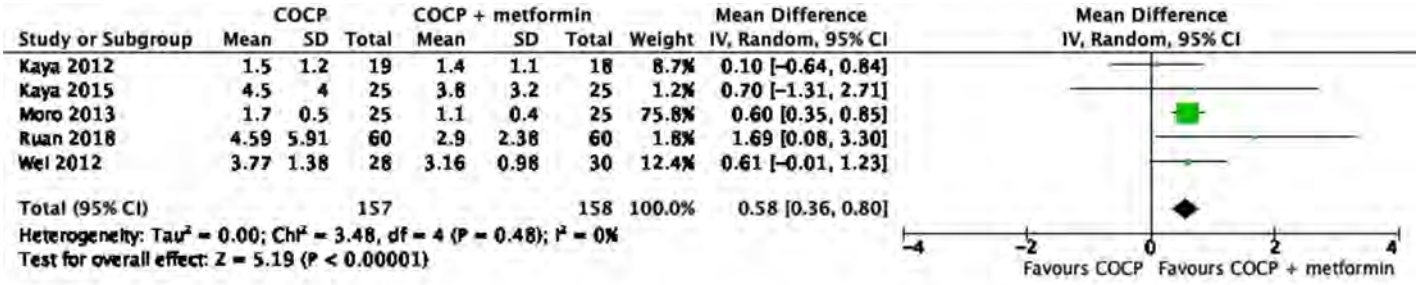


OUTCOME 21.5 FAI

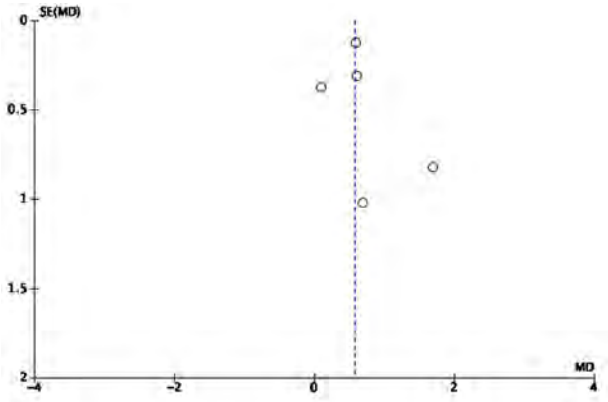
21.5.1 Individual Study Data Table

OUTCOME: FAI					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. COCP + metformin								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	COCP + met Mean	COCP + met SD	Comments
Cibula 2005		6 m	C 15 CM 13	2.8	23.11	3.7	39.93	
Moro 2013		6 m	C 25 M25	1.7	0.5	1.1	0.4	
Kaya 2012		6 m	C 19 CM 18	1.5	1.2	1.4	1.1	
Kaya 2015		6 m	C 25 CM 25	4.5	4.0	3.8	3.2	
Ruan 2018		3 m	C 60 CM 60	4.59	5.91	2.90	2.38	
Wei 2012		3 m	C 28 CM 30	3.77	1.38	3.16	0.98	

21.5.2. Forest Plot COCP vs COCP + metformin for FAI



21.5.3. Funnel plot for assessment of publication bias



OUTCOME 21.6 TOTAL TESTOSTERONE

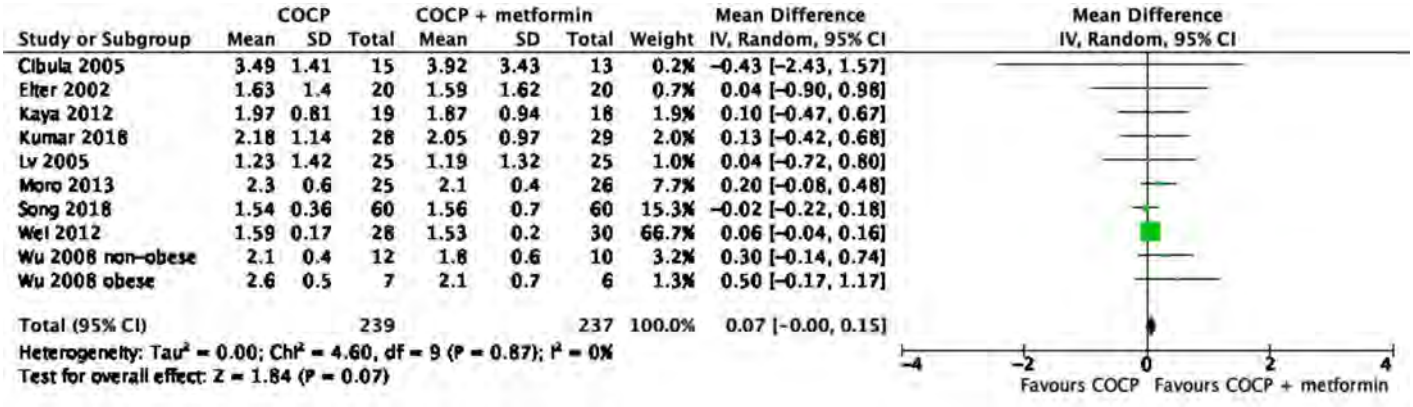
21.6.1 Individual Study Data Table

OUTCOME: Total testosterone					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. COCP + met								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	COCP + met Mean	COCP + met SD	Comments
Cibula 2005	Nmol/L	6 m	C 15 CM 13	3.49	1.41	3.92	3.43	
Elter 2002	Nmol/L	4 m	C 20 CM 20	1.63	1.4	1.59	1.62	
Feng 2016	Nmol/L	3 m	C: 41 CM: 41	18.45	6.35	15.46	6.35	Excluded due to unlikely values
Glintborg 2014-1	Nmol/L	12 m	COCP 23 CM 23	Median change - 0.36 (- 1.17; - 0.04) - 0.42 (- 1.19; 0.01), NS				
Kaya 2012	Nmol/L	6 m	C 19 CM 18	1.97	0.81	1.87	0.94	
Kaya 2015	Ng/ml	6 m	C 25 CM 25	*55 (13–131)*		*50 (19–104)*		NS
Lv 2005	Nmol/L	6 m	C 25 CM 25	1.23	1.42	1.19	1.32	
Kumar 2018	Nmol/L	6 m	C 28 CM 29	2.18	1.14	2.05	0.97	
Moro 2013	Nmol/L	6 m	C 25 CM26	2.3	0.6	2.1	0.4	
Song 2017	Nmol/L	3 m	C 60 CM 60	1.54	0.17	1.53	0.2	
Wei 2012	Nmol/L	3 m	C 28	1.59	0.17	1.53	0.20	

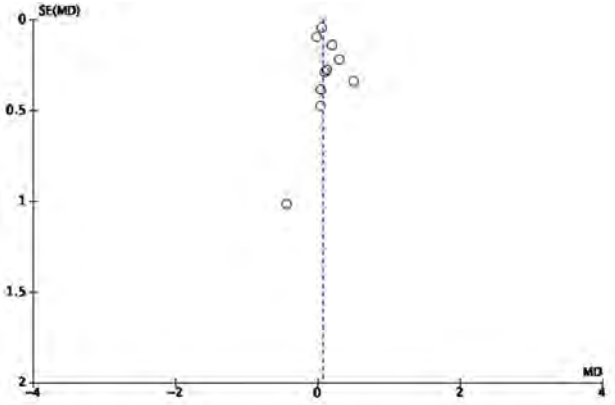
			CM 30					
Wu 2008 obese	Nmol/L	3 m	C: 7 CM 6	2.6	0.5	2.1	0.7	
Wu 2008 Non obese	Nmol/L	3 m	C: 12 CM 10	2.1	0.4	1.8	0.6	

21.6.2. Forest Plot COCP vs COCP + metformin for total testosterone

Feng excluded due to unlikely values.



21.6.3. Funnel plot for assessment of publication bias



OUTCOME 21.7 FREE TESTOSTERONE

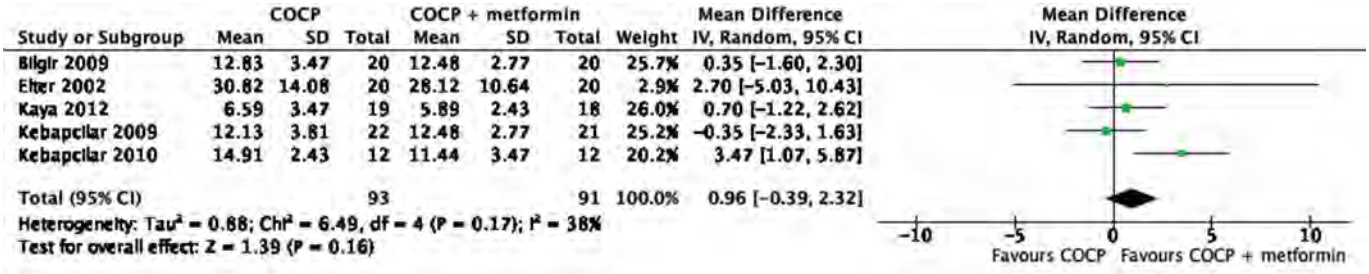
21.7.1 Individual Study Data Table

OUTCOME: Free testosterone					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. COCP+met								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	COCP+met Mean	COCP+met SD	Comments
Bilgir 2009	Pmol/L	3 months	COCP=20 COCP+met = 20	12.83	3.47	12.48	2.77	
Elter 2002	Pmol/L	4 m	C 20 CM 20	30.82	14.08	28.12	10.64	
Essah 2011	Pmol/L	3 m	C 10 CM 9	120.0	37.5	76.4	39.5	Excluded
Kaya 2012	Pmol/L	6 m	C 19 CM 18	6.59	3.47	5.89	2.43	
Kaya 2015	pg/ml	6 m	C 25 CM 25	*1.9 (0.8–4.7)* *1.8 (0.7–17) NS*				
Kebapcilar 2009	Pg/ml	3 m	C 22 CM 21	3.5	1.1	3.6	0.8	
Kebapcilar	Pg/ml	3 m	COCP 12	4.3	0.7	3.3	1.0	

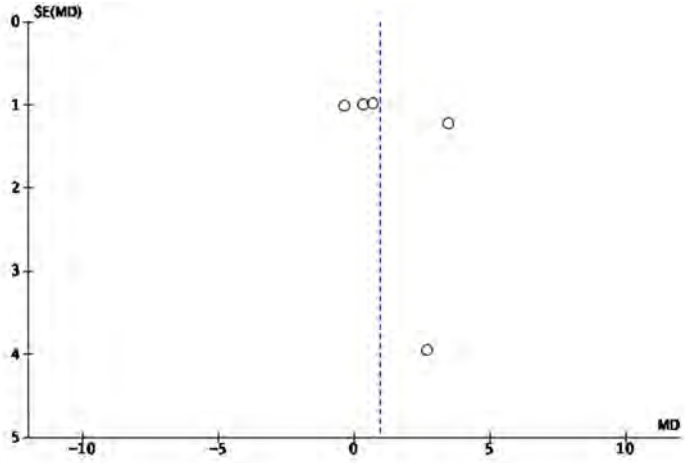
2010			CM 12					
Ruan 2018	Nmol/L	3 m	C 60 CMO 60	1.47	0.54	1.41	0.97	Excluded

21.7.2. Forest Plot COCP vs COCP + metformin for free testosterone (pmol/L)

Two studies were not included due to reporting values outside of normal ranges, considered as reporting errors, Essah 2011 (120 ± 37.5 vs. 76.5 ±39.5 pmol/L) and Ruan (1.47 ±0.54 vs. 1.41 ±0.97 nmol/L). These were excluded.



21.7.3. Funnel plot for assessment of publication bias

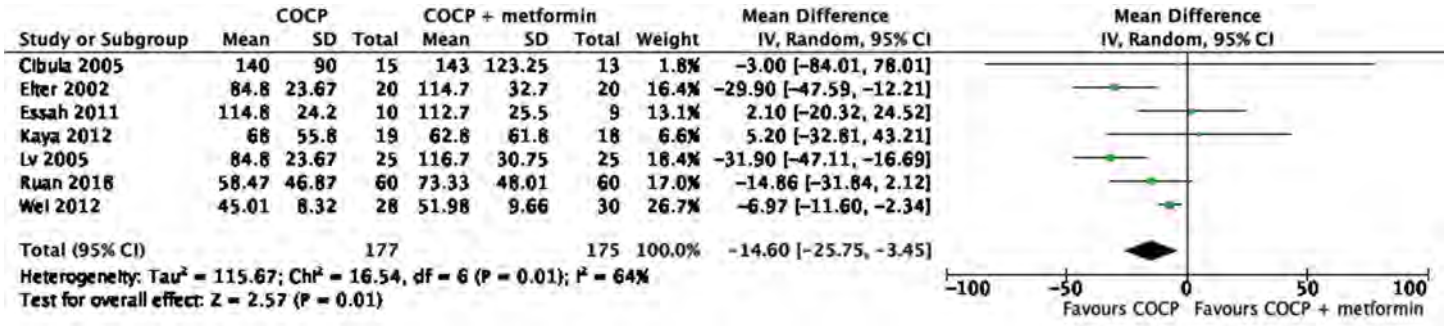


OUTCOME 21.8 SHBG

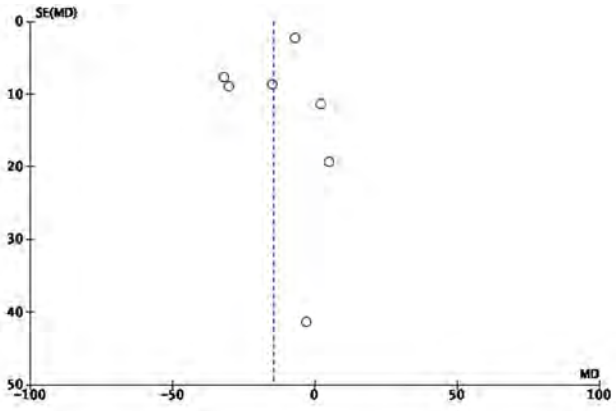
21.8.1 Individual Study Data Table

OUTCOME: SHBG					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. COCP + met								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	COCP + Met Mean	COCP + Met SD	Comments
Cibula 2005	Nmol/L	6 m	C 15 CM 13	140	90	143	123.25	
Elter 2002	Nmol/L	4 m	C 20 CM 20	84.8	23.67	114.7	32.7	
Essah 2011	Nmol/L	3 m	C 10 CM 9	114.8	24.2	112.7	25.5	
Glintborg 2014-1	Nmol/L	12 m	COCP 23 CM 19	Median change *138 (89; 162)* *106 (59; 175),* NS				
Kaya 2012	Nmol/L	6 m	C 19 CM 18	68	55.8	62.8	61.8	
Kaya 2015				*38 (18–218)* *35 (12–317) NS*				
Lv 2005	nmol/L	6 m	C 25 CM 25	84.80	23.67	116.70	30.75	
Moro 2013	Nmol/L	6 m	C 25 CM26	Median *166.2 (83.7-242)*		*166.8 (149.5-239*		
Ruan 2018	Nmol/L	3 m	C 60 MO 60	58.47	46.87	73.33	48.01	
Wei 2012	Nmol/L	3 m	C 28 CM 30	45.01	8.32	51.98	9.66	

21.8.2. Forest Plot COCP vs COCP + metformin for SHBG (nmol/L)



21.8.3. Funnel plot for assessment of publication bias

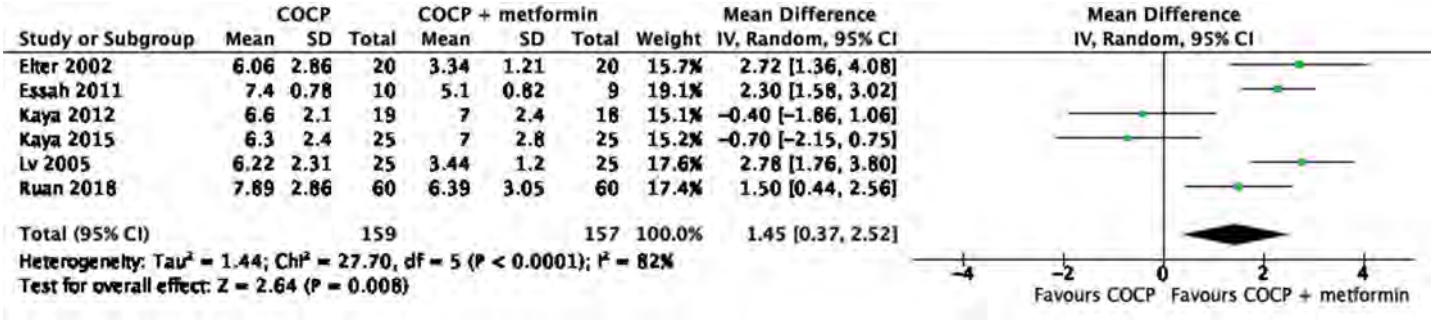


OUTCOME 21.9 ANDROSTENEDIONE

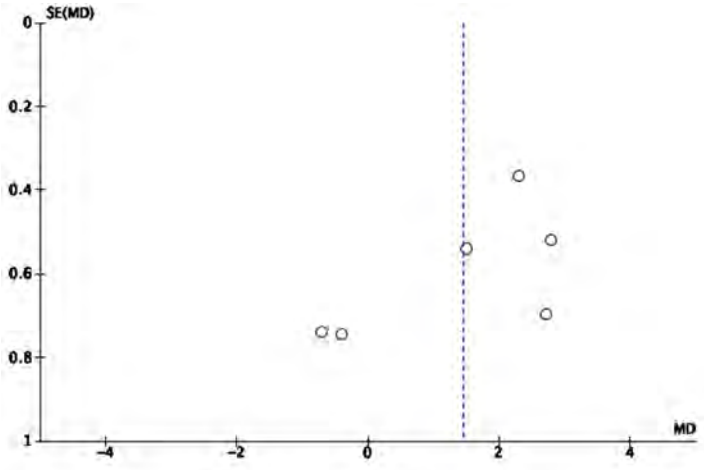
21.9.1 Individual Study Data Table

OUTCOME: androstendione					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. COCP + metformin								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	COCP + Met Mean	COCP + Met SD	Comments
Cibula 2005				Mean difference -4.0	6.4	-4.8	2.6	
Elter 2002	nmol/L	4 m	C 20 CM 20	6.06	2.86	3.34	1.21	
Essah 2011	Nmol/L	3 m	C 10 CM 9	7.4	0.78	5.1	0.82	
Kaya 2012	nmol/L	6 m	C 19 CM 18	6.6	1.2	7	2.4	
Kaya 2015	Nmol/L	6 m	C 25 C; 25	6.3	2.4	7	2.8	
Lv 2005	nmol/L	6 m	C 25 CM 25	6.22	2.31	3.44	1.20	
Moro 2013	Ng/ml	6 m	C 25 CM26	Median *2.1 (1.3-3.4)*		*2.1 (1.7-2.8)*		
Ruan 2018	Nmol/L	3 m	C 60 CMO 60	7.89	2.86	6.39	3.05	

21.9.2. Forest Plot COCP vs COCP + metformin for androstenedione (nmol/L)



21.9.3. Funnel plot for assessment of publication bias

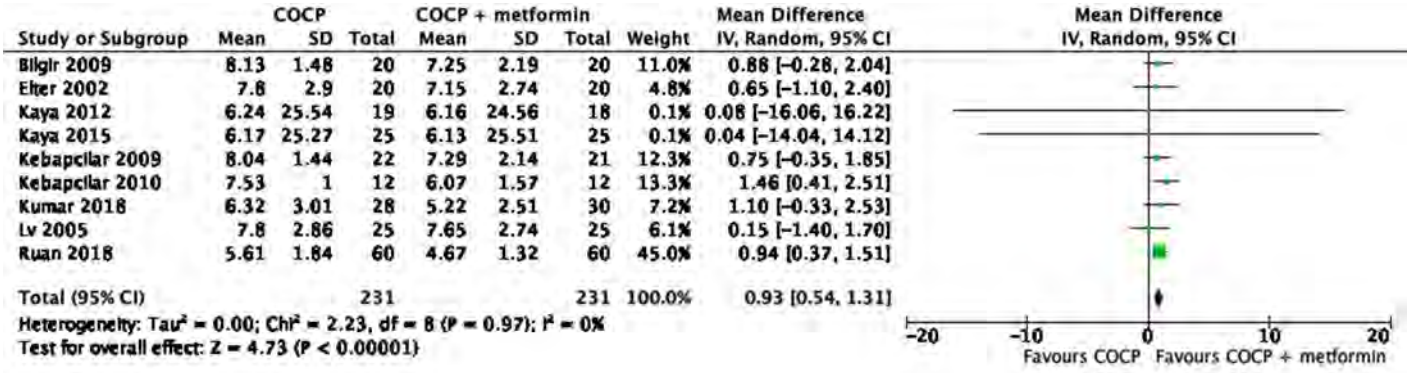


OUTCOME 21.10 DHEAS
21.10.1 Individual Study Data Table

OUTCOME: DHEAS					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. COCP+met								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	COCP+met Mean	COCP+met SD	Comments
Bilgir 2009	μg/ml Assumed meaning μg/dl, recalc to μmol/L	3 m	COCP=20 COCP+met = 20	8.13	1.48	7.25	2.19	
Cibula 2005				Mean difference -4.1	3.0	-2.5	4.0	NS
Elter 2002	μmol/L	4 m	C 20 CM 20	7.80	2.90	7.15	2.74	
Kaya 2012	μmol/L	6 m	C 19 CM 18	6.24	25.52	6.16	24.56	
Kaya 2015	μmol/L	6 m	C 25 C; 25	6.17	25.27	6.13	25.51	
Kebapcilar 2009	μg/ml Assumed meaning μg/dl, recalc to μmol/L	3 m	C 22 CM 21	8.04	1.44	7.29	2.14	
Kebapcilar 2010	μg/ml Assumed meaning μg/dl, recalc to μmol/L	3 m	C 12 CM 12	7.53	1.00	6.07	1.57	
Kumar 2018	μmol/L	6 m	C 28 M 30	6.32	3.01	5.22	2.51	
Lv 2005	μmol/L	6 m	C 25 CM 25	7.80	2.86	7.65	2.74	
Moro 2013	Ng/ml	6 m	C 25 CM26	Median *2214 (1524-3573*		*2271 (1679-2786*		
Ruan 2018	μmol/L	3 m	C 60 CMO 60	5.61	1.84	4.67	1.32	

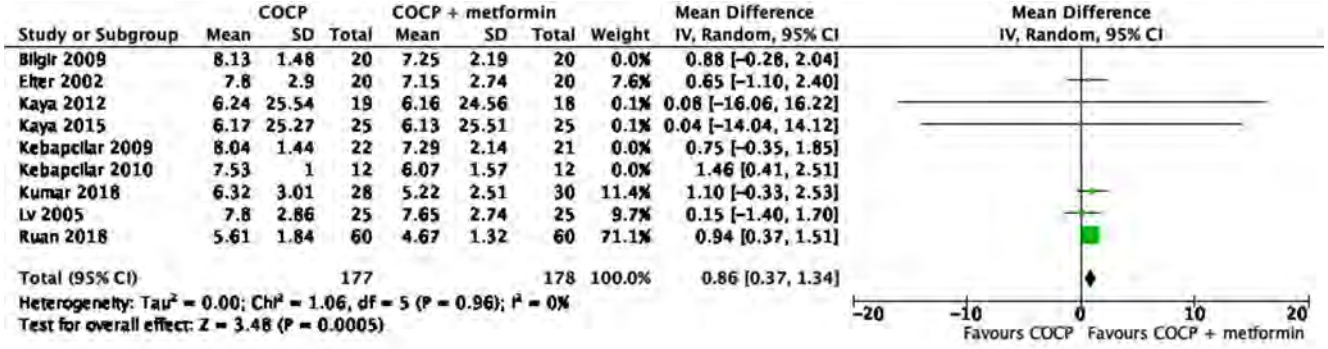
21.10.2.1. Forest Plot COCP vs COCP + metformin for DHEAS (μmol/L)

Version 1 – Bilgir, Kebapcilar 2009 and Kebapcilar 2010 all report DHEAS as μg/ml, this is considered a reporting error, and assumed meaning μg/dl. The studies were included with this assumption.

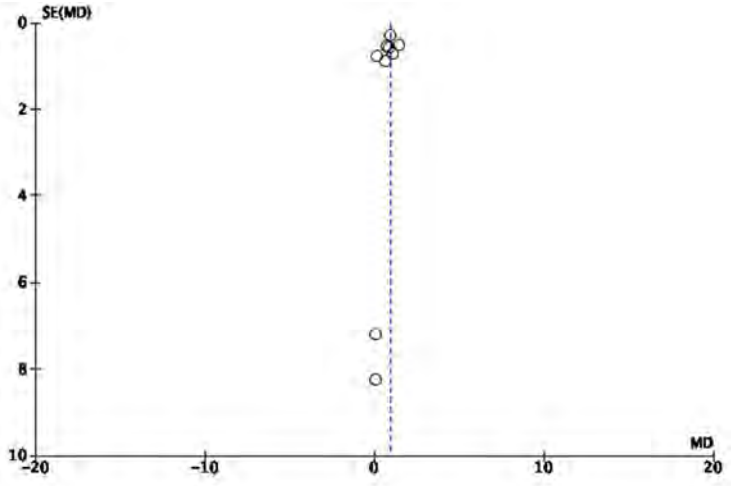


21.10.2.2. Forest Plot COCP vs COCP + metformin for DHEAS (μmol/L)

Version 2 – Sensitivity analysis without Bilgir, Kebapcilar 2009 and Kebapcilar 2010 did not change the overall results.



21.10.3. Funnel plot for assessment of publication bias, all studies included (version 1).



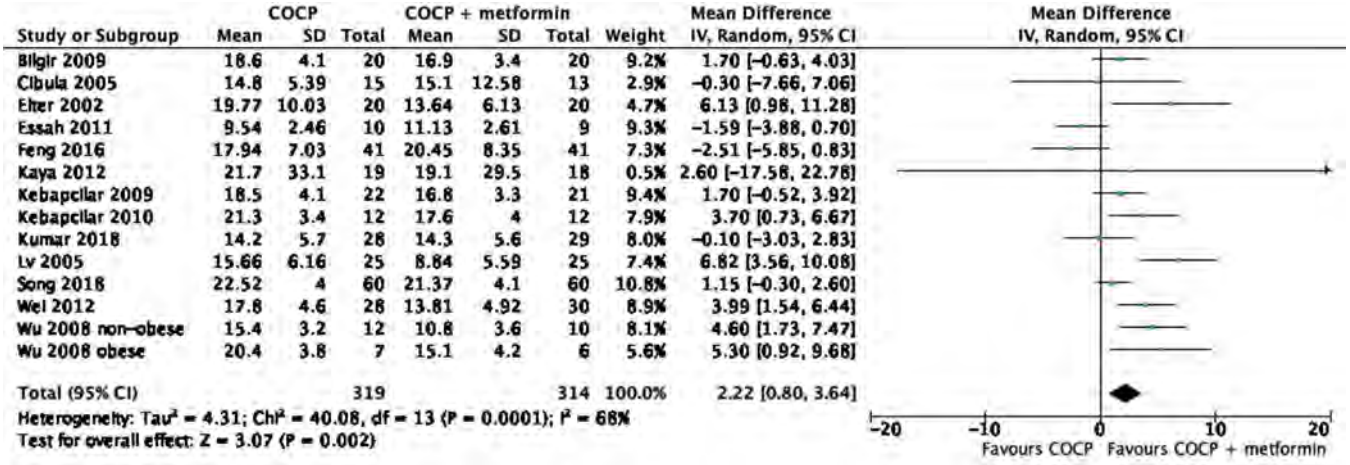
OUTCOME 21.11 INSULIN

21.11.1 Individual Study Data Table

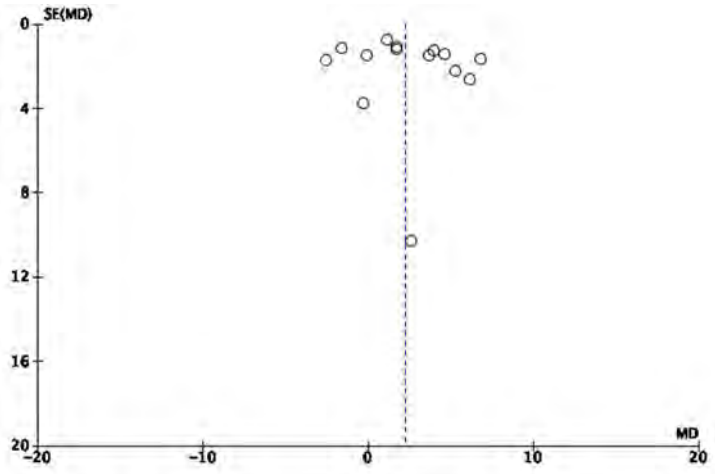
OUTCOME: fasting insulin					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. COCP+met								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	COCP+met Mean	COCP+met SD	Comments
Bilgir 2009	uIU/ml	3 m	COCP=20 COCP+met = 20	18.6	4.1	16.9	3.4	
Cibula 2005	mIU/L	6 m	C 15 CM 13	14.8	5.39	15.1	12.58	
Elter 2002	mIU/L	4 m	C 20 CM 20	19.77	10.03	13.64	6.13	
Essah 2011	Pmol/L	3 m	C 10 CM 9	66.0	17.1	77.3	18.1	
Feng 2016	uIU/ml	3 m	C: 41 CM: 41	17.94	7.03	20.45	8.35	
Glintborg 2014-1	pmol/L	12 m	COCP 23 CM 23	Median change *9 (- 6; 46)* *2 (- 22; 16).* NS				
Kaya 2012	μIU/ml	6 m	C 19 CM 18	21.7	33.1	19.1	29.5	

Kebapcilar 2009	μIU/ml	3 m	C 22 CM 21	18.5	4.1	16.8	3.3	
Kebapcilar 2010	μIU/ml	3 m	COCP 12 CM 12	21.3	3.4	17.6	4.0	
Kumar 2018	μIU/ml	6 m	C 28 CM 29	14.2	5.7	14.3	5.6	
Lv 2005	mU/L	6 m	C 25 CM 25	15.66	6.16	8.84	5.59	
Song 2017	mU/L	3 m	C 60 CM 60	22.52	4.00	21.37	4.10	
Wei 2012		3 m	C 28 CM 30	17.80	4.60	13.81	4.92	
Wu 2008 obese	mIU/L	3 m	C: 7 CM 6	20.4	3.8	15.1	4.2	
Wu 2008 Non obese	mIU/L	3 m	C: 12 CM 10	15.4	3.2	10.8	3.6	

21.11.2. Forest Plot COCP vs COCP + metformin for insulin (mIU/L)



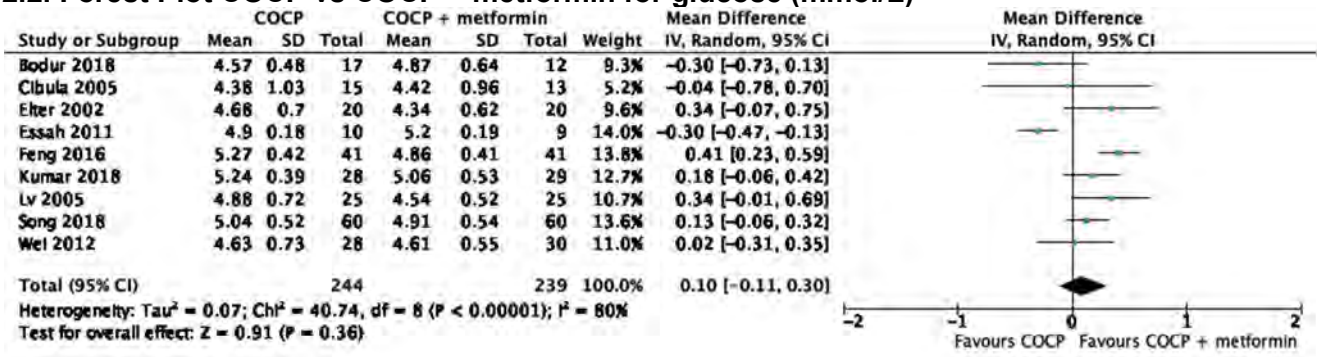
21.11.3. Funnel plot for assessment of publication bias



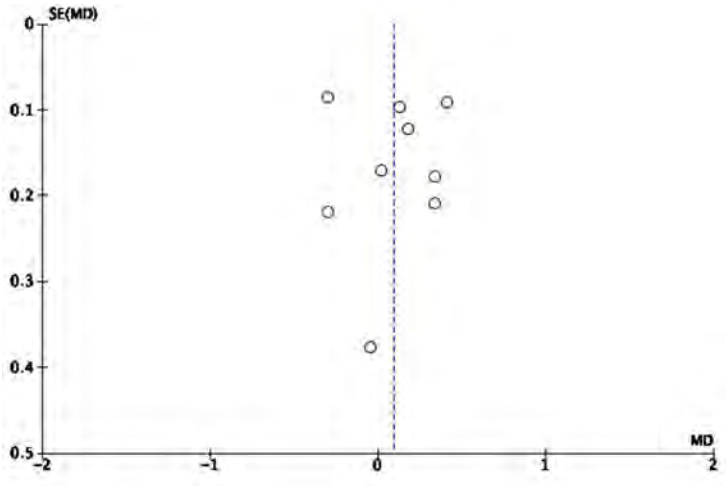
OUTCOME 21.12 GLUCOSE
21.12.1 Individual Study Data Table

OUTCOME: fasting glucose					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs.COCP +met								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	COCP+met Mean	COCP+met SD	Comments
Bodur 2018	Mg/dL (serum)	6 months	OCP=17 combo=12	82.32	8.62	87.83	11.58	
Cibula 2005	Mmol/L	6 m	C 15 CM 13	4.38	1.03	4.42	0.96	
Elter 2002	Mmol/L	4 m	C 20 CM 20	4.68	0.7	4.34	0.62	
Essah 2011	Mmol/L	3 m	C 10 CM 9	4.9	0.18	5.2	0.19	
Feng 2016	Mmol/L	3 m	C: 41 CM: 41	5.27	0.42	4.86	0.41	
Kumar 2018	Mmol/L	6 m	C 28 CM 29	5.24	0.39	5.08	0.53	
Lv 2005	mmol/L	6 m	C 25 CM 25	4.88	0.72	4.54	0.52	
Song 2017	Mmol/L	3 m	C 60 CM 60	5.04	0.52	4.91	0.54	
Wei 2012	Mmol/L	3 m	C 28 CM 30	4.63	0.73	4.61	0.55	

21.12.2. Forest Plot COCP vs COCP + metformin for glucose (mmol/L)



21.12.3. Funnel plot for assessment of publication bias

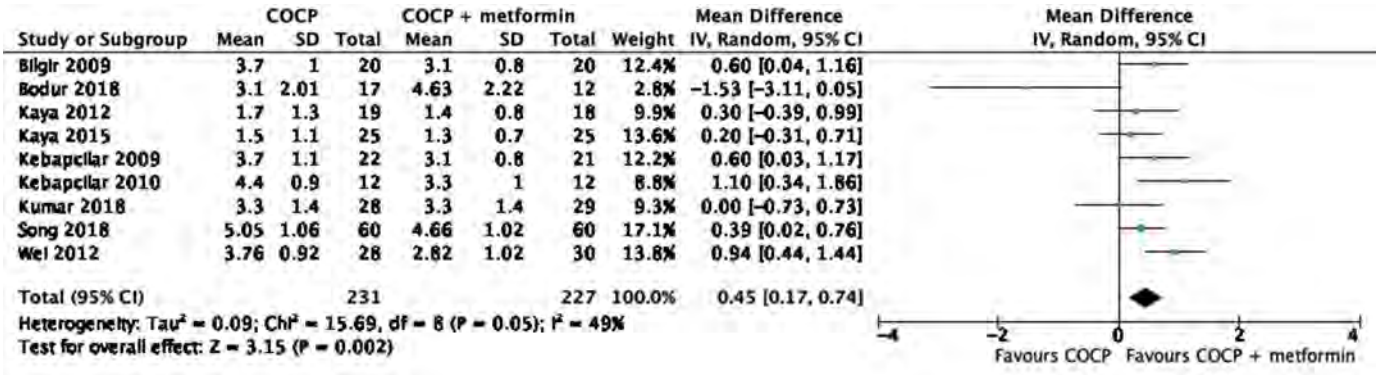


OUTCOME 21.13 HOMA-IR

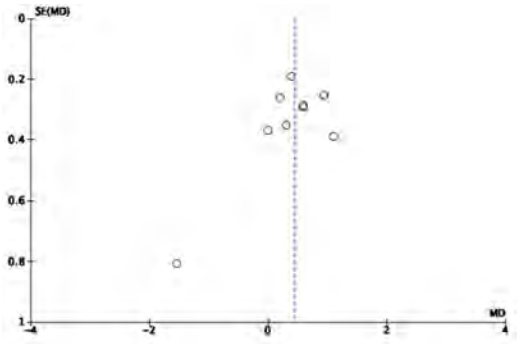
21.13.1 Individual Study Data Table

OUTCOME: HOMA-IR					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs.COCP + met								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	COCP + met Mean	COCP + met SD	Comments
Bilgir 2009	-	3 m	COCP=20 COCP+met = 20	3.7	1.0	3.1	0.8	
Bodur 2018	-	6 m	OCP=17 met=12	3.10	2.01	4.63	2.22	
Glintborg 2014-1		12 m	COCP 23 CM 23	Median change *1.7 (- 1.1; 10.4)* *- 0.6 (- 5.1; 1.8).* NS				
Kaya 2012		6 m	C 19 CM 18	1.7	1.3	1.4	0.8	
Kaya 2015		6 m	C 25 C; 25	1.5	1.1	1.3	0.7	
Kebapcilar 2009		3 m	C 22 CM 21	3.7	1.1	3.1	0.8	
Kebapcilar 2010		3 m	COCP 12 M 12	4.4	0.9	3.3	1.0	
Kumar 2018		6 m	C 28 CM 29	3.3	1.4	3.3	1.4	
Moro 2013		6 m	C 25 CM 26	Median *2.25 (1.25-2.5)*		*1.9 (1.1-3.6)*		
Song 2017		3 m	C 60 CM 60	5.05	1.06	4.66	1.02	
Wei 2012		3 m	C 28 CM 30	3.76	0.92	2.82	1.02	

21.13.2. Forest Plot COCP vs COCP + metformin for HOMA-IR



21.13.3. Funnel plot for assessment of publication bias



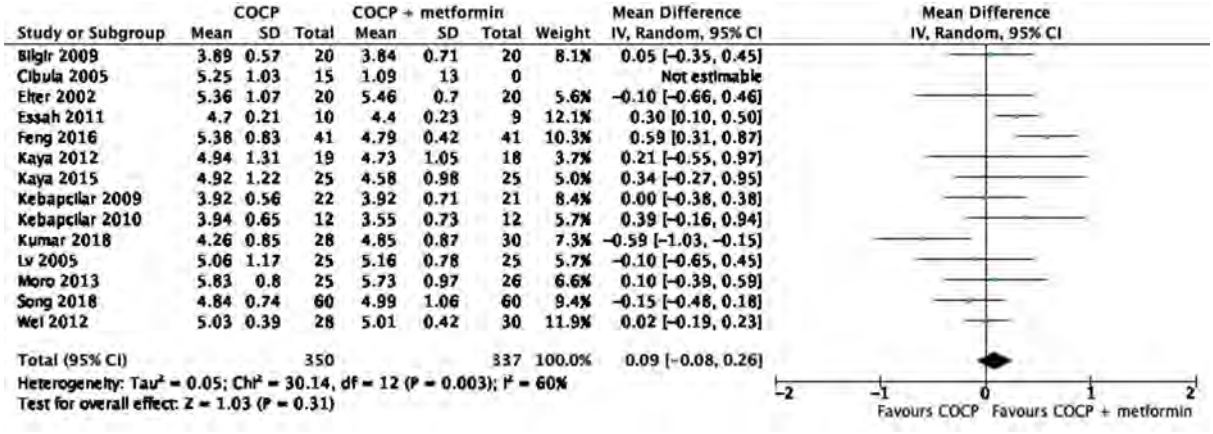
OUTCOME 21.14 OGTT
21.14.1 Individual Study Data Table

OUTCOME: OGTT					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. COCP + met								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	COCP + met Mean	COCP + met SD	Comments
Glintborg 2014-1	AUC 2 h insulin	12 m	COCP 23 CM 23	Median change 6.5 (-5.3;23.0) -0.3 (-9.0;12.3).	NS			
Kaya 2012	Insulin 2 h μIU/ml	6 m	C 19 CM 18	40.7	28.2	53.0	33.9	
Wei 2012	Nmol/L	3 m	C 28 CM 30	7.53	0.53	7.06	0.92	

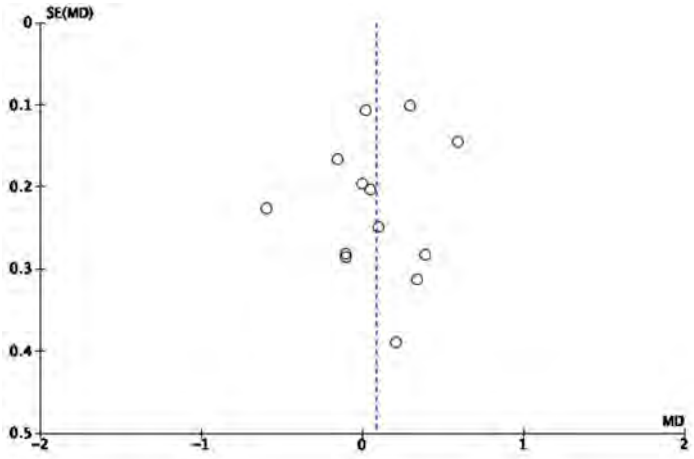
OUTCOME 21.15 CHOLESTEROL
21.15.1 Individual Study Data Table

OUTCOME: cholesterol					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. COCP+met								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	COCP+met Mean	COCP+met SD	Comments
Bilgir 2009	Mmol/L	3 months	COCP=20 COCP+met = 20	3.89	0.57	3.84	0.71	
Cibula 2005	Mmol/L	6 m	C 15 CM 13	5.25	1.03	5.52	1.09	
Elter 2002	Mmol/L	4 m	C 20 CM 20	5.36	1.07	5.46	0.7	
Essah 2011	Mmol/L	3 m	C 10 CM 9	4.7	0.21	4.4	0.23	
Feng 2016	Mmol/L	3 m	C: 41 CM: 41	5.38	0.83	4.79	0.42	
Kebapcilar 2009	Mmol/L	3 m	C 22 CM 21	3.92	0.56	3.92	0.71	
Kebapcilar 2010	Mmol/L	3 m	COCP 12 CM 12	3.94	0.65	3.55	0.73	
Kaya 2012	Mmol/L	6 m	C 19 CM 18	4.94	1.31	4.73	1.05	
Kaya 2015	Ng/ml (assumed to mean mg/dl, converted to mmol/L)	6 m	C 25 C; 25	4.92	1.22	4.58	0.98	See unit
Kumar 2018	mmol/L	6 m	C 28 M 30	4.26	0.85	4.85	0.87	
Lv 2005	mmol/L	6 m	C 25 CM 25	5.06	1.17	5.16	0.78	
Moro 2013	mmol/L	6 m	C 25 CM26	5.83	0.80	5.73	0.97	
Song 2017	Mmol/L	3 m	C 60 CM 60	4.84	0.74	4.99	1.06	
Wei 2012	mmol/L	3 m	C 28 CM 30	5.03	0.39	5.01	0.42	

21.15.2. Forest Plot COCP vs COCP + metformin for cholesterol (mmol/L)



21.15.3. Funnel plot for assessment of publication bias

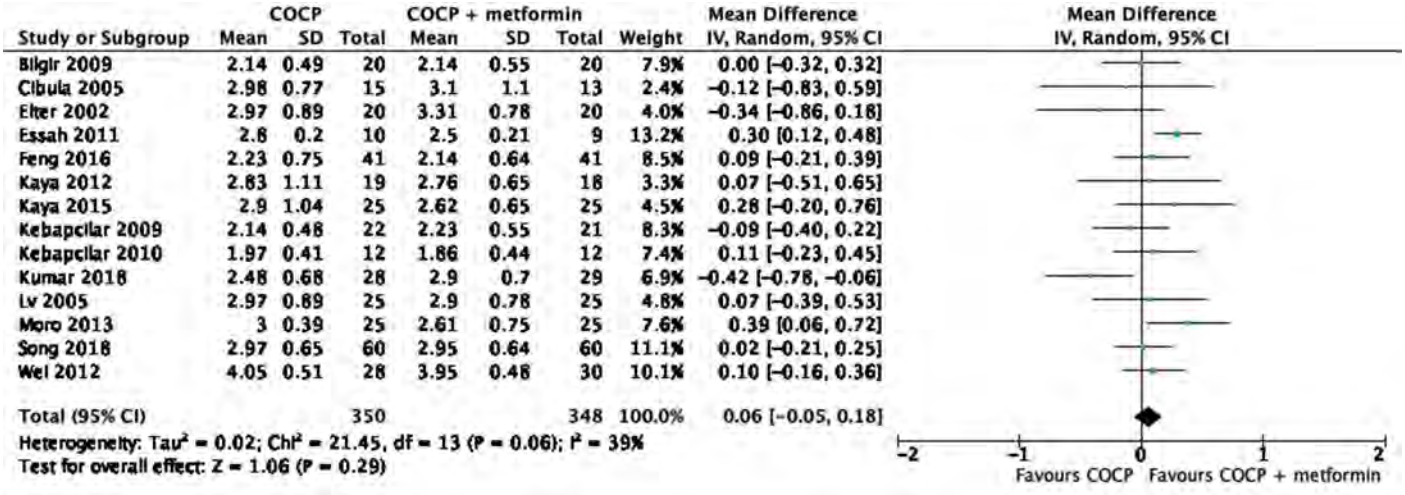


OUTCOME 21.16 LDL

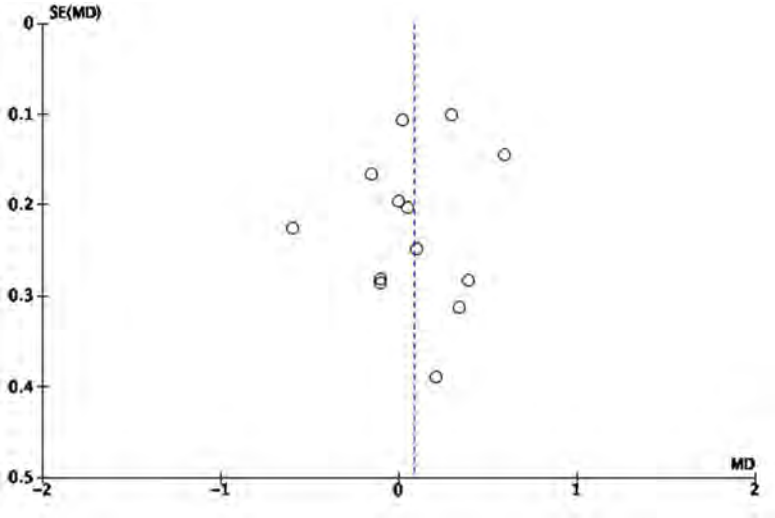
21.16.1 Individual Study Data Table

OUTCOME: LDL					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. COCP+met								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	COCP+met Mean	COCP+met SD	Comments
Bilgir 2009	Mmol/L	3 months	COCP=20 COCP+met = 20	2.14	0.49	2.14	0.55	
Cibula 2005	Mmol/L	6 m	C 15 CM 13	2.98	0.77	3.1	1.1	
Elter 2002	Mmol/L	4 m	C 20 CM 20	2.97	0.89	3.31	0.78	
Essah 2011	Mmol/L	3 m	C 10 CM 9	2.8	0.20	2.5	0.21	
Feng 2016	Mmol/L	3 m	C: 41 CM: 41	2.23	0.75	2.14	0.64	
Kaya 2012	Mmol/L	6 m	C 19 CM 18	2.83	1.11	4.73	1.05	
Kaya 2015	Ng/ml (assumed to mean mg/dl, converted to mmol/L)	6 m	C 25 C; 25	2.90	1.04	2.62	0.65	
Kebapcilar 2009	Mmol/L	3 m	C 22 CM 21	2.14	0.48	2.23	0.55	
Kebapcilar 2010	Mmol/L	3 m	C 12 CM 12	1.97	0.41	1.86	0.44	
Kumar 2018	Mmol/L	6 m	C 28 CM 29	2.48	0.68	2.90	0.70	
Lv 2005	mmol/L	6 m	C 25 CM 25	2.97	0.89	2.90	0.78	
Moro 2013	Mmol/L	6 m	C 25 M25	3.00	0.39	2.61	0.75	
Song 2017	Mmol/L	3 m	C 60 CM 60	2.97	0.65	2.95	0.64	
Wei 2012	Mmol/L	3 m	C 28 CM 30	4.05	0.51	3.95	0.48	

21.16.2. Forest Plot COCP vs COCP + metformin for LDL (mmol/L)



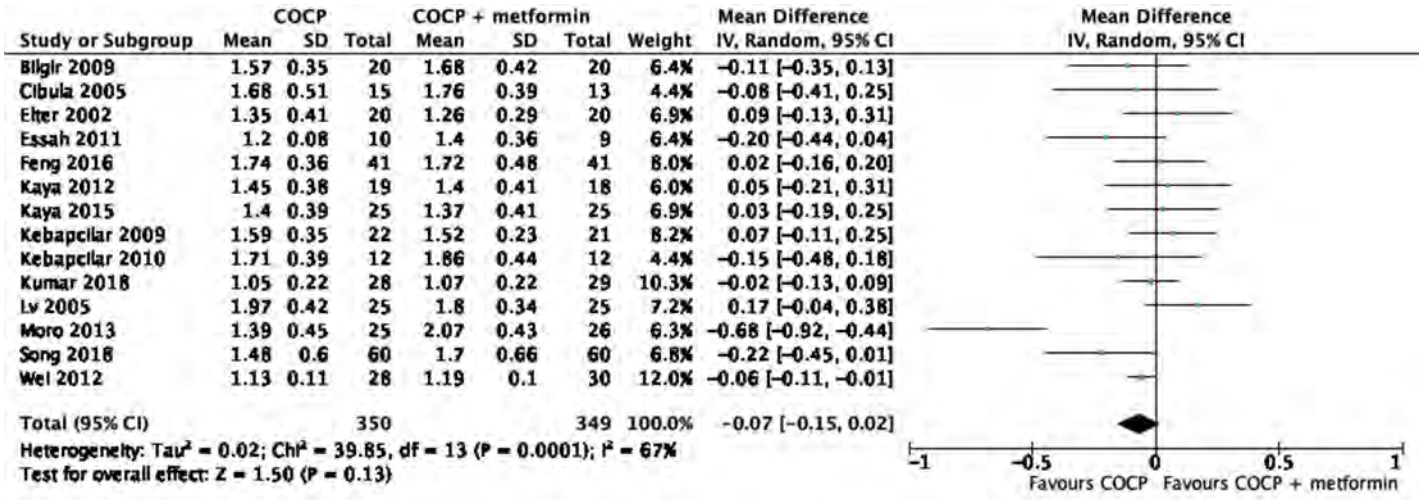
21.16.3. Funnel plot for assessment of publication bias



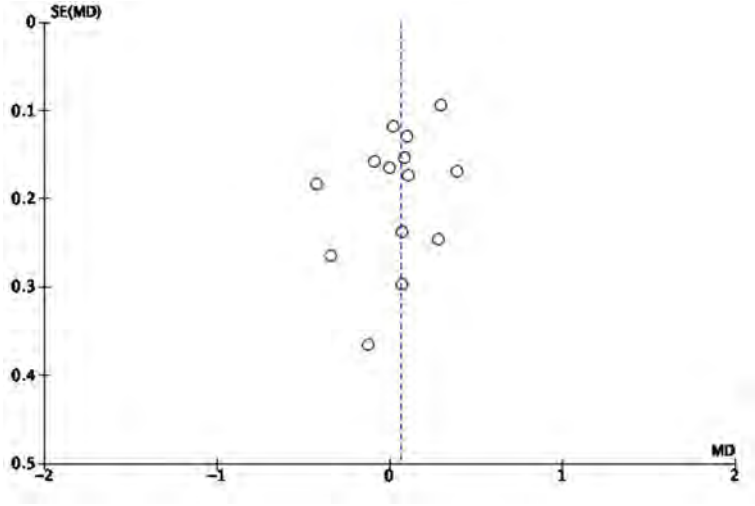
OUTCOME 21.17 HDL
21.17.1 Individual Study Data Table

OUTCOME: HDL					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. COCP+met								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	COCP+met Mean	COCP+met SD	Comments
Bilgir 2009	Mmol/L	3 months	COCP=20 COCP+met = 20	1.57	0.35	1.68	0.42	
Cibula 2005	Mmol/L	6 m	C 15 CM 13	1.68	0.51	1.76	0.39	
Elter 2002	Mmol/L	4 m	C 20 CM 20	1.35	0.41	1.26	0.29	
Essah 2011	Mmol/L	3 m	C 10 CM 9	1.2	0.08	1.4	0.36	
Feng 2016	Mmol/L	3 m	C: 41 CM: 41	1.74	0.36	1.72	0.48	
Kaya 2012	mmol/L	6 m	C 19 CM 18	1.45	0.38	1.40	0.41	
Kaya 2015	Ng/ml (assumed to mean mg/dl, converted to mmol/L)	6 m	C 25 C; 25	1.40	0.39	1.37	0.41	
Kebapcilar 2009	Mmol/L	3 m	C 22 CM 21	1.59	0.35	1.52	0.23	
Kebapcilar 2010	Mmol/L	3 m	C 12 M 12	1.71	0.39	1.86	0.44	
Kumar 2018	Mmol/L	6 m	C 28 CM 29	1.05	0.22	1.07	0.22	
Lv 2005	Mmol/L	6 m	C 25 CM 25	1.97	0.42	1.80	0.34	
Moro 2013	Mmol/L	6 m	C 25 CM26	1.39	0.45	2.07	0.43	
Song 2017	Mmol/L	3 m	C 60 CM 60	1.48	0.60	1.70	0.66	
Wei 2012	Mmol/L	3 m	C 28 CM 30	1.13	0.11	1.19	0.10	

21.17.2. Forest Plot COCP vs COCP + metformin for HDL



21.17.3. Funnel plot for assessment of publication bias

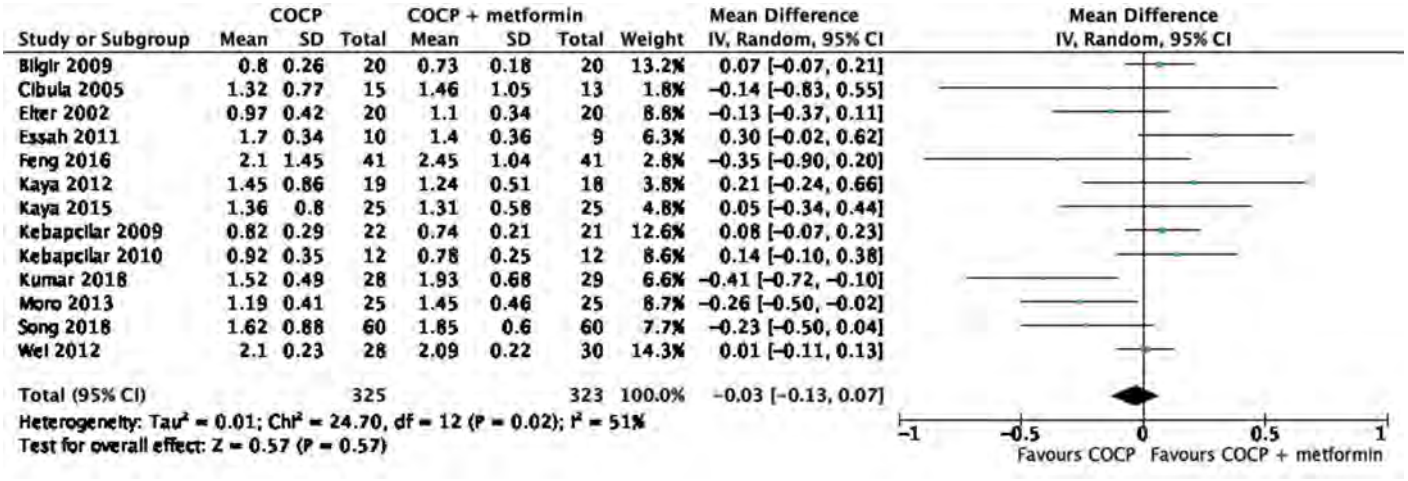


OUTCOME 21.18 TRIGLYCERIDES

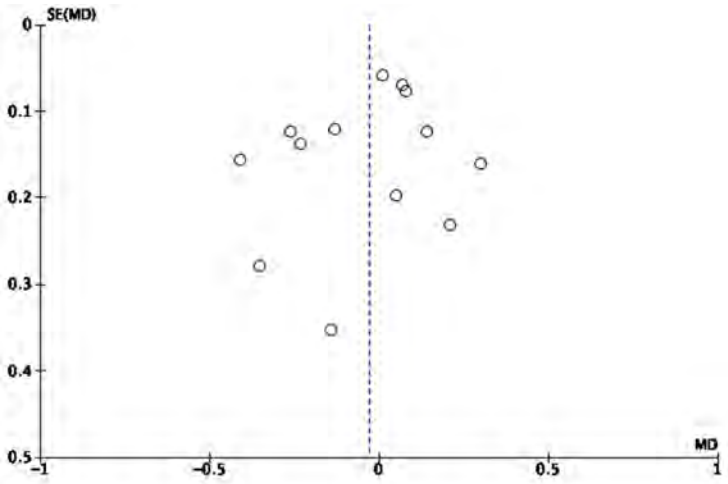
21.18.1 Individual Study Data Table

	OUTCOME: TG				OUTCOME TYPE: Continuous			
	COMPARISON (if applicable): COCP vs. COCP+met							
Author, year	Unit	Time point	N	COCP Mean	COCP SD	COCP+met Mean	COCP+met SD	Comments
Bilgir 2009	Mmol/L	3 months	COCP=20 COCP+met = 20	0.80	0.26	0.73	0.18	
Cibula 2005	Mmol/L	6 m	C 15 CM 13	1.32	0.77	1.46	1.05	
Elter 2002	Mmol/L	4 m	C 20 CM 20	0.97	0.42	1.1	0.34	
Essah 2011	Mmol/L	3 m	C 10 CM 9	1.7	0.34	1.4	0.36	
Feng 2016	Mmol/L	3 m	C: 41 CM: 41	2.10	1.45	2.45	1.04	
Kaya 2012	Mmol/L	6 m	C 19 CM 18	1.45	0.86	1.24	0.51	
Kaya 2015	Ng/ml (assumed to mean mg/dl, converted to mmol/L)	6 m	C 25 C; 25	1.36	0.80	1.31	0.58	
Kebapcilar 2009	Mmol/L	3 m	C 22 CM 21	0.82	0.29	0.74	0.21	
Kebapcilar 2010	Mmol/L	3 m	C 12 CM 12	0.92	0.35	0.78	0.25	
Kumar 2018	Mmol/L	6 m	C 28 CM 29	1.52	0.49	1.93	0.68	
Moro 2013	Mmol/L	6 m	C 25 M25	1.19	0.41	1.45	0.46	
Song 2017	Mmol/L	3 m	C 60 CM 60	1.62	0.88	1.85	0.60	
Wei 2012	Mmol/L	3 m	C 28 CM 30	2.10	0.23	2.09	0.22	

21.18.2. Forest Plot COCP vs COCP + metformin for triglycerids (mmol/L)



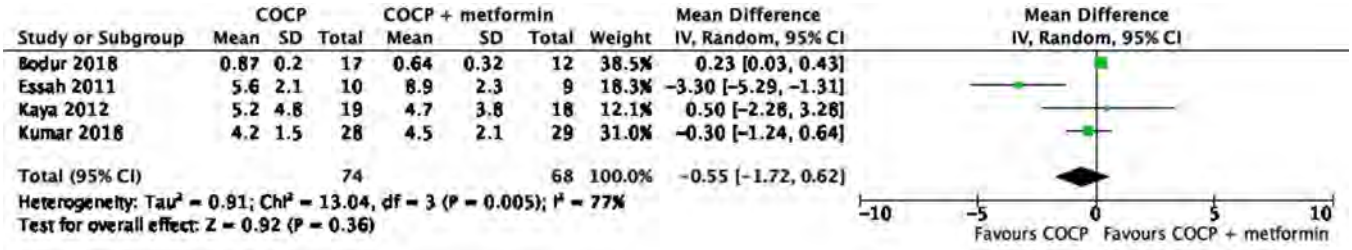
21.18.3. Funnel plot for assessment of publication bias



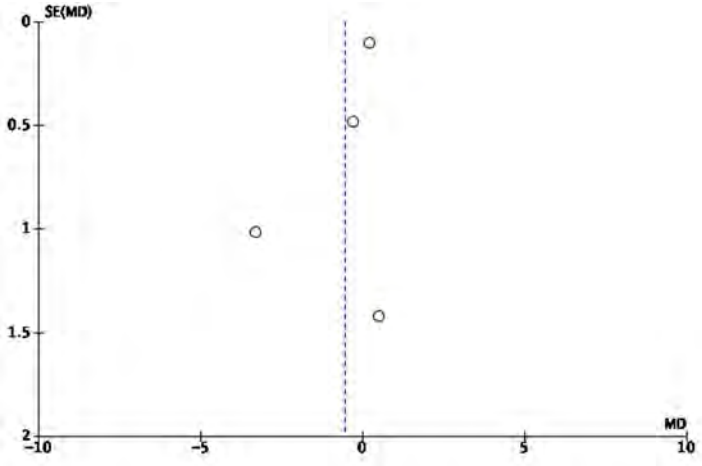
OUTCOME 21.19 CRP
21.19.1 Individual Study Data Table

OUTCOME: CRP					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): COCP vs. COCP + met								
Author, year	**Unit**	**Time point**	**N**	**COCP Mean**	**COCP SD**	**COCP + met Mean**	**COCP + met SD**	**Comments**
Bodur 2018	mg/L	6 months	OCP=17 combo=12	0.87	0.20	0.64	0.32	
Essah 2011	Mg/L	3 m	C 10 CM 9	5.6	2.1	8.9	2.3	
Kaya 2012	Reported as Mg/dl, included as mg/L	6 m	C 19 CM 18	5.2	4.8	4.7	3.8	
Kaya 2015	mg/ml	6 m	C 25 C; 25	*3.3 (3.0–24)* *3.3 (2.6–18) NS*				
Kumar 2018	Mg/L	6 m	C 28 CM 29	4.2	1.5	4.5	2.1	

21.19.2. Forest Plot COCP vs COCP + metformin for CRP (mg/L)



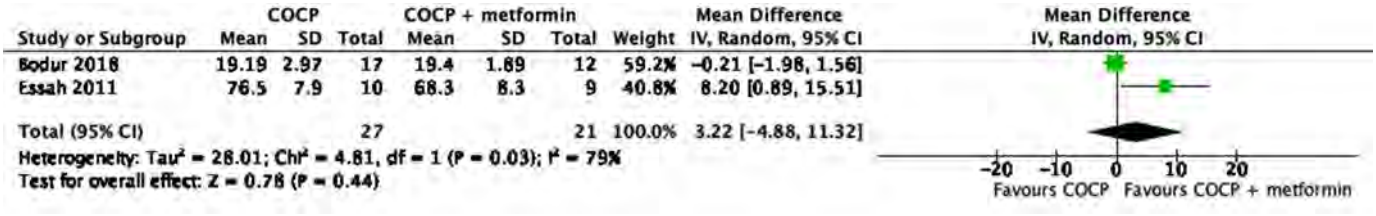
21.19.3. Funnel plot for assessment of publication bias



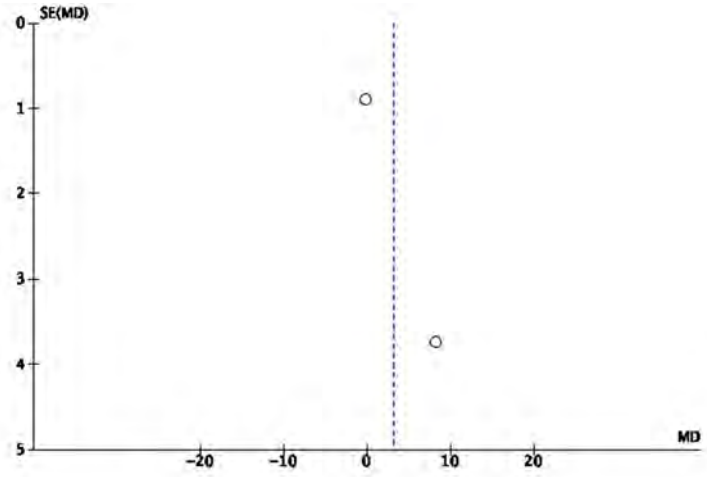
OUTCOME 21.20 PAI-1
21.20.1 Individual Study Data Table

OUTCOME: PAI-1					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): COCP vs. COCP + met								
Author, year	**Unit**	**Time point**	**N**	**COCP Mean**	**COCP SD**	**COCP + met Mean**	**COCP + met SD**	**Are these values adjusted or crude?**
Bodur 2018	Ng/ml	6 months	OCP=17 combo=12	19.19	2.97	19.40	1.89	crude
Essah 2011	Ng/ml	3 m	C 10 CM 9	76.5	7.9	68.3	8.3	

21.20.2. Forest Plot COCP vs COCP + metformin for PAI-1 (ng/ml)



21.20.3. Funnel plot for assessment of publication bias



OUTCOME 21.21 HRQoL
21.1.1 Individual Study Data Table

Altinok 2018	**Favours:** **No difference**	**Certainty** ⊕◯◯◯ VERY LOW (Due to risk of bias, indirectness, imprecision)
HRQoL mesurement	**COCP (n=23)** Median difference (IQR):	**COCP + metformin (n=23)** Median difference (IQR):
VAS 1: Facial hair growth	-1.2 (-2.9;-0.2)	-2.7 (-5.2;-1.0)
VAS 2: Body hair growth	0.7 (-2.3;0.0)	-2.4 (-4.5;0.0)
VAS 3: Acne	-1.8 (-4.0;0.0)	-2.6 (-5.3;0.0)
VAS 4: Menstrual disorder	-1.4 (-3.4;0.2)	-1.3 (-5.5;0.8)
VAS 5: Overweight	-0.2 (-2.0;0.7)	-1.6 (-2.5;-0.8)

VAS 6: PCOS	-0.2 (-2.4;1.0)	-2.1 (-3.8;0.2)
SF-36:		
PF: Physical function	0 (-4;6)	0 (-1;0)
RP: Role limitations physical	0 (0;0)	0 (0;0)
BP: Bodily pain	0 (-16;17)	0 (-6;12
GH: General health	-3 (-6;9)	0 (-2;10
VT: Vitality	-3 (-15;15)	0 (-8;8)
SF: Social function	0 (-16;13)	0 (-13;0
RE: Role limitations emotional	0 (-33;33)	0 (-17;0
MH: Mental health	-6 (-16;6)	0 (-8;4)
PCS: Summed physical scores	0 (-5;6)	2 (-2;5)
MCS: Summed mental scores	-2 (-11;9)	-2 (-6;2)

OUTCOME 21.22 ADVERSE EFFECTS

Advere seffect	Study ID	COCP	COCP + met
Nausea/vomiting	Bodur 2018	1/21	1/20
	Fonseka 2020	1/50	0/50
	Kabapcilar 2010	0/12	8/24*
	Cibula 2005	0/15	1/15
	Elter 2002	0/20	4/20
	Moro 2013	0/31	2/31
	Wu 2018	0/20	4/20
Sexual reluctance	Bodur 2018	1/21	0/20
Pregnancy	Bodur 2018	1/21	0/20
Hirsutism	Bodur 2018	1/21	1/20
Headache	Bodur 2018	0/21	1/20
	Fonseka 2020	1/50	0/50
Dizzieness	Bodur 2018	0/21	2/20
	Fonseka 2020	1/50	1/50
Unwilling weightloss	Bodur 2018	0/21	1/20
Weight increase	Wu 2018	1/20	0/20
Joint stiffness	Fonskea 2020	1/50	0/50
Breast tenderness	Fonseka 2020	1/50	0/50
Other	Song/Ruan	21/240 patients treated with COCP alone or in combination, experienced side effects including headaches, nausea, weight gain, breast tenderness, and loss of libido	9/120 patients treated with metformin alone or in combination, experienced side such as mild nausea and abdominal pain.

*COCP + metformin or metformin alone

Comparison 22: COCP vs. anti-androgen

- **EVIDENCE SUMMARY:**

One RCT with a moderate risk of bias compared EE/CPA with spironolactone 200 mg/day. No additional studies since last guideline.

- **META-ANALYSIS/DESCRIPTIVE ANALYSIS SUMMARY:**

The only outcome reported was hirsutism (FG score), where lower scores were seen after COCP treatment, very low certainty of evidence.

Included study:

Study ID	ROB	Comparisons	Country, duration	N	Mean age	Mean BMI	PCOS	Menarche age	Smokers	Comments	Outcomes relevant to this review
Spritzer 2000 (70)	Mod	1: EE/CPA 2: spironolactone 200 mg/day	Brazil 12 m	C: 9 AA: 10	22 ± 9 for all	24 ± 5 for all	NIH	NR	NR		FG score

Result from individual study:

Spritzer 2000	Certainty				**Very low** (serious risk of bias, very serious risk of imprecision)			
Outcome	Time	N	COCP Mean	COCP SD	Anti-androgen Mean	Anti-androgen SD	P value	Favours
Hirsutism /FG score)	12 m	C: 9 AA: 10	12	3	16	3.2	0.009	COCP

Comparison 23: COCP vs. COCP + antiandrogen

EVIDENCE SUMMARY:

Seven RCTs with eight publications were identified for this outcome. Four had a moderate risk of bias, and three a high risk of bias. No studies involved adolescents.
The anti-androgens used in these studies was spironolactone (Hagag, Kebapcilar 2010, Leelaphiwat, and Meyer including the follow-up publication from the same RCT by Burchall 2017, bicalutamide (Moretti), finasteride (Tartagni 2000) and cyproterone acetate (Hagag).
Since Hagag had two arms with COCP + anti-androgens, but only one arm with COCP, the combination COCP + spironolactone was used in the meta-analysis, since this was the most used combination in other studies. Information about included studies are shown below.

META-ANALYSIS/DESCRIPTIVE ANALYSIS SUMMARY:

For adults, with moderate certainty, weight was lower after COCP treatment, compared with COCP + anti-androgen treatment. There was no difference in BMI between treatments, with moderate certainty. There were no differences in biochemical hyperandrogenism, glucose metabolism or blood lipids with very low certainty.

Included studies:

Study ID	ROB	Comparisons	Country, duration	N	Mean age	Mean BMI	PCOS	Menarche age	Smokers	Comments	Outcomes relevant to this review
Hagag 2014 (71)	Mod	C) 250ug NOR + 35ug EE CA1) [250ug NOR + 35ug EE] + 100mg SPL CA2) [2mg CPA + 35ug EE] + 10mg CPA added	Israel 12 months	C: 25* CA1:72 CA2:70	C: 22±0.7 CA1: 22±0.4 CA2: 21±0.3	C: 24±0.9 CA1: 24±0.6 CA2:23.5± 0.5	Rott				FG score, fT, TT, DHEAS, A4,
Kebapcilar 2010 (48)	High	1: 35 µg EE/2mg CPA 2: 35 µg EE/2mg CPA + met 1700 mg/day 3: metformin 1700 mg/day 4: met 1700 mg/day + spiro 100 mg/day	Turkey 3 months	12/group	24.0±5.4 years; for all	1: 28.7 ±6 2: 27.6 ± 3 3: 27.8 ± 4 4: 27.6 ± 4	Rott	NR	excluded		BMI, fT, DHEAS, insulin, HOMA, TG, LDL, HDL,
Leelaphiwat 2015 (72)	High	C) 35mcg EE + 2mg CPA CA) [30mcg EE + 150mcg DSG] + 25mg SPL	Thailand 3 months	C: 16 CA: 17	C: 26.94±6.87 CA: 26.29±4.04	C: 22.96±5.35 CA: 27.15±6.37	Rott	NR	NR		Weight, BMI, WHR, FG score, TT, A4, DHEAS, SHBG, FAI, TG, chol, LDL, HDL, glucose, insulin, HOMA, OGTT
Meyer 2007 (36) Burchall 2017 (39) Hutchison 2008 (37)	Mod	HC) 35µg EE + 2mg CPA (high) LC) 20µg EE + 100µg LVG + 50mg SPL (low dose)*** M) 1g MET 2/d (2000mg/d)	Australia 6 months	HC: 31 LC: 33 M: 36	Average: 31 years	HC: 36.5 no SD LC: 35.5 no SD M: 36.3 no SD	NIH	NR	Excluded		BMI, OGTT, insulin, HOMA, testo, PAI-1, CRP, weight, Weight, BMI, glucose, insulin, HOMA, OGTT, chol, LDL, HDL, TG, CRP, TT, SHBG, FAI

Moran 2010 (38)											Moran no data used
Moretti 2018 (73)	Mod	1: OCP +BC 50 mg 2: OCP+ P.	Italy 12 months (6 month also available)	1:24 2:28	Median, IQR 1.28.1 (25.14-33.23) 2: 27.4 (25.39-30.69)	1: 26.4±6.2 2: 25.3±4.4	PCOS A phenotype	NR	NR	Different therapeutic 3rd generation OCPs were used,	mFG score, weight, BMI
Tartagni 2000 (74)	High	C) 2mg CPA + 35ug EE CA) [2mg CPA + 35ug EE] + FIN	Italy 6 months	C: 9 CA: 9	C: 22±5.1 CA: 24.1±6.1	C: 22±5.6 CA: 21.6±8.3	Author defined	NR	NR		fT, A4, DHEAS, SHBG, side effects
Vieira 2012 (75)	Mod	C) 2mg CMA + 30mcg EE CA) [2mg CMA + 30mcg EE] + 100 mg/day SPL	Brazil 12 months	C: 21 CA: 20	C: 25.0±3.8 CA: 24.4±4.3	C: 23.5 ± 4.3 CA: 26.2 ± 5.7	Rotterdam	NR	Excluded		Weight, BMI, glucose, insulin, OGTT, HOMA, chol, TG, LDL, HDL, TT, SHBG, FAI, CRP

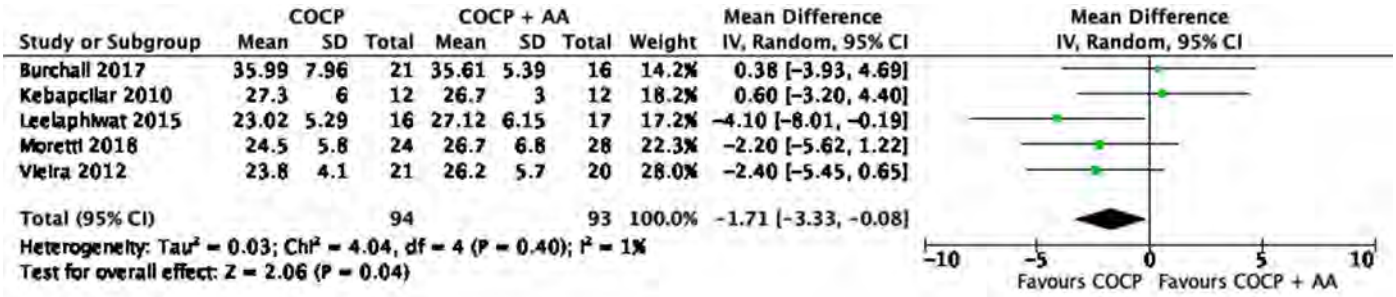
Results from the meta-analyses are shown below:

OUTCOME 23.1 BMI

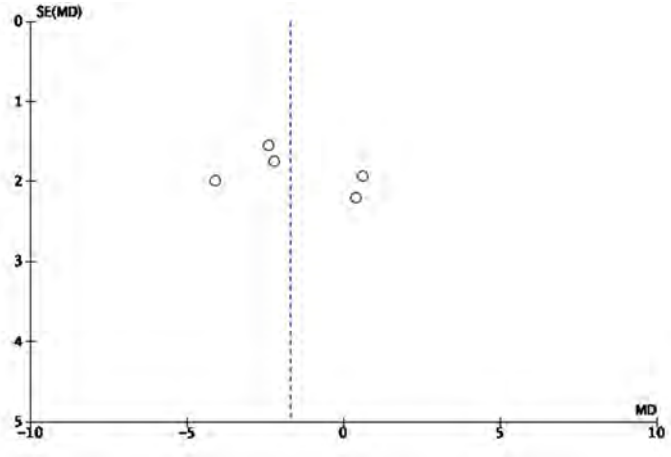
23.1.1 Individual Study Data Table

OUTCOME: BMI						OUTCOME TYPE: Continuous		
COMPARISON (if applicable): COCP vs. COCP+anti-androgen								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	COCP + AA Mean	COCP + AA SD	Comments
Burchall 2017	kg/m2	6 months	COCP=21 CA = 16	35.99	7.96	35.61	5.39	
Kebapcilar 2010		3 m	COCP 12 Met 12	27.3	6	26.7	3	
Leelaphiwat 2015	kg/m2	3 m	C:16 CA: 17	23.02	5.29	27.12	6.15	
Meyer 2007		6 m	C 31 CA 33	Mean change 0.3	1.6	Mean change -0.3	1.8	
Moretti 2018	kg/m2	12 m	C 24 CA 28	24.5	5.8	26.7	6.8	
Vieira 2012	kg/m2	12 m	C: 21 CA: 20	23.8	4.1	26.2	5.7	

23.1.2. Forest Plot COCP vs COCP + AA for BMI (kg/m2)



23.2.3. Funnel plot for assessment of publication bias

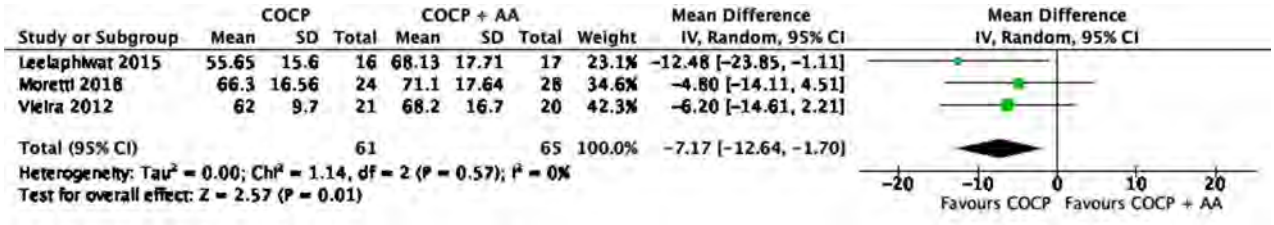


OUTCOME 23.2 WEIGHT

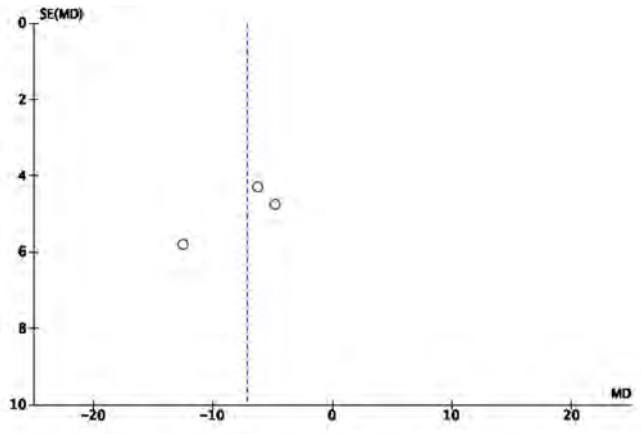
23.2.1 Individual Study Data Table

OUTCOME: weight					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. COCP + anti-androgen								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	COCP+AA Mean	COCP+AA SD	Comments
Hagag 2014	Kg, % change	12 months	1: COCP=25 2:COCP+spiro=72 3: COCP+extra CPA=70	C: +1.8±4.8		CA1: +1.3±5.6 CA2: +1.4±5.6		
Leelaphiwat 2015	kg	3 m	C:16 CA: 17	55.65	15.60	68.13	17.71	
Moretti 2018	kg	12 m	C 24 CA 28	66.3	16.56	71.1	17.64	
Vieira 2012	kg/m2	12 m	C: 21 CA: 20	62.0	9.7	68.2	16.7	

23.2.2. Forest Plot COCP vs COCP + AA for weight (kg)



23.2.3. Funnel plot for assessment of publication bias



OUTCOME 23.3 WHR
23.3.1 Individual Study Data Table

	OUTCOME: WHR				OUTCOME TYPE: Continuous			
	COMPARISON (if applicable): COCP vs. COCP + anti-androgen							
Author, year	Unit	Time point	N	COCP Mean	COCP SD	COCP+AA Mean	COCP+AA SD	Comments
Leelaphiwat 2015	-	3 m	C:16 CA: 17	0.85	0.051	0.86	0.05	

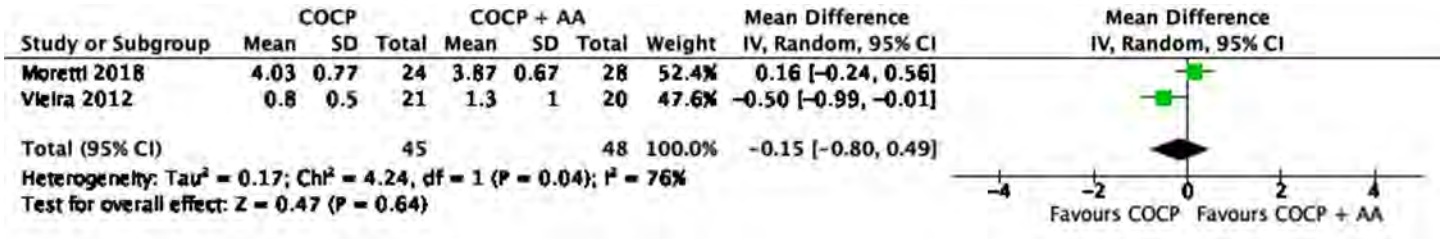
OUTCOME 23.4 HIRSUTISM
23.4.1 Individual Study Data Table

	OUTCOME: Hirsutism				OUTCOME TYPE: Continuous			
	COMPARISON (if applicable): COCP vs. COCP + anti-androgen							
Author, year	Unit	Time point	N	COCP Mean	COCP SD	COCP+AA Mean	COCP+AA SD	Comments
Hagag 2014	FG score	12 m	1: COCP=25 2:COCP+spiro=72 3: COCP+extra CPA=70	-38%±3.2 BL 14.1	0.8	2: -57%±2.4 3: -39%±2.4 BL 2: 13.8 BL3: 14.4	0.7 0.6	BL= baseline
Meyer 2007	FG score	6 m	C 31 CA 33	Mean change -2.0	3.1	Mean change -2.0	3.8	
Moretti 2018	mFG score	12 m	C 24 CA 28	12.8	5.16	15.4	5.2	
Tartagni 2000	mFG score	6 m						No data, only fgure woth bars. A significant difference between groups, favoured combo

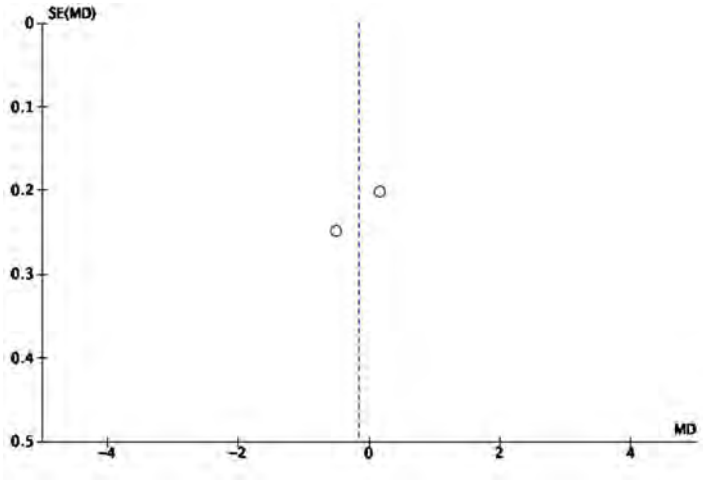
OUTCOME 23.5 FAI
23.5.1 Individual Study Data Table

	OUTCOME: FAI				OUTCOME TYPE: Continuous			
	COMPARISON (if applicable): COCP vs. COCP + anti-androgen							
Author, year	Unit	Time point	N	COCP Mean	COCP SD	COCP + AA Mean	COCP + AA SD	Comments
Meyer 2007		6 m	C 31 CA 33	Mean change -6.8	7.1	Mean change -6.3	5.2	
Moretti 2018		12 m	C24 CA 28	4.03	0.77	3.87	0.67	
Vieira 2012	-	12 m	C: 21 CA: 20	0.8	0.5	1.3	1.0	

23.5.2. Forest Plot COCP vs COCP + AA for FAI



23.5.3. Funnel plot for assessment of publication bias

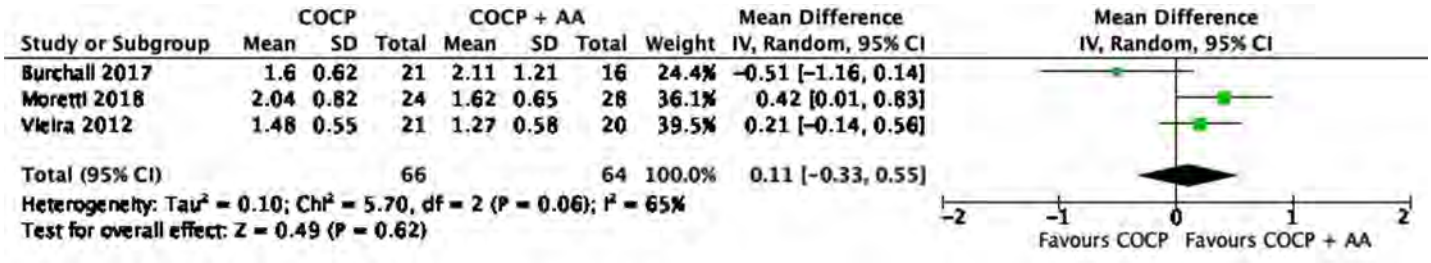


OUTCOME 23.6 TOTAL TESTOSTERONE

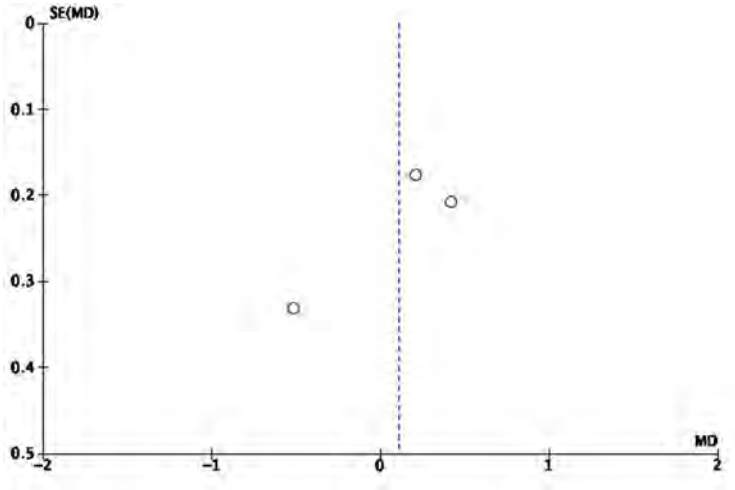
23.6.1 Individual Study Data Table

OUTCOME: Total testosterone					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. COCP + anti-androgen								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	COCP + AA Mean	COCP + AA SD	Comments
Burchall 2017	nM	6 months	COCP=21 COCP + spiro=16	1.60	0.62	2.11	1.21	crude
Hagag 2014	Nmol/L (mean change from baseline)	12 months	1: COCP=25 2:COCP+spiro=72 3: COCP+extra CPA=70	-30%±3.2		2:-31%±3.6 3:-29%±2.6		
Leelaphiwat 2015	Ng/dl	3 m	C:16 CA: 17	% change *2.86 ± 9.13*		*−0.16 ± 2.23*		
Vieira 2012	Nmol/L	12 m	C: 21 CA: 20	1.48	0.55	1.27	0.58	
Moretti 2018	Nmol/L	12 m	C24 CA 28	2.04	0.82	1.62	0.65	

23.6.2. Forest Plot COCP vs COCP + AA for total testosterone (nmol/L)



23.6.3. Funnel plot for assessment of publication bias

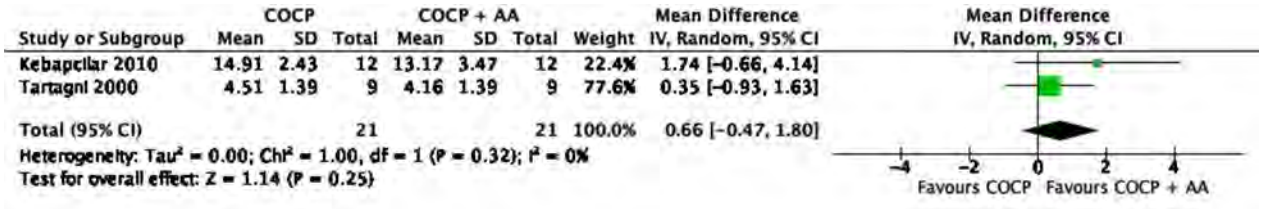


OUTCOME 23.7 FREE TESTOSTERONE

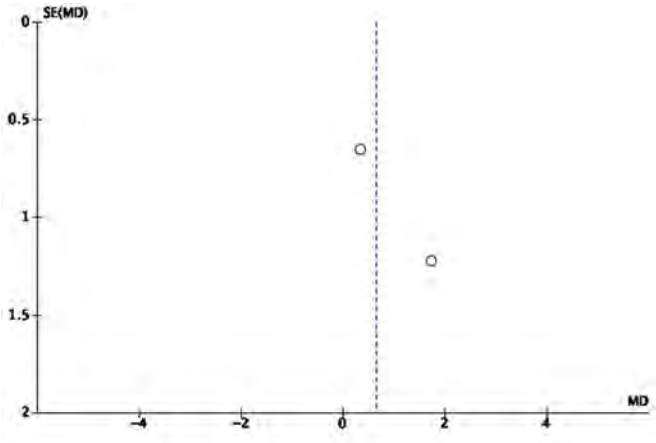
23.7.1 Individual Study Data Table

		OUTCOME: Free testosterone					OUTCOME TYPE: Continuous	
		COMPARISON (if applicable): COCP vs.COCP + AA						
Author, year	Unit	Time point	N	COCP Mean	COCP SD	COCP + AA Mean	COCP + AA SD	Comments
Kebapcilar 2010	Pmol/L	3 m	COCP 12 CA 12	14.91	2.43	13.17	3.47	
Tartagni 2000	Pmol/L	6 m	C:9 CA: 9	4.51	1.39	4.16	1.39	

23.9.2. Forest Plot COCP vs COCP + AA for free testosterone



23.9.3. Funnel plot for assessment of publication bias

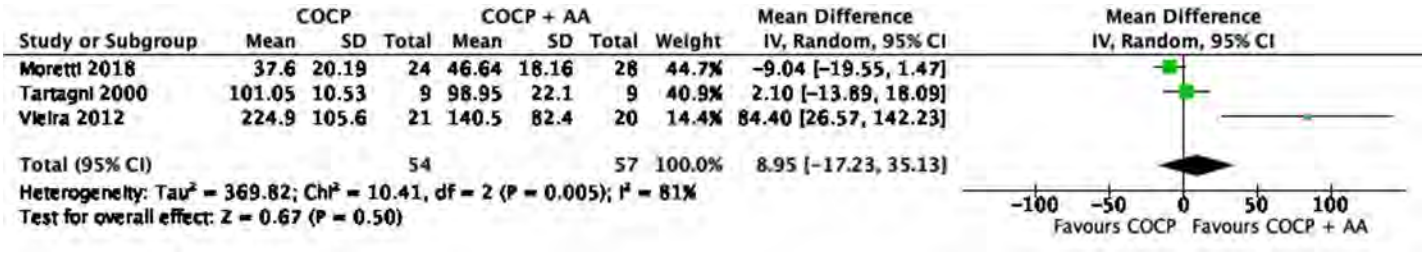


OUTCOME 23.8 SHBG

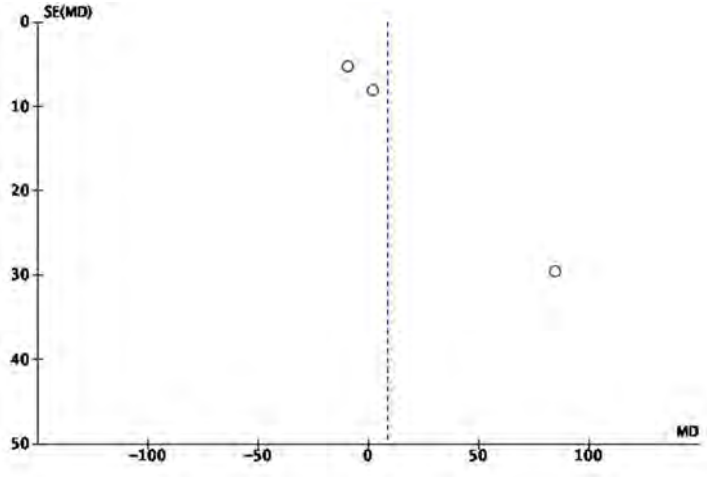
23.8.1 Individual Study Data Table

OUTCOME: SHBG					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. COCP + anti-androgen								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	COCP + AA Mean	COCP + AA SD	Comments
Leelaphiwat 2015	Mmol/L	3 m	C:16 CA: 17	% change *353.77 ± 397.10*		*168.89 ± 176.34*		
Meyer 2007	Nmol/l	6 m	C 31 CA 33	Mean change 115	76	Mean change *44.7*	43.7	
Tartagni 2000	Nmol/L	6 m	C: 9 CA: 9	101.05	10.53	98.95	22.10	
Vieira 2012	Nmol/L	12 m	C: 21 CA: 20	224.9	105.6	140.5	82.4	
Moretti 2018	Nmol/L	12 m	C24 CA 28	37.6	20.19	46.64	18.16	

23.8.2. Forest Plot COCP vs COCP + AA for SHBG (nmol/L)



23.8.3. Funnel plot for assessment of publication bias



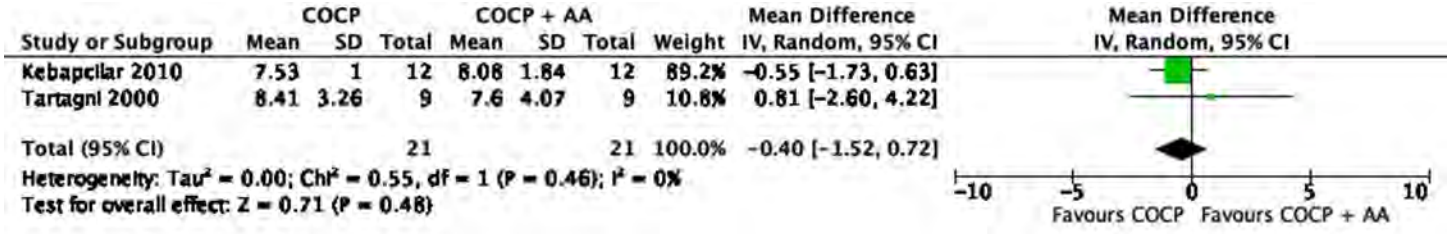
OUTCOME 23.9 ANDROSTENEDIONE
23.9.1 Individual Study Data Table

OUTCOME: androstendione				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): COCP vs. COCP+anti-androgen								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	COCP+AA Mean	COCP+AA SD	Comments
Hagag 2014	Nmol/L , % change	12 months	1: COCP=25 2:COCP+spiro=72 3: COCP+extra CPA=70	-17% ±12		2:-19% ±5 3:-21% ±6		
Leelaphiwat 2015	Ng/ml	3 m	C:16 CA: 17	% change *8.22± 37.18*		*−4.79 ± 77.56*		
Tartagni 2000	Ng/ml	6 m	C: 9 CA: 9	2.9	1.1	3.6	0.5	

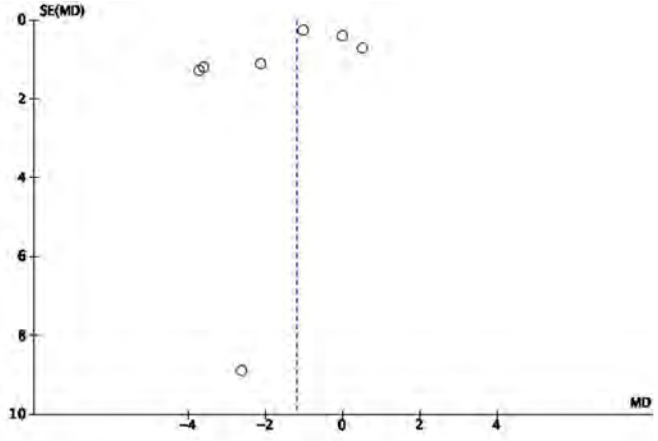
OUTCOME 23.9 DHEAS
23.9.1 Individual Study Data Table

OUTCOME: DHEAS				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): COCP vs. COCP + anti-androgen								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	COCP + AA Mean	COCP + AA SD	Comments
Hagag 2014	μmol/L, % change	12 months	1: COCP=25 2:COCP+spiro=72 3: COCP+extra CPA=70	-28% ±4.1		2: -29% ±4.6 3: -31% ±4.2		
Kebapcilar 2010	Nmol/L	3 m	C 12 CA12	7.53	1	8.08	12	
Leelaphiwat 2015	μg/dl	3 m	C:16 CA: 17	% change *−8.25 ± 37.13*		*30.30 ± 143*		
Meyer 2007	μmol/L	6 m	C 31 CA 33	Mean change -1.4	1.9	Mean change -0.7	1.1	
Tartagni 2000	Nmol/L	6 m	C: 9 CA: 9	8.41	3.26	7.6	4.07	

23.9.2. Forest Plot COCP vs COCP + AA for DHEAS (μmol/L)



23.9.3. Funnel plot for assessment of publication bias

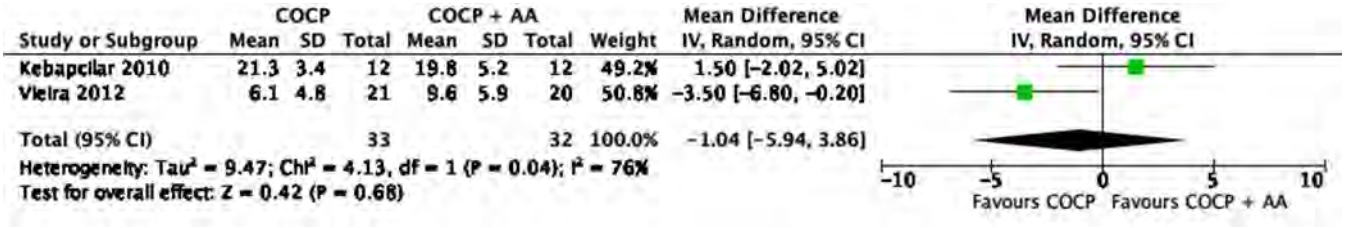


OUTCOME 23.10 INSULIN

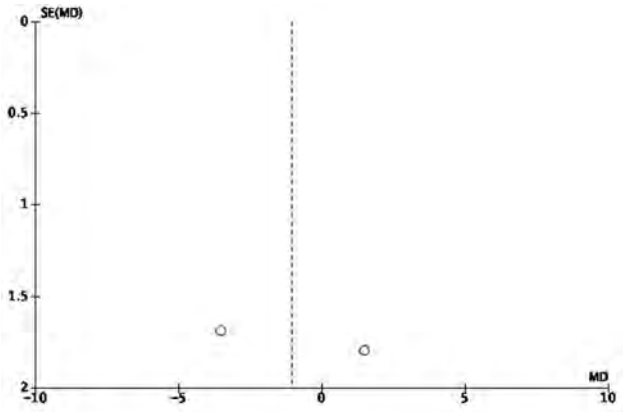
23.10.1 Individual Study Data Table

OUTCOME: fasting insulin					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. COCP + anti-androgen								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	COCP + AA Mean	COCP + AA, SD	Comments
Burchall 2017	mU/L (log transformed)	6 months	High dose COCP=21 low dose COCP + spiro = 16	Median 2.88	IQR 2.22-3.30	Median 2.88	IQR 2.36-3.14	Log transformed
Kebapcilar 2010	µIU/ml	3 m	COCP 12 CA 12	21.3	3.4	19.8	5.2	
Leelaphiwat 2015	µIU/ml	3 m	C:16 CA: 17	% change *75.12 ± 355.17*		*363.18 ±1200.77*		
Vieira 2012	µIU/ml	12 m	C: 21 CA: 20	6.1	4.8	9.6	5.9	

23.10.2. Forest Plot COCP vs COCP + AA for insulin (IU/ml)



23.9.3. Funnel plot for assessment of publication bias

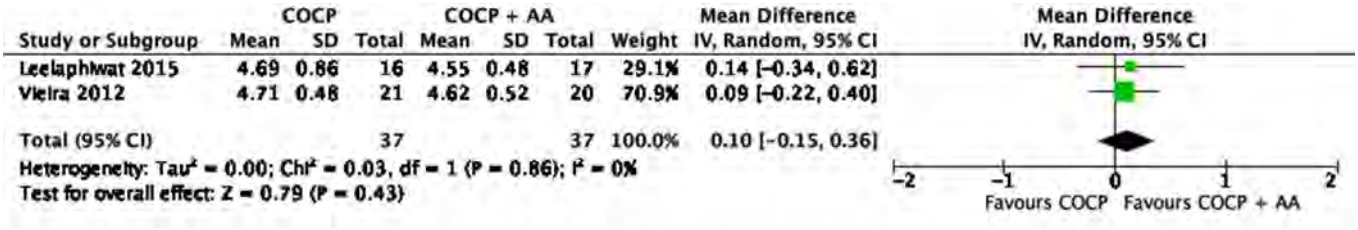


OUTCOME 23.11 GLUCOSE

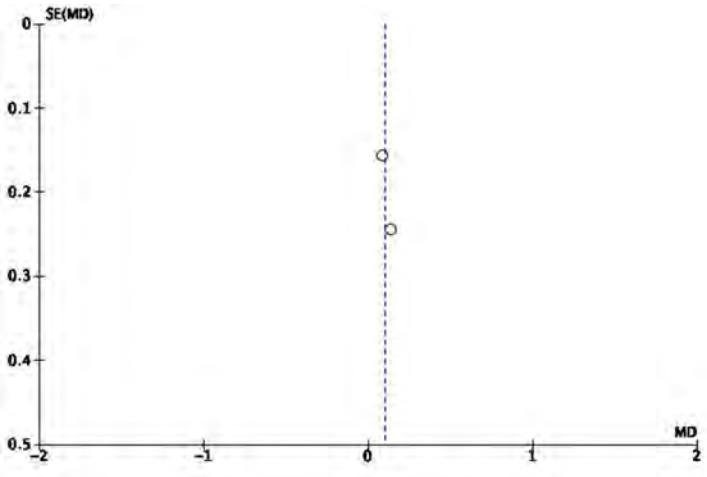
23.11.1 Individual Study Data Table

OUTCOME: fasting glucose					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs.COCP +anti-androgen								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	COCP+AA Mean	COCP+AA SD	Comments
Leelaphiwat 2015	Mmol/L	3 m	C:16 CA: 17	4.69	0.86	4.55	0.48	
Vieira 2012	Mmol/L	12 m	C: 21 CA: 20	4.71	0.48	4.62	0.52	

23.11.2. Forest Plot COCP vs COCP + AA for glucose



23.11.3. Funnel plot for assessment of publication bias

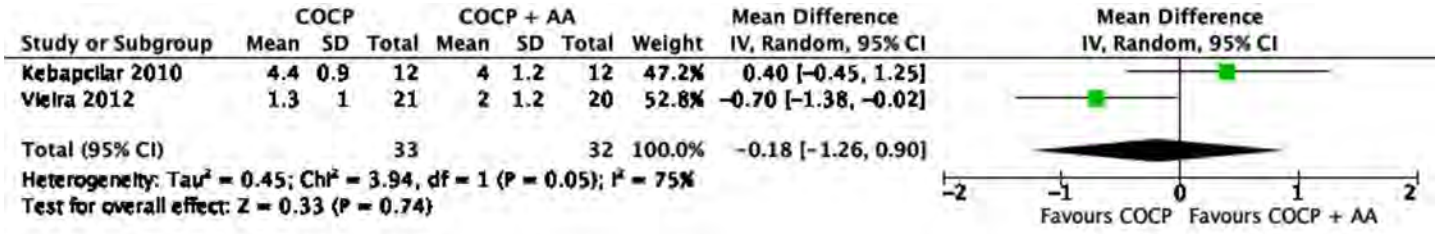


OUTCOME 23.12 HOMA-IR

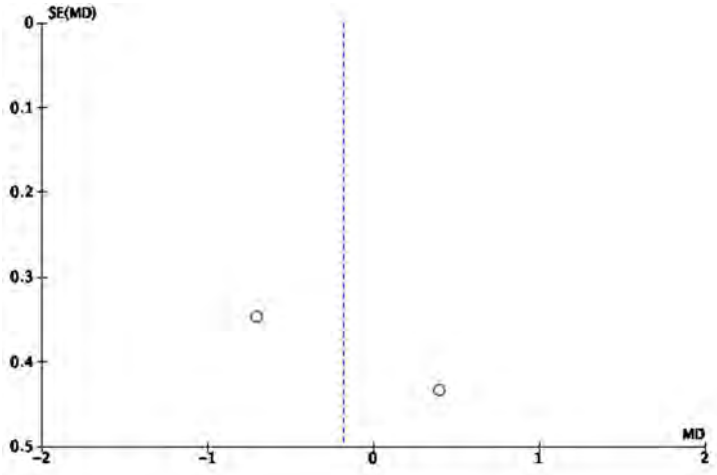
23.12.1 Individual Study Data Table

OUTCOME: HOMA-IR					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs.COCP and anti-androgen								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	COCP + AA Mean	COCP + AA SD	Comments
Burchall 2017	-	6 months	COCP + spiro=16 met=23	Median 1.17	IQR 0.54-1.63	Median 1.27	IQR 0.67-1.58	log transformed
Kebapcilar 2010		3 m	COCP 12 CA 12	4.4	0.9	4.0	1.2	
Leelaphiwat 2015		3 m	C:16 CA: 17	*76.04 ± 355.49*		*338.37 ±1138.26*		Mean % change
Vieira 2012		12 m	C: 21 CA: 20	1.3	1.0	*2.0*	1.2	

23.12.2. Forest Plot COCP vs COCP + AA for HOMA-IR



23.12.3. Funnel plot for assessment of publication bias



OUTCOME 23.13 OGTT

23.13.1 Individual Study Data Table

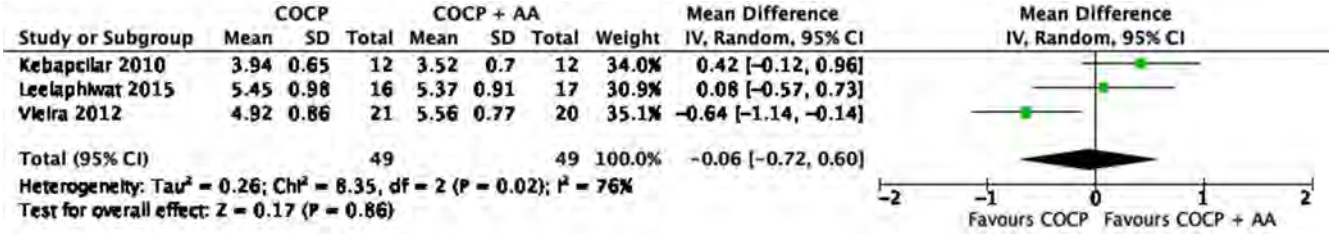
OUTCOME: OGTT					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. COCP + AA								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	COCP + AA Mean	COCP + AA SD	Comments
Burchall 2017	AUC	6 months	High dose COCP=21 low dose COCP + spiro = 16	850.88	149.21	1003.69	148.36	
Leelaphiwat 2015	2h glucose Mg/dl	3 m	C:16 CA: 17	% change *−9.51 ± 29.42*		*−12.44 ± 26.55*		

OUTCOME 23.14 CHOLESTEROL

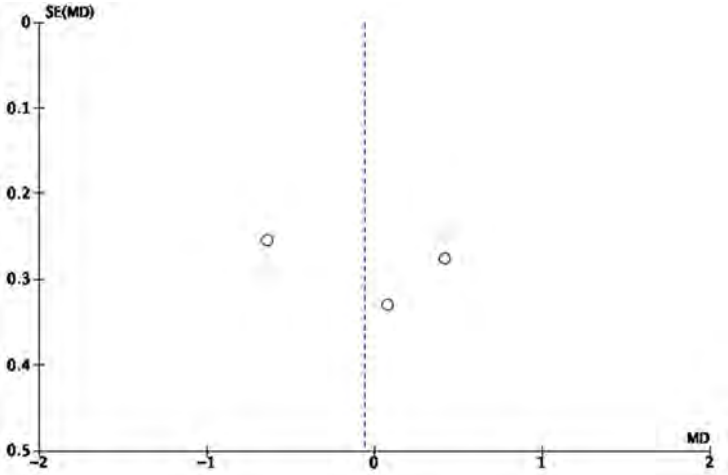
23.14.1 Individual Study Data Table

OUTCOME: cholesterol					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. COCP + anti-androgen								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	COCP + AA Mean	COCP + AA SD	Comments
Kebapcilar 2010	Mmol/L	3 m	COCP 12 CA 12	1.97	0.41	1.63	0.41	
Leelaphiwat 2015	Mmol/L	3 m	C:16 CA: 17	3.46	0.95	3.68	0.97	
Meyer 2007	Mmol/l	6m	OCP 31 OCP + AA 33	4.99		5.12		
Vieira 2012	Mmol/L	12 m	C: 21 CA: 20	2.7	0.71	3.12	0.7	

23.14.2. Forest Plot COCP vs COCP + AA for cholesterol (mmol/L)



23.14.3. Funnel plot for assessment of publication bias

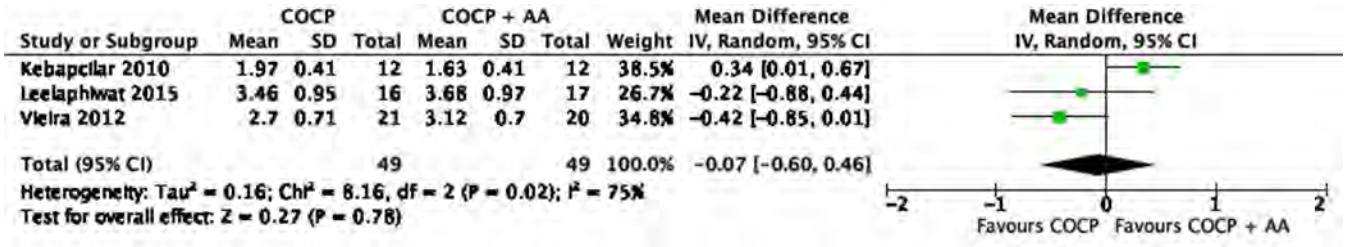


OUTCOME 23.15 LDL

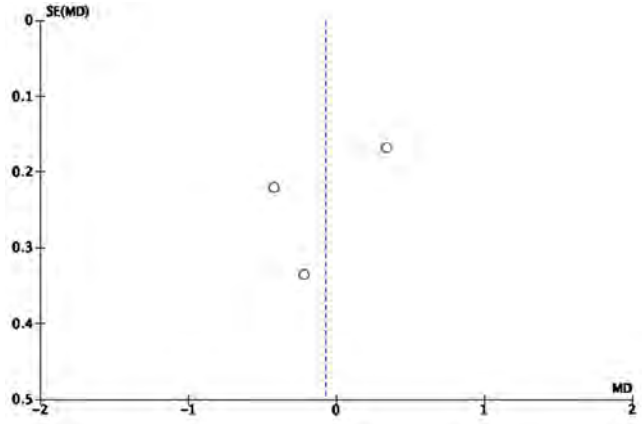
23.15.1 Individual Study Data Table

OUTCOME: LDL					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. COCP + anti-androgen								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	COCP + AA Mean	COCP + AA SD	Comments
Kebapcilar 2010	Mmol/L	3 m	C 12 CA 12	1.97	0.41	1.63	0.41	
Leelaphiwat 2015	Mmol/L	3 m	C:16 CA: 17	3.46	0.95	3.68	0.97	
Meyer 2007	Mmol/L	6 m	OCP 32 CA 33	2.78		3.28		
Vieira 2012	Mmol/L	12 m	C: 21 CA: 20	2.7	0.71	3.12	0.7	

23.15.2. Forest Plot COCP vs COCP + AA for LDL (mmol/L)



23.15.3. Funnel plot for assessment of publication bias

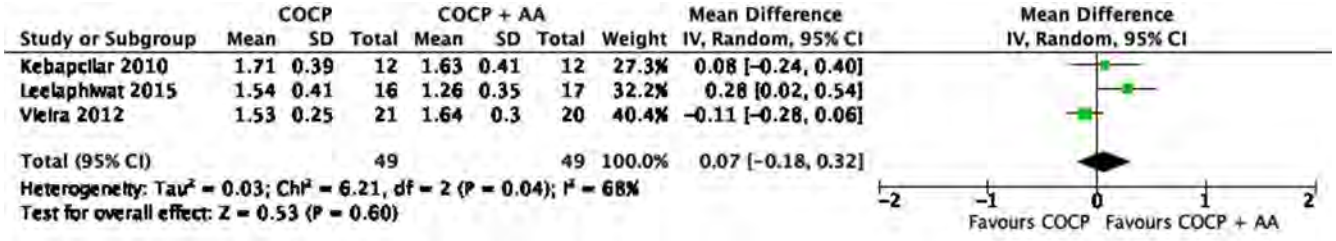


OUTCOME 23.16 HDL

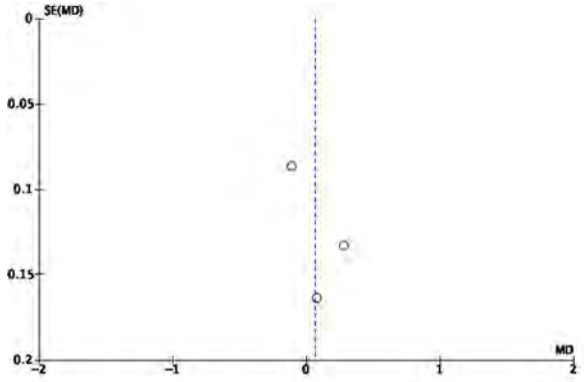
23.16.1 Individual Study Data Table

OUTCOME: HDL					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. COCP + anti-androgen								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	COCP + AA Mean	COCP + AA SD	Comments
Kebapcilar 2010	Mmol/L	3 m	C 12 CA 12	1.71	0.39	1.63	0.41	
Leelaphiwat 2015	Mmol/L	3 m	C:16 CA: 17	1.54	0.41	1.26	0.35	
Meyer 2007	Mmol/L	6 m	OCP 32 CA 33	1.46		1.22		
Vieira 2012	Mmol/L	12 m	C: 21 CA: 20	1.53	0.25	1.64	0.3	

23.16.2. Forest Plot COCP vs COCP + AA for HDL (mmol/L)



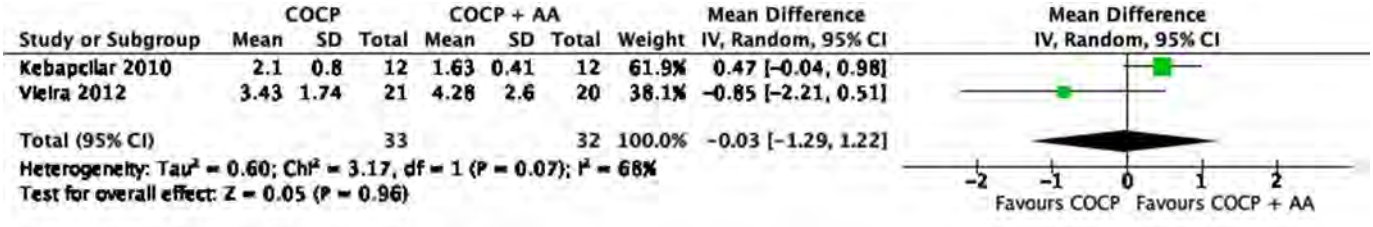
23.16.3. Funnel plot for assessment of publication bias



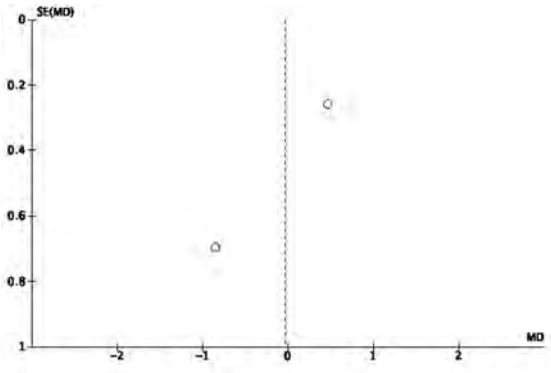
OUTCOME 23.17 TRIGLYCERIDES
23.17.1 Individual Study Data Table

OUTCOME: TG					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. COCP+anti-androgens								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	COCP+AA Mean	COCP+AA SD	Comments
Kebapcilar 2010	Mmol/L	3 m	C12 CA 12	2.1	0.8	1.63	0.41	
Vieira 2012	Mmol/L	12 m	C: 21 CA: 20	3.43	1.74	4.28	2.6	

23.17.2. Forest Plot COCP vs COCP + AA for triglycerides



23.17.3. Funnel plot for assessment of publication bias



OUTCOME 23.18 CRP
23.18.1 Individual Study Data Table

OUTCOME: CRP					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. COCP + anti-androgen								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	COCP + AA Mean	COCP + AA SD	Comments
Vieira 2012	Mg/L	12 m	C: 21 CA: 20	5.0	3.8	7.4	8.8	

OUTCOME 23.19 PAI-1
23.19.1 Individual Study Data Table

OUTCOME: PAI-1					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. COCP + AA								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	COCP + spiro Mean	COCP + spiro SD	Comments
Burchall 2017	U/ml	6 months	COCP=21 COCP + spiro=16	3.61		4.13		

OUTCOME 23.20 MENSTRUAL CYCLES
23.20.1 Individual Study Data Table

OUTCOME: Menstrual cycles					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP vs. COCP + anti-androgen								
Author, year	Unit	Time point	N	COCP Mean	COCP SD	COCP + AA Mean	COCP + AA SD	Comments
Meyer 2007	days	6 m	C 31 CA 33	Mean change -44	69.5	Mean change -61.8	96.8	
Mhao 2016			Menstrual irregularity also improved in both groups, from 14 patients, 9 of them got regular menses during metformin treatment, while 6 from 8 patients with menstrual irregularities got regular menses on EE-CA					
Sahu 2019	Cycle duration	6 m	C 44 M 42	33.8	6.9	39.9	10.2	

Adverse effects

	Study	COCP	COCP + AA
Headache	Hagag 2014	0/25	0/72
Breast tenderness	Hagag 2014	0/25	2/72
	Moretti	2/24	1/28
Nipple discharge	Hagag 2014	0/25	0/72
Vomit/nausea	Hagag 2014	1/25	0/72
	Moretti	2/24	1/28
Premenstrual pelvic pain	Hagag 2014	0/25	0/72
Menorrhagia	Hagag 2014	0/25	0/72
Menstrual spotting	Moretti	4/24	7/28
Fatigue	Hagag 2014	0/25	1/72
Decreased libido	Hagag 2014	0/25	0/72
	Moretti	0/24	1/28
Mood swings	Meyer 2007	1/35	1/38
Mood reduction	Moretti	0/24	1/28
Anemia	Moretti	2/24	1/28

Comparison 24: COCP vs. metformin + antiandrogen

▪ EVIDENCE SUMMARY:

One study was identified, Ibanez 2004 (76), including adolescents. No additional studies could be included since the last guideline.

▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

After COCP treatment, SHBG levels are higher compared with the combination of metformin + anti-androgen, with very low certainty of evidence. The combination of metformin and anti-androgen results in lower triglycerides and LDL levels, compared with COCP, with very low certainty of evidence.

Included study:

Study ID	ROB	Interventions	Setting Duration	N	Mean age	Mean BMI	PCOS	Age at menarche	Smokers	Comments	Outcomes
Ibanez 2004 (76)	Mod	1: EE 30 μg + 0.3 mg DRSP 2: Met 850 mg + flutamide 62.5 mg	Spain 9 moths	1: 16 2: 16	Mean age for all 14.6±0.3	1: *22.0 ±0.6* *2: 21.8 ±0.5*	Author defined	NR	NR	Adolescents, 2-4 yrs post menarche	BMI, FG score, Fasting glucose/insulin ratio, SHBG, Testosterone, TG, HDL, LDL,

Results are shown in the table:

Ibanez 2004	Certainty ⊕◯◯◯ VERY LOW (risk of bias, imprecision, indirectness)					
Outcome	COCP		Met + AA		P value	Favours
	Mean	SD	Mean	SD		
BMI (kg/m²)	22.5	2.0	22.0	2.4	0.53	No difference
FG score	10.9	2.8	10.4	3.6	0.66	No difference
SHBG (μg/dl)	4.5	1.6	1.1	0.4	<0.001	COCP higher
Testosterone (ng/dl)	66	40	61	20	0.66	No difference
Triglycerids (mg/dl)	97	32	53	16	<0.001	Met + AA
LDL (mg/dl)	101	28	75	20	<0.01	Met + AA
HDL (mg/dl)	75	16	66	8	0.05	No difference

Comparison 25: COCP + anti-androgen vs. metformin

- **EVIDENCE SUMMARY:**

Four different RCTs were included with five publications (36, 39, 48, 77, 78) were included. None involved adolescents. Two RCTs had a high risk of bias, one moderate and one low risk of bias. Meyer 2007 compared 20µg EE + 100µg LVG + 50mg spironolactone (n=33) with metformin 2000 mg/day (n=36) during a 6 month period (36), this study had a moderate risk of bias. A secondary publication from this RCT is Burchall 2017 (39), where hemostatic markers were examined (n= 16 vs. 23), additional outcomes could be extracted from this publication. Kebapciliar 2010 compared 35 µg EE/2mg CPA + 100mg spironolactone (n=12) with metformin 1700 mg/day (n=12) for 3 months (48). Mehrabian 2016 compared EE 30 µg + 0.15 mg LGS + 62.5 mg flutamide (n=34) with metformin 1000 mg/day (n=34) during 6 months (78). Alpanes 2017 compared 30 ug EE+ 150 ug DG + 100 mg spironolactone (n= 18) with metformin 1700 mg/day (n=13) for 12 months (77). The studies are shown below.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

Only two outcomes could be included in the meta-analysis. No differences were seen in BMI or HDL, with very low certainty of evidence. Other outcomes are reported narratively. FAI and androstenedione levels were lower after COCP + AA treatment compared with metformin, with very low certainty. Fasting glucose levels were lower after metformin, with very low certainty. In all other outcomes, there were no differences, with very low certainty.

Included studies, COCP + anti-androgen vs. metformin:

Study ID	ROB	Interventions	Setting Duration	N	Mean age	Mean BMI	PCOS	Age at menarche	Smokers	Comments	Outcomes
Alpanes 2017 (77)	High	1. 30 ug EE+ 150 ug DG + 100 mg spironolakton 2. Metformin 850 mg b.i.d.	Spain 12 months	1 = 18 2= 13	1. 25±5 2. 23±6	1. 30.6±7.9 2. 31.2±9.0	Rott AES NIH	1. 12±2 2. 12±2	NS		Frequency of menstrual dysfunction hirsutism score, serum total and free testosterone, androstenedione and DHEAS oGTT, Adverse effects
Kebapcilar 2010 (48)	High	1: 35 µg EE/2mg CPA 2: 35 µg EE/2mg CPA + met 1700 mg/day 3: metformin 1700 mg/day 4: met 1700 mg/day + spiro 100 mg/day	Turkey 3 months	12/group	24.0±5.4 years; for all	1: 28.7 ±6 2: 27.6 ± 3 3: 27.8 ± 4 4: 27.6 ± 4	Rott	NR	excluded		BMI, fT, DHEAS, insulin, HOMA, TG, LDL, HDL,
Mehrabian 2016 (78)	Low	1: EE 30 µg + 0.15 mg LGS + 62.5 mg flutaminde 2: met 1000mg/day	Iran 6 months	1:34 2:34	1: 29.0±7.7 2: 29.2±8.3	1:29.8±4.2 2:29.8±4.1	*NIH*	NR	excluded	One group with simvastain, not incl in this review	TG, glucose,CRP, HDL, insulin intolerance

Meyer 2007 (36) Burchall 2017 (39)	Mod	HC) 35µg EE + 2mg CPA (high) LC) 20µg EE + 100µg LVG + 50mg SPL (low dose)*** M) 1g MET 2/d (2000mg/d)	Australia 6 months	HC: 31 LC: 33 M: 36	Average: 31 years	HC: 36.5 no SD LC: 35.5 no SD M: 36.3 no SD	NIH	NR	Excluded		WHR, hirsutism, FAI, SHBG, DHEAS, BMI, OGTT, insulin, HOMA, testo, PAI-1, menstrual cycles, cholesterol, LDL, TG,

Results from the meta-analysis are shown below:

For other outcomes, it was not possible to perform a meta-analysis, results and GRADE are reported below.

Outcome	Author, year	Unit	Time point	N	COCP + AA	Met	COCP + AA vs. met	P value	Favours	Certainty	Importance
WHR	Meyer 2007	-	6 m	CA 33 M 36	Mean change ± SD 0.02±0.07	Mean change ± SD 0.18±0.06		NR	No difference	⊕◯◯◯ VERY LOW (1,2,3)	IMPORTANT
Hirsutism	Alpanes 2017	FG score	12 m	CA 18 M 13			Mean difference (95%CI) 4.6 (2.6-6.7)	<0.0001	No difference	⊕◯◯◯ VERY LOW (2,3,4)	CRITICAL
	Meyer 2007	FG score	6 m	CA 33 M 36	Mean change ± SD -2.0±3.8	Mean change ± SD -2.7±3.5		NR			
FAI	Meyer 2007	-	6 m	CA 33 M 36	Mean change ± SD 6.3±5.2	Mean change ± SD -2.1±9.3		NR	COCP + AA	⊕◯◯◯ VERY LOW (1,2,3)	IMPORTANT
Total testosterone	Burchall 2017	nmol/L	6 m	CA=16 M=23	Mean (SD) 2.11 (1.21)	Mean (SD) 2.10 (1.06)		NR	No difference	⊕◯◯◯ VERY LOW (2,3,4)	IMPORTANT
	Alpanes 2017	nmol/L	12 m	CA 18 M 13			Mean difference (95%CI) 1.1 (0.4-1.7)	<0.0001			
Free testosterone	Kebapcilar 2010	Pg/ml	3 m	CA 12 M 12	Mean (SD) 3.8 (1.0)	Mean (SD) 3.8 (0.7)		NR	No difference	⊕◯◯◯ VERY LOW (2,3,4)	IMPORTANT
	Alpanes 2017	pmol/L	12 m	CA 18 M 13			Mean difference (95%CI) 25 (12-39)	0.0002			

SHBG	Meyer 2007	Nmol/L	6 m	CA 33 M 36	Mean change ± SD 44.7±43.7	Mean change ± SD 7.4±35.4		NR	No difference	⊕◯◯◯ VERY LOW (1,2,3)	IMPORTANT
DHEAS	Kebapcilar 2010	μg/ml	3 m	CA 12 met 12	Mean (SD) 298 (68)	Mean (SD) 258 (57)		NR	No difference	⊕◯◯◯ VERY LOW (2,3,4)	IMPORTANT
	Alpanes 2017	μmol/L	12 m	CA 18 M 13			Mean difference (95%CI) 2.7 (1.4-4.0)	<0.0001			
	Meyer 2007	μmol/L	6 m	CA 33 M 36	Mean change ± SD -0.7±1.3	Mean change ± SD -0.37±0.4		NR			
Androstenedione	Alpanes 2017	μmol/L	12 m	CA 18 M 13			Mean difference (95%CI) 5.5 (1.8-9.2)	0.0002	COCP + AA	⊕◯◯◯ VERY LOW (2,3,4)	IMPORTANT
Insulin	Kebapcilar 2010	μIU/ml	3 m	CA 12 Met 12	Mean (SD) 19.8 (5.2)	Mean (SD) 19.0 (3.4)		NR	No difference	⊕◯◯◯ VERY LOW (2,3,4)	IMPORTANT
	Meyer 2007	U/L	6 m	CA 33 M 36	Mean change ± SD -1.67±11.1	Mean change ± SD -6.0±19.2		NR			
Fasting glucose	Mehrabian 2016	Mg/dl	6 m	CA 34 CM 34	Mean (SD) 91.0 (13.3)	Mean (SD) 78.3 (15.5)		<0.001	Met	⊕◯◯◯ VERY LOW (2,3)	IMPORTANT
HOMA-IR	Meyer 2007	-	6 m	CA 33 M 36	Mean change ± (95%CI) - 0.22 (-1.14;-0.7)	Mean change (95%CI) -1.13 (-0.6;-2.8)		NR	No difference	⊕◯◯◯ VERY LOW (2,3,4)	IMPORTANT
	Kebapcilar 2010	-	3 m	CA 12 met 12	Mean (SD) 4.0 (1.2)	Mean (SD) 3.5 (0.7)		NR			
OGTT	Meyer 2007	AUC insulin	6 m	CA 33 M 36	Mean change ± (95%CI) -34 (-1942 to 2011)	Mean change ± (95%CI) -4030 (-1489 to -6571)		NR	No difference	⊕◯◯◯ VERY LOW (2,3,4)	IMPORTANT
Abnormal glucose tolerance	Alpanes 2017	n	12 m	CA 18 M 13			OR (95%CI) 1.7 (0.7-4.4)	0.26	No difference	⊕◯◯◯ VERY LOW (1,2,3)	IMPORTANT
Menstrual cycles	Meyer 2007	days	6 m	CA 33 M 36	Mean change ± SD -61.8 ± 96.8	Mean change ± SD -47.1 ±135.2		NR	No difference	⊕◯◯◯ VERY LOW (2,3,4)	CRITICAL
Cholesterol	Kebapcilar 2010	Mg/dl	3 m	CM 12 CA 12	136 (27)	138 (28)		NR	No difference	⊕◯◯◯ VERY LOW (2,3,4)	IMPORTANT
	Meyer 2007	Mmol/L	6 m	CA 33 M 36	Mean change ± SD	Mean change ± SD		NR			

					0.19±0.85	-0.17±0.7					
LDL	Kebapcilar 2010	Mg/dl	3 m	CM 12 CA 12	63 (16)	78 (19)		NR	No difference	⊕◯◯◯ VERY LOW (2,3,4)	IMPORTANT
	Meyer 2007	Mmol/L	6 m	CA 33 M 36	Mean change ± SD 0.06±0.7	Mean change ± SD -0.04±0.7		NR			
Triglycerids	Kebapcilar 2010	Mg/dl	3 m	CM 12 CA 12	74 (39)	94 (31)		NR	No difference	⊕◯◯◯ VERY LOW (2,3,4)	IMPORTANT
	Meyer 2007	Mmol/L	6 m	CA 33 M 36	Mean change ± SD 0.13±0.6	Mean change ± SD 0.06±0.9		NR			
Dyslipidemia	Alpanes 2017	n	12 m	CA 18 M 13			OR (95%CI) 0.6 (0.2-1.8)	0.39	No difference	⊕◯◯◯ VERY LOW (2,3)	IMPORTANT
CRP	Mehrabian 2016	Mg/L	6 m	CA 34 CM 34	Mean (SD) 1.22 (0.289)	Mean (SD) 1.45 (0.479)			No difference	⊕◯◯◯ VERY LOW (2,3)	IMPORTANT
PAI-1	Burchall 2017	U/ml	6 months	COCP + spiro=16 Met=23	Mean 4.13	Mean 5.37			No difference	⊕◯◯◯ VERY LOW	IMPORTANT

1. Serious risk of bias
2. Serious risk of indirectness
3. Serious risk of imprecision
4. Very serious risk of bias

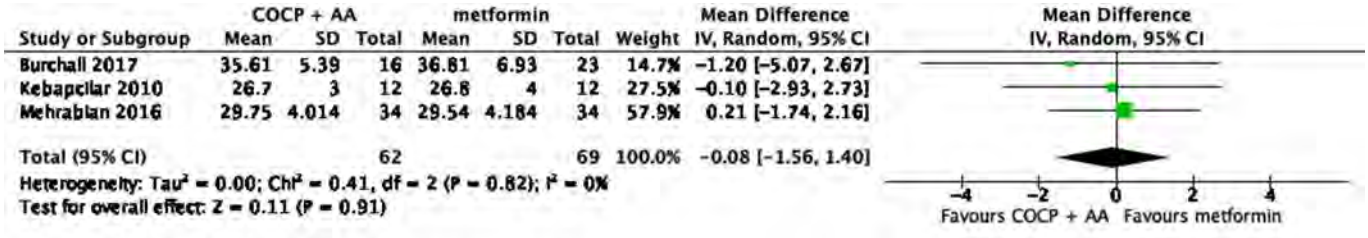
Adverse effects:

Alpanes 2017: No major adverse effects. In the metformin group, two patients dropped out because of mild but persistent gastrointestinal disturbances. One patient on COCP plus spironolactone dropped out due to a mild urticarial skin rash that resolved after stopping the medication.
Meyer 2007: One patient in the COCP plus spironolactone group withdrew due to mood swings. No adverse effects reported for metformin.
Mehrabian 2016: Reports no adverse effects. Prevalence of hypertension (BP>130/85) did not increase from baseline in any of the groups.
Kebapciliar 2010: 8/24 patients treated with metformin or metformin + COCP reported mild nausea and vomiting but this did not make patients stop the treatment. 0 side effects reported for COCP + AA.

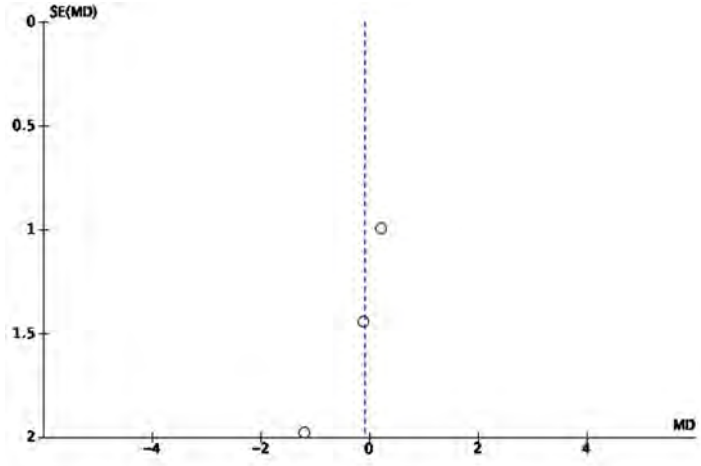
OUTCOME 25.1 BMI
25.1.1 Individual Study Data Table

OUTCOME: BMI					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP + AA vs. met - adults								
Author, year	Unit	Time point	N	COCP + AA Mean	COCP + AA SD	met Mean	met SD	Comments
Burchall 2017	kg/m2	6 months	CA = 16 met = 23	35.61	5.39	36.81	6.93	
Kebapcilar 2010	kg/m2	3 m	CA 12 Met 12	26.7	3	26.8	4	
Mehrabian 2016	kg/m2	6 m	CA 34 CM 34	29.75	4.014	29.54	4.184	

25.1.2. Forest Plot COCP + AA vs metformin for BMI (kg/m2)



25.1.3. Funnel plot for assessment of publication bias



OUTCOME 25.2 WHR

25.2.1 Individual Study Data Table

OUTCOME: WHR					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP + AA vs. met								
Author, year	Unit	Time point	N	COCP + spiro Mean	COCP + spiro SD	met Mean	met SD	Comments
Meyer2017		6 months	CA 33 M 36	Mean change ± SD 0.02±0.07		Mean change ± SD 0.18±0.06		

OUTCOME 25.3 HIRSUTISM

25.3.1 Individual Study Data Table

OUTCOME: Hirsutism					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP + AA vs. met								
Author, year	Unit	Time point	N	COCP + spiro Mean	COCP + spiro SD	met Mean	met SD	Comments
Alpanes 2017	FG score	12 m	CA 18 M 13					Mean difference (95%CI) 4.6 (2.6-6.7)
Meyer2017	FG score	6 months	CA 33 M 36	Mean change ± SD -2.0±3.8		Mean change ± SD -2.7±3.5		

OUTCOME 25.4 FAI
25.4.1 Individual Study Data Table

OUTCOME: FAI					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP + AA vs. met								
Author, year	Unit	Time point	N	COCP + spiro Mean	COCP + spiro SD	met Mean	met SD	Comments
Meyer2017	-	6 months	CA 33 M 36	Mean change ± SD 6.3±5.2		Mean change ± SD -2.1±9.3		

OUTCOME 25.5 TOTAL TESTOSTERONE
25.5.1 Individual Study Data Table

OUTCOME: Total testosterone					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP + AA vs. met								
Author, year	Unit	Time point	N	COCP + spiro Mean	COCP + spiro SD	met Mean	met SD	Comments
Burchall 2017	nM	6 months	COCP + spiro=16 met=23	2.11	1.21	2.10	1.06	
Alpanes 2017	nM	12 m	CA 18 M 13	Mean difference (95% CI) 1.1 (0.4-1.7)				

OUTCOME 25.6 FREE TESTOSTERONE
25.6.1 Individual Study Data Table

OUTCOME: Free testosterone					**OUTCOME TYPE: Continuous**			
COMPARISON (if applicable): COCP + AA vs. metformin								
Author, year	Unit	Time point	N	COCP + AA Mean	COCP + AA SD	Met Mean	Met SD	Comments
Kebapcilar 2010	Pg/ml	3 m	CA 12 met 12	3.8	1.0	3.8	0.7	
Alpanes 2017	nM	12 m	CA 18 M 13	Mean difference (95% CI) 25 (12-39)				

OUTCOME 25.7 DHEAS
25.7.1 Individual Study Data Table

OUTCOME: DHEAS					**OUTCOME TYPE: Continuous**			
COMPARISON (if applicable): COCP + anti-androgen vs metformin								
Author, year	Unit	Time point	N	COCP + AA Mean	COCP + AA SD	Met Mean	Met SD	Comments
Kebapcilar 2010	μg/ml	3 m	CA 12 met 12	298	68	258	57	
Alpanes 2017	μmol/L	12 m	CA 18 M 13	Mean difference (95% CI) 2.7 (1.4-4.0)				
Meyer 2007	μmol/L	6 m	CA 33 M 35	Mean change +/- SD -0.7 +/- 1.3 vs. -0.37 +/- 0.4				

OUTCOME 25.8 INSULIN
25.8.1 Individual Study Data Table

OUTCOME: fasting insulin	**OUTCOME TYPE: Continuous**
COMPARISON (if applicable): COCP + AA vs. met	

Author, year	Unit	Time point	N	COCP + AA Mean	COCP + AA SD	met Mean	met SD	Comments
Burchall 2017	mU/L (log transformed)	6 months	CA=21 met=23	Median 2.88	IQR 2.36-3.14	Median 2.37	IQR 2.10-3.23	Log transformed
Kebapcilar 2010	μIU/ml	3 m	CA 12 Met 12	19.8	5.2	19.0	3.4	

OUTCOME 25.9 GLUCOSE
25.9.1 Individual Study Data Table

OUTCOME: fasting glucose					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP + AA vs. met								
Author, year	Unit	Time point	N	COCP + AA Mean	COCP + AA SD	met Mean	met SD	Comments
Mehrabian 2016	Mg/dl	6 m	CA 34 CM 34	91.00	13.334	78.32	15.526	

OUTCOME 25.10 HOMA-IR
25.10.1 Individual Study Data Table

OUTCOME: HOMA-IR					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP + anti-androgen vs.met								
Author, year	Unit	Time point	N	COCP + AA Mean	COCP + AA SD	Met Mean	Met SD	Comments
Burchall 2017	- (log transformed)	6 months	CA=16 met=23	Median 1.27	IQR 0.67-1.58	Median 0. 77	IQR 0.40-1.53	Log transformed
Kebapcilar 2010		3 m	CA 12 met 12	4.0	1.2	3.5	0.7	

OUTCOME 25.11 OGTT
25.11.1 Individual Study Data Table

OUTCOME: OGTT					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP + AA vs. met								
Author, year	Unit	Time point	N	COCP + spiro Mean	COCP + spiro SD	met Mean	met SD	Comments
Burchall 2017	AUC	6 months	COCP + spiro=16 met = 23	1003.69	148.36	805.84	165.24	

OUTCOME 25.12 CHOLESTEROL
25.12.1 Individual Study Data Table

OUTCOME: cholesterol					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP + anti-androgen vs. metformin								
Author, year	Unit	Time point	N	COCP + AA Mean	COCP + AA SD	Met Mean	Met SD	Comments
Kebapcilar 2010	Mg/dl	3 m	CM 12 CA 12	136	27	138	28	
Meyer 2007	Mmol/L	6 m	CA 33 M 36	Mean change ± SD 0.19±0.85	Mean change ± SD -0.17±0.7			

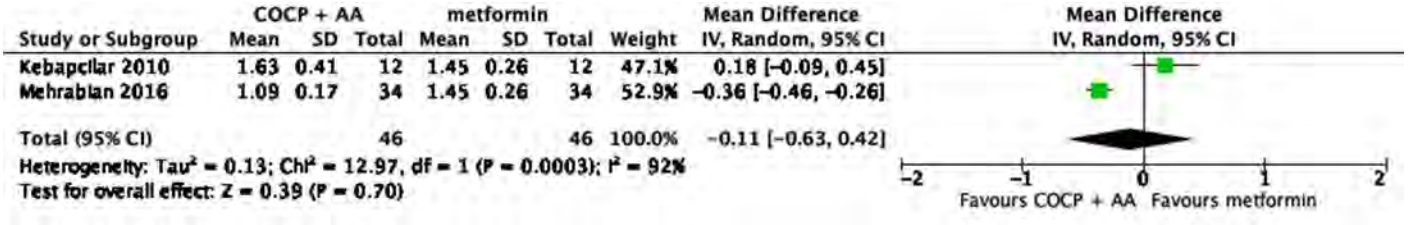
OUTCOME 25.13 LDL
25.13.1 Individual Study Data Table

OUTCOME: LDL					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP + AA vs. metformin								
Author, year	Unit	Time point	N	COCP + AA Mean	COCP + AA SD	Met Mean	Met SD	Comments
Kebapcilar 2010	Mg/dl	3 m	CA 12 Met 12	63	16	78	19	
Meyer 2007	Mmol/L	6 m	CA 33 M 36	Mean change ± SD 0.06±0.7	Mean change ± SD -0.04±0.7			

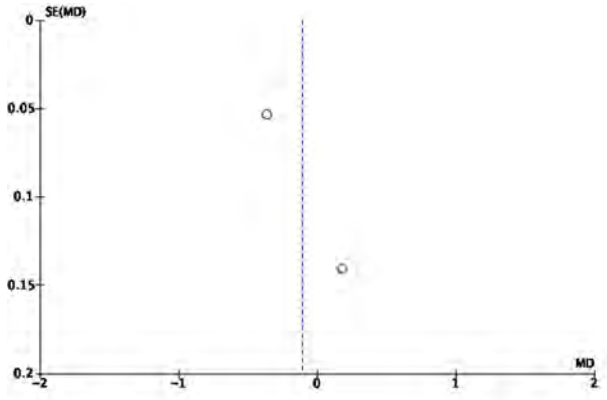
OUTCOME 25.14 HDL
25.14.1 Individual Study Data Table

OUTCOME: HDL					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP + anti-androgen vs. metformin								
Author, year	Unit	Time point	N	COCP + AA Mean	COCP + AA SD	Met Mean	Met SD	Comments
Mehrabian 2016	Mmol/L	6 m	CA 34 CM 34	1.09	0.17	1.45	0.26	
Kebapcilar 2010	Mmol/L	3 m	CA 12 Met 12	1.63	0.17	1.45	0.26	

25.14.2. Forest Plot COCP + AA vs metformin for HDL (mmol/L)



25.14.3. Funnel plot for assessment of publication bias



OUTCOME 25.15 TRIGLYCERIDES
25.15.1 Individual Study Data Table

OUTCOME: TG	OUTCOME TYPE: Continuous

COMPARISON (if applicable): COCP+anti-androgens vs. metformin								
Author, year	Unit	Time point	N	COCP+AA Mean	COCP+AA SD	Met Mean	Met SD	Comments
Kebapcilar 2010	Mg/dl	3 m	CA12 Met 12	63	16	94	31	

OUTCOME 25.16 CRP
25.16.1 Individual Study Data Table

OUTCOME: CRP				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): COCP + anti-androgen vs. metformin								
Author, year	Unit	Time point	N	COCP + AA Mean	COCP + AA SD	Met Mean	Met SD	Comments
Mehrabian 2016	Mg/L	6 m	CA 34 CM 34	1.22	0.289	1.45	0.470	

OUTCOME 25.17 PAI-1
25.17.1 Individual Study Data Table

OUTCOME: PAI-1				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): COCP + AA vs. met								
Author, year	Unit	Time point	N	COCP + spiro Mean	COCP + spiro SD	met Mean	met SD	Comments
Burchall 2017	U/ml	6 months	COCP + spiro=16 Met=23	4.13		5.37		

Comparison 26: COCP + anti androgen vs. COCP + anti androgen + met

- **EVIDENCE SUMMARY:**

One RCT, Ibanez 2005, with a moderate risk of bias, was included. This study compared COCPs containting EE/DRSP + antiandrogen (flutamide) treatment with and without metformin 850 mg/day, for 3 months. The study had two subgroups, adolescents, and young adults, and the results were reported separately.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

Results from the two subgroups were combined in a meta-analysis. Overall, there was no difference between treatments regarding BMI, SHBG, total testosterone, androstenedione, DHEAS, LDL or HDL with very low certainty of evidence.

Included studies:

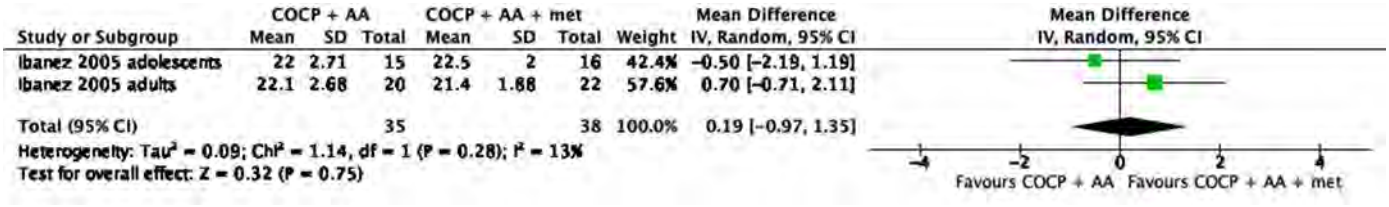
Study ID	ROB	Interventions	Setting Duration	N	Mean age	Mean BMI	PCOS	Age at menarche	Smokers	Comments	Outcomes
Ibanez 2005 (79)	Mod	1: EE 30 μg + 0.3 mg DRSP + flutamide 62.5 mg 2: : EE 30 μg + 0.3 mg DRSP + flutamide 62.5 mg + met 850 mg/day	Spain 3 months	1: 15 2:16	Mean± sem; age, 16.0 ±0.3 yr	1: 21.9 ±0.7 2: 22.4 ±0.5	Author defined	NR	NR	Adolescents, 2-6 yrs post menarche	BMI, Fasting glucose/insulin ratio, SHBG, Testosterone, A4, DHEAS, TG, HDL, LDL,
		1: EE 30 μg + 0.3 mg DRSP + flutamide 62.5 mg 2: : EE 30 μg + 0.3 mg DRSP + flutamide 62.5 mg + met 850 mg/day	Spain 3 months	1: 20 2:22	*19.3 0.4 yr; range, 16–23 yr*	1: 22.0 ±0.6 2: 21.4 ±0.5	Author defined	NR	NR	*Young women, 5–13 yr post menarche*	Fasting glucose/insulin ratio, SHBG, Testosterone, A4, DHEAS, TG, HDL, LDL,

Result from the meta-analysis:

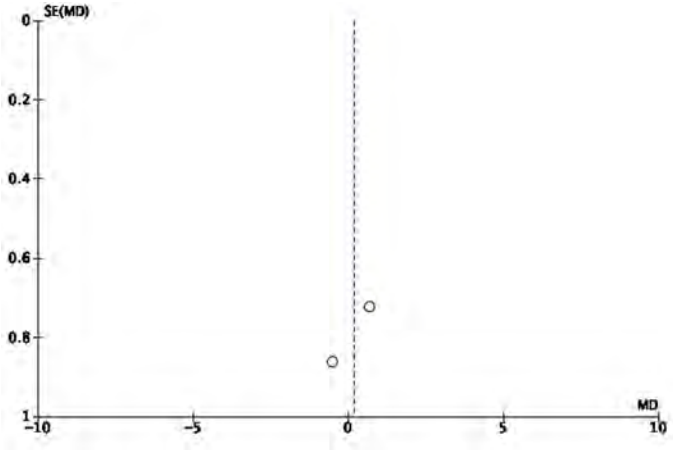
OUTCOME 26.1 BMI
26.1.1 Individual Study Data Table

	OUTCOME: BMI				OUTCOME TYPE: Continuous			
	COMPARISON (if applicable): COCP + AA vs. COCP + AA + met							
Author, year	Unit	Time point	N	COCP + AA Mean	COCP + AA SD	COCP + AA + met Mean	COCP + AA + met SD	Comments
Ibanez 2005 (adolescents)	Kg/m2	3 m	1: 15 2: 15	22.0	2.71	22.5	2.00	
Ibanez 2005 (adolescents)	Kg/m2	3 m	1: 20 2: 22	22.1	2.68	21.4	1.88	

26.1.2. Forest Plot COCP + AA vs. COCP + AA + met for BMI (kg/m2)



26.1.3. Funnel plot for assessment of publication bias

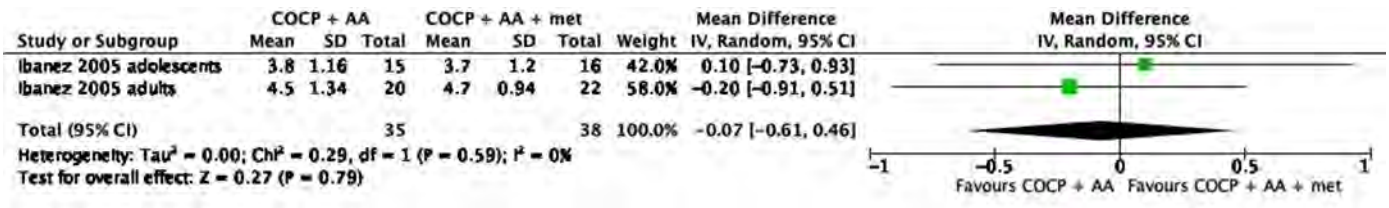


OUTCOME 26.2 SHBG

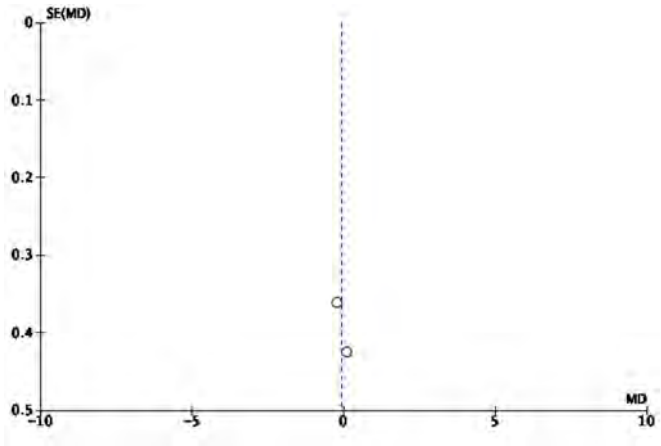
26.2.1 Individual Study Data Table

OUTCOME: SHBG					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP + AA vs. COCP + AA + met								
Author, year	Unit	Time point	N	COCP + AA Mean	COCP + AA SD	COCP + AA + met Mean	COCP + AA + met SD	Comments
Ibanez 2005 (adolescents)	(µg/dl)	3 m	1: 15 2: 15	3.8	1.16	3.7	1.20	Wrong unit? Did not convert
Ibanez 2005 (adolescents)	(µg/dl)	3 m	1: 20 2: 22	4.5	1.34	4.7	4.5	Wrong unit? Did not convert

26.922. Forest Plot COCP + AA vs. COCP + AA + met for SHBG (µg/dl), potentially wrong unit



26.2.3. Funnel plot for assessment of publication bias

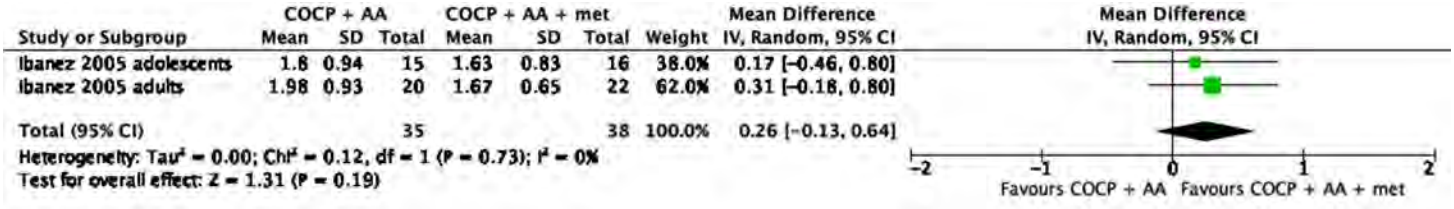


OUTCOME 26.3 TOTAL TESTOSTERONE

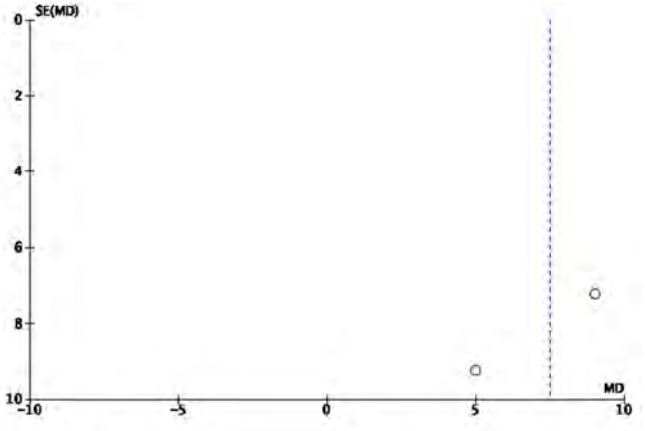
26.3.1 Individual Study Data Table

	OUTCOME: testosterone (nmol/L)				OUTCOME TYPE: Continuous			
	COMPARISON (if applicable): COCP + AA vs. COCP + AA + met							
Author, year	Unit	Time point	N	COCP + AA Mean	COCP + AA SD	COCP + AA + met Mean	COCP + AA + met SD	Comments
Ibanez 2005 (adolescents)	Nmol/L	3 m	1: 15 2: 15	1.80	0.94	1.63	0.83	
Ibanez 2005 (adolescents)	Nmol/L	3 m	1: 20 2: 22	1.98	0.93	1.67	0.65	

26.3.2. Forest Plot COCP + AA vs. COCP + AA + met for total testosterone (nmol/L)



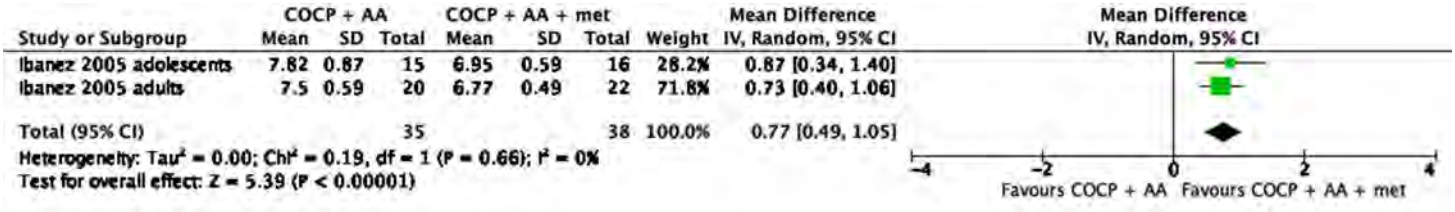
26.3.3. Funnel plot for assessment of publication bias



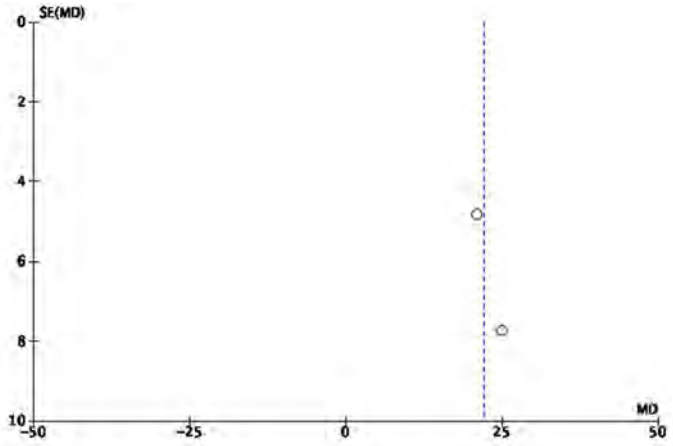
OUTCOME 26.4 ANDROSTENEDIONE
26.4.1 Individual Study Data Table

	OUTCOME: A4 (nmol/L)			OUTCOME TYPE: Continuous				
	COMPARISON (if applicable): COCP + AA vs. COCP + AA + met							
Author, year	Unit	Time point	N	COCP + AA Mean	COCP + AA SD	COCP + AA + met Mean	COCP + AA + met SD	Comments
Ibanez 2005 (adolescents)	Nmol/L	3 m	1: 15 2: 15	7.82	0.87	6.95	0.59	
Ibanez 2005 (adults)	Nmol/L	3 m	1: 20 2: 22	7.50	0.59	6.77	0.49	

26.4.2. Forest Plot COCP + AA vs. COCP + AA + met for androstenedione (nmol/L)



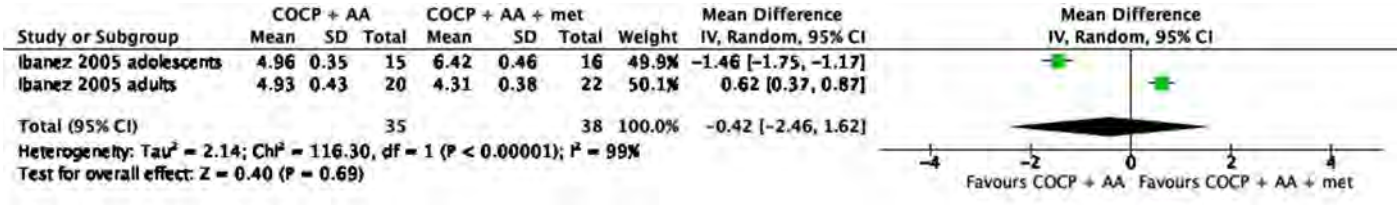
26.4.3. Funnel plot for assessment of publication bias



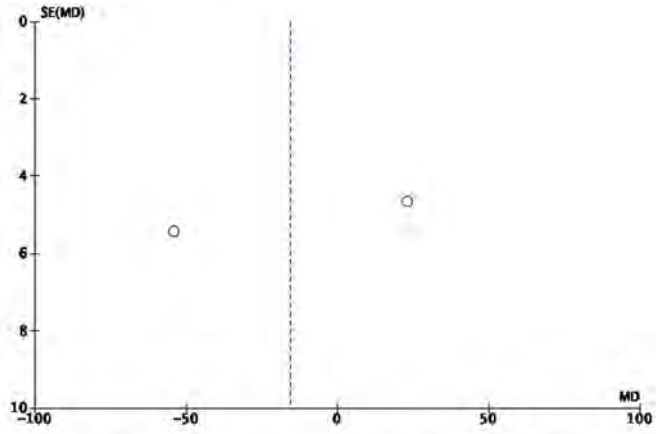
OUTCOME 26.5 DHEAS
26.5.1 Individual Study Data Table

OUTCOME: DHEAS ((µmol/L)				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): COCP + AA vs. COCP + AA + met								
Author, year	Unit	Time point	N	COCP + AA Mean	COCP + AA SD	COCP + AA + met Mean	COCP + AA + met SD	Comments
Ibanez 2005 (adolescents)	Nmol/L	3 m	1: 15 2: 15	4.96	0.35	6.42	0.46	
Ibanez 2005 (adults)	Nmol/L	3 m	1: 20 2: 22	4.93	0.43	4.31	0.38	

26.5.2. Forest Plot COCP + AA vs. COCP + AA + met for DHEAS (μmol/L)



26.5.3. Funnel plot for assessment of publication bias

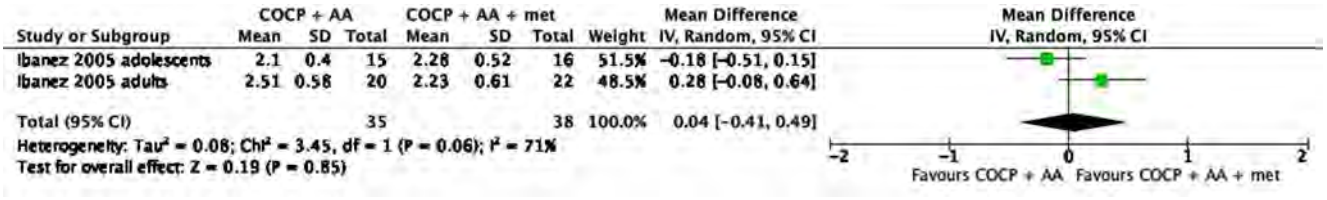


OUTCOME 26.6 LDL

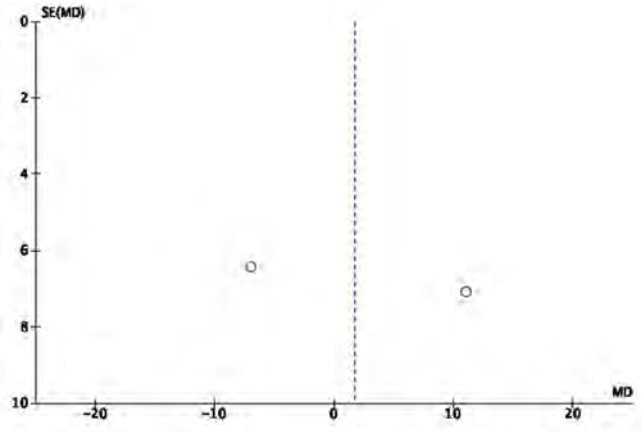
26.6.1 Individual Study Data Table

	OUTCOME: LDL (mmol/L)				OUTCOME TYPE: Continuous			
	COMPARISON (if applicable): COCP + AA vs. COCP + AA + met							
Author, year	Unit	Time point	N	COCP + AA Mean	COCP + AA SD	COCP + AA + met Mean	COCP + AA + met SD	Comments
Ibanez 2005 (adolescents)	Nmol/L	3 m	1: 15 2: 15	2.10	0.40	2.28	0.52	
Ibanez 2005 (adults)	Nmol/L	3 m	1: 20 2: 22	2.51	0.58	2.23	0.61	

26.6.2. Forest Plot COCP + AA vs. COCP + AA + met for LDL (mmol/L)



26.6.3. Funnel plot for assessment of publication bias

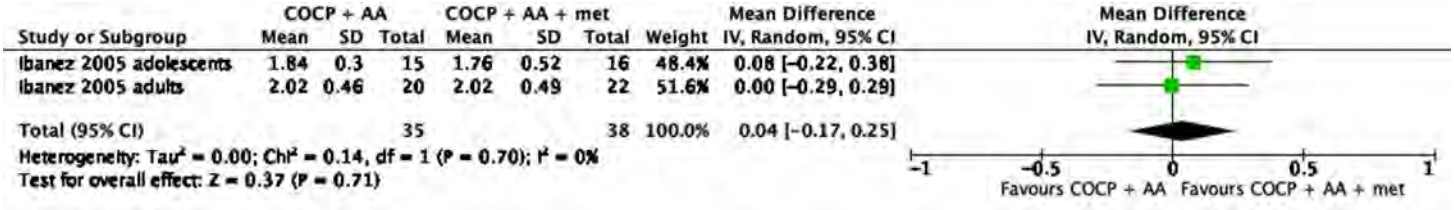


OUTCOME 26.7 HDL

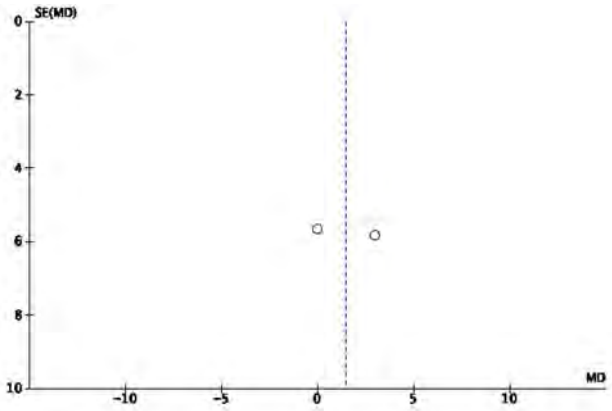
26.7.1 Individual Study Data Table

OUTCOME: HDL (mmol/L)					OUTCOME TYPE: Continuous			
COMPARISON (if applicable): COCP + AA vs. COCP + AA + met								
Author, year	Unit	Time point	N	COCP + AA Mean	COCP + AA SD	COCP + AA + met Mean	COCP + AA + met SD	Comments
Ibanez 2005 (adolescents)	Nmol/L	3 m	1: 15 2: 15	1.84	0.30	1.76	0.52	
Ibanez 2005 (adults)	Nmol/L	3 m	1: 20 2: 22	2.02	0.46	2.02	0.49	

26.7.2. Forest Plot COCP + AA vs. COCP + AA + met for HDL (mmol/L)



26.7.3. Funnel plot for assessment of publication bias

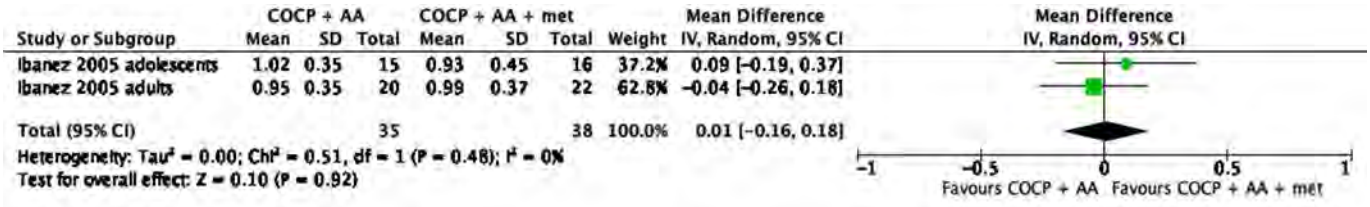


OUTCOME 26.8 TRIGLYCERIDES

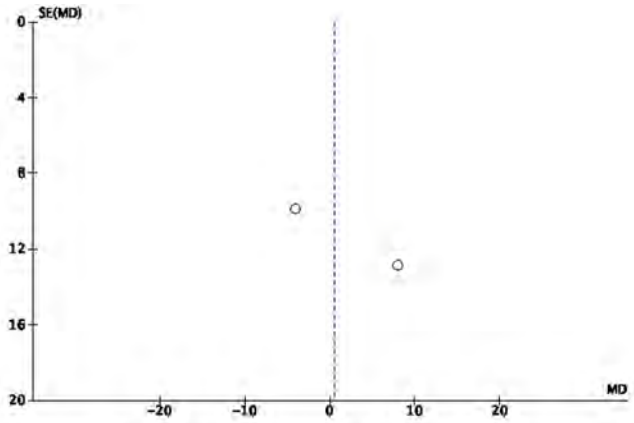
26.8.1 Individual Study Data Table

	OUTCOME: TG (mmol/L)				OUTCOME TYPE: Continuous			
	COMPARISON (if applicable): COCP + AA vs. COCP + AA + met							
Author, year	Unit	Time point	N	COCP + AA Mean	COCP + AA SD	COCP + AA + met Mean	COCP + AA + met SD	Comments
Ibanez 2005 (adolescents)	Nmol/L	3 m	1: 15 2: 15	1.02	0.35	0.93	0.45	
Ibanez 2005 (adults)	Nmol/L	3 m	1: 20 2: 22	0.95	0.35	0.99	0.37	

26.8.2. Forest Plot COCP + AA vs. COCP + AA + met for triglycerids (mmol/L)



26.8.3. Funnel plot for assessment of publication bias



Comparison 27: COCP + anti-androgen vs. COCP + metformin

- **EVIDENCE SUMMARY:**

Only one RCT was identified. The study, with a high risk of bias, compared COCP (containing CPA) + 100 mg spironolactone with COCP + metformin 1700 mg/day. The study had a duration of 3 m.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

Outcomes from this individual study are presented below. DHEAS levels were lower after COCP + metformin than after COCP + anti-androgen, with very low certainty. There were no differences in other reported outcomes, with very low certainty of evidence.

Included studies:

Study ID	ROB	Interventions	Setting Duration	N	Mean age	Mean BMI	PCOS	Age at menarche	Smokers	Outcomes
Kebapcilar 2010 (48)	High	1: 35 µg EE/2mg CPA 2: 35 µg EE/2mg CPA + met 1700 mg/day 3: metformin 1700 mg/day 4: EE/CPA + spiro 100 mg/day	Turkey 3 months	12/ group	24.0±5.4 years; for all	1: 28.7 ±6 2: 27.6 ± 3 3: 27.8 ± 4 4: 27.6 ± 4	Rott	NR	Excluded	BMI, fT, DHEAS, insulin, HOMA, TG, LDL, HDL,

Results from the individual study:

Kebapcilar 2010			⊕◯◯◯ VERY LOW (very high risk of bias, indirectness, very serious impreceion)			
Outcome	COCP + AA (n=12)		COCP + met (n=12)		P value	**Favours**
	mean	SD	mean	SD		
BMI (kg/m2)	26.7	3	26.5	3	0.87	No difference
Free testosterone (pg/ml)	3.8	1.0	3.3	1.0	0.22	No difference
DHEAS (µg/ml)	298	68	224	58	<0.01	COCP + met
Insulin (µIU/ml)	19.8	5.2	17.6	4.0	0.25	No difference
HOMA	4.0	1.2	3.3	1.0	0.12	No difference
Cholesterol (mg/dl)	136	27	137	28	0.93	No difference
LDL (mg/dl)	63	16	72	17	0.18	No difference
HDL (mg/dl)	69	12	61	10	0.08	No difference
TG (mg/dl)	74	39	69	22	0.70	No difference

Comparison 28: COCP vs. COCP + metformin + anti-androgen

▪ EVIDENCE SUMMARY:

One study with a moderate risk of bias, was identified. This Spanish study included young women and adolescents. Details are shown below.

▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

Outcomes from this individual study are presented below. SHBG levels were higher after COCP + metformin + anti-androgen, with very low certainty of evidence. There were no other differences, with very low certainty of evidence.

Included studies:

Study ID	ROB	Interventions	Setting Duration	N	Mean age	Mean BMI	PCOS	Age at menarche	Smokers	Comments	Outcomes
Ibanez 2004 (76)	Mod	1: EE 30 μg + 0.3 mg DRSP 2: EE 30 μg + 0.3 mg DRSP + Met 850 mg + flutamide 62.5 mg	Spain 9 moths	1: 11 2: 11	Mean age for all: 18.6±0.3 years	1: *21.8 ±0.7* *2: 21.7 ±0.6*	Author defined	NR	NR	Young women/adolescents 4-8 yrs post menarche	BMI, FG score, Fasting glucose/insulin ratio, SHBG, Testosterone, TG, HDL, LDL,

Results from the individual study:

Ibanez 2004	⊕◯◯◯ VERY LOW (risk of bias, indirectness, very serious imprecision)					
Outcome	**COCP**		**COCP + AA + met**		**P value**	**Favours**
	Mean	**SD**	**Mean**	**SD**		
BMI (kg/m²)	22.1	2.7	21.8	1.7	0.76	No difference
FG score	10.3	2.3	9.3	2.3	0.31	No difference
SHBG (μg/dl)	4.0	1.3	5.1	1	0.03	Higher after COCP + AA + met
Testosterone (ng/dl)	60	17	61	27	0.92	No difference
Triglycerids (mg/dl)	115	56	107	36	0.69	No difference
LDL (mg/dl)	100	20	93	23	0.45	No difference
HDL (mg/dl)	77	13	77	17	1.00	No difference
Triglycerides (mg/dl)	115	56	107	36	0.69	No difference

Comparison 29: COCP vs. SPIOMET (=metformin + anti-androgen+glucose sensitizer)

- **EVIDENCE SUMMARY:**

Two RCTs, with results pooled and with, in total, five publications were identified. COCP (EE 20 µg – LNG 100 mg) was compared with spironolactone 50 mg/d + pioglitazone 7.5 mg/d + metformin 850 mg/d (SPIOMET). The first RCT was published by Ibanez 2017 (80), with one additional publication on the same cohort by Diaz 2018 (81). Another RCT, with the same comparison, and from the same research group, was done to increase power, with no separate publication. The pooled results were published by Malpique 2019 (82), Ibanez 2020 (83) and de Zegher 2021 (84). The publication by Ibanez 2020 has the highest number of participants, as results for the primary outcome S100A4 in Malpique, not were available for all. Thus, Ibanez 2020 has been considered the main publication. FAI could be extracted from de Zegher as an additional outcome. Risk of bias was moderate. The study had a duration of 12 months.

- **META-ANALYSIS/DESCRIPTIVE ANALYSIS SUMMARY:**

Outcomes are presented in table below. With very low certainty of evidence, SPIOMET treatment results in lower BMI, FG score, insulin, HOMA, LDL and CRP levels compared with COCP. COCP treatment results in higher SHBG and lower FAI and androstenedione levels, compared with SPIOMET, with very low certainty of evidence.

Included studies

Study ID	ROB	Interventions	Setting Duration	N	Mean age	Mean BMI	PCOS	Age at menarche	Smokers	Comments	Outcomes
Ibanez 2020 (83) de Zegher 2021 (84) Malpique 2019 (82) Ibanez 2017 (80) Diaz 2018 (81)	Mod	1: EE 20 µg – levonorgestrel 100 mg 2: spironolactone 50 mg/d + pioglitazone 7.5 mg/d + metformin 850 mg/d (SPIOMET).	Spain 12 months	1=31 2=31	1: 15.9±0.2 2: 15.7±0.2	1: 24.2±0.8 2: 24.2±0.7	Hirsutism + oligomennhorea	1: 11.6±0.1 2: 11.6±0.2	NR	Adolescents Two RCTs with pooled data. Data not extracted from Ibanez 2017, Diaz 2018, Malpique 2019	BMI, hirsutism score, SHBG, TT, androstendione, insulin, HOMA, TG, LDL, HDL, CRP, From de Zegher FAI,

Ibanez 2020 has been considered the main publication. FAI could be extracted from de Zegher as an additional outcome. Results are shown below.

Ibanez 2020 de Zegher 2021	⊕◯◯◯ VERY LOW (serious risk of bias, indirectness, very serious imprecision)							
Outcome	Time point	N	COCP		SPIOMET		P value	Favours
			Mean	SD	Mean	SD		
BMI (kg/m²)	12m	31 31	24.9	4.5	23.9	3.9	<0.001	SPIOMET
FG score	12m	31 31	14	5.6	11	5.6	0.03	SPIOMET
SHBG (nmol/L)	12m	31 31	61	28	32	11	<0.001	Higher after COCP
Testosterone (nmol/L)	12m	31 31	0.7	0.6	0.8	0.6	0.51	No difference

Androstendione (nmol/L)	12m	31 31	2.5	1.1	3.5	1.7	<0.01	COCP
Fasting insulin (pmol/L)	12m	31 31	104	39	42	39	<0.001	SPIOMET
HOMA-IR	12m	31 31	3.0	1.7	1.2	0.6	<0.001	SPIOMET
LDL (mmol/L)	12m	31 31	2.7	0.6	2.2	0.6	<0.01	SPIOMET
HDL (mmol/L)	12m	31 31	1.3	0.6	1.4	0.6	0.51	No difference
Triglycerids (mmol/L)	12 m	31 31	0.75	0.3	0.67	0.3	0.30	No difference
CRP (nmol/L)	12m	31 31	24.8	21.2	6.7	5.0	<0.001	SPIOMET
FAI (from de Zegher)	6 m	58	1.4	1.1	2.9	1.7	<0.001	COCP

Comparison 30: COCP + AA1 vs. COCP + AA2

- **EVIDENCE SUMMARY:**

One RCT was identified. Hagag 2014 compared COCP (35 μg EE + 250 μg NOR) + spironolactone 100 mg with COCP (35 μg EE + 2 mg CPA) + extra 10 mg CPA. The study had a duration of 12 months and had a moderate risk of bias.

- **META-ANALYSIS/DESCRIPTIVE ANALYSIS SUMMARY:**

Outcomes are presented in table below. The combination of COCP + spironolactone resulted in a greater reduction of hirsutism compared with COCP + extra CPA, with a low certainty of evidence. Other reported outcomes (free and total testosterone, DHEAS, androstenedione) did not differ between treatments, with low certainty of evidence.

Included studies

Study ID	ROB	Interventions	Setting Duration	N	Mean age	Mean BMI	PCOS	Age at menarche	Smokers	Comments	Outcomes
Hagag 2014 (71)	Mod	CA1) [250ug NOR + 35ug EE] + 100mg SPL CA2) [2mg CPA + 35ug EE] + 10mg CPA added	srael 12 months	CA1: 72 CA2: 70	CA1: 22±0.4 CA2: 21±0.3	CA1: 24±0.6 CA2: 23.5±0.5	Rott	NR	NR		FG score, fT, TT, DHEAS, A4, side efffects

Outcomes are reported as percent change versus baseline, mean ± SE.

Outcome	COCP + sprio	COCP + extra CPA	P value	Favours
Hirsutism (FG score)	-57% ± 2.4	-39% ± 2.4	<0.001	COCP + spiro
Free testosterone (pmol/L)	-47% ± 8.7	-45% ± 3.8	NS	No difference
Total testosterone (nmol/L)	-31% ± 3.6	-29% ± 2.6	NS	No difference
DHEAS (μmol/L)	-29% ± 4.6	-31% ± 4.1	NS	No difference
Androstenedione (nmol/L)	-19% ± 5	-21% ± 6	NS	No difference

Comparison 31: Metformin vs COCP + metformin

Results are presented under Q4.3 in the technical report.

Comparison 32: COCP + metformin + lifestyle vs EE/CPA + metformin + lifestyle

- **EVIDENCE SUMMARY:**

One study, Wang 2016, with a high risk of bias was identified for this comparison. Major reasons for high risk of bias was no blinding and high attrition rate. Wang included overweight insulin-resistant women with PCOS. All women received metformin and lifestyle modification and were randomized to receive either conventional COCP (EE/DRSP) or EE/CPA for 6 months.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

Results from the single study showed no difference between treatment in any of the reported outcomes, with very low certainty of evidence.

Included study:

Study ID	ROB	Interventions	Setting Duration	N	Mean age	Mean BMI	PCOS	Age at menarche	Smokers	Comments	Outcomes
Wang 2016 (85)	High	1: 30 µg EE + 3 mg DRSP 2: 35µg EE + 2 mg CPA All received met 500 mg/day and lifestylemodification	China 6 months	1: 32 2:36	1: 23.5 ± 4.9 2: 24.3 ± 4.0	Median (IQR) 1: 23.00 (20.77, 26.76) 2: 24.07 (21.54, 26.71)	Rott	NR	Excluded	All insulin resistant and BMI>25.	BMI, WHR, glucose, inslulin, HOMA, chol, TG, LDL, HDL, FG score

Result from individual study:

Wang 2016 (85)	Certainty VERY LOW ⊕◯◯◯ (very high risk of bias, indirectness, very serious imprecision)					
Outcome	COCP + met + LS (n=32) mean.	SD	EE/CPA + met + LS (n=36) mean.	SD	P value (between changes from baseline)	Favours
BMI	Median 21.42 *(19.65, 22.51)*		Median 21.62 *(20.72, 24.65)*		0.67	No difference
WHR	0.92	0.12	0.91	0.05	0.30	No difference
Hirsutism (FG score)	Median *1.0 (0, 4.0)*		Median *2.0 (0, 3.0)*		0.23	No difference
Insulin	Median *10.75 (8.60, 13.50)*		Median *17.85 (10.30, 24.40)*		0.98	No difference
Glucose (mmol/L)	5.21	0.32	5.37	0.41	0.34	No difference
HOMA	Median *2.55 (1.92, 3.40)*		Median *3.90 (2.54, 5.89)*		0.98	No difference
OGTT (AUC glucose)	Median *467.00 (425.40, 513.40)*		Median *450.80 (425.00, 524.00)*		0.90	No difference
Cholesterol (mmol/L)	4.84	0.89	5.20	1.37	0.30	No difference
LDL (mmol/L)	2.66	0.74	2.72	0.83	0.90	No difference
HDL (mmol/L)	Median *1.67 (1.45, 1.98)*		Median *1.59 (1.36, 1.89)*		0.32	No difference
Triglycerids (mmol/L)	Median *1.30 (0.87, 1.68)*		Median *1.32 (0.88, 2.12)*		0.82	No difference

COMPARISON 1: COCP with high vs. low estrogen levels													
		Quality assessment						No. participants					
	No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	COCP + high EE	COCP + low EE	Effect, narrative summary	Favours	Certainty	Importance
Outcome: BMI													
Adults	1	RCT	no serious risk of bias	NA	no serious	very serious[1]	None	46	48	Not applicable – see narrative summary	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: WHR													
Adults	1	RCT	no serious risk of bias	NA	no serious	very serious[1]	None	46	48	Not applicable – see narrative summary	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Hirsutism													
Adults	2	RCT	no serious risk of bias	NA	serious[2]	no serious imprecision	None	66	71	Not applicable – see narrative summary*	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Total testosterone													
Adults	1	RCT	no serious risk of bias	NA	no serious	very serious[1]	None	46	48	Not applicable – see narrative summary	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: SHBG													
Adults	1	RCT	no serious risk of bias	NA	no serious	very serious[1]	None	46	48	Not applicable – see narrative summary	**High EE**	⊕⊕◯◯ LOW	IMPORTANT
Outcome: FAI													
Adults	1	RCT	no serious risk of bias	NA	no serious	very serious[1]	None	46	48	Not applicable – see narrative summary	No difference	⊕⊕◯◯ LOW	IMPORTANT

[1.] Downgraded twice due to being derived from a single study with few patients
[2.] Downgraded once for indirectness due to different ways of reporting hirsutism
*could not be meta-analysed due to one study reporting mean change and the other reporting mean at follow up.

COMPARISON 3: COCP with 1st vs. COCP with 3rd generation progestin													
		Quality assessment						No. participants					
	No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	COCP + 1st gen	COCP + 3rd gen	Effect, narrative summary	Favours	Certainty	Importance
Outcome: Total testosterone													
Adults	1	RCT	very serious[1]	NA	NA	very serious[1]	None	10	10	Not applicable – see narrative summary	**1st generation**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Free testosterone													
Adults	1	RCT	very serious[1]	NA	NA	very serious[1]	None	10	10	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: SHBG													
Adults	1	RCT	very serious[1]	NA	NA	very serious[1]	None	10	10	Not applicable – see narrative summary	**1st generation**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Androstenedione													
Adults	1	RCT	very serious[1]	NA	NA	very serious[1]	None	10	10	Not applicable – see narrative summary	**1st generation**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: DHEAS													
Adults	1	RCT	very serious[1]	NA	NA	very serious[1]	None	10	10	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT

[1] Downgraded twice for risk of bias and twice for imprecision due to being derived from a single study with a small sample size.

COMPARISON 4: COCP with 1st vs. COCP with 4th generation progestins													
	Quality assessment							No. participants		Effect, random MD [95% CI]	Favours	Certainty	Importance
	No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	COCP + 1st gen	COCP + 4th gen				
Outcome: Total testosterone													
Adults	3[1]	RCT	very serious[2]	serious[3]	no serious indirectness	no serious imprecision	none	90	90	MD 0.22 nmol/L (-0.03; 0.46)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: SHBG													
Adults	2[7]	RCT	very serious[2]	very serious[4]	no serious indirectness	serious[5]	none	30	30	MD -21.95 nmol/L (-56.93; 13.04)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Androstenedione													
Adults	2	RCT	very serious[2]	no serious inconsistency	no serious indirectness	serious[5]	none	30	30	MD 1.13 nmol/L (0.64; 1.62)	**4th generation**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: DHEAS													
Adults	3[8]	RCT	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	90	90	MD 0.78 μmol/L (0.29; 1.27)	**4th generation**	⊕⊕◯◯ LOW	IMPORTANT
Outcome: BMI													
Adults	2	RCT	very serious[2]	no serious inconsistency	serious[9]	no serious imprecision	none	119	118	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: WHR													
Adults	1	RCT	very serious[2]	NA	NA	serious[10]	none	59	58	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Hirsutism													
Adults	2	RCT	very serious[2]	NA	serious[9]	no serious imprecision	none	119	118	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Free testosterone													
Adults	1	RCT	very serious[2]	NA	NA	very serious[6]	none	10	10	Not applicable – see narrative summary	**4th generation**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Insulin													
Adults	1	RCT	very serious[2]	NA	NA	serious[10]	none	60	60	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Glucose													
Adults	1	RCT	very serious[2]	NA	NA	serious[10]	none	60	60	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: HOMA													
Adults	2	RCT	very serious[2]	NA	serious[9]	no serious imprecision	none	119	118	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Cholesterol													
Adults	1	RCT	very serious[2]	NA	NA	serious[10]	none	59	58	Not applicable – see narrative summary	**4th generation**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: LDL													
Adults	1	RCT	very serious[2]	NA	NA	serious[10]	none	59	58	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: HDL													
Adults	1	RCT	very serious[2]	NA	NA	serious[10]	none	59	58	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Triglycerides													

Adults	1	RCT	very serious[2]	NA	NA	serious[10]	none	59	58	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: CRP													
Adults	1	RCT	very serious[2]	NA	NA	serious[10]	none	59	58	Not applicable – see narrative summary	**4th generation**	⊕◯◯◯ VERY LOW	IMPORTANT

1. One additional study that could not be included in the meta-analysis, Yildizhan 2015, reported mean change from baseline, -0.34 (0.14) for first generation vs. -0.36 (0.15) nmol/L for 4th generation, p=0.42.
2. Downgraded twice as all of evidence is at high risk of bias
3. Downgraded once due to I^2 >50%
4. Downgraded twice due to I^2>50% and CIs not overlapping
5. Downgraded once due to wide CI
6. Downgraded twice due being derived from a single study with very few patients
7. One additional study, that could not be included in the meta-analysis, Yildizhan 2015 reported mean change from baseline, 9.24 (3.36) vs. 13.29 (4.7) nmol/L, p=0.001.
8. One additional study, that could not be included in the meta-analysis. Yildizhan 2015 reported mean change from baseline, -17.34 (8.74) vs. -21.43 (21.57) ug/dl, p=0.65
9. Downgraded once due to outcomes being presented in different ways
10. Downgraded once due to the evidence being derived from a single study

COMPARISON 5: COCP with 2nd vs. COCP with 3rd generation progestin													
Population	Quality assessment							No. participants		Effect estimate	Favours	Certainty	Importance
	No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	COCP + 2nd gen	COCP + 3rd gen				
Outcome: Weight													
Adults	2	RCT	very serious[1]	no serious inconsistency	serious[2]	serious[3]	None	49	46	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: BMI													
Adults	2	RCT	very serious[1]	no serious inconsistency	serious[2]	serious[3]	None	49	46	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: WHR													
Adults	1	RCT	very serious[1]	NA	NA	very serious[4]	None	26	26	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Hirsutism													
Adults	1	RCT	very serious[1]	NA	NA	very serious[4]	None	26	26	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: SHBG													
Adults	1	RCT	very serious[1]	NA	NA	very serious[4]	None	26	26	Not applicable – see narrative summary	Higher with 3rd	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: DHEAS													
Adults	1	RCT	very serious[1]	NA	NA	very serious[4]	None	26	26	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: FAI													
Adults	1	RCT	very serious[1]	NA	NA	very serious[4]	None	26	26	Not applicable – see narrative summary	**3rd generation**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Total testosterone													
Adults	1	RCT	very serious[1]	NA	NA	very serious[4]	None	26	26	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Cholesterol													
Adults	1	RCT	very serious[1]	NA	NA	very serious[4]	None	23	20	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: LDL- cholesterol													
Adults	1	RCT	very serious[1]	NA	NA	very serious[4]	None	23	20	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: HDL- cholesterol													
Adults	1	RCT	very serious[1]	NA	NA	very serious[4]	None	23	20	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Triglycerides													
Adults	1	RCT	very serious[1]	NA	NA	very serious[4]	None	23	20	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT

[1.] Downgraded twice due to the single study having a high risk of bias
[2.] Downgraded once due to the outcome being reported in different ways
[3.] Downgraded twice due to having very few patients
[4.] Downgraded twice, few patients, only one study

COMPARISON 6: COCP with 2nd vs. 4th generation progestin													
Population	**No. studies**	**Quality assessment**						**No. participants**		**Effect, narrative summary**	**Favours**	**Certainty**	**Importance**
		Design	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**COCP + 2nd gen**	**COCP + 4th gen**				
Outcome: Weight													
Adults	1	RCT	very serious[1]	NA	NA	very serious[3]	None	26	20	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: BMI													
Adults	2	RCT	very serious[1]	NA	no serious inconsistency	serious[2]	None	49	40	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: WHR													
Adults	2	RCT	very serious[1]	NA	no serious inconsistency	serious[2]	None	49	40	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Hirsutism													
Adults	1	RCT	very serious[1]	NA	NA	very serious[3]	None	26	20	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: SHBG													
Adults	1	RCT	very serious[1]	NA	NA	very serious[3]	None	26	20	Not applicable – see narrative summary	**Higher with 4th generation**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: DHEAS													
Adults	1	RCT	very serious[1]	NA	NA	very serious[3]	None	26	20	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: FAI													
Adults	1	RCT	very serious[1]	NA	NA	very serious[3]	None	26	20	Not applicable – see narrative summary	**4th generation**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Total testosterone													
Adults	1	RCT	very serious[1]	NA	NA	very serious[3]	None	26	20	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Cholesterol													
Adults	1	RCT	very serious[1]	NA	NA	very serious[3]	None	23	20	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: LDL													
Adults	1	RCT	very serious[1]	NA	NA	very serious[3]	None	23	20	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: HDL													
Adults	1	RCT	very serious[1]	NA	NA	very serious[3]	None	23	20	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Triglycerides													
Adults	1	RCT	very serious[1]	NA	NA	very serious[3]	None	23	20	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT

1. Downgraded twice due to the single study having a high risk of bias
2. Downgraded once due to the outcome being reported in different ways
3. Downgraded twice due to having very few patients
4. Downgraded twice, few patients, only one study

COMPARISON 7: COCP with 3rd vs. COCP with 4th generation progestins													
Population	**No. studies**	**Quality assessment**						**No. participants**		**Effect, random [95% CI]**	**Favours**	**Certainty**	**Importance**
		Design	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**COCP + 3rd gen**	**COCP + 4th gen**				
Outcome: BMI													
Adults	3[1]	RCT	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	59	56	MD 1.17 kg/m^2 (0.33; 2.02)	**COCP + 4th generation**	⊕⊕◯◯ LOW	CRITICAL
Outcome: Total testosterone													
Adults	2[4]	RCT	very serious[2]	serious[5]	no serious indirectness	serious[3]	none	39	39	MD 0.60 nmol/L (0.13; 1.07)	**COCP + 4th generation**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: SHBG													
Adults	2[6]	RCT	very serious[2]	very serious[7]	no serious indirectness	very serious[8]	none	39	39	MD -27.79 nmol/L (-75.47; 19.88),	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Cholesterol													
Adults	2	RCT	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	None	49	46	MD -0.16 mmol/L (-0.53; 0.22)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: LDL													
Adults	2	RCT	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	None	49	46	MD 0.26 mmol/L (0.07; 0.46)	**COCP + 4th generation**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: HDL													
Adults	2	RCT	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	None	49	46	MD -0.15 mmol/L (-0.22; -0.08),	**COCP + 3rd generation**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: WHR													
Adults	2	RCT	very serious[2]	no serious inconsistency	serious[9]	no serious imprecision	None	67	67	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Hirsutism													
Adults	2	RCT	very serious[2]	no serious inconsistency	serious[9]	no serious imprecision	None	78	79	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: FAI													
Adults	2	RCT	very serious[2]	no serious inconsistency	serious[9]	no serious imprecision	None	78	79	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Free testosterone													
Adults	1	RCT	very serious[2]	NA	NA	very serious[10]	None	10	10	Not applicable – see narrative summary	**COCP + 4th generation**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Androstenedione													

Adults	1	RCT	very serious[2]	NA	NA	very serious[10]	None	10	10	Not applicable – see narrative summary	**COCP + 4th generation**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: DHEAS													
Adults	1	RCT	very serious[2]	NA	NA	very serious[10]	None	10	10	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Insulin													
Adults	2	RCT	very serious[2]	no serious inconsistency	serious[9]	no serious imprecision	None	78	79	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Glucose													
Adults	2	RCT	very serious[2]	no serious inconsistency	serious[9]	no serious imprecision	None	78	79	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: HOMA													
Adults	2	RCT	very serious[2]	no serious inconsistency	serious[9]	no serious imprecision	None	78	79	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Triglycerides													
Adults	2	RCT	very serious[2]	no serious inconsistency	serious[9]	no serious imprecision	None	49	46	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT

[1.] Two additional studies that could not be included in the meta-analysis: Amiri 2020: reported effects using a GEE model, as shown earlier, no p values reported for this comparison; Bhattacharya 2012: reported mean change from baseline, -0.45 ± 6.75 for third generation vs. 0.11 ± 5.54 for 4th generation, p value not reported.
[2.] Downgraded twice for risk of bias as the majority of studies had a high risk of bias
[3.] Downgraded once for imprecision due to having a small number of patients
[4.] One additional study that could not be included in the meta-analysis: Bhattacharya 2012 reported mean change in TT from baseline, -0.10 ± 0.39 for third generation vs. -0.06 ± 0.32 for 4th generation, p value not reported.
[5.] Downgraded once for inconsistency due to heterogeneity (I^2>50%)
[6.] One additional study, that could not be included in the meta-analysis: Bhattacharya 2012 reported mean change in SHBG from baseline, 99.53 ± 67.52 for third generation vs. 131.52 ± 72.89 for 4th generation, p=0.035.
[7.] Downgraded twice due to I^2>50% and CIs not overlapping
[8.] Downgraded twice for imprecision due to having few participants and wide CIs
[9.] Downgraded once for indirectness due to variations in outcome reporting
[10.] Downgraded twice for imprecision due to having few patients from a single study

COMPARISON 8: COCP vs. EE/CPA													
Population	**No. studies**	**Quality assessment**						**No. participants**		**Effect, random [95% CI]**	**Favours**	**Certainty**	**Importance**
		Design	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**COCP**	**EE/ CPA**				
Outcome: BMI													
Adults	4[1]	RCT	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	None	81	89	MD 0.62 kg/m^2 (0.05; 1.20)	**EE/CPA**	⊕⊕◯◯ LOW	CRITICAL
Outcome: WHR													
Adults	2[3]	RCT	very serious[2]	no serious inconsistency	no serious indirectness	serious[16]	None	30	38	MD 0.00 (-0.01; 0.01)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: FAI													
Adults	2[6]	RCT	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	None	51	53	MD 0.14 (-0.06; 0.35)	No difference (EE/CPA if including studies outside meta-analysis[6])	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Total testosterone													
Overall	3[7]	RCT	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	None	65	67	MD 0.38 nmol/L (0.33; 0.43)	**EE/ CPA**	⊕⊕◯◯ LOW	IMPORTANT
Adults	2	RCT	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	None	51	53	MD 0.38 nmol/L (0.33; 0.43)	**EE/ CPA**	⊕⊕◯◯ LOW	IMPORTANT
Adolescents	1	RCT	very serious[2]	no serious inconsistency	no serious indirectness	very serious[14]	None	14	14	MD 0.45 nmol/L (-0.32; 1.22)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: SHBG													
Overall	3[8]	RCT	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	None	65	67	MD -5.86 nmol/L (-35.34; 23.63)	No difference	⊕⊕◯◯ LOW	IMPORTANT
Adults	2	RCT	very serious[2]	serious[24]	no serious indirectness	Serious imprecision[25]	None	51	53	MD 3.36 nmol/L (-49.79; 56.52)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Adolescents	1	RCT	very serious[2]	no serious inconsistency	no serious indirectness	very serious[14]	None	14	14	MD -12.91 nmol/L (-67.51; 41.69)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Androstenedione													
Overall	2[10]	RCT	very serious[2]	very serious[11]	no serious indirectness	very serious[12]	None	35	35	MD 0.78 nmol/L (-3.03; 4.58)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Adults	1	RCT	very serious[2]	no serious inconsistency	no serious indirectness	very serious[14]	None	15	15	MD 2.90 nmol/L 0.52; 5.28)	**EE/ CPA**	⊕◯◯◯ VERY LOW	IMPORTANT
Adolescents	1	RCT	very serious[2]	no serious inconsistency	no serious indirectness	very serious[14]	None	14	14	MD 0.97 nmol/L (-2.85; 4.79)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: DHEAS													
Overall	2[13]	RCT	very serious[2]	no serious inconsistency	no serious indirectness	very serious[14]	None	29	29	MD 1.14 nmol/L (-0.29; 2.58)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Adults	1	RCT	very serious[2]	no serious inconsistency	no serious indirectness	very serious[14]	None	15	15	MD 1.22 nmol/L (-0.68; 3.12)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Adolescents	1	RCT	very serious[2]	no serious inconsistency	no serious indirectness	very serious[14]	None	14	14	MD 1.04 nmol/L (-1.15; 2.58)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Insulin													
Overall	3[15]	RCT	serious[9]	no serious inconsistency	no serious indirectness	Serious imprecision[16]	None	43	43	MD 0.86 μU/ml (-0.78; 2.50)	No difference	⊕⊕◯◯ LOW	IMPORTANT

Adults	2	RCT	very serious[2]	no serious inconsistency	no serious indirectness	very serious[14]	None	25	25	MD 0.58 μU/ml (-1.20; 2.53)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Adolescents	1	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[14]	None	18	18	MD 2.43 μU/ml (-1.79; 6.65)	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Glucose													
Overall	3[17]	RCT	very serious[2]	very serious[11]	no serious indirectness	no serious imprecision	None	43	43	MD 0.04 mmol/L (-0.44; 0.51)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Adults	2	RCT	very serious[2]	very serious[11]	no serious indirectness	very serious[14]	None	25	25	MD 0.21 mmol/L (-0.23; 0.65)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Adolescents	1	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[14]	None	18	18	MD -0.33 mmol/L (-0.73; 0.07)	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: HOMA													
Overall	3[19]	RCT	serious[9]	no serious inconsistency	no serious indirectness	serious[20]	None	69	71	MD 0.13 (-0.40; 0.67),	No difference	⊕⊕◯◯ LOW	IMPORTANT
Adults	2	RCT	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	None	51	53	MD 0.04 (-0.57; 0.64),	No difference	⊕⊕◯◯ LOW	IMPORTANT
Adolescents	1	RCT	Not serious	no serious inconsistency	no serious indirectness	very serious[14]	None	18	18	MD 0.47 (-0.67; 1.61),	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Cholesterol													
Overall	2[21]	RCT	very serious[2]	no serious inconsistency	no serious indirectness	serious[16]	None	34	42	MD -0.59 mmol/L (-1.02; -0.16)	**COCP**	⊕◯◯◯ VERY LOW	IMPORTANT
Adults	1	RCT	very serious[2]	no serious inconsistency	no serious indirectness	very serious[14]	None	20	28	MD -0.70 (-1.27; -0.13)	**COCP**	⊕◯◯◯ VERY LOW	IMPORTANT
Adolescents	1	RCT	very serious[2]	no serious inconsistency	no serious indirectness	very serious[14]	None	14	14	MD -0.44 (-1.11; 0.23)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: LDL													
Overall	2[22]	RCT	very serious[2]	no serious inconsistency	no serious indirectness	serious[16]	None	34	42	MD -0.36 mmol/L (-0.66; -0.06)	**COCP**	⊕◯◯◯ VERY LOW	IMPORTANT
Adults	1	RCT	very serious[2]	no serious inconsistency	no serious indirectness	very serious[14]	None	20	28	MD -0.40 mmol/L (-0.77; -0.03)	**COCP**	⊕◯◯◯ VERY LOW	IMPORTANT
Adolescents	1	RCT	very serious[2]	no serious inconsistency	no serious indirectness	very serious[14]	None	14	14	MD -0.29 mmol/L (-0.81; 0.23)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: HDL													
Overall	2[23]	RCT	very serious[2]	no serious inconsistency	no serious indirectness	serious[16]	None	34	42	MD -0.08 mmol/L (-0.20; 0.04)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Adults	1	RCT	very serious[2]	no serious inconsistency	no serious indirectness	very serious[14]	None	20	20	MD -0.10 mmol/L (-0.27; 0.07)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Adolescents	1	RCT	very serious[2]	no serious inconsistency	no serious indirectness	very serious[14]	None	14	14	MD -0.06 mmol/L (-0.22; 0.10)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Hirsutism													
Adults	3	RCT	serious	no serious inconsistency	serious indirectness	No serious	None	92	90	Not applicable – see narrative summary	**EE/ CPA**	⊕⊕◯◯ LOW	CRITICAL
Outcome: Free testosterone													
Adults	2	RCT	very serious[2]	no serious inconsistency	serious indirectness	serious[16]	None	34	33	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: OGTT													
Adults	2	RCT	very serious[2]	no serious inconsistency	serious	serious[16]	None	38	37	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Triglycerides													

Adults	2	RCT	very serious[2]	no serious inconsistency	serious	serious[16]	None	37	47	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: CRP													
Adults	2	RCT	very serious[2]	no serious inconsistency	serious	serious[16]	None	56	57	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT

[1.] Two additional studies, not incl in the meta-analysis: Bhattacharya 2012 reported mean change, -0.45 ± 6.75 for a 3rd generation COCP vs. -0.59 ± 4.76 kg/m^2 for EE/CPA, p value not reported; Kahraman 2014 reported median change, −1 (−9 to 17) for a 4th generation COCP vs. −1 (−12 to 6), p=0.789.
[2.] Downgraded twice since majority of studies had a high risk of bias.
[3.] Two additional studies, not incl in the meta-analysis: Bhattacharya 2012 reported mean change, 0.00 ± 0.08 for a 3rd generation COCP vs. -0.02 ± 0.08 for EE/CPA, p value not reported; Kahraman 2014 reported median change, −4 (−31 to 35) for a 4th generation COCP vs. 0 (−11 to 14), p=0.03.
[4.] Two additional studies, not incl in the meta-analysis: Bhattacharya 2012 reported mean change in FG score, -1.69 ± 5.69 for a 3rd generation COCP vs. -5.29 ± 5.88 for EE/CPA, p=0.003.; Kahraman 2014 reported median change in % from baseline, −18 (−72 to 30) for a 4th generation COCP vs −35 (−71 to 10)), p=0.04.
[5.] Downgraded once, when also considering the results not included in the meta-analysis.
[6.] One additional study, not included in the meta-analysis: Bhattacharya 2012 reported mean change in FAI, -5.58 ± 9.15 for a 3rd generation COCP vs. -10.57 ± 7.93 for EE/CPA, p=0.001.
[7.] Two studies not included in the meta-analysis: Bhattacharya 2012 reported mean change in TT, -0.10 ± 0.39 ng/ml for a 3rd generation COCP vs. -0.03 ± 0.42 for EE/CPA, p value not reported; Kahraman 2014 reported median % change, −39 (−84 to 43) for a 4th generation COCP vs −16 (−78 to 125) for EE/CPA, p=0.087.
[8.] Two additional studies not included in the meta-analysis: Bhattacharya 2012 reported mean change, 99.53 ± 67.52 nmol/L for a 3rd generation COCP vs. -142.91 ± 60.71 for EE/CPA, p=0.02; Kahraman 2014 reported median % change (range) 178 (−57 to 897) vs. 270 (31 to 1,062) nmol/L, p=0.238.
[9.] Downgraded once since some studies had moderate or high risk of bias.
[10.] One additional study, not included in the meta-analysis: Kahraman 2014 reported median % change (range) −29 (−100 to 25) for COCP vs. −18 (−47 to 52) for EE/CPA, p=0.052.
[11.] Downgraded twice since I2>50% and CIs not overlapping
[12.] Downgraded twice due to wide CI and few patients
[13.] One additional study, not included in the meta-analysis: Kahraman 2014 reported median % change (range) −32 (−53 to 15) for COCP vs. −10 (−49 to 63) for EE/CPA, p=0.046.
[14.] Downgraded twice due to very few patients
[15.] Two additional studies, not included in the meta-analysis: Bhattacharya 2012 reported mean change, -0.02 ± 17.35 for a 3rd generation COCP vs. 6.38 ± 15.22 for EE/CPA, p value not reported; Kahraman 2014 reported median % change (range) 7 (−85 to 223) vs. 0 (−82 to 128), P=0.603.
[16.] Downgraded once due to few participants
[17.] Two additional studies not included in the meta-analysis: Bhattacharya 2012 reported mean change, -4.28 ± 11.66 for a 3rd generation COCP vs. -2.46 ± 16.86 for EE/CPA, p value not reported; Kahraman 2014 reported median % change (range) 0 (−15 to 6) vs. 0 (−10 to 18), p=0.397.
[18.] Downgraded once since CIs are not overlapping
[19.] Two additional studies, not included in the meta-analysis. Bhattacharya 2012 reported mean change, -0.28 ± 3.98 for a 3rd generation COCP vs. 1.21 ± 4.03 for EE/CPA, p value not reported; Kahraman 2014 reported median % change (range) 2 (−71 to 216) vs. −18 (−80 to 462), p=0.227.
[20.] Downgraded once since studies show results favoring different outcomes.
[21.] One additional study, not included in the meta-analysis. Kahraman 2014 reported median % change (range) 7 (−13 to 59) for COCP vs. 11 (−17 to 79) for EE/CPA, p=0.673.
[22.] One additional study, not included in the meta-analysis. Kahraman 2014 reported median % change (range) 2 (−30 to 68) vs. 5 (−16 to 63) p=0.555.
[23.] Two additional studies not included in the meta-analysis. Kahraman 2014 reported median % change (range) +5 (−42 to 45) after COCP treatment vs. +16 (−45 to 46) after EE/CPA, p=0.070. Wang 2016 reported medians, 1.67 (1.45, 1.98) mmol/L after COCP and 1.59 (1.36, 1.89) mmol/L after EE/CPA, p=0.322.
[24.] Downgraded once due to I^2>50%
[25.] Downgraded once due to wide CI

COMPARISON 9: Any COCP vs. progestogen													
Population	No. studies	Quality assessment						No. participants		Effect, random [95% CI]	Favours	Certainty	Importance
		Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	COCP	PROG				
Outcome: BMI													
Overall	2	RCT	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	None	68	69	MD 0.20 kg/m^2 (-1.40; 1.81)	No difference	⊕⊕◯◯ LOW	CRITICAL
Adults	1	RCT	very serious[1]	NA	NA	very serious[2]	None	32	31	MD 0.30 kg/m^2 (-1.92; 2.52)	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Adolescents	1	RCT	serious[3]	NA	NA	very serious[2]	None	36	38	MD 0.10 kg/m^2 (-2.23; 2.43)	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: WHR													
Overall	2	RCT	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	None	68	59	MD 0.00 (-0.16; 0.16)	No difference	⊕⊕◯◯ LOW	IMPORTANT
Adults	1	RCT	very serious[1]	NA	NA	very serious[2]	None	32	31	MD 0.00 (-0.20; 0.20)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Adolescents	1	RCT	serious[3]	NA	NA	very serious[2]	None	36	38	MD 0.00 (-0.30; 0.30)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Total testosterone													
Overall	2	RCT	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	None	68	69	MD -0.11 nmol/L (-0.46; 0.24)	No difference	⊕⊕◯◯ LOW	IMPORTANT
Adults	2	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	None	32	31	MD 0.00 nmol/L (-0.35; 0.35)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Adolescents	1	RCT	serious[3]	NA	NA	very serious[2]	None	36	38	MD -0.40 nmol/L (-1.03; 0.23)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Weight													
Adults	1	RCT	very serious[1]	NA	NA	very serious[2]	None	36	38	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Hirsutism													
Adults	1	RCT	very serious[1]	NA	NA	very serious[2]	None	32	31	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: FAI													
Adults	1	RCT	very serious[1]	NA	NA	very serious[2]	None	32	31	Not applicable – see narrative summary	COCP	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: SHBG													
Adults	1	RCT	very serious[1]	NA	NA	very serious[2]	None	32	31	Not applicable – see narrative summary	COCP higher	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: DHEAS													
Adults	1	RCT	very serious[1]	NA	NA	very serious[2]	None	32	31	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Insulin													
Adults	1	RCT	very serious[1]	NA	NA	very serious[2]	None	32	31	Not applicable – see narrative summary	Progestin	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Glucose													
Adults	1	RCT	very serious[1]	NA	NA	very serious[2]	None	32	31	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: HOMA-IR													

Adults	1	RCT	very serious[1]	NA	NA	very serious[2]	None	32	31	Not applicable – see narrative summary	No difference	⨁◯◯◯ VERY LOW	IMPORTANT
Outcome: Cholesterol													
Adults	1	RCT	very serious[1]	NA	NA	very serious[2]	None	32	31	Not applicable – see narrative summary	No difference	⨁◯◯◯ VERY LOW	IMPORTANT
Outcome: HDL													
Adults	1	RCT	very serious[1]	NA	NA	very serious[2]	None	32	31	Not applicable – see narrative summary	No difference	⨁◯◯◯ VERY LOW	IMPORTANT
Outcome: LDL													
Adults	1	RCT	very serious[1]	NA	NA	very serious[2]	None	32	31	Not applicable – see narrative summary	No difference	⨁◯◯◯ VERY LOW	IMPORTANT
Outcome: Triglycerides													
Adults	1	RCT	very serious[1]	NA	NA	very serious[2]	None	32	31	Not applicable – see narrative summary	Progestin	⨁◯◯◯ VERY LOW	IMPORTANT
Outcome: HRQoL													
Adults	1	RCT	very serious[1]	NA	NA	very serious[2]	None	36	38	Not applicable – see narrative summary	No difference	⨁◯◯◯ VERY LOW	CRITICAL

1. Downgraded twice due to high risk of bias
2. Downgraded twice for imprecision due to having a single study with few patients
3. Downgraded once due to risk of bias

COMPARISON 10: Any COCP vs controls													
Population	**No. studies**	**Quality assessment**						**No. participants**		**Effect, narrative summary**	**Favours**	**Certainty**	**Importance**
		Design	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**COCP**	**Controls**				
Outcome: Weight													
Adolescents	1	RCT	very serious[1]	NA	NA	very serious[2]	None	33	25	Not applicable – see narrative summary	**COCP**	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Testosterone													
Adolescents	1	RCT	very serious[1]	NA	NA	very serious[2]	None	33	25	Not applicable – see narrative summary	**COCP**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Insulin													
Adolescents	1	RCT	very serious[1]	NA	NA	very serious[2]	None	33	25	Not applicable – see narrative summary	**COCP**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Glucose													
Adults	1	RCT	very serious[1]	NA	NA	very serious[2]	None	17	15	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: OGTT													
Adolescents	1	RCT	very serious[1]	NA	NA	very serious[2]	None	33	25	Not applicable – see narrative summary	**Controls**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: HOMA													
Adults	1	RCT	very serious[1]	NA	NA	very serious[2]	None	17	15	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: CRP													
Adults	1	RCT	very serious[1]	NA	NA	very serious[2]	None	17	15	Not applicable – see narrative summary	**Controls**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: PAI-1													
Adults	1	RCT	very serious[1]	NA	NA	very serious[2]	None	17	15	Not applicable – see narrative summary	**Controls**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: HRQoL													
Adults	1	RCT	very serious[1]	NA	NA	very serious[2]	None	50	50	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Improvement of irregular cycles													
Adults	1	RCT	very serious[1]	NA	NA	Serious[3]	Large effect[4]	40	40	Not applicable – see narrative summary	COCP	⊕⊕◯◯ LOW	CRITICAL

[1] Downgraded twice for high risk of bias
[2] Downgraded twice for imprecision (few patients and a single study)
[3] Downgraded once for imprecision (a single study
[4] Upgraded once for large effect

COMPARISON 11: Any COCP vs placebo													
Population	**Quality assessment**							**No. participants**		**Effect, narrative summary**	**Favours**	**Certainty**	**Importance**
	No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**COCP**	**Placebo**				
Outcome: BMI													
Adolescents	1	RCT	serious[1]	NA	NA	very serious[2]	None	10	10	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Hirsutism													
Adolescents	1	RCT	serious[1]	NA	NA	very serious[2]	None	10	10	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: FAI													
Adolescents	1	RCT	serious[1]	NA	NA	very serious[2]	None	10	10	Not applicable – see narrative summary	COCP	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Testosterone													
Adolescents	1	RCT	serious[1]	NA	NA	very serious[2]	None	10	10	Not applicable – see narrative summary	COCP	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: SHBG													
Adolescents	1	RCT	serious[1]	NA	NA	very serious[2]	None	10	10	Not applicable – see narrative summary	Higher after COCP	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Insulin													
Adolescents	1	RCT	serious[1]	NA	NA	very serious[2]	None	10	10	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Glucose													
Adolescents	1	RCT	serious[1]	NA	NA	very serious[2]	None	10	10	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Cholesterol													
Adolescents	1	RCT	serious[1]	NA	NA	very serious[2]	None	10	10	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: LDL													
Adolescents	1	RCT	serious[1]	NA	NA	very serious[2]	None	10	10	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: HDL													
Adolescents	1	RCT	serious[1]	NA	NA	very serious[2]	None	10	10	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: TG													
Adolescents	1	RCT	serious[1]	NA	NA	very serious[2]	None	10	10	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: CRP													
Adolescents	1	RCT	serious[1]	NA	NA	very serious[2]	None	10	10	Not applicable – see narrative summary	Placebo	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: PAI-1													
Adolescents	1	RCT	serious[1]	NA	NA	very serious[2]	None	10	10	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT

[1] Downgraded once for risk of bias
[2] Downgraded twice for imprecision (very few patients and a single study)

COMPARISON 12: Any COCP vs lifestyle													
Population	**No. studies**	**Quality assessment**						**No. participants**		**Effect, narrative summary**	**Favours**	**Certainty**	**Importance**
		Design	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**COCP**	**Placebo**				
Outcome: BMI													
Adolescents	1	RCT	serious[1]	NA	NA	very serious[2]	None	10	8	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Hirsutism													
Adolescents	1	RCT	serious[1]	NA	NA	very serious[2]	None	10	8	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: FAI													
Adolescents	1	RCT	serious[1]	NA	NA	very serious[2]	None	10	8	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Testosterone													
Adolescents	1	RCT	serious[1]	NA	NA	very serious[2]	None	10	8	Not applicable – see narrative summary	COCP	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: SHBG													
Adolescents	1	RCT	serious[1]	NA	NA	very serious[2]	None	10	8	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Insulin													
Adolescents	1	RCT	serious[1]	NA	NA	very serious[2]	None	10	8	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Glucose													
Adolescents	1	RCT	serious[1]	NA	NA	very serious[2]	None	10	8	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Cholesterol													
Adolescents	1	RCT	serious[1]	NA	NA	very serious[2]	None	10	8	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: LDL													
Adolescents	1	RCT	serious[1]	NA	NA	very serious[2]	None	10	8	Not applicable – see narrative summary	Lifestyle	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: HDL													
Adolescents	1	RCT	serious[1]	NA	NA	very serious[2]	None	10	8	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Triglycerides													
Adolescents	1	RCT	serious[1]	NA	NA	very serious[2]	None	10	8	Not applicable – see narrative summary	Lifestyle	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: CRP													
Adolescents	1	RCT	serious[1]	NA	NA	very serious[2]	None	10	8	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: PAI-1													
Adolescents	1	RCT	serious[1]	NA	NA	very serious[2]	None	10	8	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT

[1] Downgraded once for risk of bias
[2] Downgraded twice for imprecision (very few patients and a single study)

COMPARISON 13: Any COCP vs lifestyle +/- anti-obesity treatment													
Population	**No. studies**	**Quality assessment**						**No. participants**		**Effect, narrative summary**	**Favours**	**Certainty**	**Importance**
		Design	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**COCP**	**Lifestyle +/- anti-obesity**				
Outcome: BMI													
Adults	1	RCT	serious[1]	NA	NA	very serious[1]	None	45	44	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Weight													
Adults	1	RCT	serious[1]	NA	NA	very serious[1]	None	45	44	Not applicable – see narrative summary	**Lifestyle +/- anti-obesity**	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: total testosterone													
Adults	1	RCT	serious[1]	NA	NA	very serious[1]	None	45	44	Not applicable – see narrative summary	**COCP**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: SHBG													
Adults	1	RCT	serious[1]	NA	NA	very serious[1]	None	45	44	Not applicable – see narrative summary	**COCP**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: TG													
Adults	1	RCT	serious[1]	NA	NA	very serious[1]	None	45	44	Not applicable – see narrative summary	**COCP**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: OGTT													
Adults	1	RCT	serious[1]	NA	NA	very serious[1]	None	45	44	Not applicable – see narrative summary	**Lifestyle +/- anti-obesity**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: HRQoL													
Adults	1	RCT	serious[1]	NA	NA	very serious[1]	None	45	44	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Sexual function													
Adults	1	RCT	serious[1]	NA	NA	very serious[1]	None	45	44	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Depression													
Adults	1	RCT	serious[1]	NA	NA	very serious[1]	None	45	44	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT

[1]Downgraded once for risk of bias and twice for imprecision (few patients, only one study)

COMPARISON 14: Any COCP vs. any COCP + lifestyle (+/- anti-obesity)													
Population	**No. studies**	**Quality assessment**						**No. participants**		**Effect, narrative summary**	**Favours**	**Certainty**	**Importance**
		Design	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**COCP**	**COCP+ Lifestyle +/- anti-obesity**				
Outcome: BMI													
Adults	1	RCT	serious[1]	NA	NA	very serious[2]	None	43	45	Not applicable – see narrative summary	No difference	⨁◯◯◯ VERY LOW	CRITICAL
Outcome: weight													
Adults	1	RCT	serious[1]	NA	NA	very serious[2]	None	43	45	Not applicable – see narrative summary	**COCP + Lifestyle**	⨁◯◯◯ VERY LOW	CRITICAL
Outcome: total testosterone													
Adults	1	RCT	serious[1]	NA	NA	very serious[2]	None	43	45	Not applicable – see narrative summary	No difference	⨁◯◯◯ VERY LOW	IMPORTANT
Outcome: SHBG													
Adults	1	RCT	serious[1]	NA	NA	very serious[2]	None	43	45	Not applicable – see narrative summary	No difference	⨁◯◯◯ VERY LOW	IMPORTANT
Outcome: TG													
Adults	1	RCT	serious[1]	NA	NA	very serious[2]	None	43	45	Not applicable – see narrative summary	No difference	⨁◯◯◯ VERY LOW	IMPORTANT
Outcome: OGTT													
Adults	1	RCT	serious[1]	NA	NA	very serious[2]	None	43	45	Not applicable – see narrative summary	**COCP + Lifestyle**	⨁◯◯◯ VERY LOW	IMPORTANT
Outcome: HRQoL													
Adults	1	RCT	serious[1]	NA	NA	very serious[2]	None	43	45	Not applicable – see narrative summary	No difference	⨁◯◯◯ VERY LOW	CRITICAL
Outcome: Sexual function													
Adults	1	RCT	serious[1]	NA	NA	very serious[2]	None	43	45	Not applicable – see narrative summary	No difference	⨁◯◯◯ VERY LOW	IMPORTANT
Outcome: Depression													
Adults	1	RCT	serious[1]	NA	NA	very serious[2]	None	43	45	Not applicable – see narrative summary	No difference	⨁◯◯◯ VERY LOW	IMPORTANT

[1] Downgraded once for risk of bias
[2] Downgraded twice for imprecision due to having few patients from only one study

COMPARISON 15: Lifestyle (+/- anti-obesity) vs. any COCP + lifestyle													
		Quality assessment						No. participants					
Population	No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Life style (+/- anti-obesity)	COCP + Life style	Effect, narrative summary	Favours	Certainty	Importance
	Outcome: BMI												
Adults	1	RCT	serious[1]	NA	NA	very serious[1]	None	44	43	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	CRITICAL
	Outcome: weight												
Adults	1	RCT	serious[1]	NA	NA	very serious[1]	None	44	43	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	CRITICAL
	Outcome: total testosterone												
Adults	1	RCT	serious[1]	NA	NA	very serious[1]	None	44	43	Not applicable – see narrative summary	**COCP + lifestyle**	⊕◯◯◯ VERY LOW	IMPORTANT
	Outcome: SHBG												
Adults	1	RCT	serious[1]	NA	NA	very serious[1]	None	44	43	Not applicable – see narrative summary	**Higher after COCP + lifestyle**	⊕◯◯◯ VERY LOW	IMPORTANT
	Outcome: TG												
Adults	1	RCT	serious[1]	NA	NA	very serious[1]	None	44	43	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
	Outcome: OGTT												
Adults	1	RCT	serious[1]	NA	NA	very serious[1]	None	44	43	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
	Outcome: HRQoL												
Adults	1	RCT	serious[1]	NA	NA	very serious[1]	None	44	43	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	CRITICAL
	Outcome: Sexual function												
Adults	1	RCT	serious[1]	NA	NA	very serious[1]	None	44	43	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Depression													
Adults	1	RCT	serious[1]	NA	NA	very serious[1]	None	44	43	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT

[1]Downgraded once for risk of bias and twice for imprecision (few patients, only one study)

COMPARISON 16: Any COCP vs. anti-obesity													
Population	**Quality assessment**							**No. participants**		**Effect, narrative summary**	**Favours**	**Certainty**	**Importance**
	No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**COCP**	**Anti-obesity**				
Outcome: BMI													
Adults	1	RCT	very serious[1]	NA	NA	very serious[2]	None	14	12	Not applicable – see narrative summary	**Anti-obesity**	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: weight													
Adults	1	RCT	very serious[1]	NA	NA	very serious[2]	None	14	12	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: WHR													
Adults	1	RCT	very serious[1]	NA	NA	very serious[2]	None	14	12	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Hirsutism													
Adults	1	RCT	very serious[1]	NA	NA	very serious[2]	None	14	12	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Total testosterone													
Adults	1	RCT	very serious[1]	NA	NA	very serious[2]	None	14	12	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Free testosterone													
Adults	1	RCT	very serious[1]	NA	NA	very serious[2]	None	14	12	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: SHBG													
Adults	1	RCT	very serious[1]	NA	NA	very serious[2]	None	14	12	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: DHEAS													
Adults	1	RCT	very serious[1]	NA	NA	very serious[2]	None	44	43	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Triglycerides													
Adults	1	RCT	very serious[1]	NA	NA	very serious[2]	None	10	8	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Cholesterol													
Adults	1	RCT	very serious[1]	NA	NA	very serious[2]	None	10	8	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: LDL													
Adults	1	RCT	very serious[1]	NA	NA	very serious[2]	None	10	8	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: HDL													
Adults	1	RCT	very serious[1]	NA	NA	very serious[2]	None	10	8	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Insulin													
Adults	1	RCT	very serious[1]	NA	NA	very serious[2]	None	10	8	Not applicable – see narrative summary	Anti-obesity	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Glucose													
Adults	1	RCT	very serious[1]	NA	NA	very serious[2]	None	10	8	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT

[1]Downgraded twice for risk of bias (due to the single study being high risk) and twice for imprecision (few patients, only one study)

COMPARISON 17: Any COCP vs. any COCP + anti-obesity												
	No. studies	Quality assessment						No. participants		Effect, random [95% CI]	Favours	Certainty	Importance
		Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	COCP	COCP + anti-obesity				
Outcome: BMI													
Adults	2	RCT	very serious[1]	no serious incontinency	no serious indirectness	serious[2]	none	47	45	MD 1.40 kg/m^2 (-0.93;3.73)	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Weight													
Adults	2	RCT	very serious[1]	no serious incontinency	no serious indirectness	serious[2]	none	47	45	MD 3.17 kg (-0.77;7.11)	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: WHR													
Adults	1	RCT	very serious[1]	NA	NA	very serious[7]	none	14	12	MD 0.02 (-0.03;0.07)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Hirsutism													
Adults	1	RCT	very serious[1]	NA	NA	very serious[7]	none	14	12	MD 1.42 (-0.66; 3.50)	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: FAI													
Adults	1	RCT	very serious[1]	NA	NA	serious[8]	none	60	60	MD 2.44 (0.87; 4.01)	**COCP + anti-obesity**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Total testosterone													
Adults	3	RCT	very serious[1]	no serious incontinency	no serious indirectness	no serious imprecision	none	107	105	MD 0.03 nmol/L (-0.12; 0.18)	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Free testosterone													
Adults	2[6]	RCT	very serious[1]	no serious incontinency	no serious indirectness	serious[2]	none	47	45	MD 3.56 pmol/L (-0.72;7.85)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: SHBG													
Adults	3	RCT	very serious[1]	very serious[3]	no serious indirectness	serious[4]	none	107	105	MD 18.03 nmol/L (-49.81; 85.87)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Androstenedione													
Adults	1	RCT	very serious[1]	NA	NA	serious[8]	none	60	60	MD 0.80 nmol/L (-0.44; 2.04)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: DHEAS													
Adults	2	RCT	very serious[1]	no serious incontinency	no serious indirectness	no serious imprecision	none	74	72	MD 0.79 µmol/L (0.29; 1.29)	**COCP + anti-obesity**	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Insulin													
Adults	2	RCT	very serious[1]	serious[5]	no serious indirectness	no serious imprecision	none	93	93	MD 9.61 pmol/L (-18.45; 37.68)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Glucose													
Adults	2	RCT	very serious[1]	no serious incontinency	no serious indirectness	no serious imprecision	none	93	93	MD 0.00 mmol/L (-0.17; 0.17)	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: HOMA-IR													
Adults	1	RCT	very serious[1]	NA	NA	serious[8]	none	60	60	MD 0.71 (0.15; 1.27)	**COCP + anti-obesity**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Cholesterol													

Adults	2	RCT	very serious[1]	no serious incontinency	no serious indirectness	no serious imprecision	none	74	72	MD 0.21 mmol/L (-0.02;0.44)	No difference	⨁⨁◯◯ LOW	IMPORTANT
Outcome: LDL													
Adults	3	RCT	very serious[1]	serious[5]	no serious indirectness	no serious imprecision	none	107	105	MD 0.35 mmol/L (-0.02;0.72)	No difference	⨁◯◯◯ VERY LOW	IMPORTANT
Outcome: HDL													
Adults	3	RCT	very serious[1]	very serious[3]	no serious indirectness	no serious imprecision	none	107	105	MD -0.15 mmol/L (-0.43;0.13)	No difference	⨁◯◯◯ VERY LOW	IMPORTANT
Outcome: Triglycerides													
Adults	3	RCT	very serious[1]	no serious incontinency	no serious indirectness	no serious imprecision	none	107	105	MD 0.02 mmol/L (-0.19;0.22)	No difference	⨁⨁◯◯ LOW	IMPORTANT
Outcome: CRP													
Adults	1	RCT	very serious[1]	NA	NA	serious[8]	none	60	60	MD 0.26 (-1.56; 2.08)	No difference	⨁◯◯◯ VERY LOW	IMPORTANT

1. Downgraded twice as all of evidence is derived from studies at high risk of bias
2. Downgraded once for imprecision due to small sample sizes
3. Downgraded twice due to I^2>50% and CIs not overlapping
4. Downgraded once for imprecision due to wide CIs
5. Downgraded once due to I^2>50%
6. Ruan et al. 2018 not included, reported extreme values
7. Downgraded twice due to very few participants and only one study
8. Downgraded once due to the evidence being derived from a single study

COMPARISON 18: Any COCP + metformin vs. any COCP + anti-obesity													
Population	No. studies	Quality assessment						No. participants		Effect, narrative summary	Favours	Certainty	Importance
		Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	COCP + MET	COCP + anti-obesity				
Outcome: Total testosterone													
Adults	1	RCT	Very serious	NA	no serious	serious	None	60	60	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: DHEAS													
Adults	1	RCT	Very serious	NA	no serious	serious	None	60	60	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Androstenedione													
Adults	1	RCT	Very serious	NA	no serious	serious	None	60	60	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: SHBG													
Adults	1	RCT	Very serious	NA	no serious	serious	None	60	60	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Free testosterone													
Adults	1	RCT	Very serious	NA	no serious	serious	None	60	60	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: FAI													
Adults	1	RCT	Very serious	NA	no serious	serious	None	60	60	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Triglycerides													
Adults	1	RCT	Very serious	NA	no serious	serious	None	60	60	Not applicable – see narrative summary	COCP + anti-obesity	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Cholesterol													
Adults	1	RCT	Very serious	NA	no serious	serious	None	60	60	Not applicable – see narrative summary	COCP + anti-obesity	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: LDL													
Adults	1	RCT	Very serious	NA	no serious	serious	None	60	60	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: HDL													
Adults	1	RCT	Very serious	NA	no serious	serious	None	60	60	Not applicable – see narrative summary	Higher after COCP + anti-obesity	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Insulin													
Adults	1	RCT	Very serious	NA	no serious	serious	None	60	60	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Glucose													
Adults	1	RCT	Very serious	NA	no serious	serious	None	60	60	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: HOMA													
Adults	1	RCT	Very serious	NA	no serious	serious	None	60	60	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT

All outcomes had a very low certainty of evidence due to high risk of bias (-2), imprecision (-1, only one study involving one population).

COMPARISON 19: Any COCP vs. any COCP + metformin + anti-obesity													
	No. studies	Quality assessment						No. participants		Effect, narrative summary	Favours	Certainty	Importance
		Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	COCP	COCP + met + AO				
Outcome: Total testosterone													
Adults	1	RCT	very serious[1]	NA	NA	serious[2]	None	60	60	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: DHEAS													
Adults	1	RCT	very serious[1]	NA	NA	serious[2]	None	60	60	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Androstenedione													
Adults	1	RCT	very serious[1]	NA	NA	serious[2]	None	60	60	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: SHBG													
Adults	1	RCT	very serious[1]	NA	NA	serious[2]	None	60	60	Not applicable – see narrative summary	**COCP + met + AO higher**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Free testosterone													
Adults	1	RCT	very serious[1]	NA	NA	serious[2]	None	60	60	Not applicable – see narrative summary	**COCP + met + AO**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: FAI													
Adults	1	RCT	very serious[1]	NA	NA	serious[2]	None	60	60	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Triglycerides													
Adults	1	RCT	very serious[1]	NA	NA	serious[2]	None	60	60	Not applicable – see narrative summary	**COCP**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Cholesterol													
Adults	1	RCT	very serious[1]	NA	NA	serious[2]	None	60	60	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: LDL													
Adults	1	RCT	very serious[1]	NA	NA	serious[2]	None	60	60	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: HDL													
Adults	1	RCT	very serious[1]	NA	NA	serious[2]	None	60	60	Not applicable – see narrative summary	**Higher after COCP + met + AO**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Insulin													
Adults	1	RCT	very serious[1]	NA	NA	serious[2]	None	60	60	Not applicable – see narrative summary	**COCP + met + AO**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Glucose													
Adults	1	RCT	very serious[1]	NA	NA	serious[2]	None	60	60	Not applicable – see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: HOMA													
Adults	1	RCT	very serious[1]	NA	NA	serious[2]	None	60	60	Not applicable – see narrative summary	**COCP + met + AO**	⊕◯◯◯ VERY LOW	IMPORTANT

[1] Downgraded once due to high risk of bias
[2] Downgraded once for imprecision due to the evidence being derived from a single study

COMPARISON 20: Any COCP vs. metformin													
Population	No. studies	Quality assessment						No. participants		Effect, random [95% CI]	Favours	Certainty	Importance
		Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	COCP	MET				
Outcome: BMI													
Overall	18	RCT	serious[1]	very serious[3]	no serious indirectness	no serious imprecision	none	399	417	MD 0.66 kg/m^2 (-0.02; 1.34)	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Adults	15	RCT	serious[1]	very serious[3]	no serious indirectness	no serious imprecision	none	364	379	MD 0.64 kg/m^2 (-0.06; 1.34)	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Adolescents	3	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[10]	none	35	38	MD 1.45 kg/m^2 (-2.17; 5.08)	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Weight													
Overall	7	RCT	serious[1]	very serious[3]	no serious indirectness	serious[4]	none	179	188	MD 1.23 kg (-10.36; 12.81),	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Adults	5	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	131	140	MD – 2.62 kg -6.25; 1.02)	No difference	⊕⊕◯◯ LOW	CRITICAL
Adolescents	2	RCT	serious[1]	serious[2]	no serious indirectness	very serious[5]	None	48	48	MD 12.62 kg (-3.05; 28.29)	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: WHR													
Overall (Adults)	7	RCT	serious[1]	very serious[8]	no serious indirectness	no serious imprecision	none	115	117	MD 0.01 (-0.01; 0.03),	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Hirsutism													
Overall	6	RCT	serious[1]	very serious[3]	no serious indirectness	serious[12]	none	128	122	MD -0.75 (-2.85; 1.36)	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Adults	5	RCT	serious[1]	very serious[3]	no serious indirectness	serious[12]	none	118	116	MD -0.97 (-3.37; 1.43)	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Adolescents	1	RCT	serious[1]	NA	NA	very serious[5]	None	10	6	MD 0.40 (-2.62; 3.42)	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: FAI													
Overall	8	RCT	serious[1]	very serious[3]	no serious indirectness	no serious imprecision	Large effect[9]	151	144	MD -6.43 (-8.10; -4.77)	**COCP**	⊕⊕◯◯ LOW	IMPORTANT
Adults	7	RCT	serious[1]	very serious[3]	no serious indirectness	no serious imprecision	Large effect[9]	118	116	MD -6.33 (-8.04; -4.62)	**COCP**	⊕⊕◯◯ LOW	IMPORTANT
Adolescents	1	RCT	serious[1]	NA	NA	very serious[5]	None	10	6	MD 8.50 (-15.01; -1.99)	**COCP**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Total testosterone													
Overall	18	RCT	serious[1]	serious[2]	no serious indirectness	no serious imprecision	None	417	427	MD -0.40 nmol/L (-0.54; -0.27)	**COCP**	⊕⊕◯◯ LOW	IMPORTANT
Adults	15	RCT	serious[1]	serious[2]	no serious indirectness	no serious imprecision	None	349	361	MD -0.40 nmol/L (-0.56; -0.24)	**COCP**	⊕⊕◯◯ LOW	IMPORTANT
Adolescents	3	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	None	68	66	MD -0.49 nmol/L (-0.61; -0.37)	**COCP**	⊕⊕⊕◯ MODERATE	IMPORTANT
Outcome: Free testosterone													
Overall	5	RCT	very serious[11]	serious[2]	no serious indirectness	serious imprecision[4]	None	93	105	MD -3.21 pmol/L (-4.92; -1.50)	**COCP**	⊕◯◯◯ VERY LOW	IMPORTANT
Adults	3	RCT	very serious[11]	serious[2]	no serious indirectness	no serious imprecision	None	66	79	MD -3.38 pmol/L (-5.59; -1.16)	**COCP**	⊕◯◯◯ VERY LOW	IMPORTANT
Adolescents	2	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	None	27	26	MD -3.96 pmol/L -10.59; 2.68)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT

Outcome: SHBG												
Overall	9	RCT	serious[1]	very serious[3]	no serious indirectness	no serious imprecision	Large effect[10]	191	181	MD 118.98 nmol/L (51.08; 186.88)	**Metformin (COCP ↑)**	⊕⊕◯◯ LOW	IMPORTANT
Adults	8	RCT	serious[1]	very serious[3]	no serious indirectness	no serious imprecision	Large effect[10]	181	175	MD 124.75 nmol/L (52.22; 197.29)	**Metformin (COCP ↑)**	⊕⊕◯◯ LOW	IMPORTANT
Adolescents	1	RCT	serious[1]	NA	NA	very serious[5]	None	10	6	MD 72.10 nmol/L (30.34; 113.86)	**Metformin (COCP ↑)**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Androstenedione												
Overall (Adults)	4	RCT	serious[1]	serious[2]	no serious indirectness	no serious imprecision	None	56	53	MD -3.27 nmol/L (-5.06; -1.48)	**COCP**	⊕⊕◯◯ LOW	IMPORTANT
Outcome: DHEAS												
Overall (Adults)	7[13]	RCT	serious[1]	very serious[3]	no serious indirectness	no serious imprecision	None	161	172	MD -1.19 μmol/L (-2.19; -0.18)	**COCP**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Insulin												
Overall	14	RCT	serious[1]	serious[2]	no serious indirectness	no serious imprecision	None	203	214	MD 4.11 IU/L (2.56; 5.67)	**Metformin**	⊕⊕◯◯ LOW	IMPORTANT
Adults	10	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	None	216	227	MD 3.91 IU/L (2.98; 4.85)	**Metformin**	⊕⊕⊕◯ MODERATE	IMPORTANT
Adolescents	4	RCT	serious[1]	serious[2]	no serious indirectness	serious[4]	None	70	57	MD 1.29 IU/L (-7.53; 10.12)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Glucose												
Overall	10	RCT	serious[1]	serious[2]	no serious indirectness	no serious imprecision	None	212	220	MD 0.09 mmol/L (-0.13; 0.32)	No difference	⊕⊕◯◯ LOW	IMPORTANT
Adults	9	RCT	serious[1]	serious[2]	no serious indirectness	no serious imprecision	None	202	214	MD 0.11 mmol/L (-0.13; 0.35)	No difference	⊕⊕◯◯ LOW	IMPORTANT
Adolescents	1	RCT	serious[1]	NA	NA	very serious[5]	None	10	6	MD -0.11 mmol/L (-0.76; 10.54)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: HOMA												
Overall (Adults)	11	RCT	serious[1]	very serious[3]	no serious indirectness	no serious imprecision	None	315	325	MD 0.55 (0.06; 1.05)	metformin	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Cholesterol												
Overall	13	RCT	serious[1]	very serious[3]	no serious indirectness	no serious imprecision	None	283	289	MD 0.40 mmol/L (0.14; 0.66)	metformin	⊕◯◯◯ VERY LOW	IMPORTANT
Adults	11	RCT	serious[1]	serious[2]	no serious indirectness	no serious imprecision	None	258	267	MD 0.31 mmol/L (0.05; 0.57)	metformin	⊕⊕◯◯ LOW	IMPORTANT
Adolescents	2	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[10]	None	25	22	MD 1.12 mmol/L (0.57; 1.66)	metformin	⊕⊕◯◯ LOW	IMPORTANT
Outcome: LDL												
Overall	13	RCT	serious[1]	very serious[3]	no serious indirectness	no serious imprecision	None	283	315	MD -0.08 mmol/L (-0.37; 0.22)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Adults	11	RCT	serious[1]	very serious[3]	no serious indirectness	no serious imprecision	None	258	293	MD -0.20 mmol/L (-0.51; 0.10)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Adolescents	2	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[10]	None	25	22	MD 0.92 mmol/L (0.35; 1.49)	metformin	⊕⊕◯◯ LOW	IMPORTANT
Outcome: HDL												
Overall	13	RCT	serious[1]	very serious[3]	no serious indirectness	no serious imprecision	None	283	315	MD 0.02 mmol/L (-0.09; 0.14)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Adults	11	RCT	serious[1]	very serious[3]	no serious indirectness	no serious imprecision	None	258	293	MD -0.00 mmol/L (-0.12; 0.12)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT

Adolescents	2	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[10]	None	25	22	MD 0.22mmol/L (0.00; 0.43)	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Triglycerides													
Overall	13	RCT	serious[1]	very serious[3]	no serious indirectness	no serious imprecision	None	272	287	MD 0.15 mmol/L (0.01; 0.29)	Metformin	⊕◯◯◯ VERY LOW	IMPORTANT
Adults	10	RCT	serious[1]	very serious[3]	no serious indirectness	no serious imprecision	None	258	267	MD 0.16 mmol/L (-0.00; 0.33)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Adolescents	3	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[10]	None	35	34	MD 0.13 mmol/L (-0.14; 0.39)	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: CRP													
Overall	9	RCT	serious[1]	serious[2]	no serious indirectness	no serious imprecision	None	241	242	MD 1.25 mg/L (0.69; 1.80)	metformin	⊕⊕◯◯ LOW	IMPORTANT
Adults	8	RCT	serious[1]	serious[2]	no serious indirectness	no serious imprecision	None	231	236	MD 1.15 (0.64; 1.65)	metformin	⊕⊕◯◯ LOW	IMPORTANT
Adolescents	1	RCT	serious[1]	NA	NA	very serious[5]	None	10	6	MD 6.70 (1.84; 11.56)	metformin	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: PAI-1													
Overall (Adults)	2	RCT	serious[1]	serious[2]	no serious indirectness	very serious[7]	None	27	23	MD 1.05 (-22.54; 24.65)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Menstrual cycles													
Adults	1	RCT	serious[1]	NA	NA	serious[14]	Large effect[15]	64	60	MD -6.10 days (-9.8; -2.4)	COCP	⊕⊕◯◯ LOW	CRITICAL
Outcome: HR-QoL													
Adults	3	RCT	Very serious[16]	NA	serious	no serious imprecision	None	83	81	See individual study data	No difference overall, favours COCP regarding fascial hirsutism	⊕◯◯◯ VERY LOW	CRITICAL

[1] Downgraded once as the majority of evidence is at moderate or high risk of bias
[2] Downgraded once due to I^2 >50%
[3] Downgraded twice due to I^2 >50% and CI not overlapping
[4] Downgraded once due to wide CI
[5] Downgraded twice due to very few patients
[6] Downgraded once due to I^2 >50%, but CI not overlapping
[7] Downgraded twice due to few patients and wide CI
[8] Downgraded twice due to I^2 >50% and overlapping CI
[9] Upgraded once due to large difference, not close to 0
[10] Downgraded once due to few participants
[11] Downgraded twice due to high risk of bias
[12] Downgraded once, CIs not overlapping
[13] Two studies excluded due to reporting errors, see under 20.13 for more details
[14] Downgraded once, only one study in meta-analysis
[15] Upgraded once due to large effect supported by studies that could not be included in the meta-analysis
[16] Downgraded twice since majority of studies high risk of bias
[17] Downgraded once since measures with different tools, some of them not validated

COMPARISON 21: Any COCP vs. any COCP + metformin													
Population	No. studies	Quality assessment						No. participants		Effect, random [95% CI]	Favours	Certainty	Importance
		Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	COCP	COCP + MET				
Outcome: BMI													
Adults	13	RCT	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	268	262	MD -0.28 kg/m^2 (-1.10; 0.53)	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Weight													
Adults	6	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	125	124	MD -1.52 kg (-4.42; 1.38)	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: WHR													
Adults	5	RCT	serious[1]	serious[2]	no serious indirectness	no serious imprecision	None	143	141	MD 0.00 (-0.02; 0.02),	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Hirsutism													
Adults	3	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	71	86	MD 0.99 (-0.35; 2.32),	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: FAI													
Adults	5	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	None	157	158	MD 0.58 (0.36; 0.80).	COCP + met	⊕⊕⊕◯ MODERATE	IMPORTANT
Outcome: Total testosterone													
Adults	9	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	None	239	237	MD 0.07 nmol/L (-0.00; 0.15)	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
Outcome: Free testosterone													
Adults	5	RCT	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	None	93	91	MD 0.96 pmol/L (-0.39; 2.32)	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: SHBG													
Adults	7	RCT	serious[1]	serious[2]	no serious indirectness	no serious imprecision	None	177	175	MD -14.60 nmol/L (-25.75; -3.45)	COCP	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Androstendione													
Adults	6	RCT	serious[1]	very serious[4]	no serious indirectness	no serious imprecision	None	159	157	MD 1.45 nmol/L (0.37; 2.52)	COCP + met	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: DHEAS													
Adults	6	RCT	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	None	177	178	MD 0.86 μmol/L (0.37; 1.34)	COCP + met	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Insulin													
Adults	13	RCT	serious[1]	very serious[4]	no serious indirectness	no serious imprecision	None	319	314	MD 2.22 IU/L (0.80; 3.64)	COCP + met	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Glucose													
Adults	9	RCT	serious[1]	very serious[4]	no serious indirectness	no serious imprecision	None	244	239	MD 0.10 mmol/L (-0.11; 0.30),	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: HOMA													
Adults	9	RCT	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	None	231	227	MD 0.45 (0.17; 0.74)	COCP + met	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Cholesterol													
Adults	14	RCT	serious[1]	very serious[4]	no serious indirectness	no serious imprecision	None	306	294	MD 0.09 mmol/L (-0.08; 0.26)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: LDL													
Adults	14	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	None	350	348	MD 0.06 mmol/L (-0.05; 0.18)	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT

Outcome: HDL													
Adults	14	RCT	serious[1]	serious[2]	no serious indirectness	no serious imprecision	None	350	349	MD -0.07 mmol/L (-0.15; 0.02)	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Triglycerides													
Adults	13	RCT	serious[1]	very serious[4]	no serious indirectness	no serious imprecision	None	258	267	MD 0.29 mmol/L (-0.01; 0.59)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: CRP													
Adults	4	RCT	serious[1]	very serious[4]	no serious indirectness	no serious imprecision	None	74	68	MD -0.55 mg/L (-1.72; 0.62)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: PAI-1													
Adults	2	RCT	serious[1]	serious[2]	no serious indirectness	very serious[5]	None	27	21	MD 3.22 ng/ml (-4.88; 11.32)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: **Outcome**: HR-QoL													
Adults	1	RCT	serious[1]	NA	NA	very serious[5]	None	23	23	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	CRITICAL

[1.] Downgraded once as the majority of evidence is at moderate or high risk of bias
[2.] Downgraded once due to I2 >50%
[3.] Downgraded twice due to high risk of bias
[4.] Downgraded twice due to to I2 >50% and CI not overlapping
[5.] Downgraded twice due to very few patients

COMPARISON 22: Any COCP vs. anti-androgen													
		Quality assessment						**No. participants**					
	No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**COCP**	**AA**	**Effect, random [95% CI]**	**Favours**	**Certainty**	**Importance**
Outcome: **Outcome**: Hirsutism/ FG score													
Adults	1	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[1]	none	9	10	12 ± 3 versus 16 ± 3.2, p=0.009	**COCP**	⊕◯◯◯ VERY LOW	CRITICAL

[1] Downgraded once for risk of bias and twice for imprecision (very few patients and single study)

COMPARISON 23: Any COCP vs. any COCP + anti-androgen													
Population	No. studies	Quality assessment						No. participants		Effect, random [95% CI]	Favours	Certainty	Importance
		Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	COCP	Met				
Outcome: BMI													
Adults	5	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	94	93	MD 1.71 kg/m^2 (-0.33; -0.08)	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Weight													
Adults	3	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	61	65	MD 7.17 kg (-12.64; -1.70)	**COCP**	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Total testosterone													
Adults	2	RCT	serious[1]	serious[2]	no serious indirectness	serious[3]	none	42	36	MD -0.10 nmol/L (-0.79; 0.60)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Free testosterone													
Adults	2	RCT	very serious[4]	no serious inconsistency	no serious indirectness	very serious[5]	none	21	21	MD 0.66 pmol/L (-0.47; 1.80)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: SHBG													
Adults	2	RCT	very serious[4]	very serious[6]	no serious indirectness	very serious[5]	none	30	29	MD 38.37 nmol/L (-41.72; 118.45)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: DHEAS													
Adults	2	RCT	very serious[4]	no serious inconsistency	no serious indirectness	very serious[5]	none	21	21	MD -0.40 µmol/L (-1.52; 0.72)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Insulin													
Adults	2	RCT	very serious[4]	serious[2]	no serious indirectness	serious[3]	none	33	32	MD -1.04 mU/L (-5.94; 3.86)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Glucose													
Adults	2	RCT	very serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	37	37	MD 0.10 mmol/L (-0.15; 0.36)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: HOMA													
Adults	2	RCT	very serious[4]	serious[2]	no serious indirectness	serious[3]	none	33	32	MD -0.18 (-1.26; 0.90)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Cholesterol													
Adults	3	RCT	very serious[4]	very serious[6]	no serious indirectness	serious[3]	none	49	49	MD -0.06 mmol/L (-0.72; 0.60)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: LDL													
Adults	3	RCT	very serious[4]	very serious[6]	no serious indirectness	serious[3]	none	49	49	MD -0.07 mmol/L (-0.60; 0.46)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: HDL													
Adults	3	RCT	very serious[4]	serious[2]	no serious indirectness	serious[3]	none	49	49	MD 0.07 mmol/L (-0.18; 0.32)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Triglycerides													
Adults	2	RCT	very serious[4]	serious[2]	no serious indirectness	serious[3]	none	33	32	MD -0.03 mmol/L (-1.29; 1.22)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT

1. Downgraded once as the majority of evidence is at moderate or high risk of bias
2. Downgraded once due to I^2 >50%
3. Downgraded once due to few patients
4. Downgraded twice due to high risk of bias
5. Downgraded twice due to very few patients
6. Downgraded twice due to to I^2 >50% and CI not overlapping

COMPARISON 24: Any COCP vs. metformin + anti-androgen													
Population	No. studies	Quality assessment						No. participants		Effect, narrative summary	Favours	Certainty	Importance
		Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	COCP	COCP + met + AA				
Outcome: BMI													
Adolescents	1	RCT	serious[1]	NA	NA	very serious[1]	None	16	16	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Hirsutism													
Adolescents	1	RCT	serious[1]	NA	NA	very serious[1]	None	16	16	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: SHBG													
Adolescents	1	RCT	serious[1]	NA	NA	very serious[1]	None	16	16	Not applicable; see narrative summary	**COCP higher**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Testosterone													
Adolescents	1	RCT	serious[1]	NA	NA	very serious[1]	None	16	16	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Triglycerids													
Adolescents	1	RCT	serious[1]	NA	NA	very serious[1]	None	16	16	Not applicable; see narrative summary	**Met + AA**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: LDL													
Adolescents	1	RCT	serious[1]	NA	NA	very serious[1]	None	16	16	Not applicable; see narrative summary	**Met + AA**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: HDL													
Adolescents	1	RCT	serious[1]	NA	NA	very serious[1]	None	16	16	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT

[1] Downgraded once due to risk of bias and twice due to imprecision (very few patients and only one study)

COMPARISON 25: Any COCP + anti-androgen vs. metformin												
Population	No. studies	Quality assessment						No. participants		Effect Estimate	Favours	Certainty	Importance
		Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	COCP + AA	Met				
Outcome: BMI													
Adults	3	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	62	69	MD -0.08 kg/m^2 (-1.56; 1.40)	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: HDL													
Adults	2[a]	RCT	very serious[2]	very serious[3]	no serious indirectness	serious[4]	none	46	46	MD -0.11 mmol/L (-0.46; 0.42)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: WHR													
Adults	1	RCT	serious[1]	NA	NA	very serious[5]	None	33	36	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Hirsutism													
Adults	2	RCT	very serious[2]	no serious inconsistency	no serious indirectness	serious[4]	None	51	49	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: FAI													
Adults	1	RCT	serious[1]	NA	NA	very serious[5]	None	33	36	Not applicable; see narrative summary	**COCP + AA**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Total testosterone													
Adults	2	RCT	very serious[2]	no serious inconsistency	no serious indirectness	serious[4]	None	34	36	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Free testosterone													
Adults	2	RCT	very serious[2]	no serious inconsistency	no serious indirectness	very serious[5]	None	30	25	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: SHBG													
Adults	1	RCT	serious[1]	NA	NA	very serious[5]	None	33	36	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: DHEAS													
Adults	3	RCT	very serious[2]	no serious inconsistency	no serious indirectness	serious[4]	None	66	61	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Androstenedione													
Adults	1	RCT	very serious[2]	NA	NA	very serious[5]	None	18	13	Not applicable; see narrative summary	**COCP + AA**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Insulin													
Adults	2	RCT	very serious[2]	no serious inconsistency	no serious indirectness	serious[4]	None	44	48	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Glucose													
Adults	1	RCT	no serious risk of bias	NA	NA	very serious[5]	None	34	34	Not applicable; see narrative summary	**Metformin**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: HOMA													
Adults	2	RCT	very serious[2]	no serious inconsistency	no serious indirectness	serious[4]	None	45	48	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: HOMA													
Adults	2	RCT	very serious[2]	no serious inconsistency	no serious indirectness	serious[4]	None	45	48	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: OGTT													

Adults	1	RCT	serious[1]	NA	NA	very serious[5]	None	33	36	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Abnormal glucose tolerance													
Adults	1	RCT	very serious[2]	NA	NA	very serious[5]	None	18	13	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Menstrual cycles													
Adults	1	RCT	serious[1]	NA	NA	very serious[5]	None	33	36	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Cholesterol													
Adults	2	RCT	very serious[2]	no serious inconsistency	no serious indirectness	serious[4]	None	45	48	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: LDL													
Adults	2	RCT	very serious[2]	no serious inconsistency	no serious indirectness	serious[4]	None	45	48	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Triglycerides													
Adults	2	RCT	very serious[2]	no serious inconsistency	no serious indirectness	serious[4]	None	45	48	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Dyslipidemia													
Adults	1	RCT	very serious[2]	NA	NA	very serious[5]	None	18	13	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: CRP													
Adults	1	RCT	no serious	NA	NA	very serious[5]	None	34	34	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: PAI-1													
Adults	1	RCT	serious[1]	NA	NA	very serious[5]	None	16	23	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT

1. Downgraded once as the majority of evidence is at moderate or high risk of bias
2. Downgraded twice due to high risk of bias
3. Downgraded twice due to I^2 >50% and Cis not overlapping
4. Downgraded once due to few patients
5. Downgraded twice due to the evidence being derived from a single study with a small sample size

a. One additional study, not incl in the meta-analysis. Meyer 2007 reports the mean difference between COCP + AA vs. metformin, 0.01±0.3 vs. -0.1±0.3, p value not reported.

COMPARISON 26: Any COCP + anti-androgen vs. any COCP + anti-androgen + metformin													
Population	**No. studies**	**Quality assessment**						**No. participants**		**Effect, random [95% CI]**	**Favours**	**Certainty**	**Importance**
		Design	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**COCP + AA**	**COCP + AA + Met**				
Outcome: BMI (kg/m^2)													
Overall	2	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	35	38	MD 0.19 (-0.97; 1.35)	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Adults	1	RCT	serious[1]	NA	NA	very serious[3]	none	20	22	MD 0.70 (-0.71; 2.11)	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Adolescents	1	RCT	serious[1]	NA	NA	very serious[3]	none	15	16	MD -0.50 (-2.19; 1.19)	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: SHBG (µg/dl)													
Overall	2	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	35	38	MD -0.07 (-0.61; 0.46)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Adults	1	RCT	serious[1]	NA	NA	very serious[3]	none	20	22	MD -0.20 (-0.91; 0.51)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Adolescents	1	RCT	serious[1]	NA	NA	very serious[3]	none	15	16	MD 0.10 (-0.73; 0.93)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Total testosterone (nmol/L)													
Overall	2	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	35	38	MD 0.26 (-0.13 ; 0.64)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Adults	1	RCT	serious[1]	NA	NA	very serious[3]	none	20	22	MD 0.31 (-0.18; 0.80)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Adolescents	1	RCT	serious[1]	NA	NA	very serious[3]	none	15	16	MD 0.17 (-0.46; 0.80)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Androstenedione (nmol/L)													
Overall	2	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	35	38	MD 0.77 (0.49; 1.05)	**COCP + AA + met**	⊕◯◯◯ VERY LOW	IMPORTANT
Adults	1	RCT	serious[1]	NA	NA	very serious[3]	none	20	22	MD 0.73 (0.40; 1.06)	**COCP + AA + met**	⊕◯◯◯ VERY LOW	IMPORTANT
Adolescents	1	RCT	serious[1]	NA	NA	very serious[3]	none	15	16	MD 0.87 (0.34; 1.40)	**COCP + AA + met**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: DHEAS (µmol/L)													
Overall	2	RCT	serious[1]	very serious[4]	no serious indirectness	very serious[2]	none	35	38	MD -0.42 (-2.42; 1.62)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Adults	1	RCT	serious[1]	NA	NA	very serious[3]	none	20	22	MD 0.62 (0.37; 0.87)	**COCP + AA + met**	⊕◯◯◯ VERY LOW	IMPORTANT
Adolescents	1	RCT	serious[1]	NA	NA	very serious[3]	none	15	16	MD -1.46 (-1.75; -1.17)	**COCP + AA**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: LDL (mmol/L)													
Overall	2	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	35	38	MD 0.04 (-0.41; 0.49)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Adults	1	RCT	serious[1]	NA	NA	very serious[3]	none	20	22	MD 0.28 (-0.08; 0.64)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Adolescents	1	RCT	serious[1]	NA	NA	very serious[3]	none	15	16	MD -0.18 (-0.51; 0.15)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: HDL (mmol/L)													

Overall	2	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	35	38	MD 0.04 (-0.17; 0.25)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Adults	1	RCT	serious[1]	NA	NA	very serious[3]	none	20	22	MD 0.00 (-0.29; 0.29)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Adolescents	1	RCT	serious[1]	NA	NA	very serious[3]	none	15	16	MD 0.08 (-0.22; 0.38)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Triglycerides													
Overall	2	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	35	38	MD 0.01 (-0.16; 0.18)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Adults	1	RCT	serious[1]	NA	NA	very serious[3]	none	20	22	MD -0.04 (-0.26; 0.18)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Adolescents	1	RCT	serious[1]	NA	NA	very serious[3]	none	15	16	MD 0.09 (-0.19; 0.37)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT

1. Downgraded once due to serious risk of bias
2. Downgraded twice, only one study (subgroups combined) and few patients
3. Downgraded twice, only one study and very few patients
4. Downgraded twice, high I^2 and CIs do not overlap

COMPARISON 27: Any COCP + anti-androgen vs. any COCP + metformin												
Population	No. studies	Quality assessment						No. participants		Effect estimate	Favours	Certainty	Importance
		Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	COCP + AA	COCP + Met				
Outcome: BMI													
Adults	1	RCT	very serious[1]	NA	no serious indirectness	very serious[2]	none	12	12	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Free testosterone													
Adults	1	RCT	very serious[1]	NA	no serious indirectness	very serious[2]	none	12	12	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: DHEAS													
Adults	1	RCT	very serious[1]	NA	no serious indirectness	very serious[2]	none	12	12	Not applicable; see narrative summary	**COCP + met**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Insulin													
Adults	1	RCT	very serious[1]	NA	no serious indirectness	very serious[2]	none	12	12	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: HOMA													
Adults	1	RCT	very serious[1]	NA	no serious indirectness	very serious[2]	none	12	12	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Cholesterol													
Adults	1	RCT	very serious[1]	NA	no serious indirectness	very serious[2]	none	12	12	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: LDL													
Adults	1	RCT	very serious[1]	NA	no serious indirectness	very serious[2]	none	12	12	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: HDL													
Adults	1	RCT	very serious[1]	NA	no serious indirectness	very serious[2]	none	12	12	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Triglycerides													
Adults	1	RCT	very serious[1]	NA	no serious indirectness	very serious[2]	none	12	12	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT

[1]Downgraded twice due to high risk of bias.
[2]Downgraded twice for imprecision due to few patients and only one study.

COMPARISON 28: Any COCP vs. any COCP + anti-androgen + metformin													
Population	**No. studies**	**Quality assessment**						**No. participants**		**Effect estimate**	**Favours**	**Certainty**	**Importance**
		Design	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**COCP**	**COCP + AA + Met**				
Outcome: BMI													
Adults	1	RCT	serious[1]	NA	NA	very serious[2]	none	11	11	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Hirsutism													
Adults	1	RCT	serious[1]	NA	NA	very serious[2]	none	11	11	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: SHBG													
Adults	1	RCT	serious[1]	NA	NA	very serious[2]	none	11	11	Not applicable; see narrative summary	**Higher after COCP + AA + met**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Testosterone													
Adults	1	RCT	serious[1]	NA	NA	very serious[2]	none	11	11	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	MPORTANT
Outcome: Triglycerides													
Adults	1	RCT	serious[1]	NA	NA	very serious[2]	none	11	11	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: LDL													
Adults	1	RCT	serious[1]	NA	NA	very serious[2]	none	11	11	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: HDL													
Adults	1	RCT	serious[1]	NA	NA	very serious[2]	none	11	11	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: HDL													
Adults	1	RCT	serious[1]	NA	NA	very serious[2]	none	12	12	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT

[1] Downgraded once due to moderate risk of bias.
[2] Downgraded twice for imprecision due to few patients and only one study.

COMPARISON 29: Any COCP vs. SPIOMET													
Population	**No. studies**	**Quality assessment**						**No. participants**		**Effect estimate**	**Favours**	**Certainty**	**Importance**
		Design	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**COCP**	**SPIOMET**				
Outcome: BMI													
Adolescents	1	RCT	serious[1]	NA	no serious indirectness	very serious[1]	none	31	31	Not applicable; see narrative summary	**SPIOMET**	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Hirsutism													
Adolescents	1	RCT	serious	NA	no serious indirectness	very serious[1]	none	31	31	Not applicable; see narrative summary	**SPIOMET**	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: SHBG													
Adolescents	1	RCT	serious	NA	no serious indirectness	very serious[1]	none	31	31	Not applicable; see narrative summary	**Higher after COCP**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Testosterone													
Adolescents	1	RCT	serious	NA	no serious indirectness	very serious[1]	none	31	31	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Androstenedione													
Adolescents	1	RCT	serious	NA	no serious indirectness	very serious[1]	none	31	31	Not applicable; see narrative summary	**COCP**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Insulin													
Adolescents	1	RCT	serious	NA	no serious indirectness	very serious[1]	none	31	31	Not applicable; see narrative summary	**SPIOMET**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: HOMA-IR													
Adolescents	1	RCT	serious	NA	no serious indirectness	very serious[1]	none	31	31	Not applicable; see narrative summary	**SPIOMET**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: LDL													
Adolescents	1	RCT	serious	NA	serious	very serious[1]	none	31	31	Not applicable; see narrative summary	**SPIOMET**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: HDL													
Adolescents	1	RCT	serious	NA	serious	very serious[1]	none	31	31	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Triglycerides													
Adolescents	1	RCT	serious[1]	NA	serious	very serious[1]	None	31	31	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: CRP													
Adolescents	1	RCT	serious[1]	NA	serious	very serious[1]	None	31	31	Not applicable; see narrative summary	**SPIOMET**	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: FAI													
Adolescents	1	RCT	serious[1]	NA	serious	very serious[1]	None	29	29	Not applicable; see narrative summary	**COCP**	⊕◯◯◯ VERY LOW	IMPORTANT

[1]Downgraded once for risk of bias and twice for imprecision (few patients, only one study)

COMPARISON 30: Any COCP + spironolactone vs. any COCP + extra CPA													
Population	**No. studies**	**Quality assessment**						**No. participants**		**Effect estimate**	**Favours**	**Certainty**	**Importance**
		Design	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**COCP + spiro**	**COCP + extra CPA**				
Outcome: Hirsutism													
Adults	1	RCT	serious[1]	NA	NA	serious[2]	none	72	70	Not applicable; see narrative summary	COCP + spiro	⊕⊕◯◯ LOW	CRITICAL
Outcome: Free testosterone													
Adults	1	RCT	serious[1]	NA	NA	serious[2]	none	72	70	Not applicable; see narrative summary	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Total testosterone													
Adults	1	RCT	serious[1]	NA	NA	serious[2]	none	72	70	Not applicable; see narrative summary	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: DHEAS													
Adults	1	RCT	serious[1]	NA	NA	serious[2]	none	72	70	Not applicable; see narrative summary	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Androstenedione													
Adults	1	RCT	serious[1]	NA	NA	serious[2]	none	72	70	Not applicable; see narrative summary	No difference	⊕⊕◯◯ LOW	IMPORTANT

[1]Downgraded once for risk of bias

[2]Downgraded once for imprecision (only one study)

COMPARISON 32: Any COCP + Metformin + LS vs. EE/CPA + Metformin + LS													
Population	**No. studies**	**Quality assessment**						**No. participants**		**Effect estimate**	**Favours**	**Certainty**	**Importance**
		Design	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**COCP + met + LS**	**EE/CPA + met + LS**				
Outcome: BMI													
Adults	1	RCT	very serious[1]	NA	NA	very serious[1]	none	32	36	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: WHR													
Adults	1	RCT	very serious[1]	NA	NA	very serious[1]	none	32	36	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Hirsutism													
Adults	1	RCT	very serious[1]	NA	NA	very serious[1]	none	32	36	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Insulin													
Adults	1	RCT	very serious[1]	NA	NA	very serious[1]	none	32	36	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Glucose													
Adults	1	RCT	very serious[1]	NA	NA	very serious[1]	none	32	36	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: HOMA													
Adults	1	RCT	very serious[1]	NA	NA	very serious[1]	none	32	36	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: OGTT													
Adults	1	RCT	very serious[1]	NA	NA	very serious[1]	none	32	36	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Cholesterol													
Adults	1	RCT	very serious[1]	NA	NA	very serious[1]	none	32	36	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: LDL													
Adults	1	RCT	very serious[1]	NA	NA	very serious[1]	none	32	36	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: HDL													
Adults	1	RCT	very serious[1]	NA	NA	very serious[1]	none	32	36	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Triglycerides													
Adults	1	RCT	very serious[1]	NA	NA	very serious[1]	none	32	36	Not applicable; see narrative summary	No difference	⊕◯◯◯ VERY LOW	IMPORTANT

[1] Downgraded twice for high risk of bias and twice for imprecision (few patients, only one study)

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PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 4

Question 4.2. & 4.3.

Is the oral contraceptive pill alone or in combination effective for management of hormonal and clinical PCOS features in adolescents and adults with PCOS?

BACKGROUND:

Polycystic ovary syndrome (PCOS) is a common familial endocrine disorder associated with obesity and metabolic syndrome (1). Whilst the multicomponent healthy lifestyle interventions are the core of the management, combined oral contraceptive pills (COCPs) are also required to ameliorate the clinical symptoms such as irregular menstrual cycles and hyperandrogenism in adult women and adolescents with PCOS (2, 3). COCP are also required for some adolescents who present with one PCOS feature (irregular menstrual cycles or hyperandrogenism) soon after menarche and do not full fill the adolescent diagnostic criteria for PCOS. These adolescents are considered “at risk of PCOS” and require management of their symptoms (4).

The effects of COCPs on menstrual cycle, hirsutism, androgen levels, weight, lipid profile and blood glucose levels are variably reported and depend on type of COCP used, duration of use, severity of presentation/ phenotype and adherence to the regimen, among other factors.

Different combinations of COCPs are available with heterogeneous estrogen and progestin preparations and variable pharmacological and clinical properties. Thus, the efficacy and consequences of COCPs in PCOS may vary. There is inadequate evidence to suggest the optimal COCP formulation, or dosing regimen (3, 5).

Consideration of possible adverse effects must be made before prescribing any COCPs. Absolute contraindications for COCP use include women with history of migraine with aura, deep vein thrombosis (DVT)/ pulmonary emboli (PE), known thrombogenic mutations, multiple risk factors for arterial cardiovascular disease, history of ischemic heart disease or stroke, complicated valvular heart disease, breast cancer, neuropathy, severe cirrhosis and malignant liver tumours. Women up to 6 weeks postpartum with other risk factors for venous thromboembolism (VTE) (e.g. immobility, transfusion at delivery, BMI > 30 kg/m2, postpartum haemorrhage, immediately post-caesarean delivery, preeclampsia, smoking), are also considered at high risk (6).

In the appraisal of the comparisons between different progestogens, the following needs to be considered. Progestins are classified as first to fourth generation based on when they were first available, but different generations also have some different characteristics. Current evidence suggests that COCPs containing levonorgestrel, norethisterone and norgestimate (1st, 2nd and 3rd generation progestins) are associated with the lowest relative risk of DVT/PE of the COCP preparations available. The 4th generation includes anti-androgenic progestins like drospirenone and dienogest, but also preparations with natural estrogens instead of EE, thus increasing variation when results are pooled under “4th generation preparations” Recent evidence also suggests lower VTE risk for preparations with natural estrogens. Also, according to international recommendations COCPs with 35ug EE and cyproterone acetate (CPA) should not be used first line, due to higher risk for DVT. Thus, for contraception and other indications including irregular menstrual cycles, other preparations with lower risk profiles are recommended.

Metformin is an insulin sensitizer that is used to treat impaired glucose tolerance and PCOS symptoms in adolescents and women. As metformin is cheap and available it is commonly used to treat adolescents and women with PCOS. Metformin has mild side effects of nausea, vomiting, diarrhoea, flatulence and rarely in those with renal impairment of other illnesses can have serious adverse effects such as lactic acidosis. Metformin can be used alone or in combination with COCP for PCOS (7).

The evidence of anti-obesity medications in the management of adult women with PCOS is emerging and this to be considered in addition to COCP (8).

While considering the question of effectiveness of COCP in adolescents and adult women with PCOS, all evidence was evaluated for all comparisons available within different COCP and COCP in addition to other treatments including metformin, anti-obesity medications and antiandrogens. Eighty-four studies were evaluated, 20 published after 2017 and 13 including adolescents. The relevant prioritised clinical questions were also addressed in this section.

GRADE EVIDENCE CERTAINTY	
Comparison	**GRADE for critical outcomes**
○ Comparison 1: COCP with high vs. COCP with low levels of estrogen	⊕⊕○○ LOW
○ Comparison 2: COCP with 1st vs. COCP with 2nd generation progestin	No evidence
○ Comparison 3: COCP with 1st vs. COCP with 3rd generation progestin	⊕○○○ VERY LOW
○ Comparison 4: COCP with 1st vs. COCP with 4th generation progestin	⊕○○○ VERY LOW
○ Comparison 5: COCP with 2nd vs. COCP with 3rd generation progestins	⊕○○○ VERY LOW
○ Comparison 6: COCP with 2nd vs. COCP with 4th generation progestins	⊕○○○ VERY LOW
○ Comparison 7: COCP with 3rd vs. COCP with 4th generation progestins	⊕○○○ VERY LOW
○ Comparison 8: Any COCP vs. EE/CPA	⊕⊕○○ LOW
○ Comparison 9: Any COCP vs. progestin	⊕○○○ VERY LOW
○ Comparison 10: Any COCP vs. controls	⊕○○○ VERY LOW
○ Comparison 11: Any COCP vs. placebo	⊕○○○ VERY LOW
○ Comparison 12: Any COCP vs lifestyle	⊕○○○ VERY LOW
○ Comparison 13: Any COCP vs. lifestyle +/- anti-obesity treatment	⊕○○○

	VERY LOW
○ Comparison 14: Any COCP vs. combination of COCP and lifestyle with/without anti-obesity treatment	⊕○○○ VERY LOW
○ Comparison 15: lifestyle +/- anti-obesity treatment vs. combination of COCP and lifestyle +/- anti-obesity treatment	⊕○○○ VERY LOW
○ Comparison 16: Any COCP vs. anti-obesity	⊕○○○ VERY LOW
○ Comparison 17: Any COCP vs. COCP + anti-obesity	⊕○○○ VERY LOW
○ Comparison 18: Any COCP + metformin vs. COCP + anti-obesity	⊕○○○ VERY LOW
○ Comparison 19: Any COCP vs. COCP + metformin + anti-obesity	⊕○○○ VERY LOW
○ Comparison 20: Any COCP vs. metformin (also incl. in Q4.3)	⊕○○○ VERY LOW
○ Comparison 21: Any COCP vs. COCP + metformin	⊕⊕○○ LOW
○ Comparison 22: Any COCP vs. anti-androgen (also in Q4.6, but their time limit 6 m treatment)	⊕○○○ VERY LOW
○ Comparison 23: Any COCP vs. COCP + anti-androgen androgen (also in Q4.6, with time limit of 6m)	⊕⊕⊕○ MODERATE
○ Comparison 24: Any COCP vs. metformin + anti-androgen androgen (also in Q4.6, with time limit of 6m)	⊕○○○ VERY LOW
○ Comparison 25: Any COCP + anti-androgen vs. metformin androgen (also in Q4.6, with time limit of 6m)	⊕○○○ VERY LOW
○ Comparison 26: Any COCP + anti androgen vs. COCP + anti androgen + met androgen	⊕○○○ VERY LOW

○ Comparison 27: Any COCP + anti-androgen vs. COCP + metformin androgen	⊕○○○ VERY LOW
○ Comparison 28: Any COCP vs. COCP + metformin + anti-androgen androgen (also in Q4.6)	⊕○○○ VERY LOW
○ Comparison 29: Any COCP vs. SPIOMET (=metformin + anti-androgen + glucose sensitizer) (also in Q4.6)	⊕○○○ VERY LOW
○ Comparison 30: Any COCP + AA1 vs. COCP + AA2 (reported in Q4.6)	See Q.4.6.
○ Comparison 31: Metformin vs Any COCP + metformin (reported in Q4.3)	See Q.4.3
○ Comparison 32: Any COCP + met vs. EE/CPA + met	⊕○○○ VERY LOW

Evidence to Recommendations Framework

COMPARISONS (option versus other option)

Comparison excluded due to lack of evidence:
Comparison 2: COCP with 1st vs. COCP with 2nd generation progestin
Comparisons included:
o Comparison 1: COCP with high vs. COCP with low levels of estrogen
o Comparison 3: COCP with 1st vs. COCP with 3rd generation progestin
o Comparison 4: COCP with 1st vs. COCP with 4th generation progestin
o Comparison 5: COCP with 2nd vs. COCP with 3rd generation progestins
o Comparison 6: COCP with 2nd vs. COCP with 4th generation progestins
o Comparison 7: COCP with 3rd vs. COCP with 4th generation progestins
o Comparison 8: COCP vs. EE/CPA
o Comparison 9: COCP vs. progestin
o Comparison 10: COCP vs. controls
o Comparison 11: COCP vs. placebo
o Comparison 12: COCP vs lifestyle
o Comparison 13: COCP vs. lifestyle +/- anti-obesity treatment
o Comparison 14: COCP vs. combination of COCP and lifestyle with/without anti-obesity treatment
o Comparison 15: lifestyle +/- anti-obesity treatment vs. combination of COCP and lifestyle +/- antiobesity treatment
o Comparison 16: COCP vs. anti-obesity
o Comparison 17: COCP vs. COCP + anti-obesity
o Comparison 18: COCP + metformin vs. COCP + anti-obesity
o Comparison 19: COCP vs. COCP + metformin + anti-obesity
o Comparison 20: COCP vs. metformin (also incl. in Q4.3)
o Comparison 21: COCP vs. COCP + metformin
o Comparison 22: COCP vs. anti-androgen (also in Q4.6, but their time limit 6 m treatment)
o Comparison 23: COCP vs. COCP + antiandrogen androgen (also in Q4.6, with time limit of 6m)
o Comparison 24: COCP vs. metformin +anti-androgen androgen (also in Q4.6, with time limit of 6m)
o Comparison 25: COCP +anti-androgen vs.metformin androgen (also in Q4.6, with time limit of 6m)
o Comparison 26: COCP + anti androgen vs. COCP + anti androgen + metformin + androgen
o Comparison 27: COCP + anti-androgen vs. COCP + metformin androgen
o Comparison 28: COCP vs. COCP + metformin + anti-androgen androgen (also in Q4.6)
o Comparison 29: COCP vs. SPIOMET (=metformin + anti-androgen + glucose sensitizer) (also in Q4.6)
o Comparison 30: COCP + AA1 vs. COCP + AA2 (reported in Q4.6)
o Comparison 31: Metformin vs COCP + metformin (reported in Q4.3)
o Comparison 32: COCP + met vs. EE/CPA + met

EVIDENCE-BASED RECOMMENDATION(S)

- **EBR:** The COCP could be recommended in reproductive aged adults with PCOS for management of hirsutism and/or irregular menstrual cycles.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

- **EBR:** The COCP could be considered in adolescents at risk or with a clear diagnosis of PCOS for management of hirsutism and/or irregular menstrual cycles.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

- **EBR:** Health professionals could consider that there is no clinical advantage of using high dose ethinylestradiol (≥ 30 µg) versus low dose ethinylestradiol (< 30 µg) when treating hirsutism in adults with PCOS.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

- **EBR:** General population guidelines should be considered when prescribing COCP in adults and adolescents with PCOS as specific types or doses of progestins, estrogens or combinations of COCP cannot currently be recommended.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

- **EBR:** The 35 microgram ethinyl estradiol plus cyproterone acetate preparations should be considered as second-line therapy over other COCPs, balancing benfits and adverse effects, including venous thromboembolic risks.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

- **EBR:** Progestin only oral contraceptives may be considered for endometrial protection, based on general population guidelines, acknowledging that evidence in women with PCOS is limited.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

PRACTICE POINT(S)

When prescribing COCPs in adults and adolescents with PCOS, and adolescents at risk of PCOS:

● It is important to address main presenting symptoms and consider other treatments such as cosmetic therapies.

● Shared decision-making (including accurate information and reassurance on the efficacy and safety of COCP) is recommended and likely improve adherence

- Natural estradiol preparations and the lowest effective estrogen doses (such as 20-30 micrograms of ethinyl estradiol or equivalent), need consideration, balancing efficacy, metabolic risk profile, side effects, cost and availability.
- The relatively limited evidence on COCPs specifically in PCOS needs to be appreciated with practice informed by general population guidelines.

● the relative and absolute contraindications and side effects of COCPs need to be considered and be the subject of individualised discussion

● PCOS specific risk factors such as higher weight and cardiovascular risk factors, need to be considered

GRADE CONSIDERATIONS

Justifications:

Justification for Comparison 1: COCP with high vs. COCP with low levels of estrogen

Two low risk of bias RCTs over 12 months in 193 adult women compared COCPs high (30 µg [one study]-35µg [one study) vs. low (20µg) EE. COCPs with high EE (30µg) resulted in higher SHBG levels with low certainty and no significant difference in other outcomes including hirsutism. EE was combined with DRSP in the study that evaluated more outcomes (BMI, WHR, FAI, TT). Side effects were not reported in these studies. One study was published in 2020.

Justification on Comparison 2: COCP with 1st vs 2nd generation progestin

We are unable to provide a recommendation about effectiveness of COCP with 1st vs COCP with 2nd generation progestin due to no evidence being identified.

Justification on Comparison 3: COCP with 1st vs. COCP with 3rd generation progestin

We are unable to provide a recommendation about effectiveness of COCP with 1st vs COCP with 3rd generation progestin as the available data are inconclusive and with high risk of bias.
One RCT with a high risk of bias over 3 months in 40 women (16-35 years and mean age was not reported). The study had four arms. Relevant for this comparison, chlormadinone acetate (CMA), a 1st generation progestin was compared with two different 3rd generation progestins, desogestrel (DSG) and gestodene (GSD) and was favourable for TT, SHBG and androstenedione with very low certainty. Side effects were not reported in this study.

Justification for Comparison 4: COCP with 1st vs. COCP with 4th generation progestin

We are unable to provide a recommendation about effectiveness of COCP with 1st vs COCP with 4th generation progestin to treat PCOS symptoms as the available data come from high risk of bias studies and have very low certainty.
Four RCTs with a high risk of bias over 3-24 months in 283 adult women (one study has women who were 16-35 years old). DeLeo (9) had four arms. Relevant for this comparison, chlormadinone acetate (CMA), a 1st generation progestin was compared with the 4th generation progestins drospirenone (DRSP). Both Morgante (10), Podfigurna (11) and Yildizhan (12) used the same progestins in their RCTs (DRSP).
Results from the meta-analysis showed a greater decrease in androstenedione (very low certainty) and in DHEAS (low certainty) after treatment with the 4th generation progestin. There was no difference between treatments in SHBG and total testosterone levels. With very low certainty of evidence, cholesterol and CRP levels were lower after treatment with the 4th generation progestin, compared with the 1st generation. There were no differences in other outcomes, with very low certainty of evidence.
Side effects were not reported in these studies.

Justification for Comparison 5: COCP with 2nd vs. COCP with 3rd generation progestins

3rd or 2nd generation could be considered equally effective when treating clinical hyperandrogenism.
No data assessing menstrual cycle irregularities. No specific recommendation for this comparison and will be incorporated into general recommendation.

Two RCTs with a high risk of bias over 6 months in 176 adult women. Amiri 2020 (13) was a crossover study, involving four arms. Treatment was ongoing for 6 months, then a 6-8 week washout period was allowed before change of treatment to a COCP with a different progestin. Amiri 2021 (14) was a 6 months four arm trial comparing COCPs with four different progestins. The progestins relevant for this comparison were the 2nd generation levonorgestrel (LNG) vs. 3rd generation desogestrel (DSG) in both studies.
The crossover study showed a greater decrease in FAI, and a greater increase in SHBG, after treatment with the 3rd generation progestin, with a very low certainty of evidence. There was no difference between the groups for other outcomes, including hirsutism, with a very low certainty of evidence.
Side effects were not reported in these studies.

Justification for Comparison 6: COCP with 2nd vs. COCP with 4th generation progestins
4rd or 2nd generation could be considered equally effective when treating hirsutism.
No data assessing menstrual cycle irregularities.
Two RCTs with a high risk of bias over 6 months in 176 adult women. The progestins relevant for this comparison were the 2nd generation levonorgestrel (LNG) vs. 4th generation drospirenone (DRSP) in both studies.
Results from the crossover study showed a greater decrease in FAI, and a greater increase in SHBG, after treatment with the 4th generation progestin (very low certainty of evidence) and no difference for free testosterone and DHEAS (very low certainty of evidence).
Side effects were not reported in these studies.

Justification for Comparison 7: COCP with 3rd vs. COCP with 4th generation progestins
COCP with 4th generation vs 3rd generation progestins could be considered equally effective when treating hirsutism.
Five RCTs over 3-12 months in 403 adult women were identified. One study included women 16-35 years. 4 studies have a high risk of bias and one low risk of bias. The progestins used in these studies were the 3rd generations desogestrel (DSG) and gestodene (GSD), and the 4th generations drospirenone (DRSP) and dienogest (DNG).
Total testosterone levels, androstenedione and LDL were lower, and HDL higher, after treatment with a 4th generation progestin (very low certainty of evidence) compared to 3rd generation. These differences were not clinically significant. The meta-analysis showed no difference in other outcomes, including BMI, when 4th compared with 3rd generation progestins (very low certainty of evidence).
Side effects were reported in under 60 subjects. One major adverse event reported with 3rd generation one, a case of severe lower limb pain, where Doppler showed no sign of thrombosis, but the patient discontinued treatment. Other mild side effects reported included spotting (more cases in 4th) and mastalgia and bloating (more cases with 3rd generation).

Justification for Comparison 8: Any COCP vs. EE/CPA
COCP preparations with 35 ug EE and 2 mg CPA should not be considered first line over other COCP in PCOS due to potential adverse effects and contraindications as outlined in general population guidelines.

Ten RCTs over 3-12 months were identified comparing conventional COCPs and EE/CPA including 703 subjects. Six had a high risk of bias, one moderate and three low risk of bias. Two out of 10 studies involved adolescents (use NIH criteria) and were over 12 months, one with high risk of bias and one with low. 9 out of 10 had the combination of 35 ug EE and CPA 2 mg.
Hirsutism was improved with the combination EE/CPA (very low certainty) and only reported in 2 RCT.
The meta-analysis showed that the combination EE/CPA, compared with conventional COCPs, had a beneficial effect with lower BMI, lower total testosterone. EE/CPA treatment resulted in higher levels of LDL with a low certainty of evidence and higher cholesterol (very low certainty)). In the subgroup analysis, total testosterone levels were lower after EE/CPA treatment in adults (low certainty) but not in adolescents (very low certainty). For SHBG, there were no significant differences between treatments in the adult or the adolescent subgroups, with a very low certainty of evidence.
Adverse effects were not assessed systematically. No major adverse effects were reported. Side effects were not reported in adolescent trials. Individuals on EE/CPA reported spotting, nausea and headache; and individuals on COCP reported breast tenderness. This is taking into account only reports of 50 subjects.

Justification of Comparison 9: COCP vs. progestin only
We are unable to provide a recommendation about effectiveness of COCP vs progestin only as the available data comes from moderate to high risk of bias studies and have very low certainty.

Two RCTs over 4-6 months were identified (137 subjects). One in adolescents (Chung 2014 (15)- that used Rotterdam diagnostic criteria) with a moderate risk of bias, and one in adults (16) with a high risk of bias.

In the meta-analysis, there was no difference in BMI, WHR and total testosterone (very low certainty of evidence). The other outcomes, with results only from one study, showed lower FAI and higher SHBG levels after COCP treatment and lower insulin and triglyceride levels (very low certainty of evidence). No side effects were reported. Side effects were not reported in the studies.

Justification of Comparison 10: COCP vs. controls/placebo

COCP should be recommended in women and adolescents with PCOS for the management of hyperandrogenism and/or irregular menstrual cycles.

Three RCTs (including 301 subjects, one in adolescents) compared COCPs with controls and all had a high risk of bias. There was one study published after 2017.

No meta-analysis was available. All outcomes were reported in only one study. COCP was superior to controls regarding improvement in cycle regularity (low certainty of evidence). HRQoL overall after COCP treatment, as well as in a dermatologic HRQoL questionnaire and a hirsutism HRQoL questionnaire (very low certainty of evidence). Weight, testosterone, insulin levels were lower after COCP treatment, compared with controls (very low certainty of evidence). The control group had lower after load insulin levels after an OGTT, and also had lower levels of CRP and PAI-1 compared with the group treated with COCP (very low certainty of evidence). For all other outcomes, no difference was seen between groups (very low certainty of evidence).

COCP treatment was associated with more minor adverse effects than controls. Controls reported worsening of symptoms. Adolescents using COCP complain of weight gain.

Justification of Comparison 11: COCP vs. placebo

One 6-month RCT with a moderate risk of bias including 34 adolescents diagnosed by Rotterdam criteria (17). No studies involved adults. COCP treatment resulted in lower levels of testosterone, higher SHBG and lower FAI (very low certainty of evidence). The placebo group had lower CRP levels compared with the COCP treated group (very low certainty of evidence). Mild side effects reported.

Justification of Comparison 12: COCP vs lifestyle

We are unable to provide a recommendation about effectiveness of COCP vs lifestyle as the available data come from a moderate risk of bias study and have very low certainty.

One 6-month RCT with a moderate risk of bias including 34 adolescents diagnosed by Rotterdam criteria (17). No studies involving adults.

LDL and triglycerides were lower after lifestyle treatment compared with COCP (very low certainty of evidence). Total testosterone levels were lower after COCP treatment, compared with lifestyle (very low certainty). For other outcomes, no difference was seen, with very low certainty of evidence.

Mild side effects reported.

Justification of Comparison 13: COCP vs. lifestyle +/- anti-obesity treatment

We are unable to provide a recommendation about effectiveness of COCP vs lifestyle +/- anti-obesity treatment as the available data come from a moderate risk of bias study and have very low certainty.

One RCT over 16 weeks with moderate risk of bias in 132 adult women. Anti-obesity used was sibutramine and orlistat.

Lifestyle +/-anti-obesity resulted in lower weight compared with COCP alone (very low certainty of evidence). COCP had lower total testosterone and higher SHBG, compared with lifestyle alone (very low certainty of evidence). Triglycerides were higher after COCP treatment compared with lifestyle. OGTT was better after lifestyle +/-anti-obesity (very low certainty of evidence). No report of side effects.

Justification of Comparison 14: COCP vs. combination of COCP and lifestyle with/without anti-obesity treatment

We are unable to provide a recommendation about effectiveness of COCP vs COCP and lifestyle +/- anti-obesity treatment as the available data come from a moderate risk of bias study and have very low certainty.

One RCT over 16 weeks with moderate risk of bias in 132 adult women. Anti-obesity used was sibutramine and orlistat. Combination favours weight and 2-hour OGTT (very low certainty). No report of side effects.

Justification of Comparison 15: lifestyle +/- anti-obesity treatment vs. combination of COCP and lifestyle +/- antiobesity treatment

We are unable to provide a recommendation about effectiveness of lifestyle +/- anti-obesity treatment vs COCP and lifestyle +/- anti-obesity treatment as the available data come from a moderate risk of bias study and have very low certainty.

One RCT over 16 weeks with moderate risk of bias in 132 adult women. Anti-obesity used was sibutramine and orlistat. COCP and lifestyle +/-anti-obesity favours testosterone and increases SHBG (very low certainty). No report of side effects.

Justification of Comparison 16: COCP vs. anti-obesity

We are unable to provide a recommendation about effectiveness of COCP vs anti-obesity treatment as the available data come from a high risk of bias study and have very low certainty.

One RCT with a high risk of bias compared COCP with 35 µg EE + 2 mg CPA (n=14) vs. sibutramine 10 mg/day (n=12) for 6 months in 53 adult women.

Anti-obesity medication resulted in lower BMI, lower triglycerides and lower insulin levels, compared with COCP treatment (very low certainty). No report of side effects.

Justification of Comparison 17: COCP vs. COCP + anti-obesity

Three RCTs with high risk of bias in 346 adult women (some with a BMI over 30) over 3-6 months. Sabuncu 2003 (17) compared 35 µg EE + 2 mg CPA (n=14) vs. 35 µg EE + 2 mg CPA + sibutramine 10 mg/day (n= 14) for 6 months. Song 2017 (19) compared 35 µg EE + 2 mg CPA (n=60) vs. 35 µg EE + 2 mg CPA + Orlistat 120 mgx3 (n=60). Gu 2022 (20) studied DRSP 3 mg/EE 20 µg (n=33) vs. DRSP 3 mg/EE 20 µg + Orlistat 120 mg x 3 (n=33) for 3 months.

The meta-analysis showed lower DHEAS, FAI levels and HOMA-IR after treatment with the combination COCP + anti-obesity drugs (low certainty of evidence). For all other outcomes, there were no differences between treatments (low or very low certainty of evidence).

2 RCT did not report side effects. One RCT reported mild side effects with COCP with no DVT and mild GI side effects with anti-obesity agents.

Justification of Comparison 18: COCP + metformin vs. COCP + anti-obesity

We are unable to provide a recommendation about effectiveness of COCP + metformin vs COCP + anti-obesity treatment as the available data come from a high risk of bias study and have very low certainty.

One RCT with a high risk of bias in 240 adult women over 3 months. COCP containing EE/CPA were given to both groups. One group had orlistat 120 mgx3, and one group had metformin 1500 mg/day, in addition to the COCP treatment, n=60 in both groups.

Triglycerides and cholesterol levels were lower and HDL levels higher after treatment with COCP + anti-obesity, compared with COCP + metformin (very low certainty of evidence). For other outcomes, there were no certain differences between the groups (very low certainty of evidence).

Mild side effects with COCP with no DVT and mild GI side effects with anti-obesity and metformin.

Justification of Comparison 30: COCP + AA1 vs. COCP + AA2 (reported in Q4.6)

We are unable to provide a recommendation about effectiveness of COCP plus antiandrogen 1 vs COCP antiandrogen 2 as the available data come from 1 moderate risk of bias study and have low certainty.

One 12-month RCT was identified in 142 adult women with moderate risk of bias. Hagag 2014 compared COCP (35 µg EE + 250 µg NOR) + spironolactone 100 mg with COCP (35 µg EE + 2 mg CPA) + extra 10 mg CPA.

The combination of COCP + spironolactone resulted in a greater reduction of hirsutism compared with COCP + extra CPA (low certainty of evidence). Other reported outcomes (free and total testosterone, DHEAS, androstenedione) did not differ between treatments (low certainty of evidence).

Study did not report on side effects.

Subgroup considerations:

Adolescent data is variable across the comparisons.

BMI and ethnic subgroups need to be considered.

Implementation considerations:

Potential barriers to implementation of the recommendations relate to the availability of different COCP combinations and costs of the COCP to women and health systems.

Monitoring and evaluation considerations:

Metabolic risk in particular, in adult women and adolescents with high BMI and specific ethnicities

Assess risk for impaired glucose tolerance, diabetes, dyslipidemia recognizing that risks for these consequences are higher in individuals with high BMI or specific ethnic backgrounds.

Research priorities:
Large scale population-based studies are required to capture side effects and risks in individuals with PCOS.
Large scale comparative studies in particular in adolescents are required to determine the optimal COCP preparation in relation to progestins and doses.
Efficacy on acne, hair loss and psychological outcomes.
Adverse events including weight, metabolic effects and psychological outcomes.
Progestin only preparations (including intrauterine system, implant, pill etc.)

GRADE framework

GRADE DECIDE **Interactive Evidence to Decision Framework**

● DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Extensive review and discussion on multiple preparation combinations supported the GRADE justification.

● UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Side effects are not systematically reported but overall no major side effects were reported and very few subjects did withdrew treatment due to side effects even with combinations

COCP can cause mild side effects such as spotting and breast tenderness.

● CERTAINTY OF THE EVIDENCE

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☒ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Overall certainty of evidence is low to very low.

Panel discussion:

The certainty of evidence ranges from very low to moderate (menstrual cycles, BMI, hirsutism). However evidence for hirsutism is ranked moderate and this is the main recommendation. Other outcomes have very low evidence and influenced this rating.

● VALUES

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☐ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☒ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Research evidence:

No research evidence was identified

Panel discussion:

Value to both Health professionals and consumers are likely high.

● BALANCE OF EFFECTS

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:

Individual preferences need to be considered

● COSTS

How large are the resource requirements (costs)?

Judgement:

☒ Don't know	☐ Varies	☐ Large costs	☐ Moderate costs	☐ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:

No research evidence was identified

Panel discussion:

COCP costs vary according to preparations, countries and health care systems

COCP availability might be an issue in some countries

● CERTAINTY OF COST EVIDENCE

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

No research evidence was identified

Panel discussion:

There is no evidence to comment on certainty

● COST-EFFECTIVENESS

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

No research evidence was identified

Panel discussion:

There is no evidence on cost effectiveness on COCP for management of PCOS, the cost of COCP to women and healthcare systems is generally low.

● EQUITY

What would be the impact on health equity?

Judgement:

☐ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☒ Probably increased	☐ Increased

Research evidence:

No research evidence was identified

Panel discussion:

No preferred COCP preparation and general COCP availability and low cost will increase equity.

● ACCEPTABILITY

Is the option acceptable to key stakeholders?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Majority of the key stakeholders (health care system, Health professionals and consumers) will find the recommendations acceptable. However, there will be subgroups for various reasons who will find the recommendations less acceptable.

● FEASIBILITY

Is the option feasible to implement?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☐ Probably Yes	☒ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Despite the variability in acceptance, guidelines could help address the barriers to implementation to ensure patients who are eligible for the treatment will receive it.

Education of health care professionals is essential.

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PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by ECR Lead: Johanna Melin

Other team members: Maria Forslund, Simon Alesi

Supervised, edited and supported by the Evidence Team (Aya Mousa, Jillian Tay)

GDG 4

Question 4.4.

Is metformin alone or in combination, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?

1. SELECTION CRITERIA

Table 1. PICO Criteria for Inclusion

Question	Q 4.3) Is metformin alone or in combination, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?
Clinical leads (key contacts)	**Prof Poli Mara Spritzer** Endocrinologist Universidade Federal do Rio Grande do Sul, Brazil spritzer@ufrgs.br **Dr Daniela Romualdi** Obstetrician-gynaecologist Fondazione Policlinico Universitario Agostino Gemelli, Rome, Italy daniela.romualdi@policlinicogemelli.it **A/Prof Alexia Pena Vargas** Paediatric endocrinologist The Robinson Research Institute at the University of Adelaide, Australia alexia.pena@adelaide.edu.au **Prof Selma Witchel** Paediatric endocrinologist Children's Hospital of Pittsburgh of UPMC, University of Pittsburg, USA witchelsf@upmc.edu
Allocation ranking	Level 1- New systematic review

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(language, year)*
Inclusion	Females with PCOS (diagnosed by Rotterdam, NIH or AES) of any age, ethnicity and weight. Subgroups: adolescents (10-19y), adults, pregnancy, post-menopausal. BMI subgroups informed by the most frequent presentation of the data.	Metformin alone or in combination with lifestyle, OCP, anti-androgens, anti-obesity agents. Any dose, duration of more than 6 months for hirsutism and 3 months for all other outcomes.	Placebo or any other intervention (listed in intervention) or combinations of those listed in intervention.	**Androgenicity**: Hirsutism- FG score (ethnicities), FAI, SHBG, DHEAS, testosterone, androstenedione, Irregular cycles **Metabolic**: insulin resistance HOMA, Clamp, OGTT Lipids: Chol LDL, HDL TG, CRP **Psychological**: Qol, depression **Arthropometric**: weight BMI, WHR Thromboembolic events, PAI-1 Gastrointestinal effects Vit B12 deficiency Lactic acidosis	Evidence based guidelines, systematic reviews, randomised controlled trials	English language. **New search.** No time limit
Exclusion	Females without PCOS. Use of medications for DM2, high cholesterol, serious mental illness. Statin therapy.		Agent or combination used in the intervention		Non-evidence based guidelines, non-systematic reviews, any study lower than a RCT.	

2. SEARCH STRATEGY

Table 2.1. Search details	
Search strategy source: Technical report p 788-789	
Evidence source	**Date of search 2022-07-08** **Results:**
Medline (Ovid)	688
PsychInfo (Ovid)	3
EMBASE (Ovid)	370
All EBM (Ovid)	185
CINAHL	114
Any subsequent updates - enter database and date:	

Table 2.2. Questions addressed by this search *(add more rows as needed)*:		
GDG	Q#	Question
4	4.2	Is the oral contraceptive pill alone or in combination effective for management of hormonal and clinical PCOS features in adolescents and adults with PCOS?
4	4.3	Is metformin alone or in combination, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?
4	4.6	Are anti-androgen pharmacological agents alone or in combination, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?

Table 2.3. Search strings used in OVID or other database/s –
See page 3864-3865 under Q.4.6. on anti-androgens (the same search string was used for all three questions above)

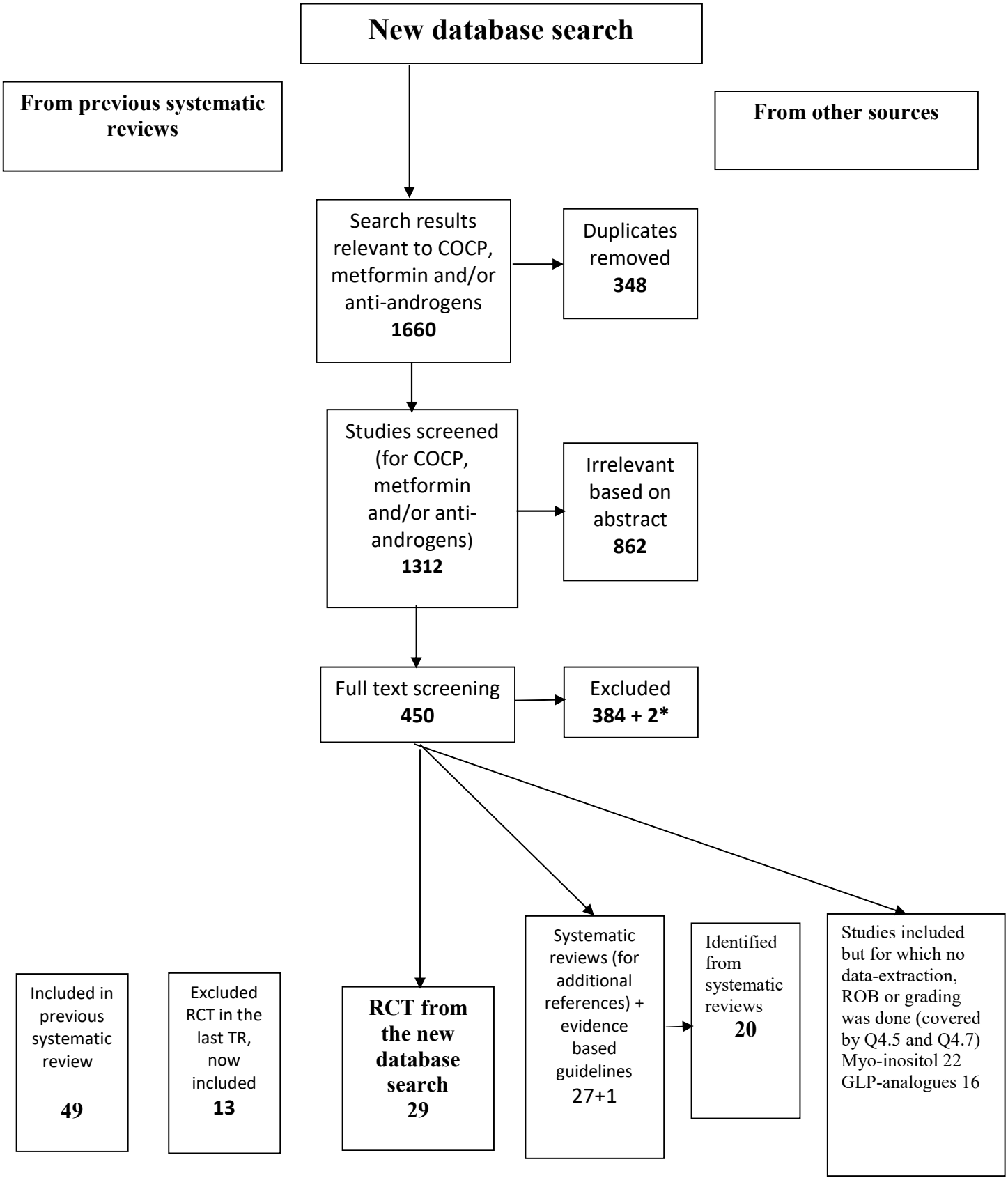
Evidence processing: Studies were selected and appraised by two reviewer/s using study selection and appraisal criteria (PICO above) established a priori. The articles were reviewed by title and abstract by two reviewers. When a decision could not be made based on title and abstract alone, full text was retrieved. Only studies that did not fit PICO for Q4.2, 4.3 or 4.6 were excluded. Full text screening was done by two reviewers. Conflicts were resolved by discussion and if needed, through contact with the evidence team/ key contacts. Included studies were double checked and approved by the clinical leads/ key contacts.

In addition to the studies included in previous guidelines, the excluded list from that search was reviewed, and studies were included if they met the current PICO.

Identified systematic reviews and evidence-based guidelines were screened manually for additional references.

In total, **111 RCTs met inclusion criteria for this review.**

3. SEARCH RESULTS - PRISMA flowchart



*Ferjan et al. 2017 and Paredes Palma et al. 2018

Altogether 49+13+29+20=111 included RCT

4. STUDY INCLUSION

Table 4.1. Included Studies

Metformin versus **placebo**:

1. Lingaiah, S.; Morin-Papunen, L.; Risteli, J.; Tapanainen, J. S.
   Metformin decreases bone turnover markers in polycystic ovary syndrome: a post hoc study
   Fertility and sterility 2019
2. Zahra, M.; Shah, M.; Ali, A.; Rahim, R.
   Effects of Metformin on Endocrine and Metabolic Parameters in Patients with Polycystic Ovary Syndrome
   Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme 2017
3. Heidari B, Lerman A, Lalia AZ, Lerman LO, Chang AY. Effect of metformin on microvascular endothelial function in polycystic ovary syndrome. *Mayo Clin Proc*. 2019
4. Bridger, T., MacDonald, S., Baltzer, F. and Rodd, C. 2006 Randomized placebo-controlled trial of metformin for adolescents with polycystic ovary syndrome.
   Archives of Pediatrics & Adolescent Medicine.
5. Chou, K.H., et al., Clinical, metabolic and endocrine parameters in response to metformin in obese women with polycystic ovary syndrome: a randomized, double blind and placebo-controlled trial. Hormone & Metabolic Research, 2003. 35(2): p. 86-91. (ROB included in last TR under Patel 2017)
6. Baillargeon, J.P, et al. Effects of metformin and rosiglitazone, alone and in combination in nonobese women with polycystic ovary syndrome and normal indices of insulin sensitivity. Fertility & Sterility, 2004 (ROB included in last TR under Patel 2017)
7. Eisenhardt, S., et al., Early effects of metformin in women with polycystic ovary syndrome: a prospective randomized, double-blind, placebo-controlled trial. Journal of Clinical Endocrinology & Metabolism, 2006. **91**(3): p. 946-52. (ROB included in last TR under Patel 2017)
8. Fleming, R., et al., Ovarian function and metabolic factors in women with oligomenorrhea treated with metformin in a randomized double blind placebo-controlled trial. Journal of Clinical Endocrinology & Metabolism, 2002. **87**(2): p. 569-74. (ROB included in last TR under Tang 2012)
9. Morin-Papunen, L., et al., Metformin improves pregnancy and live-birth rates in women with polycystic ovary syndrome (PCOS): a multicenter, double-blind, placebo controlled randomized trial. Journal of Clinical Endocrinology & Metabolism, 2012. **97**(5): p. 1492-500.
10. Hoeger, K., et al., The impact of metformin, oral contraceptives, and lifestyle modification on polycystic ovary syndrome in obese adolescent women in two randomized, placebo-controlled clinical trials. Journal of Clinical Endocrinology & Metabolism, 2008. 93(11): p. 4299-306. (ROB included in last TR under Patel 2017 (ROB own in TR)
11. Karimzadeh MA, Eftekhar M, Taheripanah R, Tayebi N, Sakhavat L, Zare F. The effect of administration of metformin on lipid profile changes and insulin resistance in patients with polycystic ovary syndrome. Middle East Fertil Soc J 2007 (ROB included in last TR under Tang 2012)
12. Kelly, C.J. and D. Gordon, The effect of metformin on hirsutism in polycystic ovary syndrome. European Journal of Endocrinology, 2002. **147**(2): p. 217-21. (ROB included in last TR under Patel 2017)
13. Lord, J., et al., The effect of metformin on fat distribution and the metabolic syndrome in women with polycystic ovary syndrome--a randomised, double-blind, placebo-controlled trial. BJOG: An International Journal of Obstetrics & Gynaecology, 2006. **113**(7): p. 817-24. (ROB included in last TR under Patel 2017)
14. Maciel, G.A., et al., Nonobese women with polycystic ovary syndrome respond better than obese women to treatment with metformin. Fertility & Sterility, 2004. **81**(2): p. 355-60. (ROB included in last TR under Patel 2017)
15. Onalan, G., et al., Predictive value of glucose-insulin ratio in PCOS and profile of women who will benefit from metformin therapy: obese, lean, hyper or normoinsulinemic? European Journal of Obstetrics, Gynecology, & Reproductive Biology, 2005. **123**(2): p. 204-11. (ROB included in last TR under Patel 2017)
16. Moghetti, P., et al. Metformin effects on clinical features, endocrine and metabolic profiles and insulin sensitivity in polycystic ovary syndrome: a randomized, double-blind, placebo-controlled 6 month trial, followed by open, long-term clinical evaluation. Journal of Clinical Endocrinology & Metabolism, 2000. 85(1):139-46. (ROB included in last TR under Patel 2017)
17. Palomba, S., et al., Insulin sensitivity after metformin suspension in normal-weight women with polycystic ovary syndrome. Journal of Clinical Endocrinology & Metabolism, 2007. **92**(8): p. 3128-35. (ROB included in last TR under Patel 2017)
18. Ng, E.H., N.M. Wat, and P.C. Ho, Effects of metformin on ovulation rate, hormonal and metabolic profiles in women with clomiphene-resistant polycystic ovaries: a randomized, double-blinded placebo-controlled trial. Human Reproduction, 2001. **16**(8): p. 1625-31. (ROB included in last TR under Tang 2012)
19. Romualdi, D., et al., Metformin effects on ovarian ultrasound appearance and steroidogenic function in normal-weight normoinsulinemic women with polycystic ovary syndrome: a randomized double-blind placebo-controlled clinical trial. Fertility & Sterility, 2010. **93**(7): p. 2303-10 (ROB included in last TR under Patel 2017)
20. Trolle, B., et al., Efficacy of metformin in obese and non-obese women with polycystic ovary syndrome: a randomized, double-blinded, placebo-controlled cross-overtrial. Human Reproduction, 2007. **22**(11): p. 2967-73. (ROB included in last TR under Patel 2017)
21. Trolle, B., et al., Adiponectin levels in women with polycystic ovary syndrome: impact of metformin treatment in a randomized controlled study. Fertility & Sterility, 2010. **94**(6): p. 2234-8. (ROB included in last TR under Patel 2017)

22. Haydardedeoglu, B., et al., Metabolic and endocrine effects of metformin and metformin plus cyclic medroxyprogesterone acetate in women with polycystic ovary syndrome. International Journal of Gynaecology & Obstetrics, 2009. **105**(1): p. 32-5.
23. Moro, F., et al., Effects of drospirenone-ethinylestradiol and/or metformin on CD4(+) CD28(null) T lymphocytes frequency in women with hyperinsulinemia having polycystic ovary syndrome: a randomized clinical trial. Reproductive Sciences, 2013. **20**(12): p. 1508-17.
24. Esfahanian, F., et al., Effect of metformin compared with hypocaloric diet on serum C-reactive protein level and insulin resistance in obese and overweight women with polycystic ovary syndrome. Journal of Obstetrics & Gynaecology Research, 2013. **39**(4): p. 806-13.
25. Fux Otta, C., et al., Clinical, metabolic, and endocrine parameters in response to metformin and lifestyle intervention in women with polycystic ovary syndrome: a randomized, double-blind, and placebo control trial. Gynecological Endocrinology, 2010. **26**(3): p. 173-8.
26. Harborne, L.R., et al., Metformin and weight loss in obese women with polycystic ovary syndrome: comparison of doses. Journal of Clinical Endocrinology & Metabolism, 2005. **90**(8): p. 4593-8.

Metformin versus **OCP** (versus **metformin+OCP):**

27. Altinok, Magda Lambaa; Ravn, Pernille; Andersen, Marianne; Glintborg, Dorte
Effect of 12-month treatment with metformin and/or oral contraceptives on health-related quality of life in polycystic ovary syndrome. Gynecological endocrinology 2018
28. Bodur, Serkan; Dundar, Ozgur; Kanat-Pektas, Mine; Kinci, Mehmet Ferdi; Tutuncu, Levent
The effects of different therapeutic modalities on cardiovascular risk factors in women with polycystic ovary syndrome: A randomized controlled study
Taiwanese journal of obstetrics & gynecology 2018
29. Fonseka, Sanjeewani; Wijeyaratne, Chandrika N.; Gawarammana, Indika B.; Kalupahana, Nishan S.; Rosairo, Shanthini; Ratnatunga, Neelakanthi; Kumarasiri, Ranjith
Effectiveness of Low-dose Ethinylestradiol/Cyproterone Acetate and Ethinylestradiol/Desogestrel with and without Metformin on Hirsutism in Polycystic Ovary Syndrome: A Randomized, Double-blind, Triple-dummy Study, Journal of Clinical & Aesthetic Dermatology 2020
30. Glintborg, D.; Mumm, H.; Holst, J. J.; Andersen, M.
Effect of oral contraceptives and/or metformin on GLP-1 secretion and reactive hypoglycaemia in polycystic ovary syndrome
Endocrine Connections 2017
31. Sahu, Asutosh; Tripathy, Priyadarshini; Mohanty, Jayashree; Nagy, Attila
Doppler analysis of ovarian stromal blood flow changes after treatment with metformin versus ethinyl estradiol-cyproterone acetate in women with polycystic ovarian syndrome: A randomized controlled trial
Journal of gynecology obstetrics and human reproduction 2019
32. Glintborg (1), D., Altinok, M. L., Mumm, H., Hermann, A. P., Ravn, P. and Andersen, M. 2014 Body composition is improved during 12 months' treatment with metformin alone or combined with oral contraceptives compared with treatment with oral contraceptives in polycystic ovary syndrome. Journal of Clinical Endocrinology & Metabolism.
33. Glintborg (2) D, Mumm H, Altinok ML, Richelsen B, Bruun JM, Andersen M. Adiponectin, interleukin-6, monocyte chemoattractant protein-1, and regional fat mass during 12-month randomized treatment with metformin and/or oral contraceptives in polycystic ovary syndrome. J Endocrinol Invest. 2014;37(8):757-64
34. Kaya, M. G., Yildirim, S., Calapkorur, B., Akpek, M., Unluhizarci, K. and Kelestimur, F. 2015 Metformin improves endothelial function and carotid intima media thickness in patients with PCOS. Gynecological Endocrinology 2015
35. Kaya, M. G.; Calapkorur, B.; Karaca, Z.; Yildirim, S.; Celik, A.; Akpek, M.; Unluhizarci, K.; Kelestimur, F.
The effects of treatment with drospirenone/ethinyl oestradiol alone or in combination with metformin on elastic properties of aorta in women with polycystic ovary syndrome
Clin Endocrinol (Oxf) Dec 2012;77(6):885-
36. Morin-Papunen (1), L., Rautio, K., Ruokonen, A., Hedberg, P., Puukka, M. and Tapanainen, J. S. 2003. Metformin reduces serum C-reactive protein levels in women with polycystic ovary syndrome. Journal of Clin Endocrinol & Metabolism Oct 2003:4649-54
37. Essah P. A., Arrowood J. A., Cheang K. I., Adawadkar S. S., Stovall D. W., and Nestler J. E., Effect of combined metformin and oral contraceptive therapy on metabolic factors and endothelial function in overweight and obese women with polycystic ovary syndrome. *Fertil. Steril 2011*
38. Feng W., Jia Y. Y., Zhang D. Y., and Shi H. R., Management of polycystic ovarian syndrome with Diane-35 or Diane-35 plus metformin, *Gynecol. Endocrinol*. 2016
39. Rautio K., Tapanainen J. S., Ruokonen A., and Morin-Papunen L. C., Effects of metformin and ethinyl estradiol-cyproterone acetate on lipid levels in obese and non-obese women with polycystic ovary syndrome., *Eur. J. Endocrinol 2005*

40. Al-Zubeidi H, Klein KO. Randomized clinical trial evaluating Metformin versus oral contraceptive pills in the treatment of adolescents with polycystic ovarian syndrome. Journal of Pediatric Endocrinology and Metabolism 2015 (ROB included in last TR under Al Khalifa 2016)

41. Christakou C, Kollias A, Piperi C, Katsikis I, Panidis D, Diamanti-Kandarakis E. The benefit-to-risk ratio of common treatments in PCOS: effect of oral contraceptives versus metformin on atherogenic markers. Hormones 2014
42. Aghamohammadzadeh N, Aliasgarzadeh A, Baglar L, Abdollahifard S, Bahrami A, Najafipour F, et al. Comparison of metformin and cyproterone-estrodiol compound effect on HS C-reactive protein and serum androgen levels in patients with polycystic ovary syndrome. Pakistan Journal of Medical Science 2010
43. El Maghraby HA, Nafee T, Guiziry D, Elnashar A. Randomized controlled trial of the effects of metformin versus combined oral contraceptives in adolescent PCOS women through a 24 months follow up period. Middle East Fertility Society Journal 2015 (ROB included in last TR under Al Khalifa 2016)
44. Elter K, Imir G, Durmusoglu F. Clinical, endocrine and metabolic effects of metformin added to ethinyl-estradiol-cyproterone acetate in non-obese women with polycystic ovarian syndrome: a randomized controlled study. Human Reproduction 2002 (ROB included in last TR under Costello 2007)
45. Harborne L, Fleming R, Lyall H, Sattar N, Norman J. Metformin or antiandrogen in the treatment of hirsutism in polycystic ovary syndrome. Journal of Clinical Endocrinology & Metabolism 2003 (ROB included in last TR under Costello 2007)
46. Bilgir O, Kebapcilar L, Taner C, Bilgir F, Kebapcilar A, Bozkaya G, et al. The effect of ethinylestradiol (EE)/cyproterone acetate (CA) and EE/CA plus metformin treatment on adhesion molecules in cases with polycystic ovary syndrome (PCOS). International Medicine 2009
47. Kilic S, Yilmaz N, Zulfikaroglu E, Erdogan G, Aydin M, Batioglu S. Inflammatory-metabolic parameters in obese and nonobese normoandrogenemic polycystic ovary syndrome during metformin and oral contraceptive treatment. Gynecological Endocrinology 2011
48. Kumar Y, Kotwal N, Singh Y, Upreti V, Somani S, Hari Kumar KV. A randomized, controlled trial comparing the metformin, oral contraceptive pills and their combination in patients with polycystic ovarian syndrome. Journal of Family Medicine and Primary Care 2018
49. Lv L, Liu Y, Sun Y, Tan K. Effects of Metformin combined with cyproterone acetate on clinical features, endocrine and metabolism of non-obese women with polycystic ovarian syndrome. Journal of Huazhong University of Science and Technology 2005
50. Meyer C, McGrath BP, Teede HJ. Effect of medical therapy on insulin resistance and the cardiovascular system in polycystic ovary syndrome. Diabetes Care 2007
51. Mhao NS, Al-Hilli SA, Hadi NR, Jamil DA, Al-Aubaidy HA. A comparative study to illustrate the benefits of using ethinyl estradiol-cyproterone acetate over metformin in patients with polycystic ovarian syndrome. Diabetes and Metabolic Syndrome: Clinical Research and Reviews 2015
52. Moran LJ, Meyer C, Hutchison SK, Zoungas S, Teede HJ. Novel inflammatory markers in overweight women with or without polycystic ovary syndrome and following pharmacological intervention. Journal of Endocrinological Investigation 2010
53. Morin-Papunen (2) L, Vauhkonen I, Koivunen R, Ruokonen A, Martikainen H, Tapanainen JS. Metformin versus ethinyl estradiol-cyproterone acetate in the treatment of nonobese women with polycystic ovary syndrome: a randomized study. The Journal of Clinical Endocrinology & Metabolism 2003 (ROB included in last TR under Costello 2007)
54. Ozgurtas T, Oktenli C, Dede M, Tapan S, Kenar L, Sanisoglu SY, et al. Metformin and oral contraceptive treatment reduced circulating asymmetric dimethylarginine (ADMA) levels in patients with polycystic ovary syndrome (PCOS). Atherosclerosis 2008 2003
55. Wu J, Zhu Y, Jiang Y, Cao Y. Effects of metformin and ethinyl estradiol-cyproterone acetate on clinical, endocrine and metabolic factors in women with polycystic ovary syndrome. Gynecological Endocrinology 2008
56. Morin-Papunen L, Vauhkonen I, Koivunen RM, Ruokonen A, Martikainen HK, Tapanainen J. Endocrine and metabolic effects of metformin versus ethinyl estradiol-cyproterone acetate in obese women with polycystic ovary syndrome: a randomized study. J Clin Endocrinol Metab 2000 (ROB included in last TR under Costello 2007)
57. Panidis D, Georgopoulos NA, Piouka A, Katsikis I, Saltamavros AD, Decavalas G, Diamanti-Kandarakis E. The impact of oral contraceptives and metformin on antiMullerian hormone serum levels in women with polycystic ovary syndrome and biochemical hyperandrogenemia. Gynecol Endocrinol 2011
58. Hutchison, S. K.; Harrison, C.; Stepto, N.; Meyer, C.; Teede, H. J.
Retinol-binding protein 4 and insulin resistance in polycystic ovary syndrome
Diabetes Care Jul 2008;31(7):1427-32
59. Kebapcilar, Levent; Yuksel, Arif; Bozkaya, Giray; Taner, Cuneyt Eftal; Kebapcilar, Ayse Gul; Bilgir, Oktay; Alacacioglu, Ahmet; Sari, Ismail
Effects of an EE/CA compared with EE/CA-metformin on serum ADMA levels in women with polycystic ovary syndrome
Central European journal of medicine 2009;4(4):423-427.
60. Luque-Ramírez, M.; Mendieta-Azcona, C.; Alvarez-Blasco, F.; Escobar-Morreale, H. F.
Effects of metformin versus ethinyl-estradiol plus cyproterone acetate on ambulatory blood pressure monitoring and carotid intima media thickness in women with the polycystic ovary syndrome
Fertil Steril Jun 2009;91(6):2527-36

61. Mehrabian, F., et al., Comparison of the effects of metformin, flutamide plus oral contraceptives, and simvastatinj on the metabolic consequences of polycystic ovary syndrome. Journal of Research in Medical Sciences, 2016. **21**(1): p. 1-7.

62. Cibula D, Fanta M, Vrbikova J, Stanicka S, Dvorakova K, hill M, et al. The effect of combination therapy with metformin and ovar contraceptives (COC) versus COC alone on insulin sensitivity, hyperandrogenism, SHBG and lipids in PCOS patients. Human reproduction (Oxford, England). 2005;20(1):180-4. (ROB included in last TR under Costello 2007)
63. Wei, W.; Zhao, H.; Wang, A.; Sui, M.; Liang, K.; Deng, H.; Ma, Y.; Zhang, Y.; Zhang, H.; Guan, Y.
A clinical study on the short-term effect of berberine in comparison to metformin on the metabolic characteristics of women with polycystic ovary syndrome Eur J Endocrinol Jan 2012;166(1):99-105.
64. Dardzinska, J.A., et al., Effects of metformin or an oral contraceptive containing cyproterone acetate on serum c-reactive protein, interleukin-6 and soluble vascular cell adhesion molecule-1 concentrations in women with polycystic ovary syndrome. Experimental & Clinical Endocrinology & Diabetes, 2014. **122**(2): p. 118-25.
65. Hoeger, K.M., et al., A randomized, 48-week, placebo-controlled trial of intensive lifestyle modification and/or metformin therapy in overweight women with polycystic ovary syndrome: a pilot study. Fertility & Sterility, 2004. **82**(2): p. 421-9
66. Allen, H.F., et al., Randomized controlled trial evaluating response to metformin versus standard therapy in the treatment of adolescents with polycystic ovary syndrome. Journal of Pediatric Endocrinology & Metabolism, 2005. **18**(8): p. 761-8.

Metformin versus **lifestyle:**
67. Elbandrawy, A. M.; Yousef, A. M.; Morgan, E. N.; Ewais, N. F.; Eid, M. M.; Elkholi, S. M.; Abdelbasset, W.K.
Effect of aerobic exercise on inflammatory markers in polycystic ovary syndrome: a randomized controlled trial
European review for medical and pharmacological sciences 2022

Metformin+lifestyle versus **lifestyle+placebo:**
68. Tiwari, Nisha; Pasrija, Shikha; Jain, Sandhya
Randomised controlled trial to study the efficacy of exercise with and without metformin on women with polycystic ovary syndrome
European Journal of Obstetrics & Gynecology & Reproductive Biology 2019
69. Tang T, Glanville J, Hayden CJ, et al. Combined lifestyle modification and metformin in obese patients with polycystic ovary syndrome. A randomized, placebo-controlled, double-blind multicentre study. Human Reproduc. 2006 ROB included in last TR)
70. Ladson, W.C. Dodson, S.D. Sweet, A.E. Archibong, A.R. Kunselman, L.M. Demers, N.I. Williams, P. Coney, R.S. Legro, The effects of metformin with lifestyle therapy in polycystic ovary syndrome: A randomized double-blind study. Fertil. Steril. 2011 (ROB included in last TR)
71. Pasquali R, Gambineri A, Biscotti D et al. Effect of long-term treatment with metformin added to hypocaloric diet on body composition, fat distribution and androgen and insulin levels in abdominally obese women with and without the polycystic ovary syndrome. The journal of clin endocrinol & metabolism. 2000. (ROB included in last TR)

OCP+anti-androgen versus **metformin:**
72. Alpanes, Macarena; Alvarez-Blasco, Francisco; Fernandez-Duran, Elena; Luque-Ramirez, Manuel; Escobar-Morreale, Hector F.
Combined oral contraceptives plus spironolactone compared with metformin in women with polycystic ovary syndrome: a one-year randomized clinical trial
European journal of endocrinology 2017
73. Ibáñez L, de Zegher F. Ethinylestradiol-drospirenone, flutamide-metformin, or both for adolescents and women with hyperinsulinemic hyperandrogenism: opposite effects on adipocytokines and body adiposity. The Journal of clinical endocrinology and metabolism. 2004;89(4):1592-7.
74. Ibáñez L, de Zegher F. Flutamide-metformin plus ethinylestradiol-drospirenone for lipolysis and antiatherogenesis in young women with ovarian hyperandrogenism: the key role of metformin at the start and after more than one year of therapy. The Journal of clinical endocrinology and metabolism. 2005;90(1):39-43.

OCP versus **OCP+anti-androgen** versus **MET**:
75. Burchall, Genia F.; Piva, Terrence J.; Ranasinha, Sanjeeva; Teede, Helena J.
Differential Effects on Haemostatic Markers by Metformin and the Contraceptive Pill: A Randomized Comparative Trial in PCOS
Thrombosis and haemostasis 2017
76. Kebapcilar, L., Taner, C. E., Kebapcilar, A. G., Alacacioglu, A. and Sari, I. 2010 Comparison of four different treatment regimens on coagulation parameters, hormonal and metabolic changes in women with polycystic ovary syndrome. Archives of Gynecology & Obstetrics. (excluded from previous report – randomization not described)

OCP versus **SPIOMET:**
77. de Zegher, Francis; Diaz, Marta; Villarroya, Joan; Cairo, Montserrat; Lopez-Bermejo, Abel; Villarroya, Francesc; Ibanez, Lourdes
The relative deficit of GDF15 in adolescent girls with PCOS can be changed into an abundance that reduces liver fat, Scientific reports 2021
78. Ibáñez, Lourdes; Díaz, Marta; García-Beltrán, Cristina; Malpique, Rita; Garde, Edurne; López-Bermejo, Abel; Zegher, Francis de
Toward a Treatment Normalizing Ovulation Rate in Adolescent Girls With Polycystic Ovary Syndrome

Journal of the Endocrine Society 2020
79. Díaz, Marta; Gallego-Escuredo, José Miguel; López-Bermejo, Abel; de Zegher, Francis; Villarroya, Francesc; Ibáñez, Lourdes
Low-Dose Spironolactone-Pioglitazone-Metformin Normalizes Circulating Fetuin-A Concentrations in Adolescent Girls with Polycystic Ovary Syndrome, International Journal of Endocrinology 2018 (all the results and outcomes are included in Ibanez et al. 2020->no ROB)
80. Ibáñez, Lourdes; del Río, Luis; Díaz, Marta; Sebastiani, Giorgia; Pozo, Óscar J.; López-Bermejo, Abel; de Zegher, Francis
Normalizing Ovulation Rate by Preferential Reduction of Hepato-Visceral Fat in Adolescent Girls With Polycystic Ovary Syndrome
Journal of adolescent health 2017 (all the results and outcomes are included in Ibanez et al 2020 ->no ROB)
81. Malpique, R.; Sanchez-Infantes, D.; Garcia-Beltran, C.; Taxeras, S. D.; Lopez-Bermejo, A.; de Zegher, F.; Ibanez, L.
Towards a circulating marker of hepato-visceral fat excess: S100A4 in adolescent girls with polycystic ovary syndrome - Evidence from randomized clinical trials
Pediatric obesity 2019 (all the results and outcomes are included in Ibanez et al. 2020 and de Zeger et al 20212020 ->no ROB)

OCP+hair removal versus **MET+hair removal:**
82. Dorgham, Nevine; Sharobim, Amin; Haggag, Hisham; El-Kalioby, Mona; Dorgham, Dina
Adding Combined Oral Contraceptives or Metformin to Laser Treatment in Polycystic Ovarian Syndrome Hirsute Patients
Journal of drugs in dermatology: JDD 2021

OCP versus **OCP+anti-obesity** versus **OCP+MET** versus **OCP+anti-obesity+MET**
83. Ruan, Xiangyan; Song, Jinghua; Gu, Muqing; Wang, Lijuan; Wang, Husheng; Mueck, Alfred O.
Effect of Diane-35, alone or in combination with orlistat or metformin in Chinese polycystic ovary syndrome patients
Archives of Gynecology & Obstetrics 2018
84. Song, Jinghua; Ruan, Xiangyan; Gu, Muqing; Wang, Lijuan; Wang, Husheng; Mueck, Alfred Otto
Effect of orlistat or metformin in overweight and obese polycystic ovary syndrome patients with insulin resistance
Gynecological endocrinology: the official journal of the International Society of Gynecological Endocrinology 2018

MET versus **anti-androgen** versus **MET+anti-androgen:**
85. Long, Tao; Zhang, Ying; Zeng, Chunping; Zheng, Siyuan; Zhou, Lin; Liu, Haiyan
Effects of Low-Dose Spironolactone Combined with Metformin or Either Drug Alone on Insulin Resistance in Patients with Polycystic Ovary Syndrome: A Pilot Study
International Journal of Endocrinology 2022
86. Gambineri, A., Pelusi, C., Genghini, S., Morselli-Labate, A. M., Cacciari, M., Pagotto, U. and Pasquali, R. 2004 Effect of flutamide and metformin administered alone or in combination in dieting obese women with polycystic ovary syndrome. Clinical Endocrinology 2004.
87. Amiri, M., et al., Effect of metformin and flutamide on anthropometric indices and laboratory tests in obese/overweight PCOS women under hypocaloric diet. Journal of Reproduction and Infertility, 2014. **15**(4): p. 205-13.
88. Gambineri, A., et al., Treatment with flutamide, metformin, and their combination added to a hypocaloric diet in overweight-obese women with polycystic ovary syndrome: a randomized, 12-month, placebo-controlled study. Journal of Clinical Endocrinology & Metabolism, 2006. **91**(10): p. 3970-80.
89. Ganie, M.A., et al., Comparison of efficacy of spironolactone with metformin in the management of polycystic ovary syndrome: an open-labeled study. The Journal of clinical endocrinology and metabolism, 2004. **89**(6): p. 2756-62.
90. Ganie, M.A., et al., Improved efficacy of low-dose spironolactone and metformin combination than either drug alone in the management of women with polycystic ovary syndrome (PCOS): a six-month, open-label randomized study. Journal of Clinical Endocrinology & Metabolism, 2013. **98**(9): p. 3599-607.
91. Mazza, A., et al., In PCOS patients the addition of low-dose spironolactone induces a more marked reduction of clinical and biochemical hyperandrogenism than metformin alone. Nutrition Metabolism & Cardiovascular Diseases, 2014. **24**(2): p. 132-9.
92. Diri, H.; Bayram, F.; Simsek, Y.; Caliskan, Z.; Kocer, D.
Comparison of Finasteride, Metformin, and Finasteride Plus Metformin in Pcos
Acta Endocrinol (Buchar) Jan-Mar 2017;13(1):84-89

Metformin+myo-inositol versus **myoinositol**:
93. Prabhakar, Priyanka; Mahey, Reeta; Gupta, Monica; Khadgawat, Rajesh; Kachhawa, Garima; Sharma, Jai Bhagwan; Vanamail, Perumal; Kumari, Rajesh; Bhatla, Neerja
Impact of myoinositol with metformin and myoinositol alone in infertile PCOS women undergoing ovulation induction cycles - randomized controlled trial
Gynecological endocrinology: the official journal of the International Society of Gynecological Endocrinology 2021

Metformin+liraglutide versus **liraglutide**:
94. Jensterle M, Kravos N, Goricar K, Janez J.

Short-term effectiveness of low dose liraglutide in combination with metformin versus high dose liraglutide alone in treatment of obese PCOS : randomized trial. BMC Endocrine Disorders 17:5, 2017.

Metformin versus **anti-diabetic (cangliflozasin, dapagliflozin, exenatide, saxagliptin, liraglutide, empagliflozin, rosiglitazone)**:

95. Cai, Meili; Shao, Xiaowen; Xing, Feng; Zhang, Yuqin; Gao, Xinyu; Zeng, Qiongjing; Dilimulati, Diliqingna; Qu, Shen; Zhang, Manna
Efficacy of canagliflozin versus metformin in women with polycystic ovary syndrome: A randomized, open-label, noninferiority trial. Diabetes, obesity & metabolism 2022
96. Elkind-Hirsch, Karen E.; Paterson, Martha S.; Seidemann, Ericka L.; Gutowski, Hanh C.
Short-term therapy with combination dipeptidyl peptidase-4 inhibitor saxagliptin/metformin extended release (XR) is superior to saxagliptin or metformin XR monotherapy in prediabetic women with polycystic ovary syndrome: a single-blind, randomized, pilot study, Fertility & Sterility 2017
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Comparing the individual effects of metformin and rosiglitazone and their combination in obese women with polycystic ovary syndrome: a randomized controlled trial
Fertility and sterility 2020
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Effect of metformin on adiponectin in PCOS: A meta-analysis and a systematic review
European Journal of Obstetrics & Gynecology & Reproductive Biology 2021
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Metformin does not improve insulin sensitivity over hypocaloric diets in women with polycystic ovary syndrome: a systematic review of 12 studies
Gynecological endocrinology: 2021
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Metformin versus the combined oral contraceptive pill for hirsutism, acne, and menstrual pattern in polycystic ovary syndrome,
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The Effect of Metformin on Polycystic Ovary Syndrome in Overweight Women: A Systematic Review and Meta-Analysis of Randomized Controlled Trials
International Journal of Endocrinology 2020
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Effects of placebo-controlled insulin-sensitizing drugs on hormonal parameters in polycystic ovary syndrome patients: A network meta-analysis, Journal of cellular biochemistry 2018
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Efficacy of Treatments for Polycystic Ovarian Syndrome Management in Adolescents
Journal of the Endocrine Society 2021
121. Kim, Chan Hee; Chon, Seung Joo; Lee, Seon Heui
Effects of lifestyle modification in polycystic ovary syndrome compared to metformin only or metformin addition: A systematic review and meta-analysis
Scientific reports 2020
122. Khatlani, Khaula; Njike, Valentine; Costales, Victoria C.
Effect of Lifestyle Intervention on Cardiometabolic Risk Factors in Overweight and Obese Women with Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis
Metabolic syndrome and related disorders 2019
123. Liu, Y.; Li, J.; Yan, Z.; Liu, D.; Ma, J.; Tong, N.
Improvement of Insulin Sensitivity Increases Pregnancy Rate in Infertile PCOS Women: A Systemic Review
Frontiers in endocrinology 2021
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The effect of metformin on homocysteine levels in patients with polycystic ovary syndrome: A systematic review and meta-analysis
Journal of Obstetrics & Gynaecology Research 2021
125. Luque-Ramírez, Manuel; Nattero-Chávez, Lía; Ortiz Flores, Andrés E.; Escobar-Morreale, Héctor F.
Combined oral contraceptives and/or antiandrogens versus insulin sensitizers for polycystic ovary syndrome: a systematic review and meta-analysis
Human reproduction update 2018
126. Patel, Roshni; Shah, Gaurang
Effect of metformin on clinical, metabolic and endocrine outcomes in women with polycystic ovary syndrome: a meta-analysis of randomized controlled trials
Current Medical Research & Opinion 2017
127. Sharpe, Abigail; Morley, Lara C.; Tang, Thomas; Norman, Robert J.; Balen, Adam H.
Metformin for ovulation induction (excluding gonadotrophins) in women with polycystic ovary syndrome
The Cochrane database of systematic reviews 2019

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Oral Metformin for Treating Dermatological Diseases: A Systematic Review
Journal of drugs in dermatology: JDD 2020

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Effect of the combined oral contraceptive pill and/or metformin in the management of polycystic ovary syndrome: A systematic review with meta-analyses
Clinical endocrinology 2019
130. Wang, Anran; Mo, Tingting; Li, Qiao; Shen, Chuangpeng; Liu, Min
The effectiveness of metformin, oral contraceptives, and lifestyle modification in improving the metabolism of overweight women with polycystic ovary syndrome: a network meta-analysis
Endocrine 2019
131. Wang, F. F.; Wu, Y.; Zhu, Y. H.; Ding, T.; Batterham, R. L.; Qu, F.; Hardiman, P. J.
Pharmacologic therapy to induce weight loss in women who have obesity/overweight with polycystic ovary syndrome: a systematic review and network meta-analysis
Obesity reviews: an official journal of the International Association for the Study of Obesity 2018
132. Weng, Shuwei; Luo, Yonghong; Zhang, Ziyu; Su, Xin; Peng, Daoquan
Effects of metformin on blood lipid profiles in nondiabetic adults: a meta-analysis of randomized controlled trials
Endocrine 2020
133. Xing, Chuan; Li, Chunzhu; He, Bing
Insulin Sensitizers for Improving the Endocrine and Metabolic Profile in Overweight Women With PCOS
The Journal of clinical endocrinology and metabolism 2020
134. Xu, Yifeng; Wu, Yanxiang; Huang, Qin
Comparison of the effect between pioglitazone and metformin in treating patients with PCOS:a meta-analysis
Archives of Gynecology & Obstetrics 2017
135. Yujie, Shang; Huifang, Zhou; Minghui, Hu; Hua, Feng; Shang, Yujie; Zhou, Huifang; Hu, Minghui; Feng, Hua
Effect of Diet on Insulin Resistance in Polycystic Ovary Syndrome
Journal of Clinical Endocrinology & Metabolism 2020
136. Zhao, Han; Xing, Chuan; Zhang, Jiaqi; He, Bing
Comparative efficacy of oral insulin sensitizers metformin, thiazolidinediones, inositol, and berberine in improving endocrine and metabolic profiles in women with PCOS: a network meta-analysis
Reproductive health 2021
137. Morley, Lara C.; Tang, Thomas; Yasmin, Ephia; Norman, Robert J.; Balen, Adam H.
Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility
The Cochrane database of systematic reviews 2017

Added from the last report:

138. Tang, T., J. M. Lord, et al.
Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility.
Cochrane Database of Systematic Reviews 2012
139. Costello M, Shrestha B, Eden J, Sjoblom P, Johnson N.
Insulin-sensitising drugs versus the combined oral contraceptive pill for hirsutism, acne and risk of diabetes, cardiovascular disease, and endometrial cancer in polycystic ovary syndrome.
Cochrane Database Syst Rev. 2007
140. Patel, R. and G. Shah, Effect of metformin on clinical, metabolic and endocrine outcomes in women with polycystic ovary syndrome: a meta-analysis of randomized controlled trials. Curr Med Res Opin, 2017. **33**(9): p. 1545-1557.

Evidence-based guidelines:

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Adolescent polycystic ovary syndrome according to the international evidence-based guideline
BMC medicine 2020

Studies on myo-inositol (included, but not for data extraction or analysis as covered by Q4.7):

1. Comparison of myo-inositol and metformin on clinical, metabolic and genetic parameters in polycystic ovary syndrome: a randomized controlled clinical trial
Jamilian, M.; Farhat, P.; Foroozanfard, F.; Afshar Ebrahimi, F.; Aghadavod, E.; Bahmani, F.; Badehnoosh, B.; Jamilian, H.; Asemi, Z.
Clinical endocrinology 2017
2. The effects of myo-inositol vs. metformin on the ovarian function in the polycystic ovary syndrome: a systematic review and meta-analysis
Azizi Kutenaei, M.; Hosseini Teshnizi, S.; Ghaemmaghami, P.; Eini, F.; Roozbeh, N.

European review for medical and pharmacological sciences 2021

3. Short-term effects of metformin and myo-inositol in women with polycystic ovarian syndrome (PCOS): a meta-analysis of randomized clinical trials
   Facchinetti, Fabio; Orru, Beatrice; Grandi, Giovanni; Unfer, Vittorio
   Gynecological endocrinology: the official journal of the International Society of Gynecological Endocrinology 2019
4. Myoinositol versus metformin pretreatment in GnRH-antagonist cycle for women with PCOS undergoing IVF: a double-blinded randomized controlled study
   Rajasekaran, Keerthana; Malhotra, Neena; Mahey, Reeta; Khadgawat, Rajesh; Kalaivani, Mani
   Gynecological endocrinology: the official journal of the International Society of Gynecological Endocrinology 2022
5. Metformin vs myoinositol: which is better in obese polycystic ovary syndrome patients? A randomized controlled crossover study
   Tagliaferri, Valeria; Romualdi, Daniela; Immediata, Valentina; De Cicco, Simona; Di Florio, Christian; Lanzone, Antonio; Guido, Maurizio
   Clinical endocrinology 2017
6. Comparision of myo-inositol versus metformin on anthropometric parameters in polycystic ovarian syndrome in women
   Nehra, J.; Kaushal, J.; Singhal, S. R.; Ghalaut, V. S.
   International Journal of Pharmacy and Pharmaceutical Sciences 2017
7. Effect of myoinositol versus metformin on biochemical profile in polycystic ovarian syndrome in women
   Nehra, J.; Kaushal, J.; Singhal, S. R.; Ghalaut, V.
   British journal of clinical pharmacology 2019
8. Comparison of myo-inositol and metformin on glycemic control, lipid profiles, and gene expression related to insulin and lipid metabolism in women with polycystic ovary syndrome: a randomized controlled clinical trial
   Shokrpour, M.; Foroozanfard, F.; Afshar Ebrahimi, F.; Vahedpoor, Z.; Aghadavod, E.; Ghaderi, A.; Asemi, Z.
   Gynecological Endocrinology 2019
9. Comparison of Effect of Metformin Versus Combination of Folic Acid/Myo-inositol in Infertile Women with Poly Cystic Ovary Syndrome Undergoing in Vitro Fertilization: A Randomized Clinical Trial
   Rastegar, F.; Rezaee, Z.; Saedi, N.; Memari, R.; Tajpour, M.
   Biomedical Research and Therapy 2021
10. The effect of myoinositol and metformin on cardiovascular risk factors in women with polycystic ovary syndrome: a randomized controlled trial
    Soldat-Stankovic, V.; Pejicic, S. P.; Stankovic, S.; Jovanic, J.; Bjekic-Macut, J.; Livadas, S.; Ognjanovic, S.; Mastorakos, G.; Micic, D.; Macut, D.
    Acta endocrinologica 2021
11. Comparison of two insulin sensitizers, metformin and myo-inositol, in women with polycystic ovary syndrome (PCOS)
    Fruzzetti, F.; Perini, D.; Russo, M.; Bucci, F.; Gadducci, A.
    Gynecological Endocrinology 2017
12. The effect of metformin and myoinositol on metabolic outcomes in women with polycystic ovary syndrome: role of body mass and adiponectin in a randomized controlled trial
    Soldat-Stankovic, V.; Popovic-Pejicic, S.; Stankovic, S.; Prtina, A.; Malesevic, G.; Bjekic-Macut, J.; Livadas, S.; Ognjanovic, S.; Mastorakos, G.; Micic, D.; Macut, D.
    Journal of endocrinological investigation 2022
13. A comparative study of myo inositol versus metformin on biochemical profile in polycystic ovarian syndrome in women
    Nehra, J.; Kaushal, J.; Singhal, S. R.; Ghalaut, V. S.
    International Journal of Pharmaceutical Sciences and Research 2017
14. Comparison of myo-inositol and metformin on mental health parameters and biomarkers of oxidative stress in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial
    Jamilian, Hamidreza; Jamilian, Mehri; Foroozanfard, Fatemeh; Afshar Ebrahimi, Faraneh; Bahmani, Fereshteh; Asemi, Zatollah
    Journal of Psychosomatic Obstetrics & Gynecology 2018
15. Changes of Serum Level of Homocysteine and Oxidative Stress Markers by Metformin and Inositol in Infertile Women with Polycystic Ovary Syndrome: a Double Blind Randomized Clinical Trial Study
    Janati, S.; Behmanesh, M. A.; Najafzadehvarzi, H.; Kassani, A.; Athari, N.; Poormoosavi, S. M.
    International Journal of Fertility and Sterility 2022
16. A comparative study of metabolic and hormonal effects of myoinositol vs. metformin in women with polycystic ovary syndrome: a randomised controlled trial
    Riju Angik, Shubhada S. Jajoo, C. Hariharan, Amogh Chimote
    Int J of Reproduction, Contraception, obstetrics and Gynecol. 2015
17. A randomised clinical trial comparing myoinositol and metformin in PCOS
    Kishan Chirania, Sujata Misra, Sandhya Behera
    Int J of Reproduction, Contraception, Obstetrics and Gynecol. 2017

18. Study on the Effect of Berberine, Myoinositol, and Metformin in Women with Polycystic Ovary Syndrome: A Prospective Randomised Study
    Neha Mishra , Ruchi Verma , Payal Jadaun
    Cureus 2022
19. A Combined Treatment with Myo-Inositol and Monacolin K Improve the Androgen and Lipid Profiles of Insulin-Resistant PCOS Patients
    Vincenzo De Leo, Maria Concetta Musacchio, Valentina Cappelli, Alessandra Di Sabatino, Claudia Tosti and Paola Piomboni
    Journal of Metabolic Syndrome 2013
20. Comparison of Clinical, Metabolic and Hormonal Effects of Metformin Versus Combined Therapy of Metformin With Myoinositol Plus D-Chiro-Inositol in Women With Polycystic Ovary Syndrome (PCOS): A Randomized Controlled Trial
    Anupama Bahadur , Hitanshi Arora , Anoosha K Ravi , Manisha Naithani , Yogesh Bahurupi , Jaya Chaturvedi , Megha Ajmani , Rajlaxmi Mundhra
    Cureus 2021
21. Comparison of metformin plus myoinositol vs metformin alone in PCOS women undergoing ovulation induction cycles: randomized controlled trial
    Anisha Agrawal , Reeta Mahey , Garima Kachhawa , Rajesh Khadgawat , Perumal Vanamail , Alka Kriplani
    Gynecol Endocrinol. 2019
22. Effect of Insulin Sensitizers on Raised Serum Anti-mullerian Hormone Levels in Infertile Women with Polycystic Ovarian Syndrome
    Neeti Chhabra , Sonia Malik
    Hum Reprod Sci. 2018

Studies on GLP-analogues (included, but not for data extraction or analysis as covered in Q4.5):

1. Elkind-Hirsch, Karen E.; Chappell, N.; Seidemann, Ericka; Storment, John; Bellanger, Drake
   Exenatide, Dapagliflozin, or Phentermine/Topiramate Differentially Affect Metabolic Profiles in Polycystic Ovary Syndrome
   Journal of Clinical Endocrinology & Metabolism 2021
2. Jensterle, Mojca; Kravos, Nika Aleksandra; Goričar, Katja; Janez, Andrej
   Short-term effectiveness of low dose liraglutide in combination with metformin versus high dose liraglutide alone in treatment of obese PCOS: randomized trial
   BMC endocrine disorders 2017
3. Liu, Xin; Zhang, Ying; Zheng, Si-Yuan; Lin, Rong; Xie, Yi-Juan; Chen, Hui; Zheng, Yong-Xiong; Liu, En; Chen, Lin; Yan, Jia-He; Xu, Wei; Mai, Ting-Ting; Gong, Yi
   Efficacy of exenatide on weight loss, metabolic parameters and pregnancy in overweight/obese polycystic ovary syndrome
   Clinical endocrinology 2017
4. Ma, Rui-Lin; Deng, Yan; Wang, Yan-Fang; Zhu, Shi-Yang; Ding, Xue-Song; Sun, Ai-Jun
   Short-term combined treatment with exenatide and metformin for overweight/obese women with polycystic ovary syndrome
   Chinese medical journal 2021
5. Salamun, Vesna; Jensterle, Mojca; Janez, Andrej; Vrtacnik Bokal, Eda
   Liraglutide increases IVF pregnancy rates in obese PCOS women with poor response to first-line reproductive treatments: a pilot randomized study
   European journal of endocrinology 2018
6. Tao, Tao; Zhang, Yi; Zhu, Yu-Chen; Fu, Jia-Rong; Wang, Yu-Ying; Cai, Jie; Ma, Jing-Yu; Xu, Yu; Gao, Yi-Ning; Sun, Yun; Fan, WuQiang; Liu, Wei
   Exenatide, Metformin, or Both for Prediabetes in PCOS: A Randomized, Open-label, Parallel-group Controlled Study
   The Journal of clinical endocrinology and metabolism 2021
7. Zheng, Siyuan; Liu, En; Zhang, Ying; Long, Tao; Liu, Xin; Gong, Yi; Mai, Tingting; Shen, Huanling; Chen, Hui; Lin, Rong; Zheng, Yongxiong; Xie, Yijuan; Wang, Fang
   Circulating zinc-alpha2-glycoprotein is reduced in women with polycystic ovary syndrome, but can be increased by exenatide or metformin treatment
   Endocrine journal 2019
8. Zheng, S.; Zhang, Y.; Long, T.; Lu, J.; Liu, X.; Yan, J.; Chen, L.; Gong, Y.; Wang, F.
   Short term monotherapy with exenatide is superior to metformin in weight loss, improving insulin resistance and inflammation in Chinese overweight/obese PCOS women
   Obesity Medicine 2017
9. Han, Yi; Li, Yingjie; He, Bing
   GLP-1 receptor agonists versus metformin in PCOS: a systematic review and meta-analysis
   Reproductive biomedicine online 2019
10. Ge, J. J.; Wang, D. J.; Song, W.; Shen, S. M.; Ge, W. H.
    The effectiveness and safety of liraglutide in treating overweight/obese patients with polycystic ovary syndrome: a meta-analysis
    Journal of endocrinological investigation 2022

11. Lyu, Xiaorui; Lyu, Taibiao; Wang, Xue; Zhu, Huijuan; Pan, Hui; Wang, Linjie; Yang, Hongbo; Gong, Fengying
The Antiobesity Effect of GLP-1 Receptor Agonists Alone or in Combination with Metformin in Overweight /Obese Women with Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis
International Journal of Endocrinology 2021
12. Panda, S. R.; Jain, M.; Jain, S.; Saxena, R.; Hota, S.
Effect of Orlistat Versus Metformin in Various Aspects of Polycystic Ovarian Syndrome: A Systematic Review of Randomized Control Trials
Journal of Obstetrics and Gynecology of India 2018
13. Mojca Jensterle Sever, Tomaz Kocjan, Marija Pfeifer, Nika Aleksandra Kravos, Andrej Janez .Short-term combined treatment with liraglutide and metformin leads to significant weight loss in obese women with polycystic ovary syndrome and previous poor response to metformin Eur J Endocrinol 2014
14. Mojca Jensterle , Nika Aleksandra Kravos , Marija Pfeifer , Tomaz Kocjan , Andrej Janez · A 12-week treatment with the long-acting glucagon-like peptide 1 receptor agonist liraglutide leads to significant weight loss in a subset of obese women with newly diagnosed polycystic ovary syndrome Hormones (Athens) 2015
15. Mojca Jensterle , Vesna Salamun , Tomaz Kocjan , Eda Vrtacnik Bokal , Andrej Janez · Short term monotherapy with GLP-1 receptor agonist liraglutide or PDE 4 inhibitor roflumilast is superior to metformin in weight loss in obese PCOS women: a pilot randomized study. J Ovarian Res 2015
16. Pratap Kumar , Shweta Arora. Orlistat in polycystic ovarian syndrome reduces weight with improvement in lipid profile and pregnancy rates. Human reproduction Sci. 2014

Excluded studies (during data extraction)

1. Ferjan, Simona; Janez, Andrej; Jensterle, Mojca
Dipeptidyl Peptidase-4 Inhibitor Sitagliptin Prevented Weight Regain in Obese Women with Polycystic Ovary Syndrome Previously Treated with Liraglutide: A Pilot Randomized Study
Metabolic syndrome and related disorders 2017 Excluded due to pretreatment with liraglutide
2. Paredes Palma, J. C.; Lopez Byhen, E.; Ibanez, L.; Balladares Macedo, L.; Paredes Palma, C.; Ramirez Velazquez, C.
Comparative treatment between sitagliptin vs. metformin, alone or in combination, in patients with polycystic ovary syndrome. A clinical entity at high risk for developing diabetes mellitus and gestational diabetes: a pilot study
Tratamiento comparativo entre sitagliptina vs. metformina, solas o en combinación, en pacientes con síndrome de ovario poliquístico. Una entidad clínica con alto riesgo para desarrollar diabetes mellitus y diabetes gestacional: 2018;81(1):15
Elsevier Doyma 2018 (met versus sitagliptin versus met+sitagliptin). Outcomes reported only in figures, no specific numbers. Randomization also not described. Appears that medication was used only 6-10 weeks

Table 4.2. Excluded studies (on full-text assessment)

Reference	Reason
Unknown. Effect of green tea pills and metformin versus placebo on the Nrf2-antioxidant system and proinflammatory cytokines, including IL-6 and TNF-a, in peripheral blood mononuclear cells of women with polycystic ovary syndrome: a single blind randomized clinica 2017.	**Wrong publication type.**
Effect of supplementation in treatment of women with polycystic ovary syndrome. Clinical trial of the effect of inofolic supplementation compared with metformin on parameters of mental health and oxidative stress in women with polycystic ovary syndrome 2017.	**Wrong publication type.**
Effect of inofolic supplementation in treatment of women with polycystic ovary syndrome. Clinical trial of the effect of inofolic supplementation compared with metformin on metabolic profiles and gene expression related to insulin and lipid in women with polycystic ovary syndrome 2017.	**Full text not obtainable.**
Comparison of oral contraceptives including Contrasmine, Etisterone and Desoceptive with Ovustop-L (LD) on clinical, biochemical and metabolic findings, and quality of life in women with polycystic ovary syndrome. A Randomized cross-over clinical trial to assess the effectiveness of oral contraceptives including Contrasmine, Etisterone and Desoceptive with Ovustop-L (LD) on clinical, biochemical and metabolic findings, and quality of life in women with polycystic o 2017.	**Full text not obtainable.**
The efficacy of Fennel infusion and cupping on ovarian failure. Comparison of ovarian cupping and fennel infusion with Metformin on oligomenorrhea and ovulation in women with polycystic ovarian syndrome: a clinical trial 2017.	**Full text not obtainable.**
Scientific Impact Paper No. 13: Metformin Therapy for the Management of Infertility in Women with Polycystic Ovary Syndrome. Obstetrician & Gynaecologist 2017, 19, 339-339, doi:10.1111/tog.12436.	**Wrong study design.**
Effect of using metformin on the incidence of gestational diabetes and preeclampsia in pregnant women with polycystic ovary. Effect of using metformin versus not using on the incidence of gestational diabetes and preeclampsia in pregnant women with polycystic ovary: A randomized clinical trial 2018.	**Wrong publication type**

?Effects of myo-inositol on induction of ovulation. Comparison the effects of myo-inositol plus clomiphene citrate with metformin plus clomiphene citrate on induction of ovulation among patients with polycystic ovarian syndrome. 2018.	**Wrong publication type**
New strategies to lose weight for women with polycystic ovary syndrome. Novel strategies in weight loss in women with polycystic ovary syndrome: does the gut microbiome play a role? 2018.	**Wrong publication type**
A study to compare the efficacy of two drugs on the success of assisted reproductive therapy in women with polycystic ovarian syndrome and undergoing treatment with IVF. Randomised Control Trial comparing the effects of Metformin to Myoinositol on ART outcome in women with PCOS undergoing IVF cycles 2018.	**Wrong publication type**
A study to compare the efficacy and adverse effects of metformin versus myoinositol plus d-chiroinositol combination therapy in polycystic ovarian syndrome. A prospective randomised comparative study of metformin versus myoinositol plus d-chiroinositol combination therapy in polycystic ovarian syndrome 2019.	**Wrong publication type**
Effect of combined electroacupuncture and medical therapy on insulin resistance in polycystic ovary syndrome patients. Combination of electroacupuncture and pharmacological treatment in improving insulin resistance (HOMA-IR) in polycystic ovary syndrome patients: a double-blind randomized clinical trial 2020.	**Wrong study design**
Study to find Effects of Chandraprabha Vati(Ayurvedic Medicine) in Polycystic Ovarian Syndrome Characterised by Small cysts in ovary with irregular,Scanty menses and excess/unwanted hairs on Face,Thighs,Abdomen etc. â??Randomized controlled clinical trial to study the efficacy OF Chandraprabha vati in PCOS.â?? 2020.	**Wrong study design**
A clinical trial to study the effect of exercise and metformin on mitochondrial health in patients with polycystic ovarian syndrome (PCOS). To assess the efficacy of moderate-intensity exercise training and metformin on mitophagy and mitochondrial phenotype in patients with polycystic ovarian syndrome (PCOS) 2020.	**Wrong publication type**
ffect of oral contraceptives on levels of adipokines, and adiposity indices in women with polycystic ovary syndrome. A randomized clinical trial to compare the effectiveness of oral contraceptives containing levonorgestrel, desogestrel, cyproterone acetate, and drospirenone on levels of adipokines, and adiposity indices in women with polycystic ovary syndrome. 2020.	**Wrong publication type**
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Expression of concern: Comparison of myo-inositol and metformin on mental health parameters and biomarkers of oxidative stress in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial The effects of fish oil omega-3 fatty acid supplementation on mental health parameters and metabolic status of patients with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. Journal of Psychosomatic Obstetrics & Gynecology 2020, 41, I-I, doi:10.1080/0167482X.2020.1842508	**Wrong publication type**
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Tehrani, F.R.; Amiri, M. Polycystic ovary syndrome in adolescents: Challenges in diagnosis and treatment. International Journal of Endocrinology and Metabolism 2019, 17, e91554, doi:http://dx.doi.org/10.5812/ijem.91554.	**Wrong study design**
Tennilä, J.; Jääskeläinen, J.; Utriainen, P.; Voutilainen, R.; Häkkinen, M.; Auriola, S.; Morin-Papunen, L.; Liimatta, J. PCOS Features and Steroid Profiles Among Young Adult Women with a History of Premature Adrenarche. Journal of Clinical Endocrinology & Metabolism 2021, 106, e3335-e3345, doi:10.1210/clinem/dgab385.	**Wrong study design**
Toosy, S.; Sodi, R.; Pappachan, J.M. Lean polycystic ovary syndrome (PCOS): an evidence-based practical approach. Journal of Diabetes and Metabolic Disorders 2018, 17, 277-285, doi:http://dx.doi.org/10.1007/s40200-018-0371-5.	**Wrong study design**
Trouva, A.; Alvarsson, M.; Calissendorff, J.; Asvold, B.O.; Vanky, E.; Hirschberg, A.L. Thyroid Status During Pregnancy in Women With Polycystic Ovary Syndrome and the Effect of Metformin. Frontiers in endocrinology 2022, 13, 772801, doi:https://dx.doi.org/10.3389/fendo.2022.772801.	**Wrong outcome**
Tso, L.O.; Costello, M.F.; Albuquerque, L.E.T.; Andriolo, R.B.; Macedo, C.R. Metformin treatment before and during IVF or ICSI in women with polycystic ovary syndrome. The Cochrane database of systematic reviews 2020, 12, CD006105, doi:https://dx.doi.org/10.1002/14651858.CD006105.pub4.	**Wrong population**
Tzotzas, T.; Karras, S.N.; Katsiki, N. Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists in the Treatment of Obese Women with Polycystic Ovary Syndrome. Current vascular pharmacology 2017, 15, 218-229, doi:https://dx.doi.org/10.2174/1570161114666161221115324.	**Wrong study design**
Udesen, P.B.; Glintborg, D.; Sorensen, A.E.; Svendsen, R.; Nielsen, N.L.S.; Wissing, M.L.M.; Andersen, M.S.; Englund, A.L.M.; Dalgaard, L.T. Metformin decreases mir-122, mir-223 and mir-29a in women with polycystic ovary syndrome. Endocrine Connections 2020, 9, 1075, doi:https://doi.org/10.1530/EC-20-0195.	**Wrong outcome**
Underdal, M.O.; Salvesen, Ø.; Henriksen, A.H.; Andersen, M.; Vanky, E. Impaired Respiratory Function in Women With PCOS Compared With Matched Controls From a Population-Based Study. Journal of Clinical Endocrinology & Metabolism 2019, 10.1210/clinem/dgz053, N.PAG-N.PAG, doi:10.1210/clinem/dgz053.	**Wrong study design**
Underdal, M.O.; Stridsklev, S.; Andresen, M.S.; Vanky, E. Metabolic health in women with PCOS-5-11 years' followup after metformin or placebo in pregnancy. Endocrine reviews 2017, 38.	**Fulltext not obtainable**
Underdal, M.O.; Stridsklev, S.; Oppen, I.H.; Høgetveit, K.; Andersen, M.S.; Vanky, E. Does Metformin Treatment During Pregnancy Modify the Future Metabolic Profile in Women With PCOS? Journal of Clinical Endocrinology & Metabolism 2018, 10.1210/jc.2018-00485, N.PAG-N.PAG, doi:10.1210/jc.2018-00485.	**Wrong population**
Vatopoulou, A.; Tziomalos, K. Management of obesity in adolescents with polycystic ovary syndrome. Expert opinion on pharmacotherapy 2020, 21, 207-211, doi:https://dx.doi.org/10.1080/14656566.2019.1701655.	**Wrong study design**

Vedtofte, L.; Foghsgaard, S.; Zierau, L.; VilsbØLl, T.; Knop, F.K. 1186-P: Lean Women with Polycystic Ovary Syndrome and Insulin Resistance Have Normal Incretin Effect, which Is Unaffected by Metformin Therapy. Diabetes 2019, 68, N.PAG-N.PAG, doi:10.2337/db19-1186-P.	**Wrong publication type**
Venter, A. Obesity, Oligomenorrhoea and PCOS in Adolescence. Obstetrics and Gynaecology Forum 2018, 28, 27-30.	**Wrong study design**
Vine, D.; Proctor, E.; Weaver, O.; Ghosh, M.; Maximova, K.; Proctor, S. A Pilot Trial: fish Oil and Metformin Effects on ApoB-Remnants and Triglycerides in Women with Polycystic Ovary Syndrome. Journal of the Endocrine Society 2021, 5, doi:https://doi.org/10.1210/jendso/bvab114.	**Wrong comparator**
Walker, K.; Decherney, A.H.; Saunders, R. Menstrual Dysfunction in PCOS. Clinical Obstetrics & Gynecology 2021, 64, 119-125, doi:10.1097/GRF.0000000000000596.	**Wrong study design**
Wang, J.; Zhu, L.; Hu, K.; Tang, Y.; Zeng, X.; Liu, J.; Xu, J. Effects of metformin treatment on serum levels of C-reactive protein and interleukin-6 in women with polycystic ovary syndrome: a meta-analysis: A PRISMA-compliant article. Medicine 2017, 96, e8183-e8183, doi:10.1097/MD.0000000000008183.	**Wrong comparator**
Wang, L.; Liang, R.; Tang, Q.; Zhu, L. An Overview of Systematic Reviews of Using Chinese Medicine to Treat Polycystic Ovary Syndrome. Evidence-based Complementary and Alternative Medicine 2021, 2021, 9935536, doi:http://dx.doi.org/10.1155/2021/9935536	**Wrong intervention**
Wang, R.; Kim, B.V.; van Wely, M.; Johnson, N.P.; Costello, M.F.; Zhang, H.; Ng, E.H.Y.; Legro, R.S.; Bhattacharya, S.; Norman, R.J., et al. Treatment strategies for women with WHO group II anovulation: systematic review and network meta-analysis. BMJ (Clinical research ed.) 2017, 356, j138, doi:https://dx.doi.org/10.1136/bmj.j138.	**Wrong population**
Wang, R.; Li, W.; Bordewijk, E.M.; Legro, R.S.; Zhang, H.; Wu, X.; Gao, J.; Morin-Papunen, L.; Homburg, R.; Konig, T.E., et al. First-line ovulation induction for polycystic ovary syndrome: an individual participant data meta-analysis. Human reproduction update 2019, 25, 717-732, doi:https://dx.doi.org/10.1093/humupd/dmz029.	**Wrong outcome**
Wang, Y.-W.; He, S.-J.; Feng, X.; Cheng, J.; Luo, Y.-T.; Tian, L.; Huang, Q. Metformin: a review of its potential indications. Drug design, development and therapy 2017, 11, 2421-2429, doi:https://dx.doi.org/10.2147/DDDT.S141675.	**Wrong study design**
Wawrzkiewicz-Jalowiecka, A.; Kowalczyk, K.; Trybek, P.; Jarosz, T.; Radosz, P.; Setlak, M.; Madej, P. In Search of New Therapeutics-Molecular Aspects of the PCOS Pathophysiology: Genetics, Hormones, Metabolism and Beyond. International journal of molecular sciences 2020, 21, doi:https://dx.doi.org/10.3390/ijms21197054.	**Wrong study design**
Wen, Y.; Ma, H.L.; Wu, X.K. Acupuncture and clomiphene interventions in PCOS conversely affect the insulin resistance profiles in early pregnancy subjects: a secondary analysis of a randomized controlled trial. Journal of obstetrics and gynaecology research 2017, 43, 160, doi:https://doi.org/10.1111/jog.13394.	**Wrong publication type**
Wenjing, L.; Hongbo, H.; Guofang, Z.; Zhanzhong, M.; Jing, L.; Fanxiang, L.; Li, W.; Hu, H.; Zou, G.; Ma, Z., et al. Therapeutic effects of puerarin on polycystic ovary syndrome: A randomized trial in Chinese women. Medicine 2021, 100, 1-8, doi:10.1097/MD.0000000000026049.	**Wrong comparator**
Witchel, S.F.; Oberfield, S.E.; Peña, A.S. Polycystic Ovary Syndrome: Pathophysiology, Presentation, and Treatment With Emphasis on Adolescent Girls. Journal of the Endocrine Society 2019, 3, 1545-1573, doi:10.1210/js.2019-00078.	**Wrong study design**
Wiweko, B.; Susanto, C. The Effect of Metformin and Cinnamon on Serum Anti-Mullerian Hormone in Women Having PCOS: a Double-Blind, Randomized, Controlled Trial. Journal of Human Reproductive Sciences 2017, 10, 31, doi:https://doi.org/10.4103/jhrs.JHRS9016.	**Wrong comparator**
Wojciechowska, A.; Osowski, A.; Jozwik, M.; Gorecki, R.; Rynkiewicz, A.; Wojtkiewicz, J. Inositols' Importance in the Improvement of the Endocrine-Metabolic Profile in PCOS. International journal of molecular sciences 2019, 20, doi:https://dx.doi.org/10.3390/ijms20225787.	**Wrong study design**
Woodward, A.; Broom, D.; Harrop, D.; Lahart, I.; Carter, A.; Dalton, C.; Metwally, M.; Klonizakis, M. The effects of physical exercise on cardiometabolic outcomes in women with polycystic ovary syndrome not taking the oral contraceptive pill: a systematic review and meta-analysis. Journal of Diabetes and Metabolic Disorders 2019, 18, 597-612, doi:http://dx.doi.org/10.1007/s40200-019-00425-y.	**Wrong intervention**
Wu, Y.; Tu, M.; Huang, Y.; Liu, Y.; Zhang, D. Association of Metformin With Pregnancy Outcomes in Women With Polycystic Ovarian Syndrome Undergoing In Vitro Fertilization: A Systematic Review and Meta-analysis. JAMA network open 2020, 3, e2011995-e2011995, doi:10.1001/jamanetworkopen.2020.11995.	**Wrong outcome**
Xie, L.; Zhang, D.; Ma, H.; He, H.; Xia, Q.; Shen, W.; Chang, H.; Deng, Y.; Wu, Q.; Cong, J., et al. The Effect of Berberine on Reproduction and Metabolism in Women with Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis of Randomized Control Trials. Evidence-based Complementary & Alternative Medicine (eCAM) 2019, 10.1155/2019/7918631, 1-15, doi:10.1155/2019/7918631.	**Wrong intervention**
Xu, J.; Zuo, Y. [Efficacy of acupuncture as adjunctive treatment on infertility patients with polycystic ovary syndrome]. Zhongguo zhen jiu = Chinese acupuncture & moxibustion 2018, 38, 358-361, doi:https://dx.doi.org/10.13703/j.0255-2930.2018.04.004.	**Wrong language**
Xu, Q.; Xie, Q. Long-term effects of prenatal exposure to metformin on the health of children based on follow-up studies of randomized controlled trials: a systematic review and meta-analysis. Springer Nature: , <Blank>, 2019; Vol. 299, pp 1295-1303.	**Wrong outcome**

Xu, Z.; Meng, L.; Pan, C.; Chen, X.; Huang, X.; Yang, H. Does oral contraceptives pretreatment affect the pregnancy outcome in polycystic ovary syndrome women undergoing ART with GnRH agonist protocol? Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology 2019, 35, 124-127, doi:https://dx.doi.org/10.1080/09513590.2018.1500535.	**Wrong study design**
Yanbo, L.; Yupei, S.; Jiping, X.; Linlin, C.; Guang, Z.; Liu, Y.; Shao, Y.; Xie, J.; Chen, L.; Zhu, G. The efficacy and safety of metformin combined with simvastatin in the treatment of polycystic ovary syndrome: A meta-analysis and systematic review. Medicine 2021, 100, 1-8, doi:10.1097/MD.0000000000026622.	**Wrong intervention**
Yang, D.; Zhao, M.; Tan, J. [Effect of polycystic ovary syndrome treated with the periodic therapy of acupuncture]. Zhongguo zhen jiu = Chinese acupuncture & moxibustion 2017, 37, 825-829, doi:https://dx.doi.org/10.13703/j.0255-2930.2017.08.007.	**Wrong language**
Yang, J.; Liu, Y.; Huang, J.; Xu, J.; You, X.; Lin, Q.; Zhang, J.; Dun, J.; Huang, S. [Acupuncture and Chinese medicine of artificial cycle therapy for insulin resistance of polycystic ovary syndrome with phlegm damp type and its mechanism]. Zhongguo zhen jiu = Chinese acupuncture & moxibustion 2017, 37, 1163-1168, doi:https://dx.doi.org/10.13703/j.0255-2930.2017.11.007.	**Wrong language**
Yao, K.; Bian, C.; Zhao, X. Association of polycystic ovary syndrome with metabolic syndrome and gestational diabetes: Aggravated complication of pregnancy (Review). Experimental and Therapeutic Medicine 2017, 14, 1271-1276, doi:http://dx.doi.org/10.3892/etm.2017.4642.	**Wrong study design**
Yen, H.; Chang, Y.-T.; Yee, F.-J.; Huang, Y.-C. Metformin Therapy for Acne in Patients with Polycystic Ovary Syndrome: A Systematic Review and Meta-analysis. American journal of clinical dermatology 2021, 22, 11-23, doi:10.1007/s40257-020-00565-5.	**Wrong outcome**
Young, C.C.; Monge, M. Polycystic Ovary Syndrome in Primary Care: It Takes a Village. Journal for Nurse Practitioners 2019, 15, 694-695, doi:10.1016/j.nurpra.2019.05.008.	**Wrong study design**
Yousuf, S.D.; Ganie, M.A.; Jeelani, S.; Mudassar, S.; Shah, Z.A.; Zargar, M.A.; Amin, S.; Wani, I.A.; Rashid, F. Effect of six-month use of oral contraceptive pills on plasminogen activator inhibitor-1 & factor VIII among women with polycystic ovary syndrome: An observational pilot study. The Indian journal of medical research 2018, 148, S151-S155, doi:https://dx.doi.org/10.4103/ijmr.IJMR_1899_17.	**Wrong study design**
Zeng, L.; Yang, K. Effectiveness of myoinositol for polycystic ovary syndrome: a systematic review and meta-analysis. Endocrine 2018, 59, 30-38, doi:https://dx.doi.org/10.1007/s12020-017-1442-y.	**Wrong intervention**
Zhang, J.; Si, Q.; Li, J. Therapeutic effects of metformin and clomiphene in combination with lifestyle intervention on infertility in women with obese polycystic ovary syndrome. Pakistan journal of medical sciences 2017, 33, 8, doi:https://doi.org/10.12669/pjms.331.11764.	**Wrong intervention**
Zhang, J.; Su, M.; Xu, L.; Yang, Z.; Yin, W.; Nie, Y.; Qiao, X.; Cheng, R.; Ma, Y. [Efficacy and metabolic safety of long-term treatment with ethinyl oestradiol/cyproterone and desogestrel/ethinyl oestradiol tablets in women with polycystic ovary syndrome]. Nan fang yi ke da xue xue bao = Journal of Southern Medical University 2018, 38, 917-922, doi:https://dx.doi.org/10.3969/j.issn.1673-4254.2018.08.03.	**Wrong language**
Zhang, S.-W.; Zhou, J.; Gober, H.-J.; Leung, W.T.; Wang, L. Effect and mechanism of berberine against polycystic ovary syndrome. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 2021, 138, 111468, doi:https://dx.doi.org/10.1016/j.biopha.2021.111468.	**Wrong study design**
Zhang, Y.; Guo, X.; Ma, S.; Ma, H.; Li, H.; Wang, Y.; Qin, Z.; Wu, X.; Han, Y.; Han, Y. The Treatment with Complementary and Alternative Traditional Chinese Medicine for Menstrual Disorders with Polycystic Ovary Syndrome. Evidence-based Complementary & Alternative Medicine (eCAM) 2021, 10.1155/2021/6678398, 1-19, doi:10.1155/2021/6678398.	**Wrong study design**
Zhao, J.; Liu, X.; Zhang, W. The Effect of Metformin Therapy for Preventing Gestational Diabetes Mellitus in Women with Polycystic Ovary Syndrome: A Meta-Analysis. Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association 2020, 128, 199-205, doi:https://dx.doi.org/10.1055/a-0603-3394.	**Fulltext not obtainable**
Zhao, Y.X.; Wang, L.J.; Gong, F.Y.; Pan, H.; Miao, H.; Duan, L.; Yang, H.B.; Zhu, H.J. [Effects of orlistat and metformin on metabolism and gonadal function in overweight or obese patients with polycystic ovary syndrome]. Zhonghua nei ke za zhi 2021, 60, 1165-1168, doi:https://dx.doi.org/10.3760/cma.j.cn112138-20210302-00171.	**Wrong language**
Zhou, K.; Zhang, J.; Xu, L.; Lim, C.E.D. Chinese herbal medicine for subfertile women with polycystic ovarian syndrome. The Cochrane database of systematic reviews 2021, 6, CD007535, doi:https://dx.doi.org/10.1002/14651858.CD007535.pub4.	**Wrong intervention**
Zimmerman, L.D.; Setton, R.; Pereira, N.; Rosenwaks, Z. Contemporary Management of Polycystic Ovarian Syndrome. Clinical obstetrics and gynecology 2019, 62, 271-281, doi:https://dx.doi.org/10.1097/GRF.0000000000000449.	**Wrong study design**

5. FINDINGS

Comparisons included:

1. Metformin versus placebo
2. Metformin+lifestyle versus placebo+lifestyle
3. Metformin versus lifestyle
4. Metformin vers OCP (also in Q4.2 – not identical)
5. Metformin vers metformin+OCP (also in Q4.2 – not identical)
6. Metformin versus anti-androgen (also in Q4.6 – identical)
7. Metformin+anti-androgen versus anti-androgen (also in Q4.6 – identical)
8. Metformin+anti-androgen versus metformin (also in Q4.6 – identical)
9. SPIOMET versus OCP (also in Q4.6 – identical)
10. Metformin versus anti-androgen+OCP (also in Q4.6 – not identical since timeline different)
11. Metformin+lifestyle versus metformin+anti-androgen+lifestyle (also in Q4.6 – not identical since timeline different)
12. Metformin+Lifestyle versus anti-androgen+lifestyle (also in Q4.6 – not identical since timeline different)
13. Metformin+anti-androgen+lifestyle versus anti-androgen+lifestyle (also in Q4.6 – not identical since timeline different)
14. Metformin+anti-androgen+lifestyle versus placebo+lifestyle (also in Q4.6 – identical)
15. Metformin versus rosiglitazone
16. Metformin versus pioglitazone
17. Metformin versus saxagliptin
18. Metformin+saxagliptin versus metformin
19. Metformin+saxagliptin versus saxagliptin
20. Metformin versus SGLT2-inhibitors
21. Metformin+liraglutide versus liraglutide
22. Metformin+myo-inositol versus myo-inositol
23. Metformin versus orlistat
24. Metformin+pioglitazone versus pioglitazone
25. Metformin+pioglitazone versus metformin
26. Metformin versus metformin+rosiglitazone
27. Metformin+rosiglitazone versus rosiglitazone
28. Metformin versus metformin (different dose)
29. Metformin versus metformin+MPA

Comparisons included in other reviews:

1. OCP versus metformin+OCP (reviewed in Q4.2)
2. OCP+metformin versus OCP+anti-obesity (reviewed in Q4.2)
3. OCP versus OCP+metformin+anti-obesity (reviewed in Q4.2)
4. Metformin+anti-androgen versus OCP (adolescents) (reviewed in Q4.2)
5. Metformin+anti-androgen+OCP versus OCP (reviewed in Q4.2)
6. Metformin+OCP versus OCP+anti-androgen (reviewed in Q4.2)

Comparison 1: Metformin versus placebo

Evidence Summary

23 randomised controlled trials (RCTs) were identified by our search. Of these RCT, 22 were included in the meta-analysis.
Of our included articles three had a low ROB, 16 had a moderate ROB and 4 had a high ROB.

Rows highlighted grey indicate studies with participants described as obese. Rows shaded green indicate that participants had BMI in the normal weight and overweight categories. We performed subgroup analyses based on BMI. As for age, there was only one study on adolescents (Hoeger et al. 2008) which is also reported separately. A major limitation in the evidence for this comparison is the lack of confidence in author reporting of units and conversions.

Meta-analysis/descriptive analysis summary

Overall:
In the meta-analysis, metformin was superior in lowering WHR (certainty very low), BMI (certainty moderate), testosterone (certainty very low), fasting glucose (certainty moderate), total cholesterol (certainty low), triglycerides (certainty low), CRP (certainty very low), PAI (certainty very low) and HOMA-IR (certainty moderate) compared to placebo.

Subanalyses according to BMI:
For PCOS-women with normal weight (BMI<25), metformin was superior in lowering FAI (certainty moderate) and fasting insulin (certainty low).
For obese PCOS women (BMI>25) metformin was superior in lowering BMI (certainty moderate), fasting glucose (certainty moderate), total cholesterol (certainty moderate) and LDL (certainty low).
Regarding individual studies, not included in the meta-analysis, Bridger et al. found that metformin was superior in improving testosterone and HDL in PCOS-women compared to placebo. The amount of girls with restored menses was also larger after metformin use compared to placebo. Certainty in the evidence for this study was low (low risk of bias but a single study with only a small amount of participants).
There was one study comparing metformin to placebo in adolescents (Hoeger et al. 2008), which found no differences in observed outcomes in metformin compared to placebo. Certainty for this study was very low (being a single, small study).
The reports suggest more gastrointestinal side effects with metformin (see table at the end of this document). Very few studies reported on side effects in specific details.

Author, year, country	Population	Sample Size per group	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Type of analysis and subgroup	ROB
Zahra et al. 2017 Pakistan	Females with PCOS aged 18–35 years	1.Metformin=20 2.Placebo=20	Metformin 500mgx 3 /day	1.26.7+/- 6.5 2. 29.6+/- 9.9	1.25.8+/- 6.1 2. 27.0+/- 6.3	Weight, BMI, f-insulin, f-gluc, HOMA	META Adults	**ROB High**
Baillargeon et al. 2004 Venezuela	Nonobese women (bmi 27), aged 17 to 40 years, who had PCOS	1.Metformin=28 2.Placebo=30	1.Metformin 850mg 2.Placebo	1.24.6+/- 0.2 2. 24.6+/-0.2	1.27.7+/- 0.9 2. 27.2+/- 0.9	Weight, whr, BMI, SHBG, T, DHEAS	META BMI<27 Adults	**ROB Moderate** included in last TR

Heidari et al. 2019 USA	Females aged 18 to 50 years with a BMI of 25 or greater who had a diagnosis of PCOS	1.Metformin=33 Placebo=15	1.metformin 1500mg/day	1.36.2+/- 10.3 2. 37.7+/- 8.1	1.32.4+/- 7.5 2.33.1+/- 5.9	Weight, whr, BMI, T, f-insulin, f-gluc, lipids, crp, HOMA	META and individual BMI>25 Adults	**ROB Moderate**
Morin-Papunen et al. 2012 Finland	Women with pcos, aged 18-39 yrs, with bmi>19	1.Metformin=106 2.placebo=111	1.Metformin 1000mgx2 (obese) Metformin 500mg+1000mg (non-obese) 2.Placebo	1: 27.1±6.3 2: 27.4±6.2	1: 28.4±3.9 2: 27.9±4.1	Weight, whr, BMI	META Adults	**ROB Moderate**
Lord et al 2006 UK	Women with anovulation and PCOS	1.Metformin=16 2.placebo=16	1) MET 500 mgx3/d 2) Placebo x3/d	1: 33.74±6.74 2: 36.37±7.46	1: 27.76±4.89 2: 30.63±4.84	Weight, whr, BMI, SHBG, T, f-insulin, f-gluc, lipids, HOMA, DHEAS	META Adults BMI>25	**ROB Low**
Lingaiah et al. 2019 Finland	Adult women with PCOS	1a. Metformin=40 (BMI<27) 1b. Metformin=17 (BMI>=27) 2a. Placebo=34 (BMI<27) 2b. Placebo=27 (BMI>=27)	1a. Metformin 500+1000mg 1b. Metformin 1000mg+1000mg	1a. 22.5 (2.2) 1b. 33.4 (4.3) 2a. 22.7 (2.6) 2b. 33.3 (4.4)	1a. 27.1 (3.1) 1b. 28.8 (3.8) 2a. 27.9 (4.2) 2b. 27.3 (5.0)	Weight, whr, BMI, SHBG, T, f-insulin, f-gluc, HOMA, DHEAS, A	META BMI<27 BMI=>27 Adults	**ROB Moderate**
Trolle et al. 2010 Denmark	women aged 18 – 45 with PCOS	1.Met=29-41 2.Placebo=29-41	1.Metformin 850mgx2/d 2.Placebox2/d	71% had BMI>30	18-45	Weight, whr, SHBG, T, f-insulin, f-gluc, lipids, HOMA	META Adults	**ROB Moderate**
Trolle et al. 2007 Denmark	Women aged 18 – 45 with PCOS	1.Met=23 2.Placebo=27	1.Metformin 850mgx2/d 2.Placebox2/d	33.8 (22.2-46.0) #	32 (21–42) #	Weight, T	META Adults	**ROB Moderate**
Naka et al 2011 Greece	Young women with PCOS (mean age 23.3 years)	1.Metformin=15 2.Placebo=14 3.Pioglitazone=14	1.Metformin 850mgx2/d 2.Placebo 3.Pioglitazone 30mg/d	1.29.4 ±6.5 2.28.3 ±4.9 3.28.5±5.4	1.22.2±3.6 2.24.3 ±6.0 3.23.6±5.1	Weight, whr, BMI, hirsutism, SHBG, T, f-insulin, f-gluc, lipids	META Adults	**ROB Moderate**
Onalan 2005 Turkey	Women with PCOS, divided according to BMI	BMI<25 1.Metformin=15 2.placebo=16	1,3,5 Metformin 500mgx1/d for 5 days, then 850mgx2 2,4,6 Placebo	1: 21.16±2.25 2: 21.96±1.52	1: 26.4±4.1 2: 27.1±4.8	Whr, BMI, hirsutism, f-insulin, f-gluc, lipids, DHEAS	META BMI<25 BMI 25-29.9 BMI>=30 Adults	**ROB high**
Chou et al. 2003 Brazil	Obese (BMI>30), non-diabetic women with PCOS	1.Metformin=14 2.Placebo=16	1.Metformin 500mgx3 2.Placebo	1.35.6+/- 4.9 2.37.4+/-6	1.24+/- 5 2. 24.5+/- 6.1	Whr, BMI, SHBG, T, f-insulin, f-gluc, lipids	META BMI>30 Adults	**ROB Moderate**
Romualdi et al. 2010 Italy	normal-weight women with PCOS (BMI 22.4, age range 19–32 yrs)	1.Metformin=13 2.Placebo=10	1.Metformin 500mgx2/d 2.Placebox2/d	1: 22.2±2.2 2: 22.3±3.9	1: 24.7±4.4 2: 27.2±2.6	Whr, BMI, hirsutism, SHBG, T, lipids, DHEAS	META Adults BMI<25	**ROB Moderate**

Eisenhardt et al. 2006 Germany	Women with PCOS, aged 21–36 yr, with menstrual disturbances and infertility and/or clinical signs of hyperandrogenism	1.Metformin=19 2.Placebo 19	1.Metformin 500mgx3 2.Placebox2	1.28.9 (23.3–34.1)* 2.32.4 (27.9 – 37.5)*	1.27.0 (24.9 – 30.7)* 2.29.7 (26.8 – 32.4)*	BMI, SHBG, T, f-insulin, f-gluc, HOMA, DHEAS	META Adults BMI>25	**ROB Low**
Fleming et al. 2002 UK	Women with oligomenorrhea (cycle length>41d; <8 cycles per year) or amenorrhea and PCOs, aged less than 35 yr	1.Metformin=26 2.Placebo=39	1.Metformin 850mgx2 2.Placebox2	1: 34.2 (31.7–36.7)* 2: 35.0 (32.6–37.3)*	1: 28.6 [26.9–30.3]* 2: 29.2 [27.5–30.7]*	BMI, SHBG, T, f-insulin, f-gluc, lipids	META Adults BMI>25	**ROB moderate**
Hoeger et al. 2008 USA	Women, aged of 12-18 yr with BMI above the 95th percentile and evidence of menstrual irregularity	1.Metformin=6 2.placebo=10 3.OCP=10 4.LS=8	1.Metformin 850mgx2/d 2. placebox2 3.30ug EE+0.15mg desogestrel	1: 34.3±6.5 2: 36.1±7.5	1: 16±1.7 2: 15.4±1.7	BMI, hirsutism, SHBG, FAI, T, f-insulin, f-gluc, lipids, crp, PAI	META BMI above the 95th percentile Adolescents	**ROB Moderate**
Hoeger et al. 2004 USA*	overweight or obese women with PCOS	1.Metformin=6 2.LS+placebo=8 3.LS+metformin=5 4.Placebo=7	1.Metformin 850mgx2/d	1: 37.1±4.9 2: 40±7.4 3: 41.7±6.2 4: 37.1±4.6	1: 29.5±6.4 2: 27.1±4.3 3: 30.4±5.4 4: 27.1±4.5	BMI, SHBG, FAI, T, f-insulin, f-gluc	META BMI=>25 Adults	**ROB Moderate**
Maciel et al. 2004 Brazil	Women with PCOS, obese (BMI>30) and non-obese (BMI<=30)	Non-obese 1.Metformin=7 2.Placebo=8	1.Metformin 500mgx3/d 2.Placebox3/d 3.Metformin 500mgx3/d 4.Placebox3/d	1: 25.3±2.1 2: 25.1±1.6	1: 22.5±1.9 2: 19.9±0.4	BMI, hirsutism, SHBG, T, f-insulin, f-gluc, lipids, A	META BMI=<30 BMI>30 Adults	**ROB Moderate**
Ng et al. 2001 Hong Kong	Infertile, Chinese women aged<40 yrs	1.Metformin=8 2.Placebo =7	1.Metformin 500mgx3 2.Placebox3	1: 24.1 (19.6-34.2) 2: 23.8 (17.9-30.8)	1: 30.5 (27-33) 2: 32.0 (26-34)	BMI, SHBG, T, f-gluc, lipids	META Adults BMI<25	**ROB Moderate** Median range
Palomba et al 2007 Italy	Normal-weight anovulatory PCOS women	1.Metformin=14 2.Placebo =13	1.Metformin 850mgx2 2.Placebox2	1: 24.3±3.1 2: 24.8±2.7	1: 22.4±2.7 2: 22.7±1.9	BMI, hirsutism, SHBG, T, DHEAS, A	META BMI<25 Adults	**ROB Moderate**
Kelly et al. 2002 UK (Crossover)	women with PCOS and hirsutism	10 in total	1) MET 500 mg/daily to 500 Mgx3/d, over 3 weeks. 2) Placebo	NR	NR	Hirsutism, SHBG, FAI, T, DHEAS	META Adults	**ROB Moderate**
Bodur et al 2018 Turkey	18–39 year old, non-obese (18–30 BMI) women with PCOS	1. metformin N=17 2. OCP N=17 3.OCP+metformin=12 4. Control N=15	1.Metformin 1700mg/day. 2. 3 mg DRSP+30ug EE 3. 3 mg DRSP+30ug EE+Metformin 1700mg/day	1.25.06 ± 3.08 2.23.45 ±3.40 3.23.82 ±2.80	1.26.24 ± 3.96 2.26.62 ±4.92 3.27.35 ±5.65	f-gluc, crp, PAI, HOMA	META BMI=<30 Adults	**ROB High**
Karimzadeh et al. 2007 Iran	Women aged 20-35 years with PCOS	1.Metformin=100 2.placebo=100	1.Metformin 500mg/day for one week and then 500mgx3/day 2.Placebo 1 tabl/day for a week, then 3 tabl/day	1.28.8+/- 3.2 2.29.5+/- 4.7	1.27.2+/- 6.8 2.28.6+/- 7.4	Lipids	META Adults BMI>25	**ROB high**

Bridger et al. 2006 Canada	Adolescents, 13 to 18 years with hyperinsulinemia and PCOS	1.Metformin=11 2.placebo=10	Metformin 750mgx2/day Placebo 1 tablx2/day	1.33.6+/- 5.6 2.30.81+/- 3.0	1.16.07+/- 0.97 2.16.08+/- 1.39	BMI, T, f-gluc, HOMA, lipids, restored menses	Individual Adolescents	**ROB low**

Results of meta-analysis

Outcome	Time point (m)	RCTs	N	Effect, random, MD	P-value	I2 (%)	Favours	Certainty
Weight (kg)	3-6	10	681	-1.84 (-3.78 to 0.10)	0.06	47	No difference	⊕⊕⊕◯ MODERATE
Sub: BMI>25	3	3	118	-0.95 (-7.25 to 5.36)	0.77	0	No difference	⊕⊕◯◯ LOW
Sub:BMI<25	3-6	2	132	-0.09 (-0.90 to 0.72)	0.83	0	No difference	⊕⊕⊕◯ MODERATE
Sub: BMI not specified	**3-6**	**5**	**431**	**-3.53 (-5.27 to -1.79)**	**<0.001**	**0**	**Metformin**	⊕⊕⊕⊕ HIGH
WHR	**3-6**	**14**	**747**	**-0.02 (-0.03 to -0.00)**	**0.04**	**75**	**Metformin**	⊕◯◯◯ VERY LOW
Sub: BMI>25	3-6	7	241	-0.02 (-0.05 to 0.01)	0.23	88	No difference	⊕◯◯◯ VERY LOW
Sub:BMI<25	**3-6**	**4**	**186**	**-0.01 (-0.02 to 0.01)**	**<0.001**	**0**	**Metformin**	⊕⊕⊕◯ MODERATE
Sub: BMI not specified	3-6	3	320	-0.00 (-0.02 to 0.02)	0.73	0	No difference	⊕⊕⊕◯ MODERATE
BMI kg/m2	**3-6**	**21**	**976**	**-0.53 (-0.95 to -0.12)**	**0.01**	**14**	**Metformin**	⊕⊕⊕◯ MODERATE
Sub: BMI>25	**3-6**	**13**	**536**	**-0.89 (-1.43 to -0.35)**	**0.001**	**0**	**Metformin**	⊕⊕⊕◯ MODERATE
Sub:BMI<25	3-6	4	139	-0.03 (-0.29 to 0.24)	0.84	0	No difference	⊕⊕⊕◯ MODERATE
Sub: BMI not specified	3-6	4	301	-0.87 (-2.30 to 0.96)	0.24	0	No difference	⊕⊕⊕◯ MODERATE
Hirsutism (FG score)	6	10	203	-0.49 (-1.51 to 0.53)	0.34	0	No difference	⊕⊕◯◯ LOW
Sub: BMI>25	6	4	58	-1.66 (-5.22 to 1.90)	0.36	24	No difference	⊕◯◯◯ VERY LOW
Sub:BMI<25	6	4	96	0.15 (-1.13 to 1.43)	0.82	0	No difference	⊕⊕◯◯ LOW
Sub: BMI not specified	6	2	49	-1.43 (-3.48 to 0.62)	0.17	0	No difference	⊕⊕⊕◯ MODERATE
SHBG (nmol/l)	3-6	17	584	-0.00 (-0.28 to 0.27)	0.98	46	No difference	⊕⊕◯◯ LOW
Sub: BMI>25	3-6	8	251	1.05 (-0.81 to 2.91)	0.27	0	No difference	⊕⊕⊕◯ MODERATE
Sub:BMI<25	3-6	5	197	-0.08 (-0.23 to 0.07)	0.29	0	No difference	⊕⊕⊕⊕ HIGH
Sub: BMI not specified	6	4	136	-2.12 (-16.14 to 11.89)	0.77	86	No difference	⊕◯◯◯ VERY LOW
FAI	3-6	9	275	-1.00 (-2.10 to 0.10)	0.08	31	No difference	⊕⊕⊕◯ MODERATE
Sub: BMI>25	3-6	4	102	-0.04 (-3.11 to 3.02)	0.98	58	No difference	⊕⊕◯◯ LOW
Sub:BMI<25	**3-6**	**3**	**124**	**-1.01 (-1.72 to -0.29)**	**0.006**	**0**	**Metformin**	⊕⊕⊕◯ MODERATE
Sub: BMI not specified	**6**	**2**	**49**	**-4.68 (-8.48 to -0.89)**	**0.02**	**0**	**Metformin**	⊕⊕⊕◯ MODERATE
Testosterone (ng/dl)	**3-6**	**18**	**636**	**-13.36 (-24.68 to -2.05)**	**0.02**	**91**	**Metformin**	⊕◯◯◯ VERY LOW

Sub: BMI>25	3-6	8	251	-3.91 (-9.16 to 1.35)	0.15	12	No difference	⊕⊕⊕◯ MODERATE
Sub:BMI<25	3-6	5	197	-25.11 (-61.89 to 11.67)	0.18	97	No difference	⊕◯◯◯ VERY LOW
Sub: BMI not specified	**6**	**5**	**188**	**-12.86 (-25.53 to -0.20)**	**0.05**	**71**	**Metformin**	⊕◯◯◯ VERY LOW
Fasting insulin mIU/l)	3-6	17	578	-3.95 (-8.42 to 0.52)	0.08	100	No difference	⊕◯◯◯ VERY LOW
Sub: BMI>25	3-6	10	279	-3.76 (-11.46 to 3.95)	0.34	100	No difference	⊕◯◯◯ VERY LOW
Sub:BMI<25	**3-6**	**2**	**105**	**-2.00 (-2.02 to -1.98)**	**0.0001**	**0**	**Metformin**	⊕⊕◯◯ LOW
Sub: BMI not specified	**3-6**	**5**	**194**	**-4.17 (-8.07 to -0.26)**	**0.04**	**70**	**Metformin**	⊕◯◯◯ VERY LOW
Fasting glucose (mg/dl)	**3-6**	**21**	**722**	**-2.39 (-3.49 to -1.30)**	**<0.0001**	**0**	**Metformin**	⊕⊕⊕◯ MODERATE
Sub: BMI>25	**3-6**	**11**	**320**	**-2.26 (-4.10 to -0.42)**	**0.02**	**0**	**Metformin**	⊕⊕⊕◯ MODERATE
Sub:BMI<25	3-6	4	178	-0.67 (-3.15 to 1.81)	0.60	0	No difference	⊕⊕⊕◯ MODERATE
Sub: BMI not specified	**3-6**	**6**	**224**	**-3.10 (-4.98 to -1.23)**	**0.001**	**20**	**Metformin**	⊕⊕⊕◯ MODERATE
Total cholesterol (mmol/l)	**3-6**	**15**	**522**	**-9.12 (-16.43 to -1.81)**	**0.01**	**32**	**Metformin**	⊕⊕◯◯ LOW
Sub: BMI>25	**3-6**	**9**	**337**	**-15.86 (-26.48 to -5.24)**	**0.003**	**33**	**Metformin**	⊕⊕◯◯ LOW
Sub:BMI<25	3-6	3	69	-4.21 (-18.04 to 9.63)	0.55	8	No difference	⊕◯◯◯ VERY LOW
Sub: BMI not specified	6	3	116	-1.42 (-11.73 to 8.89)	0.79	5	No difference	⊕⊕⊕◯ MODERATE
HDL (mmol/l)	3-6	15	609	-0.94 (-4.63 to 2.75)	0.62	71	No difference	⊕◯◯◯ VERY LOW
Sub: BMI>25	3-6	8	362	0.49 (-4.23 to 5.20)	0.84	70	No difference	⊕◯◯◯ VERY LOW
Sub:BMI<25	6	3	81	-3.19 (-12.69 to 6.40)	0.52	70	No difference	⊕◯◯◯ VERY LOW
Sub: BMI not specified	6	4	166	-1.66 (-8.21 to 4.88)	0.62	49	No difference	⊕⊕◯◯ LOW
LDL (mmol/l)	3-6	15	579	-5.48 (-11.24 to 0.29)	0.06	28	No difference	⊕⊕◯◯ LOW
Sub: BMI>25	**3-6**	**8**	**362**	**-13.44 (-23.95 to -2.92)**	**0.01**	**48**	**Metformin**	⊕⊕◯◯ LOW
Sub:BMI<25	6	3	81	-0.49 (-8.72 to 7.74)	0.91	0	No difference	⊕◯◯◯ VERY LOW
Sub: BMI not specified	6	4	136	-0.58 (-10.06 to 8.90)	0.90	0	No difference	⊕⊕⊕◯ MODERATE
Triglycerides (mmol/l)	**3-6**	**16**	**632**	**-9.72 (-18.05 to -1.40)**	**0.02**	**35**	**Metformin**	⊕⊕◯◯ LOW
Sub: BMI>25	3-6	9	427	-8.98 (-23.63 to 5.67)	0.23	60	No difference	⊕◯◯◯ VERY LOW
Sub:BMI<25	6	3	69	-5.11 (-14.42 to 4.20)	0.23	0	No difference	⊕◯◯◯ VERY LOW
Sub: BMI not specified	6	4	136	-16.09 (-34.36 to 2.18)	0.08	0	No difference	⊕⊕⊕◯ MODERATE
CRP (mg/l)	**6**	**2**	**48**	**-0.37 (-0.57 to -0.16)**	**0.0005**	**0**	**Metformin**	⊕◯◯◯ VERY LOW
PAI	**6**	**2**	**48**	**-4.99 (-6.78 to -3.21)**	**<0.00001**	**0**	**Metformin**	⊕◯◯◯ VERY LOW
HOMA-IR	**3-6**	**8**	**360**	**-0.50 (-0.91 to -0.09)**	**0.02**	**49**	**Metformin**	⊕⊕⊕◯ MODERATE
Sub: BMI>25	3-6	3	116	-0.15 (-0.68 to 0.37)	0.55	27	No difference	⊕⊕⊕⊕ HIGH
Sub: BMI not specified	**6**	**4**	**170**	**-0.95 (-1.34 to -0.56)**	**<0.00001**	**0**	**Metformin**	⊕⊕⊕◯ MODERATE

DHEAS (ug/dl)	3-6	11	375	-0.12 (-0.32 to 0.08)	0.22	47	No difference	⊕⊕◯◯ LOW
Sub:BMI>25	3-6	5	142	-0.18 (-0.63 to 0.28)	0.45	73	No difference	⊕◯◯◯ VERY LOW
Sub:BMI<25	3-6	5	213	-0.06 (-0.25 to 0.14)	0.58	0	No difference	⊕⊕⊕◯ MODERATE
Androstenedione (nmol/l)	3-6	5	174	-2.06 (-4.29 to 0.17)	0.07	69	No difference	⊕⊕⊕◯ MODERATE
Sub:BMI>25	3-6	2	58	-1.20 (-5.21 to 2.81)	0.56	56	No difference	⊕◯◯◯ VERY LOW
Sub: BMI not specified	6	2	42	-1.14 (-3.62 to 1.34)	0.37	53	No difference	⊕◯◯◯ VERY LOW

Individual studies not included in meta-analysis

Outcome	Author, year	Time point	N	Metformin	Placebo	P-value	Favours	Certainty
BMI	Bridger et al. 2006	3	Met=11 Placebo=10	Mean difference -0.16	Mean difference and 95% CI for the mean difference between groups -0.19 (-1.01 to 0.32)	NR	No difference	⊕⊕◯◯ LOW[1]
Testosterone	Bridger et al. 2006	3	Met=11 Placebo=10	Mean difference -38.3	Mean difference and 95% CI for the mean difference between groups -0.86 (infinity to -0.29)	NR	**Metformin**	⊕⊕◯◯ LOW[1]
	Heidari et al. 2019	3	Met=29 Placebo=13	Median and IQR 24 (15.5-35.5)	Median and IQR 27.5 (21.3-44)	NR	NR	⊕⊕◯◯ LOW[1]
Fasting insulin	Heidari et al. 2019	3	Met=29 Placebo=13	Median and IQR 10.2 (5.9-16)	Median and IQR 11.2 (5.4-17.9)	NR	NR	⊕⊕◯◯ LOW[1]
Fasting glucose	Bridger et al. 2006	3	Met=11 Placebo=10	Mean difference 0.31	Mean difference and 95% CI for the mean difference between groups 0.36 (-3.42 to 5.22)	NR	No difference	⊕⊕◯◯ LOW[1]
Total cholesterol	Bridger et al. 2006	3	Met=11 Placebo=10	Mean difference -0.78	Mean difference and 95% CI for the mean difference between groups -8.15 (-17.07 to 31.82)	NR	No difference	⊕⊕◯◯ LOW[1]
HDL	Bridger et al. 2006	3	Met=11 Placebo=10	Mean difference 6.98	Mean difference and 95% CI for the mean difference	NR	**Metformin**	⊕⊕◯◯ LOW[1]

					between groups -2.33 (0.78 to 18.23)			
LDL	Bridger et al. 2006	3	Met=11 Placebo=10	Mean difference -3.10	Mean difference and 95% CI for the mean difference between groups -7.76 (-12.8 to 18.23)	NR	No difference	⊕⊕◯◯ LOW[1]
Triglycerides	Bridger et al. 2006	3	Met=11 Placebo=10	Mean difference -13.13	Mean difference and 95% CI for the mean difference between groups 7.0 (-70.00 to 29.75)	NR	No difference	⊕⊕◯◯ LOW[1]
CRP	Heidari et al. 2019	3	Met=29 Placebo=13	Median and IQR 3.1 (1.4-6.2)	Median and IQR 7.2 (4.3-11.1)	NR	NR	⊕⊕◯◯ LOW[1]
Girls with restored menses	Bridger et al. 2006	3	Met=11 Placebo=10	10/11=90.9%	4/11=36.4%	1.12 to 5.58 (relative risk 2.50)	**Metformin**	⊕⊕◯◯ LOW[1]
Menstrual cycles/subject per 6 months	Baillargeon et al. 2004	6	Metformin=28 Placebo=30	Means +SD 4.6 +/- 0.77	Means +SD 2.4 +/- 6.70	0.07	No difference	⊕⊕◯◯ LOW[1]
HOMA-IR	Heidari et al. 2019	3	Met=29 Placebo=13	Median and IQR 2.1 (1.1-3.5)	Median and IQR 3.6 (1.4-6.5)	NR	NR	⊕⊕◯◯ LOW[1]
	Bridger et al. 2006	3	Met=11 Placebo=10	Mean difference -1.06	Mean difference and 95% CI for the mean difference between groups 0.86 (-9.26 to 5.42)	NR	No difference	⊕⊕◯◯ LOW[1]
DHEAS	Heidari et al. 2019	3	Met=29 Placebo=13	Median and IQR 123 (75.1-246)	Median and IQR 126 (98.5-150)	NR	NR	⊕⊕◯◯ LOW[1]
oGTT	Heidari et al. 2019	3	Met=29 Placebo=13	Means +SD 142.3 +/- 28.3	Means +SD 136.4 +/- 31.8	0.57	No difference	⊕⊕◯◯ LOW[1]

[1] Downgraded once for mod ROB and downgraded once for small number of participants

[2]

Metformin versus placebo adolescents

There was one study comparing metformin to placebo in adolescents (Hoeger et al. 2008). No statistically significant differences were found for: BMI (kg/m2); Waist (cm); Total testosterone (ng/dl); SHBG (nmol/liter); FAI; Hirsutism (FG score); Total cholesterol (mg/dl); HDL (mg/dl), LDL (mg/dl); Triglycerides (mg/dl); Fasting insulin (IU/ml); Fasting blood sugar (mg/dl); CRP (mg/l); PAI-1.

Study ID	Hoeger 2008	Certainty in effect estimates (Quality of evidence)	Very low

Outcome	Time point	N	Metformin Mean	SD	Placebo Mean	SD	P value	Favours
BMI (kg/m2)	6 months	16	35.0	8.6	35.5	6.8	NR	No difference
Waist (cm)	6 months	16	105.3	13.9	105.3	18.6	NR	No difference
Testosterone (ng/dl)	6 months	16	49.7	31.1	71.6	33.8	NR	No difference
SHBG (nmol/l)	6 months	16	21.1	8.4	19.1	9.4	NR	No difference
FAI	6 months	16	10.9	7.9	16.8	11.2	NR	No difference
Hirsutism (FGS)	6 months	16	8.2	3.4	11.6	4.9	NR	No difference
Total cholesterol (mg/dl)	6 months	16	145.3	25	157	53.2	NR	No difference
HDL (mg/dl)	6 months	16	43.5	19	43.6	8.9	NR	No difference
LDL (mg/dl)	6 months	16	92.0	15.5	114	27.1	NR	No difference
Triglycerides (mg/dl)	6 months	16	71.3	21.1	87.1	25.1	NR	No difference
Fasting insulin (IU/ml)	6 months	16	19.8	10.4	29.1	24.5	NR	No difference
Fasting glucose (mg/dl)	6 months	16	84.9	12.7	86.5	5.4	NR	No difference
CRP (mg/l)	6 months	16	2.8	2.0	4.2	2.8	NR	No difference
PAI-1	6 months	16	45.4	32.2	48.0	45.9	NR	No difference

NR; not reported; A, serious risk of bias; B, serious risk of imprecision; C, serious risk of inconsistency; D, very serious imprecision; E, indirectness

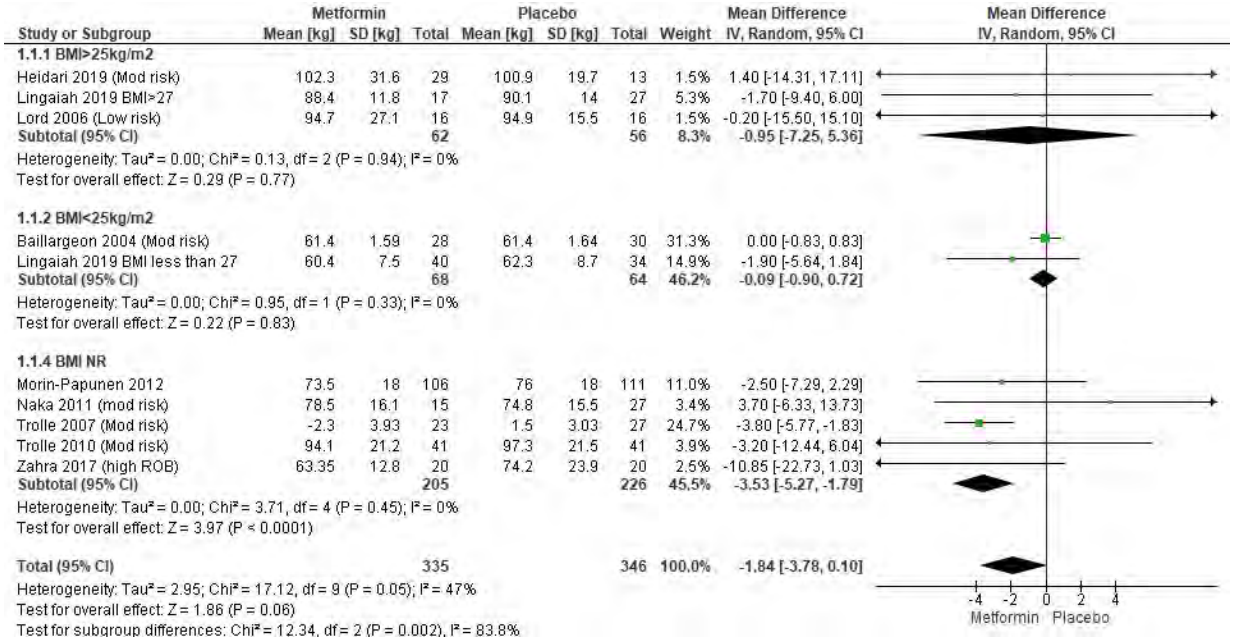
OUTCOME 1.1 WEIGHT

1.1.1 Individual Study Data Table

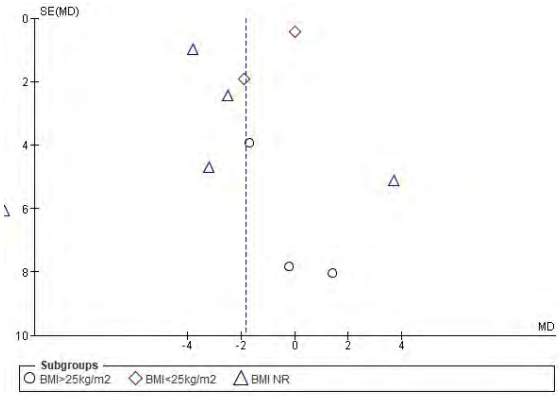
	OUTCOME: Weight					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **Placebo**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Zahra et al.2017	kg	20	63.35	12.8	20	74.2	23.9	Crude	3
Baillargeon et al. 2004	kg	28	61.4	1.59	30	61.4	1.64		6
Heidari et al. 2019	kg	29	102.3	31.6	13	100.9	19.7	BMI>=25	3

Morin-Papunen et al 2012	kg	106-128	73.5	18.0	111-125	76.0	18.0	N varies due to lacking data	3
Lord et al 2006	kg	16	94.66	27.13	16	94.90	15.51		3
Lingaiah et al. 2019	kg	17	88.4	11.8	27	90.1	14	BMI>=27	3
Lingaiah et al. 2019	kg	40	60.4	7.5	34	62.3	8.7	BMI<27	3
Trolle et al. 2010	kg	41	94.1	21.23	41	97.3	21.54		6
Trolle et al. 2007	kg	23	-2.3	3.93	27	1.5	3.03		
Naka et al 2011	kg	15	78.5	16.1	14	74.8	15.5		6

1.1.2 Forrest plot metformin versus placebo for weight (kg)



1.1.3. Funnel plot for assessment of publication bias

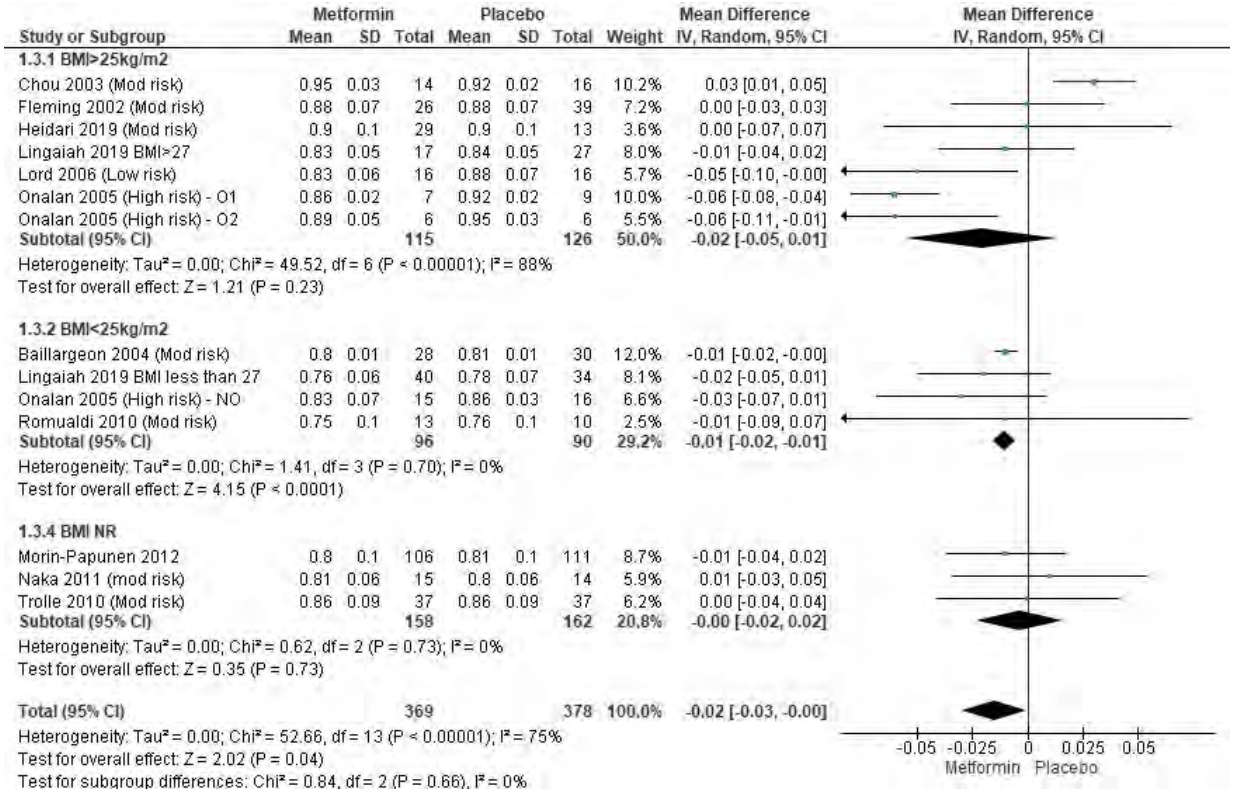


OUTCOME 1.2 WHR

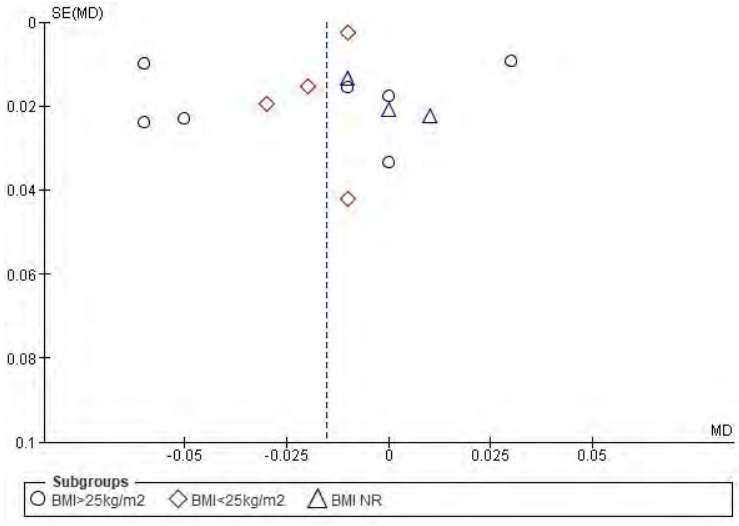
1.2.1 Individual Study Data Table

	OUTCOME: WHR					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus placebo							
Author, year	**Unit of outcome**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Baillargeon et al. 2004		28	0.8	0.01	30	0.81	0.01	Crude	6
Chou et al 2003		14	0.95	0.03	16	0.92	0.02	Crude	3
Heidari et al. 2019		29	0.9	0.1	13	0.9	0.1	BMI>=25	3
Morin-Papunen et al 2012		106-128	0.80	0.1	111-125	0.81	0.1	N varies due to lacking data	3
Lord et al 2006		16	0.83	0.06	16	0.88	0.07	Crude	3
Onalan et al. 2005		15	0.83	0.07	16	0.86	0.03	BMI<25	6
Onalan et al. 2005		7	0.86	0.02	9	0.92	0.02	BMI 25-29.9	6
Onalan et al. 2005		6	0.89	0.05	6	0.95	0.03	BMI>30	6
Romualdi et al. 2010		13	0.75	0.1	10	0.76	0.1	Crude	6
Trolle et al. 2010		37	0.86	0.09	37	0.86	0.09		6
Lingaiah et al. 2019		40	0.76	0.06	34	0.78	0.07	BMI<27	3
Lingaiah et al. 2019		17	0.83	0.05	27	0.84	0.05	BMI>=27	3
Naka et al 2011		15	0.81	0.06	14	0.80	0.06		6
Fleming et al. 2002		26	0.88	0.07	39	0.88	0.07		4
Romualdi et al. 2010		13	0.75	0.1	10	0.76	0.1		6

1.2.2. Forrest plot metformin versus placebo for WHR



1.2.3. Funnel plot for assessment of publication bias



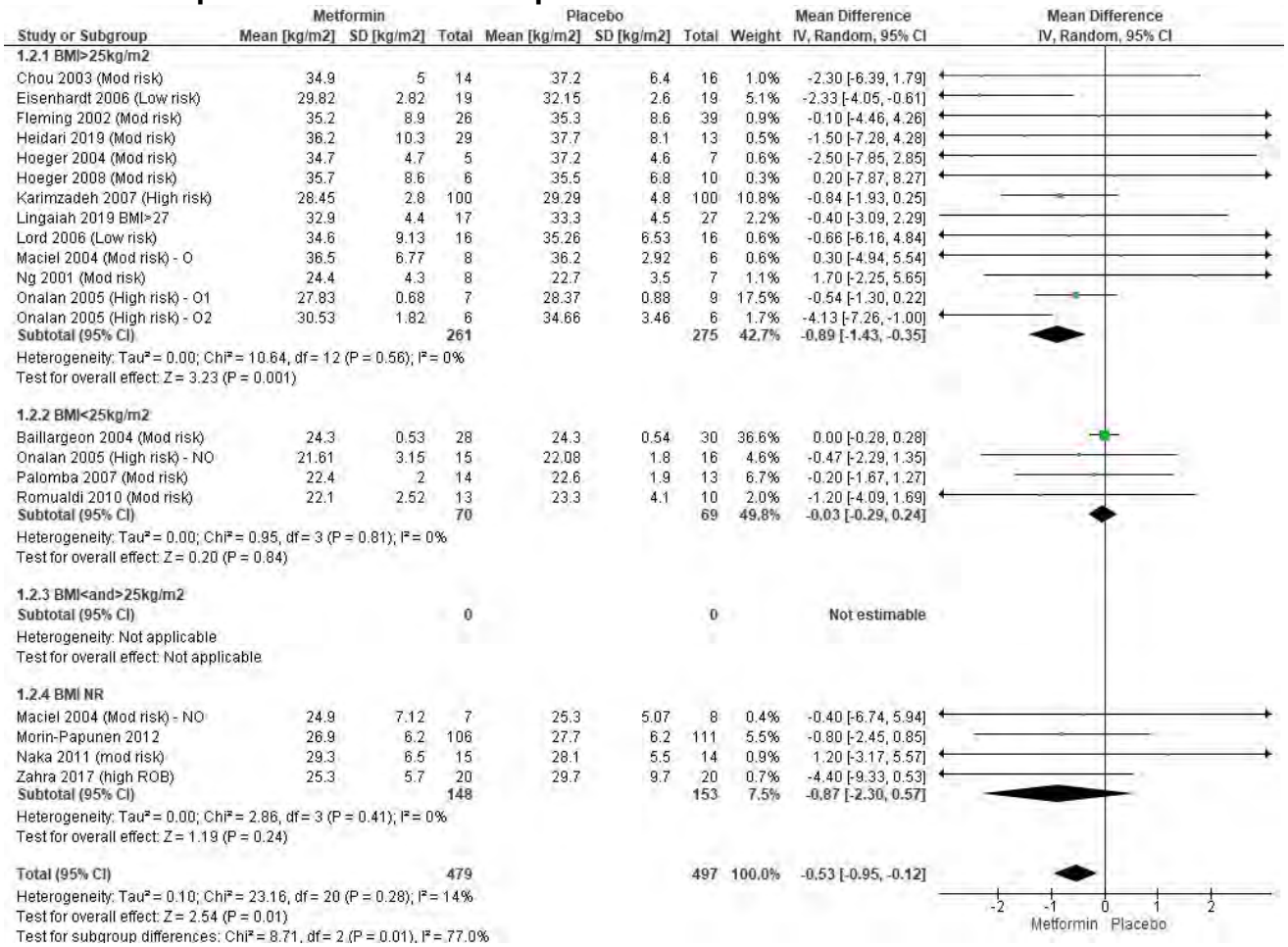
OUTCOME 1.3 BMI (kg/m2)

1.3.1 Individual Study Data Table

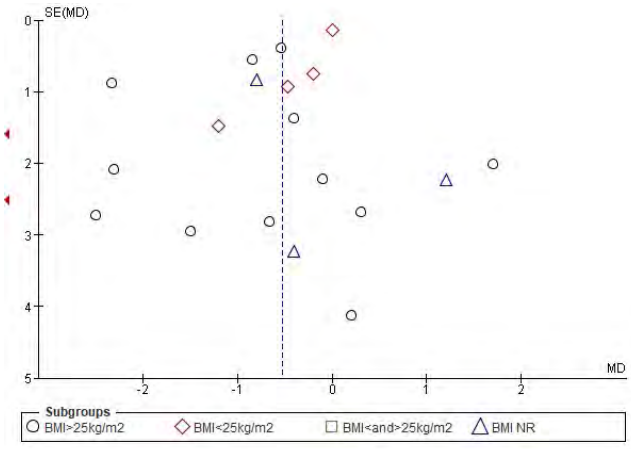
	OUTCOME: BMI					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **Placebo**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Zahra et al. 2017	Kg/m2	20	25.3	5.7	20	29.7	9.7	Crude	3
Baillargeon et al. 2004	Kg/m2	28	24.3	0.53	30	24.3	0.54	Crude	6
Chou et al 2003	Kg/m2	14	34.9	5	16	37.2	6.4	Crude	3
Eisenhardt et al 2006	Kg/m2	19	29.82	2.82	19	32.15	2.6	Crude	3
Fleming et al. 2002	Kg/m2	26	35.2	8.9	39	35.3	8.6	Crude	4
Heidari et al. 2019	Kg/m2	29	36.2	10.3	13	37.7	8.1	BMI>=25	3
Morin-Papunen et al 2012	Kg/m2	106-128	26.9	6.2	111-125	27.7	6.2	N varies due to lacking data	3
Hoeger et al. 2008	Kg/m2	6	35.7	8.6	10	35.5	6.8	Adolescents, obese (above 95 percentil)	6
Lord et al 2006	Kg/m2	16	34.6	9.13	16	35.26	6.53	Crude	3
Maciel et al. 2004	Kg/m2	7	24.9	7.12	8	25.3	5.07	BMI<=30	6
Maciel et al. 2004	Kg/m2	8	36.5	6.77	6	36.2	2.92	BMI>30	6
Lingaiah et al. 2019	Kg/m2	40	22.3	2.2	34	22.7	2.6	BMI<27	3
Lingaiah et al. 2019	Kg/m2	17	32.9	4.4	27	33.3	4.5	BMI>=27	3
Onalan et al. 2005	Kg/m2	15	21.61	3.15	16	22.08	1.8	BMI<25	6
Onalan et al. 2005	Kg/m2	7	27.83	0.68	9	28.37	0.88	BMI 25-29.9	6
Onalan et al. 2005	Kg/m2	6	30.53	182	6	34.66	3.46	BMI>30	6
Palomba et al 2007	Kg/m2	14	22.4	2.0	13	22.6	1.9	Crude	6
Ng et al. 2001	Kg/m2	8	24.4	4.3	7	22.7	3.5	Crude	3
Romualdi et al. 2010	Kg/m2	13	22.1	2.52	10	23.3	4.1	Crude	6

Naka et al 2011	Kg/m2	15	29.3	6.5	14	28.1	5.5		6
Hoeger et al 2004	Kg/m2	5	34.7	4.7	7	37.2	4.6	BMI >25	6
Karimzadeh et al. 2007	Kg/m2	100	28.45	2.8	100	29.29	4.8		3

1.3.2. Forest plot metformin versus placebo for BMI



1.3.3. Funnel plot for assessment of publication bias

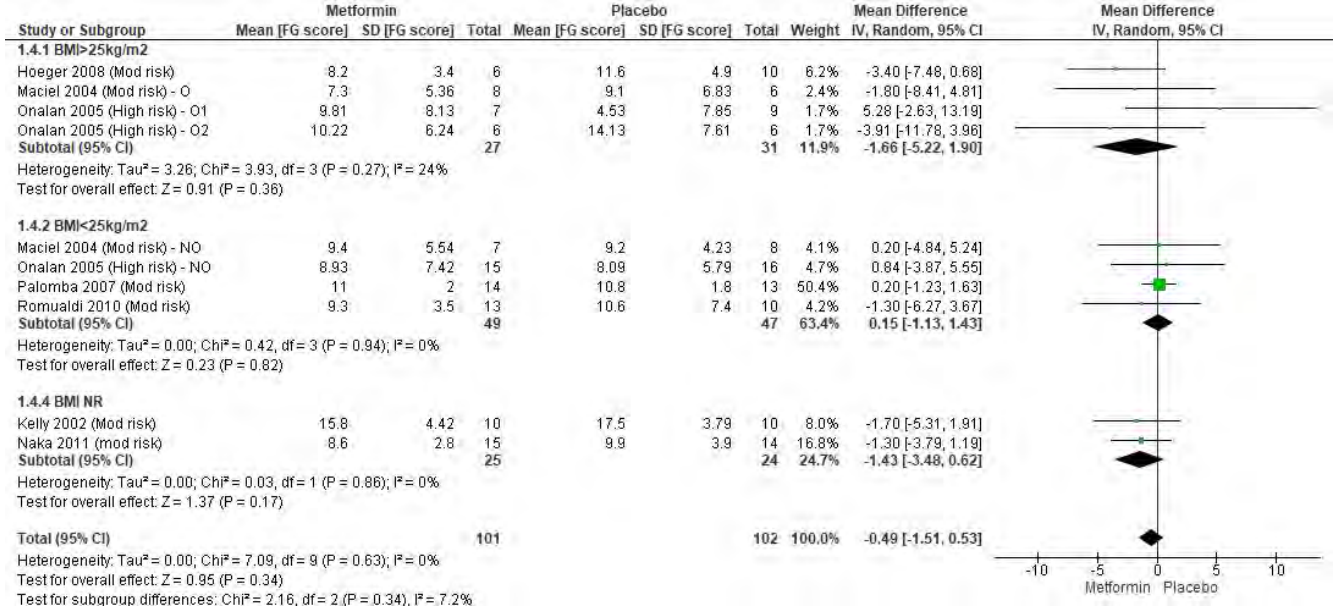


OUTCOME 1.4 Hirsutism (FGS)

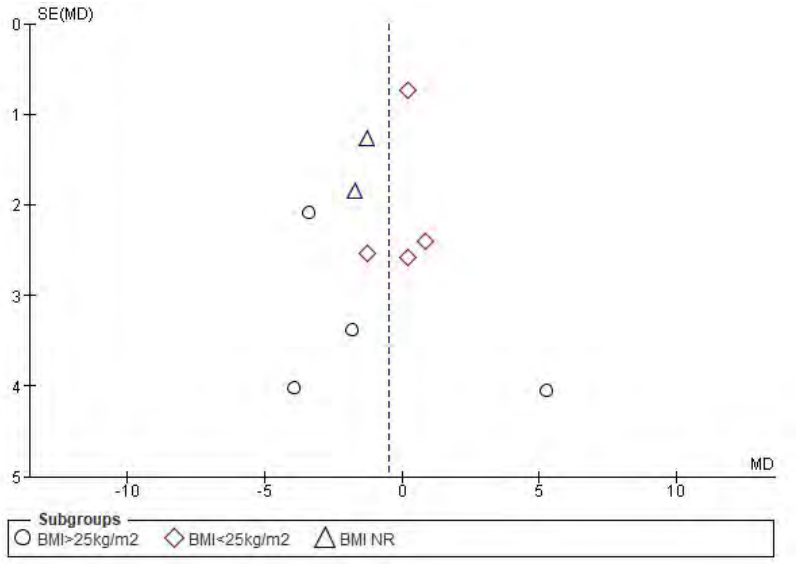
1.4.1 Individual Study Data Table

	OUTCOME: hirsutism					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus placebo							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Hoeger et al. 2008	FGS	6	8.2	3.4	10	11.6	4.9	Adolescents, obese	6
Kelly et al. 2002	FGS	10	15.8	4.42	10	17.5	3.79	Mean and sd (counted in last TR)	6
Maciel et al. 2004	FGS	7	9.4	5.54	8	9.2	4.23	BMI<=30	6
Maciel et al. 2004	FGS	8	7.3	5.36	6	9.1	6.83	BMI>30	6
Onalan et al. 2005	FGS	15	8.93	7.42	16	8.09	5.79	BMI<25	6
Onalan et al. 2005	FGS	7	9.81	8.13	9	4.53	7.85	BMI 25-29.9	6
Onalan et al. 2005	FGS	6	10.22	6.24	6	14.13	7.61	BMI>30	6
Palomba et al 2007	FGS	14	11	2	13	10.8	1.8	Crude	6
Romualdi et al. 2010	FGS	13	9.3	3.5	10	10.6	7.4	Crude	6
Naka et al 2011	FGS	15	8.6	2.8	14	9.9	3.9		6

1.4.2. Forrest plot metformin versus placebo for hirsutism



1.4.3. Funnel plot for assessment of publication bias



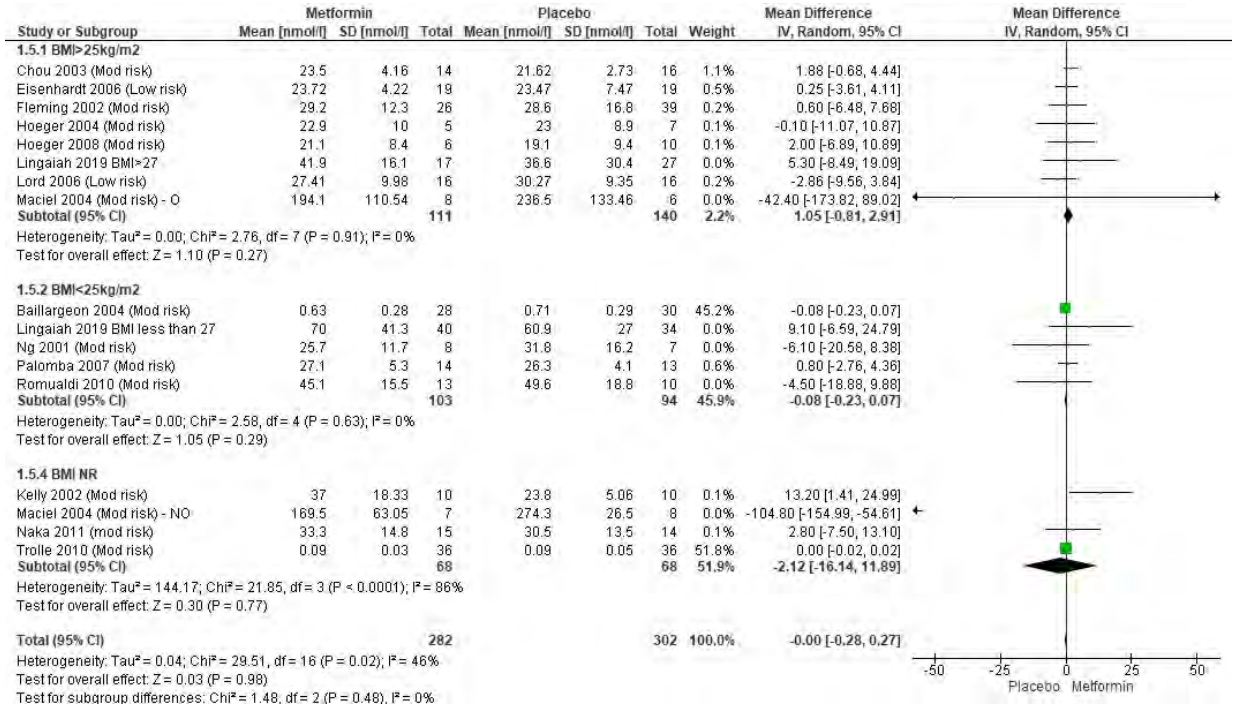
OUTCOME 1.5 SHBG (Nmol/l)

1.5.1 Individual Study Data Table

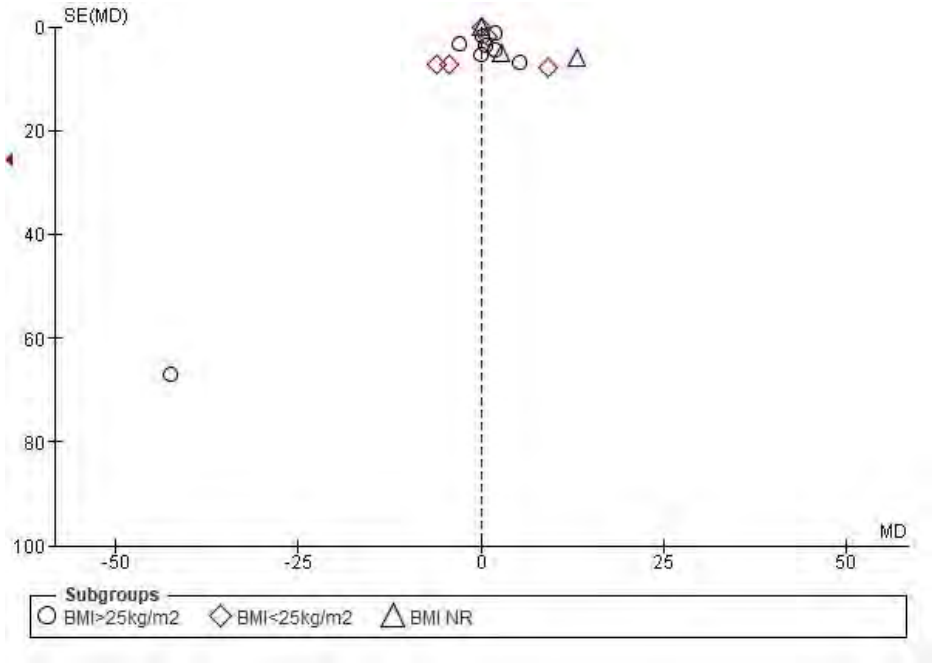
	OUTCOME: SHBG					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **Placebo**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Baillargeon et al. 2004	Nmol/l	28	0.63	0.28	30	0.71	0.29	Crude	6
Chou et al 2003	Nmol/l	14	23.5	4.16	16	21.62	2.73	Crude	3
Eisenhardt et al 2006	Nmol/l	19	23.72	4.22	19	23.47	7.47	Crude	3
Fleming et al. 2002 UK	Nmol/l	26	29.2	12.3	39	28.6	16.8	Crude	4
Hoeger et al. 2008	Nmol/l	6	21.1	8.4	10	19.1	9.4	Adolescents, obese	6
Kelly et al. 2002	Nmol/l	10	37	18.33	10	23.8	5.06	Mean and sd (counted in last TR)	6
Lord et al 2006	Nmol/l	16	27.41	9.98	16	30.27	9.35		3
Maciel et al. 2004	Nmol/l	7	169.5	63.05	8	274.3	26.5	BMI<=30	6

Maciel et al. 2004	Nmol/l	8	194.1	110.54	6	236.5	133.46	BMI>30	6
Lingaiah et al. 2019	Nmol/L	40	70.0	41.3	34	60.9	27.0	BMI<27	3
Lingaiah et al. 2019	Nmol/L	17	41.9	16.1	27	36.6	30.4	BMI>=27	3
Palomba et al 2007	Nmol/l	14	27.1	5.3	13	26.3	4.1	Crude	6
Ng et al. 2001	Nmol/l	8	25.7	11.7	7	31.8	16.2	Crude	3
Romualdi et al. 2010	Nmol/l	13	45.1	15.5	10	49.6	18.8	Crude	6
Trolle et al. 2010	Nmol/l	36	0.09	0.03	36	0.09	0.05		6
Naka et al 2011	Nmol/l	15	33.3	14.8	14	30.5	13.5		6
Hoeger et al 2004	Nmol/l	5	22.9	10	7	23	8.9		6

1.5.2. Forrest plot metformin versus placebo for SHBG



1.5.3. Funnel plot for assessment of publication bias



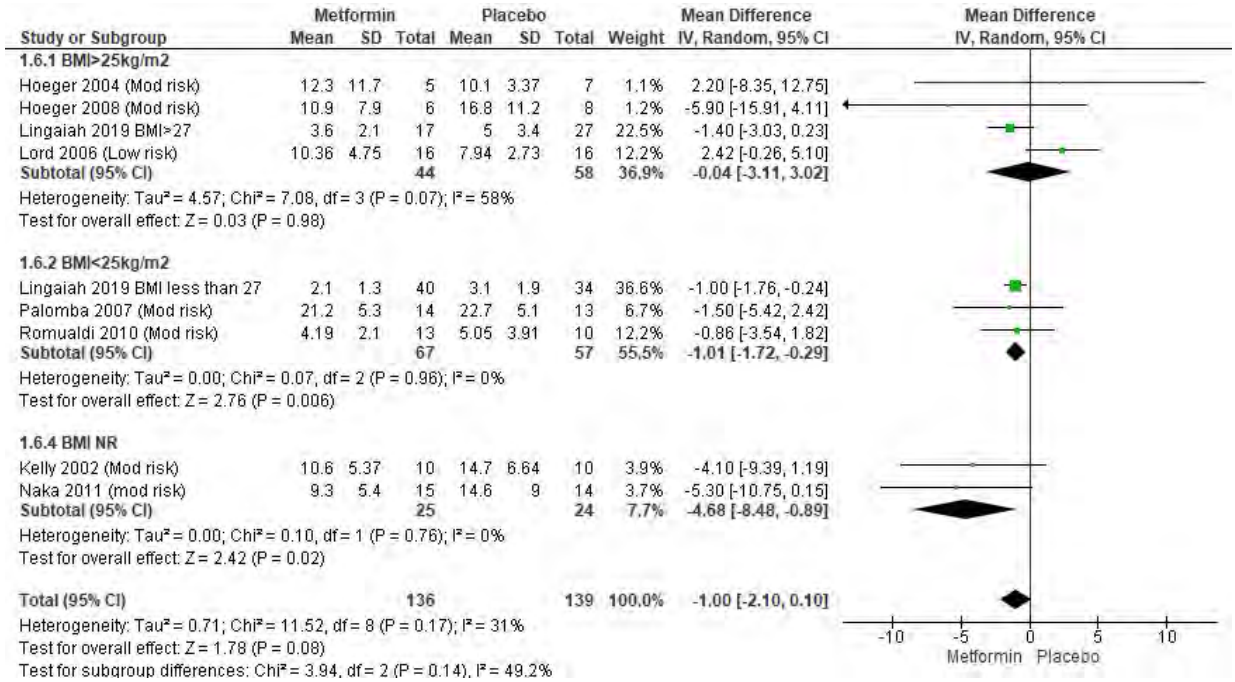
OUTCOME 1.6 FAI

1.6.1 Individual Study Data Table

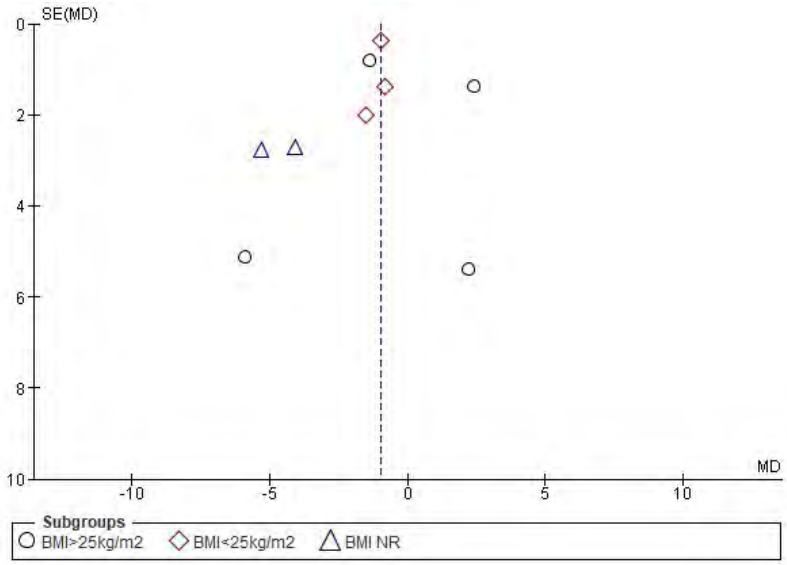
	OUTCOME: FAI					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **Placebo**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Hoeger et al. 2008		6	10.9	7.9	10	16.8	11.2	Adolescents, obese	6
Kelly et al. 2002		10	10.6	5.37	10	14.7	6.64	Mean and sd (counted in last TR)	6
Lord et al 2006		16	10.36	4.75	16	7.94	2.73		3
Palomba et al 2007		14	21.2	5.3	13	22.7	5.1	Crude	6
Romualdi et al. 2010		13	4.19	2.1	10	5.05	3.91	Crude	6
Naka et al 2011		15	9.3	5.4	14	14.6	9.0		6
Hoeger et al 2004		5	12.3	11.7	7	10.1	3.37		6

Lingaiah et al. 2019		17	3.6	2.1	27	5.0	3.4	BMI>=27	3
Lingaiah et al. 2019		40	2.1	1.3	34	3.1	1.9	BMI<27	3

1.6.2. Forrest plot metformin versus placebo for FAI



1.6.3. Funnel plot for assessment of publication bias

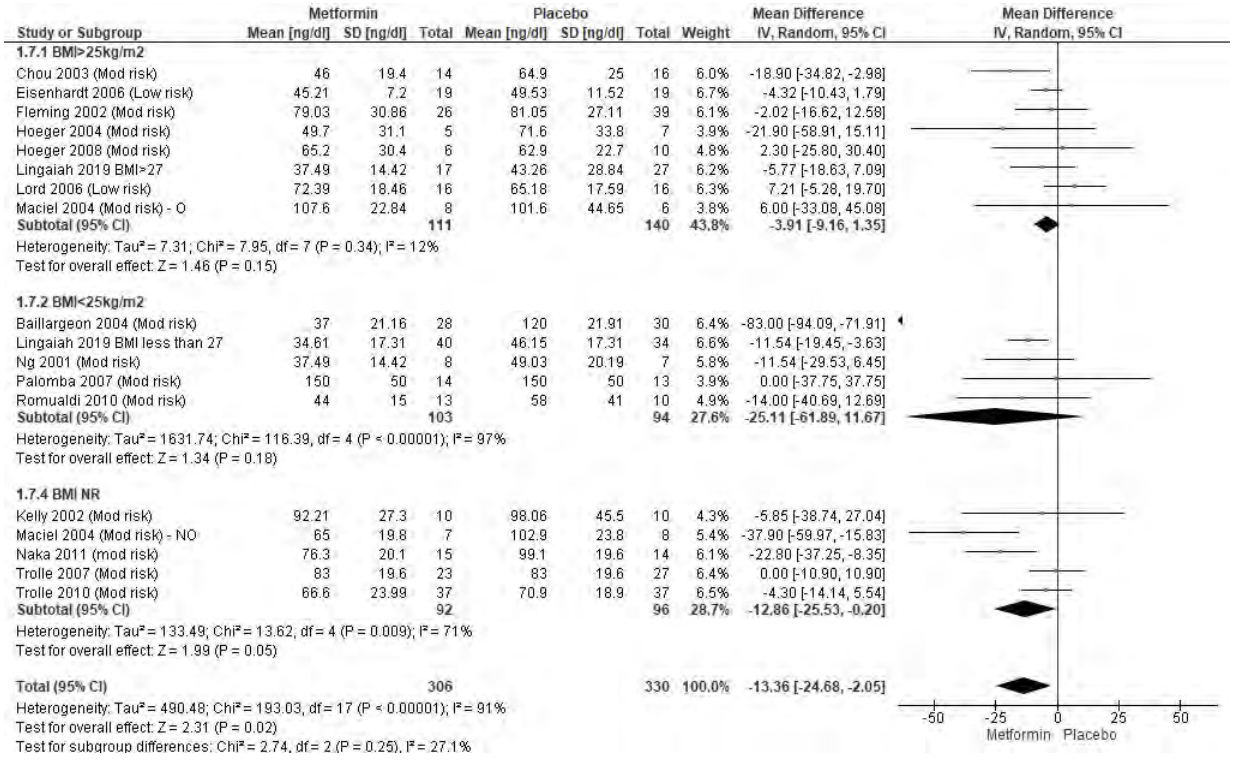


OUTCOME 1.7 Testosterone (ng/dl)

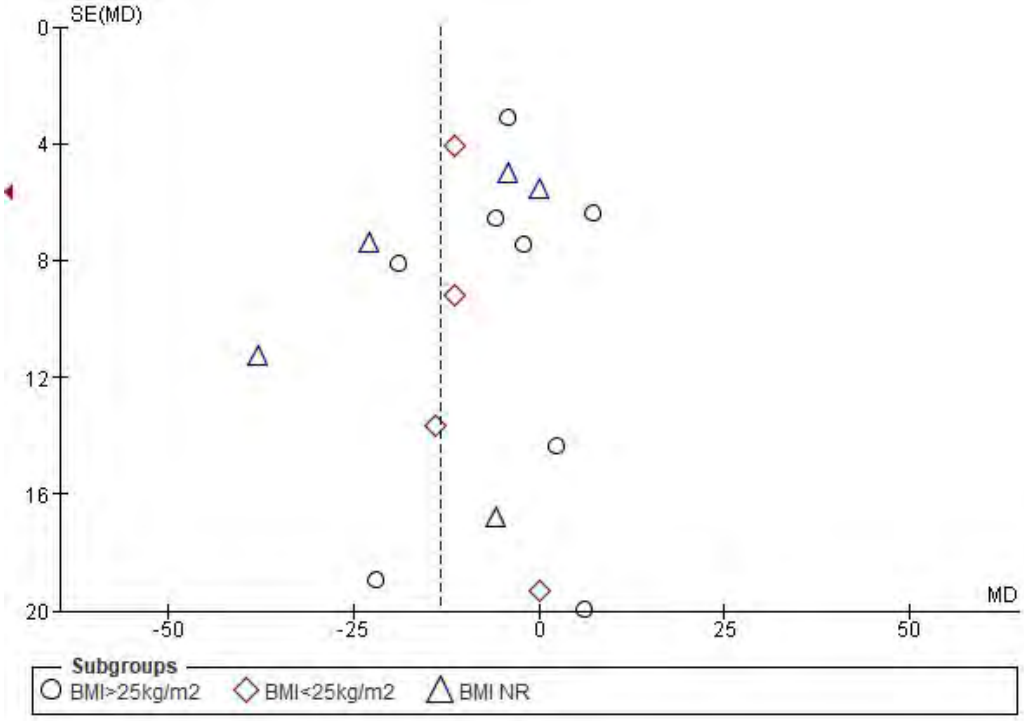
1.7.1 Individual Study Data Table

	OUTCOME: testosterone					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **Placebo**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Baillargeon et al. 2004	Ng/dl	28	37	21.16	30	120	21.91	Crude	6
Chou et al 2003	Ng/dl	14	46	19.4	16	64.9	25	Crude	3
Eisenhardt et al 2006	Ng/dl	19	45.21	7.2	19	49.53	11.52	Crude	3
Fleming et al. 2002 UK	Ng/dl	26	79.03	30.86	39	81.05	27.11	Crude	4
Hoeger et al. 2008	Ng/dl	6	49.7	31.1	10	71.6	33.8	Adolescents, obese	6
Kelly et al. 2002	Ng/dl	10	92.21	27.3	10	98.06	45.5	Mean and sd (counted in last TR)	6
Lord et al 2006	Ng/dl	16	72.39	18.46	16	65.18	17.59		3
Maciel et al. 2004	Ng/dl	7	65	19.8	8	102.9	23.8	BMI<=30	6
Maciel et al. 2004	Ng/dl	8	107.6	22.84	6	101.6	44.65	BMI>30	6
Palomba et al 2007	Ng/dl	14	150	50	13	150	50	Crude	6
Ng et al. 2001	Ng/dl	8	37.49	14.42	7	49.03	20.19	Crude	3
Romualdi et al. 2010	Ng/dl	13	44	15	10	58	41	Crude	6
Trolle et al. 2010	Ng/dl	37	66.6	23.99	37	70.9	18.90		6
Trolle et al. 2007	Ng/dl	23	83	19.6	27	83	19.6		
Naka et al 2011	ng/dl	15	76.3	20.1	14	99.1	19.6		6
Hoeger et al 2004	ng/dl	5	65.2	30.4	7	62.9	22.7		6
Lingaiah et al. 2019	Nmol/L Ng/dl	40	1.2 34.61	0.6 17.31	34	1.6 46.15	0.6 17.31	BMI<27	3
Lingaiah et al. 2019	Nmol/L Ng/dl	17	1.3 37.49	0.5 14.42	27	1.5 43.26	1.0 28.84	BMI>=27	3

1.7.2. Forrest plot metformin versus placebo for testosterone



1.7.3. Funnel plot for assessment of publication bias

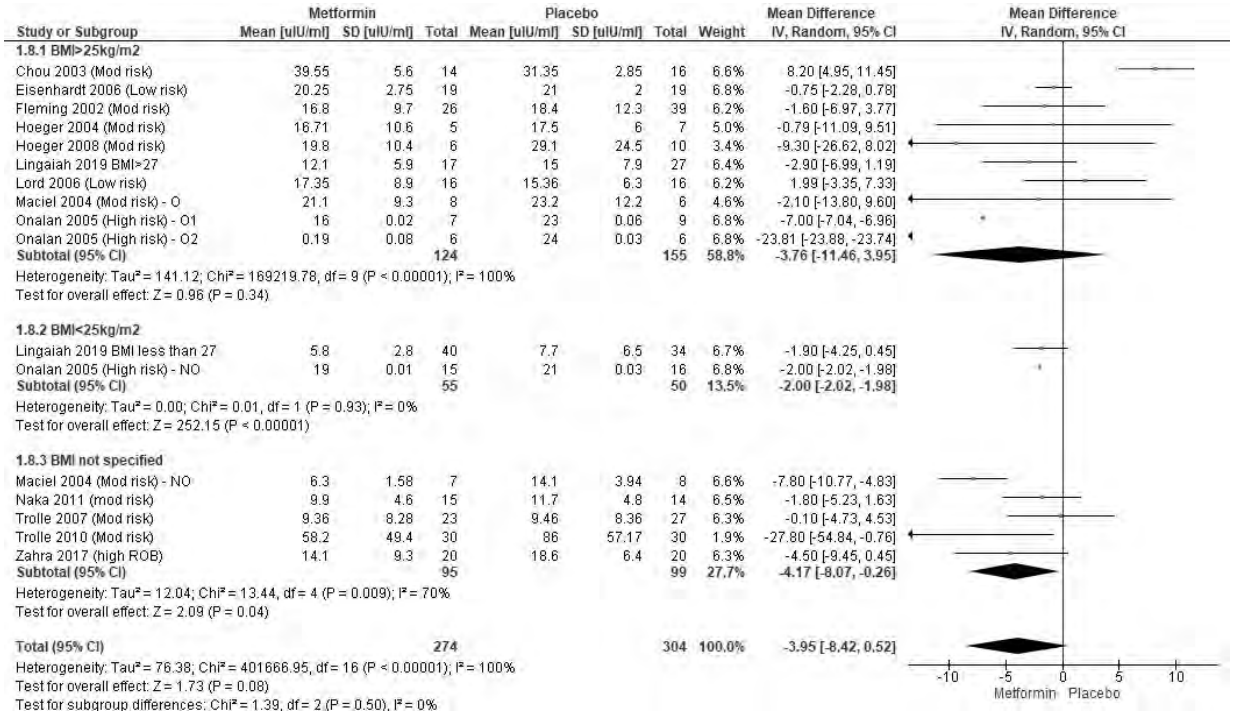


OUTCOME 1.8 Fasting insulin (uIU/ml)

1.8.1 Individual Study Data Table

	OUTCOME: fasting insulin					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **Placebo**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Zahra et al. 2017	IU/l=uIU/ml	20	14.1	9.3	20	18.6	6.4	Crude	3
Chou et al 2003	uIU/ml	14	39.55	5.6	16	31.35	2.85	Crude	3
Eisenhardt et al 2006	uIU/ml	19	20.25	2.75	19	21	2	Crude	3
Fleming et al. 2002 UK	uIU/ml	26	16.8	9.7	39	18.4	12.3	Crude	4
Hoeger et al. 2008	IU/ml	6	19.8	10.4	10	29.1	24.5	Adolescents, obese	6
Lord et al 2006	uIU/ml	16	17.35	8.9	16	15.36	6.3		3
Maciel et al. 2004	uIU/ml	7	6.3	1.58	8	14.1	3.94	BMI<=30	6
Maciel et al. 2004	uIU/ml	8	21.1	9.3	6	23.2	12.2	BMI>30	6
Onalan et al. 2005	uIU/ml	15	19	0.01	16	0.21	0.03	BMI<25	6
Onalan et al. 2005	uIU/ml	7	0.16	0.02	9	0.24	0.06	BMI 25-29.9	6
Onalan et al. 2005	uIU/ml	6	0.19	0.08	6	0.23	0.03	BMI>30	6
Trolle et al. 2010	uIU/ml	30	58.2	49.4	30	86	57.17		6
Trolle et al. 2007	uIU/ml	23	9.36	8.28	27	9.46	8.36		6
Naka et al 2011	uIU/ml	15	9.9	4.6	14	11.7	4.8		6
Hoeger et al 2004	uIU/ml	5	16.71	10.6	7	17.5	6		6
Lingaiah et al. 2019	mU/L=uIU/ml	40	5.8	2.8	34	7.7	6.5	BMI<27	3
Lingaiah et al. 2019	mU/L=uIU/ml	17	12.1	5.9	27	15.0	7.9	BMI>=27	3

1.8.2. Forrest plot metformin versus placebo for fasting insulin



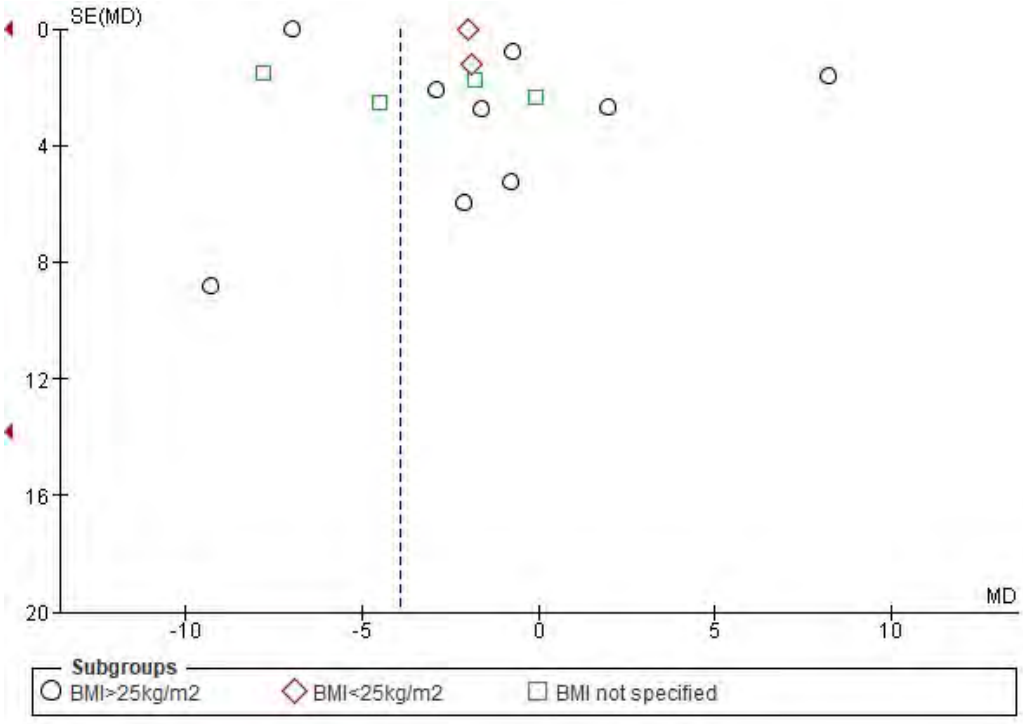
Study or Subgroup	Metformin Mean [ulU/ml]	SD [ulU/ml]	Total	Placebo Mean [ulU/ml]	SD [ulU/ml]	Total	Weight	Mean Difference IV, Random, 95% CI
1.8.1 BMI>25kg/m2								
Chou 2003 (Mod risk)	39.55	5.6	14	31.35	2.85	16	6.6%	8.20 [4.95, 11.45]
Eisenhardt 2006 (Low risk)	20.25	2.75	19	21	2	19	6.8%	-0.75 [-2.28, 0.78]
Fleming 2002 (Mod risk)	16.8	9.7	26	18.4	12.3	39	6.2%	-1.60 [-6.97, 3.77]
Hoeger 2004 (Mod risk)	16.71	10.6	5	17.5	6	7	5.0%	-0.79 [-11.09, 9.51]
Hoeger 2008 (Mod risk)	19.8	10.4	6	29.1	24.5	10	3.4%	-9.30 [-26.62, 8.02]
Lingaiah 2019 BMI>27	12.1	5.9	17	15	7.9	27	6.4%	-2.90 [-6.99, 1.19]
Lord 2006 (Low risk)	17.35	8.9	16	15.36	6.3	16	6.2%	1.99 [-3.35, 7.33]
Maciel 2004 (Mod risk) - O	21.1	9.3	8	23.2	12.2	6	4.6%	-2.10 [-13.80, 9.60]
Onalan 2005 (High risk) - O1	16	0.02	7	23	0.06	9	6.8%	-7.00 [-7.04, -6.96]
Onalan 2005 (High risk) - O2	0.19	0.08	6	24	0.03	6	6.8%	-23.81 [-23.88, -23.74]
Subtotal (95% CI)			**124**			**155**	**58.8%**	**-3.76 [-11.46, 3.95]**
Heterogeneity: Tau² = 141.12; Chi² = 169219.78, df = 9 (P < 0.00001); I² = 100%								
Test for overall effect: Z = 0.96 (P = 0.34)								
1.8.2 BMI<25kg/m2								
Lingaiah 2019 BMI less than 27	5.8	2.8	40	7.7	6.5	34	6.7%	-1.90 [-4.25, 0.45]
Onalan 2005 (High risk) - NO	19	0.01	15	21	0.03	16	6.8%	-2.00 [-2.02, -1.98]
Subtotal (95% CI)			**55**			**50**	**13.5%**	**-2.00 [-2.02, -1.98]**
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); I² = 0%								
Test for overall effect: Z = 252.15 (P < 0.00001)								
1.8.3 BMI not specified								
Maciel 2004 (Mod risk) - NO	6.3	1.58	7	14.1	3.94	8	6.6%	-7.80 [-10.77, -4.83]
Naka 2011 (mod risk)	9.9	4.6	15	11.7	4.8	14	6.5%	-1.80 [-5.23, 1.63]
Trolle 2007 (Mod risk)	9.36	8.28	23	9.46	8.36	27	6.3%	-0.10 [-4.73, 4.53]
Trolle 2010 (Mod risk)	58.2	49.4	30	86	57.17	30	1.9%	-27.80 [-54.84, -0.76]
Zahra 2017 (high ROB)	14.1	9.3	20	18.6	6.4	20	6.3%	-4.50 [-9.45, 0.45]
Subtotal (95% CI)			**95**			**99**	**27.7%**	**-4.17 [-8.07, -0.26]**
Heterogeneity: Tau² = 12.04; Chi² = 13.44, df = 4 (P = 0.009); I² = 70%								
Test for overall effect: Z = 2.09 (P = 0.04)								
Total (95% CI)			**274**			**304**	**100.0%**	**-3.95 [-8.42, 0.52]**
Heterogeneity: Tau² = 76.38; Chi² = 401666.95, df = 16 (P < 0.00001); I² = 100%								
Test for overall effect: Z = 1.73 (P = 0.08)								
Test for subgroup differences: Chi² = 1.39, df = 2 (P = 0.50), I² = 0%								

Mean Difference IV, Random, 95% CI

-10 -5 0 5 10

Metformin Placebo

1.8.3. Funnel plot for assessment of publication bias



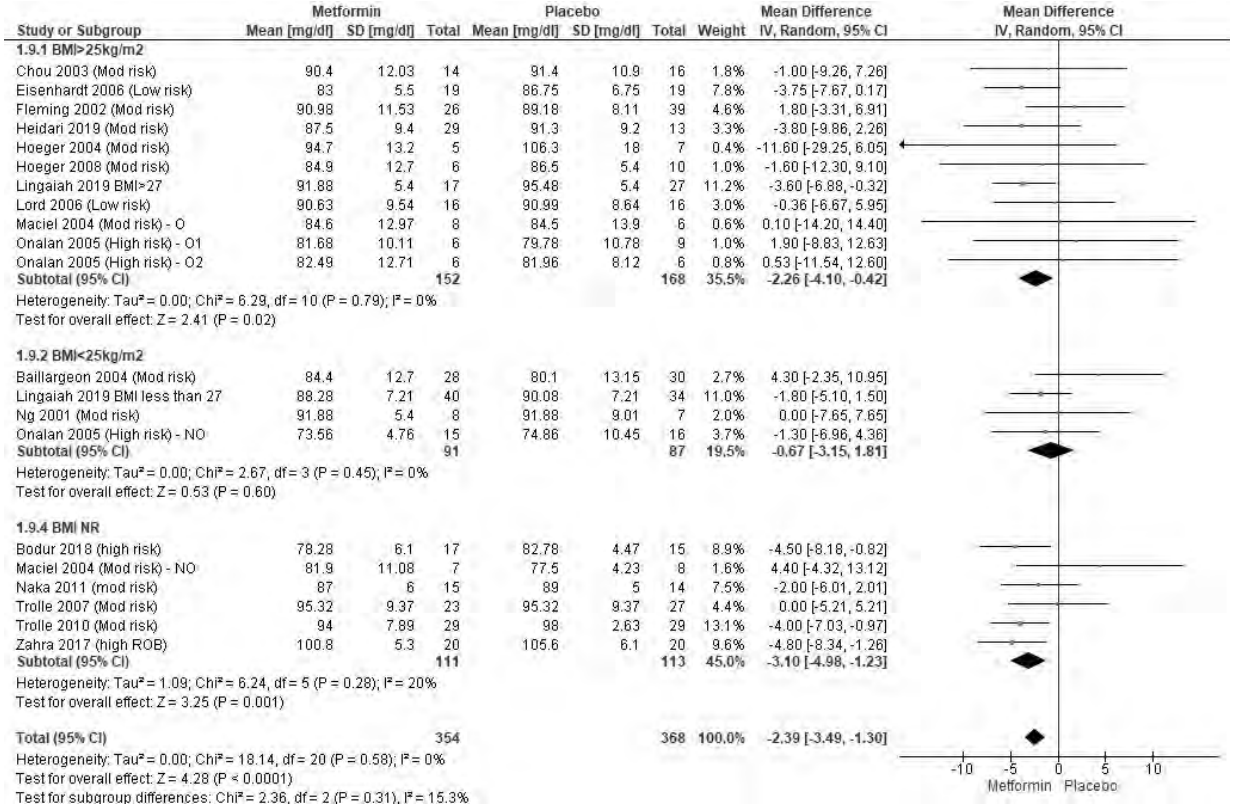
OUTCOME 1.9 Fasting glucose (mg/dl)

1.9.1 Individual Study Data Table

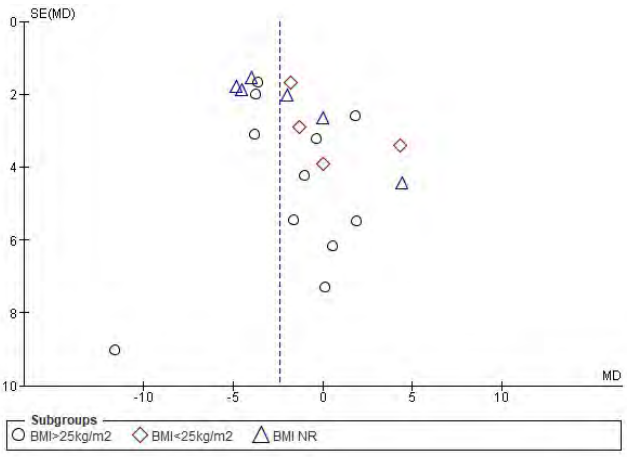
	OUTCOME: fasting glucose					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **Placebo**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Zahra et al. 2017	Mg/dl	20	100.8	5.3	20	105.6	6.1	Crude	3
Baillargeon et al. 2004	Mg/dl	28	84.4	12.70	30	80.1	13.15	Crude	6
Chou et al 2003	Mg/dl	14	90.4	12.03	16	91.4	10.9	Crude	3
Eisenhardt et al 2006	Mg/dl	19	83	5.5	19	86.75	6.75	Crude	3
Fleming et al. 2002 UK	Mg/dl	26	90.98	11.53	39	89.18	8.11	Crude	4
Bodur et al. 2018	Mg/dl	17	78.28	6.1	15	82.78	4.47	Crude	6
Heidari et al. 2019	Mg/dl	29	87.5	9.4	13	91.3	9.2	BMI>=25	3
Hoeger et al. 2008	mg/dl	6	84.9	12.7	10	86.5	5.4	Adolescents, obese	6
Lord et al 2006	Mg/dl	16	90.63	9.54	16	90.99	8.64		3
Maciel et al 2004	mg/dl	7	81.9	11.08	8	77.5	4.23	BMI<=30	6
Maciel et al. 2004	mg/dl	8	84.6	12.97	6	84.5	13.9	BMI>30	6
Lingaiah et al. 2019	mmol/L mg/dl	17	5.1 91.88	0.3 5.40	27	5.3 95.48	0.3 5.40	BMI>=27	3
Lingaiah et al. 2019	mmol/L mg/dl	40	4.9 88.28	0.4 7.21	34	5.0 90.08	0.4 7.21	BMI<27	3
Onalan et al. 2005	Mg/dl	15	73.56	4.76	16	74.86	10.45	BMI<25	6
Onalan et al. 2005	Mg/dl	7	81.68	10.11	9	79.78	10.78	BMI 25-29.9	6
Onalan et al. 2005	Mg/dl	6	82.49	12.71	6	81.96	8.12	BMI>30	6
Ng et al. 2001	Mg/dl	8	91.88	5.40	7	91.88	9.01	Crude	3
Trolle et al. 2010	Mg/dl	29	94	7.89	29	98	2.63		6
Naka et al 2011	Mg/dl	15	87	6	14	89	5		6

Trolle et al. 2007	Mg/dl	23	95.32	9.37	27	95.32	9.37		6
Hoeger et al 2004	Mg/dl	5	94.7	13.2	7	106.3	18		6
Bodur et al. 2018	Mg/dl	17	78.28	6.1	15	82.78	4.47	BMI<30	6

1.9.2. Forrest plot metformin versus placebo for fasting glucose



1.9.3. Funnel plot for assessment of publication bias

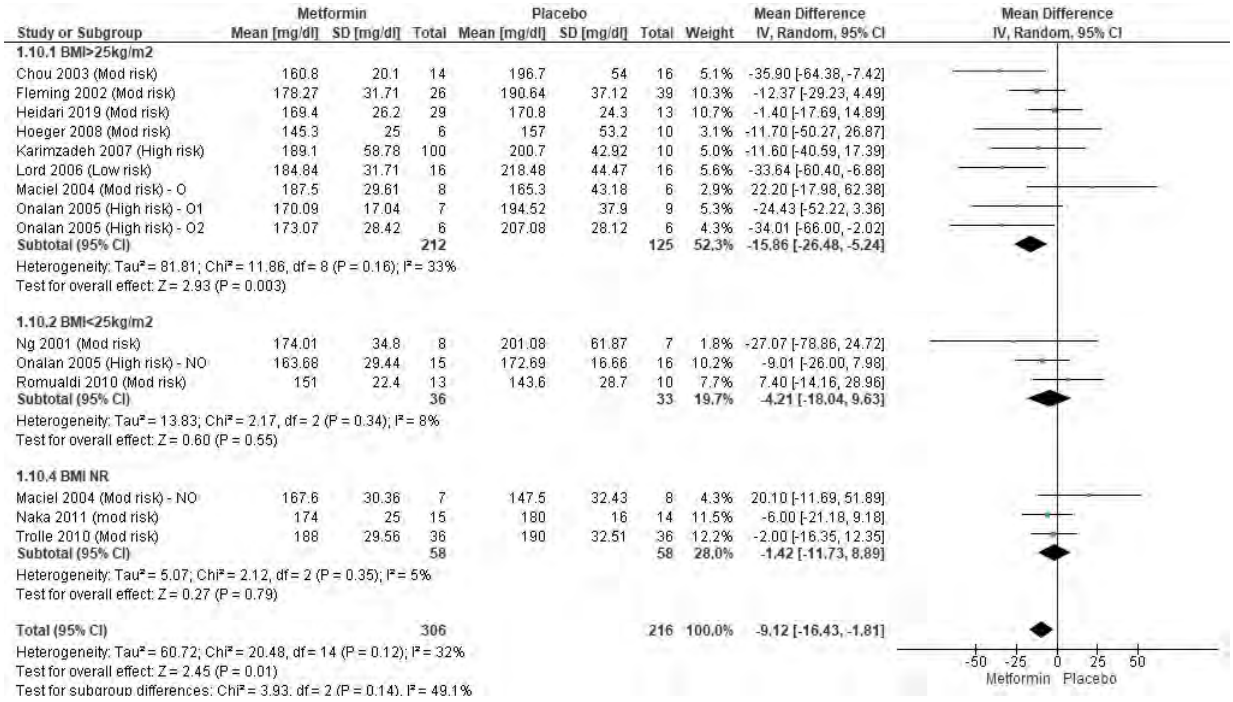


OUTCOME 1.10 Total cholesterol (mg/dl)

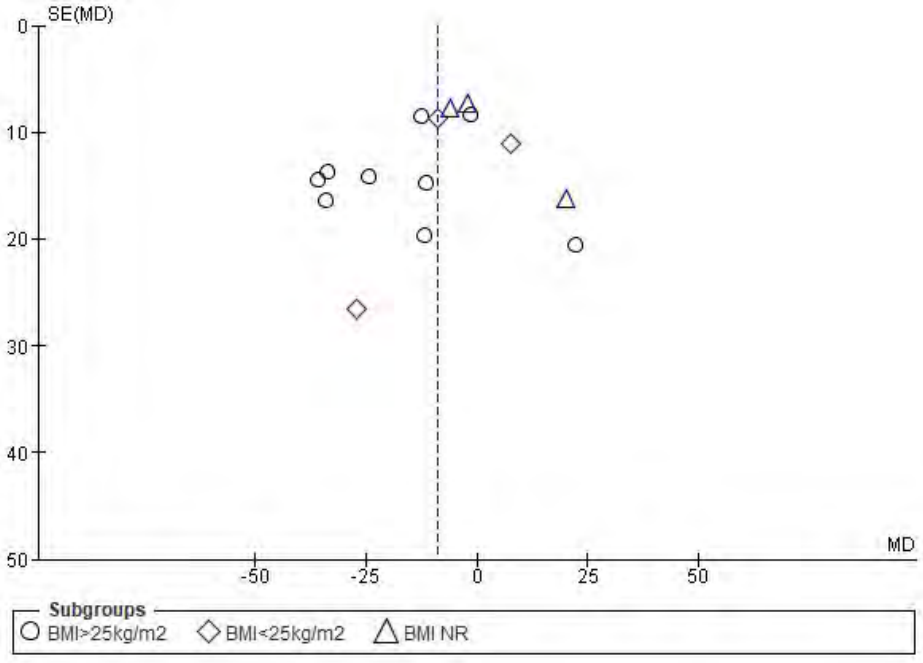
1.10.1 Individual Study Data Table

	OUTCOME: total cholesterol					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **Placebo**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Chou et al 2003	Mg/dl	14	160.8	20.1	16	196.7	54	Crude	3
Fleming et al. 2002 UK	mg/dl	26	178.27	31.71	39	190.64	37.12	Crude	4
Heidari et al. 2019	Mg/dl	29	169.4	26.2	13	170.8	24.3	Crude	3
Karimzadeh et al. 2007	Mg/dl	100	189.1	58.78	100	200.7	42.92	Crude	3
Hoeger et al. 2008	mg/dl	6	145.3	25	10	157	53.2	Adolescents, obese	6
Lord et al 2006	Mg/dl	16	184.84	31.71	16	218.48	44.47		3
Maciel et al. 2004	Mg/dl	7	167.6	30.36	8	147.5	32.43	BMI<=30	6
Maciel et al. 2004	Mg/dl	8	187.5	29.61	6	165.3	43.18	BMI>30	6
Onalan et al. 2005	Mg/dl	15	163.68	29.44	16	172.69	16.66	BMI<25	6
Onalan et al. 2005	Mg/dl	7	170.09	17.04	9	194.52	37.9	BMI 25-29.9	6
Onalan et al. 2005	Mg/dl	6	173.07	28.42	6	207.08	28.12	BMI>30	6
Ng et al. 2001	Mg/dl	8	174.01	34.80	7	201.08	61.87	Crude	3
Romualdi et al. 2010	Mg/dl	13	151	22.4	10	143.6	28.7	Crude	6
Trolle et al. 2010	Mg/dl	36	188	29.56	36	190	32.51		6
Naka et al 2011	Mg/dl	15	174	25	14	180	16		6

1.10.2. Forrest plot metformin versus placebo for total cholesterol



1.10.3. Funnel plot for assessment of publication bias

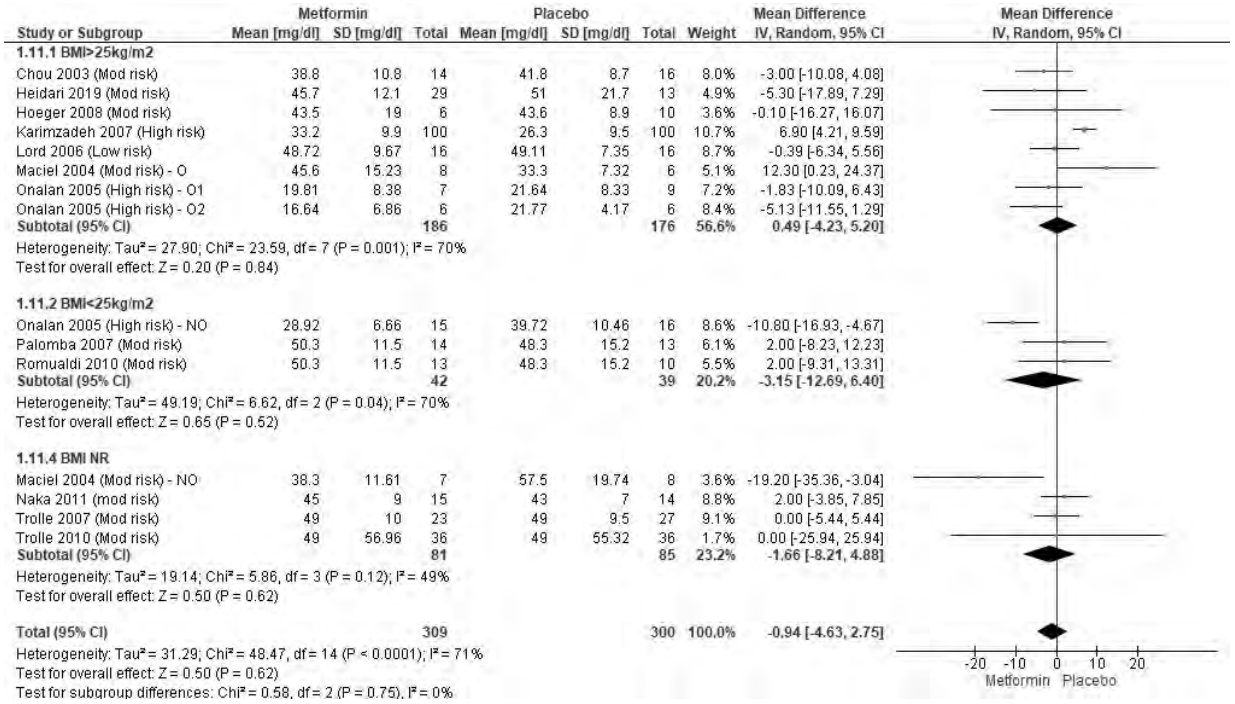


OUTCOME 1.11 HDL (mg/dl)

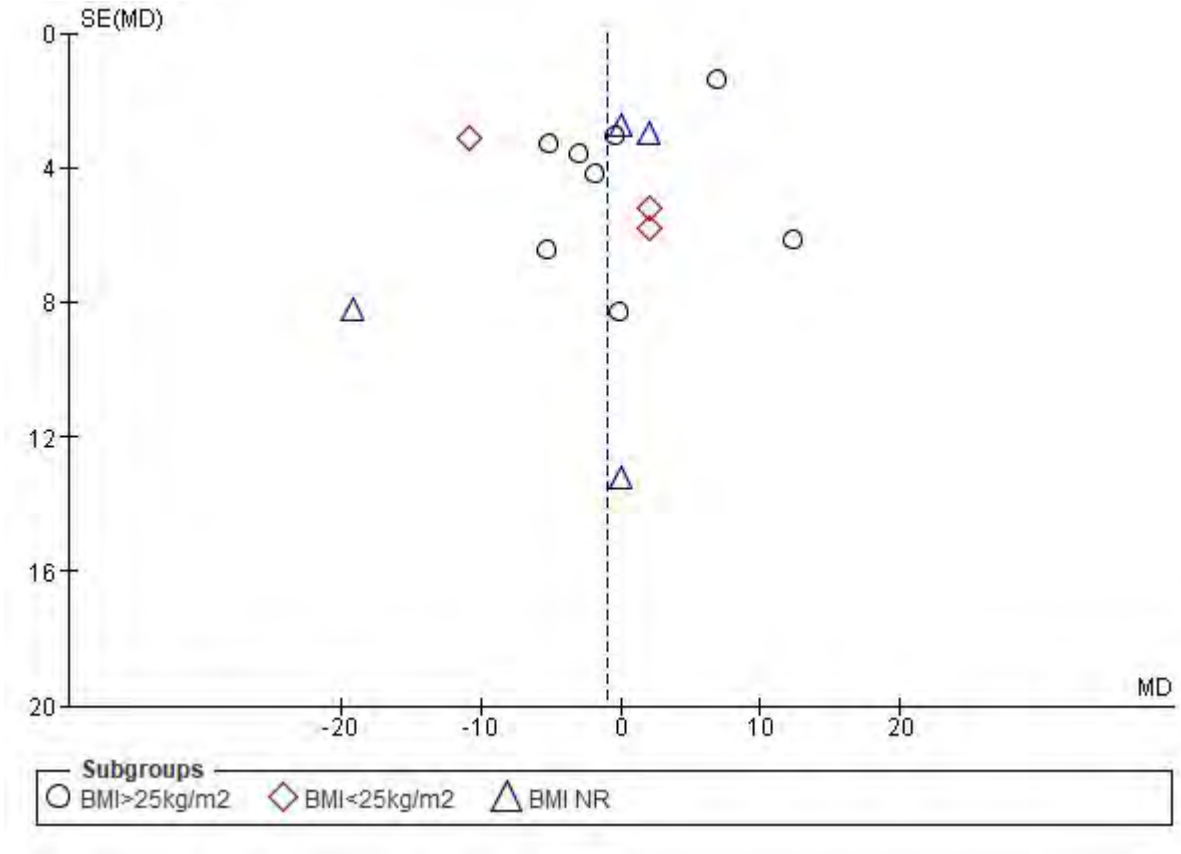
1.11.1 Individual Study Data Table

	OUTCOME: HDL					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **Placebo**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Chou et al 2003	Mg/dl	14	38.8	10.8	16	41.8	8.7	Crude	3
Heidari et al. 2019	Mg/dl	29	45.7	12.1	13	51	21.7	Crude	3
Karimzadeh et al. 2007	Mg/dl	100	33.2	9.9	100	26.3	9.5	Crude	3
Hoeger et al. 2008	mg/dl	6	43.5	19	10	43.6	8.9	Adolescents, obese	6
Lord et al 2006	Mg/dl	16	48.72	9.67	16	49.11	7.35		3
Maciel et al. 2004	Mg/dl	7	38.3	11.61	8	57.5	19.74	BMI<=30	6
Maciel et al. 2004	Mg/dl	8	45.6	15.23	6	33.3	7.32	BMI>30	6
Onalan et al. 2005	Mg/dl	15	28.92	6.66	16	39.72	10.46	BMI<25	6
Onalan et al. 2005	Mg/dl	7	19.81	8.38	9	21.64	8.33	BMI 25-29.9	6
Onalan et al. 2005	Mg/dl	6	16.64	6.86	6	21.77	4.17	BMI>30	6
Palomba et al 2007	Mg/dl	14	50.3	11.5	13	48.3	15.2	Crude	6
Romualdi et al. 2010	Mg/dl	13	50.3	11.5	10	48.3	15.2	Crude	6
Trolle et al. 2010	Mg/dl	36	49	56.96	36	49	55.32		6
Trolle et al. 2007	Mg/dl	23	49	10	27	49	9.5		6
Naka et al 2011	Mg/dl	15	45	9	14	43	7		6

1.11.2. Forrest plot metformin versus placebo for HDL



1.11.3. Funnel plot for assessment of publication bias

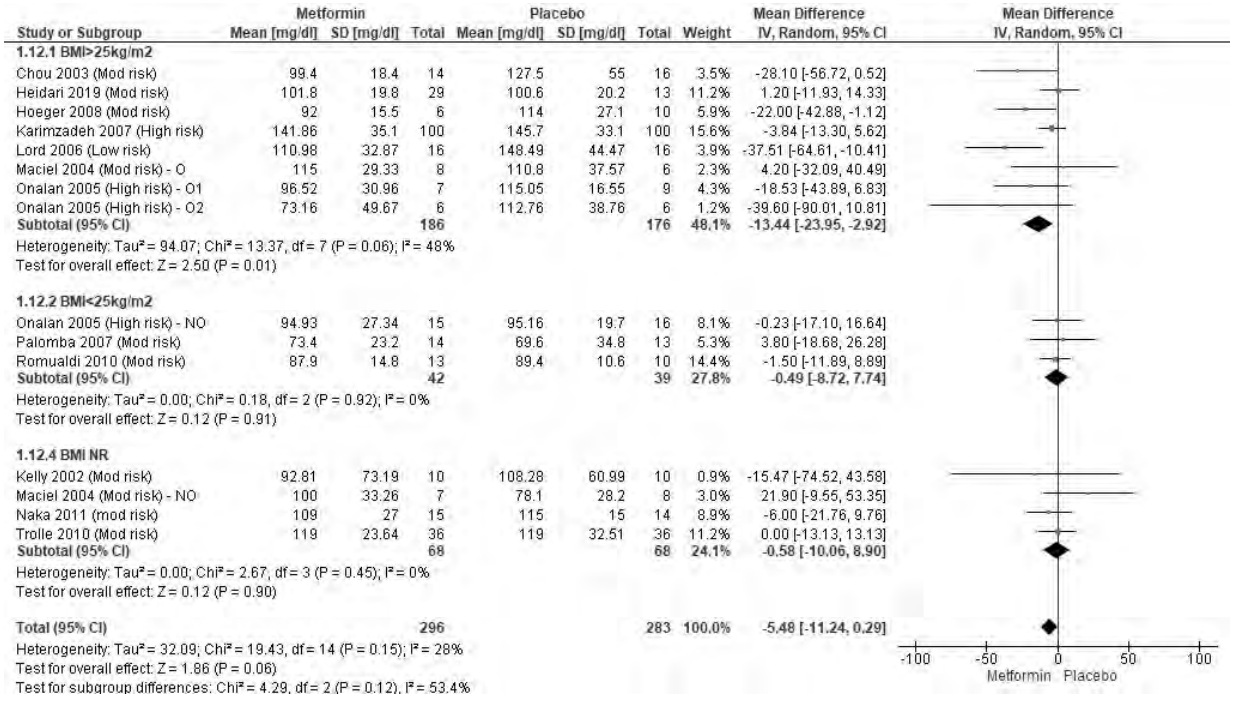


OUTCOME 1.12 LDL (mg/dl)

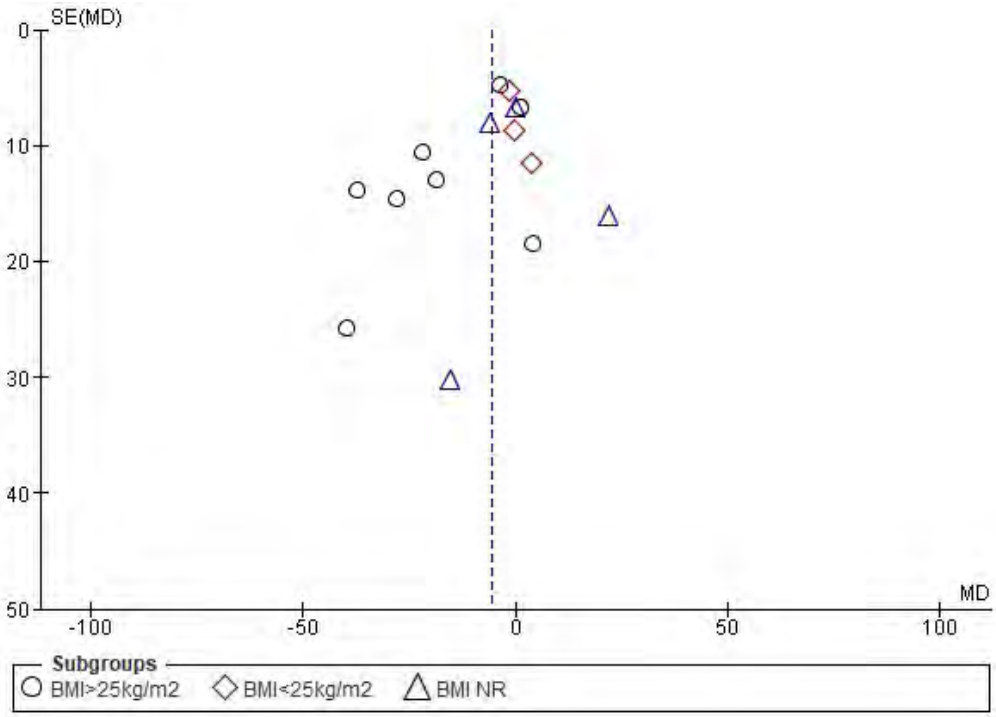
1.12.1 Individual Study Data Table

	OUTCOME: LDL					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **Placebo**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Chou et al 2003	Mg/dl	14	99.4	18.4	16	127.5	55	Crude	3
Heidari et al. 2019	Mg/dl	29	101.8	19.8	13	100.6	20.2	Crude	3
Karimzadeh et al. 2007	Mg/dl	100	141.86	35.1	100	145.7	33.1	Crude	3
Hoeger et al. 2008	mg/dl	6	92.0	15.5	10	114	27.1	Adolescents, obese	6
Kelly et al. 2002	Mg/dl	10	92.81	73.19	10	108.28	60.99	Mean and sd (counted in last TR)	6
Lord et al 2006	Mg/dl	16	110.98	32.87	16	148.49	44.47		3
Maciel et al. 2004	Mg/dl	7	100	33.26	8	78.1	28.2	BMI<=30	6
Maciel et al. 2004	Mg/dl	8	115	29.33	6	110.8	37.57	BMI>30	6
Onalan et al. 2005	Mg/dl	15	94.93	27.34	16	95.16	19.7	BMI<25	6
Onalan et al. 2005	Mg/dl	7	96.52	30.96	9	115.05	16.55	BMI 25-29.9	6
Onalan et al. 2005	Mg/dl	6	73.16	49.67	6	112.76	38.76	BMI>30	6
Palomba et al 2007	Mg/dl	14	73.4	23.2	13	69.6	34.8	Crude	6
Romualdi et al. 2010	Mg/dl	13	87.9	14.8	10	89.4	10.6	Crude	6
Trolle et al. 2010	Mg/dl	36	119	23.64	36	119	32.51		6
Naka et al 2011	Mg/dl	15	109	27	14	115	15		6

1.12.2. Forrest plot metformin versus placebo for LDL



1.12.3. Funnel plot for assessment of publication bias

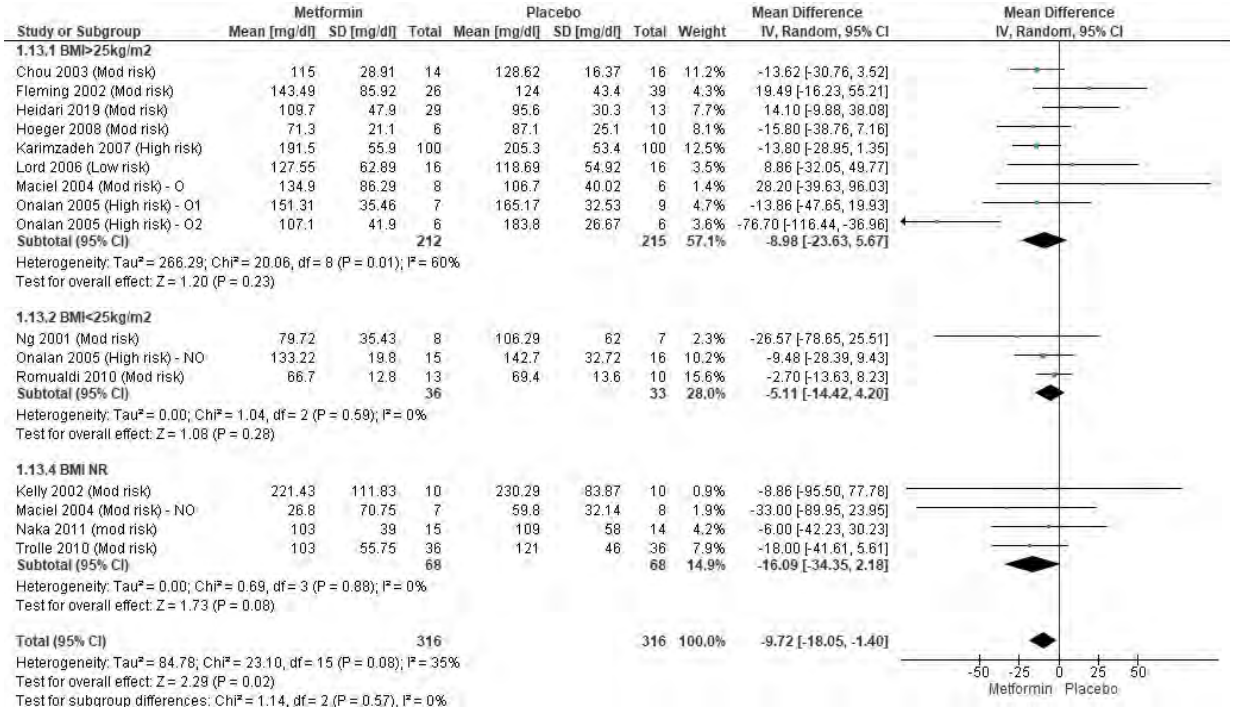


OUTCOME 1.13 Triglycerides (mg/dl)

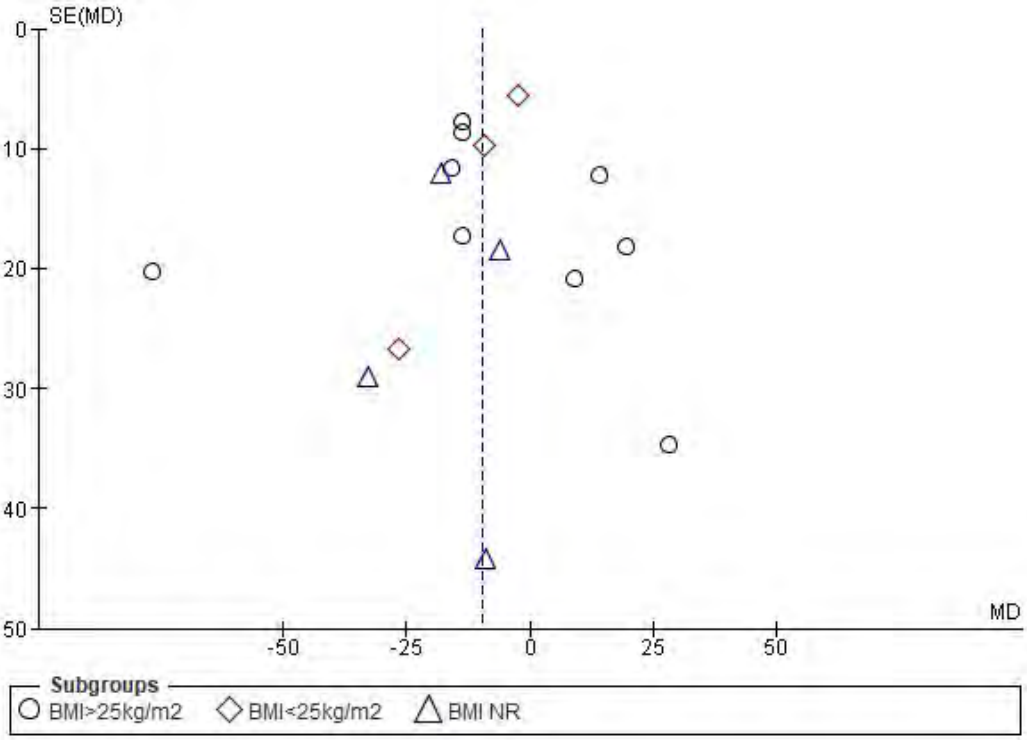
1.13.1 Individual Study Data Table

	OUTCOME: triglycerides					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **Placebo**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Chou et al 2003	Mg/dl	14	115	28.91	16	128.62	16.37	Crude	3
Fleming et al. 2002 UK	Mg/dl	26	143.49	85.92	39	124.00	43.40	Crude	4
Heidari et al. 2019	Mg/dl	29	109.7	47.9	13	95.6	30.3	Crude	3
Karimzadeh et al. 2007	Mg/dl	100	191.5	55.9	100	205.3	53.4	Crude	3
Hoeger et al. 2008	mg/dl	6	71.3	21.1	10	87.1	25.1	Adolescents, obese	6
Kelly et al. 2002	Mg/dl	10	221.43	111.83	10	230.29	83.87	Mean and sd (counted in last TR)	6
Lord et al 2006	Mg/dl	16	127.55	62.89	16	118.69	54.92		3
Maciel et al. 2004	Mg/dl	7	26.8	70.57	8	59.8	32.14	BMI<=30	6
Maciel et al. 2004	Mg/dl	8	134.9	86.29	6	106.7	40.02	BMI>30	6
Onalan et al. 2005	Mg/dl	15	133.22	19.8	16	142.7	32.72	BMI<25	6
Onalan et al. 2005	Mg/dl	7	151.31	35.46	9	165.17	32.53	BMI 25-29.9	6
Onalan et al. 2005	Mg/dl	6	107.1	41.9	6	183.8	26.67	BMI>30	6
Ng et al. 2001	Mg/dl	8	79.72	35.43	7	106.29	62.00	Crude	3
Romualdi et al. 2010	Mg/dl	13	66.7	12.8	10	69.4	13.6	Crude	6
Trolle et al. 2010	Mg/dl	36	103	55.75	36	121	46		6
Naka et al 2011	Mg/dl	15	103	39	14	109	58		6

1.13.2. Forrest plot metformin versus placebo for triglycerides



1.13.3. Funnel plot for assessment of publication bias

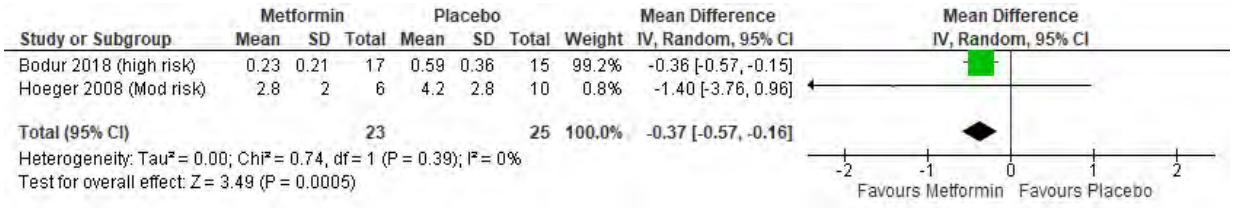


OUTCOME 1.14 CRP (mg/l)

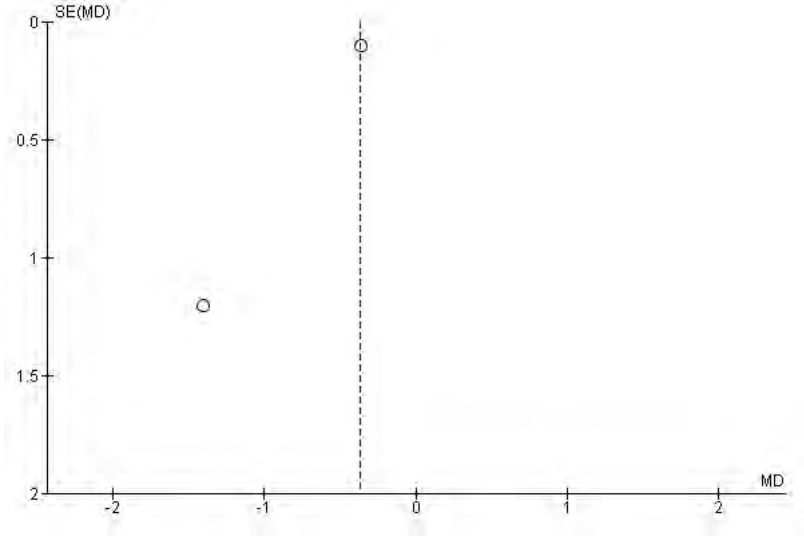
1.14.1 Individual Study Data Table

	OUTCOME: hs-CRP					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **placebo**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Bodur et al. 2018	Mg/l	17	0.23	0.21	15	0.59	0.36	Crude	6
Hoeger et al. 2008	mg/l	6	2.8	2.0	10	4.2	2.8	Adolescents, obese	6

1.14.2. Forrest plot metformin versus placebo for CRP



1.14.3. Funnel plot for assessment of publication bias

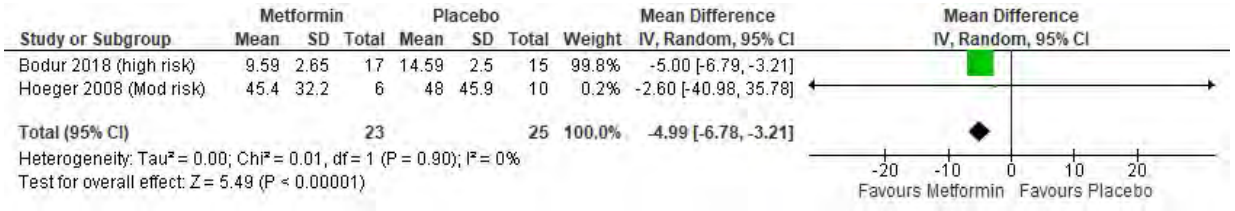


OUTCOME 1.15 PAI-1 (Ng/ml)

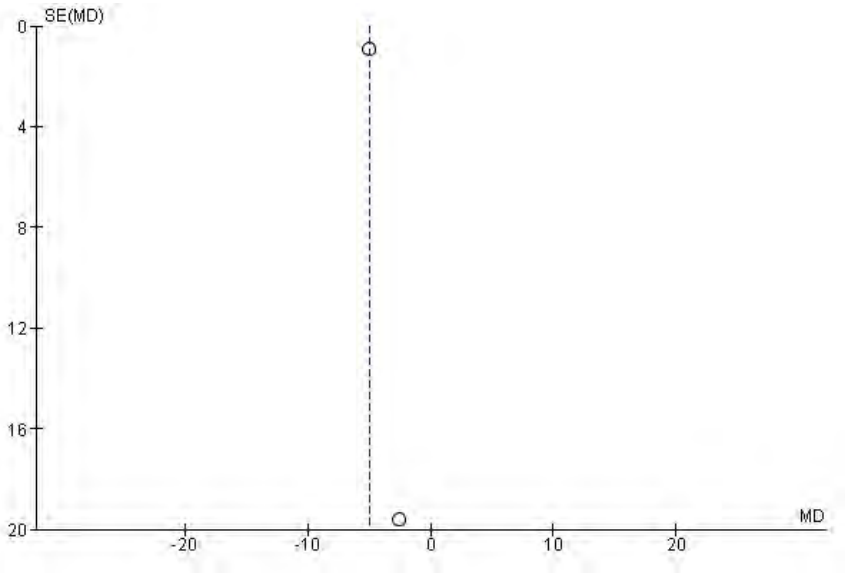
1.15.1 Individual Study Data Table

	OUTCOME: PAI-1					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **placebo**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Bodur et al. 2018	Ng/ml	17	9.59	2.65	15	14.59	2.50	Crude	6
Hoeger et al. 2008	Ng/ml	6	45.4	32.2	10	48.0	45.9	Adolescents, obese	6

1.15.2. Forrest plot metformin versus placebo for PAI-1



1.15.3. Funnel plot for assessment of publication bias

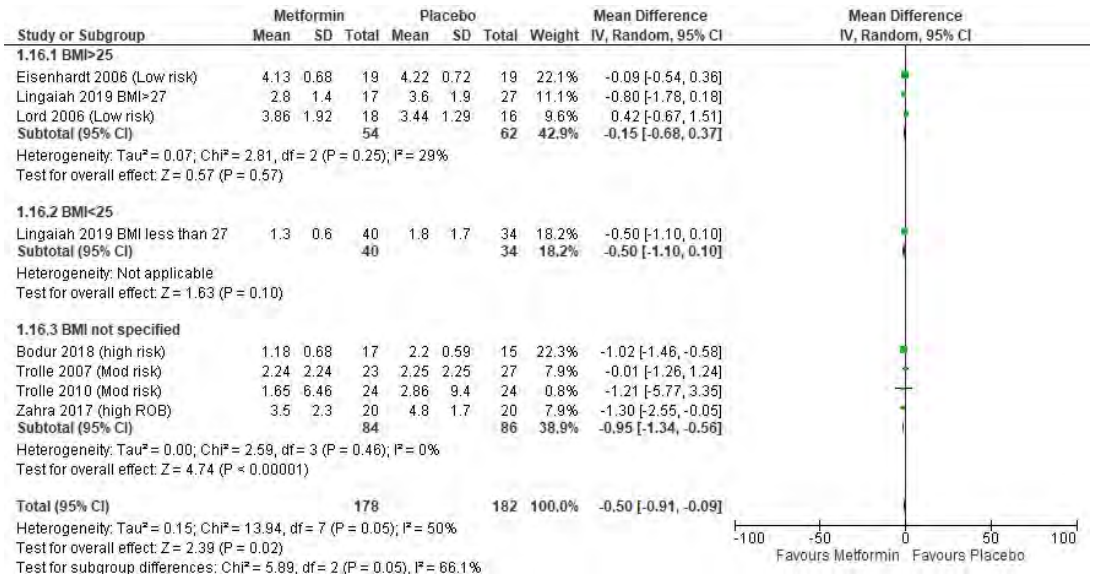


OUTCOME 1.16 HOMA-IR

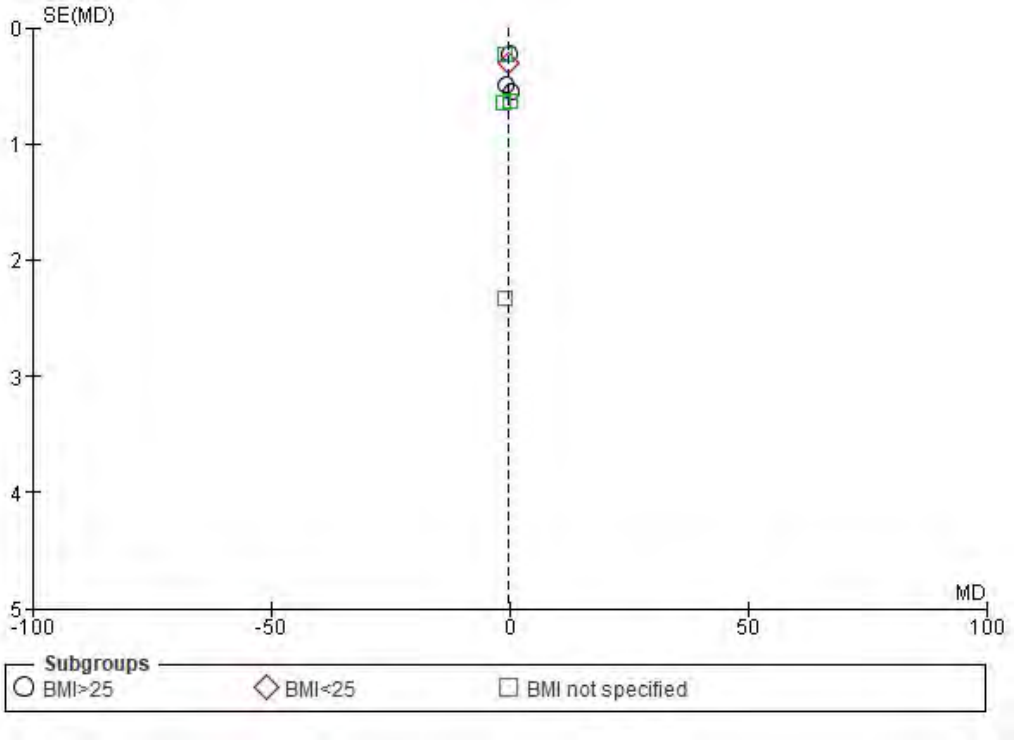
1.16.1 Individual Study Data Table

	OUTCOME: HOMA-IR					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **Placebo**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Zahra et al. 2017		20	3.5	2.3	20	4.8	1.7	Crude	3
Eisenhardt et al 2006		19	4.13	0.68	19	4.22	0.72	Crude	3
Bodur et al. 2018		17	1.18	0.68	12	2.20	0.59	Crude	6
Lord et al 2006		16	3.86	1.92	16	3.44	1.29	Crude	3
Trolle et al. 2010		24	1.65	6.46	24	2.86	9.40		6
Bodur et al. 2018		17	1.18	0.68	15	2.20	0.59	BMI<30	6
Trolle et al. 2007		23	2.24	2.24	27	2.25	2.25		6
Linghaiah et al. 2019		17	2.8	1.4	27	3.6	1.9	BMI>27	3
Linghaiah et al. 2019		40	1.3	0.6	34	1.8	1.7	BMI<27	3

1.16.2. Forrest plot metformin versus placebo for HOMA-IR



1.16.3. Funnel plot for assessment of publication bias



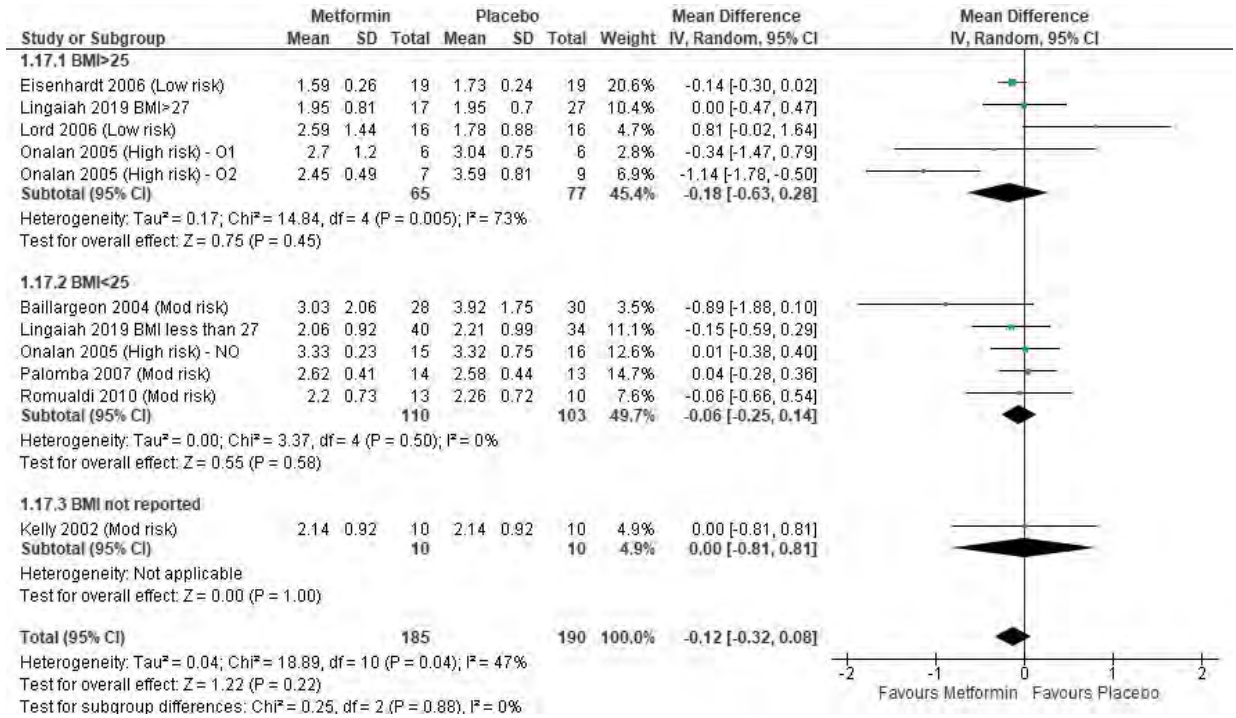
OUTCOME 1.17 DHEAS (ug/ml)

1.17.1 Individual Study Data Table

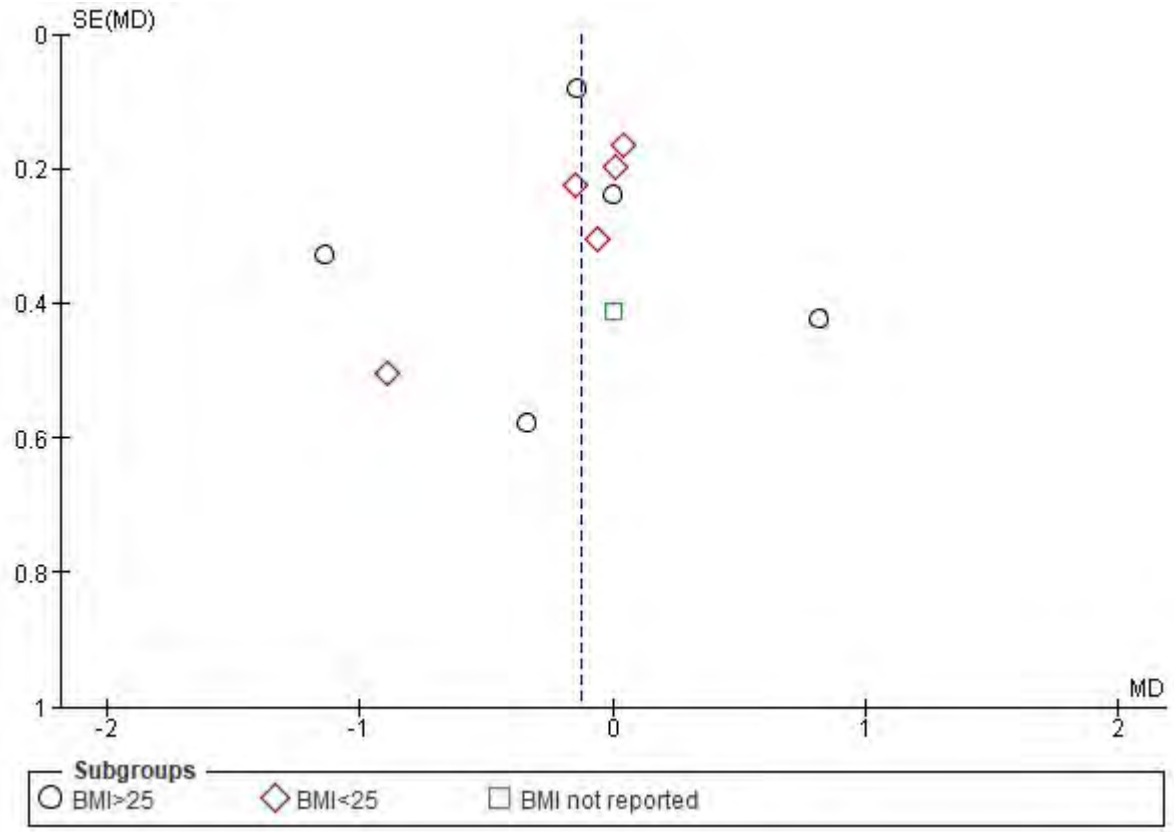
	OUTCOME: DHEAS					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **Placebo**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Baillargeon et al. 2004	Ug/ml	28	3.03	2.06	30	3.92	1.75	Crude	6
Eisenhardt et al 2006	Ug/ml	19	1.59	0.26	19	1.73	0.24	Crude	3
Kelly et al. 2002	Ug/ml	10	2.14	0.92	10	2.14	0.92	Mean and sd (counted in last TR)	6
Lord et al 2006	Ug/ml	16	2.59	1.44	16	1.78	0.88		3
Maciel et al. 2004	Ug/ml	7	0.01	0.00	8	0.01	0.00	BMI<=30	6
Maciel et al. 2004	Ug/ml	8	0.01	0.00	6	0.01	0.00	BMI>30	6

Lingaiah et al. 2019	Ug/ml	17	5.3	2.2	27	5.3	1.9	BMI>=27	3
Lingaiah et al. 2019	Ug/ml	40	5.6	2.5	34	6.0	2.7	BMI<27	3
Onalan et al. 2005	Ug/ml	15	3.33	0.23	16	3.32	0.75	BMI<25	6
Onalan et al. 2005	Ug/ml	7	2.45	0.49	9	3.59	0.81	BMI 25-29.9	6
Onalan et al. 2005	Ug/ml	6	2.7	1.2	6	3.04	0.75	BMI>30	6
Palomba et al 2007	Ug/ml	14	2.62	0.41	13	2.58	0.44	Crude	6
Romualdi et al. 2010	Ug/ml	13	2.20	0.73	10	2.26	0.72	Crude	6

1.17.2. Forrest plot metformin versus placebo for DHEAS



1.17.3. Funnel plot for assessment of publication bias



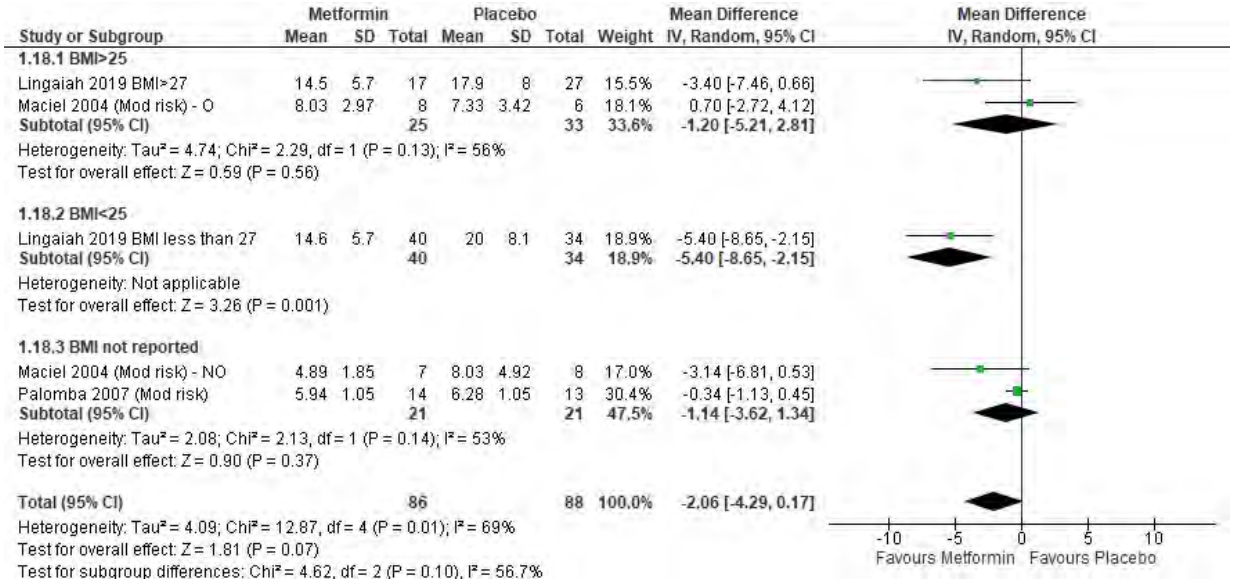
OUTCOME 1.18 Androstenedione (nmol/l)

1.18.1 Individual Study Data Table

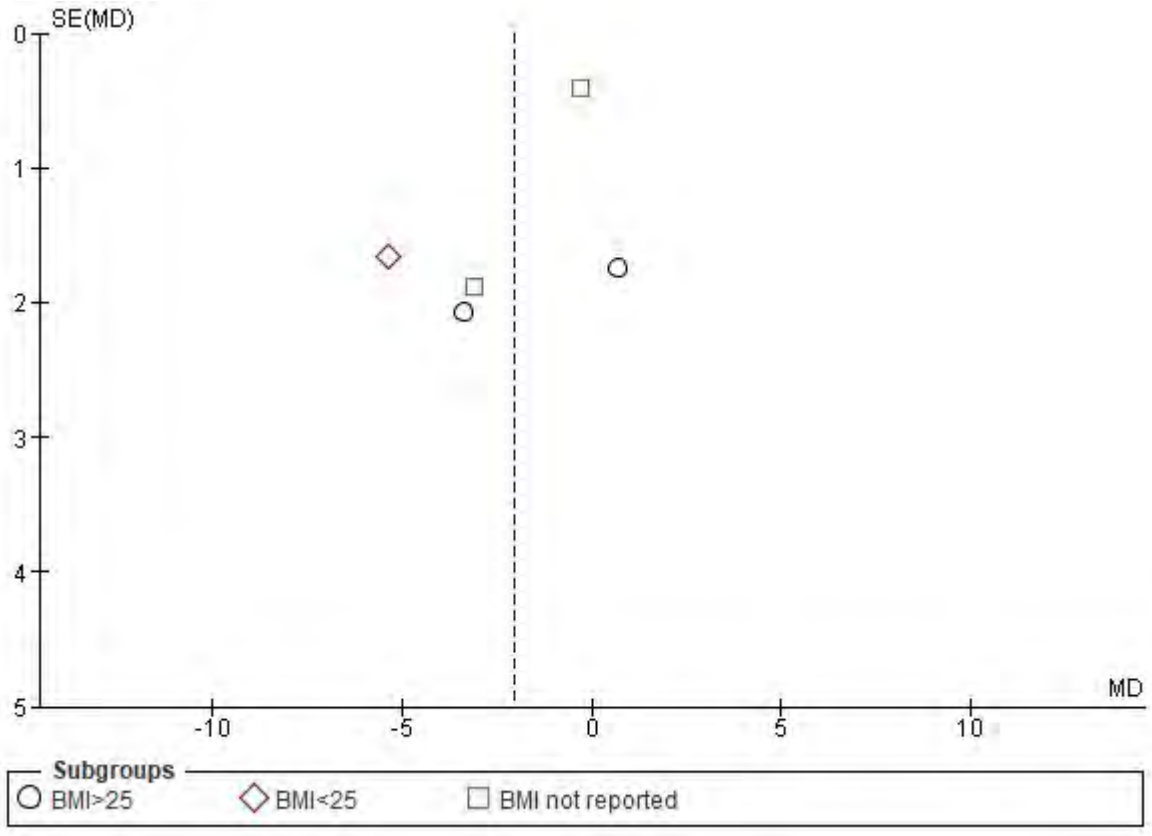
	OUTCOME: Androstenedione					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **Placebo**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Lingaiah et al. 2019	nmol/L	17	14.5	5.7	27	17.9	8.0	BMI>=27	3
Maciel et al. 2004	Ng/dl Nmol/l	7	1.4 4.89	0.53 1.85	8	2.3 8.03	1.41 4.92	BMI<=30	6
Maciel et al. 2004	Ng/dl Nmol/l	8	2.3 8.03	0.85 2.97	6	2.1 7.33	0.98 3.42	BMI>30	6
Lingaiah et al. 2019	nmol/L	40	14.6	5.7	34	20.0	8.1	BMI<27	3

Palomba et al 2007	Ng/ml Nmol/l	14	1.7 5.94	0.3 1.05	13	1.8 6.28	0.3 1.05	Crude	6

1.18.2. Forrest plot metformin versus placebo for androstenedione



1.18.3. Funnel plot for assessment of publication bias



Adverse outcomes

	Study	metformin	Placebo
Gastrointestinal side effects	Karimzadeh 2007	Nausea 30% Diarhhea 10% Vomiting 15%	0%
	Fleming 2002	15/26=57.69%	5/39=12.82%
	Ng 2001	3/8=37.5% (vomiting)	1/7=14.3% (vomiting)

Comparison 2: Metformin+lifestyle versus placebo+lifestyle

Evidence Summary

Eight randomised controlled trials (RCTs) were identified by our search. Of these RCT, all were included in the meta-analysis.
Of these studies four had a low ROB and five a moderate ROB.

Rows highlighted grey indicate studies with participants described as obese. We performed subgroup analyses based on BMI. As for age, there was only one study on adolescents (Ladson et al. 2011).

Meta-analysis/descriptive analysis summary

In the meta-analysis, metformin+lifestyle was superior in lowering testosterone for the overall group (moderate certainty). Among PCOS women without a specified BMI, WHR was significantly lower in participants with metformin+lifestyle compared to placebo and lifestyle. For other outcomes, no difference was observed. Certainty in the evidence is moderate to very low.

Regarding individual studies, not included in the meta-analysis, Tiwari et al. found that participants treated with metformin and lifestyle had less oligomenorrhea compared to placebo and lifestyle (certainty moderate). Hoeger et al. found that testosterone and FAI was significantly lower in participants treated with metformin+lifestyle compared to those who received placebo+lifestyle. Fux Otta et al. found HOMA-IR to be lower in participants treated with metformin and lifestyle. Certainty for these findings was very low.

Gastrointestinal side-effects seems to be more common in the metformin+lifestyle group (see table at the end).

Author, year, country	Population	Study Design	Sample Size per group	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Type of analysis and subgroup	ROB
Tiwari et al 2018 India	Females diagnosed as PCOS	RCT	1.Lifestyle+metformin 33 2.Lifestyle+placebo 33	6 months	1.25.2 ±4.6 2.26.3 ±3.7	1.24.3 ±3.9 2.24.5 ±4.8	Weight, whr, BMI, hirsutism	META	**ROB low**

Tang et al. 2006 UK	obese (BMI >30), oligo-/amenorrhoeic women with PCOS	RCT	1.Lifestyle+metformin 69 2.Lifestyle+placebo 74	6 months	1.37.6 ±5.0 2.38.9 ±9.5	1.29.7 ±3.7 2.29.8 ±3.8	Weight,whr, BMI	META BMI>30	ROB low
Ladson et al 2011 USA	Women with PCOS, aged 21-39 yrs	RCT Double blind	1.Lifestyle+metformin **22** 2.Lifestyle+placebo **16**	6 months	1.38.0 ±7.8 2.38.3 ±8.0	1.29 ±4.5 2.28.8 ±4.6	BMI	META	**ROB moderate**
Ladson et al 2011 USA	Women with PCOS, **adolescents**	RCT Double blind	1.Lifestyle+metformin **11** 2.Lifestyle+placebo **11**	6 months	1: 37.1±5.8 2: 35.9±6.6	1: 16.1±1.5 2: 15.4±1.2	BMI	META adolescents	**ROB low**
Fux Otta et al. 2010 Argentina	PCOS women, 20–34 years old	RCT Double blind	1.Lifestyle+metformin=14 2.Lifestyle+placebo=15	4 months	1.32.4 ±6.7 2.35.6 ±5.0	1.25.5 ±4.8 2.24.7 ±3.5	BMI	META	**ROB Moderate**
Paquali et al. 2000 Italy	Obese PCOS women with a BMI>28	RCT	1.Lifestyle+metformin=10 2.Lifestyle+placebo=8	7 months	1: 39.8±7.9 2: 39.6±6.9	1: 30.8±7.4 2: 32.3±5.0	Weight,whr, BMI, SHBG, T	META BMI>28	**ROB Moderate**
Gambineri et al. 2006 Italy	overweight-obese women with PCOS	RCT	1.Metfromin=20 2.SPL=17 3.Metfromin+SPL=20 4.Placebo=20	6 months	1.35 ±4 2.33 ±4 3.35±5 4.37±5	1.28±8 2.26 ±6 3.26±5 4.26±5	Weight, BMI, SHBG, T, hirsutism	META BMI>28	**ROB low**
Hoeger et al. 2004 USA*	overweight or obese women with PCOS	RCT	1.Metformin=6 2.LS+placebo=8 3.LS+metformin=5 4.Placebo=7	6 months	1: 37.1±4.9 2: 40±7.4 3: 41.7±6.2 4: 37.1±4.6	1:29.5±6.4 2:27.1±4.3 3:30.4±5.4 4:27.1±4.5	BMI, SHBG, FAI, T,	META BMI=>25 Adults	**ROB Moderate**
Amiri et al. 2014 Iran	overweight and obese infertile PCOS women	RCT	1.Metfromin+LS=25 2.SPL+LS=27 3.Metfromin+SPL+LS=27 4.Placebo+LS=26	6 months	>19 kg/m2 and <35 kg/m2.	18-40	Whr, BMI, SHBG, T, hirsutism	META Adults	**ROB Moderate**

Results of meta-analysis

Outcome	Time point	RCTs	N	Effect, random, MD	P-value	I2 (%)	Favours	Certainty
Weight (kg)	6-7 months	4	245	-2.82 (-6.07 to 0.42)	0.09	0	No difference	⊕⊕◯◯ LOW
Sub: BMI>25	6-7 months	3	179	-0.81 (-5.47 to 3.85)	0.73	0	No difference	⊕⊕◯◯ LOW
WHR	6-7 months	4	257	-0.01 (-0.03 to 0.01)	0.26	32	No difference	⊕⊕⊕◯ MODERATE
Sub: BMI>25	6 months	2	173	0.01 (-0.02 to 0.03)	0.63	0	No difference	⊕⊕⊕◯ MODERATE
Sub: BMI not specified	**6-7 months**	**2**	**84**	**-0.03 (-0.05 to -0.01)**	0.006	0	**Met+LS**	⊕⊕◯◯ LOW
BMI kg/m2	4-7 months	9	398	-1 (-20.2 to 0.01)	0.05	0	No difference	⊕⊕⊕◯ MODERATE
Sub: BMI>25	6-7 months	4	192	-0.80 (-2.41 to 0.82)	0.33	0	No difference	⊕⊕⊕◯ MODERATE
Sub: BMI not specified	4-6 months	5	206	-1.14 (-2.44 to 0.16)	0.09	0	No difference	⊕⊕⊕◯ MODERATE
Hirsutism (FG score)	6 months	3	156	1.17 (-1.01 to 3.35)	0.29	71	No difference	⊕⊕◯◯ LOW
SHBG (nmol/l)	6-7 months	3	109	2.26 (-1.79 to 6.31)	0.27	0	No difference	⊕⊕⊕◯ MODERATE

Testosterone (ng/dl)	**4-7 months**	**6**	**327**	**-0.06 (-0.11 to 0.00)**	**0.06**	**36**	**Met+LS**	⊕⊕⊕◯ MODERATE
Sub: BMI>25	4-6 months	3	180	-0.05 (-0.15 to 0.04)	0.28	46	No difference	⊕⊕⊕◯ MODERATE
Sub: BMI not specified	6-7 months	3	147	-0.05 (-0.13 to 0.04)	0.27	23	No difference	⊕⊕⊕◯ MODERATE
Fasting insulin mIU/l)	4-7 months	4	112	-0.45 (-2.96 to 2.06)	0.29	51	No difference	⊕⊕◯◯ LOW
Sub: BMI>25	6-7 months	2	58	-0.94 (-3.72 to 1.84)	0.51	0	No difference	⊕⊕◯◯ LOW
Sub: BMI not specified	4-6 months	2	54	1.69 (-4.13 to 7.51)	0.52	78	No difference	⊕◯◯◯ VERY LOW
Fasting glucose (mg/dl)	4-6 months	3	120	-1.36 (-6.07 to 3.36)	0.57	45	No difference	⊕⊕◯◯ LOW
OGTT (mg/dl/120min)	4-6 months	2	80	3.51 (-20.73 to 27.76)	0.78	80	No difference	⊕◯◯◯ VERY LOW
Total cholesterol (mmol/l)	4-6 months	3	202	-4.06 (-22.67 to 14.56)	0.67	74	No difference	⊕◯◯◯ VERY LOW
HDL (mmol/l)	4-6 months	3	120	-2.92 (-6.40 to 0.56)	0.10	0	No difference	⊕⊕⊕◯ MODERATE
LDL (mmol/l)	4-6 months	3	120	-3.79 (-12.84 to 5.26)	0.41	0	No difference	⊕⊕◯◯ LOW
Triglycerides (mmol/l)	4-6 months	4	242	-5.45 (-28.23 to 17.32)	0.64	34	No difference	⊕⊕◯◯ LOW
Androstenedione (nmol/l)	4-6 months	2	69	-5.06 (-69.25 to 59.13)	0.88	0	No difference	⊕◯◯◯ VERY LOW

Individual studies not included in meta-analysis

Outcome	Author, year	Time point	N	Metformin+LS	Placebo+LS	P-value	Favours	Grading
Hirsutism (FGS)	Ladson et al. 2011	6 months	M+LS=22 Placebo+LS=16	Mean change (95%CI) 1.2 (-1.1-3.6)	Mean change (95%CI) -0.2 (-2.8-2.3)	0.40	No difference	⊕◯◯◯ VERY LOW [1]
SHBG	Ladson et al. 2011	6 months	M+LS=22 Placebo+LS=16	Mean change (95%CI) 1.2 (-1.9-5.2)	Mean change (95%CI) 3.8 (-0.3-7.8)	0.43	No difference	⊕◯◯◯ VERY LOW [1]
	Hoeger et al. 2004	6 months	M+LS=5 Placebo+LS=8	Mean change +/- SD -2.5+/- 19.6	Mean change +/- SD -0.1 +/- 15.0	NR	No difference	⊕◯◯◯ VERY LOW [1]
FAI	Ladson et al. 2011	6 months	M+LS=22 Placebo+LS=16	Mean change (95%CI) -2.3 (-5.1-0.6)	Mean change (95%CI) -1.6 (-4.9-1.6)	0.76	No difference	⊕◯◯◯ VERY LOW [1]
	Hoeger et al. 2004	6 months	M+LS=5 Placebo+LS=8	Mean change +/- SD -4.1+/- 23.7	Mean change +/- SD 13.1 +/- 30.9	NR	**Metformin+LS** (by apperance)	⊕◯◯◯ VERY LOW [1]
	Gambineri et al. 2006	6 months	M+LS=20 Placebo+LS=20	Means +/- SD 4.1 +/- 4.6	Means +/- SD 3.2 +/- 2.2	0.43	No difference	⊕⊕◯◯ LOW[2]
Testosterone	Hoeger et al. 2004	6 months	M+LS=5 Placebo+LS=8	Mean change +/- SD -12.3+/- 22.7	Mean change +/- SD 7.4 +/- 29.2	NR	**Metformin+LS** (by apperance)	⊕◯◯◯ VERY LOW [1]
	Ladson et al. 2011	6 months	M+LS=22 Placebo+LS=16	Mean change (95%CI) -2.1 (-12.1-7.9)	Mean change (95%CI) -6.4 (-16.9-4.1)	0.54	No difference	⊕◯◯◯ VERY LOW [1]
Free testosterone	Amiri et al. 2014	6 months	M+LS=25 Placebo+LS=26	Means and SD 0.7 +/- 0.4	Means and SD 0.95 +/- 0.9	0.20	No difference	⊕◯◯◯ VERY LOW [1]
Fasting insulin	Ladson et al. 2011	6 months	M+LS=22 Placebo+LS=16	Mean change (95%CI) 2.7 (-6-11.4)	Mean change (95%CI) 5.1 (-6.5-16.7)	0.75	No difference	⊕◯◯◯ VERY LOW [1]
Fasting glucose	Ladson et al. 2011	6 months	M+LS=22 Placebo+LS=16	Mean change (95%CI)	Mean change (95%CI)	0.12	No difference	⊕◯◯◯ VERY LOW [1]

				-2.9 (-7.8-2.1)	2.8 (-3.1-8.7)			
Total cholesterol	Ladson et al. 2011	6 months	M+LS=22 Placebo+LS=16	Mean change (95%CI) -7.8 (-19.0-3.3)	Mean change (95%CI) -4.2 (-16.8-8.4)	0.65	No difference	⊕◯◯◯ VERY LOW [1]
HDL	Ladson et al. 2011	6 months	M+LS=22 Placebo+LS=16	Mean change (95%CI) 5.2 (1.7-8.7)	Mean change (95%CI) 7.4 (3.5-11.4)	0.35	No difference	⊕◯◯◯ VERY LOW [1]
LDL	Ladson et al. 2011	6 months	M+LS=22 Placebo+LS=16	Mean change (95%CI) -7.5 (-17.7-2.6)	Mean change (95%CI) -9.1 (-19.4-3.3)	0.94	No difference	⊕◯◯◯ VERY LOW [1]
Triglycerides	Ladson et al. 2011	6 months	M+LS=22 Placebo+LS=16	Mean change (95%CI) -14.0 (-31.1-3.0)	Mean change (95%CI) -3.9 (-23.5-15.7)	0.41	No difference	⊕◯◯◯ VERY LOW [1]
HOMA	Fux Otta et al 2010	4 months	M+LS=14 Placebo+LS=15	Means and SD 2.05 +/- 1.36	Means and SD 3.31 +/- 1.08	0.006	**Metformin+LS**	⊕◯◯◯ VERY LOW [1]
DHEAS	Gambineri et al. 2006	6 months	M+LS=20 Placebo+LS=20	Means +/- SD 2.3 +/- 0.6	Means +/- SD 2.1 +/- 1.1	0.48	No difference	⊕⊕◯◯ LOW[2]
Menstrual cycles/6months	Gambineri et al. 2006	6 months	M+LS=20 Placebo+LS=20	Means +/- SD 4.3 +/- 1.5	Means +/- SD 4.8 +/- 1.5	0.29	No difference	⊕⊕◯◯ LOW[2]
QoL-physical wellbeing	Ladson et al. 2011	6 months	M+LS=22 Placebo+LS=16	Mean change (95%CI) 0.33 (-0.25-0.90)	Mean change (95%CI) 0.61 (-0.03-1.24)	0.47	No difference	⊕◯◯◯ VERY LOW [1]
QoL-emotional wellbeing	Ladson et al. 2011	6 months	M+LS=22 Placebo+LS=16	Mean change (95%CI) -0.13 (-0.82-0.57)	Mean change (95%CI) 0.01 (-0.74-0.77)	0.77	No difference	⊕◯◯◯ VERY LOW [1]
QoL-general wellbeing	Ladson et al. 2011	6 months	M+LS=22 Placebo+LS=16	Mean change (95%CI) 0.09 (-0.46-0.65)	Mean change (95%CI) 0.62 (0.01-1.23)	0.18	No difference	⊕◯◯◯ VERY LOW [1]
Oligomenorrhea	Tiwari et al. 2018	6 months	M+LS=33 Placebo+LS=33	4/33	13/33	0.02	**Metformin+LS**	⊕⊕⊕◯ MODERATE[3]
Improvement in s-triglycerides	Tiwari et al. 2018	6 months	M+LS=33 Placebo+LS=33	0/33	2/33	0.29	No difference	⊕⊕⊕◯ MODERATE[3]
Improvement in s-cholesterol	Tiwari et al. 2018	6 months	M+LS=33 Placebo+LS=33	1/33	3/33	0.33	No difference	⊕⊕⊕◯ MODERATE[3]
oGTT	Tiwari et al. 2018	6 months	M+LS=33 Placebo+LS=33	Improvement in oGTT 0/33	Improvement in oGTT 2/33	0.29	No difference	⊕⊕⊕◯ MODERATE[3]

[1] Downgraded twice for small number of participants and once for being a moderate ROB
[2] Downgraded twice for small number of participants
[3] Downgraded once for small number of participants

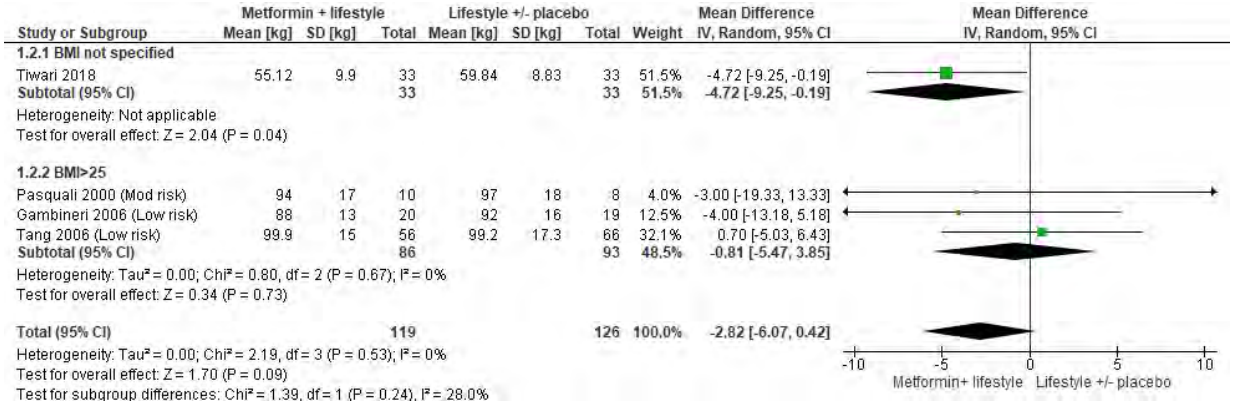
OUTCOME 2.1 WEIGHT (kg)

2.1.1 Individual Study Data Table

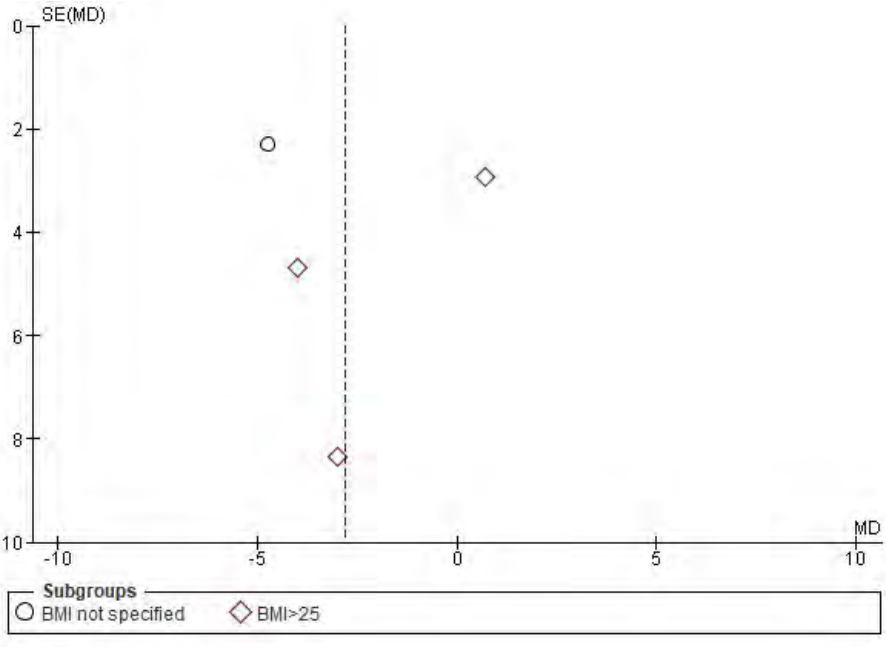
	OUTCOME: Weight					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): lifestyle+metformin versus lifestyle+placebo							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**

Tiwari et al. 2018	Kg	33	55.12	9.9	33	59.84	8.83	Crude	6
Tang et al. 2006	kg	56	99.9	15	66	99.2	17.3	BMI>30	6
Gambineri et al. 2006	Kg	20	88	14	19	93	16	BMI>=28	6
Gambineri et al. 2006	Kg	20	88	13	19	92	16	BMI>=28	12
Pasquali 2000	kg	10	94	17	8	97	18	BMI>28	7

2.1.2. Forrest plot metformin+lifestyle versus placebo+lifestyle for weight



2.1.3. Funnel plot for assessment of publication bias

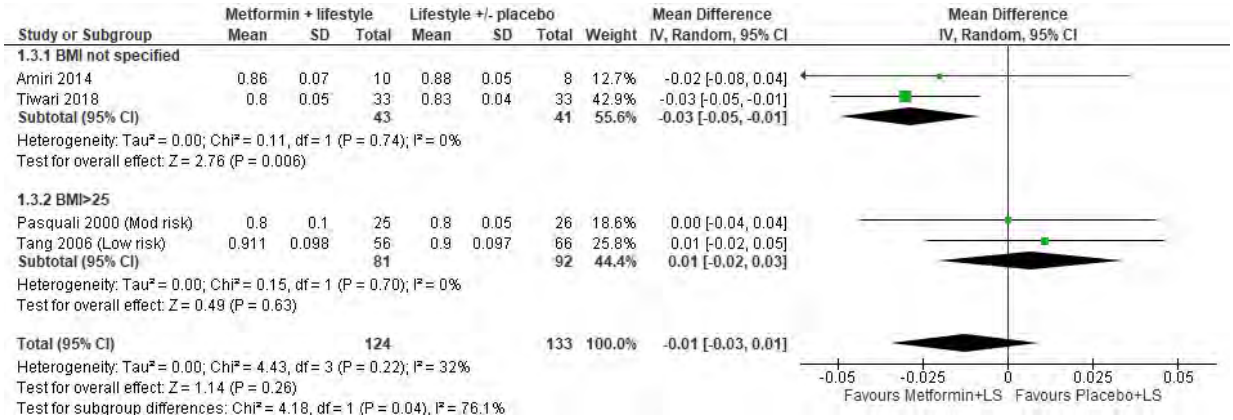


OUTCOME 2.2 WHR

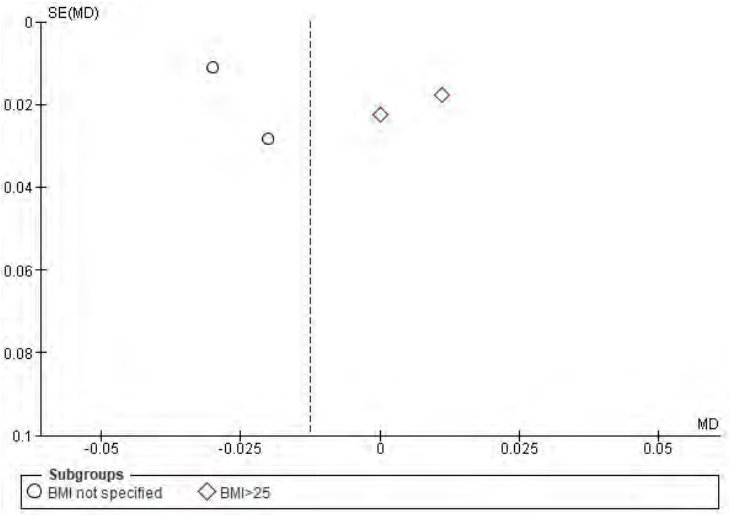
2.2.1 Individual Study Data Table

	OUTCOME: WHR					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): lifestyle+metformin versus lifestyle+placebo							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Tiwari et al. 2018		33	0.8	0.05	33	0.83	0.04	Crude	6
Tang et al. 2006		56	0.911	0.098	66	0.90	0.097	BMI>30	6
Amiri et al. 2014		25	0.8	0.1	26	0.8	0.05	crude	6
Pasquali 2000		10	0.86	0.07	8	0.88	0.05	BMI>28	7

2.2.2. Forrest plot metformin+lifestyle versus placebo+lifestyle for WHR



2.2.3. Funnel plot for assessment of publication bias

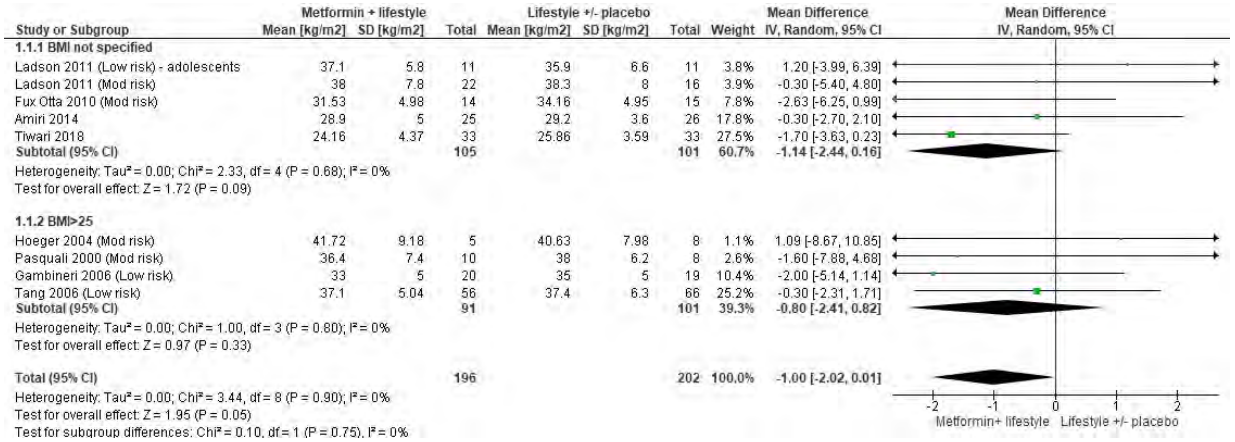


OUTCOME 2.3 BMI (kg/m2)

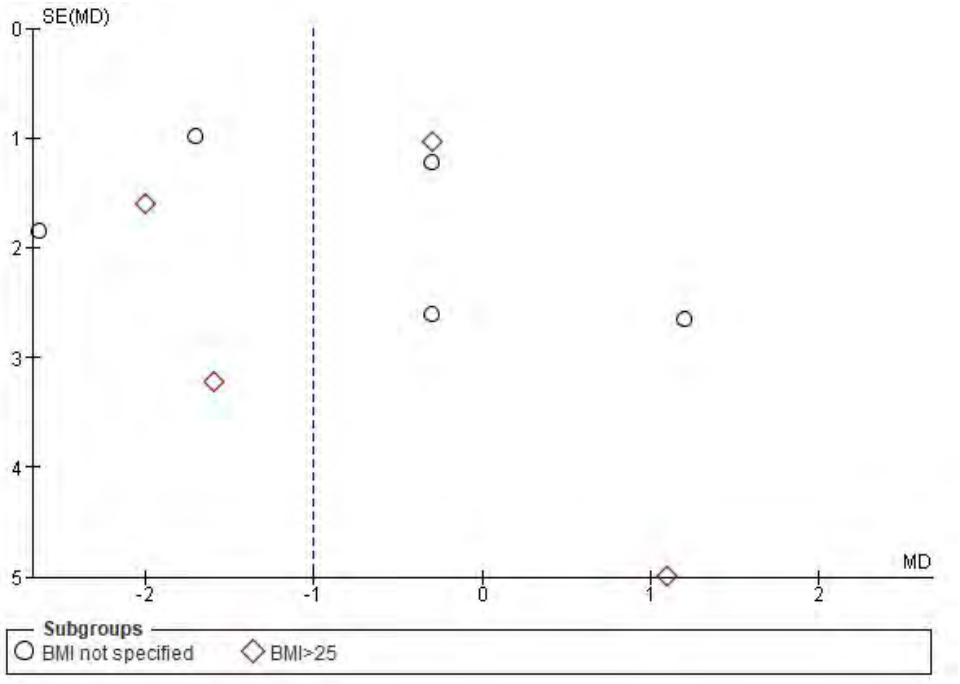
2.3.1 Individual Study Data Table

	OUTCOME: BMI						**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): lifestyle+metformin versus lifestyle+placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Tiwari et al. 2018	Kg/m2	weighted	33	24.16	4.37	33	25.86	3.59	Crude	6
Tang et al. 2006	Kg/m2	weighted	56	37.1	5.04	66	37.4	6.3	BMI>30	6
Fux Otta et al. 2010	Kg/m2	weighted	14	31.53	4.98	15	34.16	4.95	Crude	4
Amiri et al. 2014	Kg/m2	weighted	25	28.9	5	26	29.2	3.6	crude	6
Gambineri et al. 2006	Kg/m2	weighted	20	33	5	19	35	5	BMI>=28	6
Gambineri et al. 2006	Kg/m2	weighted	20	33	5	19	35	5	BMI>=28	12
Hoeger et al 2004	Kg/m2	weighted	5	41.72	9.18	8	40.63	7.98		6
Ladson et al 2011	Kg/m2	weighted	22	38	7.8	16	37.1	5.8		6
Ladson et al 2011	Kg/m2	weighted	11	38.3	8	11	35.9	6.6	adolescents	6
Pasquali 2000	Kg/m2	weighted	10	36.4	7.4	8	38.0	6.2	BMI>28	7

2.3.2. Forrest plot metformin+lifestyle versus placebo+lifestyle for BMI



2.3.3. Funnel plot for assessment of publication bias

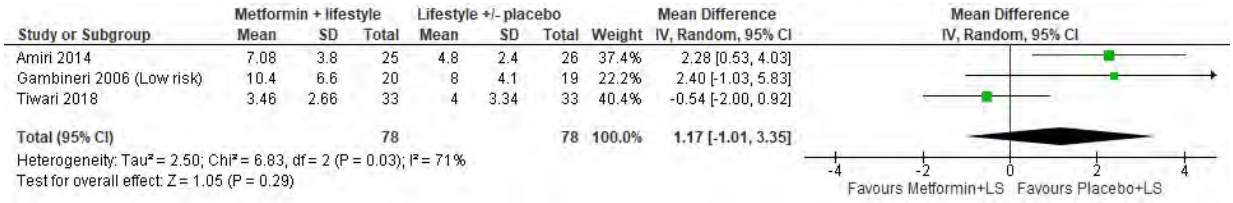


OUTCOME 2.4 Hirsutism (FGS)

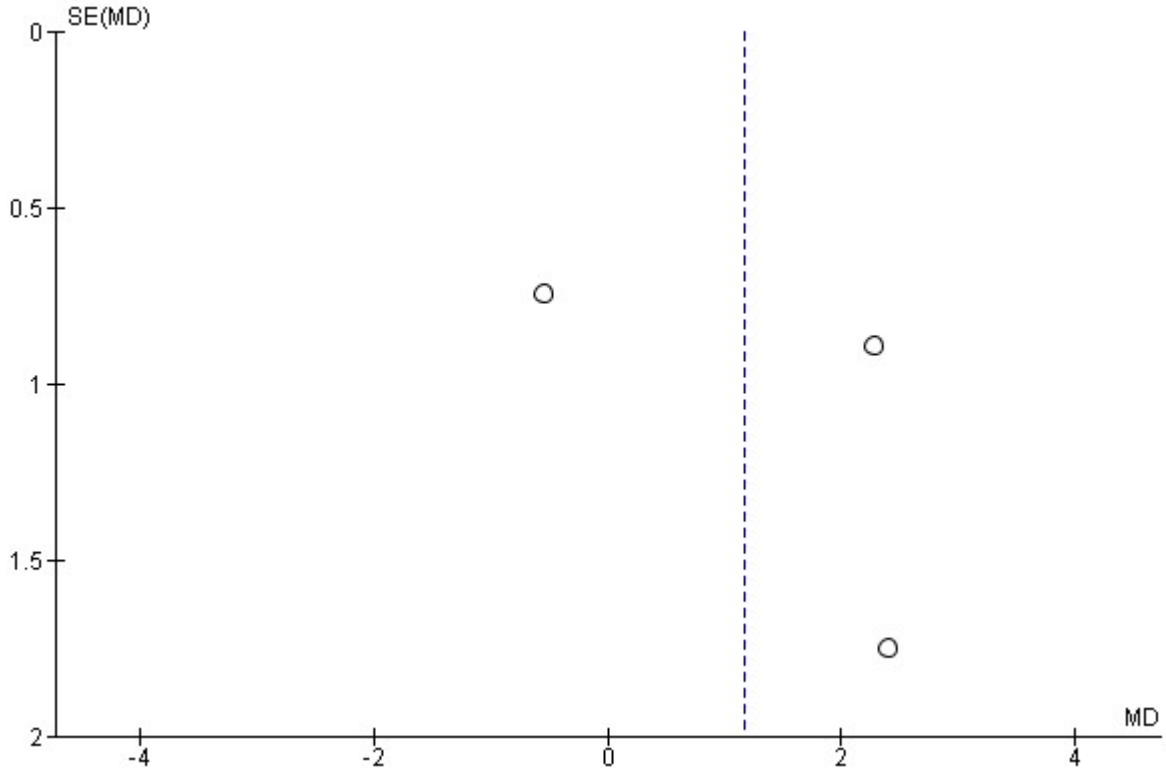
2.4.1 Individual Study Data Table

	OUTCOME: Hirsutism					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): lifestyle+metformin versus lifestyle+placebo							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Tiwari et al. 2018	points	33	3.46	2.66	33	4.0	3.34	Crude	6
Amiri et al. 2014	points	25	7.08	3.8	26	4.8	2.4	crude	6
Gambineri et al. 2006	points	20	10.9	8.6	19	8.0	5.1	BMI>=28	6
Gambineri et al. 2006	points	20	10.4	6.6	19	8.0	4.1	BMI>=28	12

2.4.2. Forrest plot metformin+lifestyle versus placebo+lifestyle for hirsutism



2.4.3. Funnel plot for assessment of publication bias



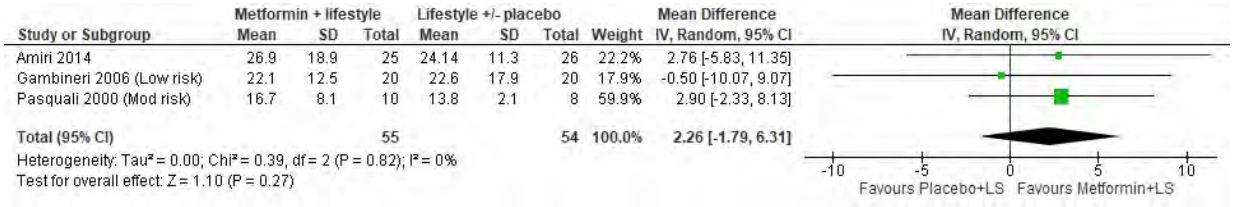
OUTCOME 2.5 SHBG (nmol/l)

2.5.1 Individual Study Data Table

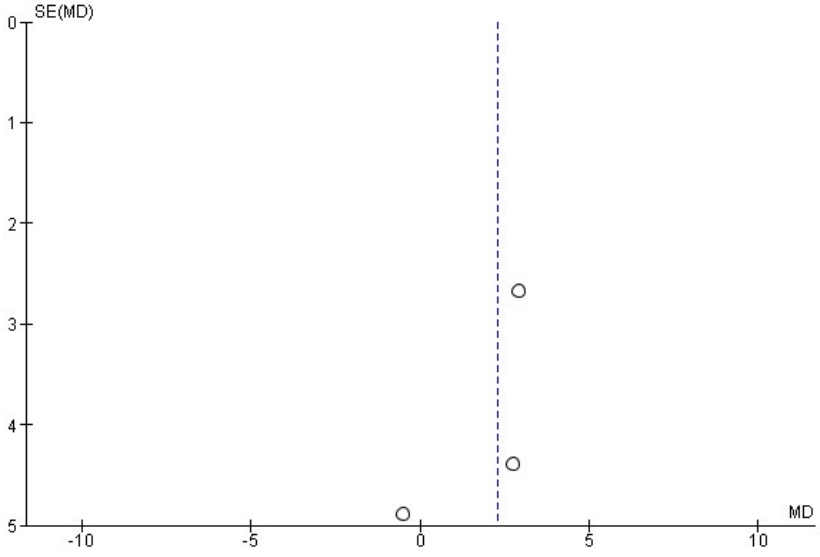
	OUTCOME: SHBG					OUTCOME TYPE: Continuous			
		COMPARISON (if applicable): lifestyle+metformin versus lifestyle+placebo							
Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	N	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	N	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Something special?	Time period (month)

Tang et al. 2006	Nmol/l	56	22.1	missing	66	21.1	missing	BMI>30	6
Amiri et al. 2014	Nmol/l	25	26.9	18.9	26	24.14	11.3		6
Gambineri et al 2006	Nmol/l	20	19.2	10.6	20	21.2	11.5		6
Gambineri et al 2006	Nmol/l	20	22.1	12.5	20	22.6	17.9		12
Pasquali et al. 2000	Nmol/l	10	16.7	8.1	8	13.8	2.1		7

2.5.2. Forrest plot metformin+lifestyle versus placebo+lifestyle for SHBG



2.5.3. Funnel plot for assessment of publication bias

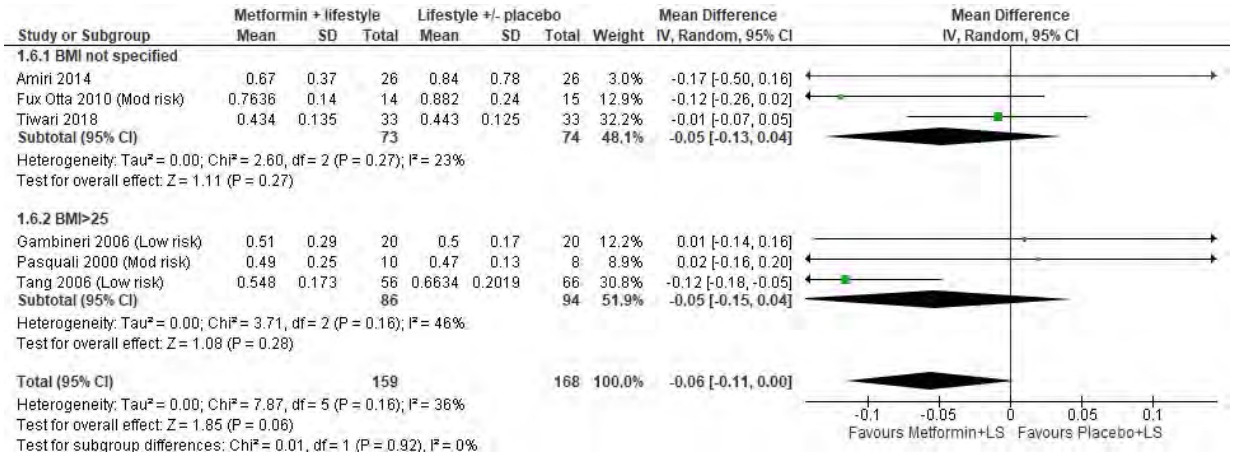


OUTCOME 2.6 Testosterone (ng/ml)

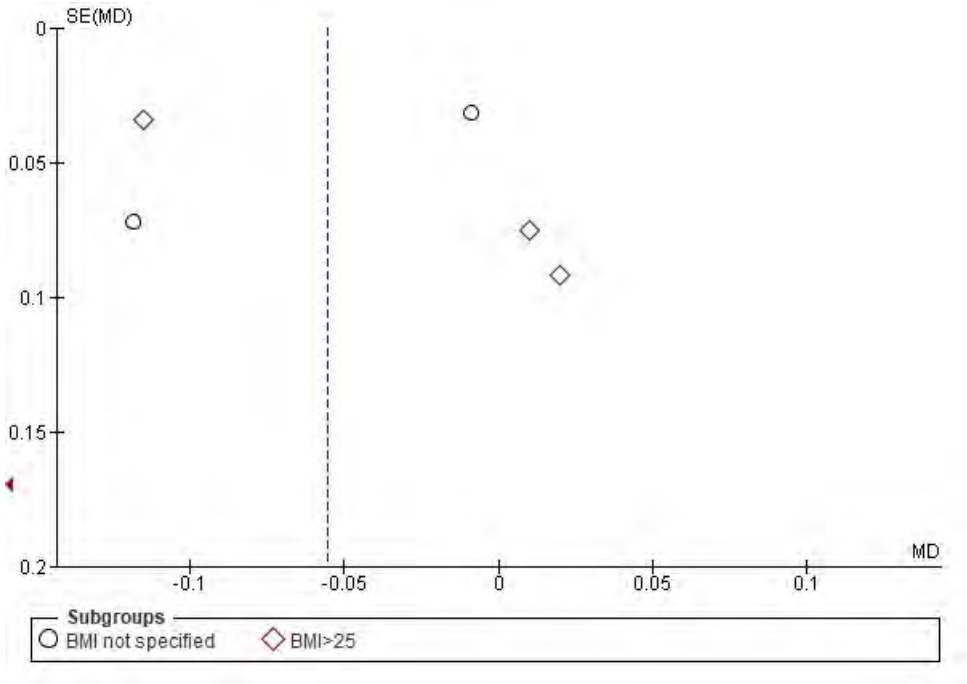
2.6.1 Individual Study Data Table

	OUTCOME: Testosterone					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin+lifestyle versus **placebo+lifestyle**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Gambineri et al 2006	Ng/ml	20	0.51	0.29	20	0.50	0.17		6
Gambineri et al 2006	Ng/ml	20	0.50	0.27	20	0.45	0.14		12
Amiri et al. 2014	pM/l ng/ml	25	2.32 0.67	1.3 0.37	26	2.9 0.84	2.7 0.78	crude	6
Pasquali 2000	Ng/ml	10	0.49	0.25	8	0.47	0.13	BMI>28	7
Fux Otta et al. 2010	Ng/ml	14	0.7636	0.14	15	0.882	0.24		4
Tiwari et al. 2018	Ng/ml	33	0.434	0.135	33	0.443	0.125		6
Tang et al. 2006	Ng/ml	56	0.548	0.173	66	0.6634	0.2019		6

2.6.2. Forrest plot metformin+lifestyle versus placebo+lifestyle for Testosterone



2.6.3. Funnel plot for assessment of publication bias

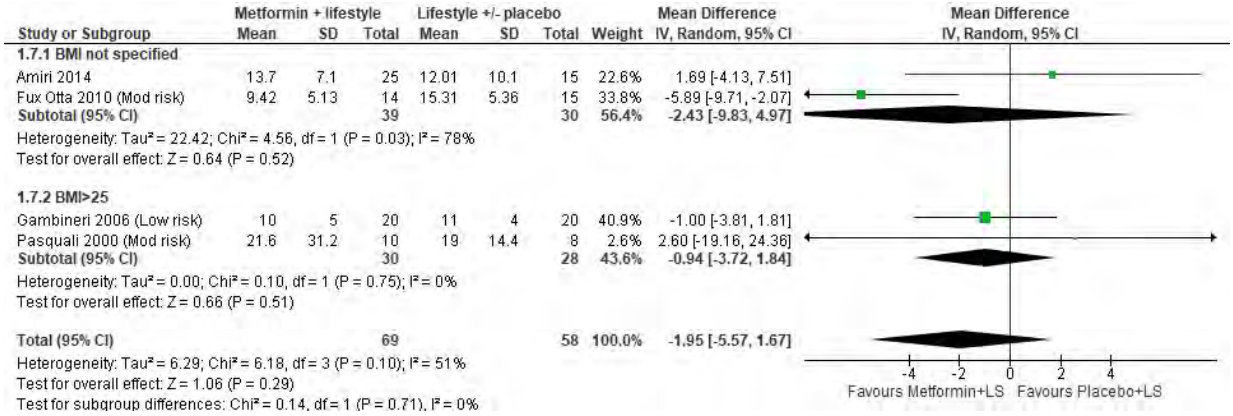


OUTCOME 2.7 Fasting insulin (uIU/ml)

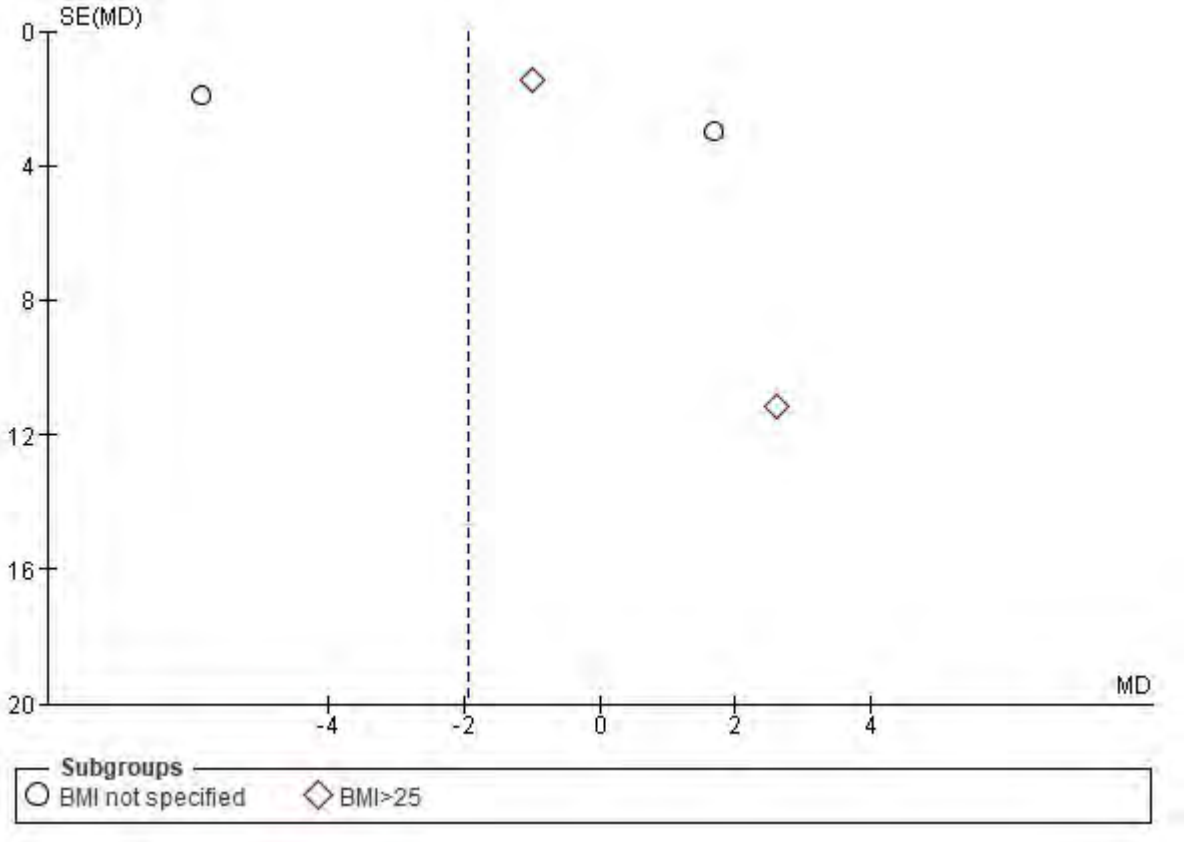
2.7.1 Individual Study Data Table

	OUTCOME: fasting insulin						**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): lifestyle+metformin versus lifestyle+placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something special?**	**Time period (month)**
Tang et al. 2006	pmol/l		56	80.7	missing	66	81.8	missing	BMI>30	6
Fux Otta et al. 2010	uIU/ml		14	9.42	5.13	15	15.31	5.36	Crude	4
Amiri et al. 2014	Pm/l		25	13.7	7.1	26	12.01	10.1	Unit??	6
Gambineri et al. 2006	uIU/ml		20	14	5	20	11	7		6
Gambineri et al. 2006	uIU/ml		20	10	5	20	11	4		12
Pasquali et al. 2000	uIU/ml		10	21.6	31.2	8	19.0	14.4		7

2.7.2. Forrest plot metformin+lifestyle vs placebo+lifestyle for fasting insulin



2.7.3. Funnel plot for assessment of publication bias

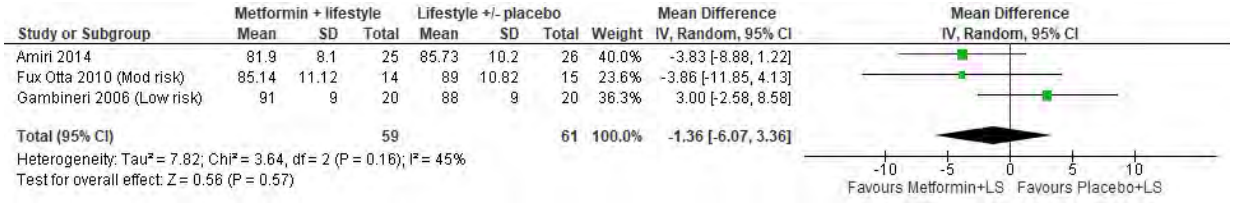


OUTCOME 2.8 Fasting glucose (mg/dl)

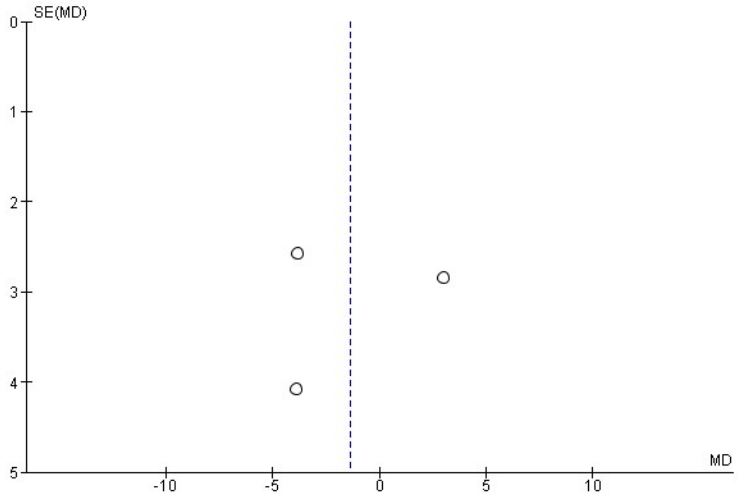
2.8.1 Individual Study Data Table

	OUTCOME: fasting glucose					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): lifestyle+metformin versus lifestyle+placebo							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something special?**	**Time period (month)**
Tang et al. 2006	mmol/l	56	4.83	missing	66	4.88	missing	BMI>30	6
Fux Otta et al. 2010	Mg/dl	14	85.14	11.12	15	89	10.82	Crude	4
Amiri et al. 2014	Mg/dl	25	81.9	8.1	26	85.73	10.2	crude	6
Gambineri et al. 2006	Mg/ml	20	91	9	20	89	10		6
Gambineri et al. 2006	Mg/ml	20	91	9	20	88	9		12

2.8.2. Forrest plot metformin+lifestyle vs placebo+lifestyle for fasting glucose



2.8.3. Funnel plot for assessment of publication bias

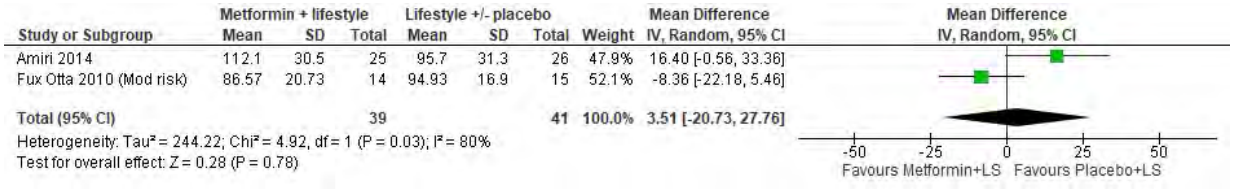


OUTCOME 2.9 OGTT (mg/dl)

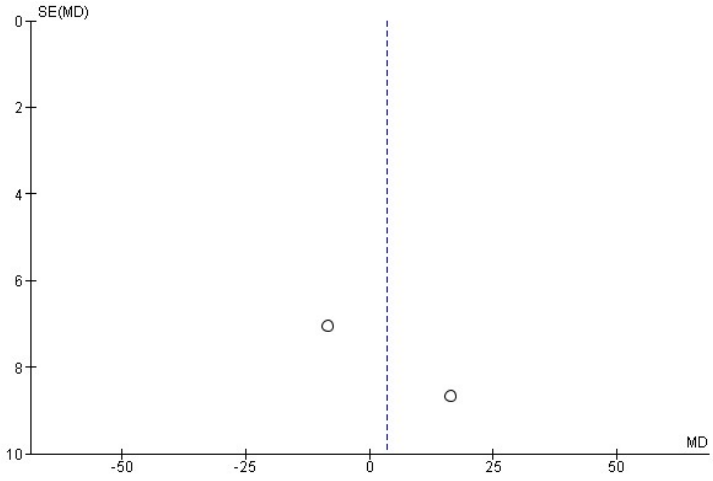
2.9.1 Individual Study Data Table

	OUTCOME: OGTT					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): lifestyle+metformin versus lifestyle+placebo							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Fux Otta et al. 2010	Mg/dl/120min	14	86.57	20.73	15	94.93	16.9	Crude	4
Amiri et al. 2014	Mg/dl/120min	25	112.1	30.5	26	95.7	31.3		6

2.9.2. Forrest plot metformin+lifestyle vs placebo+lifestyle for OGTT



2.9.3. Funnel plot for assessment of publication bias

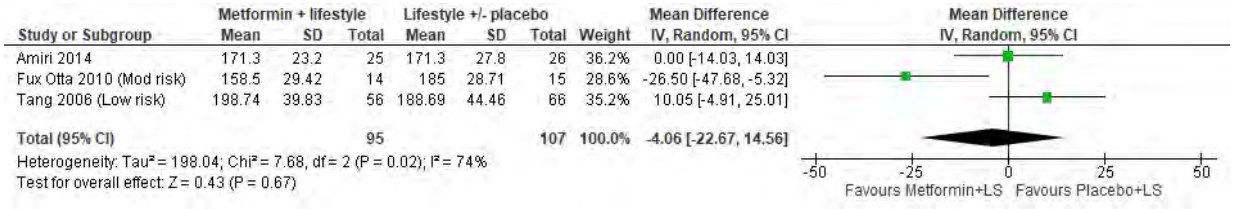


OUTCOME 2.10 Total cholesterol (mg/dl)

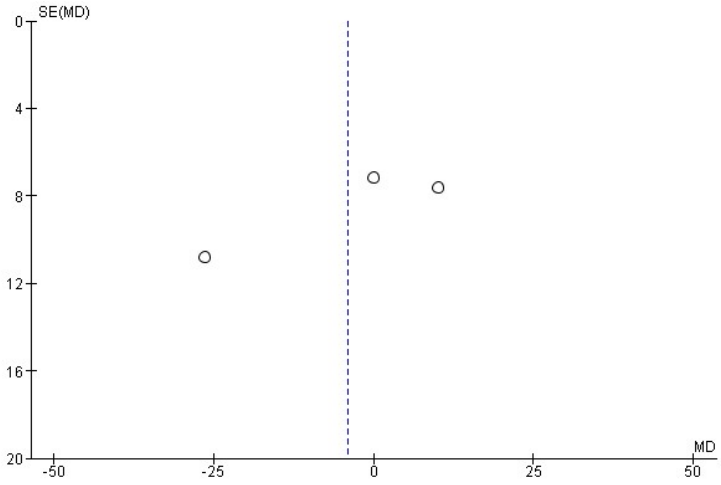
2.10.1 Individual Study Data Table

	OUTCOME: total cholesterol					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): lifestyle+metformin versus lifestyle+placebo							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Tang et al. 2006	mmol/l mg/dl	56	5.14 198.74	1.03 39.83	66	4.88 188.69	1.15 44.46	BMI>30	6
Fux Otta et al. 2010	Mg/dl	14	158.5	29.42	15	185	28.71	Crude	4
Amiri et al. 2014	mM/l	25	171.3	23.2	26	171.3	27.8	Unit?	6

2.10.2. Forrest plot metformin+lifestyle vs placebo+lifestyle for total cholesterol



2.10.3. Funnel plot for assessment of publication bias

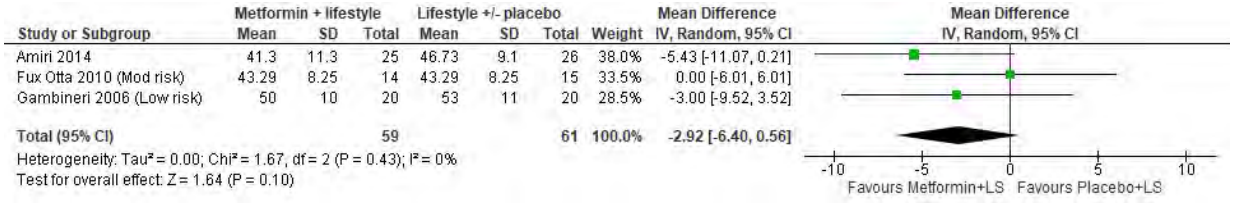


OUTCOME 2.11 HDL (mg/dl)

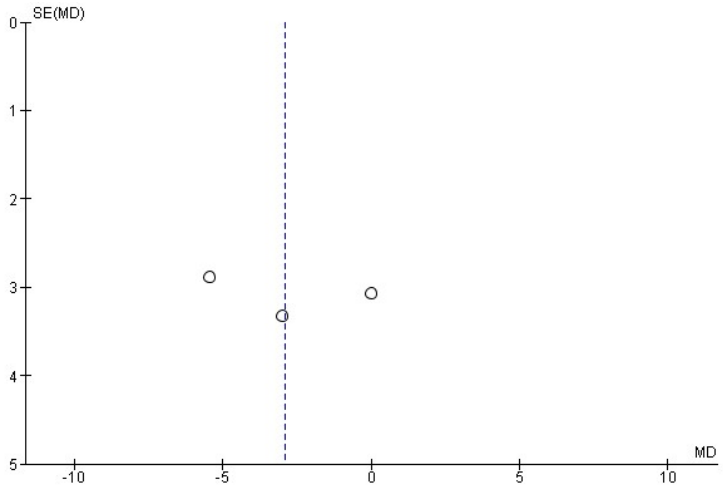
2.11.1 Individual Study Data Table

	OUTCOME: HDL					OUTCOME TYPE: Continuous			
		COMPARISON (if applicable): lifestyle+metformin versus lifestyle+placebo							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Fux Otta et al. 2010	Mg/dl	14	43.29	8.25	15	43.29	8.25	Crude	4
Amiri et al. 2014	mM/l	25	41.3	11.3	26	46.73	9.1	Unit?	6
Gambineri et al. 2006	Mg/dl	20	45	8	20	47	11		6
Gambineri et al. 2006	Mg/dl	20	50	10	20	53	11		12

2.11.2. Forrest plot metformin+lifestyle vs placebo+lifestyle for HDL



2.11.3. Funnel plot for assessment of publication bias

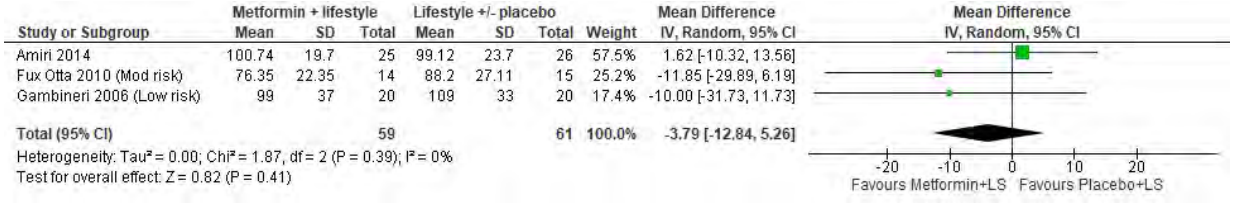


OUTCOME 2.12 LDL (mg/dl)

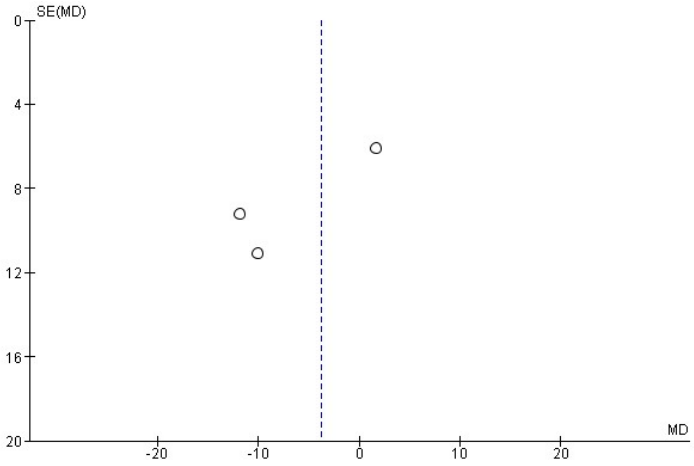
2.12.1 Individual Study Data Table

	OUTCOME: LDL					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): lifestyle+metformin versus lifestyle+placebo							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something special?**	**Time period (month)**
Fux Otta et al. 2010	Mg/dl	14	76.35	22.35	15	88.2	27.11	Crude	4
Amiri et al. 2014	mM/l	25	100.74	19.7	26	99.12	23.7	Unit?	6
Gambineri et al. 2006	Mg/dl	20	104	34	20	119	53		6
Gambineri et al. 2006	Mg/dl	20	99	37	20	109	33		12

2.12.2. Forrest plot metformin+lifestyle vs placebo+lifestyle for LDL



2.12.3. Funnel plot for assessment of publication bias

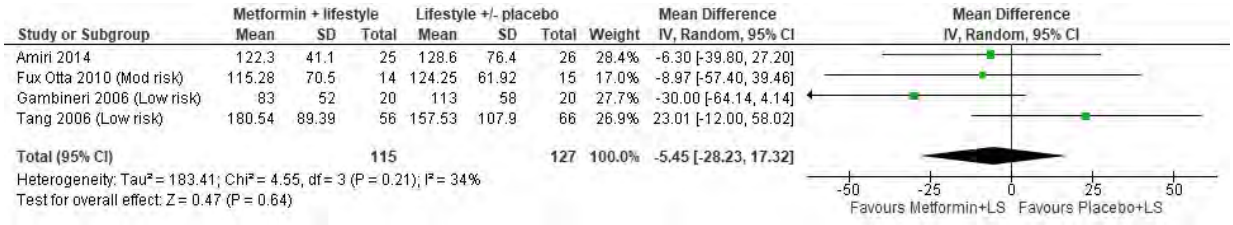


OUTCOME 2.13 Triglycerides (mg/dl)

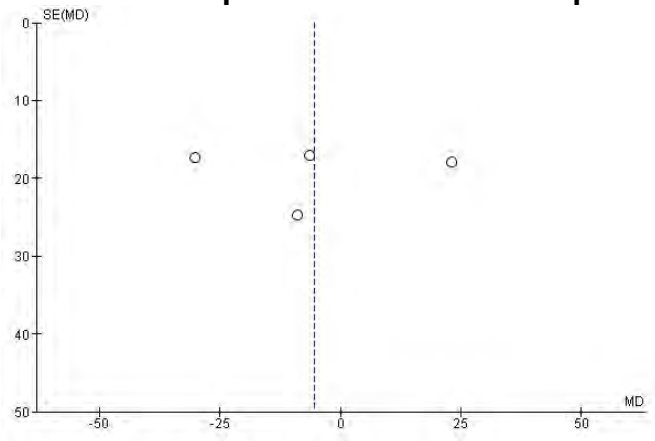
2.13.1 Individual Study Data Table

	OUTCOME: Triglycerides					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): lifestyle+metformin versus lifestyle+placebo							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something special?**	**Time period (month)**
Tang et al. 2006	mmol/l Mg/dl	56	2.04 180.54	1.01 89.39	66	1.78 157.53	1.21 107.9	BMI>30	6
Fux Otta et al. 2010	Mg/dl	14	115.28	70.5	15	124.25	61.92	Crude	4
Amiri et al. 2014	mM/l	25	122.3	41.1	26	128.6	76.4	Unit??	6
Gambineri et al. 2006	Mg/dl	20	97	36	20	101	65		6
Gambineri et al. 2006	Mg/dl	20	83	52	20	113	58		12

2.13.2. Forrest plot metformin+lifestyle vs placebo+lifestyle for triglycerides



2.13.3. Funnel plot for assessment of publication bias

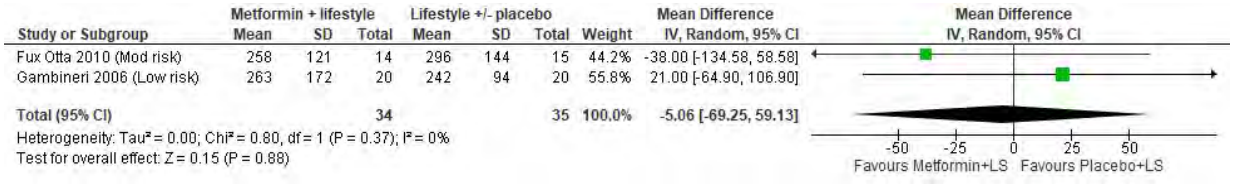


OUTCOME 2.14 Androstenedione (ng/dl)

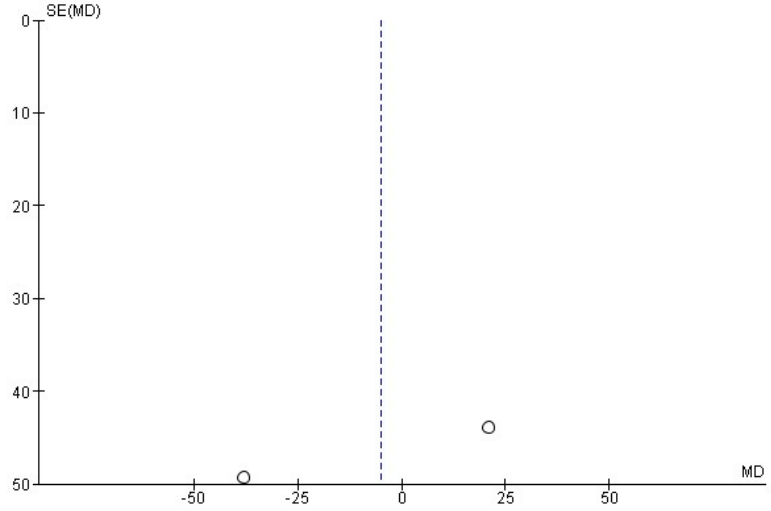
2.14.1 Individual Study Data Table

	OUTCOME: androstenedione						**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin+lifestyle versus **placebo+lifestyle**								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something special?**	**Time period (month)**
Fux Otta et al. 2010	Ng/ml		14	2.58	1.21	15	2.96	1.44	Crude	4
Gambineri et al 2006	Ng/dl		20	332	123	20	295	112		6
Gambineri et al 2006	Ng/dl		20	263	172	20	242	94		12

2.14.2. Forrest plot metformin+lifestyle vs placebo+lifestyle for androstenedione



2.14.3. Funnel plot for assessment of publication bias



Adverse outcomes

	Study	Metformin+LS	Placebo+LS
Gastrointestinal side effects	Fux Otta 2010	No serious	No serious
	Gambineri 2006	2/20	0/19
	Pasquali 2000	1/10	0/8
	Tang	11/56	6/66

Comparison 3: Metformin versus lifestyle

Evidence Summary

Three randomised controlled trials (RCTs) were identified by our search. Of these RCT, all were included in the meta-analysis.
Of these studies two had a moderate ROB and one a high ROB. All studies were on obese PCOS patients, one (Hoeger et al. 2008) on adolescents.

Meta-analysis/descriptive analysis summary

According to the meta-analysis, metformin was superior in lowering testosterone and participants with lifestyle only had an improved SHBG. For other outcomes, no difference was observed. However, certainty in the evidence is very low for all outcomes.
Regarding individual studies, not included in the meta-analysis, Esfahania et al. found that DHEAS seemed to be lower in participants using metformin compared to those with lifestyle only and WHR seemed to be lower among participants with lifestyle only. Certainty in the evidence was, however, very low for all outcomes.
Regarding adverse effects, Esfahanian et al. reported that the metformin only group had a higher amount of participants with GI related adverse effects (2/17 compared to 0/13)

Note
No new studies compared to the previous TR were identified.

Author, year, country	Population	Sample Size per group	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Type of analysis and subgroup	ROB
Esfahanian et al. 2013 Iran	Women with bmi>=27 and PCOS	1.Metformin=17 2.HC diet=13	3 months	1: 31.1±3.3 2: 34.1±5.4	1: 21.9±9.3 2: 20±4.6	BMI, WHR, T, DHEAS, f-insulin, f-gluc, lipids, HOMA, crp, adverse effects	META BMI>=27	**ROB high**
Hoeger et al. 2008 USA	Women, aged of 12-18 yr with BMI above the 95th percentile and evidence of menstrual irregularity	1.Metformin=6 2.placebo=10 3.OCP=10 4.LS=8	6 months	1: 34.3±6.5 2: 36.1±7.5	1: 16±1.7 2: 15.4±1.7	BMI, hirsutism, SHBG, FAI, T, f-insulin, f-gluc, lipids, crp, PAI	META BMI above the 95th percentile Adolescents	**ROB Moderate**

Hoeger et al. 2004 USA	Overweight or obese women with PCOS	1.Metformin=6 2.LS+placebo=8 3.LS+metformin=5 4.Placebo=7	6 months	1: 37.1±4.9 2: 40±7.4 3: 41.7±6.2 4: 37.1±4.6	1: 29.5±6.4 2: 27.1±4.3 3: 30.4±5.4 4: 27.1±4.5	BMI, SHBG, FAI, T, f-insulin, f-gluc	META BMI=>25 Adults	**ROB Moderate**

Results of meta-analysis

Outcome	Time point	RCTs	N	Effect, random, MD	P-value	I2 (%)	Favours	Certainty
BMI (kg/m2)	3-6 months	3	58	-0.53 (-3.42 to 2.35)	0.72	0	No difference	⊕◯◯◯ VERY LOW
SHBG (nmol/l)	**6 months**	**2**	**28**	**-11.05 (-20.96 to -1.14)**	**0.03**	**0**	**Lifestyle**	⊕◯◯◯ VERY LOW
Testosterone (ng/dl)	**3-6 months**	**3**	**58**	**-4.81 (-8.83 to -0.80)**	**0.02**	**0**	**Metformin**	⊕◯◯◯ VERY LOW
Fasting insulin (uIU/ml)	6 months	2	44	1.93 (-1.60 to 5.46)	0.28	0	No difference	⊕◯◯◯ VERY LOW
Fasting glucose (mg/dl)	3-6 months	3	58	-4.78 (-9.90 to 0.34)	0.07	6	No difference	⊕◯◯◯ VERY LOW
Total cholesterol (mg/dl)	3-6 months	2	44	5.00 (-27.22 to 37.22)	0.76	55	No difference	⊕◯◯◯ VERY LOW
HDL (mg/dl)	3-6 months	2	44	0.70 (-7.63 to 9.03)	0.87	0	No difference	⊕◯◯◯ VERY LOW
LDL (mg/dl)	3-6 months	2	44	0.70 (-7.63 to 9.03)	0.90	55	No difference	⊕◯◯◯ VERY LOW
Triglycerides (mg/dl)	3-6 months	2	44	-4.07 (-71.98 to 63.84)	0.91	72	No difference	⊕◯◯◯ VERY LOW
CRP (mg/dl)	3-6 months	2	44	-0.58 (-1.73 to 0.58)	0.33	0	No difference	⊕◯◯◯ VERY LOW

Individual studies not included in meta-analysis

Outcome	Author, year	Time point	N	Metformin	Lifestyle	P-value	Favours	Grading
WHR	Esfahanian et al 2013	3 months	Metformin=17 Lifestyle=13	Means +SD 0.77 +/- 0.05	Means +SD 0.70 +/- 0.05	0.001	**Lifestyle**	⊕◯◯◯ VERY LOW[1]
Hirsutism	Hoeger et al. 2008	6 months	Metformin=6 Lifestyle=8	Means +SD 8.2 +/- 3.4	Means +SD 8.2 +/- 2.0	1.0	No difference	⊕◯◯◯ VERY LOW[2]
FAI	Hoeger et al. 2008	6 months	Metformin=6 Lifestyle=8	Means +SD 10.9 +/- 7.9	Means +SD 9.5 +/- 5.3	0.56	No difference	⊕◯◯◯ VERY LOW[2]
DHEAS	Esfahanian et al 2013	3 months	Metformin=17 Lifestyle=13	Means +SD 201.7 +/- 81.3	Means +SD 293 +/- 84.4	0.003	**Metformin**	⊕◯◯◯ VERY LOW[1]
PAI	Hoeger et al. 2008	6 months	Metformin=6 Lifestyle=8	Means +SD 45.4 +/- 32.2	Means +SD 45.0 +/- 25.6	0.97	No difference	⊕◯◯◯ VERY LOW[2]
HOMA-IR	Esfahanian et al 2013	3 months	Metformin=17 Lifestyle=13	Means +SD 2.4 +/- 1.4	Means +SD 2.05 +/- 1	NR	No difference (by appearance)	⊕◯◯◯ VERY LOW[1]

[1] Downgraded twice for high ROB and downgraded twice for small number of participants

[2] Downgraded once for moderate ROB and downgraded twice for small number of participants

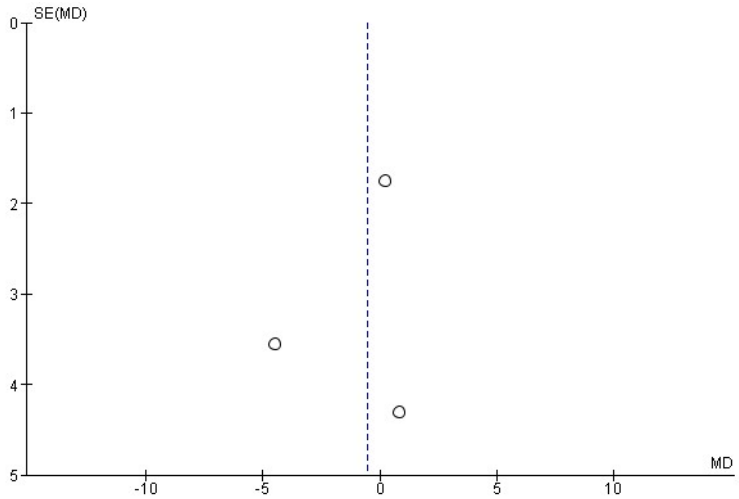
OUTCOME 3.1 BMI (kg/m2)

3.1.1 Individual Study Data Table

	OUTCOME: BMI					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **Lifestyle**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Hoeger et al. 2008	Kg/m2	6	35.7	8.6	8	34.9	7.0	Adolescents, obese	6
Esfahanian et al. 2013	Kg/m2	17	30.3	3.5	13	30.1	5.5	BMI>=27	3
Hoeger et al 2004	Kg/m2	6	36.15	5.29	8	40.63	7.98		6

3.1.2. Forrest plot metformin vs lifestyle for BMI

3.1.3. Funnel plot for assessment of publication bias

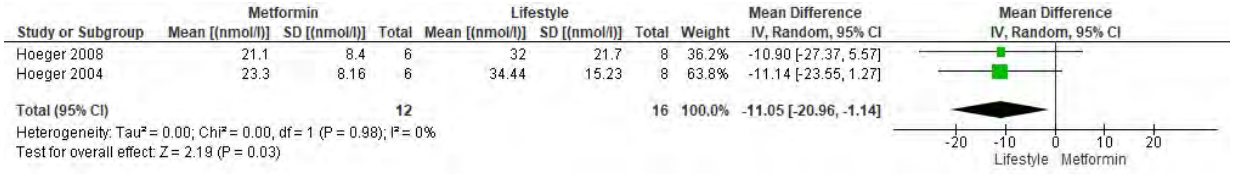


OUTCOME 3.2 SHBG (Nmol/l)

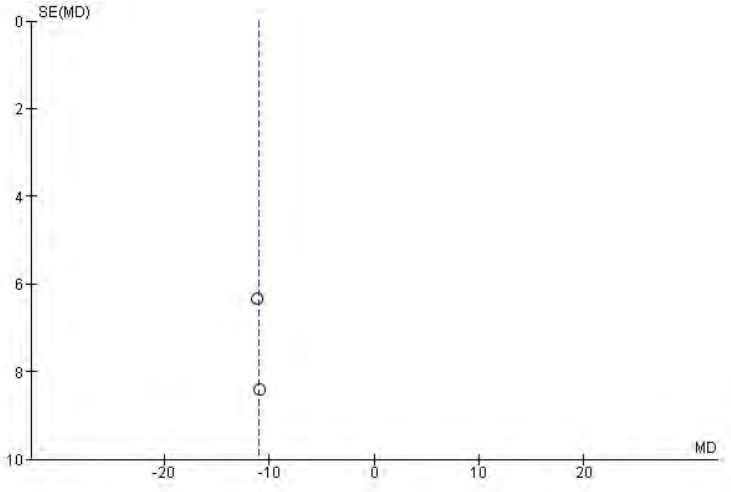
3.2.1 Individual Study Data Table

	OUTCOME: SHBG					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **Lifestyle**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Hoeger et al. 2008	Nmol/l	6	21.1	8.4	8	32.0	21.7	Adolescents, obese	6
Hoeger et al 2004	Nmol/l	6	23.77	8.16	8	34.44	15.23		6

3.2.2. Forrest plot metformin vs lifestyle for SHBG



3.2.3. Funnel plot for assessment of publication bias

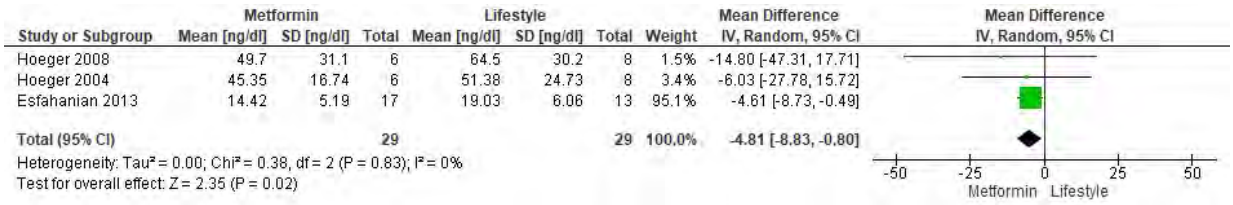


OUTCOME 3.3 Testosterone (Ng/dl)

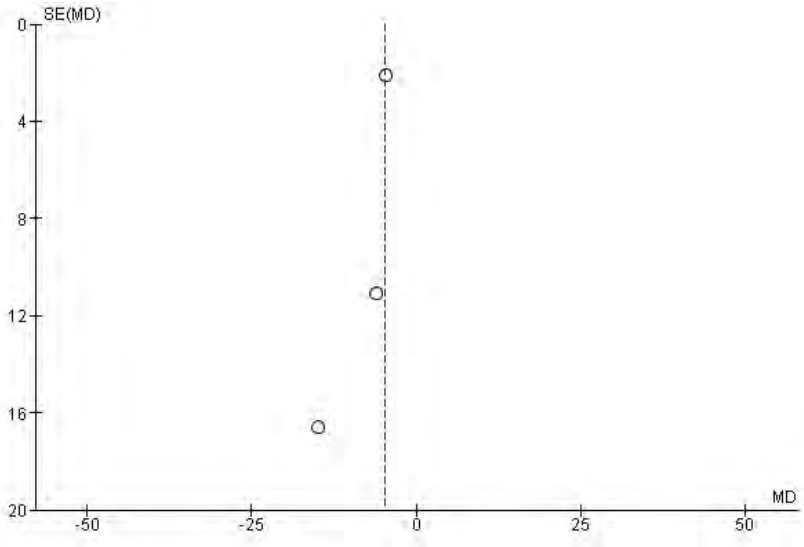
3.3.1 Individual Study Data Table

	OUTCOME: Testosterone					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **Lifestyle**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Hoeger et al. 2008	Ng/dl	6	49.7	31.1	8	64.5	30.2	Adolescents, obese	6
Esfahanian et al. 2013	Ng/dl	17	14.42	5.19	13	19.03	6.06	BMI>=27	3
Hoeger et al 2004	Ng/dl	6	45.35	16.74	8	51.38	24.73		6

3.3.2. Forrest plot metformin vs lifestyle for testosterone



3.3.3. Funnel plot for assessment of publication bias

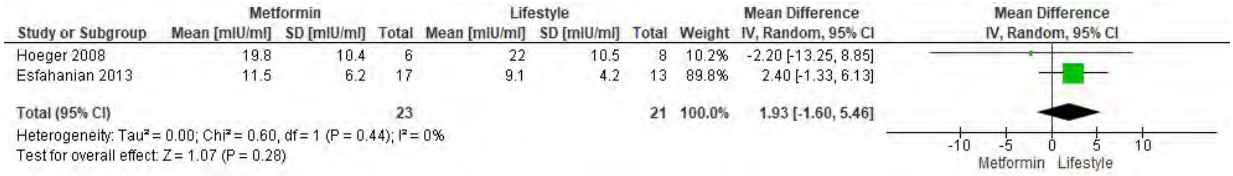


OUTCOME 3.4 Fasting insulin (mIU/ml)

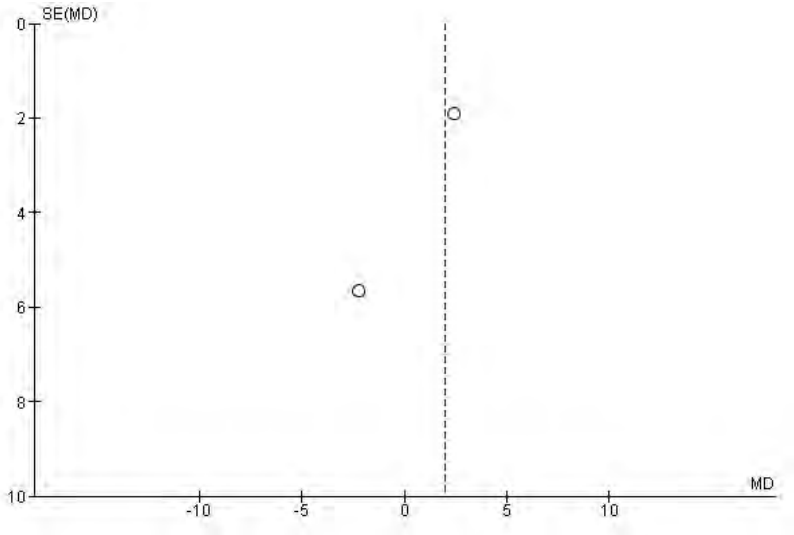
3.4.1 Individual Study Data Table

	OUTCOME: fasting insulin					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **Lifestyle**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Hoeger et al. 2008	ulU/ml	6	19.8	10.4	8	22.0	10.5	Adolescents, obese	6
Esfahanian et al. 2013	ulU/ml	17	11.5	6.2	13	9.1	4.2	BMI>=27	3

3.4.2. Forrest plot metformin vs lifestyle for fasting insulin



3.4.3. Funnel plot for assessment of publication bias

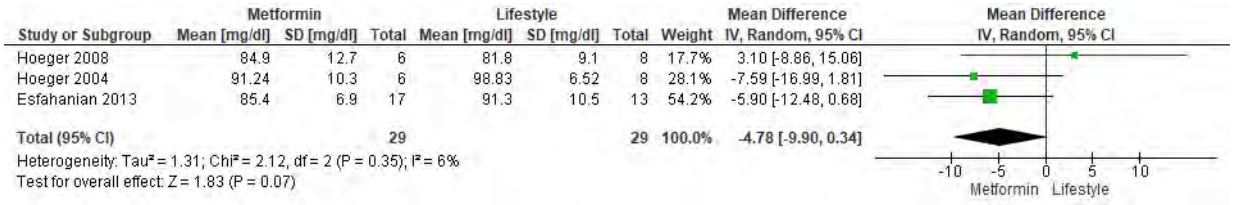


OUTCOME 3.5 Fasting glucose (mg/dl)

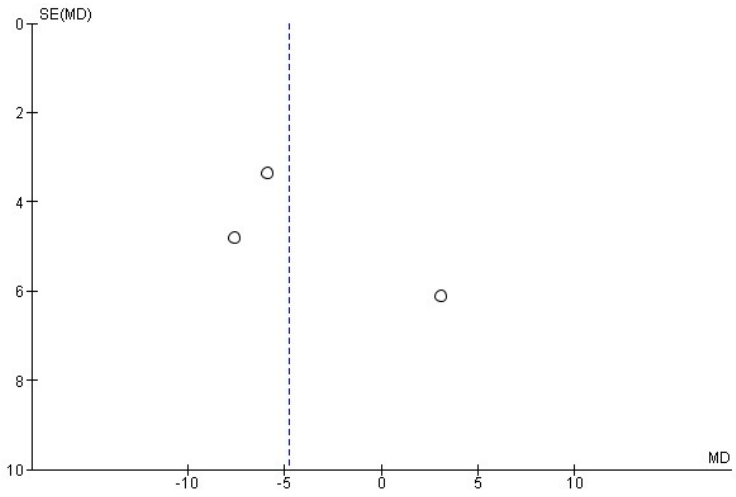
3.5.1 Individual Study Data Table

	OUTCOME: fasting glucose						**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **Lifestyle**								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**		**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Hoeger et al. 2008	Mg/dl		6	84.9	12.7	8	81.8	9.1	Adolescents, obese	6
Esfahanian et al. 2013	Mg/dl		17	85.4	6.9	13	91.3	10.5	BMI>=27	3
Hoeger et al 2004	Mg/dl		6	91.24	10.3	8	98.83	6.52		6

3.5.2. Forrest plot metformin vs lifestyle for fasting glucose



3.5.3. Funnel plot for assessment of publication bias

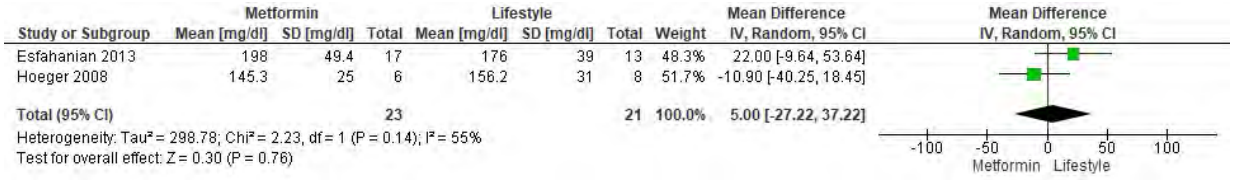


OUTCOME 3.6 Total cholesterol (mg/dl)

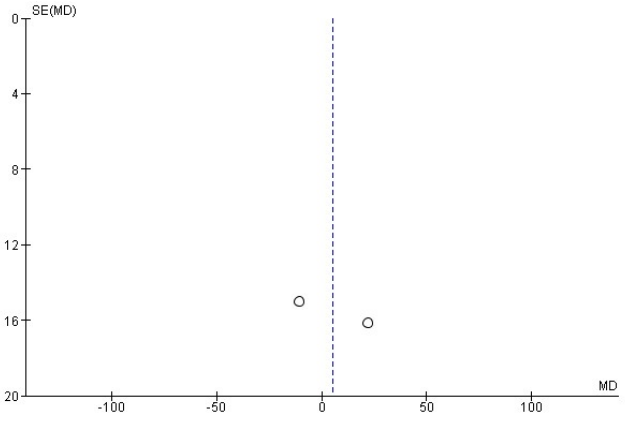
3.6.1 Individual Study Data Table

	OUTCOME: Total cholesterol						**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **Lifestyle**								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**		**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Hoeger et al. 2008	Mg/dl		6	145.3	25	8	156.2	31	Adolescents, obese	6
Esfahanian et al. 2013	mg/dl		17	198	49.4	13	176	39	BMI>=27	3

3.6.2. Forrest plot metformin vs lifestyle for total cholesterol



3.6.3. Funnel plot for assessment of publication bias

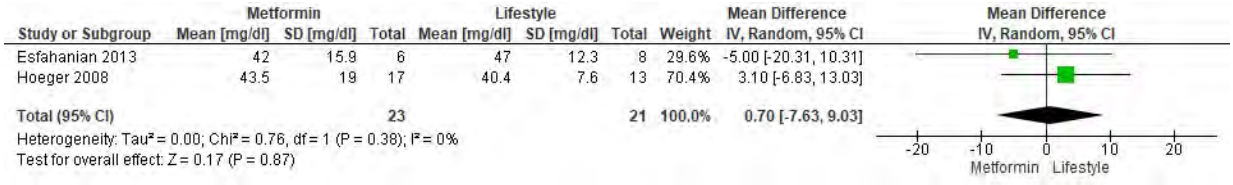


OUTCOME 3.7 HDL (mg/dl)

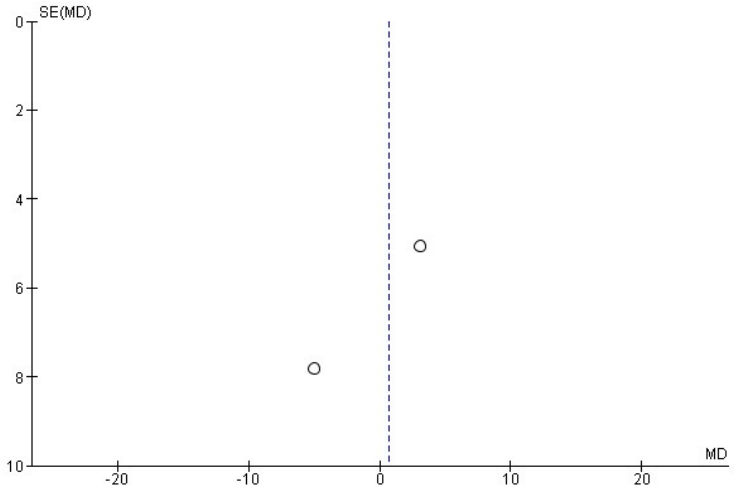
3.7.1 Individual Study Data Table

	OUTCOME: HDL					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **Lifestyle**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Hoeger et al. 2008	Mg/dl	6	43.5	19	8	40.4	7.6	Adolescents, obese	6
Esfahanian et al. 2013	mg/dl	17	42	15.9	13	47	12.3	BMI>=27	3

3.7.2. Forrest plot metformin vs lifestyle for HDL



3.7.3. Funnel plot for assessment of publication bias

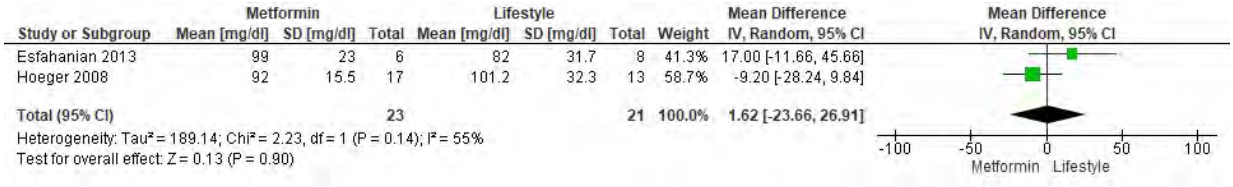


OUTCOME 3.8 LDL (mg/dl)

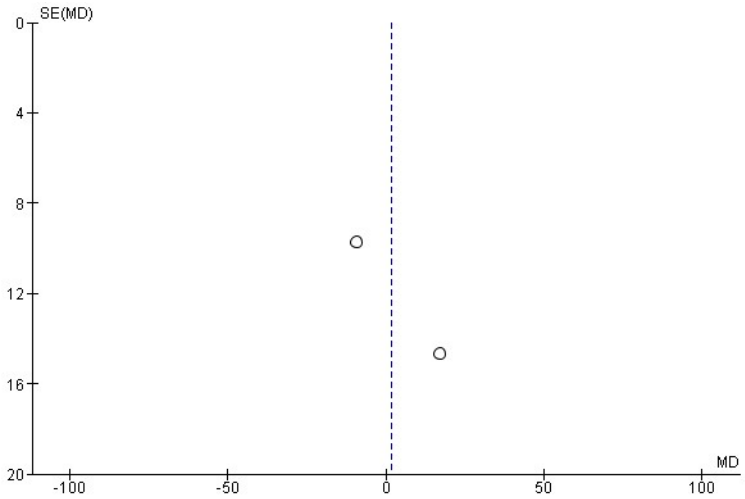
3.8.1 Individual Study Data Table

	OUTCOME: LDL					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **Lifestyle**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Hoeger et al. 2008	Mg/dl	6	92.0	15.5	8	101.2	32.3	Adolescents, obese	6
Esfahanian et al. 2013	mg/dl	17	99	23	13	82	31.7	BMI>=27	3

3.8.2. Forrest plot metformin vs lifestyle for LDL



3.8.3. Funnel plot for assessment of publication bias

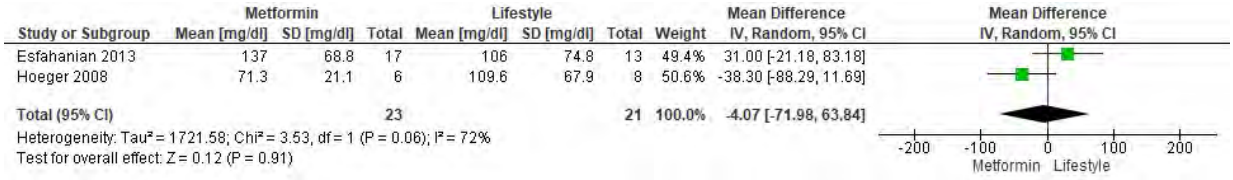


OUTCOME 3.9 Triglycerides (mg/dl)

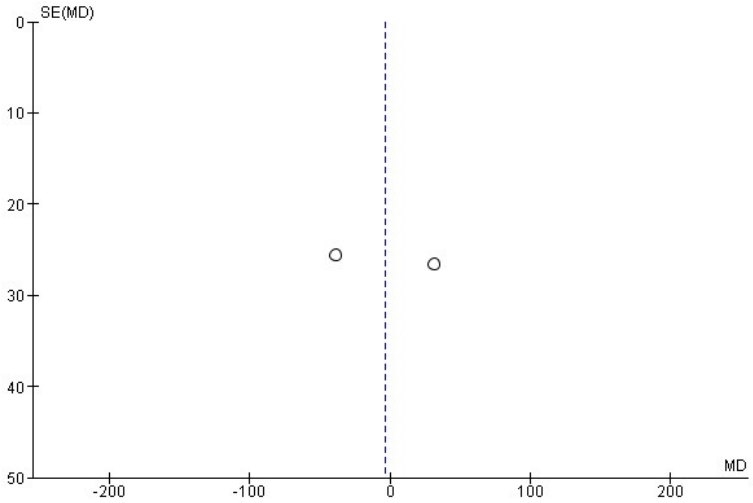
3.9.1 Individual Study Data Table

	OUTCOME: Triglycerides					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **Lifestyle**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Hoeger et al. 2008	Mg/dl	6	71.3	21.1	8	109.6	67.9	Adolescents, obese	6
Esfahanian et al. 2013	mg/dl	17	137	68.8	13	106	74.8	BMI>=27	3

3.9.2. Forrest plot metformin vs lifestyle for Triglycerides



3.9.3. Funnel plot for assessment of publication bias

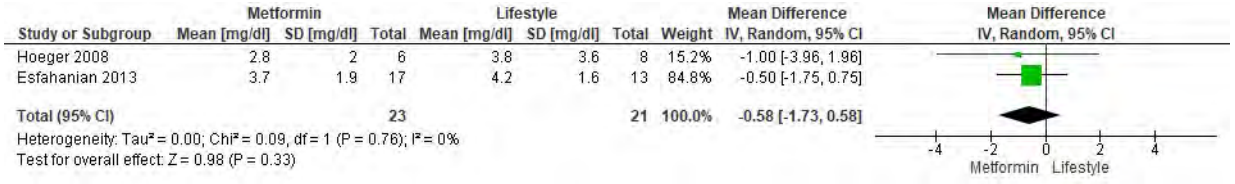


OUTCOME 3.10 Triglycerides (mg/l)

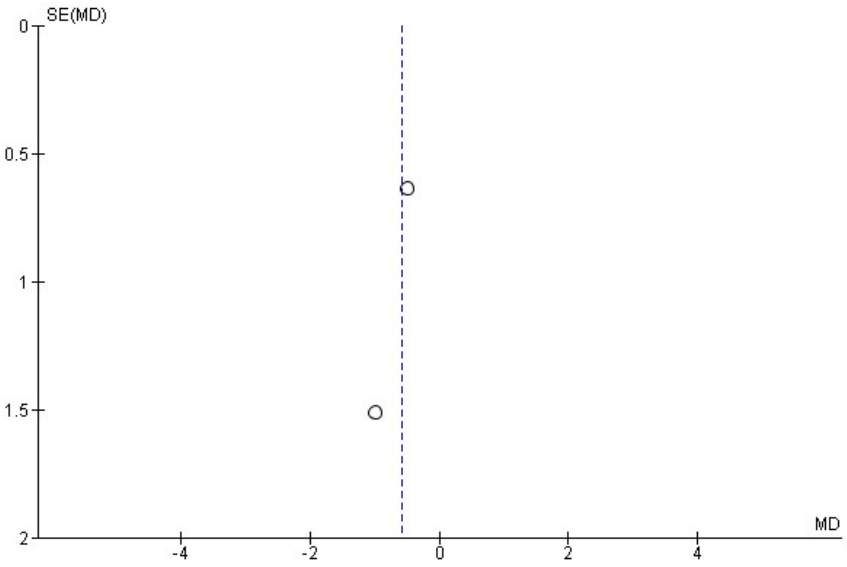
3.10.1 Individual Study Data Table

	OUTCOME: CRP						**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **Lifestyle**								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**		**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Hoeger et al. 2008	Mg/l		6	2.8	2.0	8	3.8	3.6	Adolescents, obese	6
Esfahanian et al. 2013	mg/l		17	3.7	1.9	13	4.2	1.6	BMI>=27	3

3.10.2. Forrest plot metformin vs lifestyle for CRP



3.10.3. Funnel plot for assessment of publication bias



Comparison 4: Metformin versus OCP

Evidence Summary

24 randomised controlled trials (RCTs) were identified by our search (resulting in 33 included articles). Of these RCT, 22 were included in the meta-analysis.
Of our included articles two had a low ROB, 14 had a moderate ROB and 17 had a high ROB.

We used data from original articles and performed our own conversions (in terms of units and variation) wherever means and SDs or SEs were reported.
A major limitation in the evidence for this comparison is the lack of confidence in author reporting of units and conversions.

In Panidis et al. and Christakou et al. metformin is compared to an OCP, either containing cyproterone acetate (CPA) or drospirenon (DRP). In these cases, I have included the comparison between metformin and OCPs containing CPA since this combination is more frequently used in the other studies. Note that in Q4.2 (OCP-Metformin comparison) DRP was used, explaining slightly different results and sometimes grading.

Rows highlighted grey indicate studies with participants described as obese (BMI over 25). Rows shaded green indicate that participants had BMI in the normal weight category (BMI under 25). Studies using the same data are coloured in the “author-column”. We performed subgroup analyses based on BMI (<=25, >25 or BMI not specified) and age (adults and adolescents).

Meta-analysis/descriptive analysis summary

Overall:

In the meta-analysis, metformin was superior in improving fasting insulin, total cholesterol, triglycerides, CRP and HOMA-IR (certainty low or very low).
OCP was superior in improving hyperandrogenism (SHBG, FAI, Testosterone, free testosterone, DHEAS and androstenedione) and restoring regularity in menstrual cycle (certainty moderate to very low).

Subanalyses according to BMI:

For PCOS-women with normal weight (BMI<25), metformin was superior in lowering WHR (certainty low), total cholesterol (certainty very low) and HOMA-IR (certainty moderate). OCP was better in improving hirsutism (certainty low) and androstenedione (certainty low) in PCOS-women with normal weight (BMI<25).
For obese PCOS women (BMI>25) metformin was superior in improving HDL (certainty moderate).
Metformin was superior in improving fasting insulin (certainty very low to moderate), triglycerides (certainty low) and CRP (certainty low to moderate) compared to OCP regardless of BMI. OCP was superior to metformin in improving hyperandrogenism (SHBG, FAI and Testosterone) in PCOS-women regardless of BMI (certainty low to high).

Subanalyses according to age:

For adult PCOS-women metformin was superior in improving fasting insulin (certainty moderate), whereas OCP was superior in improving hyperandrogenism (SHBG, FAI, testosterone, free testosterone) (certainty high to very low).
We found four studies on adolescents (Allen et al., Al-Zubeidi et al, El Maghraby et al. and Hoeger et al. 2008). For adolescents, metformin was superior in lowering LDL (certainty low),

whereas OCP was superior in improving SHBG and FAI (note that only one study included these outcomes).
Metformin was superior in lowering CRP and total cholesterol (certainty very low to moderate) regardless of age.

Regarding individual studies, not included in the meta-analysis, Glintborg et al. and Dardzinska et al. found that BMI, weight and CRP was significantly lower after using metformin, whereas some studies (Glintborg et al., Burchall et al., Meyer et al.) found that hyperandrogenism (SHBG, FAI, PAI and DHEAS) was better improved by using OCP.
Certainty in the evidence for the individual studies are low or very low since the studies were moderate or high risk of bias and all studies had only a small amount of participants.
Due to the lack of systematic reporting, where many studies do not report adverse effects at all, and the ones that do, not report in a similar manner, it is difficult to draw strong conclusions, but the reports suggest more gastrointestinal side effects with metformin (see table at the end of this document).
Dorgham et al. found that OCP with laser hair removal could achieve greater hair reduction and significant improvements in patients' QOL compared to metformin+laser hair removal (see table at the end of this document).

Author, year, country	Population	Sample Size per group	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Type of analysis and subgroup	ROB
Harborne et al. 2003 UK	Women with PCOS	1.Metformin=26 2.OCP=26	12 months	1.31.7 (29.5-35.5) 2.31.8 (28.4-34.4)	1.31.3 (27.9-34.7) 2.31.7 (26.8-36.5)	WHR, BMI, mFGS, SHBG, FAI, T, f-insulin, f-gluk, lipids, crp, adverse effects	META Adults BMI>25	**ROB Moderate**
Hutchinson et al 2008 Australia	Overweight women (BMI >27 kg/m2) with PCOS	1.Metformin=19 2.OCP =19	6 months	1.38.4±1.6 2.35.3±1.8	NR	WHR, SHBG, f-insulin, f-gluk, crp, lipids, HOMA	META Adults BMI>27 SEM	**ROB Moderate** Outcomes also reported in Meyer et al. 2007, Burchall et al 2017, Moran et al 2010)
Mhao et al. 2015 Iraq	Women with PCOS, age14–40 years	1.Metformin=16 2.OCP=10	3 months	1.27.2±5.4 2.30.5±5.3	NR	WHR, BMI, lipids,	META Adults	**ROB high**
Morin-Papunen et al. 2000 Finland	obese (BMI> 27) women with PCOS	1.metformin=8 2.OCP=10	6 months	1.32.5 ± 1.1 2.37.2 ±1.8	1.29.9 ± 1.5 2.29.8 ±1.0	WHR, BMI, mFGS, f-insulin, f-gluk, cycle duration, T, SHBG, A, DHEAS	META Adults BMI>27 SEM	**ROB Moderate** Outcomes also reported in Morin-Papunen et al. 2003 and Rautio et al. 2005
Morin-Papunen et al. 2003 Finland (2)	Non-obese (BMI<25) women with PCOS	1.metformin=8 2.OCP=9	6 months	1.22.5 ± 0.8 2.21.8 ±0.7	1.28.2 ± 1.4 2.28.5 ±1.7	WHR, BMI, mFGS, f-insulin, f-gluk, cycle duration, T, SHBG, A, DHEAS	META Adults BMI<25 SEM	**ROB Moderate** Outcomes also reported in Morin-Papunen

								et al. 2000 and Rautio et al. 2005
Ozgurtas et al. 2008 Turkey	Non-obese (BMI < 25), aged >18 years, women with PCOS	1.metformin=20 2.OCP=21 3.Controls=22	3 months	1.21.8 ± 01.27 2.21.72 ±1.24 3.21.4 ±1.54	NR	WHR, BMI, mFGS, T, free-T, lipids, HOMA	META Adults BMI<25	**ROB high** Controls not included in meta-analysis (no info on outcomes)
Wu et al 2008 China	Women with PCOS, aged 19-35yr, divided into obese (BMI>25) and non-obese (BMI<25)	1.Metformin obese=7 2.OCP obese=7 3. Metformin+OCP obese=6 4.Metformin non-obese=11 5.OCP non obese=12 6.Metformin+OCP non obese=10	3 months	1.25.6± 0.6 2.25.3 ±0.8 3.25.2 ±1.0 4.21.5± 1.8 5.21.4 ±1.6 6.21.6 ±1.4	1.25.6± 3.6 2.25.0 ±4.3 3.24.5 ±2.4 4.25.6± 4.2 5.26.1 ±4.6 6.25.8 ±4.0	WHR, BMI, T, f-insulin	META Adults BMI>25 BMI<25	**ROB Moderate**
Aghamohammadzadeh et al. 2010 Iran	Women with PCOS	1.Metformin=30 2.OCP=30	6 months	1.26.5 ±5.7 2.24.6 ±4.9	1.24.9 ± 11 2.22 ±5.2	Weight, T, crp,	META Adults	**ROB high**
Allen et al. 2005 USA	Obese, post-menarchal, non-sexually active adolescents, aged 12-21 years with PCOS and hyperinsulinism	1.Metformin=16 2.OCP=15	6 months	1.37.3 ±1.3 2.40.1 ±2.1	1.15.4 (13.1-18.4) 2.15.3 (12.5-21)	Weight, T, free-T, f-insulin, lipids	META Adolescents >95th percentile BMI	**ROB Low**
Cetinkalp et al 2009 Turkey	young women with PCOS	1.Metformin=47 2.Rosi=14 3.OCP=33	4 months	1.25.82 ±6.1 2.22.96 ±4.8 3.24.72±4.1	NR	Weight, BMI, T, free-T, f-insulin, f-gluk, crp, lipids, HOMA, amenorrhea, oligomenorrhea	META Adults SEM	**ROB high**
Dardzinska et al. 2014 Poland	women (age range: 18–36) with PCOS Cross-over study	1.Metformin=7 2.OCP=14	4 months	M 1st: 25.1±9.8 C 1st: 24.9±4.4	M 1st: 24.6 [23.0;26.3] C 1st: 24.9 [23.5;26.4]	Weight, T, lipids, BMI, SHBG, FAI, crp, homa, A	META Individual analysis Adults BMI<25	**ROB Moderate**
El Maghraby et al. 2015 Egypt	Girls, aged 15-20 yr with PCOS	1.Metformin=33 2.OCP=32	24 months	NR	1.17.20 ±2.0 2.16.90 ±1.6	Weight, T, f-insulin,	META Adolescents	**ROB high**
Kumar et al. 2018 India	newly diagnosed PCOS (age 18–40 year, symptom duration >6 months)	1.Metformin=30 2. OCP=28 3.Metformin+OCP=29	6 months	1.27.1 ±6 2.26.15 ±4.9 3.30.1 ±5.5	1.22±5.2 2.22.9±5 3.24.1 ±5.9	Weight, BMI, mFGS, T, f-insulin, f-gluk, crp, lipids, HOMA	META Adults BMI<25	**ROB Moderate**
Burchall et al 2017 Australia	Overweight and obese women with PCOS	1. metformin N=23 2. Low-dose OCP+spiro N=16 3.High dose OCP=21	6 months	1. 37.79 ± 6.81 2. 35.25 ± 5.71 3. 35.91 ± 8.11	1.32.16 ± 6.52 2. 35.44±6.91 3. 34.41±6.73	BMI, T, PAI	META Adults BMI not specified	Outcomes included in Meyer et al. 2007, Moran et al 2010, Hutchinson et al 2008 **ROB High**
Kilic et al 2011 Turkey	Women with PCOS aged 18-35 years	Obese: 1.Metformin=24 2.OCP=25	6months	1.31.5 ±2.2 2.27.7 ±0.9	1.28.7 ±3.7 2.29.0±3.5	BMI, HOMA	META Adults	**ROB low**

							BMI <25 BMI>25	
		Non-obese 3.Metformin=23 4.OCP=24						
Christakou et al. 2014 Greece	Premenopausal caucasian women with PCOS (BMI<25)	1.Metformin=40 2. OCP=40 3.OCP=40	6 months	1.23.0 ±0.67 2.22.4 ±0.48 3.21.8 ±6.35	1.21.5±0.5 2.23.2±0.6 3.22 ±0.6	BMI, T, crp	META Adults BMI<25	**ROB Moderate**
Hoeger et al. 2008 USA	Women, aged of 12-18 yr with BMI above the 95th percentile and evidence of menstrual irregularity	1.Metformin=6 2.placebo=10 3.OCP=10 4.LS=8	6 months	1: 34.3±6.5 2: 36.1±7.5	1: 16±1.7 2: 15.4±1.7	BMI, mFGS, SHBG, FAI, T, f-insulin, f-gluk, lipids, PAI	META Adolescents BMI>25	**ROB Moderate**
Kebapcilar et al 2010 Turkey	Women with PCOS (24.0+/-5.4 yr; BMI 27.9 +/-5.28)	1.Metformin=12 2.Metformin+OCP=12 3. OCP=12 4.OCP+SPL=12	3 months	1.27.8± 4 2.27.6 ±3 3.28.7 ±6 4.27.6±4	1.24.4± 6.2 2.24.9 ±4.8 3.23.2 ±5.1 4.23.4± 5.8	BMI, free-T, f-insulin, lipids, HOMA	META Adults	**ROB high** Outcomes also reported in Kebapcilar et al 2009 and Bilgir et al
Sahu et al 2019 India	Women aged between 18 and 35 years with PCOS	1.metformin=50 2.OCP=51	6 months	1.25.7 ± 2.6 2.25.6 ±2.7	1.27.0 ± 5.2 2.26.8 ±4.2	BMI, mFGS, SHBG, T, f-insulin, f-gluk, lipids, cycle duration, HOMA	META Adults	**ROB Moderate**
Al-Zubeidi et al. 2015 USA	Girls aged 12 and 18 yr with PCOS	1.Metformin=12 2.OCP=10	6 months	1.33.7±6 2.33.4±9	1.16 (14-18) 2.16 (15-17)	BMI, SHBG, T, free-T, f-insulin	META adolescents	**ROB high**
Moro et al. 2013 Italy	Women with PCOS aged 18 to 35 years	1.Metformin=25 2.OCP=25 3.Metformin+OCP=26	6 months	1.23.7 (20.8-28.6) 2.25.1 (21.9-28.3) 3.26.5 (21.3-30) Median (range)	1.25±5 2.26±3 3.25±4	FAI, T, lipids, BMI, WHR	META Individual Adults BMI<25	**ROB Moderate**
Panidis et al 2010 Greece	Premenopausal women with PCOS (BMI<25)	1.Metformin=15 2. OCP=15 3.OCP=15	6 months	1.21.83±1.73 2.21.69 ±2.33 3.21.04 ±1.97	1.20.53±3.1 2.22.0±2.07 3.20.67±4.13	f-insulin, f-gluk	META adults BMI<25	**ROB High**
Rautio et al. 2005 Finland*	Nonobese women BMI< 25 and obese women BMI > 27 with PCOS	1.metformin=16 2.OCP=19	6 months	1.28.7 ± 1.5 2.30.6 ±1.8	NR	lipids	META Adults	**ROB high** Same study as Morin-Papunen et al 2003 and 2000
Bodur et al 2018 Turkey	18–39 year old, non-obese (18–30 BMI) women with PCOS	1. metformin N=17 2. OCP N=17 3.OCP+metformin=12 4. Control=15	6 months	1.25.06 ± 3.08 2.23.45 ±3.40 3.23.82 ±2.80	1.26.24 ± 3.96 2.26.62 ±4.92 3.27.35 ±5.65	f-gluk, PAI, HOMA	META Adults BMI<30	**ROB High**
Luque-Ramírez 2009 Spain	Women with PCOS	1.Metformin=19 2.OCP=15	6 months	1.30.5 ±6.9 2.29.2 ±5.7	1.25.1±6.6 2.23.4±5.6	Adverse effects	META Adults	**ROB Moderate**

Morin-Papunen et al. 2003 Finland (1)	Nonobese women BMI< 25 and obese women BMI > 27 with PCOS	1.metformin=16 2.OCP=19	6 months	1.28.7 ± 1.5 2.30.6 ±1.8	NR	s-crp	META Adults	**ROB high** Same study as Morin-Papunen et al 200 and Rautio 2000 et al. 2005
Glintborg et al. 2014 (1) Denmark	White women with PCOS, aged 18-39 years, BMI <35	1. metformin N=19 2. OCP N=23 3.OCP+metformin=23	12 months	1: 25.1 (22.7–29.4)* 2: 27.3 (22.7–31.1)* 3:27.3 (24.0–30.5)P	1: 29 [24-32]* 2: 28 [23-30]* 3:30 (24-32)*	Changes in weight, bmi, f-gluc, T, SHBG, insulin, homa, mFGS	Individual median (25th and 75th quartiles)	Outcomes also reported in Altinok 2018, Glintoborg 2014 and Glintborg 2017 **ROB high**
Glintborg et al. 2014 (2) Denmark	White women with PCOS, aged 18-39 years, BMI <35	1. metformin N=19 2. OCP N=23 3.OCP+metformin=23	12 months	1: 25.1 (22.7–29.4)* 2: 27.3 (22.7–31.1)* 3:27.3 (24.0–30.5)P	1: 29 [24-32]* 2: 28 [23-30]* 3:30 (24-32)*	No data extracted	Individual median (25th and 75th quartiles)	Outcomes also reported in Altinok 2018, Glintborg 2014 and Glintborg 2017 **ROB high**
Altinok et al. 2018 Denmark	White women with PCOS, aged 18-39 years, BMI <35	1. metformin N=19 2. OCP N=23 3.OCP+metformin=23	12months	NR	NR	Changes in FAI, HR-QoL	Individual median (25th and 75th quartiles)	Outcomes also reported in Glintborg et al. 2014 and Glintborg 2017 **ROB high**
Glintborg et al 2017 Denmark	White women with PCOS, aged 18-39 years, BMI <35	1. metformin N=19 2. OCP N=23 3.OCP+metformin=23	12months	NR	NR	No data extracted	Individual median (25th and 75th quartiles)	Outcomes also reported in Glintborg et al. 2014 and Altinok 2018 **ROB high**
Meyer et al. 2007 Australia	Overweight women (BMI 27 kg/m2) with PCOS	1.Metformin=36 2.OCP (high)=31 3. OCP+SPL=33	6 months	1: 36.3 no SD 2: 36.5 no SD 3: 35.5 no SD	Average: 31 years	Change in WHR, hirsutism, FAI, DHEAS	Individual Mean change and 95%CI	**ROB Moderate** Outcomes also reported in Moran et al 2010, Burchall et al 2017, Hutchinson et al 2008
Moran et al. 2010 Australia	Overweight women (BMI 27 kg/m2) with PCOS	1.Metformin=30 2.OCP =26	6 months	NR	NR		Individual Mean change±SEM	**ROB moderate** Outcomes also reported in Meyer et al. 2007,

								Burchall et al 2017, Hutchinson et al 2008
Dorgham et al. 2021 Egypt	PCOS women, aged 18 to 40 yr with facial hirsutism	1.Met+HR=50 2.OCP+HR=50 3.HR=50	1.Metformin 500mgx1 2. EE 35 µg , cyproterone acetate 2mg	NR	NR	HLQI	Individual Mean improvement	**ROB high**

*Have reported baseline age and BMI separated by obese and non-obese groups; and both interventions were administered to each obese and non-obese group
separately, however the results are presented per intervention for all participants and not presented for each obese and non-obese group/intervention.

Results of meta-analysis

Results were subgrouped based on BMI (<=25, >25 or not specified) and age (adults and adolescents)

Outcome	Time point	RCTs	N	Effect, random, MD	P-value	I2 (%)	Favours	Certainty
Weight (kg)	4-24m	7	353	-1.25 (-12.95 to 10.44)	0.83	94	No difference	⊕◯◯◯ VERY LOW
Sub: BMI>25	6m	2	69	3.92 (-7.58 to 15.42)	0.50	23	No difference	⊕⊕◯◯ LOW
Sub:BMI<25	4-6m	2	79	-1.18 (-6.86 to 4.49)	0.68	0	No difference	⊕◯◯◯ VERY LOW
Sub: BMI not specified	4-24m	3	205	-4.97 (-26.16 to 16.22)	0.65	97	No difference	⊕◯◯◯ VERY LOW
Sub: Adults	4-6m	5	257	2.63 (-1.20 to 6.46)	0.18	2	No difference	⊕⊕◯◯ LOW
Sub: Adolescents	4-6m	2	96	-12.62 (-28.29 to 3.05)	0.11	77	No difference	⊕◯◯◯ VERY LOW
WHR	3-12m	7	191	-0.01 (-0.03 to 0.01)	0.15	63	No difference	⊕◯◯◯ VERY LOW
Sub: BMI>25	3-12m	3	83	-0.01 (-0.07 to 0.05)	0.71	85	No difference	⊕◯◯◯ VERY LOW
Sub:BMI<25	**3-6m**	**3**	**82**	**-0.01 (-0.02 to -0.00)**	**0.0008**	**0**	**Metformin**	⊕⊕◯◯ LOW
BMI kg/m2	3-12m	20	811	-0.71 (-1.52 to 0.11)	0.09	74	No difference	⊕◯◯◯ VERY LOW
Sub: BMI>25	3-12m	7	224	-1.62 (-4.28 to 1.04)	0.23	88	No difference	⊕◯◯◯ VERY LOW
Sub:BMI<25	3-6m	7	289	-0.22 (-1.00 to 0.56)	0.58	55	No difference	⊕⊕◯◯ LOW
Sub: BMI not specified	3-6m	6	298	-0.75 (-1.78 to 0.29)	0.16	11	No difference	⊕⊕◯◯ LOW
Sub: Adults	3-12m	17	742	-0.64 (-1.50 to 0.22)	0.15	77	No difference	⊕◯◯◯ VERY LOW
Sub: Adolescents	6m	3	69	-1.95 (-4.51 to 0.62)	0.14	0	No difference	⊕⊕◯◯ LOW
Hirsutism (FG score)	6-12m	6	247	0.72 (-1.40 to 2.85)	0.51	85	No difference	⊕◯◯◯ VERY LOW
Sub: BMI>25	6-12m	3	86	-0.93 (-3.65 to 1.78)	0.50	62	No difference	⊕⊕◯◯ LOW
Sub:BMI<25	**6m**	**2**	**75**	**1.73 (0.07 to 3.40)**	**0.04**	**0**	**OCP**	⊕⊕◯◯ LOW

Sub: Adults	6-12m	5	231	0.95 (-1.48 to 3.37)	0.44	88	No difference	⊕◯◯◯ VERY LOW
SHBG (nmol/l)	**3-12m**	**9**	**359**	**-116.65 (-172.78 to -60.52)**	**<0.00001**	**98**	**OCP**	⊕⊕◯◯ LOW
Sub: BMI>25	**6-12m**	**4**	**124**	**-95.79 (-118.93 to -72.66)**	**<0.00001**	**40**	**OCP**	⊕⊕⊕⊕ HIGH
Sub:BMI<25	**3-6m**	**4**	**149**	**-163.99 (-206.59 to -121.39)**	**<0.00001**	**86**	**OCP**	⊕⊕⊕◯ MODERATE
Sub: Adults	**3-12m**	**8**	**343**	**-122.12 (-183.61 to -60.64)**	**<0.00001**	**98**	**OCP**	⊕⊕◯◯ LOW
FAI	**6-12m**	**8**	**294**	**7.10 (4.92 to 9.29)**	**<0.00001**	**87**	**OCP**	⊕⊕◯◯ LOW
Sub: BMI>25	**6-12m**	**4**	**124**	**8.93 (7.80 to 10.06)**	**<0.00001**	**0**	**OCP**	⊕⊕⊕⊕ HIGH
Sub:BMI<25	**6-12m**	**4**	**170**	**5.68 (3.05 to 8.30)**	**<0.00001**	**87**	**OCP**	⊕⊕◯◯ LOW
Sub: Adults	**6-12m**	**7**	**278**	**7.00 (4.71 to 9.30)**	**<0.00001**	**89**	**OCP**	⊕⊕◯◯ LOW
Testosterone (nmol/l)	**3-24m**	**17**	**650**	**0.49 (0.31 to 0.67)**	**<0.00001**	**90**	**OCP**	⊕⊕◯◯ LOW
Sub: BMI>25	**3-12m**	**6**	**175**	**0.30 (0.02 to 0.59)**	**0.04**	**21**	**OCP**	⊕⊕⊕◯ MODERATE
Sub:BMI<25	**3-6m**	**8**	**313**	**0.63 (0.38 to 0.89)**	**<0.00001**	**60**	**OCP**	⊕⊕◯◯ LOW
Sub: BMI not specified	4-24m	3	162	0.34 (-0.06 to 0.74)	0.10	0	No difference	⊕◯◯◯ VERY LOW
Sub: Adults	**3-12m**	**14**	**581**	**0.55 (0.37 to 0.73)**	**<0.0001**	**43**	**OCP**	⊕⊕◯◯ LOW
Sub: Adolescents	6-24m	3	69	0.27 (-0.16 to 0.71)	0.44	90	No difference	⊕⊕⊕◯ MODERATE
Free testosterone (pmol/l)	**3-6m**	**5**	**198**	**3.20 (1.50 to 4.90)**	**0.0002**	**46**	**OCP**	⊕◯◯◯ VERY LOW
Sub: BMI not specified	**3-6m**	**3**	**126**	**2.26 (0.50 to 4.01)**	**0.01**	**0**	**OCP**	⊕◯◯◯ VERY LOW
Sub: Adults	**3-4m**	**3**	**145**	**3.38 (1.16 to 5.59)**	**0.003**	**59**	**OCP**	⊕◯◯◯ VERY LOW
Sub: Adolescents	6m	2	53	3.86 (-2.59 to 10.31)	0.22	0	No difference	⊕◯◯◯ VERY LOW
Fasting insulin mIU/l)	**3-12m**	**15**	**574**	**-4.31 (-5.90 to -2.72)**	**<0.00001**	**59**	**Metformin**	⊕⊕◯◯ LOW
Sub: BMI>25	**3-12m**	**6**	**169**	**-4.60 (-7.08 to -2.12)**	**0.0003**	**0**	**Metformin**	⊕⊕◯◯ LOW
Sub:BMI<25	**3-6m**	**4**	**128**	**-3.25 (-4.72 to -1.77)**	**<0.00001**	**0**	**Metformin**	⊕⊕⊕◯ MODERATE
Sub: BMI not specified	**3-24m**	**5**	**277**	**-4.77 (-8.16 to -1.39)**	**0.006**	**82**	**Metformin**	⊕◯◯◯ VERY LOW
Sub: Adults	**3-12m**	**11**	**440**	**-3.98 (-4.93 to -3.03)**	**<0.00001**	**0**	**Metformin**	⊕⊕⊕◯ MODERATE
Sub: Adolescents	6-24m	4	134	-4.19 (-11.28 to 2.90)	0.25	54	No difference	⊕◯◯◯ VERY LOW
Fasting glucose (mg/dl)	6-12m	10	429	-1.46 (-4.07 to 1.15)	0.27	50	No difference	⊕◯◯◯ VERY LOW
Sub: BMI>25	6-12m	4	124	2.89 (-2.68 to 8.46)	0.31	32	No difference	⊕⊕⊕◯ MODERATE
Sub:BMI<25	6m	3	105	-2.81 (-7.92 to 2.31)	0.28	74	No difference	⊕⊕◯◯ LOW
Sub: BMI not specified	**4-6m**	**3**	**200**	**-2.45 (-4.63 to -0.27)**	**0.03**	**0**	**Metformin**	⊕⊕⊕◯ MODERATE
Sub: Adults	4-6m	9	413	-1.58 (-4.30 to 1.15)	0.26	54	No difference	⊕⊕◯◯ LOW
Total cholesterol (mmol/l)	**3-12m**	**13**	**558**	**-0.40 (-0.66 to -0.14)**	**0.003**	**69**	**Metformin**	⊕◯◯◯ VERY LOW
Sub: BMI>25	6-12m	4	137	-0.45 (-1.16 to 0.26)	0.22	76	No difference	⊕◯◯◯ VERY LOW

Sub:BMI<25	**3-6m**	**4**	**170**	**-0.56 (-1.05 to -0.06)**	**0.03**	**80**	**Metformin**	⊕◯◯◯ VERY LOW
Sub: BMI not specified	4-6m	5	251	-0.17 (-0.35 to 0.01)	0.07	0	No difference	⊕⊕⊕◯ MODERATE
Sub: Adults	**3-12m**	**11**	**511**	**-0.31 (-0.57 to -0.05)**	**0.02**	**68**	**Metformin**	⊕◯◯◯ VERY LOW
Sub: Adolescents	**6m**	**2**	**47**	**-1.19 (-1.80 to -0.58)**	**<0.00001**	**0**	**Metformin**	⊕⊕◯◯ LOW
HDL (mmol/l)	3-12m	13	558	-0.05 (-0.18 to 0.07)	0.41	84	No difference	⊕◯◯◯ VERY LOW
Sub: BMI>25	**6-12m**	**4**	**137**	**-0.23 (-0.37 to -0.10)**	**<0.0008**	**0**	**Metformin**	⊕⊕⊕◯ MODERATE
Sub:BMI<25	3-6m	4	170	0.05 (-0.27 to 0.37)	0.75	95	No difference	⊕◯◯◯ VERY LOW
Sub: BMI not specified	3-6m	5	251	-0.01 (-0.10 to 0.08)	0.82	11	No difference	⊕⊕⊕◯ MODERATE
Sub: Adults	3-12m	11	511	-0.03 (-0.17 to 0.11)	0.65	86	No difference	⊕◯◯◯ VERY LOW
Sub: Adolescents	6m	2	47	-0.22 (-0.43 to -0.00)	0.05	0	No difference	⊕⊕◯◯ LOW
LDL (mmol/l)	3-12m	13	559	-0.15 (-0.39 to 0.09)	0.38	80	No difference	⊕◯◯◯ VERY LOW
Sub: BMI>25	6-12m	4	137	-0.21 (-0.95 to 0.53)	0.58	76	No difference	⊕⊕◯◯ LOW
Sub:BMI<25	3-6m	4	171	-0.19 (-0.52 to 0.14)	0.27	78	No difference	⊕⊕◯◯ LOW
Sub: BMI not specified	3-6m	5	251	0.03 (-0.26 to 0.31)	0.86	53	No difference	⊕⊕◯◯ LOW
Sub: Adults	3-12m	11	512	-0.02 (-0.25 to 0.21)	0.87	81	No difference	⊕◯◯◯ VERY LOW
Sub: Adolescents	**6m**	**2**	**47**	**-0.86 (-1.11 to -0.62)**	**0.002**	**0**	**Metformin**	⊕⊕◯◯ LOW
Triglycerides (mmol/l)	**3-12m**	**13**	**559**	**-0.16 (-0.31 to -0.01)**	**0.04**	**72**	**Metformin**	⊕◯◯◯ VERY LOW
Sub: BMI>25	**6-12m**	**4**	**137**	**-0.20 (-0.41 to -0.00)**	**0.05**	**0**	**Metformin**	⊕⊕◯◯ LOW
Sub:BMI<25	**3-6m**	**3**	**149**	**-0.36 (-0.73 to 0.00)**	**0.05**	**72**	**Metformin**	⊕⊕◯◯ LOW
Sub: BMI not specified	3-6m	6	273	0.00 (-0.12 to 0.12)	0.99	40	No difference	⊕⊕◯◯ LOW
Sub: Adults	3-12m	10	490	-0.18 (-0.35 to -0.00)	0.05	78	No difference	⊕◯◯◯ VERY LOW
Sub: Adolescents	6m	3	69	-0.13 (-0.39 to 0.14)	0.35	12	No difference	⊕⊕◯◯ LOW
CRP (mg/l)	**4-6m**	**9**	**403**	**-1.45 (-2.30 to -0.60)**	**0.0008**	**72**	**Metformin**	⊕⊕◯◯ LOW
Sub: BMI>25	**6m**	**3**	**81**	**-4.87 (-6.53 to -3.21)**	**<0.00001**	**0**	**Metformin**	⊕⊕◯◯ LOW
Sub:BMI<25	**6m**	**3**	**148**	**-0.82 (-1.46 to -0.19)**	**0.01**	**8**	**Metformin**	⊕⊕⊕◯ MODERATE
Sub: BMI not specified	**4-6m**	**3**	**174**	**-0.64 (-0.77 to -0.50)**	**<0.00001**	**0**	**Metformin**	⊕⊕◯◯ LOW
Sub: Adults	**4-6m**	**8**	**387**	**-1.26 (-2.04 to -0.47)**	**0.002**	**69**	**Metformin**	⊕⊕⊕◯ MODERATE
PAI	6m	2	50	-1.05 (-24.65 to 22.54)	0.93	67	No difference	⊕◯◯◯ VERY LOW
HOMA-IR	**3-6m**	**11**	**555**	**-0.59 (-1.14 to -0.04)**	**0.03**	**90**	**Metformin**	⊕◯◯◯ VERY LOW
Sub: BMI>25	6m	2	87	-0.20 (-1.02 to 0.62)	0.64	0	No difference	⊕⊕⊕◯ MODERATE
Sub:BMI<25	**3-6m**	**5**	**249**	**-0.44 (-0.80 to -0.09)**	**0.01**	**24**	**Metformin**	⊕⊕⊕◯ MODERATE
Sub: BMI not specified	3-6m	4	219	-0.77 (-2.04 to 0.51)	0.24	97	No difference	⊕⊕◯◯ LOW

DHEAS (ug/dl)	**3-6m**	**9**	**414**	**28.03 (1.09 to 54.97)**	**0.04**	**83**	**OCP**	⊕◯◯◯ VERY LOW
Sub:BMI<25	3-6m	4	146	51.77 (-22.52 to 126.06)	0.17	85	No differences	⊕◯◯◯ VERY LOW
Sub: BMI not specified	3-6m	4	250	8.76 (-19.00 to 36.52)	0.54	81	No difference	⊕◯◯◯ VERY LOW
Androstenedione (nmol/l)	**3-6m**	**4**	**106**	**3.42 (2.75 to 4.09)**	**<0.00001**	**0**	**OCP**	⊕⊕◯◯ LOW
Sub:BMI<25	**3-6m**	**3**	**88**	**3.35 (2.67 to 4.03)**	**<0.00001**	**0**	**OCP**	⊕⊕◯◯ LOW
Cycle duration	**6m**	**3**	**121**	**6.10 (2.40 to 9.80)**	**0.001**		**OCP**	⊕⊕⊕◯ MODERATE
Girls with restored menses	**6m**	**2**	**35**	**0.08 (0.01 to 0.75)**	**0.03**	**0**	**OCP**	⊕◯◯◯ VERY LOW

Individual studies not included in meta-analysis

Outcome	Author, year	Time point	N	Metformin	OCP	P-value	Favours	Grading
Weight	Glintborg et al. 2014 Glintborg et al. 2017 Altinok et al 2018	12 months	M=19 OCP=23	Median change (25th and 75th quartiles) -3.0 (-10.3 to 0.6)	Median change (25th and 75th quartiles) 1.2 (-0.8 to 3.0)	<0.05	**Metformin**	⊕◯◯◯ VERY LOW[1]
WHR	Meyer et al. 2007	6 months	M=36 OCP=31	Mean change and 95% CI 0.18 (-0.03 to 0.01)	Mean change and 95% CI 0.01 (-0.03 to 0.3)	NR	No difference	⊕⊕◯◯ LOW[2]
	Moro et al. 2013	6 months	M=25 OCP=25	Median (range) 0.84 (0.80-0.87)	Median (range) 0.78 (0.76-0.88)	NR	NR	⊕⊕◯◯ LOW[2]
BMI	Glintborg et al. 2014 Glintborg et al. 2017 Altinok et al 2018	12 months	M=19 OCP=23	Median change (25th and 75th quartiles) -1.0 (-3.7 to 0.2)	Median change (25th and 75th quartiles) 0.38 (-0.44 to 1.17)	<0.05	**Metformin**	⊕◯◯◯ VERY LOW[1]
	Dardzinska et al 2014	4 months	M=7 OCP=14	means and 95% CI 25.1 (23.8 to 27.1)	means and 95% CI 24.4 (23.2 to 26.2)	NR	No difference	⊕⊕◯◯ LOW[2]
	Moro et al. 2013	6 months	M=25 OCP=25	Median (range) 23.5 (20.4-28.3)	Median (range) 21.9 (20.4-27.8)	NR	NR	⊕⊕◯◯ LOW[2]
Hirsutism (FGS)	Glintborg et al. 2014 Glintborg et al. 2017 Altinok et al 2018	12 months	M=19 OCP=23	Median change (25th and 75th quartiles) 0 (-2 to 1)	Median change (25th and 75th quartiles) 0 (-3 to 0)	NR	No difference	⊕◯◯◯ VERY LOW[1]
	Meyer et al. 2007	6 months	M=36 OCP=31	Mean change and 95% CI -2.7 (-1.5 to -3.9)	Mean change and 95% CI -2.0 (-0.9 to -3.2)	NR	No difference	⊕⊕◯◯ LOW[2]
SHBG	Glintborg et al. 2014 Glintborg et al. 2017 Altinok et al 2018	12 months	M=19 OCP=23	Median change (25th and 75th quartiles) -9 (-2 to 19)	Median change (25th and 75th quartiles) 138 (89 to 162)	<0.001	**OCP**	⊕◯◯◯ VERY LOW[1]
	Dardzinska et al 2014	4 months	M=7 OCP=14	means and 95% CI 44 (40 to 62)	means and 95% CI 171 (156 to 221)	NR	NR	⊕⊕◯◯ LOW[2]

FAI	Glintborg et al. 2014 Glintborg et al. 2017 Altinok et al 2018	12 months	M=19 OCP=23	Median change (25th and 75th quartiles) -0.007 (-0.019 to 0.004)	Median change (25th and 75th quartiles) -0.023 (-0.034 to 0.008)	<0.05	**OCP**	⊕◯◯◯ VERY LOW[1]
	Dardzinska et al 2014	4 months	M=7 OCP=14	means and 95% CI 8.6 (7.9 to 14.0)	means and 95% CI 2.0 (1.8 to 3.2)	NR	NR	⊕⊕◯◯ LOW[2]
Testosterone	Glintborg et al. 2014 Glintborg et al. 2017 Altinok et al 2018	12 months	M=19 OCP=23	Median change (25th and 75th quartiles) -0.35 (-0.97 to -0.06)	Median change (25th and 75th quartiles) -0.36 (-1.17 to -0.04)	NR	No difference	⊕◯◯◯ VERY LOW[1]
Fasting insulin	Glintborg et al. 2014 Glintborg et al. 2017 Altinok et al 2018	12 months	M=19 OCP=23	Median change (25th and 75th quartiles) 2 (-22 to 16)	Median change (25th and 75th quartiles) 9 (-6 to 46)	NR	No difference	⊕◯◯◯ VERY LOW[1]
CRP	Dardzinska et al 2014	4 months	M=7 OCP=14	means and 95% CI 0.76 (0.62 to 2.25)	means and 95% CI 1.70 (1.65 to 3.69)	<0.05	**Metformin**	⊕⊕◯◯ LOW[2]
PAI	Burchall et al 2017	6 months	M=23 OCP=21	Mean change and 95%CI -0.87 (-1.54 to -0.19)	Mean change and 95%CI -1.91 (-2.70 to -1.12)	<0.05	**OCP**	⊕◯◯◯ VERY LOW[1]
Amenorrhea	Cetinkalp et al. 2009	4 months	M=47 OCP=33	3/47=6.38%	2/33=6.1%	0.95	No difference	⊕◯◯◯ VERY LOW[1]
Oligomenorrhea	Cetinkalp et al. 2009	4 months	M=47 OCP=33	11/47=23.4%	0/33=0%	0.04	**OCP**	⊕◯◯◯ VERY LOW[1]
HOMA-IR	Glintborg et al. 2014 Glintborg et al. 2017 Altinok et al 2018	12 months	M=19 OCP=23	Median change (25th and 75th quartiles) -0.2 (-5.5 to 4.1)	Median change (25th and 75th quartiles) 1.7 (-1.1 to 10.4)	NR	No difference	⊕◯◯◯ VERY LOW[1]
	Dardzinska et al 2014	4 months	M=7 OCP=14	means and 95% CI 1.34 (1.24 to 1.94)	means and 95% CI 1.38 (1.30 to 2.03)	NR	No difference	⊕⊕◯◯ LOW[2]
DHEAS	Meyer et al. 2007	6 months	M=36 OCP=31	Mean change and 95% CI -0.37 (-1.0 to 0.2)	Mean change and 95% CI -1.4 (-0.7 to -2.1)	<0.05	**OCP**	⊕⊕◯◯ LOW[2]
Androstenedione	Dardzinska et al 2014	4 months	M=7 OCP=14	means and 95% CI 12.2 (11.2 to 15.0)	means and 95% CI 10.1 (9.4 to 12.2)	NR	NR	⊕⊕◯◯ LOW[2]
	Moro et al. 2013	6 months	M=25 OCP=25	Median (range) 23.5 (20.4-28.3)	Median (range) 21.9 (20.4-27.8)	NR	NR	⊕⊕◯◯ LOW[2]
	Harborne et al. 2003	12	M=26 OCP=26	Changes in mean 10.4	Changes in mean 8.2	NR	NR	⊕⊕◯◯ LOW[2]
oGTT	Moran et al. 2010	6 months	1.Metformin =30 2.OCP =26	Mean change and SEM 9.1 (30)	Mean change and SEM 117.7 (27.9)	NR	No difference	⊕⊕◯◯ LOW[2]

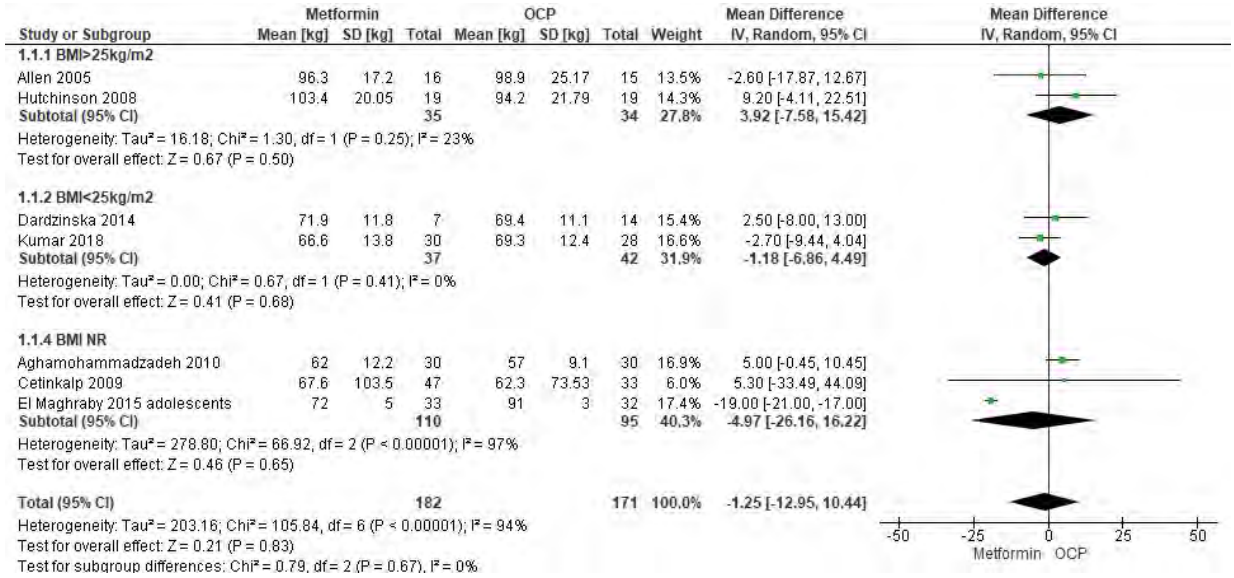
[1] Downgraded twice for high ROB and downgraded once for small number of participants
[2] Downgraded once for mod ROB and downgraded once for small number of participants

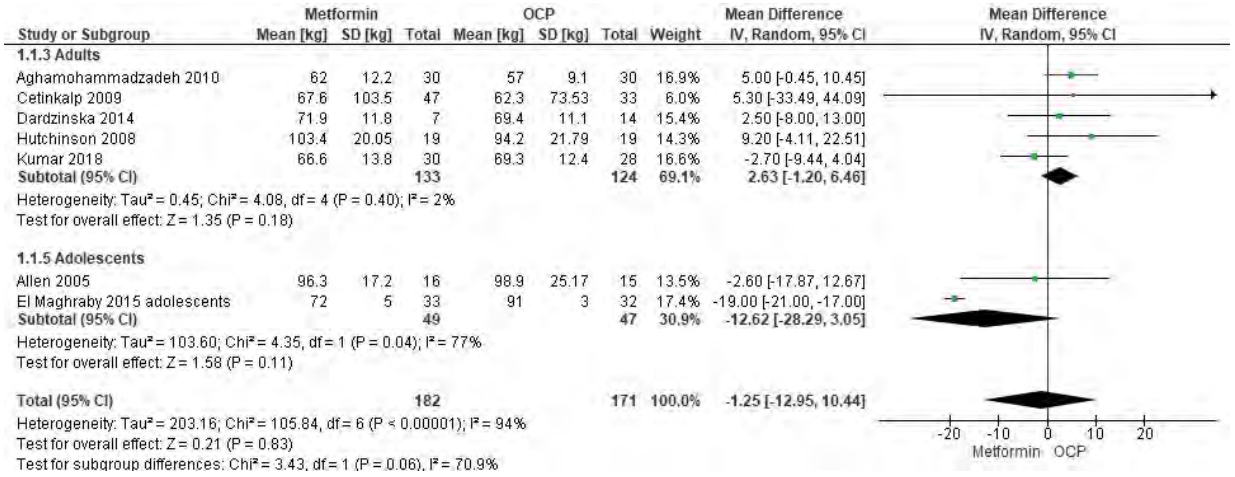
OUTCOME 4.1 weight (kg)

4.1.1 Individual Study Data Table

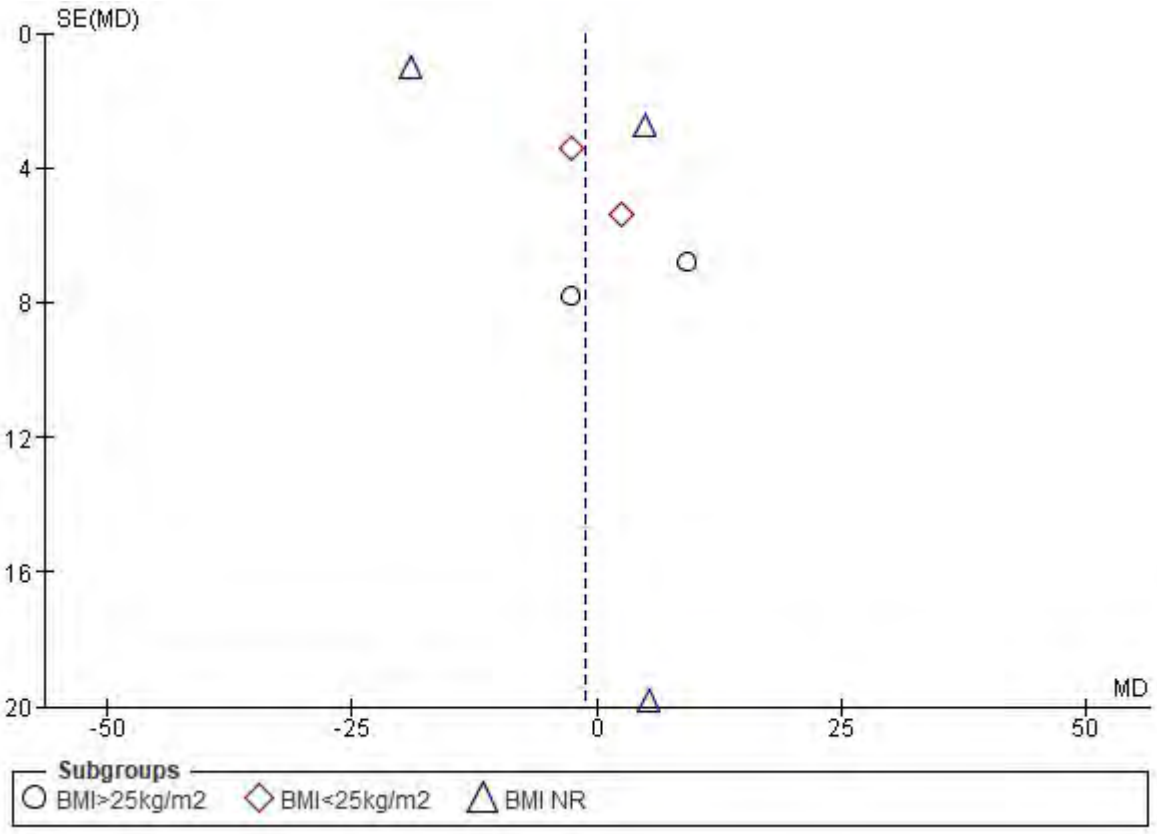
	OUTCOME: Weight						**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **OCP**								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Kumar et al.2018	kg	weighted	30	66.6	13.8	28	69.3	12.4	Crude	6
El Maghraby 2015	kg	weighted	33	72.0	5.0	32	91.0	3.0	Crude	24
Cetinkalp et al 2009	kg	weighted	47	67.6 103.5 (SD)	15.1	33	62.3 73.53 (SD)	12.8	Means+SEM	4
Aghamohammadzadeh et al. 2010	kg	weighted	30	64.8	17.1	30	60.2	13.5	Crude	3
			30	62.0	12.2	30	57.0	9.1		6
Hutchinson et al 2008	Kg	weighted	19	103.4 20.05 (SD)	4.6 (SEM)	19	94.2 21.79 (SD)	5.0 (SEM)	SEM	6
Dardzinska et al 2014	Kg	weighted	7	71.9	11.8	14	69.4	11.1		4
Allen et al. 2005	kg	weighted	16	96.3 17.2 (SEM)	4.3	15	98.9 25.17 (SEM)	6.5	Adolescents	6

4.1.2. Forrest plot metformin vs OCP for weight





4.1.3. Funnel plot for assessment of publication bias

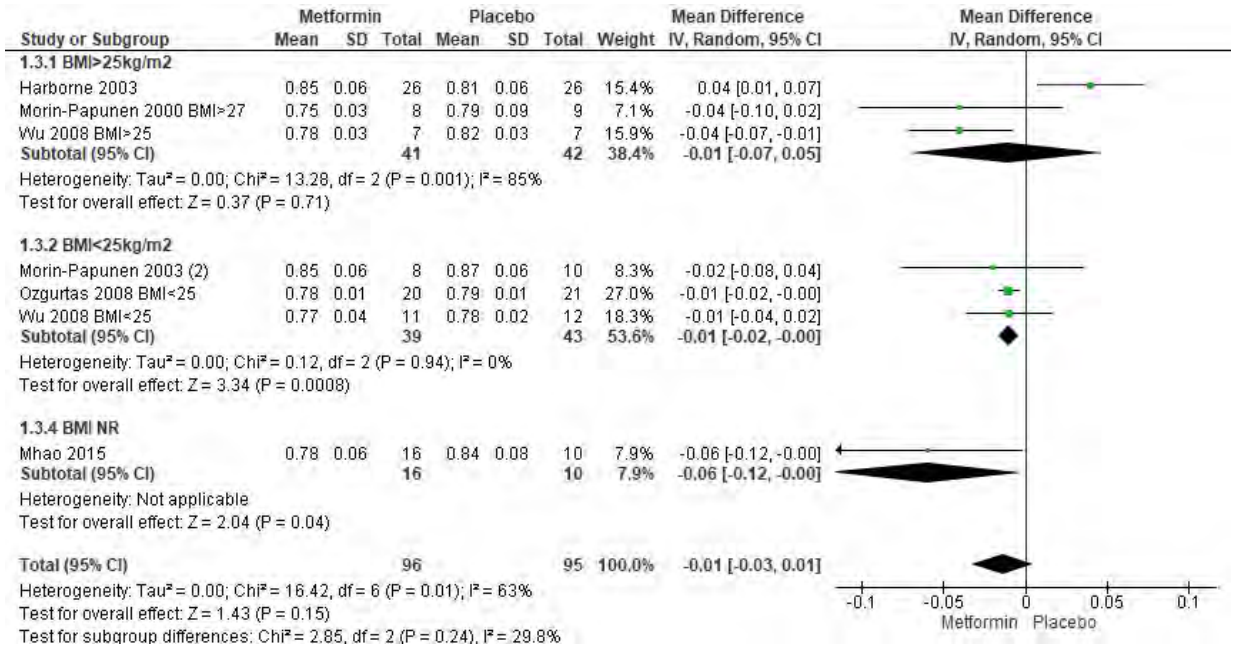


OUTCOME 4.2 WHR

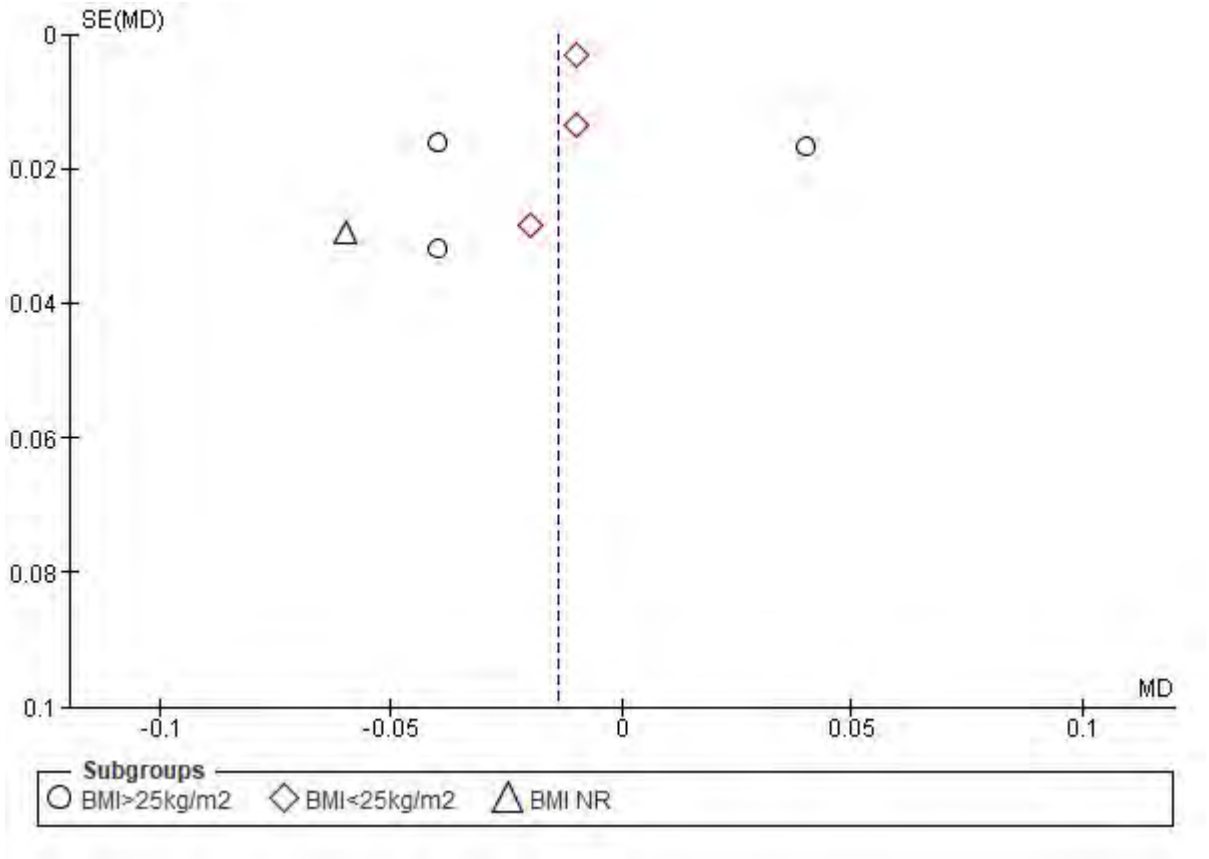
4.2.1 Individual Study Data Table

	OUTCOME: WHR					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus ocp							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra**	**Time period (month)**
Harborne et al. 2003		26	0.85	0.06	26	0.81	0.06	Crude	12
Meyer et al. 2007		36	0.18	0.06	31	0.01	0.05	Mean change and 95%CI calculated	6
Hutchinson et al 2008		19	0.9	0 (SEM)	19	0.9	0 (SEM)	SEM, pick either Hutchinson or Meyer	6
Mhao et al. 2015		16	0.78	0.06	10	0.84	0.08		3
Ozgurtas et al. 2008		20	0.78	0.01	21	0.79	0.01		3
Morin-Papunen et al. 2003 (2)		8	0.75	0.01 0.03 (SD)	9	0.79	0.03 0.09 (SD)	SEM BMI <25	6
Morin-Papunen et al. 2000 (1)		8	0.85	0.02 0.06 (SD)	10	0.87	0.02 0.06 (SD)	SEM BMI>27	6
Wu et al. 2008		7	0.78	0.03	7	0.82	0.03	BMI>25	3
Wu et al. 2008		11	0.77	0.04	12	0.78	0.02	BMI>25	3

4.2.2. Forrest plot metformin vs OCP for WHR



4.2.3. Funnel plot for assessment of publication bias



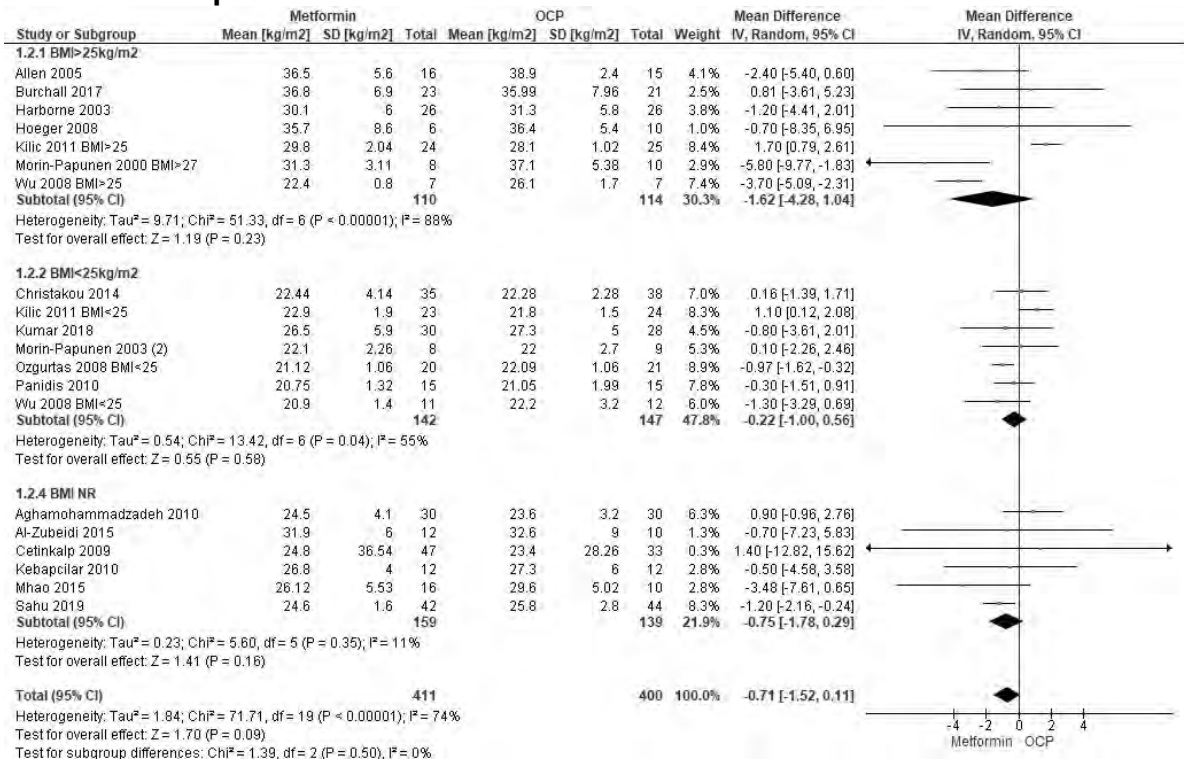
OUTCOME 4.3 BMI (kg/m2)

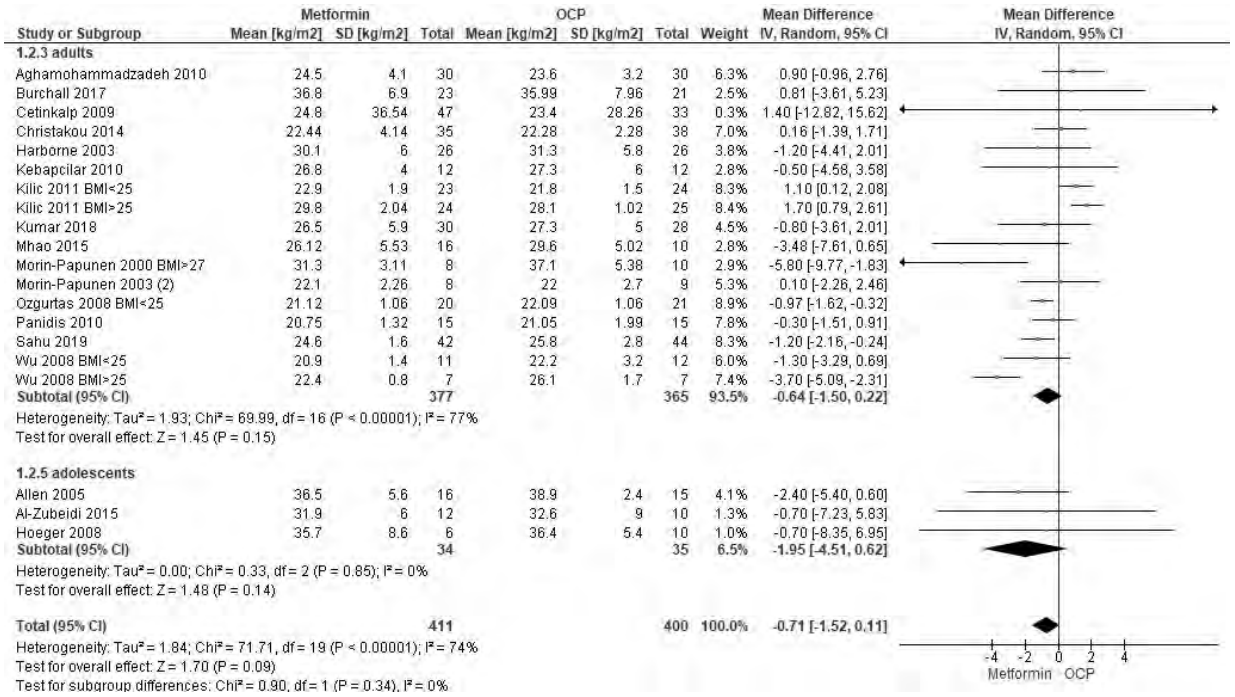
4.3.1 Individual Study Data Table

	OUTCOME: BMI					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **OCP**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Burchall et al. 2017	Kg/m2	23	36.81	6.93	21	35.99	7.96	Crude	6
Sahu et al 2019	Kg/m2	42	24.6	1.6	44	25.8	2.8	Crude	6
Kumar et al.2018	Kg/m2	30	26.5	5.9	28	27.3	5	Crude	6
Harborne et al. 2003	Kg/m2	26	30.1	6	26	31.3	5.8	Crude	12
Meyer et al. 2007	Kg/m2	36	-0.5	9.5	31	0.3	1.6	Mean change and 95%CI calculated	6
Mhao et al. 2015	Kg/m2	16	26.12	5.53	10	29.6	5.02		3

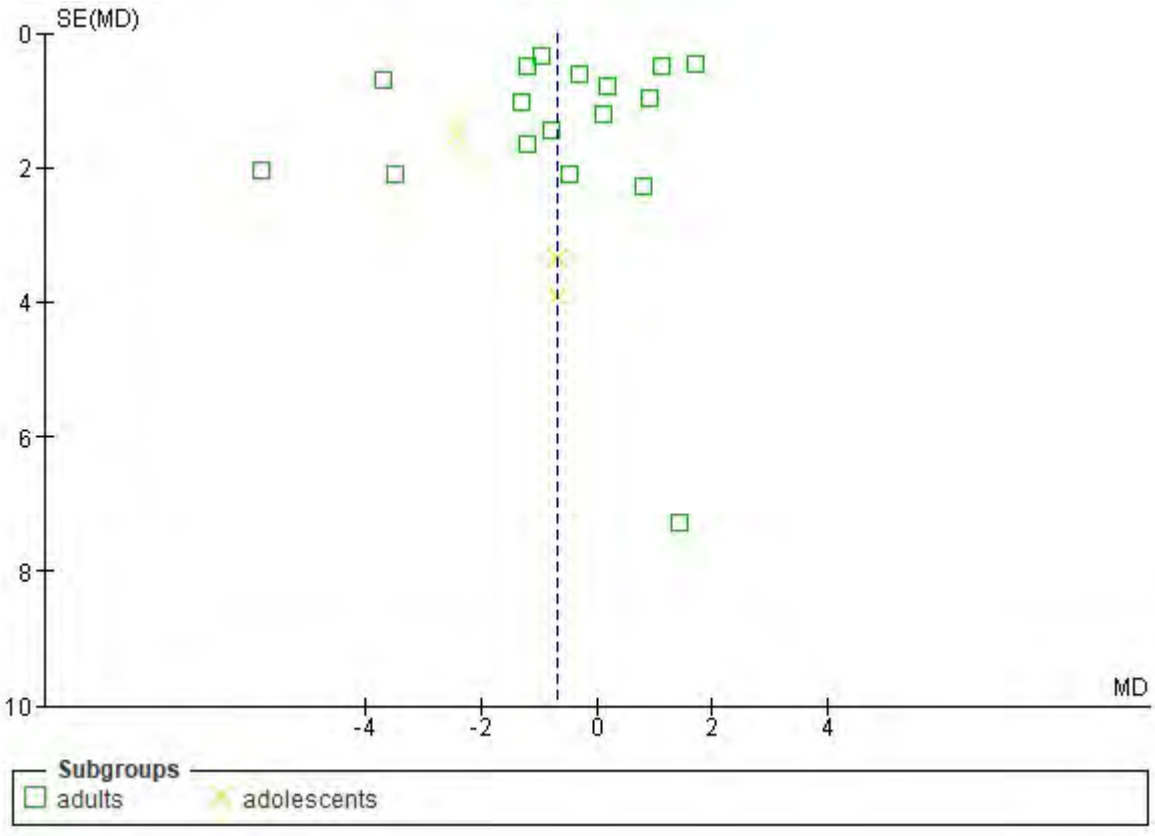
Kebapcilar et al 2010	Kg/m2	12	26.8	4	12	27.3	6		3
Ozgurtas et al. 2008	Kg/m2	20	21.12	1.06	21	22.09	1.06		3
Aghamohammadzadeh et al. 2010 Iran	Kg/m2	30	25.8	6.4	30	24.4	4.9	Crude	3
		30	24.5	4.1	30	23.6	3.2		6
Cetinkalp et al 2009	Kg/m2	47	24.8	5.33 36.54 (SD)	33	23.38	4.92 28.26 (SD)	Means+SEM	4
Hoeger et al. 2008	Kg/m2	6	35.7	8.6	10	36.4	5.4	Adolescents, obese	6
Al-Zubeidi et al. 2015 USA	Kg/m2	12	31.9	6	10	32.6	9	adolescents	6
Allen et al. 2005	Kg/m2	16	36.5	1.4 5.6	15	38.9	2.4 9.30	Adolescents SEM	6
Morin-Papunen et al. 2003 (2)	Kg/m2	8	22.1	0.8 2.26 (SD)	9	22.0	0.9 2.7 (SD)	SEM BMI <25	6
Morin-Papunen et al. 2000 (1)	Kg/m2	8	31.3	1.1 3.11 (SD)	10	37.1	1.7 5.38 (SD)	SEM BMI>27	6
Kilic et al. 2011	Kg/m2	24	29.8	2.04	25	28.1	1.02	BMI>25	6
Kilic et al. 2011	Kg/m2	23	22.9	1.9	24	21.8	1.5	BMI<25	6
Wu et al. 2008	Kg/m2	7	22.4	0.8	7	26.1	1.7	BMI>25	3
Wu et al. 2008	Kg/m2	11	20.9	1.4	12	22.2	3.2	BMI>25	3
Christakou et al. 2014	Kg/m2	35	22.44	4.14	38	22.8	2.8	CPA	6
Panidis et al. 2010	Kg/m2	15	20.75	1.32	15	21.05	1.99	CPA	6

4.3.2. Forrest plot metformin vs OCP for BMI





4.3.3. Funnel plot for assessment of publication bias

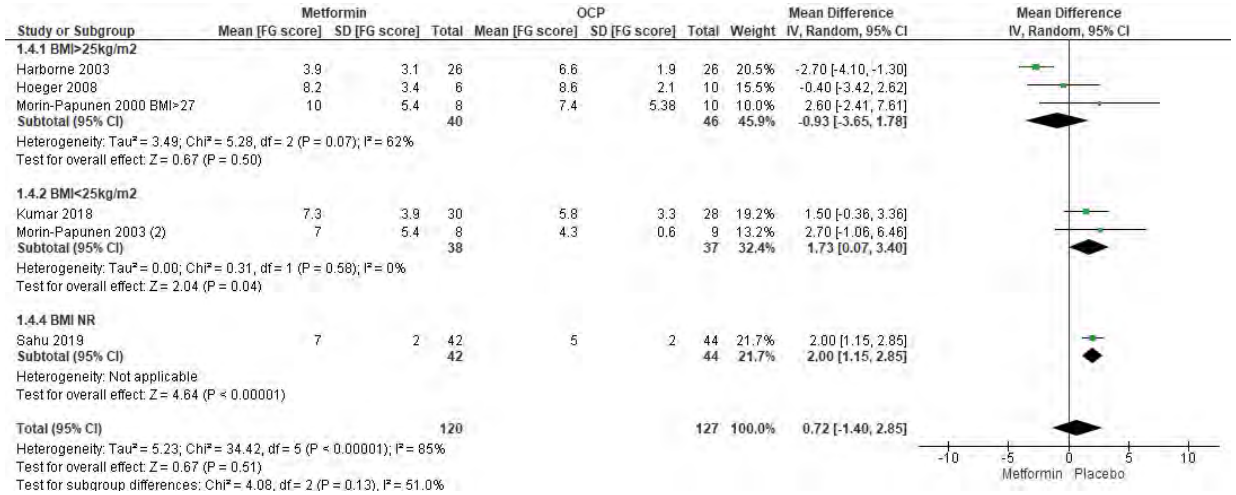


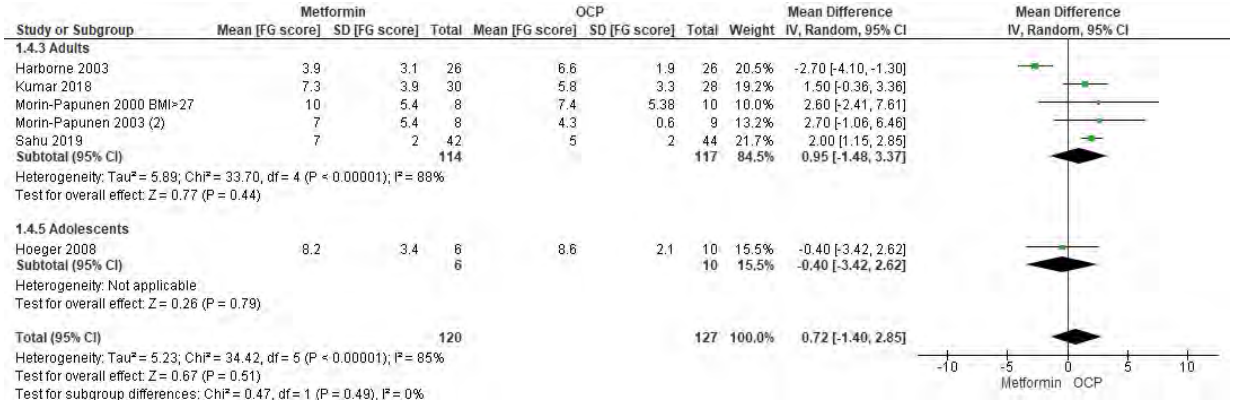
OUTCOME 4.4 hirsutism (FGS)

4.4.1 Individual Study Data Table

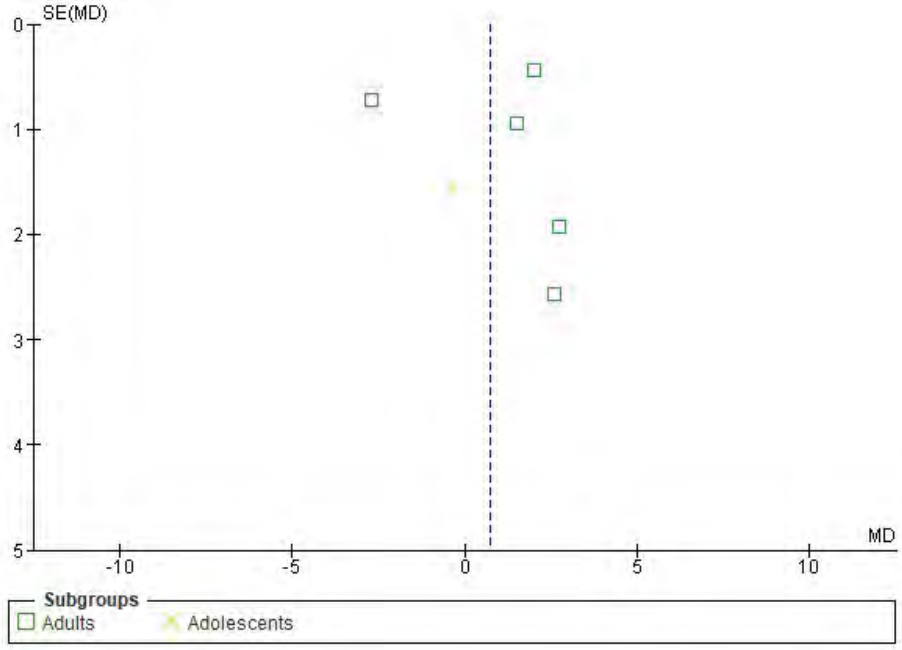
	OUTCOME: Hirsutism					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **OCP**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Sahu et al 2019	mFGS	42	7	2	44	5	2	Crude	6
Kumar et al.2018	mFGS	30	7.3	3.9	28	5.8	3.3	Crude	6
Harborne et al. 2003	mFGS	26	3.9	3.1	26	6.6	1.9	Crude	12
Hoeger et al. 2008	mfgs	6	8.2	3.4	10	8.6	2.1	Adolescents, obese	6
Morin-Papunen et al. 2003 (2)	mfgs	8	7.0	1.9 5.37 (SD)	9	4.3	0.2 0.6 (SD)	SEM BMI <25	6
Morin-Papunen et al. 2000 (1)	mfgs	8	10.0	1.9 5.37 (SD)	10	7.4	1.7 5.38 (SD)	SEM BMI>27	6

4.4.2. Forrest plot metformin vs OCP for Hirsutism





4.4.3. Funnel plot for assessment of publication bias



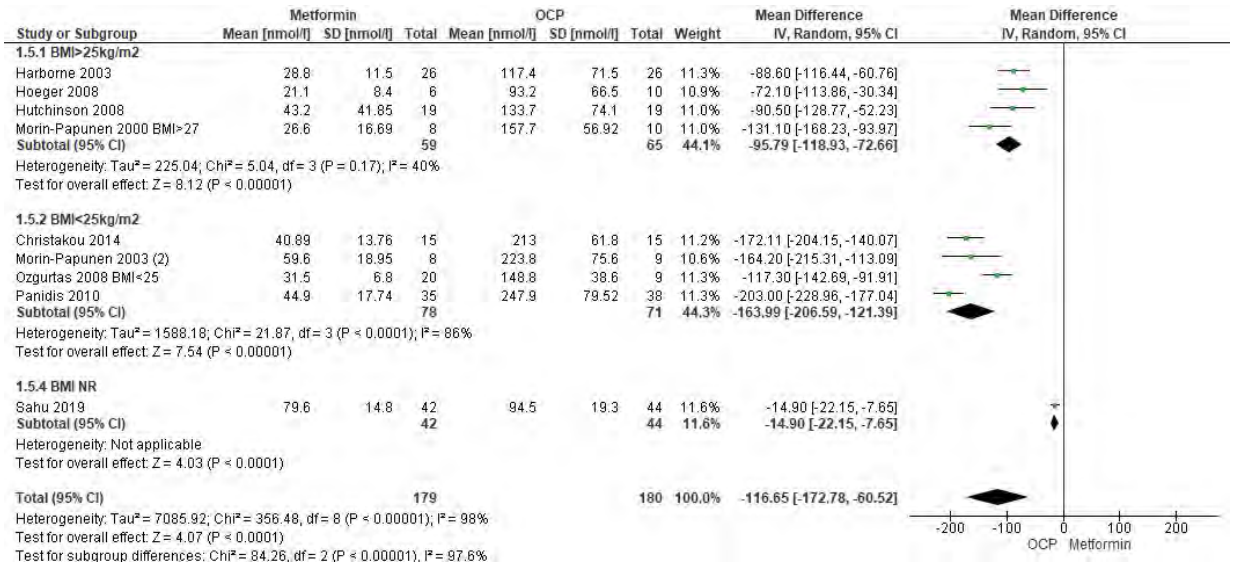
OUTCOME 4.5 SHBG (Nmol/l)

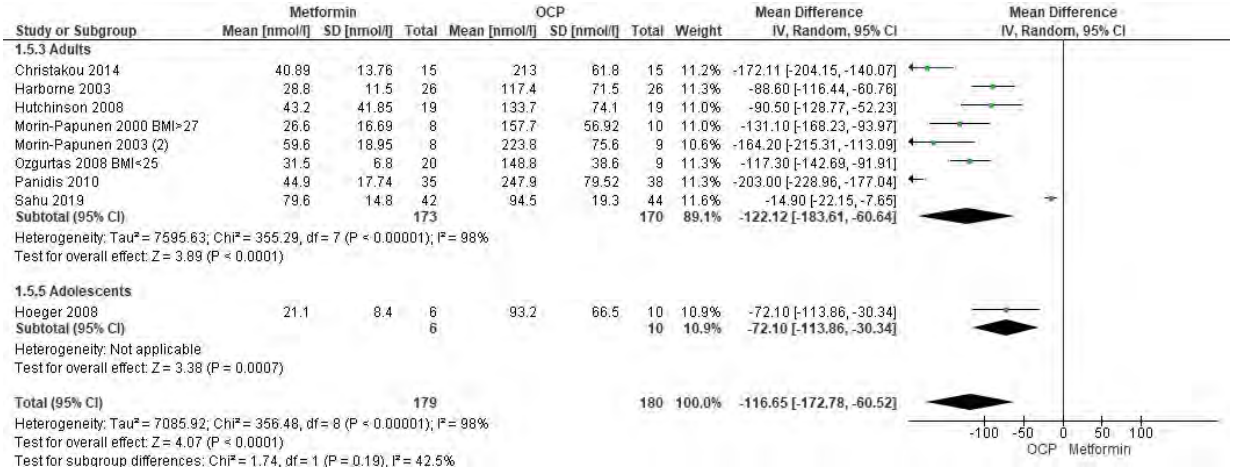
4.5.1 Individual Study Data Table

	OUTCOME: SHBG					OUTCOME TYPE: Continuous			
		COMPARISON (if applicable): metformin versus OCP							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Sahu et al 2019	Nmol/l	42	79.6	14.8	44	94.5	19.3	Adjusted	6

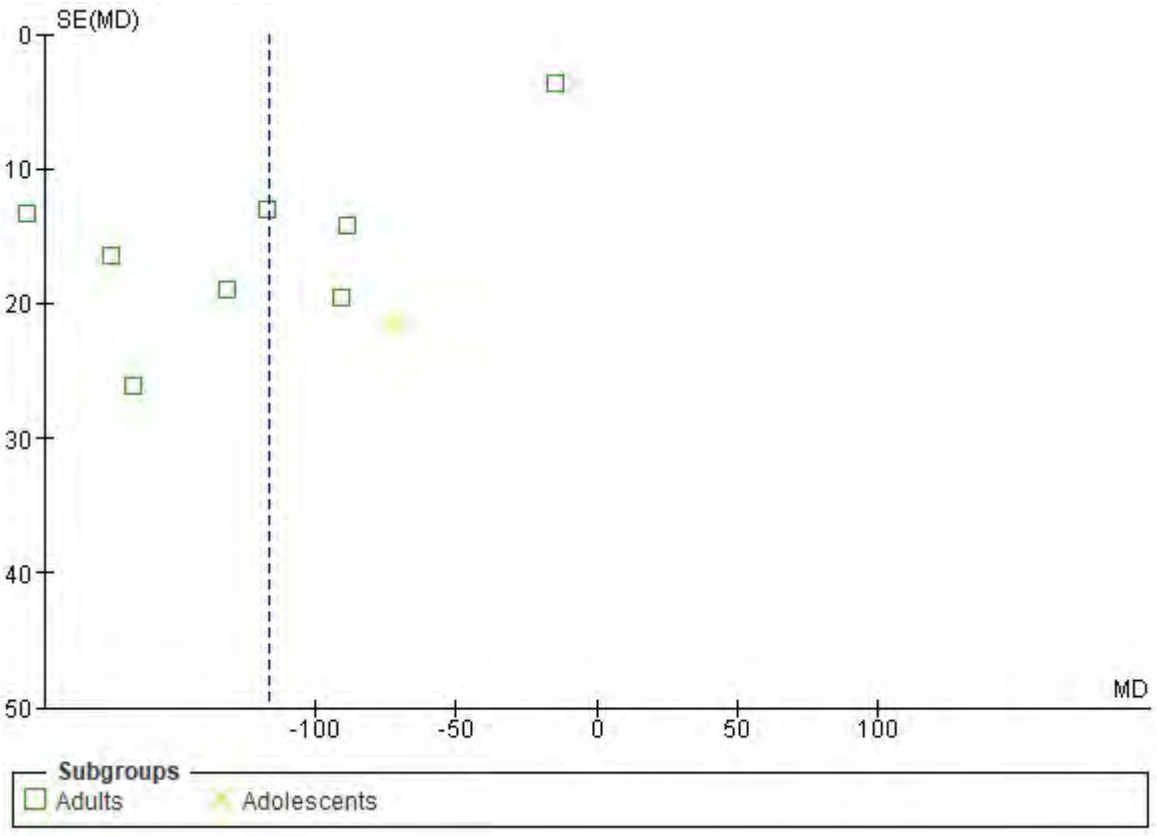
Harborne et al. 2003	Nmol/l	26	28.8	11.5	26	117.4	71.5	Crude	12
Ozgurtas et al. 2008	Nmol/l	20	31.48	6.79	21	148.75	38.63		3
Meyer et al. 2007	Nmol/l	36	7.4	35.4	31	115	76	Mean change and 95%CI calculated, pick either	6
Hutchinson et al 2008	Nmol/l	19	43.2	9.6 (SEM) 41.85 (SD)	19	133.7	17 (SEM) 74.10 (SD)	SEM, pick either	6
Hoeger et al. 2008	Nmol/l	6	21.1	8.4	10	93.2	66.5	Adolescents, obese	6
Dardzinska et al 2014	Nmol/l	7	44	40; 62	14	171	156; 221	mean and IQR so not in meta-analysis	4
Al-Zubeidi et al. 2015 USA	Nmol/l	12	18.8	0.28	10	46	0.034	adolescents	6
Morin-Papunen et al. 2000 (1)	Nmol/l	8	26.6	16.69	10	157.7	56.92	BMI>27	6
Christakou et al. 2014	Nmol/l	15	40.89	13.76	15	213	61.8	CPA	6
Morin-Papunen et al. 2003 (2)	Nmol/l	8	59.6	18.95	9	223.8	75.6	BMI<25	6
Panidis et al. 2010	Nmol/l	35	44.9	17.74	38	247.9	79.52	CPA	6

4.5.2. Forrest plot metformin vs OCP for SHBG





4.5.3. Funnel plot for assessment of publication bias

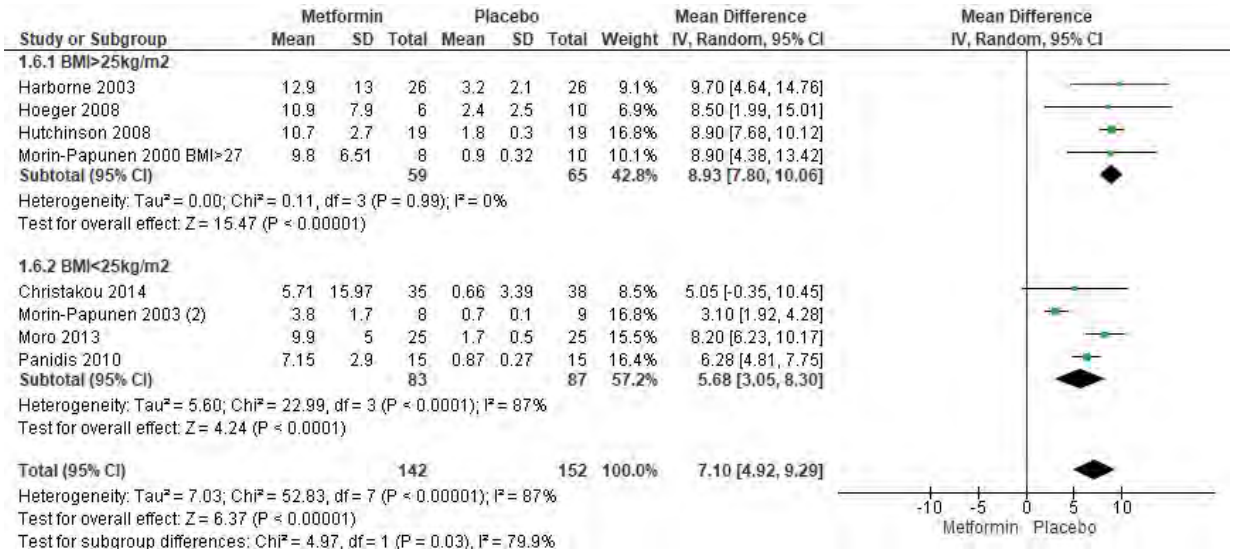


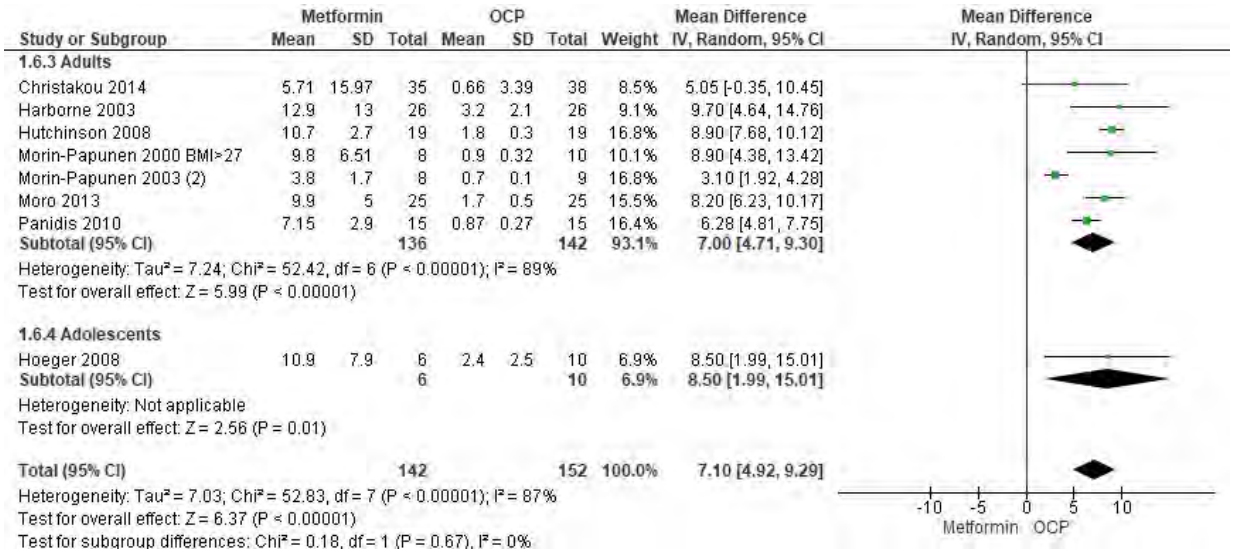
OUTCOME 4.6 FAI

4.6.1 Individual Study Data Table

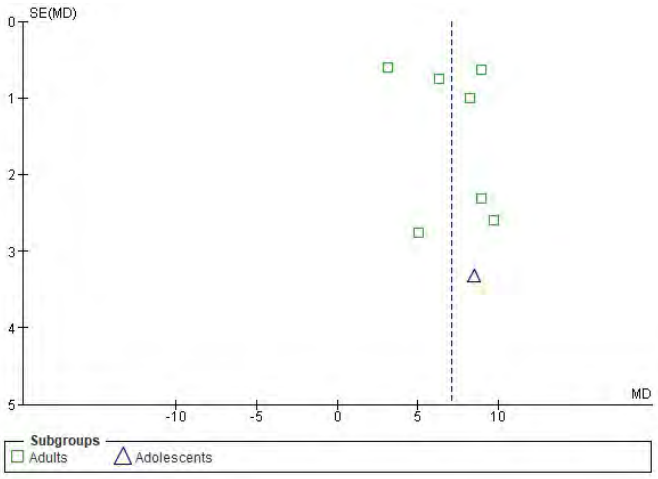
	OUTCOME: FAI					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **OCP**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Somethin g extra?**	**Time period (month)**
Harborne et al. 2003		26	12.9	13	26	3.2	2.1	Crude	12
Meyer et al. 2007		36	-2.1	9.3	31	-6.8	7.1	Mean change and 95%CI calculated	6
Hoeger et al. 2008		6	10.9	7.9	10	2.4	2.5	Adolescent s, obese	6
Moro et al. 2013		25	9.9	5	25	1.7	0.5		6
Dardzinska et al 2014		7	8.6	7.9; 14.0	14	2.0	1.8; 3.2	mean and IQR so not in meta-analysis	4
Hutchinson et al.		19	10.7	2.7	19	1.8	0.3	Pick either this or meyer	6
Morin-Papunen et al. 2003		8	3.8	0.6 1.70 (SD)	9	0.7	0.1 0.32 (SD)	BMI<25 SEM	6
Morin-Papunen et al. 2000		8	9.8	2.3 (SEM) 6.51 (SD)	10	0.9	0.1 (SEM) 0.32 (SD)	BMI>27 SEM	6
Christakou et al. 2014		35	5.71	15.97	38	0.66	3.39	CPA	6
Panidis et al. 2010		15	7.15	2.9	15	0.87	0.27	CPA	6

4.6.2. Forest plot metformin vs OCP for FAI





4.6.3. Funnel plot for assessment of publication bias



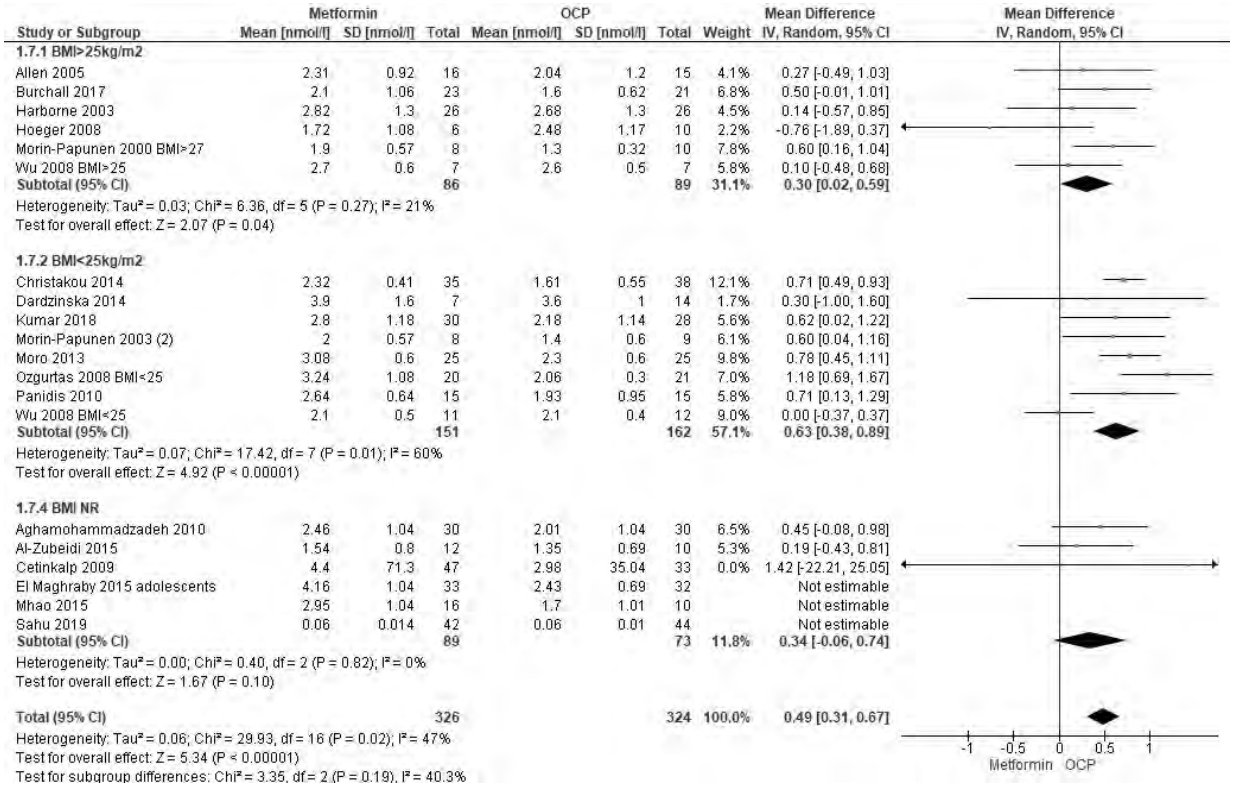
OUTCOME 4.7 Testosterone (nmol/l)

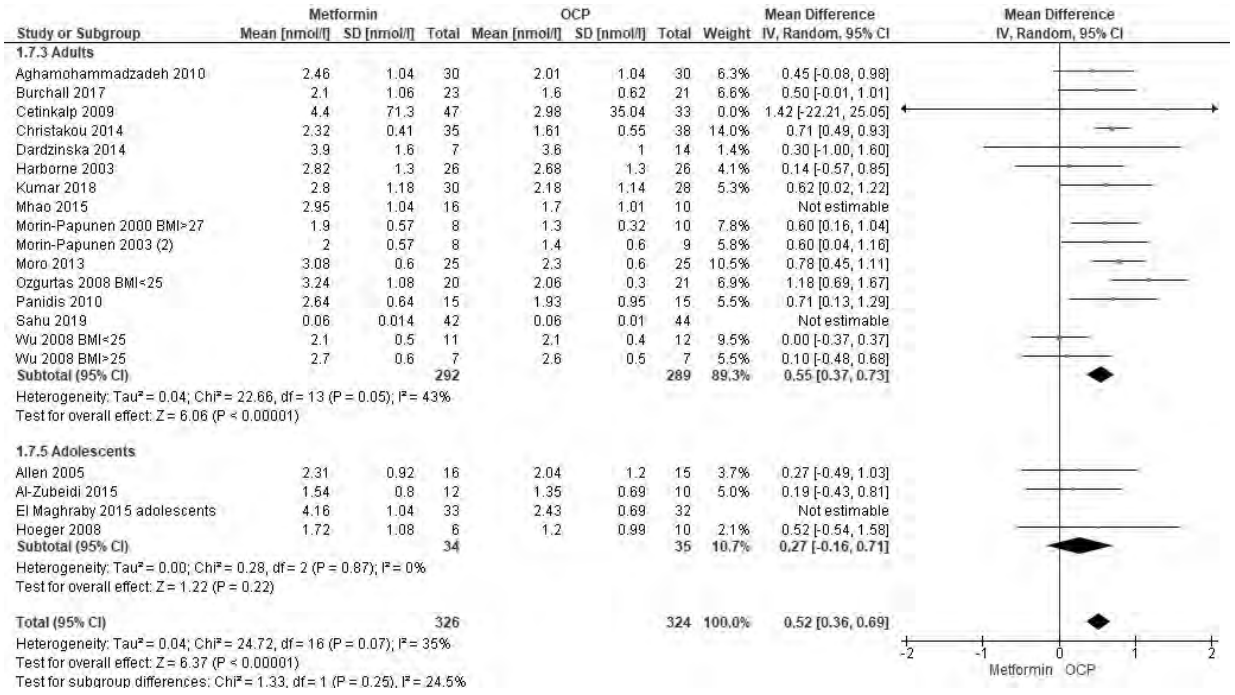
4.7.1 Individual Study Data Table

	OUTCOME: testosterone					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **OCP**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra**	**Time period (month)**
Burchall et al. 2017	Nmol/l	23	2.10	1.06	21	1.60	0.62	Crude	6
Sahu et al 2019	Ng/dl Nmol/l	42	1.8 0.062	0.4 0.0139	44	1.6 0.055	0.3 0.0104	Unit?	6
Kumar et al.2018	Ng/ml Nmol/l	30	0.81 2.8	0.34 1.18	28	0.63 2.18	0.33 1.14	Crude	6
Harborne et al. 2003	Nmol/l	26	2.82	1.3	26	2.68	1.3	Crude	12
El Maghraby 2015	Ug/ml Nmol/l	33	1.20 4.16	0.30 1.04	32	0.70 2.43	0.20 0.69	Adolescents Unit??	24
Meyer et al. 2007	Nmol/l	36	-0.2	1.3	31	-0.47	0.95	Mean change and 95%CI calculated	6
Ozgurtas et al. 2008	Nmol/l	20	03.24	1.08	21	2.06	0.30	BMI <25	3
Aghamohammadzadeh et al. 2010 Iran	Ng/ml Nmol/l	30	0.82	0.4	30	0.8	0.4	Crude	3
		30	0.71 2.46	0.3 1.04	30	0.58 2.01	0.3 1.04		6
Cetinkalp et al 2009	ng/ml Nmol/l	47	1.27 4.40	3.0 10.4 71.30 (SD)	33	0.86 2.98	1.76 6.1 35.04 (SD)	Crude SEM	4
Hoeger et al. 2008	Ng/dl Nmol/l	6	49.7 1.72	31.1 1.08	10	34.5 1.2	28.6 0.99	Adolescents, obese	6
Moro et al. 2013	Nmol/l	25	3.08	0.6	25	2.3	0.6		6
Dardzinska et al 2014	Nmol/l	7	3.9	1.6	14	3.6	1.0		4
Al-Zubeidi et al. 2015 USA	Ng/dl Nmol/l	12	44.5 1.54	23 0.80	10	39 1.35	20 0.69	adolescents	6
Allen et al. 2005	Ng/dl	16	66.8	6.6	15	58.8	8.9	Adolescents	6

	Nmol/l		2.31	0.23 0.92 (SEM)		2.04	0.31 1.20 (SEM)		
Morin-Papunen et al. 2003	Nmol/l	8	2	0.57	9	1.4	0.6	SD calculated BMI<25	6
Morin-Papunen et al. 2000	Nmol/l	8	1.9	0.57	10	1.3	0.32	SD calculated BMI>27	6
Wu et al. 2008	Nmol/l	7	2.7	0.6	7	2.6	0.5	BMI>25	3
Wu et al. 2008	Nmol/l	11	2.1	0.5	12	2.1	0.4	BMI<25	3
Christakou et al. 2014	Nmol/l	35	2.32	0.41	38	1.61	0.55	CPA	6
Panidis et al. 2010	Nmol/l	15	2.64	0.64	15	1.93	0.95	CPA	6
Mhao et al. 2015	Nmol/l	16	2.95	1.04	10	1.7	1.01		3

4.7.2. Forrest plot metformin vs OCP for Testosterone





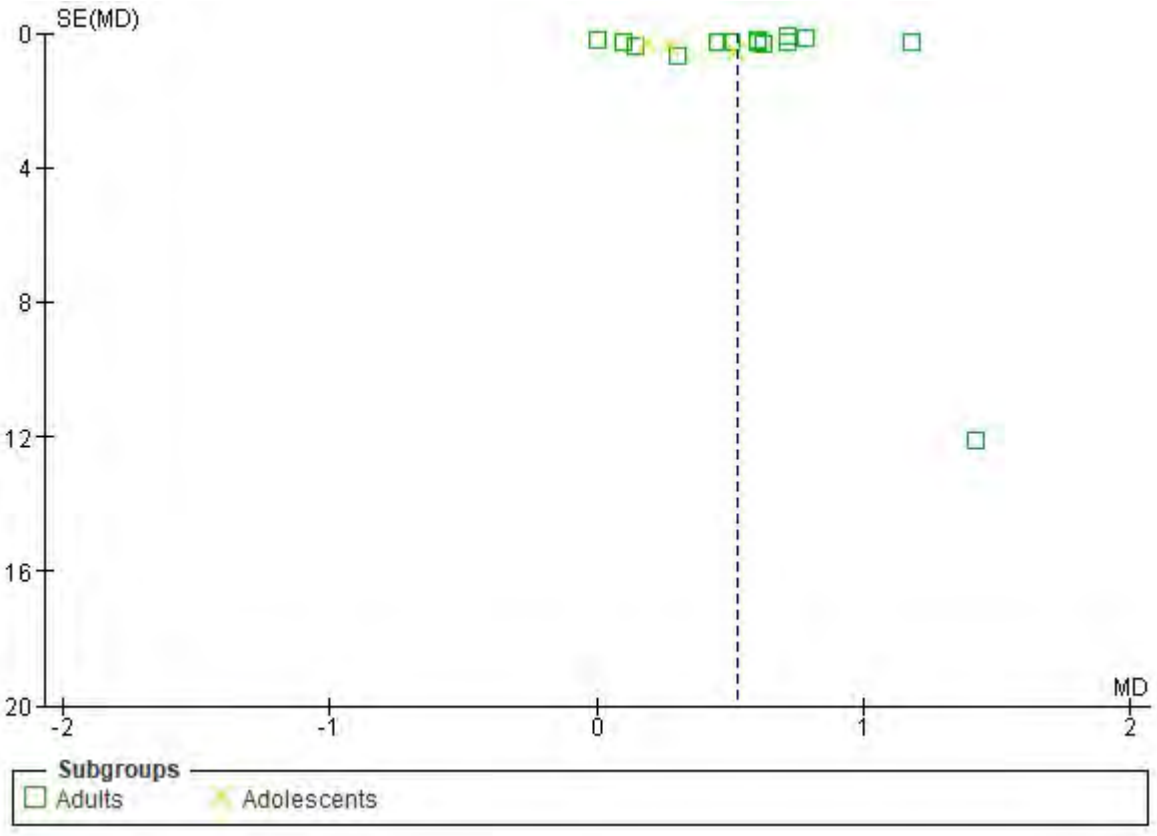
Study or Subgroup	Metformin Mean [nmol/l]	Metformin SD [nmol/l]	Metformin Total	OCP Mean [nmol/l]	OCP SD [nmol/l]	OCP Total	Weight	Mean Difference IV, Random, 95% CI
1.7.3 Adults								
Aghamohammadzadeh 2010	2.46	1.04	30	2.01	1.04	30	6.3%	0.45 [-0.08, 0.98]
Burchall 2017	2.1	1.06	23	1.6	0.62	21	6.6%	0.50 [-0.01, 1.01]
Cetinkalp 2009	4.4	71.3	47	2.98	35.04	33	0.0%	1.42 [-22.21, 25.05]
Christakou 2014	2.32	0.41	35	1.61	0.55	38	14.0%	0.71 [0.49, 0.93]
Dardzinska 2014	3.9	1.6	7	3.6	1	14	1.4%	0.30 [-1.00, 1.60]
Harborne 2003	2.82	1.3	26	2.68	1.3	26	4.1%	0.14 [-0.57, 0.85]
Kumar 2018	2.8	1.18	30	2.18	1.14	28	5.3%	0.62 [0.02, 1.22]
Mhao 2015	2.95	1.04	16	1.7	1.01	10		Not estimable
Morin-Papunen 2000 BMI>27	1.9	0.57	8	1.3	0.32	10	7.8%	0.60 [0.16, 1.04]
Morin-Papunen 2003 (2)	2	0.57	8	1.4	0.6	9	5.8%	0.60 [0.04, 1.16]
Moro 2013	3.08	0.6	25	2.3	0.6	25	10.5%	0.78 [0.45, 1.11]
Ozgurtas 2008 BMI<25	3.24	1.08	20	2.06	0.3	21	6.9%	1.18 [0.69, 1.67]
Panidis 2010	2.64	0.64	15	1.93	0.95	15	5.5%	0.71 [0.13, 1.29]
Sahu 2019	0.06	0.014	42	0.06	0.01	44		Not estimable
Wu 2008 BMI<25	2.1	0.5	11	2.1	0.4	12	9.5%	0.00 [-0.37, 0.37]
Wu 2008 BMI>25	2.7	0.6	7	2.6	0.5	7	5.5%	0.10 [-0.48, 0.68]
Subtotal (95% CI)			**292**			**289**	**89.3%**	**0.55 [0.37, 0.73]**
Heterogeneity: Tau² = 0.04; Chi² = 22.66, df = 13 (P = 0.05); I² = 43%								
Test for overall effect: Z = 6.06 (P < 0.00001)								
1.7.5 Adolescents								
Allen 2005	2.31	0.92	16	2.04	1.2	15	3.7%	0.27 [-0.49, 1.03]
Al-Zubeidi 2015	1.54	0.8	12	1.35	0.69	10	5.0%	0.19 [-0.43, 0.81]
El Maghraby 2015 adolescents	4.16	1.04	33	2.43	0.69	32		Not estimable
Hoeger 2008	1.72	1.08	6	1.2	0.99	10	2.1%	0.52 [-0.54, 1.58]
Subtotal (95% CI)			**34**			**35**	**10.7%**	**0.27 [-0.16, 0.71]**
Heterogeneity: Tau² = 0.00; Chi² = 0.28, df = 2 (P = 0.87); I² = 0%								
Test for overall effect: Z = 1.22 (P = 0.22)								
Total (95% CI)			**326**			**324**	**100.0%**	**0.52 [0.36, 0.69]**
Heterogeneity: Tau² = 0.04; Chi² = 24.72, df = 16 (P = 0.07); I² = 35%								
Test for overall effect: Z = 6.37 (P < 0.00001)								
Test for subgroup differences: Chi² = 1.33, df = 1 (P = 0.25), I² = 24.5%								

Mean Difference IV, Random, 95% CI

-2 -1 0 1 2

Metformin OCP

4.7.3. Funnel plot for assessment of publication bias

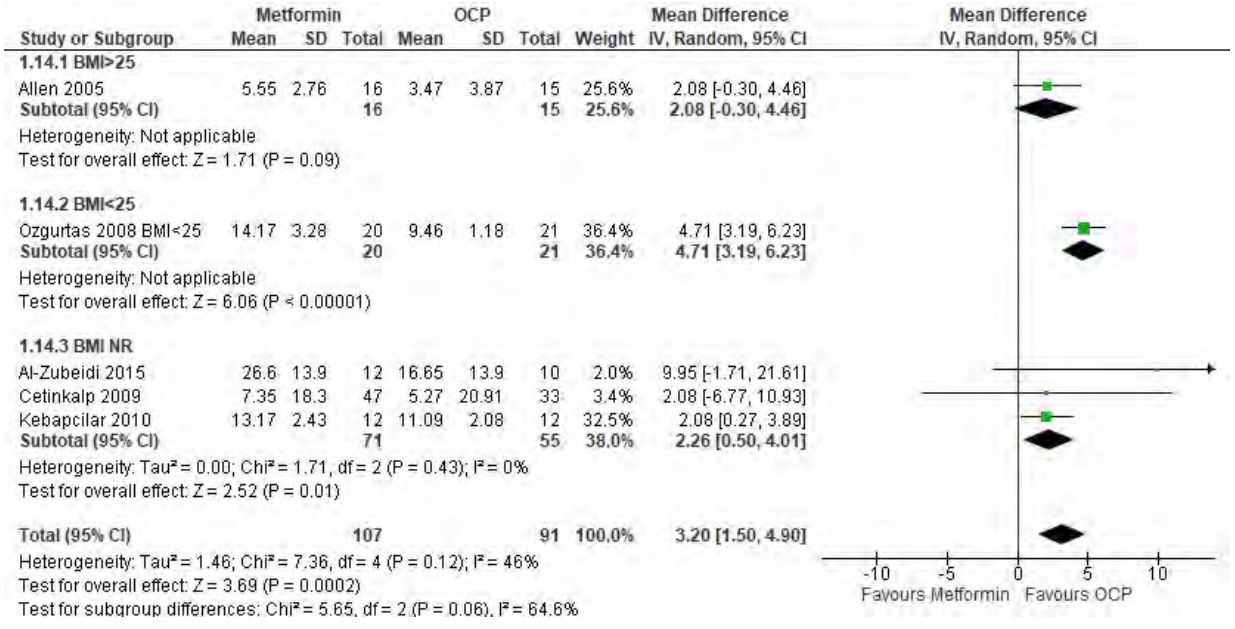


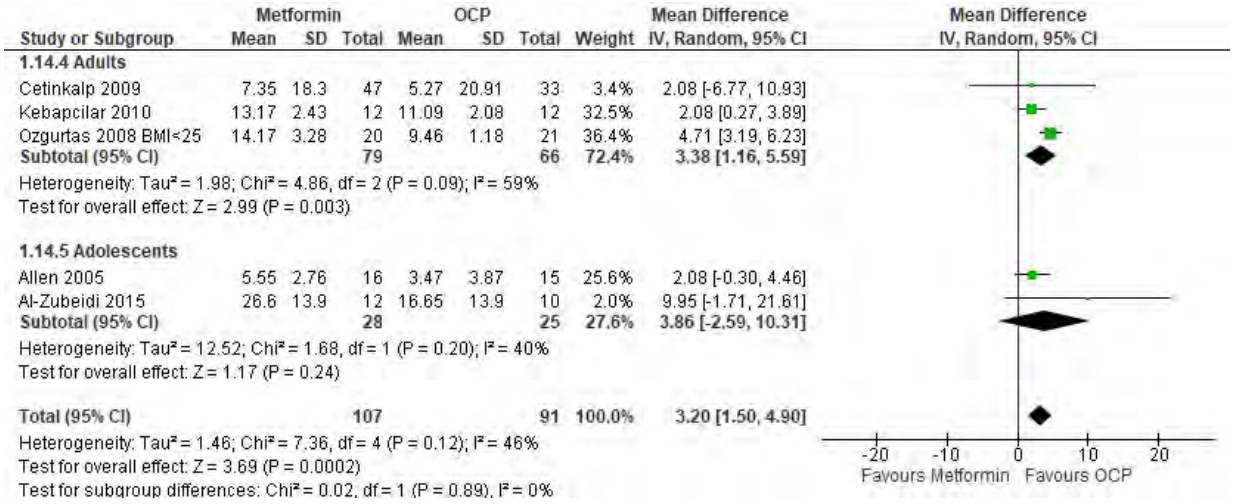
OUTCOME 4.8 Free testosterone (pmol/l)

4.8.1 Individual Study Data Table

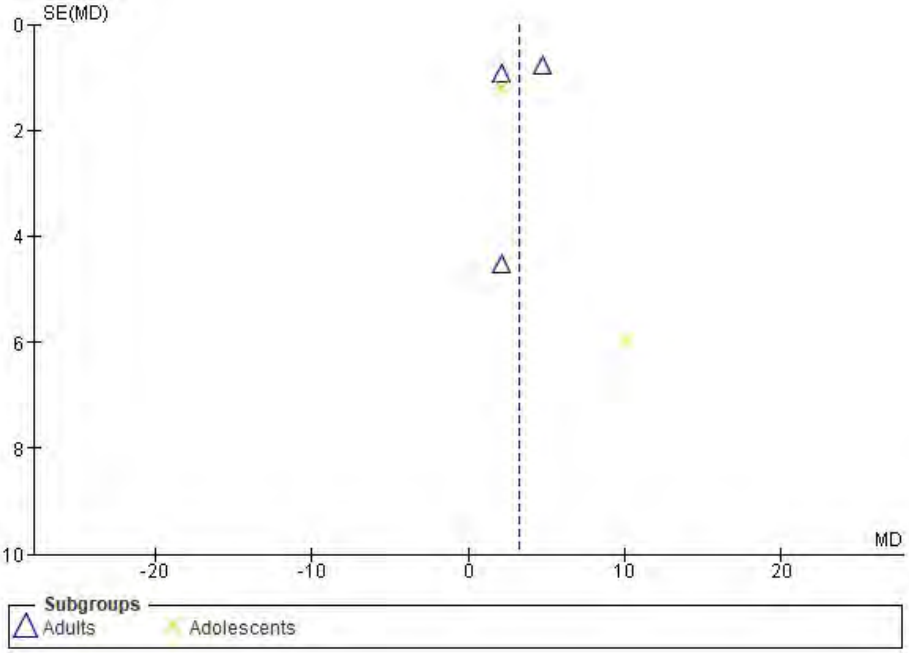
	OUTCOME: free testosterone					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **OCP**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra**	**Time period (month)**
Ozgurtas et al. 2008	pmol/l	20	14.17	3.28	21	9.46	1.18	BMI<25	3
Kebapcilar et al 2010	pg/ml pmol/l	12	3.8 13.17	0.7 2.43	12	3.2 11.09	0.6 2.08		3
Cetinkalp et al 2009	pg/ml pmol/l	47	2.12 7.35	0.77 2.67 18.30	33	1.52 5.27	1.05 3.64 20.91	Crude SEM	4
Allen et al. 2005	Ng/dl Pmol/l	16	1.6 5.55	0.2 0.69 2.76 (SEM)	15	1.0 3.47	0.3 1.0 3.87 (SEM)	Adolescents	6
Al-Zubeidi et al. 2015 USA	Pg/ml Pmol/l	12	7.7 26.7	4 13.88	10	4.8 16.65	4 13.88	adolescents	6

4.8.2. Forrest plot metformin vs OCP for Free testosterone





4.8.3. Funnel plot for assessment of publication bias



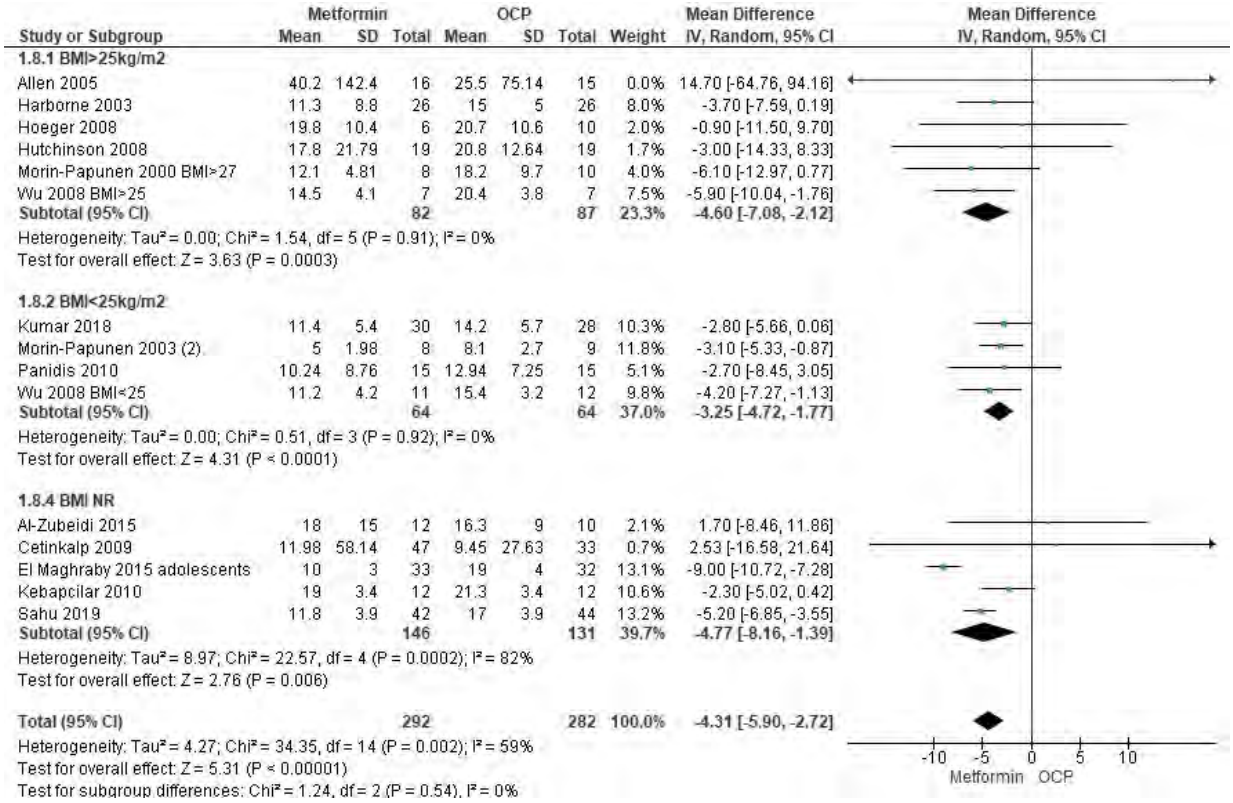
OUTCOME 4.9 fasting insulin (uIU/ml)

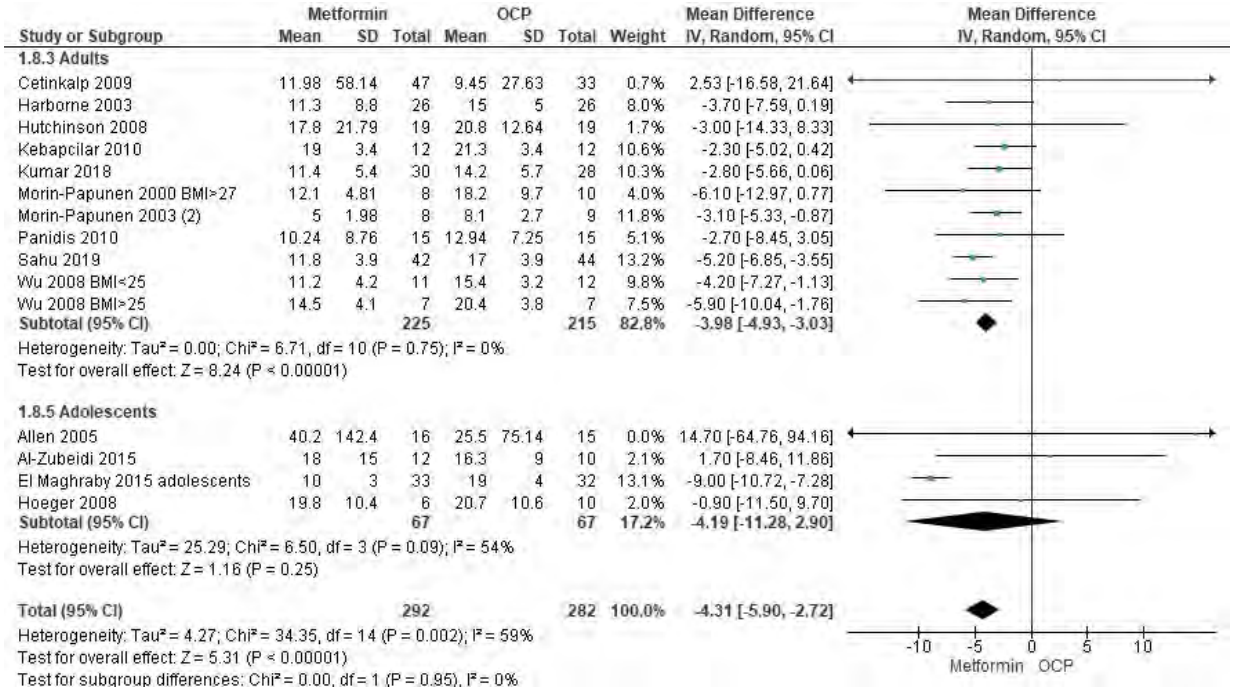
4.9.1 Individual Study Data Table

	OUTCOME: insulin					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **OCP**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**

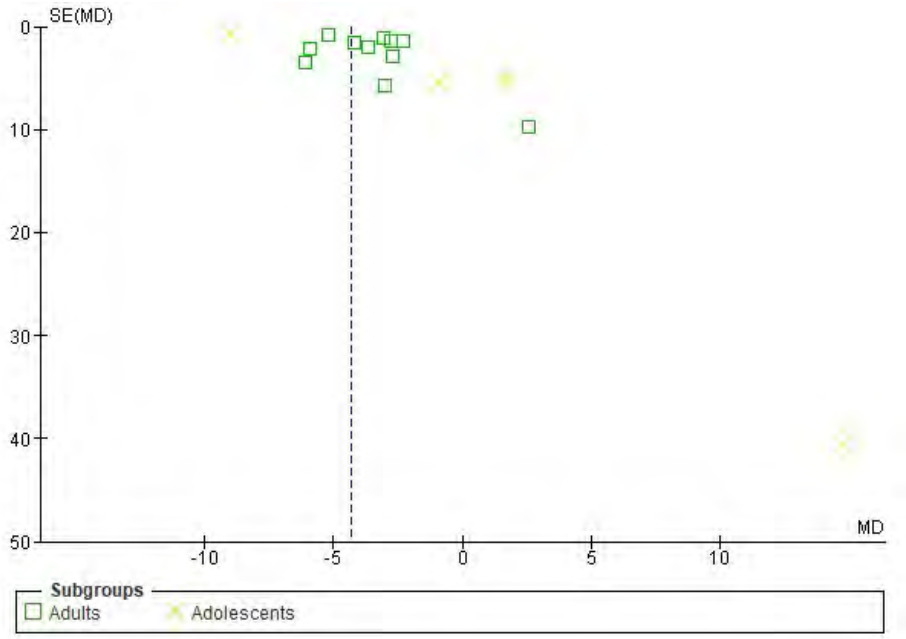
Burchall et al. 2017	mU/L	23	Median 2.37	2.10–3.23	21	Median 2.88	2.22–3.30	Median, pick either	6
Sahu et al 2019	IU/dl **uIU/ml**	42	11.8	3.9	44	17.0	3.9	Crude	6
Kumar et al.2018	**uIU/ml**	30	11.4	5.4	28	14.2	5.7	Crude	6
Harborne et al. 2003	mIU/l	26	11.3	8.8	26	15	5	Crude	12
Al-Zubeidi et al. 2015 USA	uU/ml **uIU/ml**	12	18.00	15.0	10	16.3	9	adolescents	6
El Maghraby 2015	uIU/l **uIU/ml**	33	10.0	3.0	32	19.0	4.0	Crude adolecents	24
Meyer et al. 2007	mIU/l	36	-6.0	19.2	31	1.15	14.6	Mean change and 95%CI calculated, pick either	6
Hutchinson et al 2008	mU/l **uIU/ml**	19	17.8	5 (SEM) 21.79 (SD)	19	20.8	2.9 (SEM) 12.64 (SD)	SEM, pick either	6
Kebapcilar et al 2010	uIU/ml	12	19.0	3.4	12	21.3	3.4		3
Cetinkalp et al 2009	mIU/ml **uIU/ml**	47	11.98	8.48 58.14 (SD)	33	9.45	4.81 27.63 (SD)	SEM	4
Hoeger et al. 2008	IU/ml **uIU/ml**	6	19.8	10.4	10	20.7	10.6	Adolescents, obese	6
Allen et al. 2005	uU/ml	16	40.2	35.6 142.4 (SEM)	15	25.5	19.4 75.14 (SEM)	Adolescents	6
Morin-Papunen et al. 2003 (2)	Pmol/l uIU/ml **mIU/l**	8	29.8 4.29 5	4.3 0.62 1.75 (SD) 1.98 (SD)	9	48.7 7.01 8.1	5.6 0.81 2.43 (SD) 2.7 (SD)	SEM BMI <25	6
Morin-Papunen et al. 2000 (1)	Pmol/l uIU/ml **mIU/l**	8	72.6 10.45 12.1	9.9 1.43 4.04 (SD) 4.81 (SD)	10	109.3 15.74 18.2	17.5 2.52 7.97 (SD) 9.7 (SD)	SEM BMI>27	6
Wu et al. 2008	uIU/ml	7	14.5	4.1	7	20.4	3.8	BMI>25	3
Wu et al. 2008	uIU/ml	11	11.2	4.2	12	15.4	3.2	BMI<25	3
Panidis et al. 2010	uIU/ml	15	10.24	8.76	15	12.94	7.25	CPA	6

4.9.2. Forrest plot metformin vs OCP for fasting insulin





4.9.3. Funnel plot for assessment of publication bias



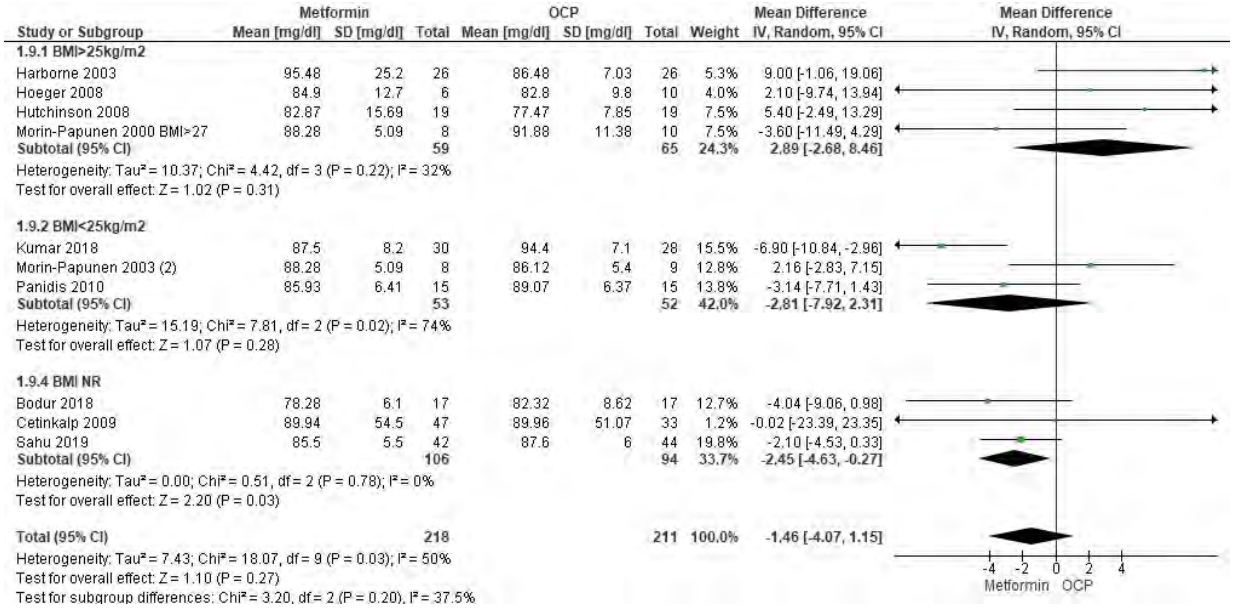
OUTCOME 4.10 fasting glucose (mg/dl)

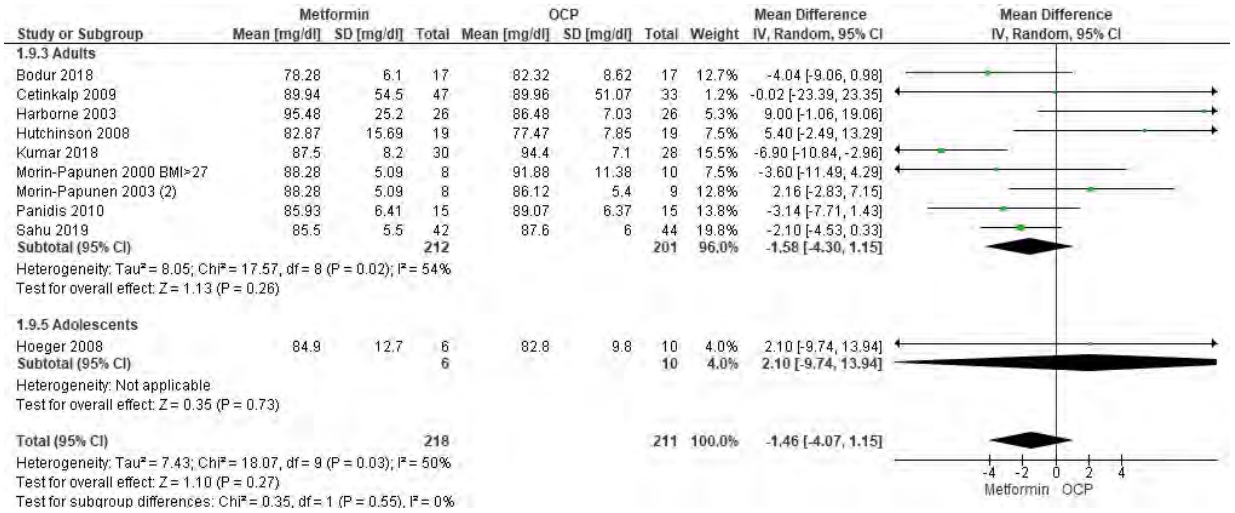
4.10.1 Individual Study Data Table

	OUTCOME: serum fasting glucose level					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **OCP**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Bodur et al. 2018	Mg/dl	17	78.28	6.1	17	82.32	8.62	BMI<30	6
Sahu et al 2019	Mg/dl	42	85.5	5.5	44	87.6	6.0	Crude	6
Kumar et al.2018	Mg/dl	30	87.5	8.2	28	94.4	7.1	Crude	6
Harborne et al. 2003	Mmol/l Mg/dl	26	5.3 95.48	1.4 25.2	26	4.8 86.48	0.39 7.03	Crude	12
Moran et al. 2010	Mmol/l	30	-0.1	0.1	26	-0.1	0.1	Mean change±SEM	6
Hutchinson et al 2008	Mmol/l Mg/dl	19	4.6 82.87	0.2 (SEM) 3.60	19	4.3 77.47	0.1 (SEM) 1.80	SEM, pick either	6

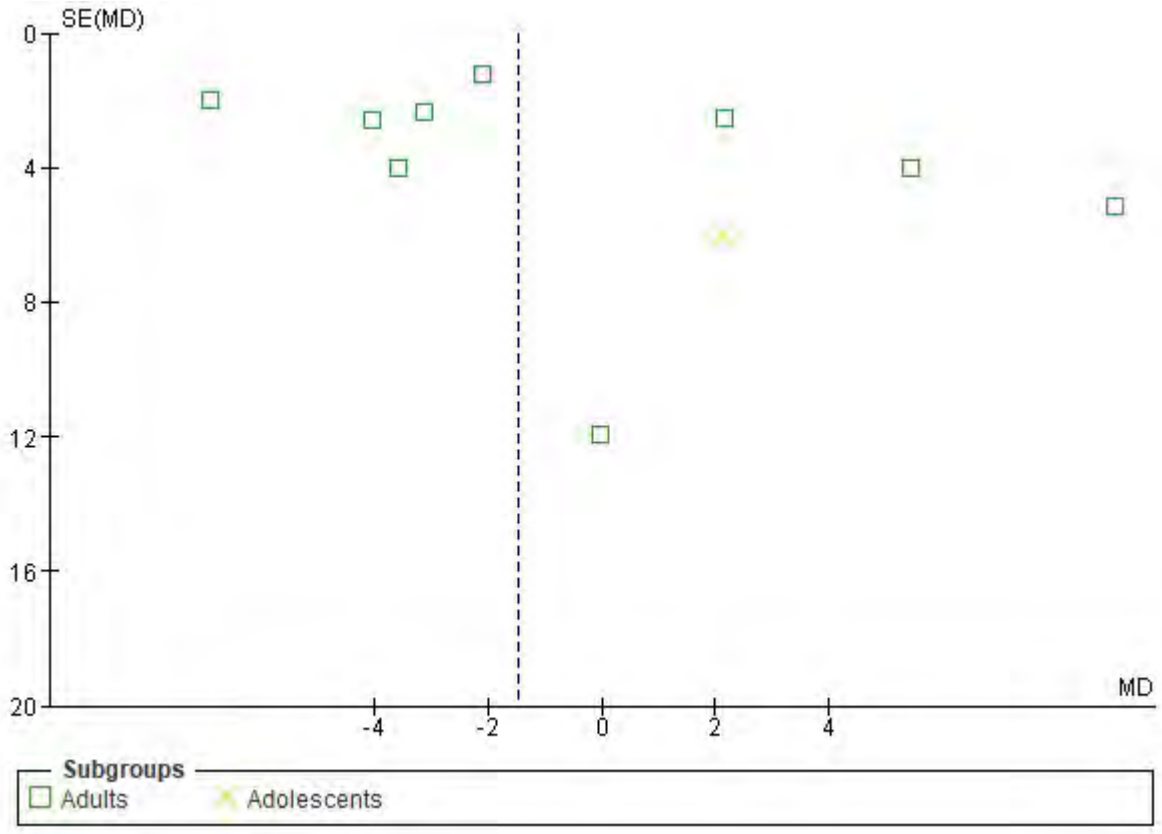
				15.69			7.85		
Cetinkalp et al 2009	Mg/dl	47	89.94	7.95 54.50	33	89.96	8.89 51.07	SEM	4
Hoeger et al. 2008	Mg/dl	6	84.9	12.7	10	82.8	9.8	Adolescents, obese	6
Morin-Papunen et al. 2003 (2)	Mmol/l Mg/dl	8	4.96 88.28	0.1 1.80 5.09 (SD)	9	4.78 86.12	0.1 1.80 5.40 (SD)	SEM BMI <25	6
Morin-Papunen et al. 2000 (1)	Mmol/l Mg/dl	8	4.9 88.28	0.1 1.80 5.09 (SD)	10	5.1 91.88	0.2 3.60 11.38 (SD)	SEM BMI>27	6
Panidis et al. 2010	Mg/dl	15	85.93	6.41	15	89.07	6.37	CPA	6

4.10.2. Forrest plot metformin vs OCP for fasting glucose





4.10.3. Funnel plot for assessment of publication bias



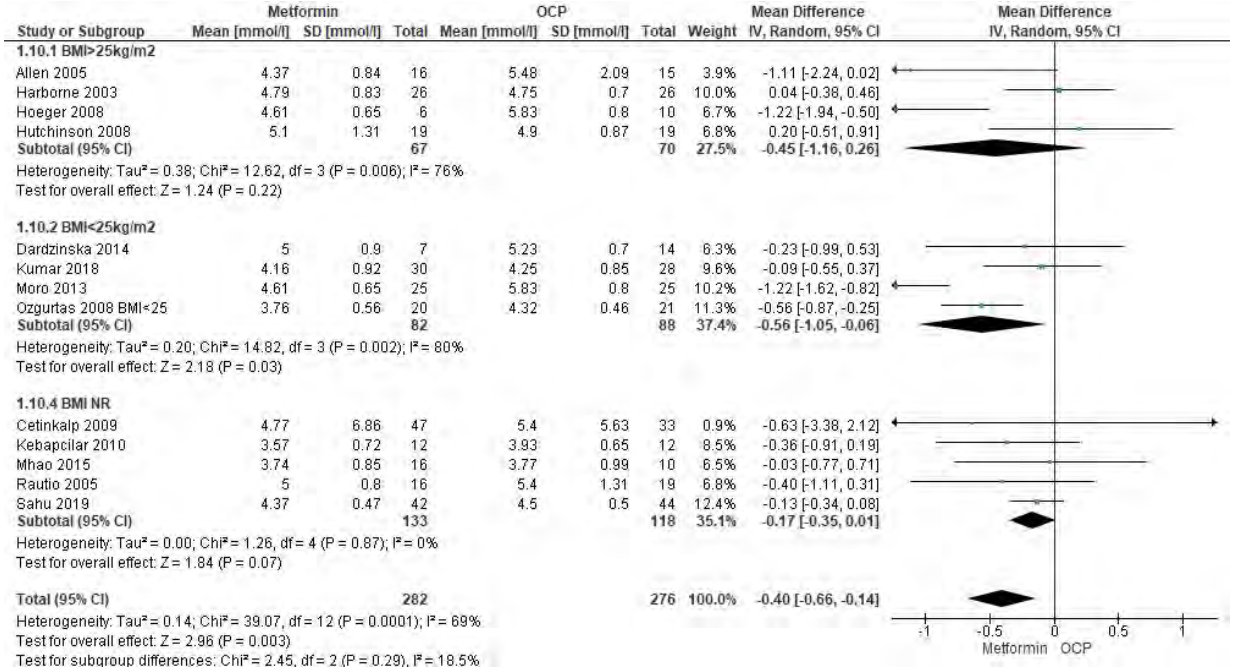
OUTCOME 4.11 Total cholesterol (mmol/l)

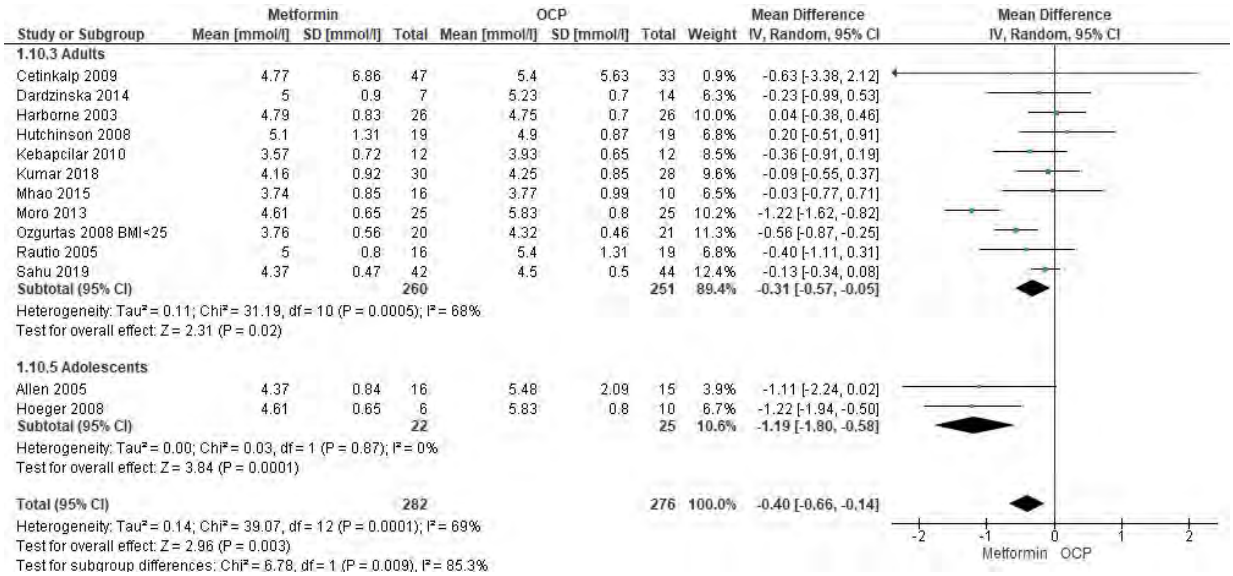
4.11.1 Individual Study Data Table

	OUTCOME: total cholesterol					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **OCP**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra**	**Time period (month)**
Sahu et al 2019	mg/dl mmol/l	42	169.0 4.37	18.2 0.47	44	174.1 4.5	19.3 0.50	Crude	6
Kumar et al. 2018	Mg/dl Mmol/l	30	160.7 4.16	35.4 0.92	28	164.3 4.25	32.8 0.85	Crude	6
Harborne et al. 2003	Mmol/l	26	4.79	0.83	26	4.75	0.7	Crude	12
Meyer et al. 2007	Mmol/l	36	-0.17	0.7	31	-0.12	0.8	Mean change and 95%CI calculated, pick either	6
Hutchinson et al 2008	Mmol/l	19	5.1	0.3 (SEM) 1.31 (SD)	19	4.9	0.2 (SEM) 0.87 (SD)	SEM, pick either	6
Mhao et al. 2015	Mg/dl Mmol/l	16	144.6 3.74	32.99 0.85	10	145.7 3.77	38.2 0.99		3
Ozgurtas et al. 2008	Mmol/l	20	3.76	0.56	21	4.32	0.46	BMI<25	3
Kebapcilar et al 2010	Mg/dl Mmol/l	12	138 3.57	28 0.72	12	152 3.93	25 0.65		3
Rautio et al. 2005	Mmol/l	16	5.1	0.2 (SE)	19	5.3	0.2 (SE)	SE	3
		16	5.0	0.2 (SE) SD=0.8	19	5.4	0.3 (SE) SD=1.31		6
Cetinkalp et al 2009	Mg/dl Mmol/l	47	184.6 4.77	38.7 1.00 6.86 (SD)	33	208.9 5.40	37.9 0.98 5.63 (SD)	SEM	4
Hoeger et al. 2008	Mg/dl Mmol/l	6	145.3 3.76	25 0.65	10	188.6 4.88	20.7 0.54	Adolescents, obese	6
Moro et al. 2013	Mmol/l	25	4.61	0.65	25	5.83	0.8		6
Dardzinska et al 2014	Mmol/l	7	5.0	0.90	14	5.23	0.7		4

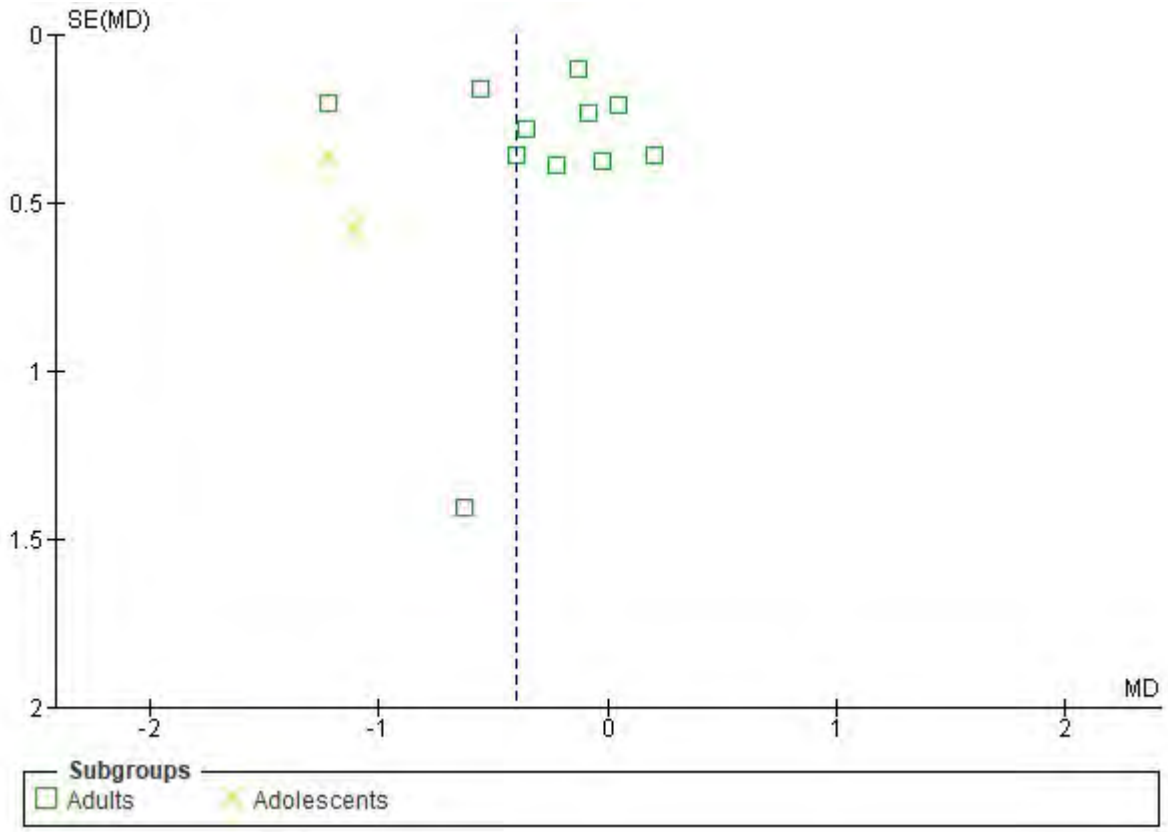
Allen et al. 2005	Mg/dl Mmol/l	16	169 4.37	8 0.21 0.84 (SEM)	15	212 5.48	21 0.54 2.09 (SEM)	Adolescents	6

4.11.2. Forrest plot metformin vs OCP for total cholesterol





4.11.3. Funnel plot for assessment of publication bias



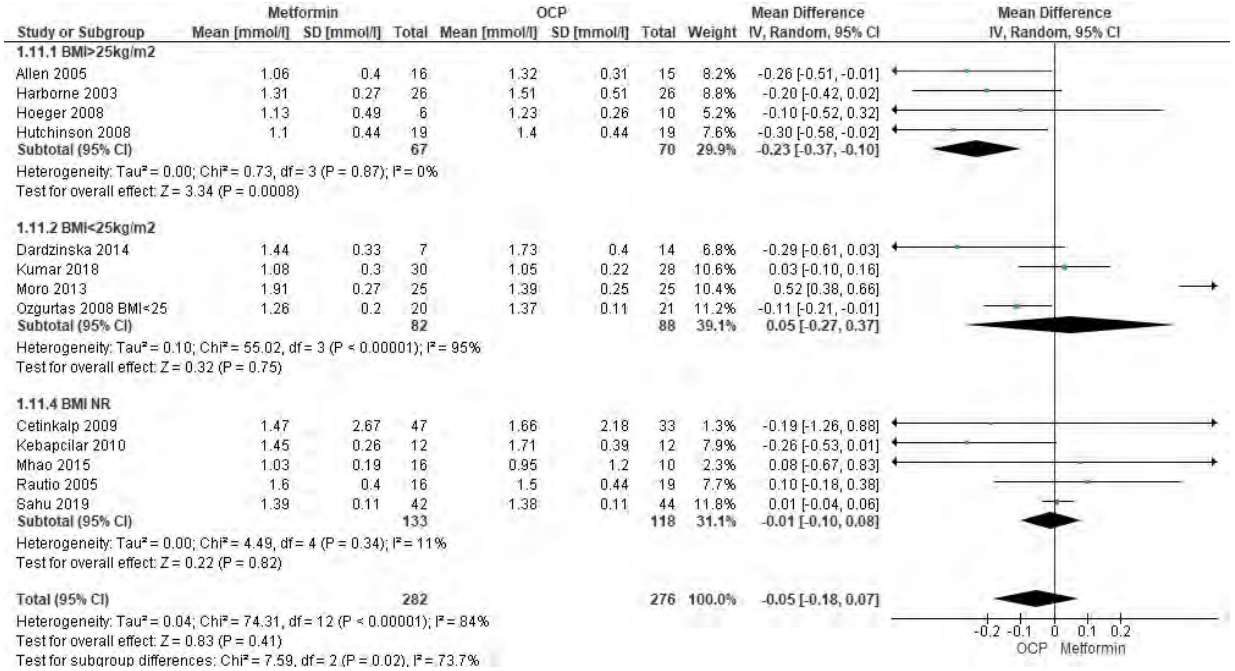
OUTCOME 4.12 HDL (mmol/l)

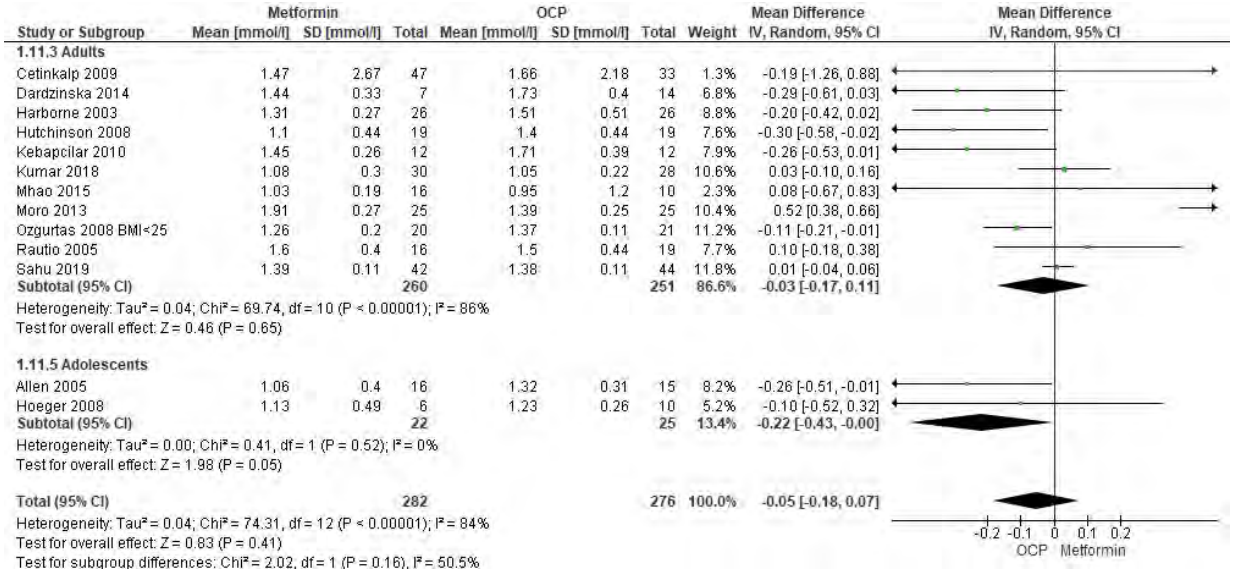
4.12.1 Individual Study Data Table

	OUTCOME: HDL					OUTCOME TYPE: Continuous			
		COMPARISON (if applicable): metformin versus OCP							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra**	**Time period (month)**
Sahu et al 2019	mg/dl Mmol/l	42	53.6 1.39	4.1 0.11	44	53.2 1.38	4.1 0.11	Crude	6
Kumar et al.2018	Mg/dl Mmol/l	30	41.7 1.08	11.7 0.30	28	40.7 1.05	8.6 0.22	Crude	6
Harborne et al. 2003	Mmol/l	26	1.31	0.27	26	1.51	0.51	Crude	12

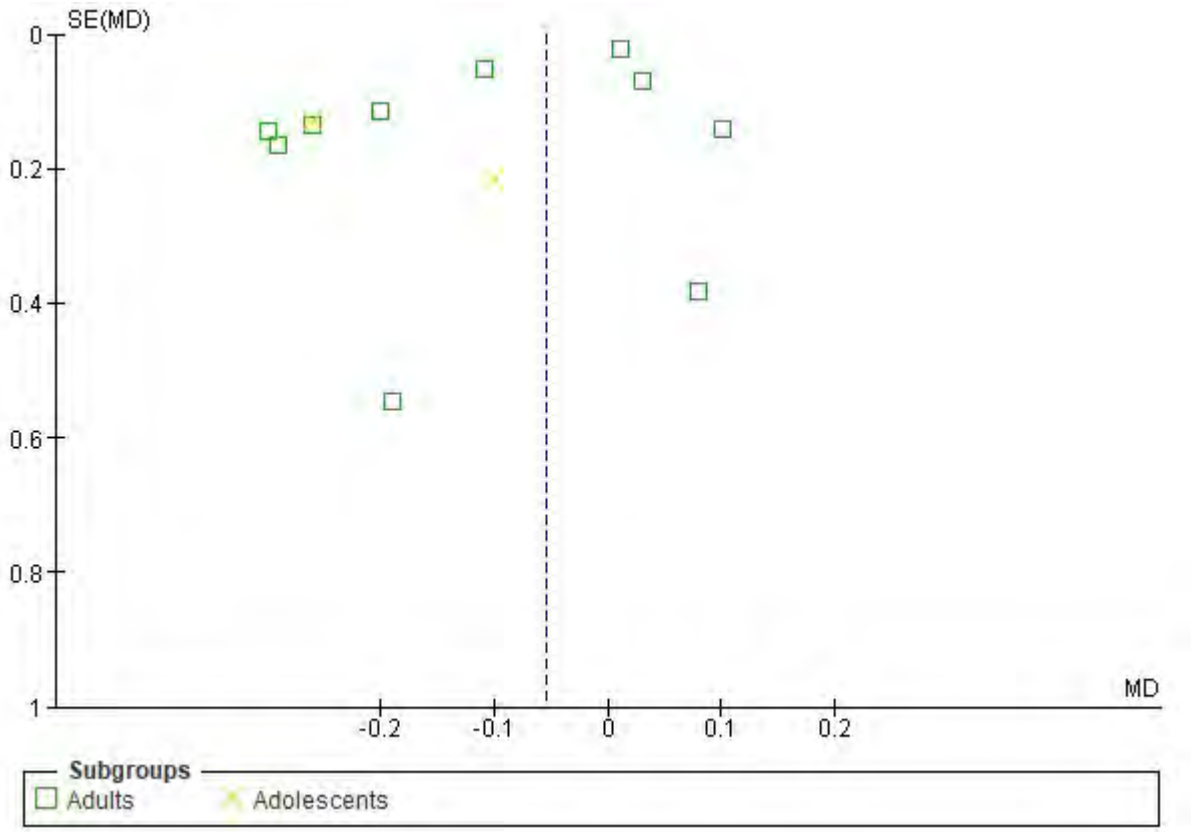
Hutchinson et al 2008	Mmol/l	19	1.1	0.1 (SEM) 0.44 (SD)	19	1.4	0.1 (SEM) 0.44 (SD)	SEM	6
Mhao et al. 2015	Mg/dl Mmol/l	16	39.8 1.03	7.43 0.19	10	36.8 0.95	46.3 1.20		3
Ozgurtas et al. 2008	Mmol/l	20	1.26	0.20	21	1.37	0.11	BMI<25	3
Kebapcilar et al 2010	Mg/dl Mmol/l	12	56 1.45	10 0.26	12	66 1.71	15 0.39		3
Rautio et al. 2005	Mmol/l	16	1.6	0.1 (SE)	19	1.5	0.1 (SE)	Crude	3
		16	1.6	0.4 (SD)	19	1.5	0.44 (SD)		6
Cetinkalp et al 2009	Mg/dl Mmol/l	47	56.7 1.47	15.06 0.39 2.67 (SD)	33	64.04 1.66	14.6 0.38 2.18 (SD)	Crude SEM	4
Hoeger et al. 2008	Mg/dl Mmol/l	6	43.5 1.13	19 0.49	10	47.6 1.23	9.9 0.26	Adolescents, obese	6
Moro et al. 2013	Mmol/l	25	1.91	0.27	25	1.39	0.25		6
Dardzinska et al 2014	Mmol/l	7	1.44	0.33	14	1.73	0.40		4
Allen et al. 2005	Mg/dl Mmol/l	16	41 1.06	4 0.10 0.4 (SEM)	15	51 1.32	3 0.08 0.31 (SEM)	Adolescents	6
Al-Zubeidi et al. 2015 USA	Mg/dl Mmol/l	12	50 1.29	10 0.26	10	38.5 0.96	Not specified	adolescents	6

4.12.2. Forrest plot metformin vs OCP for HDL





4.12.3. Funnel plot for assessment of publication bias



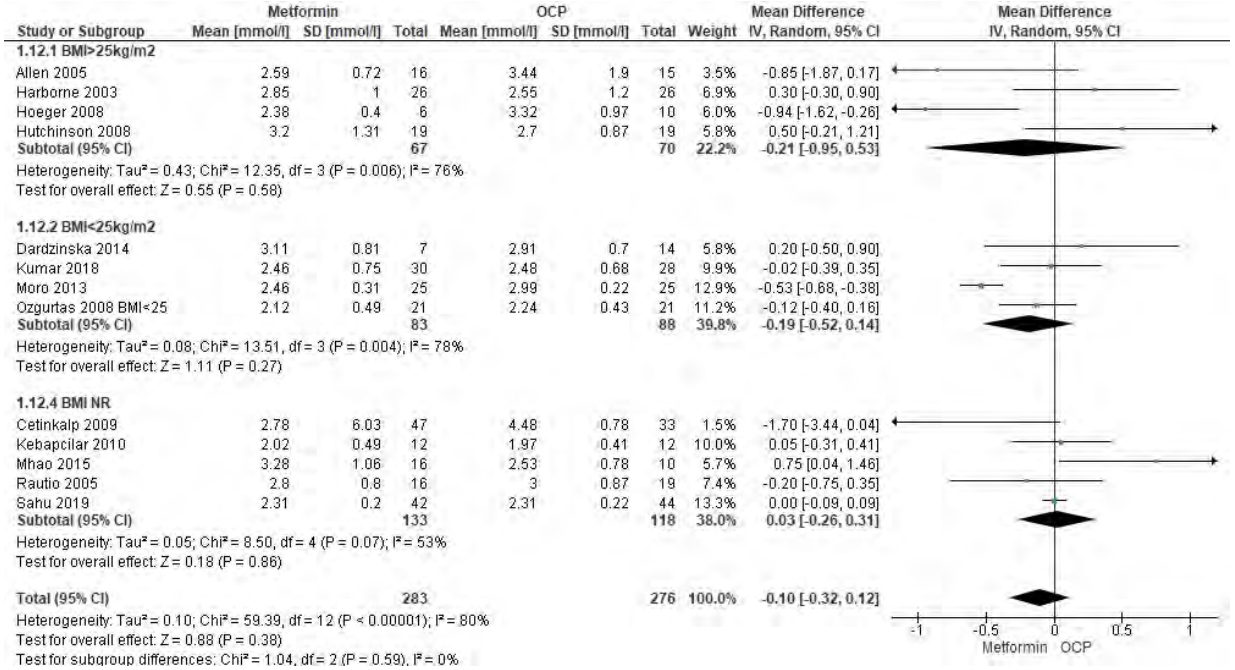
OUTCOME 4.13 LDL (mmol/l)

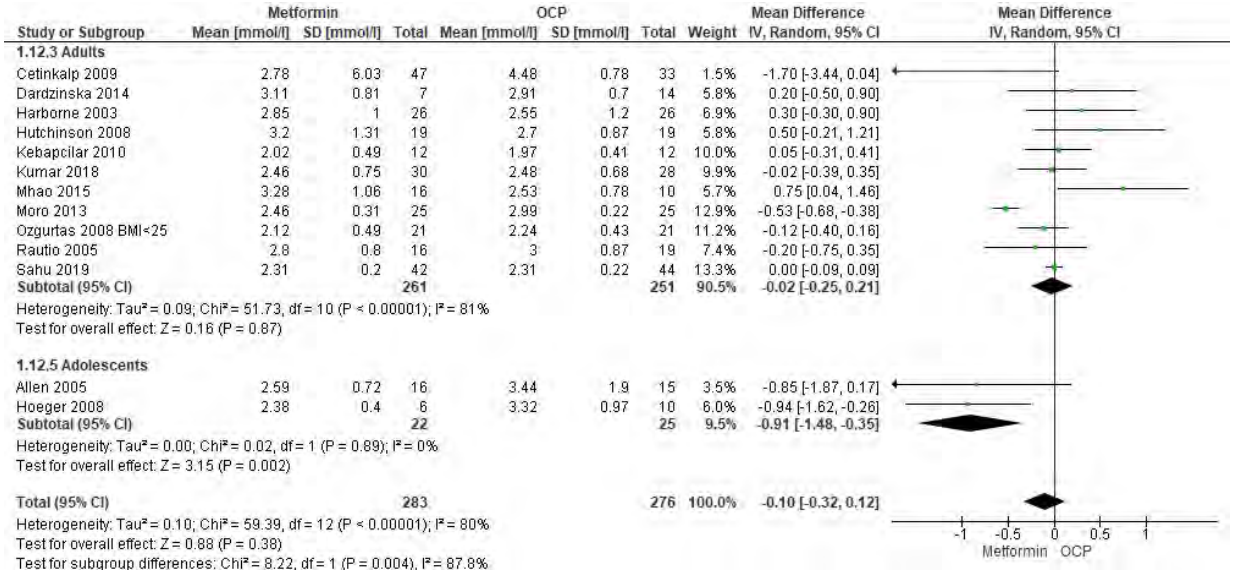
4.13.1 Individual Study Data Table

	OUTCOME: LDL					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **OCP**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Sahu et al 2019	mg/dl mmol/l	42	89.4 2.31	7.6 0.20	44	89.3 2.31	8.4 0.22	Crude	6
Kumar et al.2018	Mg/dl Mmol/l	30	95.1 2.46	28.9 0.75	28	95.8 2.48	26.3 0.68	Crude	6
Harborne et al. 2003	Mmol/l	26	2.85	1	26	2.55	1.2	Crude	12
	Mmol/l	16	2.9	0.2 (SE)	19	2.9	0.2 (SE)	Crude	3

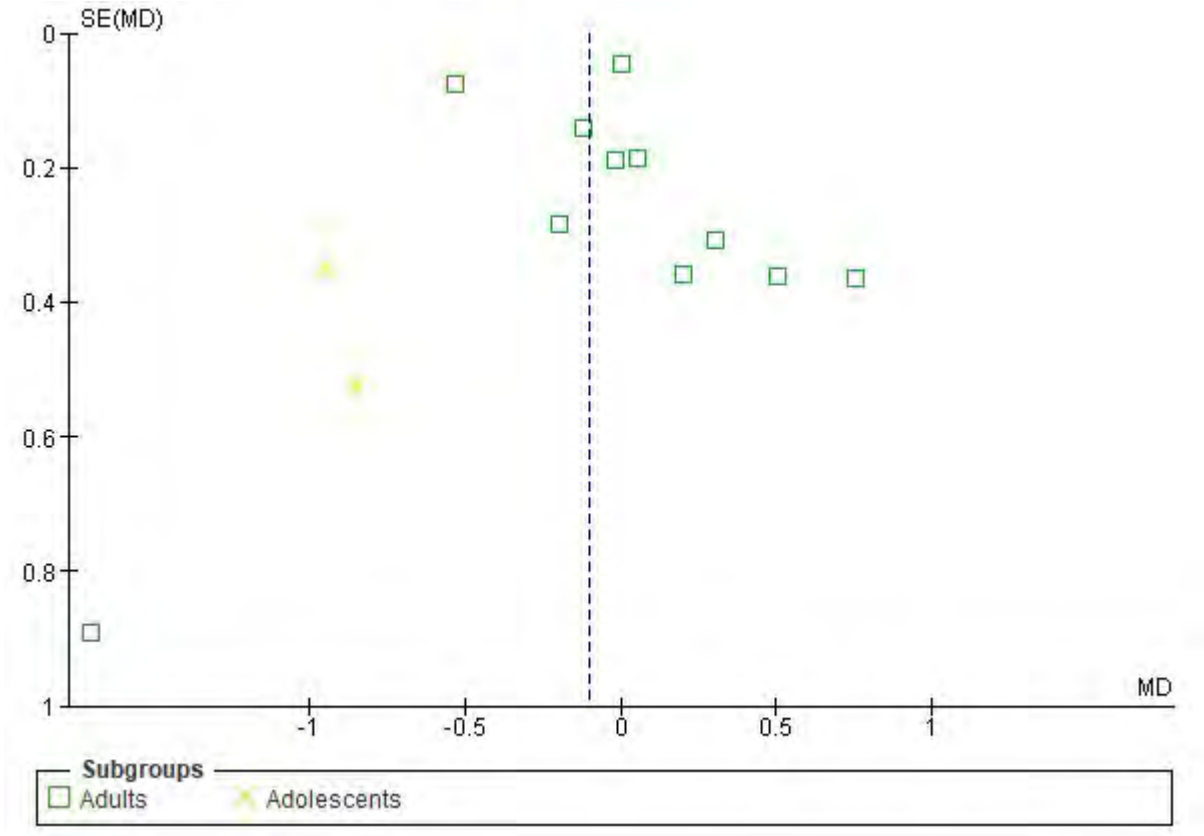
Rautio et al. 2005		16	2.8	0.2 (SE) 0.8 (SD)	19	3.0	0.2 (SE) 0.87 (SD)		6
Hutchinson et al 2008	Mmol/l	19	3.2	0.3 (SEM) 1.31 (SD)	19	2.7	0.2 (SEM) 0.87 (SD)	SEM,	6
Mhao et al. 2015	Mg/dl Mmol/l	16	126.9 3.28	41.00 1.06	10	98.0 2.53	30.0 0.78		3
Ozgurtas et al. 2008	Mmol/l	20	2.12	0.49	21	2.24	0.43	BMI<25	3
Kebapcilar et al 2010	Mg/dl Mmol/l	12	78 2.02	19 0.49	12	76 1.97	16 0.41		3
Cetinkalp et al 2009	Mg/dl Mmol/l	47	107.5 2.78	34.1 0.88 6.03 (SD)	33	123.79 3.2	30.17 0.78 4.48 (SD)	Crude	4
Hoeger et al. 2008	Mg/dl Mmol/l	6	92.0 2.38	15.5 0.40	10	128.6 3.32	37.5 0.97	Adolescents, obese	6
Moro et al. 2013	Mmol/l	25	2.46	0.31	25	2.99	0.22		6
Dardzinska et al 2014	Mmol/l	7	3.11	0.81	14	2.91	0.70		4
Allen et al. 2005	Mg/dl Mmol/l	16	100 2.59	7 0.18 0.72 (SEM)	15	133 3.44	19 0.49 1.90 (SEM)	Adolescents	6

4.13.2. Forrest plot metformin vs OCP for LDL





4.13.3. Funnel plot for assessment of publication bias

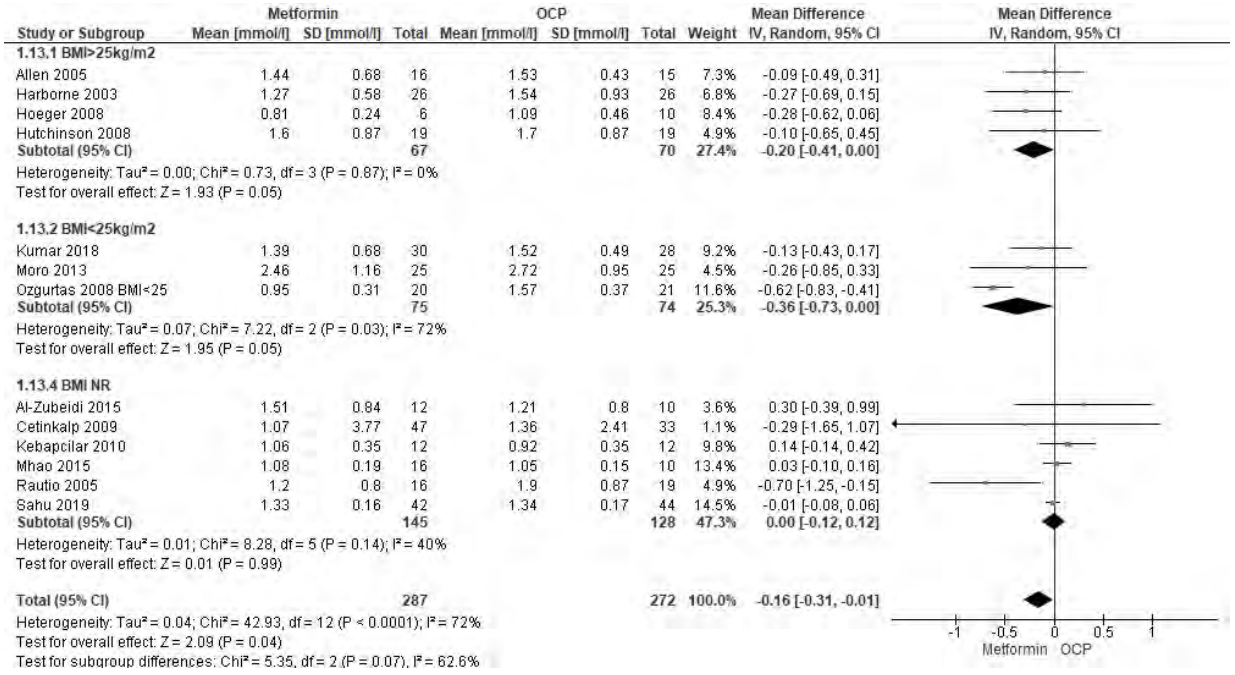


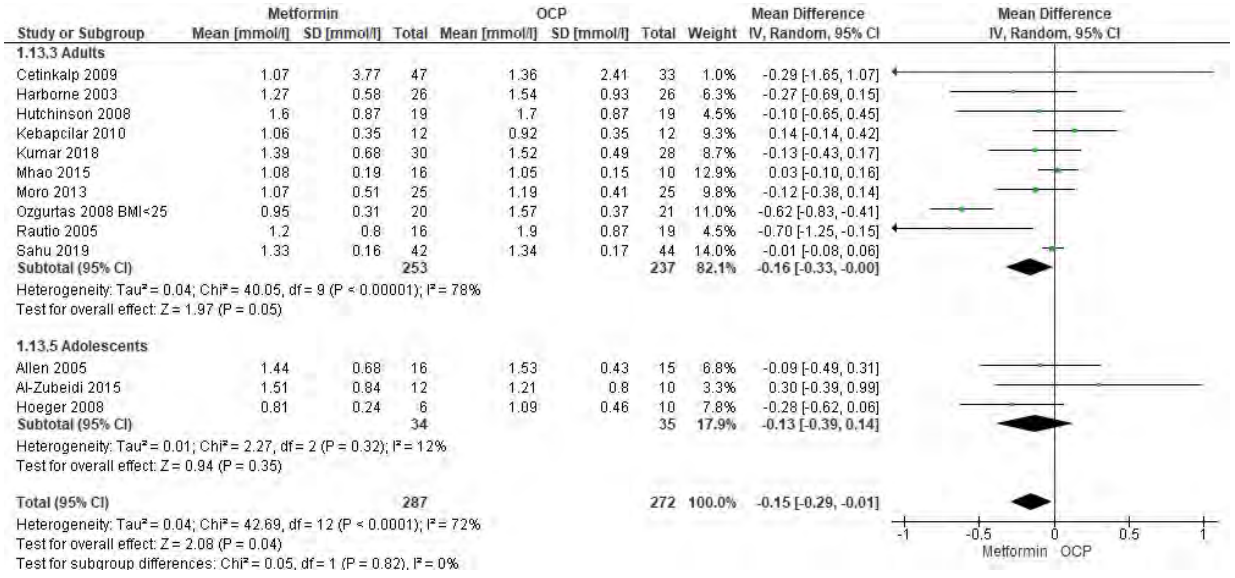
OUTCOME 4.14 Triglycerides (mmol/l)

4.14.1 Individual Study Data Table

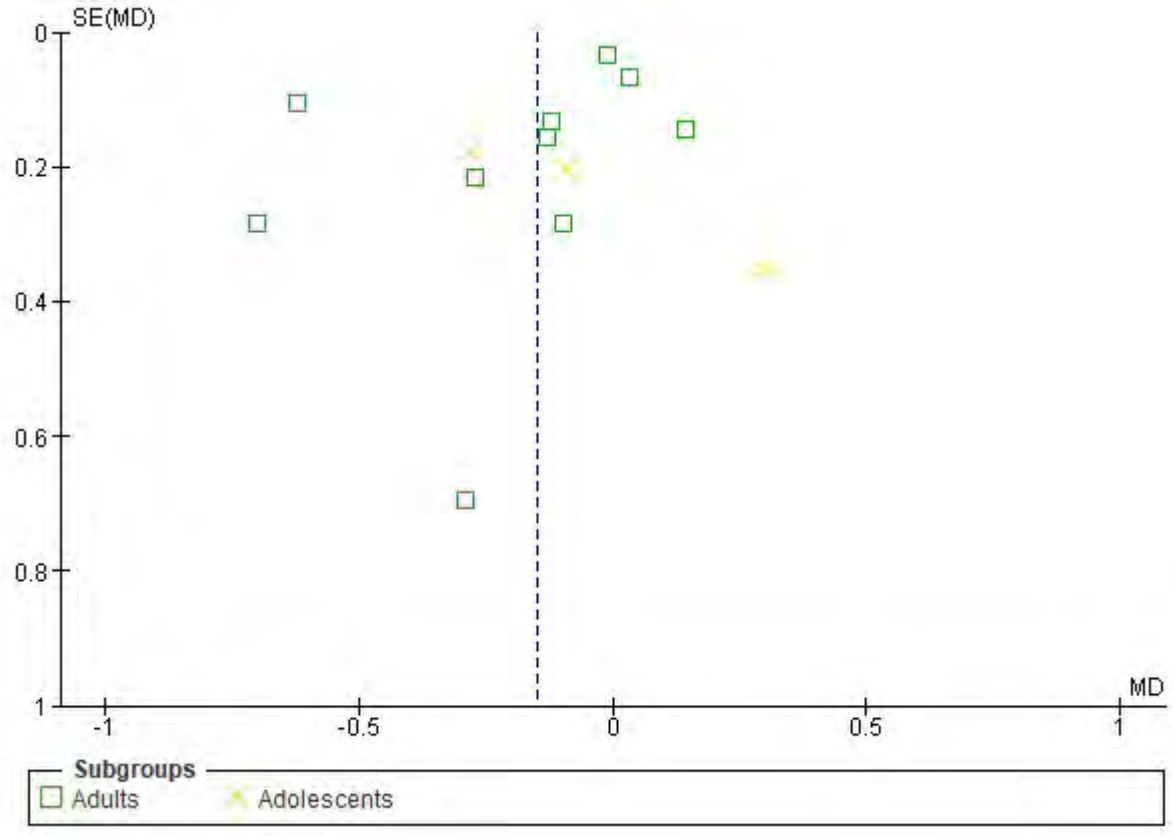
	OUTCOME: Triglycerides					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **OCP**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Sahu et al 2019	mg/dl mmol/l	42	117.5 1.33	13.9 0.16	44	118.5 1.34	15.4 0.17	Crude	6
Kumar et al.2018	Mg/dl Mmol/l	30	123 1.39	60.5 0.68	28	134.1 1.52	43.6 0.49	Crude	6
Harborne et al. 2003	Mmol/l	26	1.27	0.58	26	1.54	0.93	Crude	12
Hutchinson et al 2008	Mmol/l	19	1.6	0.2 (SEM) 0.87 (SD)	19	1.7	0.2 (SEM) 0.87 (SD)	SEM	6
Mhao et al. 2015	Mg/dl Mmol/l	16	95.7 1.08	16.6 0.19	10	92.9 1.05	13.3 0.15		3
Ozgurtas et al. 2008	Mmol/l	20	0.95	0.31	21	1.57	0.37	BMI<25	3
Kebapcilar et al 2010	Mg/dl Mmol/l	12	94 1.06	31 0.35	12	81 0.92	31 0.35		3
Rautio et al. 2005	Mmol/l	16	1.2	0.2 (SE)	19	1.8	0.1 (SE)	Crude	3
		16	1.2	0.2 (SE) 0.8 (SD)	19	1.9	0.2 (SE) 0.87 (SD)		6
Cetinkalp et al 2009	Mg/dl Mmol/l	47	94.8 1.07	48.9 0.55 3.77 (SD)	33	120.7 1.36	37.3 0.42 2.41 (SD)	SEM	4
Hoeger et al. 2008	Mg/dl Mmol/l	6	71.3 0.81	21.1 0.24	10	96.1 1.09	41.1 0.46	Adolescents, obese	6
Moro et al. 2013	Mmol/l	25	1.07	0.51	25	1.19	0.41		6
Allen et al. 2005	Mg/dl Mmol/l	16	127 1.44	15 0.17 0.68 (SEM)	15	135 1.53	10 0.11 0.43 (SEM)	Adolescents	6
Al-Zubeidi et al. 2015 USA	Mg/dl Mmol/l	12	134 1.51	74 0.84	10	107 1.21	71 0.80	adolescents	6

4.14.2. Forrest plot metformin vs OCP for Triglycerides





4.14.3. Funnel plot for assessment of publication bias



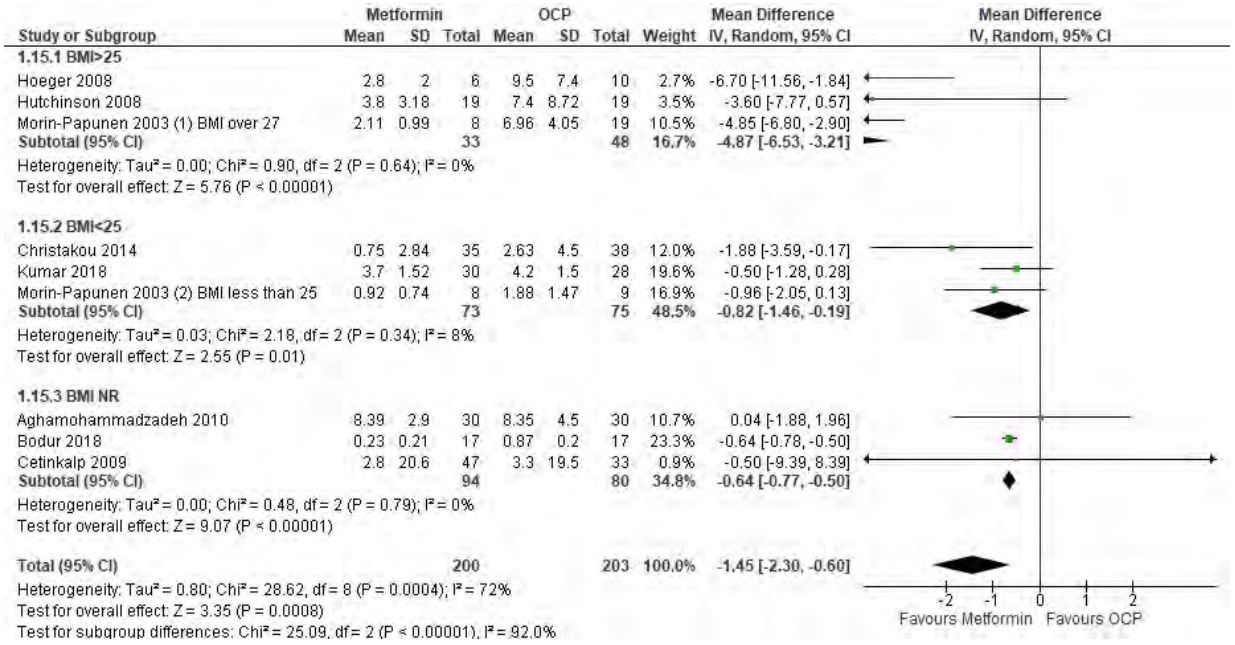
OUTCOME 4.15 CRP (mg/l)

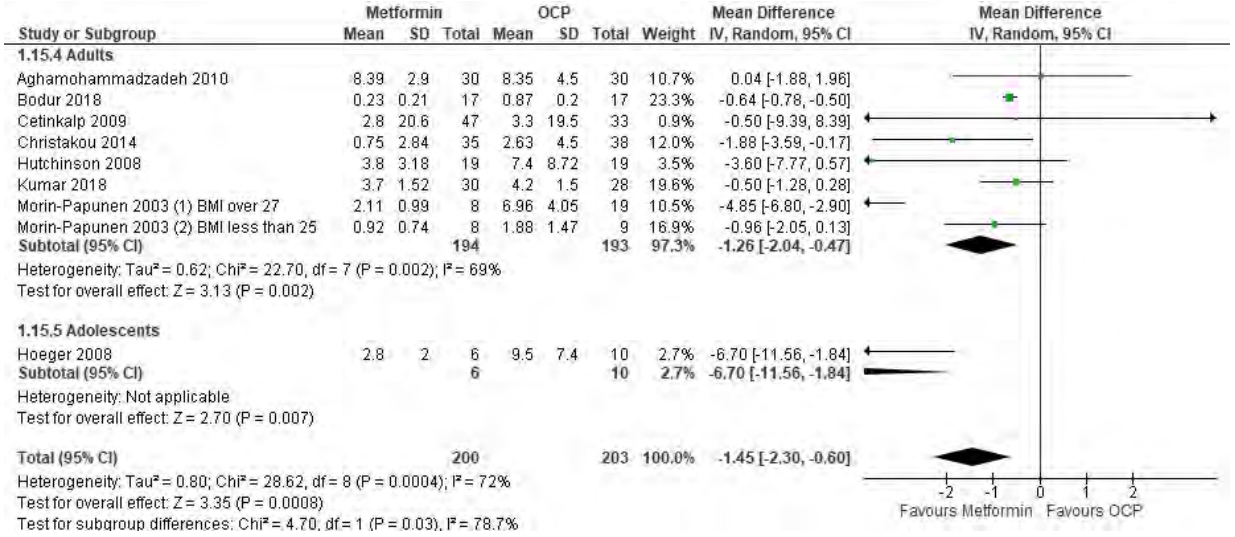
4.15.1 Individual Study Data Table

			OUTCOME: hs-CRP				OUTCOME TYPE: Continuous		
			COMPARISON (if applicable): metformin versus OCP						
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Bodur et al. 2018	Mg/l	17	0.23	0.21	17	0.87	0.20	Crude	6
Kumar et al.2018	Mg/l	30	3.7	1.52	28	4.2	1.5	Crude	6
Hutchinson et al 2008	Mg/l	19	3.8	0.73 (SEM) 3.18 (SD)	19	7.4	2.0 (SEM) 8.72 (SD)	SEM	6
Aghamohammadzadeh et al. 2010 Iran	Mg/l	30	8.27	3.5	30	8.87	3.7	Crude	3
		30	8.39	2.9	30	8.35	4.5		6

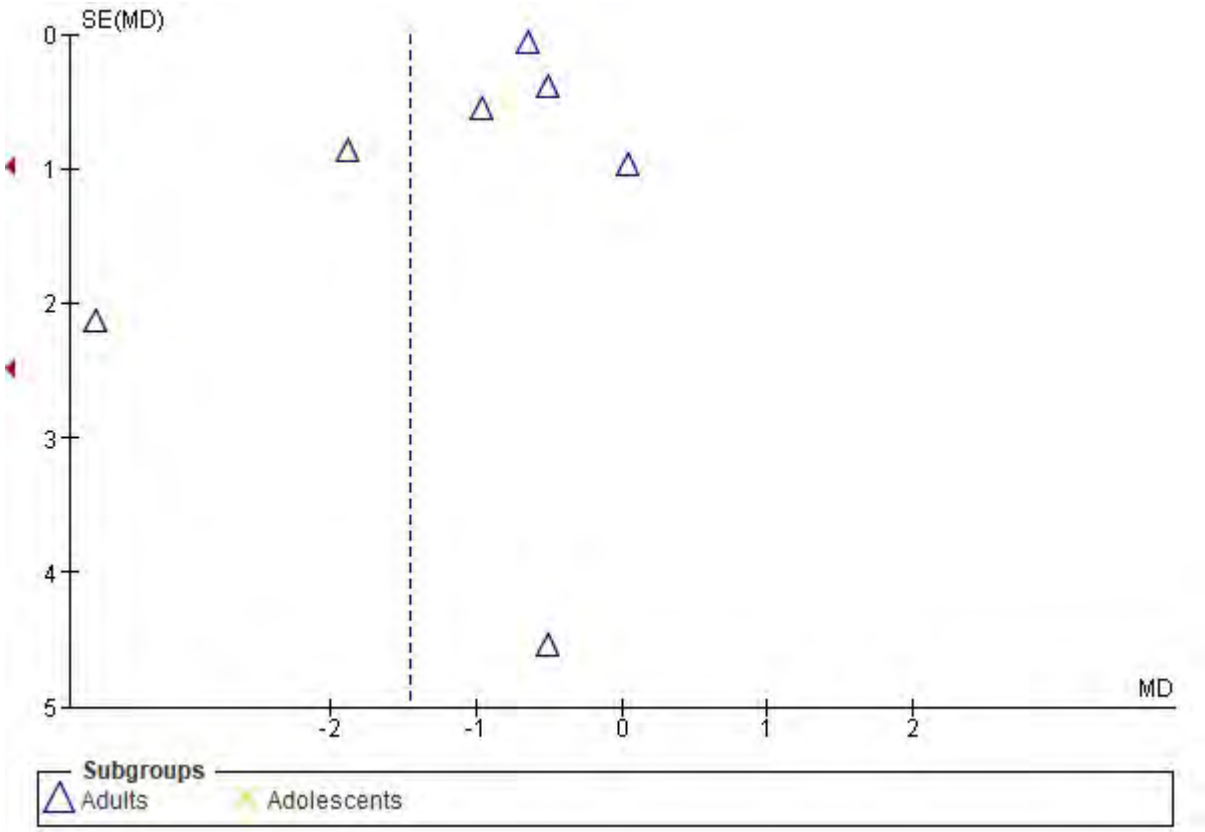
Cetinkalp et al 2009	Mg/dl Mg/l	47	0.28 2.8	0.3 20.6 (SD)	33	0.33 3.3	0.34 19.5 (SD)	SEM	4
Hoeger et al. 2008	Mg/l	6	2.8	2.0	10	9.5	7.4	Adolescents, obese	6
Morin-Papunen et al. 2003 (1)	Mg/l	8	2.11	0.99	19	6.96	4.05	BMI>27 SD	6
Morin-Papunen et al. 2003 (2)	Mg/l	8	0.92	0.74	9	1.88	1.47	BMI<25	6
Christakou	Mg/l	35	0.75	2.84	38	2.63	4.5	CPA	6

4.15.2. Forrest plot metformin vs OCP for CRP





4.15.3. Funnel plot for assessment of publication bias

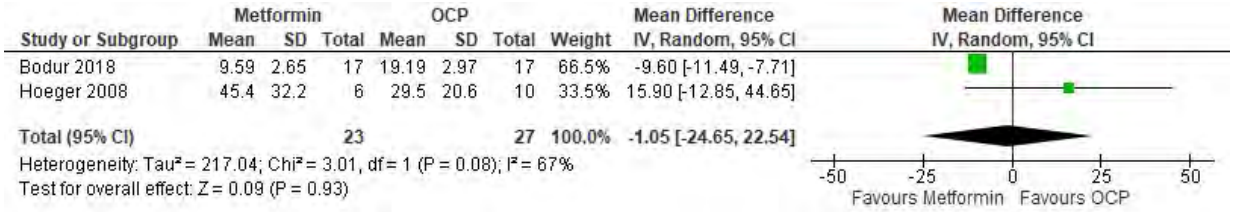


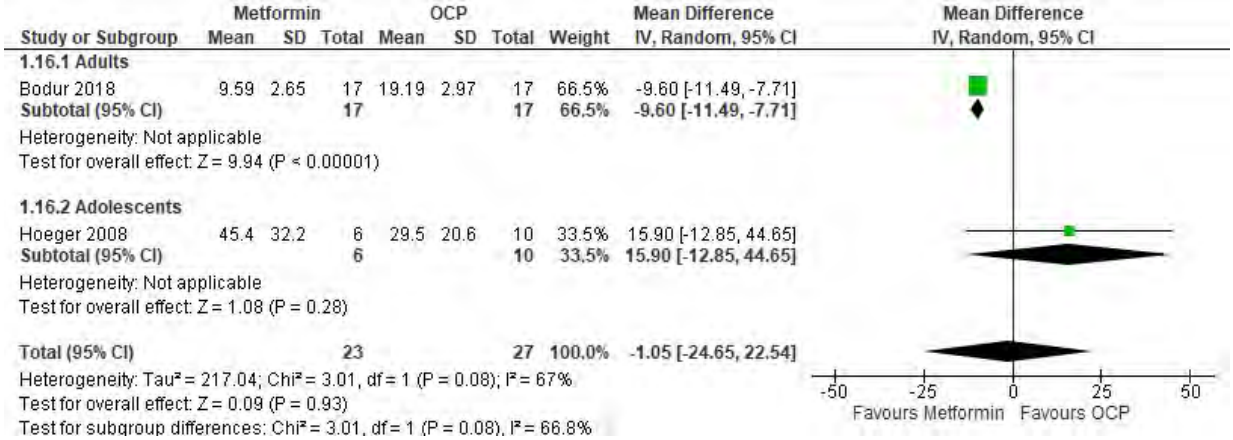
OUTCOME 4.16 PAI-1 (ng/ml)

4.16.1 Individual Study Data Table

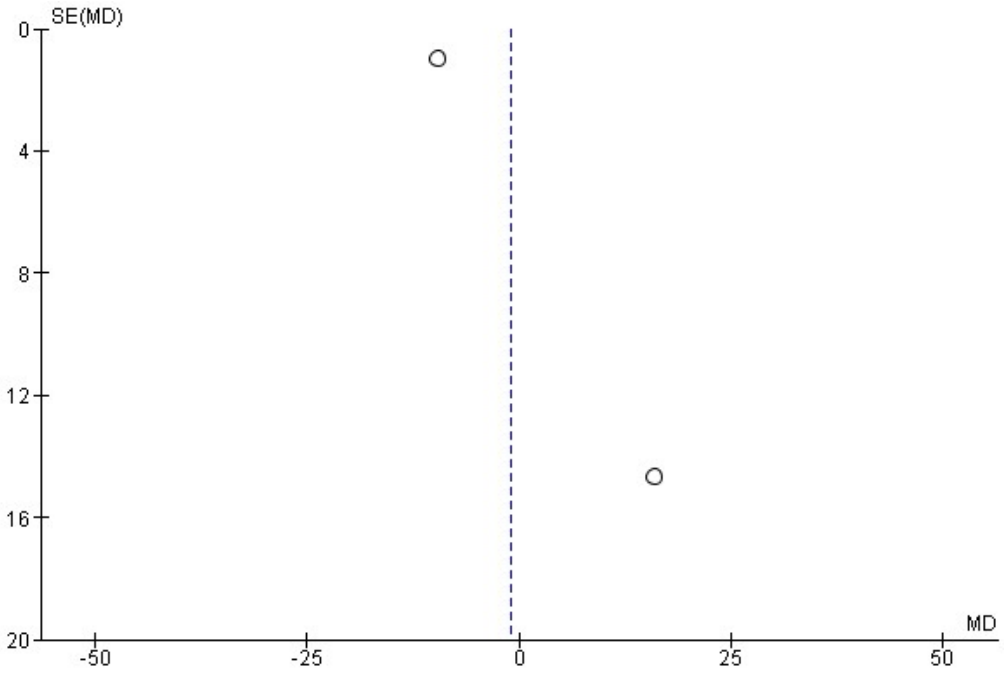
	OUTCOME: PAI-1						**OUTCOME TYPE:** Continuous		
		COMPARISON (if applicable): metformin versus **OCP**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Bodur et al. 2018	Ng/ml	17	9.59	2.65	17	19.19	2.97	Crude	6
Hoeger et al. 2008		6	45.4	32.2	10	29.5	20.6	Adolescents, obese	6

4.16.2. Forrest plot metformin vs OCP for PAI-1





4.16.3. Funnel plot for assessment of publication bias

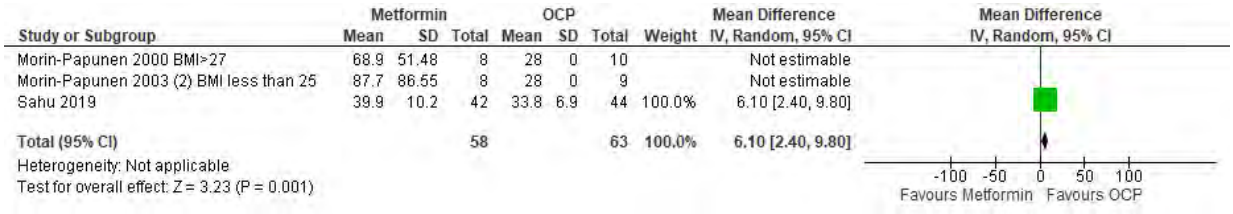


OUTCOME 4.17 Cycle duration (d)

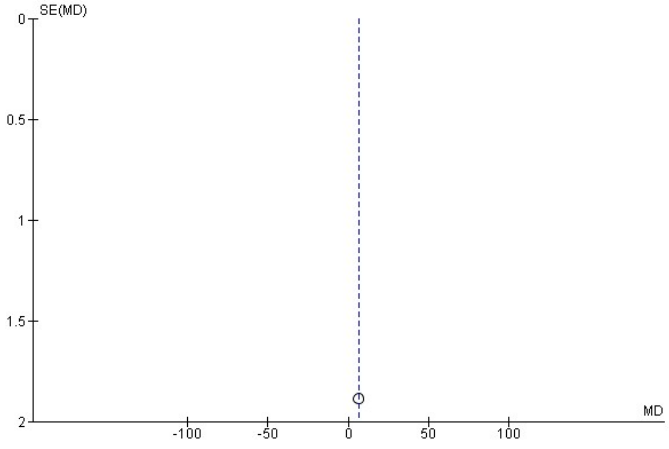
4.17.1 Individual Study Data Table

	OUTCOME: Cycle duration						**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **OCP**								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Sahu et al 2019	days	Self report	42	39.9	10.2	44	33.8	6.9	Crude	6
Morin-Papunen et al. 2003 (2)	days	Self report	8	87.7	30.6 86.55 (SD)	9	28.0	0	SEM BMI <25	6
Morin-Papunen et al. 2000 (1)	days	Self report	8	68.9	18.2 51.48 (SD)	10	28.0	0	SEM BMI>27	6

4.17.2. Forrest plot metformin vs OCP for cycle duration



4.17.3. Funnel plot for assessment of publication bias



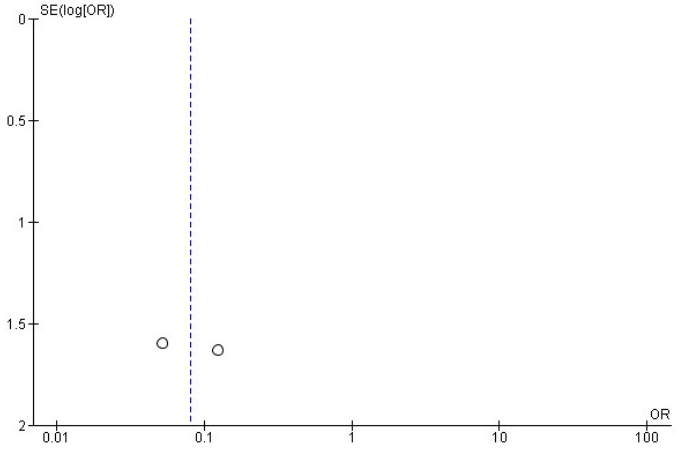
OUTCOME 4.18 Girls with restored menses (n)

4.18.1 Individual Study Data Table

OUTCOME: Girls with restored menses, BMI<25					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): metformin versus OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Something extra?**	**Time period (month)**
Morin-Papunen et al. 2003	No	Self report	4	8	9	9	BMI<25	6
Morin-Papunen et al. 2000 (1)	No	Self report	6	8	10	10	BMI>27	6

4.18.2. Forrest plot metformin vs OCP for girls with restored menses

4.18.3. Funnel plot for assessment of publication bias

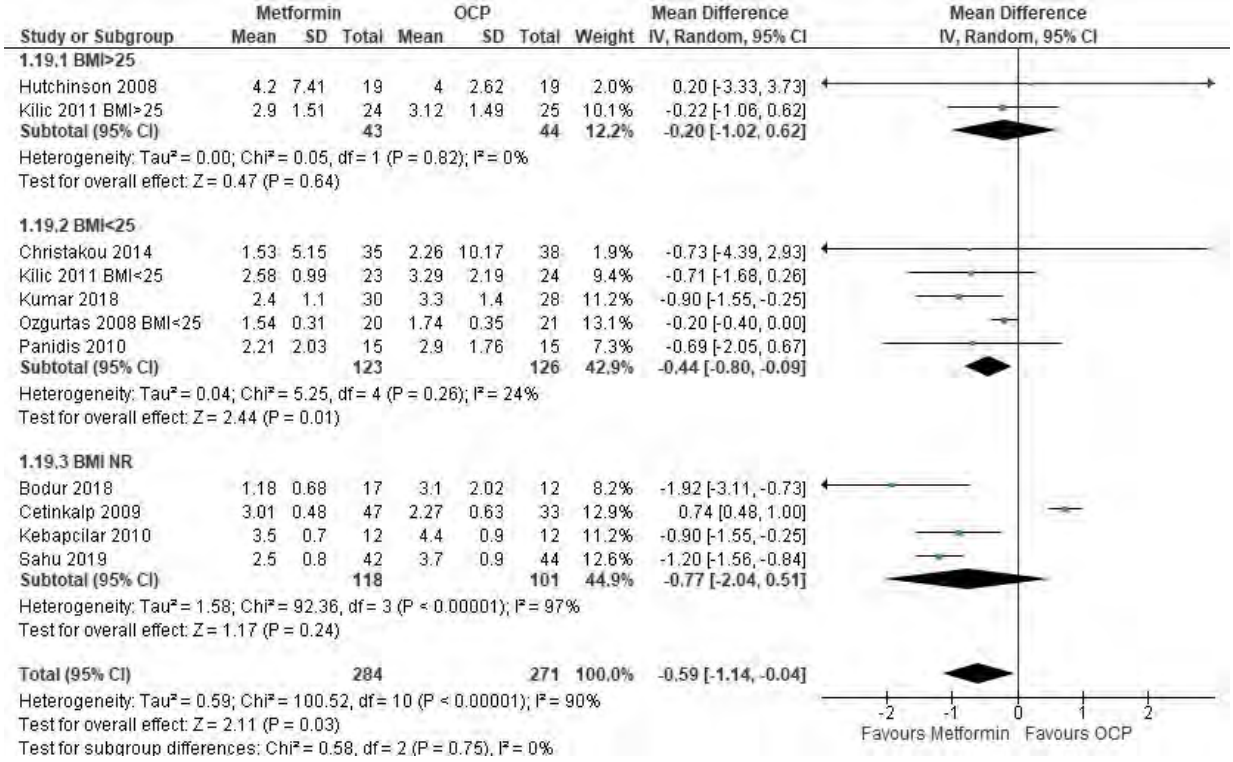


OUTCOME 4.19 HOMA-IR

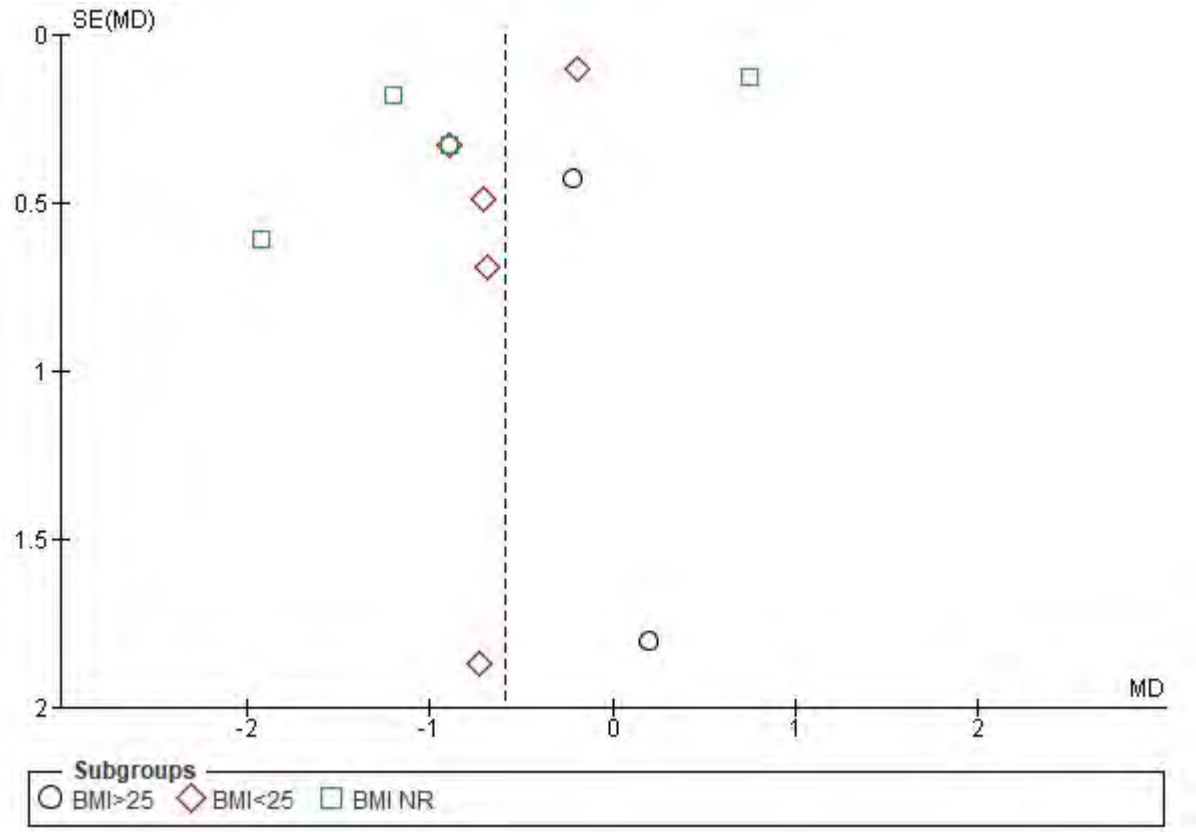
4.19.1 Individual Study Data Table

		OUTCOME: HOMA-IR				**OUTCOME TYPE:** Continuous			
			COMPARISON (if applicable): metformin versus **OCP**						
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Bodur et al. 2018		17	1.18	0.68	12	3.10	2.01	Crude	6
Sahu et al 2019		42	2.5	0.8	44	3.7	0.9	Crude	6
Ozgurtas et al. 2008		20	1.54	0.31	21	1.74	0.35	BMI<25	3
Kumar et al.2018		30	2.4	1.1	28	3.3	1.4	Crude	6
Hutchinson et al 2008		19	4.2	1.7 (SEM) 7.41 (SD)	19	4	0.6 (SEM) 2.62 (SD)	SEM BMI>27	6
Kebapcilar et al 2010		12	3.5	0.7	12	4.4	0.9		3
Cetinkalp et al 2009		47	3.01	0.07 0.48 (SD)	33	2.27	0.11 0.63 (SD)	SEM	4
Al-Zubeidi et al. 2015 USA		12	3.7	Not reported	10	3.2	Not reported	adolescents	6
Kilic et al. 2011		24	2.9	1.51	25	3.12	1.49	BMI>25	6
Kilic et al. 2011		23	2.58	0.99	24	3.29	12.19	BMI<25	6
Christakou et al. 2014		35	1.53	5.15	38	2.26	10.17	CPA	6
Panidis et al. 2010		15	2.21	2.03	15	2.9	1.76	CPA	6

4.19.2. Forrest plot metformin vs OCP for HOMA-IR



4.19.3. Funnel plot for assessment of publication bias



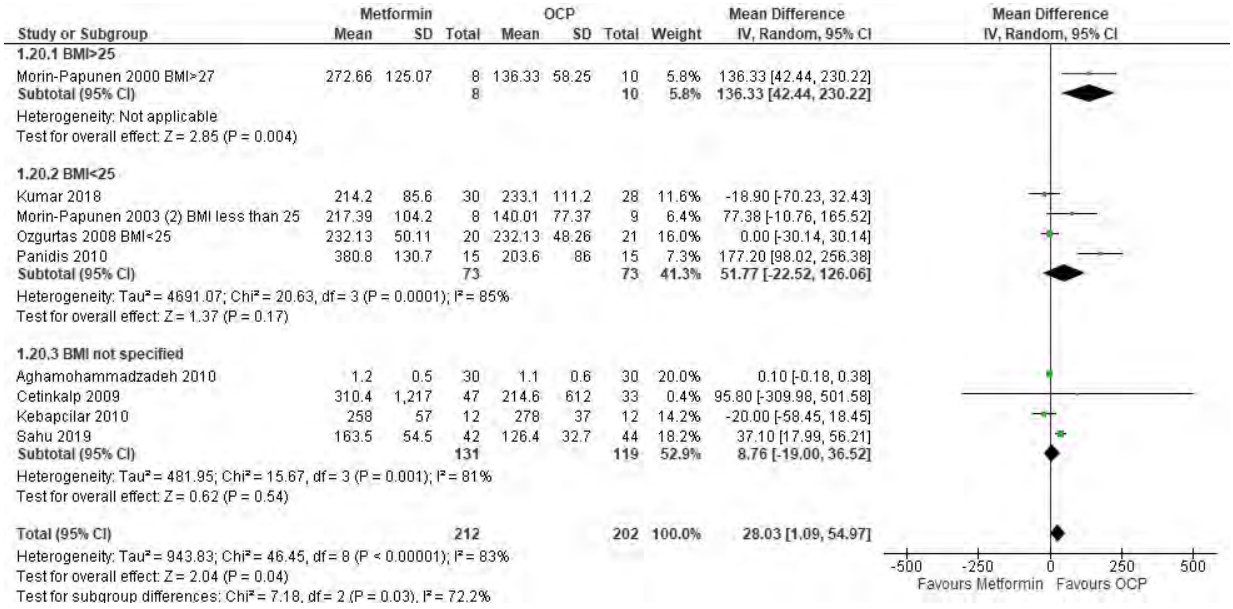
OUTCOME 4.20 DHEAS (ug/dl)

4.20.1 Individual Study Data Table

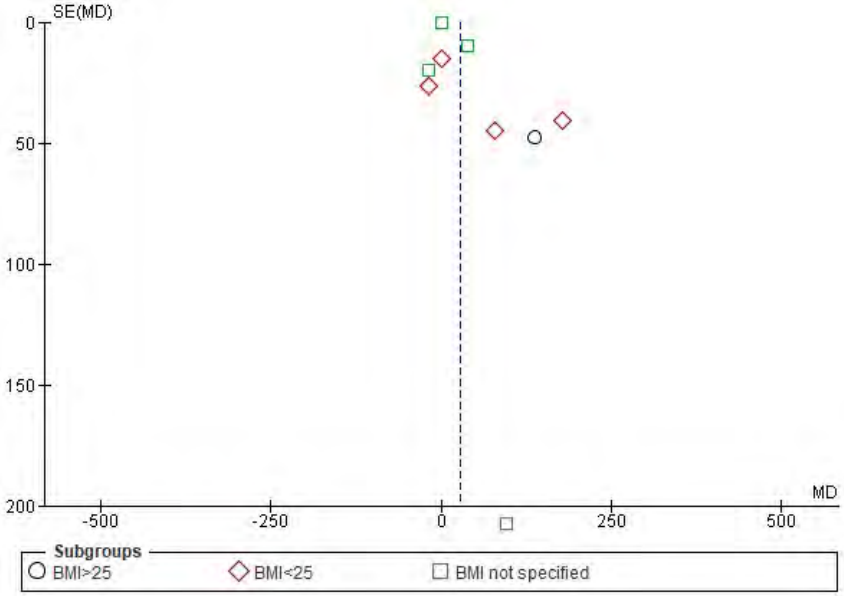
	OUTCOME: DHEAS					OUTCOME TYPE: Continuous			
		COMPARISON (if applicable): metformin versus OCP							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra**	**Time period (month)**
Sahu et al 2019	ug/dl	42	163.5	54.5	44	126.4	32.7	Crude	6
Kumar et al.2018	Ug/dl	30	214.2	85.6	28	233.1	111.2	Crude	6
Ozgurtas et al. 2008	umol/l Ug/dl	20	6.30 232.13	1.36 50.11	21	6.30 232.13	1.31 48.26		3
Kebapcilar et al 2010	Ug/ml Ug/dl	12	258 2.58	57 0.57	12	278 2.78	37 0.37		3
Aghamohammadzadeh et al. 2010 Iran	Ug/dl	30	1.8	0.9	30	1.67	1	Crude	3
		30	1.2	0.5	30	1.1	0.6		6

Cetinkalp et al 2009	Ug/dl	47	310.4	177.6 1217.56 (SD)	33	214.6	106.7 612.94 (SD)	SEM	4
Morin-Papunen et al. 2000	ug/dl	8	272.66	125.07	10	136.33	58.25	BMI>27	6
Morin-Papunen et al. 2003 (2)	Ug/dl	8	217.39	104.2	9	140.01	77.37	BMI<25	6
Panidis et al. 2010	Ug/dl	15	380.8	130.7	15	203.6	86	CPA	6

4.20.2. Forrest plot metformin vs OCP for DHEAS



4.20.3. Funnel plot for assessment of publication bias

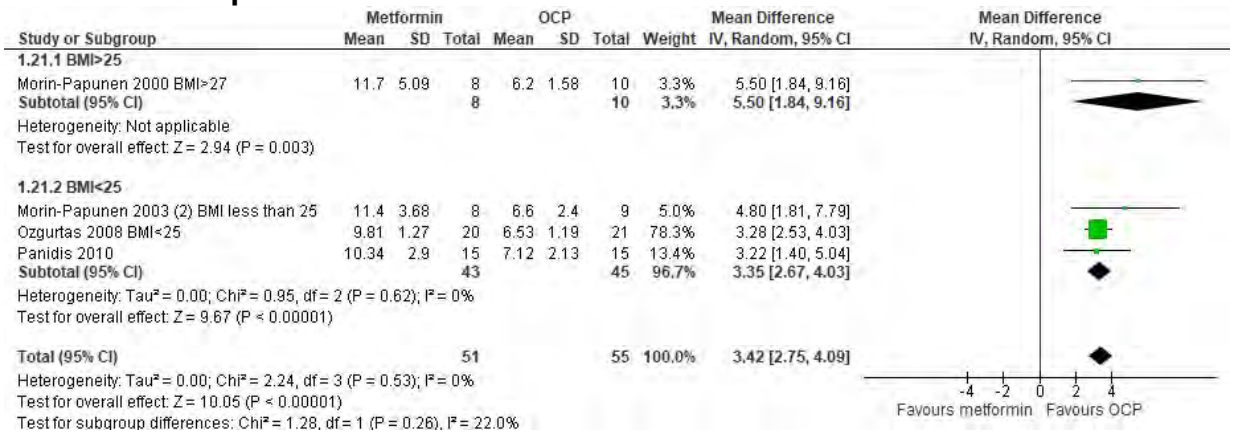


OUTCOME 4.21 Androstenedione (Nmol/l)

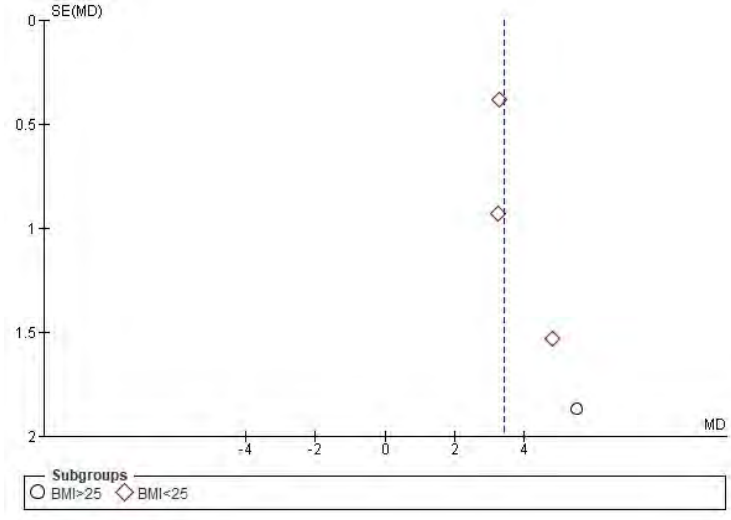
4.21.1 Individual Study Data Table

	OUTCOME: androstenedione					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): Metformin versus **OCP**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Ozgurtas et al. 2008	Nmol/l	20	9.81	1.27	21	6.53	1.19		3
Morin-Papunen et al 2000	Nmol/l	8	11.7	5.09	10	6.2	1.58	BMI>27	6
Morin-Papunen 2003 (2)	Nmol/l	8	11.4	3.68	9	6.6	2.4	BMI<25	6
Panidis et al. 2010	Nmol/l	15	10.34	2.9	15	7.12	2.13	CPA	6

4.21.2. Forrest plot metformin vs OCP for androstenedione



4.21.3. Funnel plot for assessment of publication bias



Adverse outcomes

	Study	metformin	COCP
Gastrointestinal side effects	Christakou 2014	5/40	0/40
	Harborne	3/26	0/26
	Kilic 2011	5/48	0/49
	Luque-Ramírez 2009	2/19	0/15
	Morin-Papunen 2000 (obese)	1/16	0/16
	Morin-Papunen 2003[a] (non-obese)	1/10	0/10
	Moro 2013	2/31	0/31
	Wu 2018	2/19	0/19
Nausea	Glintborg 2014	1/30	0/30
	Bodur 2018	1/29	1/21
Dizziness	Bodur 2018	2/29	0/21
Depression	Glintborg 2014	1/30	0/30
	Harborne	0/26	1/26
Sexual reluctance	Bodur 2018	0/29	1/21
Weight gain	Harborne	0/26	5/26
	Wu 2018	0/19	1/19
Weight loss	Bodur 2018	1/29	0/21
Chest pain	Harborne	0/26	1/26
Other	Dardzinska 2014	15/21 (nausea, abdominal discomfort, vomiting, diarrhoea)	10/35 (nausea, mastodynia, mood changes, abdominal discomfort, vomiting)
	Glintborg 2014	2/30 (as reported above)	3/30 (not reported which)
	El Maghraby 2015	3/32	2/33
	Luque-Ramírez 2009	Hypertension at baseline 18%, after treatment 0%	Hypertension at baseline 13%, after treatment 33%
	Bodur 2018	Pregnancy 4/29 Feeling hunger 1, hypothyroididm 1, hirsutism 1	Pregnancy 1/21, hirsutism 1.

Quality of life

HRQoL	**Favours: No difference**	**Certainty** ⊕◯◯◯ VERY LOW (Due to risk of bias, indirectness, imprecision)					
Author, year	**Measurement**	**N**	**COCP Mean**	**COCP SD**	**Met Mean**	**Met SD**	**P value**
Al-Zubeidi 2015	%	C: 10	69		76		NR

		M: 12					
Dorgham 2021	VAS (scale 0-10)	C 50 M 50	4.2	0.6	3.2	0.4	NR
	Dermatology Life Quality Index	C 50 M 50	1.0	0.6	5.0	1.5	0.001
	Hisutism Life Quality Index 0-22, none to severe problems	C 50 M 50	1.45	0.5	4.45	1.2	0.001
Altinok 2018 (reports median (IQR) differences)	VAS 1: Facial hair growth VAS 2: Body hair growth VAS 3: Acne VAS 4: Menstrual disorder VAS 5: Overweight VAS 6: PCOS		-1.2 (-2.9; -0.2) 0.7 (-2.3; 0.0) -1.8 (-4.0; 0.0) -1.4 (-3.4; 0.2) -0.2 (-2.0;0.7) -0.2 (-2.4;1.0)		0.0 (1.8; 0.2) -0.4 (-1.8; 0.0) -0.4 (-2.0; 0.1) -1 (-4; 0.7) -3.0 (-S.0;-0.2) -1.3 (-3.4;0.S)		<0.05 NR NR NR NR NR
	PF: Physical function RP: Role limitations physical BP: Bodily pain GH: General health VT: Vitality SF: Social function RE: Role limitations emotional MH: Mental health PCS: Summed physical scores MCS: Summed mental scores		0 (-4;6) 0 (0;0) 0 (-16;17) -3 (-6;9) -3 (-15;15) 0 (-16;13) 0 (-33;33) -6 (-16;6) 0 (-5;6) -2 (-11;9)		0 (0;5) 0 (-25;0) 0 (-11;1) 5 (-5;10) 5 (-20;10 0 (-13;13) 0 (-67;33) -2 (-12;8) -1 (-3;2) 1 (-11;5)		NR NR NR NR NR NR NR NR NR NR

Comparison 5: Metformin versus metformin+OCP (also in Q4.2 – not identical)

Evidence Summary

Six randomised controlled trials (RCTs) were identified by our search. Of these RCT, 5 were included in the meta-analysis.
Of these studies three had a moderate ROB and two a high ROB.

Rows highlighted grey indicate studies with participants described as obese (BMI over 25). Rows shaded green indicate that participants had BMI in the normal weight category (BMI under 25). Studies using the same data are coloured in the “author-column”. We performed subgroup analyses based on BMI (<=25, >25 or BMI not specified). All studies in this category were on adult women.

Meta-analysis/descriptive analysis summary

In the meta-analysis, metformin only was superior in lowering WHR, fasting glucose, total cholesterol and triglycerides (certainty low to very low), whereas a combination of metformin and ocp was superior in lowering testosterone (certainty low) and DHEAS (certainty very low). For other outcomes, no difference was observed. Certainty in the evidence is low or very low since the studies were moderate or high risk of bias and many studies had only a small amount of participants.

Regarding individual studies, not included in the meta-analysis, Glintborg et al. found that BMI was significantly lower after using metformin only compared to combination therapy, whereas SHBG was higher among those using combination therapy. Kumar et al. found that the metformin+OCP combination was superior when treating hirsutism. Kebapcilar et al. found that free testosterone was lower among those using combination therapy compared to those using metformin only. Glintborg et al. and Moro et al found that FAI was significantly lower after treatment with Metformin+OCP compared to metformin only. Certainty in the evidence for the individual studies are low or very low since the studies were moderate or high risk of bias and all studies had only a small amount of participants.
Only a few studies reported adverse effects separately for both groups. According to these, the risk of adverse effects appears to be fairly similar in both groups (see table at the end of this document).

Author, year, country	Population	Sample Size per group	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Type of analysis and subgroup	ROB
Kumar et al. 2018 India	newly diagnosed PCOS (age 18–40 year, symptom duration >6 months)	1.Metformin=30 2. OCP=28 3.Metformin+OCP=29	6 months	1.27.1 ±6 2.26.15 ±4.9 3.30.1 ±5.5	1.22±5.2 2.22.9±5 3.24.1 ±5.9	Weight, BMI, mFGS, T, f-insulin, f-gluk, crp, lipids, HOMA	META Adults	**ROB Moderate**
Wu et al 2008 China	Women with PCOS, aged 19-35yr, divided into obese (BMI>25) and non-obese (BMI<25)	1.Metformin obese=7 2.OCP obese=7 3. Metformin+OCP obese=6 4.Metformin non-obese=11 5.OCP non obese=12 6.Metformin+OCP non obese=10	3 months	1.25.6± 0.6 2.25.3 ±0.8 3.25.2 ±1.0 4.21.5± 1.8 5.21.4 ±1.6 6.21.6 ±1.4	1.25.6± 3.6 2.25.0 ±4.3 3.24.5 ±2.4 4.25.6± 4.2 5.26.1 ±4.6 6.25.8 ±4.0	WHR, BMI, T, f-insulin	META Adults BMI>25 BMI<25	ROB Moderate
Kebapcilar et al 2010 Turkey	Women with PCOS (24.0+/- 5.4 yr; BMI 27.9 +/-5.28)	1.Metformin=12 2.Metformin+OCP=12 3. OCP=12 4.OCP+SPL=12	3 months	1.27.8± 4 2.27.6 ±3 3.28.7 ±6 4.27.6±4	1.24.4± 6.2 2.24.9 ±4.8 3.23.2 ±5.1 4.23.4± 5.8	BMI, free-T, f-insulin, lipids, HOMA	META Adults	**ROB high**
Bodur et al 2018 Turkey	18–39 year old, non-obese (18–30 BMI) women with PCOS	1. metformin N=17 2. OCP N=17 3.OCP+metformin=12 4. Control=15	6 months	1.25.06 ± 3.08 2.23.45 ±3.40 3.23.82 ±2.80	1.26.24 ± 3.96 2.26.62 ±4.92 3.27.35 ±5.65	f-gluk, PAI, HOMA	META Adults BMI<30	**ROB High**
Moro et al. 2013 Italy	Women with PCOS aged 18 to 35 years	1.Metformin=25 2.OCP=25 3.Metformin+OCP=26	6 months	1.23.7 (20.8-28.6) 2.25.1 (21.9-28.3)	1.25±5 2.26±3 3.25±4	FAI, T, lipids, BMI, WHR	META Individual Adults BMI<25	**ROB Moderate**

				3.26.5 (21.3-30) Median (range)				
Glintborg et al. 2014 (1) Denmark	White women with PCOS, aged 18-39 years, BMI <35	1. metformin N=19 2. OCP N=23 3.OCP+metformin=23	12 months	1: 25.1 (22.7–29.4)* 2: 27.3 (22.7–31.1)* 3:27.3 (24.0–30.5)P	1: 29 [24-32]* 2: 28 [23-30]* 3:30 (24-32)*	Changes in weight, bmi, f-gluc, T, SHBG, insulin, homa, mFGS	Individual median (25th and 75th quartiles)	Outcomes also reported in Altinok 2018, Glintoborg 2014 and Glintborg 2017 **ROB high**
Glintborg et al. 2014 (2) Denmark	White women with PCOS, aged 18-39 years, BMI <35	1. metformin N=19 2. OCP N=23 3.OCP+metformin=23	12 months	1: 25.1 (22.7–29.4)* 2: 27.3 (22.7–31.1)* 3:27.3 (24.0–30.5)P	1: 29 [24-32]* 2: 28 [23-30]* 3:30 (24-32)*	No data extracted	Individual median (25th and 75th quartiles)	Outcomes also reported in Altinok 2018, Glintborg 2014 and Glintborg 2017 **(ROB high)**

Results of meta-analysis

Whenever possible, results were subgrouped based on BMI (<=25, >25 or not specified)

Outcome	Time point	RCTs	N	Effect, random, MD	P-value	I2 (%)	Favours	Certainty
Weight (kg)		4	117	-1.31 (-2.65 to 0.03)	0.06	46	No difference	⊕⊕◯◯ LOW
Sub:BMI<25		2	80	-1.38 (-3.85 to 1.09)	0.27	59	No difference	⊕⊕◯◯ LOW
WHR		**2**	**34**	**-0.03 (-0.06 to -0.01)**	**0.002**	**0**	**Metformin**	⊕◯◯◯ VERY LOW
BMI kg/m2		2	34	-1.31 (-3.07 to 0.46)	0.15	67	No difference	⊕◯◯◯ VERY LOW
Testosterone (nmol/l)		**4**	**144**	**0.64 (0.26 to 1.02)**	**0.0009**	**60**	**Metformin+OCP**	⊕⊕◯◯ LOW
Sub:BMI<25		**3**	**131**	**0.71 (0.29 to 1.13)**	**0.0001**	**66**	**Metformin+OCP**	⊕⊕◯◯ LOW
Fasting insulin mIU/l)		4	117	-0.48 (-2.54 to 1.58)	0.65	36	No difference	⊕⊕◯◯ LOW
Sub:BMI<25		2	80	-1.38 (-4.60 to 1.85)	0.40	55	No difference	⊕◯◯◯ VERY LOW
Fasting glucose (mg/dl)		**2**	**88**	**-5.90 (-11.58 to -0.22)**	**0.04**	**47**	**Metformin**	⊕◯◯◯ VERY LOW
Total cholesterol (mmol/l)		**3**	**134**	**-23.83 (-47.59 to -0.07)**	**0.05**	**79**	**Metformin**	⊕◯◯◯ VERY LOW
Sub:BMI<25		**2**	**110**	**-34.95 (-51.41 to -18.49)**	**<0.0001**	**43**	**Metformin**	⊕⊕◯◯ LOW
HDL (mmol/l)		3	134	-2.69 (-6.79 to 1.40)	0.20	12	No difference	⊕⊕◯◯ LOW
Sub:BMI<25		2	110	-2.33 (-8.38 to 3.73)	0.45	45	No difference	⊕⊕◯◯ LOW
LDL (mmol/l)		3	134	-5.54 (-17.65 to 6.57)	0.37	58	No difference	⊕◯◯◯ VERY LOW

Sub:BMI<25		2	110	-10.52 (-21.11 to 0.06)	0.05	24	No difference	⊕⊕◯◯ LOW
Triglycerides (mmol/l)		3	134	-17.86 (-63.12 to 27.40)	0.44	90	No difference	⊕◯◯◯ VERY LOW
Sub:BMI<25		**2**	**110**	**-38.59 (-57.32 to -19.86)**	**<0.0001**	**0**	**Metformin**	⊕⊕◯◯ LOW
HOMA-IR		3	112	-1.28 (-2.92 to 0.35)	0.12	92	No difference	⊕◯◯◯ VERY LOW
Sub: BMI not specified		2	53	-1.58 (-5.16 to 2.00)	0.39	96	No difference	⊕◯◯◯ VERY LOW
DHEAS (ug/dl)		**2**	**118**	**30.36 (5.69 to 55.03)**	**0.02**	**0**	**Metformin+OCP**	⊕◯◯◯ VERY LOW

Individual studies not included in meta-analysis

Outcome	Author, year	Time point	N	Metformin	Metformin+OCP	P-value	Favours	Grading
Weight	Glintborg et al. 2014 Glintborg et al. 2017 Altinok et al 2018	12 months	M=19 OCP+M=23	Median change (25th and 75th quartiles) -3.0 (-10.3 to 0.6)	Median change (25th and 75th quartiles) -1.9 (-4.9 to 3.0)	<0.05	**Metformin**	⊕◯◯◯ VERY LOW[1]
WHR	Moro et al. 2013	6 months	M=25 OCP+M=26	Median (range) 0.84 (0.80-0.87)	Median (range) 0.81 (0.77-0.85)	NR	NR	⊕⊕◯◯ LOW[2]
BMI	Glintborg et al. 2014 Glintborg et al. 2017 Altinok et al 2018	12 months	M=19 OCP+M=23	Median change (25th and 75th quartiles) -1.0 (-3.7 to 0.2)	Median change (25th and 75th quartiles) -0.78 (-1.76 to 0.03)	<0.05	**Metformin**	⊕◯◯◯ VERY LOW[1]
	Moro et al. 2013	6 months	M=25 OCP+M=26	Median (range) 23.5 (20.4-28.3)	Median (range) 24.5 (21.2-30)	NR	NR	⊕⊕◯◯ LOW[2]
Hirsutism	Glintborg et al. 2014 Glintborg et al. 2017 Altinok et al 2018	12 months	M=19 OCP+M=23	Median change (25th and 75th quartiles) 0 (-2 to 1)	Median change (25th and 75th quartiles) -4 (-7 to 0)	NR	No difference	⊕◯◯◯ VERY LOW[1]
	Kumar et al. 2018	6 months	M=30 M+OCP=29	Mean and SD 7.3 +/- 3.9	Mean and SD 4.6 +/- 2.8	NR	**Met+OCP**	⊕⊕◯◯ LOW[2]
SHBG (nmol/l)	Moro et al. 2013	6 months	M=25 OCP+M=26	Median (range) 22.5 (15-56.5)	Median (range) 166.8 (149.5-239)	NR	NR	⊕⊕◯◯ LOW[2]
	Glintborg et al. 2014 Glintborg et al. 2017 Altinok et al 2018	12 months	M=19 OCP+M=23	Median change (25th and 75th quartiles) 9 (-2 to 19)	Median change (25th and 75th quartiles) 106 (59 to 175)	<0.05	**Met+OCP**	⊕◯◯◯ VERY LOW[1]
Testosterone	Glintborg et al. 2014 Glintborg et al. 2017 Altinok et al 2018	12 months	M=19 OCP+M=23	Median change (25th and 75th quartiles) -0.35 (-0.97 to -0.06)	Median change (25th and 75th quartiles) -0.42 (-1.19 to 0.01)	NR	No difference	⊕◯◯◯ VERY LOW[1]
Free testosterone	Kebapcilar et al. 2010	12 months	M=12 OCP+M=12	Mean and SD 3.8 +/- 0.7	Mean and SD 3.3 +/- 1.0	<0.05	**Met+OCP**	⊕⊕◯◯ LOW[2]
Fasting insulin	Glintborg et al. 2014 Glintborg et al. 2017	12 months	M=19 OCP+M=23	Median change (25th and 75th quartiles) 2 (-22 to 16)	Median change (25th and 75th quartiles) -8 (-18 to 6)	NR	No difference	⊕◯◯◯ VERY LOW[1]

	Altinok et al 2018							
PAI	Bodur et al. 2018	6 months	M=17 M+OCP=12	Mean and SD 9.59 +/- 2.65	Mean and SD 19.40 +/- 1.89	<0.05	**Metformin**	⊕⊕◯◯ LOW[2]
HOMA-IR	Glintborg et al. 2014 Glintborg et al. 2017 Altinok et al 2018	12 months	M=19 OCP+M=23	Median change (25th and 75th quartiles) -0.2 (-5.5 to 4.1)	Median change (25th and 75th quartiles) -0.6 (-5.1 to 1.8)	NR	No difference	⊕◯◯◯ VERY LOW[1]
FAI	Glintborg et al. 2014 Glintborg et al. 2017 Altinok et al 2018	12 months	M=19 OCP+M=23	Median change (25th and 75th quartiles) -0.007 (-0.019 to 0.004)	Median change (25th and 75th quartiles) -0.019 (-0.029 to -0.014)	<0.05	**Met+OCP**	⊕◯◯◯ VERY LOW[1]
	Moro et al. 2013	6 months	M=25 OCP+M=26	Mean and SD 9.9 +/- 5	Mean and SD 1.1 +/- 0.4	<0.05	**Met+OCP**	⊕⊕◯◯ LOW[2]

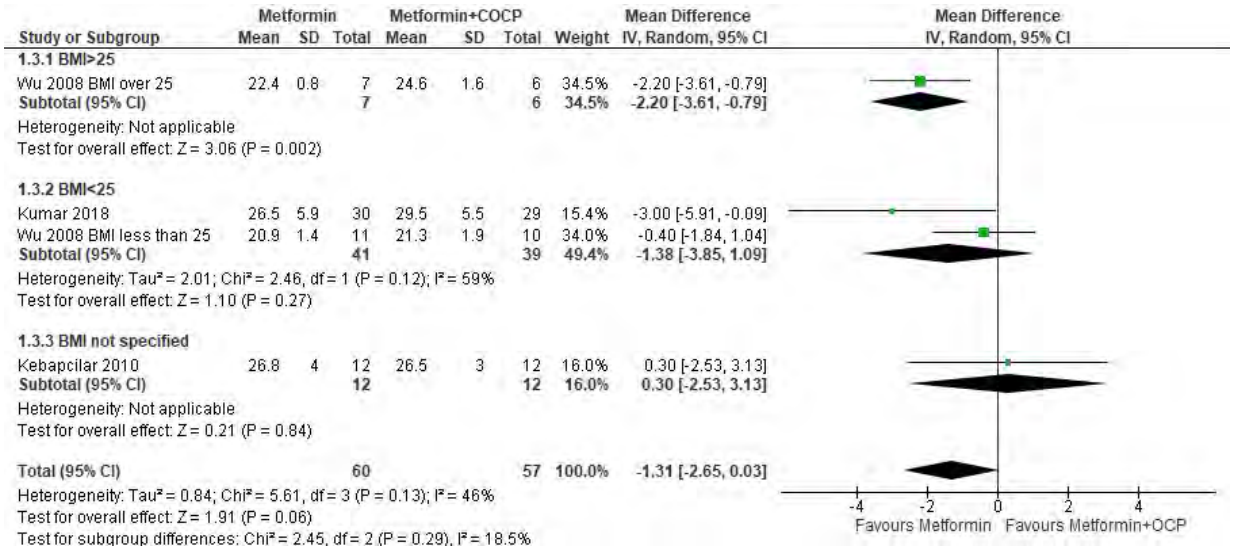
[1]Downgraded twice for high ROB and downgraded once for small number of participants
[2] Downgraded once for mod ROB and downgraded once for small number of participants

OUTCOME 5.1 Weight (kg)

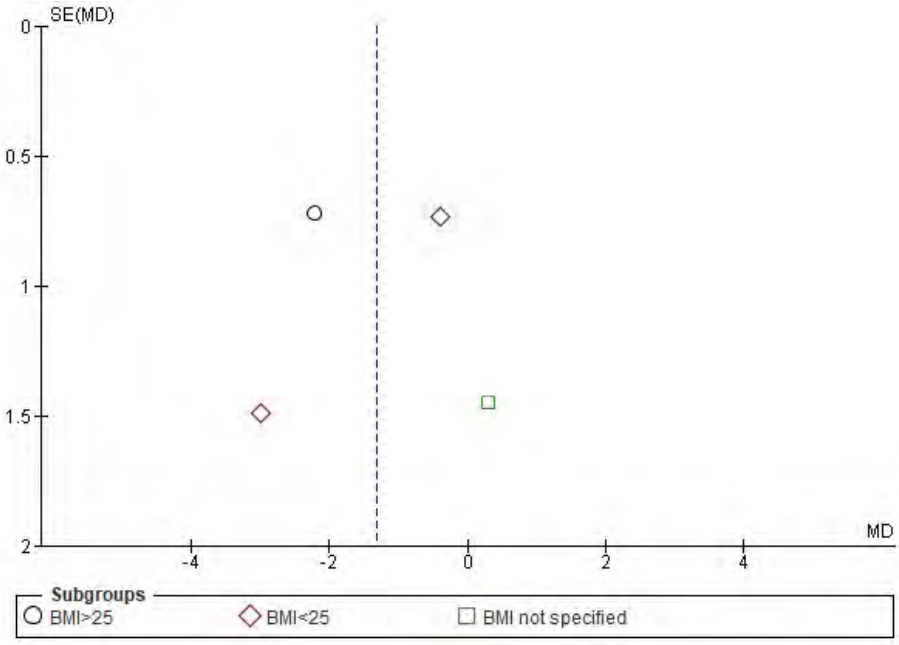
5.1.1 Individual Study Data Table

	OUTCOME: Weight				**OUTCOME TYPE:** Continuous					
	COMPARISON (if applicable): metformin versus **metformin+ OCP**									
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Wu et al. 2008	kg	weighted	7	22.4	0.8	6	24.6	1.6	BMI>25	3
Kumar et al.2018	kg	weighted	30	66.6	13.8	29	75.5	13.9	Crude	6
Wu et al. 2008	kg	weighted	7	20.9	1.4	6	21.3	1.9	BMI<25	3
Kebapcilar et al. 2010	kg	weighted	12	26.8	3	12	26.5	3		3

5.1.2. Forest plot metformin vs OCP for weight



5.1.3. Funnel plot for assessment of publication bias

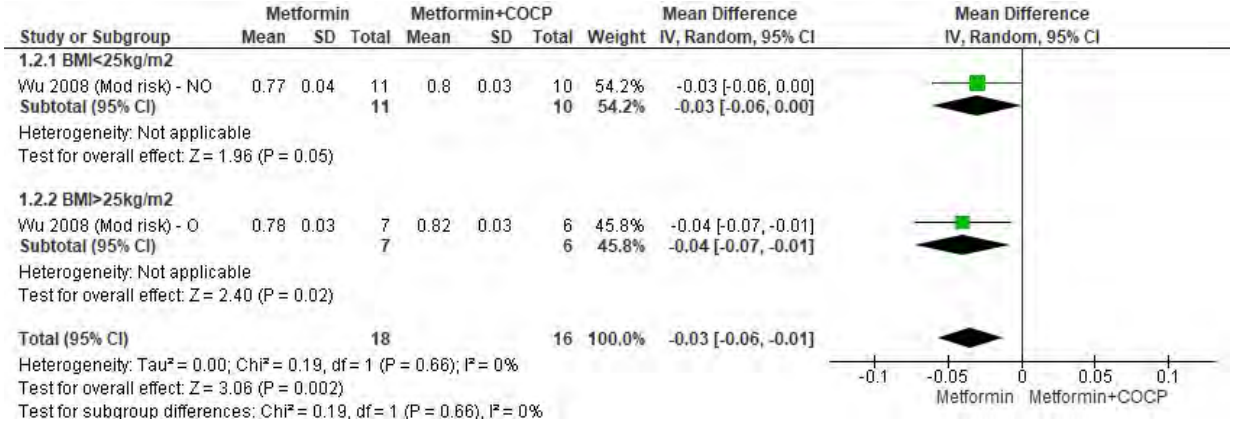


OUTCOME 5.2 WHR

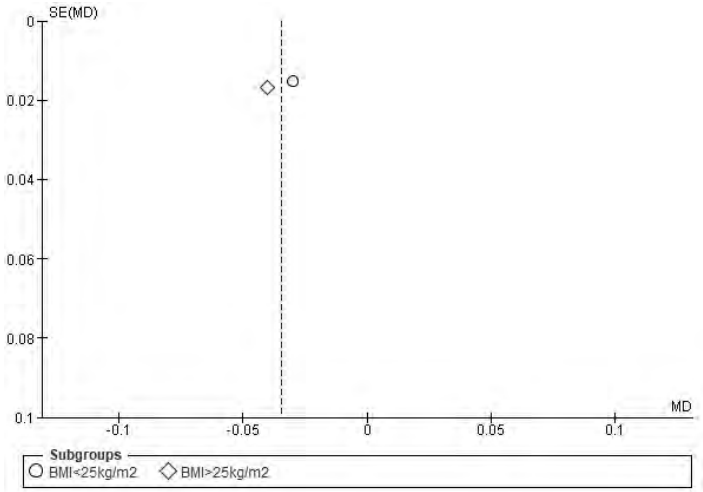
5.2.1 Individual Study Data Table

	OUTCOME: WHR					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **metformin+OCP**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Wu et al 2008		11	0.77	0.04	10	0.80	0.03	BMI<25	3
Wu et al 2008		11	0.78	0.03	10	0.82	0.03	BMI>25	3

5.2.2. Forrest plot metformin vs OCP for WHR



5.2.3. Funnel plot for assessment of publication bias

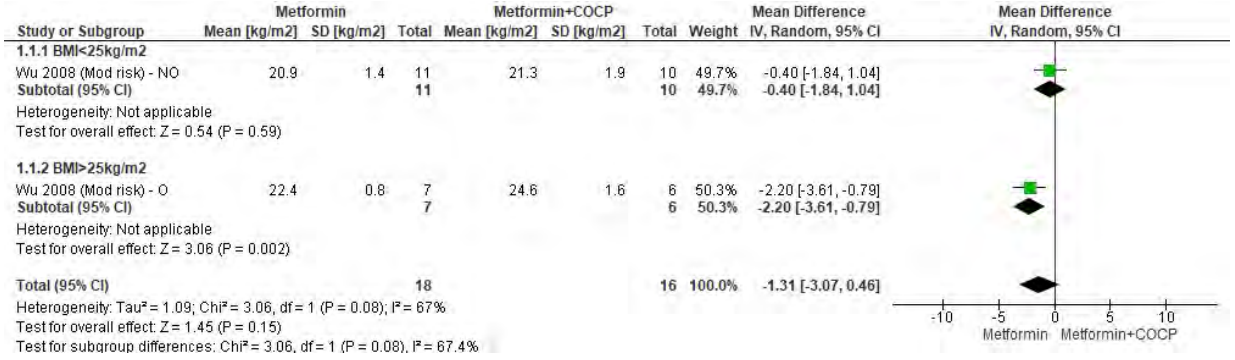


OUTCOME 5.3 BMI (kg/m2)

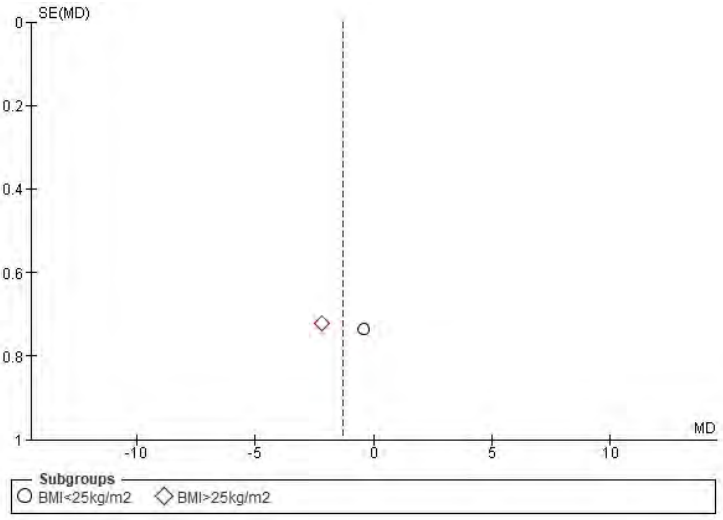
5.3.1 Individual Study Data Table

	OUTCOME: BMI					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **metformin+OCP**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Wu et al 2008	Kg/m2	11	20.9	1.4	10	21.3	1.9	BMI<25	3
Wu et al 2008	Kg/m2	7	22.4	0.8	6	24.6	1.6	BMI>25	3

5.3.2. Forrest plot metformin vs OCP for BMI



5.3.3. Funnel plot for assessment of publication bias

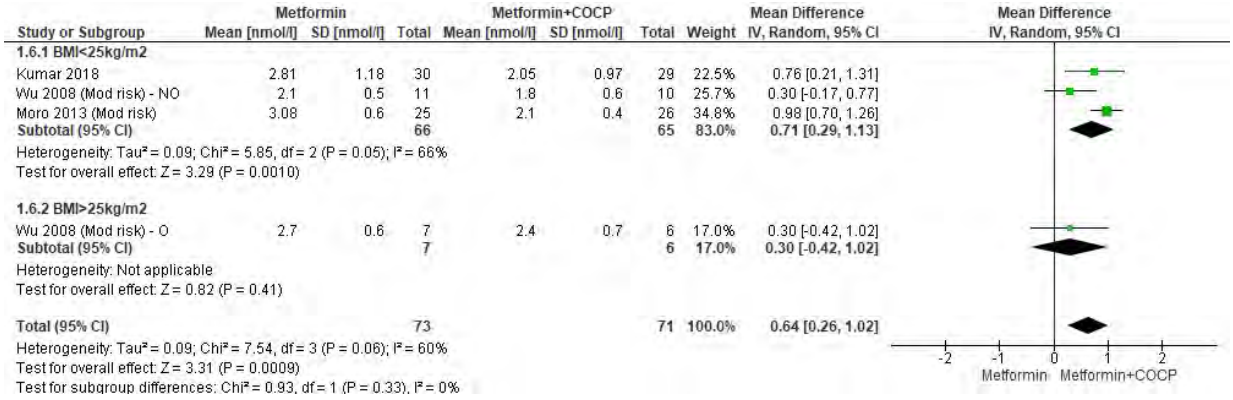


OUTCOME 5.4 Testosterone (Nmol/l)

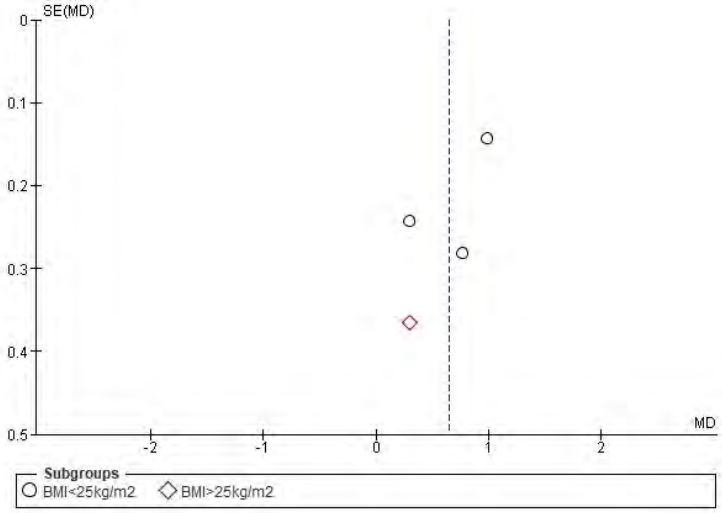
5.4.1 Individual Study Data Table

	OUTCOME: testosterone					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **metformin+OCP**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Kumar et al.2018	Ng/ml Nmol/l	30	0.81 2.81	0.34 1.18	29	0.59 2.05	0.28 0.97	Crude	6
Moro et al. 2013	Nmol/l	25	3.08	0.6	26	2.1	0.4		6
Wu et al 2008	Nmol/l	11	2.1	0.5	10	1.8	0.6	BMI<25	3
Wu et al 2008	Nmol/l	7	2.7	0.6	6	2.4	0.7	BMI>25	3

5.4.2. Forrest plot metformin vs OCP for Testosterone



5.4.3. Funnel plot for assessment of publication bias

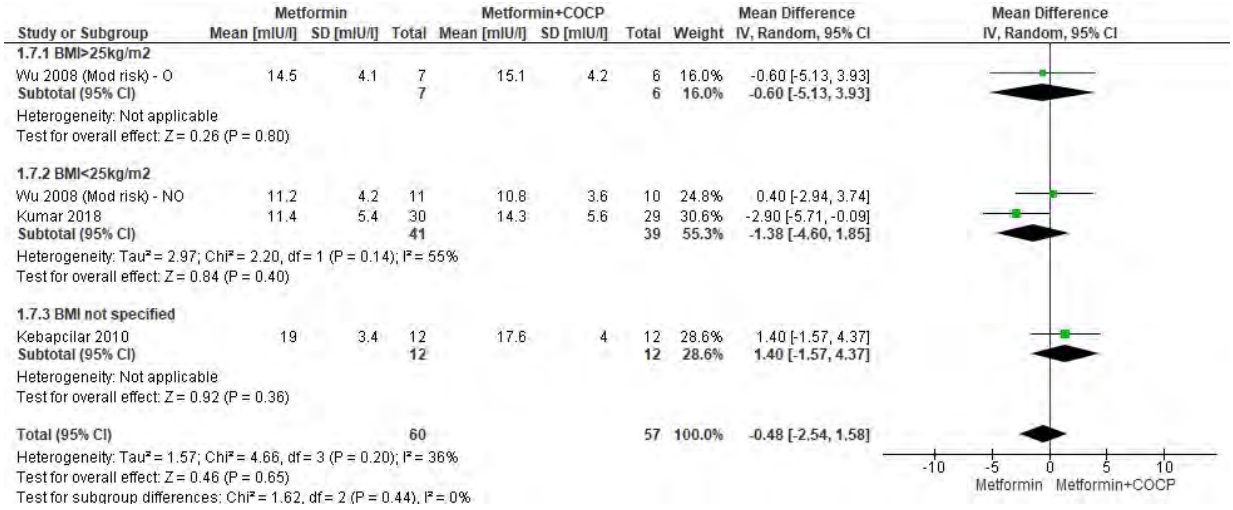


OUTCOME 5.5 Fasting insulin (uIU/ml)

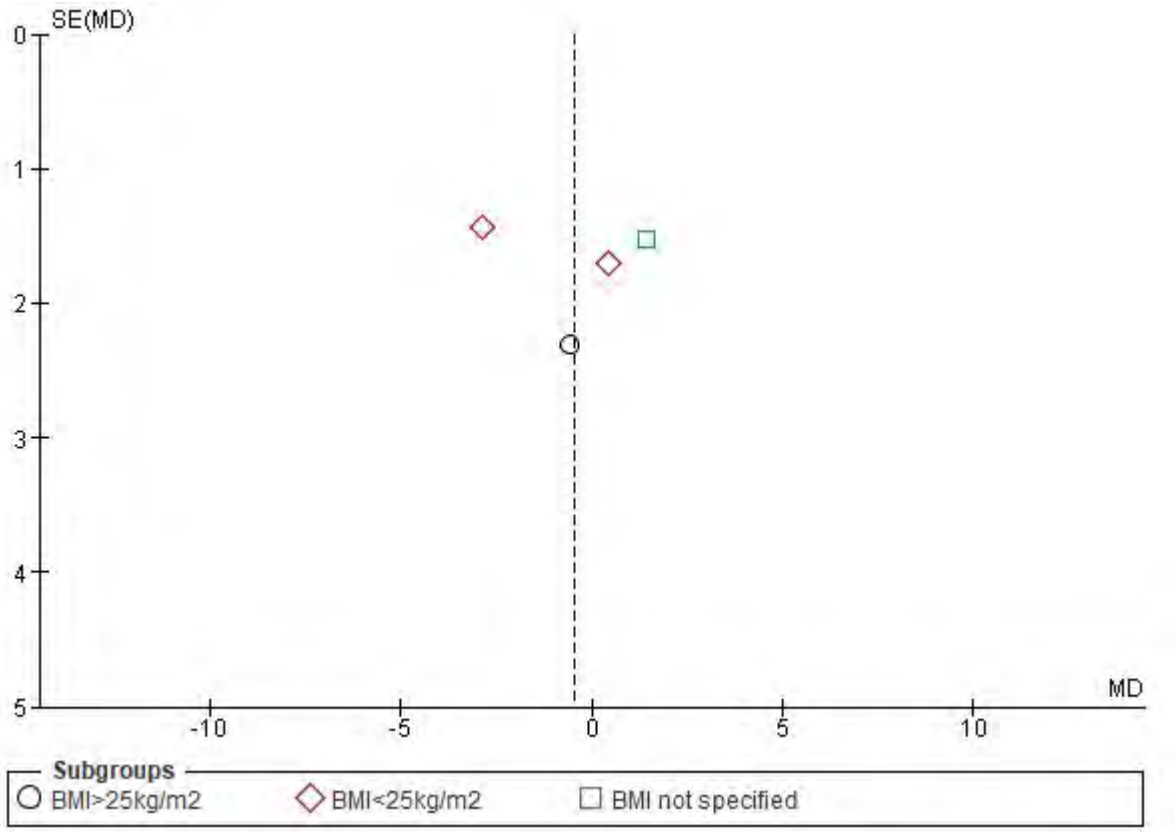
5.5.1 Individual Study Data Table

	OUTCOME: insulin				**OUTCOME TYPE:** Continuous				
	COMPARISON (if applicable): metformin versus **metformin+ OCP**								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Kumar et al.2018	ulU/ml	30	11.4	5.4	29	14.3	5.6	Crude	6
Kebapcilar et al 2010	ulU/ml	12	19.0	3.4	12	17.6	4.0		3
Wu et al 2008	ulU/ml	11	11.2	4.2	10	1.8	0.6	BMI<25	3
Wu et al 2008	ulU/ml	7	14.5	4.1	6	15.1	4.2	BMI>25	3

5.5.2. Forrest plot metformin vs OCP for fasting insulin



5.5.3. Funnel plot for assessment of publication bias

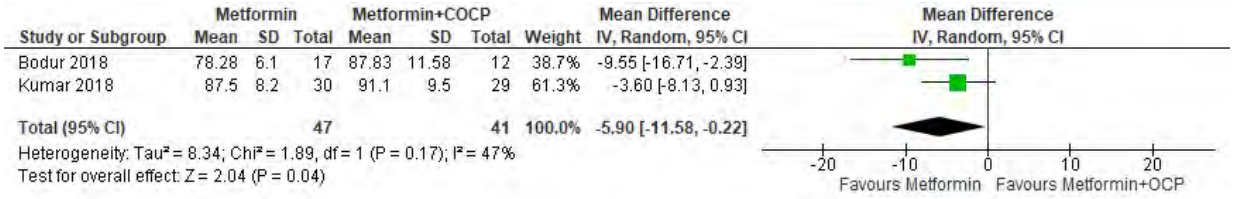


OUTCOME 5.6 Fasting glucose (mg/dl)

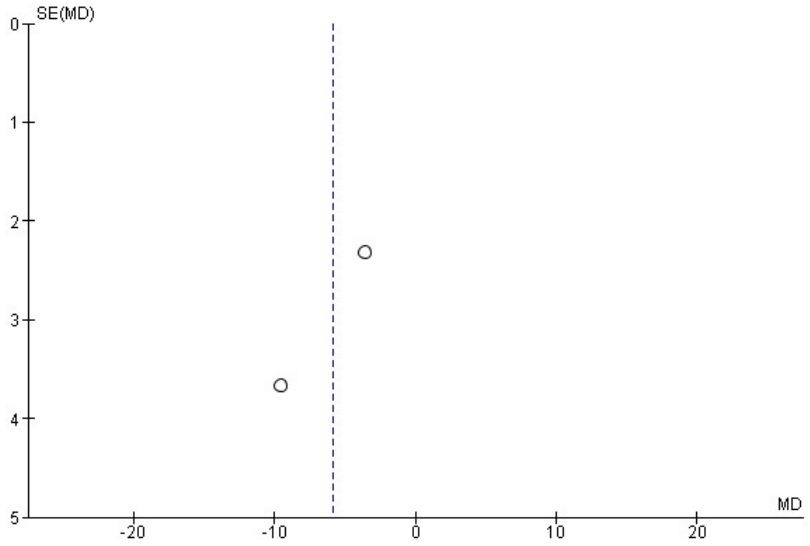
5.6.1 Individual Study Data Table

	OUTCOME: serum fasting glucose level					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **metformin+OCP**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Bodur et al. 2018	Mg/dl	17	78.28	6.1	12	87.83	11.58	Crude	6
Kumar et al.2018	Mg/dl	30	87.5	8.2	29	91.1	9.5	Crude	6

5.6.2. Forrest plot metformin vs OCP for fasting glucose



5.6.3. Funnel plot for assessment of publication bias



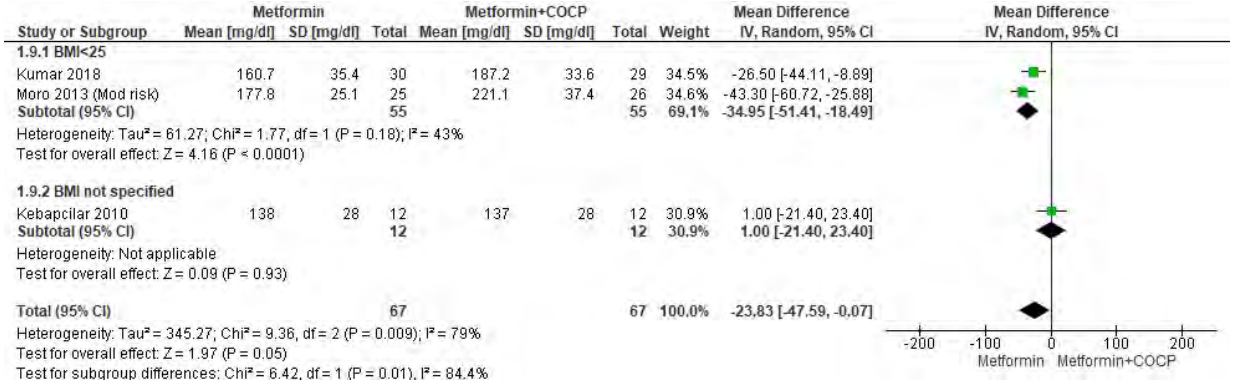
OUTCOME 5.7 Total cholesterol (mg/dl)

5.7.1 Individual Study Data Table

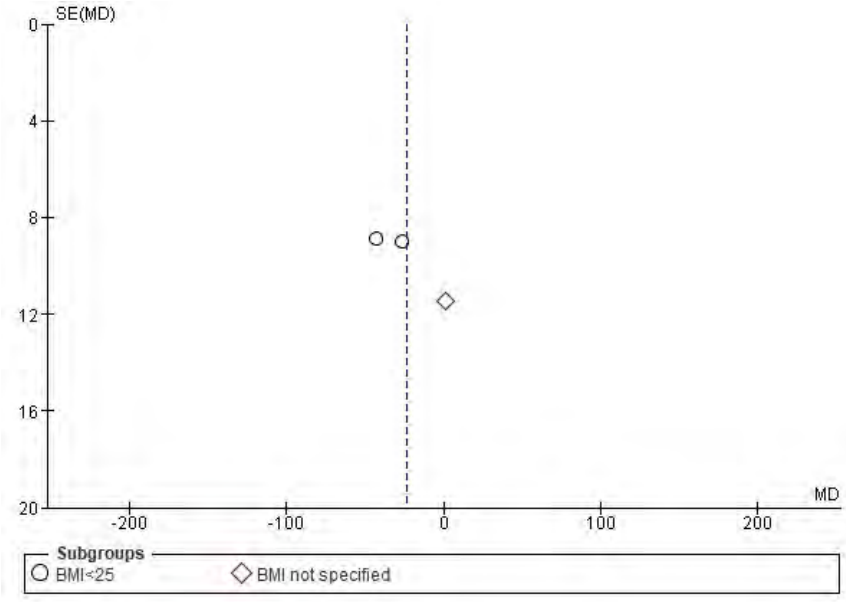
	OUTCOME: total cholesterol					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **Metformin+OCP**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Kumar et al.2018	Mg/dl	30	160.7	35.4	29	187.2	33.6	Crude	6

Kebapcilar et al 2010	Mg/dl	12	138	28	12	137	28		3
Moro et al. 2013	Mg/dl	25	177.8	25.1	26	221.1	37.4		6

5.7.2. Forrest plot metformin vs OCP for total cholesterol



5.7.3. Funnel plot for assessment of publication bias



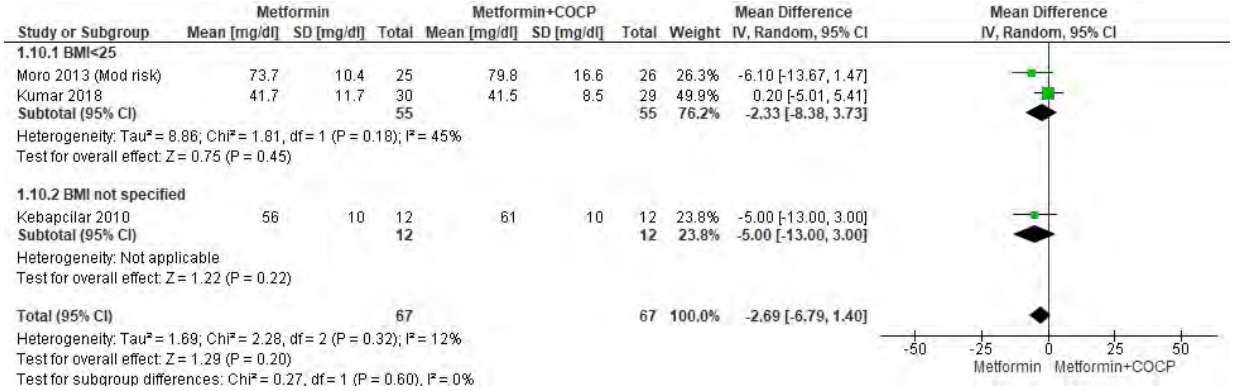
OUTCOME 5.8 HDL (mg/dl)

5.8.1 Individual Study Data Table

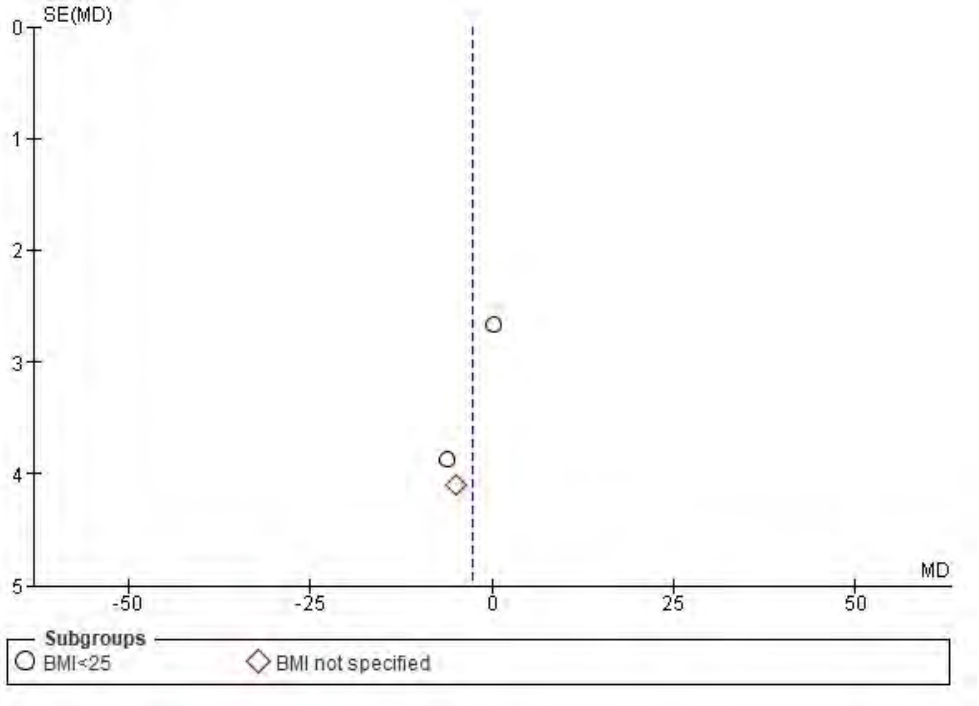
	OUTCOME: HDL		**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable): metformin versus **metformin+OCP**	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	N	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	N	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	Time period (month)
Kumar et al.2018	Mg/dl	30	41.7	11.7	29	41.5	8.5	Crude	6
Kebapcilar et al 2010	Mg/dl	12	56	10	12	61	10		3
Moro et al. 2013	Mg/dl	25	73.7	10.4	26	79.8	16.6		6

5.8.2. Forrest plot metformin vs OCP for HDL



5.8.3. Funnel plot for assessment of publication bias

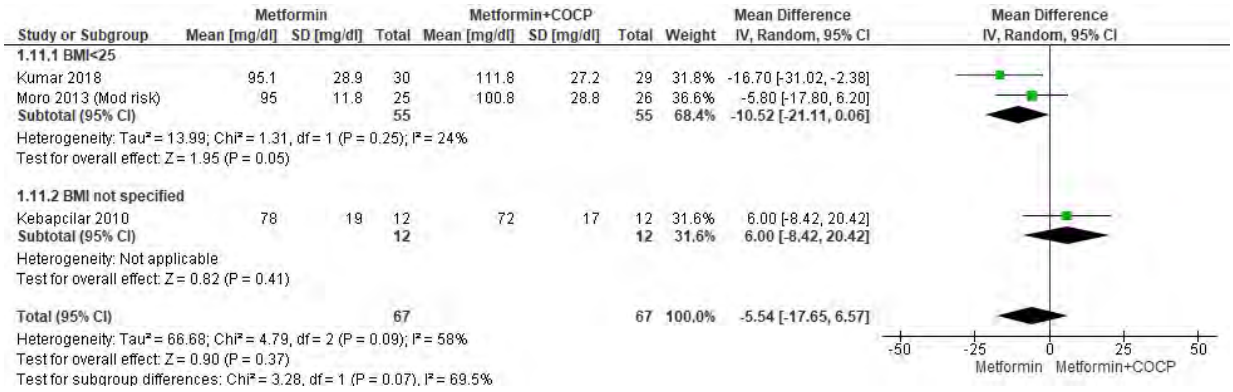


OUTCOME 5.9 LDL (mg/dl)

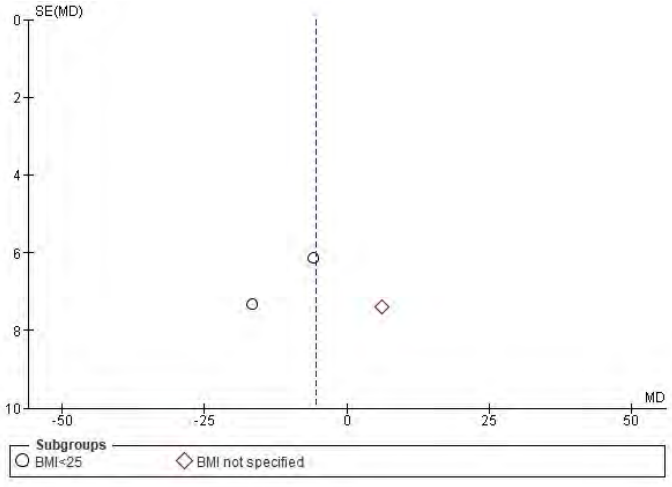
5.9.1 Individual Study Data Table

	OUTCOME: LDL					OUTCOME TYPE: Continuous			
		COMPARISON (if applicable): **metformin** versus **metformin+OCP**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Kumar et al.2018	Mg/dl	30	95.1	28.9	29	111.8	27.2	Crude	6
Kebapcilar et al 2010	Mg/dl	12	78	19	12	72	17		3
Moro et al. 2013	Mg/dl	25	95	11.8	26	100.8	28.8		6

5.9.2. Forrest plot metformin vs OCP for LDL



5.9.3. Funnel plot for assessment of publication bias

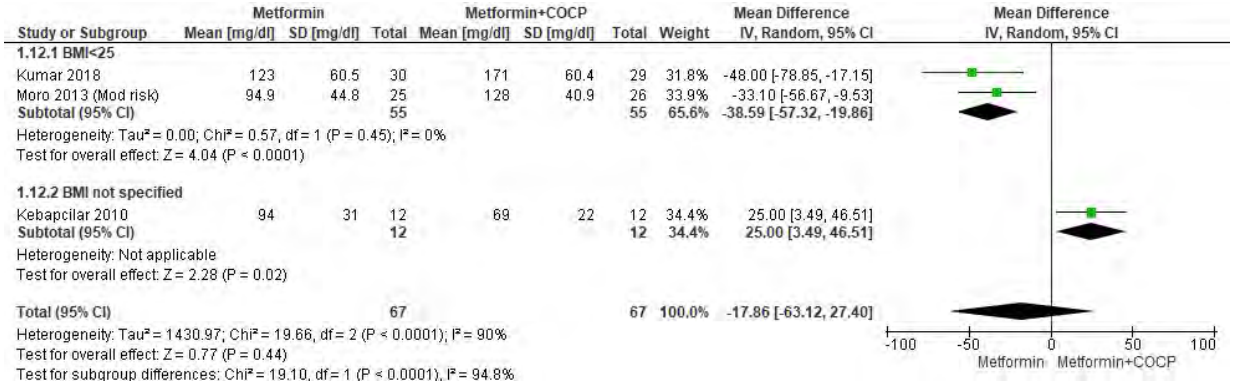


OUTCOME 5.10 Triglycerides (mg/dl)

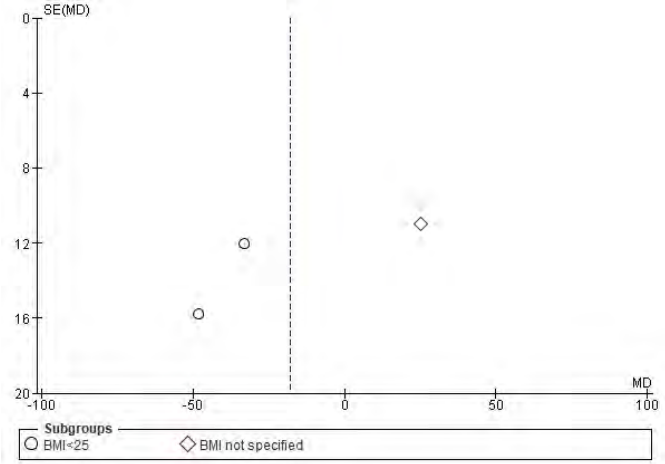
5.10.1 Individual Study Data Table

	OUTCOME: Triglycerides					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **metformin+OCP**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Kumar et al.2018	Mg/dl	30	123	60.5	29	171	60.4	Crude	6
Kebapcilar et al 2010	Mg/dl	12	94	31	12	69	22		3
Moro et al. 2013	Mg/dl	25	94.9	44.8	26	128	40.9		6

5.10.2. Forrest plot metformin vs OCP for Triglycerides



5.10.3. Funnel plot for assessment of publication bias

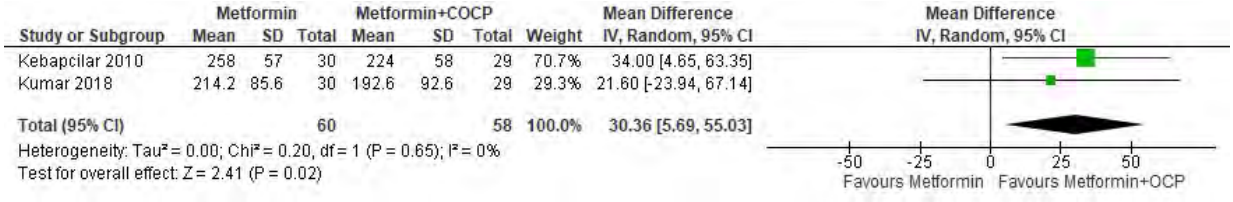


OUTCOME 5.11 DHEAS (Ug/dl)

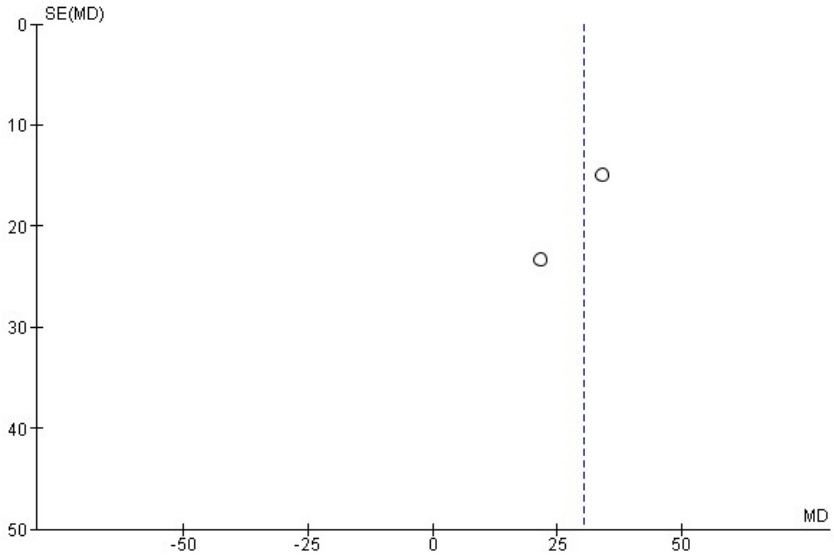
5.11.1 Individual Study Data Table

	OUTCOME: DHEAS					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **metformin+OCP**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Kumar et al.2018	Ug/dl	30	214.2	85.6	29	192.6	92.6	Crude	6
Kebapcilar et al 2010	Ug/dl	12	258	57	12	224	58		3

5.11.2. Forrest plot metformin vs OCP for DHEAS



5.11.3. Funnel plot for assessment of publication bias

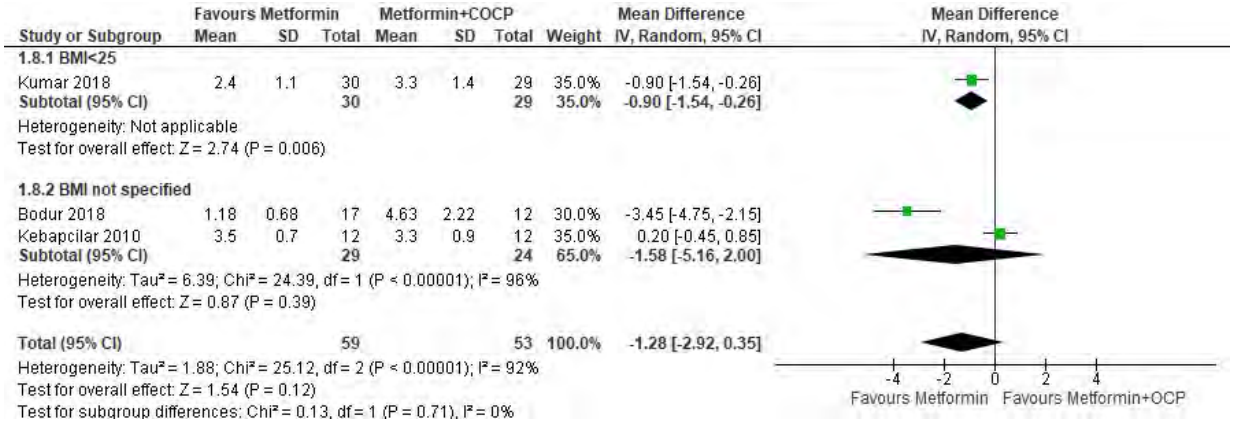


OUTCOME 5.12 HOMA-IR

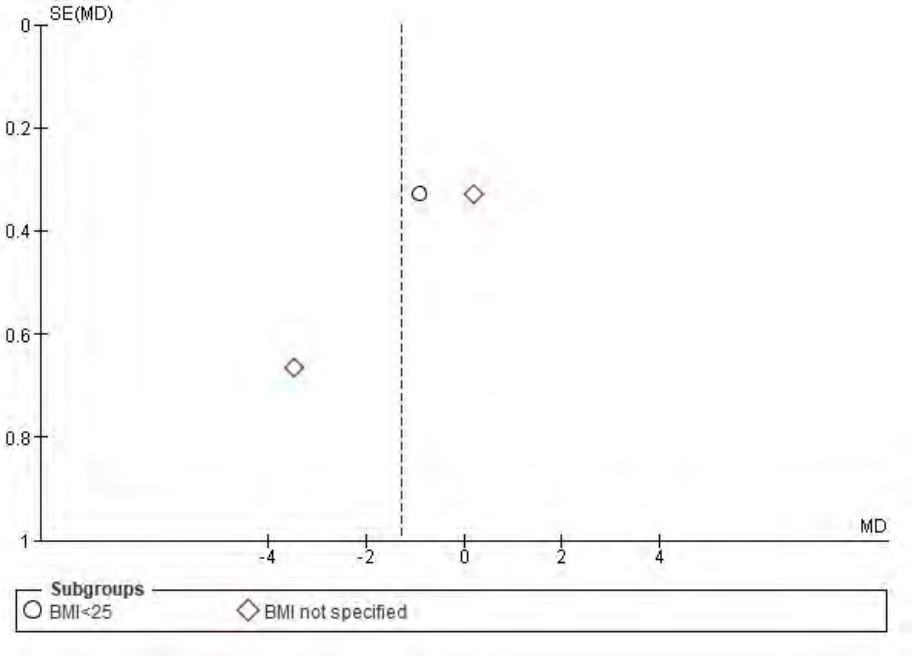
5.12.1 Individual Study Data Table

	OUTCOME: HOMA-IR		OUTCOME TYPE: Continuous						
		COMPARISON (if applicable): metformin versus metformin+OCP							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Bodur et al. 2018		17	1.18	0.68	12	4.63	2.22	BMI>30	6
Kumar et al.2018		30	2.4	1.1	29	3.3	1.4	Crude	6
Kebapcilar et al 2010		12	3.5	0.7	12	3.3	0.9		3

5.12.2. Forrest plot metformin vs OCP for HOMA-IR



5.12.3. Funnel plot for assessment of publication bias



Adverse outcomes

	Study	Metformin	Metformin+OCP
Gastrointestinal side effects	Moro 2013	2/31	2/31
	Wu 2018	2/20	4/20
	Kumar 2018	2/30	0/29
Headache	Bodur 2018	0/29	1/20
Nausea	Bodur 2018	2/29	1/29
	Glintborg 2014	1/30	3/30
Dizziness	Bodur 2018	1/29	2/20
Depression	Glintborg 2014	1/30	0/30
Weight loss	Bodur 2018	1/29	1/20
Other	Glintborg 2014	3/30 (not reported which)	2/30 (as reported above)
	Bodur 2018	hirsutism 1/29 hypothyroidism 1/29	Hirsutism 1/20

Comparison 6: Metformin versus anti-androgen (also in Q4.6 – identical)

Evidence Summary

Only one RCTs compared metformin to an anti-androgen (Diri et al. 2017). This study was rated as high risk of bias.

Meta-analysis/descriptive analysis summary

Meta-analysis was not possible with only one study. Diri et al. found that the anti-androgen finasteride reduced both androgen levels (DHEAS and SHBG) and parameters of insulin resistance (AUC-Insulin) better than metformin. For the other outcomes measured, no difference was observed.
No side effects were observed with finasteride or metformin.
Certainty in the evidence for this comparison is very low (downgraded twice for very serious risk of bias and twice for very serious risk imprecision, being a single, small study).

Author, year, country	Population	Sample Size per group	Intervention/ exposure details	PCOS criteria	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Summary of findings	Other
Diri et al. 2017 Turkey	Women with newly or previously diagnosed with PCOS	1. metformin N=19 2.Finasteride N=16 3. Metformin +finasteride N=17	1. metformin 850mgx2/d 2.finasteride 5mg/d 3. metformin 850mgx2/d+ finasteride 5mg/d	Rott	12 months	1.27.1 ± 4.3 2.37.6 ±4.1 3.35.1 ±3.6	1.26.4 ± 7.2 2.27.4 ±4.3 3.27.6±4.2	Bmi, hirsutism, shbg, free-T, dheas, A, homa-IR	Comparisons of changes in parameters in the 3 groups did not clearly show the superiority of any treatment modality	**ROB high**

Individual study

Study ID	Diri 2017							
Outcome	**Time point**	**N**	**Metformin**		**Anti-androgen**		**P value**	**Favours**
			Mean	**SD**	**Mean**	**SD**		
BMI (kg/m2)	12 months	35	26.9	4.2	26.7	2.2	NR	No difference
Hirsutism	12 months	35	11.1	5.0	11.7	5.2	NR	No difference
Free testosterone (pg/ml)	12 months	35	2.4	1.1	2.1	0.5	NR	No difference
DHEAS (ng/mll)	12 months	35	3090	1199	2421	1098	<0.05	**Anti-androgen**
SHBG (nmol/ml)	12 months	35	29.4	13.7	40.9	20.0	<0.05	**Anti-androgen**
Androstenedione (ng/ml)	12 months	35	2.3	0.7	2.6	0.6	NR	No difference
AUC-Glucose	12 months	35	11961	3542	12124	1568	NR	No difference

AUC-Insulin	12 months	35	4109	3213	1689	1652	<0.05	**Anti-androgen**
HOMA-IR	12 months	35	1.4	1.3	1.2	0.7	NR	No difference

Comparison 7: Metformin+anti-androgen versus anti-androgen (also in Q4.6 – identical)

Evidence Summary

Only one RCTs compared metformin and anti-androgen to anti-androgen only (Diri et al. 2017). This study was rated as high risk of bias.

Meta-analysis/descriptive analysis summary

Meta-analysis was not possible with only one study. Diri et al. found that anti-androgen alone was more effective in lowering HOMA-IR and AUC-insulin compared to metformin and anti-androgen in combination. For the other outcomes measured, no difference was observed.
No side effects were observed with finasteride and/or metformin.
Certainty in the evidence for this comparison is very low (downgraded twice for very serious risk of bias and twice for very serious risk imprecision, being a single, small study).

Author, year, country	Population	Sample Size per group	Intervention/ exposure details	PCOS criteria	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Summary of findings	Other
Diri et al. 2017 Turkey	Women with newly or previously diagnosed with PCOS	1. metformin N=19 2.Finasteride N=16 3. Metformin +finasteride N=17	1. metformin 850mgx2/d 2.finasteride 5mg/d 3. metformin 850mgx2/d+ finasteride 5mg/d	Rott	12 months	1.27.1 ± 4.3 2.37.6 ±4.1 3.35.1 ±3.6	1.26.4 ± 7.2 2.27.4 ±4.3 3.27.6±4.2	Bmi, hirsutism, shbg, free-T, dheas, A, homa-IR	Comparisons of changes in parameters in the 3 groups did not clearly show the superiority of any treatment modality	**ROB high**

Individual studies

Study ID	Diri 2017							
Outcome	**Time point**	**N**	**Metformin+anti-androgen Mean**	**SD**	**Anti-androgen Mean**	**SD**	**P value**	**Favours**
BMI (kg/m2)	12 months	33	26.6	4.4	26.7	2.2	NR	No difference
Hirsutism	12 months	33	12.1	5.5	11.7	5.2	NR	No difference
Free testosterone (pg/ml)	12 months	33	2.0	1.2	2.1	0.5	NR	No difference
DHEAS (ng/mll)	12 months	33	2619	1081	2421	1098	NR	No difference

SHBG (nmol/ml)	12 months	33	41.9	20.2	40.9	20.0	NR	No difference
Androstenedione (ng/ml)	12 months	33	2.5	0.6	2.6	0.6	NR	No difference
AUC-Glucose	12 months	33	13606	3522	12124	1568	NR	No difference
AUC-Insulin	12 months	33	3039	1928	1689	1652	<0.05	**Anti-androgen**
HOMA-IR	12 months	33	1.6	1.2	1.2	0.7	<0.05	**Anti-androgen**

Comparison 8: Metformin+anti-androgen versus metformin (also in Q4.6 – identical)

Evidence Summary

Only one RCTs compared metformin and anti-androgen to metformin only (Diri et al. 2017). This study was rated as high risk of bias.

Meta-analysis/descriptive analysis summary

Meta-analysis was not possible with only one study. Diri et al. found that metformin and anti-androgen in combination reduced androgen levels, whereas metformin only reduced AUC-glucose. For the other outcomes measured, no difference was observed.
No side effects were observed with finasteride and/or metformin.
Certainty in the evidence for this comparison is very low (downgraded twice for very serious risk of bias and twice for very serious risk imprecision, being a single, small study).

Author, year, country	Population	Sample Size per group	Intervention/ exposure details	PCOS criteria	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Summary of findings	Other
Diri et al. 2017 Turkey	Women with newly or previously diagnosed with PCOS	1. metformin N=19 2.Finasteride N=16 3. Metformin +finasteride N=17	1. metformin 850mgx2/d 2.finasteride 5mg/d 3. metformin 850mgx2/d+ finasteride 5mg/d	Rott	12 months	1.27.1 ± 4.3 2.37.6 ±4.1 3.35.1 ±3.6	1.26.4 ± 7.2 2.27.4 ±4.3 3.27.6±4.2	Bmi, hirsutism, shbg, free-T, dheas, A, homa-IR	Comparisons of changes in parameters in the 3 groups did not clearly show the superiority of any treatment modality	**ROB high**

Individual studies

Study ID	Diri 2017							
Outcome	**Time point**	**N**	**Metformin+anti-androgen Mean**	**SD**	**metformin Mean**	**SD**	**P value**	**Favours**
BMI (kg/m2)	12 months	36	26.6	4.4	26.9	4.2	NR	No difference
Hirsutism	12 months	36	12.1	5.5	11.1	5.0	NR	No difference
Free testosterone (pg/ml)	12 months	36	2.0	1.2	2.4	1.1	NR	No difference
DHEAS (ng/mll)	12 months	36	2619	1081	3090	1199	<0.05	**Metformin+anti-androgen**
SHBG (nmol/ml)	12 months	36	41.9	20.2	29.4	13.7	<0.05	**Metformin+anti-androgen**
Androstenedione (ng/ml)	12 months	36	2.5	0.6	2.3	0.7	NR	No difference
AUC-Glucose	12 months	36	13606	3522	11961	3542	<0.05	**Metformin**
AUC-Insulin	12 months	36	3039	1928	4109	3213	NR	No difference
HOMA-IR	12 months	36	1.6	1.2	1.4	1.3	NR	No difference

Comparison 9: SPIOMET versus OCP (also in Q4.6 – identical)

Evidence Summary

Five RCTs compared SPIOMET (spironolactone 50mgx1, pioglitazone 7.5mgx1 and metformin 850mgx1) to OCP but all studies used the same data. Outcomes from Ibanez et al. 2020 and De Zegher et al. 2019 were used, since these were the studies with the largest amount of participants. These studies were rated as moderate risk of bias.

Meta-analysis/descriptive analysis summary

Meta-analysis was not possible with only one set of data used. Ibanez et al. found that the SPIOMET reduced hirsutism, LDL-cholesterol, CRP, HOMA-IR and fasting insulin better than metformin. OCP was superior in increasing SHBG.
None of the articles reported any side effects.
Certainty in the evidence for this comparison is low (downgraded once for serious risk of bias and once for serious risk imprecision, being a single, small study).

Author, year, country	Population	Sample Size per group	Intervention/ exposure details	PCOS criteria	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Summary of findings	Other
De Zegher et al 2019 Spain	Adolescent girls with PCOS (gynaecological age>2.0 years)	SPIOMET=29 OCP=29	1.SPIOMET-group: spironolactone 50 mgx1 daily, pioglitazone 7.5 mgx1 daily and metformin 850 mgx1 daily, taken together at dinner time 2.OCP-group: 20 µg ethinyloestradiol plus 100 mg levonorgestrel (21/28 days), and placebo (7/28 days)	hirsutism, oligomenorrhea, gynaecological age>2.0 years,	12 months	NR	1.15.8 ±0.3 2.15.6 ±0.3	FAI (the rest in Ibanez et al 2020)	OCP and SPIOMET treatment were accompanied, respectively, by 1.7- and 3.4-fold rises of circulating GDF15. Post-OCP, GDF15, CRP and insulin returned towards baseline levels; post-SPIOMET, GDF15 returned also to baseline levels but CRP, insulin and liver fat remained normal	**ROB Moderate** Same outcomes in Ibanez et al. (Toward a Treatment Normalizing Ovulation Rate in Adolescent Girls with Polycystic Ovary Syndrome)?
Ibanez et al 2020 Spain	Adolescent girls with PCOS two RCT pooled (gynaecological age>2.0 years)	SPIOMET=**31** OCP=**31**	1.SPIOMET-group: spironolactone 50 mgx1 daily, pioglitazone 7.5 mgx1 daily and metformin 850 mgx1 daily, taken together at dinner time 2.OCP-group: 20 µg ethinyloestradiol plus 100 mg levonorgestrel (21/28 days), and placebo (7/28 days)	hirsutism, oligomenorrhea, gynaecological age>2.0 years,	12 months	1.24.2 ±0.7 2.24.2 ±0.7	1.15.7 ±0.2 2.15.9 ±0.2	BMI, mFGS, SHBG, T, A, free-T, f-insulin, HOMA, OGTT, triglycerides	OCP and SPIOMET treatment reduced the androgen excess comparably and had no differential effects on total-body lean or fat mass. However, SPIOMET was accompanied by more broadly normalizing effects, including on hepato-visceral fat and on circulating insulin	**ROB Moderate**
Ibanez et al 2017 Spain	Adolescent girls with PCOS	SPIOMET=**17** OCP=**17**	1.SPIOMET-group: spironolactone 50 mgx1 daily, pioglitazone 7.5 mgx1 daily and metformin 850 mgx1 daily, taken together at dinner time 2.OCP-group: 20 µg ethinyloestradiol plus 100 mg levonorgestrel (21/28 days), and placebo (7/28 days)	hirsutism, oligomenorrhea, gynaecological age>2.0 years,	12 months	1.23.4 ±0.7 2.24.0 ±0.8	1.15.8 ±0.3 2.15.9 ±0.3	No outcomes (all are in Ibanez et al 2020)	SPIOMET was followed by a 2.5-fold higher ovulation rate than OCP and by a 6-fold higher normovulatory fraction. Oligoanovulation risk after SPIOMET was 65% lower than after OCP	**ROB Moderate**

Diaz et al. 2020 Spain	nonobese adolescent girls with PCOS	SPIOMET=**17** OCP=**18**	1.SPIOMET-group: spironolactone 50 mgx1 daily, pioglitazone 7.5 mgx1 daily and metformin 850 mgx1 daily, taken together at dinner time 2.OCP-group: 20 µg ethinyloestradiol plus 100 mg levonorgestrel (21/28 days), and placebo (7/28 days)	hirsutism, oligomenorrhea, gynaecological age>2.0 years,	12 months	1.23.1 ±0.7 2.23.9 ±0.8	1.15.7 ±0.3 2.15.9 ±0.3	No outcomes (all are in Ibanez et al 2020)	A low-dose combination of insulin sensitizers and an antiandrogen—but not oral contraception—normalizes fetuin-A levels in adolescent girls with PCOS.	**ROB Moderate**
Malpique et al 2018 Spain	nonobese adolescent girls with PCOS	SPIOMET=**24** OCP=**27**	1.SPIOMET-group: spironolactone 50 mgx1 daily, pioglitazone 7.5 mgx1 daily and metformin 850 mgx1 daily, taken together at dinner time 2.OCP-group: 20 µg ethinyloestradiol plus 100 mg levonorgestrel (21/28 days), and placebo (7/28 days)	hirsutism, oligomenorrhea, gynaecological age>2.0 years,	12 months	1.25.1 ±1 2.24 ±1	1.15.8 ±0.3 2.15.7 ±0.3	No outcomes (all are in Ibanez et al 2020)	S100A4 may become a circulating marker of hepato-visceral fat excess in adolescents with PCOS	**ROB Moderate**

Individual studies

Study ID	Ibanez et al. 2020							
Outcome	**Time point**	**N**	**SPIOMET**		**OCP**		**P value**	**Favours**
			Mean	**SEM**	**Mean**	**SEM**		
BMI (kg/m2)	12 months	62	23.9	0.7	24.9	0.8	NR	No difference
Hirsutism	12 months	62	11	1	14	1	$P \leq 0.001$	**SPIOMET**
Testosterone (nmol/l)	12 months	62	0.8	0.1	0.7	0.1	NR	No difference
SHBG (nmol/ml)	12 months	62	32	2	61	5	$P \leq 0.001$	**OCP**
Androstenedione (ng/ml)	12 months	62	3.5	0.3	2.5	0.2	NR	No difference
FAI	6 months	58	2.9	0.3	1.4	0.2	NR	No difference
Triglycerides (mmol/l)	12 months	62	0.67	0.05	0.75	0.05	NR	No difference
LDL (mmol/l)	12 months	62	2.2	0.1	2.7	0.1	$P \leq 0.01$	**SPIOMET**
HDL (mmol/l)	12 months	62	1.4	0.1	1.3	0.1	NR	No difference
CRP (nmol/l)	12 months	62	6.7	0.9	24.8	3.8	$P \leq 0.001$	**SPIOMET**
Fasting Insulin (pmol/l)	12 months	62	42	7	104	7	$P \leq 0.001$	**SPIOMET**
HOMA-IR	12 months	62	1.2	0.1	3.0	0.3	$P \leq 0.01$	**SPIOMET**

Comparison 10: Metformin versus anti-androgen+OCP (also in Q4.6 – not identical since timeline is different)

Evidence Summary

Four randomised controlled trials (RCTs) and five articles reporting these outcomes were identified by our search. Of these RCT, three were included in the meta-analysis.
Of these studies, one had a low ROB (Mehrabian et al. 2016), one a moderate ROB (Meyer et al. 2009) and three a high ROB (Burchall et al. 2017, Kebapcilar et al 2010 and Alpanes et al. 2017). Rows highlighted grey below indicate studies with participants described as obese.

Meta-analysis/descriptive analysis summary

In the meta-analysis (measuring BMI, HDL and triglycerides) no differences between the two groups were observed. Certainty in the evidence is moderate to very low.
Regarding individual studies, not included in the meta-analysis, Alpanes et al observed that a combination of anti-androgen and OCP was superior in improving hyperandrogenism (hirsutism, testosterone, free testosterone, androstenedione and DHEAS). Another study found that anti-androgens combined with OCP was superior in increasing SHBG (Meyer et al. 2007) and lowering CRP (Mehrabian et al. 2016) compared to metformin only. Mehrabian et al. found that those treated with metformin had a lower fasting glucose compared to the anti-androgen+OCP-group. Certainty in the evidence for the individual studies were low or very low.
Patients using metformin reported more GI adverse effects (see table at the end).

Author, year, country	Population	Sample Size per group	Intervention/ exposure details	PCOS criteria	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Summary of findings	Other
Meyer et al. 2007 Australia	Overweight women (BMI 27 kg/m2) with PCOS	1.Metformin=36 2.OCP (high)=31 3. OCP+SPL=33	1.Metformin 1000mgx2/d 2.35µg EE + 2mg CPA (high) 3. 20µg EE + 100µg LVG + 50mg SPL (low dose)	NIH	6 months	1: 36.3 no SD 2: 36.5 no SD 3: 35.5 no SD	Average: 31 years	BMI, WHR, menstrual cycle, hirsutism, shbg, FAI, T, DHEAS, f-insulin, lipids, homa	All treatments similarly and significantly improved symptoms including hirsutism and menstrual cycle length. Insulin resistance was improved by metformin and worsened by the high-dose OCP.	**ROB Moderate** Outcomes also reported in Moran et al 2010, Burchall et al. 2017 and Hutchinson et al. 2008 Mean change and 95%CI calculated
Burchall et al 2017 Australia	Overweight and obese women with PCOS	1. metformin N=23 2. Low-dose OCP+spiro N=16 3.High dose OCP=21	1.Metformin 1000mg b.i.d. 2. 20-µg EE/100-µg levonorgestrel + spironolactone 50 mg b.i.d. 3. 35-µg EE/2-mg cyproterone acetate	NIH	6 months	1. 37.79 ± 6.81 2. 35.25 ± 5.71 3. 35.91 ± 8.11	1.32.16 ± 6.52 2. 35.44±6.91 3. 34.41±6.73	BMI, oGTT, Insulin, HOMA-IR, T, PAI-1, ADMA, PF1 and 2, TG, Fibrinolytic system,	Endothelial function improved with higher dose with some improvement in low-dose OCP + S and metformin. Aberrant coagulation was noted in both OCP groups, but not with metformin. Fibrinolysis was	Outcomes included in Meyer et al.2007, Hutchinson et al. 2008, Moran et al. 2010 **ROB High**

								Plasminogen, TAFI.	reduced with higher-dose OCP.	
Kebapcilar et al 2010 Turkey	Women with PCOS (24.0+/- 5.4 yr; BMI 27.9 +/-5.28)	1.Metformin=12 2.Metformin+OCP=12 3. OCP=12 4.OCP+SPL=12	1.Metformin 850mgx2/d 2.Metformin 850mgx2/d + EE 35ug+CPA 2mg 3. EE 35ug+CPA 2mg 4. EE 35ug+CPA 2mg+spironolactone 100mgx1/d	Rott	3 months	1.27.8± 4 2.27.6 ±3 3.28.7 ±6 4.27.6±4	1.24.4± 6.2 2.24.9 ±4.8 3.23.2 ±5.1 4.23.4± 5.8	BMI, lipids, Insulin, HOMA, dHEAS, free-T	All treatment groups showed reduced coagulation parameters, improvement of hormonal, hematological and metabolical variables. EE/CA–metformin may be a more effective due to the benefcial effect of EE/CA–metformin on insulin resistance.	**ROB high**
Alpanes et al. 2017 Spain	Women with PCOS reporting to an androgen excess outpatient clinic	1.Metformin=22 2.OCP+spiro=24	1. Metformin 425mg b.i.d. during the first week and 850mg dose b.i.d. Barrier contraception 2. OCP containing 30µg of ethinylestradiol and 150µg of desogestrel and 100mg/day of spironolactone	Presence of clinical and/or biochemical hyperandrogenism together with evidence of oligoovulation"	12 months	1. 31.2 +/- 9 2. 30.6+/- 7.9	1.23+/-6 2. 25+/-5	hirsutism score, total-T, free-T, androstenedione, DHEAS, lipids, menstrual dysfunction, weight, bmi, whr, f-gluk, f-insulin, HOMA	OCP+spiro more effective than met in terms of clinical and biochemical hyperandrogenism and menstrual bleeding. OCP+spiro decreased hirsutism score, normalized total and free T and androstenedione and reduced DHEAS	**ROB high** Reports mean difference
Mehrabian et al. 2016 Iran	Women with PCOS and metabolic syndrome	1.Metformin=34 2.OCP+SPL=34	1.Metformin 1000mg/d 2.30ug EE+0.15mg levonorgestrel+ Flutamid 62.5mg	NIH	6 months	1.29.8±4.15 2.29.8±4.16	1.29.2±8.3 2.29.0±7.7	BMI, f-gluc, lipids, crp	Metformin performed better in FBS reduction. Simvastatin had better performance in terms of reducing TG level and waist circumference	**ROB Low**

Results of meta-analysis

Outcome	Time point	RCTs	N	Effect, random, MD	P-value	I2 (%)	Favours	Certainty
BMI (kg/m2)	3-6 months	3	131	0.08 (1.40 to 1.56)	0.91	0	No difference	⊕⊕⊕◯ MODERATE
HDL (mg/dl)	3-6 months	2	92	-5.70 (-18.64 to 7.24)	0.39	87	No difference	⊕◯◯◯ VERY LOW
Triglycerides (mg/dl)	3-6 months	2	92	12.07 (-6.71 to 30.85)	0.21	0	No difference	⊕◯◯◯ VERY LOW

Individual studies

Outcome	Author, year	Time point	N	Metformin	Anti-androgen+OCP	P-value	Favours	Grading
WHR	Meyer et al. 2009	6 months	1.Metformin=36 2. OCP+SPL=33	Mean change (95% CI) 0.18 (-0.03 to 0.1)	Mean change (95% CI) 0.02 (-0.01 to 0.04)	NR	No difference	⊕⊕◯◯ LOW[1]
Menstrual cycle (d)	Meyer et al. 2009	6 months	1.Metformin=36 2. OCP+SPL=33	Mean change (95% CI) -47.1 (-1.5 to -93)	Mean change (95% CI) -61.8 (-27.3 to -96)	NR	No difference	⊕⊕◯◯ LOW[1]
Hirsutism	Alpanes et al. 2017	12 months	1.Metformin=22 2.OCP+spiro=24	Mean difference between patients (95% CI) 4.6 (2.6-6.7)		<0.0001	**AA+OCP**	⊕◯◯◯ VERY LOW[2]
	Meyer et al. 2009	6 months	1.Metformin=36 2. OCP+SPL=33	Mean change (95% CI) -2.7 (-1.5 to -3.9)	Mean change (95% CI) -2.0 (-0.7 to -3.4)	NR	No difference	⊕⊕◯◯ LOW[1]
Fasting glucose	Mehrabian et al. 2016	6 months	1.Metformin=34 2. OCP+SPL=34	Mean +/- SD 78.32 +/- 15.53	Mean +/- SD 91.00 +/- 13.33	<0.001	**Metformin**	⊕⊕⊕◯ MODERATE[3]
Fasting insulin	Meyer et al. 2009	6 months	1.Metformin=36 2. OCP+SPL=33	Mean change (95% CI) -6.0 (-12.6 to 0.4)	Mean change (95% CI) -1.67 (-2.3 to 5.6)	NR	No difference	⊕⊕◯◯ LOW[1]
	Kebapcilar et al. 2010	3 months	1.Metformin=12 2. OCP+SPL=12	Mean +/- SD 19 +/- 3.4	Mean +/- SD 19.8 +/- 5.2	NR	No difference	⊕◯◯◯ VERY LOW[4]
Testosterone	Burchall et al. 2017	6 months	1.Metformin=23 2. OCP+SPL=16	Mean +/- SD 2.10 +/- 1.06	Mean +/- SD 2.11 +/- 1.21	0.98	No difference	⊕◯◯◯ VERY LOW[4]
	Alpanes et al. 2017	12 months	1.Metformin=22 2.OCP+spiro=24	Mean difference between patients (95% CI) 1.1 (0.4-1.7)		<0.0001	**AA+OCP**	⊕◯◯◯ VERY LOW[2]
Free testosterone	Alpanes et al. 2017	12 months	1.Metformin=22 2.OCP+spiro=24	Mean difference between patients (95% CI) 25 (12-39)		0.0002	**AA+OCP**	⊕◯◯◯ VERY LOW[2]
	Kebapcilar et al. 2010	3 months	1.Metformin=12 2. OCP+SPL=12	Mean +/- SD 3.8 +/- 0.7	Mean +/- SD 3.8 +/- 1.00	NR	No difference	⊕◯◯◯ VERY LOW[4]
SHBG	Meyer et al. 2009	6 months	1.Metformin=36 2. OCP+SPL=33	Mean change (95% CI) 7.4 (-4.6 to 19.4)	Mean change (95% CI) 44.7 (60 to 29)	NR	**AA+OCP**	⊕⊕◯◯ LOW[1]
FAI	Meyer et al. 2009	6 months	1.Metformin=36 2. OCP+SPL=33	Mean change (95% CI) -2.1 (-3.1 to 3.2)	Mean change (95% CI) -6.3 (-8.1 to -4.4)	NR	No difference	⊕⊕◯◯ LOW[1]
DHEAS	Meyer et al. 2009	6 months	1.Metformin=36 2. OCP+SPL=33	Mean change (95% CI) -0.37 (-1.0 to 0.2)	Mean change (95% CI) -0.7 (-0.2 to -1.1)	NR	No difference	⊕⊕◯◯ LOW[1]
	Kebapcilar et al. 2010	3 months	1.Metformin=12 2. OCP+SPL=12	Mean +/- SD 258+/- 57	Mean +/- SD 298 +/- 68	0.12	No difference	⊕◯◯◯ VERY LOW[4]
	Alpanes et al. 2017	12 months	1.Metformin=22 2.OCP+spiro=24	Mean difference between patients (95% CI) 2.7 (1.4-4.0)		<0.0001	**AA+OCP**	⊕◯◯◯ VERY LOW[2]
Androstenedione	Alpanes et al. 2017	12 months	1.Metformin=22 2.OCP+spiro=24	Mean difference between patients (95% CI) 5.5 (1.8-9.2)		0.0002	**AA+OCP**	⊕◯◯◯ VERY LOW[2]

HOMA-IR	Meyer et al. 2009	6 months	1.Metformin=36 2. OCP+SPL=33	Mean change (95% CI) -1.13 (-0.6 to -2.8)	Mean change (95% CI) -0.22 (-1.14 to 0.7)	NR	No difference	⊕⊕◯◯ LOW[1]
	Kebapcilar et al. 2010	3 months	1.Metformin=12 2. OCP+SPL=12	Mean +/- SD 3.5+/- 0.7	Mean +/- SD 4.0 +/- 1.2	0.21	No difference	⊕◯◯◯ VERY LOW[4]
Total cholesterol (mg/dl)	Meyer et al. 2009	6 months	1.Metformin=36 2. OCP+SPL=33	Mean change (95% CI) -0.17 (-0.4 to 0.1)	Mean change (95% CI) 0.19 (-0.1 to 0.5)	NR	No difference	⊕⊕◯◯ LOW[1]
	Kebapcilar et al. 2010	3 months	1.Metformin=12 2. OCP+SPL=12	Mean +/- SD 138 +/- 28	Mean +/- SD 136 +/- 27	0.86	No difference	⊕◯◯◯ VERY LOW[4]
HDL (mg/dl)	Meyer et al. 2009	6 months	1.Metformin=36 2. OCP+SPL=33	Mean change (95% CI) -0.1 (-0.03 to -0.2)	Mean change (95% CI) 0.01 (-0.1 to 0.1)	NR	No difference	⊕⊕◯◯ LOW[1]
LDL (mg/dl)	Meyer et al. 2009	6 months	1.Metformin=36 2. OCP+SPL=33	Mean change (95% CI) -0.04 (-0.2 to 0.3)	Mean change (95% CI) 0.06 (-0.3 to 0.2)	NR	No difference	⊕⊕◯◯ LOW[1]
	Kebapcilar et al. 2010	3 months	1.Metformin=12 2. OCP+SPL=12	Mean +/- SD 78 +/- 19	Mean +/- SD 63 +/- 16	NR	No difference	⊕◯◯◯ VERY LOW[4]
Triglycerides (mg/dl)	Meyer et al. 2009	6 months	1.Metformin=36 2. OCP+SPL=33	Mean change (95% CI) 0.06 (-0.4 to 0.23)	Mean change (95% CI) 0.13 (-0.1 to 0.3)	NR	No difference	⊕⊕◯◯ LOW[1]
CRP (mg/l)	Mehrabian et al. 2016	6 months	1.Metformin=34 2. OCP+SPL=34	Mean +/- SD 1.45 +/- 0.47	Mean +/- SD 1.22 +/- 0.29	0.044	**AA+OCP**	⊕⊕⊕◯ MODERATE[3]
PAI	Burchall et al. 2017	6 months	1.Metformin=23 2. OCP+SPL=16	Mean change (95% CI) -0.87 (-1.54 to -0.19)	Mean change (95% CI) -1.49 (-2.22 to 0.75)	NR	No difference	⊕◯◯◯ VERY LOW[4]

[1] Downgraded once for mod ROB and downgraded once for small number of participants
[2] Downgraded twice for high ROB and downgraded once for small number of participants
[3] Downgraded once for small number of participants
[4] Downgraded twice for high ROB and downgraded twice for very small number of participants

OUTCOME 10.1 BMI

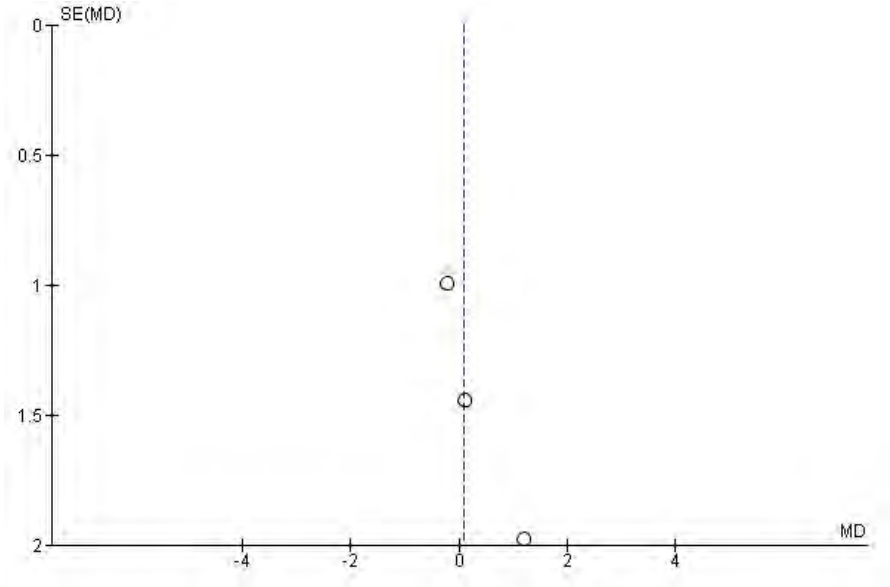
10.1.1 Individual Study Data Table

	OUTCOME: BMI									
		COMPARISON (if applicable): metformin versus **OCP+anti-androgen**								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Burchall et al. 2017	Kg/m2	weighted	23	36.81	6.93	16	35.61	5.39	Crude	6
Mehrabian et al. 2016	Kg/m2	weighted	34	29.54	4.18	34	29.75	4.01		6

Kebapcilar et al 2010	Kg/m2	weighted	12	26.8	4	12	26.7	3		3

10.1.2. Forrest plot metformin vs OCP+anti-androgen for BMI

10.1.3. Funnel plot for assessment of publication bias

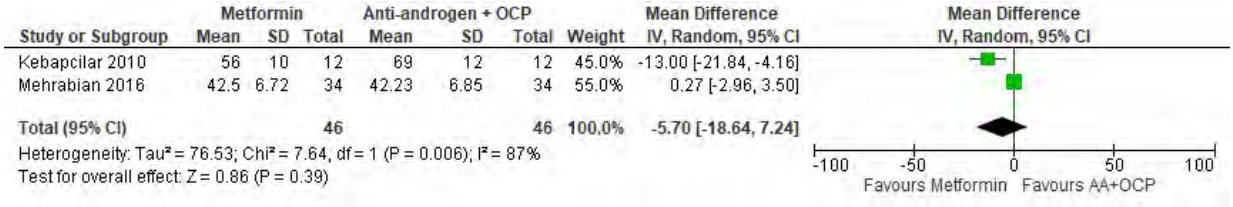


OUTCOME 10.2 HDL (mg/dl)

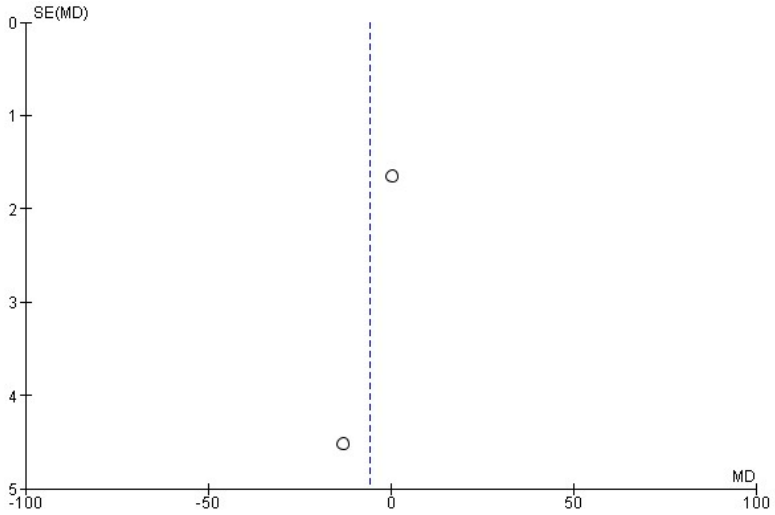
10.2.1 Individual Study Data Table

	OUTCOME: HDL					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **OCP+anti-androgen**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra**	**Time period (month)**
Kebapcilar et al 2010	Mg/dl	12	56	10	12	69	12		3
Mehrabian et al. 2016	Mg/dl	34	42.50	6.72	34	42.23	6.85	Crude	6

10.2.2. Forrest plot metformin vs OCP+anti-androgen for HDL



10.2.3. Funnel plot for assessment of publication bias

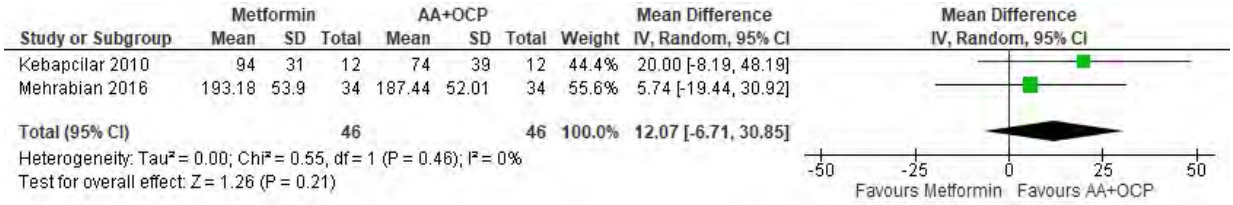


OUTCOME 10.3 Triglycerides (mg/dl)

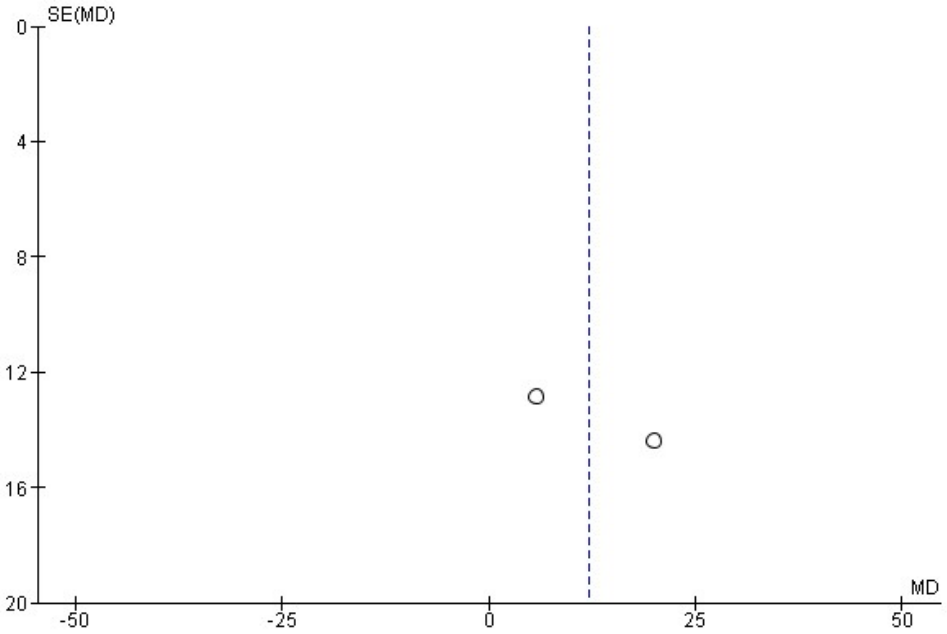
10.3.1 Individual Study Data Table

	OUTCOME: Triglycerides					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **OCP+anti-androgen**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra**	**Time period (month)**
Kebapcilar et al 2010	Mg/dl	12	94	31	12	74	39		3
Mehrabian et al. 2016	Mg/dl	34	193.18	53.90	34	187.44	52.01	Crude	6

10.3.2. Forrest plot metformin vs OCP+anti-androgen for Triglycerides



10.3.3. Funnel plot for assessment of publication bias



Adverse effects

	Study	Metformin	Anti-androgen+OCP
Gastrointestinal side effects (diarrhea,vomiting etc)	Alpanes 2017	2/22	0/24
	Kebapcilar	8/24	0
Other	Alpanes 2017	-	1/24 allergic reaction
	Meyer 2007	-	1/38 Mood swings

Comparison 11: Metformin+lifestyle versus metformin+anti-androgen+lifestyle (also in Q4.6 – not identical since timeline is different)

Evidence Summary

Five randomised controlled trials (RCTs) were identified by our search. Of these RCT, all were included in the meta-analysis.
Of these studies three had a low ROB and two a moderate ROB. All studies reported outcomes on adults. One study reported outcomes on obese PCOS-women (Gambineri et al. 2006).

Rows highlighted grey indicate studies with participants described as obese. Unfortunately, we were not able to perform any subanalyses due to a limit number of studies. A major limitation in the evidence for this comparison is the lack of confidence in author reporting of units and conversions (especially for Amiri et al., which we often had to leave out).

Meta-analysis/descriptive analysis summary

In the meta-analysis, metformin+anti-androgen+lifestyle was superior compared to metformin+lifestyle in improving hyperandrogenism (FAI and testosterone), fasting insulin and fasting glucose. For other outcomes, no difference was observed. Certainty in the evidence is low or very low.
Regarding individual studies, not included in the meta-analysis, no differences was observed. Certainty in the evidence for the individual studies were high or low.
Adverse effects seemed to be similar in both groups (see table at the end).

Note
Only one new study added, compared to the previous TR (Long et al 2022).

Author, year, country	Population	Sample Size per group	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Type of analysis and subgroup	ROB
Gambineri et al. 2006 Italy	overweight-obese women with PCOS	1.Metfromin+LS=20 2.SPL+LS=17 3.Metfromin+SPL+LS=20 4.Placebo+LS=20	6 months	1.35 ±4 2.33 ±4 3.35±5 4.37±5	1.28±8 2.26 ±6 3.26±5 4.26±5	Weight, BMI, SHBG, T, hirsutism	META BMI>28	**ROB low**
Ganie et al. 2013 India	women who met the 2006 Androgen Excess-PCOS criteria for PCOS	1.Metfromin+LS=56 2.SPL+LS=51 3.Metformin+SPL+LS=62	6 months	1: 26.0±4.1 2: 24.3±3.7 3: 24.9±4.9	1: 22.4±5.3 2: 23.6±5.2 3: 23.6±4.7	Weight, BMI, WHR, no cycles/12 months, hirsutism, T, f-insulin, f-gluc, HOMA-IR, adverse effects	META	**ROB Low**
Amiri et al. 2014 Iran	overweight and obese infertile PCOS women	1.Metfromin+LS=25 2.SPL+LS=27 3.Metfromin+SPL+LS=27 4.Placebo+LS=26	6 months	>19 kg/m$_2$ and	18-40	Whr, BMI, SHBG, T, hirsutism	META Adults	**ROB Moderate**

				<35 kg/m2.				
Long et al 2022 China	Women with PCOS aged >18yr	1. metformin+LS N=54 2. SPL+LS N=53 3.Metformin+SPL+LS=51	3 months	1.25.6 ± 4.5 2.25.9 ±6.7 3.25.4 ±3.7	1.27.0 ± 3.7 2.27.6 ±3.7 3.27.2 ±3.6	Weight, BMI, WHR, FAI, HOMA,	META Adults	**ROB Moderate**
Mazza et al. 2014 Italy	overweight/ obese patients with PCOS (BMI not specified)	1.Metformin+LS=26 2.Metformin+SPL+LS=26	6 months	1: 31.1±5 2: 32.8±5.6	1: 23.3±4.2 2: 23.1±3.8	Weight, BMI, hirsutism, shbg, FAI, T, dheas, f-insulin, f-gluc, lipids, homa	META Adult	**ROB Low**

Results of meta-analysis

Outcome	Time point	RCTs	N	Effect, random, MD	P-value	I2 (%)	Favours	Certainty
Weight (kg)	3-6 months	4	315	2.77 (-2.78 to 8.32)	0.33	79	No difference	⊕◯◯◯ VERY LOW
WHR	3-6 months	3	275	0.01 (-0.02 to 0.04)	0.51	66	No difference	⊕◯◯◯ VERY LOW
BMI (kg/m2)	3-6 months	5	367	0.30 (-0.51 to 1.12)	0.46	4	No difference	⊕⊕◯◯ LOW
Hirsutism	6 months	4	262	0.58 (-0.69 to 1.86)	0.37	41	No difference	⊕⊕◯◯ LOW
SHBG (nmol/l)	6 months	3	144	0.59 (-3.34 to 4.53)	0.77	13	No difference	⊕⊕◯◯ LOW
FAI	**3-6 months**	**3**	**197**	**1.41 (0.54 to 2.29)**	**0.002**	**0**	**Met+AA+LS**	⊕⊕◯◯ LOW
Testosterone (nmol/)	**3-6 months**	**5**	**367**	**0.26 (0.08 to 0.43)**	**0.004**	**49**	**Met+AA+LS**	⊕⊕◯◯ LOW
Fasting insulin (ulU/ml)	**3-6 months**	**4**	**315**	**1.73 (0.12 to 3.33)**	**0.04**	**15**	**Met+AA+LS**	⊕⊕◯◯ LOW
Fasting glucose (mg/dl)	**3-6 months**	**5**	**367**	**2.59 (0.38 to 4.80)**	**0.02**	**18**	**Met+AA+LS**	⊕◯◯◯ VERY LOW
Total cholesterol	3-6 months	3	209	-6.02 (-13.92 to 1.89)	0.14	0	No difference	⊕◯◯◯ VERY LOW
HDL	6 months	3	144	0.55 (-5.14 to 6.25)	0.85	55	No difference	⊕◯◯◯ VERY LOW
LDL	6 months	3	144	2.98 (-11.84 to 17.79)	0.69	27	No difference	⊕◯◯◯ VERY LOW
Triglycerides	6 months	3	144	-1.23 (-16.97 to 14.51)	0.88	0	No difference	⊕◯◯◯ VERY LOW
DHEAS (Umol/l)	6 months	2	92	0.24 (-0.45 to 0.92)	0.50	67	No difference	⊕◯◯◯ VERY LOW
HOMA-IR	3-6 months	3	275	0.21 (-0.08 to 0.51)	0.15	0	No difference	⊕⊕◯◯ LOW

Individual studies not included in meta-analysis

Outcome	Author, year	Time point	N	Metformin+LS	Metformin+AA+LS	P-value	Favours	Grading
Androstenedione	Gambineri 2006	12 months	Met+LS=20 MET+AA+LS=20	Mean +/- SD 263 +/- 172	Mean +/- SD 258 +/- 118	0.91	No difference	⊕⊕◯◯ LOW[1]

OGTT (mg/dl/120 min)	Amiri et al. 2014	6 months	Met+LS=25 MET+AA+LS=27	Mean +/- SD 112.1 +/- 30.5	Mean +/- SD 107.22+/- 25.9	0.54	No difference	⊕⊕◯◯ LOW[2]
Menstrual cycles/6months	Gambineri et al. 2006	6 months	M+LS=20 M+LS+AA=20	Means +/- SD 4.3 +/- 1.5	Means +/- SD 4.3 +/- 1.5	1.0	No difference	⊕⊕◯◯ LOW[1]
Menstrual cycles/12months	Ganie et al. 2013	6 months	M+LS=56 M+LS+AA=62	Means +/- SD 10.02 +/- 3.16	Means +/- SD 10.86 +/- 3.2	0.15	No difference	⊕⊕⊕⊕ HIGH

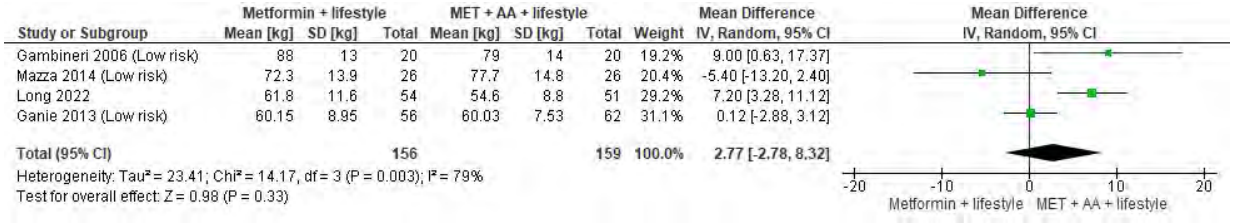
[1] Downgraded twice for small number of participants
[2] Downgraded once for mod ROB and downgraded once for small number of participants

OUTCOME 11.1 Weight (kg)

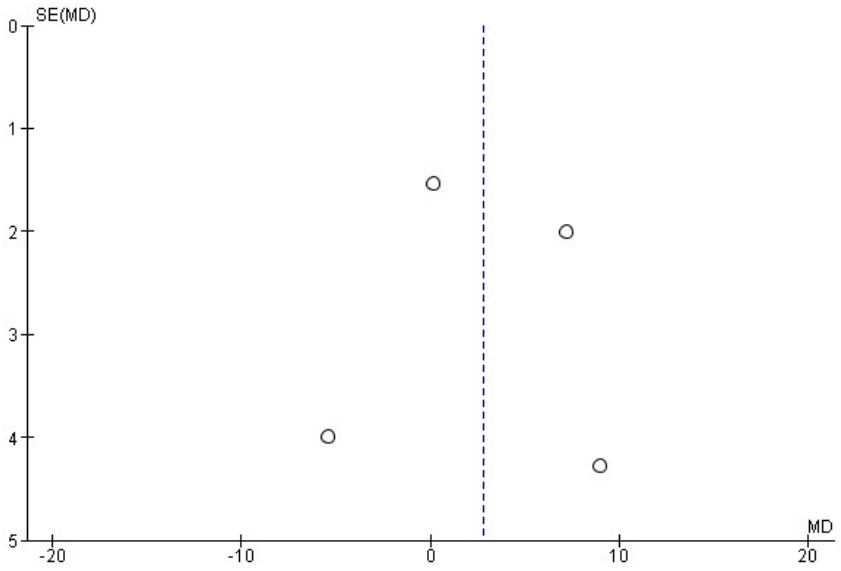
11.1.1 Individual Study Data Table

	OUTCOME: Weight					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin+lifestyle versus **metformin+anti-androgen+lifestyle**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Gambineri et al. 2006	kg	20	88	14	20	79	10	BMI>=28	6
Gambineri et al. 2006	kg	20	88	13	20	79	14	BMI>=28	12
Ganie et al. 2013	kg	56	60.15	8.95	62	60.03	7.53		6
Mazza et al. 2014	kg	26	72.3	13.9	26	77.7	14.8		6
Long et al. 2022	kg	54	60.15	8.95	51	60.03	7.53		3

11.1.2. Forrest plot metformin+lifestyle vs metformin+anti-androgen+lifestyle for weight



11.1.3. Funnel plot for assessment of publication bias

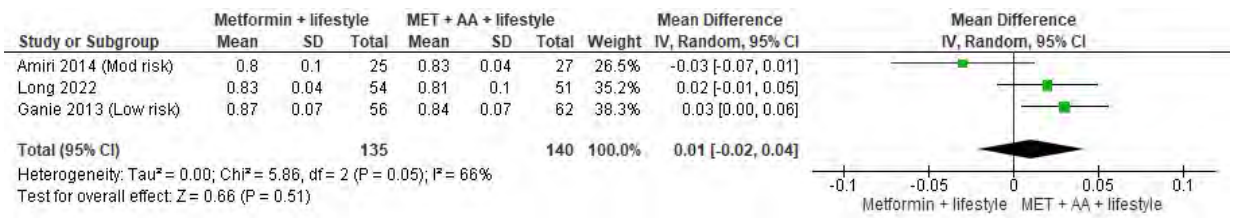


OUTCOME 11.2 WHR

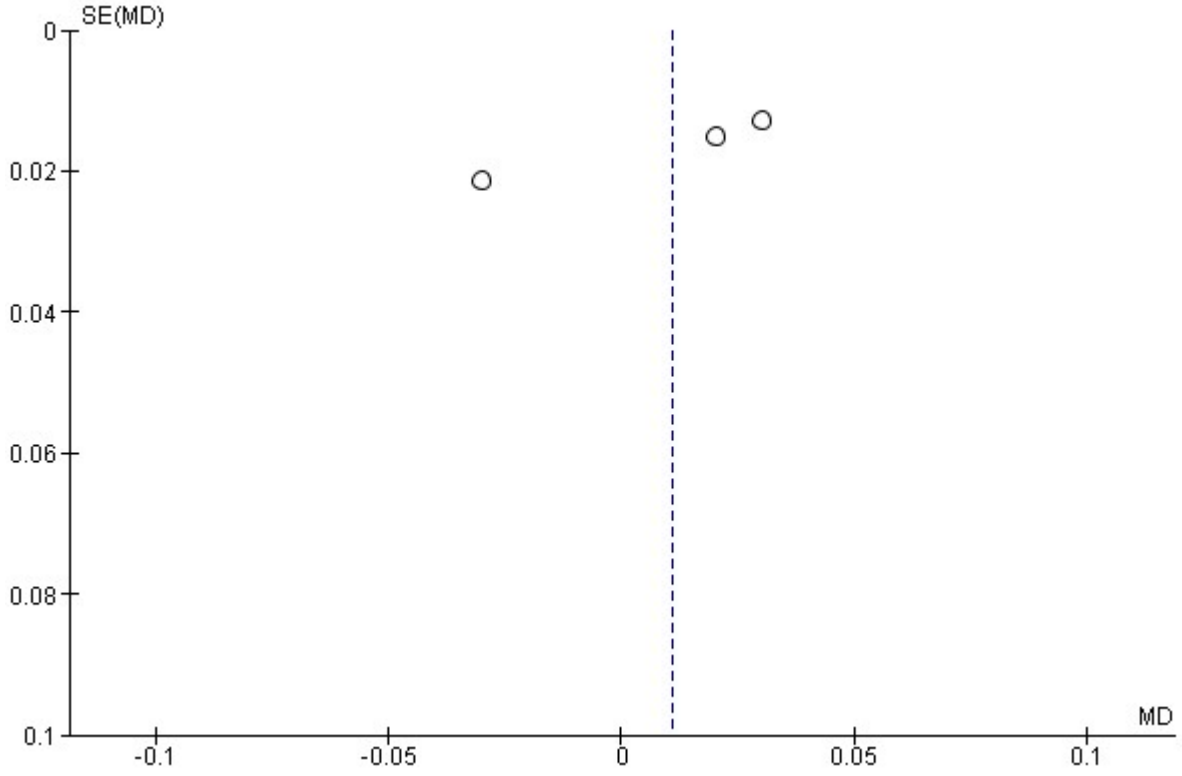
11.2.1 Individual Study Data Table

	OUTCOME: WHR					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin+lifestyle versus **metformin+anti-androgen+lifestyle**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Amiri et al. 2014		25	0.8	0.1	27	0.83	0.04	crude	6
Ganie et al. 2013		56	0.87	0.07	62	0.84	0.07		6
Long et al. 2022		54	0.83	0.04	51	0.81	0.1		3

11.2.2. Forrest plot metformin+lifestyle vs metformin+anti-androgen+lifestyle for WHR



11.2.3. Funnel plot for assessment of publication bias



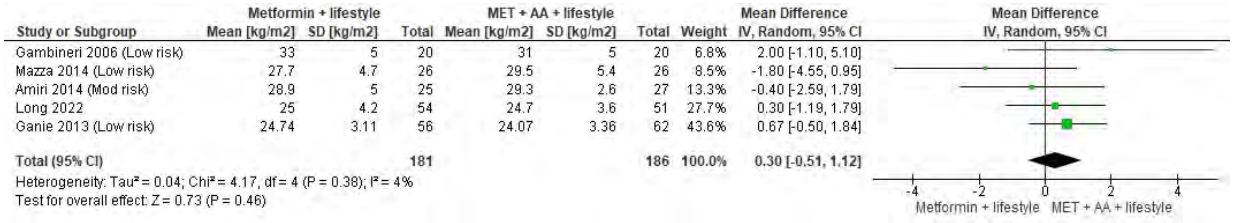
OUTCOME 11.3 BMI (kg/m2)

11.3.1 Individual Study Data Table

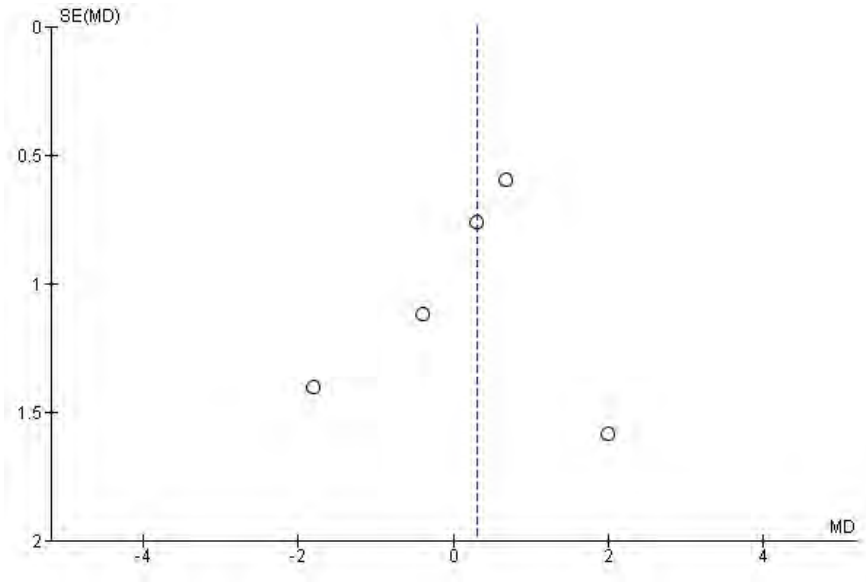
	OUTCOME: BMI						**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin+lifestyle versus **metformin+anti-androgen+lifestyle**								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Amiri et al. 2014	Kg/m2	weighted	25	28.9	5	27	29.3	2.6	crude	6
Gambineri et al. 2006	Kg/m2	weighted	20	33	5	20	31	4	BMI>=28	6
Gambineri et al. 2006	Kg/m2	weighted	20	33	5	20	31	5	BMI>=28	12
Ganie et al. 2013	Kg/m2	weighted	56	24.74	3.11	62	24.07	3.36		6

Mazza et al. 2014	Kg/m2	weighted	26	27.7	4.7	26	29.5	5.4		6
Long et al. 2022	Kg/m2	weighted	54	25	4.2	51	24.7	3.6		3

11.3.2. Forrest plot metformin+lifestyle vs metformin+anti-androgen+lifestyle for BMI



11.3.3. Funnel plot for assessment of publication bias

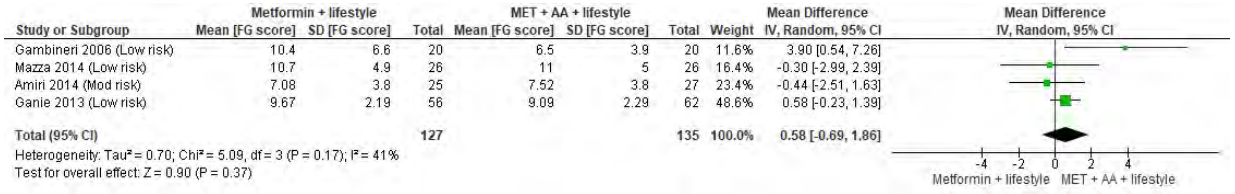


OUTCOME 11.4 Hirsutism (FGS)

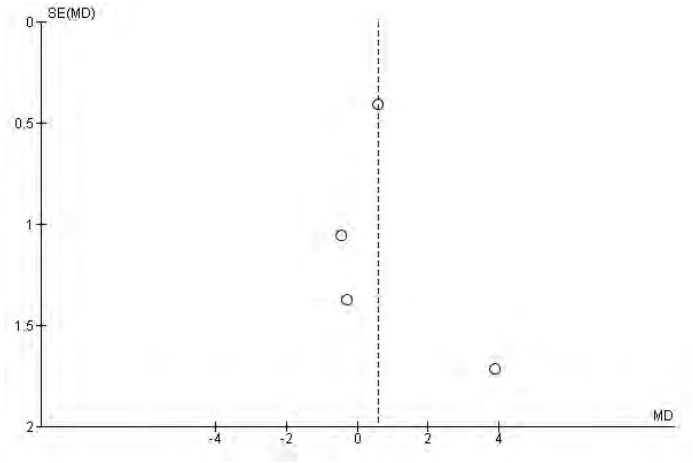
11.4.1 Individual Study Data Table

	OUTCOME: hirsutism						**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin+lifestyle versus **metformin+anti-androgen+lifestyle**								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Amiri et al. 2014	score	FGS	25	7.08	3.8	27	7.52	3.8	crude	6
Gambineri et al. 2006	score	FGS	20	10.9	8.6	20	7.9	4.3	BMI>=28	6
Gambineri et al. 2006	score	FGS	20	10.4	6.6	20	6.5	3.9	BMI>=28	12
Ganie et al. 2013	score	FGS	56	9.67	2.19	62	9.09	2.29		6
Mazza et al. 2014	score	FGS	26	10.7	4.9	26	11.0	5.0		6

11.4.2. Forrest plot metformin+lifestyle vs metformin+anti-androgen+lifestyle for hirsutism



11.4.3. Funnel plot for assessment of publication bias

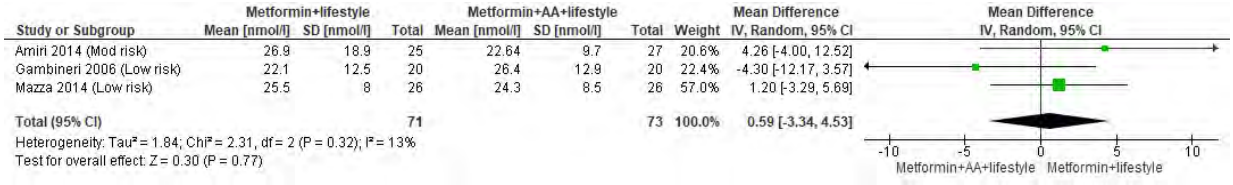


OUTCOME 11.5 SHBG (Nmol/l)

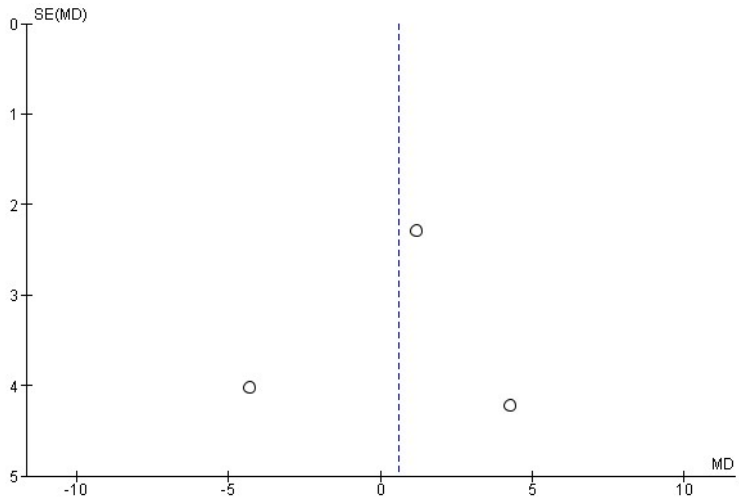
11.5.1 Individual Study Data Table

	OUTCOME: SHBG					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin+lifestyle versus **metformin+anti-androgen+lifestyle**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Amiri et al. 2014	Nmol/l	25	26.9	18.9	27	22.64	9.7	crude	6
Gambineri et al 2006	Nmol/l	20	19.2	10.6	20	26.3	14.7		6
Gambineri et al 2006	Nmol/l	20	22.1	12.5	20	26.4	12.9		12
Mazza et al. 2014	Nmol/l	26	25.5	8.0	26	24.3	8.5		6

11.5.2. Forrest plot metformin+lifestyle vs metformin+anti-androgen+lifestyle for SHBG



11.5.3. Funnel plot for assessment of publication bias

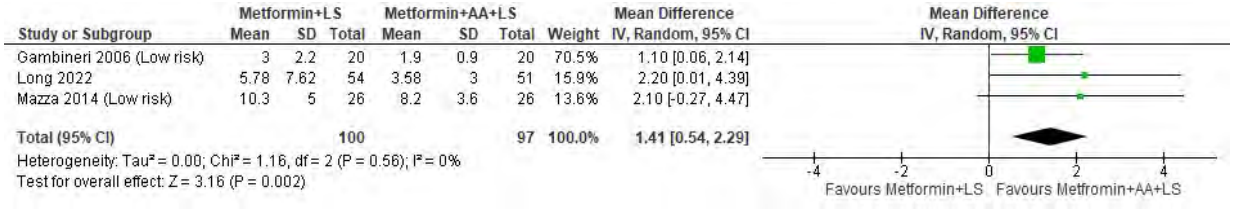


OUTCOME 11.6 FAI

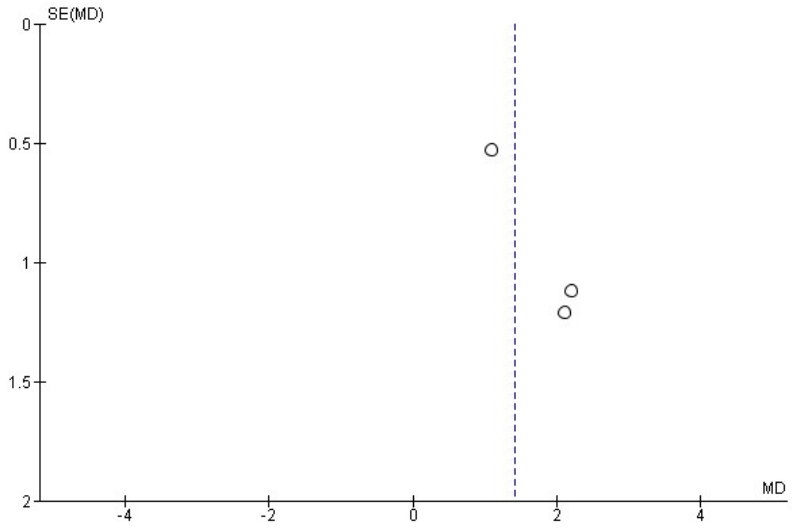
11.6.1 Individual Study Data Table

	OUTCOME: FAI					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): lifestyle+metformin+ versus lifestyle+metformin+anti-androgen							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something special?**	**Time period (month)**
Gambineri et al 2006		20	3	2.2	19	1.9	0.9		6
Long et al. 2022		54	5.78	7.62	51	3.58	3		3
Mazza et al. 2014		26	10.3	5	26	8.2	3.6		6

11.6.2. Forrest plot metformin+lifestyle vs metformin+anti-androgen+lifestyle for FAI



11.6.3. Funnel plot for assessment of publication bias

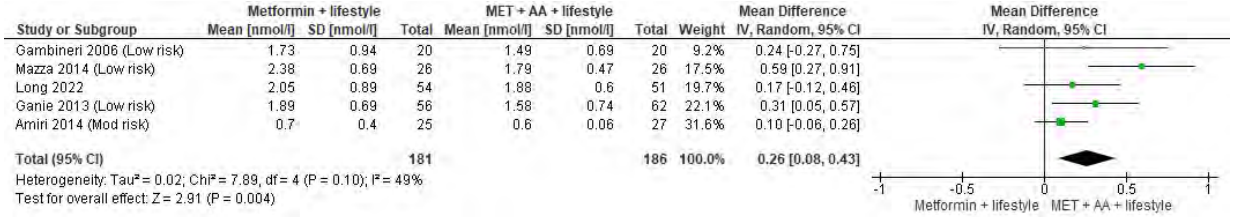


OUTCOME 11.7 Testosterone (Nmol/l)

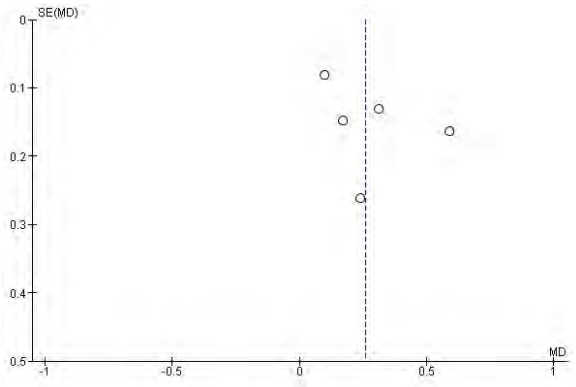
11.7.1 Individual Study Data Table

	OUTCOME: Testosterone				**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable): metformin+lifestyle versus **metformin+anti-androgen+lifestyle**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Amiri et al. 2014	Nmol/l	25	0.7	0.4	27	0.6	0.06	crude	6
Ganie et al. 2013	Nmol/l	56	1.89	0.69	62	1.58	0.74		6
Gambineri et al. 2006	Nmol/l	20	1.73	0.94	20	1.49	0.69	BMI>=28	6
Gambineri et al. 2006	Ng/ml	20	0.50	0.27	20	0.43	0.20	BMI>=28	12
Mazza et al. 2014	Nmol/l	26	2.38	0.69	26	1.79	0.47		6
Long et al. 2022	Nmol/l	54	2.05	0.89	51	1.88	0.6		3

11.7.2. Forrest plot metformin+lifestyle vs metformin+anti-androgen+lifestyle for testosterone



11.7.3. Funnel plot for assessment of publication bias

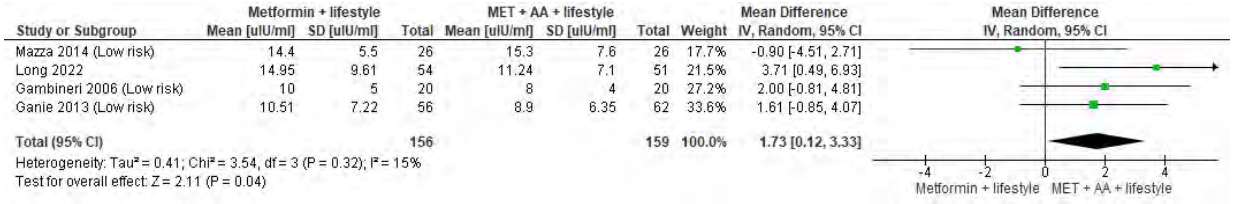


OUTCOME 11.8 Fasting insulin (uIU/ml)

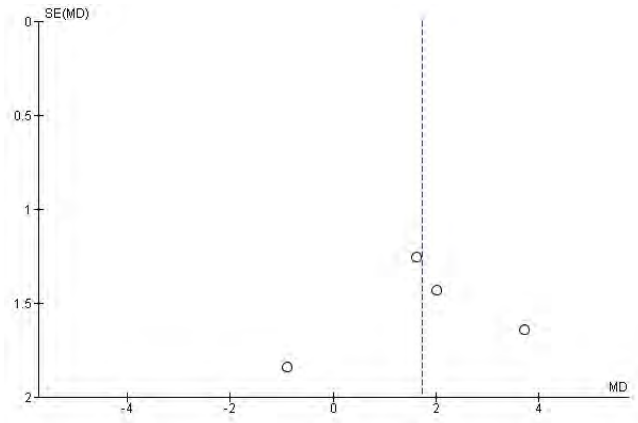
11.8.1 Individual Study Data Table

	OUTCOME: fasting insulin					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin+lifestyle versus **metformin+anti-androgen+lifestyle**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Amiri et al. 2014	Pmol/l	25	13.7	7.1	27	11.6	6.2	Unit?	6
Ganie et al. 2013	uU/ml	56	10.51	7.22	62	8.9	6.35		6
Gambineri et al 2006	uU/ml	20	14	5	20	11	5		6
Gambineri et al 2006	uU/ml	20	10	5	20	8	4		12
Mazza et al. 2014	uU/ml	26	14.4	5.5	26	15.3	7.6		6
Long et al. 2022	uU/ml	54	14.95	9.61	51	11.24	7.1		3

11.8.2. Forrest plot metformin+lifestyle vs metformin+anti-androgen+lifestyle for fasting insulin



11.8.3. Funnel plot for assessment of publication bias

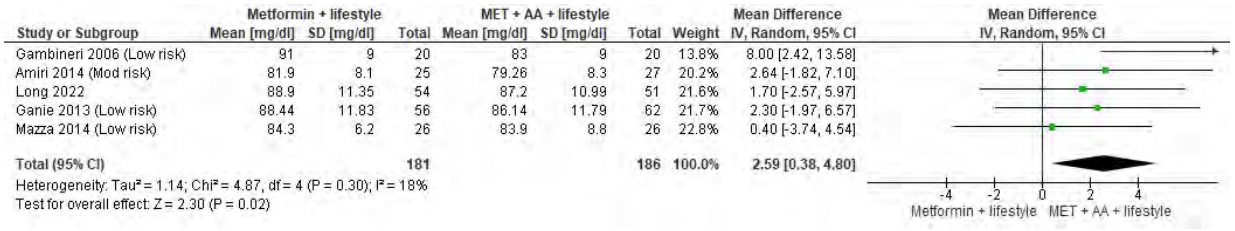


OUTCOME 11.9 Fasting glucose (mg/dl)

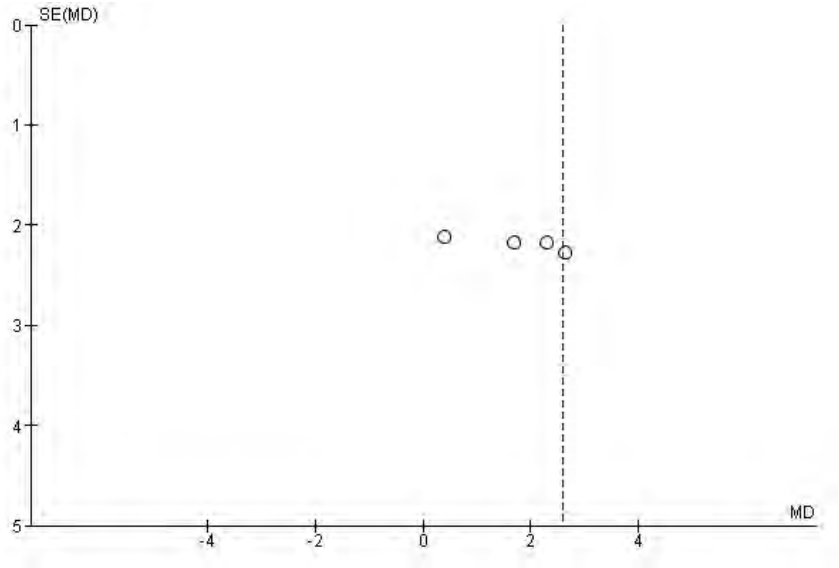
11.9.1 Individual Study Data Table

	OUTCOME: fasting glucose				**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable): metformin+lifestyle versus **metformin+anti-androgen+lifestyle**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Amiri et al. 2014	Mg/dl	25	81.9	8.1	27	79.26	8.3	crude	6
Ganie et al. 2013	Mg/dl	56	88.44	11.83	62	86.14	11.79		6
Gambineri et al 2006	Mg/dl	20	91	9	20	83	10		6
Gambineri et al 2006	Mg/dl	20	91	9	20	83	9		12
Mazza et al. 2014	Mg/dl	26	84.3	6.2	26	83.9	8.8		6
Long et al. 2022	Mmol/l Mg/dl	54	4.94 88.90	0.63 11.35	51	4.84 87.20	0.61 10.99		3

11.9.2. Forrest plot metformin+lifestyle vs metformin+anti-androgen+lifestyle for fasting glucose



11.9.3. Funnel plot for assessment of publication bias

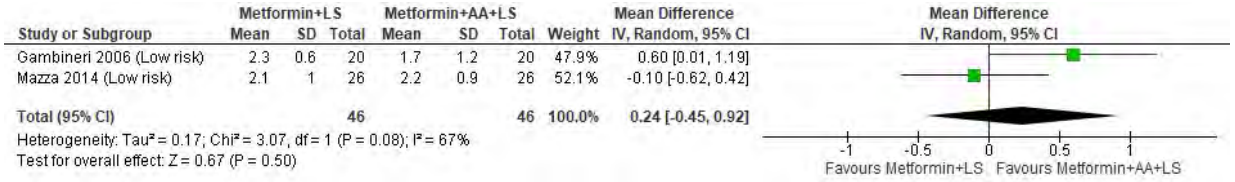


OUTCOME 11.10 DHEAS (Ug/ml)

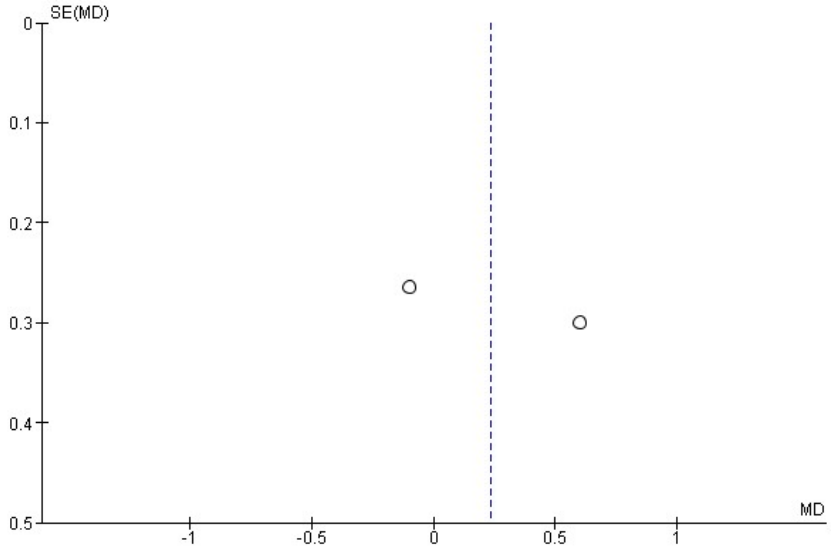
11.10.1 Individual Study Data Table

	OUTCOME: DHEAS					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin+lifestyle versus **metformin+anti-androgen+lifestyle**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Amiri et al. 2014	Ug/ml	25	222.5	129.1	27	156.08	73.6	Unit?	6
Gambineri et al 2006	Ug/ml	20	2.3	0.6	20	1.9	1.2		6
Gambineri et al 2006	Ug/ml	20	2.3	0.6	20	1.7	1.2		12
Mazza et al. 2014	Ug/ml	26	2.1	1	26	2.2	0.9		6

11.10.2. Forrest plot metformin+lifestyle vs metformin+anti-androgen+lifestyle for DHEAS



11.10.3. Funnel plot for assessment of publication bias

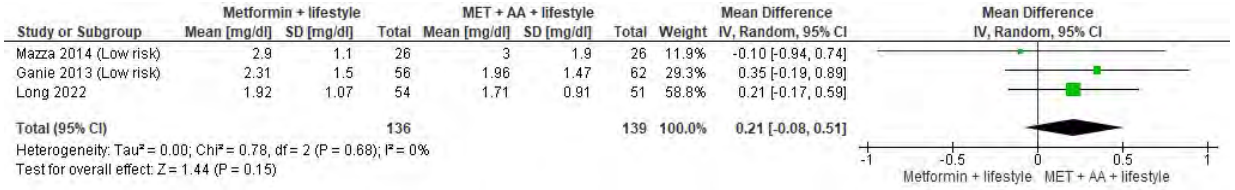


OUTCOME 11.11 HOMA-IR

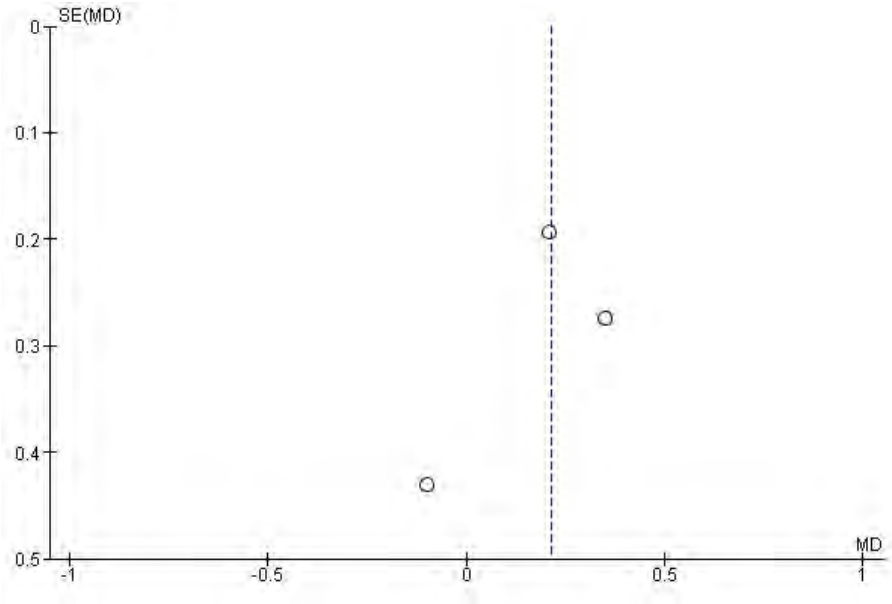
11.11.1 Individual Study Data Table

	OUTCOME: HOMA-IR					OUTCOME TYPE: Continuous			
		COMPARISON (if applicable): metformin+lifestyle versus metformin+anti-androgen+lifestyle							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Ganie et al. 2013		56	2.31	1.5	62	1.96	1.47		6
Mazza et al. 2014		26	2.9	1.1	26	3.0	1.9		6
Long et al. 2022		54	11.92	1.07	51	1.71	0.91		3

11.11.2. Forrest plot metformin+lifestyle vs metformin+anti-androgen+lifestyle for HOMA-IR



11.11.3. Funnel plot for assessment of publication bias

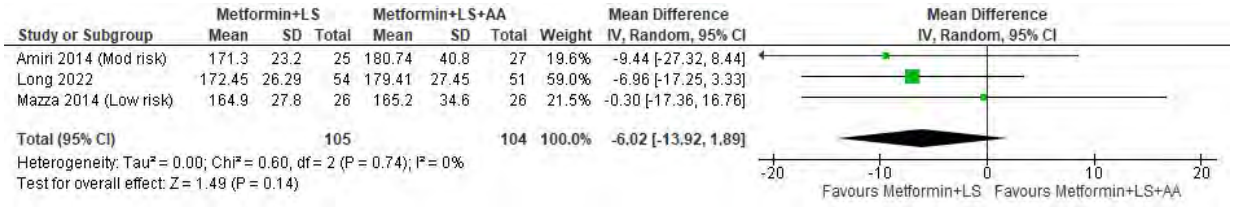


OUTCOME 11.12 Total cholesterol (mg/dl)

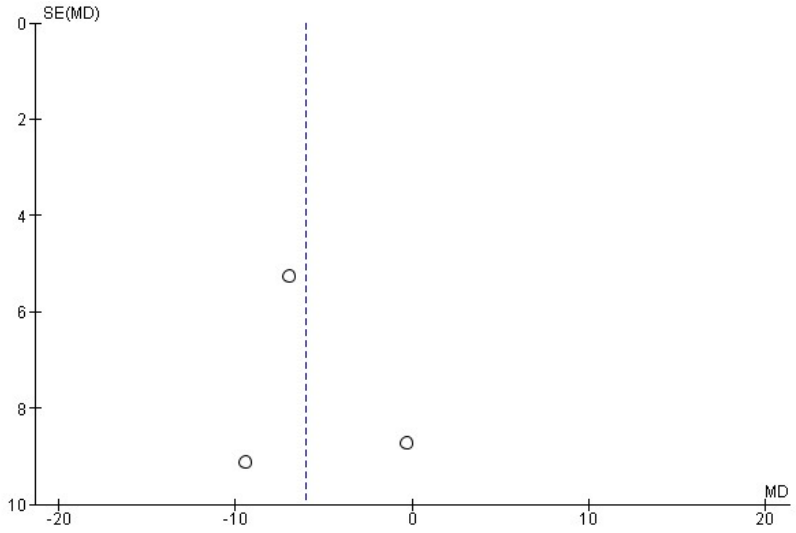
11.12.1 Individual Study Data Table

	OUTCOME: Total cholesterol					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin+lifestyle versus **metformin+anti-androgen+lifestyle**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Amiri et al. 2014	mM/l	25	171.3	23.2	27	180.74	40.8	Unit?	6
Mazza et al. 2014	Mg/dl	26	164.9	27.8	26	165.2	34.6		6
Long et al. 2022	Mg/dl	54	172.45	26.29	51	179.41	27.45		3

11.12.2. Forrest plot metformin+lifestyle vs metformin+anti-androgen+lifestyle for total cholesterol



11.12.3. Funnel plot for assessment of publication bias

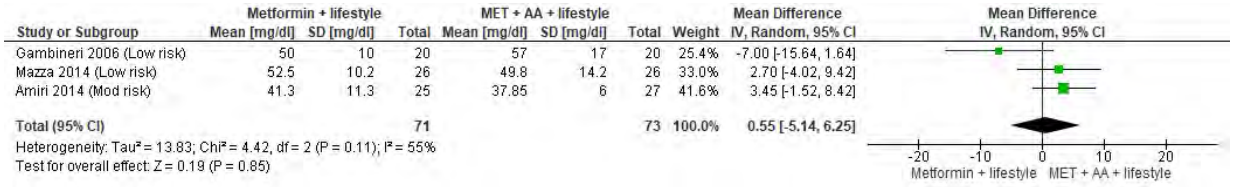


OUTCOME 11.13 HDL (mg/dl)

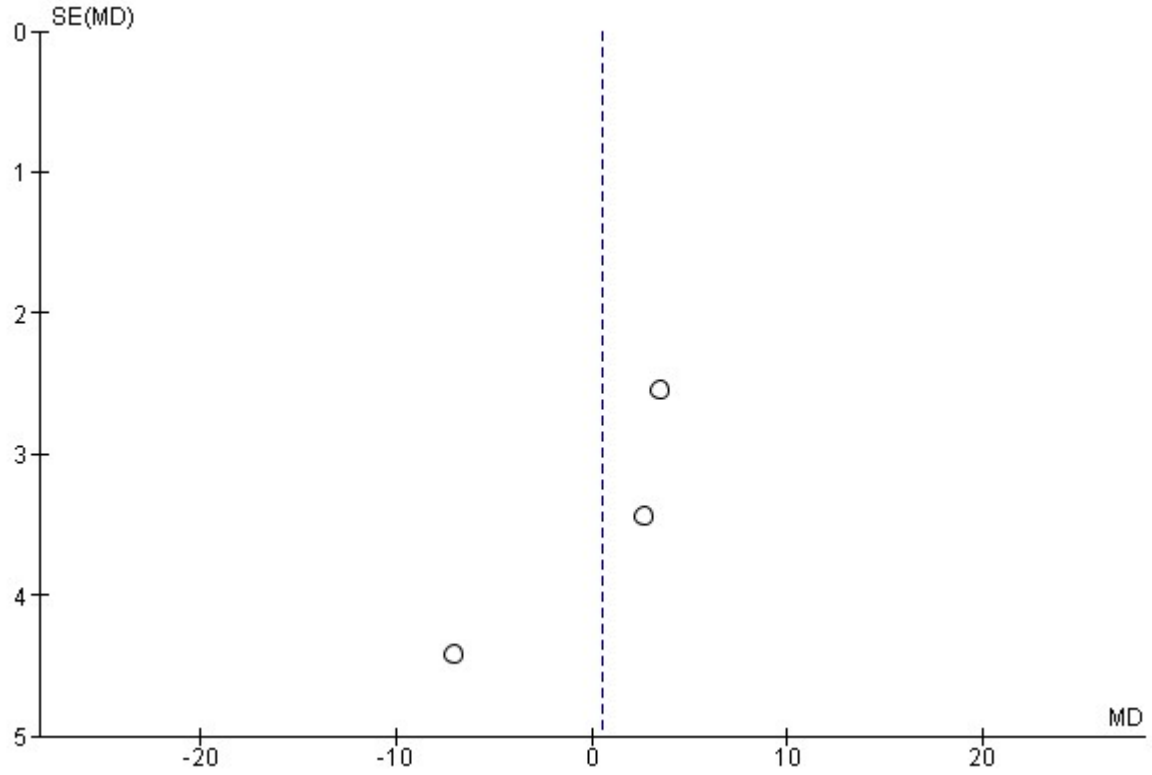
11.13.1 Individual Study Data Table

	OUTCOME: HDL					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin+lifestyle versus **metformin+anti-androgen+lifestyle**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Amiri et al. 2014	mM/l	25	41.3	11.3	27	37.85	6	Unit?	6
Gambineri et al 2006	Mg/dl	20	45	8	20	54	13		6
Gambineri et al 2006	Mg/dl	20	50	10	20	57	17		12
Mazza et al. 2014	Mg/dl	26	52.5	10.2	26	49.8	14.2		6

11.13.2. Forrest plot metformin+lifestyle vs metformin+anti-androgen+lifestyle for HDL



11.13.3. Funnel plot for assessment of publication bias



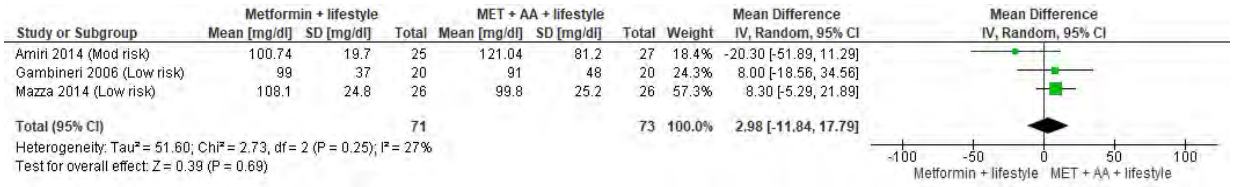
OUTCOME 11.14 LDL (mg/dl)

11.14.1 Individual Study Data Table

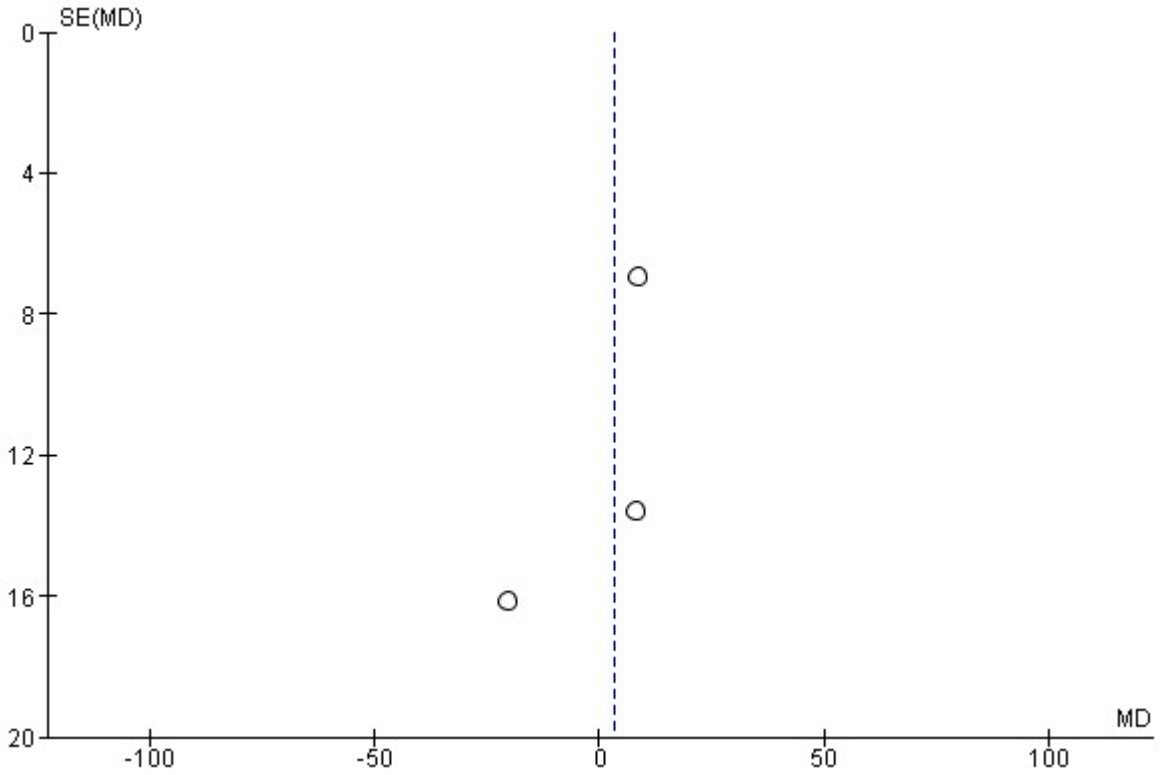
	OUTCOME: LDL					OUTCOME TYPE: Continuous			
		COMPARISON (if applicable): metformin+lifestyle versus metformin+anti-androgen+lifestyle							
Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	N	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	N	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	Time period (month)

Amiri et al. 2014	mM/l	25	100.74	19.7	27	121.04	81.2	Unit?	6
Gambineri et al 2006	mg/dl	20	104	34	20	105	26		6
Gambineri et al 2006	mg/dl	20	99	37	20	91	48		12
Mazza et al. 2014	Mg/dl	26	108.1	24.8	26	99.8	25.2		6

11.14.2. Forrest plot metformin+lifestyle vs metformin+anti-androgen+lifestyle for LDL



11.14.3. Funnel plot for assessment of publication bias

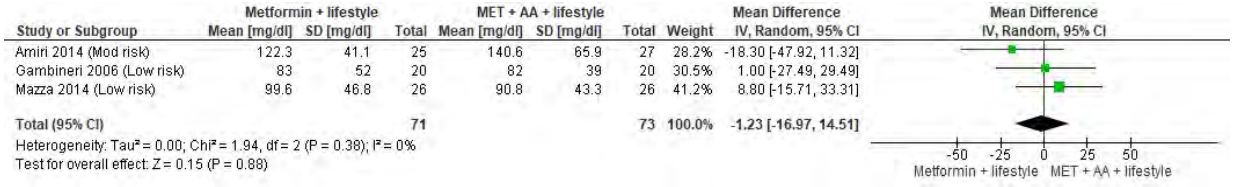


OUTCOME 11.15 Triglycerides (mg/dl)

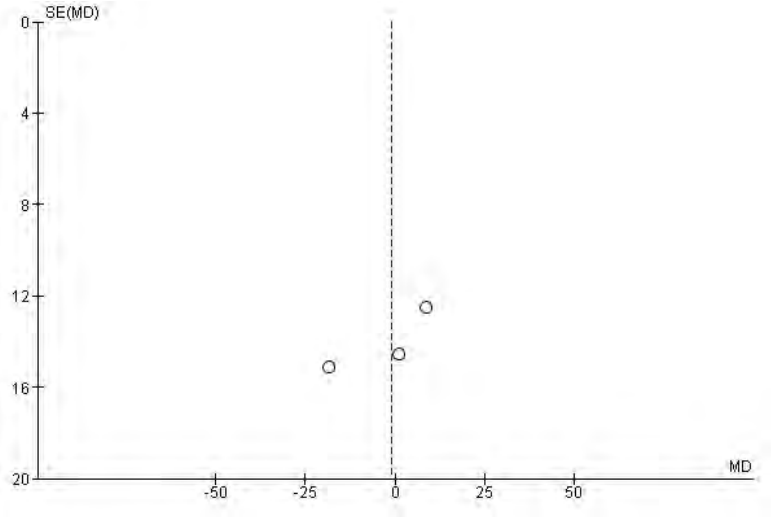
11.15.1 Individual Study Data Table

	OUTCOME: Triglycerides					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin+lifestyle versus **metformin+anti-androgen+lifestyle**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Amiri et al. 2014	mM/l	25	122.3	41.1	27	140.6	65.9	unit?	6
Gambineri et al 2006	Mg/dl	20	97	36	20	87	46		6
Gambineri et al 2006	Mg/dl	20	83	52	20	82	39		12
Mazza et al. 2014	Mg/dl	26	99.6	46.8	26	90.8	43.3		6

11.15.2. Forrest plot metformin+lifestyle vs metformin+anti-androgen+lifestyle for triglycerides



11.15.3. Funnel plot for assessment of publication bias



Adverse effects

	Study	Metformin+LS	Metformin+anti-androgen+LS
Gastrointestinal side effects (diarrhea,vomiting etc)	Long 2022	4/54	4/51
	Ganie 2013	9/56 (diarrhea)	7/62 (diarrhea) 2/62 (nausea)
Nausea	Long 2022	6/54	5/54

Comparison 12: Metformin+lifestyle versus anti-androgen+lifestyle (also in Q4.6 – not identical since timeline is different)

Evidence Summary

Five randomised controlled trials (RCTs) were identified by our search. Of these RCT, all were included in the meta-analysis.
Of these studies two had a low ROB and three a moderate ROB. All studies reported outcomes on adults. One study reported outcomes on obese PCOS-women (Gambineri et al. 2006).

Rows highlighted grey indicate studies with participants described as obese. Unfortunately, we were not able to perform any subanalyses due to a limit number of studies. A major limitation in the evidence for this comparison is the lack of confidence in author reporting of units and conversions (especially for Amiri et al., which we often had to leave out).

Meta-analysis/descriptive analysis summary

In the meta-analysis, anti-androgen+lifestyle was superior compared to metformin+lifestyle in improving hirsutism and increasing SHBG. In this meta-analysis also number of menstrual cycles/year increased with anti-androgen+lifestyle combination compared to metformin+lifestyle. For other outcomes, no difference was observed. Certainty in the evidence is low or very low.
Regarding individual studies, not included in the meta-analysis, Gambineri et al. found that participants using anti-androgen+lifestyle had a higher, more favourable HDL compared to those with metformin and lifestyle (certainty low).
Patients using metformin reported more GI adverse effects, whereas those using anti-androgens reported more polyuria and dryness of mouth (please see table at the end).

Author, year, country	Population	Sample Size per group	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Type of analysis and subgroup	ROB
Gambineri et al. 2006 Italy	overweight-obese women with PCOS	1.Metfromin+LS=20 2.SPL+LS=17 3.Metfromin+SPL+LS=20 4.Placebo+LS=20	6 months	1.35 ±4 2.33 ±4 3.35±5 4.37±5	1.28±8 2.26 ±6 3.26±5 4.26±5	Weight, BMI, SHBG, T, hirsutism	META BMI>28	**ROB low**
Ganie et al. 2004 India	Young and adolescent women with PCOS (mean age of 22.6 and mean BMI of 26.8)	1.Metfromin+LS=35 2.SPL+LS=34	6 months	1: 26.5±5.6 2: 25.9±5.0	1: 22.9±5.3 2: 23.3±5.2	BMI, WHR, no cycles/12 months, hirsutism, T, DHEAS, f-insulin, f-gluc, HOMA-IR	META Adults	**ROB Moderate**
Ganie et al. 2013 India	women who met the 2006 Androgen Excess-PCOS criteria for PCOS	1.Metfromin+LS=56 2.SPL+LS=51 3.Metformin+SPL+LS=62	6 months	1: 26.0±4.1 2: 24.3±3.7 3: 24.9±4.9	1: 22.4±5.3 2: 23.6±5.2 3: 23.6±4.7	Weight, BMI, WHR, no cycles/12 months, hirsutism, T, f-insulin, f-gluc, HOMA-IR, adverse effects	META Adults	**ROB Low**
Amiri et al. 2014 Iran	overweight and obese infertile PCOS women	1.Metfromin+LS=25 2.SPL+LS=27 3.Metfromin+SPL+LS=27 4.Placebo+LS=26	6 months	>19 kg/m_2 and <35 kg/m_2.	18-40	Whr, BMI, SHBG, T, hirsutism	META Adults	**ROB Moderate**
Long et al 2022 China	Women with PCOS aged >18yr	1. metformin+LS N=54 2. SPL+LS N=53 3.Metformin+SPL+LS=51	3 months	1.25.6 ± 4.5 2.25.9 ±6.7 3.25.4 ±3.7	1.27.0 ± 3.7 2.27.6 ±3.7 3.27.2 ±3.6	Weight, BMI, WHR, FAI, HOMA,	META Adults	**ROB Moderate**

Results of meta-analysis

Outcome	Time point	RCTs	N	Effect, random, MD	P-value	I2 (%)	Favours	Certainty
Weight (kg)	3-6 months	3	251	2.85 (-4.80 to 10.51)	0.47	85	No difference	⊕◯◯◯ VERY LOW
WHR	3-6 months	3	283	-0.00 (-0.03 to 0.02)	0.64	39	No difference	⊕⊕◯◯ LOW
BMI (kg/m2)	3-6 months	5	372	0.57 (-0.74 to 1.87)	0.40	52	No difference	⊕◯◯◯ VERY LOW
Hirsutism	**6 months**	**4**	**265**	**1.59 (0.12 to 3.06)**	**0.03**	**74**	**AA+LS**	⊕◯◯◯ VERY LOW
SHBG (nmol/l)	**6 months**	**2**	**89**	**7.70 (0.75 to 14.66)**	**0.03**	**0**	**AA+LS**	⊕◯◯◯ VERY LOW
FAI	3-6 months	2	144	0.68 (-0.51 to 1.87)	0.26	0	No difference	⊕⊕◯◯ LOW
Testosterone ng/ml)	3-6 months	4	320	0.07 (-0.13 to 0.28)	0.48	14	No difference	⊕⊕◯◯ LOW
Fasting insulin (mIU/l)	3-6 months	5	372	0.65 (-1.35 to 2.66)	0.52	54	No difference	⊕◯◯◯ VERY LOW
Fasting glucose (mg/dl)	3-6 months	5	372	-1.09 (-4.63 to 2.45)	0.54	69	No difference	⊕◯◯◯ VERY LOW
DHEAS (Umol/l)	6 months	2	106	1.02 (-1.24 to 3.27)	0.38	87	No difference	⊕◯◯◯ VERY LOW

HOMA-IR	3-6 months	3	283	-0.44 (-0.89 to 0.02)	0.06	22	No difference	⊕⊕◯◯ LOW
Number of cycles/year	**3-6 months**	**3**	**283**	**-0.88 (-1.43 to -0.33)**	**0.002**	**0**	**AA+LS**	⊕⊕◯◯ LOW

Individual studies not included in meta-analysis

Outcome	Author, year	Time point	N	Metformin+LS	Anti-androgen+LS	P-value	Favours	Grading
Total cholesterol	Long 2022	3 months	Met+LS=54 Anti-androgen+LS=53	Mean +/- SD 4.46 +/- 0.68	Mean +/- SD 4.75 +/- 0.98	0.08	No difference	⊕⊕⊕◯ MODERATE[1]
HDL	Gambineri 2006	12 months	Met+LS=20 Anti-androgen+LS=17	Mean +/- SD 50 +/- 10	Mean +/- SD 58 +/- 9	0.01	**Antiandrogen+LS**	⊕⊕◯◯ LOW[2]
LDL	Gambineri 2006	12 months	Met+LS=20 Anti-androgen+LS=17	Mean +/- SD 99 +/- 37	Mean +/- SD 88 +/- 28	0.20	No difference	⊕⊕◯◯ LOW[2]
Androstenedione	Gambineri 2006	12 months	Met+LS=20 Anti-androgen+LS=17	Mean +/- SD 263 +/- 172	Mean +/- SD 224 +/- 80	0.37	No difference	⊕⊕◯◯ LOW[2]
OGTT (mg/dl/120 min)	Amiri et al. 2014	6 months	Met+LS=25 Anti-androgen+LS=27	Mean +/- SD 112.1 +/- 30.5	Mean +/- SD 102.56 +/- 20.1	0.19	No difference	⊕⊕◯◯ LOW[3]

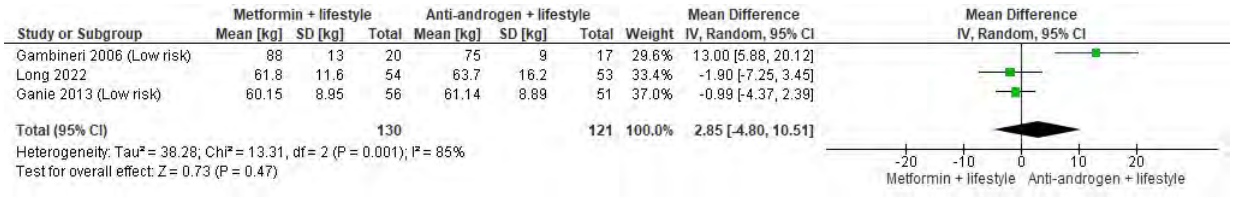
[1] Downgraded once for mod ROB
[2] Downgraded twice for small number of participants
[3] Downgraded once for mod ROB and downgraded once for small number of participants

OUTCOME 12.1 Weight (kg)

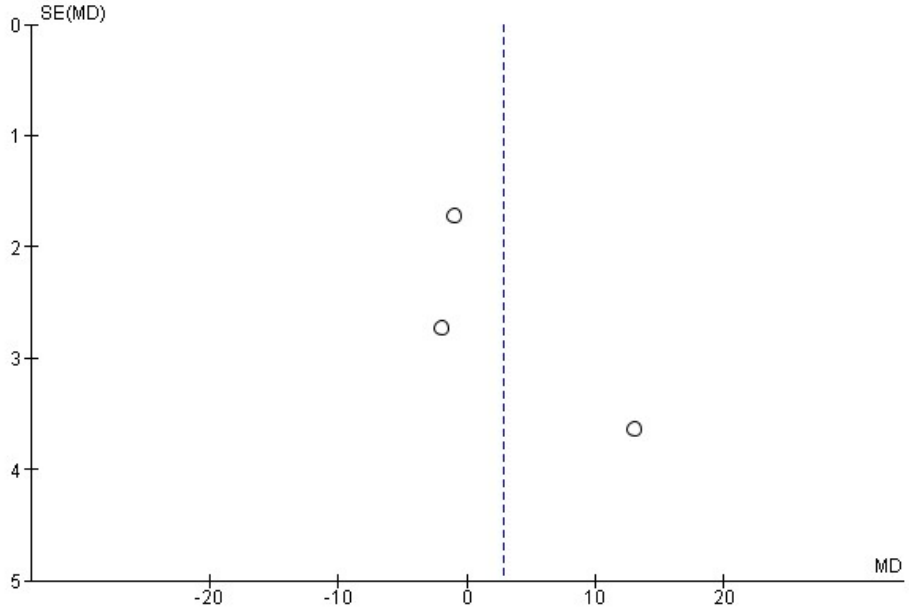
12.1.1 Individual Study Data Table

		COMPARISON (if applicable): lifestyle+metformin versus lifestyle+anti-androgen							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Gambineri et al. 2006	Kg	20	88	14	17	76	9	BMI>=28	6
Gambineri et al. 2006	Kg	20	88	13	17	75	9	BMI>=28	12
Ganie et al. 2013	kg	56	60.15	8.95	51	61.14	8.89		6
Long et al. 2022	kg	54	61.8	11.6	53	63.7	16.2		3

12.1.2. Forrest plot metformin+lifestyle vs anti-androgen+lifestyle for weight



12.1.3. Funnel plot for assessment of publication bias

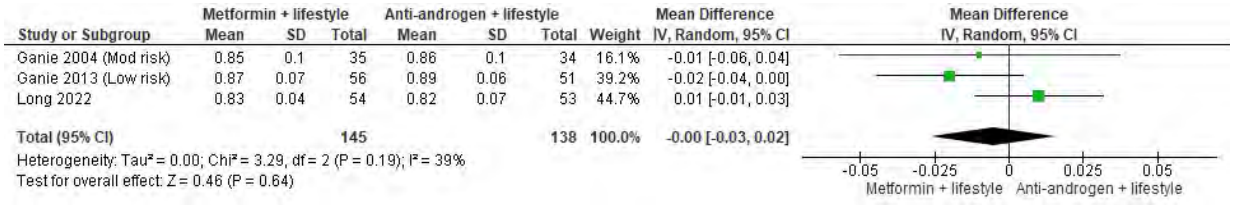


OUTCOME 12.2 WHR

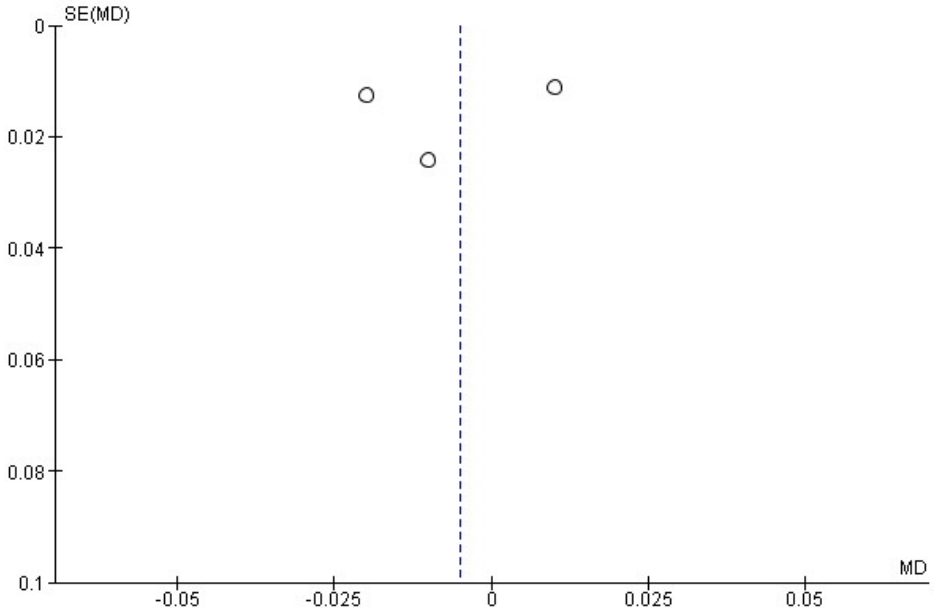
12.2.1 Individual Study Data Table

		COMPARISON (if applicable): **metformin+lifestyle** versus **anti-androgen+lifestyle**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Amiri et al. 2014		25	0.8	0.1	27	0.8	No SD	crude	6
Ganie et al. 2004		35	0.85	0.1	34	0.86	0.1	crude	6
Ganie et al. 2013		56	0.87	0.07	51	0.89	0.06	Crude	6
Long et al. 2022		54	0.83	0.04	53	0.82	0.07		3

12.2.2. Forrest plot metformin+lifestyle vs anti-androgen+lifestyle for WHR



12.2.3. Funnel plot for assessment of publication bias



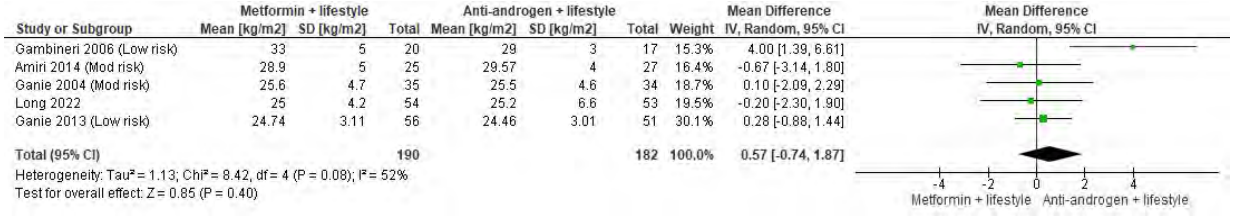
OUTCOME 12.3 BMI (kg/m2)

12.3.1 Individual Study Data Table

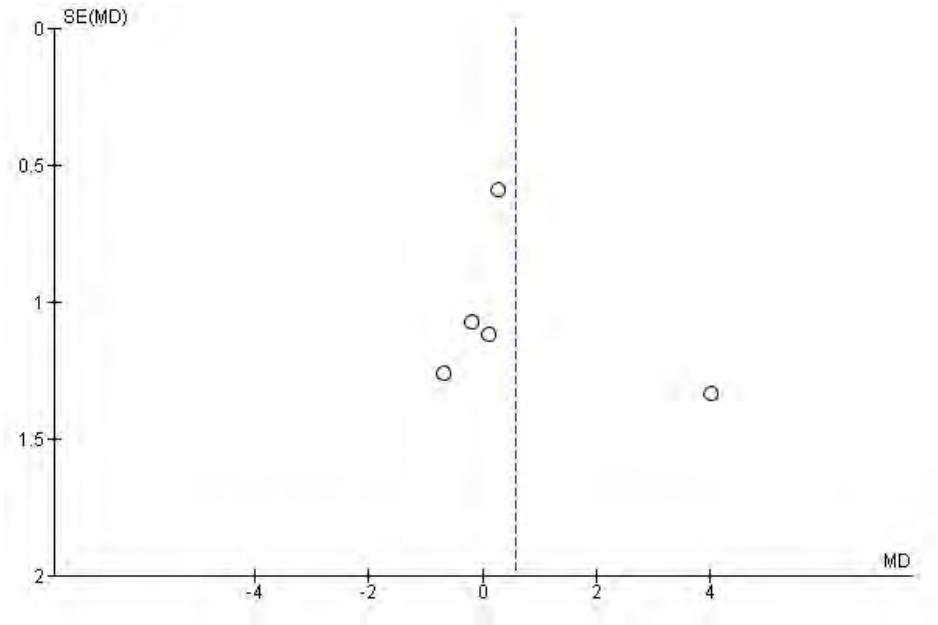
	OUTCOME: BMI						**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin+lifestyle versus **anti-androgen+lifestyle**								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Amiri et al. 2014	Kg/m2	weighted	25	28.9	5	27	29.57	4	crude	6

Gambineri et al. 2006	Kg/m2	weighted	20	33	15	17	30	3	BMI>=28	6
Gambineri et al. 2006	Kg/m2	weighted	20	33	15	17	29	3	BMI>=28	12
Ganie et al. 2004	Kg/m2	weighted	35	25.6	4.7	34	25.5	4.6	crude	6
Ganie et al. 2013	Kg/m2	weighted	56	24.74	3.11	51	24.46	3.01	crude	6
Long et al. 2022	Kg/m2	weighted	54	25	4.2	53	25.2	6.6		3

12.3.2. Forrest plot metformin+lifestyle vs anti-androgen+lifestyle for BMI



12.3.3. Funnel plot for assessment of publication bias

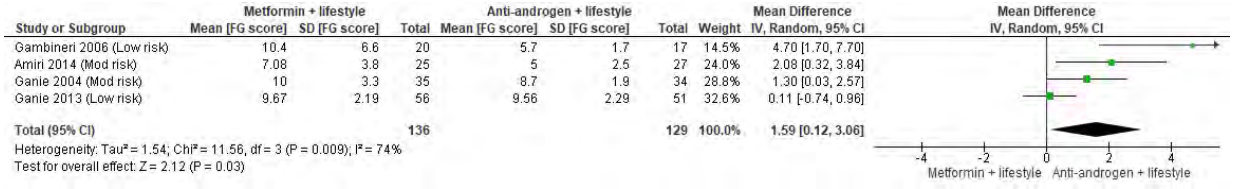


OUTCOME 12.4 Hirsutism (FGS)

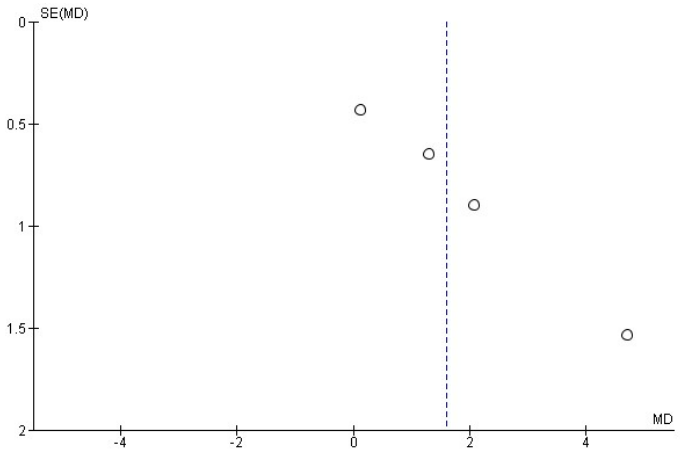
12.4.1 Individual Study Data Table

	OUTCOME: hirsutism					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin+lifestyle versus **anti-androgen+lifestyle**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Amiri et al. 2014		25	7.08	3.8	26	5	2.5	crude	6
Gambineri et al. 2006		20	10.9	8.6	17	8.4	4.0	BMI>=28	6
Gambineri et al. 2006		20	10.4	6.6	17	5.7	1.7	BMI>=28	12
Ganie et al. 2004		35	10.0	3.3	34	8.7	1.9	crude	6
Ganie et al. 2013		56	9.67	2.19	51	9.56	2.29	crude	6

12.4.2. Forrest plot metformin+lifestyle vs anti-androgen+lifestyle for hirsutism



12.4.3. Funnel plot for assessment of publication bias

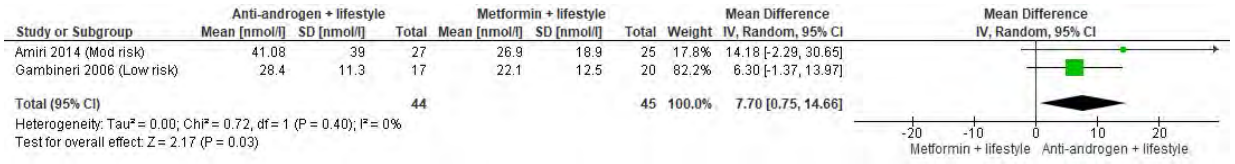


OUTCOME 12.5 SHBG (Nmol/l)

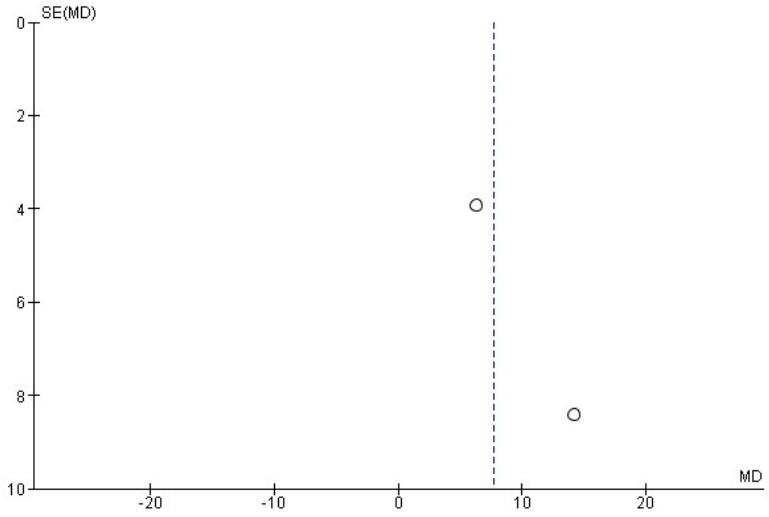
12.5.1 Individual Study Data Table

	OUTCOME: SHBG					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin+lifestyle versus **anti-androgen+lifestyle**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Amiri et al. 2014	Nmol/l	25	26.9	18.9	27	41.08	39	crude	6
Gambineri et al 2006	Nmol/l	20	19.2	10.6	17	27.6	12.6		6
Gambineri et al 2006	Nmol/l	20	22.1	12.5	17	28.4	11.3		12

12.5.2. Forrest plot metformin+lifestyle vs anti-androgen+lifestyle for SHBG



12.5.3. Funnel plot for assessment of publication bias

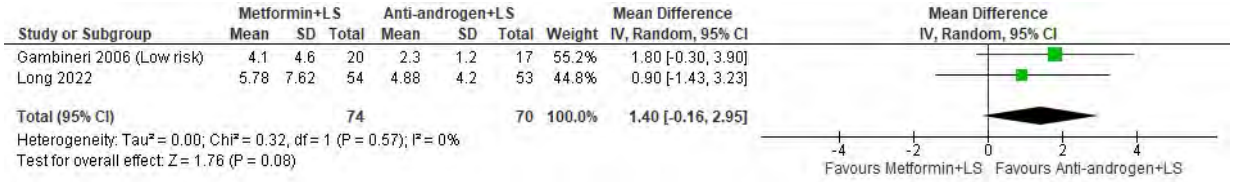


OUTCOME 12.6 FAI

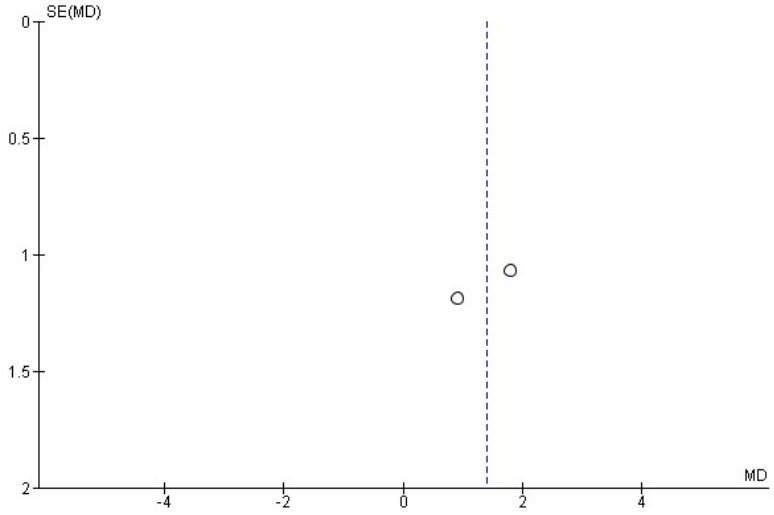
12.6.1 Individual Study Data Table

	OUTCOME: FAI					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): lifestyle+metformin versus lifestyle+anti-androgen							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something special?**	**Time period (month)**
Gambineri et al 2006		20	4.1	4.6	17	2.3	1.2		6
Long et al. 2022		54	5.78	7.62	53	4.88	4.2		3

12.6.2. Forrest plot metformin+lifestyle vs anti-androgen+lifestyle for FAI



12.6.3. Funnel plot for assessment of publication bias

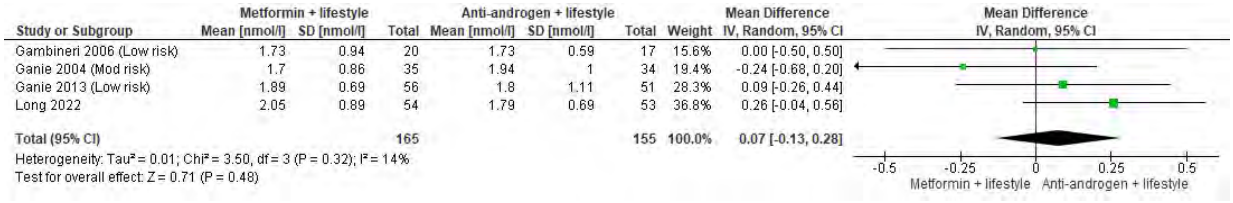


OUTCOME 12.7 Testosterone (Nmol/l)

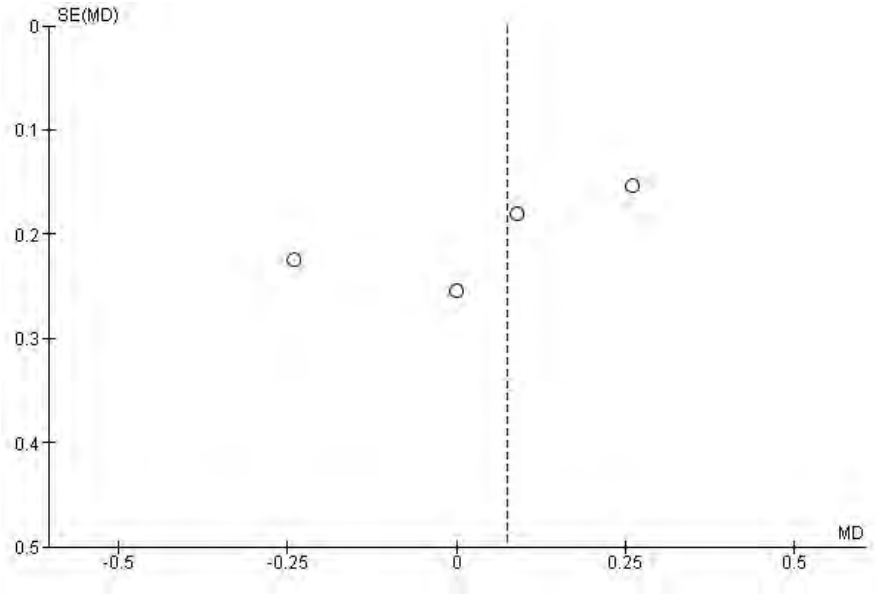
12.7.1 Individual Study Data Table

	OUTCOME: Testosterone					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin+lifestyle versus **anti-androgen+lifestyle**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Amiri et al. 2014	Nmol/l	25	0.7	0.4	27	0.55	0.2	Meta-analysis not performed due to uncertainty in unit	6
Ganie et al. 2004	Nmol/l	35	1.7	0.86	34	1.94	1.0	Crude	6
Ganie et al. 2013	Nmol/l	56	1.89	0.69	51	1.80	1.11	Crude	6
Gambineri et al. 2006	ng/ml	20	0.51	0.29	17	0.54	0.18		6
Gambineri et al. 2006	ng/ml Nmol/l	20	0.50 1.73	0.27 0.94	17	0.50 1.73	0.17 0.59		12
Long et al. 2022	Nmol/l	54	2.05	0.89	53	1.79	0.69		3

12.7.2. Forrest plot metformin+lifestyle vs anti-androgen+lifestyle for testosterone



12.7.3. Funnel plot for assessment of publication bias

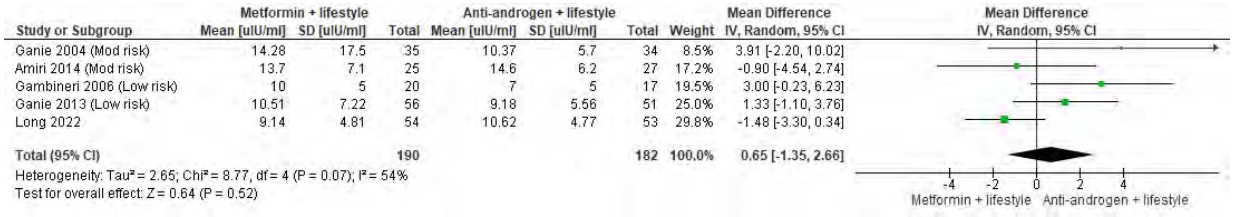


OUTCOME 12.8 Fasting insulin (uIU/ml)

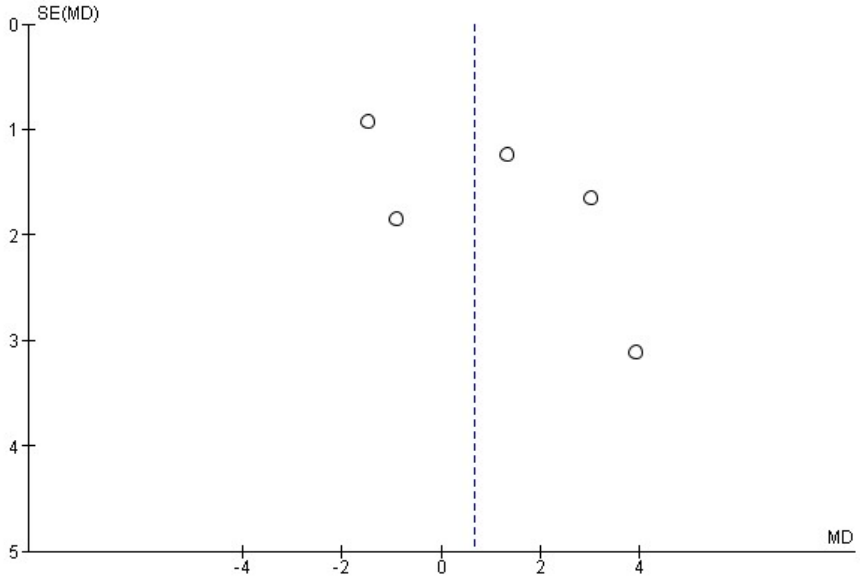
12.8.1 Individual Study Data Table

	OUTCOME: fasting insulin					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin+lifestyle versus **anti-androgen+lifestyle**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Amiri et al. 2014	pmol/l	25	13.7	7.1	27	14.6	6.2	crude	6
Ganie et al. 2004	uU/ml	35	14.28	17.5	34	10.37	5.7	crude	6
Ganie et al. 2013	uU/ml	56	10.51	7.22	51	9.18	5.56	crude	6
Gambineri et al 2006	uU/ml	20	14	5	17	11	9		6
Gambineri et al 2006	uU/ml	20	10	5	17	7	5		12
Long et al. 2022	uU/ml	54	9.14	4.81	53	10.62	4.77		3

12.8.2. Forrest plot metformin+lifestyle vs anti-androgen+lifestyle for fasting insulin



12.8.3. Funnel plot for assessment of publication bias



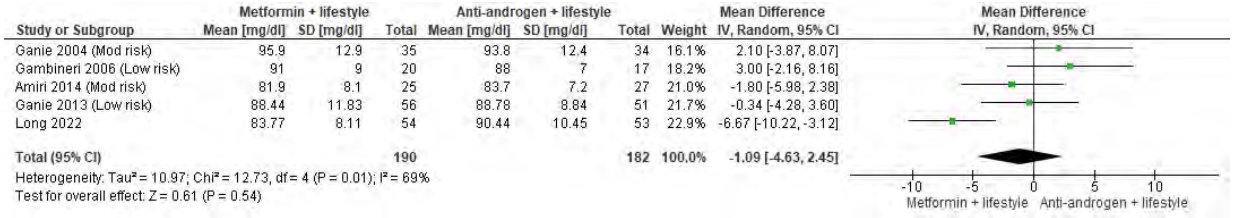
OUTCOME 12.9 Fasting glucose (mg/dl)

12.9.1 Individual Study Data Table

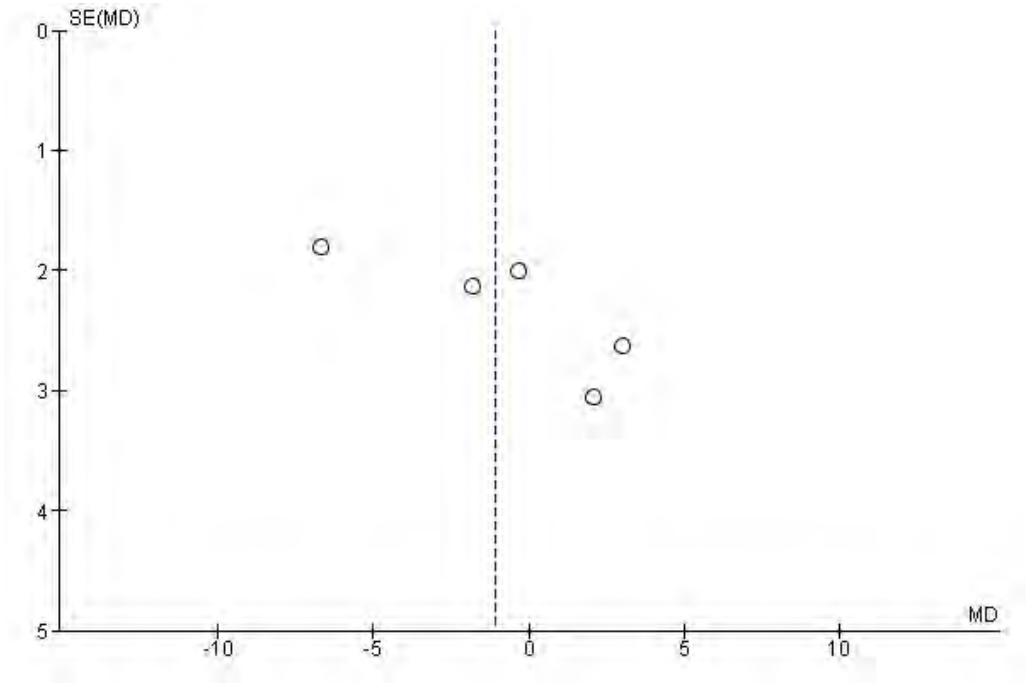
	OUTCOME: fasting glucose					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin+lifestyle versus **anti-androgen+lifestyle**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Amiri et al. 2014	Mg/dl	25	81.9	8.1	27	83.7	7.2	crude	6
Ganie et al. 2004	Mg/dl	35	95.9	12.9	34	93.8	12.4	crude	6

Ganie et al. 2013	Mg/dl	56	88.44	11.83	51	88.78	8.84		6
Gambineri et al 2006	Mg/ml	20	91	9	17	86	7	Unit?	6
Gambineri et al 2006	Mg/ml	20	91	9	17	88	7	Unit?	12
Long et al. 2022	Mg/dl	54	83.77	8.11	53	90.44	10.45		3

12.9.2. Forrest plot metformin+lifestyle vs anti-androgen+lifestyle for fasting glucose



12.9.3. Funnel plot for assessment of publication bias

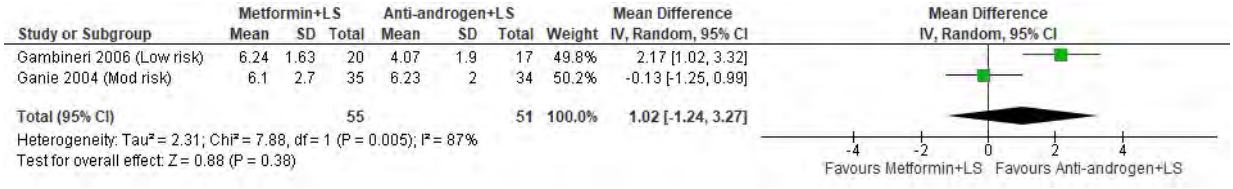


OUTCOME 12.10 DHEAS (Umol/l)

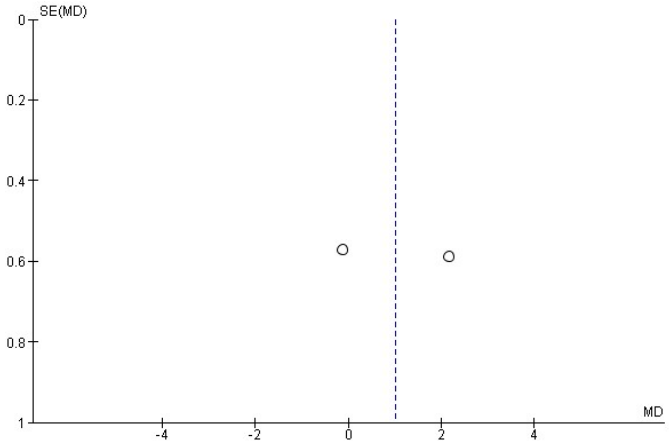
12.10.1 Individual Study Data Table

	OUTCOME: DHEAS					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin+lifestyle versus **anti-androgen+lifestyle**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Amiri et al. 2014	umol/l	25	222.5	129.1	27	145.46	81	Uncertainty in units	6
Ganie et al. 2004	Umol/l	35	6.1	2.7	34	6.23	2.0	crude	6
Gambineri et al 2006	ug/ml Umol/l	20	2.3 6.24	0.6 1.63	17	1.6 4.34	0.7 1.90		6
Gambineri et al 2006	ug/ml Umol/l	20	2.3 6.24	0.6 1.63	17	1.5 4.07	0.7 1.90		12

12.10.2. Forrest plot metformin+lifestyle vs anti-androgen+lifestyle for DHEAS



12.10.3. Funnel plot for assessment of publication bias

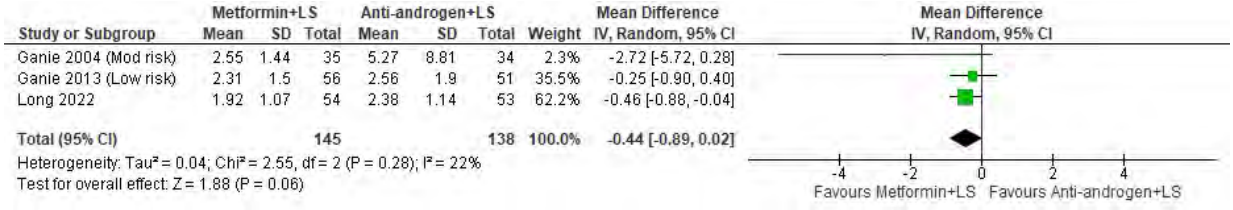


OUTCOME 12.11 HOMA-IR

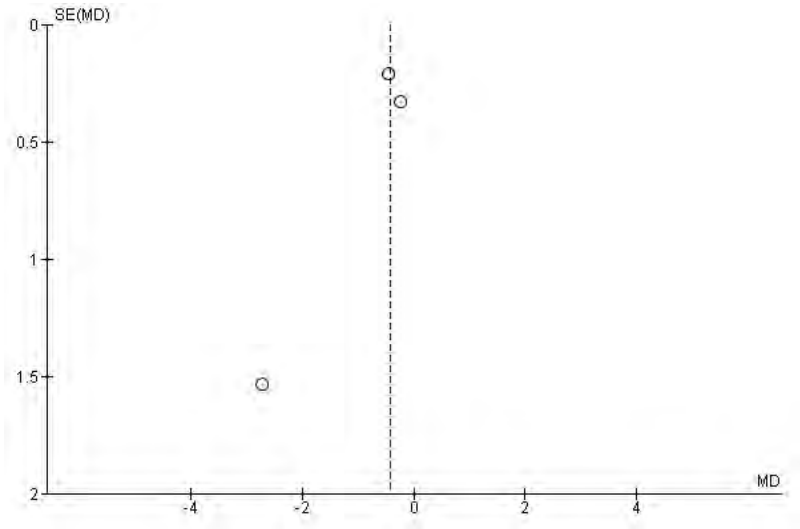
12.11.1 Individual Study Data Table

	OUTCOME: HOMA-IR					OUTCOME TYPE: Continuous			
		COMPARISON (if applicable): metformin+lifestyle versus anti-androgen+lifestyle							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Ganie et al. 2004		35	2.55	1.44	34	5.27	8.81	crude	6
Ganie et al. 2013		56	2.31	1.5	51	2.56	1.90		6
Long et al. 2022		54	1.92	1.07	53	2.38	1.14		3

12.11.2. Forrest plot metformin+lifestyle vs anti-androgen+lifestyle for HOMA-IR



12.11.3. Funnel plot for assessment of publication bias

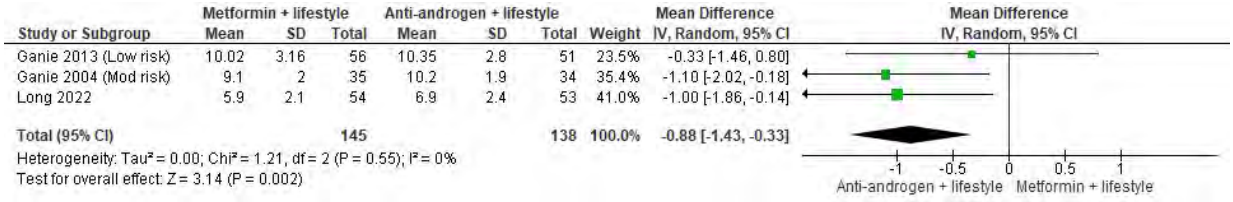


OUTCOME 12.12 Menstrual cycles/subject/12 months

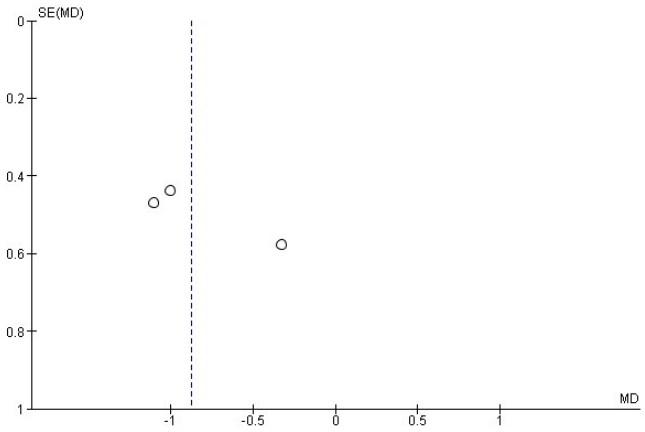
12.12.1 Individual Study Data Table

	OUTCOME: Menstrual cycles/subject per 12 months					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin+lifestyle versus **anti-androgen+lifestyle**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Ganie et al. 2004		35	9.1	2.0	34	10.2	1.9	crude	6
Ganie et al. 2013		56	10.02	3.16	51	10.35	2.8	crude	6
Long et al. 2022		54	5.9	2.1	53	6.9	2.4		3

12.12.2. Forrest plot metformin+lifestyle vs anti-androgen+lifestyle for menstrual cycles/subject/12 months



12.12.3. Funnel plot for assessment of publication bias



Adverse effects

	Study	Metformin+LS	Anti-androgen+LS
Gastrointestinal side effects (diarrhea,vomiting etc)	Long 2022	4/54	2/53
	Ganie 2013	9/56 (diarrhea)	0/51
Nausea	Long 2022	5/54	3/53
	Ganie 2013	3/56	
Other	Long 2022	0/54 (polyuria) 0/54 (dry mouth)	1/53 (polyuria) 2/53 (dry mouth)
	Ganie 2013	-	4/51 polyuria 2/51 (dry mouth) 11/51 (menstrual irregularity)

Comparison 13: Metformin+anti-androgen+lifestyle versus anti-androgen+lifestyle (also in Q4.6 – not identical since timeline is different)

Evidence Summary

Four randomised controlled trials (RCTs) were identified by our search. Of these RCT, all were included in the meta-analysis.
Of these studies two had a low ROB and two a moderate ROB.

Rows highlighted grey indicate studies with participants described as obese. Unfortunately, we were not able to perform any subanalyses due to a limit number of studies.

Meta-analysis/descriptive analysis summary

In the meta-analysis, metformin+anti-androgen+lifestyle was superior in lowering fasting glucose compared to only anti-androgen and lifestyle. For other outcomes, no difference was observed. Certainty in the evidence is low or very low.

Regarding individual studies, not included in the meta-analysis, Ganie et al. and Gambineri et al. found that HOMA-IR and menstrual cycle/6 months was significantly lower after using metformin+anti-androgen+lifestyle compared anti-androgen and lifestyle. Certainty in the evidence for the individual studies are high for HOMA-IR and low for menstrual cycles/6 months.

Author, year, country	Population	Sample Size per group	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Type of analysis and subgroup	ROB
Gambineri et al. 2006 Italy	overweight-obese women with PCOS	1.Metfromin=20 2.SPL=17 3.Metfromin+SPL=20 4.Placebo=20	6 months	1.35 ±4 2.33 ±4 3.35±5 4.37±5	1.28±8 2.26 ±6 3.26±5 4.26±5	Weight, BMI, SHBG, T, hirsutism	META BMI>28	**ROB low**

Ganie et al. 2013 India	women who met the 2006 Androgen Excess-PCOS criteria for PCOS	1.Metfromin=56 2.SPL=51 3.Metformin+SPL=62	6 months	1: 26.0±4.1 2: 24.3±3.7 3: 24.9±4.9	1: 22.4±5.3 2: 23.6±5.2 3: 23.6±4.7	Weight, BMI, WHR, no cycles/12 months, hirsutism, T, f-insulin, f-gluc, HOMA-IR, adverse effects	META Adults	**ROB Low**
Amiri et al. 2014 Iran	overweight and obese infertile PCOS women	1.Metfromin+LS=25 2.SPL+LS=27 3.Metfromin+SPL+LS=27 4.Placebo+LS=26	6 months	>19 kg/m_2 and <35 kg/m_2.	18-40	Whr, BMI, SHBG, T, hirsutism	META Adults	**ROB Moderate**
Long et al 2022 China	Women with PCOS aged >18yr	1. metformin+LS N=54 2. SPL+LS N=53 3.Metformin+SPL+LS=51	3 months	1.25.6 ± 4.5 2.25.9 ±6.7 3.25.4 ±3.7	1.27.0 ± 3.7 2.27.6 ±3.7 3.27.2 ±3.6	Weight, BMI, WHR, FAI, T, f-insulin, f-gluc	META Adults	**ROB Moderate**

Results of meta-analysis

Outcome	Time point	RCTs	N	Effect, random, MD	P-value	I2 (%)	Favours	Certainty
Weight (kg)	3-6 months	3	254	-2.51 (-8.67 to 3.65)	0.42	81	No difference	⊕◯◯◯ VERY LOW
WHR	3-6 months	2	217	-0.03 (-0.07 to 0.01)	0.11	73	No difference	⊕⊕◯◯ LOW
BMI kg/m2	3-6 months	4	307	-0.20 (-1.02 to 0.63)	0.64	0	No difference	⊕⊕◯◯ LOW
Hirsutism	6 months	3	203	0.53 (-1.55 to 2.61)	0.62	79	No difference	⊕◯◯◯ VERY LOW
SHBG (nmol/l)	6 months	2	90	-9.06 (-26.41 to 8.29)	0.31	74	No difference	⊕◯◯◯ VERY LOW
FAI	3-6 months	2	141	-0.63 (-1.40 to 0.14)	0.11	23	No difference	⊕⊕◯◯ LOW
Testosterone ng/ml)	3-6 months	4	310	-0.01 (-0.05 to 0.03)	0.62	42	No difference	⊕◯◯◯ VERY LOW
Fasting insulin (mIU/l)	3-6 months	4	307	-1.30 (-2.81 to 0.22)	0.09	0	No difference	⊕⊕◯◯ LOW
Fasting glucose (mg/dl)	3-6 months	4	307	-4.14 (-6.26 to -2.01)	0.0001	0	**Metformin+AA+LS**	⊕⊕◯◯ LOW

Individual studies not included in meta-analysis

Outcome	Author, year	Time point	N	Metformin+ AA+LS	AA+LS	P-value	Favours	Grading
DHEAS (ug/dl)	Gambineri 2006	6 months	Met++AA+LS=20 AA+LS=17	Mean +/- SD 190 +/- 120	Mean +/- SD 160 +/- 70	0.145	No difference	⊕⊕◯◯ LOW[1]
Androstenedione	Gambineri 2006	6 months	Met++AA+LS=20 AA+LS=17	Mean +/- SD 269 +/- 128	Mean +/- SD 229 +/- 88	0.06	No difference	⊕⊕◯◯ LOW[1]
HOMA_IR	Ganie et al. 2013	6 months	Met++AA+LS=62 AA+LS=51	Mean +/- SD 1.96 +/- 1.47	Mean +/- SD 2.56 +/- 1.90	<0.05	**Metformin+AA+LS**	⊕⊕⊕⊕ HIGH

Total cholesterol	Long 2022	3 months	Met+AA+LS=51 AA+LS=53	Mean +/- SD 4.64 +/- 0.71	Mean +/- SD 4.75 +/- 0.98	0.51	No difference	⊕⊕⊕◯ MODERATE[2]
HDL	Gambineri 2006	6 months	Met++AA+LS=20 AA+LS=17	Mean +/- SD 55 +/- 13	Mean +/- SD 52 +/- 13	0.07	No difference	⊕⊕◯◯ LOW[1]
LDL	Gambineri 2006	6 months	Met++AA+LS=20 AA+LS=17	Mean +/- SD 105 +/- 26	Mean +/- SD 102 +/- 28	0.45	No difference	⊕⊕◯◯ LOW[1]
Triglycerides	Gambineri 2006	6 months	Met++AA+LS=20 AA+LS=17	Mean +/- SD 87 +/- 46	Mean +/- SD 74 +/- 42	0.35	No difference	⊕⊕◯◯ LOW[1]
Menstrual cycle/6 months	Gambineri 2006	6 months	Met++AA+LS=20 AA+LS=17	Mean +/- SD 4.3 +/- 1.5	Mean +/- SD 3.2 +/- 1.2	0.017	**Metformin+AA+LS**	⊕⊕◯◯ LOW[1]
OGTT (mg/dl/120min)	Amiri 2014	6 months	Met++AA+LS=27 AA+LS=26	Mean +/- SD 107.22 +/- 25.9	Mean +/- SD 102.56 +/- 20.1	0.46	No difference	⊕⊕◯◯ LOW[3]

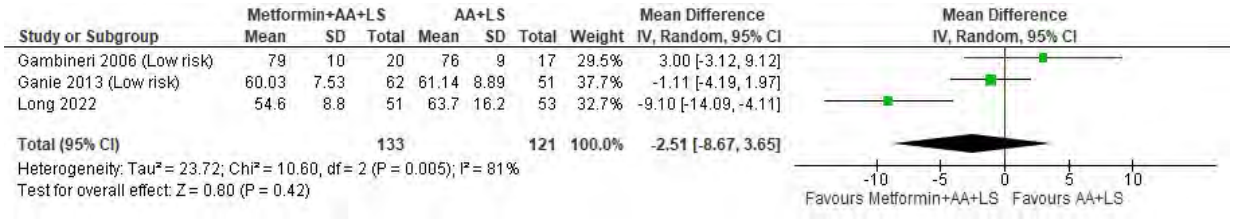
[1] Downgraded twice for small number of participants
[2] Downgraded once for mod ROB
[3] Downgraded once for mod ROB and downgraded once for small number of participants

OUTCOME 13.1 Weight (kg)

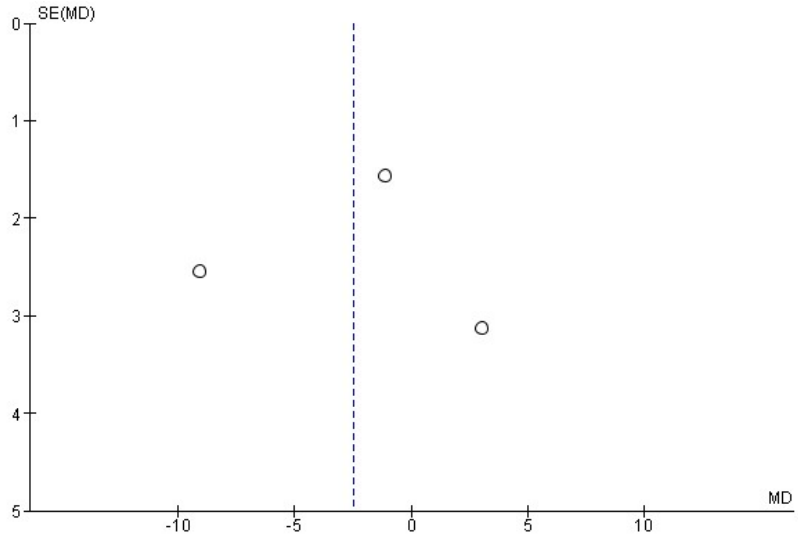
13.1.1 Individual Study Data Table

	OUTCOME: Weight						**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin+anti-androgen+ lifestyle versus anti-androgen**+lifestyle**								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Gambineri et al. 2006	kg	weighted	20	79	10	17	76	9	BMI>=28	6
Gambineri et al. 2006	kg	weighted	20	79	14	17	75	9	BMI>=28	12
Ganie et al. 2013	kg	weighted	62	60.03	7.53	51	61.14	8.89		6
Long et al. 2022	kg	weighted	51	54.6	8.8	53	63.7	16.2		3

13.1.2. Forrest plot metformin+anti-androgen+lifestyle vs anti-androgen+lifestyle for weight



13.1.3. Funnel plot for assessment of publication bias



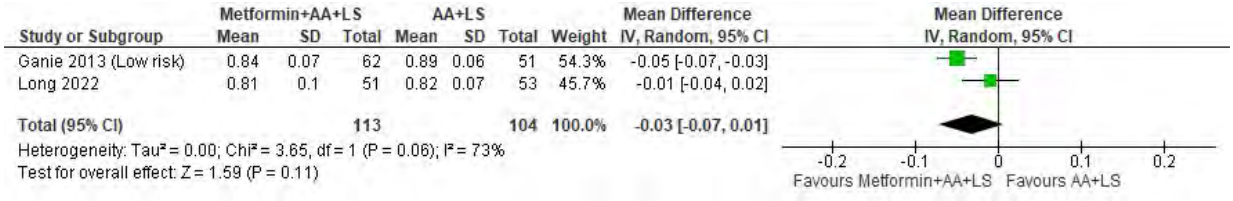
OUTCOME 13.2 WHR

13.2.1 Individual Study Data Table

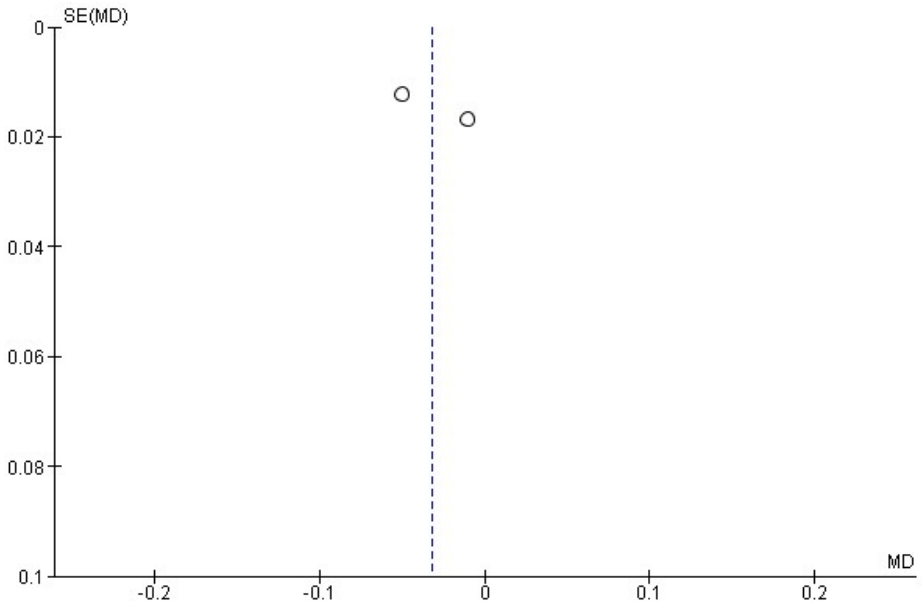
	OUTCOME: WHR					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin+anti-androgen+lifestyle versus **anti-androgen+lifestyle**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Amiri et al. 2014		27	0.83	0.04	26	0.8	No SD	crude	6
Ganie et al. 2013		62	0.84	0.07	51	0.89	0.06		6

Long et al. 2022		51	0.81	0.1	53	0.82	0.07		3

13.2.2. Forrest plot metformin+anti-androgen+lifestyle vs anti-androgen+lifestyle for WHR



13.2.3. Funnel plot for assessment of publication bias



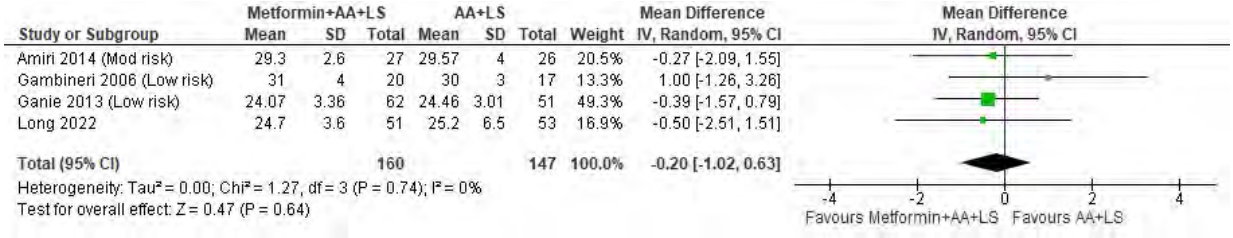
OUTCOME 13.3 BMI (kg/m2)

13.3.1 Individual Study Data Table

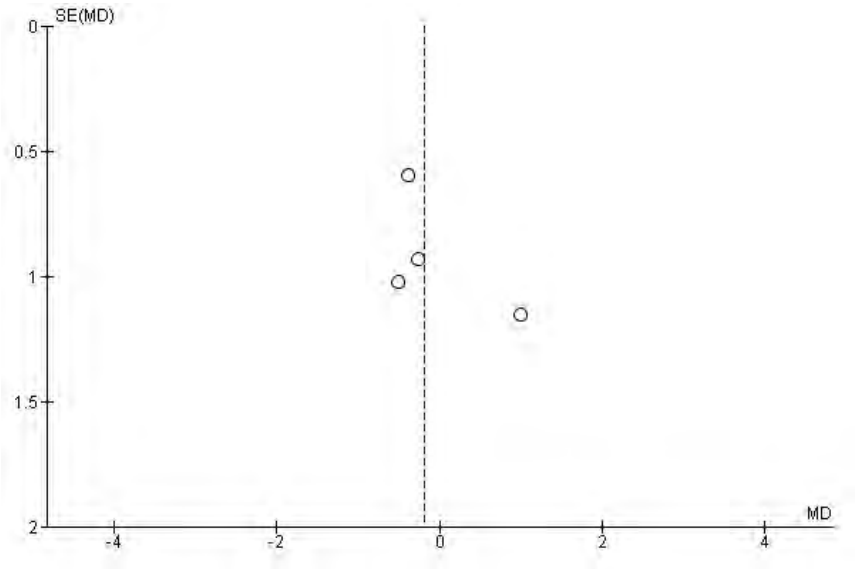
	OUTCOME: BMI		**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable): metformin+anti-androgen+lifestyle versus **anti-androgen+lifestyle**	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	N	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	N	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	Time period (month)
Amiri et al. 2014	Kg/m2	weighted	27	29.3	2.6	26	29.57	4	crude	6
Gambineri et al. 2006	Kg/m2	weighted	20	31	4	17	30	3	BMI>=28	6
Gambineri et al. 2006	Kg/m2	weighted	20	31	5	17	29	3	BMI>=28	12
Ganie et al. 2013	Kg/m2	weighted	62	24.07	3.36	51	24.46	3.01		6
Long et al. 2022	Kg/m2	weighted	51	24.7	3.6	53	25.2	6.5		3

13.3.2. Forrest plot metformin+anti-androgen+lifestyle vs anti-androgen+lifestyle for BMI



13.3.3. Funnel plot for assessment of publication bias

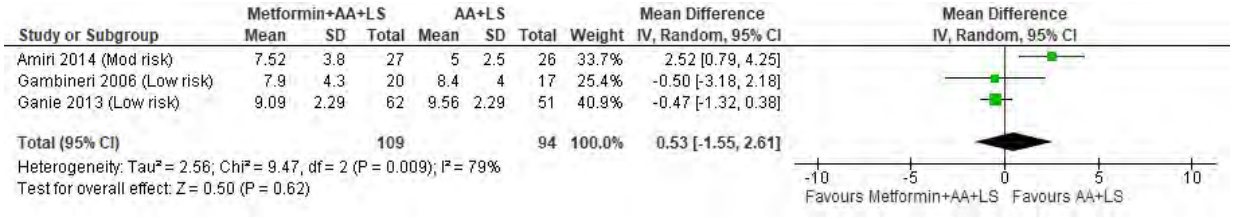


OUTCOME 13.4 Hirsutism (FGS)

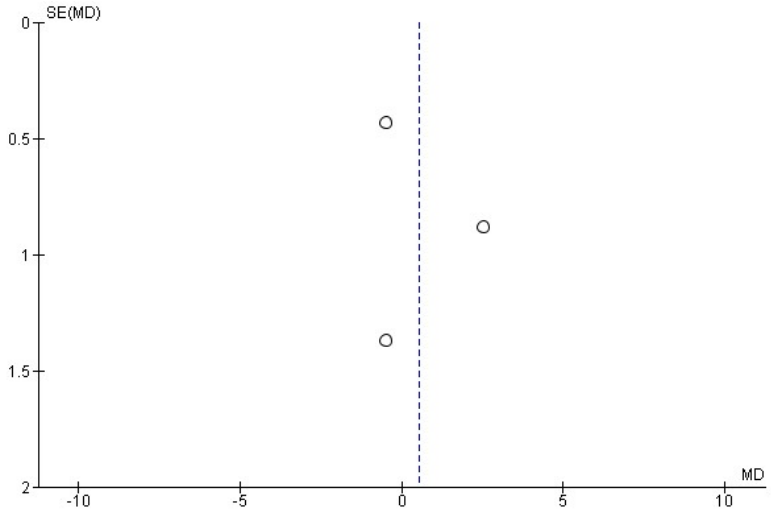
13.4.1 Individual Study Data Table

	OUTCOME: hirsutism						**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin+anti-androgen+lifestyle versus **anti-androgen+lifestyle**								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Amiri et al. 2014	score	FGS	27	7.52	3.8	26	5	2.5	crude	6
Gambineri et al. 2006	score	FGS	20	7.9	4.3	17	8.4	4.0	BMI>=28	6
Gambineri et al. 2006	score	FGS	20	6.5	3.9	17	5.7	1.7	BMI>=28	12
Ganie et al. 2013	score	FGS	62	9.09	2.29	51	9.56	2.29		6

13.4.2. Forrest plot metformin+anti-androgen+lifestyle vs anti-androgen+lifestyle for hirsutism



13.4.3. Funnel plot for assessment of publication bias

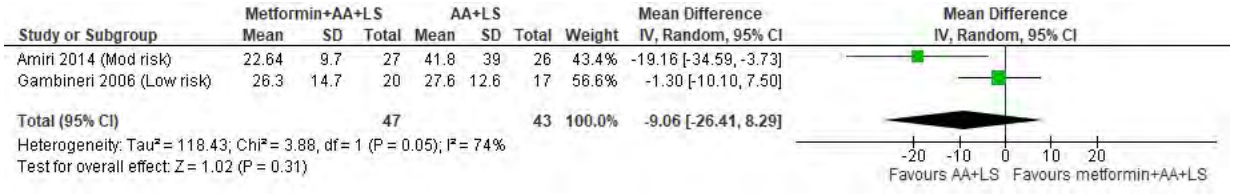


OUTCOME 13.5 SHBG (Nmol/l)

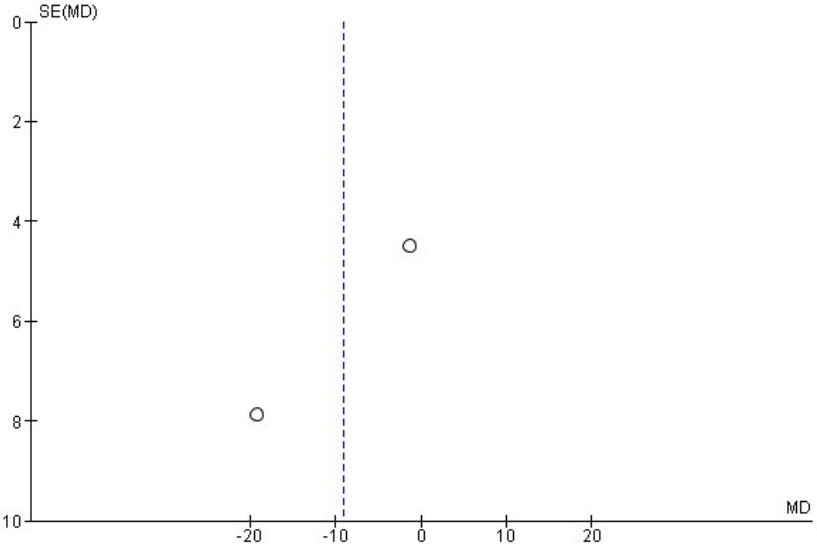
13.5.1 Individual Study Data Table

	OUTCOME: SHBG					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin+anti-androgen+lifestyle versus **anti-androgen+lifestyle**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Amiri et al. 2014	Nmol/l	27	22.64	9.7	26	41.08	39	crude	6
Gambineri et al 2006	Nmol/l	20	26.3	14.7	17	27.6	12.6		6

13.5.2. Forrest plot metformin+anti-androgen+lifestyle vs anti-androgen+lifestyle for SHBG



13.5.3. Funnel plot for assessment of publication bias

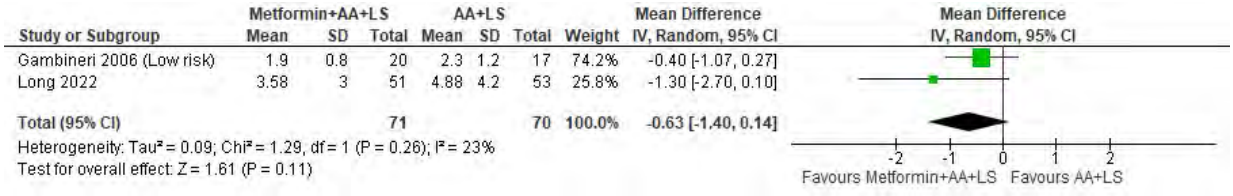


OUTCOME 13.6 FAI

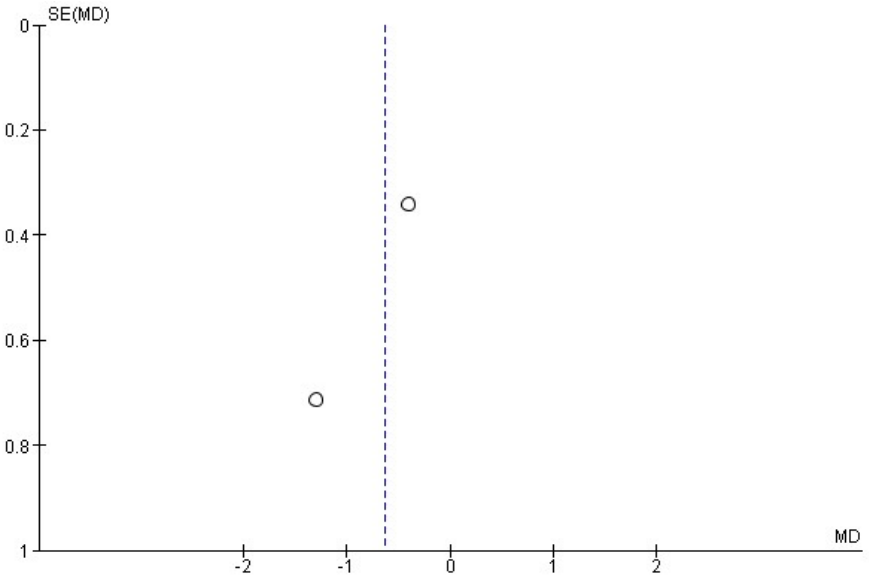
13.6.1 Individual Study Data Table

	OUTCOME: FAI					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): lifestyle+metformin+anti-androgen versus lifestyle+anti-androgen							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something special?**	**Time period (month)**
Gambineri et al 2006		20	1.9	0.8	17	2.3	1.2		6
Gambineri et al 2006		20	1.9	0.9	17	2.4	2.1		12
Long et al. 2022		51	3.58	3	53	4.88	4.2		3

13.6.2. Forrest plot metformin+anti-androgen+lifestyle vs anti-androgen+lifestyle for FAI



13.6.3. Funnel plot for assessment of publication bias



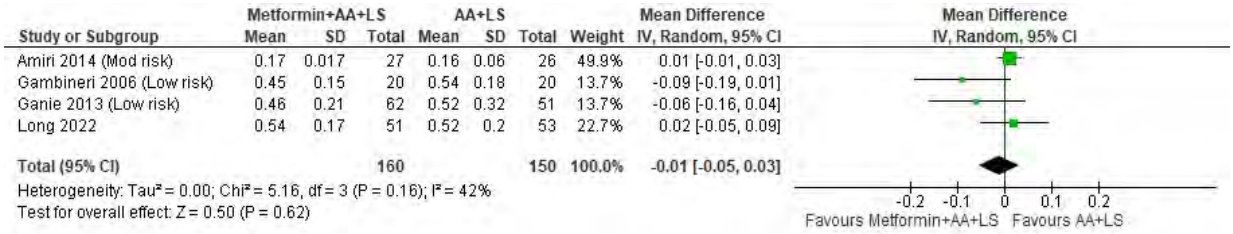
OUTCOME 13.7 Testosterone (ng/ml)

13.7.1 Individual Study Data Table

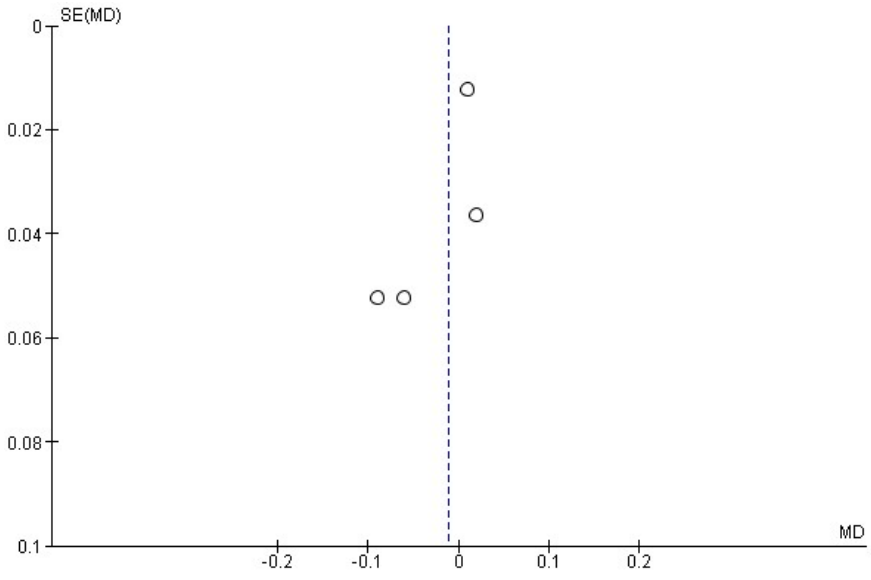
	OUTCOME: testosterone			**OUTCOME TYPE:** Continuous						
		COMPARISON (if applicable): metformin+anti-androgen+lifestyle versus **anti-androgen+lifestyle**								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Amiri et al. 2014	Nmol/l Ng/ml		27	0.6 0.17	0.06 0.017	26	0.55 0.16	0.2 0.06	crude	6

Gambineri et al 2006	Ng/ml		20	0.45	0.15	17	0.54	0.18		6
Gambineri et al 2006	Ng/ml		20	0.43	0.20	17	0.50	0.17		12
Long et al. 2022	Ng/ml		51	0.54	0.17	53	0.52	0.2		3

13.7.2. Forrest plot metformin+anti-androgen+lifestyle vs anti-androgen+lifestyle for testosterone



13.7.3. Funnel plot for assessment of publication bias

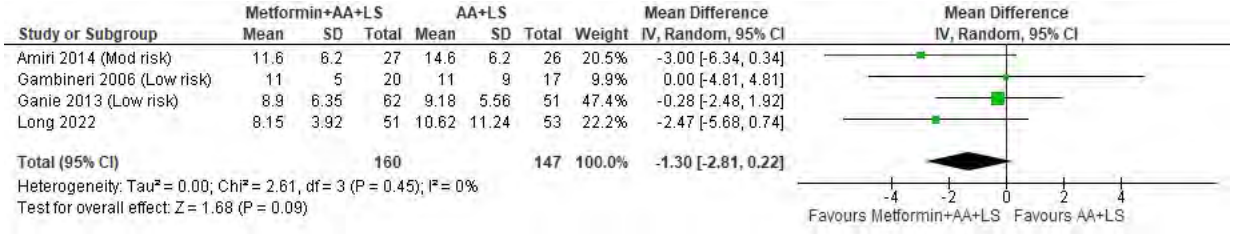


OUTCOME 13.8 Fasting insulin (uIU/ml)

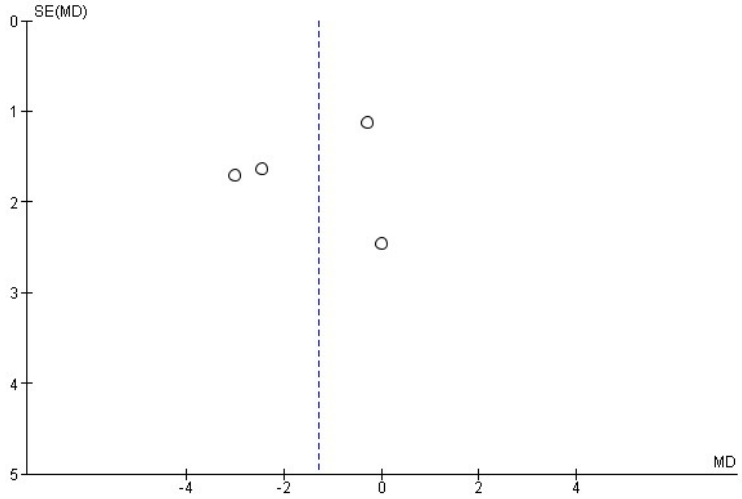
13.8.1 Individual Study Data Table

	OUTCOME: fasting insulin					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin+anti-androgen+lifestyle versus **anti-androgen+lifestyle**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Amiri et al. 2014	pM/l	27	11.6	6.2	26	14.6	6.2	Unit?	6
Ganie et al. 2013	uU/ml	62	8.9	6.35	51	9.18	5.56		6
Gambineri et al 2006	uU/ml	20	11	5	17	11	9		6
Gambineri et al 2006	uU/ml	20	8	4	17	7	5		12
Long et al. 2022	uU/ml	51	8.15	3.92	53	10.62	11.24		3

13.8.2. Forrest plot metformin+anti-androgen+lifestyle vs anti-androgen+lifestyle for fasting insulin



13.8.3. Funnel plot for assessment of publication bias

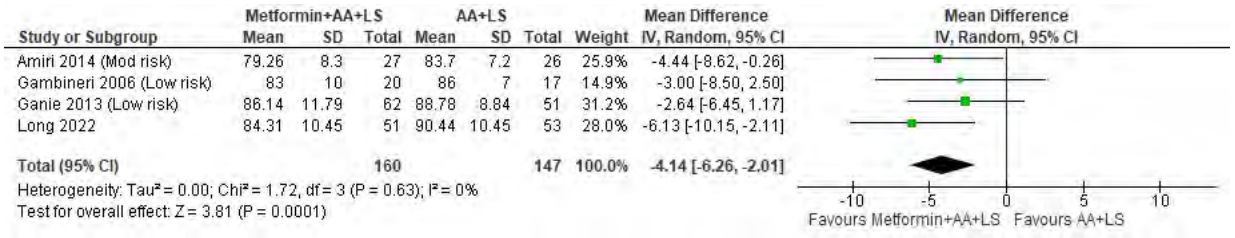


OUTCOME 13.9 Fasting glucose (mg/dl)

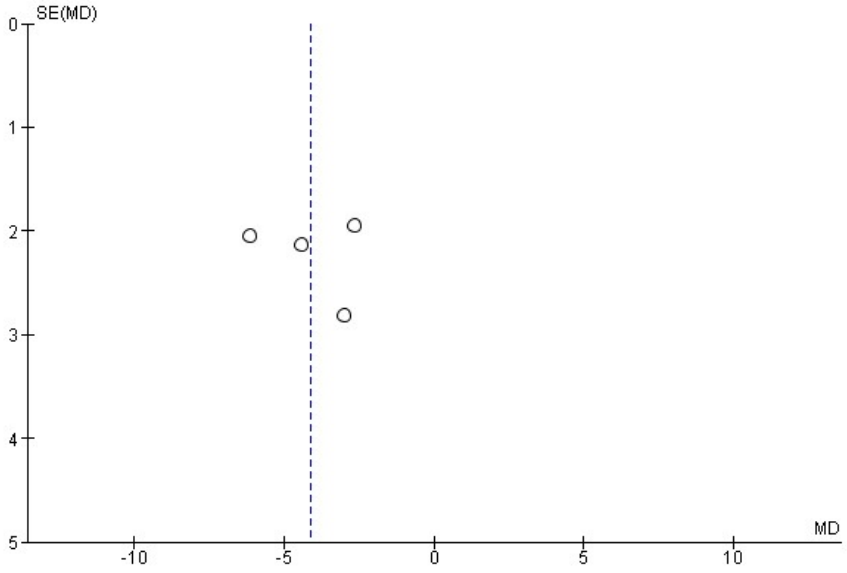
13.9.1 Individual Study Data Table

	OUTCOME: fasting glucose			**OUTCOME TYPE:** Continuous						
		COMPARISON (if applicable): metformin+anti-androgen+lifestyle versus **anti-androgen+lifestyle**								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Amiri et al. 2014	Mg/dl		27	79.26	8.3	26	83.7	7.2	crude	6
Ganie et al. 2013	Mg/dl		62	86.14	11.79	51	88.78	8.84		6
Gambineri et al 2006	mg/ml		20	83	10	17	86	7	Unit?	6
Gambineri et al 2006	mg/ml		20	83	9	17	88	7		12
Long et al. 2022	mg/dl		51	84.31	10.45	53	90.44	10.45		3

13.9.2. Forrest plot metformin+anti-androgen+lifestyle vs anti-androgen+lifestyle for fasting glucose



13.9.3. Funnel plot for assessment of publication bias



Comparison 14: Metformin+anti-androgen+lifestyle versus placebo+lifestyle (also in Q4.6 – identical)

Evidence Summary

Two randomised controlled trials (RCTs) were identified by our search. Of these RCT, both were included in the meta-analysis.
One study (Gambineri et al. 2006) had a low ROB, whereas the other one (Amiri et al. 2014) had a moderate ROB.

Rows highlighted grey indicate studies with participants described as obese.

Meta-analysis/descriptive analysis summary

In the meta-analysis, metformin+anti-androgen+lifestyle was superior in lowering fasting glucose and testosterone. For other outcomes, no difference was observed. Certainty in the evidence is very low.
Regarding individual studies, not included in the meta-analysis, Gambineri et al. found that metformin+anti-androgen+lifestyle compared anti-androgen and lifestyle was superior when it comes to lowering weight and improving the menstrual cycle. WHR was lower for those participants using placebo combined with LS. Certainty in the evidence for the individual studies are low.
None of the studies reported adverse effects.

Author, year, country	Population	Sample Size per group	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Type of analysis and subgroup	ROB
Gambineri et al. 2006 Italy	overweight-obese women with PCOS	1.Metformin+LS=20 2.SPL+LS=17 3.Metfromin+SPL+LS=20 4.Placebo+LS=20	6 months	1.35 ±4 2.33 ±4 3.35±5 4.37±5	1.28±8 2.26 ±6 3.26±5 4.26±5	Weight, BMI, SHBG, T, hirsutism	META BMI>28	**ROB low**
Amiri et al. 2014 Iran	overweight and obese infertile PCOS women	1.Metfromin+LS=25 2.SPL+LS=27 3.Metfromin+SPL+LS=27 4.Placebo+LS=26	6 months	>19 kg/m_2 and <35 kg/m_2.	18-40	Whr, BMI, SHBG, T, hirsutism	META Adults	**ROB Moderate**

Results of meta-analysis

Outcome	Time point	RCTs	N	Effect, random, MD	P-value	I2 (%)	Favours	Certainty
BMI kg/m2	6 months	2	90	-1.76 (-5.77 to 2.24)	0.39	82	No difference	⊕◯◯◯ VERY LOW
Hirsutism	6 months	2	92	1.58 (-1.13 to 4.29)	0.25	62	No difference	⊕◯◯◯ VERY LOW
SHBG (nmol/l)	6 months	2	92	1.09 (-5.23 to 7.41)	0.74	40	No difference	⊕◯◯◯ VERY LOW
Testosterone ng/ml)	6 months	2	92	-0.08 (-0.15 to 0.00)	0.04	0	**Metformin+AA+LS**	⊕◯◯◯ VERY LOW
Fasting glucose (mg/dl)	6 months	2	90	-6.29 (-10.26 to -2.33)	0.002	0	**Metformin+AA+LS**	⊕◯◯◯ VERY LOW

Individual studies not included in meta-analysis

Outcome	Author, year	Time point	N	Metformin+AA+LS	AA+LS	P-value	Favours	Grading
Weight	Gambineri 2006	6 months	Met+AA+LS=20 Placebo+LS=19	Mean +/- SD 79 +/- 10	Mean +/- SD 93 +/- 9	<0.01	**Met+AA+LS**	⊕⊕◯◯ LOW[1]
WHR	Amiri 2014	6 months	Met+AA+LS=27 Placebo+LS=26	Mean +/- SD 0.83 +/- 0.04	Mean +/- SD 0.8 +/- 0.05	<0.01	**Placebo+LS**	⊕⊕◯◯ LOW[2]
FAI	Gambineri 2006	6 months	Met+AA+LS=20 Placebo+LS=19	Mean +/- SD 1.9 +/- 0.8	Mean +/- SD 3.2 +/- 2.2	0.06	No difference	⊕⊕◯◯ LOW[1]
DHEAS (ug/ml)	Gambineri 2006	6 months	Met+AA+LS=20 Placebo+LS=19	Mean +/- SD 1.9 +/- 1.2	Mean +/- SD 2.1 +/- 1.1	0.145	No difference	⊕⊕◯◯ LOW[1]
Androstenedione	Gambineri 2006	6 months	Met+AA+LS=20 Placebo+LS=19	Mean +/- SD 258 +/- 118	Mean +/- SD 242 +/- 94	0.068	No difference	⊕⊕◯◯ LOW[1]
LDL (mg/dl)	Gambineri 2006	6 months	Met+AA+LS=20 Placebo+LS=19	Mean +/- SD 105 +/- 26	Mean +/- SD 119 +/- 53	0.446	No difference	⊕⊕◯◯ LOW[1]
Triglycerides	Gambineri 2006	6 months	Met+AA+LS=20 Placebo+LS=19	Mean +/- SD 87 +/- 46	Mean +/- SD 101 +/- 65	0.35	No difference	⊕⊕◯◯ LOW[1]
Menstrual cycle/6 months	Gambineri 2006	6 months	Met+AA+LS=20 Placebo+LS=19	Mean +/- SD 4.3 +/- 1.5	Mean +/- SD 3.2 +/- 1.2	<0.01	**Met+AA+LS**	⊕⊕◯◯ LOW[1]
OGTT (mg/dl/120 min)	Amiri 2014	6 months	Met+AA+LS=27 Placebo+LS=26	Mean +/- SD 107.22 +/- 25.9	Mean +/- SD 95.7 +/- 31.3	NS	No difference	⊕⊕◯◯ LOW[2]

[1] Downgraded twice for small number of participants

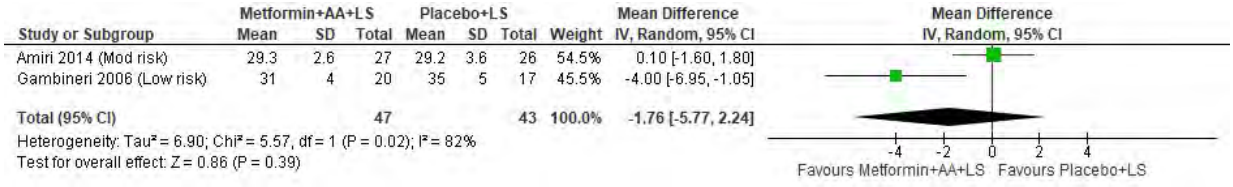
[2] Downgraded once for mod ROB and downgraded once for small number of participants

OUTCOME 14.1 BMI (kg/m2)

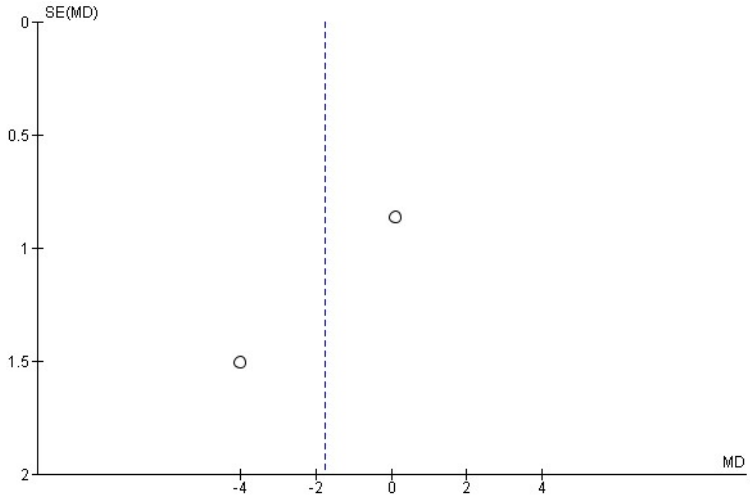
14.1.1 Individual Study Data Table

	OUTCOME: BMI						**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin+anti-androgen+lifestyle versus **placebo+lifestyle**								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Amiri et al. 2014	Kg/m2	weighted	27	29.3	2.6	26	29.2	3.6	crude	6
Gambineri et al. 2006	Kg/m2	weighted	20	31	4	19	35	5	BMI>=28	6
Gambineri et al. 2006	Kg/m2	weighted	20	31	5	19	35	5	BMI>=28	12

14.1.2. Forrest plot metformin+anti-androgen+lifestyle vs placebo+lifestyle for BMI



14.1.3. Funnel plot for assessment of publication bias

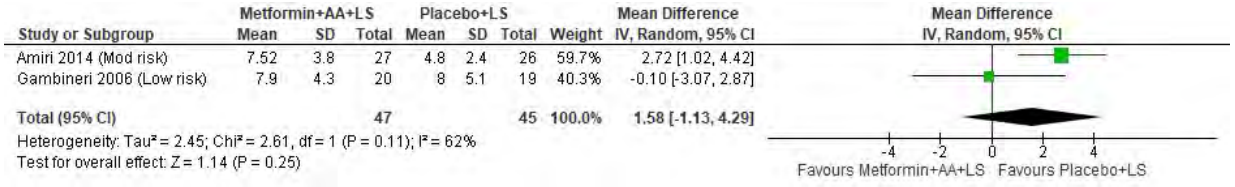


OUTCOME 14.2 Hirsutism (FGS)

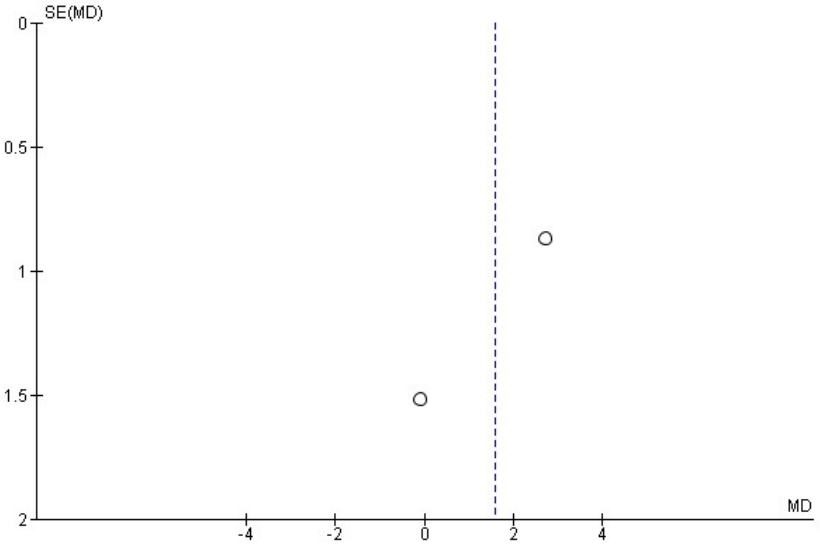
14.2.1 Individual Study Data Table

	OUTCOME: hirsutism						**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin+anti-androgen+lifestyle versus **placebo+lifestyle**								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Amiri et al. 2014	score	FGS	27	7.52	3.8	26	4.8	2.4	crude	6
Gambineri et al. 2006	score	FGS	20	7.9	4.3	19	8.0	5.1	BMI>=28	6
Gambineri et al. 2006	score	FGS	20	6.5	3.9	19	8.0	4.1	BMI>=28	12

14.2.2. Forrest plot metformin+anti-androgen+lifestyle vs placebo+lifestyle for hirsutism



14.2.3. Funnel plot for assessment of publication bias

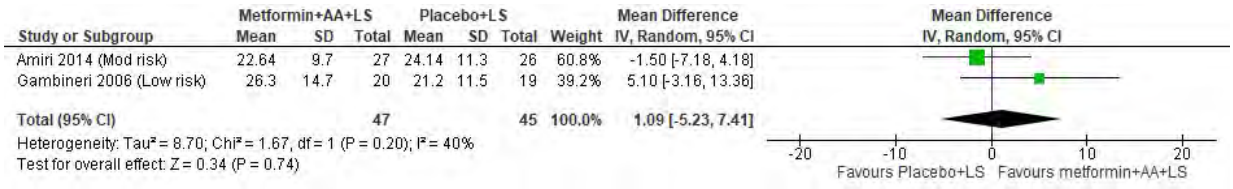


OUTCOME 14.3 SHBG (Nmol/l)

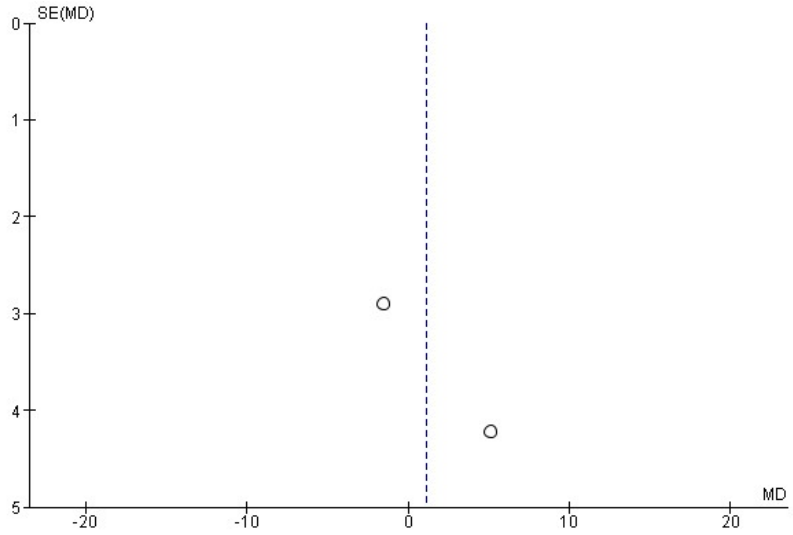
14.3.1 Individual Study Data Table

	OUTCOME: SHBG					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin+anti-androgen+lifestyle versus **placebo+lifestyle**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Amiri et al. 2014	Nmol/l	27	22.64	9.7	26	24.14	11.3	crude	6
Gambineri et al 2006	Nmol/l	20	26.3	14.7	19	21.2	11.5		6
Gambineri et al 2006	Nmol/l	20	26.4	12.9	19	22.6	17.9		12

14.3.2. Forrest plot metformin+anti-androgen+lifestyle vs placebo+lifestyle for SHBG



14.3.3. Funnel plot for assessment of publication bias

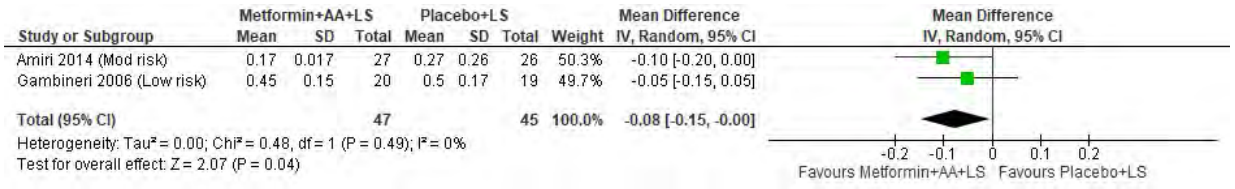


OUTCOME 14.4 Testosterone (Ng/ml)

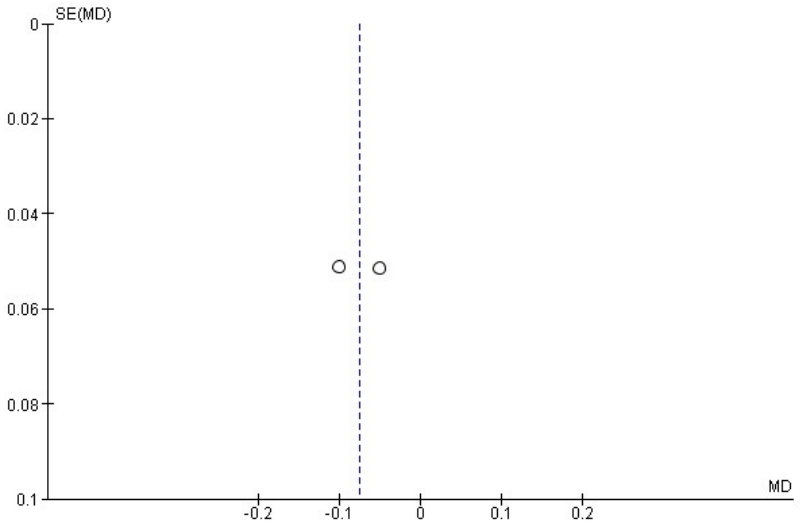
14.4.1 Individual Study Data Table

	OUTCOME: Testosterone			**OUTCOME TYPE:** Continuous					
		COMPARISON (if applicable): metformin+anti-androgen+lifestyle versus **placebo+lifestyle**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Amiri et al. 2014	nM/l ng/ml	27	0.6 0.17	0.06 0.017	26	0.95 0.27	0.9 0.26	crude	6
Gambineri et al 2006	Ng/ml	20	0.45	0.15	19	0.50	0.17		6
Gambineri et al 2006	Ng/ml	20	0.43	0.20	19	0.45	0.14		12

14.4.2. Forrest plot metformin+anti-androgen+lifestyle vs placebo+lifestyle for Testosterone



14.4.3. Funnel plot for assessment of publication bias

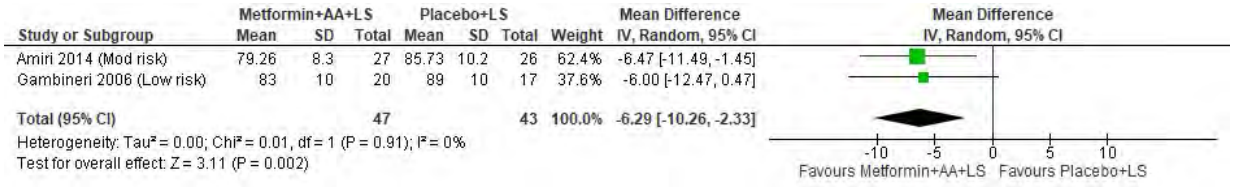


OUTCOME 14.5 Fasting glucose (Ng/ml)

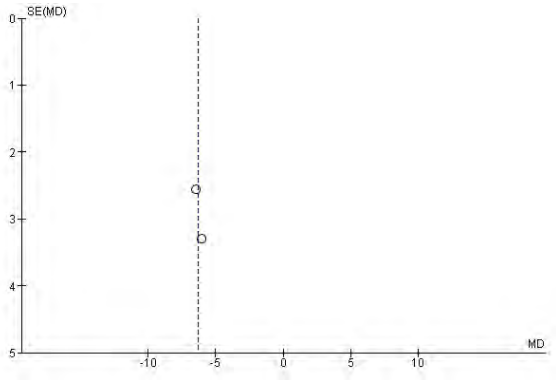
14.5.1 Individual Study Data Table

	OUTCOME: fasting glucose						**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin+anti-androgen+lifestyle versus **placebo+lifestyle**								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Amiri et al. 2014	Mg/dl		27	79.26	8.3	27	85.73	10.2	Unit?	6
Gambineri et al 2006	mg/ml		20	83	10	17	89	10		6
Gambineri et al 2006	mg/ml		20	83	9	17	88	9		12

14.5.2. Forrest plot metformin+anti-androgen+lifestyle vs placebo+lifestyle for fasting glucose



14.5.3. Funnel plot for assessment of publication bias



Comparison 15: Metformin versus rosiglitazone

Evidence Summary

Seven randomised controlled trials (RCTs), resulting in 9 articles were identified by our search. Of these RCT, all were included in the meta-analysis.
Of these articles one had a low ROB, six a moderate ROB and two a high ROB. All studies were on adult PCOS patients, one study on obese participants (BMI>=25), one on non-obese (BMI<27) and seven where the BMI was not reported. Rows highlighted grey indicate studies with participants described as obese and green indicates studies with participants described as non-obese. Studies using the same data are coloured in the “author-column”.
A major limitation in the evidence for this comparison is the lack of confidence in author reporting of units and conversions (Cetinkalp et al. 2009 and Ahmad et al. 2008).

Meta-analysis/descriptive analysis summary

Overall:
In the meta-analysis, metformin was superior in lowering weight (certainty very low) and BMI (certainty moderate), as well as improving hyperandrogenism (androstenedione and total testosterone) (certainty moderate).
Rosiglitazone was superior in improving LDL (certainty moderate).

Subanalyses according to BMI:
For PCOS-women with normal weight (BMI<27), metformin was superior in lowering testosterone (certainty very low), whereas rosiglitazone was superior in lowering fasting glucose (certainty very low). Metformin was superior in lowering weight and BMI regardless of BMI.
Note that for many outcomes subgroup analysis contained only one study and certainty is very low.

Regarding individual studies, not included in the meta-analysis, Ahmad et al found that metformin was superior in improving hirsutism (low certainty) compared to rosiglitazone. According to the study by Jensterle et al. it appears that metformin was superior in lowering triglycerides and rosiglitazone at lowering CRP (very low certainty). Menstrual cycles seemed to become more regular for participants using metformin (low certainty, Ahmad et al.).

Regarding adverse effects, Jensterle et al. and Kilicdag et al. reported participants in the metformin group to have more gastrointestinal adverse effects, whereas Jensterle found that some participants in the rosiglitazone group suffered from headache (see table at the end).

Author, year, country	Population	Sample Size per group	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Type of analysis and subgroup	ROB
Baillargeon et al. 2004 Venezuela	Nonobese women (bmi<27), aged 17 to 40 years, who had PCOS	1.Metformin=28 2.Placebo=30	6 months	1.24.6+/- 0.2 2. 24.6+/-0.2	1.27.7+/- 0.9 2. 27.2+/- 0.9	Weight, bmi, whr,mens cycle,shbg,T, DHEAS, A, f-gluc	META BMI<27 Adults	**ROB Moderate**

Jensterle et al 2008 (1) Slovenia	Women with PCOS	1.Metformin=18 2.Rosiglitazone=17	6 months	1.29.3 ±6.5 2.27.0±3.9	1.22.9 ±4.5 2.25.2±4.8	f-gluc, f-insulin, homa, bmi, dheas, A, T, free T, periods/6months	META Adults	**ROB moderate**
Jensterle et al 2008 (2) Slovenia	Women with PCOS	1.Metformin=15 2.Rosiglitazone=11	6 months	1.29.6 ±6.9 2.28.8±8.8	1.23.1 ±3.7 2.25.0±4.9	Lipids, crp (rest in Jernsterle (1)	META Adults	**ROB moderate**
Steiner et al. 2007 Germany	Women with PCOS	1.Metformin=17 2.Rosiglitazone=18	6 months	1.29.3 ±6.5 2.27.9±3.0	1.22.9 ±4.5 2.25.2±4.8	No data extracted	META Adults	Outcomes also reported in Jensterle 2008 (1) and (2), **ROB high**
Cetinkalp et al 2009 Turkey	young women with PCOS	1.Metformin=47 2.Rosi=14 3.OCP=33	4 months	1.25.82 ±6.1 2.22.96 ±4.8 3.24.72±4.1	NR	f-gluc, f-insulin, DHEAS, free-T, T, weight, bmi, hs-crp, HOMA, lipids	META Adults SEM	**ROB high**
Li et al. 2020 China	Obese Chinese women (BMI>=25) with PCOS and insulin resistance	1.Metformin+LS=68 2.Rosiglitazone+LS=67 3.Metformin+Rosiglitazone+LS=69	6 months	1.27.7 ±2.05 2.27.6 ±2.41 3.27.3±2.17	1.25.8±4.5 2.26.04 ±4.5 3.25.96±4.0	Menstrual cycle, weight, bmi, whr, mFGS, T, f-gluk, f-insulin, homa, lipids	META BMI>25	**ROB Low**
Mohiyiddeen et al 2013 UK	Women with PCOS	1.Metformin=17 2.Rosiglitazone=18	3 months	1.29.1 ±1.0 2.29.7 ±1.0	1.30.0±0.9 2.29.0 ±1.0	Weight, bmi, f-insulin, f-gluc, crp, lipids, t, shbg, fai,	META	**ROB Moderate**
Kilicdag et al. 2005 Turkey	women with PCOS	1.Metformin=15 2.Rosiglitazone=15	3 months	1.26.17 ±1.44 2.29.32±1.58	1.24.13±1.42 2.25.53 ±1.68	Weight, bmi, homa, lipids	META SEM	**ROB Moderate**
Ahmad et al. 2008 India	PCOS women aged 18-35 years, with complaints of menstrual irregularities, hirsutism, and/or sterility	1.Metformin=31 2.Rosiglitazone=30	6 months	1.27.66 ±5.44 2.26.94±5.24	1.22.81±4.52 2.23.20 ±3.36	BMI, WHR, hirsutism, menstruation, f-gluc, f-insulin, homa, T, dheas, A	META	**ROB Moderate**

Results of meta-analysis

Outcome	Time point (m)	RCTs	N	Effect, random, MD	P-value	I2 (%)	Favours	Certainty
Weight (kg)	**3-6**	**5**	**319**	**-4.39 (-7.70 to -1.08)**	**<0.001**	**92**	**Metformin**	⊕◯◯◯ VERY LOW
Sub: BMI>25	**6**	**1**	**135**	**-3.19 (-5.73 to -0.65)**	**0.01**	**NA**	**Metformin**	⊕⊕⊕◯ MODERATE
Sub: BMI<27	**6**	**1**	**58**	**-1.80 (-1.98 to -1.62)**	**<0.001**	**NA**	**Metformin**	⊕◯◯◯ VERY LOW
Sub: BMI not specified	**3-6**	**3**	**126**	**-7.55 (-9.83 to -5.27)**	**<0.001**	**NA**	**Metformin**	⊕⊕◯◯ LOW
WHR	6	3	254	0.01 (-0.01 to 0.04)	0.39	90	No difference	⊕◯◯◯ VERY LOW
Sub: BMI>25	6	1	135	-0.01 (-0.03 to 0.01)	0.29	NA	No difference	⊕⊕⊕◯

								MODERATE
Sub: BMI<27	6	1	58	0.00 (-0.00 to 0.00)	1.00	NA	No difference	⊕◯◯◯ VERY LOW
Sub: BMI not specified	**6**	**1**	**61**	**0.05 (0.03 to 0.07)**	**<0.001**	**NA**	**Rosiglitazone**	⊕◯◯◯ VERY LOW
BMI kg/m2	**3-6**	**7**	**415**	**-0.95 (-1.41 to -0.49)**	**<0.001**	**44**	**Metformin**	⊕⊕⊕◯ MODERATE
Sub: BMI>25	**6**	**1**	**135**	**-1.25 (-1.89 to -0.61)**	**0.01**	**NA**	**Metformin**	⊕⊕⊕◯ MODERATE
Sub: BMI<27	**6**	**1**	**58**	**-0.70 (-0.75 to -0.65)**	**<0.001**	**NA**	**Metformin**	⊕◯◯◯ VERY LOW
Sub: BMI not specified	3-6	5	222	-0.82 (-2.05 to 0.41)	0.19	20	No difference	⊕⊕⊕◯ MODERATE
Androstenedione (nmol/l)	**6**	**2**	**96**	**-1.79 (-2.84 to -0.74)**	**0.0009**	**0**	**Metformin**	⊕⊕◯◯ LOW
HOMA-IR	3-6	5	322	0.50 (-0.07 to 1.07)	0.08	93	No difference	⊕◯◯◯ VERY LOW
Sub: BMI>25	3	1	135	-0.09 (-0.54 to 0.36)	0.69	NA	No difference	⊕⊕⊕◯ MODERATE
Sub: BMI not specified	**3-6**	**4**	**187**	**0.74 (0.24 to 1.24)**	**0.004**	**88**	**Rosiglitazone**	⊕◯◯◯ VERY LOW
Total testosterone (nmol/l)	**3-6**	**6**	**385**	**-0.10 (-0.17 to -0.04)**	**0.003**	**0**	**Metformin**	⊕⊕⊕◯ MODERATE
Sub: BMI>25	6	1	135	-0.11 (-0.33 to 0.11)	0.33	NA	No difference	⊕⊕⊕◯ MODERATE
Sub: BMI<27	**6**	**1**	**58**	**-0.11 (-0.20 to -0.02)**	**0.02**	**NA**	**Metformin**	⊕◯◯◯ VERY LOW
Sub: BMI not specified	3-6	4	192	-0.09 (-0.21 to 0.03)	0.13	0	No difference	⊕⊕⊕◯ MODERATE
Fasting insulin (uIU/ml)	3-6	5	327	0.25 (-1.41 to 1.91)	0.77	58	No difference	⊕⊕◯◯ LOW
Sub: BMI>25	3	1	135	0.20 (-1.52 to 1.92)	0.82	NA	No difference	⊕⊕⊕◯ MODERATE
Sub: BMI not specified	3-6	4	192	0.44 (-2.06 to 2.93)	0.73	68	No difference	⊕⊕◯◯ LOW
Fasting glucose (mmol/l)	3-6	6	387	0.06 (-0.08 to 0.20)	0.37	88	No difference	⊕◯◯◯ VERY LOW
Sub: BMI>25	3	1	137	-0.11 (-0.28 to 0.06)	0.21	NA	No difference	⊕⊕⊕◯ MODERATE
Sub: BMI<27	**3**	**1**	**58**	**0.18 (0.11 to 0.25)**	**<0.001**	**NA**	**Rosiglitazone**	⊕◯◯◯ VERY LOW
Sub: BMI not specified	3-6	4	192	0.06 (-0.17 to 0.30)	0.59	90	No difference	⊕◯◯◯ VERY LOW
Total cholesterol (mmol/l)	3-6	4	261	-0.05 (-0.32 to 0.22)	0.72	43	No difference	⊕⊕◯◯ LOW
Sub: BMI>25	3	1	135	0.05 (-0.32 to 0.42)	0.79	NA	No difference	⊕⊕⊕◯ MODERATE
Sub: BMI not specified	3-6	3	126	-0.04 (-0.48 to 0.40)	0.86	47	No difference	⊕⊕◯◯ LOW
HDL (mmol/l)	3-6	4	261	0.08 (-0.09 to 0.25)	0.33	77	No difference	⊕◯◯◯ VERY LOW
Sub: BMI>25	3	1	135	0.00 (-0.08 to 0.08)	1.00	NA	No difference	⊕⊕⊕◯ MODERATE
Sub: BMI not specified	3-6	3	126	0.16 (-0.25 to 0.57)	0.45	84	No difference	⊕◯◯◯ VERY LOW
LDL (mmol/l)	**3-6**	**4**	**261**	**0.18 (0.07 to 0.30)**	**0.002**	**0**	**Rosiglitazone**	⊕⊕⊕◯ MODERATE
Sub: BMI>25	3	1	135	0.02 (-0.23 to 0.27)	0.88	NA	No difference	⊕⊕⊕◯ MODERATE
Sub: BMI not specified	**3-6**	**3**	**126**	**0.23 (0.10 to 0.36)**	**0.0007**	**0**	**Rosiglitazone**	⊕⊕⊕◯ MODERATE
DHEAS (mmol/l)	4-6	3	154	-12.27 (-30.77 to 6.23)	0.19	0	No difference	⊕⊕◯◯ LOW
Sub: BMI>25	3	1	58	-14.00 (-33.12 to 5.12)	0.15	NA	No difference	⊕◯◯◯ VERY LOW

Sub: BMI not specified	4-6	2	96	13.18 (-60.07 to 86.42)	0.72	0	No difference	⊕⊕◯◯ LOW
Triglycerides (mmol/l)	3-6	4	247	0.01 (-0.21 to 0.24)	0.90	67	No difference	⊕⊕◯◯ LOW
Sub: BMI>25	3	1	135	0.15 (-0.00 to 0.30)	0.06	NA	No difference	⊕⊕⊕◯ MODERATE
Sub: BMI not specified	3-6	3	112	-0.10 (-0.23 to 0.03)	0.13	0	No difference	⊕⊕◯◯ LOW
CRP (mg/dl)	3-4	2	96	0.20 (-0.11 to 0.52)	0.20	0	No difference	⊕⊕◯◯ LOW
Free testosterone (pmol/l)	4-6	2	96	1.00 (-1.79 to 3.80)	0.48	0	No difference	⊕⊕◯◯ LOW

Individual studies not included in the meta-analysis

Outcome	Author, year	Time point	N	Metformin	Rosiglitazone	P-value	Favours	Grading
SHBG (Nmol/l)	Mohiyiddeen et al 2013	3	M=17 R=18	Mean and SD 33.41 +/- 2.49	Mean and SD 33.28 +/- 2.60	0.13	No difference	⊕⊕◯◯ LOW[1]
Hirsutism	Ahmad et al. 2008	6	M=31 R=30	Mean and SD 6.51 +/- 1.95	Mean and SD 8.92 +/- 1.63	<0.05	**Metformin**	⊕⊕◯◯ LOW[1]
FAI	Mohiyiddeen et al 2013	3	M=17 R=18	Mean and SD 9.27 +/- 2.33	Mean and SD 8.11 +/- 1.66	0.09	No difference	⊕⊕◯◯ LOW[1]
Total cholesterol (mmol/l)	Jensterle et al. 2008	6	Met=15 Rosi=11	Median and IQR 4.59 +/- 0.93	Median and IQR 5.41 +/- 1.12	NR	No difference	⊕◯◯◯ VERY LOW[2]
HDL (mmol/l)	Jensterle et al. 2008	6	Met=15 Rosi=11	Median and IQR 1.29 +/- 0.25	Median and IQR 1.38 +/- 0.30	NR	No difference	⊕◯◯◯ VERY LOW[2]
LDL (mmol/l)	Jensterle et al. 2008	6	Met=15 Rosi=11	Median and IQR 2.87 +/- 0.84	Median and IQR 3.35 +/- 0.99	NR	No difference	⊕◯◯◯ VERY LOW[2]
Triglycerides (mmol/l)	Jensterle et al. 2008	6	Met=15 Rosi=11	Median and IQR 0.98 +/- 0.62	Median and IQR 1.48 +/- 0.88	NR	**Metformin (by appearance)**	⊕◯◯◯ VERY LOW[2]
CRP (mg/dl)	Jensterle et al. 2008	6	Met=15 Rosi=11	Median and IQR 1.92 +/- 6.18	Median and IQR 0.64 +/- 1.67	NR	**Rosiglitazone (by appearance)**	⊕◯◯◯ VERY LOW[2]
Menstrual duration	Li et al. 2020	6	Met=68 Rosi=67	Mean and SD 46.19 +/- 13.35	Mean and SD 45.07 +/- 17.50	NR	No difference	⊕⊕⊕⊕ HIGH
Menstrual cycles/subject per 6 months	Jensterle et al. 2008	6	Met=18 Rosi=17	Median and IQR 3.65 +/- 1.97	Median and IQR 4.63 +/- 1.54	0.605	No difference	⊕◯◯◯ VERY LOW[2]
Regular menstruation	Ahmad et al. 2008	6	M=31 R=30	28/31	18/30	0.01	**Metformin**	⊕⊕◯◯ LOW[1]

Oligomenorrhea	Cetinkalp et al. 2009	4	M=47 R=14	11/47 (23.4%)	2/14 (14.29%)	NR	**Rosiglitazone (by appearance)**	⊕◯◯◯ VERY LOW[3]
Amenorrhea	Cetinkalp et al. 2009	4	M=47 R=14	3/47 (6.38%)	1/14 (7.14%)	NR	No difference	⊕◯◯◯ VERY LOW[3]

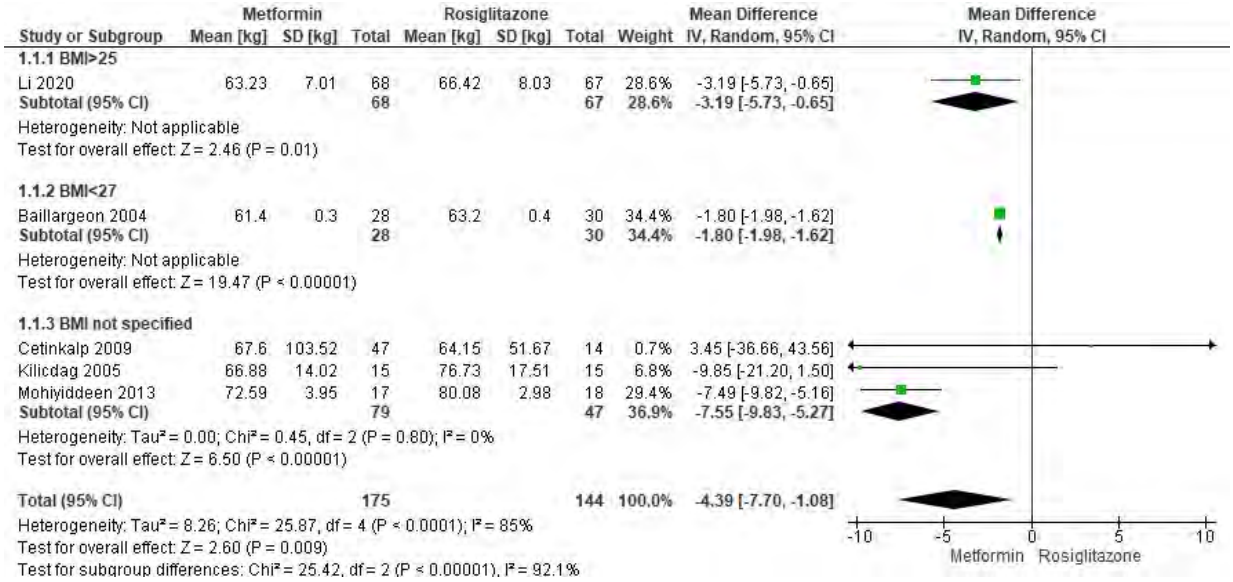
[1] Downgraded once for mod ROB and downgraded once for small number of participants
[2] Downgraded once for mod ROB and downgraded twice for very small number of participants
[3] Downgraded twice for high ROB and downgraded once for small number of participants

OUTCOME 15.1 Weight (kg)

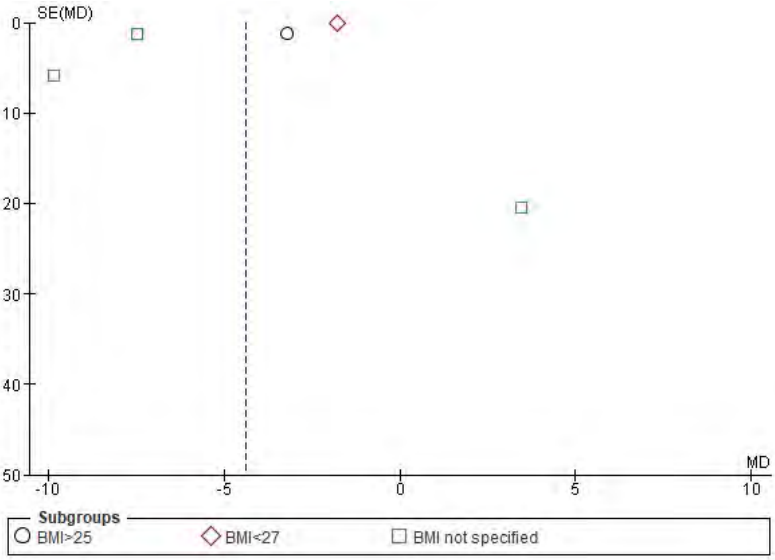
15.1.1 Individual Study Data Table

	OUTCOME: Weight					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **Rosiglitazone**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Cetinkalp et al. 2009	kg	47	67.6	15.1 103.52 (SD)	14	64.15	13.81 51.67 (SD)	SEM	4
Li et al. 2020	kg	68	63.23	7.01	67	66.42	8.03		6
Mohiyiddeen et al 2013	kg	17	72.59	3.95	18	80.08	2.98		3
Baillargeon et al. 2004	kg	28	61.4	0.3	30	63.2	0.4		6
Kilicdag et al. 2005	kg	15	66.88	3.62 14.02 (SD)	15	76.73	4.52 17.51 (SD)	mean +/- SEM	3

15.1.2. Forrest plot metformin vs rosiglitazone for weight



15.1.3. Funnel plot for assessment of publication bias



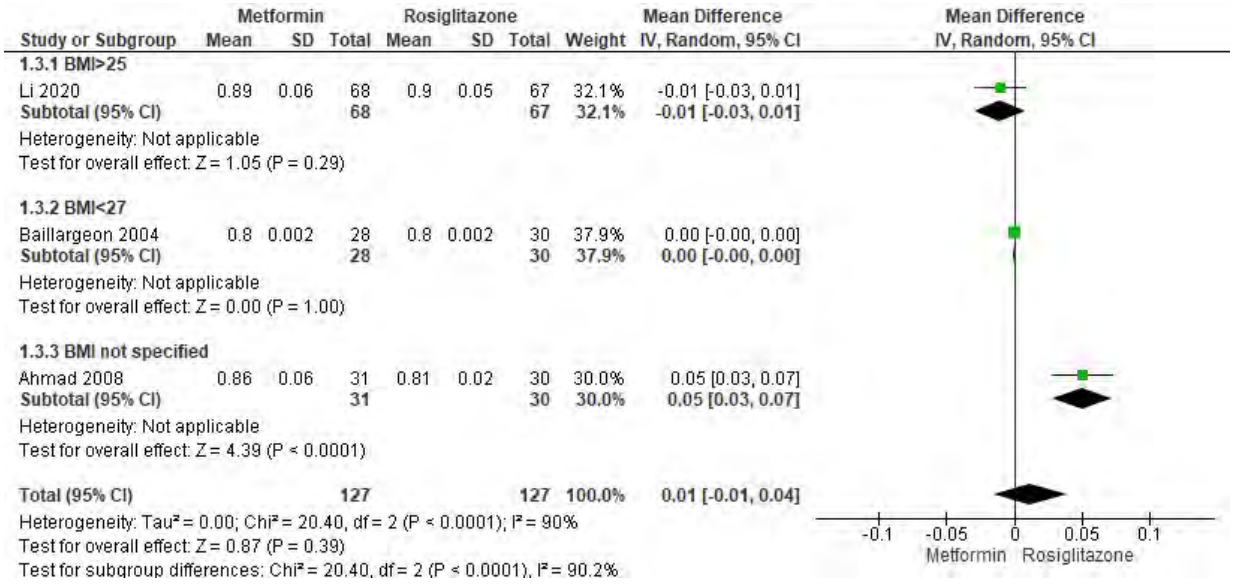
OUTCOME 15.2 WHR

15.2.1 Individual Study Data Table

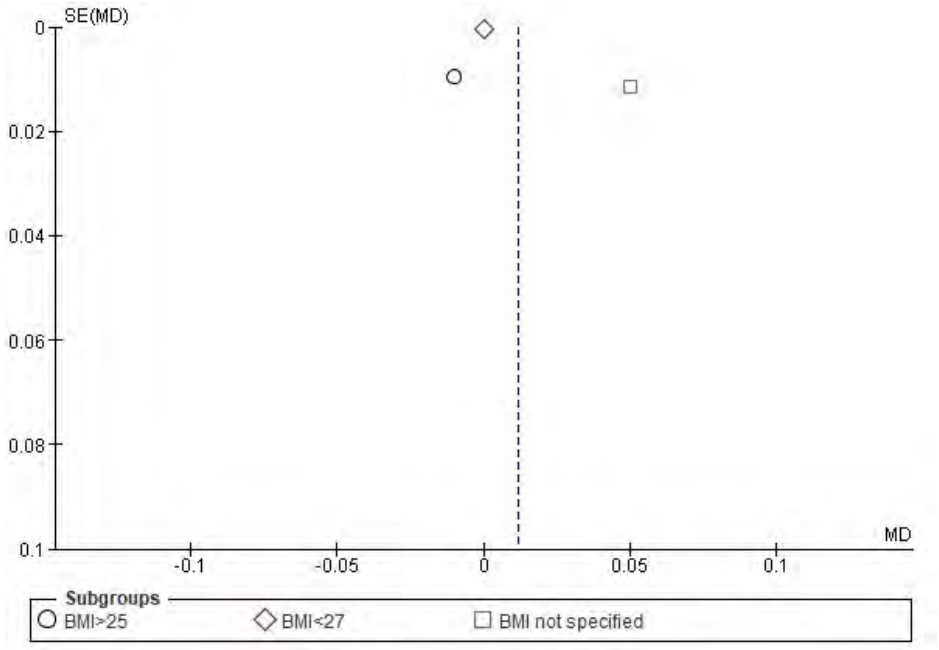
	OUTCOME: WHR		**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable): metformin versus **Rosiglitazone**	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	N	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	N	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	Time period (month)
Li et al. 2020		68	0.89	0.06	67	0.90	0.05		6
Ahmad et al. 2008		31	0.86	0.06	30	0.81	0.02		3
Ahmad et al. 2008		31	0.86	0.06	30	0.81	0.02		6
Ahmad et al. 2008		31	0.86	0.06	30	0.81	0.02		12
Baillargeon et al. 2004		28	0.80	0.002	30	0.80	0.002		6

15.2.2. Forrest plot metformin vs rosiglitazone for weight



15.2.3. Funnel plot for assessment of publication bias



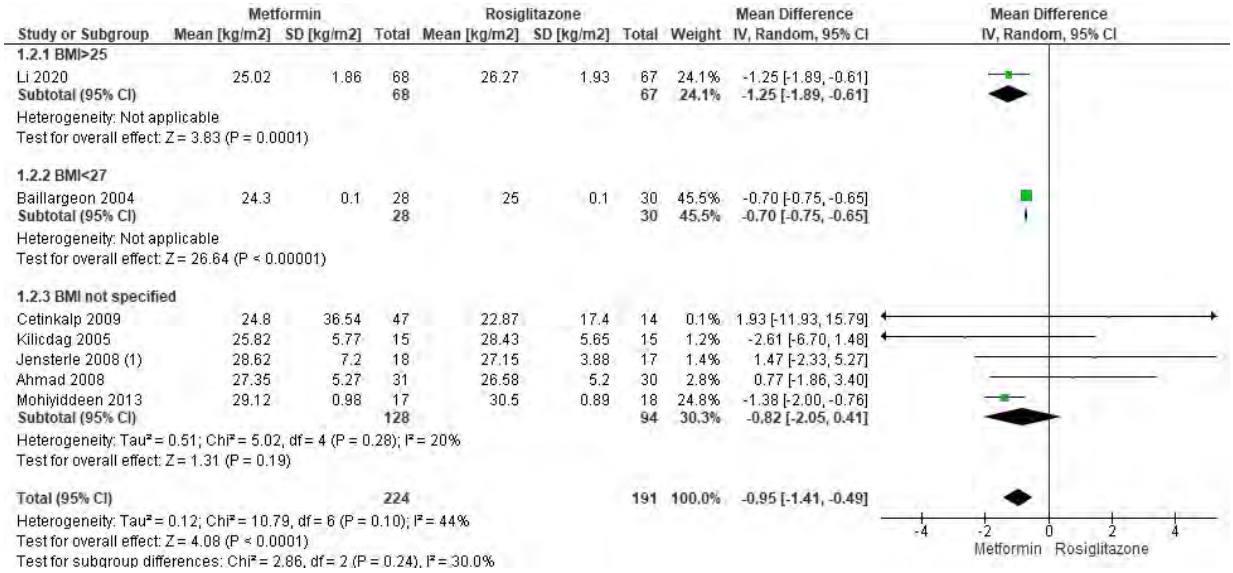
OUTCOME 15.3 BMI

15.3.1 Individual Study Data Table

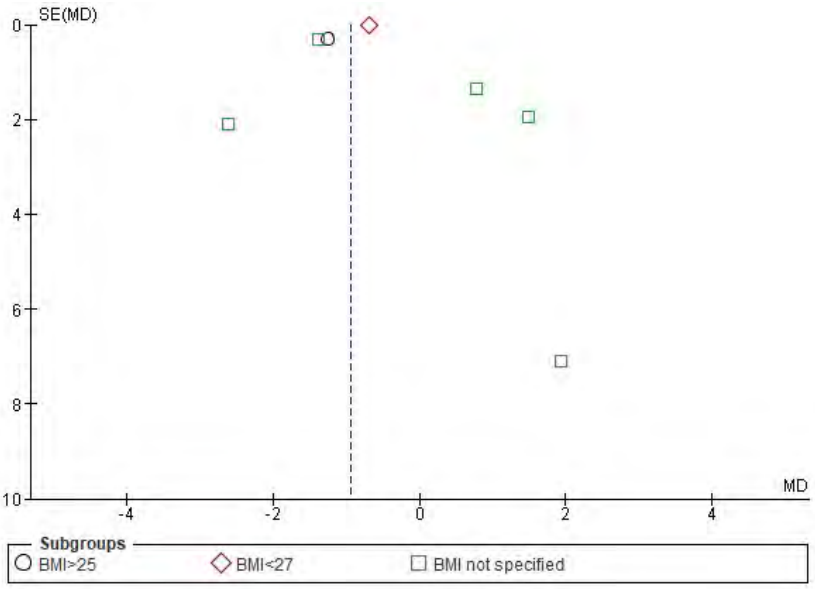
	OUTCOME: BMI						**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **Rosiglitazone**								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Cetinkalp et al. 2009	Kg/m2	weighted	47	24.8	5.33 36.54 (SD)	14	22.87	4.65 17.4 (SD)		4
Li et al. 2020	Kg/m2	weighted	68	25.02	1.86	67	26.27	1.93		6
Mohiyiddeen et al 2013	Kg/m2	weighted	17	29.12	0.98	18	30.50	0.89		3
Kilicdag et al. 2005	Kg/m2	weighted	15	25.82	1.49 5.77 (SD)	15	28.43	1.46 5.65 (SD)	mean +/- SEM	3
Ahmad et al. 2008	Kg/m2	weighted	31	27.44	5.37	30	26.78	5.2		3
Ahmad et al. 2008	Kg/m2	weighted	31	27.35	5.27	30	26.58	5.2		6
Ahmad et al. 2008	Kg/m2	weighted	31	27.50	5.25	30	27.55	6.0		12

Jensterle et al 2008 (1)	Kg/m2	weighted	18	28.62	7.20	17	27.15	3.88		6
Baillargeon et al. 2004	kg	weighted	28	24.3	0.1	30	25.0	0.1		6

15.3.2. Forrest plot metformin vs rosiglitazone for BMI



15.3.3. Funnel plot for assessment of publication bias

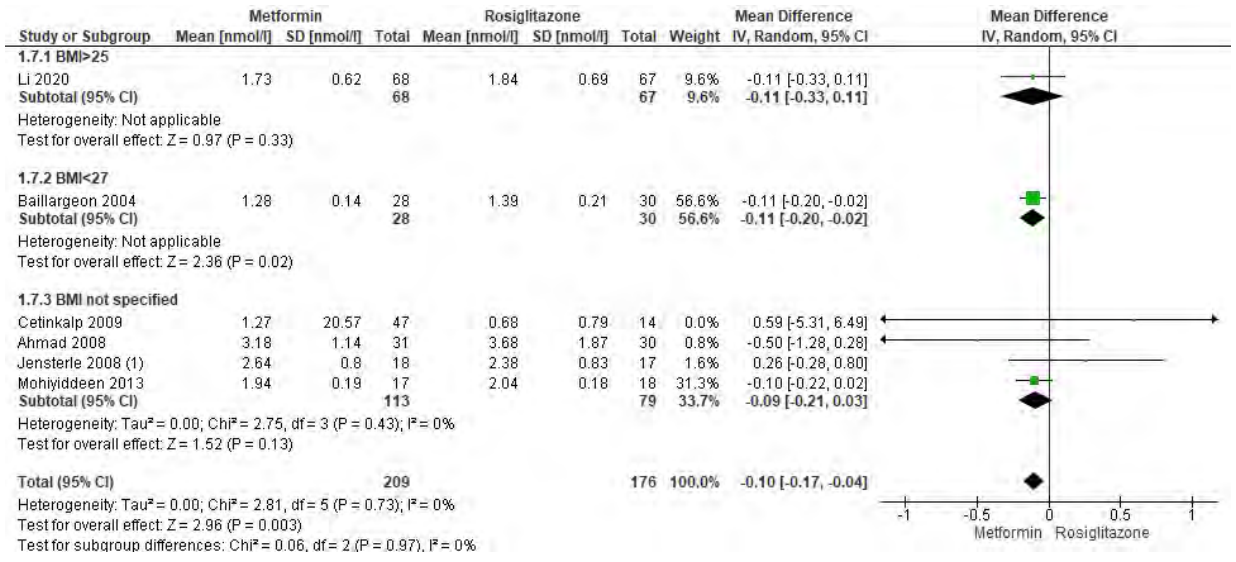


OUTCOME 15.4 Testosterone (Nmol/l)

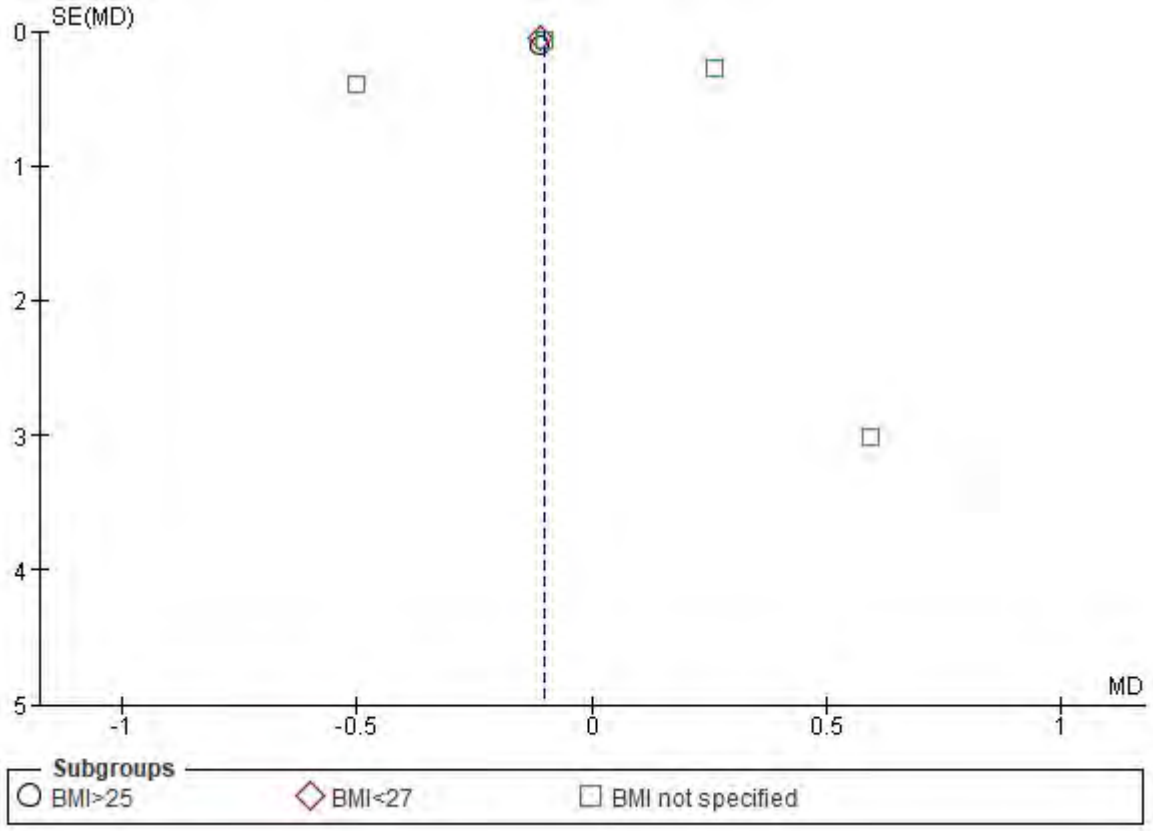
15.4.1 Individual Study Data Table

	OUTCOME: Testosterone					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **Rosiglitazone**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Cetinkalp et al. 2009	ng/ml	47	1.27	3.0 20.57 (SD)	14	0.68	0.21 0.79 (SD)		4
Li et al. 2020	Ng/ml Nmol/l	68	0.50 1.73	0.18 0.62	67	0.53 1.84	0.20 0.69		6
Mohiyiddeen et al 2013	Nmol/l	17	1.94	0.19	18	2.04	0.18		3
Ahmad et al. 2008	Pg/ml	31	0.96	0.60	30	1.49	0.45		3
Ahmad et al. 2008	Pg/ml Nmol/l	31	0.92 3.18	0.33 1.14	30	1.06 3.68	0.54 1.87		6
Ahmad et al. 2008	Pg/ml	31	0.90	0.31	30	1.01	0.64		12
Jensterle et al 2008 (1)	Nmol/l	18	2.64	0.80	17	2.38	0.83		6
Baillargeon et al. 2004	Ng/dl Nmol/l	28	37 1.28	4 0.14	30	40 1.39	6 0.21		

15.4.2. Forrest plot metformin vs rosiglitazone for testosterone



15.4.3. Funnel plot for assessment of publication bias

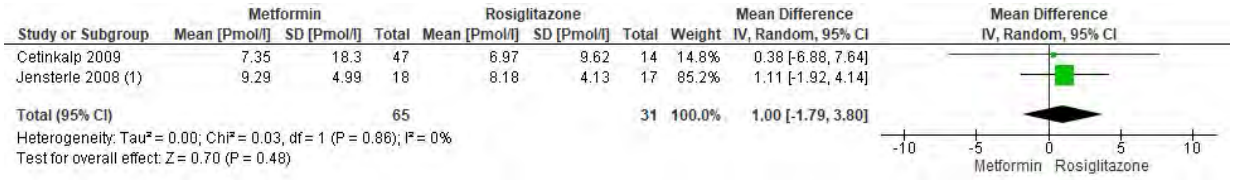


OUTCOME 15.5 Free testosterone (pmol/l)

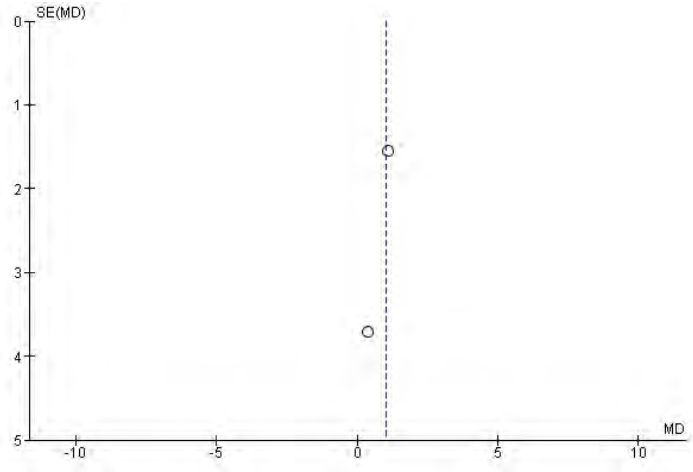
15.5.1 Individual Study Data Table

	OUTCOME: free testosterone					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **Rosiglitazone**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Cetinkalp et al. 2009	pg/ml pmol/l	47	2.12 7.35	0.77 18.3 (SD)	14	2.01 6.97	0.74 9.62 (SD)		4
Jensterle et al 2008 (1)	Pmol/l	18	9.29	4.99	17	8.18	4.13		6

15.5.2. Forrest plot metformin vs rosiglitazone for free testosterone



15.5.3. Funnel plot for assessment of publication bias



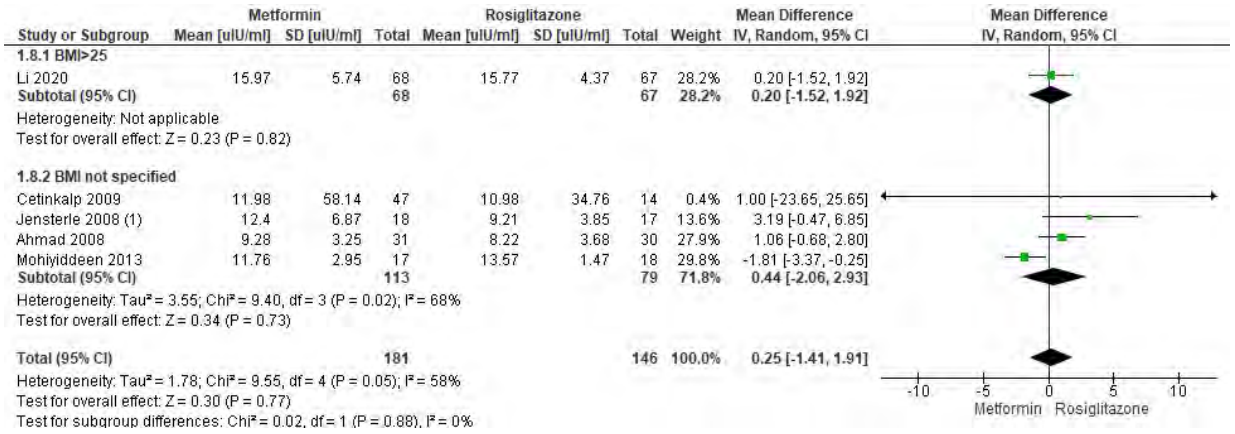
OUTCOME 15.6 Fasting insulin (uIU/ml)

15.6.1 Individual Study Data Table

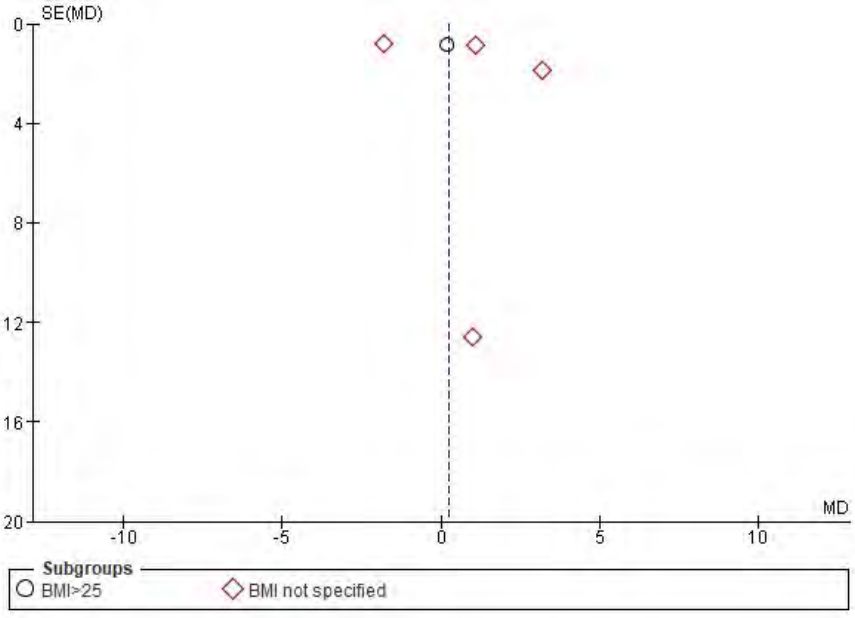
	OUTCOME: fasting insulin					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **Rosiglitazone**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Cetinkalp et al. 2009	uIU/ml	47	11.98	8.48 58.14 (SD)	14	10.98	9.29 34.76 (SD)		4
Li et al. 2020	uIU/ml	68	15.97	5.74	67	15.77	4.37		6
Mohiyiddeen et al 2013	uIU/ml	17	11.76	2.95	18	13.57	1.47		3

Ahmad et al. 2008	uIU/ml	31	9.94	2.41	30	9.55	3.11		3
Ahmad et al. 2008	uIU/ml	31	9.28	3.25	30	8.22	3.68		6
Ahmad et al. 2008	uIU/ml	31	8.94	2.39	30	8.02	3.78		12
Jensterle et al 2008 (1)	mIU/l	18	12.4	6.87	17	9.21	3.85		6

15.6.2. Forrest plot metformin vs rosiglitazone for fasting insulin



15.6.3. Funnel plot for assessment of publication bias

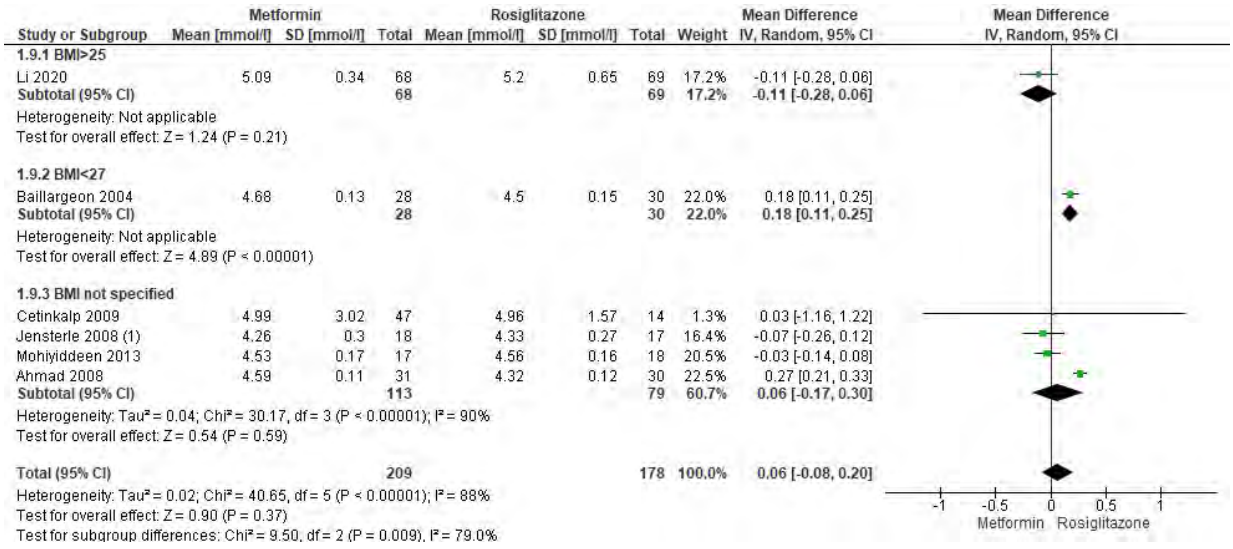


OUTCOME 15.7 Fasting glucose (mmol/l)

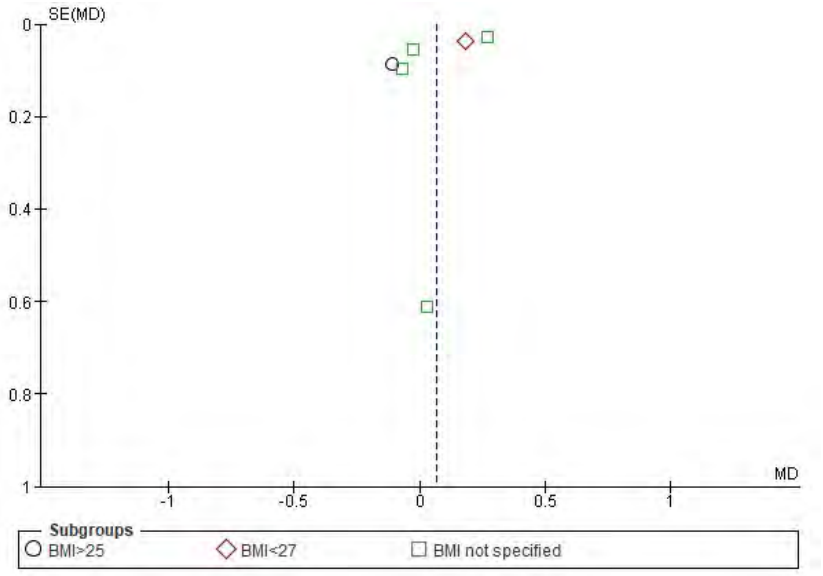
15.7.1 Individual Study Data Table

	OUTCOME: fasting glucose					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **Rosiglitazone**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Cetinkalp et al. 2009	Mg/dl	47	89.94 4.99	7.95 3.02 (SD)	14	89.3 4.96	7.51 1.57 (SD)	SEM	4
Li et al. 2020	Mmol/l	68	5.09	0.34	69	5.20	0.65		6
Mohiyiddeen et al 2013	Mmol/l	17	4.53	0.17	18	4.56	0.16		3
Ahmad et al. 2008	Mg/dl	31	80.19	1.39	30	76.80	1.56		3
Ahmad et al. 2008	Mg/dl	31	82.61 4.59	1.94 0.11	30	78.00 4.32	2.18 0.12		6
Ahmad et al. 2008	Mg/dl	31	81.94	1.29	30	77.40	1.30		12
Steiner et al. 2007	Mmol/l	17	4.26	0.30	18	4.33	0.27		6
Baillargeon et al. 2004	mg/dl mmol/l	28	84.4 4.68	2.4 0.13	30	81.0 4.5	2.7 0.15		6
Jensterle et al 2008 (1)	Mmol/l	18	4.26	0.30	17	4.33	0.27		6

15.7.2. Forrest plot metformin vs rosiglitazone for fasting glucose



15.7.3. Funnel plot for assessment of publication bias

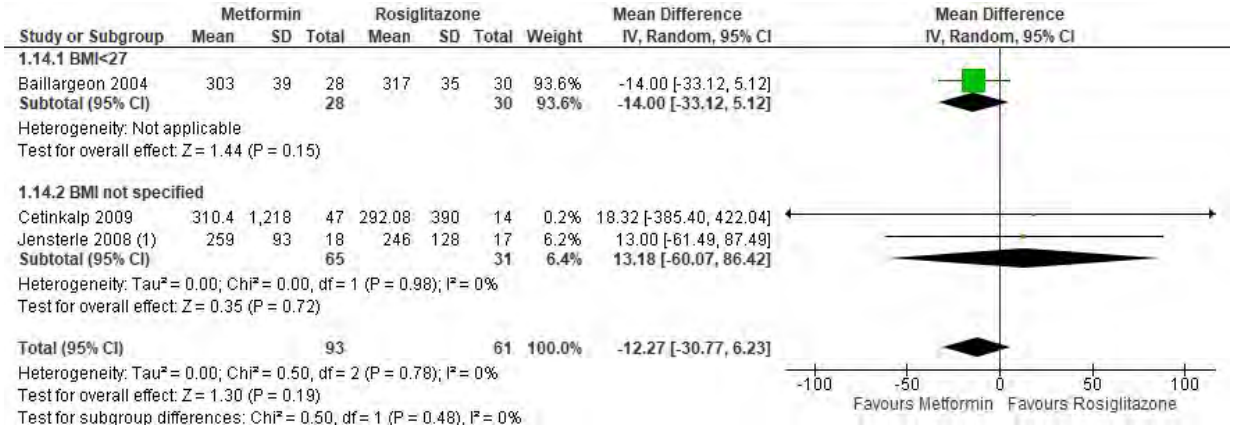


OUTCOME 15.8 DHEAS (mg/dl)

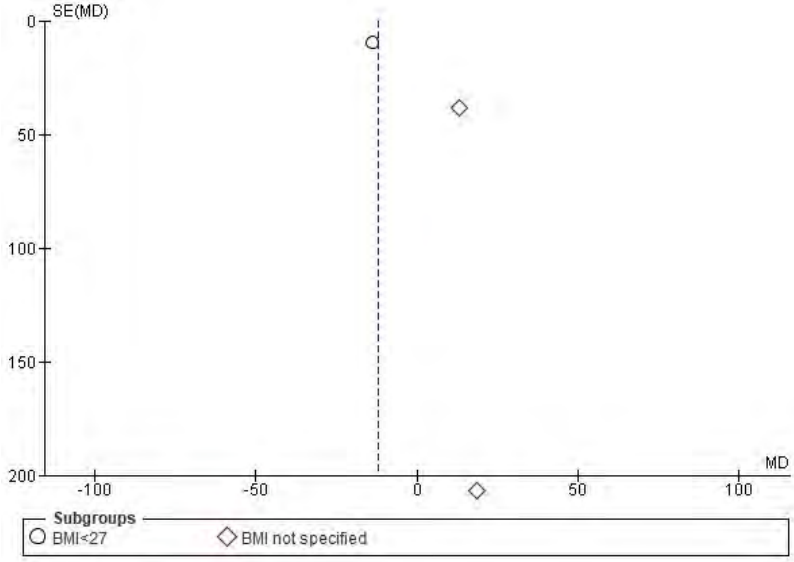
15.8.1 Individual Study Data Table

	OUTCOME: DHEAS					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **Rosiglitazone**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Cetinkalp et al. 2009	mg/dl	47	310.4	177.6 1218 (SD)	14	292.08	104.3 390 (SD)	SEM	4
Ahmad et al. 2008	Ug/ml	31	172.0	35.11	30	187.78	29.08	Unit?	3
Ahmad et al. 2008	Ug/ml	31	128.00	27.29	30	148.31	39.14	Unit?	6
Ahmad et al. 2008	Ug/ml	31	120.7	30.1	30	136.31	19.1	Unit?	12
Baillargeon et al. 2004	mg/dl	28	303	39	30	317	35	U	6
Jensterle et al 2008 (1)	Umol/l Mg/dl	18	7.02 259	2.53 93	17	6.68 246	3.48 128		6

15.8.2. Forrest plot metformin vs rosiglitazone for DHEAS



15.8.3. Funnel plot for assessment of publication bias



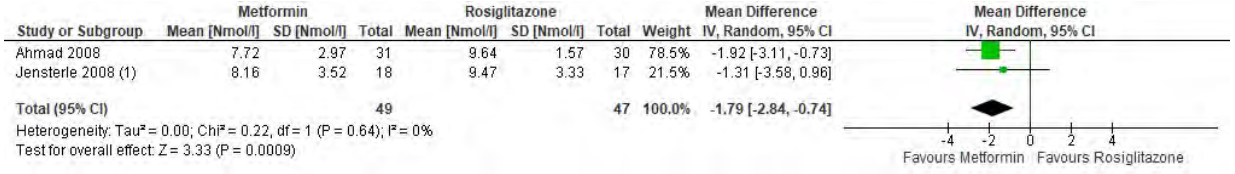
OUTCOME 15.9 androstenedione (nmol/l)

15.9.1 Individual Study Data Table

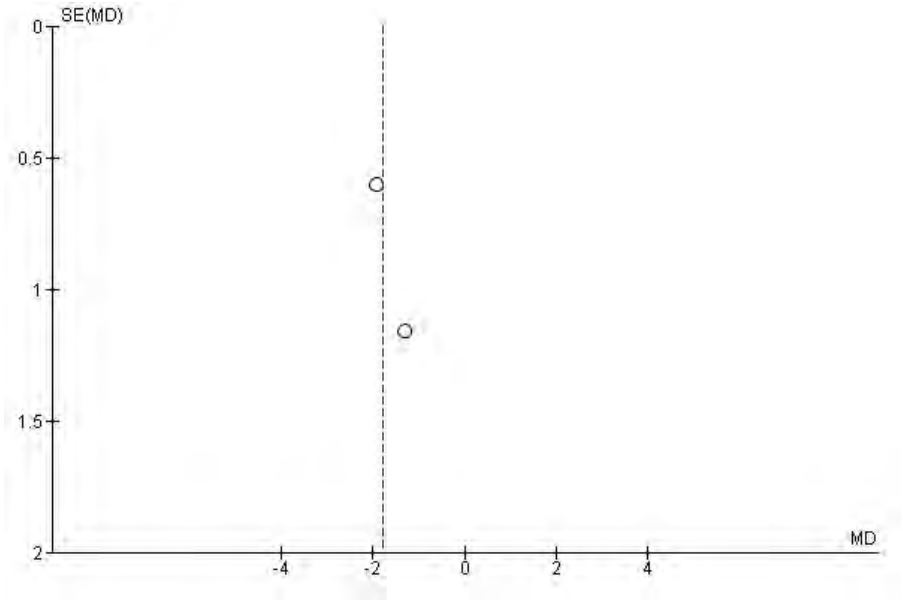
	OUTCOME: androstenedione					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **rosiglitazone**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Ahmad et al. 2008	Ng/ml	31	2.63	0.32	30	3.08	0.69		3

Ahmad et al. 2008	Ng/ml Nmol/l	31	2.21 7.72	0.85 2.97	30	2.76 9.64	0.45 1.57		6
Ahmad et al. 2008	Ng/ml	31	2.11	0.80	30	2.66	0.41		12
Jensterle et al 2008 (1)	Nmol/l	18	8.16	3.52	17	9.47	3.33		6

15.9.2. Forrest plot metformin vs rosiglitazone for androstenedione



15.9.3. Funnel plot for assessment of publication bias



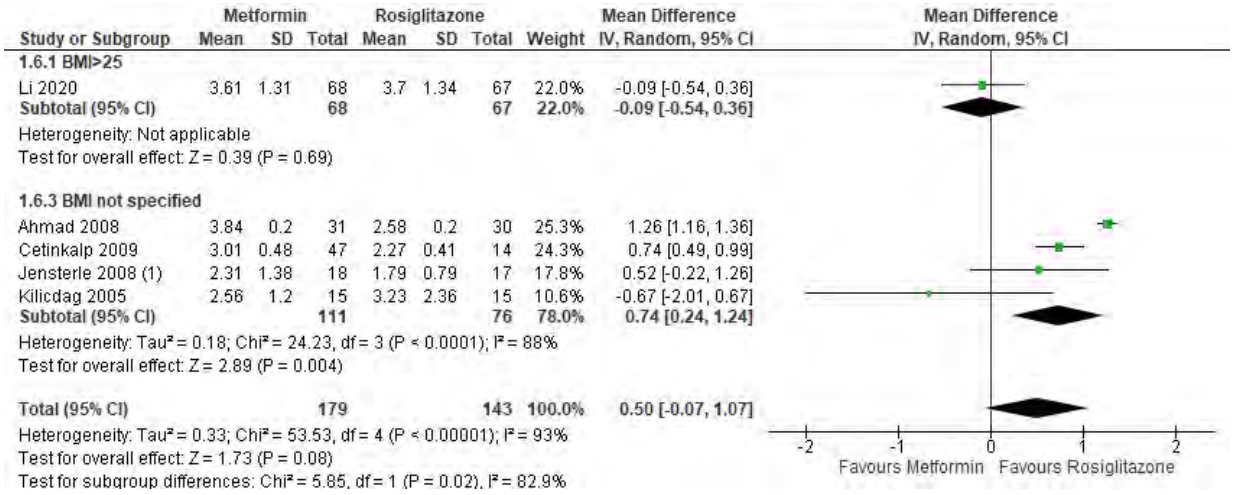
OUTCOME 15.10 HOMA-IR

15.10.1 Individual Study Data Table

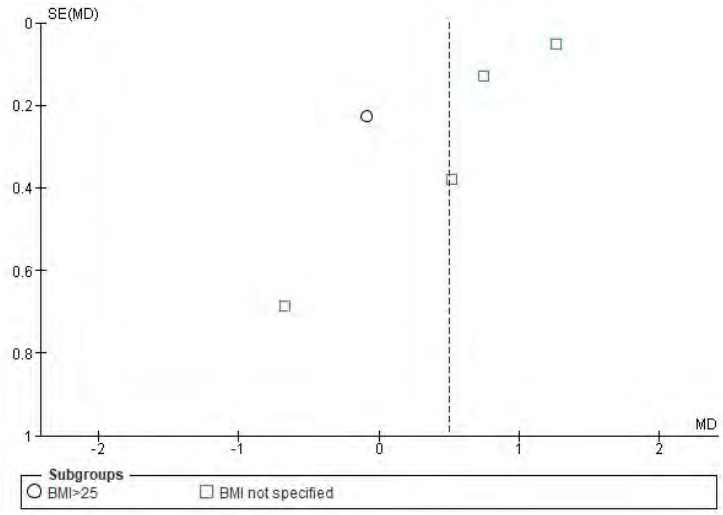
	OUTCOME: HOMA-IR					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **Rosiglitazone**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Are these values adjusted or crude?**	**Time period (month)**

							comparison group		
Cetinkalp et al. 2009		47	3.01	0.07 0.48 (SD)	14	2.27	0.11 0.41 (SD)		4
Li et al. 2020		68	3.61	1.31	67	3.70	1.34		6
Kilicdag et al. 2005		15	2.56	0.31 1.2 (SD)	15	3.23	0.61 2.36 (SD)	mean +/- SEM	3
Ahmad et al. 2008		31	3.90	0.19	30	2.77	0.22		3
Ahmad et al. 2008		31	3.84	0.20	30	2.58	0.20		6
Ahmad et al. 2008		31	2.76	0.17	30	1.90	0.16		12
Jensterle et al 2008 (1)		18	2.31	1.38	17	1.79	0.79		6

15.10.2. Forrest plot metformin vs rosiglitazone for HOMA-IR



15.10.3. Funnel plot for assessment of publication bias

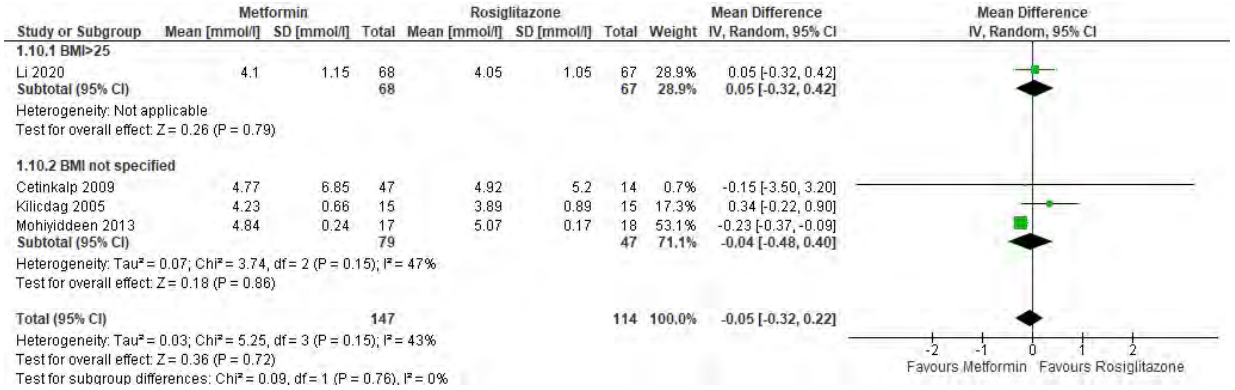


OUTCOME 15.11 Total cholesterol (mmol/l)

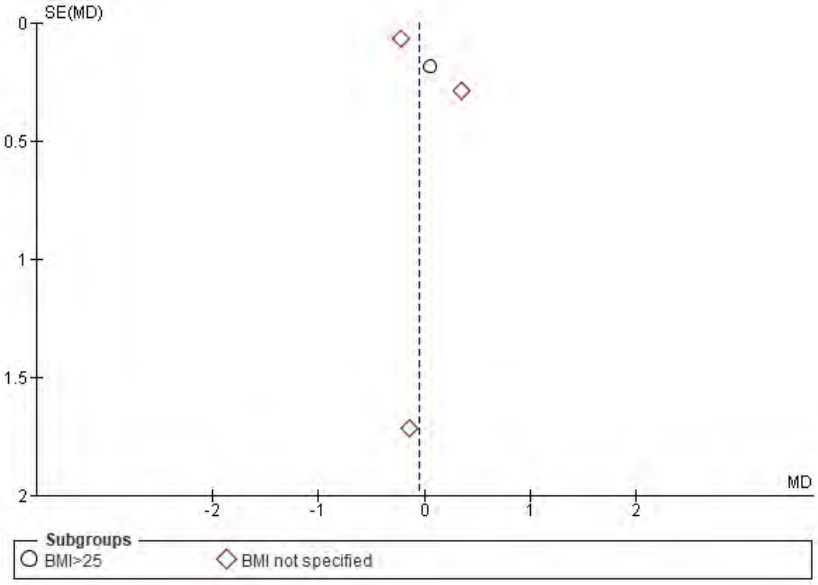
15.11.1 Individual Study Data Table

	OUTCOME: Total cholesterol						**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **Rosiglitazone**								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Cetinkalp et al. 2009	Mg/dl Mmol/l		47	184.6 4.77	38.7 6.85 (SD)	14	190.33 4.92	53.68 (5.2)	SEM	4
Li et al. 2020	Mmol/l		68	4.10	1.15	67	4.05	1.05		6
Mohiyiddeen et al 2013	Mmol/l		17	4.84	0.24	18	5.07	0.17		3
Kilicdag et al. 2005	Mg/dl Mmol/l		15	163.67 4.23	6.46 0.66 (SD)	15	150.23 3.89	8.73 0.89 (SD)	mean +/- SEM	3

15.11.2. Forrest plot metformin vs rosiglitazone for total cholesterol



15.11.3. Funnel plot for assessment of publication bias



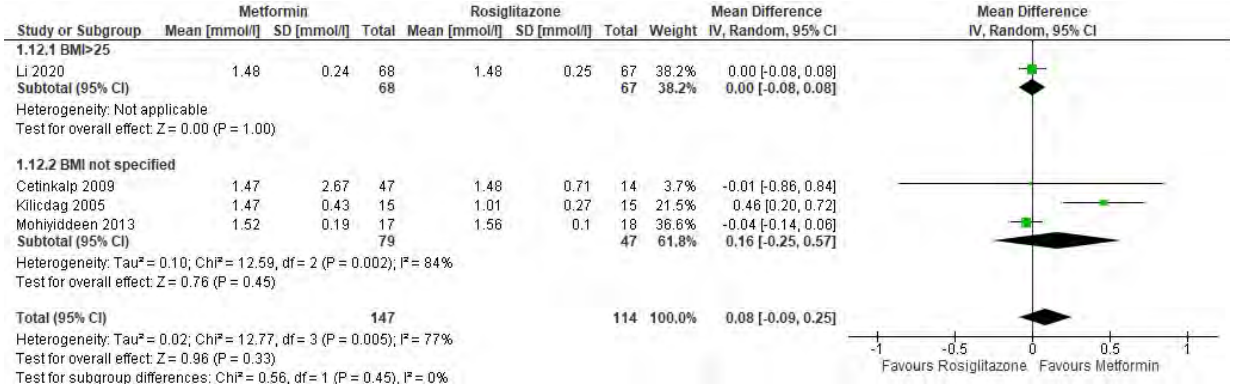
OUTCOME 15.12 HDL (mmol/l)

15.12.1 Individual Study Data Table

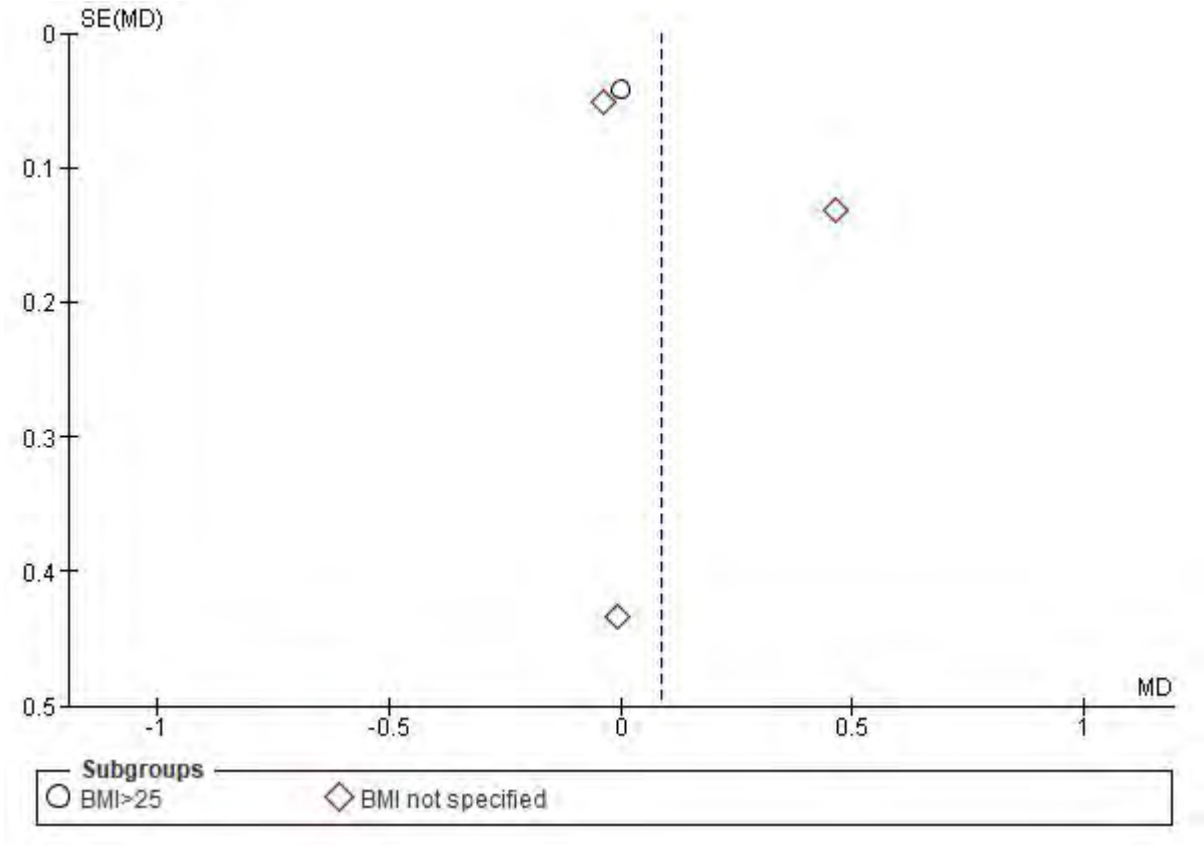
	OUTCOME: HDL					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **Rosiglitazone**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Cetinkalp et al. 2009	Mg/dl	47	56.7	15.06	14	57.27	7.4	SEM	4

	Mmol/l		1.47	2.67 (SD)		1.48	0.71 (SD)		
Li et al. 2020	Mmol/l	68	1.48	0.24	67	1.48	0.25		6
Mohiyiddeen et al 2013	Mmol/l	17	1.52	0.19	18	1.56	0.10		3
Kilicdag et al. 2005	Mg/dl	15	56.8 1.47	4.09 0.43 (SD)	15	39.2 1.01	2.52 0.27 (SD)	mean +/- SEM	3

15.12.2. Forrest plot metformin vs rosiglitazone for HDL



15.12.3. Funnel plot for assessment of publication bias

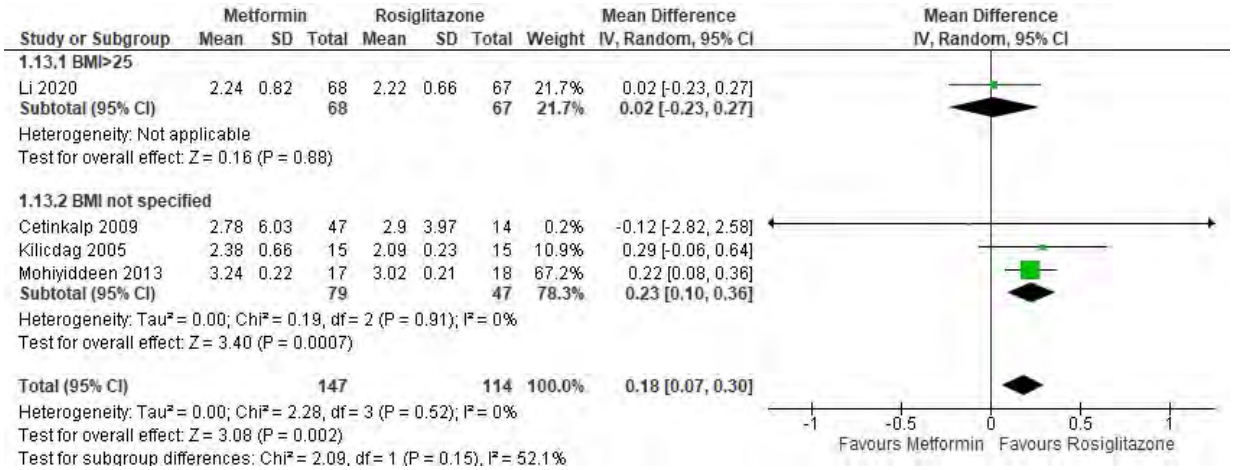


OUTCOME 15.13 LDL (mmol/l)

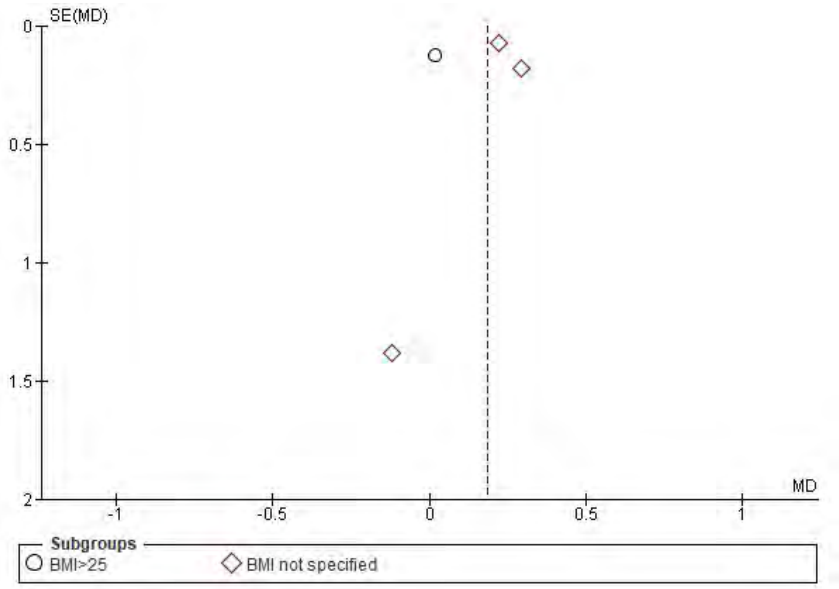
15.13.1 Individual Study Data Table

	OUTCOME: LDL					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **Rosiglitazone**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Cetinkalp et al. 2009	Mg/dl Mmol/l	47	107.5 2.78	34.1 6.03 (SD)	14	112.08 2.9	40.8 3.97 (SD)	SEM	4
Li et al. 2020	Mmol/l	68	2.24	0.82	67	2.22	0.66		6
Mohiyiddeen et al 2013	Mmol/l	17	3.24	0.22	18	3.02	0.21		3
Kilicdag et al. 2005	Mg/dl Mmol/l	15	92.20 2.38	6.55 0.66 (SD)	15	80.7 2.09	2.30 0.23 (SD)	mean +/- SEM	3

15.13.2. Forrest plot metformin vs rosiglitazone for LDL



15.13.3. Funnel plot for assessment of publication bias

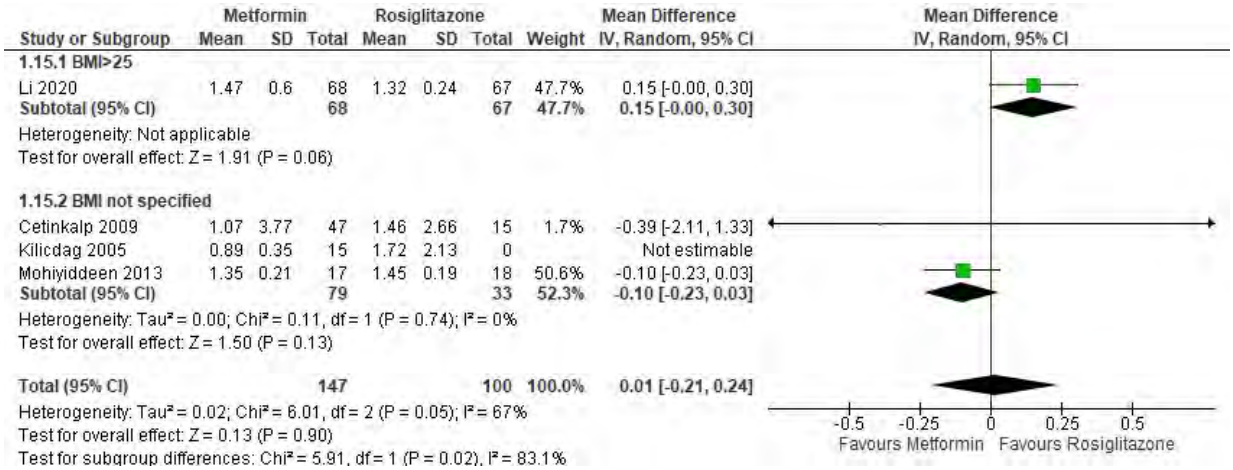


OUTCOME 15.14 Triglycerides (mmol/l)

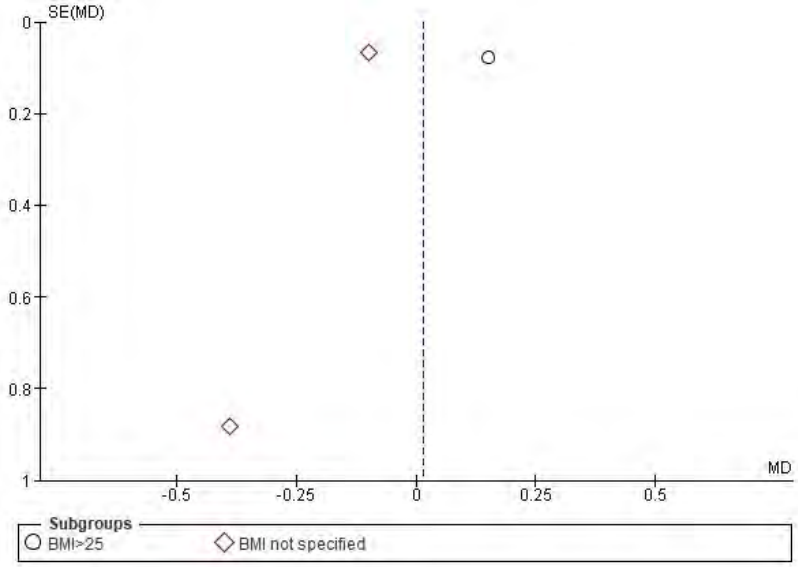
15.14.1 Individual Study Data Table

	OUTCOME: triglycerides					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **Rosiglitazone**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**
Cetinkalp et al. 2009	Mg/dl Mmol/l	47	94.8 1.07	48.9 3.77 (SD)	14	129.58 1.46	62.9 2.66 (SD)		4
Li et al. 2020	Mmol/l	68	1.47	0.60	67	1.32	0.24		6
Mohiyiddeen et al 2013	Mmol/l	17	1.35	0.21	18	1.45	0.19		3
Kilicdag et al. 2005	Mg/dl Mmol/l	15	78.87 0.89	7.71 0.35 (SD)	15	152.46 1.72	48.42 2.13 (SD)	mean +/- SEM	3

15.14.2. Forrest plot metformin vs rosiglitazone for Triglycerides



15.14.3. Funnel plot for assessment of publication bias



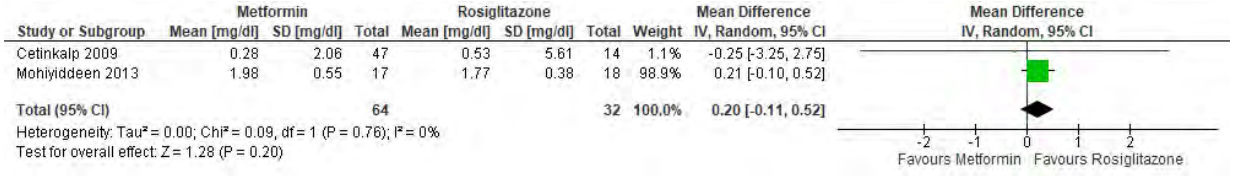
OUTCOME 15.15 CRP (mg/l)

15.15.1 Individual Study Data Table

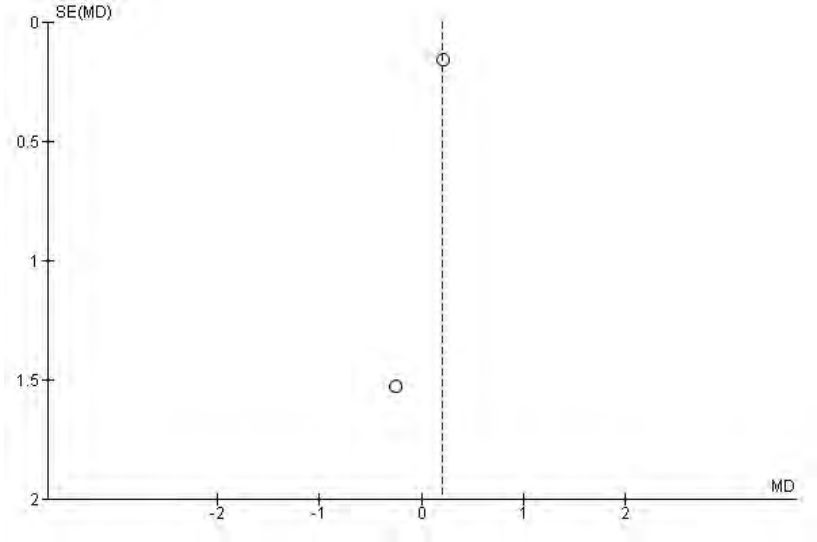
	OUTCOME: hs-CRP					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **Rosiglitazone**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**Time period (month)**

Cetinkalp et al. 2009	Mg/l	47	0.28	0.3 2.06 (SD)	14	0.53	1.5 5.61 (SD)		4
Mohiyiddeen et al 2013	Mg/l	17	1.98	0.55	18	1.77	0.38		3

15.15.2. Forrest plot metformin vs rosiglitazone for CRP



15.15.3. Funnel plot for assessment of publication bias



Adverse effects

	Study	Metformin	Rosiglitazone
Gastrointestinal side effects (diarrhea,vomiting etc)	Jensterle 2008 (1)	4/18	0/17
	Kilicdag	3/15	0/15
Headache	Jensterle 2008 (1)	0/18	3/17

Comparison 16: Metformin versus pioglitazone

Evidence Summary

Six randomised controlled trials (RCTs) were identified by our search. Of these RCT, all were included in the meta-analysis.
Of these studies two had a moderate ROB and four a high ROB. All studies were on adult PCOS patients, two studies on obese participants (BMI>=25) and four where the BMI was not reported. Rows highlighted grey indicate studies with participants described as obese.
A major limitation in the evidence for this comparison is the lack of confidence in author reporting of units and conversions (Shahebrahimi et al).

Meta-analysis/descriptive analysis summary

In the meta-analysis, metformin was superior in lowering WHR in obese women (certainty very low) whereas pioglitazone was superior in improving FAI (certainty moderate).
Regarding individual studies, not included in the meta-analysis, Ortega-Gonzales et al found that metformin was superior in improving free testosterone and androstenedione (very low certainty).
We did not find any reports on adverse effects.

Author, year, country	Population	Sample Size per group	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Type of analysis and subgroup	ROB
Naka et al 2011 Greece	Young women with PCOS (mean age 23.3 years)	1.Metformin=15 2.Placebo=14 3.Pioglitazone=14	6 months	1.29.4 ±6.5 2.28.3 ±4.9 3.28.5±5.4	1.22.2±3.6 2.24.3 ±6.0 3.23.6±5.1	Weight, bmi, WHR, f-gluc, f-insulin, lipids, hirsutism, T, SHBG, FAI	META	**ROB Moderate**
Ortega-Gonzales et al. 2005 Mexico	Women with PCOS, aged 18–35 yr, whose chief complaints were hirsutism	1.Metformin=18 2.Pioglitazone=17	6 months	1.34.1 ±1.6 2.32.2 ±1.0	1.29.0±0.8 2.28.8 ±0.9	Weight, bmi, WHR, hirsutism, f-gluc, f-insulin, HOMA, lipids, dheas, free-T, A	META Means and SEM BMI>=25	**ROB high**
Shahebrahimi et al 2016 Iran	Women with PCOS, aged 20–49 years	1.Metformin=28 2.Pioglitazone=28	3 months	1.27.71 ±4.36 2.28.28±4.49	1.27.5±3.68 2.27.6 ±5.91	Weight, bmi, f-gluc, lipids, T, f-insulin, dheas	META	**ROB high**
Sohrevardi et al. 2016 Iran	women with PCOS, aged 18-40 years, with irregular menses and infertility	1.Metformin=22 2.Pioglitazone=21 3. Metformin+Pioglitazone=23	3 months	1.27.5 ±3.6 2.27.2±4.7 3.28.5 ±3.2	1.28.72±6.3 2.27.52 ±5.0 3.30.73 ±6.2	Weight, bmi, WHR, f-gluc, f-insulin, homa, lipids, dheas, T	META	**ROB high**
Cho et al. 2009 UK	obese hyperandrogenic, anovulatory Caucasian women with PCOS	1.Metformin=10 2.Orlistat=10 3.Pioglitazone=10	3 months	1.34.3 ±1.8 2.37.4±2.7 3.36.2±1.8	NR	Homa, insulin, shbg, bmi, fai	META Means and SEM BMI>=25	**ROB Moderate**

Sangeeta et al. 2012 India	Women of age 18–30 years with PCOS	1.Metformin=43 2.Pioglitazone=42	6 months	NR	NR	Hirsutism, lipids, f-insulin, homa, T, shbg, FAI	META	**ROB high**

Results of meta-analysis

Outcome	Time point	RCTs	N	Effect, random, MD	P-value	I2 (%)	Favours	Certainty
Weight (kg)	3-6	4	163	-1.09 (-5.22 to 3.03)	0.60	0	No difference	⊕◯◯◯ VERY LOW
Sub: BMI>25	6	1	35	-1.80 (-11.45 to 7.85)	0.71	NA	No difference	⊕◯◯◯ VERY LOW
Sub: BMI not specified	3-6	3	128	-0.94 (-5.50 to 3.62)	0.69	0	No difference	⊕⊕◯◯ LOW
WHR	3-6	3	107	-0.01 (-0.05 to 0.04)	0.83	81	No difference	⊕◯◯◯ VERY LOW
Sub: BMI>25	**6**	**1**	**35**	**-0.06 (-0.10 to -0.02)**	**0.005**	**NA**	**Metformin**	⊕◯◯◯ VERY LOW
Sub: BMI not specified	3-6	2	72	0.02 (-0.00 to 0.04)	0.10	0	No difference	⊕⊕◯◯ LOW
BMI kg/m2	3-6	5	183	-1.09 (-2.54 to 0.37)	0.14	0	No difference	⊕⊕⊕◯ MODERATE
Sub: BMI>25	3-6	2	55	-2.26 (-5.45 to 0.93)	0.16	0	No difference	⊕◯◯◯ VERY LOW
Sub: BMI not specified	3-6	3	128	-0.78 (-2.41 to 0.86)	0.35	0	No difference	⊕⊕⊕◯ MODERATE
HOMA-IR	3	4	183	1.33 (-0.18 to 2.85)	0.08	88	No difference	⊕◯◯◯ VERY LOW
Sub: BMI>25	3	2	55	0.17 (-0.56 to 0.89)	0.65	0	No difference	⊕◯◯◯ VERY LOW
Sub: BMI not specified	3	2	128	2.68 (-1.75 to 7.12)	0.24	95	No difference	⊕◯◯◯ VERY LOW
Total testosterone (ng/dl)	3-6	4	213	-4.86 (-12.37 to 2.65)	0.20	25	No difference	⊕⊕◯◯ LOW
Fasting insulin (IU/ml)	3-6	6	268	3.12 (-3.48 to 9.72)	0.35	95	No difference	⊕⊕◯◯ LOW
Sub: BMI>25	3-6	2	55	0.76 (-2.56 to 4.08)	0.65	0	No difference	⊕◯◯◯ VERY LOW
Sub: BMI not specified	3-6	4	213	3.89 (-4.68 to 12.47)	0.37	97	No difference	⊕⊕◯◯ LOW
Fasting glucose (mg/dl)	3-6	4	163	1.22 (-2.58 to 5.01)	0.53	68	No difference	⊕⊕◯◯ LOW
Sub: BMI>25	6	1	35	0.10 (-5.32 to 5.52)	0.97	NA	No difference	⊕◯◯◯ VERY LOW
Sub: BMI not specified	3-6	3	128	1.42 (-3.39 to 6.23)	0.56	77	No difference	⊕⊕◯◯ LOW
Total cholesterol (mg/dl)	3-6	5	248	3.57 (-18.33 to 25.46)	0.75	90	No difference	⊕◯◯◯ VERY LOW
Sub: BMI>25	3	1	35	7.00 (-13.66 to 27.66)	0.51	NA	No difference	⊕◯◯◯ VERY LOW
Sub: BMI not specified	3-6	4	213	2.53 (-24.47 to 29.53)	0.85	92	No difference	⊕◯◯◯ VERY LOW
HDL (mg/dl)	3-6	5	248	-7.08 (-15.67 to 1.50)	0.11	93	No difference	⊕◯◯◯ VERY LOW
Sub: BMI>25	3	1	35	-4.30 (-11.26 to 2.66)	0.23	NA	No difference	⊕◯◯◯ VERY LOW
Sub: BMI not specified	3-6	4	213	-7.73 (-17.60 to 2.14)	0.12	94	No difference	⊕◯◯◯ VERY LOW
LDL (mg/dl)	3-6	4	163	-3.91 (-21.19 to 13.36)	0.68	70	No difference	⊕◯◯◯ VERY LOW

Sub: BMI>25	3	1	35	8.20 (-8.58 to 24.98)	0.34	NA	No difference	⊕◯◯◯ VERY LOW
Sub: BMI not specified	3-6	3	128	-8.46 (-30.62 to 13.71)	0.45	71	No difference	⊕◯◯◯ VERY LOW
DHEAS (ug/dl)	3-6	3	134	-19.76 (-44.43 to 4.92)	0.12	0	No difference	⊕⊕◯◯ LOW
Sub: BMI>25	6	1	35	-36.60 (-112.03 to 38.83)	0.34	NA	No difference	⊕◯◯◯ VERY LOW
Sub: BMI not specified	3-6	2	99	-17.74 (-43.85 to 8.38)	0.18	0	No difference	⊕◯◯◯ VERY LOW
Triglycerides (mg/dl)	3-6	4	163	9.06 (-14.39 to 32.51)	0.45	58	No difference	⊕◯◯◯ VERY LOW
Sub: BMI>25	3	1	35	-19.10 (-52.34 to 14.14)	0.26	NA	No difference	⊕◯◯◯ VERY LOW
Sub: BMI not specified	3-6	3	128	1704 (-6.48 to 40.56)	0.16	47	No difference	⊕◯◯◯ VERY LOW
SHBG	3-6	3	134	-18.21 (-46.99 to 10.58)	0.22	97	No difference	⊕⊕◯◯ LOW
Sub: BMI>25	3	1	20	-6.70 (-15.57 to 2.17)	0.14	NA	No difference	⊕◯◯◯ VERY LOW
Sub: BMI not specified	6	2	114	-23.88 (-63.48 to 15.71)	0.24	97	No difference	⊕⊕◯◯ LOW
FAI	**3-6**	**3**	**134**	**2.46 (1.42 to 3.50)**	**<0.001**	**6**	**Pioglitazone**	⊕⊕⊕◯ MODERATE
Sub: BMI>25	3	1	20	1.40 (-0.72 to 3.52)	0.20	NA	No difference	⊕◯◯◯ VERY LOW
Sub: BMI not specified	**6**	**2**	**114**	**2.80 (1.72 to 3.88)**	**<0.001**	**0**	**Pioglitazone**	⊕⊕⊕◯ MODERATE
Hirsutism	6	3	149	0.28 (-0.83 to 1.39)	0.62	0	No difference	⊕⊕⊕◯ MODERATE
Sub: BMI>25	6	1	35	0.70 (-1.26 to 2.66)	0.48	NA	No difference	⊕◯◯◯ VERY LOW
Sub: BMI not specified	6	2	114	0.09 (-1.26 to 1.43)	0.90	0	No difference	⊕⊕⊕◯ MODERATE

Individual studies not included in meta-analysis

Outcome	Author, year	Time point	N	Metformin	Pioglitazone	P-value	Favours	Grading
Free testosterone (pg/ml)	Ortega-Gonzales et al. 2005	6	M=18 P=17	Mean and SD 1.81 +/- 0.29	Mean and SD 2.12 +/- 0.35	0.004	**Metformin**	⊕◯◯◯ VERY LOW[1]
Androstenedione (ng/ml)	Ortega-Gonzales et al. 2005	6	M=18 P=17	Mean and SD 2.07 +/- 0.14	Mean and SD 2.50 +/- 0.26	<0.001	**Metformin**	⊕◯◯◯ VERY LOW[1]
Oligomenorrhea	Shahebrahimi et al 2016	3	M=28 P=28	13/28	11/28	0.52	No difference	⊕◯◯◯ VERY LOW[2]
Amenorrhea	Shahebrahimi et al 2016	3	M=28 P=28	0/28	1/28	NR	No difference	⊕◯◯◯ VERY LOW[2]

[1] Downgraded twice for small number of participants and twice for being a high ROB
[2] Downgraded once for small number of participants and twice for being a high ROB

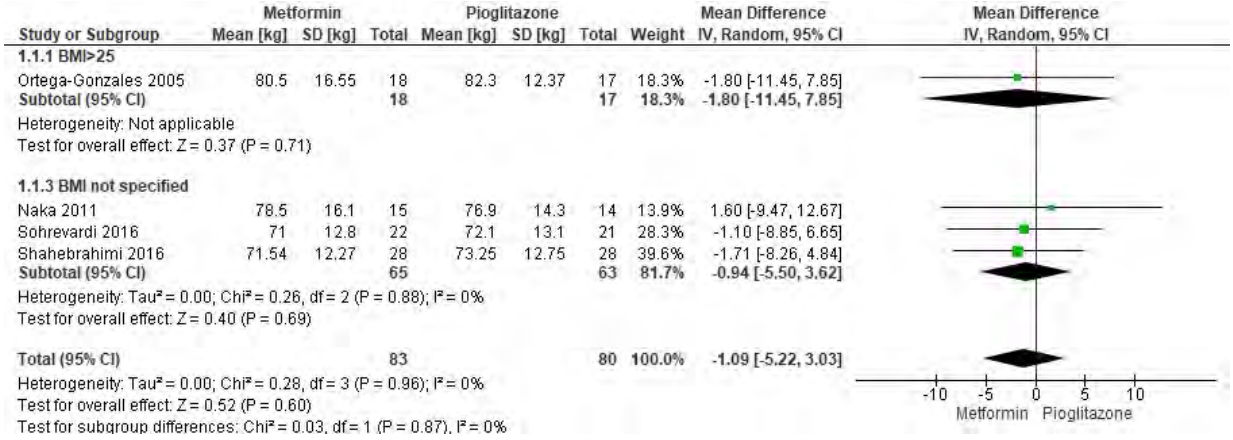
OUTCOME 16.1 weight (kg)

16.1.1 Individual Study Data Table

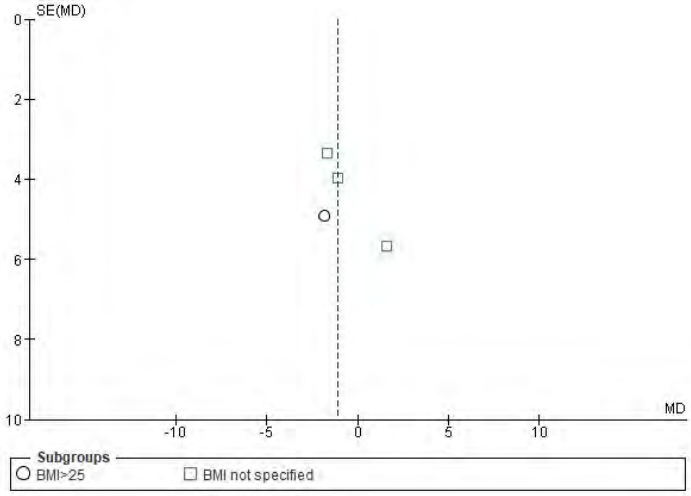
	OUTCOME: Weight		**OUTCOME TYPE:** Continuous

		COMPARISON (if applicable): **metformin** versus **pioglitazone**								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Naka et al 2011	kg	weighted	15	78.5	16.1	14	76.9	14.3		6
Ortega-Gonzales et al. 2005	kg	weighted	18	80.5	3.9 16.55 (SD)	17	82.3	3.0 12.37 (SD)	Mean+SEM	6
Shahebrahimi et al 2016	kg	weighted	28	71.54	12.27	28	73.25	12.75		3
Sohrevardi et al. 2016	kg	weighted	22	71	12.8	21	72.1	13.1		3

16.1.2. Forrest plot metformin vs pioglitazone for weight



16.1.3. Funnel plot for assessment of publication bias

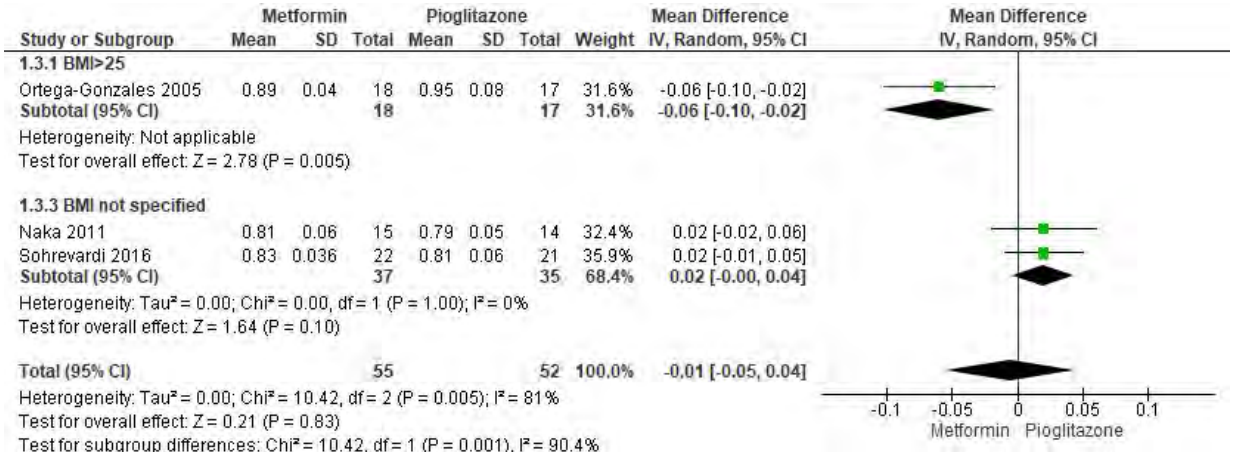


OUTCOME 16.2 WHR

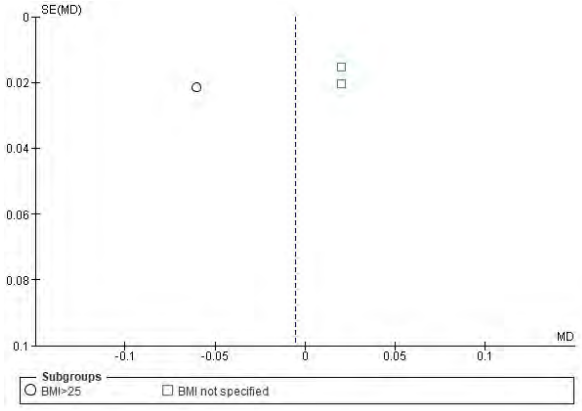
16.2.1 Individual Study Data Table

	OUTCOME: WHR			**OUTCOME TYPE:** Continuous					
		COMPARISON (if applicable): metformin versus **pioglitazone**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Naka et al 2011		15	0.81	0.06	14	0.79	0.05		6
Ortega-Gonzales et al. 2005		18	0.89	0.01 0.04 (SD)	17	0.95	0.02 0.08 (SD)	Mean+SEM	6
Sohrevardi et al. 2016		22	0.83	0.036	21	0.81	0.06		3

16.2.2. Forrest plot metformin vs pioglitazone for WHR



16.2.3. Funnel plot for assessment of publication bias

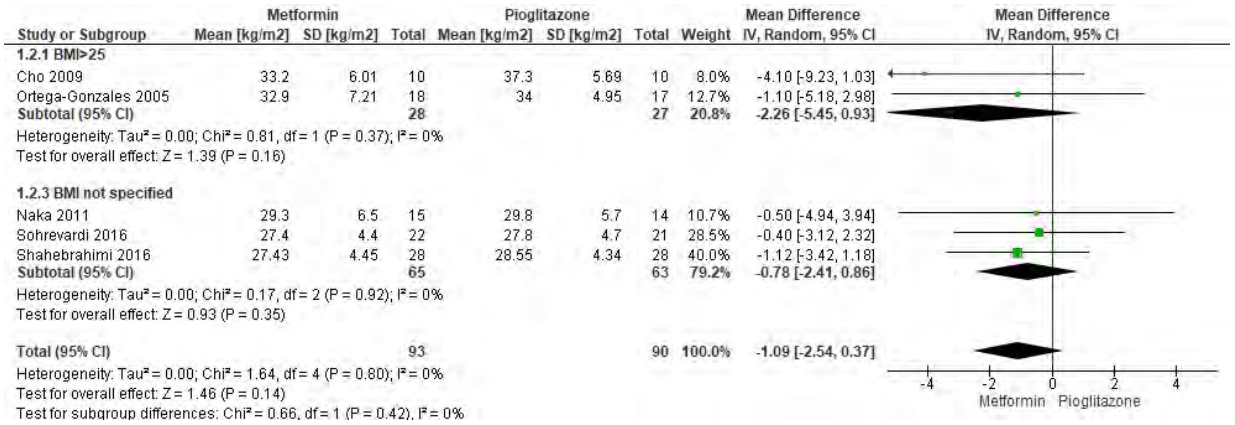


OUTCOME 16.3 BMI

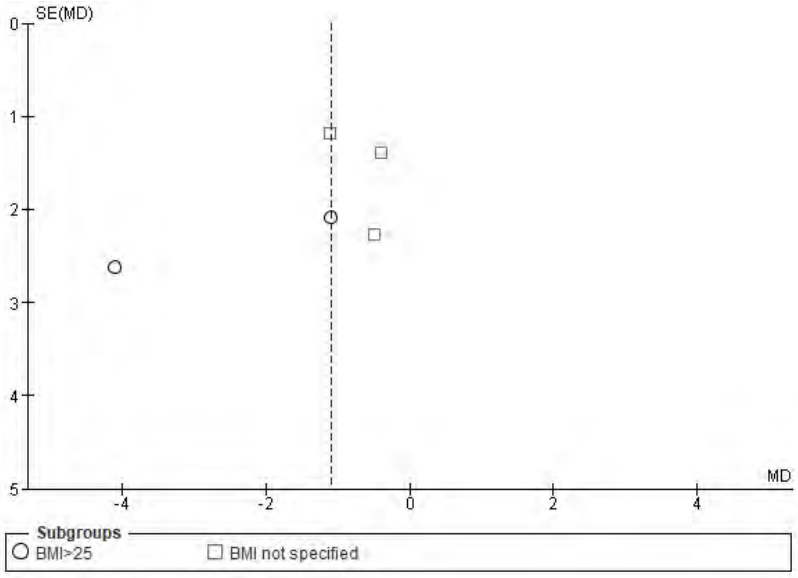
16.3.1 Individual Study Data Table

	OUTCOME: BMI						**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **pioglitazone**								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Naka et al 2011	Kg/m2	weight	15	29.3	6.5	14	29.8	5.7		6
Ortega-Gonzales et al. 2005	Kg/m2	weighted	18	32.9	1.7 7.21 (SD)	17	34.0	1.2 4.95 (SD)	Mean+SEM	6
Shahebrahimi et al 2016	Kg/m2	weighted	28	27.43	4.45	28	28.55	4.34		3
Sohrevardi et al. 2016	Kg/m2	weighted	22	27.4	4.4	21	27.8	4.7		3
Cho et al. 2009	Kg/m2	weighted	10	33.2	1.9 6.01 (SD)	10	37.3	1.8 5.69 (SD)	Mean+SEM	3

16.3.2. Forrest plot metformin vs pioglitazone for BMI



16.3.3. Funnel plot for assessment of publication bias

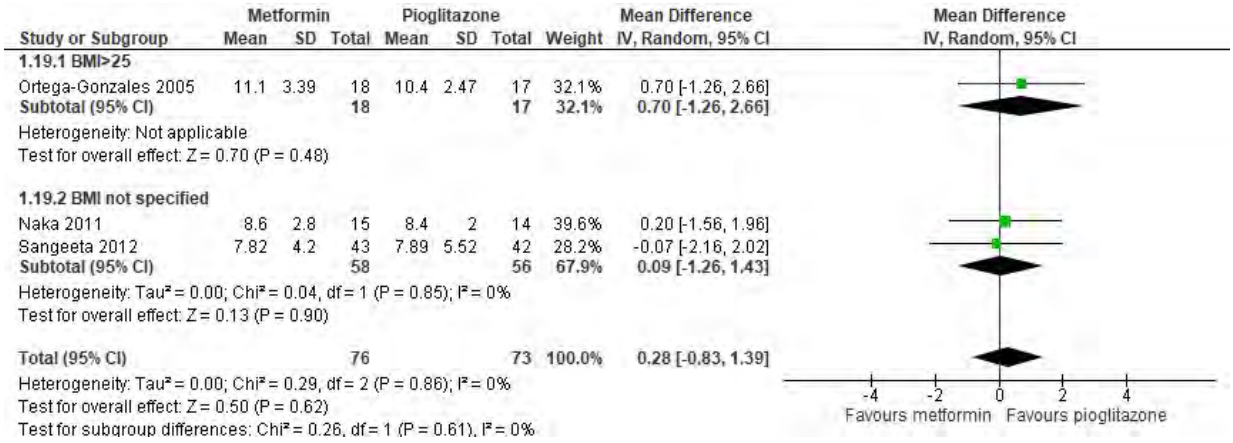


OUTCOME 16.4 Hirsutism

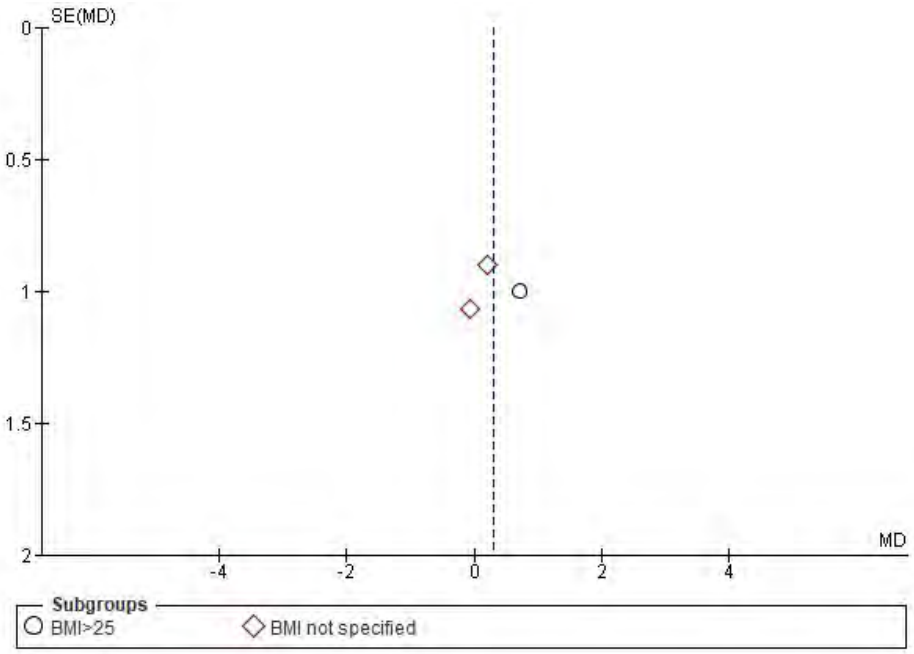
16.4.1 Individual Study Data Table

	OUTCOME: hirsutism						**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **pioglitazone**								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Sangeeta et al. 2012	score	FGS	43	7.82	4.2	42	7.89	5.52		6
Naka et al 2011	score	FGS	15	8.6	2.8	14	8.4	2.0		6
Ortega-Gonzales et al. 2005	score	FGS	18	11.1	1.7 3.39 (SD)	17	10.4	0.6 2.47 (SD)	Mean+SEM	6

16.4.2. Forrest plot metformin vs pioglitazone for hirsutism



16.4.3. Funnel plot for assessment of publication bias

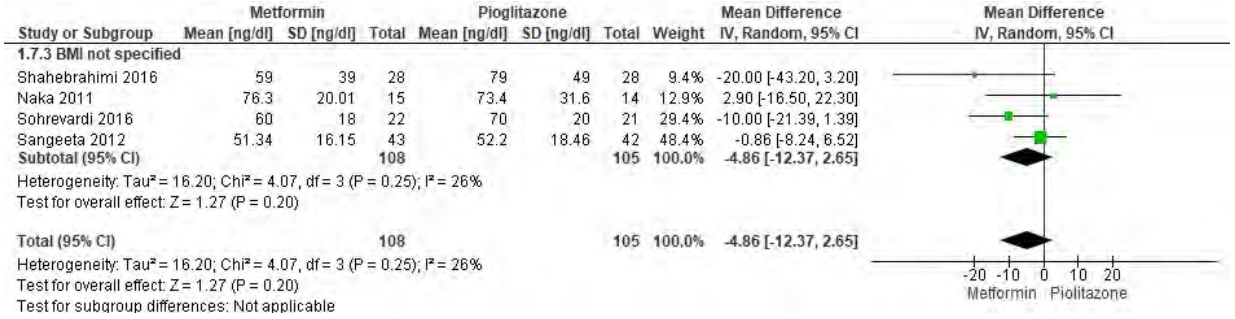


OUTCOME 16.5 Testosterone (ng/dl)

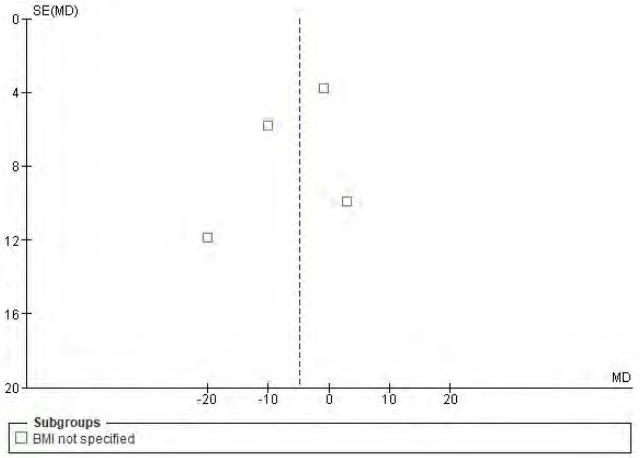
16.5.1 Individual Study Data Table

	OUTCOME: Testosterone					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **pioglitazone**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Sangeeta et al. 2012	Nmol/l Ng/dl	43	1.78 51.34	0.56 16.15	42	1.81 52.2	0.64 18.46		6
Naka et al 2011	ng/dl	15	76.3	20.1	14	73.4	31.6		6
Shahebrahimi et al 2016	Ng/dl	28	0.59	0.39	28	0.79	0.49	Unit?	3
Sohrevardi et al. 2016	Ug/l Ng/dl	22	0.6 60	0.18 18	21	0.7 70	0.2 20		3

16.5.2. Forrest plot metformin vs pioglitazone for testosterone



16.5.3. Funnel plot for assessment of publication bias

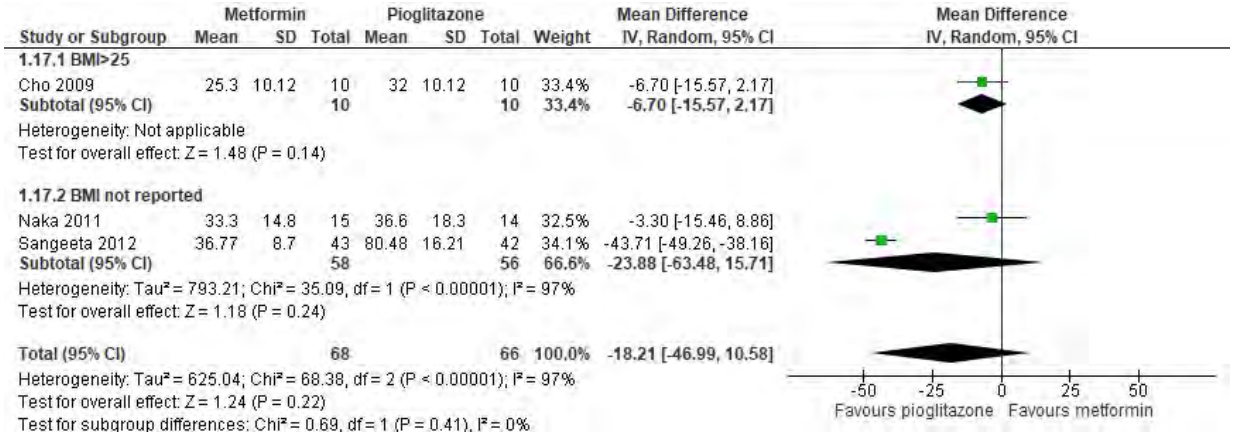


OUTCOME 16.6 SHBG (nmol/l)

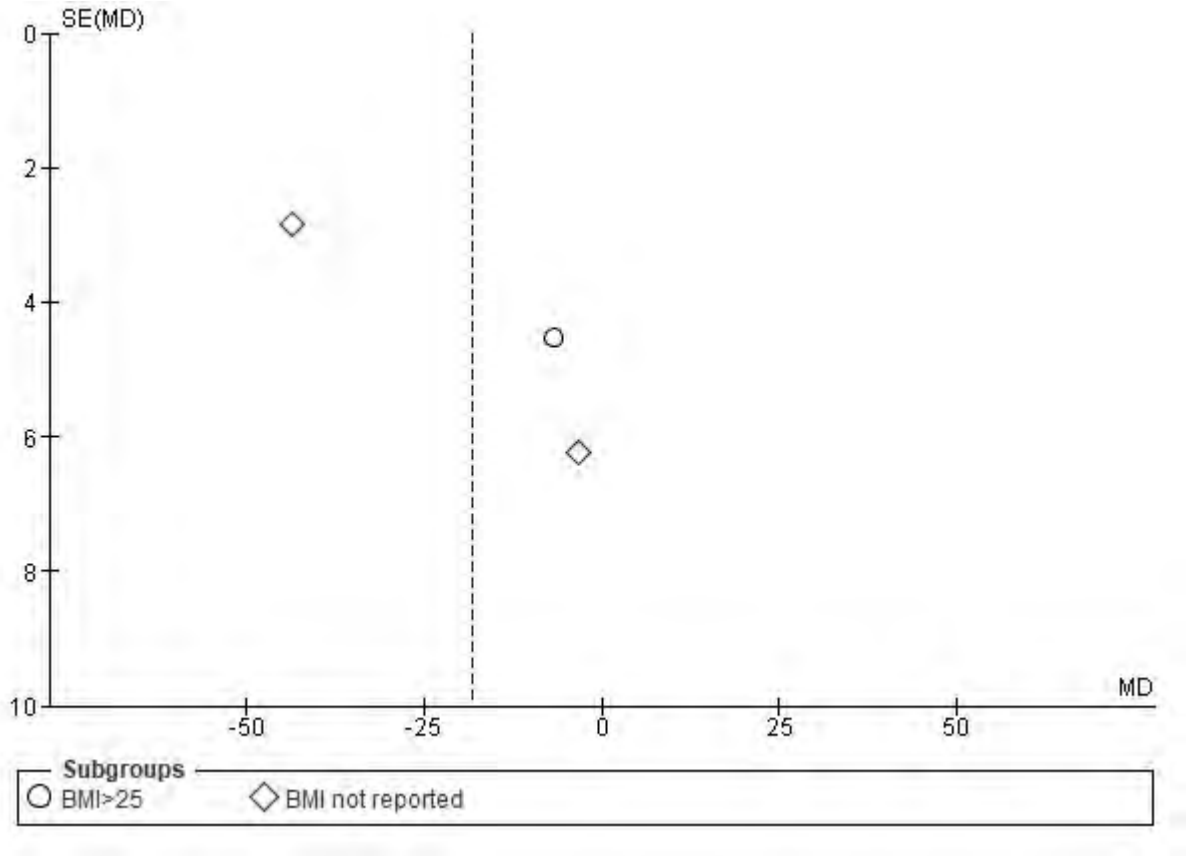
16.6.1 Individual Study Data Table

	OUTCOME: SHBG					OUTCOME TYPE: Continuous			
		COMPARISON (if applicable): metformin versus pioglitazone							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Sangeeta et al. 2012	Nmol/l	43	36.77	8.7	42	80.48	16.21		6
Naka et al 2011	Nmol/l	15	33.3	14.8	14	36.6	18.3		6
Cho et al. 2009	Nmol/l	10	25.3	3.2 10.12 (SD)	10	32	3.2 10.12 (SD)	Mean+SEM	3

16.6.2. Forrest plot metformin vs pioglitazone for SHBG



16.6.3. Funnel plot for assessment of publication bias



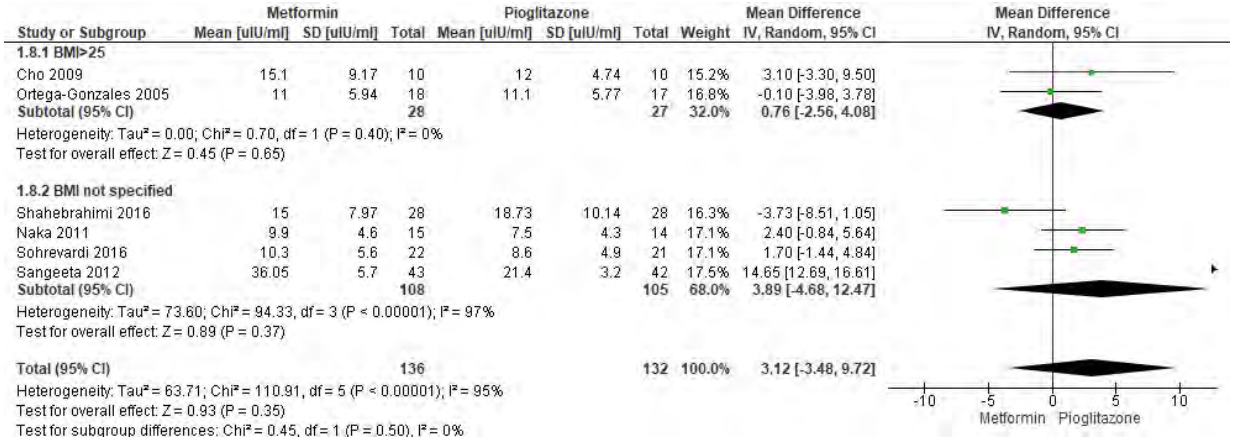
OUTCOME 16.7 fasting insulin (uIU/ml)

16.7.1 Individual Study Data Table

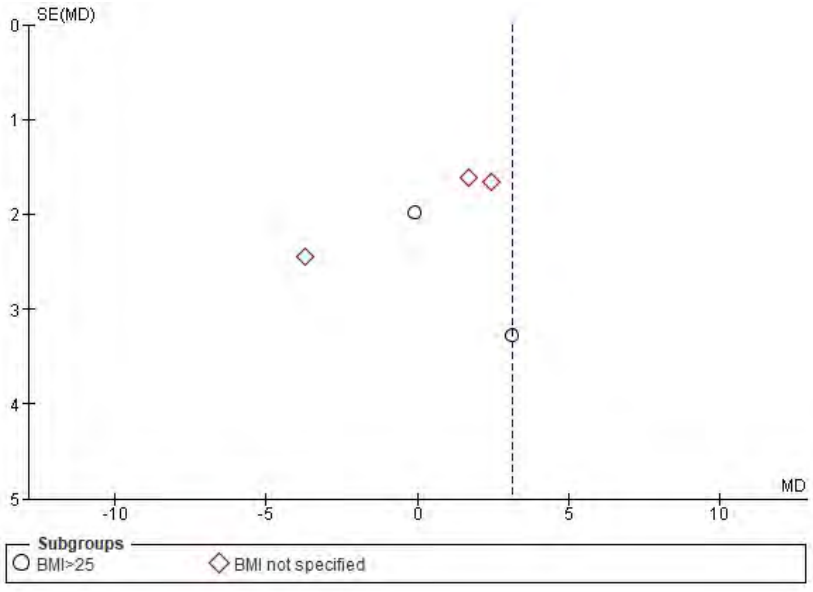
	OUTCOME: fasting insulin					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **pioglitazone**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Sangeeta et al. 2012	uU/ml	43	36.05	5.7	42	21.4	3.2		6
Naka et al 2011	uU/ml	15	9.9	4.6	14	7.5	4.3		6
Ortega-Gonzales et al. 2005	uU/ml	18	11.0	1.4 5.94 (SD)	17	11.1	1.4 5.77 (SD)	Mean+SEM	6
Shahebrahimi et al 2016	uU/ml	28	15	7.97	28	18.73	10.14		3

Sohrevardi et al. 2016	uU/ml	22	10.3	5.6	21	8.6	4.9		3
Cho et al. 2009	uU/ml	10	15.1	2.9 9.17 (SD)	10	12.0	1.5 4.74 (SD)	Mean+SEM	3

16.7.2. Forrest plot metformin vs pioglitazone for fasting insulin



16.7.3. Funnel plot for assessment of publication bias

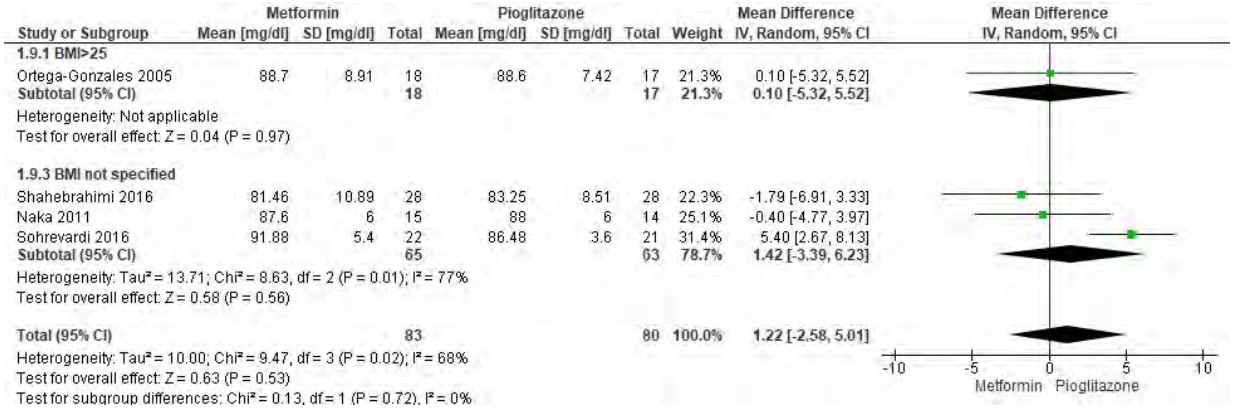


OUTCOME 16.8 fasting glucose (mg/dl)

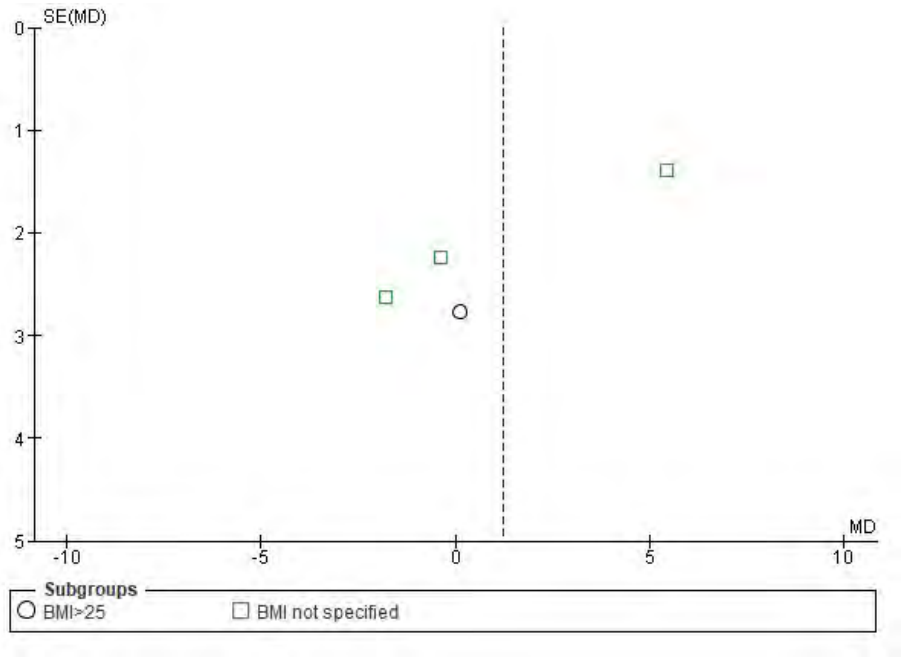
16.8.1 Individual Study Data Table

	OUTCOME: serum fasting glucose level		**OUTCOME TYPE:** Continuous						
		COMPARISON (if applicable): metformin versus **pioglitazone**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Naka et al 2011	Mg/dl	15	87.6	6	14	88	6		6
Ortega-Gonzales et al. 2005	Mg/dl	18	88.7	2.1 8.91 (SD)	17	88.6	1.8 7.42 (SD)	Mean+SEM	6
Shahebrahimi et al 2016	Mg/dl	28	81.46	10.89	28	83.25	8.51		3
Sohrevardi et al. 2016	Mmol/l Mg/dl	22	5.1 91.88	0.3 5.4	21	4.8 86.48	0.2 3.6		3

16.8.2. Forrest plot metformin vs pioglitazone for fasting glucose



16.8.3. Funnel plot for assessment of publication bias

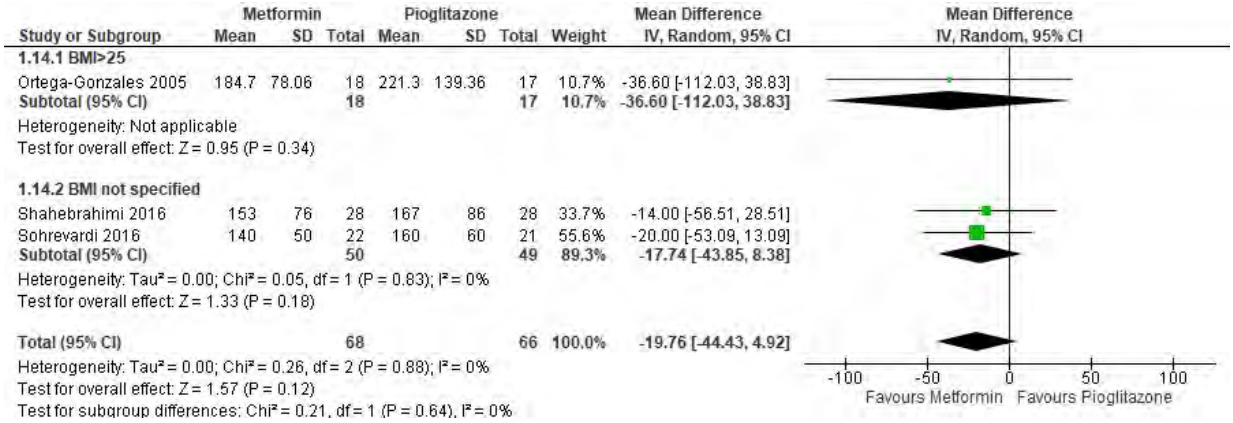


OUTCOME 16.9 DHEAS (ug/dl)

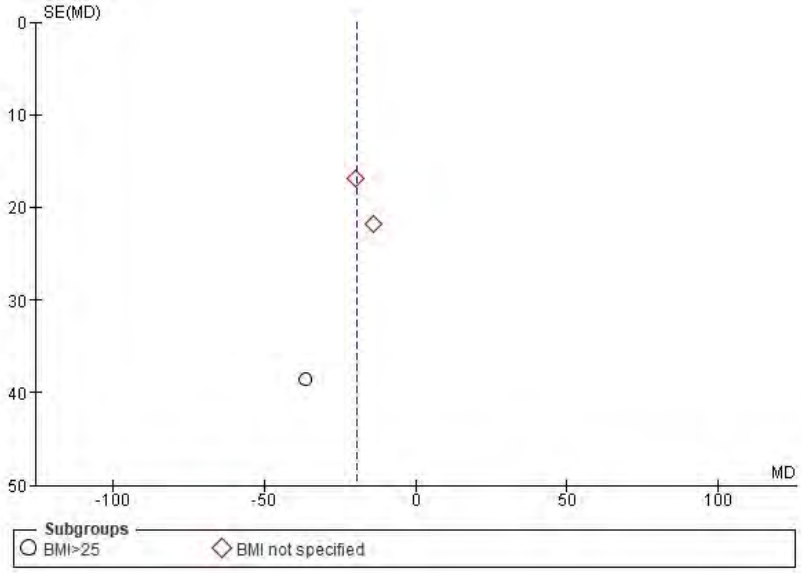
16.9.1 Individual Study Data Table

	OUTCOME: DHEAS					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **pioglitazone**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Ortega-Gonzales et al. 2005	Ug/dl	18	184.7	18.4	17	221.3	33.8	Mean+SEM	6
Shahebrahimi et al 2016		28	1.53 153	0.76 76	28	1.67 167	0.86 86	DHEA, no unit specified, ug/dl?	3
Sohrevardi et al. 2016	Mg/l Ug/dl	22	1.4 140	0.5 50	21	1.6 160	0.6 60		3

16.9.2. Forrest plot metformin vs pioglitazone for DHEAS



16.9.3. Funnel plot for assessment of publication bias

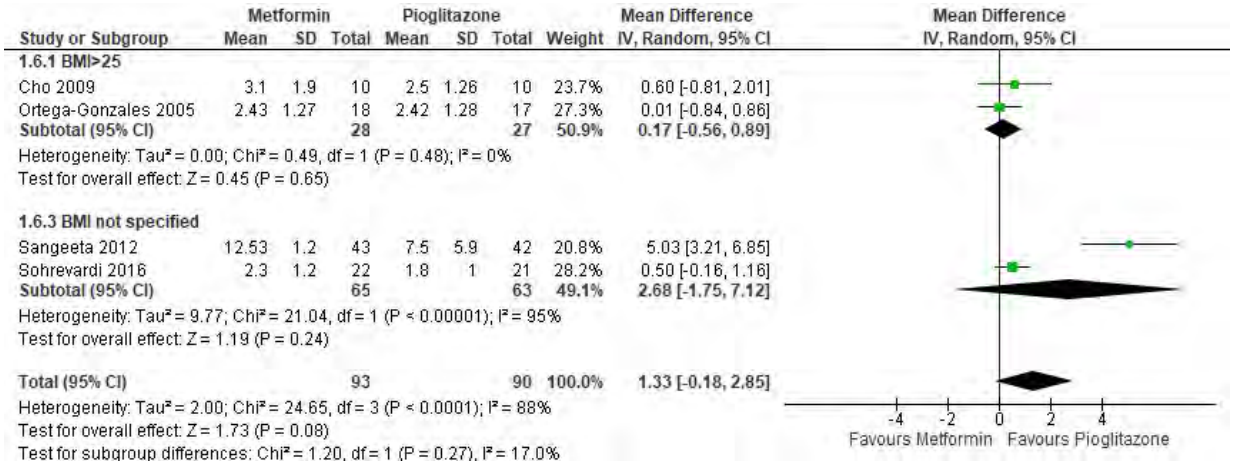


OUTCOME 16.10 HOMA-IR

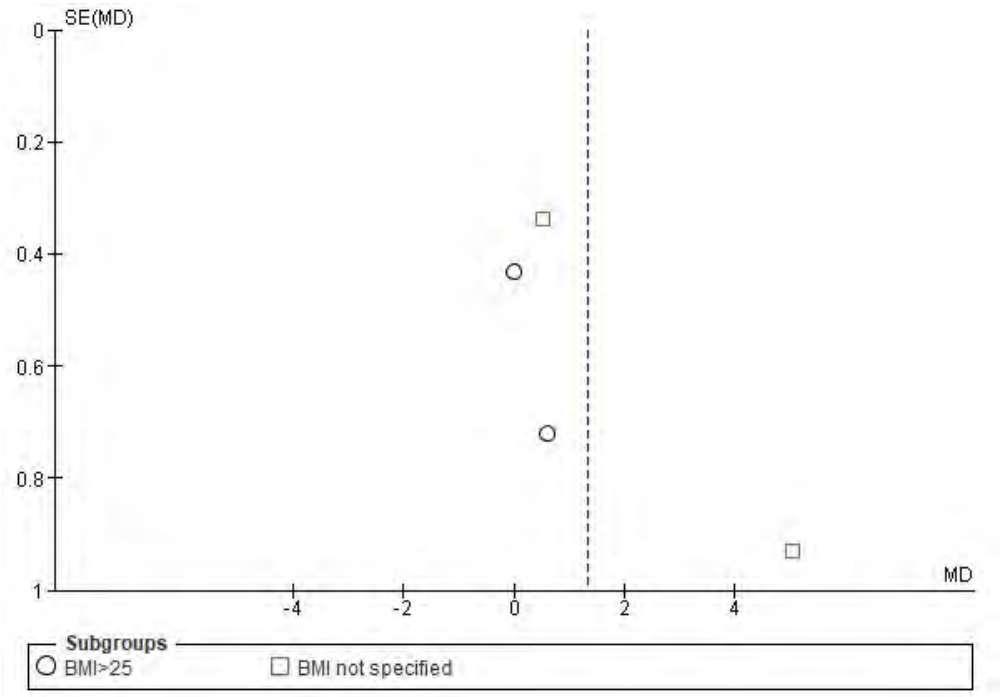
16.10.1 Individual Study Data Table

	OUTCOME: HOMA-IR					OUTCOME TYPE: Continuous			
		COMPARISON (if applicable): metformin versus pioglitazone							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Sangeeta et al. 2012		43	12.53	1.2	42	7.5	5.9		6
Ortega-Gonzales et al. 2005		18	2.43	0.3 1.27 (SD)	17	2.42	0.31 1.28 (SD)	Mean+SEM	6
Sohrevardi et al. 2016		22	2.3	1.2	21	1.8	1		3
Cho et al. 2009		10	3.1	0.6 1.9 (SD)	10	2.5	0.4 1.26 (SD)	Mean+SEM	3

16.10.2. Forrest plot metformin vs pioglitazone for HOMA-IR



16.10.3. Funnel plot for assessment of publication bias

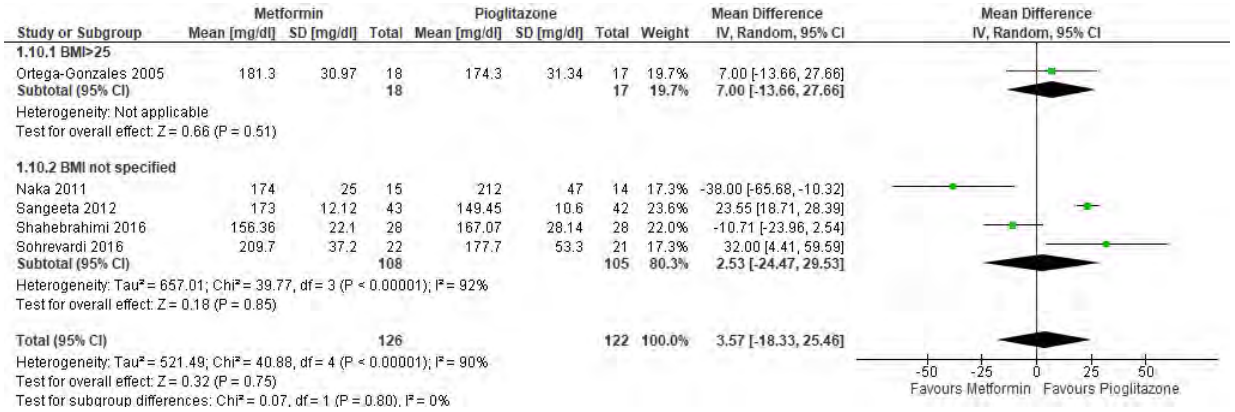


OUTCOME 16.11 total cholesterol (mg/dl)

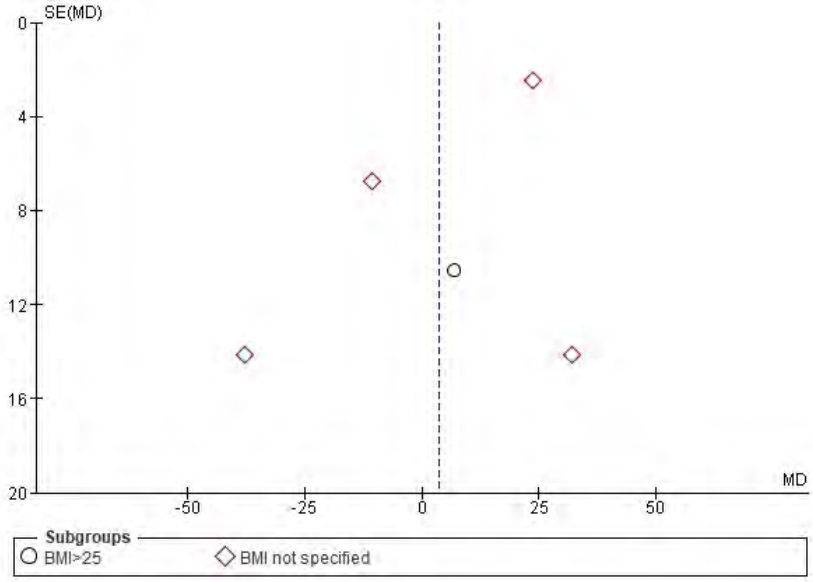
16.11.1 Individual Study Data Table

	OUTCOME: total cholesterol					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **pioglitazone**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Sangeeta et al. 2012	Mg/dl	43	173.00	12.12	42	149.45	10.6		6
Naka et al 2011	Mg/dl	15	174	25	14	212	47		6
Ortega-Gonzales et al. 2005	Mg/dl	18	181.3	7.3 30.97 (SD)	17	174.3	7.6 31.34 (SD)	Mean+SEM	6
Shahebrahimi et al 2016	Mg/dl	28	156.36	22.10	28	167.07	28.14		3
Sohrevardi et al. 2016	Mg/dl	22	209.7	37.2	21	177.7	53.3		3

16.11.2. Forrest plot metformin vs pioglitazone for total cholesterol



16.11.3. Funnel plot for assessment of publication bias



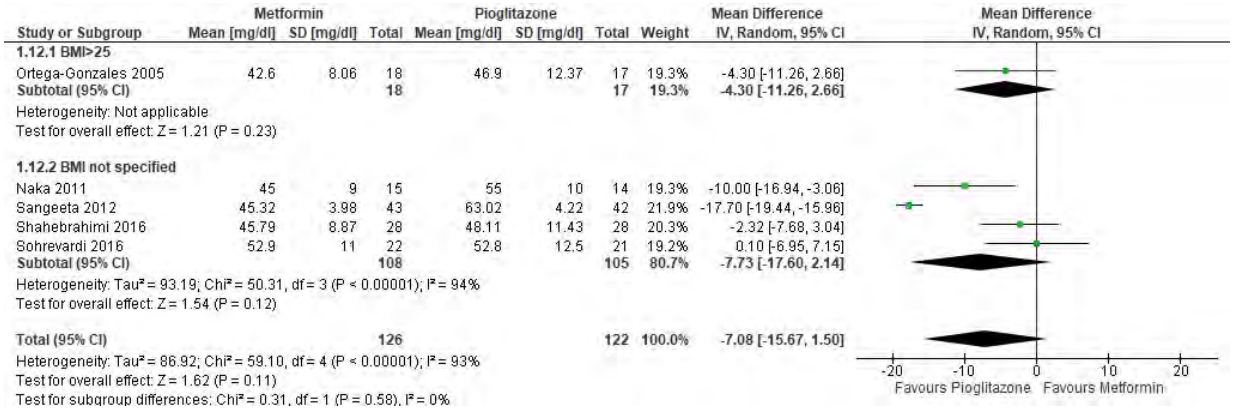
OUTCOME 16.12 HDL (mg/dl)

16.12.1 Individual Study Data Table

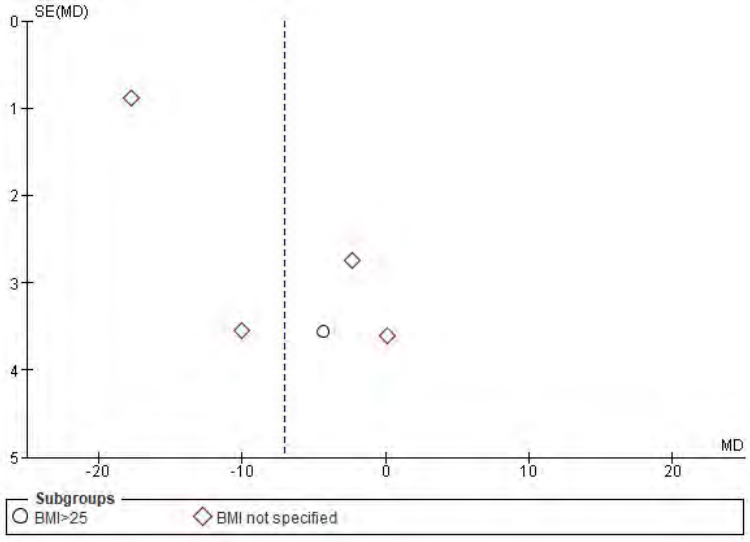
	OUTCOME: HDL					OUTCOME TYPE: Continuous			
		COMPARISON (if applicable): metformin versus pioglitazone							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Sangeeta et al. 2012	Mg/dl	43	45.32	3.98	42	63.02	4.22		6

Naka et al 2011	Mg/dl	15	45	9	14	55	10		6
Ortega-Gonzales et al. 2005	Mg/dl	18	42.6	1.9 8.06 (SD)	17	46.9	3.0 12.37 (SD)	Mean+SEM	6
Shahebrahimi et al 2016	Mg/dl	28	45.79	8.87	28	48.11	11.43		3
Sohrevardi et al. 2016	Mg/dl	22	52.9	11	21	52.8	12.5		3

16.12.2. Forrest plot metformin vs pioglitazone for HDL



16.12.3. Funnel plot for assessment of publication bias

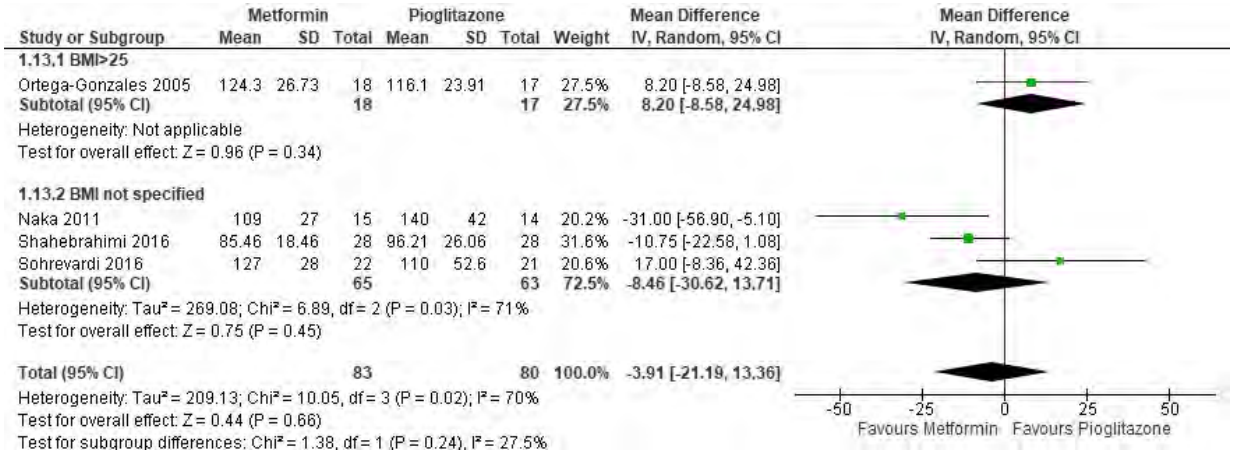


OUTCOME 16.13 LDL (mg/dl)

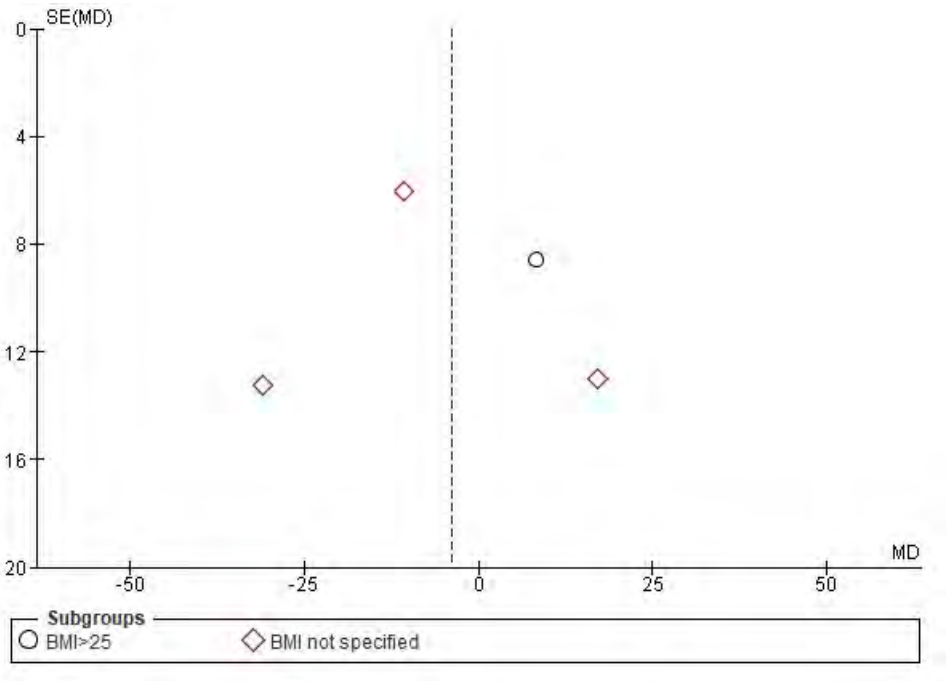
16.13.1 Individual Study Data Table

	OUTCOME: LDL					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **pioglitazone**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Sangeeta et al. 2012	Mg/dl	43	19.1	1.33	42	25.9	1.66		6
Naka et al 2011	Mg/dl	15	109	27	14	140	42		6
Ortega-Gonzales et al. 2005	Mg/dl	18	124.3	6.3 26.73 (SD)	17	116.1	5.8 23.91 (SD)	Mean+SEM	6
Shahebrahimi et al 2016	Mg/dl	28	85.46	18.46	28	96.21	26.06		3
Sohrevardi et al. 2016	Mg/dl	22	127	28	21	110	52.6		3

16.13.2. Forrest plot metformin vs pioglitazone for LDL



16.13.3. Funnel plot for assessment of publication bias

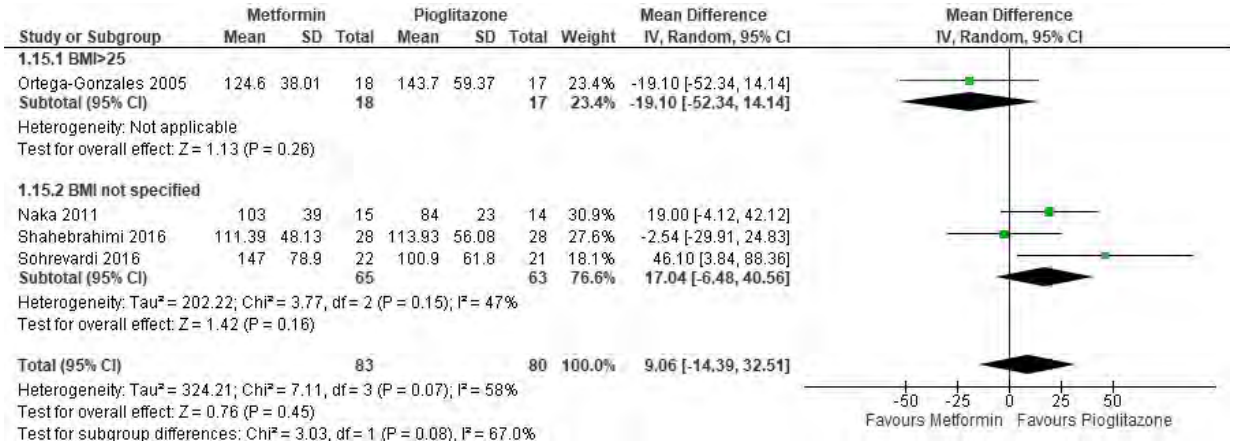


OUTCOME 16.14 Triglycerides (mg/dl)

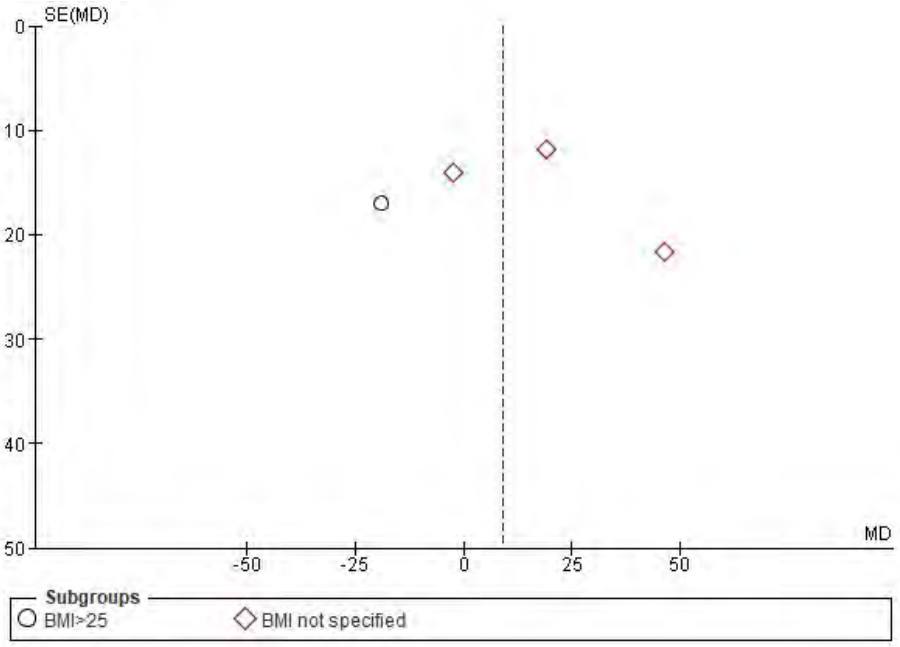
16.14.1 Individual Study Data Table

	OUTCOME: Triglycerides					**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): metformin versus **pioglitazone**							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Naka et al 2011	Mg/dl	15	103	39	14	84	23		6
Ortega-Gonzales et al. 2005	Mg/dl	18	124.6	8.96 38.01 (SD)	17	143.7	14.4 59.37 (SD)	Mean+SEM	6
Shahebrahimi et al 2016	Mg/dl	28	111.39	48.13	28	113.93	56.08		3
Sohrevardi et al. 2016	Mg/dl	22	147	78.9	21	100.9	61.8		3

16.14.2. Forrest plot metformin vs pioglitazone for Triglycerides



16.14.3. Funnel plot for assessment of publication bias

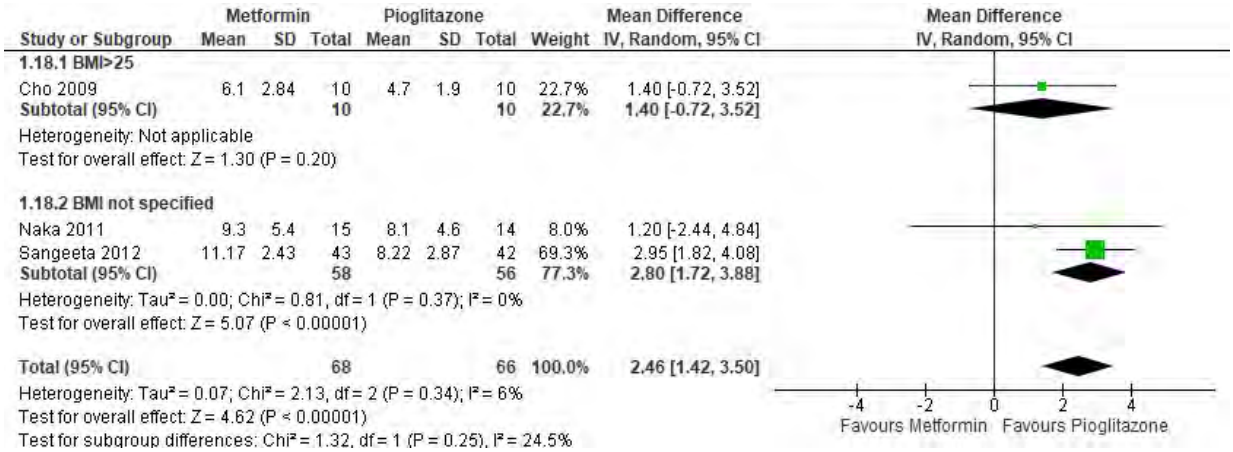


OUTCOME 16.15 FAI

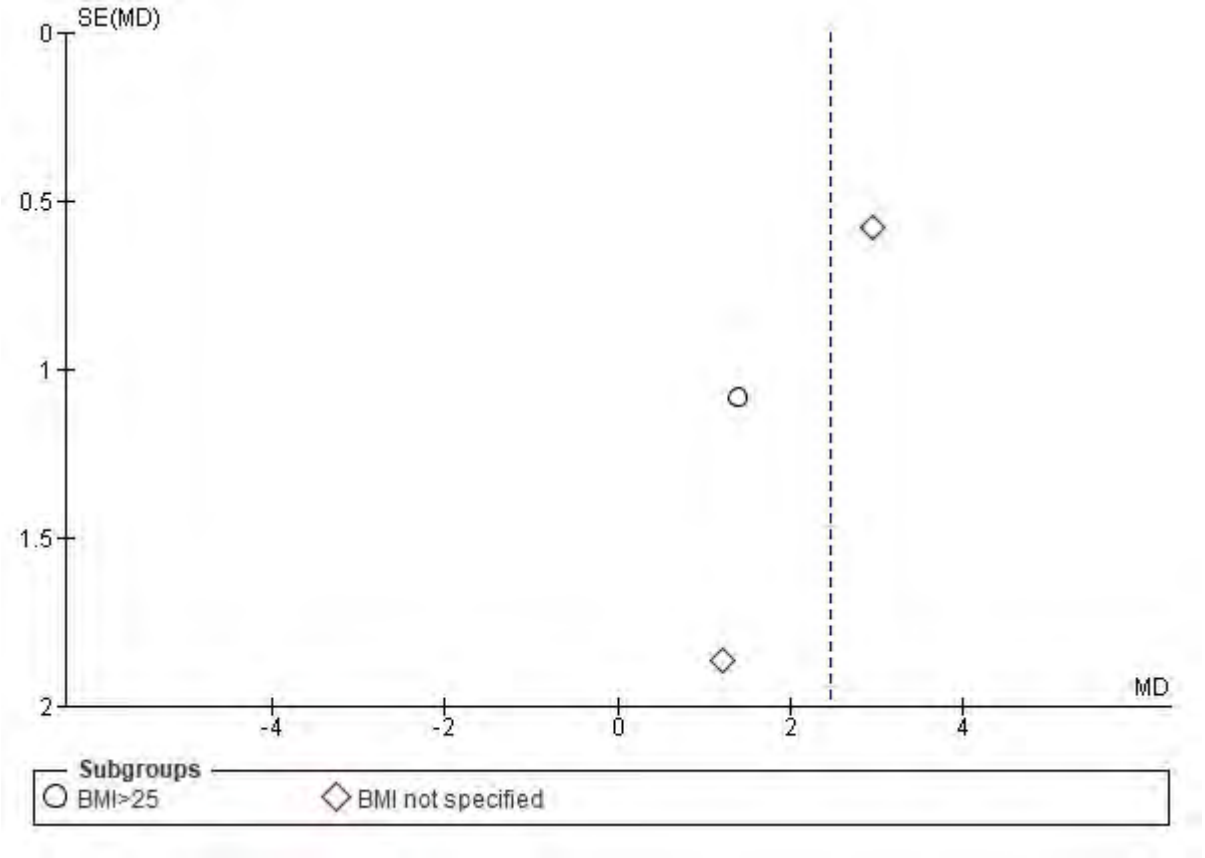
16.15.1 Individual Study Data Table

	OUTCOME: FAI					OUTCOME TYPE: Continuous			
		COMPARISON (if applicable): metformin versus pioglitazone							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**N**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**N**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Something extra?**	**Time period (month)**
Sangeeta et al. 2012		43	11.17	2.43	42	8.22	2.87		6
Naka et al 2011		15	9.3	5.4	14	8.1	4.6		6
Cho et al. 2009		10	6.1	0.9 2.84 (SD)	10	4.7	0.6 1.9 (SD)	Mean+SEM	3

16.15.2. Forrest plot metformin vs pioglitazone for FAI



16.15.3. Funnel plot for assessment of publication bias



Comparison 17: Metformin versus saxagliptin

Evidence Summary

Only one RCTs compared metformin to saxagliptin (Elkind-Hirsch et al. 2016). This study was rated as low risk of bias.

Meta-analysis/descriptive analysis summary

Meta-analysis was not possible with only one study. Elkind-Hirsch et al. found that saxagliptin was more effective than metformin in lowering triglycerides and increasing SHBG, whereas metformin was superior in decreasing testosterone and LDL among PCOS women with prediabetic hyperglycemia. For the other outcomes measured, no difference was observed. The article states that “saxagliptin was well tolerated in this trial. The addition of SAXA to MET therapy did not lead to an increase in the incidence of gastrointestinal side effects, which are typically associated with metformin treatment alone. No clinically meaningful differences between treatment groups in the overall incidence of clinical adverse experiences, serious clinical adverse experiences, or laboratory adverse experiences were observed. The incidence of study discontinuation due to adverse events over 16 weeks was similar across arms.”
Certainty in the evidence for this comparison is low (downgraded twice for very serious risk of imprecision, being a small, single study).

Author, year, country	Population	Sample Size per group	Intervention/ exposure details	PCOS criteria	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Summary of findings	Other
Elkind-Hirsch et al 2016 USA	Patients with PCOS (aged 18–42 years) and prediabetic hyperglycemia	1.Metformin=12 2.Saxagliptin=11 3.Metformin+Saxagliptin=11	1.Metformin 2000mg/d 2.Saxagliptin 5mg/d 3. Metformin 2000mg/d+Saxagliptin 5mg/d	NIH	4 months	1.42.1 ±7.3 2.37.2 ±6.8 3.43.8±10.5	1.29.9±7 2.28.6 ±6.6 3.29.6±8	f-gluc, HOMA-IR, lipids, WHR, BMI, menstrual interval, T, A, SHBG, DHEAS, FAI	Treatment with SAXA-MET was superior to either drug alone in terms of clinical and metabolic benefits in prediabetic patients with PCOS.	**ROB low**

Individual studies

Study ID	Elkind-Hirsch 2016							
Outcome	**Time point**	**N**	**Metformin**		**Saxagliptin**		**P value**	**Favours**
			Mean	**SD**	**Mean**	**SD**		
BMI (kg/m2)	4 months	23	42	7.7	36.7	7.4	0.09	No difference
WHR	4 months	23	0.66	0.7	0.6	0.1	0.78	No difference
Testosterone (nmol/l)	4 months	23	1.1	0.42	1.5	0.52	0.04	**Metformin**
DHEAS (umol/l)	4 months	23	4.7	1.5	5.35	2.3	0.43	No difference
SHBG (nmol/l)	4 months	23	20	11	32	14	0.02	**Saxagliptin**
FAI	4 months	23	6.3	2.8	5.5	3.4	0.54	No difference
Total cholesterol (mmol/l)	4 months	23	4.7	0.62	5.0	1.7	0.58	No difference
HDL (mmol/l)	4 months	23	1.06	0.3	1.06	0.2	1.0	No difference
LDL (mmol/l)	4 months	23	2.82	0.6	3.21	1.3	0.03	**Metformin**
Triglycerides (mmol/l)	4 months	23	1.86	0.7	1.54	0.7	0.001	**Saxagliptin**
Fasting glucose (mmol/l)	4 months	23	5.4	0.7	5.3	0.51	0.82	No difference
HOMA-IR	4 months	23	5.9	3.7	4.4	2.9	0.28	No difference
Menstrual cycle (d)	4 months	23	81	44	58	29	0.07	No difference

Comparison 18: Metformin+saxagliptin versus metformin

Evidence Summary

Only one RCTs compared metformin and saxagliptin to metformin (Elkind-Hirsch et al. 2016). This study was rated as low risk of bias.

Meta-analysis/descriptive analysis summary

Meta-analysis was not possible with only one study. Elkind-Hirsch et al. found that metformin and saxagliptin was more effective than metformin only in lowering triglycerides, increasing SHBG and shortening menstrual cycle among PCOS women with prediabetic hyperglycemia. For the other outcomes measured, no difference was observed.
The article states that “saxagliptin was well tolerated in this trial. The addition of SAXA to MET therapy did not lead to an increase in the incidence of gastrointestinal side effects, which are typically associated with metformin treatment alone. No clinically meaningful differences between treatment groups in the overall incidence of clinical adverse experiences, serious clinical adverse experiences, or laboratory adverse experiences were observed. The incidence of study discontinuation due to adverse events over 16 weeks was similar across arms.”
Certainty in the evidence for this comparison is low (downgraded twice for very serious risk of imprecision, being a small, single study).

Author, year, country	Population	Sample Size per group	Intervention/ exposure details	PCOS criteria	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Summary of findings	Other
Elkind-Hirsch et al 2016 USA	Patients with PCOS (aged 18–42 years) and prediabetic hyperglycemia	1.Metformin=12 2.Saxagliptin=11 3.Metformin+Saxagliptin=11	1.Metformin 2000mg/d 2.Saxagliptin 5mg/d 3. Metformin 2000mg/d+Saxagliptin 5mg/d	NIH	4 months	1.42.1 ±7.3 2.37.2 ±6.8 3.43.8±10.5	1.29.9±7 2.28.6 ±6.6 3.29.6±8	f-gluc, HOMA-IR, lipids, WHR, BMI, menstrual interval, T, A, SHBG, DHEAS, FAI	Treatment with SAXA-MET was superior to either drug alone in terms of clinical and metabolic benefits in prediabetic patients with PCOS.	**ROB low**

Individual studies

Study ID	Elkind-Hirsch 2016							
Outcome	**Time point**	**N**	**Metformin+Saxagliptin Mean**	**SD**	**Metformin Mean**	**SD**	**P value**	**Favours**
BMI (kg/m2)	4 months	23	42	10.2	42	7.7	1.00	No difference

WHR	4 months	23	0.65	0.08	0.66	0.7	1.0	No difference
Testosterone (nmol/l)	4 months	23	1.1	0.73	1.1	0.42	1.0	No difference
DHEAS (umol/l)	4 months	23	3.83	1.8	4.7	1.5	0.21	No difference
SHBG (nmol/l)	4 months	23	31	10	20	11	0.01	**Met+Saxa**
FAI	4 months	23	4.3	3.5	6.3	2.8	0.08	No difference
Total cholesterol (mmol/l)	4 months	23	4.6	0.54	4.7	0.62	0.68	No difference
HDL (mmol/l)	4 months	23	1.06	0.2	1.06	0.3	1.0	No difference
LDL (mmol/l)	4 months	23	2.95	0.5	2.82	0.6	0.57	No difference
Triglycerides (mmol/l)	4 months	23	1.33	0.4	1.86	0.7	0.02	**Met+Saxa**
Fasting glucose (mmol/l)	4 months	23	5.0	0.36	5.4	0.7	0.08	No difference
HOMA-IR	4 months	23	3.6	2.1	5.9	3.7	0.06	No difference
Menstrual cycle (d)	4 months	23	36	11	81	44	<0.001	**Met+Saxa**

Comparison 19: Metformin+saxagliptin versus saxagliptin

Evidence Summary

Only one RCTs compared metformin and saxagliptin to saxagliptin (Elkind-Hirsch et al. 2016). This study was rated as low risk of bias.

Meta-analysis/descriptive analysis summary

Meta-analysis was not possible with only one study. Elkind-Hirsh found that a combination treatment with metformin and saxagliptin is superior compared to saxagliptin when it comes to shortening menstrual cycle among PCOS women with prediabetic hyperglycemia.
The article states that “saxagliptin was well tolerated in this trial. The addition of SAXA to MET therapy did not lead to an increase in the incidence of gastrointestinal side effects, which are typically associated with metformin treatment alone. No clinically meaningful differences between treatment groups in the overall incidence of clinical adverse experiences, serious clinical adverse experiences, or laboratory adverse experiences were observed. The incidence of study discontinuation due to adverse events over 16 weeks was similar across arms.”
Certainty in the evidence for this comparison is low (downgraded twice for very serious risk of imprecision, being a small, single study).

Author, year, country	Population	Sample Size per group	Intervention/ exposure details	PCOS criteria	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Summary of findings	Other
Elkind-Hirsch et al 2016 USA	Patients with PCOS (aged 18–42 years) and prediabetic hyperglycemia	1.Metformin=12 2.Saxagliptin=11 3.Metformin+Saxagliptin=11	1.Metformin 2000mg/d 2.Saxagliptin 5mg/d 3. Metformin 2000mg/d+Saxagliptin 5mg/d	NIH	4 months	1.42.1 ±7.3 2.37.2 ±6.8 3.43.8±10.5	1.29.9±7 2.28.6 ±6.6 3.29.6±8	f-gluc, HOMA-IR, lipids, WHR, BMI, menstrual interval, T, A, SHBG, DHEAS, FAI	Treatment with SAXA-MET was superior to either drug alone in terms of clinical and metabolic benefits in prediabetic patients with PCOS.	**ROB low**

Individual studies

Study ID	Elkind-Hirsch 2016							
Outcome	**Time point**	**N**	**Metformin+Saxagliptin**		**Saxagliptin**		**P value**	**Favours**
			Mean	**SD**	**Mean**	**SD**		
BMI (kg/m2)	4 months	22	42	10.2	36.7	7.4	0.16	No difference
WHR	4 months	22	0.65	0.08	0.6	0.1	0.20	No difference
Testosterone (nmol/l)	4 months	22	1.1	0.73	1.5	0.52	0.14	No difference
DHEAS (umol/l)	4 months	22	3.83	1.8	5.35	2.3	0.08	No difference
SHBG (nmol/l)	4 months	22	31	10	32	14	0.85	No difference
FAI	4 months	22	4.3	3.5	5.5	3.4	0.78	No difference
Total cholesterol (mmol/l)	4 months	22	4.6	0.54	5.0	1.7	0.70	No difference
HDL (mmol/l)	4 months	22	1.06	0.2	1.06	0.2	1.0	No difference
LDL (mmol/l)	4 months	22	2.95	0.5	3.21	1.3	0.54	No difference
Triglycerides (mmol/l)	4 months	22	1.33	0.4	1.54	0.7	0.39	No difference
Fasting glucose (mmol/l)	4 months	22	5.0	0.36	5.3	0.51	0.21	No difference
HOMA-IR	4 months	22	3.6	2.1	4.4	2.9	0.22	No difference
Menstrual cycle (d)	4 months	22	36	11	58	29	<0.001	**MET+SAXA**

Comparison 20: Metformin versus SGLT2-inhibitors

Evidence Summary

Two RCTs compared metformin to SGLT2inhibitors. One compared metformin to empagliflozin (Javed et al. 2019), whereas the other one compared metformin to canagliflozin (Cai et al. 2022). Both studies were rated as moderate risk of bias.

Meta-analysis/descriptive analysis summary

Meta-analysis was not possible with only one study comparing metformin to empagliflozin. Javed et al. found that empagliflozin improved weight and BMI reduction in overweight and obese women with PCOS (BMI=>25). No changes were seen in hormonal or metabolic parameters. There were no adverse events in the metformin-group. In the empagliflozin-group, two patients reported adverse events (headache and dizziness=1 and mild rash=1) which were however believed to be unrelated to the study drug. As this was a randomized open-label study, it was rates as having a moderate risk of bias. Certainty in the evidence for this comparison is very low (downgraded once for serious risk of bias and twice for very serious risk imprecision, being a small study).

Meta-analysis was also not possible with only one study comparing metformin to canagliflozin. Cai et al. found that canagliflozin lowered DHEAS in women with PCOS. Otherwise there were no differences in the outcomes compared. This study was rated as having a moderate risk of bias due to no blinding and protocol published in retrospect. Certainty in the evidence for this comparison is very low (downgraded once for serious risk of bias and twice for very serious risk imprecision, being a small study).

Author, year, country	Population	Sample Size per group	Intervention/ exposure details	PCOS criteria	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Summary of findings	Other
Javed et al. 2019 UK	Overweight and obese women (BMI>=25) with PCOS	1.Metformin=20 2.Empagliflozin=19	1.Metformin 1500mg/d 2.Empagliflozin 25mg/d	Rott	3 months	1.38.7 ±7.8 2.37.1 ±6.8	1.31.5±20 2.26.0 ±8.0	Weight, bmi, FAI, T, SHBG, A, DHEAS, f-gluc, f-insulin, homa, lipids, crp	A significant improvement in anthropometric parameters and body composition could be observed in overweight and obese women with PCOS after 12 weeks of treatment with empagliflozin compared to metformin, although no changes were seen in hormonal or metabolic parameters.	**ROB moderate**
Cai et al 2022 China	Women aged 18 to 45 years with PCOS and IR	1.Metformin=29 2.Canagliflozin=30	1.Metformin 1500/2000mg/d 2.Canagliflozin 100mg/d	Rott	3 months	1.27.95 (26.22 to 29.69) 2.27.26 (25.55 to 28.99) Mean (95% CI)	1.27.83 (25.97 to 29.68) 2.28.58 (26.72 to 30.43) Mean (95% CI)	Weight, bmi, whr, menstrual cycles, homa, f-gluc, f-insulin, lipids, T, A, DHEAS, SHBG	canagliflozin was not inferior to metformin in PCOS patients with IR, which suggests that sodium-glucose cotransporter-2 inhibitors should be considered as effective drugs in the treatment of PCOS patients with IR.	**ROB Moderate**

Individual studies

Study ID	Javed 2019					
Outcome	**Time point**	**N**	**Metformin Mean SD**	**Empagliflozin Mean SD**	**P value**	**Favours**

Weight	3 months	39	110.1	25.7	101.5	16.3	<0.05	**empagliflozin**
BMI (kg/m2)	3 months	39	39.2	7.9	36.6	6.0	<0.05	**empagliflozin**
Testosterone (nmol/l)	3 months	39	1.5	1.2	1.6	0.6	NR	No difference
SHBG (nmol/l)	3 months	39	19.5	14.5	19.2	8.5	NR	No difference
FAI	3 months	39	8.0	6.4	9.4	3.6	NR	No difference
Androstenedione (nmol/l)	3 months	39	5.0	2.8	5.7	1.9	NR	No difference
DHEAS (umol/l)	3 months	39	5.8	3.0	6.2	2.1	NR	No difference
Total cholesterol (mmol/l)	3 months	39	4.5	0.9	4.7	1.1	NR	No difference
HDL (mmol/l)	3 months	39	1.1	1.9	1.1	0.2	NR	No difference
LDL (mmol/l)	3 months	39	2.8	0.9	2.7	1.1	NR	No difference
Triglycerides (mmol/l)	3 months	39	1.2	0.7	1.4	0.9	NR	No difference
Fasting insulin (uIU/ml)	3 months	39	14.0	22.7	12.7	14.4	NR	No difference
Fasting glucose (mmol/l)	3 months	39	4.4	0.6	4.5	0.6	NR	No difference
CRP (mg/l)	3 months	39	5.1	10.9	3.3	5.9	NR	No difference
HOMA-IR	3 months	39	3.2	4.9	2.4	2.7	NR	No difference

Study ID	Cai 2022							
Outcome	**Time point**	**N**	**Metformin (29) Least Squares Means 95% CI**		**Canagliflozin (30) Least Squares Means 95% CI**		**P value**	**Favours**
Weight	3 months	59	-2.68	-3.93 to –1.43	-2.82	-3.97 to -1.66	0.876	No difference
BMI (kg/m2)	3 months	59	-0.90	-1.46 to -0.35	-1.04	-1.56 to -0.53	0.727	No difference
WHR	3 months	59	-0.01	-0.03 to 0.01	-0.02	-0.04 to 0.00	0.513	No difference
Testosterone (nmol/l)	3 months	59	-0.00	-0.25 to 0.24	-0.15	-0.38 to 0.08	0.411	No difference
SHBG (nmol/l)	3 months	59	-13.58	-31.21 to 4.05	-4.84	-19.40 to 9.75	0.472	No difference
Androstenedione (ng/ml)	3 months	59	0.04	-0.49 to 0.56	-0.48	-1.04 to 0.09	0.199	No difference
DHEAS (umol/l)	3 months	59	36.52	-16.31 to 89.35	-68.96	-126.36 to -11.55	0.013	**Canagliflozin**
Total cholesterol (mmol/l)	3 months	59	-0.00	-0.23 to 0.24	0.17	-0.05 to 0.39	0.329	No difference
HDL (mmol/l)	3 months	59	0.13	-0.04 to 0.30	0.02	-0.17 to 0.13	0.211	No difference
LDL (mmol/l)	3 months	59	-0.03	-0.28 to 0.34	0.22	0.06 to 0.51	0.378	No difference
Triglycerides (mmol/l)	3 months	59	-0.23	-0.44 to -0.03	-0.36	-0.54 to -0.17	0.393	No difference
Fasting insulin (ng/ml)	3 months	59	-3.97	-7.97 to 0.03	-7.70	-11.46 to -3.94	0.196	No difference
Fasting glucose (ng/ml)	3 months	59	-0.23	-0.41 to -0.05	-0.23	-0.40 to -0.06	0.995	No difference
Free testosterone (pg/ml)	3 months	59	0.30	-0.44 to 1.04	0.30	-0.30 to 0.89	0.991	No difference
HOMA-IR	3 months	59	0.29	0.08 to 0.50	0.42	0.23 to 0.62	0.382	No difference
Menstrual cycles/year	3 months	59	1.37	0.63 to 2.11	1.34	0.66 to 2.02	0.950	No difference

Comparison 21: Metformin+liraglutide versus liraglutide

Evidence Summary

Only one RCTs compared metformin and liraglutide to liraglutide only (Jensterle et al. 2017). This study was rated as high risk of bias as there was no blinding. Note that other comparisons between metformin and liraglutide are included in Q4.5.

Meta-analysis/descriptive analysis summary

Meta-analysis was not possible with only one study. Jensterle et al. found that liraglutide only was more effective in lowering BMI, whereas metformin and liraglutide combined was more effective in lowering LDL-cholesterol. Note that the liraglutide dose was different in the two groups observed.
The most common side effects in the liraglutide-group were nausea (8/14) and diarrhea (5/14). Vomiting occurred in 1/14 patients and 2/14 mild headache were documented. Adverse effects reported in combination-group were nausea (6/14), mild diarrhea (6/14), and insomnia (1/14). No side effect was documented by 6/14 in the liraglutide-group and 8/14 in the combination-group. No subject withdrew because of the adverse events in either group.

Certainty in the evidence for this comparison is very low (downgraded twice for serious risk of bias and twice for very serious risk imprecision, being a single, small study).

Author, year, country	Population	Sample Size per group	Intervention/ exposure details	PCOS criteria	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Summary of findings	Other
Jensterle et al. 2017 Slovenia	Obese (bmi >30) PCOS women	1.Metformin+liraglutide=14 2.Liraglutide=14	1. Metformin 1000mgx2/d+liraglutide 1.2mg/d (s.c.) 2.Liraglutide 3mg/d (s.c.)	Rott	3 months	1.37.5 ±5.3 2.39.2 ±5.5	1.31.6±5.9 2.34.6±6.1	BMI, weight, T, free T, shbg, ogtt, homa, lipids	Short-term interventions with COMBO and LIRA3 both led to significant improvement of measures of obesity in obese PCOS, LIRA3 being superior to COMBO. However, COMBO further improved androgen profile beyond weight reduction and was associated with better tolerability.	**ROB high**

Individual studies

Study ID	Jensterle 2017							
Outcome	**Time point**	**N**	**Metformin+Liraglutide**		**Liraglutide**		**P value**	**Favours**
			Mean	**SD**	**Mean**	**SD**		
Weight	3 months	28	98.9	10.3	104.7	14.8	0.062	No difference
BMI (kg/m2)	3 months	28	36.2	5.5	37.0	5.5	0.050	**Liraglutide**

Androstenedione (nmol/l)	3 months	28	8.6	3.5	7.7	3.4	0.376	No difference
Testosterone (nmol/l)	3 months	28	1.5	0.8	1.2	0.5	0.285	No difference
Free testosterone (pmol/l)	3 months	28	11.0	4.2	9.7	3.8	0.482	No difference
SHBG (nmol/l)	3 months	28	47.2	90.4	46.9	54.5	0.376	No difference
Total cholesterol (mg/dl)	3 months	28	4.5	1.0	4.8	0.8	0.094	No difference
HDL (mg/dl)	3 months	28	1.3	0.2	1.2	0.3	0.793	No difference
LDL (mg/dl)	3 months	28	2.7	0.9	3.0	0.7	0.038	**Metformin+LIRA**
Triglycerides (mg/dl)	3 months	28	1.2	0.5	1.6	0.6	0.128	No difference
Fasting insulin (mIU/l)	3 months	28	16.8	13.2	19.4	10.4	0.571	No difference
Fasting glucose (mmol/l)	3 months	28	5.0	0.3	5.1	0.4	0.734	No difference
HOMA-IR	3 months	28	3.7	3.0	4.4	2.4	0.427	No difference

Comparison 22: Metformin+myo-inositol versus myo-inositol

Evidence Summary

Only one RCTs compared metformin and myo-inositol to myo-inositol only (Prabhakar et al. 2021). This study was rated as moderate risk of bias as the information on whether the study is open labelled or blinded is lacking. Note that other comparisons between metformin and myo-inositol are included in Q4.7

Meta-analysis/descriptive analysis summary

Meta-analysis was not possible with only one study. This study reported standardized mean difference (SMD) and 95% CI. Prabhakar et al. did not find any differences in the study groups for outcomes observed.
The combination group reported more adverse events (84.2%) than the myo-inositol group (18.7%). One patient in the combination group discontinued due to nausea, vomiting and severe gastric pain. Liver function tests were normal in both groups.
Certainty in the evidence for this comparison is very low (downgraded once for serious risk of bias and twice for very serious risk imprecision, being a single, small study).

Author, year, country	Population	Sample Size per group	Intervention/ exposure details	PCOS criteria	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Summary of findings	Other
Prabhakar et al. 2021 India	PCOS women with infertility (BMI<30)	1.Metformin+myoinositol=36 2.myoinositol=40	1. Metformin 500mgx3/d+myoinositol 4g/d 2.Myoinositol 4g/d	Rott	3 months	1.25.4 ±2.47 2.25.4 ±2.46	1.28.3 ±3.4 2.27.9 ±3.1	BMI, WHR, T, HOMA, lipids	After 3 months of therapy, both study groups had comparable improvement in metabolic and hormonal parameters.	**ROB moderate**

Individual studies

Study ID	Prabhakar et al 2021				
Outcome	**Time point**	**N**	**SMD**	**95% CI**	**Favours**
BMI (kg/m2)	3 months	76	-0.21	-0.66 to 0.25	No difference
WHR	3 months	76	-0.28	-0.73 to 0.17	No difference
Testosterone	3 months	76	0.14	-0.31 to 0.59	No difference
Total cholesterol (mg/dl)	3 months	76	-0.26	-0.72 to 0.19	No difference
HDL (mg/dl)	3 months	76	0.24	-0.21 to 0.69	No difference
LDL (mg/dl)	3 months	76	0.26	-0.19 to 0.71	No difference
Triglycerides (mg/dl)	3 months	76	-0.15	-0.60 to 0.30	No difference
HOMA-IR	3 months	76	-0.21	-0.66 to 0.24	No difference

Comparison 23: Metformin versus orlistat

Evidence Summary

Only one RCTs compared metformin to orlistat (Cho et al. 2009). This study was rated as moderate risk of bias.

Meta-analysis/descriptive analysis summary

Meta-analysis was not possible with only one study. Cho et al. found no differences in metformin compared to orlistat for the outcomes measured.
The article did not report on adverse effects. Certainty in the evidence for this comparison is very low (downgraded once for being a moderate ROB study and twice for very serious risk of imprecision, being a small, single study).

Author, year, country	Population	Sample Size per group	Intervention/ exposure details	PCOS criteria	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Summary of findings	Other

Cho et al. 2009 UK	obese hyperandrogenic, anovulatory Caucasian women with PCOS	1.Metformin=10 2.Orlistat=10 3.Pioglitazone=10	1.Metformin 500mgx3/d 2.Orlistat 120mgx3/d 3.Pioglitazone 45mg/d	Rott	3 months	1.34.3 ±1.8 2.37.4±2.7 3.36.2±1.8	NR	Homa, insulin, shbg, bmi, fai	Only orlistat reduced both IR and its variability significantly, though all three drugs were effective in reducing hyperandrogenism within the 12-week period of the study	**ROB Moderate**

Individual studies

Study ID	Cho 2009							
Outcome	**Time point**	**N**	**Metformin**		**Orlistat**		**P value**	**Favours**
			Mean	**SEM (SD)**	**Mean**	**SEM (SD)**		
BMI (kg/m2)	3 months	20	33.2	1.9 (6.01)	35.2	2.4 (7.59)	0.51	No difference
SHBG (nmol/l)	3 months	20	25.3	3.2 (10.12)	29.5	5.1 (16.13)	0.49	No difference
FAI	3 months	20	6.1	0.9 (2.85)	6.9	1.6 (5.06)	0.17	No difference
Fasting insulin (uU/ml)	3 months	20	15.1	2.9 (9.17)	17.7	2.3 (7.27)	0.38	No difference
HOMA-IR	3 months	20	3.1	0.6 (1.90)	3.7	0.5 (1.58)	0.44	No difference

Comparison 24: Metformin+pioglitazone versus pioglitazone

Evidence Summary

Only one RCTs compared metformin and pioglitazone to pioglitazone (Sohrevardi et al. 2016). This study was rated as high risk of bias.

Meta-analysis/descriptive analysis summary

Meta-analysis was not possible with only one study. Sohrevardi et al. found that treatment with a combination of metformin and pioglitazone was superior in lowering testosterone compared to pioglitazone only, whereas pioglitazone only was better in lowering fasting glucose.
In the combination group two women withdrew from the study because of intolerable gastric discomfort. Pioglitazone was well tolerated and
no patients discontinued pioglitazone because of side-effects.
Certainty in the evidence for this comparison is very low (downgraded twice for very serious risk of bias and twice for very serious risk imprecision, being a single, small study).

Author, year, country	Population	Sample Size per group	Intervention/ exposure details	PCOS criteria	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Summary of findings	Other
Sohrevardi et al. 2016 Iran	Women with PCOS, aged 18-40 years, with irregular menses and infertility	1.Metformin=22 2.Pioglitazone=21 3. Met+Pio=23	1.Metformin 500mgx3/d 2.Pioglitazone 30mg/d 3. Metformin 500mgx3/d+Pioglitazone 30mg/d	Rott	3 months	1.27.5 ±3.6 2.27.2±4.7 3.28.5 ±3.2	1.28.72±6.3 2.27.52 ±5.0 3.30.73 ±6.2	Weight, bmi, WHR, f-gluc, f-insulin, homa, lipids, dheas, T	only metformin ameliorated hyperandrogenemia in women with PCOS. Treatment with combination of metformin and pioglitazone did not show more benefit than monotherapy with each drug alone.	**ROB high**

Individual studies

Study ID	Sohrevardi 2016							
Outcome	**Time point**	**N**	**Metformin+Pioglitazone Mean**	**SD**	**Pioglitazone Mean**	**SD**	**P value**	**Favours**
Weight	3 months	44	71.5	9.8	72.1	13.1	0.86	No difference
BMI (kg/m2)	3 months	44	28	3.4	27.8	4.7	0.87	No difference
WHR	3 months	44	0.82	0.049	0.81	0.055	0.53	No difference
Testosterone (ug/l)	3 months	44	0.6	0.1	0.7	0.2	0.04	**Metformin+Pioglitazone**
DHEAS (mg/l)	3 months	44	1.5	0.8	1.6	0.6	0.64	No difference
Total cholesterol (mg/dl)	3 months	44	197	35.6	177.7	53.3	0.16	No difference
HDL (mg/dl)	3 months	44	55.7	13.2	52.8	12.5	0.45	No difference
LDL (mg/dl)	3 months	44	124	29.8	110	52.6	0.28	No difference
Triglycerides (mg/dl)	3 months	44	114.3	78.5	100.9	61.8	0.53	No difference
Fasting insulin (uIU/ml)	3 months	44	7.3	4.3	8.6	4.9	0.35	No difference
Fasting glucose (mmol/l)	3 months	44	5	0.4	4.8	0.2	0.03	**Pioglitazone**
HOMA-IR	3 months	44	1.6	0.8	1.8	1	0.47	No difference

Comparison 25: Metformin versus metformin+pioglitazone

Evidence Summary

Only one RCTs compared metformin to metformin and pioglitazone (Sohrevardi et al. 2016). This study was rated as high risk of bias.

Meta-analysis/descriptive analysis summary

Meta-analysis was not possible with only one study. Sohrevardi et al. found that treatment with a combination of metformin and pioglitazone was superior in lowering fasting insulin and HOMA-IR. Otherwise, no significant differences were found when comparing metformin to metformin and pioglitazone.
In the metformin group, two subjects withdrew from the study because of severe gastrointestinal side effects. In the combination group two women withdrew from the study because of intolerable gastric discomfort.
Certainty in the evidence for this comparison is very low (downgraded twice for very serious risk of bias and twice for very serious risk imprecision, being a single, small study).

Author, year, country	Population	Sample Size per group	Intervention/ exposure details	PCOS criteria	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Summary of findings	Other
Sohrevardi et al. 2016 Iran	Women with PCOS, aged 18-40 years, with irregular menses and infertility	1.Metformin=22 2.Pioglitazone=21 3. Met+Pio=23	1.Metformin 500mgx3/d 2.Pioglitazone 30mg/d 3. Metformin 500mgx3/d+Pioglitazone 30mg/d	Rott	3 months	1.27.5 ±3.6 2.27.2±4.7 3.28.5 ±3.2	1.28.72±6.3 2.27.52 ±5.0 3.30.73 ±6.2	Weight, bmi, WHR, f-gluc, f-insulin, homa, lipids, dheas, T	only metformin ameliorated hyperandrogenemia in women with PCOS. Treatment with combination of metformin and pioglitazone did not show more benefit than monotherapy with each drug alone.	**ROB high**

Individual studies

Study ID	Sohrevardi 2016							
Outcome	**Time point**	**N**	**Metformin Mean**	**SD**	**Metformin+Pioglitazone Mean**	**SD**	**P value**	**Favours**
Weight	3 months	45	71	12.8	71.5	9.8	0.88	No difference
BMI (kg/m2)	3 months	45	27.4	4.4	28	3.4	0.61	No difference
WHR	3 months	45	0.83	0.036	0.82	0.049	0.43	No difference
Testosterone (ug/l)	3 months	45	0.6	0.18	0.6	0.1	1.0	No difference
DHEAS (mg/l)	3 months	45	1.4	0.5	1.5	0.8	0.92	No difference
Total cholesterol (mg/dl)	3 months	45	209.7	37.2	197	35.6	0.24	No difference
HDL (mg/dl)	3 months	45	52.9	11	55.7	13.2	0.44	No difference
LDL (mg/dl)	3 months	45	127	28	124	29.8	0.73	No difference
Triglycerides (mg/dl)	3 months	45	147	78.9	114.3	78.5	0.16	No difference
Fasting insulin (uIU/ml)	3 months	45	10.3	5.6	7.3	4.3	0.04	**Metformin+Pioglitazone**
Fasting glucose (mmol/l)	3 months	45	5.1	0.3	5	0.4	0.34	No difference
HOMA-IR	3 months	45	2.3	1.2	1.6	0.8	0.02	**Metformin+Pioglitazone**

Comparison 26: Metformin versus metformin+rosiglitazone

Evidence Summary

Only one RCTs compared metformin to metformin and rosiglitazone (Li et al. 2020). This study was rated as low risk of bias.

Meta-analysis/descriptive analysis summary

Meta-analysis was not possible with only one study. Li et al. found that metformin alone was more effective for decreasing weight and BMI. Note that the metformin-dose was higher (1500mg/d) in the metformin-only group compared to the combination group (metformin 1000mg/d). Metformin in combination with rosiglitazone was more effective for decreasing total cholesterol and triglycerides. Metformin only increased HDL better than Metformin+Rosiglitazone in combination.
When metformin was administered at a dosage of 1,500 mg/day, 51 patients experienced nausea, loss of appetite, diarrhea, and dizziness. Most of these patients gradually adapted within 1 to 5 weeks, except for one patient who could not tolerate a dosage of 1,500 mg/day and withdrew from the study with a dosage reduced to 1,000 mg/day. No side effects related to rosiglitazone were reported throughout the study.

Certainty in the evidence for this comparison is moderate (downgraded once for serious risk of imprecision, being a small, single study).

Author, year, country	Population	Sample Size per group	Intervention/ exposure details	PCOS criteria	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Summary of findings	Other
Li et al. 2020 China	Obese Chinese women (BMI>=25) with PCOS and insulin resistance	1.Metformin+LS=68 2.Rosiglitazone+LS=67 3.Metformin+Rosiglitazone+LS=69	1.metformin 1500mg/d 2.Rosiglitazone 4mg/d 3.Metformin 1000mg/d +Rosiglitazone 4mg/d	Rott	6 months	1.27.7 ±2.05 2.27.6 ±2.41 3.27.3±2.17	1.25.8±4.5 2.26.04 ±4.5 3.25.96±4.0	Menstrual cycle, weight, bmi, whr, mFGS, T, f-gluk, f-insulin, homa, lipids	metformin along with lifestyle modification should be recommended for obese, insulin-resistant women with PCOS. Rosiglitazone alone or combined with metformin plus lifestyle modification should be considered for the women with abnormal lipid profiles	**ROB Low**

Individual studies

Study ID	Li 2020							
Outcome	**Time point**	**N**	**Metformin**		**Metformin+Rosiglitazone**		**P value**	**Favours**
			Mean	**SD**	**Mean**	**SD**		
Weight	6 months	137	63.23	7.01	66.47	8.10	<0.025	**Metformin**
BMI (kg/m2)	6 months	137	25.02	1.86	25.94	2.22	<0.025	**Metformin**
WHR	6 months	137	0.89	0.060	0.90	0.058	NR	No difference

Testosterone (ng/ml)	6 months	137	0.50	0.18	0.46	0.19	NR	No difference
Hirsutism (mFGS)	6 months	137	2 (median)	0,6 (IQR)	2 (median)	0,6 (IQR)	NR	No difference
Total cholesterol (mmol/l)	6 months	137	4.10	1.15	3.78	0.76	<0.025	**Metformin+Rosiglitazone**
HDL (mmol/l)	6 months	137	1.48	0.24	1.38	0.27	<0.025	**Metformin**
LDL (mmol/l)	6 months	137	2.24	0.82	2.22	0.79	NR	No difference
Triglycerides (mmol/l)	6 months	137	1.47	0.60	1.29	0.68	<0.025	**Metformin+Rosiglitazone**
Fasting insulin (mIU/l)	6 months	137	15.97	5.74	15.65	5.17	NR	No difference
Fasting glucose (mmol/l)	6 months	137	5.09	0.34	5.14	0.58	NR	No difference
HOMA-IR	6 months	137	3.61	1.31	3.63	1.50	NR	No difference
Menstrual cycle (d)	6 months	137	46.19	13.35	43.65	15.14	NR	No difference

Comparison 27: Metformin+rosiglitazone versus rosiglitazone

Evidence Summary

Only one RCTs compared metformin and rosiglitazone to rosiglitazone (Li et al. 2020). This study was rated as low risk of bias.

Meta-analysis/descriptive analysis summary

Meta-analysis was not possible with only one study. Li et al. found that metformin in combination with rosiglitazone was more effective for decreasing total testosterone and total cholesterol. Rosiglitazone only increased HDL better than Metformin+Rosiglitazone in combination.
When metformin was administered at a dosage of 1,500 mg/day, 51 patients experienced nausea, loss of appetite, diarrhea, and dizziness. Most of these patients gradually adapted within 1 to 5 weeks, except for one patient who could not tolerate a dosage of 1,500 mg/day and withdrew from the study with a dosage reduced to 1,000 mg/day. No side effects related to rosiglitazone were reported throughout the study.

Certainty in the evidence for this comparison is moderate (downgraded once for serious risk of imprecision, being a small, single study).

Author, year, country	Population	Sample Size per group	Intervention/ exposure details	PCOS criteria	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Summary of findings	Other
Li et al. 2020 China	Obese Chinese women (BMI>=25) with PCOS and insulin resistance	1.Metformin+LS=68 2.Rosiglitazone+LS=67 3.Metformin+Rosiglitazone+LS=69	1.metformin 1500mg/d 2.Rosiglitazone 4mg/d 3.Metformin 1000mg/d +Rosiglitazone 4mg/d	Rott	6 months	1.27.7 ±2.05 2.27.6 ±2.41 3.27.3±2.17	1.25.8±4.5 2.26.04 ±4.5 3.25.96±4.0	Menstrual cycle, weight, bmi, whr, mFGS, T, f-gluk, f-insulin, homa, lipids	metformin along with lifestyle modification should be recommended for obese, insulin-resistant women with PCOS. Rosiglitazone alone or combined with metformin plus lifestyle modification should be considered for the women with abnormal lipid profiles	**ROB Low**

Individual studies

Study ID	Li 2020							
Outcome	**Time point**	**N**	**Metformin+Rosiglitazone Mean**	**SD**	**Rosiglitazone Mean**	**SD**	**P value**	**Favours**
Weight	6 months	136	66.47	8.10	66.42	8.03	NR	No difference
BMI (kg/m2)	6 months	136	25.94	2.22	26.27	1.93	NR	No difference
WHR	6 months	136	0.90	0.058	0.90	0.052	NR	No difference
Testosterone (ng/ml)	6 months	136	0.46	0.19	0.53	0.20	<0.025	**Metformin+Rosiglitazone**
Hirsutism (mFGS)	6 months	136	2 (median)	0,6 (IQR)	2 (median)	0,6 (IQR)	NR	No difference
Total cholesterol (mmol/l)	6 months	136	3.78	0.76	4.05	1.05	<0.025	**Metformin+Rosiglitazone**
HDL (mmol/l)	6 months	136	1.38	0.27	1.48	0.25	<0.025	**Rosiglitazone**
LDL (mmol/l)	6 months	136	2.22	0.79	2.22	0.66	NR	No difference
Triglycerides (mmol/l)	6 months	136	1.29	0.68	1.32	0.24	NR	No difference
Fasting insulin (mIU/l)	6 months	136	15.65	5.17	15.77	4.37	NR	No difference
Fasting glucose (mmol/l)	6 months	136	5.14	0.58	5.20	0.65	NR	No difference
HOMA-IR	6 months	136	3.63	1.50	3.70	1.34	NR	No difference
Menstrual cycle (d)	6 months	136	43.65	15.14	45.07	17.50	NR	No difference

Comparison 28: Metformin versus metformin (different dose)

Evidence Summary

Only one RCTs compared metformin with different doses (Harborne et al. 2005). This study was rated as high risk of bias.

Meta-analysis/descriptive analysis summary

Meta-analysis was not possible with only one study. Harborne et al. found that there was no difference between the two interventions. Other relevant outcomes were mentioned in this study, however no useable data was reported.
Certainty in the evidence for this comparison is very low (downgraded twice for very serious risk of bias and once for serious risk imprecision, being a small study). The study didn't report adverse effects.

Author, year, country	Population	Sample Size per group	Intervention/ exposure details	PCOS criteria	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Summary of findings	Other
Harborne et al. 2005 UK	Obese women with PCOS	1.42 2.41	1.Metformin 500mgx3=1500mg/d 2.Metformin 850mgx3=2550mg/d	Author defined	8 months	All participants: 37.2 (35.9, 38.5)	NR	weight	Weight loss is a feature of protracted metformin therapy in obese women with PCOS, with greater weight reduction potentially achievable with higher doses.	**ROB high**

Individual studies

Study ID	Harborne 2005							
Outcome	**Time point**	**N**	**Metformin 1500mg/d Mean**	**SD**	**Metformin 2550mg/d Mean**	**SD**	**P value**	**Favours**
Weight	8 months	83	101.9	19.90	92.7	14.57	0.08	No difference

Comparison 29: Metformin versus metformin+MPA

Evidence Summary

Only one RCTs compared metformin to metformin and MPA (medroxyprogesterone acetate) (Haydardedeoglu et al. 2009). This study was rated as moderate risk of bias.

Meta-analysis/descriptive analysis summary

A meta-analysis was not possible to perform with only one study. Haydardedeoglu et al. found that metformin only was superior for lowering testosterone and free testosterone compared to metformin combined with cyclic MPA and metformin only was also superior in increasing HDL. Certainty in the evidence for this comparison is very low (downgraded once for serious risk of bias and twice for very serious risk imprecision, being a small study).
Note: in the previous TR, this study was included in the comparison of metformin versus OCP. Since MPA is a progestin and in that way different from the other OCPs, it is analysed separately.

Author, year, country	Population	Sample Size per group	Intervention/ exposure details	PCOS criteria	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Summary of findings	Other
Haydardedeoglu 2009 Turkey	Women with PCOS	1.Metformin=20 2.Metformin+MPA=20	1.Metformin 850mgx2/d 2. Metformin 850mgx2/d+MPA 5mgx2/d (day 15-25)	Rott	3 months	1.25.8 ±5.6 2.25.9 ±5.7	1.24.4±5.5 2.25±6.1	Weight, bmi, T, free-T, DHEAS, f-insulin, f-gluc, OGTT, lipids, HOMA	There were no adverse effects of short-term cyclic MPA plus metformin treatment on metabolic parameters or insulin resistance in patients with PCOS over a 3-month treatment period	ROB Moderate

Individual studies

Study ID	Haydardedeoglu 2009							
Outcome	**Time point**	**N**	**Metformin**		**Metformin+MPA**		**P value**	**Favours**
			Mean	**SD**	**Mean**	**SD**		
Weight	3 months	40	65.89	14.02	65.06	15.85	0.86	No difference
BMI (kg/m2)	3 months	40	25.41	5.77	24.94	6.13	0.80	No difference
DHEAS (ng/ml)	3 months	40	2579.87	1655.66	2655,37	1934.61	0.89	No difference
Testosterone (ng/ml)	3 months	40	0.66	0.35	1.02	0.34	0.001	**Metformin**
Free testosterone (pg/ml)	3 months	40	2.78	1.23	5.19	1.23	<0.001	**Metformin**
Total cholesterol (mg/dl)	3 months	40	161.93	25.02	163.43	30.7	0.87	No difference

HDL (mg/dl)	3 months	40	56.8	15.84	48	11.18	0.04	**Metformin**
LDL (mg/dl)	3 months	40	94.6	25.38	100.37	31.17	0.52	No difference
Triglycerides (mg/dl)	3 months	40	76.86	29.87	96.31	44.94	0.11	No difference
Fasting insulin (mg/dl)	3 months	40	11.91	5.63	11.14	4.8	0.64	No difference
Fasting glucose (mg/dl)	3 months	40	87.06	7.58	89.25	6.65	0.33	No difference
HOMA-IR	3 months	40	2.56	0.68	2.5	1.21	0.85	No difference
OGTT	3 months	40	108.78	35.42	106.56	26.13	0.82	No difference

7. Study Characteristics Table- ***Metformin versus placebo – Adults and adolescents***

Author, year, country	Population	Study Design	Sample Size per group	Intervention / exposure details	PCOS criteria	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Summary of findings	Other
Lingaiah et al. 2019 Finland	Adult women with PCOS	RCT	1a. Metformin=40 (BMI<27) 1b. Metformin=17 (BMI>=27) 2a. Placebo=34 (BMI<27) 2b. Placebo=27 (BMI>=27)	1a. Metformin 500+1000mg 1b. Metformin 1000mg+1000 mg	ESHRE ASRM Rott	3 months	1a. 22.5 (2.2) 1b. 33.4 (4.3) 2a. 22.7 (2.6) 2b. 33.3 (4.4)	1a. 27.1 (3.1) 1b. 28.8 (3.8) 2a. 27.9 (4.2) 2b. 27.3 (5.0)	T, SHBG, FAI, DHEAS, A, f-gluk, f-ins, HOMA, BMI, WHR, weight	Small decrease in weight and BMI in the obese group after metformin. T and f-gluc decreased, and the Matsuda index increased. Non-obese group treated with metformin, T, FAI and A decreased	**ROB Moderate**
Zahra et al. 2017 Pakistan	Females with PCOS aged 18–35 years	RCT	1.Metformin=20 2.Placebo=20	Metformin 500mgx 3 /day	Author defined	3 months	1.26.7+/- 6.5 2. 29.6+/- 9.9	1.25.8+/- 6.1 2. 27.0+/- 6.3	Weight, BMI, fasting glucose, insulin, HOMA-IR	Metformin treatment showed significant improvement in systolic and diastolic blood pressures. In addition, an improvement in the hormonal profile in the form of reduction in LH, FSH, and visfatin levels was observed.	**ROB High**
Heidari et al. 2019 USA	Females aged 18 to 50 years with a BMI of 25 or greater who had a diagnosis of PCOS	RCT	1.Metformin=33 Placebo=15	1.metformin 1500mg/day	Rott	3 months	1.36.2+/- 10.3 2. 37.7+/- 8.1	1.32.4+/- 7.5 2.33.1+/- 5.9	Bmi, weight, ogtt,f-gluc, insulin, HOMA, DHEAS, T, CRP, lipids	In metformin-treated participants, there was a significant decrease in body weight (*P*<.05), f-gluc (*P*<.01), f-insulin (*P*<.05), HOMA-IR (*P*<.05), total cholesterol	**ROB Moderate**

										(*P*<.05), and T(*P*<.001) after 3 months of treatment.	
Baillargeon et al. 2004 Venezuela	Nonobese women (bmi 27), aged 17 to 40 years, who had PCOS	RCT double-blind	1.Metformin=28 2.Placebo=30	1.Metformin 850mg 2.Placebo	Own	6 months	1.24.6+/- 0.2 2. 24.6+/-0.2	1.27.7+/- 0.9 2. 27.2+/- 0.9	Weight, bmi, whr,mens cycle,shbg,T, DHEAS, A, f-gluc	Metformin is useful in the treatment of nonobese women with PCOS who have normal clinical indices of insulin sensitivity	**ROB Moderate**
Chou et al. 2003 Brazil	Obese (BMI>30), non-diabetic women with PCOS	RCT double-blind	1.Metformin=14 2.Placebo=16	1.Metformin 500mgx3 2.Placebo	Own	3 months	1.35.6+/- 4.9 2.37.4+/-6	1.24+/- 5 2. 24.5+/- 6.1	BMI, whr,shbg, t, f-insulin, f-gluc, lipids	Metformin-group lower T and tot-cholesterol, other parameters did not differ.	**ROB Moderate**
Eisenhardt et al. 2006 Germany	Women with PCOS, aged 21–36 yr, with menstrual disturbances and infertility and/or clinical signs of hyperandrogenism	RCT double-blind	1.Metformin=19 2.Placebo 19	1.Metformin 500mgx3 2.Placebox2	Rott	3 months	1.28.9 (23.3–34.1)* 2.32.4 (27.9 –37.5)*	1.27.0 (24.9 –30.7)* 2.29.7 (26.8 –32.4)*	BMI, SHBG, T, DHEAS, f-insulin, f-gluc, t-cholesterol	IR is a baseline predictor of clinical efficacy in metformin treatment in PCOS women measured by improved menstrual cyclicity and ovulatory function.	**ROB Low**
Fleming et al. 2002 UK	Women with oligomenorrhea (cycle length>41d; <8 cycles per year) or amenorrhea and PCOs, aged less than 35 yr	RCT double-blind	1.Metformin=26 2.Placebo=39	1.Metformin 850mgx2 2.Placebox2	NR	4 months	1: 34.2 (31.7–36.7)* 2: 35.0 (32.6–37.3)*	1: 28.6 [26.9–30.3]* 2: 29.2 [27.5–30.7]*	BMI, WHR, SHBG, T, f-insulin, f-gluc, cholesterol, triglycerides	Metabolic risk factor benefits of metformin were not observed in the morbidly obese subgroup of patients (bmi > 37). No change in f-gluc, f-insulin, or insulin responses to glucose challenge was recorded	**ROB moderate**
Karimzadeh et al. 2007 Iran	Women aged 20-35 years with PCOS	RCT	1.Metformin=100 2.placebo=100	1.Metformin 500mg/day for one week and then 500mgx3/day	Rott	3 months	1.28.8+/- 3.2 2.29.5+/- 4.7	1.27.2+/- 6.8 2.28.6+/- 7.4	Lipids	Metformin increased ovulation and pregnancy rates and decreased lipids	**ROB high**

				2.Placebo 1 tabl/day for a week, then 3 tabl/day							
Bridger et al. 2006 Canada	Adolescents, 13 to 18 years with hyperinsulinemia and PCOS	RCT double-blind	1.Metformin=11 2.placebo=10	Metformin 750mgx2/day Placebo 1 tablx2/day	Own	3 months	1.33.6+/- 5.6 2.30.81+/- 3.0	1.16.07+/- 0.97 2.16.08+/- 1.39	BMI, T, f-gluc, HOMA, lipids, restored menses	A significant decline in T with metformin compared with placebo The relative risk of menses was 2.50 times higher in the metformin group compared with the placebo. There were no significant changes in bmi, hirsutism, triglyceride levels, or total and low-density lipoprotein cholesterol levels.	**ROB low**
Morin-Papunen et al. 2012 Finland	Women with pcos, aged 18-39 yrs, with bmi>19	RCT double-blind	1.Metformin=106 2.placebo=111	1.Metformin 1000mgx2 (obese) Metformin 500mg+1000 mg (non-obese) 2.Placebo	Rott	3 months	1: 27.1±6.3 2: 27.4±6.2	1: 28.4±3.9 2: 27.9±4.1	Weight, whr, bmi	Obese women especially seem to benefit from 3 months' pretreatment with metformin and its combination thereafter with routine ovulation induction in anovulatory infertility.	**ROB Moderate**
Hoeger et al. 2008 USA	Women, aged of 12-18 yr with BMI above the 95th percentile and evidence of menstrual irregularity	RCT	1.Metformin=6 2.placebo=10 3.OCP=10 4.LS=8	1.Metformin 850mgx2/d 2. placebox2 3.30ug EE+0.15mg desogestrel	Author defined	6 months	1: 34.3±6.5 2: 36.1±7.5	1: 16±1.7 2: 15.4±1.7	BMI, PAI, FG, SHBG, FAI, T, f-gluc, lipids,crp	LS modification and OCs reduce androgens and increase SHBG in obese adolescents with PCOS. Metformin, in combination with LS modification and OC, reduces central adiposity, reduces	**ROB Moderate**

										total testosterone, and increases HDL, but does not enhance overall weight reduction.	
Hoeger et al. 2004 USA*	overweight or obese women with PCOS	RCT	1.Metformin=6 2.LS+placebo=8 3.LS+metformin=5 4.Placebo=7	1.Metformin 850mgx2/d	NIH	6 months	1: 37.1±4.9 2: 40±7.4 3: 41.7±6.2 4: 37.1±4.6	1: 29.5±6.4 2: 27.1±4.3 3: 30.4±5.4 4: 27.1±4.5	BMI, shbg, FAI, T, f-insulin, f-gluc	Weight reduction might play the most significant role in restoration of ovulation in obese women with PCOS	**ROB Moderate**
Esfahanian et al. 2013 Iran	women with bmi>=27 and PCOS	RCT	1.Metformin=17 2.HC diet=13	1.Metformin 1000-2000mg/d 2.HC diet – for 5-10% weight reduction	Rott	3 months	1: 31.1±3.3 2: 34.1±5.4	1: 21.9±9.3 2: 20±4.6	BMI, WHR, T, DHEAS, f-insulin, f-gluc, lipids, HOMA, crp, adverse effects	weight reduction was equally efficient with Metformin and LS and in decreasing hs-CRP levels. Metformin was more effective in improving insulin resistance in obese and overweight PCOS women	**ROB high**
Kelly et al. 2002 UK (Crossover)	women with PCOS and hirsutism	RCT double-blind	10 in total	1) MET 500 mg/daily to 500 Mgx3/d, over 3 weeks. 2) Placebo	Author defined	6 months (8wk washout)	NR	NR	Hirsutism, SHBG, FAI, T, DHEAS, lipids	metformin results in a significant improvement in hair growth compared with placebo.	**ROB Moderate**
Lord et al 2006 UK	Women with anovulation and PCOS	RCT double-blind	1.Metformin=16 2.placebo=16	1) MET 500 mgx3/d 2) Placebo x3/d	Author defined	3 months	1: 33.74±6.74 2: 36.37±7.46	1: 27.76±4.89 2: 30.63±4.84	Weight, bmi, whr, shbg, fai, T, DHEAS, f-insulin, f-gluc, lipids, HOMA	no significant differences in fat distribution. The metformin group had lower total cholesterol and HDL but there was no treatment effect on androgens, insulin, insulin resistance, triglycerides.	**ROB Low**
Moghetti et al. 2000 Italy	Caucasian women with PCOS, ages between 18–35 yr	RCT Double-blind	1.Metformin 2.Placebo N=NR	1) MET, 500 mg/daily 1st week	Author defined	6 months	1: 27.1±1.5 2: 32.6±1.1	1: 23.9±1.2 2: 21.4±1.4	BMI, WHR, SHBG, F-insulin, F-gluc, lipids,	metformin treatment reduced hyperinsulinemia and	**ROB high**

				to 500 mgx2 for next week, to 500 mgx3 further 24 wks. 2) Placebo					adverse effects No data extracted while N not reported	hyperandrogenemia, independently of changes in body weight.	
Onalan 2005 Turkey	Women with PCOS divided according to BMI	RCT Double-blind	BMI<25 1.Metformin=15 2.placebo=16 BMI 25-29.9 3.Metformin=7 4.placebo=9 BMI>30 5.Metformin=6 6.placebo=6	1,3,5 Metformin 500mgx1/d for 5 days, then 850mgx2 2,4,6 Placebo	Author defined	6 months	1: 21.16±2.25 2: 21.96±1.52 3: 28.1±1 4: 28.2±0.7 3: 31.6±1.1 4: 32.2±3.2	1: 26.4±4.1 2: 27.1±4.8 3: 24.6±4.8 4: 27.3±4.4 3: 31.8±4.0 4: 621.2±5.5	BMI, WHR, FG, DHEAS, f-insulin, f-gluc, lipids	We observed a significant decrease in WHR following metformin therapy in the normoinsulinemic overweight sub-group. Metformin had a significant effect on hirsutism scores in hyperinsulinemic lean women and decreased DHEAS levels in the lean hyperinsulinemic and normoinsulinemic groups.	**ROB high**
Palomba et al 2007 Italy	Normal-weight anovulatory PCOS women	RCT	1.Metformin=14 2.Placebo =13	1.Metformin 850mgx2 2.Placebox2	Author defined	6 months	1: 24.3±3.1 2: 24.8±2.7	1: 22.4±2.7 2: 22.7±1.9	Bmi, hirsutism, shbg, fai, T, DHEAS, A, lipids,	Metformin administration exerts beneficial effects on peripheral insulin sensitivity	**ROB Moderate**
Ng et al. 2001 Hong Kong	Infertile, Chinese women aged<40 yrs	RCT double-blind	1.Metformin=8 2.Placebo =7	1.Metformin 500mgx3 2.Placebox3	NR	3 months	1: 24.1 (19.6-34.2) 2: 23.8 (17.9-30.8)	1: 30.5 (27-33) 2: 32.0 (26-34)	BMI, shbg, T, f-gluc, lipids, adverse effects	Metformin did not increase ovulation rate despite reduction of bmi, s-testosterone and fasting leptin	**ROB Moderate**
Romualdi et al. 2010 Italy	normal-weight women with PCOS (BMI 22.4, age range 19–32 yrs)	RCT double-blind	1.Metformin=13 2.Placebo=10	1.Metformin 500mgx2/d 2.Placebox2/d	Rott	6 months	1: 22.2±2.2 2: 22.3±3.9	1: 24.7±4.4 2: 27.2±2.6	BMI, whr, hirsutism, shbg,fai, T, DHEAS, lipids	Metformin improves the menstrual pattern and ultrasonographic ovarian features in normoinsulinemic	**ROB Moderate**

										PCOS women. These effects seem to be independent of the insulin-lowering properties of the drug.	
Trolle et al. 2007 Denmark	women aged 18 – 45 with PCOS	RCT double-blind	1.Metformin=23 2.Placebo=27	1.Metformin 850mgx2/d 2.Placebox2/d	Rott	6 months	33.8 (22.2–46.0) Mean (5-95% percentiles)	1.32 (21-42) Mean (5-95% percentiles)	Weight, T, f-insulin, f-gluc, HDL, HOMA,	Metformin treatment lowered weight and systolic blood pressure and increased HDL in women with PCOS. In post-hoc analysis it increased insulin sensitivity and lowered testosterone in obese women. Non-obese women did not benefit from metformin.	**ROB Moderate**
Trolle et al. 2010 Denmark	women aged 18 – 45 with PCOS	RCT double-blind	1.Met=29-41 2.Placebo=29-41	1.Metformin 850mgx2/d 2.Placebox2/d	Rott	6 months	71% had BMI>30	18-45	Weight, WHR, SHBG, T, f-insulin, f-gluc, lipids, HOMA	In PCOS, adiponectin levels are closely linked to insulin resistance, HDL cholesterol, and abdominal adiposity and unaffected by metformin.	**ROB Moderate**
Maciel et al. 2004 Brazil	Women with PCOS, obese (BMI>30) and non-obese (BMI<=30)	RCT double-blind	Non-obese 1.Metformin=7 2.Placebo=8 Obese 3.Metformin=8 4.Placebo=6	1.Metformin 500mgx3/d 2.Placebox3/d 3.Metformin 500mgx3/d 4.Placebox3/d	NR	6 months	1: 25.3±2.1 2: 25.1±1.6 3: 37.2±1.7 4: 35.8±1.5	1: 22.5±1.9 2: 19.9±0.4 3: 20.5±1.9 4: 21.1±0.7	BMI, FG, shbg, T, DHEAS, A, f-insulin, f-gluc, lipids	Nonobese patients respond better than obese patients to a 1.5 g/day metformin regimen	**ROB Moderate**

*Means and SDs taken from Naderpoor 2015 because the original article reported percentage change from baseline and Naderpoor obtained means and SDs.

7. Study Characteristics Table- ***Metformin versus OCP+anti-androgen versus anti-androgen– Adults and adolescents***

Author, year, country	Population	Study Design	Sample Size per group	Intervention/ exposure details	PCOS criteria	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Summary of findings	Other
Alpanes et al. 2017 Spain	Women with PCOS reporting to an androgen excess outpatient clinic	RCT	1.Metformin=22 2.OCP+spiro=24	1. Metformin 425mg b.i.d. during the first week and 850mg dose b.i.d. Barrier contraception 2. OCP containing 30µg of ethinylestradiol and 150µg of desogestrel and 100mg/day of spironolactone	Presence of clinical and/or biochemical hyperandrogenism together with evidence of oligoovulation"	12months	1. 31.2 +/- 9 2. 30.6+/- 7.9	1.23+/-6 2. 25+/-5	hirsutism score, total-T, free-T, androstenedione, DHEAS, menstrual dysfunction, cardiometabolic orders, abnormal glucose intolerance, dyspipidemia, hypertension. weight, bmi, waist circumference, whr, f-gluk, f-insulin, HOMA	OCP+spiro more effective than met in terms of clinical and biochemical hyperandrogenism and menstrual bleeding. OCP+spiro decreased hirsutism score, normalized total and free T and androstenedione and reduced DHEAS	**ROB high**
Burchall et al 2017 Australia	Overweight and obese women with PCOS	RCT	1. metformin N=23 2. Low-dose OCP+spiro N=16 3.High dose OCP=21	1.Metformin 1000mg b.i.d. 2. 20-µg EE/100-µg levonorgestrel + spironolactone 50 mg b.i.d. 3. 35-µg EE/2-mg cyproterone acetate	NIH	6 months	1. 37.79 ± 6.81 2. 35.25 ± 5.71 3. 35.91 ± 8.11	1.32.16 ± 6.52 2. 35.44±6.91 3. 34.41±6.73	BMI, oGTT, Insulin, HOMA-IR, T, PAI-1, ADMA, PF1 and 2, TG, Fibrinolytic system, Plasminogen, TAFI.	Endothelial function improved with higher dose with some improvement in low-dose OCP + S and metformin. Aberrant coagulation was noted in both OCP groups, but not with metformin. Fibrinolysis was reduced with higher-dose OCP.	Outcomes included in Meyer et al. 2007, Hutchinson et al. and Moran et al. 2010 **ROB High**

Long et al 2022 China	Women with PCOS aged >18yr	RCT	1. metformin N=54 2. SPL N=53 3.Metformin+SPL=51	1.Metformin 1500mg/d 2.Spironolactone 40mg/d 2.Metformin 1500mg/d+Spironolactone 40mg/d	Rott	3 months	1.25.6 ± 4.5 2.25.9 ±6.7 3.25.4 ±3.7	1.27.0 ± 3.7 2.27.6 ±3.7 3.27.2 ±3.6	Weight, BMI, WHR, FAI, HOMA,	No differences in any parameters between the metformin and spironolactone groups (all P > 0.05). In the combined group, after 12 weeks of treatment, HOMA-IR was lower than in the metformin and spironolactone groups	**ROB Moderate**
Gambineri et al 2004 Italy	Obese (BMI>28) women with PCOS	RCT	1. metformin N=10 2.Placebo N=10 3. FLUT N=10 4.Metformin+FLUT=10	1. metformin 850mgx2/d 2.Placebo 3. FLUT 250mgx2 4.Metformin 850mgx2/d +FLUT 250mgx2/d	Rott	6 months	1.37.0 ± 5.9 2.37.6 ±4.1 3.35.1 ±3.6 3.34.4 ±4.4	1.26.1 ± 4.5 2.27.1 ±3.6 3.27.1 ±5.8 3.27.7 ±4.1	**HOMA**	Metformin, flutamide or the combined metformin + flutamide treatment appears to have a more favourable outcome on body fat distribution, androgens, lipids, hirsutism and menses.	**ROB Moderate** Outcomes included in Gambineri et al. 2006
Diri et al. 2017 Turkey	Women with newly or previously diagnosed with PCOS	RCT	1. metformin N=19 2.Finasteride N=16 3. Metformin +finasteride N=17	1. metformin 850mgx2/d 2.finasteride 5mg/d 3. metformin 850mgx2/d+ finasteride 5mg/d	Rott	6 months	1.27.1 ± 4.3 2.37.6 ±4.1 3.35.1 ±3.6	1.26.4 ± 7.2 2.27.4 ±4.3 3.27.6±4.2	Bmi, hirsutism, shbg, free-T, dheas, A, homa-IR	Comparisons of changes in parameters in the 3 groups did not clearly show the superiority of any treatment modality	**ROB high**
Ibanez et al. 2004 Spain	Young women/adolescents 4-8 yrs post menarche	RCT	1. metformin+AA=16 2.OCP=16	1. Met 850 mg + flutamide 62.5 mg 2. EE 30 g + 0.3 mg DRSP	Author defined	9 months	1. 21.8 ±0.5 2. 22.0 ±0.6	Mean age for all 14.6±0.3	BMI, FG score, Fasting glucose/insulin ratio, SHBG, Testosterone, TG, HDL, LDL	Low-dose flutamide is a pivotal component within the first contraceptive combination therapy that has been shown to attenuate the hypoadiponectinemia, ovarian vascular hyper-resistance,	**ROB Moderate**

										lean mass deficit, and central adiposity of young women with PCOS.	
Ibanez et al. 2005 Spain	Adolescents, 2-6 yrs post menarche	RCT	1. met+AA+OCP=16 2.OCP+AA=15	1. EE 30 g + 0.3 mg DRSP + flutamide 62.5 mg + met 850 mg/day 2. EE 30 g + 0.3 mg DRSP + flutamide 62.5 mg	Author defined	3 months	1.22.4 ±0.5 2.21.9±0.7	Mean± sem for all 16.0±0.3	BMI, Fasting glucose/insulin ratio, SHBG, T, A4, DHEAS, TG, HDL, LDL,	Met proved to be a pivotal component of a prime combination therapy that attenuates the dysadipocytokinemia, the lean mass deficit, and the central adiposity of young patients with polycystic ovary syndrome.	**ROB Moderate**

7. Study Characteristics Table- *Metformin versus OCP versus OCP+metformin – Adults and adolescents*

Author, year, country	Population	Study Design	Sample Size per group	Intervention/ exposure details	PCOS criteria	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Summary of findings	Other
Bodur et al 2018 Turkey	18–39 year old, non-obese (18–30 BMI) women with PCOS	RCT	1. metformin N=17 2. OCP N=17 3.OCP+metformin =12 4.Control	1.Metformin 1700mg/day. 2. 3 mg DRSP+30ug EE 3. 3 mg DRSP+30ug EE+Metformin 1700mg/day	Rott	6 months	1.25.06 ± 3.08 2.23.45 ±3.40 3.23.82 ±2.80	1.26.24 ± 3.96 2.26.62 ±4.92 3.27.35 ±5.65	Changes in adiponectin, hs-CRP, Apolipoprotein, PAI-1, homocysteine	Hs-CRP and PAI-1 levels increased in the OCP-group. In metformin-group hs-CRP and PAI-1 decreased. HOMA-IR values increased in the metformin-group and metformin+OCP-group and decreased in the OCP-group. S-gluc did not change in any of the groups.	**ROB High**
Glintborg et al. 2014 (1) Denmark	White women with PCOS, aged 18-39	RCT	1. metformin N=19 2. OCP N=23 3.OCP+metformin =23	1.Metformin 2000mg/day.	Rott	12 months	1: 25.1 (22.7–29.4)* 2: 27.3 (22.7–31.1)*	1: 29 [24-32]* 2: 28 [23-30]* 3:30 (24-32)*	Changes in weight, bmi, f-gluc, T, SHBG,	Treatment with M and M+OCP were superior to OCP regarding weight and regional fat mass. OCP	Outcomes also reported in Altinok 2018 and

	years, BMI <35			2. 150mg desogestrel+30ug ethinylestradiol 3. 150mg desogestrel+30ug ethinylestradiol +Metformin 2000mg/day			3:27.3 (24.0–30.5)P		insulin, homa, mFGS median (25th and 75th quartiles)	and M+OCP were superior to M regarding reduction in free T levels	Glintborg 2017 **ROB high**
Glintborg et al. 2014 (2) Denmark	White women with PCOS, aged 18-39 years, BMI <35	RCT	1. metformin N=19 2. OCP N=23 3.OCP+metformin =23	1.Metformin 2000mg/day. 2. 150mg desogestrel+30ug ethinylestradiol 3. 150mg desogestrel+30ug ethinylestradiol +Metformin 2000mg/day	Rott	12 months	1: 25.1 (22.7–29.4)* 2: 27.3 (22.7–31.1)* 3:27.3 (24.0–30.5)P	1: 29 [24-32]* 2: 28 [23-30]* 3:30 (24-32)*	No outcomes extracted	Long-term treatment with M alone or in combination with OCP was associated with improved body composition compared to OCP, whereas inflammatory markers were unchanged. OCP was not associated with increased inflammatory markers despite a small but significant weight gain.	Outcomes also reported in Altinok 2018, Glintborg 2014 and Glintborg 2017 **ROB high**
Altinok et al. 2018 Denmark	White women with PCOS, aged 18-39 years, BMI <35	RCT	1. metformin N=19 2. OCP N=23 3.OCP+metformin =23	1.Metformin 2000mg/day. 2. 150mg desogestrel+30ug ethinylestradiol 3. 150mg desogestrel+30ug ethinylestradiol +Metformin 2000mg/day	Rott	12months	NR	NR	No outcomes extracted	HRQoL changes were comparable between 12-month randomized M and/or OCP treatment in relatively healthy and lean women with PCOS.	Outcomes also reported in Glintborg et al. 2014 and Glintborg 2017 **ROB high**
Glintborg et al 2017 Denmark	White women with PCOS, aged 18-39 years, BMI <35	RCT	1. metformin N=19 2. OCP N=23 3.OCP+metformin =23	1.Metformin 2000mg/day. 2. 150mg desogestrel+30ug ethinylestradiol 3. 150mg desogestrel+30ug ethinylestradiol +Metformin 2000mg/day	Rott	12months	NR	NR	No outcomes extracted	AUC GLP-1 levels were unchanged during treatment. Increased risk of hypoglycemia during metformin +OCP could be associated with increased insulin secretion	Outcomes also reported in Glintborg et al. 2014 and Altinok 2018 ROB high

Kaya et al. 2012 Turkey	Thirty-seven women with PCOS (mean age: 23·1 ± 5·0)	RCT	1.metformin+OCP =25 2.OCP=25	1. drospirenone 3 mg/ EE 3 ug and metformin 850x2/day 2. drospirenone 3 mg/ EE 3 mg	Rott	6 months	1.31.7 ± 7.3 2.26.4 ±6.2	1.23± 4.5 2.23.2 ±5.4	Weight, BMI, lipids, SHBG, T, FAI, A, DHEAS, HOMA, CRP	We demonstrated an improvement in the elastic parameters of the aorta by adding metformin to OCP treatment. We suggest that metformin plus OCP treatment may decrease cardiovascular disease risk in women with PCOS.	**ROB High**
Kaya et al. 2015 Turkey	Women with PCOS, aged 17-37 years	RCT	1.metformin+OCP =25 2.OCP=25	1. drospirenone 3 mg/ EE 3 ug and metformin 850x2/day 2. drospirenone 3 mg/ EE 3 mg	Rott	6 months	1.29.8 ± 6.9 2.26.7 ±5.7	1.24± 4 2.23 ±5	Weight, BMI, lipids, SHBG, T, FAI, A, DHEAS, HOMA, CRP	adding metformin to OCP treatment may have beneficial effect on FMD and CIMT that represent vascular function in patients with PCOS. These results suggest that adding metformin to OCP treatment for PCOS could preserve the cardiovascular system and improve it.	**ROB High**
Sahu et al 2019 India	Women aged between 18 and 35 years with PCOS	RCT	1.metformin=50 2.OCP=51	1.Metformin 1000mg/day 2. 35 mg of ethinylestradiol plus 2 mg of cyproterone acetate	Rott	6 months	1.25.7 ± 2.6 2.25.6 ±2.7	1.27.0 ± 5.2 2.26.8 ±4.2	BMI, WC, cycle duration, hirsutism score, SHBG, DHEAS, lipids, f-glucose, f-insulin, HOMA-IR	OCP resulted in a higher reduction in LH and androgens whereas metformin resulted in significant reduction in BMI, WC and insulin resistance.	**ROB Moderate**
Essah et al 2011 USA	Overweight women with PCOS	RCT double -blind	1.Metformin+OCP =9 2.OCP=10	1.35ug EE + 0.18/ 0.215/ 0.25mg NOR + Metformin 500mgx3/d (1500mg/d) 2. 35ug EE + 0.18/ 0.215/ 0.25mg NOR (+ placebo)	Rott	3 months	1.36.2 ± 2.5 2.32.6 ±2.3	NR	Insulin sensitivity and other glycaemic measures flow-mediated dilatation, inflammatory and vascular markers	Both treatments had similar effects on androgen levels, lipid profile, insulin sensitivity, and serum inflammatory markers, but flow-mediated dilatation increased by 69.0% in the metformin+OCP group while it remained unchanged in the OCP group.	**ROB low**
Feng et al. 2016 China	Women with PCOS (age 26–32 years;	RCT	1.Metformin+OCP =41 2.OCP=41	1.35ug EE + 2mg CPA] +	Rott	3 months	1.29.5 ±4.4 2.27.8 ±4.2	1.27.9 ± 3.8 2.28.6 ±3.0	Anthropometric measures Hirsutism scores	OCP+metformin had shown reduced fat percentage levels and	**ROB moderate**

	mean, 29.0 years)			Met 450mg-850mgx 2/d 2. 35ug EE + 2mg CPA					Acne scores Endocrine parameters	improved glucose and lipid metabolism	
Aghamohammadzadeh et al. 2010 Iran	Women with PCOS	RCT	1.Metformin=30 2.OCP=30	1. Metformin 1000mgx1/d 2. EE 35µg plus Cyproterone acetate 2mg	NIH	6 months	1.26.5 ±5.7 2.24.6 ±4.9	1.24.9 ± 11 2.22 ±5.2	T, DHEAS, hs-crp, weight, BMI	there were no significant differences in the effects of these two drugs on serum testosterone, DHEA-S and hs-CRP levels.	**ROB high**
Rautio et al. 2005 Finland	Nonobese women BMI< 25 and obese women BMI > 27 with PCOS	RCT	1.metformin=16 2.OCP=19	1.Metformin 500 mgx2 daily for 3 months, then 1000 mgx2 daily for 3 months 2. ethinyl estradiol 35 ug, cyproterone acetate 2 mg	Homburg	6 months	1.28.7 ± 1.5 2.30.6 ±1.8	NR	lipids	metformin treatment had beneficial effects on lipid profile and blood pressure, and therefore it could be useful in the prevention of cardiovascular complications in these women	**ROB high** Outcomes also reported in Morin-Papunen et al 2003
Bilgir et al. 2009 Turkey	Women with PCOS	RCT	1.Metformin+OCP =20 2.OCP=20	1.35ug EE + 2mg CPA] + Met 850mgx 2/d 2. 35ug EE + 2mg CPA	Rott	3 months	1.28.2 ±4.3 2.28.2 ±6.0	1.25.2±4.6 2.24.3±5.7	BMI, lipids, insulin, HOMA-IR, DHEAS, free-T	EE/CA+metformin treatment reduced inflammation markers in cases with PCOS compared to EE/CA treatment.	**ROB high**
Christakou et al. 2014 Greece	Premenopausal caucasian women with PCOS (BMI<25)	RCT	1.Metformin=40 2. OCP=40 3.OCP=40	1.Metformin 425 mgx2 daily for one week, then 850 mgx2 daily for 6 months 2. ethinyl estradiol 30 ug, drospirenon 3 mg 3. 35 µg ethinylestradiol and 2 mg cyproterone acetate	NIH	6 months	1.23.0 ±0.67 2.22.4 ±0.48 3.21.8 ±6.35	1.21.5±0.5 2.23.2±0.6 3.22 ±0.6	BMI, HOMA-IR, T, SHBG, FAI, CRP	CRP was decreased with metformin but increased with ocp.	**ROB Moderate**
Elter et al 2002 Turkey	Women with PCOS, aged 16-36 yr	RCT	1.Metformin+OCP =20 2.OCP=20	1.Metformin 500mgx3/d, 500mgx2 for adequate compliance+ 35µg EE + 2mg CPA 2. 35µg EE + 2mg CPA	Own	4 months	1.22.74 ±2.66 2.21.83 ±1.40	1.24.90±6.6 2.23.45±6.1	BMI, WHR, SHBG, T, f-insulin, f-gluc, lipids,	MET+OCP had decreases in BMI and WHR and a sign increase in insulin sens compared to OCP-group. Adding MET improved A and SHBG compared with OCP alone	**ROB Moderate**
Kumar et al. 2018	newly diagnosed	RCT	1.Metformin=30 2. OCP=28	1. metformin 500 mg/day, gradually	Rott	6 months	1.27.1 ±6 2.26.15 ±4.9	1.22±5.2 2.22.9±5	Weight, BMI, mFGS, lipids, f-	Met+OCP improves the hyperandrogenism, body	**ROB Moderate**

India	PCOS (age 18–40 year, symptom duration >6 months)		3.Metformin+OCP =29	increased to 2000 mg/day over 1 month 2. EE 35 mcg and cyproterone acetate 2 mg 3. metformin 500 mg/day, gradually increased to 2000 mg/day over 1 month +EE 35 mcg and cyproterone acetate 2 mg			3.30.1 ±5.5	3.24.1 ±5.9	gluk, f-insulin, HOMA-IR, T, DHEAS	composition, and reduces the inflammatory markers better than Met or OCP alone	
Kilic et al 2011 Turkey	Women with PCOS aged 18-35 years	RCT	Obese: 1.Metformin=24 2.OCP=25 Non-obese 3.Metformin=23 4.OCP=24	1,3:Metformin 850mgx2/d (1700mg) 2,4: 0.03mg EE + 0.15mg DSG	Rott	6months	1.31.5 ±2.2 2.27.7 ±0.9 3.23.3 ±1.6 4.21.6 ±1.4	1.28.7 ±3.7 2.29.0±3.5 3.26.3 ±3.0 4.26.7 ±3.8	BMI, HOMA-IR, CRP	Metformin improved hormonal and metabolic parameters and decreased ADMA and homocysteine levels possibly independent of BMI. Use of OCP in obese and nonobese patients with PCOS with impaired glucose tolerance increased ADMA and hs-CRP levels and created an increase in the metabolic risk	**ROB low**
Harborne et al. 2003 UK	Women with PCOS	RCT	1.Metformin=26 2.OCP=26	1.Metformin 500mgx3/d 2.35µg EE + 2mg CPA	Rott	12 months	1.31.7 (29.5-35.5) 2.31.8 (28.4-34.4)	1.31.3 (27.9-34.7) 2.31.7 (26.8-36.5)	BMI, WHR, mFGS, SHBG, FAI, T, f-insulin, f-gluc, lipids	OCP was responsible for profound suppression of androgen activity, in contrast to metformin, which induced negligible change. However, metformin did reduce markers of insulin resistance.	**ROB Moderate**
Al-Zubeidi et al. 2015 USA	Girls aged 12 and 18 yr with PCOS	RCT	1.Metformin=12 2.OCP=10	1.Metformin 2000mg/day 2. 30ug EE+1mg NORA/d	NIH	6 months	1.33.7±6 2.33.4±9	1.16 (14-18) 2.16 (15-17)	f-insulin, QoL	BMI decreased in all patients (metformin p=0.004, OCP p=0.045). FT decreased significantly only with OCP.	**ROB high**

El Maghraby et al. 2015 Egypt	Girls, aged 15-20 yr with PCOS	RCT	1.Metformin=33 2.OCP=32	1. Metformin 1700mg/d 2. 30ug EE+15mg progestin/d	Rott	24 months	NR	1.17.20 ±2.0 2.16.90 ±1.6	weight	Metformin and OCP have comparable therapeutic effectiveness on cycle regularity and hirsutism. Metformin showed a improvement in metabolic syndrome, while OCP was associated with a deterioration of metabolic syndrome.	**ROB high**
Lv et al. 2005 China	Women with PCOS, aged 16--36 years	RCT	1.OCP+Metformin =25 2.OCP=25	1.Metformin 500mg/d+CPA 2.CPA	Own	6 months	1.22.10±2.46 2.21.8±1.37	1.24.5±5.6 2.24.35±5.1	BMI, WHR, T, A, DHEAS, SHBG, f-gluc, f-insulin, lipids	in the OCP+ metformin group, BMI and WHR were decreased, while insulin sensitivity was significantly decreased as compared with those before treatment. In CPA group, no significant changes were found before and after treatment.	**ROB high**
Mehrabian et al. 2016 Iran	Women with PCOS and metabolic syndrome	RCT	1.Metformin=34 2.OCP+SPL=34	1.Metformin 1000mg/d 2.30ug EE+0.15mg levonorgestrel+ Flutamid 62.5mg	NIH	6 months	1.29.8±4.15 2.29.8±4.16	1.29.2±8.3 2.29.0±7.7	BMI, f-gluc, lipids, crp	Metformin performed better in FBS reduction. Simvastatin had better performance in terms of reducing TG level and waist circumference	**ROB Low**
Meyer et al. 2007 Australia	Overweight women (BMI 27 kg/m2) with PCOS	RCT	1.Metformin=36 2.OCP (high)=31 3. OCP+SPL=33	1.Metformin 1000mgx2/d 2.35µg EE + 2mg CPA (high) 3. 20µg EE + 100µg LVG + 50mg SPL (low dose)	NIH	6 months	1: 36.3 no SD 2: 36.5 no SD 3: 35.5 no SD	Average: 31 years	BMI, WHR, menstrual cycle, hirsutism, shbg, FAI, T, DHEAS, f-insulin, lipids, homa	All treatments similarly and significantly improved symptoms including hirsutism and menstrual cycle length. Insulin resistance was improved by metformin and worsened by the high-dose OCP.	**ROB Moderate** Outcomes also reported in Moran et al 2010, Hutchinson et al. 2008, Burchall et al. 2017
Hutchinson et al 2008 Australia	Overweight women (BMI 27 kg/m2) with PCOS	RCT	1.Metformin=19 2.OCP =19	1.Metformin 1000mgx2/d 2.35µg EE + 2mg CPA (high)	NIH	6 months	1.38.4±1.6 2.35.3±1.8	NR	Weight, WHR, crp, SHBG, BMI, T	Metformin improved insulin resistance by 35%, whereas the OCP worsened insulin resistance by 33%. However, RBP4 increased	**ROB Moderate** Outcomes also reported in Meyer et al. 2007, Burchall

										nonsignificantly in both group	et al 2017, Moran etl al 2010
Mhao et al. 2015 Iraq	Women with PCOS, age14–40 years	RCT	1.Metformin=16 2.OCP=10	1. Metformin 500mgx2/d 2. EE 35 ug – CPA 2 mg	NR	3 months	1.27.2±5.4 2.30.5±5.3	NR	BMI, WHR, lipids	metformin improved lipids; glucose homeostasis and BMI, however, OCP is superior in improving the clinical manifestation of patients with PCOS, (menstrual cycle regulation, hyperandrogenic state)	**ROB high**
Moran et al. 2010 Australia	Overweight women (BMI 27 kg/m2) with PCOS	RCT	1.Metformin=30 2.OCP =26	1.Metformin 1000mgx2/d 2.35µg EE + 2mg CPA (high)	NIH	6 months	NR	NR	f-gluc, oGTT, CRP	Alterations in leptin between women with and without PCOS and following pharmacological interventions are primarily related to adiposity and not IR. Aldosterone was reduced equivalently with metformin and the OCP despite differential effects on IR.	**ROB moderate** Outcomes also reported in Meyer et al. 2007, Hutchinson et al. 2008, Moran et al. 2010
Morin-Papunen et al. 2000 Finland	obese (BMI> 27) women with PCOS	RCT	1.metformin=8 2.OCP=10	1. Metformin 500mgx2/d 3 months (1000mg), then 1000mgx2/d next 3 months (2000mg) 2. ethinyl estradiol 35 ug, cyproterone acetate 2 mg	Hombur g	6 months	1.32.5 ± 1.1 2.37.2 ±1.8	1.29.9 ± 1.5 2.29.8 ±1.0	Period, b-gluc, hirsutism, adverse effects	Metformin decreased the WHR, T and insulin and improved oxidative glucose utilization and menstrual cyclicity. OCP decreased T and increased SHBG	**ROB Moderate** Outcomes also reported in Morin-Papunen et al. 2003
Morin-Papunen et al. 2003 Finland (2)	Non-obese (BMI<25) women with PCOS	RCT	1.metformin=8 2.OCP=9	1. Metformin 500mgx2/d 3 months (1000mg), then 1000mgx2/d next 3 months (2000mg) 2. ethinyl estradiol 35 ug, cyproterone acetate 2 mg	Hombur g	6 months	1.22.5 ± 0.8 2.21.8 ±0.7	1.28.2 ± 1.4 2.28.5 ±1.7	Period, b-gluc, hirsutism, adverse effects	EE-CA seems to be an efficient for hyperandrogenic symptoms, but its possible negative effects on insulin and glucose metabolism have to be taken into consideration in nonobese subjects. Metformin improved	**ROB Moderate** Outcomes also reported in Morin-Papunen et al. 2000

										hyperandrogenism, hyperinsulinemia, and menstrual cyclicity. Thus, similarly to obese PCOS women, nonobese PCOS subjects with anovulation may also benefit from metformin	
Morin-Papunen et al. 2003 Finland (1)	Nonobese women BMI< 25 and obese women BMI > 27 with PCOS	RCT	1.metformin=16 2.OCP=19	1.Metformin 500 mgx2 daily for 3 months, then 1000 mgx2 daily for 3 months 2. ethinyl estradiol 35 ug, cyproterone acetate 2 mg	Hombur g	6 months	1.28.7 ± 1.5 2.30.6 ±1.8	NR	s-crp	During metformin treatment, serum CRP levels decreased significantly at 6 months in the whole study population and especially in obese subjects. In contrast, the treatment with ethinyl estradiol-cyproterone acetate increased serum CRP levels	**ROB high** Outcomes also reported in Morin-Papunen et al. 2003, 2000
Ozgurtas et al. 2008 Turkey	Non-obese (BMI < 25), aged >18 years, women with PCOS	RCT	1.metformin=20 2.OCP=21 3.Controls=22	1. metformin 850 mgx2/d 2. 35ug EE and 2 mg CPA	Rott	3 months	1.21.8 ± 01.27 2.21.72 ±1.24 3.21.4 ±1.54	NR	BMI, WHR, HOMA-IR, lipids, T, free-T, A, DHEAS, SHBG Controls not included in meta-analysis (no info on outcomes)	ADMA concentrations in non-obese, non-hypertensive and young women with PCOS are significantly higher than healthy controls and they improved by a 3-month course of metformin and oral contraceptive treatments.	**ROB high**
Panidis et al 2010 Greece	Premenopausal women with PCOS (BMI<25)	RCT	1.Metformin=15 2. OCP=15 3.OCP=15	1.Metformin 850 mgx2/d 2. EE 30 ug, drospirenon 3 mg 3. 35 µg EE and 2 mg CPA	NIH	6 months	1.21.83±1.73 2.21.69 ±2.33 3.21.04 ±1.97	1.20.53±3.1 2.22.0±2.07 3.20.67±4.13	A, DHEAS, insulin, glucose (rest are reported in Christakou et al)	AMH serum levels were decreased under treatment with 35 mg ethinylestradiol plus 2 mg cyproterone acetate, due to decrease in androgens and suppression of gonadotropins.	**ROB High**

Wu et al 2008 China	Women with PCOS, aged 19-35yr, divided into obese (BMI>25) and non-obese (BMI>25)	RCT	1.Metformin obese=7 2.OCP obese=7 3. Metformin+OCP obese=6 4.Metformin non-obese=11 5.OCP non obese=12 6.Metformin+OCP non obese=10	1.Metformin 500mgx3/d 2. 35µg EE + 2mg CPA 3. Metformin 500mgx3/d+35µg EE + 2mg CPA	Rott	3 months	1.25.6± 0.6 2.25.3 ±0.8 3.25.2 ±1.0 4.21.5± 1.8 5.21.4 ±1.6 6.21.6 ±1.4	1.25.6± 3.6 2.25.0 ±4.3 3.24.5 ±2.4 4.25.6± 4.2 5.26.1 ±4.6 6.25.8 ±4.0	BMI, WHR, T, Insulin	Metformin+OCP may be more effective in suppressing the hyperandrogenemia of obese and non-obese PCOS patients than metformin alone and may reduce insulin levels more than OCP alone.	**ROB Moderate**
Kebapcilar et al 2010 Turkey	Women with PCOS (24.0+/- 5.4 yr; BMI 27.9 +/-5.28)	RCT	1.Metformin=12 2.Metformin+OCP =12 3. OCP=12 4.OCP+SPL=12	1.Metformin 850mgx2/d 2.Metformin 850mgx2/d + EE 35ug+CPA 2mg 3. EE 35ug+CPA 2mg 4. EE 35ug+CPA 2mg+spironolactone 100mgx1/d	Rott	3 months	1.27.8± 4 2.27.6 ±3 3.28.7 ±6 4.27.6±4	1.24.4± 6.2 2.24.9 ±4.8 3.23.2 ±5.1 4.23.4± 5.8	BMI, lipids, Insulin, HOMA, dHEAS, free-T	All treatment groups showed reduced coagulation parameters, improvement of hormonal, hematological and metabolical variables. EE/CA–metformin may be a more effective due to the benefcial effect of EE/CA–metformin on insulin resistance.	**ROB high** Outcomes also reported in Kebapcilar et al 2009 and Bilgir et al
Kebapcilar et al 2009 Turkey	Women with PCOS	RCT	1.Metformin+OCP =21 2.OCP=22	1.Metformin 850mgx2/d + EE 35ug+CPA 2mg 2. EE 35ug+CPA 2mg	Rott	3 months	1.28.7± 4.4 2.27.2 ±6.2	1.25.1± 4.4 2.24.1 ±5.6	BMI, lipids, Insulin, HOMA, dHEAS, free-T	Adding metformin to EE/ CA therapy in PCOS may beneficial endothelium effects associated with reduction of ADMA levels	**ROB high** Outcomes also reported in Kebapcilar et al 2009 and Bilgir et al
Bilgir et al. 2009 Turkey	Women with PCOS	RCT	1.Metformin+OCP =20 2.OCP=20	1.35ug EE + 2mg CPA] + Met 850mgx 2/d 2. 35ug EE + 2mg CPA	Rott	3 months	1.28.2 ±4.3 2.28.2 ±6.0	1.25.2±4.6 2.24.3±5.7	BMI, lipids, insulin, HOMA-IR, DHEAS, free-T	EE/CA+metformin treatment reduced inflammation markers in cases with PCOS compared to EE/CA treatment.	**ROB high** Outcomes also reported in Kebapcilar et al 2009 and Bilgir et al
Luque-Ramírez 2009 Spain	Women with PCOS	RCT	1.Metformin=19 2.OCP=15	1.Metformin 1700mg/d 2. 35ug EE + 2mg CPA	NIH	6 months	1.30.5 ±6.9 2.29.2 ±5.7	1.25.1±6.6 2.23.4±5.6	Adverse effects	Metformin treatment decreased daytime ABPM recordings whereas Diane35 Diario exerted the opposite effect. The safer blood pressure profile of metformin should be considered in PCOS patients	**ROB Moderate**

Cibula 2005 Czech Republic	Women with PCOS	RCT	1.Metformin+OCP =13 2.OCP=15	1. Metformin 500mgx3/d+ 35ug EE + 250ug NOR 2. 35ug EE + 250ug NOR	Own	6 months	1.24.7 ±4.9 2.22.1 ±3.1	1.23.8±5.4 2.23.2±4.6	Weight, BMI, SHBG, FAI, T, f-insulin, f-gluc, lipids, adverse effects	Metformin caused a more significant decrease in the free androgen index but had no additional positive impact on lipids, insulin sensitivity, SHBG or testosterone.	**ROB Moderate**
Wei et al. 2012 China	Women with PCOS and insulin resistance	RCT	1.Metformin+OCP =30 2.OCP=28 (Berberine+OCP= 31)	1.Metformin500mgx3/ d+35ug EE+2mg CPA 2. 35ug EE+2mg CPA	Rott	3 months	1.62.98 ±5.2 2.65.13 ±5.1	1.26.03±2.8 2.26.75±2.6	BMI, WHR, f-gluc, f-insulin, OGTT, HOMA, lipids, T, SHBG, FAI	Intake of Berberine improved some of the metabolic and hormonal derangements in a group of treated Chinese women with PCOS.	**ROB Moderate**
Moro et al. 2013 Italy	Women with PCOS aged 18 to 35 years	RCT	1.Metformin=25 2.OCP=25 3.Metformin+OCP =26	1.Metformin 500mgx3 2.30ug EE+3mg drsp 3. Metformin 500mgx3 30ug EE+3mg drsp	Rott	6 months	1.23.7 (20.8-28.6) 2.25.1 (21.9-28.3) 3.26.5 (21.3-30) Median (range)	1.25±5 2.26±3 3.25±4	FAI, T, lipids	In women with hyperinsulinemic PCOS, combined therapy with DRSP/EE and metformin may reduce cardiovascular risk.	**ROB Moderate**
Dardzinska et al. 2014 Poland	women (age range: 18–36) with PCOS Cross-over study	RCT	1.Metformin=7 2.OCP=14	1Metformin 850mgx2/d 2.EE 35ug+CPA 2mg	Rott	4 months	M 1st: 25.1±9.8 C 1st: 24.9±4.4	M 1st: 24.6 [23.0;26.3] C 1st: 24.9 [23.5;26.4]	Weight, lipids, adverse events (rest mean and IQR so extracted but not used in meta-analysis)	Treatment with EE-CPA containing OC for 4 months in women with PCOS significantly raises serum CRP.	**ROB Moderate**
Allen et al. 2005 USA	obese, post-menarchal, non-sexually active adolescents aged 12-21 years with PCOS and hyperinsulinism	RCT	1.Metformin=16 2.OCP=15	M) 1000mg MET/day C) 35ug EE + 0.25mg NOR/day	Author defined	6 months	1.37.3 ±1.3 2.40.1 ±2.1	1.15.4 (13.1-18.4) 2.15.3 (12.5-21)	Weight, f-insulin,	Adolescents with PCOS treated with metformin or OCP experienced similar beneficial outcomes including reduction in androgen levels, weight loss, and increased insulin sensitivity. The choice of a treatment agent for long-term use will depend on safety profiles, therapeutic goals and patient adherence.	**ROB Low**

7. Study Characteristics Table- *Metformin versus Metformin+MPA – Adults and adolescents*

Author, year, country	Population	Study Design	Sample Size per group	Intervention/ exposure details	PCOS criteria	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Summary of findings	Other
Haydardedeoglu 2009 Turkey	Women with PCOS	RCT	1.Metformin=20 2.Metformin+P=20	1.Metformin 850mgx2/d 2. Metformin 850mgx2/d+MPA 5mgx2/d (day 15-25)	Rott	3 months	1.25.8 ±5.6 2.25.9 ±5.7	1.24.4±5.5 2.25±6.1	Weight, bmi, T, free-T, DHEAS, f-insulin, f-gluc, OGTT, lipids, HOMA	There were no adverse effects of short-term cyclic MPA plus metformin treatment on metabolic parameters or insulin resistance in patients with PCOS over a 3-month treatment period	**ROB Moderate**

7. Study Characteristics Table- *SPIOMET versus OCP – Adults and adolescents*

Author, year, country	Population	Study Design	Sample Size per group	Intervention/ exposure details	PCOS criteria	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Summary of findings	Other
De Zegher et al 2019 Spain	Adolescent girls with PCOS (gynaecological age>2.0 years)	RCT	SPIOMET=29 OCP=29	1.SPIOMET-group: spironolactone 50 mgx1 daily, pioglitazone 7.5 mgx1 daily and metformin 850 mgx1 daily, taken together at dinner time 2.OCP-group: 20 µg ethinyloestradiol plus 100 mg levonorgestrel (21/28 days), and placebo (7/28 days)	hirsutism, oligomenorrhea, gynaecological age>2.0 years,	12 months	NR	1.15.8 ±0.3 2.15.6 ±0.3	FAI (the rest in Ibanez et al 2020)	OCP and SPIOMET treatment were accompanied, respectively, by 1.7- and 3.4-fold rises of circulating GDF15. Post-OCP, GDF15, CRP and insulin returned towards baseline levels; post-SPIOMET, GDF15 returned also to baseline levels but CRP, insulin and liver fat remained normal	**ROB Moderate** Outcomes also reported in Ibanez et al. 2020.

Ibanez et al 2020 Spain	Adolescent girls with PCOS two RCT pooled (gynaecological age>2.0 years)	RCT	SPIOMET=**31** OCP=**31**	1.SPIOMET-group: spironolactone 50 mgx1 daily, pioglitazone 7.5 mgx1 daily and metformin 850 mgx1 daily, taken together at dinner time 2.OCP-group: 20 µg ethinyloestradiol plus 100 mg levonorgestrel (21/28 days), and placebo (7/28 days)	hirsutism, oligomenorrhea, gynaecological age>2.0 years,	12 months	1.24.2 ±0.7 2.24.2 ±0.7	1.15.7 ±0.2 2.15.9 ±0.2	BMI, mFGS, SHBG, T, A, free-T, f-insulin, HOMA, OGTT, triglycerides	OCP and SPIOMET treatment reduced the androgen excess comparably and had no differential effects on total-body lean or fat mass. However, SPIOMET was accompanied by more broadly normalizing effects, including on hepato-visceral fat and on circulating insulin	**ROB Moderate**
Ibanez et al 2017 Spain	Adolescent girls with PCOS	RCT	SPIOMET=**17** OCP=**17**	1.SPIOMET-group: spironolactone 50 mgx1 daily, pioglitazone 7.5 mgx1 daily and metformin 850 mgx1 daily, taken together at dinner time 2.OCP-group: 20 µg ethinyloestradiol plus 100 mg levonorgestrel (21/28 days), and placebo (7/28 days)	hirsutism, oligomenorrhea, gynaecological age>2.0 years,	12 months	1.23.4 ±0.7 2.24.0 ±0.8	1.15.8 ±0.3 2.15.9 ±0.3	No outcomes (all are in Ibanez et al 2020)	SPIOMET was followed by a 2.5-fold higher ovulation rate than OCP and by a 6-fold higher normovulatory fraction. Oligoanovulation risk after SPIOMET was 65% lower than after OCP	**ROB Moderate** Outcomes also reported in Ibanez et al. 2020.
Diaz et al. 2020 Spain	nonobese adolescent girls with PCOS	RCT	SPIOMET=**17** OCP=**18**	1.SPIOMET-group: spironolactone 50 mgx1 daily, pioglitazone 7.5 mgx1 daily and metformin 850 mgx1 daily, taken together at dinner time 2.OCP-group: 20 µg ethinyloestradiol plus 100 mg levonorgestrel (21/28 days), and placebo (7/28 days)	hirsutism, oligomenorrhea, gynaecological age>2.0 years,	12 months	1.23.1 ±0.7 2.23.9 ±0.8	1.15.7 ±0.3 2.15.9 ±0.3	No outcomes (all are in Ibanez et al 2020)	A low-dose combination of insulin sensitizers and an antiandrogen—but not oral contraception—normalizes fetuin-A levels in adolescent girls with PCOS.	**ROB Moderate** Outcomes also reported in Ibanez et al. 2020.
Malpique et al 2018 Spain	nonobese adolescent girls with PCOS	RCT	SPIOMET=**24** OCP=**27**	1.SPIOMET-group: spironolactone 50 mgx1 daily, pioglitazone 7.5 mgx1 daily and metformin 850 mgx1	hirsutism, oligomenorrhea, gynaecological age>2.0 years,	12 months	1.25.1 ±1 2.24 ±1	1.15.8 ±0.3 2.15.7 ±0.3	No outcomes (all are in Ibanez et al 2020)	S100A4 may become a circulating marker of hepato-visceral fat excess in adolescents with PCOS	**ROB Moderate** Outcomes also reported

				daily, taken together at dinner time 2.OCP-group: 20 µg ethinyloestradiol plus 100 mg levonorgestrel (21/28 days), and placebo (7/28 days)							in Ibanez et al. 2020.

7. Study characteristics Table - OCP versus **OCP+anti-obesity** versus **MET+anti-obesity** versus **OCP+anti-obesity+MET**

Author, year, country	Population	Study Design	Sample Size per group	Intervention/ exposure details	PCOS criteria	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Summary of findings	Other
Song et al. 2018 China	Women, aged 18-40 yrs, BMI>=24 with PCOS	RCT	1.OD=60 2.MD=60 3.OMD=60 4.D=60	1.Orlistat 120mgx3/d+35ugEE and 2mgCPA 2.Metformin500mgx3/d+35ugEE and 2mgCPA 3. Orlistat 120mgx3/d+Metformin 500mgx3/d+35ug EE and 2mg CPA 4. 35ugEE and 2mg CPA	Rott	3 months	1.27.9 ±4.1 2.27.0 ±3.5 3.28.8 ±3.4 4.28.6 ±4.9	1.26.8 ±4.1 2.28.6 ±5.1 3.27.6 ±4.6 4.27.7 ±5.0	T, lipids, f-insulin, f-gluc, HOMA-IR,	orlistat is more effective in reducing weight and lipid profile than metformin	**ROB high** Outcomes also reported in Ruan et al. 2018
Ruan et al. 2018 China	Women, aged 18-40 yrs, BMI>=24 with PCOS	RCT	1.OD=60 2.MD=60 3.OMD=60 4.D=60	1.Orlistat 120mgx3/d+35ugEE and 2mgCPA 2.Metformin500mgx3/d+35ugEE and 2mgCPA 3. Orlistat 120mgx3/d+Metformin 500mgx3/d+35ug EE and 2mg CPA 4. 35ugEE and 2mg CPA	Rott	3 months	1.27.9 ±4.1 2.27.0 ±3.5 3.28.8 ±3.4 4.28.6 ±4.9	1.26.8 ±4.1 2.28.6 ±5.1 3.27.6 ±4.6 4.27.7 ±5.0	DHEAS, A, SHBG, FAI, free-T	Diane-35 in combination with orlistat or metformin is more efective in reducing androgen than Diane-35 alone. Orlistat is more efective in reducing body fat percentage than metformin. In addition, orlistat has mild side-efects and is better tolerated compared with metformin.	.**ROB high** Outcomes also reported in song et al. 2018

7. Study characteristics Table - Metformin versus **Metformin** (different dose)

Author, year, country	Population	Study Design	Sample Size per group	Intervention/ exposure details	PCOS criteria	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Summary of findings	Other
Harborne et al. 2005 UK	Obese women with PCOS	RCT	1.42 2.41	1.Metformin 500mgx3=1500mg/d 2.Metformin 850mgx3=2550mg/d	Author defined	8 months	All participants : 37.2 (35.9, 38.5)	NR	weight	Weight loss is a feature of protracted metformin therapy in obese women with PCOS, with greater weight reduction potentially achievable with higher doses.	**ROB high**

7. Study Characteristics Table- ***Met+OCP versus OCP – Adults and adolescents***

Author, year, country	Population	Study Design	Sample Size per group	Intervention/ exposure details	PCOS criteria	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Summary of findings	Other
Fonseka et al. 2020 Sri Lanka	Females with PCOS aged 18-40yr	Double-blind RCT	1.20 2.23 3.26 4.30	1.OCP= *EE35ug+Cyproterone acetate 2mg* *2. OCP EE20ug+desogestrel 0,15mg* *3. Metformin 500mgx1 +OCP EE35ug+Cyproterone acetate 2mg* *4. Metformin 500mgx1+OCP EE20ug+desogestrel 0,15mg*	Rotterdam	12 months	1.28.3 ±6.9 2.26.7 ±4.9 3.27.9±4.9 4.27.2 ±4.3	1.23.4 ±5.1 2.22.4 ±6.5 3.24.8±6.2 4.27.9 ±6.9	mFGS	EE/CPA and EE/DES were equally effective in improving hirsutism in PCOS, with no added benefit from low-dose metformin.	**ROB low**

7. Study Characteristics Table- ***Metformin versus Metformin+lifestyle– Adults and adolescents***

Author, year, country	Population	Study Design	Sample Size per group	Intervention/ exposure details	PCOS criteria	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Summary of findings	Other
Elbandrawy et al. 2022 Egypt	Females aged 25-35 years diagnosed with PCOS	RCT	1.20 2.20	1.metformin 1500mg/day 2.metformin 1500mg/day+aerobic excerise	Rotterdam	3 months	1.28.6 ±2.2 2.28.6 ±1.4	1.30.7 ±3.0 2.29.4 ±3.5	CRP	The findings showed a significant reduction in IL-6, TNF-α, and CRP values in both AEM and M groups. The AEM-group showed a greater reduction in IL-6, TNF-α, and CRP.	**ROB moderate**

7. Study Characteristics Table- lifestyle+metformin versus lifestyle+placebo – ***Adults and adolescents***

Author, year, country	Population	Study Design	Sample Size per group of those analyzed	Intervention/ exposure details	PCOS criteria	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Summary of findings	Other
Tiwari et al 2018 India	Females diagnosed as PCOS	RCT	*1.Lifestyle+metformin 33* *2.Lifestyle+placebo 33*	*1.* lifestyle+ Metformin 1700mg/d *2.Lifestyle+placebo*	Rott	6 months	1.25.2 ±4.6 2.26.3 ±3.7	1.24.3 ±3.9 2.24.5 ±4.8	Androgenic parameters (mFGS, T), antropometric parameters (BMI, WHR), biochemical parameters (OGTT, triglycerides, s-cholesterol), clinical parameters (oligomenorrhea)	The mean difference in mFGS at 0, 3 and 6months were statistically significant in both groups. On comparing groupA (lifestyle+placebo) with groupB (lifestyle+met) at 6months, significant improvement was found in menstrual cycle symptoms (55.17% vs 83.33%), mean weight loss (1.08 kg vs 2.5 kg), waist circumference reduction (2.56 cm vs 4.75 cm) and change in mean waist hip ratio (0.02vs0.04). Significant changes were noted in OGTT and Serum testosterone level at 6months in GroupB (lifestyle+met), but not in Group A (lifestyle+placebo)	**ROB low**
Tang et al. 2006	obese (BMI >30), oligo-	RCT	*1.Lifestyle+metformin 69*	*1. Metformin 850mgx2/d*	Rott	6 months	1.37.6 ±5.0 2.38.9 ±9.5	1.29.7 ±3.7 2.29.8 ±3.8	BMI, weight, WHR, T, SHBG,	Metformin does not improve weight loss or menstrual frequency in obese	**ROB low**

UK	/amenorrhoeic women with PCOS		*2.Lifestyle+placebo 74*	*2.Placebo-tablx2/d*					FAI, f-gluc, f-insulin, lipids, menses/6months	patients with PCOS. Weight loss alone through lifestyle changes improves menstrual frequency	
Ladson et al 2011 USA	Women with PCOS, aged 21-39 yrs	RCT Double blind	1.Lifestyle+metformin 22 2.Lifestyle+placebo 16	1.Metformin 500mgx4/d + LS 2.placebo+LS	NIH	6 months	1.38.0 ±7.8 2.38.3 ±8.0	1.29 ±4.5 2.28.8 ±4.6	FGS, T, sHBG, FAI, lipids, f-gluc, f-insulin, QoL	The addition of metformin to lifestyle therapy produced little reproductive or glycemic benefit in women with PCOS, although our study had limited power owing to a high dropout rate	**ROB moderate**
Ladson et al 2011 USA	Women with PCOS, adolescents	RCT Double blind	1.Lifestyle+metformin 11 2.Lifestyle+placebo 11	1.Metformin 500mgx4/d + LS 2.placebo+LS	NIH	6 months	1: 37.1±5.8 2: 35.9±6.6	1: 16.1±1.5 2: 15.4±1.2	BMI	The addition of metformin to lifestyle therapy produced little reproductive or glycemic benefit in women with PCOS, although our study had limited power owing to a high dropout rate	**ROB low**
Fux Otta et al. 2010 Argentina	PCOS women, 20–34 years old	RCT Double blind	*1.Lifestyle+metformin=14* *2.Lifestyle+placebo=15*	*1.Metformin 750mgx2/d* *2.Placebox2/d*	NIH	4 months	1.32.4 ±6.7 2.35.6 ±5.0	1.25.5 ±4.8 2.24.7 ±3.5	BMI, WHR, lipids, f-gluc, OGTT, f-insulin, HOMA, T, DHEAS, A	metformin has an additive effect to diet and exercise to improve parameters of hyperandrogenism and insulin resistance	**ROB Moderate**
Paquali et al. 2000 italiy	Obese PCOS women with a BMI>28	RCT	*1.Lifestyle+metformin=10* *2.Lifestyle+placebo=8*	*1. Metformin 850mgx2/d*	Rott	7 months	1: 39.8±7.9 2: 39.6±6.9	1: 30.8±7.4 2: 32.3±5.0		Metformin had a greater reduction of body weight and abdominal fat, particularly the visceral depots, and a more consistent decrease of serum insulin, testosterone, and leptin concentrations.	**ROB Moderate**

7. Study Characteristics Table- **Metformin+hair removal** versus **OCP+hair removal** versus **hair removal** – ***Adults and adolescents***

Author, year, country	Population	Study Design	Sample Size per group	Intervention/ exposure details	PCOS criteria	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Summary of findings	Other
Dorgham et al. 2021 Egypt	PCOS women, aged 18 to 40 yr with facial hirsutism	RCT	1.Met+HR=50 2.OCP+HR=50 3.HR=50	1.Metformin 500mgx1 2. EE 35 µg , cyproterone acetate 2mg	Rott	6 months	NR	NR	HLQI	OCP with laser hair removal can achieve greater hair reduction, significant improvements in patients' QOL, and	**ROB high**

										better maintenance compared to metformin+ laser hair removal or conducting alone	

7. Study Characteristics Table- Metformin+myo-inositol versus **myoinositol** – ***Adults and adolescents***

Author, year, country	Population	Study Design	Sample Size per group	Intervention/ exposure details	PCOS criteria	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Summary of findings	Other
Prabhakar et al. 2021 India	PCOS women with infertility	RCT	1.Metformin+myoinositol=50 2.myoinositol=55	1. Metformin 500mgx3/d+myoinositol 4g/d 2.Myoinositol 2gx2/d	Rott	3 months	1.25.4 ±2.47 2.25.4 ±2.46	1.28.3 ±3.4 2.27.9 ±3.1	BMI, WHR, T, HOMA, lipids Reports mean difference and 95% CI	After 3 months of therapy, both study groups had comparable improvement in metabolic and hormonal parameters.	**ROB moderate**

7. Study Characteristics Table- Metformin+liraglutide versus **liraglutide** – ***Adults and adolescents***

Author, year, country	Population	Study Design	Sample Size per group	Intervention/ exposure details	PCOS criteria	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Summary of findings	Other
Jensterle et al. 2017 Slovenia	Obese (bmi >30) PCOS women	RCT	1.Metformin+liraglutide=14 2.Liraglutide=14	1. Metformin 1000mgx2/d+liraglutide 1.2mg/d (s.c.) 2.Liraglutide 3mg/d (s.c.)	Rott	3 months	1.37.5 ±5.3 2.39.2 ±5.5	1.31.6±5.9 2.34.6±6.1	BMI, weight, T, free T, shbg, ogtt, homa, lipids	Short-term interventions with COMBO and LIRA3 both led to significant improvement of measures of	**ROB high**

										obesity in obese PCOS, LIRA3 being superior to COMBO. However, COMBO further improved androgen profile beyond weight reduction and was associated with better tolerability.	

7. Study Characteristics Table- Metformin versus **anti-diabetic versus OCP** – ***Adults and adolescents***

Author, year, country	Population	Study Design	Sample Size per group	Intervention/ exposure details	PCOS criteria	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Summary of findings	Other
Cetinkalp et al 2009 Turkey	young women with PCOS	RCT	1.Metformin=47 2.Rosi=14 3.OCP=33	1.Metformin 2000mg/d 2.Rosiiglitazone 4mg/d 3.35ug EE+ 2mg CPA	Rott	4 months	1.25.82 ±6.1 2.22.96 ±4.8 3.24.72±4.1	NR	f-gluc, f-insulin, DHEAS, free-T, T, weight, bmi, hs-crp, HOMA, lipids	OCP is more effective than rosiglitazone and metformin in improving menstrual pattern and reducing free-t MET is more effective in reducing fasting insulin levels than OCP	**ROB high** Note, also OCP
Cai et al 2022 China	Women aged 18 to 45 years with PCOS and IR	RCT	1.Metformin=29 2.Canagliflozin=30	1.Metformin 1500/2000mg/d 2.Canagliflozin 100mg/d	Rott	3 months	1.27.95 (26.22 to 29.69) 2.27.26 (25.55 to 28.99) Mean (95% CI)	1.27.83 (25.97 to 29.68) 2.28.58 (26.72 to 30.43) Mean (95% CI)	Weight, bmi, whr, menstrual cycles, homa, f-gluc, f-insulin, lipids, T, A, DHEAS, SHBG Mean (95% CI)	Canagliflozin was not inferior to metformin in PCOS patients with IR, which suggests that sodium-glucose cotransporter-2 inhibitors should be considered as	**ROB Moderate**

										effective drugs in the treatment of PCOS patients with IR.	
Elkind-Hirsch et al 2016 USA	Patients with PCOS (aged 18–42 years) and prediabetic hyperglycemia	RCT	1.Metformin=12 2.Saxagliptin=11 3.Metformin+Saxagliptin=11	1.Metformin 2000mg/d 2.Saxagliptin 5mg/d 3. Metformin 2000mg/d+Saxagliptin 5mg/d	NIH	4 months	1.42.1 ±7.3 2.37.2 ±6.8 3.43.8±10.5	1.29.9±7 2.28.6 ±6.6 3.29.6±8	f-gluc, HOMA-IR, lipids, WHR, BMI, menstrual interval, T, A, SHBG, DHEAS, FAI	Treatment with SAXA-MET was superior to either drug alone in terms of clinical and metabolic benefits in prediabetic patients with PCOS.	**ROB low**
Javed et al. 2019 UK	women with PCOS	RCT	1.Metformin=20 2.Empagliflozin=19	1.Metformin 1500mg/d 2.Empagliflozin 25mg/d	Rott	3 months	1.38.7 ±7.8 2.37.1 ±6.8	1.31.5±20 2.26.0 ±8.0	Weight, bmi, FAI, T, SHBG, A, DHEAS, f-gluc, f-insulin, homa, lipids, crp	A significant improvement in anthropometric parameters and body composition, in overweight and obese women with PCOS after 12 weeks of treatment with empagliflozin compared to metformin, although no changes were seen in hormonal or metabolic parameters.	**ROB moderate**
Li et al. 2020 China	Obese Chinese women (BMI>=25) with PCOS and insulin resistance	RCT	1.Metformin+LS=68 2.Rosiglitazone+LS=67 3.Metformin+Rosiglitazone+LS=69	1.metformin 1500mg/d 2.Rosiglitazone 4mg/d 3.Metformin 1000mg/d +Rosiglitazone 4mg/d	Rott	6 months	1.27.7 ±2.05 2.27.6 ±2.41 3.27.3±2.17	1.25.8±4.5 2.26.04 ±4.5 3.25.96±4.0	Menstrual cycle, weight, bmi, whr, mFGS, T, f-gluk, f-insulin, homa, lipids	metformin along with lifestyle modification should be recommended for obese, insulin-resistant women with PCOS. Rosiglitazone alone or combined with metformin plus lifestyle modification should be considered for the women with	**ROB Low**

										abnormal lipid profiles	
Sangeeta et al. 2012 India	Women of age 18–30 years with PCOS	RCT double blinded	1.Metformin=43 2.Pioglitazone=42	1.Metformin 500mgx2/d 2.Pioglitazone 15mgx1/d	Rott	6 months	NR	NR	Hirsutism, lipids, f-insulin, homa, T, shbg, FAI	pioglitazone may be a better treatment option as far as protection from tendency to development of diabetes is conscerned. The rise in serum SHBG levels and decline in free androgen index and L/H ratio are more remarkable with pioglitazone	**ROB high**
Mohiyiddeen et al 2013 UK	Women with PCOS	RCT	1.Metformin=17 2.Rosiglitazone=18	1.Metformin 500mgx2/d 2.Rosiglitazone 4mgx1/d	Rott	3 months	1.29.1 ±1.0 2.29.7 ±1.0	1.30.0±0.9 2.29.0 ±1.0	Weight, bmi, f-insulin, f-gluc, crp, lipids, t, shbg, fai,	rosiglitazone and metformin, has comparable benefi cial impacts on metabolic, hormonal and morphological features of PCOS but no obvious eff ect on vascular parameters in a population of predominantly mild PCOS	**ROB Moderate**
Naka et al 2011 Greece	Young women with PCOS (mean age 23.3 years)	RCT	1.Metformin=15 2.Placebo=14 3.Pioglitazone=14	1.Metformin 850mgx2/d 2.Placebo 3.Pioglitazone 30mg/d	Rott	6 months	1.29.4 ±6.5 2.28.3 ±4.9 3.28.5±5.4	1.22.2±3.6 2.24.3 ±6.0 3.23.6±5.1	Weight, bmi, WHR, f-gluc, f-insulin, lipids, hirsutism, T, SHBG, FAI	treatment with metformin or pioglitazone for 6 months induces a similar beneficial effect on endothelial function; this may be partially attributed to an improvement in insulin resistance	**ROB Moderate** Note, also placebo
Ortega-Gonzales et al. 2005	Women with PCOS, aged 18–35 yr, whose	RCT	1.Metformin=18 2.Pioglitazone=17	1.Metformin 850mgx3/d 2.Pioglitazone 30mg/d	Rott	6 months	1.34.1 ±1.6 2.32.2 ±1.0	1.29.0±0.8 2.28.8 ±0.9	Weight, bmi, WHR, hirsutism, f-gluc, f-insulin,	pioglitazone is as effective as metformin in	**ROB high**

Mexico	chief complaints were hirsutism								HOMA, lipids, dheas, free-T, A Means and SEM reported	improving insulin sensitivity and hyperandrogenism, despite an increase in body weight, bmi and the WHR associated with pioglitazone	
Shahebrahimi et al 2016 Iran	Women with PCOS, aged 20–49 years	RCT	1.Metformin=28 2.Pioglitazone=28	1.Metformin 500mgx3/d 2.Pioglitazone 30mg/d	Rott	3 months	1.27.71 ±4.36 2.28.28±4.49	1.27.5±3.68 2.27.6 ±5.91	Weight, bmi, f-gluc, lipids, T, f-insulin, dheas	Although we were not able to recommend one treatment regime over the other, pioglitazone offers a useful, alternate treatment in women with PCOS who are not able to tolerate metformin.	**ROB high**
Sohrevardi et al. 2016 Iran	women with PCOS, aged 18-40 years, with irregular menses and infertility	RCT	1.Metformin=22 2.Pioglitazone=21 3. Metformin+Pioglitazone=23	1.Metformin 500mgx3/d 2.Pioglitazone 30mg/d 3. Metformin 500mgx3/d+Pioglitazone 30mg/d	Rott	3 months	1.27.5 ±3.6 2.27.2±4.7 3.28.5 ±3.2	1.28.72±6.3 2.27.52 ±5.0 3.30.73 ±6.2	Weight, bmi, WHR, f-gluc, f-insulin, homa, lipids, dheas, T	only metformin ameliorated hyperandrogenemia in women with PCOS. Treatment with combination of metformin and pioglitazone did not show more benefit than monotherapy with each drug alone.	**ROB high**
Kilicdag et al. 2005 Turkey	women with PCOS	RCT	1.Metformin=15 2.Rosiglitazone=15	1.Metformin 850mgx2/d 2.Rosiglitazone 4mgx1/d	NIH	3 months	1.26.17 ±1.44 2.29.32±1.58	1.24.13±1.42 2.25.53 ±1.68	Weight, bmi, dheas, T, free-T, homa, lipids	metformin and rosiglitazone therapy result in a significant increase in plasma Hcy concentrations, without significant changes in BMI and IR that could result in increased cardiovascular risk.	**ROB Moderate**

Ahmad et al. 2008 India	PCOS women aged 18-35 years, with complaints of menstrual irregularities, hirsutism, and/or sterility	RCT	1.Metformin=31 2.Rosiglitazone=30	1.Metformin 850mgx2/d 2.Rosiglitazone 2mgx2/d	NIH	3, 6, 12 months	1.27.66 ±5.44 2.26.94±5.24	1.22.81±4.52 2.23.20 ±3.36	BMI, WHR, hirsutism, menstruation, f-gluc, f-insulin, homa, T, dheas, A	rosiglitazone seems to improve insulin resistance relatively earlier; while metformin had an earlier and more sustained benefit on hyperandrogenemia.	**ROB Moderate**
Cho et al. 2009 UK	obese hyperandrogenic, anovulatory Caucasian women with PCOS	RCT	1.Metformin=10 2.Orlistat=10 3.Pioglitazone=10	1.Metformin 500mgx3/d 2.Orlistat 120mgx3/d 3.Pioglitazone 45mg/d	Rott	3 months	1.34.3 ±1.8 2.37.4±2.7 3.36.2±1.8	NR	Homa, insulin, shbg, bmi, fai Means and SEM reported	Only orlistat reduced both IR and its variability significantly, though all three drugs were effective in reducing hyperandrogenism within the 12-week period of the study	**ROB Moderate**
Steiner et al. 2007 Germany	Women with PCOS	RCT	1.Metformin=17 2.Rosiglitazone=18	1.Metformin 850mgx2/d 2.Rosiglitazone 4mg/d	NIH	6 months	1.29.3 ±6.5 2.27.9±3.0	1.22.9 ±4.5 2.25.2±4.8	f-gluc, f-insulin, homa, bmi, periods/month	an increase in insulin sensitivity was observed, especially in the rosiglitazone arm.	**ROB high**
Jensterle et al 2008 (1) Slovenia	Women with PCOS	RCT	1.Metformin=18 2.Rosiglitazone=17	1.Metformin 850mgx2/d 2.Rosiglitazone 4mg/d	NICHD	6 months	1.29.3 ±6.5 2.27.0±3.9	1.22.9 ±4.5 2.25.2±4.8	f-gluc, f-insulin, homa, bmi, dheas, A, T, free T, periods/6months	therapy with insulin sensitizers resulted in marked improvement in adipose tissue GLUT4 mRNA expression in PCOS patients, rosiglitazone being more effective when compared with metformin.	**ROB moderate** Outcomes also reported in Jensterle et al. 2008
Jensterle et al 2008 (2) Slovenia	Women with PCOS	RCT	1.Metformin=15 2.Rosiglitazone=11	1.Metformin 850mgx2/d 2.Rosiglitazone 4mg/d	NICHD	6 months	1.29.6 ±6.9 2.28.8±8.8	1.23.1 ±3.7 2.25.0±4.9	Lipids, crp (rest in Jernsterle (1)	therapy with insulin sensitizers, MET and ROSI, resulted in marked improvement of endothelial function in young PCOS patients without clinically evident	**ROB moderate** Outcomes also reported in Jensterle

										atherosclerosis who were not severely insulin resistant. Neither drug was superior to the other	et al. 2008

7. Study Characteristics Table- Metformin+LS versus **anti-androgen+LS versus met+anti-androgen+LS versus placebo+LS – *Adults and adolescents***

Author, year, country	Population	Study Design	Sample Size per group	Intervention/ exposure details	PCOS criteria	Duration	Mean BMI (kg/m2)	Mean Age (y)	Outcomes	Summary of findings	Other
Amiri et al. 2014 Iran	overweight and obese infertile PCOS women	RCT	1.Metfromin+LS=25 2.SPL+LS=27 3.Metfromin+SPL+LS=27 4.Placebo+LS=26	1.Metfromin 850mgx2/d 2.Flutamid 250mgx2/d 3. Metfromin 850mgx2/d + Flutamid 250mgx2/d 4.Placebo	Rott	6 months	>19 kg/m_2 and <35 kg/m_2.	18-40	BMI, WHR, hirsutism, T, DHEAS, f-insulin, f-gluc, OGTT, lipids	Using combination of metformin and flutamide improves anthropometric indices and laboratory tests in obese/overweight PCOS women under hypocaloric diet	**ROB moderate**
Gambineri et al. 2006 Italy	overweight-obese women with PCOS	RCT	1.Metfromin=20 2.SPL=17 3.Metfromin+SPL=20 4.Placebo=20	1.Metfromin 500mgx3/d 2.Flutamid 250mgx2/d 3. Metfromin 500mgx3/d + Flutamid 250mgx2/d 4.Placebo	Rott	6/12 months	1.35 ±4 2.33 ±4 3.35±5 4.37±5	1.28±8 2.26 ±6 3.26±5 4.26±5	BMI, weight, hirsutism, frequency of menstruation Weight, bmi, T, free-T, A, DHEAS, SHBG, f-gluc, f-insulin, HOMA, lipids	SPL improved more than placebo the menstrual pattern, f-gluc, insulin sensitivity, LDL, whereas metformin decreased f-gluc. The combination of the two drugs maintained the specific effect of each of the compounds, without any additive or synergistic effect.	**ROB Low**
Ganie et al. 2004 India	Women with PCOS (mean age of 22.6 and mean BMI of 26.8)	RCT	1.Metfromin=35 2.SPL=34	1.Metformin 500mgx2/d 2.Spironolactone 25mgx2/d	NIH	6 months	1: 26.5±5.6 2: 25.9±5.0	1: 22.9±5.3 2: 23.3±5.2	BMI, WHR, no cycles/12 months, hirsutism, T, DHEAS, f-	Spironolactone appears better than metformin in the treatment of hirsutism, menstrual cycle	**ROB Moderate**

									insulin, f-gluc, HOMA-IR	frequency, and hormonal derangements and is associated with fewer adverse events.	
Ganie et al. 2013 India	women who met the 2006 Androgen Excess-PCOS criteria for PCOS	RCT	1.Metfromin=56 2.SPL=51 3.Metformin+SPL=62	1.Metformin 500mgx2/d 2.Spironolactone 50mg/d 3. Metformin 500mgx2/d and Spironolactone 50mg/d	Androgen excess	6 months	1: 26.0±4.1 2: 24.3±3.7 3: 24.9±4.9	1: 22.4±5.3 2: 23.6±5.2 3: 23.6±4.7	Weight, BMI, WHR, no cycles/12 months, hirsutism, T, f-insulin, f-gluc, HOMA-IR, adverse effects	The combination of low-dose spironolactone with metformin seems superior to either drug alone in terms of clinical benefits and compliance in women with PCOS.	**ROB Low**
Mazza et al. 2014 Italy	overweight/ obese patients with PCOS.	RCT	1.Metformin+LS=26 2.Metformin+SPL+LS=26	1.Metformin 1700mg/d 2.Metformin 1700mg/d+spironolactone 25mg/d	Rott	6 months	1: 31.1±5 2: 32.8±5.6	1: 23.3±4.2 2: 23.1±3.8	Weight, BMI, hirsutism, shbg, FAI, T, dheas, f-insulin, f-gluc, lipids, homa	In PCOS patients the addition of low-dose spironolactone induces a more marked reduction of clinical and biochemical hyperandrogenism than metformin alone	**ROB Low**

Grade assessments and evidence profile

Comparison 1: Metformin versus placebo

	Comparison: Metformin-Placebo											
	Quality assessment						No of participants					
	No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Met**	**Placebo**	**Effect, random, MD**	**Favours**	**Certainty**	**Importance**
Weight (kg)												
Overall	10	RCT	Serious[1]	No serious	No serious	No serious	335	346	-1.84 (-3.78 to 0.10)	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
BMI>25	3	RCT	Serious[1]	No serious	No serious	Serious[6]	62	56	-0.95 (-7.25 to 5.36)	No difference	⊕⊕◯◯ LOW	IMPORTANT
BMI<25	2	RCT	Serious[1]	No serious	No serious	No serious	68	64	-0.09 (-0.90 to 0.72)	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
BMI NS	5	RCT	No serious	No serious	No serious	No serious	205	226	**-3.53 (-5.27 to -1.79)**	**Metformin**	⊕⊕⊕⊕ HIGH	IMPORTANT
WHR												
Overall	14	RCT	Serious[1]	Very serious[4]	No serious	No serious	369	378	-0.02 (-0.03 to -0.00)	**Metformin**	⊕◯◯◯ VERY LOW	IMPORTANT
BMI>25	7	RCT	Serious[1]	Very serious[4]	No serious	No serious	115	126	-0.02 (-0.05 to 0.01)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI<25	4	RCT	Serious[1]	No serious	No serious	No serious	96	90	-0.01 (-0.02 to 0.01)	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
BMI NS	3	RCT	Serious[1]	No serious	No serious	No serious	158	162	-0.00 (-0.02 to 0.02)	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
BMI												
Overall	21	RCT	Serious[1]	No serious	No serious	No serious	479	497	**-0.53 (-0.95 to -0.12)**	**Metformin**	⊕⊕⊕◯ MODERATE	CRITICAL
BMI>25	13	RCT	Serious[1]	No serious	No serious	No serious	261	275	**-0.89 (-1.43 to -0.35)**	**Metformin**	⊕⊕⊕◯ MODERATE	CRITICAL
BMI<25	4	RCT	Serious[1]	No serious	No serious	No serious	70	69	-0.03 (-0.29 to 0.24)	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
BMI NS	4	RCT	Serious[1]	No serious	No serious	No serious	148	153	-0.87	No difference	⊕⊕⊕◯	CRITICAL

									(-2.30 to 0.96)		MODERATE	
Hirsutism (FG score)												
Overall	10	RCT	Serious[1]	No serious	No serious	Serious[6]	101	102	-0.49 (-1.51 to 0.53)	No difference	⊕⊕◯◯ LOW	IMPORTANT
BMI>25	4	RCT	Serious[1]	No serious	No serious	Very serious[5]	27	31	-1.66 (-5.22 to 1.90)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI<25	4	RCT	Serious[1]	No serious	No serious	Serious[7]	49	47	0.15 (-1.13 to 1.43)	No difference	⊕⊕◯◯ LOW	IMPORTANT
BMI NS	2	RCT	No serious	No serious	No serious	Serious[7]	25	24	-1.43 (-3.48 to 0.62)	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
SHBG (nmol/l)												
Overall	17	RCT	Serious[1]	Serious[3]	No serious	No serious	282	302	-0.00 (-0.28 to 0.27)	No difference	⊕⊕◯◯ LOW	IMPORTANT
BMI>25	8	RCT	Serious[1]	No serious	No serious	No serious	111	140	1.05 (-0.81 to 2.91)	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
BMI<25	5	RCT	No serious	No serious	No serious	No serious	103	94	-0.08 (-0.23 to 0.07)	No difference	⊕⊕⊕⊕ HIGH	IMPORTANT
BMI NS	4	RCT	Serious[1]	Serious[3]	No serious	Serious[6]	68	68	-2.12 (-16.14 to 11.89)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
FAI												
Overall	9	RCT	No serious	Serious[3]	No serious	No serious	136	139	-1.00 (-2.10 to 0.10)	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
BMI>25	4	RCT	No serious	Serious[3]	No serious	Serious[7]	44	58	-0.04 (-3.11 to 3.02)	No difference	⊕⊕◯◯ LOW	CRITICAL
BMI<25	3	RCT	No serious	No serious	No serious	Serious[7]	67	57	**-1.01 (-1.72 to -0.29)**	**Metformin**	⊕⊕⊕◯ MODERATE	CRITICAL
BMI NS	2	RCT	No serious	No serious	No serious	Serious[6]	25	24	**-4.68 (-8.48 to -0.89)**	**Metformin**	⊕⊕⊕◯ MODERATE	CRITICAL
Testosterone (ng/dl)												
Overall	18	RCT	No serious	Very serious[4]	No serious	Serious[6]	306	330	**-13.36 (-24.68 to -2.05)**	**Metformin**	⊕◯◯◯ VERY LOW	IMPORTANT
BMI>25	8	RCT	No serious	No serious	No serious	Serious[6]	111	140	-3.91 (-9.16 to 1.35)	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
BMI<25	5	RCT	No serious	Very serious[4]	No serious	Serious[6]	103	94	-25.11 (-61.89 to 11.67)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI NS	5	RCT	No serious	Very serious[4]	No serious	Serious[6]	92	96	**-12.86 (-25.53 to -0.20)**	**Metformin**	⊕◯◯◯ VERY LOW	IMPORTANT
Fasting insulin uIU/ml)												
Overall	17	RCT	Serious[1]	Very serious[4]	No serious	Serious[6]	274	304	-3.95	No difference	⊕◯◯◯	IMPORTANT

									(-8.42 to 0.52)		VERY LOW	
BMI>25	10	RCT	Serious[1]	Very serious[4]	No serious	Serious[6]	124	155	-3.76 (-11.46 to 3.95)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI<25	2	RCT	Serious[1]	No serious	No serious	Serious[7]	55	50	**-2.00 (-2.02 to -1.98)**	**Metformin**	⊕⊕◯◯ LOW	IMPORTANT
BMI NS	5	RCT	Serious[1]	Very serious[4]	No serious	Serious[6]	95	99	**-4.17 (-8.07 to -0.26)**	**Metformin**	⊕◯◯◯ VERY LOW	IMPORTANT
Fasting glucose (mg/dl)												
Overall	21	RCT	Serious[1]	No serious	No serious	No serious	354	368	**-2.39 (-3.49 to -1.30)**	**Metformin**	⊕⊕⊕◯ MODERATE	IMPORTANT
BMI>25	11	RCT	Serious[1]	No serious	No serious	No serious	152	168	**-2.26 (-4.10 to -0.42)**	**Metformin**	⊕⊕⊕◯ MODERATE	IMPORTANT
BMI<25	4	RCT	Serious[1]	No serious	No serious	No serious	91	87	-0.67 (-3.15 to 1.81)	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
BMI NS	6	RCT	Serious[1]	No serious	No serious	No serious	111	113	**-3.10 (-4.98 to -1.23)**	**Metformin**	⊕⊕⊕◯ MODERATE	IMPORTANT
Total cholesterol (mg/dl)												
Overall	15	RCT	Serious[1]	No serious	No serious	Serious[6]	306	216	**-9.12 (-16.43 to -1.81)**	**Metformin**	⊕⊕◯◯ LOW	IMPORTANT
BMI>25	9	RCT	Serious[1]	No serious	No serious	Serious[6]	212	125	**-15.86 (-26.48 to -5.24)**	**Metformin**	⊕⊕◯◯ LOW	IMPORTANT
BMI<25	3	RCT	Serious[1]	No serious	No serious	Very serious[5]	36	33	-4.21 (-18.04 to 9.63)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI NS	3	RCT	No serious	No serious	No serious	Serious[6]	58	58	-1.42 (-11.73 to 8.89)	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
HDL (mg/dl)												
Overall	15	RCT	Serious[1]	Serious[3]	No serious	Serious[6]	309	300	-0.94 (-4.63 to 2.75)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI>25	8	RCT	Serious[1]	Serious[3]	No serious	Serious[6]	186	176	0.49 (-4.23 to 5.20)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI<25	3	RCT	Serious[1]	Serious[3]	No serious	Very serious[5]	42	39	-3.19 (-12.69 to 6.40)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI NS	4	RCT	No serious	Serious[3]	No serious	Serious[6]	81	85	-1.66 (-8.21 to 4.88)	No difference	⊕⊕◯◯ LOW	IMPORTANT
LDL (mg/dl)												
Overall	15	RCT	Serious[1]	No serious	No serious	Serious[6]	296	283	-5.48 (-11.24 to 0.29)	No difference	⊕⊕◯◯ LOW	IMPORTANT
BMI>25	8	RCT	Serious[1]	No serious	No serious	Serious[6]	186	176	**-13.44 (-23.95 to -2.92)**	**Metformin**	⊕⊕◯◯ LOW	IMPORTANT

BMI<25	3	RCT	Serious[1]	No serious	No serious	Very serious[5]	42	39	-0.49 (-8.72 to 7.74)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI NS	4	RCT	No serious	No serious	No serious	Serious[6]	68	68	-0.58 (-10.06 to 8.90)	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
Triglycerides (mg/dl)												
Overall	16	RCT	Serious[1]	No serious	No serious	Serious[6]	316	316	**-9.72 (-18.05 to -1.40)**	**Metformin**	⊕⊕◯◯ LOW	IMPORTANT
BMI>25	9	RCT	Serious[1]	Serious[3]	No serious	Serious[6]	212	215	-8.98 (-23.63 to 5.67)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI<25	3	RCT	Serious[1]	No serious	No serious	Very serious[5]	36	33	-5.11 (-14.42 to 4.20)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI NS	4	RCT	No serious	No serious	No serious	Serious[6]	68	68	-16.09 (-34.36 to 2.18)	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
CRP (mg/l)												
Overall	2	RCT	Very serious[2]	No serious	No serious	Serious[7]	23	25	**-0.37 (-0.57 to -0.16)**	**Metformin**	⊕◯◯◯ VERY LOW	IMPORTANT
PAI												
Overall	2	RCT	Very serious[2]	No serious	No serious	Serious[7]	23	25	**-4.99 (-6.78 to -3.21)**	**Metformin**	⊕◯◯◯ VERY LOW	IMPORTANT
HOMA-IR												
Overall	8	RCT	Serious[1]	No serious	No serious	No serious	176	182	**-0.50 (-0.91 to -0.10)**	**Metformin**	⊕⊕⊕◯ MODERATE	CRITICAL
BMI>25	3	RCT	No serious	No serious	No serious	No serious	52	62	-0.15 (-0.68 to 0.37)	No difference	⊕⊕⊕⊕ HIGH	CRITICAL
BMI NS	4	RCT	Serious[1]	No serious	No serious	No serious	84	86	**-0.95 (-1.34 to -0.56)**	**Metformin**	⊕⊕⊕◯ MODERATE	CRITICAL
DHEAS (ug/dl)												
Overall	11	RCT	Serious[1]	Serious[3]	No serious	No serious	185	190	-0.12 (-0.32 to 0.08)	No difference	⊕⊕◯◯ LOW	IMPORTANT
BMI<25	5	RCT	Serious[1]	Very serious[4]	No serious	No serious	65	77	-0.18 (-0.63 to 0.28)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI NS	5	RCT	Serious[1]	No serious	No serious	No serious	110	103	-0.06 (-0.25 to 0.14)	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
Androstenedione (nmol/l)												
Overall	5	RCT	No serious	Serious[3]	No serious	No serious	86	88	-2.06 (-4.29 to 0.17)	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
BMI>25	2	RCT	No serious	Serious[3]	No serious	Very serious[5]	25	33	-1.20 (-5.21 to 2.81)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT

BMI NS	2	RCT	No serious	Serious[3]	No serious	Very serious[8]	21	21	-1.14 (-3.62 to 1.34)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT

[1] Downgraded once as the majority of studies are low to moderate ROB but 1-3 high ROB
[2] Downgraded twice as one study is high ROB and one moderate ROB
[3] Downgraded once as I^2 is close to or >50% but CI partly overlapping
[4] Downgraded twice as I^2 very high and CI not overlapping
[5] Downgraded twice as the CI is wide and there are few participants
[6] Downgraded once as the CI is wide
[7] Downgraded once as there are only a few participants
[8] Downgraded twice as there are very few participants

Comparison 2: Metformin+lifestyle versus placebo+lifestyle

Grade assessments and evidence profile

	Comparison: Metformin+LS – Placebo+LS											
	Quality assessment						No of participants					
	No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Met +LS**	**PLB+ LS**	**Effect, random, MD**	**Favours**	**Certainty**	**Importance**
Weight (kg)												
Overall	4	RCT	Serious[1]	No serious	No serious	Serious[4]	119	126	-2.82 (-6.07 to 0.42)	No difference	⊕⊕◯◯ LOW	IMPORTANT
BMI>25	3	RCT	Serious[1]	No serious	No serious	Serious[4]	86	93	-0.81 (-5.47 to 3.85)	No difference	⊕⊕◯◯ LOW	IMPORTANT
WHR												
Overall	4	RCT	Serious[1]	No serious	No serious	No serious	124	133	-0.01 (-0.03 to 0.01)	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
BMI>25	2	RCT	Serious[1]	No serious	No serious	No serious	81	92	0.01 (-0.02 to 0.03)	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
BMI NS	2	RCT	Serious[1]	No serious	No serious	Serious[3]	43	41	**-0.03 (-0.05 to -0.01)**	**Met+LS**	⊕⊕◯◯ LOW	IMPORTANT
BMI (kg/m2)												

Overall	9	RCT	Serious[1]	No serious	No serious	No serious	196	202	-1 (-2.02 to 0.01)	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
BMI>25	4	RCT	Serious[1]	No serious	No serious	No serious	91	101	-0.80 (-2.41 to 0.82)	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
BMI NS	5	RCT	Serious[1]	No serious	No serious	No serious	105	101	-1.14 (-2.44 to 0.16)	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Hirsutism												
Overall	3	RCT	Serious[1]	Serious[2]	No serious	No serious	78	78	1.17 (-1.01 to 3.35)	No difference	⊕⊕◯◯ LOW	IMPORTANT
SHBG												
Overall	3	RCT	Serious[1]	No serious	No serious	No serious	55	54	2.26 (-1.79 to 6.31)	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
Testosterone												
Overall	6	RCT	Serious[1]	No serious	No serious	No serious	159	168	**-0.06 (-0.11 to 0.00)**	**Met+LS**	⊕⊕⊕◯ MODERATE	IMPORTANT
BMI>25	3	RCT	Serious[1]	No serious	No serious	No serious	86	94	-0.05 (-0.15 to 0.04)	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
BMI NS	3	RCT	Serious[1]	No serious	No serious	No serious	73	74	-0.05 (-0.13 to 0.04)	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
Fasting insulin uIU/ml)												
Overall	4	RCT	Serious[1]	Serious[2]	No serious	No serious	69	58	-0.45 (-2.96 to 2.06)	No difference	⊕⊕◯◯ LOW	IMPORTANT
BMI>25	2	RCT	Serious[1]	No serious	No serious	Serious[4]	30	28	-0.94 (-3.72 to 1.84)	No difference	⊕⊕◯◯ LOW	IMPORTANT
BMI NS	2	RCT	Serious[1]	Serious[2]	No serious	Serious[4]	39	30	1.69 (-4.13 to 7.51)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Fasting glucose (mg/dl)												
Overall	3	RCT	Serious[1]	No serious	No serious	Serious[4]	59	61	-1.36 (-6.07 to 3.36)	No difference	⊕⊕◯◯ LOW	IMPORTANT
OGTT												
Overall	2	RCT	Serious[1]	Serious[2]	No serious	Very serious[5]	39	41	3.51 (-20.73 to 27.76)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Total cholesterol												
Overall	3	RCT	Serious[1]	Serious[2]	No serious	Serious[4]	95	107	-4.06 (-22.67 to 14.56)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
HDL (mg/dl)												

Overall	3	RCT	Serious[1]	No serious	No serious	No serious	59	61	-2.92 (-6.40 to 0.56)	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
LDL (mg/dl)												
Overall	3	RCT	Serious[1]	No serious	No serious	Serious[4]	59	61	-3.79 (-12.84 to 5.26)	No difference	⊕⊕◯◯ LOW	IMPORTANT
Triglycerides (mg/dl)												
Overall	4	RCT	Serious[1]	No serious	No serious	Serious[4]	115	127	-5.45 (-28.23 to 17.32)	No difference	⊕⊕◯◯ LOW	IMPORTANT
Androstenedione												
Overall	2	RCT	Serious[1]	No serious	No serious	Very serious[5]	34	35	-5.06 (-69.25 to 59.13)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT

[1] Downgraded once as the studies are at low or moderate risk of bias
[2] Downgraded once as I^2 is close to or >50% but CI partly overlapping
[3] Downgraded once as number of participants is low
[4] Downgraded once as the CI is wide
[5] Downgraded twice as number of participants is low and CI wide

Comparison 3: Metformin versus lifestyle

Grade assessments and evidence profile

	Comparison: Metformin – LS											
	Quality assessment						No of participants					
	No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Met**	**LS**	**Effect, random, MD**	**Favours**	**Certainty**	**Importance**
BMI												

Overall	3	RCT	Serious[1]	No serious	Serious[3]	Very serious[4]	29	29	-0.53 (-3.42 to 2.35)	No difference	⊕◯◯◯ VERY LOW	CRITICAL
SHBG												
Overall	2	RCT	Serious[1]	No serious	Serious[3]	Very serious[6]	12	16	**-11.05 (-20.96 to -1.14)**	**Lifestyle**	⊕◯◯◯ VERY LOW	IMPORTANT
Testosterone												
Overall	3	RCT	Serious[1]	No serious	Serious[3]	Very serious[4]	29	29	**-4.81 (-8.83 to -0.80)**	**Metformin**	⊕◯◯◯ VERY LOW	IMPORTANT
Fasting insulin												
Overall	2	RCT	Serious[1]	No serious	Serious[3]	Very serious[6]	23	21	1.93 (-1.60 to 5.46)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Fasting glucose												
Overall	2	RCT	Serious[1]	No serious	Serious[3]	Very serious[4]	29	29	-4.78 (-9.90 to 0.34)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Total cholesterol												
Overall	2	RCT	Serious[1]	Serious[2]	Serious[3]	Very serious[6]	23	21	5.00 (-27.22 to 37.22)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
HDL												
Overall	2	RCT	Serious[1]	No serious	Serious[3]	Very serious[6]	23	21	0.70 (-7.63 to 9.03)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
LDL												
Overall	2	RCT	Serious[1]	Serious[2]	Serious[3]	Very serious[6]	23	21	0.70 (-7.63 to 9.03)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Triglycerides												
Overall	2	RCT	Serious[1]	Serious[2]	Serious[3]	Very serious[6]	23	21	-4.07 (-71.98 to 63.84)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
CRP												
Overall	2	RCT	Serious[1]	No serious	Serious[3]	Very serious[6]	23	21	-0.58 (-1.73 to 0.58)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT

[1] Downgraded once as studies are high ROB and moderate ROB
[2] Downgraded once as I^2 is close to or >50% but CI partly overlapping
[3] Downgraded once as only obese patients included in the group
[4] Downgraded twice as the CI is wide and there are few studies
[5] Downgraded once as there are only a few participants
[6] Downgraded twice as there are very few participants

Comparison 4: Metformin versus OCP

Grade assessments and evidence profile

	Comparison: Metformin-OCP											
	Quality assessment						No of participants					
	No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Met**	**OCP**	**Effect, random, MD**	**Favours**	**Certainty**	**Importance**
Weight (kg)												
Overall	7	RCT	Serious[1]	Very serious[11]	No serious	Serious[15]	182	171	-1.25 (-12.95 to 10.44)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI>25	2	RCT	No serious	No serious	No serious	Very serious[14]	35	34	3.92 (-7.58 to 15.42)	No difference	⊕⊕◯◯ LOW	IMPORTANT
BMI<25	3	RCT	Serious[2]	No serious	No serious	Very serious[14]	37	42	-1.18 (-6.86 to 4.49)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI NS	2	RCT	Very serious[3]	Very serious[11]	No serious	Serious[15]	110	95	-4.97 (-26.16 to 16.22)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Adults	5	RCT	Serious[4]	No serious	No serious	Serious[15]	133	124	2.63 (-1.20 to 6.46)	No difference	⊕⊕◯◯ LOW	IMPORTANT
Adolesc	2	RCT	Serious[5]	Serious[10]	No serious	Very serious[14]	49	47	-12.62 (-28.29 to 3.05)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
WHR												
Overall	8	RCT	Serious[4]	Very serious[11]	Serious[13]	No serious	115	114	-0.01 (-0.03 to 0.01)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI>25	4	RCT	Serious[2]	Very serious[11]	No serious	No serious	60	61	-0.01 (-0.07 to 0.05)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI<25	3	RCT	Serious[4]	No serious	No serious	Serious[16]	39	43	**-0.01 (-0.02 to -0.00)**	**Metformin**	⊕⊕◯◯ LOW	IMPORTANT
BMI kg/m2												
Overall	20	RCT	Serious[7]	Very serious[11]	No serious	No serious	411	400	-0.71 (-1.52 to 0.11)	No difference	⊕◯◯◯ VERY LOW	CRITICAL
BMI>25	7	RCT	Serious[6]	Very serious[11]	No serious	Serious[15]	110	114	-1.62 (-4.28 to 1.04)	No difference	⊕◯◯◯ VERY LOW	CRITICAL

BMI<25	7	RCT	Serious[7]	Serious[10]	No serious	No serious	142	147	-0.22 (-1.00 to 0.56)	No difference	⊕⊕◯◯ LOW	CRITICAL
BMI NS	6	RCT	Very serious[18]	No serious	No serious	No serious	159	139	-0.75 (-1.78 to 0.29)	No difference	⊕⊕◯◯ LOW	CRITICAL
Adults	17	RCT	Serious[7]	Very serious[11]	No serious	No serious	377	365	-0.64 (-1.50 to 0.22)	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Adolesc	3	RCT	Serious[7]	No serious	No serious	Serious[16]	34	35	-1.95 (-4.51 to 0.62)	No difference	⊕⊕◯◯ LOW	CRITICAL
Hirsutism (FG score)												
Overall	6	RCT	Serious[2]	Very serious[11]	No serious	Serious[15]	120	127	0.72 (-1.40 to 2.85)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI>25	3	RCT	Serious[2]	Serious[10]	No serious	Serious[16]	40	46	-0.93 (-3.65 to 1.78)	No difference	⊕⊕◯◯ LOW	IMPORTANT
BMI<25	2	RCT	Serious[2]	No serious	No serious	Serious[16]	38	37	**1.73 (0.07 to 3.40)**	**OCP**	⊕⊕◯◯ LOW	IMPORTANT
Adults	5	RCT	Serious[2]	Very serious[11]	No serious	Serious[15]	114	117	0.95 (-1.48 to 3.37)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
SHBG (nmol/l)												
Overall	9	RCT	Serious[4]	Very serious[11]	No serious	No serious	179	180	**-116.65 (-172.78 to -60.52)**	**OCP**	⊕⊕◯◯ LOW[19]	IMPORTANT
BMI>25	4	RCT	Serious[2]	No serious	No serious	No serious	59	65	**-95.79 (-118.93 to -72.66)**	**OCP**	⊕⊕⊕⊕ HIGH[19]	IMPORTANT
BMI<25	4	RCT	Serious[4]	Serious[10]	No serious	No serious	78	71	**-163.99 (-206.59 to -121.39)**	**OCP**	⊕⊕⊕◯ MODERATE[19]	IMPORTANT
Adults	8	RCT	Serious[4]	Very serious[11]	No serious	No serious	173	170	**-122.12 (-183.61 to -60.64)**	**OCP**	⊕⊕◯◯ LOW[19]	IMPORTANT
FAI												
Overall	8	RCT	Serious[4]	Very serious[11]	No serious	No serious	142	152	**7.10 (4.92 to 9.29)**	**OCP**	⊕⊕◯◯ LOW[19]	CRITICAL
BMI>25	4	RCT	Serious[2]	No serious	No serious	No serious	59	65	**8.93 (7.80 to 10.06)**	**OCP**	⊕⊕⊕⊕ HIGH[19]	CRITICAL
BMI<25	4	RCT	Serious[4]	Very serious[11]	No serious	No serious	83	87	**5.68 (3.05 to 8.30)**	**OCP**	⊕⊕◯◯ LOW[19]	CRITICAL
Adults	7	RCT	Serious[8]	Very serious[11]	No serious	No serious	136	142	**7.00 (4.71 to 9.30)**	**OCP**	⊕⊕◯◯ LOW[19]	CRITICAL
Testosterone (nmol/l)												

Overall	20	RCT	Serious[7]	Serious[10]	No serious	No serious	326	324	**0.49 (0.31 to 0.67)**	**OCP**	⊕⊕◯◯ LOW	IMPORTANT
BMI>25	6	RCT	Serious[7]	No serious	No serious	No serious	86	89	**0.30 (0.02 to 0.59)**	**OCP**	⊕⊕⊕◯ MODERATE	IMPORTANT
BMI<25	8	RCT	Serious[7]	Serious[10]	No serious	No serious	151	162	**0.63 (0.38 to 0.89)**	**OCP**	⊕⊕◯◯ LOW	IMPORTANT
BMI NS	6	RCT	Serious[7]	Very serious[11]	No serious	No serious	89	73	0.34 (-0.06 to 0.74)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Adults	16	RCT	Serious[7]	Serious[10]	No serious	No serious	350	343	**0.55 (0.37 to 0.73)**	**OCP**	⊕⊕◯◯ LOW	IMPORTANT
Adolesc	4	RCT	Serious[7]	No serious	No serious	No serious	67	67	0.27 (-0.16 to 0.71)	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
Free testosterone (pmol/l)												
Overall	5	RCT	Very serious[3]	Serious[10]	No serious	Serious[15]	107	91	**3.20 (1.50 to 4.90)**	**OCP**	⊕◯◯◯ VERY LOW	IMPORTANT
BMI NS	3	RCT	Very serious[3]	No serious	No serious	Serious[15]	71	55	**2.26 (0.50 to 4.01)**	**OCP**	⊕◯◯◯ VERY LOW	IMPORTANT
Adults	3	RCT	Very serious[3]	Serious[10]	No serious	No serious	79	66	**3.38 (1.16 to 5.59)**	**OCP**	⊕◯◯◯ VERY LOW	IMPORTANT
Adolesc	2	RCT	Serious[9]	No serious	No serious	Very serious[14]	28	25	3.86 (-2.59 to 10.31)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Fasting insulin mIU/l)												
Overall	15	RCT	Serious[7]	Serious[10]	No serious	No serious	292	282	**-4.31 (-5.90 to -2.72)**	**Metformin**	⊕⊕◯◯ LOW	IMPORTANT
BMI>25	6	RCT	Serious[2]	No serious	No serious	Serious[15]	82	87	**-4.60 (-7.08 to -2.12)**	**Metformin**	⊕⊕◯◯ LOW	IMPORTANT
BMI<25	4	RCT	Serious[4]	No serious	No serious	No serious	64	64	**-3.25 (-4.72 to -1.77)**	**Metformin**	⊕⊕⊕◯ MODERATE	IMPORTANT
BMI NS	5	RCT	Serious[4]	Very serious[11]	No serious	Serious[15]	146	131	**-4.77 (-8.16 to -1.39)**	**Metformin**	⊕◯◯◯ VERY LOW	IMPORTANT
Adults	11	RCT	Serious[4]	No serious	No serious	No serious	225	215	**-3.98 (-4.93 to -3.03)**	**Metformin**	⊕⊕⊕◯ MODERATE	IMPORTANT
Adolesc	4	RCT	Serious[7]	Serious[10]	No serious	Serious[15]	67	67	-4.19 (-11.28 to 2.90)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Fasting glucose (mg/dl)												
Overall	10	RCT	Serious[5]	Serious[10]	No serious	No serious	218	211	-1.46 (-4.07 to 1.15)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI>25	4	RCT	Serious[2]	No serious	No serious	No serious	59	65	2.89 (-2.68 to 8.46)	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT

BMI<25	3	RCT	Serious[4]	Serious[10]	No serious	No serious	53	52	-2.81 (-7.92 to 2.31)	No difference	⊕⊕◯◯ LOW	IMPORTANT
BMI NS	3	RCT	Serious[4]	No serious	No serious	No serious	106	94	**-2.45 (-4.63 to -0.27)**	**Metformin**	⊕⊕⊕◯ MODERATE	IMPORTANT
Adults	9	RCT	Serious[4]	Serious[10]	No serious	No serious	212	201	-1.58 (-4.30 to 1.15)	No difference	⊕⊕◯◯ LOW	IMPORTANT
Total cholesterol (mmol/l)												
Overall	13	RCT	Serious[5]	Very serious[11]	No serious	No serious	282	276	**-0.40 (-0.66 to -0.14)**	**Metformin**	⊕◯◯◯ VERY LOW	IMPORTANT
BMI>25	4	RCT	Serious[2]	Very serious[11]	No serious	No serious	67	70	-0.45 (-1.16 to 0.26)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI<25	4	RCT	Serious[4]	Very serious[11]	No serious	No serious	82	88	**-0.56 (-1.05 to -0.06)**	**Metformin**	⊕◯◯◯ VERY LOW	IMPORTANT
BMI NS	5	RCT	Serious[4]	No serious	No serious	No serious	133	118	-0.17 (-0.35 to 0.01)	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
Adults	11	RCT	Serious[4]	Very serious[11]	No serious	No serious	260	251	**-0.31 (-0.57 to -0.05)**	**Metformin**	⊕◯◯◯ VERY LOW	IMPORTANT
Adolesc	2	RCT	Serious[4]	No serious	No serious	Serious[16]	22	25	**-1.19 (-1.80 to -0.58)**	**Metformin**	⊕⊕◯◯ LOW	IMPORTANT
HDL (mmol/l)												
Overall	13	RCT	Serious[5]	Very serious[11]	No serious	No serious	282	276	-0.05 (-0.18 to 0.07)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI>25	4	RCT	Serious[2]	No serious	No serious	No serious	67	70	**-0.23 (-0.37 to -0.10)**	**Metformin**	⊕⊕⊕◯ MODERATE	IMPORTANT
BMI<25	4	RCT	Serious[4]	Very serious[11]	No serious	No serious	82	88	0.05 (-0.27 to 0.37)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI NS	5	RCT	Serious[4]	No serious	No serious	No serious	133	118	-0.01 (-0.10 to 0.08)	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
Adults	11	RCT	Serious[4]	Very serious[11]	No serious	No serious	260	251	-0.03 (-0.17 to 0.11)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Adolesc	2	RCT	Serious[4]	No serious	No serious	Serious[16]	22	25	-0.22 (-0.43 to -0.00)	No difference	⊕⊕◯◯ LOW	IMPORTANT
LDL (mmol/l)												
Overall	13	RCT	Serious[5]	Very serious[11]	No serious	No serious	283	276	-0.15 (-0.39 to 0.09)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI>25	4	RCT	Serious[2]	Serious[10]	No serious	No serious	67	70	-0.21 (-0.95 to 0.53)	No difference	⊕⊕◯◯ LOW	IMPORTANT
BMI<25	4	RCT	Serious[4]	Serious[10]	No serious	No serious	83	88	-0.19 (-0.52 to 0.14)	No difference	⊕⊕◯◯ LOW	IMPORTANT

BMI NS	5	RCT	Serious[4]	Serious[10]	No serious	No serious	133	118	0.03 (-0.26 to 0.31)	No difference	⊕⊕◯◯ LOW	IMPORTANT
Adults	11	RCT	Serious[4]	Very serious[11]	No serious	No serious	261	251	-0.02 (-0.25 to 0.21)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Adolesc	2	RCT	Serious[4]	No serious	No serious	Serious[16]	22	25	**-0.86 (-1.11 to -0.62)**	**Metformin**	⊕⊕◯◯ LOW	IMPORTANT
Triglycerides (mmol/l)												
Overall	13	RCT	Serious[5]	Very serious[11]	No serious	No serious	287	272	**-0.16 (-0.31 to -0.01)**	**Metformin**	⊕◯◯◯ VERY LOW	IMPORTANT
BMI>25	4	RCT	Serious[2]	No serious	No serious	No serious	67	70	**-0.20 (-0.41 to -0.00)**	**Metformin**	⊕⊕◯◯ LOW	IMPORTANT
BMI<25	3	RCT	Serious[4]	Serious[10]	No serious	No serious	75	74	**-0.36 (-0.73 to 0.00)**	**Metformin**	⊕⊕◯◯ LOW	IMPORTANT
BMI NS	6	RCT	Serious[4]	Serious[10]	No serious	No serious	145	128	0.00 (-0.12 to 0.12)	No difference	⊕⊕◯◯ LOW	IMPORTANT
Adults	10	RCT	Serious[4]	Very serious[11]	No serious	No serious	253	237	**-0.18 (-0.35 to -0.00)**	**Metformin**	⊕◯◯◯ VERY LOW	IMPORTANT
Adolesc	3	RCT	Serious[7]	No serious	No serious	Serious[16]	34	35	-0.13 (-0.39 to 0.14)	No difference	⊕⊕◯◯ LOW	IMPORTANT
CRP (mg/l)												
Overall	9	RCT	Serious[4]	Serious[10]	No serious	No serious	200	203	**-1.45 (-2.30 to -0.60)**	**Metformin**	⊕⊕◯◯ LOW	IMPORTANT
BMI>25	3	RCT	Serious[2]	No serious	No serious	Serious[16]	33	48	**-4.87 (-6.53 to -3.21)**	**Metformin**	⊕⊕◯◯ LOW	IMPORTANT
BMI<25	2	RCT	Serious[2]	No serious	No serious	No serious	73	75	**-0.82 (-1.46 to -0.19)**	**Metformin**	⊕⊕⊕◯ MODERATE	IMPORTANT
BMI NS	4	RCT	Serious[4]	No serious	No serious	No serious	94	80	**-0.64 (-0.77 to -0.50)**	**Metformin**	⊕⊕◯◯ LOW	IMPORTANT
Adults	8	RCT	Serious[4]	Serious[10]	No serious	No serious	194	193	**-1.26 (-2.04 to -0.47)**	**Metformin**	⊕⊕⊕◯ MODERATE	IMPORTANT
PAI-1												
Overall	2	RCT	Serious[4]	Serious[10]	Serious[13]	Very serious[14]	23	27	-1.05 (-24.65 to 22.54)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
HOMA-IR												
Overall	11	RCT	Serious[5]	Very serious[11]	Serious[13]	No serious	284	271	**-0.59 (-1.14 to -0.04)**	**Metformin**	⊕◯◯◯ VERY LOW	CRITICAL
BMI>25	2	RCT	No serious	No serious	No serious	Serious[16]	43	44	-0.20 (-1.02 to 0.62)	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
BMI<25	5	RCT	Serious[5]	No serious	No serious	No serious	123	126	**-0.44 (-0.80 to -0.09)**	**Metformin**	⊕⊕⊕◯ MODERATE	CRITICAL

BMI NS	4	RCT	Serious[4]	Very serious[11]	Serious[12]	No serious	118	101	-0.77 (-2.04 to 0.51)	No difference	⊕⊕◯◯ LOW	CRITICAL
DHEAS (ug/dl)												
Overall	9	RCT	Serious[4]	Very serious[11]	Serious[13]	No serious	212	202	**28.03 (1.09 to 54.97)**	**OCP**	⊕◯◯◯ VERY LOW	IMPORTANT
BMI<25	4	RCT	Serious[4]	Very serious[11]	No serious	Serious[15]	73	73	51.77 (-22.52 to 126.06)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI NS	4	RCT	Serious[4]	Very serious[11]	Serious[12]	Serious[15]	131	119	8.76 (-19.00 to 36.52)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Androstenedione (nmol/l)												
Overall	4	RCT	Serious[4]	No serious	Serious[13]	No serious	51	55	**3.42 (2.75 to 4.09)**	**OCP**	⊕⊕◯◯ LOW	IMPORTANT
BMI<25	3	RCT	Serious[4]	No serious	No serious	Serious[16]	43	45	**3.35 (2.67 to 4.03)**	**OCP**	⊕⊕◯◯ LOW	IMPORTANT
Cycle duration												
Overall	3	RCT	Serious[4]	Not estimable	No serious	Serious[16]	58	63	**6.10 (2.40 to 9.80)**	**OCP**	⊕⊕⊕◯ MODERATE[19]	CTITICAL
Girls with restored menses												
Overall	2	RCT	Serious[2]	No serious	Serious[13]	Serious[16]	16	19	**0.08 (0.01 to 0.75)**	**OCP**	⊕◯◯◯ VERY LOW	CRITICAL

[1] Downgraded once as studies high to low risk of bias (3/7 high ROB)
[2] Downgraded once as all studies moderate ROB
[3] Downgraded twice as all studies high ROB
[4] Downgraded once as all studies high or moderate ROB
[5] Downgraded once as studies low, moderate and high ROB
[6] Downgraded once as 4 studies moderate, 2 low, 1 high ROB (weight 2,5%)
[7] Downgraded once as studies high to low risk of bias
[8] Downgraded once as 6 studies moderate, 1 high ROB (weight 16.4%)
[9] Downgraded once as one study high and one low ROB
[10] Downgraded once as I^2 is close to or >50% but CI partly overlapping
[11] Downgraded twice as I^2 very high and CI not overlapping
[12] Downgraded once as no information on what BMI the patients in the studies had
[13] Downgraded once as no adolescents in the overall group
[14] Downgraded twice as the CI is wide and there are few studies
[15] Downgraded once as the CI is wide

[16] Downgraded once as there are only a few participants
[17] Not downgraded since there is only one study with a large CI containing only a small amount of the participants
[18] Downgraded twice as all studies but one is high ROB
[19] Upgraded once due to large effect

Comparison 5: Metformin versus metformin+OCP (also in Q4.2 – not identical)

Grade assessments and evidence profile

	Comparison: Metformin-Metformin+OCP											
	Quality assessment						No of participants					
	No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Met**	**Met+ OCP**	**Effect, random, MD**	**Favours**	**Certainty**	**Importance**
Weight (kg)												
Overall	4	RCT	Serious[1]	Serious[2]	No serious	No serious	60	57	-1.31 (-2.65 to 0.03)	No difference	⊕⊕◯◯ LOW	IMPORTANT
BMI<25	2	RCT	Serious[1]	Serious[2]	No serious	No serious	41	39	-1.38 (-3.85 to 1.09)	No difference	⊕⊕◯◯ LOW	IMPORTANT
WHR												
Overall	2	RCT	Serious[1]	No serious	No serious	Very serious[9]	18	16	-0.03 (-0.06 to -0.01)	**Metformin**	⊕◯◯◯ VERY LOW	IMPORTANT
BMI (kg/m2)												
Overall	2	RCT	Serious[1]	Serious[2]	No serious	Very serious[9]	18	16	-1.31 (-3.07 to 0.46)	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Testosterone (ng/dl)												
Overall	4	RCT	Serious[1]	Serious[2]	No serious	No serious	73	71	0.64 (0.26 to 1.02)	**Metformin+OCP**	⊕⊕◯◯ LOW	IMPORTANT
BMI<25	3	RCT	Serious[1]	Serious[2]	No serious	No serious	66	65	0.71 (0.29 to 1.13)	**Metformin+OCP**	⊕⊕◯◯ LOW	IMPORTANT
Fasting insulin uIU/ml)												

Overall	4	RCT	Serious[1]	No serious	No serious	Serious[7]	60	57	-0.48 (-2.54 to 1.58)	No difference	⊕⊕◯◯ LOW	IMPORTANT
BMI<25	2	RCT	Serious[1]	Serious[2]	No serious	Very serious[6]	41	39	-1.38 (-4.60 to 1.85)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Fasting glucose (mg/dl)												
Overall	2	RCT	Serious[1]	Serious[2]	Serious[5]	Very serious[6]	47	41	-5.90 (-11.58 to -0.22)	**Metformin**	⊕◯◯◯ VERY LOW	IMPORTANT
Total cholesterol (mg/dl)												
Overall	3	RCT	Serious[1]	Serious[2]	No serious	Serious[7]	67	67	-23.83 (-47.59 to -0.07)	**Metformin**	⊕◯◯◯ VERY LOW	IMPORTANT
BMI<25	2	RCT	Serious[1]	No serious	No serious	Serious[7]	55	55	-34.95 (-51.41 to -18.49)	**Metformin**	⊕⊕◯◯ LOW	IMPORTANT
HDL (mg/dl)												
Overall	3	RCT	Serious[1]	No serious	No serious	Serious[7]	67	67	-2.69 (-6.79 to 1.40)	No difference	⊕⊕◯◯ LOW	IMPORTANT
BMI<25	2	RCT	Serious[1]	No serious	No serious	Serious[7]	55	55	-2.33 (-8.38 to 3.73)	No difference	⊕⊕◯◯ LOW	IMPORTANT
LDL (mg/dl)												
Overall	3	RCT	Serious[1]	Serious[2]	No serious	Serious[7]	67	67	-5.54 (-17.65 to 6.57)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI<25	2	RCT	Serious[1]	No serious	No serious	Serious[7]	55	55	-10.52 (-21.11 to 0.06)	No difference	⊕⊕◯◯ LOW	IMPORTANT
Triglycerides (mg/dl)												
Overall	3	RCT	Serious[1]	Very serious[3]	No serious	Serious[7]	67	67	-17.86 (-63.12 to 27.40)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI<25	2	RCT	Serious[1]	No serious	No serious	Serious[7]	55	55	-38.59 (-57.32 to -19.86)	**Metformin**	⊕⊕◯◯ LOW	IMPORTANT
HOMA-IR												
Overall	3	RCT	Serious[1]	Very serious[3]	No serious	No serious	59	53	-1.28 (-2.92 to 0.35)	No difference	⊕◯◯◯ VERY LOW	CRITICAL
BMI NS	2	RCT	Very serious[5]	Very serious[3]	No serious	Very serious[6]	30	29	-1.58 (-5.16 to 2.00)	No difference	⊕◯◯◯ VERY LOW	CRITICAL
DHEAS (ug/dl)												
Overall	3	RCT	Serious[1]	No serious	No serious	Serious[7]	60	58	30.36 (5.69 to 55.03)	**Metformin+OCP**	⊕◯◯◯ VERY LOW	IMPORTANT

[1] Downgraded once as the studies are at moderate or high risk of bias
[2] Downgraded once as I^2 is close to or >50% but CI partly overlapping
[3] Downgraded twice as I^2 very high and CI not overlapping

[4] Downgraded once as no information on what BMI the patients in the studies had
[5] Downgraded twice as both studies are at high risk of bias
[6] Downgraded twice as the CI is wide and there are few participants
[7] Downgraded once as the CI is wide
[8] Downgraded once as there are only a few studies
[9] Downgraded twice as there are very few participants

Comparison 6: Metformin versus anti-androgen (also in Q4.6 – identical)

Grade assessments and evidence profile

	Comparison: Metformin – anti-androgen (also in AA, Q4.6) Time point 12 months											
	Quality assessment						No of participants					
	No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Met 19**	**AA 16**	**P-value**	**Favours**	**Certainty**	**Importance**
BMI kg/m2												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	19	16	NR	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Hirsutism												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	19	16	NR	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Free testosterone												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	19	16	NR	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
DHEAS												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	19	16	<0.05	**Anti-androgen**	⊕◯◯◯ VERY LOW	IMPORTANT
SHBG												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	19	16	<0.05	**Anti-androgen**	⊕◯◯◯ VERY LOW	IMPORTANT
Androstenedione												

Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	19	16	NR	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
AUC-glucose												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	19	16	NR	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
AUC-insulin												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	19	16	<0.05	**Anti-androgen**	⊕◯◯◯ VERY LOW	IMPORTANT
HOMA-IR												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	19	16	NR	No difference	⊕◯◯◯ VERY LOW	CRITICAL

[1] Downgraded twice due to the evidence being derived from a single high risk of bias study

[2] Downgraded twice due to having a small number of studies/ participants

Comparison 7: Metformin+anti-androgen versus anti-androgen (also in Q4.6 – identical)

Grade assessments and evidence profile

	Comparison: Metformin+anti-androgen – anti-androgen (also in AA Q4.6) Timepoint 12 months											
	Quality assessment						No of participants					
	No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Met +AA 17**	**AA 19**	**P-value**	**Favours**	**Certainty**	**Importance**
BMI kg/m2												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	17	16	NR	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Hirsutism												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	17	16	NR	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Free testosterone												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	17	16	NR	No difference	⊕◯◯◯ VERY LOW	IMPORTANT

DHEAS												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	17	16	NR	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
SHBG												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	17	16	NR	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Androstenedione												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	17	16	NR	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
AUC-glucose												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	17	16	NR	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
AUC-insulin												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	17	16	<0.05	**Anti-androgen**	⊕◯◯◯ VERY LOW	IMPORTANT
HOMA-IR												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	17	16	<0.05	**Anti-androgen**	⊕◯◯◯ VERY LOW	CRITICAL

[1] Downgraded twice due to the evidence being derived from a single high risk of bias study

[2] Downgraded twice due to having a small number of studies/ participants

Comparison 8: Metformin+anti-androgen versus metformin (also in Q4.6 – identical)

Grade assessments and evidence profile

	Comparison: Metformin – anti-androgen (Identical to Q4.6)											
	Quality assessment						No of participants					
	No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Met +AA 17**	**Met 19**	**P-value**	**Favours**	**Certainty**	**Importance**
BMI kg/m2												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	17	19	NR	No difference	⊕◯◯◯ VERY LOW	CRITICAL

Hirsutism											
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	17	19	NR	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Free testosterone											
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	17	19	NR	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
DHEAS											
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	17	19	<0.05	**Metformin+anti-androgen**	⊕◯◯◯ VERY LOW	IMPORTANT
SHBG											
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	17	19	<0.05	**Metformin+anti-androgen**	⊕◯◯◯ VERY LOW	IMPORTANT
Androstenedione											
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	17	19	NR	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
AUC-glucose											
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	17	19	<0.05	**Metformin**	⊕◯◯◯ VERY LOW	IMPORTANT
AUC-insulin											
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	17	19	NR	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
HOMA-IR											
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	17	19	NR	No difference	⊕◯◯◯ VERY LOW	CRITICAL

[1] Downgraded twice due to the evidence being derived from a single high risk of bias study

[2] Downgraded twice due to having a small number of studies/ participants

Comparison 9: SPIOMET versus OCP (also in Q4.6 – identical)

Grade assessments and evidence profile

	Comparison: SPIOMET – OCP (also in AA Q4.6) Timeline 6-12 months											
	Quality assessment						No of participants					
	No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**SPIOMET 31**	**OCP 31**	**P-value**	**Favours**	**Certainty**	**Importance**
BMI kg/m2												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Serious[2]	31	31	NR	No difference	⊕⊕◯◯ LOW	CRITICAL
Hirsutism												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Serious[2]	31	31	$P \leq 0.001$	**SPIOMET**	⊕⊕◯◯ LOW	IMPORTANT
Testosterone												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Serious[2]	31	31	NR	No difference	⊕⊕◯◯ LOW	IMPORTANT
SHBG												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Serious[2]	31	31	$P \leq 0.001$	**OCP**	⊕⊕◯◯ LOW	IMPORTANT
Androstenedione												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Serious[2]	31	31	NR	No difference	⊕⊕◯◯ LOW	IMPORTANT
FAI												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Serious[2]	29	29	NR	No difference	⊕⊕◯◯ LOW	CRITICAL
Triglycerides												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Serious[2]	31	31	NR	No difference	⊕⊕◯◯ LOW	IMPORTANT
LDL												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Serious[2]	31	31	$P \leq 0.01$	**SPIOMET**	⊕⊕◯◯ LOW	IMPORTANT
HDL												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Serious[2]	31	31	NR	No difference	⊕⊕◯◯ LOW	IMPORTANT
CRP												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Serious[2]	31	31	$P \leq 0.001$	**SPIOMET**	⊕⊕◯◯ LOW	IMPORTANT
Fasting insulin												

Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Serious[2]	31	31	$P \leq 0.001$	**SPIOMET**	⊕⊕◯◯ LOW	IMPORTANT
HOMA-IR												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Serious[2]	31	31	$P \leq 0.01$	**SPIOMET**	⊕⊕◯◯ LOW	CRITICAL

[1] Downgraded once due to the evidence being derived from a moderate risk of bias study

[2] Downgraded once due to having a small number of studies/ participants

Comparison 10: Metformin versus anti-androgen+OCP (also in Q4.6 – not identical since timeline is different)

Grade assessments and evidence profile

	Comparison: Metformin – AA+OCP											
	Quality assessment						No of participants					
	No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Met**	**AA+ OCP**	**Effect, random, MD**	**Favours**	**Certainty**	**Importance**
BMI												
Overall	3	RCT	Serious[1]	No serious	No serious	No serious	69	62	0.08 (1.40 to 1.56)	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
HDL												
Overall	2	RCT	Serious[1]	Serious[2]	No serious	Very serious[4]	46	46	-5.70 (-18.64 to 7.24)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Triglycerides												
Overall	2	RCT	Serious[1]	No serious	No serious	Very serious[4]	46	46	12.07 (-6.71 to 30.85)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT

[1] Downgraded once as studies are low ROB and high ROB
[2] Downgraded once as I^2 is close to or >50% but CI partly overlapping
[3] Downgraded once as patients with different BMI included in the group
[4] Downgraded twice as the CI is wide and there are few studies

Comparison 11: Metformin+lifestyle versus metformin+anti-androgen+lifestyle (also in Q4.6 – not identical since timeline is different)

Grade assessments and evidence profile

	Comparison: Metformin+LS – Metformin+AA+LS (Also in Q4.6)											
	Quality assessment						No of participants					
	No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Met +LS**	**Met+ AA+ LS**	**Effect, random, MD**	**Favours**	**Certainty**	**Importance**
Weight												
Overall	4	RCT	Serious[1]	Serious[2]	Serious[4]	Serious[7]	156	159	2.77 (-2.78 to 8.32)	No difference	⊕◯◯◯ VERY LOW	
WHR												
Overall	3	RCT	Serious[1]	Serious[2]	Serious[4]	No serious	135	140	0.01 (-0.02 to 0.04)	No difference	⊕◯◯◯ VERY LOW	
BMI												
Overall	5	RCT	Serious[1]	No serious	Serious[4]	No serious	181	186	0.30 (-0.51 to 1.12)	No difference	⊕⊕◯◯ LOW	CRITICAL
Hirsutism												
Overall	4	RCT	Serious[1]	No serious	Serious[4]	No serious	127	135	0.58 (-0.69 to 1.86)	No difference	⊕⊕◯◯ LOW	IMPORTANT
SHBG												
Overall	3	RCT	Serious[1]	No serious	Serious[4]	No serious	71	73	0.59 (-3.34 to 4.53)	No difference	⊕⊕◯◯ LOW	IMPORTANT
FAI												
Overall	3	RCT	Serious[1]	No serious	Serious[4]	No serious	100	97	**1.41 (0.54 to 2.29)**	**Met+AA+LS**	⊕⊕◯◯ LOW	CRITICAL
Testosterone												
Overall	5	RCT	Serious[1]	No serious	Serious[4]	No serious	181	186	**0.26 (0.08 to 0.43)**	**Met+AA+LS**	⊕⊕◯◯ LOW	IMPORTANT
Fasting insulin												
Overall	4	RCT	Serious[1]	No serious	Serious[4]	No serious	156	159	**1.73 (0.12 to 3.33)**	**Met+AA+LS**	⊕⊕◯◯	IMPORTANT

										LOW	
Fasting glucose											
Overall	5	RCT	Serious[1]	No serious	Serious[4]	Serious[7]	181	186	**2.59 (0.38 to 4.80)**	**Met+AA+LS**	⊕◯◯◯ VERY LOW	IMPORTANT
Total cholesterol											
Overall	3	RCT	Serious[1]	No serious	Serious[4]	Serious[7]	105	104	-6.02 (-13.92 to 1.89)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
HDL											
Overall	3	RCT	Serious[1]	Serious[2]	Serious[4]	Serious[7]	71	73	0.55 (-5.14 to 6.25)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
LDL											
Overall	3	RCT	Serious[1]	No serious	Serious[4]	Serious[7]	71	73	2.98 (-11.84 to 17.79)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Triglycerides											
Overall	3	RCT	Serious[1]	No serious	Serious[4]	Serious[7]	71	73	-1.23 (-16.97 to 14.51)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
DHEAS											
Overall	2	RCT	No serious	Serious[2]	Serious[4]	Serious[6]	46	46	0.24 (-0.45 to 0.92)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
HOMA-IR											
Overall	3	RCT	Serious[1]	No serious	Serious[4]	No serious	136	139	0.21 (-0.08 to 0.51)	No difference	⊕⊕◯◯ LOW	CRITICAL

[1] Downgraded once as studies are low ROB and moderate ROB
[2] Downgraded once as I^2 is close to or >50% but CI partly overlapping
[3] Downgraded twice as I^2 very high and CI not overlapping
[4] Downgraded once as patients with different BMI included in the group
[5] Downgraded twice as the CI is wide and there are few studies
[6] Downgraded once as there are only a few participants
[7] Downgraded once as the CI is wide

Comparison 12: Metformin+lifestyle versus anti-androgen+lifestyle (also in Q4.6 – not identical since timeline is different)

Grade assessments and evidence profile

	Comparison: Metformin+LS – AA+LS (Also in Q4.6)											
	Quality assessment						No of participants					
	No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Met +LS**	**AA+ LS**	**Effect, random, MD**	**Favours**	**Certainty**	**Importance**
Weight												
Overall	3	RCT	Serious[1]	Very serious[3]	Serious[4]	Serious[7]	130	121	2.85 (-4.80 to 10.51)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
WHR												
Overall	3	RCT	Serious[1]	No serious	Serious[4]	No serious	145	138	-0.00 (-0.03 to 0.02)	No difference	⊕⊕◯◯ LOW	IMPORTANT
BMI												
Overall	5	RCT	Serious[1]	Serious[2]	Serious[4]	No serious	190	182	0.57 (-0.74 to 1.87)	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Hirsutism												
Overall	4	RCT	Serious[1]	Very serious[3]	Serious[4]	No serious	136	129	**1.59 (0.12 to 3.06)**	**AA+LS**	⊕◯◯◯ VERY LOW	IMPORTANT
SHBG												
Overall	2	RCT	Serious[1]	No serious	Serious[4]	Very serious[5]	44	45	**7.70 (0.75 to 14.66)**	**AA+LS**	⊕◯◯◯ VERY LOW	IMPORTANT
FAI												
Overall	2	RCT	Serious[1]	No serious	Serious[4]	No serious	74	70	0.68 (-0.51 to 1.87)	No difference	⊕⊕◯◯ LOW	CRITICAL
Testosterone												
Overall	4	RCT	Serious[1]	No serious	Serious[4]	No serious	165	155	0.07 (-0.13 to 0.28)	No difference	⊕⊕◯◯ LOW	IMPORTANT
Fasting insulin												
Overall	5	RCT	Serious[1]	Serious[2]	Serious[4]	Serious[6]	190	182	0.65 (-1.35 to 2.66)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Fasting glucose												
Overall	5	RCT	Serious[1]	Serious[2]	Serious[4]	Serious[6]	190	182	-1.09 (-4.63 to 2.45)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
DHEAS												
Overall	2	RCT	Serious[1]	Very serious[3]	Serious[4]	Very serious[5]	55	51	1.02 (-1.24 to 3.27)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
HOMA-IR												
Overall	3	RCT	Serious[1]	No serious	Serious[4]	No serious	145	138	-0.44 (-0.89 to 0.02)	No difference	⊕⊕◯◯ LOW	CRITICAL

Number of cycles/year												
Overall	3	RCT	Serious[1]	No serious	Serious[4]	No serious	145	138	**-0.88 (-1.43 to -0.33)**	**AA+LS**	⊕⊕◯◯ LOW	CRITICAL

[1] Downgraded once as studies are low ROB and moderate ROB
[2] Downgraded once as I^2 is close to or >50% but CI partly overlapping
[3] Downgraded twice as I^2 very high and CI not overlapping
[4] Downgraded once as patients with different BMI and age included in the group
[5] Downgraded twice as the CI is wide and there are few studies
[6] Downgraded once as there are only a few participants
[7] Downgraded once as the CI is wide

Comparison 13: Metformin+anti-androgen+lifestyle versus anti-androgen+lifestyle (also in Q4.6 – not identical since timeline is different)

Grade assessments and evidence profile

	Comparison: Metformin+AA+LS – AA+LS											
	Quality assessment						No of participants					
	No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Met +AA +LS**	**Met+ AA**	**Effect, random, MD**	**Favours**	**Certainty**	**Importance**
Weight (kg)												
Overall	3	RCT	Serious[1]	Very serious[3]	Serious[5]	Serious[7]	133	121	-2.51 (-8.67 to 3.65)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
WHR												
Overall	2	RCT	Serious[1]	Serious[2]	No serious	No serious	113	104	-0.03 (-0.07 to 0.01)	No difference	⊕⊕◯◯ LOW	IMPORTANT
BMI (kg/m2)												
Overall	4	RCT	Serious[1]	No serious	Serious[5]	No serious	160	147	-0.20	No difference	⊕⊕◯◯	CRITICAL

									(-1.02 to 0.63)		LOW	
Hirsutism												
Overall	3	RCT	Serious[1]	Very serious[3]	Serious[5]	Serious[7]	109	94	0.53 (-1.55 to 2.61)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
SHBG												
Overall	2	RCT	Serious[1]	Serious[2]	Serious[5]	Very serious[6]	47	43	-9.06 (-26.41 to 8.29)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
FAI												
Overall	2	RCT	Serious[1]	No serious	Serious[5]	No serious	71	70	-0.63 (-1.40 to 0.14)	No difference	⊕⊕◯◯ LOW	CRITICAL
Testosterone												
Overall	4	RCT	Serious[1]	Serious[2]	Serious[5]	No serious	160	150	-0.01 (-0.05 to 0.03)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Fasting insulin												
Overall	4	RCT	Serious[1]	No serious	Serious[5]	No serious	160	147	-1.30 (-2.81 to 0.22)	No difference	⊕⊕◯◯ LOW	IMPORTANT
Fasting glucose												
Overall	4	RCT	Serious[1]	No serious	Serious[5]	No serious	160	147	-4.14 (-6.26 to -2.01)	**Metformin+AA +LS**	⊕⊕◯◯ LOW	IMPORTANT

[1] Downgraded once as the studies are at moderate and high risk of bias
[2] Downgraded once as I^2 is close to or >50% but CI partly overlapping
[3] Downgraded twice as I^2 very high and CI not overlapping
[4] Downgraded once as no information on what BMI the patients in the studies had
[5] Downgraded once as patients with different BMI included in the overall group
[6] Downgraded twice as the CI is wide and there are few studies
[7] Downgraded once as the CI is wide

Comparison 14: Metformin+anti-androgen+lifestyle versus placebo+lifestyle (also in Q4.6 – identical)

Grade assessments and evidence profile

	Comparison: Metformin+AA+LS – AA+LS (Identical to Q4.6)

	Quality assessment						No of participants					
	No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Met +AA +LS**	**PLB+ AA**	**Effect, random, MD**	**Favours**	**Certainty**	**Importance**
BMI (kg/m2)												
Overall	2	RCT	Serious[1]	Very serious[3]	Serious[4]	Very serious[5]	47	43	-1.76 (-5.77 to 2.24)	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Hirsutism												
Overall	2	RCT	Serious[1]	Serious[2]	Serious[4]	Very serious[5]	47	45	1.58 (-1.13 to 4.29)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
SHBG												
Overall	2	RCT	Serious[1]	No serious	Serious[4]	Very serious[5]	47	45	1.09 (-5.23 to 7.41)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Testosterone												
Overall	2	RCT	Serious[1]	No serious	Serious[4]	Serious[6]	47	45	-0.08 (-0.15 to 0.00)	**Metformin+ AA+LS**	⊕◯◯◯ VERY LOW	IMPORTANT
Fasting glucose												
Overall	2	RCT	Serious[1]	No serious	Serious[4]	Very serious[5]	47	43	-6.29 (-10.26 to -2.33)	**Metformin+ AA+LS**	⊕◯◯◯ VERY LOW	IMPORTANT

[1] Downgraded once as one study is low ROB and one moderate ROB
[2] Downgraded once as I^2 is close to or >50% but CI partly overlapping
[3] Downgraded twice as I^2 very high and CI not overlapping
[4] Downgraded once as patients with different BMI included in the group

Comparison 15: Metformin versus rosiglitazone

Grade assessments and evidence profile

	Comparison: Metformin – Rosiglitazone					
	Quality assessment	No of participants				

	No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Met	ROSI	Effect, random, MD	Favours	Certainty	Importance
Weight (kg)												
Overall	5	RCT	Serious[2]	Very serious[4]	No serious	Serious[5]	175	144	**-4.39 (-7.70 to -1.08)**	**Metformin**	⊕◯◯◯ VERY LOW	IMPORTANT
BMI>25	1	RCT	No serious	Not applicable	Not applicable	Serious[5]	68	67	**-3.19 (-5.73 to -0.65)**	**Metformin**	⊕⊕⊕◯ MODERATE	IMPORTANT
BMI<27	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[8]	28	30	**-1.80 (-1.98 to -1.62)**	**Metformin**	⊕◯◯◯ VERY LOW	IMPORTANT
BMI NS	3	RCT	Serious[2]	No serious	No serious	Serious[5]	79	47	**-7.55 (-9.83 to -5.27)**	**Metformin**	⊕⊕◯◯ LOW	IMPORTANT
WHR												
Overall	3	RCT	Serious[1]	Very serious[4]	No serious	No serious	127	127	0.01 (-0.01 to 0.04)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI>25	1	RCT	No serious	Not applicable	Not applicable	Serious[7]	68	67	-0.01 (-0.03 to 0.01)	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
BMI<27	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[8]	28	30	0.00 (-0.00 to 0.00)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI NS	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[8]	31	30	**0.05 (0.03 to 0.07)**	**Rosiglitazone**	⊕◯◯◯ VERY LOW	IMPORTANT
BMI (kg/m2)												
Overall	7	RCT	Serious[2]	No serious	No serious	No serious	224	191	**-0.95 (-1.41 to -0.49)**	**Metformin**	⊕⊕⊕◯ MODERATE	CRITICAL
BMI>25	1	RCT	No serious	Not applicable	Not applicable	Serious[7]	68	67	**-1.25 (-1.89 to -0.61)**	**Metformin**	⊕⊕⊕◯ MODERATE	CRITICAL
BMI<27	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[8]	28	30	**-0.70 (-0.75 to -0.65)**	**Metformin**	⊕◯◯◯ VERY LOW	CRITICAL
BMI NS	5	RCT	Serious[2]	No serious	No serious	No serious	128	94	-0.82 (-2.05 to 0.41)	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Androstenedione												
Overall	2	RCT	Serious[2]	No serious	No serious	Serious[6]	49	47	**-1.79 (-2.84 to -0.74)**	**Metformin**	⊕⊕◯◯ LOW	IMPORTANT
HOMA-IR												
Overall	5	RCT	Serious[1]	Very serious[4]	No serious	No serious	179	143	0.50 (-0.07 to 1.07)	No difference	⊕◯◯◯ VERY LOW	CRITICAL

BMI>25	1	RCT	No serious	Not applicable	Not applicable	Serious[7]	68	67	-0.09 (-0.54 to 0.36)	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
BMI NS	4	RCT	Serious[2]	Very serious[4]	No serious	No serious	111	76	**0.74 (0.24 to 1.24)**	**Rosiglitazone**	⊕◯◯◯ VERY LOW	CRITICAL
Total testosterone												
Overall	6	RCT	Serious[2]	No serious	No serious	No serious	209	176	**-0.10 (-0.17 to -0.04)**	**Metformin**	⊕⊕⊕◯ MODERATE	IMPORTANT
BMI>25	1	RCT	No serious	Not applicable	Not applicable	Serious[7]	68	67	-0.11 (-0.33 to 0.11)	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
BMI<27	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[8]	28	30	**-0.11 (-0.20 to -0.02)**	**Metformin**	⊕◯◯◯ VERY LOW	IMPORTANT
BMI NS	4	RCT	Serious[2]	No serious	No serious	No serious	113	79	-0.09 (-0.21 to 0.03)	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
Fasting insulin												
Overall	5	RCT	Serious[2]	Serious[3]	No serious	No serious	181	146	0.25 (-1.41 to 1.91)	No difference	⊕⊕◯◯ LOW	IMPORTANT
BMI>25	1	RCT	No serious	Not applicable	Not applicable	Serious[7]	68	67	0.20 (-1.52 to 1.92)	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
BMI NS	4	RCT	Serious[2]	Serious[3]	No serious	No serious	113	79	0.44 (-2.06 to 2.93)	No difference	⊕⊕◯◯ LOW	IMPORTANT
Fasting glucose												
Overall	6	RCT	Serious[2]	Very serious[4]	No serious	No serious	209	178	0.06 (-0.08 to 0.20)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI>25	1	RCT	No serious	Not applicable	Not applicable	Serious[7]	68	69	-0.11 (-0.28 to 0.06)	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
BMI<27	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[8]	28	30	**0.18 (0.11 to 0.25)**	**Rosiglitazone**	⊕◯◯◯ VERY LOW	IMPORTANT
BMI NS	4	RCT	Serious[2]	Very serious[4]	No serious	No serious	113	79	0.06 (-0.17 to 0.30)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Total cholesterol												
Overall	4	RCT	Serious[2]	Serious[3]	No serious	No serious	147	114	-0.05 (-0.32 to 0.22)	No difference	⊕⊕◯◯ LOW	IMPORTANT
BMI>25	1	RCT	No serious	Not applicable	Not applicable	Serious[7]	68	67	0.05 (-0.32 to 0.42)	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
BMI NS	3	RCT	Serious[2]	Serious[3]	No serious	No serious	79	47	-0.04 (-0.48 to 0.40)	No difference	⊕⊕◯◯ LOW	IMPORTANT

HDL											
Overall	4	RCT	Serious[2]	Very serious[4]	No serious	No serious	147	114	0.08 (-0.09 to 0.25)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI>25	1	RCT	No serious	Not applicable	Not applicable	Serious[7]	68	67	0.00 (-0.08 to 0.08)	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
BMI NS	3	RCT	Serious[2]	Very serious[4]	No serious	No serious	79	47	0.16 (-0.25 to 0.57)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
LDL											
Overall	4	RCT	Serious[2]	No serious	No serious	No serious	147	114	**0.18 (0.07 to 0.30)**	**Rosiglitazone**	⊕⊕⊕◯ MODERATE	IMPORTANT
BMI>25	1	RCT	No serious	Not applicable	Not applicable	Serious[7]	68	67	0.02 (-0.23 to 0.27)	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
BMI NS	3	RCT	Serious[2]	No serious	No serious	No serious	79	47	**0.23 (0.10 to 0.36)**	**Rosiglitazone**	⊕⊕⊕◯ MODERATE	IMPORTANT
DHEAS											
Overall	3	RCT	Serious[2]	No serious	No serious	Serious[5]	93	61	-12.27 (-30.77 to 6.23)	No difference	⊕⊕◯◯ LOW	IMPORTANT
BMI<27	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[8]	28	30	-14.00 (-33.12 to 5.12)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI NS	2	RCT	Serious[2]	No serious	No serious	Serious[5]	65	31	13.18 (-60.07 to 86.42)	No difference	⊕⊕◯◯ LOW	IMPORTANT
Triglycerides											
Overall	4	RCT	Serious[2]	Serious[3]	No serious	No serious	147	100	0.01 (-0.21 to 0.24)	No difference	⊕⊕◯◯ LOW	IMPORTANT
BMI>25	1	RCT	No serious	Not applicable	Not applicable	Serious[7]	68	67	0.15 (-0.00 to 0.30)	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
BMI NS	3	RCT	Serious[2]	No serious	No serious	Serious[6]	79	33	-0.10 (-0.23 to 0.03)	No difference	⊕⊕◯◯ LOW	IMPORTANT
CRP											
Overall	2	RCT	Serious[2]	No serious	No serious	Serious[6]	64	32	0.20 (-0.11 to 0.52)	No difference	⊕⊕◯◯ LOW	IMPORTANT
Free testosterone											
Overall	2	RCT	Serious[2]	No serious	No serious	Serious[6]	65	31	1.00 (-1.79 to 3.80)	No difference	⊕⊕◯◯ LOW	IMPORTANT

[1] Downgraded once as one study that is moderate risk of bias

[2] Downgraded once as one study high risk of bias and the rest moderate or low risk of bias
[3] Downgraded once as I^2 is close to or >50% but CI partly overlapping
[4] Downgraded twice as I^2 is high and CI is not overlapping
[5]Downgraded once as CI wide
[6]Downgraded once as number of participants is low
[7]Downgraded once as only one study
[8]Downgraded twice as only one study with a small number of participants

Comparison 16: Metformin versus pioglitazone

Grade assessments and evidence profile

	Comparison: Metformin – Pioglitazone											
	Quality assessment						No of participants					
	No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Met**	**PIO**	**Effect, random, MD**	**Favours**	**Certainty**	**Importance**
Weight (kg)												
Overall	4	RCT	Very serious[2]	No serious	No serious	Serious[5]	83	80	-1.09 (-5.22 to 3.03)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI>25	1	RCT	Very serious[2]	Not applicable	Not applicable	Very serious[6]	18	17	-1.80 (-11.45 to 7.85)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI NS	3	RCT	Serious[1]	No serious	No serious	Serious[5]	65	63	-0.94 (-5.50 to 3.62)	No difference	⊕⊕◯◯ LOW	IMPORTANT
WHR												
Overall	3	RCT	Serious[1]	Very serious[4]	No serious	Serious[5]	55	52	-0.01 (-0.05 to 0.04)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI>25	1	RCT	Very serious[2]	Not applicable	No serious	Very serious[6]	18	17	**-0.06 (-0.10 to -0.02)**	**Metformin**	⊕◯◯◯ VERY LOW	IMPORTANT
BMI NS	2	RCT	Serious[1]	No serious	No serious	Serious[5]	37	35	0.02 (-0.00 to 0.04)	No difference	⊕⊕◯◯ LOW	IMPORTANT
BMI (kg/m2)												
Overall	5	RCT	Serious[1]	No serious	No serious	No serious	93	90	-1.09	No difference	⊕⊕⊕◯	CRITICAL

									(-2.54 to 0.37)		MODERATE	
BMI>25	2	RCT	Serious[1]	No serious	No serious	Very serious[6]	28	27	-2.26 (-5.45 to 0.93)	No difference	⊕◯◯◯ VERY LOW	CRITICAL
BMI NS	3	RCT	Serious[1]	No serious	No serious	No serious	65	63	-0.78 (-2.41 to 0.86)	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
HOMA-IR												
Overall	4	RCT	Serious[1]	Very serious[4]	No serious	No serious	93	90	1.33 (-0.18 to 2.85)	No difference	⊕◯◯◯ VERY LOW	CRITICAL
BMI>25	2	RCT	Serious[1]	No serious	No serious	Very serious[6]	28	27	0.17 (-0.56 to 0.89)	No difference	⊕◯◯◯ VERY LOW	CRITICAL
BMI NS	2	RCT	Serious[1]	Very serious[4]	No serious	No serious	65	63	2.68 (-1.75 to 7.12)	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Testosterone												
Overall	4	RCT	Serious[1]	No serious	No serious	Serious[5]	108	105	-4.86 (-12.37 to 2.65)	No difference	⊕⊕◯◯ LOW	IMPORTANT
Fasting insulin												
Overall	6	RCT	Serious[1]	No serious	No serious	Serious[5]	136	132	3.12 (-3.48 to 9.72)	No difference	⊕⊕◯◯ LOW	IMPORTANT
BMI>25	2	RCT	Serious[1]	No serious	No serious	Very serious[6]	28	27	0.76 (-2.56 to 4.08)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI NS	4	RCT	Serious[1]	No serious	No serious	Serious[5]	108	105	3.89 (-4.68 to 12.47)	No difference	⊕⊕◯◯ LOW	IMPORTANT
Fasting glucose												
Overall	4	RCT	Serious[1]	Serious[2]	No serious	Serious[5]	83	80	1.22 (-2.58 to 5.01)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI>25	1	RCT	Very serious[2]	No serious	No serious	Very serious[6]	18	17	0.10 (-5.32 to 5.52)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI NS	3	RCT	Serious[1]	Serious[2]	No serious	Serious[5]	65	63	1.42 (-3.39 to 6.23)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Total cholesterol												
Overall	5	RCT	Serious[1]	Very serious[4]	No serious	Serious[5]	126	122	3.57 (-18.33 to 25.46)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI>25	1	RCT	Very serious[2]	Not applicable	No serious	Very serious[6]	18	17	7.00 (-13.66 to 27.66)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI NS	4	RCT	Serious[1]	Very serious[4]	No serious	Serious[5]	108	105	2.53 (-24.47 to 29.53)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
HDL												
Overall	5	RCT	Serious[1]	Very serious[4]	No serious	Serious[5]	126	122	-7.08 (-15.67 to 1.50)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT

BMI>25	1	RCT	Very serious[2]	Not applicable	No serious	Very serious[6]	18	17	-4.30 (-11.26 to 2.66)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI NS	4	RCT	Serious[1]	Very serious[4]	No serious	Serious[5]	108	105	-7.73 (-17.60 to 2.14)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
LDL												
Overall	4	RCT	Serious[1]	Serious[3]	No serious	Serious[5]	83	80	-3.91 (-21.19 to 13.36)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI>25	1	RCT	Very serious[2]	Not applicable	No serious	Very serious[6]	18	17	8.20 (-8.58 to 24.98)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI NS	3	RCT	Serious[1]	Serious[3]	No serious	Serious[5]	65	63	-8.46 (-30.62 to 13.71)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
DHEAS												
Overall	3	RCT	Serious[1]	No serious	No serious	Serious[5]	68	66	-19.76 (-44.43 to 4.92)	No difference	⊕⊕◯◯ LOW	IMPORTANT
BMI>25	1	RCT	Serious[1]	No serious	No serious	Very serious[6]	18	17	-36.60 (-112.03 to 38.83)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI NS	2	RCT	Serious[1]	No serious	No serious	Very serious[6]	50	49	-17.74 (-43.85 to 8.38)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Triglycerides												
Overall	4	RCT	Serious[1]	Serious[3]	No serious	Serious[5]	83	80	9.06 (-14.39 to 32.51)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI>25	1	RCT	Very serious[2]	Not applicable	No serious	Very serious[6]	18	17	-19.10 (-52.34 to 14.14)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI NS	3	RCT	Serious[1]	Serious[3]	No serious	Serious[5]	65	63	17.04 (-6.48 to 40.56)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
SHBG												
Overall	3	RCT	Serious[1]	No serious	No serious	Serious[5]	68	66	-18.21 (-46.99 to 10.58)	No difference	⊕⊕◯◯ LOW	IMPORTANT
BMI>25	1	RCT	Serious[1]	No serious	No serious	Very serious[6]	10	10	-6.70 (-15.57 to 2.17)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI NS	2	RCT	Serious[1]	No serious	No serious	Serious[5]	58	56	-23.88 (-63.48 to 15.71)	No difference	⊕⊕◯◯ LOW	IMPORTANT
FAI												
Overall	3	RCT	Serious[1]	No serious	No serious	No serious	68	66	**2.46 (1.42 to 3.50)**	**Pioglitazone**	⊕⊕⊕◯ MODERATE	CRITICAL
BMI>25	1	RCT	Very serious[2]	Not applicable	No serious	Very serious[7]	10	10	1.40 (-0.72 to 3.52)	No difference	⊕◯◯◯ VERY LOW	CRITICAL
BMI NS	2	RCT	Serious[1]	No serious	No serious	No serious	58	56	**2.80 (1.72 to 3.88)**	**Pioglitazone**	⊕⊕⊕◯ MODERATE	CRITICAL

Hirsutism												
Overall	3	RCT	Serious[1]	No serious	No serious	No serious	76	73	0.28 (-0.83 to 1.39)	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
BMI>25	1	RCT	Serious[1]	Not applicable	No serious	Very serious[7]	18	17	0.70 (-1.26 to 2.66)	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI NS	2	RCT	Serious[1]	No serious	No serious	No serious	58	56	0.09 (-1.26 to 1.43)	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT

[1] Downgraded once as the studies are at high or moderate risk of bias
[2] Downgraded twice due to one study at high risk of bias
[3] Downgraded once as I^2 is close to or >50% but CI partly overlapping
[4] Downgraded twice as I^2 is high and CI is not overlapping
[5] Downgraded once as the CI is wide
[6]Downgraded twice as number of participants is low and CI wide
[7]Downgraded twice as number of participants is very low

Comparison 17: Metformin versus saxagliptin

Grade assessments and evidence profile

	Comparison: Metformin – Saxagliptin											
	Quality assessment						No of participants					
	No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Met 12**	**SAXA 11**	**P-value**	**Favours**	**Certainty**	**Importance**
BMI kg/m2												
Overall	1	RCT	No serious	Not applicable	Not applicable	Very serious[1]	12	11	NR	No difference	⊕⊕◯◯ LOW	CRITICAL
WHR												
Overall	1	RCT	No serious	Not applicable	Not applicable	Very serious[1]	12	11	NR	No difference	⊕⊕◯◯ LOW	IMPORTANT
Testosterone												
Overall	1	RCT	No serious	Not applicable	Not applicable	Very serious[1]	12	11	NR	No difference	⊕⊕◯◯ LOW	IMPORTANT

DHEAS											
Overall	1	RCT	No serious	Not applicable	Not applicable	Very serious[1]	12	11	NR	No difference	⊕⊕◯◯ LOW	IMPORTANT
SHBG											
Overall	1	RCT	No serious	Not applicable	Not applicable	Very serious[1]	12	11	NR	No difference	⊕⊕◯◯ LOW	IMPORTANT
FAI											
Overall	1	RCT	No serious	Not applicable	Not applicable	Very serious[1]	12	11	NR	No difference	⊕⊕◯◯ LOW	CRITICAL
Total cholesterol											
Overall	1	RCT	No serious	Not applicable	Not applicable	Very serious[1]	12	11	NR	No difference	⊕⊕◯◯ LOW	IMPORTANT
HDL											
Overall	1	RCT	No serious	Not applicable	Not applicable	Very serious[1]	12	11	NR	No difference	⊕⊕◯◯ LOW	IMPORTANT
LDL											
Overall	1	RCT	No serious	Not applicable	Not applicable	Very serious[1]	12	11	NR	No difference	⊕⊕◯◯ LOW	IMPORTANT
Triglycerides											
Overall	1	RCT	No serious	Not applicable	Not applicable	Very serious[1]	12	11	0.001	**Saxagliptin**	⊕⊕◯◯ LOW	IMPORTANT
Fasting glucose											
Overall	1	RCT	No serious	Not applicable	Not applicable	Very serious[1]	12	11	NR	No difference	⊕⊕◯◯ LOW	IMPORTANT
HOMA-IR											
Overall	1	RCT	No serious	Not applicable	Not applicable	Very serious[1]	12	11	NR	No difference	⊕⊕◯◯ LOW	CRITICAL
Menstrual cycle (d)											
Overall	1	RCT	No serious	Not applicable	Not applicable	Very serious[1]	12	11	NR	No difference	⊕⊕◯◯ LOW	CRITICAL

[1] Downgraded twice due to having a small number of studies/ participants

Comparison 18: Metformin+saxagliptin versus metformin

Grade assessments and evidence profile

	Comparison: Metformin+saxagliptin – Metformin

	Quality assessment						No of participants					
	No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Met+SAXA 11**	**SAXA 12**	**P-value**	**Favours**	**Certainty**	**Importance**
BMI kg/m2												
Overall	1	RCT	No serious	Not applicable	Not applicable	Very serious[1]	11	12	NR	No difference	⊕⊕◯◯ LOW	CRITICAL
WHR												
Overall	1	RCT	No serious	Not applicable	Not applicable	Very serious[1]	11	12	NR	No difference	⊕⊕◯◯ LOW	IMPORTANT
Testosterone												
Overall	1	RCT	No serious	Not applicable	Not applicable	Very serious[1]	11	12	NR	No difference	⊕⊕◯◯ LOW	IMPORTANT
DHEAS												
Overall	1	RCT	No serious	Not applicable	Not applicable	Very serious[1]	11	12	NR	No difference	⊕⊕◯◯ LOW	IMPORTANT
SHBG												
Overall	1	RCT	No serious	Not applicable	Not applicable	Very serious[1]	11	12	NR	No difference	⊕⊕◯◯ LOW	IMPORTANT
FAI												
Overall	1	RCT	No serious	Not applicable	Not applicable	Very serious[1]	11	12	NR	No difference	⊕⊕◯◯ LOW	CRITICAL
Total cholesterol												
Overall	1	RCT	No serious	Not applicable	Not applicable	Very serious[1]	11	12	NR	No difference	⊕⊕◯◯ LOW	IMPORTANT
HDL												
Overall	1	RCT	No serious	Not applicable	Not applicable	Very serious[1]	11	12	NR	No difference	⊕⊕◯◯ LOW	IMPORTANT
LDL												
Overall	1	RCT	No serious	Not applicable	Not applicable	Very serious[1]	11	12	NR	No difference	⊕⊕◯◯ LOW	IMPORTANT
Triglycerides												
Overall	1	RCT	No serious	Not applicable	Not applicable	Very serious[1]	11	12	0.004	**MET+SAXA**	⊕⊕◯◯ LOW	IMPORTANT
Fasting glucose												
Overall	1	RCT	No serious	Not applicable	Not applicable	Very serious[1]	11	12	NR	No difference	⊕⊕◯◯ LOW	IMPORTANT
HOMA-IR												

Overall	1	RCT	No serious	Not applicable	Not applicable	Very serious[1]	11	12	NR	No difference	⊕⊕◯◯ LOW	CRITICAL
Menstrual cycle (d)												
Overall	1	RCT	No serious	Not applicable	Not applicable	Very serious[1]	11	12	0.03	**Met+Saxa**	⊕⊕◯◯ LOW	CRITICAL

[1] Downgraded twice due to having a small number of studies/ participants

Comparison 19: Metformin+saxagliptin versus saxagliptin

Grade assessments and evidence profile

	Comparison: Metformin+saxagliptin – Metformin											
	Quality assessment						No of participants					
	No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Met+ SAXA 11**	**SAXA 11**	**P-value**	**Favours**	**Certainty**	**Importance**
BMI kg/m2												
Overall	1	RCT	No serious	Not applicable	Not applicable	Very serious[1]	11	11	NR	No difference	⊕⊕◯◯ LOW	CRITICAL
WHR												
Overall	1	RCT	No serious	Not applicable	Not applicable	Very serious[1]	11	11	NR	No difference	⊕⊕◯◯ LOW	IMPORTANT
Testosterone												
Overall	1	RCT	No serious	Not applicable	Not applicable	Very serious[1]	11	11	NR	No difference	⊕⊕◯◯ LOW	IMPORTANT
DHEAS												
Overall	1	RCT	No serious	Not applicable	Not applicable	Very serious[1]	11	11	NR	No difference	⊕⊕◯◯ LOW	IMPORTANT
SHBG												
Overall	1	RCT	No serious	Not applicable	Not applicable	Very serious[1]	11	11	NR	No difference	⊕⊕◯◯ LOW	IMPORTANT
FAI												
Overall	1	RCT	No serious	Not applicable	Not applicable	Very serious[1]	11	11	NR	No difference	⊕⊕◯◯ LOW	CRITICAL

Total cholesterol												
Overall	1	RCT	No serious	Not applicable	Not applicable	Very serious[1]	11	11	NR	No difference	⊕⊕◯◯ LOW	IMPORTANT
HDL												
Overall	1	RCT	No serious	Not applicable	Not applicable	Very serious[1]	11	11	NR	No difference	⊕⊕◯◯ LOW	IMPORTANT
LDL												
Overall	1	RCT	No serious	Not applicable	Not applicable	Very serious[1]	11	11	NR	No difference	⊕⊕◯◯ LOW	IMPORTANT
Triglycerides												
Overall	1	RCT	No serious	Not applicable	Not applicable	Very serious[1]	11	11	NR	No difference	⊕⊕◯◯ LOW	IMPORTANT
Fasting glucose												
Overall	1	RCT	No serious	Not applicable	Not applicable	Very serious[1]	11	11	NR	No difference	⊕⊕◯◯ LOW	IMPORTANT
HOMA-IR												
Overall	1	RCT	No serious	Not applicable	Not applicable	Very serious[1]	11	11	NR	No difference	⊕⊕◯◯ LOW	CRITICAL
Menstrual cycle (d)												
Overall	1	RCT	No serious	Not applicable	Not applicable	Very serious[1]	11	11	NR	**MET+SAXA**	⊕⊕◯◯ LOW	CRITICAL

[1] Downgraded twice due to having a small number of studies/ participants

Comparison 20: Metformin versus SGLT2-inhibitors

Grade assessments and evidence profile

	Comparison: Metformin- Empagliflozin											
	Quality assessment						No of participants					
	No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Met 20**	**Emp 19**	**P-value**	**Favours**	**Certainty**	**Importance**
Weight (kg)												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	20	19	<0.05	**empagliflozin**	⊕◯◯◯ VERY LOW	IMPORTANT
BMI kg/m2												

Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	20	19	<0.05	**empagliflozin**	⊕◯◯◯ VERY LOW	CRITICAL
SHBG												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	20	19	NR	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
FAI												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	20	19	NR	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Testosterone												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	20	19	NR	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Fasting insulin												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	20	19	NR	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Fasting glucose												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	20	19	NR	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Total cholesterol												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	20	19	NR	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
HDL												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	20	19	NR	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
LDL												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	20	19	NR	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Triglycerides												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	20	19	NR	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
CRP												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	20	19	NR	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
HOMA-IR												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	20	19	NR	No difference	⊕◯◯◯ VERY LOW	CRITICAL
DHEAS												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	20	19	NR	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Androstenedione												

Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	20	19	NR	No difference	⊕◯◯◯ VERY LOW	IMPORTANT

[1] Downgraded once due to the evidence being derived from a single moderate risk of bias study

[2] Downgraded twice due to having a small number of studies/ participants

Grade assessments and evidence profile

	Comparison: Metformin- Canagliflozin											
	Quality assessment						No of participants					
	No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Met 29**	**Can 30**	**P-value**	**Favours**	**Certainty**	**Importance**
Weight (kg)												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	29	30	0.876	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
WHR												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	29	30	0.513	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI kg/m2												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	29	30	0.727	No difference	⊕◯◯◯ VERY LOW	CRITICAL
SHBG												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	29	30	0.472	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Testosterone												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	29	30	0.411	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Free testosterone												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	29	30	0.991	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Fasting insulin												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	29	30	0.196	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Fasting glucose												

Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	29	30	0.995	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Total cholesterol												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	29	30	0.329	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
HDL												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	29	30	0.211	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
LDL												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	29	30	0.378	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Triglycerides												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	29	30	0.393	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
HOMA-IR												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	29	30	0.382	No difference	⊕◯◯◯ VERY LOW	CRITICAL
DHEAS												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	29	30	0.013	**Canagliflozin**	⊕◯◯◯ VERY LOW	IMPORTANT
Androstenedione												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	29	30	0.199	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Menstrual cycles/year												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	29	30	0.950	No difference	⊕◯◯◯ VERY LOW	CRITICAL

[1] Downgraded once due to the evidence being derived from a single moderate risk of bias study

[2] Downgraded twice due to having a small number of studies/ participants

Comparison 21: Metformin+liraglutide versus liraglutide

Grade assessments and evidence profile

	Comparison: Metformin+liraglutide – liraglutide											
	Quality assessment						No of participants					
	No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Met+ LIRA 14**	**Met 14**	**P-value**	**Favours**	**Certainty**	**Importance**
Weight												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	14	14	0.062	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI kg/m2												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	14	14	0.050	**Liraglutide**	⊕◯◯◯ VERY LOW	CRITICAL
Androstenedione												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	14	14	0.376	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Testosterone												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	14	14	0.285	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Free testosterone												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	14	14	0.482	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
SHBG												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	14	14	0.376	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Total cholesterol												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	14	14	0.094	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
HDL												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	14	14	0.793	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
LDL												

Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	14	14	0.038	**Metformin+LIRA**	⨁◯◯◯ VERY LOW	IMPORTANT
Triglycerides												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	14	14	0.128	No difference	⨁◯◯◯ VERY LOW	IMPORTANT
Fasting insulin												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	14	14	0.571	No difference	⨁◯◯◯ VERY LOW	IMPORTANT
Fasting glucose												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	14	14	0.734	No difference	⨁◯◯◯ VERY LOW	IMPORTANT
HOMA-IR												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	14	14	0.427	No difference	⨁◯◯◯ VERY LOW	CRITICAL

[1] Downgraded twice due to the evidence being derived from a single high risk of bias study

[2] Downgraded twice due to having a small number of studies/ participants

Comparison 22: Metformin+myo-inositol versus myo-inositol

Grade assessments and evidence profile

	Comparison: Metformin+myo-inositol – myo-inositol											
	Quality assessment						No of participants					
	No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Met +MI 36**	**MI 40**	**P-value**	**Favours**	**Certainty**	**Importance**
BMI kg/m2												

Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	36	40	NR	No difference	⊕◯◯◯ VERY LOW	CRITICAL
WHR												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	36	40	NR	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Testosterone												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	36	40	NR	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Total cholesterol												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	36	40	NR	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
HDL												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	36	40	NR	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
LDL												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	36	40	NR	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Triglycerides												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	36	40	NR	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
HOMA-IR												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	36	40	NR	No difference	⊕◯◯◯ VERY LOW	CRITICAL

[1] Downgraded once due to the evidence being derived from a single, moderate risk of bias study

[2] Downgraded twice due to having a small number of studies/ participants and being a single study

Comparison 23: Metformin versus orlistat

Grade assessments and evidence profile

	Comparison: Metformin – Orlistat					
	Quality assessment	No of participants				

	No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Met 10	ORL 10	P-value	Favours	Certainty	Importance
BMI kg/m2												
Overall	1	RCT	Serious[2]	Not applicable	Not applicable	Very serious[1]	10	10	0.51	No difference	⊕◯◯◯ VERY LOW	CRITICAL
SHBG												
Overall	1	RCT	Serious[2]	Not applicable	Not applicable	Very serious[1]	10	10	0.49	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
FAI												
Overall	1	RCT	Serious[2]	Not applicable	Not applicable	Very serious[1]	10	10	0.17	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Fasting insulin												
Overall	1	RCT	Serious[2]	Not applicable	Not applicable	Very serious[1]	10	10	0.38	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
HOMA-IR												
Overall	1	RCT	Serious[2]	Not applicable	Not applicable	Very serious[1]	10	10	0.44	No difference	⊕◯◯◯ VERY LOW	CRITICAL

[1] Downgraded twice due to having a small number of studies/ participants

[2] Downgraded once as being a single, moderate risk study

Comparison 24: Metformin+pioglitazone versus pioglitazone

Grade assessments and evidence profile

	Comparison: Metformin+Pioglitazone - Pioglitazone											
	Quality assessment						No of participants					
	No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Met+ PIO 23	PIO 21	P-value	Favours	Certainty	Importance
Weight (kg)												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	23	21	0.86	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI kg/m2												

Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	23	21	0.87	No difference	⊕◯◯◯ VERY LOW	CRITICAL
WHR												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	23	21	0.53	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Testosterone												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	23	21	0.04	**Metformin+Pio**	⊕◯◯◯ VERY LOW	IMPORTANT
DHEAS												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	23	21	0.64	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Total cholesterol												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	23	21	0.16	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
HDL												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	23	21	0.45	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
LDL												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	23	21	0.28	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Triglycerides												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	23	21	0.53	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Fasting insulin												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	23	21	0.35	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Fasting glucose												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	23	21	0.03	**Pioglitazone**	⊕◯◯◯ VERY LOW	IMPORTANT
HOMA-IR												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	23	21	0.47	No difference	⊕◯◯◯ VERY LOW	CRITICAL

[1] Downgraded twice due to the evidence being derived from a single high risk of bias study

[2] Downgraded twice due to having a small number of studies/ participants

Comparison 25: Metformin versus metformin+pioglitazone

Grade assessments and evidence profile

	Comparison: Metformin – Metformin+Pioglitazone											
	Quality assessment						No of participants					
	No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Met 22**	**Met+ Pio 23**	**P-value**	**Favours**	**Certainty**	**Importance**
Weight (kg)												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	22	23	0.88	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI kg/m2												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	22	23	0.61	No difference	⊕◯◯◯ VERY LOW	CRITICAL
WHR												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	22	23	0.43	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Testosterone												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	22	23	1.0	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
DHEAS												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	22	23	0.92	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Total cholesterol												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	22	23	0.24	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
HDL												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	22	23	0.44	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
LDL												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	22	23	0.73	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Triglycerides												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	22	23	0.16	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Fasting insulin												

Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	22	23	0.04	**Metformin+Pioglitazone**	⊕◯◯◯ VERY LOW	IMPORTANT
Fasting glucose												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	22	23	0.34	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
HOMA-IR												
Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	22	23	0.02	**Metformin+Pioglitazone**	⊕◯◯◯ VERY LOW	CRITICAL

[1] Downgraded twice due to the evidence being derived from a single high risk of bias study

[2] Downgraded twice due to having a small number of studies/ participants

Comparison 26: Metformin versus metformin+rosiglitazone

Grade assessments and evidence profile

	Comparison: Metformin – Metformin+Rosiglitazone											
	Quality assessment						No of participants					
	No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Met 68**	**Met+ Rosi 69**	**P-value**	**Favours**	**Certainty**	**Importance**
Weight (kg)												
Overall	1	RCT	No serious	Not applicable	Not applicable	Serious[1]	68	69	<0.025	**Metformin**	⊕⊕⊕◯ MODERATE	IMPORTANT
BMI kg/m2												
Overall	1	RCT	No serious	Not applicable	Not applicable	Serious[1]	68	69	<0.025	**Metformin**	⊕⊕⊕◯ MODERATE	CRITICAL
SHBG												
Overall	1	RCT	No serious	Not applicable	Not applicable	Serious[1]	68	69	NR	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
FAI												
Overall	1	RCT	No serious	Not applicable	Not applicable	Serious[1]	68	69	NR	No difference	⊕⊕⊕◯ MODERATE	CRITICAL

Testosterone											
Overall	1	RCT	No serious	Not applicable	Not applicable	Serious[1]	68	69	NR	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
Fasting insulin											
Overall	1	RCT	No serious	Not applicable	Not applicable	Serious[1]	68	69	NR	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
Fasting glucose											
Overall	1	RCT	No serious	Not applicable	Not applicable	Serious[1]	68	69	NR	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
Total cholesterol											
Overall	1	RCT	No serious	Not applicable	Not applicable	Serious[1]	68	69	<0.025	**Metformin+Rosiglitazone**	⊕⊕⊕◯ MODERATE	IMPORTANT
HDL											
Overall	1	RCT	No serious	Not applicable	Not applicable	Serious[1]	68	69	<0.025	**Metformin**	⊕⊕⊕◯ MODERATE	IMPORTANT
LDL											
Overall	1	RCT	No serious	Not applicable	Not applicable	Serious[1]	68	69	NR	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
Triglycerides											
Overall	1	RCT	No serious	Not applicable	Not applicable	Serious[1]	68	69	<0.025	**Metformin+Rosiglitazone**	⊕⊕⊕◯ MODERATE	IMPORTANT
CRP											
Overall	1	RCT	No serious	Not applicable	Not applicable	Serious[1]	68	69	NR	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
HOMA-IR											
Overall	1	RCT	No serious	Not applicable	Not applicable	Serious[1]	68	69	NR	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
DHEAS											
Overall	1	RCT	No serious	Not applicable	Not applicable	Serious[1]	68	69	NR	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
Androstenedione											
Overall	1	RCT	No serious	Not applicable	Not applicable	Serious[1]	68	69	NR	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
Menstrual cycle											
Overall	1	RCT	No serious	Not applicable	Not applicable	Serious[1]	68	69	NR	No difference	⊕⊕⊕◯ MODERATE	CRITICAL

[1] Downgraded once due to being a single study

Comparison 27: Metformin+rosiglitazone versus rosiglitazone

Grade assessments and evidence profile

	Comparison: Metformin+Rosiglitazone - Rosiglitazone											
	Quality assessment						No of participants					
	No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Met+ Rosi 69**	**Rosi 67**	**P-value**	**Favours**	**Certainty**	**Importance**
Weight (kg)												
Overall	1	RCT	No serious	Not applicable	Not applicable	Serious[1]	69	67	NR	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
BMI kg/m2												
Overall	1	RCT	No serious	Not applicable	Not applicable	Serious[1]	69	67	NR	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
SHBG												
Overall	1	RCT	No serious	Not applicable	Not applicable	Serious[1]	69	67	NR	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
FAI												
Overall	1	RCT	No serious	Not applicable	Not applicable	Serious[1]	69	67	NR	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Testosterone												
Overall	1	RCT	No serious	Not applicable	Not applicable	Serious[1]	69	67	<0.025	**Metformin+Rosiglitazone**	⊕⊕⊕◯ MODERATE	IMPORTANT
Fasting insulin												
Overall	1	RCT	No serious	Not applicable	Not applicable	Serious[1]	69	67	NR	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
Fasting glucose												
Overall	1	RCT	No serious	Not applicable	Not applicable	Serious[1]	69	67	NR	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
Total cholesterol												
Overall	1	RCT	No serious	Not applicable	Not applicable	Serious[1]	69	67	<0.025	**Metformin+Rosiglitazone**	⊕⊕⊕◯ MODERATE	IMPORTANT
HDL												

Overall	1	RCT	No serious	Not applicable	Not applicable	Serious[1]	69	67	<0.025	**Rosiglitazone**	⊕⊕⊕◯ MODERATE	IMPORTANT
LDL												
Overall	1	RCT	No serious	Not applicable	Not applicable	Serious[1]	69	67	NR	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
Triglycerides												
Overall	1	RCT	No serious	Not applicable	Not applicable	Serious[1]	69	67	NR	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
CRP												
Overall	1	RCT	No serious	Not applicable	Not applicable	Serious[1]	69	67	NR	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
HOMA-IR												
Overall	1	RCT	No serious	Not applicable	Not applicable	Serious[1]	69	67	NR	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
DHEAS												
Overall	1	RCT	No serious	Not applicable	Not applicable	Serious[1]	69	67	NR	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
Androstenedione												
Overall	1	RCT	No serious	Not applicable	Not applicable	Serious[1]	69	67	NR	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
Menstrual cycle												
Overall	1	RCT	No serious	Not applicable	Not applicable	Serious[1]	69	67	NR	No difference	⊕⊕⊕◯ MODERATE	CRITICAL

[1] Downgraded once due to being a single study

Comparison 28: Metformin versus metformin (different dose)

Grade assessments and evidence profile

	Comparison: Metformin 1500mg/d – metformin 2550mg/d											
	Quality assessment						No of participants					
	No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Met 42**	**Met 41**	**P-value**	**Favours**	**Certainty**	**Importance**
Weight (kg)												

Overall	1	RCT	Very serious[1]	Not applicable	Not applicable	Serious[2]	42	41	0.08	No difference	⊕◯◯◯ VERY LOW	IMPORTANT

[1] Downgraded twice due to the evidence being derived from a single high risk of bias study
[2] Downgraded once due to having a small number of studies/ participants

Comparison 29: Metformin versus metformin+MPA

Grade assessments and evidence profile

	Comparison: Metformin – Metformin+MPA											
	Quality assessment						No of participants					
	No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Met 20**	**Met+ MPA 20**	**P-value**	**Favours**	**Certainty**	**Importance**
Weight (kg)												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	20	20	0.86	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
BMI kg/m2												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	20	20	0.80	No difference	⊕◯◯◯ VERY LOW	CRITICAL
DHEAS												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	20	20	0.89	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Testosterone												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	20	20	0.001	**Metformin**	⊕◯◯◯ VERY LOW	IMPORTANT
Free testosterone												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	20	20	<0.001	**Metformin**	⊕◯◯◯ VERY LOW	IMPORTANT
Total cholesterol												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	20	20	0.87	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
HDL												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	20	20	0.04	**Metformin**	⊕◯◯◯ VERY LOW	IMPORTANT
LDL												

Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	20	20	0.52	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Triglycerides												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	20	20	0.11	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Fasting insulin												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	20	20	0.64	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Fasting glucose												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	20	20	0.33	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
HOMA-IR												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	20	20	0.85	No difference	⊕◯◯◯ VERY LOW	CRITICAL
OGTT												
Overall	1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	20	20	0.82	No difference	⊕◯◯◯ VERY LOW	IMPORTANT

[1] Downgraded once due to the evidence being derived from a single moderate risk of bias study

[2] Downgraded twice due to having a small number of studies/ participants

QUALITY APPRAISAL. RANDOMISED CONTROLLED TRIALS

Study ID	Aghamohammadzadeh 2010
Study Citation	Aghamohammadzadeh N, Aliasgarzadeh A, Baglar L, Abdollahifard S, Bahrami A, Najafipour F, et al. Comparison of metformin and cyproteroneestrodiol compound effect on hs c-reactive protein and serum androgen levels in patients with poly cystic ovary syndrome. Pakistan journal of medical sciences. 2010;26(2):347-51.
Study Country	Iran
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS
PCOS diagnostic criteria	NIH
Presence of infertility	*Not reported*
Presence of other condition/s	*Not reported*
Medication History	*No*
N per group	*Allocated/randomised: 35 to each group* *Assessed at end of study: 30 in each group*
Setting	*specialty and sub specialty clinics of Tabriz University (Medical Sciences).*
Intervention	*EE 35 μg + CPA 2 mg*
Comparison	*Meformin 1000 mg/d*
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*CRP, androgens*
Follow up Duration	*3 + 6 months*
Summary Result/s	*No significant differences between COCP and metformin.*
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT	

Does the study have a clearly focused question and/or PICO?	**Yes** Partial No Not reported	*The aim of our study was to compare the effects of Metformin and Cyproterone-estradiol compound on CRP and androgens level in patients with PCOS.*
Does the study have specified inclusion/exclusion criteria?	**Yes** Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	**Yes** Partial No Not reported	
Inclusion criteria	Yes **Partial** No Not reported	*patients with PCOS from specialty and sub specialty clinics of Tabriz University (Medical Sciences). We used the National Institutes of Health criteria for diagnosis of patients. Not clearly stated specific inclusion criteria.*
Exclusion criteria	**Yes** Partial No Not reported	*rheumatic disease, infective disease, therapy for hirsutism and scalp hair loss such as spironolactone and finasteride and therapy for acne such as antibi-otics.*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No **Not reported**	*Patients randomly divided in two equal groups.*
	Was allocation to intervention group concealed?	Yes Partial No **Not reported**	
PERFORMANC	**Were patients blind to intervention group?**	Yes Partial No **Not reported**	

	Were investigators and care providers blind to intervention group?	Yes Partial No **Not reported**	
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No **Not reported**	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No **Not reported**	
	Were all outcomes measured in a standard, valid and reliable way?	Yes **Partial** No Not reported	*Yes for blood tests, not reported for anthropometry*
	Were outcomes assessed objectively and independently?	Yes **Partial** No Not reported	*Yes for blood tests, not reported for anthropometry*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	14% COCP 14% met	*COCP 5/35 = 14%* *Met 5/35 = 14%*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial **No** Not reported	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No **Not reported**	*No protocol*

CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes **Partial** No Not reported	*Only BMI, andorgens and CRP at baseline reported, not other baseline criteria such as age.*
	If confounding was present, was it controlled for?	Yes Partial **No** Not reported	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No **Not reported**	
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No **Not reported**	
	If statistical analysis was undertaken, was this appropriate?	Yes **Partial** No Not reported	*T tests were used, no reports on if data was normally distributed*
COMMENTS			
What is the overall risk of bias?		Low Moderate **High** Insufficient information	*Randomization not described. Lack of baseline data. No protocol,*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

Study ID	Ahmad 2008
Study Citation	Ahmad, Jamal; Shukla, Nidhi; Khan, Abdur Rahman; Ahmed, Faiz; Siddiqui, M. Asim Comparison of metabolic effects of metformin and rosiglitazone in the management of polycystic ovary syndrome (PCOS): A prospective, parallel, randomized, open-label study Diabetes & metabolic syndrome clinical research & reviews 2008;2(1):37-46
Study Country	India
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	PCOS women aged 18-35 years, with complaints of menstrual irregularities, hirsutism, and/or sterility
PCOS diagnostic criteria	NIH
Presence of infertility	For some
Presence of other condition/s	Menstrual irregularities, hirsutism
Medication History	-
N per group	*Allocated/randomised:* 1.Metformin=35 2.Rosiglitazone=35 *Assessed: Metformin=31* *Rosiglitazone=30*
Setting	Seventy non-diabetic, euthyroid, normoprolactinemic women aged 18-35 years, attending the outpatient endocrinology clinic with complaints of menstrual irregularities, hirsutism, and/or sterility were recruited.
Intervention	1.Metformin 850mgx2/d
Comparison	2.Rosiglitazone 2mgx2/d
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	BMI, WHR, hirsutism, menstruation, f-gluc, f-insulin, homa, T, dheas, A

Follow up Duration	3, 6 and 12 months	
Summary Result/s	Rosiglitazone seems to improve insulin resistance relatively earlier; while metformin had an earlier and more sustained benefit on hyperandrogenemia.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*The present study was undertaken to evaluate and compare the efficacy of metformin versus rosiglitazone on insulin resistance and hyperandrogenemia in women with PCOS*
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	
Inclusion criteria	Yes Partial No Not reported	PCOS was diagnosed by the presence of (i) chronic ovulatory dysfunction–oligomenorrhea (cycle length > 45 days) or amenorrhea (cycle length > 6 months), (ii) evidence of hyperandrogenemia, whether clinical (hirsutism with F—G score of >8) or biochemical (serum concentration of testosterone)
Exclusion criteria	Yes Partial No Not reported	other causes such as CAH, androgen secreting tumors, hyperprolactinemia and Cushing's syndrome.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS — **Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*-Subjects were randomly allocated into two group using random number tables.* -prospective, parallel, randomized, open-label study
SELECTION BIAS — **Was allocation to intervention group concealed**	Yes Partial No Not reported	

PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	Met - 4/35=11.4% Rosi- 5/35=14.3%
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis	Yes Partial No Not reported	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*However, no p-values were reported to report similarity at baseline. This was done via visual inspection.*
	If confounding was present, was it controlled for?	Yes Partial Not reported No	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*There was sufficient randomisation, but open-label design indicates no blinding so there was potentially performance and detection bias.*

Study ID	Alpanes 2017
Study Citation	Alpañés M, Álvarez-Blasco F, Fernández-Durán E, Luque-Ramírez M, Escobar-Morreale HF. Combined oral contraceptives plus spironolactone compared with metformin in women with polycystic ovary syndrome: a one-year randomized clinical trial. European journal of endocrinology / European Federation of Endocrine Societies. 2017;177(5):399-408.
Study Country	Spain
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS
PCOS diagnostic criteria	Rotterdam (fulfills NIH/AES criteria)
Presence of infertility	Excluded
Presence of other condition/s	
Medication History	-
N per group	*Randomised to COC + spir:* 24 assigned, 18 completed *Randomized to metformin.:* 22 assigned, 13 completed
Setting	*Androgen excess outpatient clinic, Madrid, Spain*
Intervention	30 μg EE+ 150 μg DG (Microdiol, Merck Sharp & Dohme de España, S.A. Madrid, Spain) given 21/28 days + 100 mg spironolactone (Aldactone, Pfizer, S.L., Alcobendas, Spain)
Comparison	*Metformin* (Dianben, Merck, S.L., Mollet del Vallés, Spain) 850 mg b.i.d. (total 1700 mg/day)
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Hirsutism score, BMI, waist circumference and waist-to-hip ratio after three, six, nine and 12 months of treatment.* *Androgenic profile and OGTT after overnight fasting.*
Follow up Duration	*12 months*

Summary Result/s	Compared with metformin, COC plus spironolactone caused larger decreases in hirsutism score, total and free testosterone and menstrual dysfunction.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	**Yes** Partial No Not reported	*The aim was to compare COC + spiro vs. met to compare treatment efficacy and safety in terms of cardiometabolic risk factors and adverse events.*
Does the study have specified inclusion/exclusion criteria?	**Yes** Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	**Yes** Partial No Not reported	
Inclusion criteria	**Yes** Partial No Not reported	*Diagnosis of PCOS required the presence of clinical and/or biochemical hyperandrogenism together with evidence of oligoovulation. Specific etiologies such as nonclassic 21-hydroxylase deficiency, hyperprolactinemia, hypothyroidism, Cushing's syndrome and androgen-secreting tumors had been excluded.* *Hirsutism was defined by a modified Ferriman–Gallwey score ≥8 points. Biochemical hyperandrogenism was defined by total testosterone ≥2.3 nmol/L, calculated free testosterone ≥35 pmol/L, androstendione ≥15.7 nmol/L and/or dehydroepiandrosterone sulfate ≥9.5 µmol/L.* *Ovulatory dysfunction required the presence of menstrual dysfunction (menstrual cycle length: ≤ 26 or > 35 days) or evidence of luteal phase defect in women with normal menstrual cycles (day 20–24 serum progesterone concentrations: ≤12.7 pmol/L).*
Exclusion criteria	**Yes** Partial No Not reported	*Patients seeking fertility and those with previous surgical treatment of PCOS or medical treatment with hormonal contraceptives, antiandrogens, insulin sensitizers or drugs that might interfere with blood pressure regulation, lipid profile or carbohydrate metabolism for the previous three months, history of serious illness including hypertension, diabetes mellitus, or cardiovascular*

			events, pregnancy, contraindication for the use of metformin, COC or spironolactone and drug or alcohol abuse.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	**Yes** Partial No Not reported	*Stratified block randomization one-to-one ratio. Blocks of ten sealed opaque envelopes (five per arm of treatment) served for treatment assignment. Stratification for obesity, defined by a body mass index (BMI) ≥30 kg/m2, was accomplished by using separate blocks for non-obese and for obese women.*
	Was allocation to intervention group concealed?	Yes Partial **No** Not reported	*No masking method was used after randomization.*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial **No** Not reported	
	Were investigators and care providers blind to intervention group?	Yes Partial **No** Not reported	
	Aside from the experimental intervention, were the groups treated the same?	Yes **Partial** No Not reported	*Met group started on lower dose first week, and were advised to use barrier conception.*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No **Not reported**	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes **Partial** No Not reported	*Yes for blood samples. Not reported for anthropometric and hirsutism outcomes.*

	Were outcomes assessed objectively and independently?	Yes **Partial** No Not reported	*Yes for blood samples. Not reported for anthropometric and hirsutism outcomes.*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	25% treatment 41% control/ comparison	*COC + spiro: 24 assigned, 18 with ongoing treatment after 12 months = 25% dropout.* *24 included in ITT analysis = 100%.* *Met: 22 assigned, 13 with ongoing treatment after 12 months = 41% dropout. 22 included in ITT analysis = 100%.*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	**Yes** Partial No Not reported	*ITT*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	**Yes** Partial No Not reported	*Protocol published is in Spanish but seems to include the reported outcomes.*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes **Partial** No Not reported	*Partial* *SHBG levels seem to be higher at baseline in COC+spiro group. Met group has higher FG score at baseline.*
	If confounding was present, was it controlled for?	Yes Partial **No** Not reported	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial **No** Not reported	

	Was the study sufficiently powered to detect any differences between the groups?	**Yes** Partial No Not reported	
	If statistical analysis was undertaken, was this appropriate?	Yes **Partial** No Not reported	*No absolute results presented, only % change from baseline for some outcomes, and not for both groups.*
COMMENTS			
What is the overall risk of bias?		Low Moderate **High** Insufficient information	*High dropout rate, most results not presented as numbers with appropriate measures. Group allocation probably known to the ones who performed hirsutism assessment (not reported)*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

Study ID	Altinok 2018
Study Citation	Altinok, Magda Lambaa; Ravn, Pernille; Andersen, Marianne; Glintborg, Dorte Effect of 12-month treatment with metformin and/or oral contraceptives on health-related quality of life in polycystic ovary syndrome Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology 2018;34(10):859-863
Study Country	Denmark
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	White women with PCOS, aged 18-39 years, BMI <35

PCOS diagnostic criteria	Rotterdam
Presence of infertility	Not reported
Presence of other condition/s	Eight participants had prescriptions of antidepressants at trial-start M (n = 3), M + OCP (n = 3) and OCP (n =2)
Medication History	Eight participants had prescriptions of antidepressants at trial-start M (n = 3), M + OCP (n = 3) and OCP (n =2)
N per group	*Allocated/randomised: Metformin-group 30* *OCP-group 30* *Metformin+OCP 30* *Assessed at end of study: Metformin-group 19* *OCP-group 23* *Metformin+OCP 23*
Setting	Patients were recruited from the Department of Endocrinology, Odense University Hospital, and from local fertility clinics and Departments of Gynecology.
Intervention	Metformin 1000+1000 mg/d (M was slowly up titrated with 500 mg/day/week). M was paused 4 weeks and OCP 12 weeks prior to evaluation. Barrier contraception during the study period or an intrauterine device implanted. All patients were given general advice on lifestyle intervention.
Comparison	OCP-group: 150 mg desogestrel+30 µg ethinylestradiol Metformin+OCP: Metformin 1000+1000 mg/d and 150 mg desogestrel+30 µg ethinylestradiol. All patients were given general advice on lifestyle intervention.
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Weight, BMI (kg/m2), FG-total, Total T, FAI, SHBG (nmol/l), Health-related quality of life
Follow up Duration	12 months
Summary Result/s	HRQoL changes were comparable between 12- month randomized M and/or OCP treatment in relatively healthy and lean women with PCOS.

ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	To assess changes in HRQoL during a 12-month randomized treatment with M, OCP or M + OCP in PCOS.

Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	
Inclusion criteria	Yes Partial No Not reported	White women, aged 18–39 years and with body mass index (BMI) < 35 kg/m2. Patients who fulfilled the Rotterdam criteria for PCOS
Exclusion criteria	Yes Partial No Not reported	Pregnancy, medical diseases, untreated depression or eating disorders, diabetes or contraindications for M or OCP
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported
	Was allocation to intervention group concealed?	Yes Partial No Not reported
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported

	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	Patients with Metformin only consented to use a barrier contraception during the study period or have an intrauterine device implanted.
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	*Metformin-group 11/30=36.7%* *OCP-group 7/30=23.3%* *Metformin+OCP 7/30=23.3%*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Only remaining participants*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	

CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*SOS missing*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	Oral contraceptive pills and metformin tablets were sponsored by Sandoz but they were not involved in the economy, planning of the project, or writing of the article.
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	The power of the study was calculated using the area under the curve for serum insulin during two hours oral glucose tolerance test as the primary end point. No previous randomized controlled trials has examined the effect of M and/or OCP on HRQoL during 12-month treatment.
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	
COMMENTS		*High dropout rate, no baseline data regarding important confounders, unclear randomization and blinding process.*	
What is the overall risk of bias?		Low Moderate High Insufficient information	
Did risk of bias differ by outcome *(eg. primary outcome was*		*No – all outcomes high risk of bias*	

low risk but rest were high)?	

Study ID	Bilgir 2009
Study Citation	*Bilgir O, Kebapcilar L, Taner C, Bilgir F, Kebapcilar A, Bozkaya G, et al. The effect of ethinylestradiol (EE)/cyproterone acetate (CA) and EE/CA plus metformin treatment on adhesion molecules in cases with polycystic ovary syndrome (PCOS). Intern Med. 2009;48(14):1193-9.*
Study Country	Turkey
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS
PCOS diagnostic criteria	Rotterdam
Presence of infertility	*Not reported*
Presence of other condition/s	
Medication History	*No*
N per group	*Allocated/randomised: 20 in each group* *Assessed at end of study: 20 in each group*
Setting	*Not reported, study performed in Turkey,*
Intervention	*EE 35 µg plus CPA 2 mg (Diane Nova, Shering, Germany; 21 days per month followed by a 7-day pill-free period*
Comparison	*EE 35 µg plus CPA 2 mg (Diane Nova, Shering, Germany; 21 days per month followed by a 7-day pill-free period + metformin (Glucophage, Merck Lipha Lab, Lyon, France; 850 mg twice daily).*
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Lipid profile, androgens, insulin, and HOMA-IR values* *Adhesion molecules*
Follow up Duration	*3 months*
Summary Result/s	*EE/CA+metformin treatment reduced inflammation markers in cases with PCOS compared to EE/CA treatment.*
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT	

Does the study have a clearly focused question and/or PICO?	**Yes** Partial No Not reported	*Adhesion molecules were evaluated before and 3 months after treatment to observe the response to EE/CA and EE/CA plus metformin treatment with respect to chronic inflammation previously detected in PCOS.*
Does the study have specified inclusion/exclusion criteria?	**Yes** Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	**Yes** Partial No Not reported	
Inclusion criteria	**Yes** Partial No Not reported	*All cases with PCOS were evaluated based on the Rotterdam criteria. All patients fulfilled the diagnostic criteria; that is, at least two of the three criteria: polycystic ovaries on ultrasonography, clinical and/ or biochemical signs of hyperandrogenism, and oligo- and/ or anovulation. All women had normal thyroid, renal and hepatic functions.* *Not reported if this was inclusion criteria.*
Exclusion criteria	**Yes** Partial No Not reported	*Women who had received any medication (e.g., insulin-sensitizing drugs, oral contraceptives, antiandrogens, statins, aspirin, NSAIDs, warfarin, antidepressant medication, corticosteroids, ASA, GnRH agonists or antagonists) in the preceding 3 months were excluded. Furthermore, patients with hypertension and electrocardiographic changes suggestive of coronary artery disease, a history of angina or myocardial infarction, any known vascular, diabetes mellitus, known coagulation abnormalities, hyperprolactinemia, spontaneous abortion, bulimia or anorexia, any systemic disease,* *infection or inflammatory diseases were excluded from the study.*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No **Not reported**	*randomly divided into two groups*
	Was allocation to intervention group concealed?	Yes Partial No **Not reported**	

PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No **Not reported**	
	Were investigators and care providers blind to intervention group?	Yes Partial No **Not reported**	
	Aside from the experimental intervention, were the groups treated the same?	**Yes** Partial No Not reported	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No **Not reported**	
	Were all outcomes measured in a standard, valid and reliable way?	**Yes** Partial No Not reported	
	Were outcomes assessed objectively and independently?	**Yes** Partial No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	0% COCP 0% COCP + met	*COCP 0/20* *COCP + met 0/20*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	**Yes** Partial No Not reported	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No **Not reported**	*Not reported* *This is difficult to determine if there isn't a protocol.*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	**Yes** Partial No Not reported	
	If confounding was present, was it controlled for?	Yes Partial **No** Not reported	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No **Not reported**	
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No **Not reported**	
	If statistical analysis was undertaken, was this appropriate?	**Yes** Partial No Not reported	
COMMENTS			
What is the overall risk of bias?		Low Moderate **High** Insufficient information	*Randomization not described, no blinding, no protocol.*

Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	

Study ID	Bodur 2018
Study Citation	Bodur S, Dundar O, Kanat-Pektas M, Kinci MF, Tutuncu L. The effects of different therapeutic modalities on cardiovascular risk factors in women with polycystıc ovary syndrome: A randomızed controlled study. Taiwan J Obstet Gynecol. 2018;57(3):411-6.
Study Country	Turkey
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Non-obese women with PCOS aged 18-39 years
PCOS diagnostic criteria	Rotterdam
Presence of infertility	*Not reported*
Presence of other condition/s	
Medication History	*No*
N per group	*OCP: 21* *Met:29* *Combo: 20* *Controls:17*
Setting	*Outpatient gynaecology clinic of the Haydarpasa Training Hospital,Istanbul, Turkey*
Intervention	*3 mg DRSP in combination with 30 µg EE (Yasmin™ pills, Schering AG, Germany).*
Comparison	*Met: 1700 mg metformin per day (Glucophage® 850 mg tablets, Merck Pharmaceuticals, Turkey).* *Combo: 3 mg DRSP and 30 µg EE in combination with 1700 mg metformin per day.* *Controls: No treatment*

Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Primary not stated. Antropometry, glucose metabolism, inflammatory and hematostatic factors.*	
Follow up Duration	*6 months*	
Summary Result/s	*Six cycles of treatments with OC alone may cause metabolic variables to deteriorate in non-obese women with PCOS. The addition of metformin to OC may ameliorate some aspects of this effect.*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	**Yes** Partial No Not reported	*This study was designed to evaluate the effects of different therapeutic modalities (3 mg DRSP/ 30 µg EE, 1700 mg metformin and in combination) on cardiovascular risk factors, including metabolic risk factors, haemostatic risk factors, and markers of low-grade inflammation in non-obese women with PCOS.*
Does the study have specified inclusion/exclusion criteria?	**Yes** Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	**Yes** Partial No Not reported	
Inclusion criteria	**Yes** Partial No Not reported	*Non-obese (18-30 BMI) women with PCOS according to Rotterdam criteria receiving care at the outpatient gynaecology clinic of the Haydarpasa Training Hospital. Clinical or biochemical hyperandrogenism was detected if the modified Ferriman-Gallwey score was higher than 8, acne was present and serum concentrations of total and/ or free testosterone were increased. Oligomenorrhoea was defined when menstruation occurred six times a year at most. Polycystic ovaries were visualized by ultrasonography when increased stromal echogenicity was peripher-ally surrounded by more than 10 follicles with a diameter of 2-8 mm*
Exclusion criteria	**Yes** Partial	*Those patients who had systemic disorders and were receiving therapies that could affect*

		No Not reported	*carbohy-drate and lipid metabolism were excluded from the study. Patients reporting contraindications for oral contraceptives and metformin were also excluded from the study.*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes **Partial** No Not reported	*randomized into four subgroups by a computerized method*
	Was allocation to intervention group concealed?	Yes Partial No **Not reported**	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No **Not reported**	
	Were investigators and care providers blind to intervention group?	Yes Partial No **Not reported**	
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No **Not reported**	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No **Not reported**	
	Were all outcomes measured in a standard, valid and reliable way?	**Yes** Partial No Not reported	
	Were outcomes assessed objectively and independently?	**Yes** Partial No Not reported	

ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	19% treatment (OCP) Met: 41% Combo: 40% Controls: 13%	*OCP 4/21 dropouts = 19%* *Met: 12/29 dropouts = 41%* *Combo 8/20 dropouts = 40%* *Controls 2/17 dropouts = 13%*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No **Not reported**	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No **Not reported**	*Not reported* *No protocol.*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	**Yes** Partial No Not reported	
	If confounding was present, was it controlled for?	Yes Partial **No** Not reported	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial **No** Not reported	

	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No **Not reported**	
	If statistical analysis was undertaken, was this appropriate?	**Yes** Partial No Not reported	
COMMENTS		*Lack of blinding and high dropout rate not similar between groups key reason for high RoB*	
What is the overall risk of bias?		Low Moderate **High** Insufficient information	Lack of blinding and high dropout rate not similar between groups key reason for high RoB
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No – all outcomes high risk of bias*	

Study ID	Bridger 2006
Study Citation	Bridger, T.; MacDonald, S.; Baltzer, F.; Rodd, C. Randomized placebo-controlled trial of metformin for adolescents with polycystic ovary syndrome Arch Pediatr Adolesc Med Mar 2006;160(3):241-6
Study Country	Canada
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Adolescents, 13 to 18 years with hyperinsulinemia and PCOS
PCOS diagnostic criteria	Author defined. All subjects had chronic oligomenorrhea (<6 menses in the preceding year) and clinical or biochemical evidence of hyperandrogenism

Presence of infertility	No	
Presence of other condition/s	No	
Medication History	*No*	
N per group	*Allocated/randomised: Metformin-group 11* *placebo-group 11* *Assessed at end of study, Metformin-group 11* *placebo-group 10*	
Setting	Adolescents with PCOS and hyperinsulinemia from the Endocrinology and Adolescent Medicine clinics of the Montreal Children's Hospital (Montreal, Quebec) between 1999 and 2002. Participants were 13-18 years old and had a history of menarche at least 2 years prior to enrollment	
Intervention	Metformin 750mgx2/day	
Comparison	Placebo 1 tablx2/day	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	BMI, , T, f-gluc, HOMA, lipids, girls with restored menses	
Follow up Duration	3 months	
Summary Result/s	A significant decline in T with metformin compared with placebo The relative risk of menses was 2.50 times higher in the metformin group compared with the placebo. There were no significant changes in bmi, hirsutism, triglyceride levels, or total and low-density lipoprotein cholesterol levels.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	To determine whether metformin or placebo could, in conjunction with healthy lifestyle counseling, decrease serum testosterone levels and related aberrations in adolescents with hyperandrogenism, hyperinsulinemia, and polycystic ovarian syndrome.
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	

If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	
Inclusion criteria		Yes Partial No Not reported	Adolescents, 13 to 18 years with chronic oligomenorrhea (<6 menses in the preceding year) and clinical or biochemical evidence of hyperandrogenism
Exclusion criteria		Yes Partial No Not reported	Exclusion criteria included diabetes mellitus, renal or hepatic disease, pregnancy, allergies to metformin, taking oral contraceptives in the 6 months prior to enrolment, or taking medications that could influence the effects of insulin or androgens
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Patients were randomized by draw sequential sampling, without replacement
	Was allocation to intervention group concealed?	Yes Partial No Not reported	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*placebo-controlled, double- blind trial*
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	

DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	*Metformin-group 0/11=0%* *placebo-group 1/11=9.1%*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)	Yes Partial No Not reported	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Differences in BMI*

	If confounding was present, was it controlled for?	Yes Partial No Not reported	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*Aventis Phar- maceutical, Laval, Quebec, supplied metformin and an identical appearing placebo*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Sample size was based on power calculations and the pub- lished effects of metformin treatment in adult women. We ap- proached eligible candidates sequentially until this goal was achieved, and baseline demographic features did not differ be- tween participants and nonparticipants
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

Study ID	Burchall 2017

Study Citation	Burchall, Genia F.; Piva, Terrence J.; Ranasinha, Sanjeeva; Teede, Helena J. Differential Effects on Haemostatic Markers by Metformin and the Contraceptive Pill: A Randomized Comparative Trial in PCOS Thrombosis and haemostasis 2017;117(11):2053-2062
Study Country	Australia
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Overweight and obese women with PCOS
PCOS diagnostic criteria	NIH
Presence of infertility	No
Presence of other condition/s	BMI – metformin group = 37.79 ± 6.81 Low dose OCP+spiro=35.25 ± 5.71 Higher-dose OCP= 35.91 ± 8.11
Medication History	*No*
N per group	*Allocated/randomised: metformin-group N=37* *Low-dose OCP+spiro N=38* *High dose OCP=35* *Assessed at end of study: metformin-group N=23* *Low-dose OCP+spiro N=16* *High dose OCP=21* Not all participants had samples available for haemostatic measurements.
Setting	The women were recruited from community advertisements and studied between 2003 and 2005. The study was performed retrospectively on biobanked samples.
Intervention	Participants received standard diet and lifestyle advice at the screening visit. Three months later, women were randomly allocated. Metformin 1000mgx2/day with dose titrated up over 4 weeks starting at 500 mgx2/dday.
Comparison	Participants received standard diet and lifestyle advice at the screening visit. Low-dose OCP+Spiro: 20-µg EE/100-µg levonorgestrel combined with spironolactone 50 mgx2/day High-dose OCP: 35-µg EE/2-mg cyproterone acetate

Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	BMI, oGTT, Insulin, HOMA-IR, T, PAI-1, ADMA, PF1 and 2, TG, Fibrinolytic system, Plasminogen, TAFI.	
Follow up Duration	Metabolic, hormonal and haemostatic markers were assessed at baseline and after 6 months of intervention.	
Summary Result/s	Endothelial function improved with higher dose with some improvement in low-dose OCP + S and metformin. Aberrant coagulation was noted in both OCP groups, but not with metformin. Fibrinolysis was reduced with higher-dose OCP. Study suggests an additional dimension of treatment (haemostatic system effects) that favours metformin treatment over the OCP in PCOS.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	To investigate and compare haemostatic impacts of common pharmacological treatments and explore relationships with hormonal and metabolic variables in PCOS.
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	
Inclusion criteria	Yes Partial No Not reported	PCOS was diagnosed after medical review by the study team based on the NIH criteria that includes irregular menstrual cycles (<21 or >35 days) and clinical (hirsutism, acne) or biochemical (elevation of at least one circulating ovarian androgen) hyperandrogenism.
Exclusion criteria	Yes Partial No Not reported	Exclusion criteria were secondary causes of amenorrhea and hyperandrogenism (congenital adrenal hyperplasia, androgen-secreting tumours, Cushing's syndrome, hyperprolactinaemia, thyroid dysfunction, adrenal disorders and pregnancy), smoking and diabetes.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	At randomization subjects were allocated to one of three groups based on computer-generated random numbers. Open label study
	Was allocation to intervention group concealed?	Yes Partial No Not reported	Open label study
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	Open label study
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	Open label study. End-point sample collection was completed by a research nurse who was blinded to the treatment allocation.
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	End-point sample collection was completed by a research nurse who was blinded to the treatment allocation.
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	*metformin-group N=14/37=37.8%* *low-dose OCP+spiro N=22/38=57.9%* *high dose OCP=14/35=40%* Not all participants had samples available for haemostatic measurements.

	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	There was no significant difference in age between the three interventional groups. Other variables not reported.
	If confounding was present, was it controlled for?	Yes Partial No Not reported	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Prior sample size calculation was made to ensure adequate statistical power to detect statistical significance, although the study was slightly underpowered in the low-dose OCP + S group

	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	
COMMENTS		Moderate - Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.	
What is the overall risk of bias?		Low Moderate High Insufficient information	*High drop outrate/lost to follow up and no blinding key reason for high RoB*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	Cai 2022
Study Citation	Cai, Meili; Shao, Xiaowen; Xing, Feng; Zhang, Yuqin; Gao, Xinyu; Zeng, Qiongjing; Dilimulati, Diliqingna; Qu, Shen; Zhang, Manna Efficacy of canagliflozin versus metformin in women with polycystic ovary syndrome: A randomized, open-label, noninferiority trial Diabetes, obesity & metabolism 2022;24(2):312-320
Study Country	China
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women aged 18 to 45 years with PCOS and IR
PCOS diagnostic criteria	Rotterdam
Presence of infertility	NR
Presence of other condition/s	Insulin resistance
Medication History	No
N per group	*Allocated/randomised:* 1. Metformin=35 2. Canagliflozin=33

	Assessed: 1. Metformin=29 2. Canagliflozin=30	
Setting	A randomized open-label study in the Department of Endocrinology, Shanghai Tenth People's Hospital between July 2019 and April 2021. 68 PCOS patients with IR who were aged 18 to 45 years were finally enrolled	
Intervention	Metformin 500mgx2 the first week, then Metformin 1500-2000mg/d	
Comparison	Canagliflozin 100mg/d	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Weight, bmi, whr, menstrual cycles, homa, f-gluc, f-insulin, lipids, T, A, DHEAS, SHBG	
Follow up Duration	3 months	
Summary Result/s	canagliflozin was not inferior to metformin in PCOS patients with IR	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	To determine the safety and efficacy of canagliflozin in comparison to metformin in polycystic ovary syndrome (PCOS) patients with insulin resistance (IR).
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	
Inclusion criteria	Yes Partial No Not reported	-PCOS patients with IR who were aged 18 to 45 years -Diagnosis of PCOS was based on the Rotterdam diagnosis criteria (2003)

Exclusion criteria		Yes Partial No Not reported	-younger than 18 years or older than 45 years -mental illness that rendered the individual unable to provide informed consent -severe hepatic and renal dysfunction and/or heart failure -taking/having taken traditional Chinese medicine, contraceptives, SGLT2 inhibitors, metformin, glucagon-like peptide-1 or pioglitazone in the previous 3 months -current or recent participation in another clinical trial -strong fertility needs within half a year of the study period.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	randomized, in a 1:1 ratio, to either a canagliflozin or a metformin group, using blocked randomization (block size: 6). Sequentially numbered, sealed, opaque envelopes were used for allocation concealment.
	Was allocation to intervention group concealed?	Yes Partial No Not reported	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	The participants were advised to use adequate contraception while receiving canagliflozin.

DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	1. Metformin=6/35=17.1% 2. Canagliflozin=3/33=9.1%
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*The intention to treat population was used to analyse the safety of canagliflozin versus metformin and the pre-protocol population was used to analyse the efficacy of canagliflozin versus metformin*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	clinical trial registration number was NCT04700839. *Protocol published at the end of the study period*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	

	If confounding was present, was it controlled for?	Yes Partial Not reported No	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*Funding not reported*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	
COMMENTS		*No blinding, protocol published in retrospect*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate*

Study ID	*Cetinkalp 2009*
Study Citation	Cetinkalp S, Karadeniz M, Erdogan M, Ozgen G, Saygl F, Ylmaz C. The effects of rosiglitazone, metformin, and estradiol-cyproterone acetate on lean patients with polycystic ovary syndrome. The Endocrinologist (Baltimore, Md). 2009;19(3):94-7.
Study Country	Turkey
BRIEF CHARACTERISTICS OF RCT	

Patient/population/ participants	Women with PCOS	
PCOS diagnostic criteria	Rotterdam	
Presence of infertility	*Not reported*	
Presence of other condition/s		
Medication History	*No*	
N per group	*Allocated/randomised: 100 included, 94 randomized* *Assessed at end of study:* *COCP:33* *Met: 47* *Rosiglitazone:14 (not included in this systematic review)*	
Setting	*Not reported*	
Intervention	35ug EE +2 mg CPA	
Comparison	metformin 2g/day	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	BMI, weight, TG, Chol, LDL, HDL, insulin, glucose, HOMA, DHEAS, free T, TT, CRP, oligo-/amenorrhea, FG score	
Follow up Duration	*4 months*	
Summary Result/s	*ECA is more effective than insulin-sensitizing drugs such as rosiglitazone and metformin in improving menstrual pattern and reducing serum free-testosterone levels. MET, an insulin-sensitizing drug, is more effective in reducing fasting insulin levels than the ECA.*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	**Yes** Partial No Not reported	*The present study aims to compare the clinical, biochemical, and hormonal changes in PCOS patients on MET, ROSI, and ECA therapy.*
Does the study have specified inclusion/exclusion criteria?	**Yes** Partial No Not reported	

If there were specified inclusion/ exclusion criteria, were these appropriate?		**Yes** Partial No Not reported	
Inclusion criteria		**Yes** Partial No Not reported	*Young women with PCOS were included in our study. PCOS was defined by the Rotterdam PCOS consensus criteria.*
Exclusion criteria		**Yes** Partial No Not reported	Patients who had DM, hyperprolactinemia, congenital adrenal hyper-plasia (diagnosed with the adrenocorticotropic hormone stimulation test), thyroid disorders, Cushing syndrome, hypertension, hepatic or renal dysfunction were excluded from the study. Use of confounding medications, such as oral contraceptive agents, antihypertensive medications, and insulin sensitizing drugs were also excluded.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No **Not reported**	*Only reported that randomization was used*
	Was allocation to intervention group concealed?	Yes Partial No **Not reported**	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No **Not reported**	
	Were investigators and care providers blind to intervention group?	Yes Partial No **Not reported**	
	Aside from the experimental intervention, were the groups treated the same?	**Yes** Partial No Not reported	

DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No **Not reported**	
	Were all outcomes measured in a standard, valid and reliable way?	**Yes** Partial No Not reported	
	Were outcomes assessed objectively and independently?	Yes **Partial** No Not reported	*Yes for blood tests, not reported for anthropometry.*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison **Not reported**	*Overall 6/100 dropouts, not reported for specific groups*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No **Not reported**	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No **Not reported**	*No protocol*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes **Partial** No Not reported	*Age not reported*

	If confounding was present, was it controlled for?	Yes Partial **No** Not reported	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No **Not reported**	
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No **Not reported**	
	If statistical analysis was undertaken, was this appropriate?	Yes **Partial** No Not reported	*Only Mann-Whitney U test and Wilcoxon rank sum test were used, no reports on data distribution*
COMMENTS			
What is the overall risk of bias?		Low Moderate **High** Insufficient information	*High due to not describing randomization, no Consort flow chart, no description of group allocation for dropouts, no baseline data for age.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	Cho 2009

Study Citation	Cho, L. W.; Kilpatrick, E. S.; Keevil, B. G.; Coady, A. M.; Atkin, S. L. Effect of metformin, orlistat and pioglitazone treatment on mean insulin resistance and its biological variability in polycystic ovary syndrome Clin Endocrinol (Oxf) Feb 2009;70(2):233-7
Study Country	UK
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Obese, hyperandrogenic, anovulatory Caucasian women with PCOS
PCOS diagnostic criteria	Rott
Presence of infertility	No
Presence of other condition/s	Obesity
Medication History	
N per group	*Allocated/randomised:* 1.Metformin=10 2.Orlistat=10 3.Pioglitazone=10 *Assessed:* 1.Metformin=10 2.Orlistat=10 3.Pioglitazone=10
Setting	Thirty obese hyperandrogenic, anovulatory Caucasian women with PCOS [BMI 36·0 ± 1·2 kg/m2 and age of 26·4 ± 1·5 year (mean ± SEM)] were recruited from the Hull Royal Infirmary endocrinology clinic, where they were referred by their primary care physicians for investigation of menstrual abnormalities, with or without hirsutism.
Intervention	1.Metformin 500mgx3/d
Comparison	2.Orlistat 120mgx3/d 3.Pioglitazone 45mg/d
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Homa, insulin, shbg, bmi, fai
Follow up Duration	3 months

Summary Result/s	Only orlistat reduced both IR and its variability significantly, though all three drugs were effective in reducing hyperandrogenism within the 12-week period of the study	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	To compare the change in IR and its variability before and after treatment with insulin sensitization through metformin and pioglitazone, compared to that induced by weight loss with orlistat
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	*Exclusion criteria were vague (no specified medication)*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	
Inclusion criteria	Yes Partial No Not reported	all patients had oligomenorrhea or amenorrhoea, hyperandrogenaemia and polycystic ovaries on transvaginal ultrasound.
Exclusion criteria	Yes Partial No Not reported	None were on any medications that would alter their IR at the time or for the preceding 3 months of entering the trial. Diabetes was excluded by a 75-g oral glucose tolerance test.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS **Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Randomized, open labelled parallel study randomized using a computer program
SELECTION BIAS **Was allocation to intervention group concealed**	Yes Partial No Not reported	
PERFORMANC **Were patients blind to intervention group?**	Yes Partial No Not reported	

	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	0% in all groups
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis	Yes Partial No Not reported	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	

CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Age not reported*
	If confounding was present, was it controlled for?	Yes Partial Not reported No	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*Funded by Hull university but conflict of interest not reported*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Describes power calculation, but not for what difference*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	
COMMENTS		*No blinding, no protocol, conflict of interest not reported, all relevant baseline values not reported.*	
What is the overall risk of bias?		Low Moderate High Insufficient information	

Study ID	Christakou 2014

Study Citation	Christakou C, Kollias A, Piperi C, Katsikis I, Panidis D, Diamanti-Kandarakis E. The benefit-to-risk ratio of common treatments in PCOS: effect of oral contraceptives versus metformin on atherogenic markers. Hormones (Athens). 2014;13(4):488-97.
Study Country	Greece
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS
PCOS diagnostic criteria	NIH
Presence of infertility	*Not reported*
Presence of other condition/s	
Medication History	*No*
N per group	*Allocated/randomised: 40 / group randomized* *Assessed at end of study:* *EE/CPA:38* *EE/DRSP: 36* *Met: 35*
Setting	Outpatient Departments of Endocrinology of the two participant University Hospitals in Thessaloniki and in Athens, between 2008 and 2010
Intervention	35ug EE +2 mg CPA
Comparison	30 35ug EE + 3mg DRSP metformin 1700 mg/day
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	BMI, HOMA, TT, SHBG, FAI, CRP
Follow up Duration	*3 + 6 months*
Summary Result/s	Metformin as well as the OCP containing cyproterone acetate were effective in reducing serum AGEs while the OCP containing drospirenone had a marginal lowering effect on this marker
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT	

Does the study have a clearly focused question and/or PICO?	**Yes** Partial No Not reported	To compare effects of COCP and metformin on atherosclerotic markers incl CRP and advanced glycated end products in lean women with PCOS
Does the study have specified inclusion/exclusion criteria?	**Yes** Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	**Yes** Partial No Not reported	
Inclusion criteria	**Yes** Partial No Not reported	PCOS according to NIH criteria. All the participants were lean (BMI <25 kg/m2), in good health and nonsmokers or had quit smoking for more than a year at baseline. Not stated if this was exclusion criteria
Exclusion criteria	**Yes** Partial No Not reported	Patients were excluded from participation if they were pregnant or planning to become pregnant, were breastfeeding, had a his-tory of current or recent (within 6 months) use of oral contraceptives, antidiabetics, or antiandrogens, or had any contraindications to metformin therapy including renal or hepatic impairment.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	**Yes** Partial No Not reported	After completing baseline evaluation, patients were randomized in a 1:1:1 ratio Randomization was performed by random number tables. The patient number treatment codes were held by a third party.
	Was allocation to intervention group concealed?	Yes Partial **No** Not reported	
PERFORMANC	**Were patients blind to intervention group?**	Yes Partial **No** Not reported	

	Were investigators and care providers blind to intervention group?	Yes Partial No **Not reported**	
	Aside from the experimental intervention, were the groups treated the same?	**Yes** Partial No Not reported	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	**Yes** Partial No Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	**Yes** Partial No Not reported	
	Were outcomes assessed objectively and independently?	**Yes** **Partial** No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	***EE/CPA 5%*** ***EE/DRSP 10%*** ***Met 13%***	EE/CPA 2/40=5% EE/DRSP 4/40=10% met 5/40=13%
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial **No** Not reported	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No **Not reported**	*No protocol*

CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes **Partial** No Not reported	Matched for age, BMI and WHR. HOMA differed at baseline.
	If confounding was present, was it controlled for?	Yes **Partial** No Not reported	Correlation between HOMA and primary outcomes were checked, no correlations
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial **No** Not reported	
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No **Not reported**	
	If statistical analysis was undertaken, was this appropriate?	**Yes** Partial No Not reported	
COMMENTS			
What is the overall risk of bias?		Low **Moderate** High Insufficient information	Moderate due to only partly described randomization process, no blinding
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	De Zegher
Study Citation	de Zegher, Francis; Diaz, Marta; Villarroya, Joan; Cairo, Montserrat; Lopez-Bermejo, Abel; Villarroya, Francesc; Ibanez, Lourdes The relative deficit of GDF15 in adolescent girls with PCOS can be changed into an abundance that reduces liver fat Scientific reports 2021;11(1):7018
Study Country	Spain
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Adolescent girls with PCOS two RCT pooled (gynaecological age>2.0 years)
PCOS diagnostic criteria	Inclusion criteria were hirsutism (modifed Ferriman-Gallwey score>8), oligomenorrhea (menstrual intervals>45 day), gynaecological age>2.0 years, and absence of sexual activity.
Presence of infertility	No
Presence of other condition/s	hyperandrogenism
Medication History	No
N per group	Allocated/randomised: SPIOMET-group=36 OCP-group=35 Assessed at end of study: SPIOMET-group=29 OCP-group=29
Setting	A post-hoc study of two previous randomised studies in adolescent girls with PCOS
Intervention	Mediterranean diet and regular exercise were recommended to all study participants. SPIOMET-group: spironolactone 50 mgx1 daily, pioglitazone 7.5 mg once daily and metformin 850 mg once daily, taken together at dinner time.
Comparison	Mediterranean diet and regular exercise were recommended to all study participants; OCP-group: 20 µg ethinyloestradiol plus 100 mg levonorgestrel (21/28 days), and placebo (7/28 days)

Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Birthweight, GDF15, CRP, HOMA-IR, adiponectin, abdominal fat, hepatic fat, lipids, FAI, testosterone	
Follow up Duration	12 months with medication. Results of outcomes are shown at baseline, 6 months with medication and 6 months after medication stopped (i.e. 18 months after the study begun)	
Summary Result/s	OCP and SPIOMET treatment were accompanied, respectively, by 1.7- and 3.4-fold rises of circulating GDF15. Post-OCP, the circulating concentrations of GDF15, CRP and insulin returned towards baseline levels; post-SPIOMET, there appeared to be prolonged benefts: GDF15 returned also to baseline levels but CRP, insulin and liver fat remained normal, while circulating HMW adiponectin remained elevated.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	To test the hypothesis that PCOS in non-obese adolescents is characterised by low concentrations of circulating GDF15, when judged by the degree of CRP and insulin drive. To study the effects of OCP versus SPIOMET on circulating GDF15
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	
Inclusion criteria	Yes Partial No Not reported	a) hirsutism (modifed Ferriman-Gallwey score>8) b) oligomenorrhea (menstrual intervals>45 day), c) gynaecological age>2.0 years d) absence of sexual activity.
Exclusion criteria	Yes Partial No Not reported	Exclusion criteria were 21-hydroxylase defciency; glucose intolerance or diabetes; evidence of thyroid, liver, or kidney dysfunction; hyperprolactinemia; and any prior use of medications affecting gonadal/adrenal function, or carbohydrate/lipid metabolism
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	open-label, randomized, controlled design? On the other hand they say that the OCP group got OCP+placebo
	Was allocation to intervention group concealed?	Yes Partial No Not reported	*Open label*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	Open label
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*Not reported for anthropomety, yes for blood samples*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	*SPIOMET-group 7/36=19.4%* *OCP 6/35=17.1%*

	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Not reported*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	
	If confounding was present, was it controlled for?	Yes Partial No Not reported	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	

	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	
COMMENTS		*Conflicting information on randomization and drop-outs key reason for moderate RoB*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No – all outcomes similar*	

Study ID	Diri 2017
Study Citation	Diri, H.; Bayram, F.; Simsek, Y.; Caliskan, Z.; Kocer, D. Comparison of Finasteride, Metformin, and Finasteride Plus Metformin in Pcos. *Acta Endocrinol (Buchar)* **2017**, *13*, 84-89, doi:10.4183/aeb.2017.84.
Study Country	Turkey
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS
PCOS diagnostic criteria	Rotterdam
Presence of infertility	*No*
Presence of other condition/s	*None*
Medication History	*None*
N per group	*Randomised to FIN: n = 16; Randomised to MET: n = 19; Randomised to MET + FIN: n = 17*

Setting	*Patients admitted to the outpatient Endocrinology clinic of Erciyes University medical school, Turkey*	
Intervention	5mg/day FIN (Proscar, Merck Sharp Dohme, UK);	
Comparison/s	850mg twice daily metformin (Glukofen, Sandoz, Turkey); 5mg/day FIN (Proscar, Merck Sharp Dohme, UK) + 850mg twice daily metformin (Glukofen, Sandoz, Turkey).	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	BMI, SHBG, Free T, DHEAS, Adrostenedione. HOMA-IR, AUC-Glucose, AUC-Insulin	
Follow up Duration	12 months	
Summary Result/s	Whilst each individual group showed benefit within the groups, comparisons in changes between the groups in parameters of any particular treatment modality. However, finasteride alone significantly reduced both androgen levels and parameters of insulin resistance. Metformin was not inferior to finasteride in the treatment of hyperandrogenism.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Yes
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes
Inclusion criteria	Yes Partial No Not reported	Yes *This study enrolled 70 patients admitted to the outpatient Endocrinology clinic of Erciyes University Medical School and either newly or previously diagnosed with PCOS.*
Exclusion criteria	Yes Partial No Not reported	Yes - *Patients with chronic systemic diseases, continuous drug use, and those who were treated for PCOS during the previous year were excluded.*

INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	No *Stated it was randomised but no protocol for randomisation provided*
	Was allocation to intervention group concealed?	Yes Partial No Not reported	No *They were informed of the side effects, thus they were aware of which drugs they were taking.*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	Partial
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	Partial *During the first week of treatment, metformin was administered at a dose of 425 mg twice daily to avoid gastrointestinal side effects, and thereafter at a dose of 850 mg twice daily. Compared to other treatments that did not have this dose ramp up.*
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	Partial
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	Yes
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Partial
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	No

ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	Not reported
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	No
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported – no protocol
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	Partial - *Some yes, but others such as SHBG and E2 were not similar at baseline*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	No
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	Partial – no information on funding

	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported – no power calculations made.
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	**High -** *This is due to lack of blinding of participants, attrition bias, and drop-out rate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

Study ID	Dorgham 2021
Study Citation	Dorgham N, Sharobim A, Haggag H, El-Kalioby M, Dorgham D. Adding Combined Oral Contraceptives or Metformin to Laser Treatment in Polycystic Ovarian Syndrome Hirsute Patients. J Drugs Dermatol. 2021;20(3):302-6.
Study Country	Egypt
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS and facial hirsutism
PCOS diagnostic criteria	Rotterdam
Presence of infertility	*Not reported*

Presence of other condition/s	*Facial hirsutism*	
Medication History	*No*	
N per group	*Allocated/randomised: 50/group* *Assessed at end of study: 50/group*	
Setting	*Not stated where, but single center in Cairo, Egypt*	
Intervention	*Laser only*	
Comparison	*1: Laser + metformin* (Glucophage® 500 mg; Merck Serono, Darmstadt, Germany); 2: Laser + COCP, 35 μg EE + 2 mg CPA (Diane-35®; Bayer AG, Leverkusen, Germany).	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	HR-QoL (VAS, Dermatology Life Quality Index (DLQI) Hisutism Life Quality Index) (HLQI))	
Follow up Duration	*6 m*	
Summary Result/s	Combining hormonal treatment with laser hair removal can achieve greater hair reduction, significant improvements in patients' QOL, and better maintenance as compared with when combining metformin with laser hair removal or conducting alone.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	**Yes** Partial No Not reported	Assessing the impact of adding combined oral contraceptives (COCs) or metformin to laser hair removal on the quality of life of polycystic ovarian syndrome (PCOS) patients with hirsutism.
Does the study have specified inclusion/exclusion criteria?	**Yes** Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	**Yes** Partial No Not reported	
Inclusion criteria	**Yes** Partial No	*T*he inclusion criteria were an age of 18 to 40 years with a confirmed diagnosis of PCOS according to

		Not reported	the Rotterdam criteria10 and facial hirsutism as assessed by the Ferriman–Gallwey score.
Exclusion criteria		**Yes** Partial No Not reported	Hirsute patients with other dermatological and/or systemic diseases were considered ineligible for inclusion. Patients with any contraindication to receiving laser or hormonal treatments (eg, history of DVT) were also excluded.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	**Yes** Partial No Not reported	Patients were randomly divided into three equal groups. An independent person created the allocation sequence using computer-generated random numbers. Allocation was concealed using sequentially numbered, opaque sealed envelopes kept by the attending nurse.
	Was allocation to intervention group concealed?	**Yes** Partial No Not reported	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No **Not reported**	
	Were investigators and care providers blind to intervention group?	Yes Partial No **Not reported**	
	Aside from the experimental intervention, were the groups treated the same?	**Yes** Partial No Not reported	
DEDETECTION	**Were outcome assessors blind to intervention group?**	Yes Partial No **Not reported**	

	Were all outcomes measured in a standard, valid and reliable way?	Yes **Partial** No Not reported	Self-reported outcome for QoL, change from start measured on VAS by treating physician
	Were outcomes assessed objectively and independently?	**Yes** Partial No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison **Not reported**	
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No **Not reported**	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No **Not reported**	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No **Not reported**	Baseline data other then QoL data not reported
	If confounding was present, was it controlled for?	Yes Partial No **Not reported**	

OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No **Not reported**	
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No **Not reported**	
	If statistical analysis was undertaken, was this appropriate?	**Yes** Partial No Not reported	
COMMENTS			
What is the overall risk of bias?		Low Moderate **High** Insufficient information	No baseline data, no reports on of dropouts, no blinding
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

Study ID	Elbandrawy 2022
Study Citation	Elbandrawy, A. M.; Yousef, A. M.; Morgan, E. N.; Ewais, N. F.; Eid, M. M.; Elkholi, S. M.; Abdelbasset, W. K. Effect of aerobic exercise on inflammatory markers in polycystic ovary syndrome: a randomized controlled trial European review for medical and pharmacological sciences 2022;26(10):3506-3513
Study Country	Cairo
BRIEF CHARACTERISTICS OF RCT	

Patient/population/ participants	Females aged 25-35 years diagnosed with PCOS [mean age of 26.7±2.3, BMI of 23.6±3.5kg/m2
PCOS diagnostic criteria	Rotterdam
Presence of infertility	Not reported
Presence of other condition/s	No
Medication History	No
N per group	Allocated/randomised: Metformin 20 Metformin+AE-group 20 Assessed at end of study: Metformin 20 Metformin+AE-group 20
Setting	Normal-weight women with PCOS were recruited from the Outpatient Clinic of Gynecology, Kasr Al-Aini University Hospital, Egypt
Intervention	Metformin 1500mg daily.
Comparison	A treadmill was used for walking aerobic exercise. All participants were allowed to hold a support bar if necessary. Participants assigned to the aerobic exercise group were invited to undertake three sessions of supervised exercise training each week for 12 consecutive weeks. Each session lasted approximately 60 min. The aerobic exercises consisted in walking on the treadmill for 30 minutes at a 0% slope, including three phases: the warming-up phase, which consisted in walking on the treadmill for 5 minutes at low intensity (30% of MHR), the actual phase, which consisted in walking on the treadmill for 20 min at moderate intensity (60-70% of MHR), and the cooling phase, which consisted in walking on the treadmill for 5 minutes at low intensity (30% of MHR). The MHR was calculated according to the equation (220-age). In addition Metformin 1500mg daily
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	IL-6, TNF-α, and CRP at baseline and after 12 weeks of intervention.
Follow up Duration	3 months
Summary Result/s	The findings showed a significant reduction in IL-6, TNF-α, and CRP values in both AEM and M groups (p=0.001, p=0.01,

	respectively) after the end of the 12 weeks of the intervention. However, the AEM-group showed a greater reduction in IL-6, TNF-α, and CRP (p=0.01, p = 0.01 and p=0.001, respectively)	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	To examine the potential effects of aerobic exercise on interleukin-6 (IL6), tumor necrosis factor (TNF), and C-reactive protein (CRP) in PCOS women.
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	
Inclusion criteria	Yes Partial No Not reported	Women with PCOS had to meet two of the following criteria: a medical history of hyperandrogenic oligo/ amenorrhea (8 menses per year) and PCO on ultrasonography of more than 10 ovarian follicles 2-9 mm in diameter, or clinical hirsutism (a modified Ferriman-Gallwey score of 8 or higher was considered diagnostic of hirsutism)
Exclusion criteria	Yes Partial No Not reported	No participation in an exercise training program in the last 3 months hyperandrogenism, such as congenital adrenal hyperplasia, thyroid dysfunction, and hyperprolactinemia. Additional exclusion criteria for this study were renal or hepatic dysfunction.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS **Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Participants who met the inclusion criteria were randomly assigned to one of the two groups. A computer-generated random table was used for randomization. At the baseline and after 12 weeks of the intervention, only one independent investigator, who was blinded to group allocation, conducted the testing procedures.

	Was allocation to intervention group concealed?	Yes Partial No Not reported	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*Impossible, as only one group had aerobic activity*
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	"At the baseline and after 12 weeks of the intervention, only one independent investigator, who was blinded to group allocation, conducted the testing procedures." So investigators yes, care provider no
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	Participants in the AE+Met-group were given a separate familiarization session prior to the aerobic training session, during which they were introduced to the aerobic exercise protocol as well as all measurement procedures.
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Anthropometrical measurements not reported
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	One independent investigator, who was blinded to group allocation, conducted the testing procedures.
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	*Metformin-group 0/20=0%* *AE+Metformin-group 0/20=0%*

	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*No reports on hyperandrogenism or matabolic hormones*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	

	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

Study ID	Elkind-Hirsch 2016
Study Citation	Elkind-Hirsch, Karen E.; Paterson, Martha S.; Seidemann, Ericka L.; Gutowski, Hanh C. Short-term therapy with combination dipeptidyl peptidase-4 inhibitor saxagliptin/metformin extended release (XR) is superior to saxagliptin or metformin XR monotherapy in prediabetic women with polycystic ovary syndrome: a single-blind, randomized, pilot study Fertility & Sterility 2017;107(1):253-260.e1
Study Country	USA
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	PCOS women, aged 18–42 years with prediabetic hyperglycemia
PCOS diagnostic criteria	NIH
Presence of infertility	No
Presence of other condition/s	prediabetic hyperglycemia determined by a 75-gram oral glucose tolerance test
Medication History	NR
N per group	*Allocated/randomised:* 1. Metformin=13 2. Saxagliptin=12

	3. Metformin+Saxagliptin=13 *Assessed:* 1. Metformin=12 2. Saxagliptin=11 3. Metformin+Saxagliptin=11	
Setting	Healthy, premenopausal patients with PCOS, aged 18-42 years and with impaired glucose regulation were enrolled in the study from March 2014 to January 2016.	
Intervention	1.Metformin 2000mg/d	
Comparison	2.Saxagliptin 5mg/d 3. Metformin 2000mg/d+Saxagliptin 5mg/d	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	f-gluc, HOMA-IR, lipids, WHR, BMI, menstrual interval, T, A, SHBG, DHEAS, FAI	
Follow up Duration	4 months	
Summary Result/s	Treatment with SAXA-MET was superior to either drug alone in terms of clinical and metabolic benefits in prediabetic patients with PCOS.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	To evaluate efficacy with the dipeptidyl peptidase-4 inhibitor saxagliptin (SAXA), metformin extended release (MET), and combination (SAXA-MET) in patients with polycystic ovary syndrome (PCOS) and impaired glucose regulation.
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	

If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	
Inclusion criteria	Yes Partial No Not reported	Polycystic ovary syndrome was defined according to NIH. Eligible patients were required to have the combination of irregular periods (cycle length outside 21– 35 days or fewer than eight cycles per year) together with biochemical evidence of hyperandrogenism (total T >50 ng/dL or free androgen index [FAI] >3.87. Prediabetic hyperglycemia was determined by a 75-g oral glucose tolerance test (OGTT) and included PCOS patients with impaired fasting glucose, IGT, or both (impaired fasting glucose/IGT)
Exclusion criteria	Yes Partial No Not reported	DM, smokers, suspected pregnancy, desiring pregnancy, or injectable hormonal contraceptive use within 6 months; and use of oral contraceptives, other steroid hormones, drugs that affect gastrointestinal motility or carbohydrate metabolism, and/or antiobesity drugs within 3 months before study entry
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS **Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	All patients were allocated to 1 of these 3 groups according to computer-generated random numbers using a block randomization method. The primary investigator was blinded to all treatment arms. Prospective, randomized, single-blind drug study
SELECTION BIAS **Was allocation to intervention group concealed?**	Yes Partial No Not reported	
PERFORMANC **Were patients blind to intervention group?**	Yes Partial No Not reported	

	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	The primary investigator was blinded to all treatment arms.
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	1. Metformin=1/13=7.69% 2. Saxagliptin=1/12=8.33% 3. Metformin+Saxagliptin=2/13=15.4%
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Clinical Trial Registration Number: NCT02022007

CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	
	If confounding was present, was it controlled for?	Yes Partial Not reported No	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	Main author served on an advisory board for AstraZeneca and has received research grant support from Novo Nordisk, Bayer, and Merck, Sharp and Dohme. Research grant from AstraZeneca Pharmaceuticals
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Power calculations were done*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Low*

Study ID	Fonseka 2020

Study Citation	Fonseka S, Wijeyaratne CN, Gawarammana IB, Kalupahana NS, Rosairo S, Ratnatunga N, et al. Effectiveness of Low-dose Ethinylestradiol/Cyproterone Acetate and Ethinylestradiol/Desogestrel with and without Metformin on Hirsutism in Polycystic Ovary Syndrome: A Randomized, Double-blind, Triple-dummy Study. J Clin Aesthet Dermatol. 2020;13(7):18-23.
Study Country	Sri Lanka
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS aged 18-40 yrs, with mFG score ≥8.
PCOS diagnostic criteria	Rotterdam
Presence of infertility	*Not reported*
Presence of other condition/s	
Medication History	*No*
N per group	*COCP EE/CPA = 20* *COCP EE/DSG = 23* *EE/CPA + met = 26* *EE/DSG + met = 30*
Setting	*Patients attending medical and gynecology clinics at teaching hospitals in Kandy and Peradeniya, Sri Lanka*
Intervention	*EE 35 μg + CPA 2mg*
Comparison	*EE 20 μg + DSG 0.15 mg* *Met + EE 35 μg + CPA 2mg* *Met + EE 20 μg + DSG 0.15 mg*
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Hirsutism: Hair density, hair diameter, and hair growth rate* *mFG score* *VAS hirsutism self assessment*
Follow up Duration	*6 + 12 months*
Summary Result/s	*EE/CPA and EE/DSG were equally effective in improving hirsutism in PCOS, with no added benefit from low-dose metformin.*
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT	

Does the study have a clearly focused question and/or PICO?	**Yes** Partial No Not reported	The objective was to determine the effectiveness of ethinylestradiol/cyproterone EE/CPA) and ethinylestradiol/desogestrel (EE/DES) both alone and in combination with low-dose metformin on hirsutism in women with PCOS.
Does the study have specified inclusion/exclusion criteria?	**Yes** Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	**Yes** Partial No Not reported	
Inclusion criteria	**Yes** Partial No Not reported	Eligible subjects included those aged 18 to 40 years with PCOS diagnosed in accordance with the 2003 Rotterdam Consensus Conference criteria with a modified Ferriman-Gallway score (mFGS) of hirsutism of eight points or more.
Exclusion criteria	**Yes** Partial No Not reported	*Patients with secondary causes of hyperandrogenism, significant comorbidities such as diabetes, contraindications to the use of trial drugs, or who were taking any form of hormonal contraceptives or antiandrogens three months prior to starting the study and seeking fertility were excluded.*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	**Yes** Partial No Not reported	*Simple randomization to four study arms was completed using a computer-generated random number table.*
	Was allocation to intervention group concealed?	**Yes** Partial No Not reported	According to the list generated by a random number generator, a piece of paper indicating the study arm (A, B, C, or D) was placed inside serially-numbered, sealed, opaque envelopes. When a participant was recruited, the patient's name, address, and telephone number were written on the envelope. Treatment was started according to the assigned arm (A, B, C, or D). All logistics were overseen by an administrator who was not involved in the rest of the study.

PERFORMANCE BIAS	**Were patients blind to intervention group?**	**Yes** Partial No Not reported	*Subjects of all four arms were prescribed three drugs using appropriate placebos.* *The active tablets were removed from the commercial packings and placed in adhesive polythene bags*
	Were investigators and care providers blind to intervention group?	**Yes** Partial No Not reported	*All the investigators, the statistician, and the involved patients were blinded to the treatment; the pharmacist who dispensed the drugs was not.*
	Aside from the experimental intervention, were the groups treated the same?	**Yes** Partial No Not reported	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	**Yes** Partial No Not reported	*a single examiner who was blinded to the therapy conduct the assessments and intra-observer variability was minimized by using the same photographic scale of mFGS to score the hirsutism.*
	Were all outcomes measured in a standard, valid and reliable way?	**Yes** Partial No Not reported	
	Were outcomes assessed objectively and independently?	**Yes** Partial No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	20% EE/CPA 8% *EE/DSG* *0% EE/CPA + met* *3% EE/DSG +met*	*COCP EE/CPA: randomized 25, dropout 5 = 20%* *COCP EE/DSG: randomized 25, dropout 2 = 8%* *EE/CPA + met: randomized 26, dropout 0 = 0%* *EE/DSG + met: randomized 31, dropout 1 = 3%*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial **No** Not reported	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	**Yes** Partial No Not reported	*Protocol followed*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes **Partial** No Not reported	*Baseline characteristics did not differ significantly except for age, which was higher in met + EE/DSG group*
	If confounding was present, was it controlled for?	Yes Partial **No** Not reported	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial **No** Not reported	
	Was the study sufficiently powered to detect any differences between the groups?	Yes **Partial** No Not reported	
	If statistical analysis was undertaken, was this appropriate?	**Yes** Partial No Not reported	*A two-way mixed analysis of variance (ANOVA) model for repeated measures was used during the analysis. Additionally, a one-way ANOVA and categorical data analytical methods were used wherever appropriate.* *Before applying the two-way mixed ANOVA model, significant outliers in each variable were excluded. Where sphericity was not assured, the Greenhouse-Geisser or Huynh-Feldt test was used to calculate the p-values*
COMMENTS			

What is the overall risk of bias?	**Low** Moderate High Insufficient information	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		

Study ID	Gambineri 2004
Study Citation	Gambineri, A.; Pelusi, C.; Genghini, S.; Morselli-Labate, A. M.; Cacciari, M.; Pagotto, U.; Pasquali, R. Effect of flutamide and metformin administered alone or in combination in dieting obese women with polycystic ovary syndrome Clin Endocrinol (Oxf) Feb 2004;60(2):241-9
Study Country	Italy
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Obese (BMI>28) women with PCOS
PCOS diagnostic criteria	Rott
Presence of infertility	No
Presence of other condition/s	Obesity
Medication History	-
N per group	*Allocated/randomised:* 1. metformin N=10 2.Placebo N=10 3. FLUT N=10 4.Metformin+FLUT=10 *Assessed:* 1. metformin N=10 2.Placebo N=8 3. FLUT N=9 4.Metformin+FLUT=10

Setting	Forty obese women with PCOS were enrolled in the study. After a 1-month diet, according to single blind design, the patients were allocated to treatment with placebo, metformin (850 mg/orally, twice daily), flutamide (250 mg/orally, twice daily) or metformin (850 mg/orally, twice daily) + flutamide (250 mg/orally, twice daily) for the following 6 months, while continuing hypocaloric dieting.	
Intervention	1. metformin 850mgx2/d 2.Metformin 850mgx2/d +FLUT 250mgx2/d	
Comparison	Placebo FLUT 250mgx2/d	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Weight, bmi, T, free-T, A, DHEAS, SHBG, f-gluc, f-insulin, HOMA, lipids	
Follow up Duration	6 months	
Summary Result/s	Metformin, flutamide or the combined metformin + flutamide treatment appears to have a more favourable outcome on body fat distribution, androgens, lipids, hirsutism and menses.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	To investigate the effects of long-term metformin and flutamide, given alone or in combination and added to a hypocaloric diet, on body weight and fat distribution, androgens, metabolic and clinical status, in a group of obese women with PCOS
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	

Inclusion criteria		Yes Partial No Not reported	-BMI > 28 and abdominal fat distribution, defined - -WHR> 0·80 (WHO, 1997). The diagnosis of PCOS was made according to the presence of oligo/ amenorrhoea, hyperandrogenism [supranormal testosterone levels according to our reference values (0·39 ± 0·18 ng/ml)] and ovarian ultrasounds
Exclusion criteria		Yes Partial No Not reported	-thyroid, cardiovascular, renal or liver dysfunction, based on clinical examination and routine laboratory findings. -Cushing's syndrome and congenital adrenal hyperplasia, DM medication or significantly modified their body weight for 3 months before the study
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	"randomly placed, according to a single-blind design"
	Was allocation to intervention group concealed?	Yes Partial No Not reported	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	All women were placed, for the first month, on a standardized hypocaloric diet (1200–1400 kCal/daily) containing 50% carbohydrates, 30% lipids and 20% proteins
DED ETEC	**Were outcome assessors blind to**	Yes Partial No	

	intervention group?	Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	1. metformin N=0/10=0% 2.Placebo N=2/10 =20% 3. FLUT N=1/10=10% 4.Metformin+FLUT=0/10=0%
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	

	If confounding was present, was it controlled for?	Yes Partial Not reported	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	
If statistical analysis was undertaken, was this appropriate?		Yes Partial No Not reported	
COMMENTS		*Most of the content regarding blinding and randomisation leads to moderate RoB here.*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate*

Study ID	*Glintborg 2014*
Study Citation	Glintborg D, Altinok ML, Mumm H, Hermann AP, Ravn P, Andersen M. Body composition is improved during 12 months' treatment with metformin alone or combined with oral contraceptives compared with treatment with oral contraceptives in polycystic ovary syndrome. The Journal of clinical endocrinology and metabolism. 2014;99(7):2584-91.

Study Country	Denmark	
BRIEF CHARACTERISTICS OF RCT		
Patient/population/ participants	Women with PCOS	
PCOS diagnostic criteria	Rotterdam	
Presence of infertility	*Not reported*	
Presence of other condition/s	-	
Medication History	*No*	
N per group	*Allocated/randomised: 30 to each group* *Assessed at end of study:* *COCP=23* *Met=19* *Combo=23*	
Setting	*Patients recruited from the department of Endocrinol-ogy, Odense University Hospital, and from local fertility clinics and Departments of Gynecology.*	
Intervention	*30 μg EE + 150 mg DSG*	
Comparison	*-Metformin 1000 mg b.i.d. (2000 mg/day)* *-Combo met + COCP*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*body composition, hyperandrogenism, metabolic markers*	
Follow up Duration	*12 months*	
Summary Result/s	*Met treatment alone or in combination with COCP was associated with weight loss and improved body composition compared with COCP alone, whereas free T levels decreased during met + COCP or COCP.*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	**Yes** Partial No Not reported	*The primary aim of the present study was to evaluate whether treatment with metformin alone or combined with OCP resulted in a more advantageous body compo-sition than treatment with OCP alone*

Does the study have specified inclusion/exclusion criteria?	**Yes** Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	**Yes** Partial No Not reported	
Inclusion criteria	**Yes** Partial No Not reported	*Patients with PCOS according to Rotterdam criteria. Other inclusion criteria not stated.*
Exclusion criteria	**Yes** Partial No Not reported	*Patients with diabetes (fasting plasma glucose ≥ 7.0 mmol/L and/or HbA1c 44 mmol/mol), elevated liver enzymes, renal dysfunction, congestive heart disease, depression, and eating dis-orders were not included in the study. Obese patients [body mass index (BMI) ≥ 35 kg/m2] and patients with other contraindications for COCP (previous or family history of thrombosis or breast cancer, coagulatory defects, and heavy smokers) were not included in the study. Patients were not included if they were pregnant or expressed a wish for conception during the study period.*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS **Did the study have an adequate method of randomisation?**	Yes Partial No **Not reported**	
SELECTION BIAS **Was allocation to intervention group concealed?**	Yes Partial No **Not reported**	
PERFORMANC **Were patients blind to intervention group?**	Yes Partial No **Not reported**	

	Were investigators and care providers blind to intervention group?	Yes Partial No **Not reported**	
	Aside from the experimental intervention, were the groups treated the same?	Yes **Partial** No Not reported	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No **Not reported**	
	Were all outcomes measured in a standard, valid and reliable way?	**Yes** Partial No Not reported	
	Were outcomes assessed objectively and independently?	Yes **Partial** No Not reported	*Not reported for clinical examinations, yes for blood tests and DXA scans*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	23% COCP 37% met 23% combo	*COCP 7/30=23%* *Met 11/30=37%* *Combo 7/30=23%*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No **Not reported**	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	**Yes** Partial No Not reported	

CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	**Yes** Partial No Not reported	
	If confounding was present, was it controlled for?	Yes **Partial** No Not reported	*In a multiple regression model, BMI and FAI was included*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial **No** Not reported	
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No **Not reported**	
	If statistical analysis was undertaken, was this appropriate?	**Yes** Partial No Not reported	
COMMENTS			
What is the overall risk of bias?		Low Moderate **High** Insufficient information	*Randomization not described, many dropouts, uneven distribution of dropouts and dropouts differed in BMI at baseline compared with completers.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

Study ID	Heidari 2019
Study Citation	Heidari, Behnam; Lerman, Amir; Lalia, Antigoni Z.; Lerman, Lilach O.; Chang, Alice Y. Effect of Metformin on Microvascular Endothelial Function in Polycystic Ovary Syndrome Mayo Clinic proceedings 2019;94(12):2455-2466
Study Country	USA
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Females aged 18 to 50 years with a BMI of 25 or greater who had a diagnosis of PCOS
PCOS diagnostic criteria	Rotterdam
Presence of infertility	Not reported
Presence of other condition/s	BMI of 25 or greater
Medication History	*No*
N per group	*Allocated/randomised: Metformin-group 33* *placebo-group 15* *Assessed at end of study: Metformin-group 29* *Placebo13*
Setting	An open-label study of women with PCOS randomized to metformin vs no treatment at Mayo Clinic in Rochester, Minnesota, from March 24, 2014, to November 18, 2016
Intervention	Metformin 1500mg/day
Comparison	placebo
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Bmi, weight, ogtt,f-gluc, insulin, HOMA, DHEAS, T, CRP, lipids
Follow up Duration	3 months
Summary Result/s	In metformin-treated participants, there was a significant decrease in body weight (P<.05), f-gluc (P<.01), f-insulin (P<.05), HOMA-IR (P<.05), total cholesterol (P<.05), and T(P<.001) after 3 months of treatment
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT	

Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	"to determine whether specific metabolic, hormonal, or phenotypic features of PCOS might be associated with metformin's effect in PCOS on peripheral microvascular endothelial function or if metformin can improve endothelial function in women with PCOS and endothelial dysfunction."
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	
Inclusion criteria	Yes Partial No Not reported	Criteria of both oligoanovulation and androgen excess were required for inclusion in the study to increase the likelihood of insulin resistance. Oligoanovulation was defined as less than 9 menses per year or the absence of a progesterone increase above 10 ng/mL in the luteal phase (days 20–22 of menstrual cycle) in women with monthly menses. Androgen excess was defined as elevated testosterone or dehydroepiandrosterone sulfate, severe acne, androgenic alopecia, or clinical hirsutism (Ferriman-Gallwey score >8).
Exclusion criteria	Yes Partial No Not reported	Exclusion criteria included elevated prolactin level, untreated hypothyroidism or hyperthyroidism, Cushing syndrome, congenital adrenal hyperplasia, diabetes, creatinine level greater than 1.5 mg/dL (to convert to µmol/L, multiply by 88.4), pregnancy, breastfeeding, smoking, taking oral contraceptive pills or other medications that would affect androgen levels, insulin sensitivity, or endothelial function.

INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	an open-label randomized study. The randomization is not described
	Was allocation to intervention group concealed?	Yes Partial No Not reported	Open label design
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	Open label design
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	Participants randomized to the no treatment arm had the option to continue the study for an additional 3 months, during which they received metformin and completed an additional set of study measurements after metformin treatment
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	

ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	*Metformin-group 4/33=12.1%* *placebo-group 2/15=13.3%*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Registration number:NCT02086526
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	
	If confounding was present, was it controlled for?	Yes Partial No Not reported	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*Two of the authors are consultants for medical companies*

	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	
COMMENTS		*Moderate*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*No blinding*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

Study ID	Ibanez 2020
Study Citation	Ibáñez L, Díaz M, García-Beltrán C, Malpique R, Garde E, López-Bermejo A, et al. Toward a Treatment Normalizing Ovulation Rate in Adolescent Girls With Polycystic Ovary Syndrome. J Endocr Soc. 2020;4(5):bvaa032.
Study Country	Spain
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Adolescent girls with PCOS two RCT pooled (gynaecological age>2.0 years)
PCOS diagnostic criteria	Inclusion criteria were hirsutism (modifed Ferriman-Gallwey score>8), oligomenorrhea (menstrual intervals>45 day), gynaecological age>2.0 years, and absence of sexual activity.
Presence of infertility	No

Presence of other condition/s	hyperandrogenism	
Medication History	*No*	
N per group	*Allocated/randomised: SPIOMET-group 36* *OCP-group 35* *Assessed at end of study: SPIOMET-group 31* *OCP-group 31*	
Setting	A post-hoc study of two previous randomised studies in adolescent girls with PCOS conducted in the Adolescent Endocrinology Unit of Sant Joan de Déu University Hospital, Barcelona, Spain. Mediterranean diet and regular exercise were recommended to all study participants	
Intervention	20 µg EE plus 100 mg LNG (21/28 days), and placebo (7/28 days)	
Comparison	SPIOMET-group: spironolactone 50 mgx1 daily, pioglitazone 7.5 mg once daily and metformin 850 mg once daily	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	BMI, hirsutism score, SHBG, T, androstenedione, free-testosterone, free-androstenedione, f-insulin, HOMA-IR, oGTT,, CRP lipids	
Follow up Duration	12 months	
Summary Result/s	OCP and SPIOMET treatment reduced the androgen excess comparably and had no differential effects on total-body lean or fat mass. However, SPIOMET was accompanied by more broadly normalizing effects, including on hepato-visceral fat and on circulating insulin	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	**Yes** Partial No Not reported	Reports on pooled results from two RCTs. The limited power of the first study (N = 34) prompted the launch of a second study with virtually identical design. The primary endpoint was posttreatment ovulation rate; secondary outcomes included hirsutism score, fasting insulin, androgens, lipids, high-molecular-weight (HMW) adiponectin, C-reactive protein (CRP), carotid intima-media thickness (cIMT), body composition, and hepato-visceral fat
Does the study have specified	**Yes** Partial No	

inclusion/exclusion criteria?	Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	**Yes** Partial No Not reported	
Inclusion criteria	**Yes** Partial No Not reported	a) hirsutism (modifed Ferriman-Gallwey score>8) b) oligomenorrhea (menstrual intervals>45 day), c) gynaecological age>2.0 years d) absence of sexual activity.
Exclusion criteria	**Yes** Partial No Not reported	Exclusion criteria were 21-hydroxylase defciency; glucose intolerance or diabetes; evidence of thyroid, liver, or kidney dysfunction; hyperprolactinemia; and any prior use of medications affecting gonadal/adrenal function, or carbohydrate/lipid metabolism
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS – **Did the study have an adequate method of randomisation?**	**Yes** Partial No Not reported	Randomization (1:1) for study medication was webbased (http://www.SealedEnvelope.com), using random permuted blocks, with strata for age (<16.0 or >16.0 years) and BMI (<24.0 or ≥24.0 kg/m2).
SELECTION BIAS – **Was allocation to intervention group concealed?**	**Yes** Partial No Not reported	
PERFORMANCE BIAS – **Were patients blind to intervention group?**	Yes Partial **No** Not reported	
PERFORMANCE BIAS – **Were investigators and care providers blind to intervention group?**	Yes Partial No **Not reported**	

	Aside from the experimental intervention, were the groups treated the same? moderate	**Yes** Partial No Not reported	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial **No** Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	**Yes** Partial No Not reported	
	Were outcomes assessed objectively and independently?	**Yes** Partial No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	11% COCP 14% SPIOMET	COCP 4/35=11% SPIOMET 5/36=14%
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No **Not reported**	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	**Yes** Partial No Not reported	

CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	**Yes** Partial No Not reported	
	If confounding was present, was it controlled for? **Low**	Yes Partial No Not reported	*NA*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial **No** Not reported	
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No **Not reported**	
	If statistical analysis was undertaken, was this appropriate?	**Yes** Partial No Not reported	
COMMENTS			
What is the overall risk of bias?		Low **Moderate** High Insufficient information	Moderate due to no blinding, outcome assessors not blinded,
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

Study ID	Javed 2019
Study Citation	Javed, Z.; Papageorgiou, M.; Deshmukh, H.; Rigby, A. S.; Qamar, U.; Abbas, J.; Khan, A. Y.; Kilpatrick, E. S.; Atkin, S. L.; Sathyapalan, T. Effects of empagliflozin on metabolic parameters in polycystic ovary syndrome: a randomized controlled study Clinical endocrinology 2019;90(6):805
Study Country	UK
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	PCOS women, aged 18–45 years and BMI>=25
PCOS diagnostic criteria	Rotterdam
Presence of infertility	No
Presence of other condition/s	Overweight, bmi>=25
Medication History	NR
N per group	*Allocated/randomised:* 1. Metformin=20 2. Empagliflozin=20 *Assessed:* 1. Metformin=20 2. Empagliflozin=19
Setting	An open-label, randomized, comparative study in women with PCOS was performed in the Academic Diabetes, Endocrinology and Metabolism research centre at Hull Royal Infirmary.
Intervention	1.Metformin 1500mg/d
Comparison	Empagliflozin 25mg/d
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Weight, bmi, FAI, T, SHBG, A, DHEAS, f-gluc, f-insulin, homa, lipids, crp
Follow up Duration	3 months

Summary Result/s	A significant improvement in anthropometric parameters and body composition, in overweight and obese women with PCOS after 12 weeks of treatment with empagliflozin compared to metformin, although no changes were seen in hormonal or metabolic parameters.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	The aim of this study was to compare the effects of empagliflozin vs metformin on anthropometric and body composition, hormonal and metabolic parameters in women with PCOS.
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	
Inclusion criteria	Yes Partial No Not reported	Aged 18-45 years BMI ≥25 kg/m^2 diagnosed with PCOS based on the Rotterdam criteria [biochemical hyperandrogenism, as indicated by a free androgen index (FAI) >4, and self-reported oligomenorrhea (cycle length >35 days and 9 or fewer periods per year) or amenorrhoea (absence of menses for a period ≥3 months)
Exclusion criteria	Yes Partial No Not reported	-differential diagnoses on classical 21-hydroxylase deficiency, hyperprolactinaemia, Cushing's disease and androgen-secreting tumours were excluded from participation. -pregnancy or intention to become pregnant, breastfeeding, documented use of oral hormonal contraceptives and hormone-releasing implants, metformin or other insulin-sensitizing medications, clomiphene citrate or oestrogen modulators, GnRH modulators and

			Minoxidil, DM, history or presence of malignant neoplasms within the last 5 years, pancreatitis (acute or chronic), recurrent UTI or gastrointestinal tract surgery, ongoing, inadequately controlled thyroid disorder and known hypersensitivity to the investigational medicinal products or any of their excipients.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	randomized on a 1:1 ratio using an online web-based randomization service (**https://www.sealedenvelope.com**) to receive either empagliflozin 25 mg (Jardiance) or metformin A randomized open-label study
	Was allocation to intervention group concealed?	Yes Partial No Not reported	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	
DEDET ECTION	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	

	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	Metformin 0/20=0% Empagliflozin 1/20=5%
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis	Yes Partial No Not reported	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Clinical Trial Registration Number: NCT03008551
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Age seemed to differ but this was adjusted for*
	If confounding was present, was it controlled for?	Yes Partial Not reported No	*adjusted for BMI and age where relevant*

OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	
COMMENTS		*No blinding*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate*

Study ID	Jensterle 2008 (1)
Study Citation	Jensterle, M.; Janez, A.; Mlinar, B.; Marc, J.; Prezelj, J.; Pfeifer, M. Impact of metformin and rosiglitazone treatment on glucose transporter 4 mRNA expression in women with polycystic ovary syndrome Eur J Endocrinol Jun 2008;158(6):793-801
Study Country	Slovenia
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS
PCOS diagnostic criteria	NICHD (National Institute of Child Health and Human Development)
Presence of infertility	NR
Presence of other condition/s	*NR*

Medication History	*NR*
N per group	*Allocated/randomised:* 1.Metformin=18 2.Rosiglitazone=17 *Assessed:* 1.Metformin=17 2.Rosiglitazone=16
Setting	"We recruited 35 women with PCOS as classified according to the National Institute of Child Health and Human Development (NICHD) criteria" (not reported where and in what kind of hospital)
Intervention	1.Metformin 850mgx2/d
Comparison	2.Rosiglitazone 4mg/d
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	f-gluc, f-insulin, homa, bmi, dheas, A, T, free T, periods/6months
Follow up Duration	6 months
Summary Result/s	Therapy with insulin sensitizers resulted in marked improvement in adipose tissue GLUT4 mRNA expression in PCOS patients, rosiglitazone being more effective when compared with metformin.

ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	To explore whether the well-known clinical, hormonal and metabolic efficacy of metformin or rosiglitazone treatment is reflected in the modulation of adipocyte GLUT4 mRNA expression in patients with PCOS.
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	
Inclusion criteria	Yes Partial No Not reported	PCOS was classified according to the National Institute of Child Health and Human Development (NICHD) criteria

Exclusion criteria		Yes Partial No Not reported	Possible Cushing's syndrome or congenital (nonclassic) adrenal hyperplasia was excluded. Additional exclusion criteria were type 1 or type 2 diabetes mellitus, a significant cardiovascular or hepatic disease, and the use of medications known or suspected to affect reproductive or metabolic functions, within 60 days prior to study entry
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	"As a method of randomization, the RAND programme in Excel was used"
	Was allocation to intervention group concealed	Yes Partial No Not reported	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	

	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	Met 1/18=5.6% Rosi 1/17=5.9%
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis	Yes Partial No Not reported	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	
	If confounding was present, was it controlled for?	Yes Partial Not reported No	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	

	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Lack of blinding*

Study ID	Jensterle 2008 (2)
Study Citation	Jensterle, M.; Sebestjen, M.; Janez, A.; Prezelj, J.; Kocjan, T.; Keber, I.; Pfeifer, M. Improvement of endothelial function with metformin and rosiglitazone treatment in women with polycystic ovary syndrome Eur J Endocrinol Oct 2008;159(4):399-406
Study Country	Slovenia
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS
PCOS diagnostic criteria	NICHD (National Institute of Child Health and Human Development)
Presence of infertility	NR
Presence of other condition/s	*NR*
Medication History	*NR*
N per group	*Allocated/randomised:* 1.Metformin=15 2.Rosiglitazone=13

	Assessed: 1.Metformin=15 2.Rosiglitazone=11	
Setting	"We recruited 28 women with PCOS as classified according to the National Institute of Child Health and Human Development (NICHD) criteria" (not reported where and in what kind of hospital)	
Intervention	1.Metformin 850mgx2/d	
Comparison	2.Rosiglitazone 4mg/d	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	f-gluc, f-insulin, homa, bmi, dheas, A, T, free T, periods/6months, lipids	
Follow up Duration	6 months	
Summary Result/s	Therapy with insulin sensitizers, MET and ROSI, resulted in marked improvement of endothelial function in young PCOS patients without clinically evident atherosclerosis who were not severely insulin resistant. Neither drug was superior to the other.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	To explore whether the well-known clinical, hormonal and metabolic efficacy of metformin or rosiglitazone treatment is reflected in the modulation of adipocyte GLUT4 mRNA expression in patients with PCOS.
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	
Inclusion criteria	Yes Partial No Not reported	PCOS was classified according to the National Institute of Child Health and Human Development (NICHD) criteria
Exclusion criteria	Yes Partial No	Possible Cushing's syndrome or congenital (nonclassic) adrenal hyperplasia was excluded. Additional exclusion criteria were type 1 or type 2

		Not reported	diabetes mellitus, a significant cardiovascular or hepatic disease, and the use of medications known or suspected to affect reproductive or metabolic functions, within 60 days prior to study entry
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	"As a method of randomization, the RAND programme in Excel was used"
	Was allocation to intervention group concealed	Yes Partial No Not reported	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*One person was blinded but no reporting on the others - All measurements were carried out by the same investigator who was blinded for the treatment assignment of the patients and also for the post- or pretreatment status, since there were more studies on endothelial dysfunction in PCOS going on simultaneously making that possible.*
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	

	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	Met 0/15=0% Rosi 2/13=15.4%
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis	Yes Partial No Not reported	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	
	If confounding was present, was it controlled for?	Yes Partial Not reported No	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	

	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	
COMMENTS		*No blinding, no protocol*	
What is the overall risk of bias?		Low Moderate High Insufficient information	

Study ID	Jensterle 2017
Study Citation	Jensterle et al., *BMC Endocrine Disorders 17 :5*, 2017
Study Country	Slovenia
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS and obesity
PCOS diagnostic criteria	Rotterdam
Presence of infertility	*Not reported*
Presence of other condition/s	*bmi>30*
Medication History	*No*
N per group	*Lira 3 mg 14, Combo N =14*
Setting	outpatients Department for Endocrinology, Diabetes and Metabolic Diseases University Medical Center Ljubljana
Intervention	*Liraglutide 3mg qd*

Comparison	*Combo: Metformin 1000mg BID and Liraglutide 1.2 mg qd*	
Co-intervention	*none*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	The primary outcome of the study was mean change in measures of obesity. Secondary outcomes included metabolic and hormonal changes	
Follow up Duration	*12 weeks*	
Summary Result/s	Short-term interventions with COMBO and LIRA3 both led to significant improvement of measures of obesity in obese PCOS, LIRA3 being superior to COMBO. However, COMBO further improved androgen profile beyond weight reduction and was associated with better tolerability.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	compare the combination of metformin and low dose liraglutide 1.2 mg to high dose liraglutide 3 mg alone on measures of obesity in obese PCOS.
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	type A phenotype of PCOS diagnosed by ASRM-ESHRE Rotterdam criteria including concomitant presence of a) hyperandrogenemia on either the biochemical or the clinical level, b) menses abnormalities and c) PCO morphology; age 18 years to menopause and obesity (body mass index: BMI ≥ 30)
Exclusion criteria	Yes Partial No Not reported	Patients with history of carcinoma, significant cardiovascular, kidney or hepatic disease and the use of medications known to affect reproductive or metabolic functions within prior to study entry
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Not reported*
	Was allocation to intervention group concealed?	Yes Partial No Not reported	*Not reported*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*No*
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*Not reported*
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	*30 patients:* *Combo: 1/15= 6.6%* *(1 study protocol violation)* *Lira3 1/15 = 6.6%* *(1 study protocol violation)*

	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Yes*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*yes*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*yes*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Not reported*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*Not reported*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Yes,* To detect a statistically significant difference between groups of approximately 2.5 kg in weight loss with 80% power, each group had to consist of 14 patients.
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*yes*

COMMENTS	*Lack blinding key reason for high RoB*	
What is the overall risk of bias?	Low Moderate High Insufficient information	*High (no blinding)*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*No – all outcomes high risk of bias*	

Study ID	Karimzadeh 2007
Study Citation	Karimzadeh, Mohamad Ali; Eftekhar, Maryam; Taheripanah, Robabeh; Tayebi, Naeimeh; Sakhavat, Leili; Zare, Fatemeh The effect of administration of metformin on lipid profile changes and insulin resistance in patients with polycystic ovary syndrome Middle East Fertility Society journal 2007;12(3):174
Study Country	Iran
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women aged 20-35 years with PCOS
PCOS diagnostic criteria	Rotterdam
Presence of infertility	Yes
Presence of other condition/s	menstrual disorder, hirsutism and infertility
Medication History	
N per group	*Allocated/randomised: Metformin-group 100* *placebo-group 100* *Assessed at end of study, not reported*
Setting	200 women with PCOS (age 20- 35 years) who were referred to clinic because of menstrual disorder, hirsutism and infertility.
Intervention	Metformin 500mg/day for one week and then 500mgx3/day

Comparison	Placebo 1 tabl/day for a week, then 3 tabl/day	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Lipids	
Follow up Duration	3 months	
Summary Result/s	Metformin increased ovulation and pregnancy rates and decreased lipids compared to placebo	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	To evaluate the effects of metformin on lipid profile changes, insulin resistance, BMI, Ovulation and pregnancy rates in patients affected by PCOS
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	
Inclusion criteria	Yes Partial No Not reported	women (age 20- 35 years) with PCOS who were referred due to menstrual disorder, hirsutism and infertility.
Exclusion criteria	Yes Partial No Not reported	other endocrinological abnormalities such as hyperprolactinaemia, and thyroid dysfunction, Cushing syndrome, congenital adrenal hyperplasia.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Then patients were randomly (Randomization was performed using computergenerated sequences that were sealed in number opaque envelopes) divided into two groups.
	Was allocation to intervention group concealed?	Yes Partial No Not reported	Both women and the doctor were blinded to the content of tablet which had identical appearance and were packaged by the clinic pharmacist

PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)	Yes Partial No Not reported	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Not reported*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	
	If confounding was present, was it controlled for?	Yes Partial No Not reported	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	
COMMENTS		*Attrition not reported, no protocol, no reports regarding funding or conflict of interest, no description on blood analysis*	
What is the overall risk of bias?		Low Moderate High	

	Insufficient information	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		

Study ID	*Kaya 2012*
Study Citation	Kaya MG, Calapkorur B, Karaca Z, Yildirim S, Celik A, Akpek M, et al. The effects of treatment with drospirenone/ethinyl oestradiol alone or in combination with metformin on elastic properties of aorta in women with polycystic ovary syndrome. Clin Endocrinol (Oxf). 2012;77(6):885-92.
Study Country	Turkey
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS
PCOS diagnostic criteria	AES
Presence of infertility	*NR*
Presence of other condition/s	
Medication History	*No*
N per group	*Allocated/randomised: COCP 19, COCP + met 18* *Assessed at end of study: COCP 19, COCP + met 18*
Setting	*women newly diagnosed with PCOS in the Department of Endocrinology of Erciyes University, Turkey*
Intervention	30 µg EE/3mg DRSP
Comparison	30 µg EE/3 mgDRSP + met

Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	BMI, weight, SHBG, TT, fT, FAI, androstendione, DHEAS, insulin, HOMA, TG, LDL, HDL, CRP,	
Follow up Duration	*6 months*	
Summary Result/s	an improvement in the elastic parameters of the aorta by adding metformin to OCP treatment.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	**Yes** Partial No Not reported	The aim of this study was to investigate the effects of treatment with drospirenone/ethinyl oestradiol (E/E) alone or in combination with metformin on the elastic properties of the aorta in women with PCOS
Does the study have specified inclusion/exclusion criteria?	**Yes** Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	**Yes** Partial No Not reported	
Inclusion criteria	**Yes** Partial No Not reported	Patients were selected from women newly diagnosed with PCOS in the Department of Endocrinology of Erciyes University according to the Androgen Excess and PCOS Society criteria
Exclusion criteria	**Yes** Partial No Not reported	Exclusion criteria included diabetes mellitus, hypertension, hy- perlipidaemia, corticosteroid use, oral contraceptive use, sys- temic disease (hepatic, renal, cardiac), use of drugs affecting insulin resistance, smoking, aortic disease (coarctation, aneu- rism, Marfan syndrome or history of aortic surgery), evidence of ongoing infection, presence of severe valve disease, pregnancy or inflammation and insufficient echocardiography view
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No **Not reported**	Consecutively randomized into two different treatment arms
	Was allocation to intervention group concealed?	Yes Partial No **Not reported**	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No **Not reported**	
	Were investigators and care providers blind to intervention group?	Yes Partial No **Not reported**	
	Aside from the experimental intervention, were the groups treated the same?	**Yes** Partial No Not reported	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes **Partial** No Not reported	Echocardiographic examinations were performed before and after 6 months of treatment by the same physician (BC) who was unaware of the patients' treatment group.
	Were all outcomes measured in a standard, valid and reliable way?	**Yes** Partial No Not reported	
	Were outcomes assessed objectively and independently?	**Yes** Partial No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	0 %	*0 dropouts*

	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	**Yes** Partial No Not reported	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No **Not reported**	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial **No** Not reported	BMI differed, 26 in combo vs 32 in COCP group. Other baseline parameters did not differ.
	If confounding was present, was it controlled for?	Yes Partial **No** Not reported	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes **Partial** No Not reported	No conflict of interest, but funding not reported.
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No **Not reported**	
	If statistical analysis was undertaken, was this appropriate?	**Yes** Partial No Not reported	

COMMENTS		
What is the overall risk of bias?	Low Moderate **High** Insufficient information	Randomization process not described properly, was decribed as consecutively randomized. Baseline characteristics differed between groups.
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		

Study ID	Kaya 2015
Study Citation	Kaya MG, Yildirim S, Calapkorur B, Akpek M, Unluhizarci K, Kelestimur F. Metformin improves endothelial function and carotid intima media thickness in patients with PCOS. Gynecol Endocrinol. 2015;31(5):401-5.
Study Country	Turkey
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS, aged 17-37 years
PCOS diagnostic criteria	AES
Presence of infertility	Not reported
Presence of other condition/s	*No*
Medication History	*No*
N per group	*Allocated/randomised:* *Metformin+OCP 25* *OCP 25* *Assessed at end of study: drop-out not reported*
Setting	Women with PCOS in the Department of Endocrinology at Erciyes University Hospital, aged 17–37 years

Intervention	drospirenone 3 mg/ EE 3 mg with a 28-d cycle (21 hormone pills followed by 7 placebo pills)	
Comparison	drospirenone 3 mg/ EE 3 mg with a 28-d cycle (21 hormone pills followed by 7 placebo pills) and metformin 850 mg twice a day	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Weight, BMI, lipids, SHBG, T, FAI, A, DHEAS, HOMA, CRP	
Follow up Duration	6 months	
Summary Result/s	adding metformin to OCP treatment may have beneficial effect on FMD and CIMT that represent vascular function in patients with PCOS. These results suggest that adding metformin to OCP treatment for PCOS could preserve the cardiovascular system and improve it.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	**Yes** Partial No Not reported	to investigate the effects of treatment with drospirenone/ ethinyl estradiol (EE) alone or in combination with metformin on the flow-mediated vasodilatation (FMD) and carotid intima media thickness (CIMT) in women with PCOS.
Does the study have specified inclusion/exclusion criteria?	**Yes** Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	**Yes** Partial No Not reported	
Inclusion criteria	**Yes** Partial No Not reported	Newly diagnosed women with PCOS, aged 17–37 years. PCOS was defined as the presence of two of the following criteria after the exclusion of other etiologies: (i) polycystic ovaries on ultrasound examination, (ii) chronic oligomenorrhea or amenorrhea, (iii) clinical or biochemical evidence of hyperandrogenism
Exclusion criteria	**Yes** Partial No Not reported	DM, corticosteroid use, use of drugs affecting insulin resistance, hyperlipidemia, hypertension, oral contraceptive use, evidence of ongoing infection, presence of severe valve disease, pregnancy, systemic disease (hepatic, renal,

			cardiac), smoking, aortic disease (coarctation, aneurism, Marfan syndrome or history of aortic surgery).
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No **Not reported**	
	Was allocation to intervention group concealed?	Yes Partial No **Not reported**	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No **Not reported**	
	Were investigators and care providers blind to intervention group?	Yes Partial No **Not reported**	
	Aside from the experimental intervention, were the groups treated the same?	**Yes** Partial No Not reported	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No **Not reported**	
	Were all outcomes measured in a standard, valid and reliable way?	**Yes** Partial No Not reported	After overnight fasting, blood samples were obtained from the subjects during the follicular phase of the menstrual cycle, except in those with amenorrhea.
	Were outcomes assessed objectively and independently?	**Yes** Partial No Not reported	

ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	0 %	
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)? **High**	Yes Partial No Not reported	*NA*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No **Not reported**	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	**Yes** Partial No Not reported	
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*NA*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes **Partial** No Not reported	No conflict of interest, funding not reported.

	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No **Not reported**	
	If statistical analysis was undertaken, was this appropriate?	**Yes** Partial No Not reported	
COMMENTS		*Randomization-process reported poorely*	
What is the overall risk of bias?		Low Moderate **High** Insufficient information	Unclear randomization, no blinding.

Study ID	Kebapcilar 2009
Study Citation	Kebapcilar L, Yuksel A, Bozkaya G, Taner CE, Kebapcilar AG, Bilgir O, et al. Effects of an EE/CA compared with EE/CA-metformin on serum ADMA levels in women with polycystic ovary syndrome. Central European journal of medicine. 2009;4(4):423-7.
Study Country	Turkey
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS
PCOS diagnostic criteria	Rotterdam
Presence of infertility	*Not reported*
Presence of other condition/s	
Medication History	*No*
N per group	*Allocated/randomised: COCP 22, COCP + met 21*

	Assessed at end of study: COCP 22, COCP + met 21	
Setting	*Not reported. Study conducted in Turkey.*	
Intervention	35 µg EE/2mg CPA	
Comparison	35 µg EE/2mg CPA + met 1700 mg/day	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	BMI, fT, DHEAS, insulin, HOMA, TG, LDL, HDL,	
Follow up Duration	*3 months*	
Summary Result/s	Adding metformin to OCP treatment, improved all lipid profiles, HOMA-IR, insulin, androgens and also ADMA levels after 3 months of therapy.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	**Yes** Partial No Not reported	The aim of the study was to investigate EE/CA alone and EE/CA combined with metformin treatments on serum asymmetric dimethylarginine levels in women with PCOS.
Does the study have specified inclusion/exclusion criteria?	**Yes** Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	**Yes** Partial No Not reported	
Inclusion criteria	**Yes** Partial No Not reported	Women with PCOS according to Rotterdam criteria
Exclusion criteria	**Yes** Partial No Not reported	Women with hypertension, diabetes, history of coronary heart disease, known coagulation abnormalities and current smokers and cronic alcohol users were also not included.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No **Not reported**	Patients were randomly assigned to one of two treatment groups.
	Was allocation to intervention group concealed?	Yes Partial No **Not reported**	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No **Not reported**	
	Were investigators and care providers blind to intervention group?	Yes Partial No **Not reported**	
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No **Not reported**	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No **Not reported**	
	Were all outcomes measured in a standard, valid and reliable way?	**Yes** Partial No Not reported	
	Were outcomes assessed objectively and independently?	**Yes** Partial No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	0 %	No subjects were lost during the follow up and none of the 43 patients had stopped the therapies because of adverse effects

	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	**Yes** Partial No Not reported	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No **Not reported**	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	**Yes** Partial No Not reported	
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*NA*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No **Not reported**	
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No **Not reported**	
	If statistical analysis was undertaken, was this appropriate?	**Yes** Partial No Not reported	

COMMENTS		
What is the overall risk of bias?	Low Moderate **High** Insufficient information	Randomization not described, no blinding
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		

Study ID	Kebapcilar 2010
Study Citation	Kebapcilar L, Taner CE, Kebapcilar AG, Alacacioglu A, Sari I. Comparison of four different treatment regimens on coagulation parameters, hormonal and metabolic changes in women with polycystic ovary syndrome. Arch Gynecol Obstet. 2010;281(1):35-42.
Study Country	Turkey
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS
PCOS diagnostic criteria	Rotterdam
Presence of infertility	*Not reported*
Presence of other condition/s	
Medication History	*No*
N per group	*Allocated/randomised: 12/group* *Assessed at end of study: 12/group*
Setting	*Not reported*
Intervention	35 µg EE/2mg CPA (Diane Nova, Shering, Germany; 21 days per month followed by a 7-day pill-free period),

Comparison	1: 35 µg EE/2mg CPA + met 1700 mg/day 2: : metformin 1700 mg/day 3: : met 1700 mg/day + spiro 100 mg/day metformin: Glucophage, Merck Lipha Lab, Lyon, France; 850 mg twice daily), spironolactone (Aldactone, ARIS, Turkey; 100 mg/daily)	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	BMI, fT, DHEAS, insulin, HOMA, TG, LDL, HDL,	
Follow up Duration	*3 months*	
Summary Result/s	In all treatment groups, reduced levels of coagulation parameters were observed, improvement of hormonal, hematological and metabolical variables by most probably reducing insulin levels. Among the treatment groups, EE/CA–metformin may be a more effective therapeutic option than the other protocols and this may be due to the benefcial effect of EE/CA–metformin on insulin resistance	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	**Yes** Partial No Not reported	To determine the effects of different treatment regimens on the hormonal features, metabolic parameters, and hematologic variables in women with PCOS
Does the study have specified inclusion/exclusion criteria?	**Yes** Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	**Yes** Partial No Not reported	
Inclusion criteria	**Yes** Partial No Not reported	Patients with PCOS (24.0+/-5.4 years; BMI 27.9+/-5.28) were included in the study. PCOS was diagnosed according to Rotterdam. All women had normal thyroid, renal and hepatic functions.
Exclusion criteria	**Yes** Partial No Not reported	Women who had any medication (e.g., antihypertensives, oral anti-diabetics, oral contraceptives, antiandrogens, statins, warfarin, antidepressant medication, and GnRH agonists and antagonists) in the preceding 3 months were not included. Women who are current smokers and with hypertension, diabetes, histor y of coronary heart

			disease, known coagulation abnormalities were also excluded.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No **Not reported**	Patients were randomly assigned to one of four treatment groups and each group contained 12 participants
	Was allocation to intervention group concealed?	Yes Partial No **Not reported**	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No **Not reported**	
	Were investigators and care providers blind to intervention group?	Yes Partial No **Not reported**	
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No **Not reported**	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No **Not reported**	
	Were all outcomes measured in a standard, valid and reliable way?	**Yes** Partial No Not reported	
	Were outcomes assessed objectively and independently?	**Yes** Partial No Not reported	

ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	0 %	0 None of the 48 patients had stopped the therapies because of adverse effects.
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	**Yes** Partial No Not reported	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No **Not reported**	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes **Partial** No Not reported	Patient groups were well matched for all parameters, except HDL cholesterol levels at baseline
	If confounding was present, was it controlled for?	Yes Partial **No** Not reported	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial **No** Not reported	

	Was the study sufficiently powered to detect any differences between the groups?	**Yes** Partial No Not reported	
	If statistical analysis was undertaken, was this appropriate?	**Yes** Partial No Not reported	
COMMENTS			
What is the overall risk of bias?		Low Moderate **High** Insufficient information	Randomization not described, no blinding.
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

Study ID	Kilicdag 2005
Study Citation	Kilicdag, E. B.; Bagis, T.; Zeyneloglu, H. B.; Tarim, E.; Aslan, E.; Haydardedeoglu, B.; Erkanli, S. Homocysteine levels in women with polycystic ovary syndrome treated with metformin versus rosiglitazone: a randomized study Hum Reprod Apr 2005;20(4):894-9
Study Country	Turkey
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS
PCOS diagnostic criteria	NIH
Presence of infertility	No

Presence of other condition/s	-
Medication History	-
N per group	*Allocated/randomised:* 1.Metformin=15 2.Rosiglitazone=15 *Assessed:* 1.Metformin=15 2.Rosiglitazone=15
Setting	This study was conducted in the Department of Obstetrics and Gynecology of Baskent University School of Medicine, Adana, Turkey. Between April 2002 and June 2003, 30 women with PCOS participated in this prospective randomized study
Intervention	1.Metformin 850mgx2/d
Comparison	2.Rosiglitazone 4mg/d
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Weight, bmi, dheas, T, free-T, homa, lipids
Follow up Duration	3 months
Summary Result/s	Metformin and rosiglitazone therapy result in a significant increase in plasma Hcy concentrations, without significant changes in BMI and IR that could result in increased cardiovascular risk.

ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	To examine the effects of short-term metformin and rosiglitazone therapy, especially on serum levels of Hcy and other cardiovascular factors such as lipid profile and insulin resistance, in patients with PCOS.
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	

If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	
Inclusion criteria		Yes Partial No Not reported	All patients with oligomenorrhoea (a cycle length of 45 days or six periods per year) or amenorrhoea, who also had evidence of hyperandrogenism [a hirsutism score >7, according to Ferriman and Gallway] and/or an elevated serum testosterone level
Exclusion criteria		Yes Partial No Not reported	-other causes of hyperandrogenism. -subjects treated with hormonal medications within 3 months
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Patients were randomized to two groups by an allocation sequence generated from a random number table and assigned through consecutively numbered opaque, sealed envelopes.
	Was allocation to intervention group concealed	Yes Partial No Not reported	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	
DE DE	**Were outcome assessors blind to**	Yes Partial	

	intervention group?	No Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	O% in both groups
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis	Yes Partial No Not reported	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*HDL level was significantly different*

	If confounding was present, was it controlled for?	Yes Partial Not reported No	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	
COMMENTS		*No blinding, no protocol*	
What is the overall risk of bias?		Low Moderate High Insufficient information	

Study ID	Kumar 2018
Study Citation	Kumar Y, Kotwal N, Singh Y, Upreti V, Somani S, Hari Kumar KVS. A randomized, controlled trial comparing the metformin, oral contraceptive pills and their combination in patients with polycystic ovarian syndrome. J Family Med Prim Care. 2018;7(3):551-6.
Study Country	India
BRIEF CHARACTERISTICS OF RCT	

Patient/population/ participants	Newly diagnosed PCOS (age 18–40 year, symptom duration >6 months)	
PCOS diagnostic criteria	Rotterdam	
Presence of infertility	No	
Presence of other condition/s	*No*	
Medication History	*No*	
N per group	*Allocated/randomised:* 1. Metformin=30 2. OCP=30 3.OCP+Metformin=30 *Assessed at end of study:* 1. Metformin=30 2. OCP=28 3.OCP+Metformin=29	
Setting	A randomized, controlled, prospective interventional study in a tertiary care, teaching hospital of the armed forces. The participants were recruited from the endocrinology/medicine/gynecology clinic of our hospital. Included were 90 newly diagnosed patients with PCOS (aged between 18 and 40 years, symptom duration >6 months, premenopausal, and normal thyroid function).	
Intervention	OCP-group: EE 35 mcg and cyproterone acetate 2 mg	
Comparison	Metformin: 500 mg/day, gradually increased to 2000 mg/day over 1 month Metformin+OCP-group: metformin 500 mg/day, gradually increased to 2000 mg/day over 1 month +EE 35 mcg and cyproterone acetate 2 mg	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Weight, BMI, mFGS, lipids, f-gluc, f-insulin, HOMA-IR, TT, DHEAS	
Follow up Duration	6 months	
Summary Result/s	Met+OCP improves hyperandrogenism and body composition and reduces the inflammatory markers better than Met or OCP alone	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes **Partial** No	to determine the effect of metformin and OCP either alone or in combination in women with PCOS. (previous reports have given conflicting results

		Not reported	about the clinical, hormonal, and reproductive outcomes)
Does the study have specified inclusion/exclusion criteria?		**Yes** Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?		**Yes** Partial No Not reported	
Inclusion criteria		**Yes** Partial No Not reported	Newly diagnosed patients with PCOS according to Rotterdam (aged between 18 and 40 years, symptom duration >6 months, premenopausal, and normal thyroid function)
Exclusion criteria		**Yes** Partial No Not reported	Patients with a history of using any drug therapy (insulin sensitizers, hormone therapy, calcium, and Vitamin D), use of other drugs that affect the body composition and androgen levels (insulin, glucocorticoids), and pregnancy or lactation.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	**Yes** Partial No Not reported	The patients were divided into three groups using a computer-generated random sequence numbering
	Was allocation to intervention group concealed?	Yes Partial No **Not reported**	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No **Not reported**	
	Were investigators and care providers blind to intervention group?	Yes Partial No **Not reported**	

	Aside from the experimental intervention, were the groups treated the same?	**Yes** Partial No Not reported	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No **Not reported**	
	Were all outcomes measured in a standard, valid and reliable way?	**Yes** Partial No Not reported	
	Were outcomes assessed objectively and independently?	**Yes** Partial No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	7% COCP 0% met 3% COCP + met	1. Metformin=0/30=0% 2. OCP=2/30=6.7% 3.OCP+Metformin=1/30=3.3%
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)? moderate	Yes Partial **No** Not reported	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No **Not reported**	

CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes **Partial** No Not reported	All the three groups were comparable in the clinical presentation and the symptomatology. However, patients in Group 3 had higher BMI and IR in comparison to other groups.
	If confounding was present, was it controlled for?	Yes Partial **No** Not reported	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial **No** Not reported	
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial **No** Not reported	
	If statistical analysis was undertaken, was this appropriate?	Yes **Partial** No Not reported	
COMMENTS			
What is the overall risk of bias?		Low **Moderate** High Insufficient information	No blinding, groups differed partially at baseline

Study ID	Li 2020
Study Citation	Li, Y.; Tan, J.; Wang, Q.; Duan, C.; Hu, Y.; Huang, W.

	Comparing the individual effects of metformin and rosiglitazone and their combination in obese women with polycystic ovary syndrome: a randomized controlled trial Fertility and sterility 2020;113(1):197
Study Country	China
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Obese Chinese women (BMI>=25) with PCOS and insulin resistance
PCOS diagnostic criteria	Rotterdam
Presence of infertility	NR
Presence of other condition/s	Overweight, bmi>=25
Medication History	patients exhibiting insulin resistance
N per group	*Allocated/randomised:* 1. Metformin+LS=68 2. Rosiglitazone+LS=67 3.Metformin+Rosiglitazone+LS=69 *Assessed:* 1. Metformin+LS=61 2. Rosiglitazone+LS=63 3.Metformin+Rosiglitazone+LS=61
Setting	Prospective randomized controlled trial that took place between December 2013 and September 2016 at the Reproductive Endocrinology Division, West China Second University Hospital of Sichuan University, People's Republic of China
Intervention	1.Metformin 1500mg/d+lifestyle
Comparison	2.Rosiglitazone 4mg/d+lifestyle 3.Metformin 1000mg/d +Rosiglitazone 4mg/d+lifestyle

	During the study, all participants were advised to undergo lifestyle modification, including dietary adjustments and moderate-strength physical exercises three times a week for 40 minutes per session	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Menstrual cycle, weight, bmi, whr, mFGS, T, f-gluk, f-insulin, homa, lipids	
Follow up Duration	6 months	
Summary Result/s	Metformin along with lifestyle modification should be recommended for obese, insulin-resistant women with PCOS. Rosiglitazone alone or combined with metformin plus lifestyle modification should be considered for the women with abnormal lipid profiles	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	to compare the clinical and biochemical metabolic effects of metformin, rosiglitazone, and their combination in obese, insulin-resistant Chinese women with PCOS
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	
Inclusion criteria	Yes Partial No Not reported	-women from 18 to 35 years of age -patients with obesity, a BMI>=25 -patients exhibiting insulin resistance, homeostatic model assessment of insulin resistance (HOMA-IR) index >=2.77
Exclusion criteria	Yes Partial No Not reported	-patients with hyperprolactinemia, hypo- or hyperthyroidism, or abnormal liver, kidney, or heart function -patients affected by hypertension, diabetes mellitus, or severe mental illness or with a personal history of cardiovascular events -patients who had taken oral contraceptives, glucocorticoids, antiandrogen agents, ovulation induction agents, diabetic drugs, or other steroid agents within 3 months

INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	A prospective, randomized, open-label study. Women were randomly allocated to the treatment group according to computer-generated random numbers, using a block randomization method (1:1:1) with random block size of 6 or 10
	Was allocation to intervention group concealed?	Yes Partial No Not reported	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	

ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	1. Metformin+LS=7/68=10.3% 2. Rosiglitazone+LS=4/67=6.0% 3.Metformin+Rosiglitazone+LS=8/69=11.6%
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis	Yes Partial No Not reported	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Chinese Clinical Trial Registry Center (ChiCTR-TRC-13003642)
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	
	If confounding was present, was it controlled for?	Yes Partial Not reported No	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*Funding not reported*

	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	
COMMENTS		*Not blinded, but unlikely to affect outcome.*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*Low*

Study ID	Lingaiah 2019
Study Citation	Lingaiah, S.; Morin-Papunen, L.; Risteli, J.; Tapanainen, J. S. Metformin decreases bone turnover markers in polycystic ovary syndrome: a post hoc study Fertility and sterility 2019;112(2):362
Study Country	Finland
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Adult women with PCOS, non-obese (BMI <27) and obese (BMI>=27)
PCOS diagnostic criteria	Rotterdam
Presence of infertility	Yes
Presence of other condition/s	No
Medication History	No
N per group	*Assessed at end of study: Metformin-group BMI <27, 40* *Placebo-group, BMI<27, 34*

	Metformin-group BMI >=27, 17 *Placebo-group, BMI>=27, 27*	
Setting	*Post hoc analysis among a subset of subjects from a large cohort of subjects in a prospective multi-center, placebo-controlled randomized study on the effects of metformin on miscarriage, pregnancy, and live-birth rates. Only the subjects examined at Oulu University Hospital were included in the study.*	
Intervention	*Non-obese women (BMI < 27 kg/m2) received metformin (Diformin; Leiras) at a dose of 500 mg + 1,000 mg daily* *Obese women (BMI R 27 kg/m2) received metformin at a dose of 1,000 mgx2 daily.*	
Comparison	Placebo tablets	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	T, SHBG, FAI, DHEAS, A, f-gluk, f-ins, HOMA, BMI, WHR, weight.	
Follow up Duration	3 months	
Summary Result/s	Metformin treatment, was associated with reduced bone turnover, as suggested by reductions in markers of bone formation and resorption, leading to slower bone remodeling in premenopausal women with PCOS. Small decrease in weight and BMI in the obese group after metformin. T and f-gluc decreased, and the Matsuda index increased. Non-obese group treated with metformin, T, FAI and A decreased	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	to investigate the effects of metformin on bone turnover markers in women with PCOS
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	

Inclusion criteria		Yes Partial No Not reported	Women aged 18–39 yr at entry, with a BMI greater than 19 kg/m^2 and diagnosed with PCOS according to Rotterdam criteria
Exclusion criteria		Yes Partial No Not reported	type 2 DM, active liver disease (alanine aminotransferase >100 IU/liter), history of cardiac or renal failure, hormone medication, alcohol use, and regular smoking.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Randomization was performed by the hospital pharmacy with 1:1 allocation in random blocks of 10 using two computer-generated lists, one for the nonobese and one for the obese women. Metformin and placebo tablets were provided by Leiras (Turku, Finland) and prepacked in opaque identical containers of 100 tablets and consecutively numbered for each woman according to the randomization schedule. Each woman was assigned a number and received the tablets in the corresponding container. Randomization codes remained blinded until the database lock had taken place. The patients and all study site personnel were blinded to the study drug codes
	Was allocation to intervention group concealed?	Yes Partial No Not reported	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	

DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Blood samples were collected in a fasting state at baseline and at 3 months of treatment with metformin/placebo and were stored at 20 C until the time of analysis.
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Weight and waist and hip circumferences (measured to the nearest centimetre with a soft tape at the narrowest part of the torso and at the widest part of the gluteal region) were assessed at each visit, and the waist to hip ratio (WHR) was calculated.
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	0 % in this study (only participants who completed study included in post hoc) met-group 16.9%, placebo 21.2% in original study
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	intention to treat analysis
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	

	If confounding was present, was it controlled for?	Yes Partial No Not reported	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	
COMMENTS		*Moderate*	
What is the overall risk of bias?		Low Moderate High Insufficient information	Unclear attrition
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No – all outcomes moderate risk of bias*	

Study ID	Long 2022
Study Citation	Long, Tao; Zhang, Ying; Zeng, Chunping; Zheng, Siyuan; Zhou, Lin; Liu, Haiyan

	Effects of Low-Dose Spironolactone Combined with Metformin or Either Drug Alone on Insulin Resistance in Patients with Polycystic Ovary Syndrome: A Pilot Study International Journal of Endocrinology 2022;():1-8
Study Country	China
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS aged >18yr
PCOS diagnostic criteria	Rott
Presence of infertility	No
Presence of other condition/s	No
Medication History	-
N per group	*Allocated/randomised:* 1. Metformin=63 2. SPL=63 3. Metformin+SPL=63 *Assessed at end of study:* 1. Metformin=54 2. SPL=53 3. Metformin+SPL=51
Setting	A single center, randomized, open-label, pilot study of patients with PCOS,aged >18 yrs at the third Affiliated Hospital of Guangzhou Medical University between 01/2014 and 01/2016
Intervention	1.Metformin 1500mg/d 2.Metformin 1500mg/d+Spironolactone 40mg/d
Comparison	3.Spironolactone 40mg/d
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Weight, BMI, WHR, FAI, HOMA,
Follow up Duration	3 months
Summary Result/s	No differences in any parameters between the metformin and spironolactone groups (all $P > 0.05$). In the combined group, after 12 weeks of treatment, HOMA-IR was lower than in the metformin and spironolactone groups

ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	To compare the effects of low-dose spironolactone combined with metformin or either drug alone on IR and functional improvement in patients with PCOS, as well as compliance, safety, and incidence of adverse effects through a prospective randomized open-label study.
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	
Inclusion criteria	Yes Partial No Not reported	(1) age >18 years; (2) history of sexual life; and (3) agreed to use barrier contraception within 12 weeks.
Exclusion criteria	Yes Partial No Not reported	(1) other endocrine diseases such as hyperprolactinemia and congenital adrenal hyperplasia (CAH), or hyperprolactinemia and other endocrine diseases that led to hyperandrogenism, such as Cushing's syndrome, CAH, and androgen-secreting tumors; (2) patients with immune diseases, cancer, type 1 diabetes, or history of type 2 diabetes; (3) medications within 12 weeks, including cortisol, antidepressants, hypoglycemic agents, hormonal contraceptives, ovulation-inducing drugs, or other drugs that affect the metabolism of glycolipids and sex hormones; (4) pregnant or lactating women within the recent 6 months or those with pregnancy plan within 3 months; (5) patients with speech impairment or those with disabilities who cannot understand the experimental requirements; (6) patients with severe organ failure such as liver or renal function, or mental disorders; (7) patients with immunodeficiency or HIV infection;

			(8) history of drug abuse and alcohol dependence in the past 5 years; (9) history of pancreatitis or pancreatectomy; or (10) participated in any clinical trials within 3 months
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	The participants were randomized 1 :1 : 1 to one of three groups according to a random number table: the metformin group, spironolactone group, and metformin + spironolactone group. This was an open-label study
	Was allocation to intervention group concealed?	Yes Partial No Not reported	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	

	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	1. Metformin=9/63=14.3% 2. SPL=10/63=15.9% 3. Metformin+SPL=12/63=19.0%
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	
	If confounding was present, was it controlled for?	Yes Partial Not reported	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	

	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	
COMMENTS		*No blinding, not ITT, no protocol*	
What is the overall risk of bias?		Low Moderate High Insufficient information	

Study ID	Luque-Ramírez 2009
Study Citation	Luque-Ramírez M, Mendieta-Azcona C, Alvarez-Blasco F, Escobar-Morreale HF. Effects of metformin versus ethinyl-estradiol plus cyproterone acetate on ambulatory blood pressure monitoring and carotid intima media thickness in women with the polycystic ovary syndrome. Fertility and sterility. 2009;91(6):2527-36.
Study Country	Spain
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS
PCOS diagnostic criteria	Rotterdam
Presence of infertility	*Not reported*
Presence of other condition/s	
Medication History	*No*
N per group	*Allocated/randomised: COCP 15; metformin 19* *Assessed at end of study: COCP 15; metformin 12*

Setting	*Academic hospital, Madrid, Spain*	
Intervention	35 µg EE/2mg CPA	
Comparison	1700 mg met/day	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*The study was designed for ambulatory blood pressure monitoring and carotid intima media thickness Outcome of interest for this review is adverse effects*	
Follow up Duration	*24 w*	
Summary Result/s	Metformin treatment decreased daytime ABPM recordings whereas EE + CPA exerted the opposite effect. The safer blood pressure profile of metformin should be considered in PCOS patients who present with a history of hypertension or who are at risk for this disorder.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	**Yes** Partial No Not reported	To compare the effects of metformin versus an antiandrogenic contraceptive pill on ambulatory blood pressure monitoring (ABPM) and carotid intima media thickness (CIMT) in women with polycystic ovary syn- drome (PCOS)
Does the study have specified inclusion/exclusion criteria?	Yes **Partial** No Not reported	vague for inclusion, none for exclusion?
If there were specified inclusion/ exclusion criteria, were these appropriate?	**Yes** Partial No Not reported	
Inclusion criteria	**Yes** Partial No Not reported	34 consecutive PCOS patients were recruited.
Exclusion criteria	**Yes** Partial No Not reported	None of the patients had a personal history of hypertension, diabetes mellitus, or cardiovascular events, or had received treatment with oral contraceptives, antiandrogens, insulin sensitizers, or drugs that might interfere with blood pressure regulation for the previous 6 months.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Did the study have an adequate method of randomisation?**	**Yes** Partial No Not reported	Simple randomization was conducted using blocksof 10 sealed opaque envelopes assigning five patients to re-ceive Diane35Diario and five patients to receive metformin.Randomization allocated 15 patients to Diane35Diario and19 patients to metformin.
	Was allocation to intervention group concealed?	**Yes** Partial No Not reported	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial **No** Not reported	
	Were investigators and care providers blind to intervention group?	Yes Partial No **Not reported**	
	Aside from the experimental intervention, were the groups treated the same?	**Yes** Partial No Not reported	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No **Not reported**	
	Were all outcomes measured in a standard, valid and reliable way?	**Yes** Partial No Not reported	
	Were outcomes assessed objectively and independently?	**Yes** Partial No Not reported	

ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	0% COCP 37% met	COCP 0/15 met 7/19=37%
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	**Yes** Partial No Not reported	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	**Yes** Partial No Not reported	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	**Yes** Partial No Not reported	
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*NA*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No **Not reported**	

	Was the study sufficiently powered to detect any differences between the groups?	**Yes** Partial No Not reported	
	If statistical analysis was undertaken, was this appropriate?	**Yes** Partial No Not reported	
COMMENTS			
What is the overall risk of bias?		Low **Moderate** High Insufficient information	No blinding, high dropout rate in one arm, but intention to treat analysis
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

Study ID	Lv 2005
Study Citation	Lv L, Liu Y, Sun Y, Tan K. Effects of metformin combined with cyproterone acetate on clinical features, endocrine and metabolism of non-obese women with polycystic ovarian syndrome. J Huazhong Univ Sci Technolog Med Sci. 2005;25(2):194-7.
Study Country	China
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS
PCOS diagnostic criteria	The presence of: (1) chronic anovulatroy disorders such as oligomenorrhea, anovulatory cycles, or secondary amenorrhea; (2) the ratio of LH/FSH was>2 and (or) the plasma testosterone (T) level was>2.6 nmol/L;

	(3) 10 or more follicles 2--8 mm in diameter) in one or both ovaries by transvaginal ultrasound examination;	
Presence of infertility	*Not reported*	
Presence of other condition/s		
Medication History	*No*	
N per group	*Allocated/randomised:* *Assessed at end of study: 25/group*	
Setting		
Intervention	35 µg EE/2mg CPA	
Comparison	35 µg EE/2mg CPA + met 500 mg/day	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	BMI, WHR, TT, A4, DHEAS, SHBG,	
Follow up Duration	*6 months*	
Summary Result/s	Combined use of EE/CPA and metformin could improve insulin sensitivity and further suppress hyperandrogenism in non-obese women with PCOS	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes **Partial** No Not reported	To explore the effects of metformin combined with cyproterone acetate (CPA) on the clinical features, endocrine and metabolism of the patients with polycystic ovarian syndrome
Does the study have specified inclusion/exclusion criteria?	**Yes** Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	**Yes** Partial No Not reported	
Inclusion criteria	**Yes** Partial No	PCOS was defined as the presence of: (1) chronic anovulatroy disorders such as oligomenorrhea, anovulatory cycles, or secondary amenorrhea; (2) the ratio of LH/FSH was>2 and (or) the plasma

		Not reported	testosterone (T) leve was>2.6 nmol/L; (3) 10 or more follicles (2--8 mm in diameter) in one or both ovaries by trans- vaginal ultrasound examination
Exclusion criteria		**Yes** Partial No Not reported	other known endocrinological disease, and those taking drugs known to affect carbohydrate or lipid metabolism and OGTT re- sults during the 6 months preceding the study were excluded.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No **Not reported**	The subjects were randomized to either the CPA group (n=25) or to the CPA+metformin group (n=25).
	Was allocation to intervention group concealed?	Yes Partial No **Not reported**	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No **Not reported**	
	Were investigators and care providers blind to intervention group?	Yes Partial No **Not reported**	
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No **Not reported**	
DEDET ECTION	**Were outcome assessors blind to intervention group?**	Yes Partial No **Not reported**	

	Were all outcomes measured in a standard, valid and reliable way?	**Yes** Partial No Not reported	
	Were outcomes assessed objectively and independently?	**Yes** Partial No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	**Not reported**	
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No **Not reported**	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	**Yes** Partial No Not reported	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	**Yes** Partial No Not reported	
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*NA*

OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No **Not reported**	
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No **Not reported**	
	If statistical analysis was undertaken, was this appropriate?	**Yes** Partial No Not reported	
COMMENTS			
What is the overall risk of bias?		Low Moderate **High** Insufficient information	randomization poorley described, no blinding, no info on drop outs, unclear aim
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

Study ID	Mhao 2016
Study Citation	Mhao NS, Al-Hilli AS, Hadi NR, Jamil DA, Al-Aubaidy HA. A comparative study to illustrate the benefits of using ethinyl estradiol-cyproterone acetate over metformin in patients with polycystic ovarian syndrome. Diabetes Metab Syndr. 2016;10(1 Suppl 1):S95-8.
Study Country	Iraq
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS

PCOS diagnostic criteria	Rotterdam
Presence of infertility	*Some were seeking due to infertility, proportion not stated.*
Presence of other condition/s	
Medication History	*No*
N per group	*Allocated/randomised:* *Assessed at end of study: COCP 10, met 16 (dropouts not reported)*
Setting	The participants were attending the infertility clinic, the teaching hospital, seeking treatment for their infertility and/or cycle abnormalities. Iraq.
Intervention	EE 30 µg /CMA 2mg
Comparison	met 1000 mg/day
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	BMI, WHR, FG score, chol, HDL, LDL, TG, TT, OGTT
Follow up Duration	*3 months*
Summary Result/s	Metformin is beneficial in improving lipids, glucose homeostasis and BMI, but EE/CPA is superior in improving the clinical manifestations of PCOS including menstrual disturbances and hyperandrogenism.

ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes **Partial** No Not reported	To illustrate the clinical and biochemical effects of ethinylestradiol-cyproteroneacetate(EE-AC) and metformin in this disease.
Does the study have specified inclusion/exclusion criteria?	Yes **Partial** No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes **Partial** No Not reported	

Inclusion criteria		Yes **Partial** No Not reported	women with PCOS (no definition) seeking for infertility and/or cycle abnormailities
Exclusion criteria		Yes Partial **No** Not reported	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No **Not reported**	"This was a randomized control trial study, done on twenty-six female patients already diagnosed as cases of PCOS. Participants were divided into two study groups"
	Was allocation to intervention group concealed?	Yes Partial No **Not reported**	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No **Not reported**	
	Were investigators and care providers blind to intervention group?	Yes Partial No **Not reported**	
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No **Not reported**	
DEDET ECTION	**Were outcome assessors blind to intervention group?**	Yes Partial No **Not reported**	

	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No **Not reported**	
	Were outcomes assessed objectively and independently?	Yes Partial No **Not reported**	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison **Not reported**	
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No **Not reported**	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No **Not reported**	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes **Partial** No Not reported	Age not reported at baseline
	If confounding was present, was it controlled for?	Yes Partial **No** Not reported	

OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial **No** Not reported	
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No **Not reported**	
	If statistical analysis was undertaken, was this appropriate?	Yes **Partial** No Not reported	Baseline variables not reported, not adjusted
COMMENTS			
What is the overall risk of bias?		Low Moderate **High** Insufficient information	No reports on ranomization, blinding, dropouts, age at baseline, PCOS criteria not defined
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

Study ID	Mohiyiddeen 2013
Study Citation	Mohiyiddeen, L.; Watson, A. J.; Apostolopoulos, N. V.; Berry, R.; Alexandraki, K. I.; Jude, E. B. Effects of low-dose metformin and rosiglitazone on biochemical, clinical, metabolic and biophysical outcomes in polycystic ovary syndrome J Obstet Gynaecol Feb 2013;33(2):165-70
Study Country	UK
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS
PCOS diagnostic criteria	Rotterdam

Presence of infertility	NR
Presence of other condition/s	irregular periods
Medication History	-
N per group	*Allocated/randomised:* 1. Metformin=20 2. Rosiglitazone=20 *Assessed:* 1. Metformin=17 2. Rosiglitazone=18
Setting	Women with PCOS who attended the gynaecological outpatient clinic as a result of irregular periods
Intervention	1.Metformin 500mgx2/d
Comparison	2.Rosiglitazone 4mgx1/d
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Weight, bmi, f-insulin, f-gluc, crp, lipids, t, shbg, fai
Follow up Duration	3 months
Summary Result/s	Rosiglitazone and metformin, has comparable beneficial impacts on metabolic, hormonal and morphological features of PCOS but no obvious effect on vascular parameters in a population of predominantly mild PCOS

ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	To compare the effect of low-dose metformin and rosiglitazone on clinical, biochemical, ultrasound features and endothelial function in patients with polycystic ovary syndrome (PCOS)
Does the study have specified	Yes Partial No	

inclusion/exclusion criteria?	Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	
Inclusion criteria	Yes Partial No Not reported	The diagnosis for PCOS was based on the criteria adapted from the Rotterdam consensus. These criteria include hyperandrogenism, chronic anovulation and polycystic ovaries.
Exclusion criteria	Yes Partial No Not reported	Secondary causes such as non-classical adrenal 21-hydroxylase deficiency, hyperprolactinaemia and androgen-secreting neoplasms
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS **Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Randomisation using a computer generated system into two groups The study had an open design, as one of the investigators in the study knew the dosage for safety reasons. The rest of the research team as well as the senior sonographer who performed the ovarian scans were blinded to the randomisation
SELECTION BIAS **Was allocation to intervention group concealed**	Yes Partial No Not reported	
PERFORMANCE BIAS **Were patients blind to intervention group?**	Yes Partial No Not reported	
PERFORMANCE BIAS **Were investigators and care providers blind to intervention group?**	Yes Partial No Not reported	

	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	1. Metformin=3/20=15% 2. Rosiglitazone=2/20=10%
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis	Yes Partial No Not reported	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	

CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	
	If confounding was present, was it controlled for?	Yes Partial Not reported No	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*Funding not reported*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	
COMMENTS		*No protocol, patients not blinded*	
What is the overall risk of bias?		Low Moderate High Insufficient information	

Study ID	Naka 2011

Study Citation	Naka, K. K.; Kalantaridou, S. N.; Kravariti, M.; Bechlioulis, A.; Kazakos, N.; Calis, K. A.; Makrigiannakis, A.; Katsouras, C. S.; Chrousos, G. P.; Tsatsoulis, A.; Michalis, L. K. Effect of the insulin sensitizers metformin and pioglitazone on endothelial function in young women with polycystic ovary syndrome: a prospective randomized study Fertil Steril Jan 2011;95(1):203-9
Study Country	Greece
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Young women with PCOS (mean age 23.3 years)
PCOS diagnostic criteria	Rotterdam
Presence of infertility	NR
Presence of other condition/s	NR
Medication History	-
N per group	*Allocated/randomised:* 1. Metformin=15 2. Placebo=15 2. Pioglitazone=15 *Assessed:* 1. Metformin=15 2. Placebo=14 2. Pioglitazone=14
Setting	University Hospital endocrinology outpatient clinic
Intervention	1.Metformin 850mgx2/d
Comparison	2.Placebo 3.Pioglitazone 30mg/d

Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Weight, bmi, WHR, f-gluc, f-insulin, lipids, hirsutism, T, SHBG, FAI	
Follow up Duration	6 months	
Summary Result/s	treatment with metformin or pioglitazone for 6 months induces a similar beneficial effect on endothelial function; this may be partially attributed to an improvement in insulin resistance	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	To compare the effect of two different insulin sensitizers, metformin and pioglitazone, on endothelial function in women with PCOS
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	
Inclusion criteria	Yes Partial No Not reported	At least two of the following three features were present: oligo-ovulation or anovulation (fewer than six menstrual cycles in the preceding year), hyperandrogenism, and polycystic ovaries
Exclusion criteria	Yes Partial No Not reported	congenital adrenal hyperplasia, hyperprolactinemia, thyroid disease, or Cushing's syndrome) [1] prior treatment (in the past 6 months) known to affect vascular endothelial function (vitamins, antioxidants, cardiovascular medications); [2] prior treatment (in the past 6 months) with oral contraceptives, antiandrogens, glucocorticoids, or infertility medications; [3] history of cardiovascular disease or diabetes; or [4] excessive alcohol use (more than two drinks a day)
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS **Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	-A prospective, randomized, open-label study - participants were assigned randomly following a computergenerated list of randomization into three groups

	Was allocation to intervention group concealed	Yes Partial No Not reported	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*The metformin group took their doses twice daily, whereas the pioglitazone group took it once daily, and the no treatment group did not receive a placebo.*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	1. Metformin=0/15=0% 2. Placebo=1/15=6.7% 3. Pioglitazone=1/15=6.7%

	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis	Yes Partial No Not reported	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	
	If confounding was present, was it controlled for?	Yes Partial Not reported No	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*Funding not reported*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Based on their power calculations from previous studies*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	

COMMENTS	*Lack of blinding (open-label)*
What is the overall risk of bias?	Low Moderate High Insufficient information
Study ID	Ortega-Gonzales 2005
Study Citation	Ortega-González, C.; Luna, S.; Hernández, L.; Crespo, G.; Aguayo, P.; Arteaga-Troncoso, G.; Parra, A. Responses of serum androgen and insulin resistance to metformin and pioglitazone in obese, insulin-resistant women with polycystic ovary syndrome J Clin Endocrinol Metab Mar 2005;90(3):1360-5
Study Country	Mexico
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS, aged 18–35 yr, BMI>=25, whose chief complaints were hirsutism and/or sterility
PCOS diagnostic criteria	Rotterdam
Presence of infertility	In some
Presence of other condition/s	Obesity and hirsutism
Medication History	-
N per group	*Allocated/randomised:* 1. Metformin=25 2. Pioglitazone=27 *Assessed:* 1. Metformin=18 2. Pioglitazone=17
Setting	Women with PCOS, aged 18–35 yr, whose chief complaints were hirsutism and/or sterility, were recruited from the outpatient Endocrinology and Sterility Clinics of the Instituto Nacional de Perinatologı´a.
Intervention	1.Metformin 850mgx3/d
Comparison	2.Pioglitazone 30mg/d

Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Weight, bmi, WHR, hirsutism, f-gluc, f-insulin, HOMA, lipids, dheas, free-T, A	
Follow up Duration	6 months	
Summary Result/s	pioglitazone is as effective as metformin in improving insulin sensitivity and hyperandrogenism, despite an increase in body weight, bmi and the WHR associated with pioglitazone	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	To compare the effectiveness of pioglitazone and metformin in ameliorating IR and hyperandrogenism in obese women with PCOS and IR who were naive to previous treatment with drugs intended to improve insulin sensitivity.
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	
Inclusion criteria	Yes Partial No Not reported	The diagnosis of PCOS was based on at least two of the three following abnormalities: oligomenorrhea or amenorrhea, a serum androstenedione concentration more than 2.9 ng/ml, or a serum free testosterone more than 2.5 pg/ml and polycystic ovaries by ultrasound. All women had a BMI >=25 kg/m2 , acanthosis nigricans, fasting hyperinsulinemia greater than 16 IU/ml and a fasting glucose to insulin ratio of less than 4.5
Exclusion criteria	Yes Partial No Not reported	impaired glucose tolerance test or type 2 DM, hyperprolactinemia, thyroid disorders, late-onset congenital adrenal hyperplasia, and Cushing's syndrome. Use of clomiphene citrate, oral contraceptives, antiandrogens, or drugs to control their appetite during the previous 6 months.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Randomization was by random number tables. The patients' number treatment codes were retained until the end of the trial in a sealed envelope by a third party who did not participate in the study; patients' names were disclosed after completion of the study. Because the drugs had different daily dose schedules (i.e. once a day for pioglitazone and three times a day for metformin), the study had an open design
	Was allocation to intervention group concealed	Yes Partial No Not reported	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	

ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	1. Metformin=7/25=28% 2. Pioglitazone=10/27=37%
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis	Yes Partial No Not reported	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Trial registration number: CN-00503724
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	
	If confounding was present, was it controlled for?	Yes Partial Not reported No	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	

	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*High drop-out number, 28-37%*

Study ID	*Ozgurtas 2008*
Study Citation	Ozgurtas T, Oktenli C, Dede M, Tapan S, Kenar L, Sanisoglu SY, et al. Metformin and oral contraceptive treatments reduced circulating asymmetric dimethylarginine (ADMA) levels in patients with polycystic ovary syndrome (PCOS). Atherosclerosis. 2008;200(2):336-44.
Study Country	Turkey
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS with a chief complaint of irregular menstrual cycles and/or clinical hyperandrogenism.
PCOS diagnostic criteria	Rotterdam
Presence of infertility	
Presence of other condition/s	

Medication History	*No*	
N per group	*Allocated/randomised: 22/group* *Assessed at end of study: COCP 21; met 20*	
Setting	obstetrics and gynecology outpatient clinic, Turkey	
Intervention	35 µg EE + 2 mg CPA	
Comparison	met 1700mg/day	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	BMI, WHR, HOMA, chol, TG, HDL, LDL, TT, fT, A4, DHEAS, SHBG	
Follow up Duration	*3 months*	
Summary Result/s	circulating (asymmetric dimethylarginine) ADMA concentrations in non-obese, non-hypertensive and young women with PCOS are significantly higher than healthy controls and they improved by a 3-month course of metformin and oral contraceptive treatments	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	**Yes** Partial No Not reported	(1) to determine circulating ADMA concentrations in 44 women with PCOS and 22 age- and BMI-matched healthy controls, (2) to evaluate its correlations with insulin resistance, gonadotrophins, and androgen secretion, and (3) to compare effects of metformin and ethinylestradiol–cyproterone acetate (EE/CPA) treatments on circulating ADMA concentrations
Does the study have specified inclusion/exclusion criteria?	**Yes** Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	**Yes** Partial No Not reported	
Inclusion criteria	**Yes** Partial No	PCOS was made according to the criteria proposed at the Rotterdam revised consensus meeting BMI < 25 kg/m2, aged >18 years, normal tsh and prl

		Not reported	
Exclusion criteria		**Yes** Partial No Not reported	subjects with possible ovarian tumors, congenital adrenal hyperplasia, BMI greater than 25 kg/m 2 , any chronic disease that could interfere with the absorption, distribution, metabolism or excretion of met- formin or EE/CPA, renal or liver disease,
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No **Not reported**	The subjects were randomised to receive either metformin or monophasic oral contraceptive
	Was allocation to intervention group concealed?	Yes Partial No **Not reported**	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No **Not reported**	
	Were investigators and care providers blind to intervention group?	Yes Partial No **Not reported**	
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No **Not reported**	
DEDETECTION	**Were outcome assessors blind to intervention group?**	Yes Partial No **Not reported**	

	Were all outcomes measured in a standard, valid and reliable way?	**Yes** Partial No Not reported	
	Were outcomes assessed objectively and independently?	**Yes** Partial No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	5% COCP 9% met	COCP 1/22=5% Met 2/22=9%
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No **Not reported**	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No **Not reported**	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	**Yes** Partial No Not reported	
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*NA*

OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No **Not reported**	
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No **Not reported**	
	If statistical analysis was undertaken, was this appropriate?	**Yes** Partial No Not reported	
COMMENTS			
What is the overall risk of bias?		Low Moderate **High** Insufficient information	Randomization not described, no blinding
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

Study ID	*Panidis 2011*
Study Citation	Panidis D, Georgopoulos NA, Piouka A, Katsikis I, Saltamavros AD, Decavalas G, et al. The impact of oral contraceptives and metformin on anti-Müllerian hormone serum levels in women with polycystic ovary syndrome and biochemical hyperandrogenemia. Gynecol Endocrinol. 2011;27(8):587-92.
Study Country	Greece
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS

PCOS diagnostic criteria	NIH
Presence of infertility	*Not reported*
Presence of other condition/s	
Medication History	*No*
N per group	*Allocated/randomised:* *Assessed at end of study: 15/group*
Setting	*Outpatient endocrine clinic, Greece*
Intervention	35 µg EE + 2 mg CPA
Comparison	1: 3 mg DRSP/30 mcg EE 2: metformin 1700mg/day
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Primary outcome AMH: Relevant outcomes for this review: BMI, HOMA, glucose, insulin, TT, A4, DHEAS, SHBG, FAI
Follow up Duration	*6 months*
Summary Result/s	AMH serum levels were significantly decreased under treatment with 35 microg ethinylestradiol plus 2 mg cyproterone acetate, due to decrease in androgens and suppression of gonadotropins.

ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	**Yes** Partial No Not reported	To assess the impact of metformin and of two different oral contraceptives (OCs) containing cyproterone acetate and drospirenone, on serum anti-Müllerian hormone (AMH) levels, in a cohort of women with polycystic ovary syndrome
Does the study have specified inclusion/exclusion criteria?	**Yes** Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	**Yes** Partial No Not reported	

Inclusion criteria		**Yes** Partial No Not reported	Only normal weight (BMI<25)were included in the study. Diagnosis of PCOS was based on the presence of: chronic anovulation (fewer than six spontaneous bleeding episodes per year), and biochemical hyperandrogenemia in accordance with NIH
Exclusion criteria		**Yes** Partial No Not reported	Other common causes of hyperandrogenism such as prolactino- ma, congenital adrenal hyperplasia, Cushing syndrome and virilizing ovarian or adrenal tumours were excluded.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes **Partial** No Not reported	Randomisation was non-blind and was based on patients' chronological presence at the outpatient endocrine infirmary,
	Was allocation to intervention group concealed?	Yes Partial **No** Not reported	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial **No** Not reported	
	Were investigators and care providers blind to intervention group?	Yes Partial **No** Not reported	
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No **Not reported**	
DEDET ECTION	**Were outcome assessors blind to intervention group?**	Yes Partial No **Not reported**	

	Were all outcomes measured in a standard, valid and reliable way?	**Yes** Partial No Not reported	
	Were outcomes assessed objectively and independently?	**Yes** Partial No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	0%	*0 dropouts*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	**Yes** Partial No Not reported	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No **Not reported**	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	**Yes** Partial No Not reported	
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*NA*

OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes **Partial** No Not reported	Funding not reported
	Was the study sufficiently powered to detect any differences between the groups?	Yes **Partial** No Not reported	By including a minimum of 15 patients in each study group, the probability is 90% that the study will detect a treatment difference at a two sided 5.0% significance level.
	If statistical analysis was undertaken, was this appropriate?	Yes **Partial** No Not reported	”We prefer to use non-parametric methods as fewer assumptions have to be made"
COMMENTS			
What is the overall risk of bias?		Low Moderate **High** Insufficient information	Randomization in chronological order, no blinding, no protocol,
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

Study ID	Prabhakar 2021
Study Citation	Prabhakar, Priyanka; Mahey, Reeta; Gupta, Monica; Khadgawat, Rajesh; Kachhawa, Garima; Sharma, Jai Bhagwan; Vanamail, Perumal; Kumari, Rajesh; Bhatla, Neerja Impact of myoinositol with metformin and myoinositol alone in infertile PCOS women undergoing ovulation induction cycles - randomized controlled trial Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology 2021;37(4):332-336
Study Country	India
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	PCOS women with infertility

PCOS diagnostic criteria	Rotterdam	
Presence of infertility	Yes	
Presence of other condition/s	No	
Medication History	No	
N per group	*Allocated/randomised:* 1. Metformin+myoinositol=57 2.myoinositol =59 *Assessed:* 1. Metformin+myoinositol=50 2.myoinositol=55	
Setting	Total 130 infertile PCOS women (Rotterdam criteria) attending infertility clinic were screened for the study	
Intervention	1. Metformin 500mgx3/d+myoinositol 4g/d	
Comparison	2.Myoinositol 2gx2/d	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	BMI, WHR, T, HOMA, lipids	
Follow up Duration	3 months	
Summary Result/s	After 3 months of therapy, both study groups had comparable improvement in metabolic and hormonal parameters.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	to compare the efficacy of the combination of metformin and myoinositol with myoinositol alone in terms of clinical pregnancy rate among infertile PCOS women.
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	

If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*No exclusion criteria (other diseases for example)*
Inclusion criteria		Yes Partial No Not reported	women aged 20–38 years who failed to conceive for >12 months, BMI <30 and bilateral patent tubes on hysterosalpingography/laparoscopy with mild male factor infertility and those women willing to participate and follow-up in the study
Exclusion criteria		Yes Partial No Not reported	*Not clearly stated, those who did not fullfill inclsuion?*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Patients were randomized into two groups according to computer-generated randomization table.
	Was allocation to intervention group concealed?	Yes Partial No Not reported	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	
DED ETEC	**Were outcome assessors blind to**	Yes Partial No	

	intervention group?	Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	1. Metformin+myoinositol=7/57=12.3% 2.myoinositol=4/59=6.8%
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*All except total cholesterol*
	If confounding was present, was it controlled for?	Yes Partial Not reported No	

OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate*

Study ID	Sahu 2019
Study Citation	Sahu A, Tripathy P, Mohanty J, Nagy A. Doppler analysis of ovarian stromal blood flow changes after treatment with metformin versus ethinyl estradiol-cyproterone acetate in women with polycystic ovarian syndrome: A randomized controlled trial. J Gynecol Obstet Hum Reprod. 2019;48(5):335-9.
Study Country	India
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS, all with menstrual irregularities
PCOS diagnostic criteria	Rotterdam
Presence of infertility	*Not reported*
Presence of other condition/s	

Medication History	*No*	
N per group	*Allocated/randomised: COCP 51; metformin 50* *Assessed at end of study: COCP 44; metformin 42*	
Setting	*Department of Obstetrics and Gynecology, SCB Medical College, Cuttack, India*	
Intervention	*35 ug EE + 2 mg CPA 21/7*	
Comparison	*metformin 500 mg x 2*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Primary:* ovarian stromal blood flow *Relevant for this review: BMI, cycle duration, hirsutism, TT, SHBG, DHEAS, chol, HDL, LDL, TG, glucose, insulin, HOMA*	
Follow up Duration	*6 months*	
Summary Result/s	*Treatment with both OCP and metformin leads to a reduction in ovarian stromal vascularization in PCOS women perhaps through different mechanisms and this reduction is more prominent with OCP*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	**Yes** Partial No Not reported	To evaluate the effects of oral contraceptive pill (OCP) and metformin at the end of 6 months of treatment on ovarian stromal blood flow by using pulsed and color Doppler in women with PCOS.
Does the study have specified inclusion/exclusion criteria?	**Yes** Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	**Yes** Partial No Not reported	
Inclusion criteria	**Yes** Partial No Not reported	PCOS according to Rotterdam criteria
Exclusion criteria	**Yes** Partial No	Women were excluded if they were known to have congenital adrenal hyperplasia, pituitary insufficiency, persistent hyperprolactinemia, current or previous cardiovascular, hepatic or renal

		Not reported	dysfunction, diabetes, if they had used ovulation induction drugs, oral hypoglycemic agents, OCPs, or anti-androgens within the last 3 months.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	**Yes** Partial No Not reported	Simple randomization was performed using random number table
	Was allocation to intervention group concealed?	Yes Partial **No** Not reported	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial **No** Not reported	
	Were investigators and care providers blind to intervention group?	Yes Partial **No** Not reported	
	Aside from the experimental intervention, were the groups treated the same?	Yes **Partial** No Not reported	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial **No** Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	**Yes** Partial No Not reported	
	Were outcomes assessed objectively and independently?	**Yes** Partial No Not reported	

ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	COCP 14% Met 16%	COCP 7/51=14% Met 8/50=16%
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial **No** Not reported	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	**Yes** Partial No Not reported	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	**Yes** Partial No Not reported	
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*NA*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial **No** Not reported	

	Was the study sufficiently powered to detect any differences between the groups?	**Yes** Partial No Not reported	
	If statistical analysis was undertaken, was this appropriate?	**Yes** Partial No Not reported	
COMMENTS			
What is the overall risk of bias?		Low **Moderate** High Insufficient information	No blinding
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

Study ID	Sangeeta 2012
Study Citation	Sangeeta, S. Metformin and pioglitazone in polycystic ovarian syndrome: a comparative study J Obstet Gynaecol India Oct 2012;62(5):551-6
Study Country	India
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women of age 18–30 years with PCOS
PCOS diagnostic criteria	Rotterdam
Presence of infertility	NR
Presence of other condition/s	NR
Medication History	

N per group	*Allocated/randomised:* 1. Metformin=50 2. Pioglitazone=50 *Assessed:* 1. Metformin=43 2. Pioglitazone=42	
Setting	A randomized, double-blinded, comparative study conducted at Gandhi Hospital—a tertiary care centre and a teaching hospital for graduation and post-graduation in medicine at Hyderabad, Andhra Pradesh, India	
Intervention	1.Metformin 500mgx2/d	
Comparison	2.Pioglitazone 15mgx1/d	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Hirsutism, lipids, f-insulin, homa, T, shbg, FAI	
Follow up Duration	6 months	
Summary Result/s	Pioglitazone may be a better treatment option as far as protection from tendency to development of diabetes is concerned. The rise in serum SHBG levels and decline in free androgen index and L/H ratio are more remarkable with pioglitazone	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	To evaluate the effect of metformin and pioglitazone on insulin resistance, ovulation and hyperandrogenism in women with PCOS
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	

If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	
Inclusion criteria	Yes Partial No Not reported	Age 18-30 yrs the presence of two out of the following three criteria after the exclusion of other criteria: (1) oligo and/or anovulation, (2) hyperandrogenism (clinical and/or biochemical), and (3) polycystic ovaries, (12 or more follicles of 2–9 mm in diameter or ovarian volume[10 cc)
Exclusion criteria	Yes Partial No Not reported	(1) Pregnancy and nursing, (2) Significant liver impairment, (3) Significant renal impairment, (4) Neoplastic disease, (5) Cardiovascular diseases, (6) Cushing's disease, (7) Hypothyroidism, (8) Hyperprolactinemia, and (9) Any drug intake-like Anti-diabetic (or) Oestrogen and progesterone.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS – **Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	"This is a randomized, double-blinded, comparative study" "randomly allocated to two groups" *Randomised but method not demonstrated*
SELECTION BIAS – **Was allocation to intervention group concealed?**	Yes Partial No Not reported	
PERFORMANCE BIAS – **Were patients blind to intervention group?**	Yes Partial No Not reported	*As randomized and double-blinded*
PERFORMANCE BIAS – **Were investigators and care providers blind to intervention group?**	Yes Partial No Not reported	

	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Different treatment regimen - MET group was b.i.d and pioglitazone was 15 OD.*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	1. Metformin=7/50=14% 2. Pioglitazone=8/50=16%
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis	Yes Partial No Not reported	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	

CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Age and bmi (or weight, WHR) at baseline not reported*
	If confounding was present, was it controlled for?	Yes Partial Not reported No	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	The power of the study for different variables was found to be 79.3–100 % except F–G grading for hirsutism (5 %) and serum testosterone (5.6 %) (power calculation done with the help of standard statistical tools). Done posthoc
	If statistical analysis was undertaken, was this appropriate? Moderate	Yes Partial No Not reported	
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Randomization poorley described, no info on baseline age and bmi.*

Study ID	Shahebrahimi 2016

Study Citation	Shahebrahimi, K.; Jalilian, N.; Bazgir, N.; Rezaei, M. Comparison clinical and metabolic effects of metformin and pioglitazone in polycystic ovary syndrome Indian J Endocrinol Metab Nov-Dec 2016;20(6):805-809	
Study Country	Iran	
BRIEF CHARACTERISTICS OF RCT		
Patient/population/ participants	Women with PCOS, aged 20–49 years	
PCOS diagnostic criteria	Rotterdam	
Presence of infertility	Not reported	
Presence of other condition/s	-	
Medication History	-	
N per group	*Allocated/randomised:* 1. Metformin=28 2. Pioglitazone=28 *Assessed:* ?	
Setting	the Obstetrics and Gynecology Clinic of Imam Reza Hospital, Kermanshah, Iran, from May 2012 to April 2013	
Intervention	1.Metformin 500mgx3/d	
Comparison	2.Pioglitazone 30mg/d	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Weight, bmi, f-gluc, lipids, T, f-insulin, dheas	
Follow up Duration	3 months	
Summary Result/s	Although we were not able to recommend one treatment regime over the other, pioglitazone offers a useful, alternate treatment in women with PCOS who are not able to tolerate metformin.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No	This study compares the effects of 2 types of insulin sensitizer drugs, metformin and pioglitazone, on

		Not reported	clinical, metabolic, and endocrine characteristics of women with PCOS.
Does the study have specified inclusion/exclusion criteria?		Yes Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	
Inclusion criteria		Yes Partial No Not reported	the presence of at least 2 of the following 3 criteria: (1) Oligo/anovulation, (2) clinical or biochemical signs of hyperandrogenism including hirsutism, acne, or increased serum testosterone, and (3) polycystic ovaries by vaginal ultrasound
Exclusion criteria		Yes Partial No Not reported	Diabetes mellitus, abnormal liver function tests, known cardiac or renal disease, smoking, age <20 yrs, adrenal disorders including congenital adrenal hyperplasia and Cushings syndrome, thyroid disorders and hyperprolactinemia.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	"56 subjects aged 20–49 years were randomly divided into 2 treatment groups"
	Was allocation to intervention group concealed	Yes Partial No Not reported	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	

	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	
	Were outcomes assessed objectively and independently? moderate	Yes Partial No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis	Yes Partial No Not reported	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	

CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Not compared statistically, seems to differ in some baseline factors such as BP and acne*
	If confounding was present, was it controlled for?	Yes Partial Not reported No	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Randomization not described, no blinding, baseline factors differ*

Study ID	Sohrevardi 2016

Study Citation	Sohrevardi, S. M.; Nosouhi, F.; Hossein Khalilzade, S.; Kafaie, P.; Karimi-Zarchi, M.; Halvaei, I.; Mohsenzadeh, M. Evaluating the effect of insulin sensitizers metformin and pioglitazone alone and in combination on women with polycystic ovary syndrome: An RCT Int J Reprod Biomed Dec 2016;14(12):743-754
Study Country	Iran
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS, aged 18-40 years, with irregular menses and infertility
PCOS diagnostic criteria	Rotterdam
Presence of infertility	Yes
Presence of other condition/s	Irregular menses
Medication History	-
N per group	*Allocated/randomised:* 1.Metformin=28 2.Pioglitazone=28 3. Metformin+Pioglitazone=28 *Assessed:* 1.Metformin=22 2.Pioglitazone=21 3. Metformin+Pioglitazone=23
Setting	Eighty four women with PCOS, aged 18-40 years old, with irregular menses and infertility and/or clinical sign of hyperandrogenism (hirsutism and acne) were recruited from Department of Gynecology, Shahid Sadoughi Hospital Yazd, Iran. between April 2014 to May 2015.
Intervention	1.Metformin 500mgx3/d
Comparison	2.Pioglitazone 30mg/d 3. Metformin 500mgx3/d+Pioglitazone 30mg/d
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Weight, bmi, WHR, f-gluc, f-insulin, homa, lipids, dheas, T
Follow up Duration	3 months

Summary Result/s	Only metformin ameliorated hyperandrogenemia in women with PCOS. Treatment with combination of metformin and pioglitazone did not show more benefit than monotherapy with each drug alone	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	to determine the effect of metformin and pioglitazone on clinical, hormonal and metabolic parameters in women with PCOS.
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	
Inclusion criteria	Yes Partial No Not reported	The presence of at least 2 of the following 3 criteria: (1) Oligo/anovulation, (2) clinical or biochemical signs of hyperandrogenism including hirsutism, acne, or increased serum testosterone, and (3) polycystic ovaries by vaginal ultrasound
Exclusion criteria	Yes Partial No Not reported	Thyroid dysfunction, hyperprolactinemia, Cushing's syndrome, any androgen-secreting tumors, DM (fasting plasma glucose >7 mmol/L), nonclassical 21- hydroxylase deficiency, autoimmune disease, central nervous system disease, significant hypertension, past hysterectomy, abnormal liver or kidney functions or active liver disease (ALT >2.5 the upper limit of normal range), and known heart disease, pregnancy and lactation were excluded from the study.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Before initiation of the study, all patients were allocated to three different groups in sequences provided by computer program generating random number. All subjects received a sealed envelope including the number 1 or 2 or 3 which was corresponding to metformin, pioglitazone and combination therapy, respectively. In our study because commercially accessible pills were applied, there was no blinding after randomization, therefore, investigator and subjects could be aware of the actual treatment.
	Was allocation to intervention group concealed	Yes Partial No Not reported	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	
	Were outcomes assessed objectively and independently?	Yes Partial No	

		Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	1.Metformin=6/28=21.4% 2.Pioglitazone=7/28=25% 3. Metformin+Pioglitazone 5/28=17.9%
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis	Yes Partial No Not reported	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Differs in HOMA-IR*
	If confounding was present, was it controlled for?	Yes Partial Not reported No	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	

	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	
COMMENTS		*No blinding, no protocol, High drop-out 18-25%*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*High drop-out 18-25%*

Study ID	Song 2018
Study Citation	Song J, Ruan X, Gu M, Wang L, Wang H, Mueck AO. Effect of orlistat or metformin in overweight and obese polycystic ovary syndrome patients with insulin resistance. Gynecological endocrinology. 2018;34(5):413-7.
Study Country	China
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS Same participants in Ruan 2018
PCOS diagnostic criteria	Rotterdam
Presence of infertility	*Not reported*
Presence of other condition/s	
Medication History	*No*
N per group	*Allocated/randomised: 60/group*

	Assessed at end of study: 60/group	
Setting	*Department of Gynecological Endocrinology, Beijing Obstetrics and Gynecology Hospital, Capital Medical University (Beijing, China)*	
Intervention	*35 µg EE + 2 mg CPA*	
Comparison	*1: 35 µg EE + 2 mg CPA + Orlistat 120 mgx3* *2: 35 µg EE + 2 mg CPA + metformin 1500 mg/day* *3: 35 µg EE + 2 mg CPA + Orlistat 120 mgx3 + metformin 1500 mg/day*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*TT, chol, LDL, HDL, glucose, insulin, HOMA,* *From Ruan* *TT, DHEAS, androstendione, SHBG, FAI, adverse effects*	
Follow up Duration	*3 months*	
Summary Result/s	*There was a decrease in body weight and BMI in all groups, but the decrease in the COCP + orlistat and COCP + orlistat + metformin groups was larger.*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	**Yes** Partial No Not reported	*To evaluate the effect of orlistat or metformin combined with Diane-35 on anthropometric, hormonal and metabolic parameters in overweight and obese polycystic ovary syndrome(PCOS) patients with insulin resistance (fasting insulin>10 mIU/L).*
Does the study have specified inclusion/exclusion criteria?	**Yes** Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	**Yes** Partial No Not reported	
Inclusion criteria	**Yes** Partial No Not reported	*Chinese, age 18–40 years, body mass index (BMI) 24 kg/m2, fasting insulin (FINS)>10 mIU/L, no dietary modification for the preceding 3 months, diagnosis PCOS according the Rotterdam criteria, exclusion of other etiologies (congenital adrenal*

		hyperplasia, Cushing's syndrome, androgen-secreting neoplasms, hyperprolactinemia and thyroid disease).
Exclusion criteria	**Yes** Partial No Not reported	*Exclusion of other etiologies (congenital adrenal hyperplasia, Cushing's syndrome, androgen-secreting neoplasms, hyperprolac-tinemia and thyroid disease). Further exclusion criteria were ischemic heart disease, vascular disease, type-2 diabetes with ketoacidosis, renal or hepatic impairment, severe infection and malignant tumor*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No **Not reported**
	Was allocation to intervention group concealed?	Yes Partial No **Not reported**
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No **Not reported**
	Were investigators and care providers blind to intervention group?	Yes Partial No **Not reported**
	Aside from the experimental intervention, were the groups treated the same?	**Yes** Partial No Not reported
DEDETECTION	**Were outcome assessors blind to intervention group?**	Yes Partial No **Not reported**

	Were all outcomes measured in a standard, valid and reliable way?	Yes **Partial** No Not reported	Anthropometry not specified
	Were outcomes assessed objectively and independently?	Yes **Partial** No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	0%	
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	**Yes** Partial No Not reported	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No **Not reported**	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes **Partial** No Not reported	All baseline characteristics not compared statistically.
	If confounding was present, was it controlled for?	Yes Partial **No** Not reported	

OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial **No** Not reported	
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No **Not reported**	
	If statistical analysis was undertaken, was this appropriate?	**Yes** Partial No Not reported	
COMMENTS			
What is the overall risk of bias?		Low Moderate **High** Insufficient information	Randomization not described, no blinding, no protocol
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

Study ID	Steiner 2007
Study Citation	Steiner, C. A.; Janez, A.; Jensterle, M.; Reisinger, K.; Forst, T.; Pfützner, A. Impact of treatment with rosiglitazone or metformin on biomarkers for insulin resistance and metabolic syndrome in patients with polycystic ovary syndrome J Diabetes Sci Technol Mar 2007;1(2):211-7
Study Country	Germany
BRIEF CHARACTERISTICS OF RCT	

Patient/population/ participants	Women with PCOS	
PCOS diagnostic criteria	NIH	
Presence of infertility	No	
Presence of other condition/s	-	
Medication History	-	
N per group	*Allocated/randomised:* 1.Metformin=17 2.Rosiglitazone=18 *Assessed: 1.*Metformin=16 2.Rosiglitazone=17	
Setting	Thirty-five women with clinically confirmed PCOS diagnosis were included in the study [age (mean±SD): 24.7±4.8 years; body mass index: 27.4±6.0 kg/m2 (unclear in which country and what hospital)	
Intervention	1.Metformin 850mgx2/d	
Comparison	2.Rosiglitazone 4mg/d	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	f-gluc, f-insulin, homa, bmi, periods/month	
Follow up Duration	6 months	
Summary Result/s	An increase in insulin sensitivity was observed, especially in the rosiglitazone arm.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	To explore whether treatment of patients with PCOS with two different insulin sensitizing drugs has an impact on newly described biomarkers for metabolic syndrome A little vague
Does the study have specified	Yes Partial No	

inclusion/exclusion criteria?	Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	
Inclusion criteria	Yes Partial No Not reported	PCOS as classified according to National Institute of Child Health and Human Development criteria
Exclusion criteria	Yes Partial No Not reported	- Possible Cushing's syndrome or congenital (nonclassic) adrenal hyperplasia was excluded. -type 1 or type 2 diabetes mellitus, significant cardiovascular or hepatic disease, and the use of medications known or suspected to affect reproductive or metabolic functions within 60 days of study entry.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	The patients were randomly allocated to a 6-month treatment
	Was allocation to intervention group concealed	Yes Partial No Not reported	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	

	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Fasting bloodsamples? How where weight measured?*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	1.Metformin=1/17=5.9% 2.Rosiglitazone=1/18=5.6%
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis	Yes Partial No Not reported	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	

CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	
	If confounding was present, was it controlled for?	Yes Partial Not reported No	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*Andreas Pfützner and Andrej Janez are consultants to Glaxo-Smith- Kline, the manufacturer of rosiglitazone.*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	
COMMENTS		*Randomization not described, no protocol, possible conflict of interest*	
What is the overall risk of bias?		Low Moderate High Insufficient information	

Study ID	Tiwari 2018

Study Citation	Tiwari, Nisha; Pasrija, Shikha; Jain, Sandhya Randomised controlled trial to study the efficacy of exercise with and without metformin on women with polycystic ovary syndrome European Journal of Obstetrics & Gynecology & Reproductive Biology 2019;234():149-154
Study Country	India
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Females with PCOS (aged and bmi not specified)
PCOS diagnostic criteria	Rotterdam
Presence of infertility	Not reported
Presence of other condition/s	*No*
Medication History	*No*
N per group	*Allocated/randomised: Lifestyle+metformin 33* *Lifestyle+placebo 33* *Assessed at end of study: Lifestyle+metformin 31* *Lifestyle+placebo 31*
Setting	This randomised double blinded placebo controlled trial was carried out in a district hospital in Delhi over a period of one year
Intervention	All women were advised to do marching at the same place for 30 min three days a week for 3 months in the department under supervision. The exercise was monitored by the investigator to ensure a heart rate 120 beats/min. For the next 3 months all women continued the exercise at home without supervision In addition Metformin 1700mg daily
Comparison	All women were advised to do marching at the same place for 30 min three days a week for 3 months in the department under supervision. The exercise was monitored by the investigator to ensure a heart rate 120 beats/min. For the next 3 months all women continued the exercise at home without supervision In addition placebo
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Androgenic parameters (mFGS, T), antropometric parameters (BMI, WHR), biochemical parameters (OGTT, triglycerides, s-cholesterol), clinical parameters (oligomenorrhea)

Follow up Duration	6 months	
Summary Result/s	The mean difference in mFGS at 0, 3 and 6months were statistically significant in both groups. On comparing groupA (lifestyle+placebo) with groupB (lifestyle+met) at 6months, significant improvement was found in menstrual cycle symptoms (55.17% vs 83.33%), mean weight loss (1.08 kg vs 2.5 kg), waist circumference reduction (2.56 cm vs 4.75 cm) and change in mean waist hip ratio (0.02vs0.04). Significant changes were noted in OGTT and Serum testosterone level at 6months in GroupB (lifestyle+met), but not in Group A (lifestyle+placebo)	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	1. To study the efficacy of exercise in improving clinical symptoms, anthropometry, glucose tolerance and laboratory profile in women with PCOS. 2. To study the combined efficacy of exercise and metformin on above parameters in women with polycystic ovary syndrome.
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	
Inclusion criteria	Yes Partial No Not reported	“Women diagnosed as PCOS on the basis of the Rotterdam criteria, willing to participate in the study, follow the exercise schedule and not on any regular exercise regime”.
Exclusion criteria	Yes Partial No Not reported	“diseases like adrenal hyperplasia, cushing syndrome etc”
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Women included in the study were divided into two groups by block randomisation with sealed envelope system. Sister-in-charge of Outpatient Department prepared eleven large envelopes each containing six smaller envelopes, three each of group A and B. All selected women were divided into groups of six, depending upon their time of selection. Each time one big envelope was opened and smaller envelopes were randomly chosen by women according to which their group was assigned. Those labelled "A" received placebo along with exercise and those labelled "B" received metformin with exercise. The sister-in-charge kept the record as to which patient belonged to which group and gave metformin/placebo as per the randomisation, such that till the end of the study neither the patients nor the investigator had any knowledge regarding who belonged to which group, thus making the study double blind. At the end of the study group distribution was collected from sister-in-charge and analysed.
	Was allocation to intervention group concealed?	Yes Partial No Not reported	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	
DE DE	**Were outcome assessors blind to**	Yes Partial	

	intervention group?	No Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	*Lifestyle+metformin 2/33=6.1%* *Lifestyle+placebo 2/33 =6.1%*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Trial registration after publication*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	

	If confounding was present, was it controlled for?	Yes Partial No Not reported	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Power calculation described, but not for what outcome and relevant difference*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

Study ID	Wei 2012
Study Citation	Wei W, Zhao H, Wang A, Sui M, Liang K, Deng H, et al. A clinical study on the short-term effect of berberine in comparison to

	metformin on the metabolic characteristics of women with polycystic ovary syndrome. European journal of endocrinology / European Federation of Endocrine Societies. 2012;166(1):99-105.
Study Country	China
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS, all insulin resistant
PCOS diagnostic criteria	Rotterdam
Presence of infertility	*not reported*
Presence of other condition/s	
Medication History	*No*
N per group	*Allocated/randomised:* *Assessed at end of study:* COCP=28; COCP + met=30
Setting	
Intervention	35 µg EE + 2 mg CPA + placebo
Comparison	35 µg EE + 2 mg CPA + met 1500 mg/day (The RCT also included barbiturate, not incl here)
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Weight, WHR, BMI, glucose, inslulin, OGTT, HOMA, chol, TG, LDL, HDL, TT, SHBG, FAI
Follow up Duration	*3 months*
Summary Result/s	Although, the 3-month treatment period led to decrease in concentrations of insulin and androgens as it was reported elsewhere, we could not confirm significant effect of MET on weight change and lipid profile as it was shown by others. Three months may be too short a time to demonstrate the effect of MET on metabolic abnormalities sufficiently. Furthermore, MET is associated with a higher incidence of nausea, vomiting, and other gastrointestinal disturbances.
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT	

Does the study have a clearly focused question and/or PICO?	**Yes** Partial No Not reported	This study aimed to assess whether use of BBR, considered to be an insulin sensing agent, is effective in the treatment of endocrine characteristics of PCOS and to compare these effects with MET therapy. The outcome measures in this study included change in anthropometric measures and hormonal and metabolic indices in a group of insulin-resistant Chinese women with PCOS.
Does the study have specified inclusion/exclusion criteria?	**Yes** Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	**Yes** Partial No Not reported	
Inclusion criteria	**Yes** Partial No Not reported	subjects with PCOS according to Rotterdam criteria and insulin resistance (IR was assessed by HOMA-IR ≥ 3.8 or fasting glucose insulin ratio (FGIR) ≤ 4.5.
Exclusion criteria	**Yes** Partial No Not reported	Exclusion conditions included the following systemic and endocrine disorders: late-onset congenital adrenal hyperplasia, Cushing's syndrome, thyroid dysfunction, hyperprolactinemia, diabetes mellitus, coronary artery disease, and spontaneous abortion. Furthermore, subjects accepting treatment with medications known to alter insulin hemodynamics, ovulation induction, anti-obesity, or oral contraceptives (OCs) within 3 months were excluded from the study
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS – **Did the study have an adequate method of randomisation?**	**Yes** Partial No Not reported	Randomization was based on a computer-generated code in blocks of six. A copy of the code was stored in a sealed envelope by personnel not involved in the trial.
SELECTION BIAS – **Was allocation to intervention group concealed?**	**Yes** Partial No Not reported	

PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No **Not reported**	
	Were investigators and care providers blind to intervention group?	Yes Partial No **Not reported**	
	Aside from the experimental intervention, were the groups treated the same?	**Yes** Partial No Not reported	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No **Not reported**	
	Were all outcomes measured in a standard, valid and reliable way?	**Yes** Partial No Not reported	
	Were outcomes assessed objectively and independently?	**Yes** Partial No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	10% COCP 14% met	COCP: 3/31=10% COCP + met: 5/36=14%
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial **No** Not reported	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No **Not reported**	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	**Yes** Partial No Not reported	
	If confounding was present, was it controlled for?	Yes Partial **No** Not reported	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial **No** Not reported	
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No **Not reported**	
	If statistical analysis was undertaken, was this appropriate?	**Yes** Partial No Not reported	
COMMENTS			
What is the overall risk of bias?		Low **Moderate** High Insufficient information	No blinding, no protocol

Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	

Study ID	Zahra 2017
Study Citation	Zahra, M.; Shah, M.; Ali, A.; Rahim, R. Effects of Metformin on Endocrine and Metabolic Parameters in Patients with Polycystic Ovary Syndrome Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme 2017;49(2):103-108
Study Country	Pakistan
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Females with PCOS aged 18–35 years
PCOS diagnostic criteria	Vaguely reported see inclusion criteria
Presence of infertility	Not reported
Presence of other condition/s	No
Medication History	No
N per group	*Allocated/randomised: 30 (metformin group) and 30 (placebo)* *Assessed at end of study: 20 (metformin group) and 20 (placebo)*
Setting	This was a randomized, placebo-controlled study, conducted in 2 tertiary care hospitals (Hayatabad Medical Complex and Leady Reading Hospital, Peshawar, Pakistan)
Intervention	Metformin, according to body weight with a maximum dose of 500mg 3 times/day
Comparison	Placebo tablets 3 times/day
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Weight, BMI, fasting glucose, insulin, HOMA-IR, LH, FSH, visfatin, INSL-3, systolic and diastolic bp.
Follow up Duration	3 months

Summary Result/s	Metformin treatment showed significant improvement in systolic and diastolic blood pressures. In addition, an improvement in the hormonal profile in the form of reduction in LH, FSH, and visfatin levels was observed.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	to evaluate the effects of metformin on insulin resistance in PCOS and to determine its relation with neo-hormones INSL-3 and visfatin
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	18-35 year old females with PCOS. The diagnosis of PCOS was based on females having disturbed ovulatory function with chronic oligomenorrhea or amenorrhea, typical appearance of polycystic ovaries by ultrasound examination (according to ESHRE, ASRM), hirsutism, or elevated serum androgens
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Those females who dropped metformin in this 3 months period (due to socioeconomic reasons) or those were not willing for follow-up vis - its were excluded from the study.*
Inclusion criteria	Yes Partial No Not reported	18-35 year old females with PCOS. The diagnosis of PCOS was based on females having disturbed ovulatory function with chronic oligomenorrhea or amenorrhea, typical appearance of polycystic ovaries by ultrasound examination (according to ESHRE, ASRM), hirsutism, or elevated serum
Exclusion criteria	Yes Partial No Not reported	-Those who quit metformin in this 3 months period (due to socioeconomic reasons) -not willing for follow-up visits -Patients on antihypertensive drugs were also excluded from the study
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	The methods section only states: “The participants were then randomly divided into 2 groups”
	Was allocation to intervention group concealed?	Yes Partial No	

		Not reported	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Venous blood sample was obtained after overnight fast, for arthropometic measures it was not reported.
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	
ATTRITIO N BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	In the original study: Metformin-group 10/30=33.3% Placebo-group 10/30=33.3% Some dropouts excluded!

	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Baseline weight and BMI seems to be different (higher in placebo group). Also INSL-3 and visfatin differs at baseline.*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	

	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	
COMMENTS		*High*	
What is the overall risk of bias?		Low Moderate High Insufficient information	The randomization process poorly described, many drop-outs, differences in baseline variables.
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No – all outcomes high risk of bias*	

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 4

Question 4.4.

Is metformin alone or in combination, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?

BACKGROUND:

Metformin, an insulin sensitizer, has been widely used for the prevention/management of prediabetes and type 2 diabetes in general population mild side effects of nausea, vomiting, diarrhoea, and flatulence (1,2). Metformin has additional benefits on weight loss in the combined treatment with lifestyle changes (3). Metformin has also been regularly evaluated alone or combined with oral contraceptive pills (OCP) and/ or antiandrogen drugs in randomized controlled trials in adult and adolescent women with PCOS (4). Its main action is in the liver with suppression of gluconeogenesis and hepatic glucose output, but it also enhances peripheral insulin action and reduces glucose absorption from the digestive tract, with no significant direct effect on pancreatic insulin production (5). Indeed, as women with PCOS present higher prevalence of insulin resistance, and the compensatory hyperinsulinemia has been linked to ovarian androgen secretion, metformin could be acting on the interface of metabolic and reproductive features of PCOS (6,7,8,9). In recent years, randomized clinical trials have emerged also looking for evidence of possible benefits and safety of combining metformin with antidiabetic or anti-obesity drugs, with or without OCP, anti-androgens and lifestyle on clinical, metabolic, and hormonal outcomes in adult and adolescent girls with PCOS, which is summarized in the present topic.

The usual dose of metformin for PCOS is 1000 to 2500 mg per day, although doses of up to 2000 mg have been trialled in PCOS. A limitation can be mild side effects, which are predominantly gastroenterological consisting of abdominal discomfort, nausea, and diarrhea. These symptoms are usually dose dependent and time-limited and can be minimized by gradually building up the dose of metformin over a period of 1–2 months. Initial doses should be 250–500 mg/day taken just before the main meal. In the case gastrointestinal side effects recidivate, the current dose may be reduced for a period of 7–10 days, followed by a resumption of the increasing dosage schedule (10,11). Vitamin B12 levels may also be affected on longer term metformin, especially in high risk populations.

GRADE EVIDENCE CERTAINTY	
Comparison	**GRADE for critical outcomes**
○ **Comparison 1:** Metformin versus placebo	⨁⨁◯◯ LOW
○ **Comparison 2:** Metformin + lifestyle versus placebo + lifestyle	⨁⨁⨁◯ MODERATE
○ **Comparison 3:** Metformin versus lifestyle	⨁◯◯◯ VERY LOW
○ **Comparison 4:** Metformin versus OCP (also in Q4.2 – not identical)	⨁◯◯◯ VERY LOW
○ **Comparison 5:** Metformin versus metformin + OCP (also in Q4.2 – not identical)	⨁◯◯◯ VERY LOW
○ **Comparison 6:** Metformin versus anti-androgen (also in Q4.6 – identical)	⨁◯◯◯ VERY LOW
○ **Comparison 7:** Metformin + anti-androgen versus anti-androgen (also in Q4.6 – identical)	⨁◯◯◯ VERY LOW
○ **Comparison 8:** Metformin + anti-androgen versus metformin (also in Q4.6 – identical)	⨁◯◯◯ VERY LOW
○ **Comparison 9:** SPIOMET versus OCP (also in Q4.6 – identical)	⨁⨁◯◯ LOW
○ **Comparison 10:** Metformin versus anti-androgen + OCP (also in Q4.6 – not identical since timeline different)	⨁⨁⨁◯ MODERATE
○ **Comparison 11:** Metformin + lifestyle versus metformin + anti-androgen + lifestyle (also in Q4.6 – not identical since timeline different)	⨁⨁◯◯ LOW
○ **Comparison 12:** Metformin + Lifestyle versus anti-androgen + lifestyle (also in Q4.6 – not identical since timeline different)	⨁◯◯◯ VERY LOW

○ **Comparison 13:** Metformin + anti-androgen + lifestyle versus anti-androgen + lifestyle (also in Q4.6 – not identical since timeline different)	⊕⊕◯◯ LOW
○ **Comparison 14:** Metformin + anti-androgen + lifestyle versus placebo + lifestyle (also in Q4.6 – identical)	⊕◯◯◯ VERY LOW
○ **Comparison 15:** Metformin versus rosiglitazone	⊕◯◯◯ VERY LOW
○ **Comparison 16:** Metformin versus pioglitazone	⊕◯◯◯ VERY LOW
○ **Comparison 17:** Metformin versus saxagliptin	⊕⊕◯◯ LOW
○ **Comparison 18:** Metformin + saxagliptin versus metformin	⊕⊕◯◯ LOW
○ **Comparison 19:** Metformin + saxagliptin versus saxagliptin	⊕⊕◯◯ LOW
○ **Comparison 20:** Metformin versus SGLT2-inhibitors	⊕◯◯◯ VERY LOW
○ **Comparison 21:** Metformin + liraglutide versus liraglutide	⊕◯◯◯ VERY LOW
○ **Comparison 22:** Metformin + myo-inositol versus myo-inositol	⊕◯◯◯ VERY LOW
○ **Comparison 23:** Metformin versus orlistat	⊕◯◯◯ VERY LOW
○ **Comparison 24:** Metformin + pioglitazone versus pioglitazone	⊕◯◯◯ VERY LOW
○ **Comparison 25:** Metformin + pioglitazone versus metformin	⊕◯◯◯ VERY LOW
○ **Comparison 26:** Metformin versus metformin + rosiglitazone	⊕⊕⊕◯

	MODERATE
○ **Comparison 27:** Metformin + rosiglitazone versus rosiglitazone	⨁⨁⨁◯ MODERATE
○ **Comparison 28:** Metformin versus metformin (different dose)	⨁◯◯◯ VERY LOW
○ **Comparison 29:** Metformin versus metformin + MPA	⨁◯◯◯ VERY LOW

Evidence to Recommendations Framework

COMPARISONS (option versus other option)

Comparison 1: Metformin versus placebo
Comparison 2: Metformin + lifestyle versus placebo + lifestyle
Comparison 3: Metformin versus lifestyle

EVIDENCE-BASED RECOMMENDATION(S)

- **EBR:** Metformin alone should be considered in adults with PCOS and a BMI ≥ 25 kg/m2 for anthropometric, and metabolic outcomes including insulin resistance, glucose, and lipid profiles.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

- **EBR:** Metformin alone could be considered in adolescents at risk of or with PCOS for cycle regulation, acknowledging limited evidence.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

- **CR:** Metformin alone may be considered in adult women with PCOS and BMI < 25 kg/m^2, acknowledging limited evidence.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

PRACTICE POINT(S)

Where metformin is prescribed the following need to be considered:

- Shared decision making needs to consider feasibility and effectiveness of active lifestyle intervention.

Women should be informed that metformin and active lifestyle intervention have similar efficacy.

- Mild adverse effects, including gastrointestinal side-effects that are generally dose dependent and self-limiting
- Starting at a low dose, with 500mg increments 1-2 weekly and extended-release preparations may minimise side effects and improve adherence.
- Suggested maximum daily dose is 2.5g in adults and 2g in adolescents.
-
- Use appears safe long-term, based on use in other populations, however indications for ongoing requirement needs to be considered
- Use may be associated with low vitamin B12 levels, especially in those with risk factors for low vitamin B12 (e.g. diabetes, post bariatric surgery, pernicious anaemia, vegan diet etc.), where monitoring should be considered,
-

GRADE CONSIDERATIONS

Justifications:
In adult women with PCOS, metformin alone, at doses 1000 -2000 mg/d favour BMI reduction and metabolic outcomes, such as fasting glucose, HOMA-IR (moderate certainty), total cholesterol, triglycerides (low certainty), as well as testosterone (low certainty) and possibly WHR and shortening cycles (very low certainty). In women with BMI<25 metformin is superior to placebo in decreasing FAI (moderate certainty).
Metformin in combination with lifestyle favour improvement on testosterone (moderate certainty) and menstrual cycles/6 months (very low certainty). There is no significant effect on hirsutism (low certainty).
Women using metformin had more adverse gastrointestinal effects compared to placebo (moderate certainty). Side effects are not well reported.

Subgroup considerations:
In women with PCOS and BMI>25 metformin alone versus placebo favours decreasing BMI (moderate certainty)
In women with PCOS and BMI>25 metformin in combination with active lifestyle intervention was superior in lowering testosterone vs. lifestyle only.
Only 2 studies included 55 adolescent girls and suggested this could favor improving lipid profile, testosterone and restoring cycles, with very low quality of evidence.

Implementation considerations:
Metformin is widely prescribed for the management of type 2 diabetes and has been used in many countries to treat women and adolescents with PCOS. It is of low cost and widely available but side effects are present.
Metformin should be implemented after active lifestyle intervention but significant barriers for implementation of active lifestyle intervention may be present.

Monitoring and evaluation considerations:
Ensure contraception for women on metformin only (without OCP) treatment and not planning pregnancy at short-term
Gastrointestinal side effects are common in individuals taking metformin and should be monitored as they will impact on adherence. Considerations should be made to change to extended-release preparation if metformin is not well tolerated or there are adherence issues.

Research priorities:
Vitamin B12 status should also be the subject of further research to inform frequency of monitoring unless women are vegetarian.
The need for high-quality, well-designed, and adequately powered studies in adults and mainly in adolescents, suggested in the previous TR, remains current, with detailed reports on metformin-related adherence and adverse effects.
Importantly, these studies in women and adolescents require evaluation of different doses, extended-release preparations, and longer duration of treatment.
Need for studies to examine the impact of metformin on acne, hair loss, psychosexual function?
Studies in women across the BMI range to understanding any potential differential effect of metformin associated with BMI

GRADE framework

GRADE DECIDE **Interactive Evidence to Decision Framework**

• DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Metformin versus placebo

Twenty-three RCT addressing the outcomes of interest were identified and of these, 22 were included in the meta-analysis. One of them was in adolescents.

-Metformin, when compared to placebo, was superior in lowering the following outcomes: BMI (moderate certainty), WHR (very low certainty), testosterone (very low certainty), fasting glucose (moderate certainty), HOMA-IR (certainty moderate) total cholesterol (low certainty), triglycerides (low certainty), CRP (very low certainty), PAI (very low certainty); and in shortening the menstrual cycle (very low certainty).

-In sub analyses, for BMI>25 metformin was superior in lowering BMI, fasting glucose and total cholesterol (moderate certainty for all) and LDL (low certainty). For BMI<25, metformin was superior in lowering FAI (moderate certainty) and fasting insulin (low certainty)

-There was no significant difference in hirsutism score (low certainty). There were no significant differences in the following outcomes: SHBG, DHEAS, androstenedione, HDL.

It is important to remain cautious due to low to very low certainty in effect estimates and the quality of evidence across most of the outcomes.

- Regarding adolescents, one study was analysed as an individual study and showed metformin was superior in improving testosterone and HDL and in restoring menses. Certainty in the evidence for this study was low (low risk of bias but a single study with only a small number of participants, as reported by the evidence team). The other study found no differences in observed outcomes in metformin compared to placebo (low certainty for this single, small study).

Metformin + lifestyle versus placebo + lifestyle

Eight RCTs that address this comparison were identified and included in the meta-analysis. One of them also analysed adolescents separately.

-Metformin in combination with lifestyle when compared to placebo in combination with lifestyle, was superior in lowering testosterone (moderate certainty).

-Metformin + lifestyle was superior in increasing menstrual cycles/6 months (very low certainty).

-In a sub-analysis that included 2 studies in the meta-analysis, in which the BMI was not specified, metformin + lifestyle was superior in lowering WHR (low certainty).

-There were no significant differences for the other outcomes with certainty in the evidence being moderate to very low.

Metformin versus lifestyle

Three RCTs addressing this comparison were identified and included in the meta-analysis.

All studies were in women of a higher weight and adolescents with PCOS, one of them on 22 adolescents. No new studies from the previous analysis were identified.

-Metformin in comparison to lifestyle was superior in lowering testosterone and lifestyle was superior in increasing SHBG. While not statistically significant, fasting glucose tended to favour metformin.

-No differences were observed for the other outcomes: BMI, fasting insulin, total cholesterol, HDL, LDL, triglycerides, CRP.

However, it is important to remain cautious since the certainty in effect estimates and the quality of evidence is very low for all outcomes

- Concerning individual studies, not included in the meta-analysis, in one study DHEAS seemed to be lower in the metformin group vs. lifestyle WHR seemed to be lower in the lifestyle group vs. metformin. However, certainty in the evidence was very low for these outcomes.

Panel discussion:

See justifications above.

● UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Adverse gastrointestinal effects were more frequent in the metformin group x placebo and in the metformin + lifestyle group x placebo + lifestyle (moderate certainty).

Panel discussion:

Metformin gastrointestinal side effects versus difficulty implementing lifestyle intervention

● CERTAINTY OF THE EVIDENCE

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☐ Very low	☒ Low	☐ Moderate	☐ High

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Very low to moderate certainty evidence depending on the comparisons and outcomes. Data on side effects are limited.

● VALUES

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☐ Important uncertainty or variability	☒ Possibly important uncertainty or variability	☐ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Research evidence:

No research evidence was identified

Studies are warranted to define the value that consumers or health professionals place on the outcomes especially in the context of metformin not being approved for PCOS. Some relevant outcomes seem to be weight, quality of life, cycles, hirsutism, GI side-effects.

Panel discussion:

Lack of evidence creates challenges

● BALANCE OF EFFECTS

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

No research evidence was identified.

Panel discussion:

Challenges with lack of adequate evidence.

● COSTS

How large are the resource requirements (costs)?

Judgement:

☐ Don't know	☐ Varies	☐ Large costs	☐ Moderate costs	☒ Negligible costs or savings	☒ Moderate savings	☐ Large savings

Research evidence:

No research evidence was identified

Panel discussion:

Lifestyle intervention may be expensive to women and health systems, as in healthy food, and metformin is low in cost.

● CERTAINTY OF COST EVIDENCE

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

No research evidence was identified

Panel discussion:

Unclear.

● COST-EFFECTIVENESS

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

No research evidence was identified

Panel discussion:

No clear evidence.

● EQUITY

What would be the impact on health equity?

Judgement:

☐ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☒ Probably increased	☐ Increased

Research evidence:

No research evidence was identified

Panel discussion:

Lifestyle intervention may be expensive to women and health systems, as in healthy food, and metformin is low in cost.

● ACCEPTABILITY

Is the option acceptable to key stakeholders?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Health care professionals might not accept metformin as it is not approved for PCOS this might change with education.

Public health may not accept medication over lifestyle.

Women with PCOS might not accept this option due to side effects or dosing schedule.

● FEASIBILITY

Is the option feasible to implement?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Low cost and accessible.

Evidence to Recommendations Framework

COMPARISONS (option versus other option)

Comparison 4: Metformin versus OCP
Comparison 5: Metformin versus metformin + OCP
Comparison 9: SPIOMET versus OCP

EVIDENCE-BASED RECOMMENDATION(S)

- **EBR:** COCP could be used over metformin for management of hirsutism and irregular menstrual cycles in PCOS.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

- **EBR:** Metformin could be used over COCP for metabolic indications in PCOS.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

- **EBR:** The combination of COCP and metformin could be considered to offer little additional clinical benefit over COCP or metformin alone, in adults with PCOS with a BMI $\leq$ 30 kg/m2.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

PRACTICE POINT(S)

- **PP:** In combination with the COCP, metformin may be most beneficial in high metabolic risk groups including those with a BMI >30 kg/m^2, diabetes risk factors, impaired glucose tolerance or high-risk ethnic groups.
- **PP:** Where COCP is contraindicated, not accepted or not tolerated, metformin may be considered for irregular menstrual cycles. For hirsutism, other interventions may be needed.

GRADE CONSIDERATIONS

Justifications:

[COMP 4] In adult women with PCOS, metformin, at doses 1000 -2000 mg/d favours improvement on metabolic outcomes. In turn OCP is more effective in improving clinical and laboratorial hyperandrogenism and restoring regularity in menstrual cycle (moderate to very low certainty). To note, even if OCP is better for hyperandrogenism, studies confirm that metformin may decrease androgen levels and probably ameliorate cycles, depending on the effective dose and time of exposition. Among the 22 RCT included in the meta-analysis, various include adolescent girls but few studied only this population.

[COMP 5] Metformin + OCP is more effective in lowering testosterone (low certainty) and DHEAS (very low certainty) compared to metformin only. There were no studies with adolescent girls in for this comparison

[COMP 9] Evidence on SPIOMET is very limited and only available in Spain. Two RCTs, with results pooled and with, in total, five publications were identified. COCP (EE 20 µg – LNG 100 mg) was compared with spironolactone 50 mg/d + pioglitazone 7.5 mg/d + metformin 850 mg/d (SPIOMET).

The first RCT was published in 2017, with one additional publication on the same cohort, one year later. Another RCT, with the same comparison, and from the same research group, was done to increase power, with no separate publication. The pooled results were reported in three publications in the next years, one of them with the highest number of participants, being considered the main publication. FAI could be extracted from the more recent study, as an additional outcome.
Risk of bias was moderate. The study had a duration of 12 months. Only effect on hirsutism, no effect on testosterone.

Subgroup considerations:
Inadequate evidence in those with BMI ≥ 30 kg/m2 and adolescents.

Implementation considerations:
The off-label status of metformin in PCOS needs to be discussed with the patient in the context of heavily evidence-based recommendations.

Monitoring and evaluation considerations:
Metformin approval by policy regulators to enable monitoring and evaluation of guideline recommendation.

Research priorities:
Adolescents and BMI ≥30 kg/m2 groups
For metformin, COCP and combinations

GRADE framework

GRADE DECIDE **Interactive Evidence to Decision Framework**

● DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

Judgement:

☒ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Metformin versus OCP

24 RCTs (33 articles) addressing the comparison of metformin and OCP were identified and of these, 22 were included in the meta-analysis.

-Metformin, compared to OCP, was superior in improving fasting insulin, total cholesterol, triglycerides, CRP and HOMA-IR (low or very low certainty). For women with BMI<25: metformin was also superior in lowering WHR (low certainty), total cholesterol (very low certainty) and HOMA-IR (moderate certainty). Regarding women with BMI >25, metformin was superior in improving HDL (moderate certainty).

-OCP was superior in improving hyperandrogenism (SHBG, FAI, Testosterone, free testosterone, DHEAS and androstenedione) and restoring regularity in the menstrual cycle (moderate to very low certainty). For women with BMI<25: OCP was also better in improving hirsutism (low certainty) and androstenedione (low certainty)

-Regarding adolescents, metformin was superior in lowering LDL (low certainty), whereas OCP was superior in improving SHBG and FAI (note that only one study included these outcomes).

Metformin versus metformin + OCP

Six RCTs were identified for this comparison and of these, 5 were included in the meta-analysis.

-Metformin alone, compared to the combination with OCP, was superior in lowering WHR, fasting glucose, total cholesterol (low to very low certainty for all), and triglycerides (in the sub analysis with BMI<25, low certainty)

-The combination of metformin and OCP was superior in lowering testosterone (low certainty) and DHEAS (very low certainty).

- No differences were observed for the other outcomes, but the certainty in effect estimates and the quality of evidence is low or very low.

- Regarding individual studies, not included in the meta-analysis for some outcomes, the combination metformin and OCP was superior on improving hirsutism, SHBG levels, free testosterone and FAI. In turn, metformin only was found to be superior in lowering BMI.

Again, the certainty in the evidence for the individual studies are low or very low (studies with moderate or high risk of bias and most with small sample sizes).

SPIOMET versus OCP

Five RCTs comparing SPIOMET (spironolactone 50mgx1, pioglitazone 7.5mgx1 and metformin

850mgx1) with OCP were identified. However, all studies used the same set of data and therefore, it was not possible to perform a meta-analysis. The outcomes of the two studies with the largest sample size were used .

-SPIOMET was superior in reducing hirsutism, LDL-cholesterol, CRP, HOMA-IR and fasting insulin compared to OCP.

-OCP increased SHBG more than SPIOMET. QOE for these comparisons are low

Panel discussion:

As above.

● UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Gastrointestinal side effects seem to be more frequent with metformin

The frequency of adverse effects is similar between metformin alone or metformin +OCP groups

There were no side effects reported for SPIOMET or OCP.

Systematic effects are not systematically reported.

Panel discussion:

Favours this option for not combining metformin and COCP as it offers little additional benefit beyond monotherapy.

● CERTAINTY OF THE EVIDENCE

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☐ Very low	☒ Low	☐ Moderate	☐ High

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

This rating refers to combination treatment with metformin and COCP.

● VALUES

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☐ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☒ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Research evidence:

No research evidence was identified

Some women with PCOS and especially those not using OCP have expectations on restoration of cycles.

Panel discussion:

● BALANCE OF EFFECTS

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:

See above

● COSTS

How large are the resource requirements (costs)?

Judgement:

☐ Don't know	☐ Varies	☐ Large costs	☐ Moderate costs	☒ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:

No research evidence was identified

Combination might increase costs

Panel discussion:

Metformin is low cost so omitting the combination treatment offers little cost savings.

● CERTAINTY OF COST EVIDENCE

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

No research evidence was identified

Panel discussion:

● COST-EFFECTIVENESS

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

No research evidence was identified

Panel discussion:

Unclear

● EQUITY

What would be the impact on health equity?

Judgement:

☐ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☒ Probably increased	☐ Increased

Research evidence:

No research evidence was identified

Panel discussion:

Policy regulators' approval of metformin use in PCOS will increase equity.

● ACCEPTABILITY

Is the option acceptable to key stakeholders?

Judgement:

☐ Don't know	☒ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Policy regulators may not wish to cover the cost of metformin.

● FEASIBILITY

Is the option feasible to implement?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☐ Probably Yes	☒ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Aligns with current practice recommendations.

Evidence to Recommendations Framework

COMPARISONS (option versus other option)
Comparison 28: Metformin versus metformin (different dose) – This data is considered in the metformin versus placebo comparison

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8. Diamanti-Kandarakis E, Dunaif A. Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. Endocr Rev 2012;33(6):981-1030.

9. Nestler JE, Jakubowicz DJ, de Vargas AF, Brik C, Quintero N, Medina F. Insulin stimulates testosterone biosynthesis by human thecal cells from women with polycystic ovary syndrome by activating its own receptor and using inositolglycan mediators as the signal transduction system. J Clin Endocrinol Metab 1998;83(6):2001-5.

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PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by ECR Lead: Carolyn Ee

Other team members: Alyse Goldberg, Vibhuti Rao, Jing Liu, Sandro Graca

Supervised, edited and supported by the Evidence Team (Aya Mousa, Jillian Tay)

GDG 4

Question 4.5.

Are anti-obesity pharmacological agents alone or in combination, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?

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Table 1. PICO Criteria for Inclusion – Not to be adapted To be used by evidence team to decide which studies will be included when screening search results.	
Question	Q 4.5 Are anti-obesity pharmacological agents alone or in combination, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?
Clinical leads (key contacts)	**Prof Bulent Yildiz** Endocrinologist Hacettepe University, Turkey byildiz@hacettepe.edu.tr **A/Prof Alexia Pena Vargas** Paediatric endocrinologist The Robinson Research Institute at the University of Adelaide, Australia alexia.pena@adelaide.edu.au **Dr Carolyn Ee** General practitioner Western Sydney University, Australia C.Ee@westernsydney.edu.au **Prof Selma Witchel** Paediatric endocrinologist Children's Hospital of Pittsburgh of UPMC, University of Pittsburg, USA witchelsf@upmc.edu
Allocation ranking	Level 1- New systematic review

1. SELECTION CRITERIA

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(language, year)*
Inclusion	Females with PCOS (diagnosed by Rotterdam, NIH or AES) of any age, ethnicity and weight. Subgroups: adolescents (10-19y), adults, post-menopausal. BMI subgroups overweight and each class of obesity BMI>25-29.9, 30-34.9, 35-40, >40	Anti-obesity pharmacological agents alone (Orlistat, GLP1RA, phentermine/topiramate, lorcaserin, naltrexone/bupropion, or any other anti-obesity pharmacological agent) or in combination with lifestyle, metformin, OCP, anti-androgens. All doses Duration: min 3 months	Placebo or any other intervention (listed in intervention) or combinations of those listed in intervention. Bariatric surgery alone or in combination with listed interventions.	Androgenicity: Hirsutism- FG score (ethnicities), FAI, testosterone (free/total), SHBG, DHEAS, androstenedione, Irregular cycles Metabolic: fasting glucose, fasting insulin, HOMA-IR, QUICKI, OGTT: 120 min glucose and insulin, 30/60/90 min glucose and insulin where available, AUC glucose, AUC insulin, Matsuda index, Euglycemic hyperinsulinemic clamp. Lipids: Chol LDL, HDL TG, CRP Psychological: Qol, depression Arthropometric: weight BMI, WHR, waist circumference, % with >5% or > 10% weight loss , fat mass, fat free mass, % body fat Gastrointestinal effects Fertility: Menstrual regularity, Live birth rate, pregnancy rate (biochemical or clinical ultrasound), ovulation, single and multiple pregnancies, miscarriage rate, adverse events (including pre term delivery, growth restriction, low birth weight, stillbirth. Pregnancy complications, pre-eclampsia, hyperglycaemia, hypertension in pregnancy, gestational diabetes, perinatal morbidity, fetal macrosomia, caesarean.) Adverse events	Evidence based guidelines, systematic reviews, randomised controlled trials. Crossover trials will be included but only the phase before the crossover will be included in outcomes.	English language. New search Limit to last 10 years - decision from 2018
Exclusion	Females without PCOS.	Metformin alone	Agent or combination used in the intervention.		Non-evidence based guidelines, non-systematic reviews, any study lower than a RCT. Quasi randomised trials.	

2. SEARCH STRATEGY

Table 2.1. Search details

Search strategy source: *[enter doi or 2018 technical report page number where search string was derived]*

Evidence source	Date of search
Medline (Ovid)	22 July 2022
PsychInfo (EBSCO)	22 July 2022
EMBASE (Ovid)	22 July 2022
CINAHL (EBSCO)	22 July 2022

Table 2.2. Questions addressed by this search *(add more rows as needed)*:

GDG	Q#	Question
4	4.5	Are anti-obesity pharmacological agents alone or in combination, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?

Table 2.3. Search strings used in OVID or other database/s – *please save a screenshot of search results to submit alongside this template*

OVID and EMBASE Medline	CINAHL/Psychinfo
1 exp Polycystic Ovary Syndrome/ 49396 2 poly?cystic ovar*.mp. 50776 3 PCO#.mp. 71172 4 (stein?leventhal or leventhal).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy] 1525 5 anovulat*.mp. 16658 6 oligo?ovulat*.mp. 179 7 (ovar* adj5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*)).mp. 60215 8 1 or 2 or 3 or 4 or 5 or 6 or 7 107933 9 exp Anti-Obesity Agents/ 26934 10 Obesity/dt, th [Drug Therapy, Therapy] 62364 11 ((anti?obesity or obesity or weight loss) and (agent* or drug* or therap*)).mp. 497216 12 orlistat.mp. or exp Orlistat/ 9517 13 sibutramine.mp. 6130 14 exp Appetite Depressants/ 94233	Please see pdf attachments

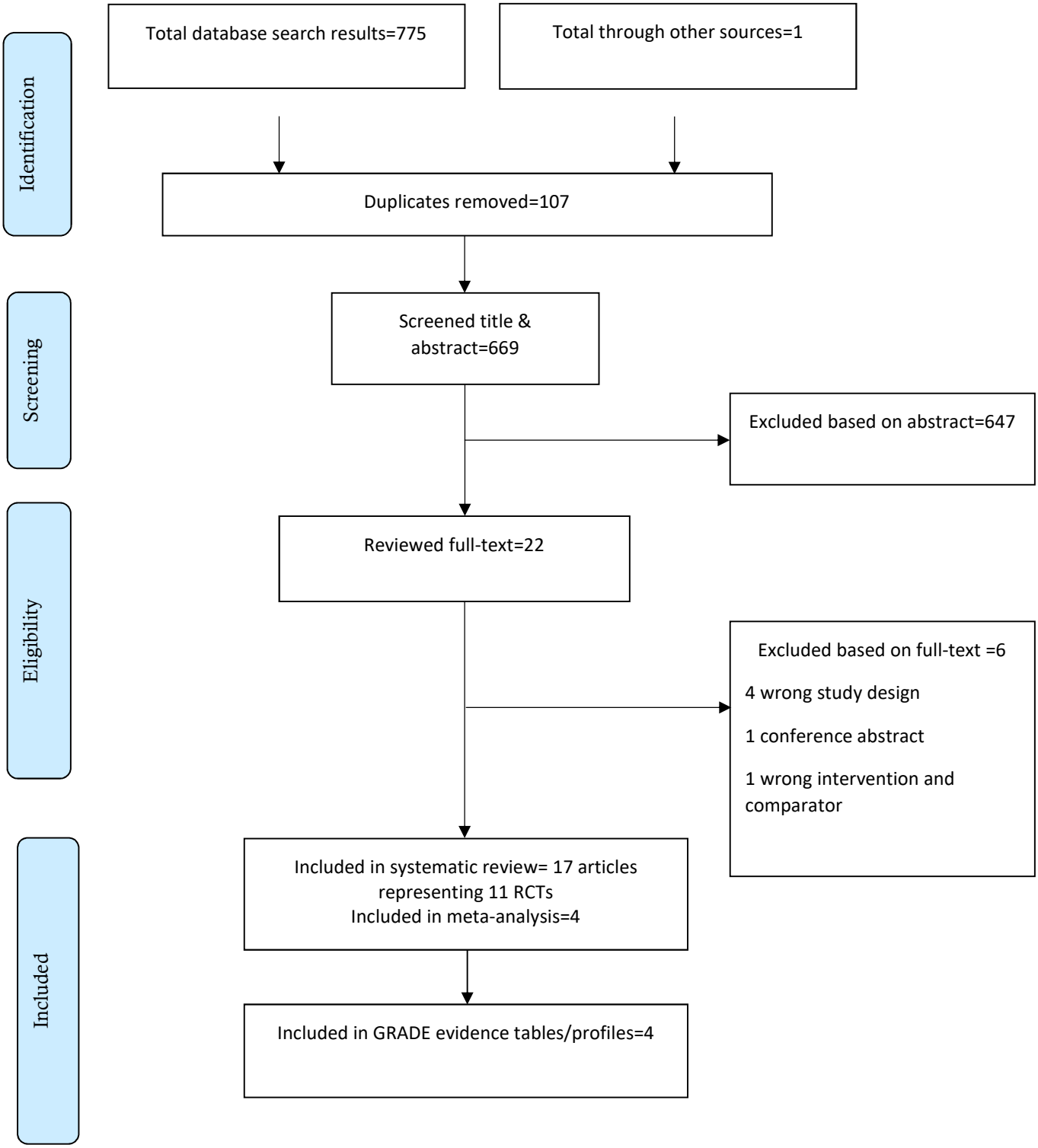
15 exp Appetite Depressants/ 94233 16 appetite suppressant*.mp. 1487 17 exp Glucagon-Like Peptide 1/ or Glucagon-Like Peptide 1 agonist.mp. 32498 18 (GLP-1 adj2 agonist*).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy] 10048 19 semaglutide.mp. 3397 20 tirzepatide.mp. 310 21 liraglutide.mp. 15050 22 dulaglutide.mp. 2796 23 exenatide.mp. or exp Exenatide/ 15334 24 lixisenatide.mp. 2560 25 albiglutide.mp. 1485 26 Lorcaserin.mp. 1842 27 phentermine.mp. or exp Phentermine/ 5217 28 topiramate.mp. or Topiramate/ 31119 29 naltrexone.mp. or exp Naltrexone/ 28800 30 exp Bupropion/ or buproprion.mp. 23012 31 incretin.mp. 15542 32 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 688891 33 8 and 32 9353 34 randomized controlled trial.pt. 575128 35 controlled clinical trial.pt. 94983 36 randomi*ed.ab. 1665228 37 placebo.ab. 565580 38 drug therapy.fs. 6697085 39 randomly.ab. 901041 40 trial.ab. 1500989 41 groups.ab. 5706526 42 34 or 35 or 36 or 37 or 38 or 39 or 40 or 4113488139 43 33 and 42 5456 44 exp animals/ not humans.sh. 33866843 45 43 not 44 1276 46 limit 45 to last 10 years 643	

843

47	limit 46 to english language	627	
48	remove duplicates from 47	613	

Evidence processing: Studies were selected and appraised by 2 reviewer/s in consultation with the evidence team/ key contact using study selection and appraisal criteria (PICO above) established a priori. The articles were reviewed by title and abstract by 2 reviewers. Any disagreements were resolved by discussion. Full text articles were retrieved and independently reviewed by two reviewers. All data extraction and risk of bias assessment was conducted independently by two reviewers.

3. SEARCH RESULTS - PRISMA flowchart



4. STUDY INCLUSION

Table 4.1. Included Studies (full citation with doi)- *add more rows as needed*

1. Elkind-Hirsch, K. E., Chappell, N., Seidemann, E., Storment, J., & Bellanger, D. (2021). Exenatide, Dapagliflozin, or Phentermine/Topiramate Differentially Affect Metabolic Profiles in Polycystic Ovary Syndrome. *The Journal of clinical endocrinology and metabolism, 106*(10), 3019-3033. doi:https://dx.doi.org/10.1210/clinem/dgab408

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Related manuscripts

Li, R., Mai, T., Zheng, S., & Zhang, Y. (2022). Effect of metformin and exenatide on pregnancy rate and pregnancy outcomes in overweight or obese infertility PCOS women: long-term follow-up of an RCT. *Archives of Gynecology and Obstetrics*(6ys, 8710213). doi:https://dx.doi.org/10.1007/s00404-022-06700-3

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8. Nylander, M., Frossing, S., Kistorp, C., Faber, J., & Skouby, S. O. (2017). Liraglutide in polycystic ovary syndrome: a randomized trial, investigating effects on thrombogenic potential. *Endocrine connections, 6*(2), 89-99. doi:https://dx.doi.org/10.1530/EC-16-0113

Related manuscripts

i. **Nylander, M., Frossing, S., Clausen, H. V., Kistorp, C., Faber, J., & Skouby, S. O. (2017). Effects of liraglutide on ovarian dysfunction in polycystic ovary syndrome: a randomized clinical trial. *Reproductive Biomedicine Online, 35*(1), 121-127. doi:https://dx.doi.org/10.1016/j.rbmo.2017.03.023**

ii. **Frossing, S., Nylander, M., Chabanova, E., Frystyk, J., Holst, J. J., Kistorp, C., . . . Faber, J. (2018). Effect of liraglutide on ectopic fat in polycystic ovary syndrome: A randomized clinical trial. *Diabetes, Obesity & Metabolism, 20*(1), 215-218. doi:https://dx.doi.org/10.1111/dom.13053**

iii. **Frossing, S., Nylander, M., Kistorp, C., Skouby, S. O., & Faber, J. (2018). Effect of liraglutide on atrial natriuretic peptide, adrenomedullin, and copeptin in PCOS. *Endocrine connections, 7*(1), 115-123. doi:https://dx.doi.org/10.1530/EC-17-0327**

9. Song, J., Ruan, X., Gu, M., Wang, L., Wang, H., & Mueck, A. O. (2018). Effect of orlistat or metformin in overweight and obese polycystic ovary syndrome patients with insulin resistance. *Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology, 34*(5), 413-417. doi:https://dx.doi.org/10.1080/09513590.2017.1407752 *Related manuscripts* Ruan, X., Song, J., Gu, M., Wang, L., Wang, H., & Mueck, A. O. (2018). Effect of Diane-35, alone or in combination with orlistat or metformin in Chinese polycystic ovary syndrome patients. *Archives of Gynecology and Obstetrics, 297*(6), 1557-1563. doi:https://dx.doi.org/10.1007/s00404-018-4762-0
10. Tao, T., Zhang, Y., Zhu, Y.-C., Fu, J.-R., Wang, Y.-Y., Cai, J., . . . Liu, W. (2021). Exenatide, Metformin, or Both for Prediabetes in PCOS: A Randomized, Open-label, Parallel-group Controlled Study. *The Journal of clinical endocrinology and metabolism, 106*(3), e1420-e1432. doi:https://dx.doi.org/10.1210/clinem/dgaa692
11. Zheng, S., Zhang, Y., Long, T., Lu, J., Liu, X., Yan, J., . . . Wang, F. (2017). Short term monotherapy with exenatide is superior to metformin in weight loss, improving insulin resistance and inflammation in Chinese overweight/obese PCOS women. *Obesity Medicine, 7*, 15-20. doi:https://doi.org/10.1016/j.obmed.2017.06.003 *Related manuscripts* Zheng, S., Liu, E., Zhang, Y., Long, T., Liu, X., Gong, Y., . . . Wang, F. (2019). Circulating zinc-alpha2-glycoprotein is reduced in women with polycystic ovary syndrome, but can be increased by exenatide or metformin treatment. *Endocrine Journal, 66*(6), 555-562. doi:https://dx.doi.org/10.1507/endocrj.EJ18-0153

Table 4.2. Studies awaiting classification

Reference
1. Jensterle, M., Kravos, N. A., Pfeifer, M., Kocjan, T., & Janez, A. (2015). A 12-week treatment with the long-acting glucagon-like peptide 1 receptor agonist liraglutide leads to significant weight loss in a subset of obese women with newly diagnosed polycystic ovary syndrome. *Hormones (Athens, Greece), 14*(1), 81-90. doi: https://dx.doi.org/10.1007/BF03401383
2. Jensterle, M., Salamun, V., Kocjan, T., Vrtacnik Bokal, E., & Janez, A. (2015). Short term monotherapy with GLP-1 receptor agonist liraglutide or PDE 4 inhibitor roflumilast is superior to metformin in weight loss in obese PCOS women: a pilot randomized study. *Journal of ovarian research, 8*(101474849), 32. doi:https://dx.doi.org/10.1186/s13048-015-0161-3
3. Jensterle Sever, M., Kocjan, T., Pfeifer, M., Kravos, N. A., & Janez, A. (2014). Short-term combined treatment with liraglutide and metformin leads to significant weight loss in obese women with polycystic ovary syndrome and previous poor response to metformin. *European journal of endocrinology, 170*(3), 451-459. doi:https://dx.doi.org/10.1530/EJE-13-0797
4. Kumar, P., & Arora, S. (2014). Orlistat in polycystic ovarian syndrome reduces weight with improvement in lipid profile and pregnancy rates. *Journal of Human Reproductive Sciences, 7*(4), 255-261. doi:https://dx.doi.org/10.4103/0974-1208.147492
5. Salamun, V., Jensterle, M., Janez, A., & Vrtacnik Bokal, E. (2018). Liraglutide increases IVF pregnancy rates in obese PCOS women with poor response to first-line reproductive treatments: a pilot randomized study. *European journal of endocrinology, 179*(1), 1-11. doi:https://dx.doi.org/10.1530/EJE-18-0175

Table 4.3. Studies excluded on full text assessment	
Reference	**Reason**
1. Jensterle, M., Kravos, N. A., Goricar, K., & Janez, A. (2017). Short-term effectiveness of low dose liraglutide in combination with metformin versus high dose liraglutide alone in treatment of obese PCOS: randomized trial. *BMC Endocrine Disorders, 17*(1), 5. doi:https://dx.doi.org/10.1186/s12902-017-0155-9	Wrong intervention and comparator – liraglutide + metformin v liraglutide
2. Min, Min; Ruan, Xiangyan; Wang, Husheng; Cheng, Jiaojiao; Luo, Suiyu; Xu, Zhongting; Li, Meng; Mueck, Alfred Otto. Effect of orlistat during individualized comprehensive life-style intervention on visceral fat in overweight or obese PCOS patients. *Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology* / 2022;(8807913):1-5, England 2022 / https://dx.doi.org/10.1080/09513590.2022.2089108	Wrong study design – described as a clinical cohort study, no randomisation applied.
3. Salamun V.; Jensterle M.; Janez A.; Vrtacnik Bokal E. Short term intervention with liraglutide and metformin increased fertility potential in a subset of obese PCOS proceeding IVF. *Human Reproduction / 2017;32(Supplement 1)*:i291-i292. Netherlands Oxford University Press 2017	Conference abstract
4. Salehpour, Saghar; Hosseini, Sedighe; Nazari, Leila; Saharkhiz, Nasrin; Zademodarres, Shahrzad. Effects of orlistat on serum androgen levels among iranian obese women with polycystic ovarian syndrome. *JBRA assisted reproduction* / 2018;22(3):180-184 Brazil 2018 . https://dx.doi.org/10.5935/1518-0557.20180033	Wrong study design – pre-post single arm study
5. Genetic variability in GLP-1 receptor is associated with inter-individual differences in weight lowering potential of liraglutide in obese women with PCOS: a pilot study. Jensterle, Mojca; Pirs, Bostjan; Goricar, Katja; Dolzan, Vita; Janez, Andrej/ *European journal of clinical pharmacology* / 2015;71(7):817-24, Germany 2015 / https://dx.doi.org/10.1007/s00228-015-1868-1	Wrong study design – pre-post single arm study
6. Jensterle, Mojca; Kocjan, Tomaz; Kravos, Nika Aleksandra; Pfeifer, Marija; Janez, Andrej Short-term intervention with liraglutide improved eating behavior in obese women with polycystic ovary syndrome. *Endocrine research* / 2015;40(3):133-8. England 2015 https://dx.doi.org/10.3109/07435800.2014.966385	Wrong study design – pre-post single arm study

5. DATA EXTRACTION

DICHOTOMOUS OUTCOMES

1. Exenatide

i. Exenatide v Dapagliflozin

Sample sizes: EXE=20, DAPA=17

OUTCOME: Gastrointestinal effects (Nausea)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Exenatide versus Dapagliflozin (DAPA)								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			5		0		Crude	NA

OUTCOME: Other AE (Yeast infection)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Exenatide versus Dapagliflozin (DAPA)								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

Elkind-Hirsch et al. 2021			0		4		Crude	NA

OUTCOME: Other AE (Injection site reaction: irritation, nodule, rash, redness, itching)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Exenatide versus Dapagliflozin (DAPA)								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			5		0		Crude	NA

OUTCOME: Other AE (Urinary tract infection: burning urination)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Exenatide versus Dapagliflozin (DAPA)								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			0		2		Crude	NA

OUTCOME: Other AE (Vaginal irritation)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Exenatide versus Dapagliflozin (DAPA)								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			0		1		Crude	NA

OUTCOME: Other AE (Rapid heartbeat)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Exenatide versus Dapagliflozin (DAPA)								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			0		1		Crude	NA

OUTCOME: Other AE (Light headed)	**OUTCOME TYPE:** Dichotomous

COMPARISON (if applicable): Exenatide versus Dapagliflozin (DAPA)								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			0		1		Crude	NA

OUTCOME: Other AE (Prolong menstrual bleeding)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Exenatide versus Dapagliflozin (DAPA)								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			0		1		Crude	NA

ii. Exenatide + dapagliflozin v dapagliflozin

Sample size: EXE + DAPA=20, DAPA=17

OUTCOME: Other AE (Yeast infection)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Exenatide + Dapagliflozin (DAPA) versus DAPA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			5		4		Crude	NA

OUTCOME: Other AE (Injection site reaction: irritation, nodule, rash, redness, itching)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Exenatide + Dapagliflozin (DAPA) versus DAPA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			4		0		Crude	NA

OUTCOME: Other AE (Urinary tract infection: burning urination)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Exenatide + Dapagliflozin (DAPA) versus DAPA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			2		2		Crude	NA

OUTCOME: Other AE (Vaginal irritation)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Exenatide + Dapagliflozin (DAPA) versus DAPA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			1		1		Crude	NA

OUTCOME: Other AE (Rapid heartbeat)	**OUTCOME TYPE:** Dichotomous
COMPARISON (if applicable): Exenatide + Dapagliflozin (DAPA) versus DAPA	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Elkind-Hirsch et al. 2021			0		1		Crude	NA

OUTCOME: Other AE (Light headed)			**OUTCOME TYPE:** Dichotomous					
COMPARISON (if applicable): Exenatide + Dapagliflozin (DAPA) versus DAPA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			0		1		Crude	NA

OUTCOME: Other AE (Prolong menstrual bleeding)	**OUTCOME TYPE:** Dichotomous
COMPARISON (if applicable): Exenatide + Dapagliflozin (DAPA) versus DAPA	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Elkind-Hirsch et al. 2021			1		1		Crude	NA

iii. Exenatide v metformin

a. Exenatide v metformin

Sample sizes:

Zheng: EXE=31, MET=32

Tao: EXE=50, MET=50

OUTCOME: Gastrointestinal effects (Nausea)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Exenatide versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Zheng et al. 2019 (Zheng et al. 2017)			6		3		Crude	NA

OUTCOME: Gastrointestinal effects (nausea and vomiting)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Exenatide versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in**	**Mean (specify if median) or median in control /**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

				intervention / exposure group	**comparison group**	**comparison group**		
Tao et al. 2021			2		2		Crude	NA

OUTCOME: Gastrointestinal effects (Diarrhea)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Exenatide versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Zheng et al. 2019 (Zheng et al. 2017)			0		2		Crude	NA

OUTCOME: Gastrointestinal effects (Bloating)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Exenatide versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

						comparison group		
Zheng et al. 2019 (Zheng et al. 2017)			2		2		Crude	NA

OUTCOME: Gastrointestinal effects (Vomiting)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Exenatide versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Zheng et al. 2019 (Zheng et al. 2017)			4		2		Crude	NA

OUTCOME: Gastrointestinal effects (Gastrointestinal spasm)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Exenatide versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in**	**Mean (specify if median) or median in control /**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

				intervention / exposure group	**comparison group**	**comparison group**		
Zheng et al. 2019 (Zheng et al. 2017)			1		1		Crude	NA

OUTCOME: Gastrointestinal effects (Stomachache)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Exenatide versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Zheng et al. 2019 (Zheng et al. 2017)			0		2		Crude	NA

OUTCOME: Gastrointestinal effects (Constipation)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Exenatide versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in**	**Mean (specify if median) or median in control /**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

				intervention / exposure group	**comparison group**	**comparison group**		
Zheng et al. 2019 (Zheng et al. 2017)			0		2		Crude	NA

OUTCOME: Other adverse effects (Dizziness)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Exenatide versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Zheng et al. 2019 (Zheng et al. 2017)			2		0		Crude	NA

OUTCOME: Other adverse effects (Headache)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Exenatide versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in**	**Mean (specify if median) or median in control /**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

				intervention / exposure group	**comparison group**	**comparison group**		
Tao et al. 2021			0		1		Crude	NA

OUTCOME: Other adverse effects (Weakness)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Exenatide versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Zheng et al. 2019 (Zheng et al. 2017)			2		0		Crude	NA

OUTCOME: Other adverse effects (Subcutaneous induration)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Exenatide versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

						comparison group		
Zheng et al. 2019 (Zheng et al. 2017)			1		0		Crude	NA

b. Exenatide + oral contraceptive pill v metformin + oral contraceptive pill

Sample size:

Non-pregnancy outcomes: EXE=78, MET=80

Pregnancy outcomes: EXE=72, MET=75

OUTCOME: Live birth				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): EXE + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Liu et al. 2017 (Li 2022)		Delivery after 28 weeks	48		47		Crude	NA

OUTCOME: Pregnancy rate - biochemical	**OUTCOME TYPE:**

Data extraction – dichotomous outcomes

COMPARISON (if applicable): EXE + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Liu et al. 2017		Positive B-HCG test either in urine or serum without the development of a gestational sac	9		10		Crude	NA

OUTCOME: Pregnancy rate – clinical				**OUTCOME TYPE:**				
COMPARISON (if applicable): EXE + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Liu et al. 2017		Singleton viable fetus on transvaginal ultrasound between 6 and 9 weeks 6 days gestation	48		47		Crude	NA

OUTCOME: Singleton pregnancies				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): EXE + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Liu et al. 2017			8		8		Crude	NA

OUTCOME: Twin pregnancies				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): EXE + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Liu et al. 2017		Twin pregnancies per clinical intrauterine pregnancies and confirmed by ultrasound	1		2		Crude	NA

OUTCOME: Miscarriage rate					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): EXE + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Liu et al. 2017 - (Li 2022)		Pregnancy loss before 28 weeks	9		10		Crude	NA

OUTCOME: Preterm delivery					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): EXE + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Liu et al. 2017 (Li 2022)		Delivery between week 29 and week 36+6	7	NA	5	NA	Crude	NA

OUTCOME: Hypertension in pregnancy				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): EXE + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Liu et al. 2017		Hypertension developed during pregnancy without pre existing hypertention	1		0		Crude	NA

OUTCOME: Gestational diabetes				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): EXE + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Liu et al. 2017		IADPSG criteria	4		4		Crude	NA

OUTCOME: Fetal macrosomia					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): EXE + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Liu et al. 2017		Neonatal birthweight ≥4000g	1		1		Crude	NA

OUTCOME: Fetal polydactyly					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): EXE + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Liu et al. 2017 (Li 2022)			0		1		Crude	NA

OUTCOME: Fetal patent ductus arteriosus	**OUTCOME TYPE:** Dichotomous

COMPARISON (if applicable): EXE + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Liu et al. 2017 (Li 2022)			0		1		Crude	NA

OUTCOME: Fetal atrial septal defect					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): EXE + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Liu et al. 2017 (Li 2022)			1		0		Crude	NA

OUTCOME: Gastrointestinal effects (Nausea)	**OUTCOME TYPE:** Dichotomous
COMPARISON (if applicable): EXE + OCP vs MET + OCP	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Liu et al. 2017			13		7		Crude	NA

OUTCOME: Gastrointestinal effects (nausea and vomiting)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): EXE + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Tao et al. 2021			2		2		Crude	NA

OUTCOME: Gastrointestinal effects (Diarrhea)0				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): EXE + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in**	**Mean (specify if median) or median in control /**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

				intervention / exposure group	**comparison group**	**comparison group**		
Liu et al. 2017			0		4		Crude	NA

OUTCOME: Gastrointestinal effects (Bloating)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): EXE + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Liu et al. 2017			4		4		Crude	NA

OUTCOME: Gastrointestinal effects (Vomiting)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): EXE + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

Liu et al. 2017			6		3		Crude	NA

OUTCOME: Gastrointestinal effects (Stomachache)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): EXE + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Liu et al. 2017 (Li 2022)			0		4		Crude	NA

OUTCOME: Gastrointestinal effects (Constipation)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): EXE + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

Liu et al. 2017 (Li 2022)			0		4		Crude	NA

OUTCOME: Other adverse effects (Dizziness)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): EXE + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Liu et al. 2017 (Li 2022)			2		0		Crude	NA

OUTCOME: Subcutaneous induration with rash at the injection site				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): EXE + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

						comparison group		
Liu et al. 2017 (Li 2022)			2		0		Crude	NA

OUTCOME: Hypoglycemic events					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): EXE + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Liu et al. 2017 (Li 2022)			0		0		Crude	NA

iv. Exenatide + Metformin v Metformin alone

a. Exenatide + Metformin v Metformin

Sample sizes: EXE+MET=50, MET=50

OUTCOME: Gastrointestinal effects (nausea and vomiting)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Exenatide + Metformin versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Tao et al. 2021			0		2		Crude	NA

OUTCOME: Other adverse effects (Headache)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Exenatide + Metformin versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Tao et al. 2021			0		1		Crude	NA

b. Exenatide + Metformin + oral contraceptive pill vs Metformin + oral contraceptive pill

Sample sizes: EXE+MET=19, MET=21

OUTCOME: Gastrointestinal effects (Nausea)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Exenatide + MET + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Ma et al. 2021			11		10		Crude	NA

OUTCOME: Gastrointestinal effects (Diarrhea)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Exenatide + MET + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Ma et al. 2021			9		11		Crude	NA

OUTCOME: Gastrointestinal effects (Bloating)	**OUTCOME TYPE:** Dichotomous

COMPARISON (if applicable): Exenatide + MET + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Ma et al. 2021			6		2		Crude	NA

OUTCOME: Gastrointestinal effects (Vomiting)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Exenatide + MET + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Ma et al. 2021			2		3		Crude	NA

OUTCOME: Gastrointestinal effects (Stomachache)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Exenatide + MET + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in**	**Mean (specify if median) or median in control /**	**SD (or specify if other measure: SE, IQR or 95% CI)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

				intervention / exposure group	**comparison group**	**in control/ comparison group**		
Ma et al. 2021			0		2		Crude	NA

OUTCOME: Gastrointestinal effects (Constipation)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Exenatide + MET + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Ma et al. 2021			2		1		Crude	NA

OUTCOME: Other adverse effects (Headache)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Exenatide + MET + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

Ma 2021			2		1			

OUTCOME: Other adverse effects (Fatigue)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Exenatide + MET + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Ma et al. 2021			3		2		Crude	NA

OUTCOME: Other adverse effects (Dizzy)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Exenatide + MET + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Ma et al. 2021			1		1		Crude	NA

OUTCOME: Other adverse effects (Urticaria)	**OUTCOME TYPE:** Dichotomous

COMPARISON (if applicable): Exenatide + MET + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Ma et al. 2021			1		0		Crude	NA

OUTCOME: Other adverse effects (Injection site pain)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Exenatide + MET + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Ma et al. 2021			2		0		Crude	NA

OUTCOME: Other adverse effects (Injection site itchy)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Exenatide + MET + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in**	**Mean (specify if median) or median in control /**	**SD (or specify if other measure: SE, IQR or 95% CI)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

				intervention / exposure group	**comparison group**	**in control/ comparison group**		
Ma et al. 2021			12		0		Crude	NA

OUTCOME: Other adverse effects (Subcutaneous induration)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Exenatide + MET + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Ma et al. 2021			11		0		Crude	NA

v. Exenatide v Phentermine/Topiramate

Sample sizes: EXE=20, PT=16

OUTCOME: Gastrointestinal effects (Nausea)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Exenatide versus Phentermine/Topiramate								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in**	**Mean (specify if median) or median in control /**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

				intervention / exposure group	**comparison group**	**comparison group**		
Elkind-Hirsch et al. 2021			5		2		Crude	NA

OUTCOME: Gastrointestinal effects (Upset stomach)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Exenatide versus Phentermine/Topiramate								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			0		1		Crude	NA

OUTCOME: Other AE (Injection site irritation)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Exenatide versus Phentermine/Topiramate								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

						comparison group		
Elkind-Hirsch et al. 2021			3		0		Crude	NA

OUTCOME: Other AE (Injection site rash, itch)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Exenatide versus Phentermine/Topiramate								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			2		0		Crude	NA

OUTCOME: Other AE (Rapid Heart Rate)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Exenatide versus Phentermine/Topiramate								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

						comparison group		
Elkind-Hirsch et al. 2021			0		1		Crude	NA

OUTCOME: Other AE (Light headed)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Exenatide versus Phentermine/Topiramate								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			0		1		Crude	NA

OUTCOME: Other AE (Fatigue)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Exenatide versus Phentermine/Topiramate								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

						comparison group		
Elkind-Hirsch et al. 2021			0		2		Crude	NA

OUTCOME: Other AE (Insomnia)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Exenatide versus Phentermine/Topiramate								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			0		3		Crude	NA

OUTCOME: Other AE (headache)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Exenatide versus Phentermine/Topiramate								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

						comparison group		
Elkind-Hirsch et al. 2021			0		2		Crude	NA

OUTCOME: Other AE (Kidney stone)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Exenatide versus Phentermine/Topiramate								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			0		1		Crude	NA

vi. Exenatide v Dapagliflozin + Metformin

Sample sizes: EXE=20, DAPA + MET=19

OUTCOME: Gastrointestinal effects (Nausea)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Exenatide versus DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			5		1		Crude	NA

OUTCOME: Gastrointestinal effects (Upset stomach)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Exenatide versus DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			0		5		Crude	NA

OUTCOME: Other AE (Yeast infection)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Exenatide versus DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			0		5		Crude	NA

OUTCOME: Other AE (Injection site reaction: irritation, nodule, rash, redness, itching)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Exenatide versus DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			5		0		Crude	NA

OUTCOME: Other AE (Urinary tract infection: burning urination)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Exenatide versus DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			0		1		Crude	NA

OUTCOME: Other AE (Frequent urination)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Exenatide versus DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			0		1		Crude	NA

OUTCOME: Other AE (Stuffy nose)	**OUTCOME TYPE:** Dichotomous
COMPARISON (if applicable): Exenatide versus DAPA + MET	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Elkind-Hirsch et al. 2021			0		1		Crude	NA

2. Liraglutide

i. Liraglutide v placebo

a. Liraglutide v placebo

Sample sizes: LIRA 44, Placebo 21 unless otherwise stated

OUTCOME: Adverse effects: nausea					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Liraglutide vs Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Nylander 2017*	%	Medical interview	78.7% (n=14)	Not listed	13.0% (n=3)	Not listed	Crude	NA

OUTCOME: AE - Vomiting	**OUTCOME TYPE:** Continuous

COMPARISON (if applicable): Liraglutide vs Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Nylander 2017	%	Count	10.6% (n=5/47)	Not listed	0	0	Crude	NA

OUTCOME: AE – Diarrhoea					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Liraglutide vs Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Nylander 2017	%	Count	10.6% (n=5/47)	Not listed	4.4% (n=1/23)	Not listed	Crude	NA

OUTCOME: AE - Constipation	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Liraglutide vs Placebo	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Nylander 2017*	%	Count	25.5% (n=12/47)	Not listed	0	0	Crude	NA

OUTCOME: AE - Injection site reaction (bruising, redness, itching)				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide vs Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Nylander 2017	%	Count	6.4% (n=3/47)	Not listed	0	0	Crude	NA

OUTCOME: AE – Ructus / heartburn	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Liraglutide vs Placebo	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Nylander 2017	%	Count	17.0%	Not listed	0	0	Crude	NA

OUTCOME: AE – Gastroenteritis				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide vs Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Nylander 2017	%	Count	10.6% (n=8/47)	Not listed	8.7% (n=2/23)	Not listed	Crude	NA

OUTCOME: AE – Epigastrial pain	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Liraglutide vs Placebo	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Nylander 2017	%	Count	17.0% (n=8/47)	Not listed	0	0	Crude	NA

OUTCOME: AE – Gallstone related pain				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide vs Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Nylander 2017	%	Count	6.4% (n=3/47)	Not listed	4.4% (n=1/23)	Not listed	Crude	NA

OUTCOME: AE – Cholecystectomy	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Liraglutide vs Placebo	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Nylander 2017	%	Count	4.3% (n=2/47)	Not listed	0	0	Crude	NA

OUTCOME: AE – Hypotension				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide vs Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Nylander 2017	%	Count	2.1% (n=1/47)	Not listed	0	0	Crude	NA

OUTCOME: AE – Tachycardia	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Liraglutide vs Placebo	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Nylander 2017	%	Count	2.1% (n=1/47)	Not listed	0	0	Crude	NA

OUTCOME: AE – Syncope				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide vs Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Nylander 2017	%	Count	2.1% (n=1/47)	Not listed	0	0	Crude	NA

OUTCOME: AE – Dizziness	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Liraglutide vs Placebo	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Nylander 2017	%	Count	8.5% (n=4/47)	Not listed	0	0	Crude	NA

OUTCOME: AE – Headache				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide vs Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Nylander 2017	%	Count	0	0	13.0% (n=3/23)	Not listed	Crude	NA

OUTCOME: AE – Upper respiratory tract infection	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Liraglutide vs Placebo	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Nylander 2017	%	Count	14.9%	n=7 (of 47)	17.4%	n=4 (of 23)	Crude	NA

OUTCOME: AE – Urinary tract infection				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide vs Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Nylander 2017	%	Count	4.3%	n=2 (of 47)	0	0	Crude	NA

OUTCOME: AE – Hair loss	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Liraglutide vs Placebo	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Nylander 2017	%	Count	2.1%	n=1 (of 47)	0	0	Crude	NA

OUTCOME: AE – Joint pain				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide vs Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Nylander 2017	%	Count	2.1% (n=1/47)	Not listed	0	0	Crude	NA

b. Liraglutide + lifestyle v placebo + lifestyle

Sample size: LIRA + LS=44, Placebo + LS=23

OUTCOME: Adverse effects: nausea				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide + lifestyle vs Placebo + lifestyle								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch 2022	%	Count	25.5% (n/37/47)	Not listed	11% (n=3/23)	Not listed	Crude	NA

OUTCOME: AE - Vomiting				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide + lifestyle vs Placebo + lifestyle								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch 2022	%	Count	9% (n=5_	Not listed	0	0	Crude	NA

OUTCOME: AE – Diarrhoea				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide + lifestyle vs Placebo + lifestyle								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch 2022	%	Count	7.3% (n=4)	Not listed	0	0	Crude	NA

OUTCOME: AE - Constipation				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide + lifestyle vs Placebo + lifestyle								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch 2022	%	Count	5.5% (n=3)	Not listed	3.7% (n=1)	Not listed	Crude	NA

OUTCOME: AE - Heartburn				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide + lifestyle vs Placebo + lifestyle								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch 2022	%	Count	3.6% (n=1)	Not listed	3.7% (n=1)	Not listed	Crude	NA

OUTCOME: AE - Reflux				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide + lifestyle vs Placebo + lifestyle								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch 2022	%	Count	3.6% (n=2)	Not listed	0	0	Crude	NA

OUTCOME: AE - Indigestion				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide + lifestyle vs Placebo + lifestyle								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch 2022	%	Count	3.6%	n=2	0	0	Crude	NA

OUTCOME: AE - Prolonged menstrual bleeding				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide + lifestyle vs Placebo + lifestyle								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch 2022	%	Count	5.5% (n=3)	Not listed	3.7%	Not listed	Crude	NA

OUTCOME: AE - Injection site reaction (bruising, redness, itching)				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide + lifestyle vs Placebo + lifestyle								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch 2022	%	Count	5.5% (n=3)	Not listed	0	0	Crude	NA

OUTCOME: AE - No menstrual cycles				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide + lifestyle vs Placebo + lifestyle								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch 2022	%	Count	0	0	3.7% (n=1)	Not listed	Crude	NA

OUTCOME: AE - COVID19				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide + lifestyle vs Placebo + lifestyle								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch 2022	%	Count	0	0	3.7%	n=1	Crude	NA

3. Semaglutide

i. Semaglutide v Placebo

Sample size: Semaglutide 13, placebo 12

OUTCOME: eg. Nausea and vomiting					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): eg. Semaglutide vs placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Jensterle 2021	n	NA	9		1		Crude	NA

4. Phentermine/Topiramate

i. Phentermine/Topiramate v Dapagliflozin

Sample sizes: PT=13, Dapa=17

OUTCOME: Gastrointestinal effects (Nausea)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Phentermine/topiramate vs Dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			2		0		Crude	NA

OUTCOME: Gastrointestinal effects (Upset stomach)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Phentermine/topiramate vs Dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

Elkind-Hirsch et al. 2021			1		0		Crude	NA

OUTCOME: Other AE (Yeast infection)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Phentermine/topiramate vs Dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			0		4		Crude	NA

OUTCOME: Other AE (Urinary tract infection: burning urination)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Phentermine/topiramate versus Dapagliflozin (DAPA)								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			0		2		Crude	NA

OUTCOME: Other AE (Vaginal irritation)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Phentermine/topiramate versus Dapagliflozin (DAPA)								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			0		1		Crude	NA

OUTCOME: Other AE (Rapid heartbeat)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Phentermine/topiramate versus Dapagliflozin (DAPA)								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			1		1		Crude	NA

OUTCOME: Other AE (Light headed)	**OUTCOME TYPE:** Dichotomous
COMPARISON (if applicable): Phentermine/topiramate versus Dapagliflozin (DAPA)	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Elkind-Hirsch et al. 2021			1		1		Crude	NA

OUTCOME: Other AE (Fatigue)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Phentermine/topiramate vs Dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			2		0		Crude	NA

OUTCOME: Other AE (Insomnia)	**OUTCOME TYPE:** Dichotomous
COMPARISON (if applicable): Phentermine/topiramate vs Dapa	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Elkind-Hirsch et al. 2021			3		0		Crude	NA

OUTCOME: Other AE (Headache)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Phentermine/Topiramate versus Dapagliflozin (DAPA)								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			2		0		Crude	NA

OUTCOME: Other AE (Kidney stone)	**OUTCOME TYPE:** Dichotomous
COMPARISON (if applicable): Phentermine/Topiramate versus Dapagliflozin (DAPA)	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Elkind-Hirsch et al. 2021			1		0		Crude	NA

OUTCOME: Other AE (Prolong menstrual bleeding)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Phentermine/Topiramate versus Dapagliflozin (DAPA)								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			0		1		Crude	NA

ii. Phentermine/Topiramate v Dapagliflozin + Metformin

Sample sizes: PT=13, DAPA+Met=19

OUTCOME: Gastrointestinal effects (Nausea)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Phentermine/topiramate vs DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			2		1		Crude	NA

OUTCOME: Gastrointestinal effects (Upset stomach)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Phentermine/topiramate vs DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			1		5		Crude	NA

OUTCOME: Other AE (Yeast infection)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Phentermine/topiramate vs DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			0		5		Crude	NA

OUTCOME: Other AE (Injection site reaction: irritation, nodule, rash, redness, itching)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Phentermine/topiramate vs DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			0		0		Crude	NA

OUTCOME: Other AE (Urinary tract infection: burning urination)	**OUTCOME TYPE:** Dichotomous

COMPARISON (if applicable): Phentermine/Topiramate versus DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			0		1		Crude	NA

OUTCOME: Other AE (Frequent urination)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Phentermine/topiramate versus DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			0		1		Crude	NA

OUTCOME: Other AE (Rapid heartbeat)	**OUTCOME TYPE:** Dichotomous
COMPARISON (if applicable): Phentermine/topiramate versus DAPA + MET	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Elkind-Hirsch et al. 2021			1		0		Crude	NA

OUTCOME: Other AE (Light headed)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Exenatide versus DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			1		0		Crude	NA

OUTCOME: Other AE (Fatigue)	**OUTCOME TYPE:** Dichotomous
COMPARISON (if applicable): Phentermine/topiramate vs Dapa	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Elkind-Hirsch et al. 2021			2		0		Crude	NA

OUTCOME: Other AE (Insomnia)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Phentermine/topiramate vs Dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			3		0		Crude	NA

OUTCOME: Other AE (Headache)	**OUTCOME TYPE:** Dichotomous
COMPARISON (if applicable): Phentermine/topiramate versus DAPA + MET	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Elkind-Hirsch et al. 2021			2		0		Crude	NA

OUTCOME: Other AE (Kidney stone)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Phentermine/Topiramate versus DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			1		0		Crude	NA

iii. Phentermine/Topiramate v Exenatide + Dapagliflozin

Sample sizes: PT=13, EXE+DAPA=20

OUTCOME: Gastrointestinal effects (Nausea)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Phentermine/topiramate vs EXE + DAPA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			2		1		Crude	NA

OUTCOME: Gastrointestinal effects (Upset stomach)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Phentermine/topiramate vs EXE + DAPA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			1		5		Crude	NA

OUTCOME: Other AE (Yeast infection)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Phentermine/topiramate vs EXE + DAPA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			0		5		Crude	NA

OUTCOME: Other AE (Urinary tract infection: burning urination)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Phentermine/Topiramate versus EXE + DAPA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			0		1		Crude	NA

OUTCOME: Other AE (Frequent urination)	**OUTCOME TYPE:** Dichotomous
COMPARISON (if applicable): Phentermine/topiramate versus EXE + DAPA	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Elkind-Hirsch et al. 2021			0		1		Crude	NA

OUTCOME: Other AE (Rapid heartbeat)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Phentermine/topiramate versus EXE + DAPA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			1		0		Crude	NA

OUTCOME: Other AE (Light headed)	**OUTCOME TYPE:** Dichotomous
COMPARISON (if applicable): Exenatide versus EXE + DAPA	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Elkind-Hirsch et al. 2021			1		0		Crude	NA

OUTCOME: Other AE (Fatigue)					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Phentermine/topiramate vs Dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			2		0		Crude	NA

OUTCOME: Other AE (Insomnia)	**OUTCOME TYPE:** Dichotomous
COMPARISON (if applicable): Phentermine/topiramate vs Dapa	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Elkind-Hirsch et al. 2021			3		0		Crude	NA

OUTCOME: Other AE (Headache)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Phentermine/topiramate versus EXE + DAPA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			2		0		Crude	NA

OUTCOME: Other AE (Kidney stone)	**OUTCOME TYPE:** Dichotomous
COMPARISON (if applicable): Phentermine/Topiramate versus EXE + DAPA	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Elkind-Hirsch et al. 2021			1		0		Crude	NA

OUTCOME: Other AE (Yeast infection)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Phentermine/Topiramate versus EXE + DAPA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			0		5		Crude	NA

OUTCOME: Other AE (Injection site irritation)	**OUTCOME TYPE:** Dichotomous
COMPARISON (if applicable): Phentermine/Topiramate versus EXE + DAPA	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Elkind-Hirsch et al. 2021			0		4		Crude	NA

OUTCOME: Other AE (Urinary tract infection: Burning urination)				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Phentermine/Topiramate versus EXE + DAPA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			0		2		Crude	NA

OUTCOME: Other AE (Vaginal irritation)	**OUTCOME TYPE:** Dichotomous
COMPARISON (if applicable): Phentermine/Topiramate versus EXE + DAPA	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Elkind-Hirsch et al. 2021			0		1		Crude	NA

OUTCOME: Other AE (Prolonged menstrual bleeding)			**OUTCOME TYPE:** Dichotomous					
COMPARISON (if applicable): Phentermine/Topiramate versus EXE + DAPA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021			0		1		Crude	NA

5. Orlistat

i. Orlistat + lifestyle v placebo + lifestyle

Sample sizes:

Moini: Orlistat 43, placebo + lifestyle 43

OUTCOME: Urgency to go to the bathroom				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Orlistat + lifestyle vs placebo + lifestyle								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Moini 2015	%	Count	Percentage only – 54%	NA	0	NA	Crude	NA

OUTCOME: Oily spotting in undergarments				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Orlistat + lifestyle vs placebo + lifestyle								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Moini 2015	%	Count	Percentage only – 30%	NA	0	NA	Crude	NA

OUTCOME: Oily or fatty stool				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Orlistat + lifestyle vs placebo + lifestyle								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Moini 2015	%	Count	Percentage only – 22%	NA	0	NA	Crude	NA

OUTCOME: Headaches				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Orlistat + lifestyle vs placebo + lifestyle								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Moini 2015	%	Count	Percentage only – 3%	NA	5%	NA	Crude	NA

OUTCOME: Dizziness	**OUTCOME TYPE:** Continuous

COMPARISON (if applicable): Orlistat + lifestyle vs placebo + lifestyle								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Moini 2015	%	Count	0	NA	9%	NA	Crude	NA

OUTCOME: Diarrhoea/constipation				OUTCOME TYPE: Continuous				
COMPARISON (if applicable): Orlistat + lifestyle vs placebo + lifestyle								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Moini 2015	%	Count	0	NA	16%	NA	Crude	NA

ii. Orlistat + lifestyle + OCP v Metformin + lifestyle + OCP

Sample size: Orlistat 60, Metformin 60

OUTCOME: Gastrointestinal AE				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Orlistat (+lifestyle + OCP) vs Metformin (+LS + OCP)								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in metformin group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Song 2017	N	NA	2		3		Crude	NA

iii. Orlistat + lifestyle + OCP v lifestyle + OCP

Sample sizes:

Song 2017: Orlistat=60, Control=60

OUTCOME: Gastrointestinal AE					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Orlistat + LS + OCP v LS + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Song 2017	N	NA	2		0	-	Crude	NA

iv. Orlistat + Metformin + OCP + lifestyle v Metformin + OCP + lifestyle

Sample sizes: Orlistat 60, Met 60

OUTCOME: eg. Gastrointestinal AE					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): eg. Orlistat + Metformin + OCP vs Metformin alone + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Song 2017	N	NA	9	-	3	-	Crude	NA

CONTINUOUS OUTCOMES

***** Where a meta-analysis was not possible, statistically significant between-group differences are marked with an asterisk***

1. Exenatide

i. Exenatide v Dapagliflozin

Sample sizes: EXE=20, DAPA=17

OUTCOME: Androgenicity:FAI					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): exanetide vs dapa (Dapagliflozin)								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021		competitive binding immunoenzymatic assays with direct chemiluminometric technology (Beckman Coulter Access 2).	5.3	0.72	4.7	0.8	Crude	NA

OUTCOME: Androgenicity: Total testosterone	**OUTCOME TYPE:** Continuous

COMPARISON (if applicable): exanetide vs dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	Ng/dl	SHBG: TT concentration was measured with an automated chemiluminescent microparticle immunoassay, the Architect second-generation testosterone assay (Abbott Diagnostics) with 5 ng/dL as the minimum detectable concentration of TT	38.8	4	35	4.4	Crude	NA

OUTCOME: Androgenicity DHEAS	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): exanetide vs dapa	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Elkin-Hirsch 2021	Mcg/dL	competitive binding immunoenzymatic assays with direct chemiluminometric technology (Beckman Coulter Access 2).	165	22	187	24	Crude	NA

OUTCOME: Metabolics: Fasting glucose				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): exanetide vs dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	Mg/dl	glucose	91	1.9	93	2.1	Crude	NA

		analyzer using the glucose oxidase method (Glucose Reagent Kit, Bayer).						

OUTCOME: Metabolics: HOMA- IR				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): exanetide vs dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021		was calculated using the equation: fasting insulin concentration (µIU/mL) × fasting glucose concentration (mmol/L) 22.5	3.5	0.55	3.4	0.6	Crude	NA

OUTCOME: Metabolics: Matsuda Index SI OGTT	**OUTCOME TYPE:** Continuous

COMPARISON (if applicable): exanetide vs dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021		Serum insulin was determined in all samples in duplicate by microparticle enzyme immunoassay (Abbott AxSYM System, Abbott Laboratories).	3.16	0.6	3.6	0.7	Crude	NA

OUTCOME: Lipids: Tot cholesterol					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): exanetide vs dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

Elkin-Hirsch 2021	Mg/dl	standard enzymatic colorimetric assays on an automated clinical chemistry analyzer	189	10	186	11	Crude	NA

OUTCOME: Lipids: LDL					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): exanetide vs dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	Mg/dl	calculated according to the Friedewald equation	119	9	113.5	10	Crude	NA

OUTCOME: Lipids: HDL	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): exanetide vs dapa	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Elkin-Hirsch 2021	Mg/dl	standard enzymatic colorimetric assays on an automated clinical chemistry analyzer	42.5	2	43	2.2	Crude	NA

OUTCOME: Lipids: TG					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): exanetide vs dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	Mg/dl	standard enzymatic colorimetric assays on an	130	12	132	13	Crude	na

		automated clinical chemistry analyzer						

OUTCOME: Antropometric: weight					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): exanetide vs dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	kg		100.4	3.7	102.6	4	Crude	NA

OUTCOME: Antropometric: BMI					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): exanetide vs dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

Elkin-Hirsch 2021	Kg/m2		37.3	1.1	37.4	1.2	Crude	NA

OUTCOME: Antropometric: WHR				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): exanetide vs dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021		WC was measured at the narrowest level midway between the rib cage and the iliac crest and hip circumference measured at the widest level over the buttocks while the participants were in the standing position	0.825	0.016	0.79	0.017	Crude	NA

		using a flexible measuring tape.						

OUTCOME: Antropometric: WC				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): exanetide vs dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	Cm	narrowest level midway between the rib cage and the iliac crest	104	3	101	3.2	Crude	NA

OUTCOME: Antropometric: fat free mass /lean BM				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): exanetide vs dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in**	**Mean (specify if median) or median in control /**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

				intervention / exposure group	**comparison group**	**comparison group**		
Elkin-Hirsch 2021	kg	Participants in hospital gowns were positioned in the supine position on the DXA table, and instructed to keep their arms separated from their trunk, hands placed flat on the table, palms facing down, away from their thighs adjacent to the side of the body, and their legs separated from one another	52.3	1.6	52.2	1.7	Crude	NA

OUTCOME: Antropometric: fat mass	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): exanetide vs dapa	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Elkin-Hirsch 2021	kg	Participants in hospital gowns were positioned in the supine position on the DXA table, and instructed to keep their arms separated from their trunk, hands placed flat on the table, palms facing down, away from their thighs adjacent to the side of the body, and their legs separated from one another	47.6	2.4	47.8	2.6	Crude	NA

OUTCOME: Antropometric: % body fat					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): exanetide vs dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021		Participants in hospital gowns were positioned in the supine position on the DXA table, and instructed to keep their arms separated from their trunk, hands placed flat on the table, palms facing down, away from their thighs adjacent to the side of the body, and their legs separated from one another	46.1	1.1	46.4	1.2	Crude	NA

ii. Exenatide + Dapagliflozin v Dapagliflozin

Statistically significant between-group differences are marked with *

Sample sizes: EXE+DAPA=20, DAPA=17

OUTCOME: Androgenicity:FAI					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): exanetide and dapa vs dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021		competitive binding immunoenzymatic assays with direct chemiluminometric technology (Beckman Coulter Access 2).	5.2	0.73	4.7	0.8	Crude	NA

OUTCOME: Androgenicity: Total testosterone	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): exanetide and dapa vs dapa	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Elkin-Hirsch 2021	Ng/dl	SHBG: TT concentration was measured with an automated chemiluminescent microparticle immunoassay, the Architect second-generation testosterone assay (Abbott Diagnostics) with 5 ng/dL as the minimum detectable concentration of TT	40.6	4	35	4.4	Crude	NA

OUTCOME: DHEAS				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Exenatide + Dapagliflozin (DAPA) versus DAPA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021	mcg/dL	competitive binding immunoenzymatic assays with direct chemiluminometric technology (Beckman Coulter Access 2).	169	0.22	187	24	Crude	NA

OUTCOME: Metabolics: Fasting glucose				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): exanetide and dapa vs dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in**	**Mean (specify if median) or median in control /**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

				intervention / exposure group	**comparison group**	**comparison group**		
Elkin-Hirsch 2021	Mg/dl	glucose analyzer using the glucose oxidase method (Glucose Reagent Kit, Bayer).	87.5	1.9	93	2.1	Crude	NA

OUTCOME: Metabolics: HOMA- IR				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): exanetide and dapa vs dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021		was calculated using the equation: fasting insulin concentration (µIU/mL) × fasting glucose	2.6	0.55	3.4	0.6	Crude	NA

		concentration (mmol/L) 22.5						

OUTCOME: Matsuda index: sensitivity index (SI)			**OUTCOME TYPE:** Continuous					
COMPARISON (if applicable): Exenatide + Dapagliflozin (DAPA) versus DAPA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021		OGTT, Serum insulin was determined in all samples in duplicate by microparticle enzyme immunoassay (Abbott AxSYM System, Abbott Laboratories).	3.9	0.6	3.6	0.7	Crude	NA

OUTCOME: Total cholesterol				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Exenatide + Dapagliflozin (DAPA) versus DAPA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021	mg/dL		190	15	186	11	Crude	NA

OUTCOME: Lipids: LDL				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): exanetide and dapa vs dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	Mg/dl	calculated according to the Friedewald equation	115	9	113.5	10	Crude	NA

OUTCOME: Lipids: HDL					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): exanetide and dapa vs dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	Mg/dl	standard enzymatic colorimetric assays on an automated clinical chemistry analyzer	41	2	43	2.2	Crude	NA

OUTCOME: Triglycerides (TG)					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Exenatide + Dapagliflozin (DAPA) versus DAPA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

Elkind-Hirsch et al. 2021	mg/dL		112	12	132	13	Crude	NA

OUTCOME: Antropometric: weight				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): exanetide and dapa vs dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021*	kg		98	3.7	102.6	4	Crude	NA

OUTCOME: Antropometric: BMI				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): exanetide and dapa vs dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

Elkin-Hirsch 2021*	Kg/m2		36.7	1.1	37.4	1.2	Crude	NA

OUTCOME: Waist-to-hip ratio (WHR)				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Exenatide + Dapagliflozin (DAPA) versus DAPA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch et al. 2021		WC was measured at the narrowest level midway between the rib cage and the iliac crest and hip circumference measured at the widest level over the buttocks while the participants were in the standing position	0.86	0.016	0.79	0.017	Crude	NA

		using a flexible measuring tape.						

OUTCOME: Antropometric: WC				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): exanetide and dapa vs dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	cm	narrowest level midway between the rib cage and the iliac crest	105	3	101	3.2	Crude	NA

OUTCOME: Antropometric: fat free mass /lean BM				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): exanetide +dapa vs dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in**	**Mean (specify if median) or median in control /**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

				intervention / exposure group	**comparison group**	**comparison group**		
Elkin-Hirsch 2021	kg	Participants in hospital gowns were positioned in the supine position on the DXA table, and instructed to keep their arms separated from their trunk, hands placed flat on the table, palms facing down, away from their thighs adjacent to the side of the body, and their legs separated from one another	51.8	1.6	52.2	1.7	Crude	NA

OUTCOME: Antropometric: fat mass	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): exanetide +dapa vs dapa	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Elkin-Hirsch 2021*	kg	Participants in hospital gowns were positioned in the supine position on the DXA table, and instructed to keep their arms separated from their trunk, hands placed flat on the table, palms facing down, away from their thighs adjacent to the side of the body, and their legs separated from one another	44.9	2.4	47.8	2.6	Crude	NA

OUTCOME: Antropometric: % body fat					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): exanetide +dapa vs dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021*	%	Participants in hospital gowns were positioned in the supine position on the DXA table, and instructed to keep their arms separated from their trunk, hands placed flat on the table, palms facing down, away from their thighs adjacent to the side of the body, and their legs separated from one another	44.8	1.1	46.4	1.2	Crude	NA

Exenatide v Metformin

a. Exenatide v Metformin

Statistically significant between-group differences are marked with *

Sample sizes:

Zheng: EXE=31, MET=32

Tao: EXE=50, MET=50

OUTCOME: mFG score					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Exenatide versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Zheng et al. 2019 (Zheng et al. 2017)	NA		6.9	1.6	6.8	1.7	Crude	NA

OUTCOME: Free androgen index (FAI)	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Exenatide versus Metformin	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Zheng et al. 2019*	NA	FAI = T [nmol/L] × 100/SHBG [nmol/L]	7.28	2.54	7.66	2.73	Crude	NA
Tao et al. 2021			Median=7.74	IQR=4.90-12.60	Median=8.50	IQR=3.89-12.61	Crude	NA

OUTCOME: Total testosterone (T)				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Exenatide versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Zheng et al. 2019	nmol/L	Blood	1.75	0.78	1.91	1.12	Crude	NA
Tao et al. 2021	nmol/L	Liquid chromatography	Median=2.03	IQR=1.72-2.45	1.86	0.82	Crude	NA

		mass spectometry						

OUTCOME: SHBG				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): eg. Exenatide vs Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Zheng et al. 2019	Nmol/L	Blood	37.16	4.59	36.04	4.48	Crude	NA
Tao 2021	Nmol/L	Chemiluminescence (Elecsys Auto analyser, Roche, USA)	27.2 (Median)	19.4 – 35.5 (IQR)	23.15 (median)	15.88 – 35.28 (IQR)		

OUTCOME: Dehydroepiandronate sulfate (DHEAS)				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Exenatide versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI)**	**Mean (specify if median) or median in control /**	**SD (or specify if other measure: SE, IQR or 95%**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

				in intervention / exposure group	**comparison group**	**CI) in control/ comparison group**		
Zheng et al. 2019	µg/dL	Blood	265.86	10.60	268.61	10.44	Crude	NA
Tao et al. 2021	ng/ml	Chemiluminescence (Elecsys Auto analyser, Roche, USA)	Median=211.00	IQR=160.75-266.25	Median=246.00	IQR=230.00-302.25	Crude	NA

OUTCOME: Dehydroepiandronate sulfate (DHEAS) – Converted to µmol/L			**OUTCOME TYPE:** Continuous					
COMPARISON (if applicable): Exenatide versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Zheng et al. 2019	µg/dL	Blood	7.22	0.29	7.29	0.28	Crude	NA
Tao et al. 2021	ng/ml	Chemiluminescence (Elecsys Auto	Median=211.00	IQR=160.75-266.25	Median=246.00	IQR=230.00-302.25	Crude	NA

		analyser, Roche, USA)						

OUTCOME: Androstenedione				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Exenatide versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Tao et al. 2021	µg/ml	Chemiluminescence (Elecsys Auto analyser, Roche, USA)	Median=3.28	IQR=2.66- 3.71	Median=3.31	IQR=2.61- 3.37	Crude	NA

OUTCOME: Fasting glucose				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Exenatide versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

Zheng et al. 2019	mmol/L	Fasting venous blood	4.74	0.51	4.76	0.41	Crude	NA
Tao et al. 2021	mmol/L	Automatic analyser (Roche/Hitachi modular analytics D2400 and E170 module, Roche, USA)	4.85	0.08	4.74	0.07	Crude	NA

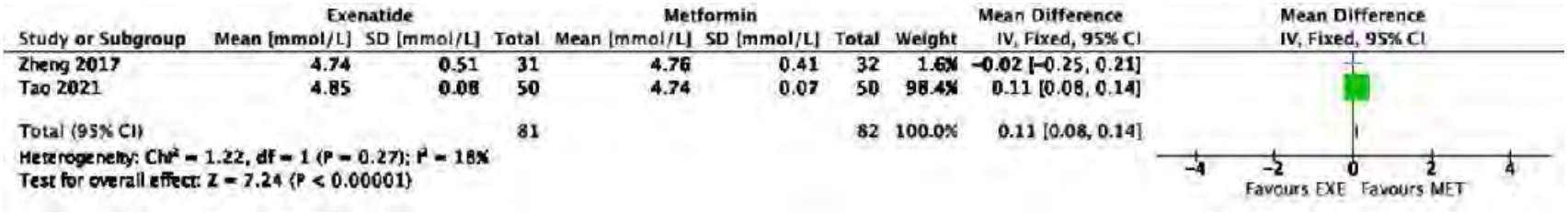


Figure 1 Forest plot: Exenatide v metformin - fasting glucose

OUTCOME: Fasting insulin (FINS)	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Exenatide versus Metformin	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Zheng et al. 2019	mU/L	Fasting venous blood	13.12	2.24	13.65	2.12	Crude	NA
Tao et al. 2021	mIU/L	Chemiluminescence (Elecsys Auto analyser, Roche, USA)	16.47	0.96	15.66	0.22	Crude	NA

OUTCOME: Fasting insulin (FINS) – converted to pmol/L					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Exenatide versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Zheng et al. 2019	Pmol/L	Fasting venous blood	78.72	13.44	81.90	12.72	Crude	NA
Tao et al. 2021	Pmol/L	Chemiluminescence (Elecsys Auto	98.82	5.76	93.96	1.32	Crude	NA

		analyser, Roche, USA)						

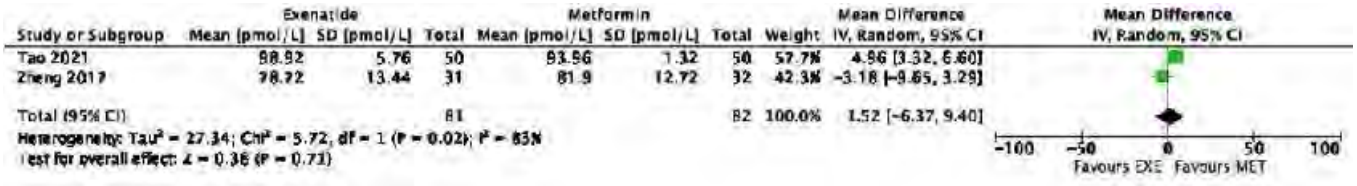


Figure 2 Forest plot: Exenatide v metformin - fasting insulin

OUTCOME: Homeostasis model assessment of insulin resistance (HOMA-IR)				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Exenatide versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Zheng et al. 2019	NA	The homeostasis model assessment of insulin resistance (HOMA-IR) =	2.68	1.09	2.91	1.11	Crude	NA

		fasting blood glucose (FBG) (mmol/L) × fasting insulin (FINS) (mU/L)/22.5.						
Tao et al. 2021	NA		4.13	0.55	3.36	0.24	Crude	NA

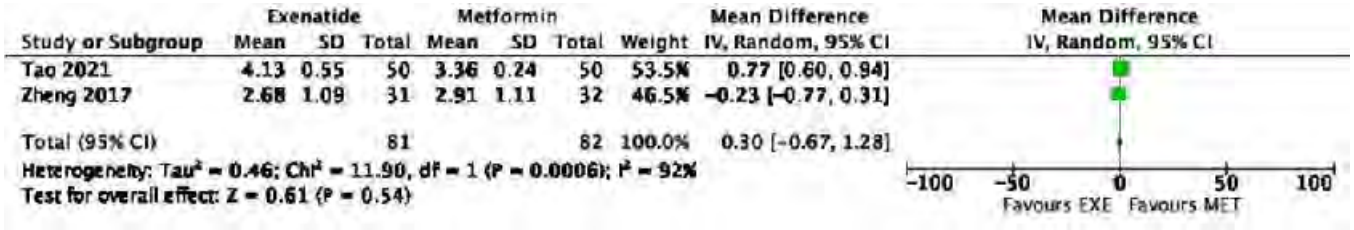


Figure 3 Forest plot:Exenatide v metformin - HOMA-IR

OUTCOME: 2-h post-glucose load plasma glucose (2hPBG)				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Exenatide versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

						comparison group		
Zheng et al. 2019*	mmol/L	OGTT 75g	6.21	0.46	5.76	1.15	Crude	NA

OUTCOME: 2-h postglucose load blood insulin (2hINS)					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Exenatide versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Zheng et al. 2019	mU/L	OGTT 75g	92.42	4.5	108.03	4.65	Crude	NA
Tao et al. 2021*	mIU/L	OGTT	127.06	11.81	85.17	6.47	Crude	NA

OUTCOME: 2hr-insulin (converted to pmol/L)	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): eg. Exenatide vs Metformin	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Zheng et al. 2019	Pmol/L	75g OGTT	554.52	121.68	648.18	129.96	Crude	NA
Tao 2021*	Pmol/L	75g OGTT	762.36	70.86	511.02	38.82	Crude	NA

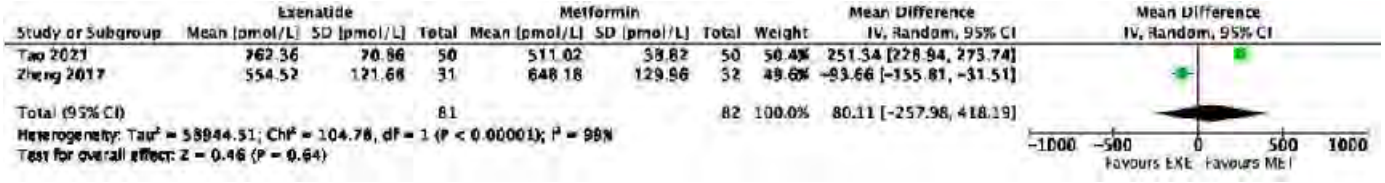


Figure 4 Forest plot: Exenatide v metformin - 2 hour insulin

OUTCOME: AUC glucose				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Exenatide versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in**	**Mean (specify if median) or median in control /**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

				intervention / exposure group	**comparison group**	**comparison group**		
Zheng et al. 2019	mmol/L × h	OGTT 75g	21.25	2.30	20.87	2.56	Crude	NA

OUTCOME: AUC insulin				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Exenatide versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Zheng et al. 2019*	mU/L × h	OGTT 75g	198.78	10.65	233.66	12.23	Crude	NA

OUTCOME: Insulin secretion index (Matsuda)				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): eg. Exenatide vs Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg,**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention**	**Mean (specify if median) or median in control /**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

	mmol/L, etc.)			**/ exposure group**	**comparison group**	**comparison group**		
Zheng et al. 2017*	NA	1/FINS (mU/L)*FBG(mmol/L)	0.017	0.007	0.016	0.007	Crude	NA

OUTCOME: Total cholesterol (TC)				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Exenatide versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Zheng et al. 2019*	mmol/L	Fasting venous blood	4.77	0.82	4.49	0.86	Crude	NA
Tao et al. 2021	mmol/L	Automatic analyser (Roche/Hitachi modular analytics D2400 and E170 module, Roche, USA)	Median=4.70	IQR=4.34, 4.94	Median=4.66	IQR=4.49- 4.76	Crude	NA

OUTCOME: Low-density lipoprotein cholesterol (LDL-C)				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Exenatide versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Zheng et al. 2019	mmol/L	Fasting venous blood	3.42	1.05	3.37	1.07	Crude	NA
Tao et al. 2021	mmol/L	Automatic analyser (Roche/Hitachi modular analytics D2400 and E170 module, Roche, USA)	Median=2.71	IQR= 2.33- 3.03	Median=2.52	IQR=2.21- 2.59	Crude	NA

OUTCOME: High-density lipoprotein cholesterol (HDL-C)				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Exenatide versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in**	**Mean (specify if median) or median in control /**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

				intervention / exposure group	**comparison group**	**comparison group**		
Zheng et al. 2019	mmol/L	Fasting venous blood	1.27	0.66	1.43	0.52	Crude	NA
Tao et al. 2021	mmol/L	Automatic analyser (Roche/Hitachi modular analytics D2400 and E170 module, Roche, USA)	Median=1.19	IQR=1.03-1.27	Median=1.24	IQR=1.18- 1.28	Crude	NA

OUTCOME: Triglycerides (TG)				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Exenatide versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Zheng et al. 2019	mmol/L	Fasting venous blood	1.51	0.92	1.53	0.84	Crude	NA
Tao et al. 2021	mmol/L	Automatic analyser	Median=1.26	IQR=0.93- 1.52	Median=1.38	IQR=1.26-1.44)	Crude	NA

		(Roche/Hitachi modular analytics D2400 and E170 module, Roche, USA)						

OUTCOME: Highly sensitive C-reactive protein (hs-CRP)				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Exenatide versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Zheng et al. 2019*	mg/L	Fasting venous blood	1.61	1.21	1.93	0.86	Crude	NA

OUTCOME: Weight				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Exenatide versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in**	**Mean (specify if median) or median in control /**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

				intervention / exposure group	**comparison group**	**comparison group**		
Zheng et al. 2019	kg		66.64	3.76	68.49	3.50	Crude	NA
Tao et al. 2021	kg		Median=74.55	IQR=68.00-85.25	Median=76.00	IQR=68.50-82.00	Crude	NA

OUTCOME: BMI				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Exenatide versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Zheng et al. 2019	kg/m2		26.12	2.28	27.27	3.50	Crude	NA
Tao et al. 2021	kg/m2		Median=28.46	IQR=25.69-31.37	Median=28.19	IQR=25.91-30.86	Crude	NA

OUTCOME: Waist-to-hip ratio (WHR)

OUTCOME TYPE: Continuous			**COMPARISON (if applicable):** Exenatide versus Metformin					
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Zheng et al. 2019	NA	NA	0.86	0.30	0.87	0.28	Crude	NA

OUTCOME: Waist circumference (WC)			**OUTCOME TYPE:** Continuous					
COMPARISON (if applicable): Exenatide versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Zheng et al. 2019	cm	Tape measure	85.16	3.63	90.52	3.30	Crude	NA

OUTCOME: Menstrual regularity (menstrual periods/year)	**OUTCOME TYPE:** Continuous

COMPARISON (if applicable): Exenatide versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Zheng et al. 2019 (Zheng et al. 2017)	times/yr		6.52	2.27	6.17	2.17	Crude	NA

b. Exenatide + oral contraceptive pill v Metformin + oral contraceptive pill

Statistically significant between-group differences are marked with *

Sample size:

Non-pregnancy outcomes: EXE=78, MET=80

Pregnancy outcomes: EXE=72, MET=75

OUTCOME: Fasting glucose							**OUTCOME TYPE:** Continuous	
COMPARISON (if applicable): EXE + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

						comparison group		
Liu et al. 2017	mmol/L	Standard glucose oxidase means (Beckman Coulter Glucose Analyser, Beckman Coulter Inc, Fullerton, CA, USA)	4.98	0.44	4.85	0.38	Crude	NA

OUTCOME: Fasting insulin (FINS)					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): EXE + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Liu et al. 2017*	mU/L	IRMA (Bio Source Europe SA, Nivelles, Belgium)	12.12	4.24	13.47	4.24	Crude	NA

OUTCOME: Fasting insulin (FINS) – converted to pmol/L				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): EXE + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Liu et al. 2017*	Pmol/L	Fasting venous blood	72.72	25.44	80.82	25.44	Crude	NA

OUTCOME: Homeostasis model assessment of insulin resistance (HOMA-IR)				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): EXE + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Liu et al. 2017*	NA		2.92	1.31	3.30	1.00	Crude	NA

OUTCOME: 2-h post-glucose load plasma glucose (2hPBG)				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): EXE + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Liu et al. 2017*	mmol/L	OGTT 75g	7.12	1.15	7.37	1.04	Crude	NA

OUTCOME: 2-h postglucose load blood insulin (2hINS)				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): EXE + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Liu et al. 2017*	mU/L	OGTT 75g	76.93	67.03	104.39	37.02	Crude	NA

OUTCOME: 2hr-insulin (converted to pmol/L)	**OUTCOME TYPE:** Continuous

COMPARISON (if applicable): eg. Exenatide vs Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Liu 2017	Pmol/L	75g OGTT	461.58	402.18	626.34	222.12	Crude	NA

OUTCOME: Total cholesterol (TC)					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): EXE + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Liu et al. 2017	mmol/L	Fasting venous blood	4.70	0.86	4.62	0.89	Crude	NA

OUTCOME: Low-density lipoprotein cholesterol (LDL-C)	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): EXE + OCP vs MET + OCP	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Liu et al. 2017	mmol/L	Fasting venous blood	2.79	0.97	2.69	0.83	Crude	NA

OUTCOME: High-density lipoprotein cholesterol (HDL-C)				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): EXE + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Liu et al. 2017	mmol/L	Fasting venous blood	1.32	0.33	1.35	0.23	Crude	NA

OUTCOME: Triglycerides (TG)	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): EXE + OCP vs MET + OCP	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Liu et al. 2017	mmol/L	Fasting venous blood	1.78	0.81	1.34	0.43	Crude	NA

OUTCOME: Highly sensitive C-reactive protein (hs-CRP)				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): EXE + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Liu et al. 2017*	mg/L	Fasting venous blood	2.30	1.34	3.23	1.49	Crude	NA

OUTCOME: Weight	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): EXE + OCP vs MET + OCP	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Liu et al. 2017*	kg		68.66	9.66	68.17	4.56	Crude	NA

OUTCOME: BMI					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): EXE + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Liu et al. 2017*	kg/m2		26.04	3.52	27.20	1.80	Crude	NA

OUTCOME: Waist-to-hip ratio (WHR) **OUTCOME TYPE:** Continuous
COMPARISON (if applicable): EXE + OCP vs MET + OCP

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Liu et al. 2017	NA	NA	0.87	0.07	0.89	0.05	Crude	NA

OUTCOME: Waist circumference (WC)					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): EXE + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Liu et al. 2017*	cm	Tape measure	83.92	9.72	84.44	5.27	Crude	NA

OUTCOME: Body fat percentage	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): EXE + OCP vs MET + OCP	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Liu et al. 2017*	%	DEXA	39.37	3.71	40.14	2.99	Crude	NA

OUTCOME: Menstrual frequency					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): EXE + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Liu et al. 2017*	Ratio of actual menses to expected menses (expected = 12 periods in 52 weeks)		0.90	0.13	0.68	0.03	Crude	NA

iii. Exenatide + Metformin v Metformin alone

a. Exenatide + Metformin v Metformin

Sample sizes: EXE+MET=50, MET=50

OUTCOME: Free androgen index (FAI)				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Exenatide + Metformin versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Tao et al. 2021			Median= 10.44	IQR= 6.41-13.87	Median= 8.50	IQR= 3.89-12.61	Crude	NA

OUTCOME: Total testosterone (T)				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Exenatide + Metformin versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Tao et al. 2021	nmol/L		Median= 1.89	IQR= 1.39-2.69	1.86	0.82	Crude	NA

OUTCOME: Sex hormone binding globulin (SHBG)				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Exenatide + Metformin versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Tao et al. 2021	nmol/L		Median= 24.07	IQR= 18.10-29.70	Median= 23.15	IQR= 15.88-35.28	Crude	NA

OUTCOME: Dehydroepiandrosterone (DHEAS)				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Exenatide + Metformin versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Tao et al. 2021	ng/ml		Median= 234.50	IQR= 201.00-291.25	Median= 246.00	IQR= 230.00-302.25	Crude	NA

OUTCOME: Androstenedione (A2)				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Exenatide + Metformin versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Tao et al. 2021	µg/dL		Median= 2.66	IQR= 2.23-3.76	Median= 3.31	IQR= 2.61-3.37	Crude	NA

OUTCOME: Fasting plasma glucose (FBG)				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Exenatide + Metformin versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Tao et al. 2021	mmol/L		5.10	0.10	4.74	0.07	Crude	NA

OUTCOME: Fasting insulin

OUTCOME TYPE: Continuous								
COMPARISON (if applicable): Exenatide + Metformin versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Tao et al. 2021	mIU/L		18.69	1.66	15.66	0.22	Crude	NA

OUTCOME: Fasting insulin (converted to pmol/L)			**OUTCOME TYPE:** Continuous					
COMPARISON (if applicable): Exenatide + Metformin versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Tao et al. 2021	Pmol/L		112.14	9.96	93.96	1.32	Crude	NA

OUTCOME: HOMA-IR				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Exenatide + Metformin versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Tao et al. 2021			4.26	0.41	3.36	0.24	Crude	NA

OUTCOME: 120min glucose from OGTT				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Exenatide + Metformin versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Tao et al. 2021	mmol/L	75g OGTT	2.25	0.17	3.02	0.21	Crude	NA

OUTCOME: 120min insulin from OGTT	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Exenatide + Metformin versus Metformin	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Tao et al. 2021*	mIU/L	75g OGTT	120.85	12.02	85.17	6.47	Crude	NA

OUTCOME: Total cholesterol (TC)				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Exenatide + Metformin versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Tao et al. 2021	mmol/L		Median= 4.60	IQR= 4.31-5.21	Median= 4.66	IQR= 4.49-4.76	Crude	NA

OUTCOME: LDL	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): eg. EXE + MET vs MET	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Tao 2021*	mmol/L	Fasting venous blood	2.81(Median)	2.51 – 3.21 (IQR)	2.52 (Median)	2.21 – 2.59 (IQR)	Crude	NA

OUTCOME: High-density lipoprotein (HDL)					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Exenatide + Metformin versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Tao et al. 2021	mmol/L		Median= 1.12	IQR= 0.99-1.24	Median= 1.24	IQR= 1.18-1.28	Crude	NA

OUTCOME: Triglyceride (TG)	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Exenatide + Metformin versus Metformin	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Tao et al. 2021	mmol/L		Median= 1.19	IQR= 1.04-1.80	Median= 1.38	IQR= 1.26-1.44	Crude	NA

OUTCOME: Weight				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Exenatide + Metformin versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Tao et al. 2021	kg		76.65	13.18	Median=76.00	IQR= 68.50-82.00	Crude	NA

OUTCOME: BMI	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Exenatide + Metformin versus Metformin	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Tao et al. 2021	kg/m2		29.17	4.80	Median= 28.19	IQR= 25.91-30.86	Crude	NA

b. Exenatide + Metformin + oral contraceptive pill v Metformin + oral contraceptive pill

Sample sizes: EXE+MET=19, MET=21

OUTCOME: Total testosterone (T)					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Exenatide + MET + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Ma et al. 2021*	ng/mL		0.57	0.25	0.56	0.20	Crude	NA

OUTCOME: Dehydroepiandrosterone (DHEAS)	**OUTCOME TYPE:** Continuous

COMPARISON (if applicable): Exenatide + MET + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Ma et al. 2021	µg/dL		261.60	133.86	261.55	120.16	Crude	NA

OUTCOME: Fasting plasma glucose (FBG)					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Exenatide + MET + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Ma et al. 2021*	mmol/L		4.93	0.47	5.19	0.51	Crude	NA

OUTCOME: Fasting insulin **OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Exenatide + MET + OCP vs MET + OCP

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Ma et al. 2021	µIU/mL		23.0	10.16	21.81	8.26	Crude	NA

OUTCOME: HOMA-IR					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Exenatide + MET + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Ma et al. 2021			Median=4.70	IQR= 4.20–6.21	Median=4.80	IQR=3.47–6.39	Crude	NA

OUTCOME: QUICKI	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Exenatide + MET + OCP vs MET + OCP	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Ma et al. 2021			Median=0.30	IQR= 0.29–0.31	Median=0.30	IQR= 0.29–0.32	Crude	NA

OUTCOME: 120min glucose from OGTT				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Exenatide + MET + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Ma et al. 2021	Mmol/L	75g OGTT	6.66	1.41	8.54	1.74	Crude	NA

OUTCOME: 120min insulin from OGTT	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Exenatide + MET + OCP vs MET + OCP	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Ma et al. 2021*	µIU/mL	75g OGTT	124.82	82.54	131.71	61.96	Crude	NA

OUTCOME: Matsuda index					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Exenatide + MET + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Ma et al. 2021*			Median=1.92	IQR=1.44–2.47	Median=1.81	IQR=1.42–2.76	Crude	NA

OUTCOME: Total cholesterol (TC)	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Exenatide + MET + OCP vs MET + OCP	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Ma et al. 2021*	mmol/L		5.13	0.99	5.64	0.88	Crude	NA

OUTCOME: LDL					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): eg. EXE + MET vs MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Ma 2021	Mmol/L	Fasting venous blood	2.98	0.83	3.37	0.78	Crude	NA

OUTCOME: High-density lipoprotein (HDL)	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Exenatide + MET + OCP vs MET + OCP	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Ma et al. 2021	mmol/L		1.44	0.34	1.45	0.36	Crude	NA

OUTCOME: Triglyceride (TG)					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Exenatide + MET + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Ma et al. 2021*	mmol/L		Median=2.0	IQR=1.59–3.20	Median= 2.46	IQR= 1.56–3.61	Crude	NA

OUTCOME: hsCRP	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Exenatide + MET + OCP vs MET + OCP	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Ma et al. 2021	mg/L		Median=4.18	IQR=1.74–9.99	Median= 2.57	IQR= 2.18–5.30	Crude	NA

OUTCOME: Weight					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Exenatide + MET + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Ma et al. 2021*	kg		78.57	10.94	77.05	9.75	Crude	NA

OUTCOME: BMI	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Exenatide + MET + OCP vs MET + OCP	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Ma et al. 2021*	kg/m2		29.40	3.32	29.63	2.80	Crude	NA

OUTCOME: Waist circumference (WC)				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Exenatide + MET + OCP vs MET + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Ma et al. 2021*	cm		92.70	8.71	94.98	8.13	Crude	NA

iv. Exenatide v Phentermine/Topiramate

Sample sizes: EXE=20, PT=16

OUTCOME: Androgenicity:FAI					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): exanetide vs Phentermine/Topiramate								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021		competitive binding immunoenzymatic assays with direct chemiluminometric technology (Beckman Coulter Access 2).	5.3	0.72	5.0	0.8	Crude	NA

OUTCOME: Androgenicity: Total testosterone					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): exanetide vs Phentermine/Topiramate								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention**	**Mean (specify if median) or median in control /**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

				/ exposure group	**comparison group**	**comparison group**		
Elkin-Hirsch 2021	Ng/dl	SHBG: TT concentration was measured with an automated chemiluminescent microparticle immunoassay, the Architect second-generation testosterone assay (Abbott Diagnostics) with 5 ng/dL as the minimum detectable concentration of TT	38.8	4	45.5	4.5	Crude	NA

OUTCOME: Androgenicity DHEAS				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): exanetide vs Phentermine/Topiramate								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

Elkin-Hirsch 2021	Mcg/dL	competitive binding immunoenzymatic assays with direct chemiluminometric technology (Beckman Coulter Access 2).	165	22	201	24	Crude	NA

OUTCOME: Metabolics: Fasting glucose				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): exanetide vs Phentermine/Topiramate								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	Mg/dl	glucose analyzer using the glucose oxidase method (Glucose Reagent Kit, Bayer).	91	1.9	91.4	2.2	Crude	NA

OUTCOME: Metabolics: HOMA- IR	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): exanetide vs Phentermine/Topiramate	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Elkin-Hirsch 2021		was calculated using the equation: fasting insulin concentration (µIU/mL) × fasting glucose concentration (mmol/L) 22.5	3.5	0.55	3.2	0.62	Crude	NA

OUTCOME: Metabolics: Matsuda Index SI OGTT					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): exanetide vs Phentermine/Topiramate								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021		Serum insulin was determined in all samples in duplicate by microparticle	3.16	0.6	4.7	0.7	Crude	NA

		enzyme immunoassay (Abbott AxSYM System, Abbott Laboratories).						

OUTCOME: Lipids: Tot cholesterol				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): exanetide vs Phentermine/Topiramate								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	Mg/dl	standard enzymatic colorimetric assays on an automated clinical chemistry analyzer	189	10	178	12	Crude	NA

OUTCOME: Lipids: LDL	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): exanetide vs Phentermine/Topiramate	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Elkin-Hirsch 2021	Mg/dl	calculated according to the Friedewald equation	119	9	105	16	Crude	NA

OUTCOME: Lipids: HDL					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): exanetide vs Phentermine/Topiramate								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	Mg/dl	standard enzymatic colorimetric assays on an automated clinical chemistry analyzer	42.5	2	44	2.3	Crude	NA

OUTCOME: Lipids: TG				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): exanetide vs Phentermine/Topiramate								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	Mg/dl	standard enzymatic colorimetric assays on an automated clinical chemistry analyzer	130	12	110	13	Crude	na

OUTCOME: Antropometric: weight				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): exanetide vs Phentermine/Topiramate								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

Elkin-Hirsch 2021	kg		100.4	3.7	97	4.1	Crude	NA

OUTCOME: Antropometric: BMI				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): exanetide vs Phentermine/Topiramate								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	Kg/m2		37.3	1.1	35.3	1.3	Crude	NA

OUTCOME: Antropometric: WHR				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): exanetide vs Phentermine/Topiramate								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

Elkind-Hirsch et al. 2021		WC was measured at the narrowest level midway between the rib cage and the iliac crest and hip circumference measured at the widest level over the buttocks while the participants were in the standing position using a flexible measuring tape.	0.825	0.016	0.81	0.018	Crude	NA

OUTCOME: Antropometric: WC				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): exanetide vs Phentermine/Topiramate								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	Cm	narrowest level midway between the rib cage and the iliac crest	104	3	101	3.2	Crude	NA

OUTCOME: Antropometric: fat free mass /lean BM				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): exanetide vs Phentermine/Topiramate								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	kg	Participants in hospital gowns were positioned in the supine position on the DXA table, and instructed to keep their arms separated from their trunk, hands placed flat on the table, palms facing down, away from their thighs adjacent to the side of the body, and their legs separated from one another	52.3	1.6	51.7	1.8	Crude	NA

OUTCOME: Antropometric: fat mass					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): exanetide vs Phentermine/Topiramate								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	kg	Participants in hospital gowns were positioned in the supine position on the DXA table, and instructed to keep their arms separated from their trunk, hands placed flat on the table, palms facing down, away from their thighs adjacent to the side of the body, and their legs separated from one another	47.6	2.4	44.5	2.8	Crude	NA

OUTCOME: Antropometric: % body fat					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): exanetide vs Phentermine/Topiramate								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021		Participants in hospital gowns were positioned in the supine position on the DXA table, and instructed to keep their arms separated from their trunk, hands placed flat on the table, palms facing down, away from their thighs adjacent to the side of the body, and their legs separated from one another	46.1	1.1	45.2	1.2	Crude	NA

v. Exenatide v Dapagliflozin + Metformin

Sample sizes: EXE=20, DAPA + MET=19

OUTCOME: Androgenicity:FAI					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): exanetide vs DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021		competitive binding immunoenzymatic assays with direct chemiluminometric technology (Beckman Coulter Access 2).	5.3	0.72	5.7	0.74	Crude	NA

OUTCOME: Androgenicity: Total testosterone					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): exanetide vs DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI)**	**Mean (specify if median) or median in control /**	**SD (or specify if other measure: SE, IQR or 95%**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

				in intervention / exposure group	comparison group	CI) in control/ comparison group		
Elkin-Hirsch 2021	Ng/dl	SHBG: TT concentration was measured with an automated chemiluminescent microparticle immunoassay, the Architect second-generation testosterone assay (Abbott Diagnostics) with 5 ng/dL as the minimum detectable concentration of TT	38.8	4	39.5	4.1	Crude	NA

OUTCOME: Androgenicity DHEAS				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): exanetide vs DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

Elkin-Hirsch 2021	Mcg/dL	competitive binding immunoenzymatic assays with direct chemiluminometric technology (Beckman Coulter Access 2).	165	22	189	23	Crude	NA

OUTCOME: Metabolics: Fasting glucose				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): exanetide vs DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	Mg/dl	glucose analyzer using the glucose oxidase method (Glucose Reagent Kit, Bayer).	91	1.9	89	2.0	Crude	NA

OUTCOME: Metabolics: HOMA- IR	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): exanetide vs DAPA + MET	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Elkin-Hirsch 2021		was calculated using the equation: fasting insulin concentration (µIU/mL) × fasting glucose concentration (mmol/L) 22.5	3.5	0.55	3.3	0.57	Crude	NA

OUTCOME: Metabolics: Matsuda Index SI OGTT			**OUTCOME TYPE:** Continuous					
COMPARISON (if applicable): exanetide vs DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021		Serum insulin was determined in all samples in duplicate by microparticle	3.16	0.6	4.8	0.6	Crude	NA

		enzyme immunoassay (Abbott AxSYM System, Abbott Laboratories).						

OUTCOME: Lipids: Tot cholesterol					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): exanetide vs DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	Mg/dl	standard enzymatic colorimetric assays on an automated clinical chemistry analyzer	189	10	192	11	Crude	NA

OUTCOME: Lipids: LDL	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): exanetide vs DAPA + MET	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Elkin-Hirsch 2021	Mg/dl	calculated according to the Friedewald equation	119	9	121	9.5	Crude	NA

OUTCOME: Lipids: HDL					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): exanetide vs DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	Mg/dl	standard enzymatic colorimetric assays on an automated clinical chemistry analyzer	42.5	2	45	2	Crude	NA

OUTCOME: Lipids: TG				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): exanetide vs DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	Mg/dl	standard enzymatic colorimetric assays on an automated clinical chemistry analyzer	130	12	105	12	Crude	na

OUTCOME: Antropometric: weight				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): exanetide vs DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

Elkin-Hirsch 2021	kg		100.4	3.7	101.2	3.8	Crude	NA

OUTCOME: Antropometric: BMI				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): exanetide vs DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	Kg/m2		37.3	1.1	37	1.2	Crude	NA

OUTCOME: Antropometric: WHR				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): exanetide vs DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

Elkind-Hirsch et al. 2021		WC was measured at the narrowest level midway between the rib cage and the iliac crest and hip circumference measured at the widest level over the buttocks while the participants were in the standing position using a flexible measuring tape.	0.825	0.016	0.83	0.016	Crude	NA

OUTCOME: Antropometric: WC				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): exanetide vs DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	Cm	narrowest level midway between the rib cage and the iliac crest	104	3	101.3	3	Crude	NA

OUTCOME: Antropometric: fat free mass /lean BM					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): exanetide vs DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	kg	Participants in hospital gowns were positioned in the supine position on the DXA table, and instructed to keep their arms separated from their trunk, hands placed flat on the table, palms facing down, away from their thighs adjacent to the side of the body, and their legs separated from one another	52.3	1.6	52.9	1.6	Crude	NA

OUTCOME: Antropometric: fat mass					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): exanetide vs DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	kg	Participants in hospital gowns were positioned in the supine position on the DXA table, and instructed to keep their arms separated from their trunk, hands placed flat on the table, palms facing down, away from their thighs adjacent to the side of the body, and their legs separated from one another	47.6	2.4	48	2.5	Crude	NA

OUTCOME: Antropometric: % body fat					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): exanetide vs DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021		Participants in hospital gowns were positioned in the supine position on the DXA table, and instructed to keep their arms separated from their trunk, hands placed flat on the table, palms facing down, away from their thighs adjacent to the side of the body, and their legs separated from one another	46.1	1.1	46.1	1.1	Crude	NA

2. Liraglutide

i. Liraglutide v placebo

a. Liraglutide v placebo

Sample sizes: LIRA 44, Placebo 21 unless otherwise stated

OUTCOME: Androgenicity: FAI					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Liraglutide vs Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Nylander 2017		Total testosterone x 100 / SHBG	Difference at week 26 –1.34	Difference at week 26 (95% CI) (–2.19 to −0.48)	Difference at week 26 0.80	Difference at week 26 (95% CI) (–0.42 to 2.01)	Crude	na

OUTCOME: Androgenicity: Free Testosterone	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Liraglutide vs Placebo	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Nylander 2017*	nmol/L	Determined using liquid chromatography and double mass spectrometry (UPLC-MSMS TQ-S System, Waters Corporation, Milford, MA, USA), with inter-assay coefficients of variability 12% or less for all.	Difference at week 26 –0.005	Difference at week 26 (95% CI) (–0.009 to −0.001)	Difference at week 26 0.004	Difference at week 26 (95% CI) (–0.003 to 0.011)	Crude	NA

*p=0.05

OUTCOME: Androgenicity: Tot Testosterone	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Liraglutide vs Placebo	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Nylander 2017	nmol/L	Determined using liquid chromatography and double mass spectrometry (UPLC-MSMS TQ-S System, Waters Corporation, Milford, MA, USA), with inter-assay coefficients of variability 12% or less for all.	Difference at week 26 –0.07	Difference at week 26 (95% CI) (–0.25 to 0.10)	Difference at week 26 0.15	Difference at week 26 (95% CI) (–0.10 to 0.39)	Crude	NA

OUTCOME: Androgenicity: SHBG					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Liraglutide vs Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention**	**Mean (specify if median) or median in control /**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

				/ exposure group	comparison group	comparison group		
Nylander 2017*	nmol/L	Measured using a sandwich chemiluminescence immunometric method (Immulite 2000, Siemens Healthcare GmbH, Erlangen, Germany) with inter-assay coefficients of variability less than 7%	Difference at week 26 7.4	Difference at week 26 (95% CI) (4.1 to 10.7)	Difference at week 26 2.0	Difference at week 26 (95% CI) (–2.9 to 7.0)	Crude	NA

*p<0.05

OUTCOME: Androgenicity: androstenedione				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide vs Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

Nylander 2017	nmol/L	Determined using liquid chromatography and double mass spectrometry (UPLC-MSMS TQ-S System, Waters Corporation, Milford, MA, USA), with inter-assay coefficients of variability 12% or less for all.	Difference at week 26 –0.69	Difference at week 26 (95% CI) (–1.44 to 0.06)	Difference at week 26 0.76	Difference at week 26 (95% CI) (–0.39 to 1.92)	Crude	NA

OUTCOME: Fasting glucose				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide vs Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Nylander 2017*	mM	"in-house routine analysis"	"Mean reduction of 0.24mM (95% CI 0.05 to 0.43) in the LIRA group compared to placebo"				Crude	NA

OUTCOME: hsCRP				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide vs Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Nylander 2017	mg/L		Difference at week 26 0.85 (n=42) *missing 3 from baseline ratio from logarithmic transformed numbers	Difference at week 26 (95% CI) (0.70–1.03) (n=42) *missing 3 from baseline ratio from logarithmic transformed numbers	Difference at week 26 0.75 (n=18) *missing 2 from baseline ratio from logarithmic transformed numbers	Difference at week 26 (95% CI) (0.43–1.30) (n=18) *missing 2 from baseline ratio from logarithmic transformed numbers	Crude	NA

OUTCOME: Metabolic: Matsuda/ISOGTT				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide vs Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Frøssing 2018			Difference at week 26 0.41	Difference at week 26 0.19	Difference at week 26 0.34	Difference at week 26 0.24	Crude	NA

OUTCOME: Total cholesterol				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide vs Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in**	**Mean (specify if median) or median in control /**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

				intervention / exposure group	**comparison group**	**comparison group**		
Frossing 2018	nmol/L		Difference at week 26 0.03	Difference at week 26 0.09	Difference at week 26 0.08	Difference at week 26 0.09	Crude	NA

OUTCOME: LDL cholesterol					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Liraglutide vs Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Frøssing 2018	nmol/L		Difference at week 26 0.14	Difference at week 26 0.09	Difference at week 26 0.13	Difference at week 26 0.09	Crude	NA

OUTCOME: HDL cholesterol				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide vs Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Frøssing 2018	nmol/L		Difference at week 26 −0.01	Difference at week 26 0.02	Difference at week 26 0.01	Difference at week 26 0.03	Crude	NA

OUTCOME: Triglyceride				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide vs Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

Frøssing 2018	nmol/L		Difference at week 26 median (IQR) −0.22	Difference at week 26 (95% CI) (−0.36 to −0.09)	Difference at week 26 median (IQR) −0.11	Difference at week 26 (95% CI) (−0.37 to 0.14)	Crude	NA

OUTCOME: Anthropometrics: weight				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide vs Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Frøssing 2018*	Kg	Assessed in light clothing, after overnight fasting.	Difference at week 26 −5.2	Difference at week 26 0.7	Difference at week 26 0.2	Difference at week 26 0.9	Crude	NA

OUTCOME: Anthropometrics: BMI	**OUTCOME TYPE:** Continuous

COMPARISON (if applicable): Liraglutide vs Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Frøssing 2018*	kg/m2 (change in)		Difference at week 26 −1.9	Difference at week 26 0.3	Difference at week 26 0.1	Difference at week 26 0.3	Crude	NA

OUTCOME: Anthropometrics: WHR			**OUTCOME TYPE:** Continuous					
COMPARISON (if applicable): Liraglutide vs Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Frøssing 2018*	**CHANGE in WHR**		Difference at week 26	Difference at week 26	Difference at week 26	Difference at week 26	Crude	NA

			0.01	0.01	0.04	0.01		

OUTCOME: Anthropometrics: WC				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide vs Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Frøssing 2018*	cm	Waist circumference was measured by a single observer in a standardized way: half way between the 12th rib and the anterior superior iliac spine.	Difference at week 26 –4.1	Difference at week 26 1.1	Difference at week 26 1.1	Difference at week 26 1.5	Crude	NA

OUTCOME: Anthropometrics: Fat free mass/lean body mass	**OUTCOME TYPE:** Continuous

COMPARISON (if applicable): Liraglutide vs Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Frøssing 2018*	Kg Change	DXA	Difference at week 26 −2.4	Difference at week 26 0.4	Difference at week 26 Median (p25-75) 0.1	Difference at week 26 [95% CI] 0.4	Crude	NA

OUTCOME: Fat mass				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide vs Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

Frøssing 2018*	Kg	DXA	Difference at week 26 −2.6	Difference at week 26 0.5	Difference at week 26 0.3	Difference at week 26 0.7	Crude	NA

OUTCOME: Anthropometrics: % body fat					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Liraglutide vs Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Frøssing 2018	**Change in %**	DXA	Difference at week 26 −0.9	Difference at week 26 0.34	Difference at week 26 −0.03	Difference at week 26 0.4	Crude	NA

OUTCOME: Mense/year				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide vs Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Nylander 2017*- not complete data	Bleeding ratio difference at week 26	Bleeding ratio was defined as number of menstrual bleedings divided by study period (months). A bleeding ratio of 1.0 corresponds to six menses in six months, i.e. a cycle length of 30.4 days. A cycle length of 35 days corresponds to a bleeding ratio of 0.87 (365 days/35 days/month)/12 months = 0.87).	Difference at week 26 0.28 *missing 2	Difference at week 26 (95% CI) (0.20 to 0.36) *missing 2	Difference at week 26 0.14 *missing 3	Difference at week 26 (95% CI) (0.02 to 0.26) *missing 3	Crude	NA

b. Liraglutide + Lifestyle v Placebo + Lifestyle

Sample size: LIRA + LS=44, Placebo + LS=23

OUTCOME: Androgenicity: FAI					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Liraglutide + lifestyle vs Placebo + lifestyle								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch 2022*		Calculated from the TT concentration (nmol/L) and concentration of SHBG (nM/L)x100 SHBG was analyzed using competitive binding immunoenzymatic assays with direct chemiluminometric technology (Beckman Coulter	5.98	SEM 0.6	6.4	SEM 0.75	Crude	NA

		Access 2, Brea CA). TT levels were measured with an automated chemiluminescent micro-particle immunoassay, the Architect second-generation testosterone assay (Abbott Diagnostics, Abbott Park, IL) with 5 ng/dL as the minimum detectable concentration of TT.						

OUTCOME: Androgenicity: Tot Testosterone				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide + lifestyle vs Placebo + lifestyle								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

						comparison group		
Elkind-Hirsch 2022	ng/dl	TT levels were measured with an automated chemiluminescent microparticle immunoassay, the Architect second-generation testosterone assay (Abbott Diagnostics, Abbott Park, IL) with 5 ng/dL as the minimum detectable concentration of TT.	45.4	SEM 3	46.8	SEM 4.1	Crude	NA

OUTCOME: Androgenicity: DHEAS	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Liraglutide + lifestyle vs Placebo + lifestyle	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Elkind-Hirsch 2022	Mcg/dl	competitive binding immunoenzymatic assays with direct chemiluminometric technology (Beckman Coulter Access 2, Brea CA).	177.1	SEM 14.2	171.3	SEM 16.8	Crude	NA

OUTCOME: Metabolic: fasting Glucose				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide + lifestyle vs Placebo + lifestyle								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch 2022*	mg/dL	Plasma glucose levels were determined using	90.2	SEM 1.3	94.3	SEM 2.2	Crude	NA

		the glucose oxidase method (Glucose Reagent Kit, Bayer Newbury, UK).						

OUTCOME: Metabolic: HOMA IR				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide + lifestyle vs Placebo + lifestyle								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch 2022*		Plasma glucose levels were determined using the glucose oxidase method (Glucose Reagent Kit, Bayer Newbury, UK). Serum insulin was quantified by microparticle	4.1	SEM 0.6	5.2	SEM 1.1	Crude	NA

		enzyme immunoassay (Abbott AxSYM System, Abbott Laboratories, Abbott Park, IL).						

*p=0.05

OUTCOME: Metabolic: Matsuda/IS_{OGTT}				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide + lifestyle vs Placebo + lifestyle								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch 2022*		Plasma glucose levels were determined using the glucose oxidase method (Glucose Reagent Kit, Bayer Newbury, UK).	3.7	SEM 0.4	3	SEM 0.5	Crude	NA

		Serum insulin was quantified by microparticle enzyme immunoassay (Abbott AxSYM System, Abbott Laboratories, Abbott Park, IL). OGTT-stimulated concentrations of glucose and insulin such as Matsuda's insulin sensitivity index (SIOGTT)						

OUTCOME: Total cholesterol				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide + lifestyle vs Placebo + lifestyle								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in**	**Mean (specify if median) or median in control /**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

				intervention / exposure group	**comparison group**	**comparison group**		
Elkind-Hirsch 2022	mg/dL	Measured on an automated clinical chemistry analyzer	176	SEM 5.3	178	SEM 8.8	Crude	NA

OUTCOME: LDL cholesterol				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide + lifestyle vs Placebo + lifestyle								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch 2022	mg/dL	measured on an automated clinical chemistry analyzer	113.4	SEM 5	112.4	SEM 8.2	Crude	NA

OUTCOME: HDL cholesterol					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Liraglutide + lifestyle vs Placebo + lifestyle								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch 2022	Mg/dl	automated clinical chemistry analyzer,	41	1.8	42	2.3	Crude	NA

OUTCOME: Triglyceride					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Liraglutide + lifestyle vs Placebo + lifestyle								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch 2022*	mg/dL	measured on an automated clinical	109	SEM 7.7	114	SEM 11	Crude	NA

		chemistry analyzer						

OUTCOME: Anthropometrics: weight				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide + lifestyle vs Placebo + lifestyle								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch 2022*	Kg	Wearing light clothing, the nearest 0.1kg	104.7	SEM 2.9	117.9	SEM 5	Crude	NA

OUTCOME: Anthropometrics: BMI				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide + lifestyle vs Placebo + lifestyle								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

						comparison group		
Elkind-Hirsch 2022*	kg/m2		39.1	SEM 1.1	43.4	SEM 1.8	Crude	NA

OUTCOME: Anthropometrics: WHR					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Liraglutide + lifestyle vs Placebo + lifestyle								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch 2022*		Calculated as WC divided by HC	0.81	SEM 0.01	0.83	SEM 0.02	Crude	NA

OUTCOME: Anthropometrics: WC	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Liraglutide + lifestyle vs Placebo + lifestyle	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Elkind-Hirsch 2022*	cm	Measured at the narrowest point between the iliac crest and the lowest rib during minimal respiration	101	SEM 2.0	110	SEM 3.3	Crude	NA

OUTCOME: Anthropometrics: % with 5 % loss				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide + lifestyle vs Placebo + lifestyle								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch 2022*	%	count	25/44 57%		5/23 22%		Crude	NA

OUTCOME: Anthropometrics: % with 10 % loss				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide + lifestyle vs Placebo + lifestyle								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch 2022*	%	count	13/44 29.5%		8.7%		Crude	NA

OUTCOME: Anthropometrics: Fat free mass/lean body mass				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide + lifestyle vs Placebo + lifestyle								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch 2022		Total and regional body composition was determined using	54.1	SEM 1.1	58.2	SEM 1.9	Crude	NA

		DXA (Hologic Discovery A model, Hologic, Inc., Waltham, MA) at the start and completion of the study trial. For each region of the whole body (head, trunk, arms, and legs), fat and lean body mass were determined, expressed as mass (g). The total fat mass percentage was calculated by dividing the weight of the total fat mass (kg) by BW.						

OUTCOME: Anthropometrics: % body fat	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Liraglutide + lifestyle vs Placebo + lifestyle	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Elkind-Hirsch 2022*	%	Total and regional body composition was determined using DXA (Hologic Discovery A model, Hologic, Inc., Waltham, MA) at the start and completion of the study trial. For each region of the whole body (head, trunk, arms, and legs), fat and lean body mass were determined, expressed as mass (g). Total fat mass % = weight of the total fat mass (kg) / BW	46.0	SEM 0.9	47.9	SEM 0.9	Crude	NA

OUTCOME: Mense/year				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Liraglutide + lifestyle vs Placebo + lifestyle								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkind-Hirsch 2022*	counting	Frequency of menses per year	8.65	SEM 0.4	4.8	SEM 0.7	Crude	NA

3. Semaglutide

i. Semaglutide v Placebo

Sample size: Semaglutide 13, placebo 12

OUTCOME: eg. fasting glucose					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Semaglutide vs Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Jensterle 2021	Mmol/L	a standard glucose oxidase method (Beckman Coulter Glucose Analyzer, Beckman Coulter Inc CA, USA).	4.8	0.3	5.2	0.6	Crude	NA

OUTCOME: eg. fasting insulin	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Semaglutide vs Placebo	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Jensterle 2021*	mU/l	Insulin was determined by immunoradiometric assay (Biosource Europe S.A., Nivelles, Belgium	14.57	10.34	14.79	8.13	Crude	NA

OUTCOME: eg. HOMA-IR				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Semaglutide vs Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Jensterle 2021			3.13	2.17	3.38	1.87	Crude	NA

OUTCOME: eg. Glucose at 120 Min OGTT	**OUTCOME TYPE:** Continuous

COMPARISON (if applicable): Semaglutide v Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Jensterle 2021*	Mmol/L	a standard glucose oxidase method (Beckman Coulter Glucose Analyzer, Beckman Coulter Inc CA, USA).	5	0.8	5.9	1.3	Crude	NA

OUTCOME: eg. Insulin at 120 min OGTT			**OUTCOME TYPE:** Continuous					
COMPARISON (if applicable): Semaglutide vs Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

Jensterle 2021	mIU/l	immunoradiometric assay (Biosource Europe S.A., Nivelles, Belgium	59.21	26.17	99.8	99.92	Crude	NA

OUTCOME: Total cholesterol				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Semaglutide vs Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	Method of measurement	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Jensterle 2021	Mmol/l	Adiva 1800, Siemens analyzer	4.58	1.01	5.42	1.05	Crude	NA

OUTCOME: LDL cholesterol	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Semaglutide vs Placebo	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Jensterle 2021	Mmol/l	Adiva 1800, Siemens analyzer	2.78	0.78	3.3	0.71	Crude	NA

OUTCOME: HDL cholesterol					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Semaglutide vs Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Jensterle 2021*	Mmol/l	Adiva 1800, Siemens analyzer	1.28	0.29	1.32	0.24	Crude	NA

OUTCOME: TG	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Semaglutide vs Placebo	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Jensterle 2021	Mmol/l	Adiva 1800, Siemens analyzer	1.56	1.17	1.98	1.53	Crude	NA

OUTCOME: Weight				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Semaglutide vs Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Jensterle 2021*	Kg	Scale	95.6	13.3	100.7	14.8	Crude	NA

OUTCOME: BMI	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Semaglutide vs Placebo	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Jensterle 2021*	Kg/m2		34.8	3.2	36.1	4.2	Crude	NA

OUTCOME: Waist circumference				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Semaglutide vs Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Jensterle 2021*	Cm	Tape measure	99.7	10.7	109.8	14.6	Crude	NA

OUTCOME: eg. Visceral adipose tissue	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): eg. Semaglutide vs placebo	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Jensterle 2021*	g	DEXA	632	215	766	237	Crude	NA

4. Phentermine/Topiramate

i. Phentermine/Topiramate v Dapagliflozin

Sample sizes: PT=13, Dapa=17

OUTCOME: Androgenicity: FAI					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Phentermine/Topiramate vs Dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021		competitive binding immunoenzymatic assays with direct chemiluminometric technology (Beckman Coulter Access 2).	5.0	0.8	4.7	0.8	Crude	NA

OUTCOME: Androgenicity: Total testosterone					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Phentermine/Topiramate vs Dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI)**	**Mean (specify if median) or median in control /**	**SD (or specify if other measure: SE, IQR or 95%**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

				in intervention / exposure group	**comparison group**	**CI) in control/ comparison group**		
Elkin-Hirsch 2021	Ng/dl	SHBG: TT concentration was measured with an automated chemiluminescent microparticle immunoassay, the Architect second-generation testosterone assay (Abbott Diagnostics) with 5 ng/dL as the minimum detectable concentration of TT	45.5	4.5	35	4.4	Crude	NA

OUTCOME: Androgenicity DHEAS				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Phentermine/Topiramate vs Dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

Elkin-Hirsch 2021	Mcg/dL	competitive binding immunoenzymatic assays with direct chemiluminometric technology (Beckman Coulter Access 2).	201	24	187	24	Crude	NA

OUTCOME: Metabolics: Fasting glucose				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Phentermine/Topiramate vs Dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	Mg/dl	glucose analyzer using the glucose oxidase method (Glucose Reagent Kit, Bayer).	91.4	2.2	93	2.1	Crude	NA

OUTCOME: Metabolics: HOMA- IR	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Phentermine/Topiramate vs Dapa	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Elkin-Hirsch 2021		was calculated using the equation: fasting insulin concentration (µIU/mL) × fasting glucose concentration (mmol/L) 22.5	3.2	0.62	3.4	0.6	Crude	NA

OUTCOME: Metabolics: Matsuda Index SI OGTT				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Phentermine/Topiramate vs Dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021		Serum insulin was determined in all samples in duplicate by microparticle	4.7	0.7	3.6	0.7	Crude	NA

		enzyme immunoassay (Abbott AxSYM System, Abbott Laboratories).						

OUTCOME: Lipids: Tot cholesterol					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Phentermine/topiramate vs Dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	Mg/dl	standard enzymatic colorimetric assays on an automated clinical chemistry analyzer	178	12	186	11	Crude	NA

OUTCOME: Lipids: LDL	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Phentermine/topiramate vs Dapa	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Elkin-Hirsch 2021	Mg/dl	calculated according to the Friedewald equation	105	16	113.5	10	Crude	NA

OUTCOME: Lipids: HDL					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): exanetide vs dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	Mg/dl	standard enzymatic colorimetric assays on an automated clinical chemistry analyzer	44	2.3	43	2.2	Crude	NA

OUTCOME: Lipids: TG				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Phentermine/topiramate vs Dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	Mg/dl	standard enzymatic colorimetric assays on an automated clinical chemistry analyzer	110	13	132	13	Crude	na

OUTCOME: Antropometric: weight				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Phentermine/topiramate vs Dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

Elkin-Hirsch 2021*	kg		97	4.1	102.6	4	Crude	NA

OUTCOME: Anthropometric: BMI				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Phentermine/topiramate vs Dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021*	Kg/m2		35.3	1.3	37.4	1.2	Crude	NA

OUTCOME: Antropometric: WHR				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Phentermine/topiramate vs Dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

Elkind-Hirsch et al. 2021		WC was measured at the narrowest level midway between the rib cage and the iliac crest and hip circumference measured at the widest level over the buttocks while the participants were in the standing position using a flexible measuring tape.	0.81	0.018	0.79	0.017	Crude	NA

OUTCOME: Antropometric: WC				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Phentermine/topiramate vs Dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	Cm	narrowest level midway between the rib cage and the iliac crest	97	3.4	101	3.2	Crude	NA

OUTCOME: Antropometric: fat free mass /lean BM					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Phentermine/topiramate vs Dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	kg	Participants in hospital gowns were positioned in the supine position on the DXA table, and instructed to keep their arms separated from their trunk, hands placed flat on the table, palms facing down, away from their thighs adjacent to the side of the body, and their legs separated from one another	51.7	1.8	52.2	1.7	Crude	NA

OUTCOME: Antropometric: fat mass					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Phentermine/topiramate vs Dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021*	kg	Participants in hospital gowns were positioned in the supine position on the DXA table, and instructed to keep their arms separated from their trunk, hands placed flat on the table, palms facing down, away from their thighs adjacent to the side of the body, and their legs separated from one another	44.5	2.8	47.8	2.6	Crude	NA

OUTCOME: Antropometric: % body fat					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Phentermine/topiramate vs Dapa								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021*		Participants in hospital gowns were positioned in the supine position on the DXA table, and instructed to keep their arms separated from their trunk, hands placed flat on the table, palms facing down, away from their thighs adjacent to the side of the body, and their legs separated from one another	45.2	1.2	46.4	1.2	Crude	NA

ii. Phentermine/Topiramate v Dapagliflozin + Metformin

Sample sizes: PT=13, DAPA+Met=19

OUTCOME: Androgenicity: FAI					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Phentermine/Topiramate vs DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021		competitive binding immunoenzymatic assays with direct chemiluminometric technology (Beckman Coulter Access 2).	5.0	0.8	5.7	0.74	Crude	NA

OUTCOME: Androgenicity: Total testosterone					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Phentermine/Topiramate vs DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention**	**Mean (specify if median) or median in control /**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

				/ exposure group	**comparison group**	**comparison group**		
Elkin-Hirsch 2021	Ng/dl	SHBG: TT concentration was measured with an automated chemiluminescent microparticle immunoassay, the Architect second-generation testosterone assay (Abbott Diagnostics) with 5 ng/dL as the minimum detectable concentration of TT	45.5	4.5	39.5	4.1	Crude	NA

OUTCOME: Androgenicity DHEAS				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Phentermine/Topiramate vs DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

Elkin-Hirsch 2021	Mcg/dL	competitive binding immunoenzymatic assays with direct chemiluminometric technology (Beckman Coulter Access 2).	201	24	189	23	Crude	NA

OUTCOME: Metabolics: Fasting glucose				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Phentermine/Topiramate vs DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	Mg/dl	glucose analyzer using the glucose oxidase method (Glucose Reagent Kit, Bayer).	91.4	2.2	89	2.0	Crude	NA

OUTCOME: Metabolics: HOMA- IR	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Phentermine/Topiramate vs DAPA + MET	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Elkin-Hirsch 2021		was calculated using the equation: fasting insulin concentration (µIU/mL) × fasting glucose concentration (mmol/L) 22.5	3.2	0.62	3.3	0.57	Crude	NA

OUTCOME: Metabolics: Matsuda Index SI OGTT					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Phentermine/Topiramate vs DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021		Serum insulin was determined in all samples in duplicate by microparticle	4.7	0.7	4.8	0.6	Crude	NA

		enzyme immunoassay (Abbott AxSYM System, Abbott Laboratories).						

OUTCOME: Lipids: Tot cholesterol				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Phentermine/topiramate vs DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	Mg/dl	standard enzymatic colorimetric assays on an automated clinical chemistry analyzer	178	12	192	11	Crude	NA

OUTCOME: Lipids: LDL	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Phentermine/topiramate vs DAPA + MET	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Elkin-Hirsch 2021	Mg/dl	calculated according to the Friedewald equation	105	16	121	9.5	Crude	NA

OUTCOME: Lipids: HDL					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): exanetide vs DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	Mg/dl	standard enzymatic colorimetric assays on an automated clinical chemistry analyzer	44	2.3	45	2	Crude	NA

OUTCOME: Lipids: TG				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Phentermine/topiramate vs DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	Mg/dl	standard enzymatic colorimetric assays on an automated clinical chemistry analyzer	110	13	105	12	Crude	na

OUTCOME: Antropometric: weight				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Phentermine/topiramate vs DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

Elkin-Hirsch 2021*	kg		97	4.1	101.2	3.8	Crude	NA

OUTCOME: Anthropometric: BMI				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Phentermine/topiramate vs DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021*	Kg/m2		35.3	1.3	37	1.2	Crude	NA

OUTCOME: Antropometric: WHR				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Phentermine/topiramate vs DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

Elkind-Hirsch et al. 2021		WC was measured at the narrowest level midway between the rib cage and the iliac crest and hip circumference measured at the widest level over the buttocks while the participants were in the standing position using a flexible measuring tape.	0.81	0.018	0.83	0.016	Crude	NA

OUTCOME: Antropometric: WC				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Phentermine/topiramate vs DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021*	Cm	narrowest level midway between the rib cage and the iliac crest	97	3.4	101.3	3	Crude	NA

OUTCOME: Antropometric: fat free mass /lean BM					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Phentermine/topiramate vs DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	kg	Participants in hospital gowns were positioned in the supine position on the DXA table, and instructed to keep their arms separated from their trunk, hands placed flat on the table, palms facing down, away from their thighs adjacent to the side of the body, and their legs separated from one another	51.7	1.8	52.9	1.6	Crude	NA

OUTCOME: Antropometric: fat mass					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Phentermine/topiramate vs DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021*	kg	Participants in hospital gowns were positioned in the supine position on the DXA table, and instructed to keep their arms separated from their trunk, hands placed flat on the table, palms facing down, away from their thighs adjacent to the side of the body, and their legs separated from one another	44.5	2.8	48	2.5	Crude	NA

OUTCOME: Antropometric: % body fat					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Phentermine/topiramate vs DAPA + MET								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021*		Participants in hospital gowns were positioned in the supine position on the DXA table, and instructed to keep their arms separated from their trunk, hands placed flat on the table, palms facing down, away from their thighs adjacent to the side of the body, and their legs separated from one another	45.2	1.2	46.1	1.1	Crude	NA

iii. Phentermine/Topiramate v Exenatide + Dapagliflozin

Sample sizes: PT=13, EXE+DAPA=20

OUTCOME: Androgenicity: FAI					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Phentermine/Topiramate vs EXE + DAPA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021		competitive binding immunoenzymatic assays with direct chemiluminometric technology (Beckman Coulter Access 2).	5.0	0.8	5.2	0.73	Crude	NA

OUTCOME: Androgenicity: Total testosterone					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Phentermine/Topiramate vs EXE + DAPA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention**	**Mean (specify if median) or median in control /**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

				/ exposure group	comparison group	comparison group		
Elkin-Hirsch 2021	Ng/dl	SHBG: TT concentration was measured with an automated chemiluminescent microparticle immunoassay, the Architect second-generation testosterone assay (Abbott Diagnostics) with 5 ng/dL as the minimum detectable concentration of TT	45.5	4.5	40.6	4	Crude	NA

OUTCOME: Androgenicity DHEAS				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Phentermine/Topiramate vs EXE + DAPA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

Elkin-Hirsch 2021	Mcg/dL	competitive binding immunoenzymatic assays with direct chemiluminometric technology (Beckman Coulter Access 2).	201	24	169	0.22	Crude	NA

OUTCOME: Metabolics: Fasting glucose				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Phentermine/Topiramate vs EXE + DAPA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	Mg/dl	glucose analyzer using the glucose oxidase method (Glucose Reagent Kit, Bayer).	91.4	2.2	87.5	1.9	Crude	NA

OUTCOME: Metabolics: HOMA- IR	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Phentermine/Topiramate vs EXE + DAPA	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Elkin-Hirsch 2021		was calculated using the equation: fasting insulin concentration (µIU/mL) × fasting glucose concentration (mmol/L) 22.5	3.2	0.62	3.4	0.6	Crude	NA

OUTCOME: Metabolics: Matsuda Index SI OGTT				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Phentermine/Topiramate vs EXE + DAPA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021		Serum insulin was determined in all samples in duplicate by microparticle	4.7	0.7	3.9	0.6	Crude	NA

		enzyme immunoassay (Abbott AxSYM System, Abbott Laboratories).						

OUTCOME: Lipids: Tot cholesterol				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Phentermine/topiramate vs EXE + DAPA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	Mg/dl	standard enzymatic colorimetric assays on an automated clinical chemistry analyzer	178	12	190	15	Crude	NA

OUTCOME: Lipids: LDL	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Phentermine/topiramate vs EXE + DAPA	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Elkin-Hirsch 2021	Mg/dl	calculated according to the Friedewald equation	105	16	115	9	Crude	NA

OUTCOME: Lipids: HDL					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): exanetide vs EXE + DAPA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	Mg/dl	standard enzymatic colorimetric assays on an automated clinical chemistry analyzer	44	2.3	41	2	Crude	NA

OUTCOME: Lipids: TG				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Phentermine/topiramate vs EXE + DAPA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021*	Mg/dl	standard enzymatic colorimetric assays on an automated clinical chemistry analyzer	110	13	112	12	Crude	na

OUTCOME: Antropometric: weight				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Phentermine/topiramate vs EXE + DAPA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

Elkin-Hirsch 2021	kg		97	4.1	98	3.7	Crude	NA

OUTCOME: Anthropometric: BMI				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Phentermine/topiramate vs EXE + DAPA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	Kg/m2		35.3	1.3	36.7	1.1	Crude	NA

OUTCOME: Anthropometric: WHR				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Phentermine/topiramate vs EXE + DAPA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

Elkind-Hirsch et al. 2021		WC was measured at the narrowest level midway between the rib cage and the iliac crest and hip circumference measured at the widest level over the buttocks while the participants were in the standing position using a flexible measuring tape.	0.81	0.018	0.86	0.016	Crude	NA

OUTCOME: Antropometric: WC				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Phentermine/topiramate vs EXE + DAPA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	Cm	narrowest level midway between the rib cage and the iliac crest	97	3.4	105	3	Crude	NA

OUTCOME: Antropometric: fat free mass /lean BM					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Phentermine/topiramate vs EXE + DAPA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	kg	Participants in hospital gowns were positioned in the supine position on the DXA table, and instructed to keep their arms separated from their trunk, hands placed flat on the table, palms facing down, away from their thighs adjacent to the side of the body, and their legs separated from one another	51.7	1.8	51.8	1.6	Crude	NA

OUTCOME: Antropometric: fat mass					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Phentermine/topiramate vs EXE + DAPA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021	kg	Participants in hospital gowns were positioned in the supine position on the DXA table, and instructed to keep their arms separated from their trunk, hands placed flat on the table, palms facing down, away from their thighs adjacent to the side of the body, and their legs separated from one another	44.5	2.8	44.9	2.4	Crude	NA

OUTCOME: Antropometric: % body fat					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Phentermine/topiramate vs EXE + DAPA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Elkin-Hirsch 2021		Participants in hospital gowns were positioned in the supine position on the DXA table, and instructed to keep their arms separated from their trunk, hands placed flat on the table, palms facing down, away from their thighs adjacent to the side of the body, and their legs separated from one another	45.2	1.2	44.8	1.1	Crude	NA

5. Orlistat

i. Orlistat + lifestyle v placebo + lifestyle

Sample sizes:

Moini: Orlistat 43, placebo + lifestyle 43

OUTCOME: Total testosterone					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Orlistat + lifestyle vs placebo + lifestyle								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Moini 2015	ng/ml	ELISA (Monobid, USA)	63.95	1.63	81.60	4.64	Crude	NA

OUTCOME: Fasting glucose	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Orlistat + lifestyle vs placebo + lifestyle	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Moini 2015	Mg/dL	Photometry (Parsazmoon, Iran)	107.05	4.24	106.35	4.24	Crude	NA

OUTCOME: Fasting insulin				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Orlistat + lifestyle vs placebo + lifestyle								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Moini 2015	µu/mL	ELISA	17.20	6.72	17.34	7.27	Crude	NA

OUTCOME: HOMA-IR	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Orlistat + lifestyle vs placebo + lifestyle	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Moini 2015	NA	FPG x FINS / 405	3.43	1.11	3.41	1.42	Crude	NA

OUTCOME: LDL				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Orlistat + lifestyle vs placebo + lifestyle								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Moini 2015*	Mg/dL	phytometry	71.18	2.34	99.63	5.8	Crude	NA

OUTCOME: HDL	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Orlistat + lifestyle vs placebo + lifestyle	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Moini 2015*	Mg/dL	phytometry	54.13	2.32	49.23	1.47	Crude	NA

OUTCOME: TG				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Orlistat + lifestyle vs placebo + lifestyle								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Moini 2015*	Mg/dL	phytometry	128.34	16.52	158.98	11.93	Crude	NA

OUTCOME: Weight	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Orlistat + lifestyle vs placebo + lifestyle	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Moini 2015*	Kg	Scales	76.25	4.3	79.15	4.51	Crude	NA

OUTCOME: BMI				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Orlistat + lifestyle vs placebo + lifestyle								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Moini 2015*	Kg/m^2	Scale	27.16	1.93	28.57	1.9	Crude	NA

OUTCOME: WHR	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Orlistat + lifestyle vs placebo + lifestyle	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Moini 2015	cm	Tape measure	0.76	0.03	0.86	0.03	Crude	NA

ii. Orlistat + lifestyle + OCP v Metformin + lifestyle + OCP

Sample size: Orlistat 60, Metformin 60

OUTCOME: FAI				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Orlistat (+lifestyle + OCP) vs Metformin (+LS + OCP)								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in metformin group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Song 2017	NA	ADVIA Centaur XP immunoassay	2.15	1.91	2.90	2.38	Crude	NA

OUTCOME: Free testosterone				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Orlistat (+lifestyle + OCP) vs Metformin (+LS + OCP)								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in metformin group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Song 2017	nmol/L	Immunoassay	1.41	0.97	1.37	0.85	Crude	NA

OUTCOME: Total testosterone				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Orlistat (+lifestyle + OCP) vs Metformin (+LS + OCP)								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in metformin group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Song 2017	Ng/dL	Immunoassay	44.28	18.92	44.92	20.26	Crude	NA

OUTCOME: SHBG				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Orlistat (+lifestyle + OCP) vs Metformin (+LS + OCP)								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in metformin group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
OUTCOME: DHEA				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Orlistat (+lifestyle + OCP) vs Metformin (+LS + OCP)								
Song 2017	nmol/L	Immunoassay	72.41	15.33	73.33	48.01	Crude	NA
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in metformin group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Kumar 2014	ng/dL	Immune electric chermluminence method	% change: 10.6	% change SE 5.75	% change: -4.98	% change SE 4.66	Crude	NA
Song 2017	µg/dL	Immunoassay	175.02	38.10	172.29	48.83	Crude	NA

OUTCOME: Androstenedione				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Orlistat (+lifestyle + OCP) vs Metformin (+LS + OCP)								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in metformin group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Song 2017	nmol/L	Immunoassay	7.09	3.99	6.39	3.05		

OUTCOME: Fasting glucose				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Orlistat (+lifestyle + OCP) vs Metformin (+LS + OCP)								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in metformin group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

Song 2017	mmol/L	Synchron LX20 chemistry analyser	5.02	0.88	4.91	0.54	Crude	NA

OUTCOME: Fasting insulin				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Orlistat (+lifestyle + OCP) vs Metformin (+LS + OCP)								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in metformin group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Song 2017	mIU/L	Chemistry analyser	19.36	7.46	21.37	4.1		

OUTCOME: HOMA-IR				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Orlistat (+lifestyle + OCP) vs Metformin (+LS + OCP)								
Author, year	**Unit of outcome (e.g. g, mg, µg,**	**Method of measurement**	**Mean (specify if median) in intervention/**	**SD (or specify if other measure:**	**Mean (specify if median) or median in**	**SD (or specify if other measure:**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

	mmol/L, etc.)		**exposure group**	**IQR, SE or 95% CI) in intervention / exposure group**	**metformin group**	**SE, IQR or 95% CI) in control/ comparison group**		
Song 2017	NA	NR	4.34	1.96	4.66	1.02		

OUTCOME: Total cholesterol				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Orlistat (+lifestyle + OCP) vs Metformin (+LS + OCP)								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in metformin group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Song 2017	mmol/L	Chemistry analyser	4.61	0.57	4.99	1.06	Crude	NA

OUTCOME: LDL	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Orlistat (+lifestyle + OCP) vs Metformin (+LS + OCP)	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in metformin group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Song 2017	mmol/L	Chemistry analyser	2.75	0.99	2.95	0.64		

OUTCOME: HDL				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Orlistat (+lifestyle + OCP) vs Metformin (+LS + OCP)								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in metformin group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Song 2017	Mmol/L	Chemistry analyser	2.01	0.99	1.7	0.66	Crude	NA

OUTCOME: TG				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Orlistat (+lifestyle + OCP) vs Metformin (+LS + OCP)								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in metformin group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Song 2017	Mmol/L	Chemistry analyser	1.56	0.44	1.85	0.6	Crude	NA

iii. Orlistat + lifestyle + OCP v lifestyle + OCP

Sample sizes:

Gu 2022: Orlistat=33, Control-33

Song 2017: Orlistat=60, Control=60

OUTCOME: FAI					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Orlistat + LS + OCP v LS + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Song 2017*	NA	ADVIA Centaur XP immunoassay	2.15	1.91	4.59	5.91	Crude	NA

OUTCOME: Free testosterone					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Orlistat + LS + OCP v LS + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

						comparison group		
Gu 2022	pg/mL*	NR	2.90	1.72	3.8	3.32	Crude	NA
Song 2017	nmol/L	Immunoassay	1.41	0.97	1.47	0.54	Crude	NA

*unable to convert values – implausible

OUTCOME: Total testosterone					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Orlistat + LS + OCP v LS + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Gu 2022	pg/mL	NR	353.53	172.06	386.16	158.83	Crude	NA
Song 2017	Ng/dL	Immunoassay	44.28	18.92	44.29	10.30	Crude	NA

OUTCOME: SHBG	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Orlistat + LS + OCP v LS + OCP	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Gu 2022	Nmol/L	NR	136.24	58.23	120.19	55.44	Crude	NA
Song 2017	nmol/L	Immunoassay	72.41	15.33	58.47	46.87	Crude	NA

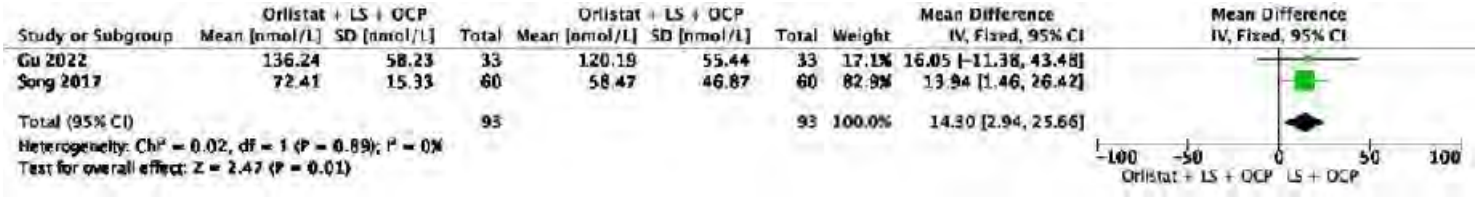


Figure 5 Forest plot: Orlistat + lifestyle + OCP vs lifestyle + OCP - SHBG

OUTCOME: DHEAS					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Orlistat + LS + OCP v LS + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

						comparison group		
Song 2017*	µg/dL	Immunoassay	175.02	38.10	206.85	67.75	Crude	NA

OUTCOME: Androstenedione				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Orlistat + LS + OCP v LS + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Song 2017	nmol/L	Immunoassay	7.09	3.99	7.89	2.86	Crude	NA

OUTCOME: Fasting glucose				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Orlistat + LS + OCP v LS + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

						comparison group		
Gu 2022	mmol/L	NR	5.17	0.54	5.16	0.4	Crude	NA
Song 2017	mmol/L	Synchron LX20 chemistry analyser	5.02	0.88	5.04	0.52	Crude	NA

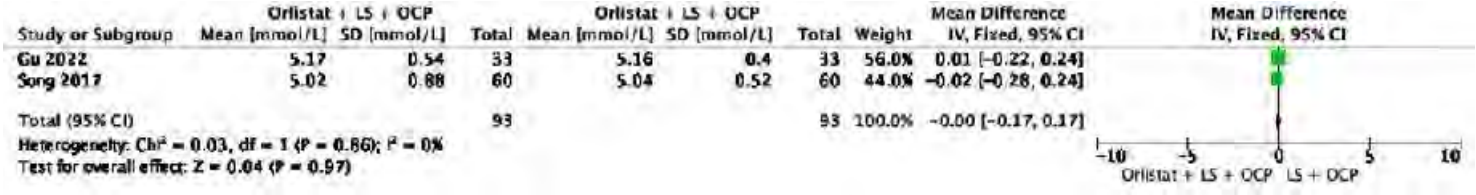


Figure 6 Forest plot: Orlistat + lifestyle + OCP v lifestyle + OCP - fasting glucose

OUTCOME: FINS	**OUTCOME TYPE:** Continuous

COMPARISON (if applicable): Orlistat + LS + OCP v LS + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Gu 2022	pmol/L	NR	109.13	59.18	102.12	49.96	Crude	NA
Song 2017	mIU/L	Chemistry analyser	19.36	7.46	22.52	4.00	Crude	NA

OUTCOME: FINS – converted to pmol/L				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Orlistat + LS + OCP v LS + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Gu 2022	pmol/L	NR	109.13	59.18	102.12	49.96	Crude	NA
Song 2017	pmol/L	Chemistry analyser	116.16	44.76	135.12	24	Crude	NA

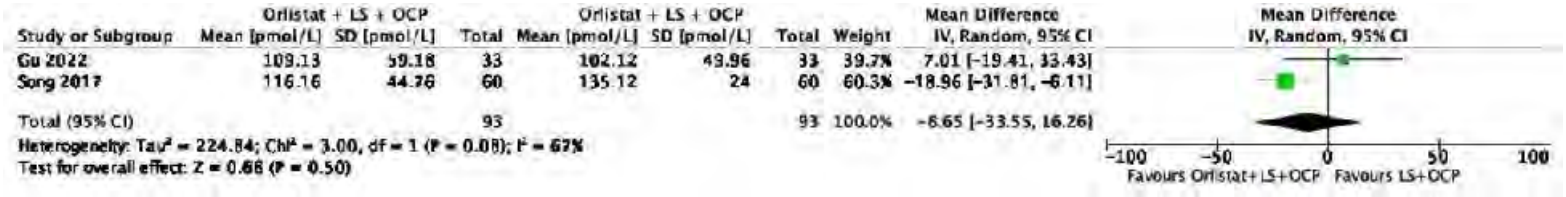


Figure 7 Forest plot: Orlistat + lifestyle + OCP v lifestyle + OCP - fasting insulin

OUTCOME: HOMA-IR				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Orlistat + LS + OCP v LS + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Song 2017	NA	NR	4.34	1.96	5.05	1.06	Crude	NA

OUTCOME: Total Cholesterol	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Orlistat + LS + OCP v LS + OCP	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Gu 2022	mmol/L	NR	Median=4.63	IQR=0.88	Median=4.83	IQR=0.72	Crude	NA
Song 2017	mmol/L	Chemistry analyser	4.61	0.57	4.84	0.74	Crude	NA

OUTCOME: LDL					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Orlistat + LS + OCP v LS + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Gu 2022*	mmol/L	NR	2.38	0.55	3.02	0.64	Crude	NA
Song 2017	mmol/L	Chemistry analyser	2.75	0.99	2.97	0.65	Crude	NA

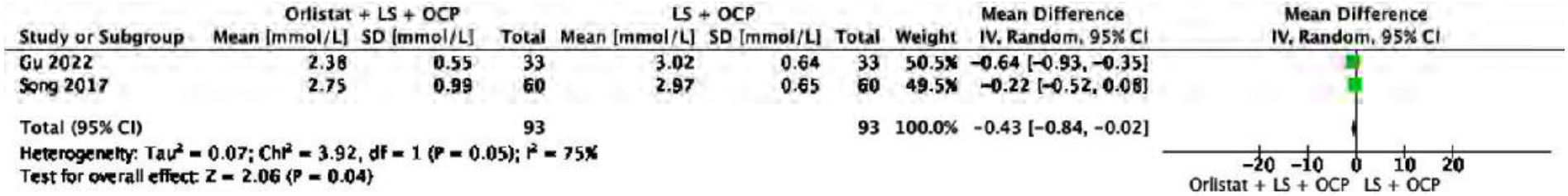


Figure 8 Forest plot: Orlistat + lifestyle + OCP v lifestyle + OCP - LDL cholesterol

OUTCOME: HDL					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Orlistat + LS + OCP v LS + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Gu 2022	mmol/L	NR	1.3	0.3	1.36	0.25	Crude	NA
Song 2017	Mmol/L	Chemistry analyser	2.01	0.99	1.48	0.6	Crude	NA

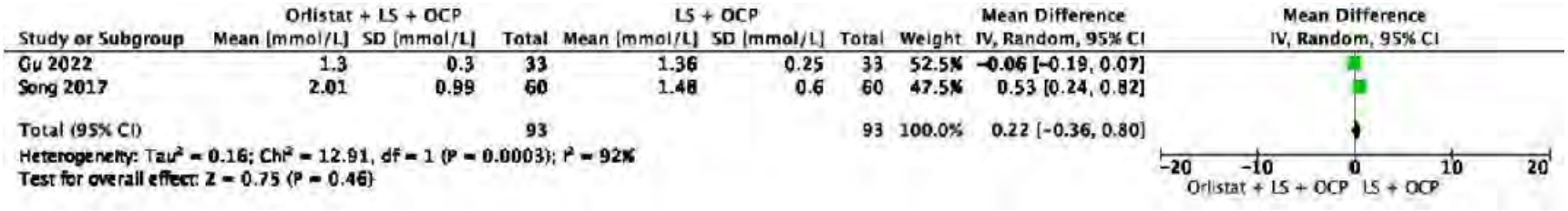


Figure 9 Forest plot: Orlistat + lifestyle + OCP v lifestyle + OCP – HDL cholesterol

OUTCOME: Triglycerides					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Orlistat + LS + OCP v LS + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Gu 2022	mmol/L	NR	2.12	0.97	1.95	0.8	Crude	NA
Song 2017	Mmol/L	Chemistry analyser	1.56	0.44	1.62	0.88	Crude	NA

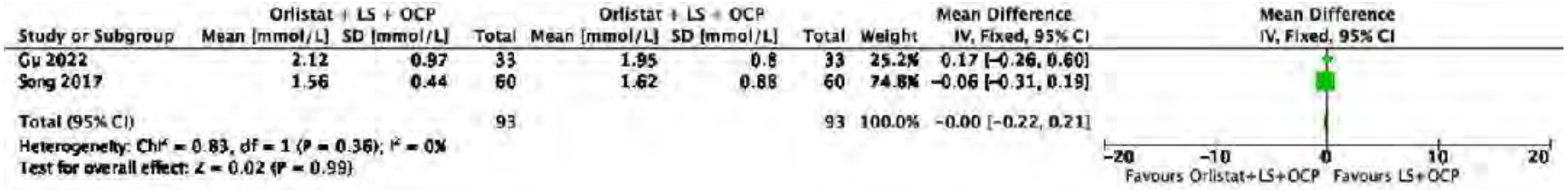


Figure 10 Forest plot: Orlistat + lifestyle + OCP v lifestyle + OCP - triglycerides

OUTCOME: CRP					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): Orlistat + LS + OCP v LS + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Gu 2022*	mg/L	NR	4.43	3.69	4.69	3.84	Crude	NA

OUTCOME: Weight	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Orlistat + LS + OCP v LS + OCP	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Gu 2022*	Kg	scales	69.9	7.86	75.52	9.35	Crude	NA

OUTCOME: BMI				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Orlistat + LS + OCP v LS + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Gu 2022*	Kg/m2		26.26	3.12	27.02	3.31	Crude	NA

OUTCOME: Waist circumference	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): Orlistat + LS + OCP v LS + OCP	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Gu 2022	Cm		86.17	8.47	89.13	8.87	Crude	NA

OUTCOME: % body fat				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Orlistat + LS + OCP v LS + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Gu 2022*	%	Measured by an MC/MES00-042 muscle function analyzer (Maidakang,Beijing, China)	43.13	8.89	43.3	5.71	Crude	NA

iv. Orlistat + Metformin + OCP + lifestyle v Metformin + OCP + lifestyle

Sample size: Orlistat 60 + MET 60, MET 60

OUTCOME: eg. FAI				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): eg. Orlistat + Metformin + OCP vs Metformin alone + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Song 2017	NA	Advia Centaur XP immunoassay	Median 3.01	IQR 3.24	Median 2.9	IQR 2.38	Crude	NA

OUTCOME: eg. Free testosterone				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): eg. Orlistat + Metformin + OCP vs Metformin alone + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

						comparison group		
Song 2017	Nmol/L	Advia Centaur XP immunoassay	1.19	0.67	1.37	0.85	Crude	NA

OUTCOME: eg. Total testosterone				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): eg. Orlistat + Metformin + OCP vs Metformin alone + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Song 2017	ng/dL	Advia Centaur XP immunoassay	43.13	12.94	44.92	20.26	Crude	NA

OUTCOME: eg. SHBG	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): eg. Orlistat + Metformin + OCP vs Metformin alone + OCP	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Song 2017	nmol/L	Advia Centaur XP immunoassay	85.41	67.51	73.33	48.01	Crude	NA

OUTCOME: eg. DHEA					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): eg. Orlistat + Metformin + OCP vs Metformin alone + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Song 2017	µg/dL	Advia Centaur XP immunoassay	177.72	94.93	172.29	48.83	Crude	NA

OUTCOME: eg. Androstenedione	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): eg. Orlistat + Metformin + OCP vs Metformin alone + OCP	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Song 2017	Nmol/L	Advia Centaur XP immunoassay	7.51	2.98	6.39	3.05	Crude	NA

OUTCOME: eg. Fasting glucose				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): eg. Orlistat + Metformin + OCP vs Metformin alone + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Song 2017	Mmol/L	Synchron LX20 chemistry analyzer (Beckman Coulter, America)	5.03	0.62	4.91	0.54	Crude	NA

OUTCOME: eg. Fasting insulin					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): eg. Orlistat + Metformin + OCP vs Metformin alone + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Song 2017	mIU/L	ADVIA Centaur XP immunoassay system (Siemens, Germany)	20.61	4.48	21.37	4.1	Crude	NA

OUTCOME: eg. HOMA-IR					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): eg. Orlistat + Metformin + OCP vs Metformin alone + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Song 2017	NA	fasting insulin (mIU/L) x fasting glucose (mmol/L) / 22.5	4.58	1.06	4.66	1.02	Crude	NA

OUTCOME: eg. Total cholesterol				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): eg. Orlistat + Metformin + OCP vs Metformin alone + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Song 2017	mmol/L	Chemistry analyser	4.81	0.67	4.99	1.06	Crude	NA

OUTCOME: eg. LDL				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): eg. Orlistat + Metformin + OCP vs Metformin alone + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Song 2017	mmol/L	Chemistry analyser	2.79	0.67	2.95	0.64	Crude	NA

OUTCOME: eg. HDL					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): eg. Orlistat + Metformin + OCP vs Metformin alone + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Song 2017	mmol/L	Chemistry analyser	1.85	0.43	1.7	0.66	Crude	NA

OUTCOME: eg. TG					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): eg. Orlistat + Metformin + OCP vs Metformin alone + OCP								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Song 2017	mmol/L	Chemistry analyser	1.94	1.2	1.85	0.60	Crude	NA

Note: Orlistat + Metformin was superior to Metformin for body fat %reduction – reported in body of manuscript.

(Numerical data is not provided in the numerical tables)

6. STUDY CHARACTERISTICS AND QUALITY APPRAISAL

1. Exenatide

i. Elkind-Hirsch 2021

Study ID	*Elkind-Hirsch 2021*
Study Citation	*Elkind-Hirsch et al., J Clin Endocrinol Metab 106:3019-3033, 2021*
Study Country	*USA*
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	*Women with PCOS age 18-45*
PCOS diagnostic criteria	*NIH 1990*
Presence of infertility	*not reported*
Presence of other condition/s	*Obese , BMI 30-45, premenopausal*
Medication History	*No*
N per group	*130 at baseline,* *11 were ineligible* *119 met criteria assigned to 1 of 5 treatment groups* *End of study:* *Exenatide n=20* *Dapagliflozin n= 17* *Exenatide and Dapa n= 20* *Dapa and metformin n = 19* *Phentermine/Topiramate n = 16* *Allocated/randomised: 119 (23 Exenatide; 22 Dapagliflozin plus Exenatide; 23 Dapagliflozin; 26 Dapagliflozin/Glucophage; 25 Phentermine-Topiramate)*

Setting	*Woman's Hospital Endocrine and Weight Loss Clinic, USA*
Intervention	*1. Exenatide once weekly (Bydureon),; 2 mg weekly,* *2. dapagliflozin (Farxiga) 10 mg daily,* *3. Exenatide and DAPA (2 mg weekly/10 mg daily),* *4. Combined dapagliflozin/metformin XR (Xigduo) were provided* *by AstraZeneca Pharmaceuticals (DAPA 10 mg/MET 2000 mg XR daily),* *5. weight loss medication, PHEN/TPM (PHEN 7.5 mg/* *TPM 46 mg ER daily)* *treated for 24 weeks.*
Comparison	***DAPA**: 10 mg daily;* ***combined DAPA/MET** (DAPA 10 mg/MET 2000 mg XR daily),* *for 24 weeks*
Co-intervention	*Counselling concerning the benefits of lifestyle modification through diet and exercise;* *Encouragement to increase daily exercise (eg, walking, using stairs)*
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*FAI, total testosterone, DHEAS* *fasting glucose, HOMA-IR, Matsuda index: Sensitivity index (SI)* *Total cholesterol, LDL, HDL, TG,* *Weight, BMI, WHR, WC, body fat %, Fat mass, Fat free mass-Lean BM* *N of single pregnancies* *Gastrointestinal effects (Nausea, Upset stomach), Other AE (Yeast infection, Injection site reaction: irritation, nodule, rash, redness, itching, Urinary tract infection: burning*

	urination, Frequent urination, Vaginal irritation, Rapid heartbeat, Light headed, Stuffy nose, Fatigue, Insomnia, Headache, Kidney stone, Prolong menstrual bleeding) *after 24 weeks of treatment*	
Follow up Duration	*24 weeks*	
Summary Result/s	*Dual therapy with EQW/DAPA was superior to either alone, DAPA/MET and PHEN/TPM in terms of clinical and metabolic benefits* *EQW/DAPA and PHEN/TPM resulted in the most loss of weight and total body fat by DXA, and WC. Despite equivalent reductions in BMI and WC with PHEN/TPM, only EQW/DAPA and EQW resulted in significant improvements in MBG, SI, and IS. Reductions in fasting glucose, testosterone, FAI, and BP were seen with all drugs.*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* GLP-1RA and SGLT2i, in combination and alone, SGLT2i plus MET vs a comparator weight loss medication in obese, nondiabetic women with PCOS
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No	Yes Eligible participants were required to have the combination of irregular periods (cycle length outside 21-35 days or < 8 cycles/year) together with biochemical evidence of hyperandrogenism (total

	Not reported	testosterone [TT] > 50 ng/dL, or free androgen index [FAI] > 3.87) (16) and exclusion of known disorders for bleeding irregularities and androgen excess. obese class I, II, and III (BMI > 30 < 45) and agreement to use effective contraception consistently during therapy
Exclusion criteria	Yes Partial No Not reported	Yes Diabetic individuals, current smokers, suspected pregnancy, desiring pregnancy, or injectable hormonal contraceptive use within 6 months and use of oral contraceptives, other steroid hormones, drugs that affect gastrointestinal motility or carbohydrate metabolism, and/or antiobesity drugs within 3 months prior to study entry.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Yes* All participants were assigned to 1 of these 5 groups based on computer-generated random numbers using a block randomization method.
	Was allocation to intervention group concealed?	Yes Partial No Not reported	*yes*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*No*

	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*Yes* "All investigators were blinded to drug treatment."
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*

ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	*Obese women with PCOS* *1. Exenatide once weekly (Bydureon),; 2 mg weekly,* *3/23= 13%* *(1 dropout request by patient, 2 pregnant)* *2. dapagliflozin (Farxiga) 10 mg daily: 6/23=26%* *(1 patient moved, 1 concern about meds, 2 not complaint, 1 removed from study by physician, 1 major surgery)* *3. Exenatide and DAPA (2 mg weekly/10 mg daily): 2/22= 9%* *(1 side effects, 1 non compliant)* *4. Combined dapagliflozin/metformin XR (Xigduo)* *(DAPA 10 mg/MET 2000 mg XR daily): 7/26=27%* *(4 not tolerate side effects, 1 personal reason, 1 non compliant, 1 gallstone and GI problems)* *5. weight loss medication, PHEN/TPM (PHEN 7.5 mg/* *TPM 46 mg ER daily) : 9/25=36%* *(5 side effects, 1 non compliant, 2 pregnant, 1 reaction to med)*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Yes (page 3024: When baseline comparisons were analyzed there were no consistent differences between the treatment groups for intent-to-treat participants as well asparticipants completing the trial (see Table 1).*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*yes.AG* *Clinicaltrials.gov NCT02635386*

CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*yes*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Not reported*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*Partial- disclosed as per:* *K.E.H reports receiving grant support from Novo* *Nordisk and Astra-Zeneca, serves on an advisory board for Astra Zeneca Pharmaceuticals, and is a consultant for EMD Serono.* *N.C. and J.S. report grant support from Ferring Pharmaceuticals.* *E.S. and D.B. have nothing to disclose.*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Yes* *The sample size had a statistical power of 0.80 and* *2-sided P value of less than .05 and was calculated to be* *22 for each group.*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*yes*
COMMENTS		*Lack blinding of medication to participant and some conflict of interest from author*	
What is the overall risk of bias?		Low Moderate High	*Moderate- meds not blinded to participants*

	Insufficient information	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*No –*	

iii. Tao 2021

Study ID	Tao 2021
Study Citation	Tao et.al. Exenatide, Metformin, or Both for Prediabetes in PCOS: A Randomized, Open-label, Parallel-group Controlled Study *The Journal of Clinical Endocrinology & Metabolism*, 2021, Vol. 106, No. 3, e1420–e1432 doi:10.1210/clinem/dgaa692
Study Country	China
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	*Premenopausal women with PCOS age 18-45, with prediabetes and overweight/obesity*
PCOS diagnostic criteria	*Rotterdam*
Presence of infertility	*Not reported*
Presence of other condition/s	*BMI ≥25kg/m²* *Prediabetes – presence of IFG (FBG 5.6-6.9mmol/L) and/or IGT (PPG levels for the 75-g OGTT between 7.8-11.0mmol/L) and/or HbA1c 5.7-6.4%.*
Medication History	*No*
N per group	*Allocated/randomised: 183 (61 EXE+MET; 61 EXE; 61 MET)* *Assessed at end of study: 150 (: 50 (EXE + MET), 50 (MET), 50 (EXE)*

Setting	*University teaching hospital, Renji Hospital Affiliated to Shanghai Jiaotong University School of Medicine, Shanghai, China*	
Intervention	*Exenatide once daily injection) (Byetta) 10-20ug plus metformin 1500mg-2000mg daily for 12 weeks* *Exenatide once daily (Byetta) without Metformin* *Initial dose was 10 μg/day and increased to 20 μg/day after 1 month*	
Comparison	*Metformin (Glucophage) 1500mg-2000mg orally daily for 12 weeks* *Initiated at 500mg tds for 1 week and increased to 1000mg bd after 1 week*	
Co-interventions	*"All patients received guidance concerning diet and exercise as appropriate"*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Primary outcomes: Remission of prediabetes (normal OGTT after 12 weeks treatment* *Secondary: anthropometric, hormonal, metabolic - FBG, Fasting insulin, HOMA-IR, 2-hour glucose increment in OGTT, TG, total cholesterol(TC), HDL, and low-density lipoprotein (LDL),* *free androgen index (FAI), free testosterone (FT), Total testosterone (T), sex hormone binding globulin (SHBG), dehydroepiandrosterone (DHEAS), androstenedione (A2)*	
Follow up Duration	*12 weeks*	
Summary Result/s	*Compared with MET monotherapy, EXE alone or EXE+MET achieved a higher rate of remission of prediabetes among patients with PCOS by improving postprandial insulin secretion*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* *The aim was to evaluate EXE, MET and a combination of the two for clinical efficacy for prediabetes in women with PCOS.*
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	*Yes*

If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* *Diagnosed according to Rotterdam criteria* *18-45 years old* *BMI ≥25* *Diagnosed with prediabetes – presence of IFG (FBG 5.6-6.9mmol/L) and/or IGT (PPG levels for the 75-g OGTT between 7.8-11.0mmol/L) and/or HbA1c 5.7-6.4%.* *Premenopausal* *First onset of PCOS that had not received any hypoglycemic medications in the preceding 3 months, or received diet and behavioural interventions for 3 months but still meeting OGTT criteria for prediabetes.*
Exclusion criteria	Yes Partial No Not reported	*Yes* *subjects with self- reported allergy to either glucagon-like peptide 1 receptor agonists (GLP-1RA) or MET; subjects with severe liver function test abnormality (defined as alanine aminotransferase [ALT] 2.5 times or higher than the upper limit of normal range), or renal dysfunction (serum creatinine >132 μmol/L, and/or estimated glomerular filtration rate <60 mL/ min/1.73 m^2), hypertension (>160/100 mmHg), active infection, secondary diabetes, and subjects with active alcohol misuse, pregnancy, or breast feeding.*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS – **Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Yes* *Computer generated*

	Was allocation to intervention group concealed?	Yes Partial No Not reported	*Not reported* *"All eligible patients were randomly assigned… using the random number created by a computer-generated coding system".*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*No*
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*Not reported*
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*

ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	*EXE + Met = 11/61 = 18%* *Reasons: Poor compliance 11* *MET = 11/61 = 18%* *Reasons: Poor compliance 8, AE 3* *EXE = 11/61 = 18%* *Reasons: Poor compliance 9, AE 2*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*No* *ITT analysis not described, per protocol described only.*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*No* *Clinical trial registration states that improvement of fatty liver (ultrasonography) was a secondary outcome measure . This was not reported and there are no related publications.*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Yes* *No difference for age or any parameters*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Partial – modelling done for primary outcome of remission of prediabetes but this was not relevant to our review*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No* *Authors reported they had no COIs*

	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Yes* *Sample size calculation reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS		*Lack of allocation concealment and blinding key reason for high ROB*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*High*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No – all outcomes high risk of bias*	

iii. Zheng 2017/2019

Study ID	*Zheng 2017; Zheng 2019*
Study Citation	*Zheng, S., Liu, E., Zhang, Y., Long, T., Liu, X., Gong, Y., ... & Wang, F. (2019). Circulating zinc-α2-glycoprotein is reduced in women with polycystic ovary syndrome, but can be increased by exenatide or metformin treatment. Endocrine Journal, 66(6), 555-562. (APA)* *Zheng, S., Zhang, Y., Long, T., Lu, J., Liu, X., Yan, J., ... & Wang, F. (2017). Short term monotherapy with exenatide is superior to metformin in weight loss, improving insulin resistance and inflammation in Chinese overweight/obese PCOS women. Obesity Medicine, 7, 15-20.*
Study Country	China

BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	*Women with PCOS, age 18-40* *Overweight and obese (Chinese Obesity Working Group standard)*
PCOS diagnostic criteria	*Rotterdam*
Presence of infertility	*NR*
Presence of other condition/s	*Overweight/obese*
Medication History	*NR*
N per group	*Allocated/randomised: 82 (41 Exenatide 10ug bid sc, 41 metformin 1000mg bid)* *Assessed at end of study: 63 (31 Exenatide, 32 metformin)*
Setting	*Third Affiliated Hospital of Guangzhou Medical University, Endocrinology Department (Outpatients)*
Intervention	*Exenatide (Byetta, Baxter Pharmaceutical Solutions, 2.4mls/vessel) dose was 10ug bid for 12 weeks*
Comparison	*Metformin (US-Shanghai Squibb Pharmaceuticals, 500mg/tablet) dose was 1000mg bid for 12 weeks*
Co-interventions	*All patients receive diet and exercise advice*
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Weight, WC, BMI, WHR, TC, TG, HDL-C, LDL-C, hs-CRP, metabolic (e.g. fasting glucose, FINS, HOMA-IR, 2hPBG, 2hINS, AUC glucose, AUC insulin, FAI, SHBG, DHEAS, T at pre-treatment baseline and after 12-week treatment* *mFG score, Matsuda index [insulin secretion index (ISI)], Menstrual regularity (menstrual periods), Gastrointestinal effects (nausea, diarrhea, Bloating, Vomiting, Gastrointestinal spasm, stomachache, constipation), Other adverse effects (dizziness, weakness, subcutaneous induration)*
Follow up Duration	*12 weeks (post-test)*
Summary Result/s	*Exenatide was more effective than metformin in reducing body weight, waist circumference, 2hr glucose, fasting insulin, 2 hr insulin, HOMA-IR, AUC-insulin, FAI and hs-CRP.*

ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*The purpose of the study was to observe characteristics of serum ZAG (not reported) and its relationship with endocrine and metabolic indicators of PCOS patients, and to explore the effects of exenatide or metformin on serum ZAG levels in overweight/obese PCOS patients.*
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes - reported* *Rotterdam* *Age 18-40* *Obese/overweight*
Exclusion criteria	Yes Partial No Not reported	*Yes* *Not overweight/obese* *Hyperprolactinemia, congenital adrenal hyperplasia, other adrenal or ovarian tumours that produce testosterone*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS – **Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Not reported* *The study reported that participants were "randomly and equally assigned" but did not describe the method of randomisation.*

	Was allocation to intervention group concealed?	Yes Partial No Not reported	*Not reported* *There was no reporting of how allocation was concealed.*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*No* *No blinding was reported however as interventions have different delivery systems, it is likely that participants were not blinded.*
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*Not reported*
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes* *They both received the same lifestyle advice*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*

ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	*Exenatide group: 10/41= 24.4%* *Metformin group: 9/41 = 22.0%*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Not reported*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Partial* *The trial was registered. Menstrual cycle was specified in the registration but not reported in this paper.*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Partial* *Only age was reported. No t-test was performed on baseline variables.*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Partial* *Outcomes not adjusted for age*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No* *The authors declared no conflicts of interest. Funding was obtained from the National Natural Science Foundation of China (No. 81200607) and the project of the Key Laboratory for Major Obstetric Diseases of Guangdong Higher Education Institutes (No. 2012Z05)*

	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS		*Lack of randomisation, allocation concealment and blinding key reason for high RoB*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*High*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No – all outcomes high risk of bias*	

iv. Liu 2017/Li 2022

Study ID	Liu 2017/Li 2022
Study Citation	*Li et al., Archives of Gynecology and Obstetrics. 1-11, 2022* Liu et al. *Clinical Endocrinology* 2017; 87:767-774.
Study Country	China
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	*Women with PCOS (18-40) with overweight/obesity and attempting to conceive, with no other cause for female infertility and no male infertility.*
PCOS diagnostic criteria	*Rotterdam*

Presence of infertility	*Yes; without contraception, no male infertility for 2 years and not pregnant*
Presence of other condition/s	*Overweight/obese (BMI ≥ 24kg/m^2)* *Infertility*
Medication History	*Not reported*
N per group	*Allocated/randomised: 176 (88 pre-gestational Exenatide 12 weeks then metformin 12 weeks, 88 metformin 24 weeks)* **note that Li 2022 reports 160 randomised due to some participants not wanting to have ART at the centre)* *Assessed at 12 weeks: 158 (78 Exenatide, 80 metformin – all outcomes except pregnancy) (Note Li 2022 reports 72 and 75)* *Assessed at 64 weeks: 147 (72 Exenatide, 75 metformin – pregnancy only)*
Setting	*Third Affiliated Hospital of Guangzhou Medical University, Endocrinology Outpatients department.*
Intervention	*Pre-gestational Exenatide (Amylin Pharmaceuticals Inc, San Diego, USA) 10ug bd for 12 weeks, followed by Metformin 1000mg bd for 12 weeks.* *Exenatide was commenced at 5ugbd, and participants who could not tolerate AEs were instructed to reduce the dose to 5ug bd.* *In the second phase (after 12 weeks) Exenatide was ceased and participants commenced on Metformin at a dose of 500mg bd then titrating up by 500mg every 3 days to a final dose of 1000mg bd.*
Comparison	*Metformin (Bristol-Myers Squibb Co. New York, USA) 1000mg bd for 24 weeks.* *Commenced at 500mg bd then titrated up by 500mg every 3 days up to a dose of 1000mg bd.*
Co-interventions	• ***Lifestyle interventions (diet and exercise) were actively promoted in both groups according to international guidelines (ADA Standards of Medical Care 2018).*** • ***Combined OCP and barrier contraception in the first phase (12 weeks) (cyproterone and ethinyl estradiol, Bayer Technology and Engineering Co., Ltd., Leverkusen, Germany)*** • ***ART as needed in second phase. All participants were instructed to have regular intercourse (2-3 times weekly). Ovulation assessment and ART were offered to participants who failed successful pregnancy. OI was given***

	for 3 cycles, then IVF-ET was provided once. Metformin was ceased upon confirmation of pregnancy.	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Androgenecity (FAI, testosterone, SHBG), Metabolic (Fasting gluc/insulin, 120min gluc/insulin, HOMA-IR), Lipids, hs-CRP, Anthropometric (weight, BMI, WHR, WC, body composition), pregnancy rate, incidence of miscarriage, preterm delivery, menstrual frequency ratio, live birth rate, the ratio of cumulative number of pregnancies to total number, mild or moderate gastrointestinal (GI) discomfort, hypoglycemic events*	
Follow up Duration	*12 weeks (androgens, metabolic, lipids, anthropometric etc)* *64 weeks (pregnancy outcomes)*	
Summary Result/s	*In overweight/obese Chinese women with PCOS, 12 weeks of exenatide therapy significantly reduced body weight and central adiposity, insulin resistance, inflammatory markers and menstrual cycles compared to metformin. Pregestational exenatide for 12 weeks followed by metformin was more likely to result in spontaneous pregnancy than metformin, however there was no difference in pregnancy rate after ART.*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* *The study aimed to assess treatment effects associated with Metformin or exenatide on body weight, fat mass, glycemic control, IR, hormonal levels, inflammatory markers and safety after 12 weeks of treatment and compare the conception rate in the second 12-week period in overweight/obese women with PCOS.*
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* *Inclusion criteria:* *(i) is 18-40 years old; (ii) is OW/OB (body mass index [BMI] ≥24 kg/m^2); (iii) has been without contraception for more than 2 years and has not been pregnant; (iv) is attempting to become pregnant; (v) has at least one*

		unobstructed fallopian tube and a normal uterine cavity; and (vi) has a male partner with normal semen test.
Exclusion criteria	Yes Partial No Not reported	*Yes* *diagnosis of type 1 or type 2 diabetes mellitus; severe cardiovascular, kidney or liver disease (liver enzyme was more than 2 times the normal value); thyroid dysfunction; history of carcinoma; the use of drugs considered or suspected to affect the metabolic or reproductive systems in the past 3 months; or a male partner with oligospermia, asthenospermia, semen abnormal liquefaction, sexual dysfunction, or genital malformation that caused infertility.*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Yes* *Computer generated.*
	Was allocation to intervention group concealed?	Yes Partial No Not reported	*Not reported*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*No* *There is no mention of blinding of participants. Given that Exenatide is sc it would not be possible to blind.*
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*Not reported*

	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	*Exenatide group (note the two papers reported different numbers of individuals randomised. First paper reported 88 women per arm, second paper reported 80 women per arm)* *12 weeks 10/88 = 11.4% (According to Liu 2017)* *End of study 16/88 = 18.2%* *Metformin group* *12 weeks 8/88 = 9.1%* *End of study 13/88 = 14.8%*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Yes*

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*No* *There was no published protocol. However the trial registration specifies that the aim was to examine the effects of metformin, spironolactone and GLP-1 RAs. The main indicators were insulin resistance and glycolipid metabolism index, insulin resistance and beta cell function, and sex hormone levels.* *Not reported are: adipokine levels, beta cell function.*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Yes* *Groups were compared with one-way ANOVA for key variables such as age, weight.*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Not reported*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No* *The authors declared no COI.*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Yes* *A sample size calculation was performed. 45 per group was required for body weight as the primary variable.*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Partial* *Potential confounders were not taken into account.*
COMMENTS		*Lack of blinding and allocation concealment and selective outcome reporting are key reasons for moderate ROB.*	

What is the overall risk of bias?	Low Moderate High Insufficient information	*High*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*No – all outcomes high risk of bias*	

v. Ma 2021

Study ID	Ma 2021
Study Citation	Ma et.al. Short-term combined treatment with exenatide and metformin for overweight/obese women with polycystic ovary syndrome. Chinese Medical Journal *134(23):2882–2889,* 2021 10.1097/CM9.0000000000001712
Study Country	China
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	*Women with PCOS age 18-40, with overweight/obesity*
PCOS diagnostic criteria	*Rotterdam*
Presence of infertility	*Not reported*
Presence of other condition/s	overweight/obese (body mass index [BMI] ≥25 kg/m2 *No diabetes*
Medication History	*Not reported*
N per group	*Allocated/randomised: 50 (25 EXE + MET, 25 MET)* *Assessed at end of study: 40 (19 EXE + MET, 21 MET)*
Setting	*Outpatients from University teaching hospital, Department of Obstetrics and Gynaecology outpatients (Peking Union Medical College Hospital, Beijing, China)*

Intervention	*Exenatide once weekly (Bydureon) 2mg plus metformin 500mg tds for 12 weeks* *Metformin initiated at 250mg daily and increased by 250mg daily up to 500mg tds*
Comparison	*Metformin (Glucophage) 500mg tds for 12 weeks* *Metformin initiated at 250mg daily and increased by 250mg daily up to 500mg tds*
Co-interventions	*Diane-35 (ethinylestradiol 0.035 mg and cyproterone acetate 2 mg, Bayer, Leverkusen, Germany) for 21 consecutive days from the first day of menstruation or progesterone withdrawal hemorrhage, and the next cycle began after 7 days of withdrawal. Lifestyle intervention was not actively promoted*
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Primary outcomes: Anthropometric changes* *Secondary: changes in reproductive hormone levels, glucose and lipids, CRP*
Follow up Duration	*12 weeks*
Summary Result/s	*Combination therapy with exenatide once weekly and metformin was more effective than metformin alone for reducing body weight, BMI, waist circumference, and improving insulin sensitivity in women with PCOS and overweight/obesity.*

ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* *The aim was to assess the therapeutic efficacy of exenatide once weekly and metformin on body weight as well as endocrinological parameters in overweight/obese women with PCOS. The hypothesis included that EXE+MET had better efficacy in inducing weight loss and improving IR than MET alone.*
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial	*Yes* *Diagnosed according to Rotterdam criteria*

	No Not reported	*18-40 years old* *BMI ≥25*
Exclusion criteria	Yes Partial No Not reported	*Yes* *Patients with diabetes; history of cancer; personal or family history of multiple endocrine neoplasia type 2; severe cardiovascular, kidney, or liver diseases; and use of statins or other drugs known or suspected to affect reproductive or metabolic functions within 3 months before entering the study*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Yes* *"A simple computer-generated randomization process. The randomized codes in this study were generated electronically using a two-block randomization technique to create a treatment allocation spreadsheet."*
	Was allocation to intervention group concealed?	Yes Partial No Not reported	*Not reported* *A treatment allocation spreadsheet was created but there is no information about whether allocation was actually concealed.*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*No*
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*Not reported*

	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	*EXE + Met = 6/25 = 24%* *Reasons: Gastrointestinal reaction 1, Change in residence due to covid 5* *MET = 4/25 = 16%* *Reasons: Gastrointestinal reaction 1, change in residence due to covid 2, pregnant 1*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Yes*

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*No* *Clinical trial registration states proportion of subjects who lost 5% and 10% of BW, BP, menstrual cycle, acne severity score, ovarian volume, follicular number. These were not reported.*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Yes* *No difference for age or any parameters*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Not reported*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*Partial.* *"Conflicts of interest: None."* *The information of funding was not reported.*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Yes* *Sample size calculation reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS		*Lack of allocation concealment and blinding key reason for high ROB*	
What is the overall risk of bias?		Low Moderate High	*High*

	Insufficient information	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*No – all outcomes high risk of bias*	

2. Liraglutide

i. Nylander 2017

Study ID	Nylander 2017
Study Citation	Nylander et al., *Reproductive Biomedicine Online 35,1 (2017): 121-127* *Related manuscripts:* • **Nylander, M., Frossing, S., Clausen, H. V., Kistorp, C., Faber, J., & Skouby, S. O. (2017). Effects of liraglutide on ovarian dysfunction in polycystic ovary syndrome: a randomized clinical trial. *Reproductive Biomedicine Online, 35*(1), 121-127. doi:https://dx.doi.org/10.1016/j.rbmo.2017.03.023** • **Frossing, S., Nylander, M., Chabanova, E., Frystyk, J., Holst, J. J., Kistorp, C., . . . Faber, J. (2018). Effect of liraglutide on ectopic fat in polycystic ovary syndrome: A randomized clinical trial. *Diabetes, Obesity & Metabolism, 20*(1), 215-218. doi:https://dx.doi.org/10.1111/dom.13053** • **Frossing, S., Nylander, M., Kistorp, C., Skouby, S. O., & Faber, J. (2018). Effect of liraglutide on atrial natriuretic peptide, adrenomedullin, and copeptin in PCOS. *Endocrine connections, 7*(1), 115-123. doi:https://dx.doi.org/10.1530/EC-17-0327**
Study Country	Denmark
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS and overweight/obesity
PCOS diagnostic criteria	Rotterdam
Presence of infertility	*Not reported*

Presence of other condition/s	*BMI>25 and or insulin resistance (*fasting plasma C-peptide >0.6 nmol/L)
Medication History	use of hormonal contraceptives within six weeks, injectable hormonal contraceptives within six months and antidiabetic or antihypertensive drugs within three months prior to randomization led to exclusion.
N per group	*72 randomized (48 LIRA, 24 placebo)* *65 analysed (44 LIRA, 21 placebo)*
Setting	Enrolled from social media (www.facebook.com/PCOSkliniskforsoeg), from private practicing gynecologists and from our outpatient PCOS clinic, securing external validity. *Herlev Gentofte Hospital, University of Copenhagen, Denmark.*
Intervention	*Liraglutide 1.8 mg qd x 26 weeks,) administered subcutaneously 1.8 mg/day, starting at 0.6 mg/day and 1.2 mg/day for the first and second week, respectively – for 26 weeks.*
Comparison	*Placebo (Novo Nordisk A/S), provided identically packed*
Co-interventions	*None*
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Primary outcome was the difference between the groups in change from baseline to follow-up in endogenous thrombin potential (ETP) measured by thrombin generation test (TGT). Secondary outcomes were differences between groups in change from baseline to follow-up in other parameters of TGT (described in 'Assays' subsection) as well as plasma levels of vWF, PAI-1 and hsCRP. Other: Adverse effects
Follow up Duration	*26 weeks*
Summary Result/s	In overweight women with PCOS, liraglutide intervention caused an approximate 5% weight loss. There possible beneficial effects on marker of VTE. *After six months, the liraglutide group had a mean weight loss of 5.2 kg (95% CI 3.0 to 7.5, P < 0.0001) and mean reductions in fasting glucose and HbA1c of 0.24 mM (95% CI 0.05 to 0.43, P < 0.05) and 1.4 mmol/mol (95% CI 0.3 to 2.5, P < 0.05), respectively, compared with the placebo group.*

ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*The aim was to determine if* intervention with the GLP-1 analog liraglutide, in overweight women with PCOS, would lead to a beneficial reduction in VTE and CVD risk markers: thrombin generation, vWF, PAI-1 and hsCRP, possibly due to a weight loss
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	≥18 years, premenopausal and had PCOS according to Rotterdam criteria, i.e., minimum two of the three (1) oligo-/amenorrhea (cycle >35 days), (2) clinical (Ferriman–Gallwey score ≥8) or biochemical hyperandrogenism (total or free testosterone levels above reference: >1.8 nmol/L and >0.034 nmol/L, respectively) and (3) polycystic ovaries (≥12 follicles (2–9 mm) and/or volume >10 mL in at least one ovary) on transvaginal

		ultrasound. Other causes to bleeding irregularities and androgen excess were excluded. The women should have BMI ≥25 kg/m2 and/or insulin resistance defined as fasting plasma C-peptide >0.6 nmol/L at screening.
Exclusion criteria	Yes Partial No Not reported	pregnancy, breastfeeding, smoking >10 cigarettes/ day, diabetes, hypertension, overt inflammatory disease, use of herbal medicine or medications known to affect the hemostatic system. The use of hormonal contraceptives within six weeks, injectable hormonal contraceptives within six months and antidiabetic or antihypertensive drugs within three months prior to randomization led to exclusion.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Yes* *Women were randomized, in blocks of six, to 26 weeks of intervention with liraglutide or placebo in a 2:1 ratio.* .
	Was allocation to intervention group concealed?	Yes Partial No Not reported	*yes*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*yes*

	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*yes*
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	*Liraglutide:4/48 =8.3%* *2 lost to follow up* *2 abdominal pain* *Placebo:3/24=12%* *1 lost to follow up* ***1- Withdrew consent- "personal reasons"*** *1-Gall stone related abdominal pain*

	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Yes*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*yes*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*yes*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Not reported*

OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*Partial:* K and J F have given lectures at NovoNordisk sponsored symposia. C K is a member of a NovoNordisk Advisory board. J F is a member of NovoNordisk Advisory board with regard to liraglutide treatment in diabetes. **Funding** M N was supported by a grant from the University of Copenhagen throughout the study period. The study was investigator-initiated and funded by Novo Nordisk A/S, who contributed with study and placebo drug and with a grant, covering preparation of the study as well as expenses to laboratory measures. The funds were unconditioned in relation to study design, collection, analysis and interpretation of data as well as on writing the manuscript, but Novo Nordisk A/S had access to the manuscript prior to submission.
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	no A sample size calculation based on an estimated standard deviation of 130 units obtained from in-house data, declared 63 subjects, randomized 2:1, needed for 80% power to find a difference in effect size of 100 nmol/min of ETP. SG
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*yes*
COMMENTS		*Conflict of interest for authors led to moderate*	

	Despite being a randomised, double-blind RCT, possible ROB from selection bias (recruiting participants from social media might have caused, i.e. including only resourceful and highly motivated women), and possible recall bias (participants did not keep a bleeding diary before inclusion, and the reported bleeding ratio at baseline). *Sample size (lack of power) and authors' financing / position as member of NovoNordisk Advisory board with regard to liraglutide treatment in diabetes – Novo Nordisk A/S contributed with study and placebo drug and with a grant, covering preparation of the study as well as expenses to laboratory measures*	
What is the overall risk of bias?	Low Moderate High Insufficient information	*moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*No – all outcomes moderate*	

ii. Elkind-Hirsch 2022

Study ID	Elkind-Hirsch 2022
Study Citation	Elkind-Hirsch 2022., *Fertil Steril* 118:371–81, 2022
Study Country	USA
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	*Women with PCOS age 18-45, with BMI>30 kg/m2*
PCOS diagnostic criteria	*NIH*
Presence of infertility	*not reported*
Presence of other condition/s	*BMI>30 kg/m2, irregular periods (cycle length outside 21–35 days or 50 ng/dL, with biochemical hyperandrogenism (total testosterone >50 ng/dL or free androgen index [FAI] >3.87)*

Medication History	*No*	
N per group	*Allocated/randomised: 82 (55 LIRA 3, 27 placebo)* *Assessed at end of study: 67 (44 Lira 3, 23 placebo)*	
Setting	*University teaching hospital with patients from endocrinology clinics and weight management clinic, Louisiana, USA*	
Intervention	*Liraglutide 3 mg/day x 32 weeks*	
Co-intervention	*Lifestyle recommendations:* - ***diet of 500–800 kcal/day reduction made up of 50% carbohydrates, 20% proteins, and 30% of fat with increased consumption of fiber, whole grains, cereals, fruits, and vegetables*** - ***at least 30 minutes of moderate-intensity physical activity daily.***	
Comparison	*placebo* *(identical prefilled pen by Novo Nordisk A/S)*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	- ***Primary: Changes in body mass and FAI.*** - ***Anthropometrics, circulating hormones, menstrual regularity, markers of glycemic control, and lipid profiles after 32 weeks*** - ***Safety was assessed in all patients who received at least one dose of the study drug.***	
Follow up Duration	*32 weeks*	
Summary Result/s	*In the obese group, liraglutide 3mg was more effective in reducing body weight, androgenicity and cardiometabolic parameters compared with placebo*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	yes	YES The aim of this 32-week trial was to evaluate the efficacy and safety of LIRA 3 mg compared with placebo (PL) for reducing BW and hyperandrogenism in women with obesity and PCOS
Does the study have specified inclusion/exclusion criteria?	Yes	*Yes*

If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes	*Yes*
Inclusion criteria		Yes	YES PCOS (NIH) with a body mass index of at least 30 kg/m2 - **irregular periods (cycle length outside 21–35 days or** <8 cycles per year) together with biochemical hyperandrogenism (total testosterone [TT] >50 ng/dL, or free androgen index [FAI] >3.87) and exclusion of known disorders for bleeding irregularities and androgen excess. Also must have agreement to use effective contraception consistently during the therapy
Exclusion criteria		Yes	Yes diabetes diagnosis, smoking within 6 months, pregnancy or lactation, clinically significant systemic disease, uncontrolled hypertension, acute pancreatitis, injectable hormonal contraceptive use within 6 months, use of oral contraceptives, other steroid hormones, drugs that affect gastrointestinal motility or carbohydrate metabolism, and/or anti-obesity drugs within 3 months before study entry.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes	YES Participants were randomly allocated (2:1) on the basis of computer-generated random numbers using the block randomization method
	Was allocation to intervention group concealed?	Yes Partial No Not reported	*yes*

PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*yes*
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*yes*
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*yes*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*

ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	*LIRA 3 mg 11/55= 20%* *(6 intolerable SE of nausea, 2 non compliant, 1 concern about medication, 2 pregnancy)* *Placebo: 4/27= 14.8%* *(2 no benefits of meds, 1 gall bladder surgery, 1 covid exposure and need to quarantine)*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Yes*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*yes*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Yes*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*yes*

OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*Partial* *This study was supported by an investigator-initiated research grant from Novo Nordisk awarded to main author (K.E.H.).* *K.E.H. reports receiving grant support from Novo Nordisk, Dexcom, AstraZeneca, and Ortho Diagnostics, serves on advisory board for NovoNordisk and AstraZeneca and is a consultant for EMD Serono, NovoNordisk, and Lilly; honoraria from NovoNordisk.* *N.C. reports grant support from Ferring Pharmaceuticals.* *J.S. reports grant support from Ferring Pharmaceuticals.* *E.S. has nothing to disclose.* *D.B. has nothing to disclose.*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Yes.* To calculate the sample size, we used the standard formula suggested for clinical trials by considering a type I error (a) of 0.05 and a type II error (b) of 0.20 (power ¼80%). Sample size calculation revealed that 57 participants randomized in a 2:1 ratio (LIRA 3 mg:PL) were needed. Using a 30% dropout rate, the study was designed to recruit 82 participants; enroll 54 LIRA 3 mg and 28 PL participants to ensure that the number of subjects completing the study (38 LIRA 3 mg/19 PL) as derived by the sample size calculation was met.
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*yes*

COMMENTS	*Declared conflict of interest*	
What is the overall risk of bias?	Low Moderate High Insufficient information	*low*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*no*	

3. Semaglutide

i. Jensterle 2021

Study ID	Jensterle 2021
Study Citation	Jensterle M et al., *Diabetes Research and Clinical Practice* 178: 2027
Study Country	Slovenia
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS and obesity
PCOS diagnostic criteria	Rotterdam
Presence of infertility	Not reported
Presence of other condition/s	*Obesity: BMI criteria no reported*
Medication History	Use of medications that cause clinically significant weight gain or loss were excluded
N per group	*30 recruited* *25 concluded the study* *Semaglutide 13* *Placebo 12*

Setting	academic outpatient clinics in University Medical Centre Ljubljana, Slovenia
Intervention	*Semaglutide* initiated at a dose of 0.5 mg once weekly for the first 4 weeks, and increased to 1.0 mg once weekly for the remaining treatment period Total 16 weeks
Comparison	*Placebo pen*
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Changes in fat storage in tongue (primary), and anthropometrics at 16 weeks*
Follow up Duration	*16 weeks*
Summary Result/s	*Semaglutide treated patients lost significantly more fat in the tongue, compared with placebo. The lingual fat reduction correlates with significant reduction in BMI, body weight and waist and neck circumference.*

ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Partial* To evaluate the effect of the latest GLP-1RA semaglutide, which is also in clinical development for weight management, on fat storage in the tongue of obese women, and its relationships with several clinical and laboratory parameters.
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	*Partial* *although BMI cutoff not mentioned*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Partial* *Cannot tell for inclusion as they were not well reported* *In the clinical trial registry and protocol states 18-50 (in protocol 18 – menopause), BMI >30*

Inclusion criteria	Yes Partial No Not reported	*Partial* *Diagnosis using Rotterdam was described, no other inclusion criteria were described apart from "30 women with PCOS and obesity was recruited". No description of obesity cutoff or age*
Exclusion criteria	Yes Partial No Not reported	Any known serious chronic illness, including diabetes, angina pectoris, coronary heart disease, congestive heart failure, severe renal and hepatic impairment, inflammatory bowel disease, gastroparesis, cancer, chronic obstructive lung disease, psychiatric and neurological disease. Use of medications that cause clinically significant weight gain or loss, previous bariatric surgery, a history of idiopathic acute pancreatitis, a family or personal history of multiple endocrine neoplasia type 2 or familial medullary thyroid carcinoma, current smoking, pregnancy, expecting pregnancy or breast feeding, allergy to any of the ingredients of the study medication and anticipated change in lifestyle (e.g. eating, exercise or sleeping pattern) during the trial. Subjects with contraindications for magnetic resonance imaging (MRI) scanning (implants, claustrophobia etc) were also excluded.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Yes* *From protocol – RAND randomisation function is used*
	Was allocation to intervention group concealed?	Yes Partial No Not reported	*Partial* *Allocated by study nurse using a subject randomisation list.*

PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*Yes – protocol states participants were blinded*
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*Partial* *the person randomising and the main investigator were not blinded.*
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*Yes*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes, but not all reported*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*

ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?** **Please also record reasons for withdrawal in each group**	X% treatment X% control/ comparison Not reported	*Obese women with PCOS* *Semaglutide = 2/15= 13%* *Placebo = 3/15 = 20 %* *Reasons for withdrawal: Due to the COVID-19 pandemic*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Yes*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*No* *The protocol states a number of other outcomes such as taste discrimination, gastric emptying, blood pressure, menstrual regularity which were not reported in this paper.*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*yes*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Not reported*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*Partial* *Author is a Medical Director of Novo Nordisk in Eastern Europe and has received honoraria and research support for a wide range of pharmaceutical companies*

	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Yes*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*yes*
COMMENTS		*Moderate – while study is single-blinded, there is a conflict of interest and selective outcome reporting.*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No – all outcomes moderate*	

4. Orlistat

i. Moini 2015

Study ID	Moini 2015
Study Citation	Moini et. al. Effect of Orlistat on weight loss, hormonal and metabolic profiles in women with polycystic ovarian syndrome: a randomized double-blind placebo-controlled trial.
Study Country	Iran
BRIEF CHARACTERISTICS OF RCT	

Patient/population/ participants	Women with PCOS and overweight/obesity
PCOS diagnostic criteria	Rotterdam
Presence of infertility	Not reported
Presence of other condition/s	Overweight/obesity
Medication History	*No – exclusion criteria stated no history of taking. Hormonal medications in the last six months*
N per group	*Allocated/randomised: 50 orlistat, 50 placebo* *Assessed at end of study: 43 orlistat, 43 placebo*
Setting	*Gynecology clinic at a University hospital*
Intervention	*Orlistat 120mg three times a day for 3 months, Aburaihan Pharmaceutical Company*
Comparison	*Placebo identical in shape, manufactured by Aburaihan Pharmaceutical Company (same company)*
Co-interventions	*Lifestyle interventions:* *Hypocaloric MUFA diet 1200-1800 kcal/day, 55% carbohydrates, 30% fat, 15% protein.* *Encouraged to walk 30 mins/day* *Weekly exercise diaries showed that consistency of exercise was 74.8% in the intervention and 77% in the control group.*
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Anthropometric, FBG, FI, HOMA-IR, total testosterone, TG, HDL, LDL.*
Follow up Duration	*3 months*
Summary Result/s	*Between-group differences for weight, BMI, WHR, TG, LDL and HDL but not testosterone, FINs, FBG, HOMA-IR*
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT	

Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* *The aim was to determine the effects of combined orlistat and conventional hypocaloric diet compared to diet alone in overweight/obese women with PCOS*
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* *Diagnosis according to Rotterdam* *Reproductive age (19-38)* *BMI >25* *No history of taking hormonal medications in last 6 months* *No current dietary modifications or in the past 6 months*
Exclusion criteria	Yes Partial No Not reported	*Yes* *History of cholestasis, liver disease, renal disease, malabsorption, hypothyroidism.*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS **Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Yes* *Random number table.*

	Was allocation to intervention group concealed?	Yes Partial No Not reported	*Not reported*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*Yes*
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*Yes* *A member of the study team who was blinded to both groups visited each participant monthly.*
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*Yes*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*

ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?** **Please also record reasons for withdrawal in each group**	X% treatment X% control/ comparison Not reported	*Orlistat = 7/50 = 14%* *3 - lack of compliance for follow-up visits* *2 - concerns about treatment/side effects* *1 - presence of medical conditions* *1 - use of different medical treatments* *Placeb = 7/50 = 14%* *4 - lack of compliance for follow-up visits* *1 - concerns about treatment/side effects* *2 - use of different medical treatments*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Yes*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Not reported* *This is difficult to determine if there isn't a protocol or trial registration.*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Partial* *No t-test was reported for age .No other details were reported. Mean age was 27.42 + 3.31 in control and 26.8 + 5.16 in the intervention group.*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Not reported*

OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No* *The authors declared no COI*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Partial* *Potential confounders not adjusted for*
COMMENTS		*Double blinded RCT*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*Unclear*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

ii. Song 2017

Study ID	Song 2017/Ruan 2018
Study Citation	*Effect of Diane-35, alone or in combination with orlistat or metformin in Chinese polycystic ovary syndrome patients.* *Ruan, Xiangyan; Song, Jinghua; Gu, Muqing; Wang, Lijuan; Wang, Husheng; Mueck, Alfred O* *Archives of gynecology and obstetrics / 2018;297(6):1557-1563* *Germany 2018 /*

	Effect of orlistat or metformin in overweight and obese polycystic ovary syndrome patients with insulin resistance. *Song, Jinghua; Ruan, Xiangyan; Gu, Muqing; Wang, Lijuan; Wang, Husheng; Mueck, Alfred Otto* *Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology / 2018;34(5):413-417* *England 2018 /*
Study Country	China
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS and overweight/obesity (BMI≥24)
PCOS diagnostic criteria	Rotterdam
Presence of infertility	Not reported
Presence of other condition/s	Insulin resistance (fasting insulin > 10mIU/L) Overweight/obesity
Medication History	No history of taking medication or dietary modification currently or for the preceding 3 months.
N per group	*Allocated/randomised: 240 (numbers in each group not reported – so the assumption is 60 per group for:* 1. ***Orlistat + Diane,*** 2. ***Metformin + Diane*** 3. ***Orlistat + Metformin + Diane,*** 4. ***Diane only*** *Assessed at end of study: 240*
Setting	*Patients attending the Department of Gynaecological Endocrinology in a University Hospital in Beijing, China*
Intervention	*Orlistat 120mg tds*
Comparison	*Metformin titrated up to 500mg tds* *Diane-35, 2mg cyproterone acetate and 35 μg ethinylestradiol) once daily for 21 days per cycle*

Co-interventions	*Based on each patient's basal energy requirements and on an estimation of the typical activity level, at baseline, a dietician prescribed:* - ***an individualized low-fat diet, and*** - ***moderate daily physical activity.***	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Hormonal, metabolic, anthropometric*	
Follow up Duration	*12 weeks/3 months*	
Summary Result/s	*Improvements in body weight, BMI, and HDL in the Orlistat + Diane and Orlistat + Metformin + Diane groups compared to Diane alone.* *DHEA was lower in all groups compared to Diane alone.* *SHBG was higher in the Orlistat + Metformin group compared to Diane alone.* *FAI was lower in the Orlistat group compared to Diane alone.* *Orlistat has mild side-effects and is better tolerated compared with metformin*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* *The aim was to evaluate the effect of Diane-24 alone or in combination with orlistat or metformin on androgen and body fat % in Chinese overweight and obese PCOS patients.*
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No	*Chinese women* *Age 18-40* *BMI ≥ 24*

		Not reported	*FINS > 10mIU/L* *No history of taking medication or dietary modification currently or for preceding 3 months*
Exclusion criteria		Yes Partial No Not reported	*Ischemic heart disease* *Clinical evident vascular disease* *T2D with ketoacidosis* *Renal / hepatic impairment* *Severe infection* *Malignant tumour*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Yes – random number table*
	Was allocation to intervention group concealed?	Yes Partial No Not reported	*Not reported*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*No*
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*Not reported*

	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?** **Please also record reasons for withdrawal in each group**	X% treatment X% control/ comparison Not reported	*No dropouts* *"All 240 included subjects completed the 12-week study period."*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Yes*

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Not reported* *This is difficult to determine if there isn't a protocol or trial registration*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Yes*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Not reported*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No* *The authors report no COI*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Partial* *Confounders not reported*
COMMENTS		*Lack of allocation concealment and blinding*	
What is the overall risk of bias?		Low Moderate High	*High*

	Insufficient information	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*No – all outcomes high risk of bias*	

iii. Gu 2022

Study ID	Gu 2022
Study Citation	*Effect on the cardiovascular independent risk factor lipoprotein(a) in overweight or obese PCOS patients with ethinyl-estradiol/drospirenone alone or plus orlistat.* *Gu, Muqing; Ruan, Xiangyan; Li, Yanqiu; Li, Tianhe; Yin, Chenghong; Mueck, Alfred O* *Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology / 2022;38(7):598-602 England 2022 /* *doi:10.1080/09513590.2022.2078805*
Study Country	China
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	*Women with PCOS and overweight/obesity (BMI ≥24)*
PCOS diagnostic criteria	*Rotterdam*
Presence of infertility	*Not reported*
Presence of other condition/s	*Overweight/obesity (BMI ≥ 24kg/m²)*
Medication History	*No hormonal contraceptives/concomitant medications that interact with OCP for 2 cycles before/throughout the study*
N per group	*Allocated/randomised: 66 (33 Orlistat + OCP, 33 OCP alone)*

	Assessed at end of study: not explicitly described as there was no reporting of dropouts in the study but assume 66	
Setting	*Department of Obstetrics and Gynecology in a University Hospital in Beijing*	
Intervention	*Orlistat 120mg tds + OCP (drospirenone 3mg/ethinylestradiol 20μg in a 24-active/4-inert pill combination) once daily*	
Comparison	*OCP alone (drospirenone 3mg/ethinylestradiol 20μg in a 24-active/4-inert pill combination) once daily*	
Co-interventions	*Lifestyle interventions: dietician prescribed personalised balanced nutrition diet based on resting energy expenditure*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Anthropometric, metabolic, inflammatory markers, hormonal*	
Follow up Duration	*3 months*	
Summary Result/s	*CRP, LDL-C, Weight, BMI, WC, body fat percentage were improved in the Orlistat + OCP group compared to OCP alone*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* *The aim was to investigate the effect of orlistat with the OCP vs OCP alone for the cardiovascular independent risk factor lipoprotein A*
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*

Inclusion criteria	Yes Partial No Not reported	*18-40* *BMI ≥24* *Rotterdam criteria*
Exclusion criteria	Yes Partial No Not reported	*Contraindications for OCP use* *Use of antilipidemic agents* *T2D* *CVD* *Renal/hepatic impairment* *Severe infections* *Hormonal contraceptives/concomitant meds that interact with OCP in previous 2 cycles*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS – **Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Not reported* *Sequence generation not reported*
SELECTION BIAS – **Was allocation to intervention group concealed?**	Yes Partial No Not reported	*Not reported*
PERFORMANCE BIAS – **Were patients blind to intervention group?**	Yes Partial No Not reported	*No*
PERFORMANCE BIAS – **Were investigators and care providers blind to intervention group?**	Yes Partial No Not reported	*Not reported*

	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?** **Please also record reasons for withdrawal in each group**	X% treatment X% control/ comparison Not reported	*Not explicitly reported but as the authors did not mention dropouts, assume 0%*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Yes*

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Not reported* *This is difficult to determine if there isn't a protocol.*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Partial* *"All individuals were matched according to age and BMI at the study baseline." – **but** "the Orlistat + OCP group had significantly higher serum CRP-concentrations than the OCP alone group."* *"Other characteristics were not significantly different between the groups at baseline. "*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Not reported*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No* *The authors report no COI*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Yes* *Sample size calculation was reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Not reported*

COMMENTS	*Lack of reporting of randomisation sequence generation and blinding key reason for high RoB*	
What is the overall risk of bias?	Low Moderate High Insufficient information	*High*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*No – all outcomes high risk of bias*	

7. Study Characteristics Table

Author, year, country	Population/ Setting	Study Design	Sample Size per group	Intervention/ exposure details	Comparison/ control details	Co-interventions	Follow up Duration	Outcomes	Summary of findings
Elkind-Hirsch 2021	Women with PCOS and BMI30-45, Endocrine and Weight Loss Clinic	Single blinded five arm RCT	Exenatide 20 Dapa 17 Exenatide + Dapa 20 Dapa + metformin 19 Phentermine-topiramate 16	Exenatide 2 mg Weekly Exenatide 2mg weekly + dapaglifozin 10mg/day Phentermine 7.5mg/Topiramate 46mg ER daily	Dapa 10 mg/day Dapa + metformin XE 10mg/2000mg	Diet and exercise counselling, encouragement to increase daily exercise	24 weeks	FAI, total testosterone, DHEAS fasting glucose, HOMA-IR, *Matsuda index: Sensitivity index (SI)* Total cholesterol, LDL, HDL, TG, Weight, BMI, WHR, WC, body fat %, Fat mass, Fat free mass-Lean BM Gastrointestinal effects Other AE	There were no differences between groups for metabolic outcomes. There was no difference between EXE and DAPA, EXE and PT, or PT and EXE/DAPA for any outcomes. EXE/DAPA resulted in most loss of weight and total body fat and WC and was superior to DAPA or DAPA/MET for body weight, BMI, total fat mass and total body fat %, and to DAPA/MET for WC. EXE/DAPA was superior to PT for triglycerides but not for any other outcomes. Phen/TM was more effective in promoting weight loss (body weight and BMI) than Dapa or Dapa/Met. PT resulted in greater reduction in body fat and body fat % than DAPA and DAPA/MET, and in waist circumference than DAPA/Met. However there were no significant between-group differences for WHR. All treatments resulted in a reduction in lean BM.

									GI AEs were most common with nausea most common in EXE group. The highest loss rate was from the PT group because of unpleasant AEs e.g. headache, insomnia and fatigue.
Tao et al. 2021	Overweight/obese PCOS patients with prediabetes; in hospital	Parallel Open-label RCT	Exenatide =50 Metformin=50	Exenatide (10-20 μg daily) sc	Metformin (1500-2000 mg daily)	Guidance on diet and exercise	12 weeks	Hormonal: free androgen index (FAI), Total testosterone (T), sex hormone binding globulin (SHBG), dehydroepiandrosterone (DHEAS), androstenedione (A2) FBG, Fasting insulin, HOMA-IR, 120min glucose from OGTT TG, total cholesterol(TC), HDL, and low-density lipoprotein (LDL), Weight, BMI, Gastrointestinal effects, Other adverse effects (headache)	MET resulted in lower FBG than EXE + MET. There was no difference between groups for measures of insulin sensitivity except for 2hr insulin which was lower in the the MET group compared to EXE or EXE+MET. There was a greater reduction in LDL cholesterol in the MET group compared to EXE+ MET. There was no difference between groups for weight and BMI. Note that the authors reported a higher remission rate of prediabetes in the EXE and EXE+ MET groups compared to MET.
Zheng et al., 2019/Zheng et al. 2017, China	Women with PCOS (18 to 40 years old); Endocrinology Department of Hospital (outpatients)	Parallel RCT	Exenatide = 31 Metformin = 32	Exenatide 10 μg, twice a day sc (20 μg total)	Metformin 1,000 mg, twice a day (2g total)	Diet and exercise advice	12 weeks (after test at baseline)	mFG score, FAI, T, SHBG, DHEAS, fasting glucose, FINS, HOMA-IR, 2hPBG, 2hINS, AUC glucose, AUC insulin, Matsuda index [insulin secretion index (ISI)], TC, LDL-C, HDL-C, TG, hs-CRP,	Exenatide was more effective than metformin in improving body weight, BMI, waist circumference, 2 hr insulin, HOMA-IR, AUC-insulin, Matsuda index, and hs-CRP. Metformin was more effective at reducing total cholesterol. Metformin was better tolerated than Exenatide in the first 8 weeks.

								Weight, WC, BMI, WHR, Menstrual regularity (menstrual periods), Gastrointestinal effects (nausea, diarrhea, Bloating, Vomiting, Gastrointestinal spasm, stomachache, constipation), Other adverse effects (dizziness, weakness, subcutaneous induration)	Exenatide was twice as likely to cause nausea in the first 8 weeks.
Li et al., 2022, China/Liu et al., 2017, China	Women with PCOS (18 to 40 years old); Endocrinology Department of Hospital (outpatients)	Crossover, open label RCT	<u>Liu 2017</u> Exenatide + lifestyle instructions = 78 Metformin + lifestyle instructions = 80 <u>Li 2022 (64 weeks – pregnancy outcomes)</u> Exenatide + lifestyle instructions = 72 Metformin + lifestyle instructions = 75	<u>Li 2022</u> First stage: Exenatide 5 μg, twice daily sc for 4 weeks and increased to 10 μg twice daily after 4 weeks; 5 μg twice a day (for those who could not tolerate adverse events) Second stage: Metformin, 500 mg, twice a day and titrating up to 1000 mg twice daily by 500 mg every 3 days <u>Liu 2017</u>	Li 2022 First stage: Metformin 500 mg, twice a day and titrated by 500 mg every 3 days up to 1000 mg twice a day for 12 weeks Second stage: Metformin 1000 mg twice a day <u>Liu 2017</u> Metformin, 500 mg once a day and gradually reached 1000 mg twice a day after 1 week	Lifestyle: Diet and exercise were actively promoted in both groups according to international guidelines (ADA Standards of Medical Care 2018). OCP for first 12 weeks: A low-dose hormonal contraceptive pill cyproterone and ethinyl estradiol	12 weeks (all outcomes except pregnancy/repro) – at completion of first phase of the crossover trial (ie EXE v MET) 64 weeks (pregnancy/reproductive0	FAI, T, SHBG, fasting glucose, FINS, HOMA-IR, 2hPBG, 2hINS, TC, LDL-C, HDL-C, TG, hs-CRP, Weight, WC, BMI, WHR, % Body fat Reproductive: menstrual regularity, pregnancy rate, miscarriage rate, preterm delivery, live birth	In overweight or obese infertility PCOS, pregestational exenatide treatment resulted in more spontaneous pregnancy likely due to greater weight reduction and improvement of insulin resistance compared with metformin treatment without obvious benefit on overall pregnancy rate after ART or pregnancy outcomes of successful conceived women. EXE resulted in more weight loss, improved fat percentage and BMI, lower WC and WHR, more menstrual cycles, lower hs-CRP, and improved insulin sensitivity (FINS, 2-hr insulin, HOMA-IR). AE: GI discomfort more frequent in the EXE group.

				First 12-week period: Exenatide 10 µg once a day and increased to 10 µg twice a day after 1 week, Second 12-week period:Metformin 1000 mg twice a day,		ART as needed in second phase.			
Ma et al. 2021	Overweight/obese women with PCOS; Department of Obstetrics and Gynecology in hospital	Parallel Open-label RCT	Exenatide+Metformin=19 Metformin=21	Exenatide (2 mg once a week) + Metformin (500 mg three times a day)	Metformin (500 - 1500 mg daily)	OCP (Diane-35 (ethinylestradiol 0.035 mg and cyproterone acetate 2 mg)	12 weeks	Hormonal:Total testosterone, DHEAS, Metabolic: Fasting plasma glucose, Fasting insulin, HOMA-IR, QUICKI, OGTT 2 h PG, OGTT 2 h insulin, Matsuda index Lipids:Total cholesterol, LDL-c, HDL-c, TG, hsCRP, Anthropometric: Weight, BMI, Waist circumference, Gastrointestinal effects Other adverse effects	Metformin combined with Exenatide was more effective than Metformin alone in reducing body weight, BMI, and waist circumference and improving some but not all metabolic outcomes (2hr insulin, Matsuda, Total cholesterol, TG, HDL, fasting gluc) in overweight/obese women with PCOS. Total testosterone was higher in the EXE+MET group compared to the MET group at end of treatment.
Nylander 2017 (Frossing 2018x2, Nylander 2017)	Women with PCOS ≥18 years BMI ≥25 kg/m2 and/or insulin resistance defined as fasting plasma C-peptide >0.6	double blind RCT	Liraglutide 1.8 mg 44 Placebo 21	Liraglutide 1.8 mg	Placebo	None	26 weeks	Hormonal (FAI, Free and total testosterone, SHBG, Androstenedione) Metabolic (fasting gluc, Matsuda) Lipids (TC, LDL, HDL, TG)	Improved free testosterone, SHBG, fasting glucose, weight, BMI, WHR, WC, fat mass, and bleeding ratio in the liraglutide group compared to placebo There was more lean mass lost in the liraglutide group compared to placebo

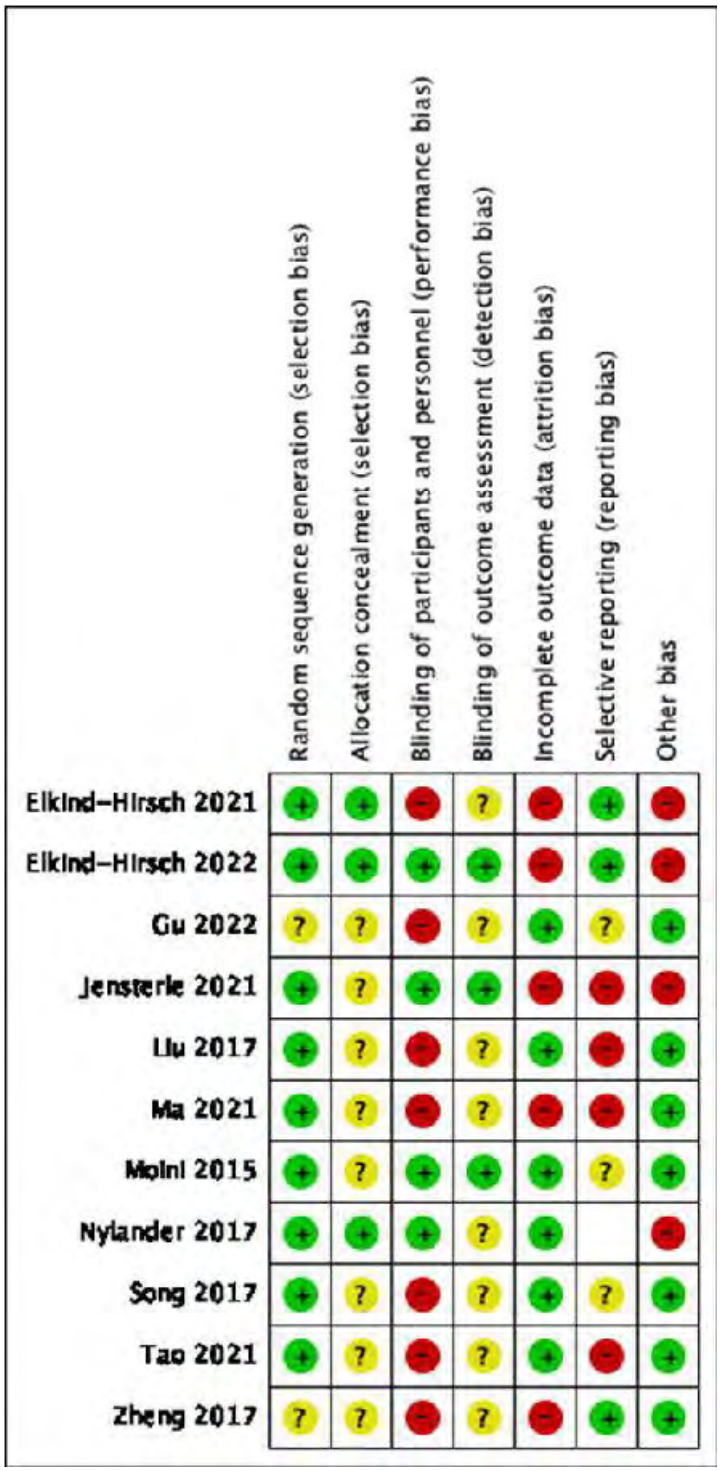
	nmol/L at screening. Herlev Gentofte Hospital, University of Copenhagen, Denmark.							Hs-CRP Anthropometric (Weight, BMI, WHR, WC, FFM, FM, %body fat) Reproductive (bleeding ratio) AEs (GI and other)	The most prevalent adverse effects were nausea (liraglutide 79% versus placebo 13%, P < 0.01), primarily seen in the start-up phase, and constipation (26% versus 0%, P < 0.01). Gallstone-related pain was experienced by 6% of women in the liraglutide group and 4% in the placebo group (NS)
Elkind-Hirsch 2022	Women with PCOS and BMI>30, Age 18-46, Outpatient Endocrinology and weight management clinic, USA.	double blind RCT	Liraglutide 3 mg = 44 Placebo= 23	Liraglutide 3 mg daily	Placebo (identical prefilled pen)	Lifestyle: diet of 500–800 kcal/day reduction made up of 50% carbohydrates, 20% proteins, and 30% of fat with increased consumption of fiber, whole grains, cereals, fruits, and vegetables at least 30 minutes of moderate-intensity physical activity daily.	32 weeks	Hormonal (FAI, Total testosterone, DHEA) Metabolic (fasting gluc, HOMA-IR, Matsuda) Lipids (TC, LDL, HDL, TG) Anthropometric (Weight, BMI, WHR, WC, % 5% and 10% weight loss, FFM, FM, % body fat) Reproductive (menstrual cycles/year) AEs (GI and other)	Liraglutide 3mg daily improved FAI but not total testosterone and DHEA compared to placebo Liraglutide improved all measures of glucose metabolism and insulin resistance (fasting gluc, HOMA-IR, Matsuda), and body weight, central adiposity, body composition compared to placebo but there was no difference in fat free mass between groups. There was no difference between groups for lipids except for triglycerides Women in the liraglutide group had more menstrual periods than the placebo group Women in the liraglutide group complained of more nausea, vomiting, diarrhoea, constipation, reflux, indigestion, prolonged menstrual bleeding, injection site induration although statistical analysis for between-group comparisons were not reported.

									The placebo group reported more COVID-19 infections and absence of menstrual cycles.
Moini 2015	Women with PCOS and overweight/obesity;Gynecology Clinic in University hospital in Iran	Parallel double blind RCT	Orlistat = 43 Placebo = 43	Orlistat 120mg tds	Placebo	Hypocaloric MUFA diet Encouraged to walk 30 mins/day	3 months	Hormonal: Total testosterone Metabolic: Fasting glucose, FINS, HOMA-IR Lipids: LDL, HDL, TG Anthropometric: Weight, BMI, WHR AEs	Between-group differences for weight, BMI, WHR, TG, LDL and HDL but not testosterone, FINs, FBG, HOMA-IR
Gu 2022	Women with PCOS (Rotterdam), 18-40y.o., overweight / obese (BMI ≥ 24) Department of Gynecological Endocrinology, Beijing Obstetrics and Gynecology Hospital, Capital Medical University, Beijing, China	Parallel open-label RCT	Orlistat + LS + OCP = 33 LS + OCP alone = 33	Orlistat 120mg 3x day, plus OCP and lifestyle: OCP (DRSP 3mg / EE 20 μg in a 24-active/4-inert pill regimen; Lifestyle: Personalized balanced nutrition diet based on the patient's resting energy expenditure.	OCP alone (DRSP 3mg / EE 20 μg in a 24-active/4-inert pill regimen) and lifestyle (Personalized balanced nutrition diet based on the patient's resting energy expenditure)	OCP and lifestyle (Personalized balanced nutrition diet based on the patient's resting energy expenditure)	3 months	Hormonal (free/total testosterone, SHBG) Metabolic (Fasting glucose, fasting insulin) Lipids (TC, HDL, LDL, TG) CRP Anthropometric (weight, BMI, WC, % body fat)	Reductions in LDL-C, weight, BMI, WC, BFP, CRP and FT were significantly greater in in the Orlistat + OCP group.
Song 2017	Chinese women diagnosed with PCOS according to	Parallel, open-label, RCT	Orlistat + Diane-35 + Lifestyle = 60	**(1) Orlistat, 120 mg 3x daily before each meal + cointerventio**	**(3) Lifestyle + Diane alone** **(4) Metformin + lifestyle + Diane**	Lifestyle in all groups - Based on each patient's basal energy	12 weeks	Hormonal (FAI, Free/total testosterone, SHBG, DHEAS, Androstenedione)	Compared to Diane-35 alone: - DHEA-S significantly decreased in all groups - SHBG significantly increased in the Orlistat + Metformin group

	Rotterdam criteria Age 18–40 years BMI ≥ 24 kg/m2 FINS > 10 mIU/L, No dietary modification for the preceding 3 months Patients attending the Department of Gynecological Endocrinology, Beijing Obstetrics and Gynecology Hospital, Capital Medical University (Beijing, China).		Metformin + Diane-35 + Lifestyle = 60 Orlistat + Metformin + Diane + lifestyle = 60 Diane-35 + Lifestyle = 60	**ns of Lifestyle + Diane** **(2) Orlistat + Metformin + Diane + Lifestyle**	Metformin: up to 1.5g daily.	requirements and on an estimation of the typical activity level, at baseline, a dietician prescribed: - an individualized low-fat diet, and moderate daily physical activity. Diane-35 (2mg cyproterone acetate and 35 lg ethinylestradiol) 1x daily during the 3 cycles, at the same time for 21 days in all groups		Metabolic (Fasting glucose, fasting insulin, HOMA-IR) Lipids (TC, HDL, LDL, TG) Anthropometric (Weight, BMI, WC, Fat mass, % Body fat) – no data available apart from differences between groups and unlabelled figures, contacted authors for numerical data but no response AEs	- FAI significantly decreased in the Orlistat group There were no between-group differences for metabolic outcomes. Both Orlistat and Orlistat + Metformin increased HDL compared to Diane alone Both Orlistat and Orlistat + Metformin were superior to Diane alone for reducing body weight and BMI Orlistat + Metformin was superior to Metformin for body fat %reduction (Numerical data is not provided in the numerical tables) There was no difference in other anthropometric outcomes between Orlistat and Orlistat v Metformin. There were no between-group differences between Orlistat and Metformin. Orlistat has mild side-effects and is better tolerated compared with metformin.
Jensterle 2021	Women with PCOS and obesity, academic centre in Slovenia	Single blinded placebo-controlled trial	Semaglutide 13 Placebo 12	Semaglutide 1 mg once weekly for 16 weeks	Placebo	None	16 weeks	Metabolic: fasting gluc, FINS, HOMA-IR, 120 min gluc and insulin Lipids: Total chol, LDL, HDL, TG	Semaglutide was superior to placebo for body weight, BMI, waist circumference, HDL, visceral body fat, plasma insulin and 120min glucose Nausea and vomiting were reported in the semaglutide group but were transient and mild-moderate in severtiy

								Anthropometric: weight, BMI, WC, visceral body fat AEs	

8. Risk of Bias summary



9. GRADE ASSESSMENTS AND EVIDENCE PROFILE

1. Introduction

Meta-analyses were conducted on the following comparisons:

1. Exenatide v Metformin (2 RCTs) (Zheng, Zhang et al. 2017, Tao, Zhang et al. 2021)

2. Orlistat + lifestyle + OCP v lifestyle + OCP (2 RCTs) (Song, Ruan et al. 2018, Gu, Ruan et al. 2022)

For the following comparisons, a meta-analysis was not possible on any outcomes either due to the comparison only having one representative RCT or RCTs reporting non-parametric data (median and IQR) or change scores without any information on standard deviation or standard error. We have provided a narrative synthesis for convenience.

Exenatide v DAPA (Dapagliflozin)

Exenatide + DAPA v DAPA

Exenatide + OCP v MET (Metformin) + OCP

Exenatide + MET v MET alone

Exenatide + MET + OCP (Oral Contraceptive Pill) v MET + OCP alone

Exenatide v Phentermine/Topiramate

Exenatide v DAPA + MET

Liraglutide v Placebo

Liraglutide + LS (lifestyle) v Placebo + LS

Semaglutide v Placebo

Phentermine/Topiramate v DAPA

Phentermine/Topiramate v DAPA + MET

Phentermine/Topiramate v EXE + DAPA

Orlistat + LS v LS +-placebo

Orlistat + LS v MET + LS

Orlistat + LS + OCP v MET + LS + OCP

Orlistat + LS + OCP + MET v MET + LS + OCP

2. Narrative Syntheses

EVIDENCE SUMMARY

We found 16 manuscripts[1-16] representing 11 trials and 996 participants. Four trials were included in meta-analyses[5,16-18] . All studies enrolled women with overweight/obesity and/or insulin resistance. There were no studies on adolescents. Five studies trialled exenatide [1,10,11,16,18], three orlistat [5,12,17], two liraglutide [2,13], one semaglutide [19] and one phentermine-topiramate as well as exenatide [1]. Four studies were placebo-controlled [2,12,13,19], four used metformin as a comparator [10,11,16,20], two trials used the oral contraceptive pill (OCP) and lifestyle [5,17] alone, and one trial used metformin and lifestyle [17].

The majority of trials were at unclear risk of selection bias, mainly due to failure to specify if or how allocation was concealed. More than half of trials were at high risk of performance bias due to lack of blinding of participants and personnel, three quarters were at unclear risk of detection bias, and less than half were at low risk for reporting bias. More than a quarter of trials were at high risk of other bias, mainly due to conflicts of interest.

META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY

Exenatide

There was no difference between exenatide and metformin for androgenicity, most metabolic outcomes, most lipid outcomes and anthropometric outcomes. There was very low certainty evidence that metformin was superior to exenatide for fasting glucose, while EXE was superior to MET for AUC insulin and the Matsuda index. Exenatide + OCP was superior to metformin + OCP for most but not all metabolic, anthropometric outcomes and reproductive outcomes, while there were no between-group differences for androgenicity and lipids.

There was no difference between exenatide + metformin (+-OCP) and metformin alone (+- OCP) for androgenicity, most metabolic outcomes, and most lipid parameters. MET was superior to EXE + MET for 120 minute insulin and LDL cholesterol. EXE +MET + OCP was superior to MET + OCP for change in fasting glucose, 120 minute glucose, and 120 minute insulin. EXE + MET + OCP was superior to MET + OCP for body weight, BMI and WC although there was no difference between EXE + MET and MET alone for weight and BMI.

There was no difference between exenatide and phentermine/topiramate for androgenicity, metabolic, lipids, or anthropometric outcomes.

Liraglutide

Liraglutide (+-lifestyle) was superior to placebo (+- lifestyle) for menstrual cycles and some but not all androgenicity and metabolic outcomes but not for lipids. Liraglutide was superior to placebo for anthropometric outcomes including weight and fat mass. However, liraglutide alone resulted in more lean body mass loss than placebo, but this was not seen when liraglutide was combined with lifestyle interventions.

Semaglutide

Semaglutide was superior to placebo for some but not all metabolic outcomes and lipid parameters, and anthropometric measures including visceral body fat.

Orlistat

Orlistat was superior to placebo for anthropometric and lipid outcomes but not for androgenicity or metabolic outcomes. Orlistat + lifestyle + OCP was superior to lifestyle + OCP alone for some but not all androgenicity outcomes, lipid and anthropometric outcomes while there were no differences for metabolic outcomes. There was low certainty evidence that orlistat + lifestyle + OCP is superior to lifestyle + OCP alone for SHBG, LDL, and CRP and that there is no difference between groups for HDL, fasting insulin, and triglycerides.

There were no between-group differences for orlistat vs metformin or orlistat + metformin vs metformin alone for androgens, metabolic, lipids and anthropometric outcomes. The only exception was that orlistat + metformin was superior to metformin alone for body fat % reduction.

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i. Exenatide v DAPA – single trial (Elkind-Hirsch 2021)

Benefits: There was no statistically significant difference between EXE and DAPA for any of the outcomes in the study which are: Hormonal (FAI, TT, DHEAS), Metabolic (FBG, HOMA-IR, Matsuda), Lipids (TC, LDL, HDL, TG), Anthropometric (weight, BMI, WHR, WC, fat free mass, fat mass, fat %).

There was very serious imprecision (single trial, sample size 37 for these two arms) and the trial was rated at moderate risk of bias due to lack of blinding of the participants and potential conflicts of interest due to pharmaceutical industry funding.

Risks: GI AEs were the most common in the EXE group.

ii. Exenatide + DAPA v DAPA – single trial (Elkind-Hirsch 2021)

Benefits: EXE + DAPA was superior to DAPA alone for the outcomes of body weight, BMI, fat mass and % body fat. There were no between group differences for the other anthropometric outcomes of WHR, WC, and fat free mass, and no differences for hormonal (FAI, TT, DHEAS), Metabolic (FBG, HOMA-IR, Matsuda) and lipids (TC, LDL, HDL, TG).

There was very serious imprecision (single trial, sample size 37 for these two arms) and the trial was rated at moderate risk of bias due to lack of blinding of the participants and potential conflicts of interest due to pharmaceutical industry funding.

Risks: Injection site reactions were reported in the EXE + DAPA group (4/20).

iii. Exenatide v Metformin – two trials (Tao 2021, Zheng 2017), MA for four outcomes

a. *Exenatide v Metformin*

Benefits: See GRADE for HOMA-IR, FINS, FBG, 2hr insulin

There was no difference between groups for mFG (1 trial - Zheng), total testosterone (2 trials), SHBG (2 trials), DHEA (2 trials), androstenedione (1 trial – Tao), AUC glucose (1 trial – Zheng), LDL cholesterol (2 trials), HDL (2 trials), triglycerides (2 trials), weight (2 trials), BMI (2 trials), WHR (1 trial – Zheng), WC (1 trial – Zheng), and menstrual regularity (1 trial – Zheng).

EXE was superior to MET for FAI in one trial (Zheng) but not in another (Tao). MET was superior to EXE for 2hr glucose, Matsuda index and total cholesterol (1 trial – Zheng). EXE was superior to MET for AUC insulin (1 trial – Zheng) and hsCRP (1 trial – Zheng)

There was very serious imprecision (very small sample sizes and very small number of studies) and both trials were rated at high risk of bias due to unclear sequence generation, allocation concealment and lack of blinding.
Risks: Nausea was more frequent in the EXE group (Zheng) and more participants in the EXE group withdrew due to AEs (Zheng).

b. *Exenatide + OCP v Metformin + OCP – single trial (Liu 2017)*

Benefits:

EXE + OCP was superior to MET + OCP for metabolic outcomes (FINS, HOMA-IR, 2hr insulin, 2 hr glucose) and for most but not all anthropometric outcomes. Mean post treatment BMI, WC and body fat % were lower in the EXE + OCP group compared to MET + OCP. Mean post treatment weight was higher in the MET + OCP group compared to EXE + OCP (68.66kg v 68.17kg).

The ratio of actual menses to expected menses was higher in the EXE + OCP group compared to MET + OCP (0.90 v 0.68).

Mean post treatment hsCRP was lower in the EXE + OCP group compared to the MET + OCP group (2.30 mg/L v 3.23 mg/L).

There were no differences between EXE + OCP and MET + OCP for the following outcomes: Metabolic (FBG, 2hr insulin), Lipids (TC, LDL, HDL, TG), anthropmetric (WHR)

There was serious imprecision (single trial, sample size 158 for non-pregnancy outcomes, 147 for pregnancy outcomes) and the trial was rated at high risk of bias due to black of blinding, unclear allocation concealment, and selective outcome reporting.

Risk:

There was no difference between groups for miscarriage, twin pregnancy, preterm delivery, GDM, gestational hypertension, fetal macrosomia.

GI AEs were more frequent in the EXE + OCP group compared with MET + OCP.

iv. Exenatide + Metformin V Metformin

a. *Exenatide + Metformin V Metformin – single trial (Tao 2021)*

Benefits: There were no between-group differences between EXE + MET v MET for FAI, TT, SHBG, DHEAS, Androstenedione, FBG, FINS, HOMA-IR, 2hr gluc, Total cholesterol, HDL, TG, weight and BMI.

MET was superior to EXE + MET for 2 hr insulin and LDL cholesterol.

There was very serious imprecision (very small sample sizes and very small number of studies) and the trial was rated at high risk of bias due to unclear sequence generation, allocation concealment and lack of blinding.

Risks: No AEs were reported in the EXE + MET group although AEs were not well reported overall – only in the context of reason for withdrawal.

b. *Exenatide + oral contraceptive pill + Metformin v oral contraceptive pill + Metformin – single trial (Ma 2021)*

Benefits: EXE + MET was superior to MET for FBG, 2hr insulin, TC, TG, BMI, and WC.

MET was superior to EXE + MET for TT, Matsuda index, and weight.

There were no between group differences for DHEAS, FINS, HOMA-IR, QUICKI, 2 hr glucose, LDL, HDL, hsCRP.

There was very serious imprecision (very small sample sizes and very small number of studies) and the trial was rated at high risk of bias due to unclear sequence generation, allocation concealment and lack of blinding.

Risks: there was more bloating in the EXE + MET group but other GI AEs were comparable. There were injection site reactions in the EXE+MET group.

v. Exenatide v Phentermine/Topiramate – single study (Elkind-Hirsch 2021)

Benefits: There were no between group differences for any outcomes (Hormonal – FAI/TT/DHEAS), metabolic (FBG, HOMA-IR, Matsuda), Lipids (TC, LDL, HDL, TG), anthropometric (Weight, BMI, WHR, WC, body fat %, Fat mass, Fat free mass-Lean BM).

There was very serious imprecision (single trial, sample size 37 for these two arms) and the trial was rated at moderate risk of bias due to lack of blinding of the participants and potential conflicts of interest due to pharmaceutical industry funding.

Risks: Nausea was more common with EXE while other AEs were more common in the PT group such as insomnia, rapid heart rate and dizziness

vi. Exenatide v Dapagliflozin + Metformin – single trial (Elkind-Hirsch 2021)

Benefits: There were no between group differences for any outcomes (Hormonal – FAI/TT/DHEAS), metabolic (FBG, HOMA-IR, Matsuda), Lipids (TC, LDL, HDL, TG), anthropometric (Weight, BMI, WHR, WC, body fat %, Fat mass, Fat free mass-Lean BM).

There was very serious imprecision (single trial, sample size 37 for these two arms) and the trial was rated at moderate risk of bias due to lack of blinding of the participants and potential conflicts of interest due to pharmaceutical industry funding.

Risks: Nausea was more common in the EXE group and upset stomach, yeast infection and urinary symptoms in the DAPA + MET group.

vii. Liraglutide v placebo

a. *Liraglutide v placebo – single trial (Nylander 2017)*

Benefits: LIRA was superior to placebo for TT, SHBG, FBG, weight, BMI, WHR, WC,fat mass, and menstrual cycles.

LIRA resulted in more lean body mass loss compared to placebo.

There were no between group differences for FAI, Androstenedione, hsCRP, Matsuda index, Lipids (TC, LDL, HDL, TG), % body fat.

There was very serious imprecision (single trial, small sample size) and the trial was rated at moderate risk of bias due to potential conflict of interest

Risks: GI AEs were more common in the LIRA group.

b. Liraglutide + lifestyle v placebo + lifestyle – single trial (Elkind-Hirsch 2022)

Benefits: LIRA was superior to placebo for FAI, FBG, HOMA-IR, Matsuda, TG, weight, BMI, WHR, WC, % with 5% weight loss, % with 10% wt loss, % body fat, menstrual cycle.

There were no between-group differences for TT, DHEAS, TC, HDL, LDL, fat free mass.

There was very serious imprecision (single trial, small sample size) and the trial was rated low for risk of bias.

Risks: Women in the liraglutide group complained of more nausea, vomiting, diarrhoea, constipation, reflux, indigestion, prolonged menstrual bleeding, injection site induration

The placebo group reported more COVID-19 infections and absence of menstrual cycles.

viii. Semaglutide v placebo – single trial (Jensterle 2021)

Benefits: Semaglutide was superior to placebo for body weight, BMI, waist circumference, HDL, visceral body fat, fasting insulin and 120min glucose.

There were no between-group differences for FBG, HOMA-IR, 2-hr insulin, TC, LDL, and TG.

There was very serious imprecision (single trial, very small sample size) and the study was rated at moderate risk of bias due to potential conflict of interest and selective outcome reporting.

Benefits: There was more nausea in the semaglutide group.

ix. Phentermine/topiramate v Dapagliflozin – single trial (Elkind-Hirsch 2021)

Benefits: PT was superior to DAPA for body weight, BMI, body fat mass and body fat %.

There were no between-group differences for hormonal outcomes (FAI, TT, DHEAS), metabolic outcomes (FBG, HOMA-IR, Matsuda), lipids (TC, HDL, LDL, TG), central adiposity (WC, WHR) and fat free mass.

There was very serious imprecision (single trial, sample size 37 for these two arms) and the trial was rated at moderate risk of bias due to lack of blinding of the participants and potential conflicts of interest due to pharmaceutical industry funding.

Risks: PT caused nausea, upset stomach, insomnia, headache and fatigue, while DAPA caused urinary symptoms and vaginal irritation.

x. Phentermine/topiramate v Dapagliflozin + Metformin

Benefits: PT was superior to DAPA + MET for body weight, BMI, body fat mass and body fat %.

There were no between-group differences for hormonal outcomes (FAI, TT, DHEAS), metabolic outcomes (FBG, HOMA-IR, Matsuda), lipids (TC, HDL, LDL, TG), central adiposity (WC, WHR) and fat free mass.

There was very serious imprecision (single trial, sample size 37 for these two arms) and the trial was rated at moderate risk of bias due to lack of blinding of the participants and potential conflicts of interest due to pharmaceutical industry funding.

Risks: PT caused more fatigue, headache, rapid heart rate, and insomnia.

xi. Phentermine/topiramate v Exenatide + Dapagliflozin

Benefits: EXE/DAPA was superior to PT for triglycerides. There were no between-group differences for the other outcomes: Hormonal (FAI, TT, DHEAS), Metabolic (FBG, HOMA-IR, Matsuda), Lipids (TC, LDL, HDL), Anthropometric (weight, BMI, WHR, WC, fat free mass, fat mass, fat %).

There was very serious imprecision (single trial, sample size 37 for these two arms) and the trial was rated at moderate risk of bias due to lack of blinding of the participants and potential conflicts of interest due to pharmaceutical industry funding.

Risks: EXE/DAPA caused more upset stomach, yeast infection. PT caused more fatigue, insomnia and headache.

xii. Orlistat + lifestyle v placebo + lifestyle – single trial (Moini 2015)

Benefits: Orlistat was superior to placebo for LDL, HDL, TG, and weight.

There were no between-group differences for TT, FBG, FINS, HOMA-IR, and WHR.

There was serious imprecision (single study, small sample size - 96) and the study was rated at unclear risk of bias due to lack of reporting of allocation concealment and no protocol/trial registration available to determine selective outcome reporting.

Risks: More than half of women reported urgency to go to the bathroom and 30% reported oily spotting in undergarments. About one in five women reported oily or fatty stool.

xiii. Orlistat + lifestyle + oral contraceptive pill v Metformin + lifestyle + oral contraceptive pill – single trial (Song 2017)

Benefits: There were no between-group differences for Hormonal (FAI, Free/total testosterone, SHBG, DHEAS, Androstenedione), Metabolic (Fasting glucose, fasting insulin, HOMA-IR), Lipids (TC, HDL, LDL, TG) and Anthropometric (Weight, BMI, WC, Fat mass, % Body fat) outcomes.

There was serious imprecision (single study) and the study was rated at high risk of bias due to lack of information on allocation concealment and lack of blinding.

Risks: A small proportion of participants reported GI AEs with orlistat (flatulence and oily spotting).

xiv. Orlistat + lifestyle + OCP v lifestyle + OCP – two trials (Gu 2022 and Song 2017), MA for six outcomes

Benefits: Orlistat was superior to LS and OCP alone for SHBG (low certainty) and LDL (low certainty).

Orlistat was superior to LS and OCP alone for body weight, BMI, DHEAS, FAI (1 trial - Song), CRP (1 trial - Gu), weight (2 trials), BMI (2 trials), and % body fat (1 trial – Gu). Note that numerical data on endpoint weight and BMI were not available from the Song trial as only a figure with no data labels was presented.

There was no difference between groups on meta-analysis for FBG, FINS, HDL and TG.

There was no difference between groups for free or total testosterone (2 trials), androstenedione (1 trial – Song), HOMA-IR (1 trial – Song), total cholesterol (2 trials), waist circumference (1 trial - Gu).

There was serious imprecision (small number of trials, small sample sizes) and both trials were rated at high risk of bias due to lack of reporting of randomisation and allocation concealment and lack of blinding.

Risks: A small proportion of participants reported GI AEs with orlistat (flatulence and oily spotting).

xv. Orlistat + Metformin + OCP + LS v Metformin + OCP + LS – single trial (Song 2017)

Benefits: Orlistat + Metformin was superior to metformin for body fat % reduction (numerical data not available). There were no between-group differences for other outcomes: Hormonal (FAI, Free/total testosterone, SHBG, DHEAS, Androstenedione), Metabolic (Fasting glucose, fasting insulin, HOMA-IR), Lipids (TC, HDL, LDL, TG) and Anthropometric (Weight, BMI, WC, Fat mass).

There was serious imprecision (single study) and the study was rated at high risk of bias due to lack of information on allocation concealment and lack of blinding.

Risks: A small proportion of participants reported GI AEs with orlistat (flatulence and oily spotting).

1. GRADE Comparisons

i. Exenatide v Metformin

COMPARISON: Exenatide v Metformin												
	Quality assessment						No. participants					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**EXE**	**MET**	**Effect, fixed [95% CI]**	**Favours**	**Certainty**	**Importance**
Outcome: HOMA-IR												
2	RCT	serious[1]	Serious inconsistency[3]	no serious indirectness	Very serious imprecision[2]	none	81	82	MD 0.30 (-0.67, 1.28)*	NS	⨁◯◯◯ VERY LOW	
Outcome: Fasting insulin (pmol/L)												
2	RCT	serious[1]	Serious inconsistency[3]	no serious indirectness	Very serious imprecision[2]	none	81	82	MD 1.52 (-6.37, 9.40)*	NS	⨁◯◯◯ VERY LOW	
Outcome: Fasting glucose (mmol/L)												
2	RCT	serious[1]	No serious inconsistency	no serious indirectness	Very serious imprecision[2]	none	81	82	MD 0.11 (0.08, 0.14)	MET	⨁◯◯◯ VERY LOW	
Outcome: 2 hr OGTT insulin (pmol/L)												
2	RCT	serious[1]	Serious inconsistency[3]	no serious indirectness	Very serious imprecision[2]	none	81	82	MD 80.11 (-257.98, 418.19)*	NS	⨁◯◯◯ VERY LOW	

1 Downgraded one level for unclear sequence generation and allocation concealment, and lack of blinding

2 Downgraded two levels for very small sample sizes and very small number of studies

3 Downgraded one level for inconsistent direction of effect and high heterogeneity

*random effects

ii. Orlistat + lifestyle + OCP v lifestyle + OCP

COMPARISON: Orlistat + LS + OCP v LS + OCP												
	Quality assessment						No. participants					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Orlistat + LS + OCP**	**LS + OCP**	**Effect, fixed [95% CI]**	**Favours**	**Certainty**	**Importance**
Outcome: SHBG (nmol/L)												
2	RCT	serious[1]	No serious inconsistency	No serious indirectness	Serious imprecision[2]	none	93	93	MD 14.30 (2.94, 25.66)	Orlistat (for higher SHBG)	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Fasting glucose (mmol/L)												
2	RCT	serious[1]	No serious inconsistency	No serious indirectness	Serious imprecision[2]	none	93	93	MD -0.00 (-0.17, 0.17)	NS	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Fasting insulin (pmol/L)												
2	RCT	serious[1]	Serious inconsistency[3]	No serious indirectness	Serious imprecision[2]	none	93	93	MD -8.65 (-33.55, 16.26)*	NS	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: LDL (mmol/L)												
2	RCT	serious[1]	No serious inconsistency	No serious indirectness	Serious imprecision[2]	none	93	93	MD -0.43 (-0.84, -0.02)*	Orlistat	⊕⊕◯◯ LOW	IMPORTANT
Outcome: HDL cholesterol (mmol/L)												
2	RCT	serious[1]	Serious inconsistency[3]	No serious indirectness	Serious imprecision[2]	none	93	93	MD 0.22 (-0.36, 0.80)*	NS	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Triglycerides (mmol/L)												
2	RCT	serious[1]	No serious inconsistency	No serious indirectness	Serious imprecision[2]	none	93	93	MD -0.00 (-0.22, 0.21)	NS	⊕⊕◯◯ LOW	IMPORTANT

1 downgrade one level for lack of reporting of allocation concealment, no reporting of sequence generation in one study, and lack of blinding.

2 downgrade one level for small number of studies and small sample sizes

3 downgrade one level for inconsistent direction of effect, limited overlap of confidence intervals, and high heterogeneity

*random effects

NS= not statistically significant

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PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 4

Question 4.5.

Are anti-obesity pharmacological agents alone or in combination, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?

BACKGROUND:

Unhealthy higher weight is increasing in prevalence throughout the world. Depending on the dataset and ethnicity, 50-70% of women with PCOS are of significantly higher weight and have insulin resistance adversely affecting fertility and psychological health and increasing metabolic risks including type 2 diabetes mellitus and metabolic syndrome. Weight loss improves outcomes as previously outlined.

In class II (BMI 35-40 kg/m^2) and class III (≥40 kg/m2) higher weight, lifestyle interventions are not durably effective.

Higher weight is also a significant concern for many affected adolescents and women with PCOS. Whilst lifestyle change has a key role in the management of higher weight, the role of anti-obesity pharmacological agents in achieving weight loss and potential associated health benefits is increasingly recognised with recent guidelines (1,2), and systematic reviews (3) in the area. However, the role of these agents in PCOS and in reproductive-aged women remains unclear.

Semaglutide, liraglutide, phentermine/topiramate, naltrexone/bupropion and orlistat are approved anti-obesity medications in adults, each of which has been compared to placebo in randomised controlled trials. These medications are increasingly being used in adults for assistance with weight loss. However, there is limited available data in women with PCOS.

Only the agents approved for weight loss have been considered in malign evidence-based recommendations.

GRADE EVIDENCE CERTAINTY	
Comparison	**GRADE for critical outcomes**
○ **Comparison 1:** Exenatide v DAPA – single trial	⨁◯◯◯ VERY LOW
○ **Comparison 2:** Exenatide + DAPA v DAPA – single trial	⨁◯◯◯ VERY LOW
○ **Comparison 3:** Exenatide v Metformin- meta-analysis	⨁◯◯◯ VERY LOW
○ **Comparison 4 (a):** Exenatide + Metformin v Metformin- single trial	⨁⨁◯◯ LOW
○ **Comparison 4 (b):** Exenatide + oral contraceptive pill + Metformin v oral contraceptive pill + Metformin – single trial	⨁◯◯◯ VERY LOW
○ **Comparison 5:** Exenatide v Phentermine/Topiramate – single study	⨁◯◯◯ VERY LOW
○ **Comparison 6:** Exenatide v Dapagliflozin + Metformin – single trial	⨁◯◯◯ VERY LOW
○ **Comparison 7 (a):** Liraglutide v Placebo – single trial	⨁⨁◯◯ LOW
○ **Comparison 7 (b):** Liraglutide + lifestyle v placebo + lifestyle- single trial	⨁⨁◯◯ LOW
○ **Comparison 8**: Semaglutide v placebo – single trial	⨁◯◯◯ VERY LOW
○ **Comparison 9:** Phentermine/topiramate v Dapagliflozin – single trial	⨁◯◯◯ VERY LOW
○ **Comparison 10:** Phentermine/topiramate v Dapagliflozin + Metformin	⨁◯◯◯ VERY LOW

○ **Comparison 11:** Phentermine/topiramate v Exenatide + Dapagliflozin	⊕○○○ VERY LOW
○ **Comparison 12:** Orlistat + lifestyle v placebo + lifestyle – single trial	⊕⊕○○ LOW
○ **Comparison 13:** Orlistat + lifestyle + oral contraceptive pill v Metformin + lifestyle + oral contraceptive pill – single trial	⊕⊕○○ LOW
○ **Comparison 14:** Orlistat + LS + OCP v LS + OCP- meta-analysis	⊕○○○ VERY LOW
○ **Comparison 15:** Orlistat + Metformin + OCP + LS v Metformin + OCP + LS – single trial	⊕⊕○○ LOW

Evidence to Recommendations Framework

COMPARISONS (option versus other option)

Anti-obesity versus placebo
Anti-obesity versus lifestyle

CONCENSUS RECOMMENDATION

- **CR:** Anti-obesity medications including liraglutide, semaglutide, both glucagon-like peptide-1 (GLP-1) receptor agonists and orlistat, could be considered, in addition to active lifestyle intervention, for the management of higher weight in adult women with PCOS as per general population guidelines.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

PRACTICE POINT(S)

- Health professionals should ensure concurrent effective contraception when pregnancy is possible, for women who take GLP-1 receptor agonists, as pregnancy safety data are lacking.
- Gradual dose escalation for GLP-1 receptor agonists is recommended to reduce gastrointestinal adverse effects.

Shared decision making, when discussing GLP-1 receptor agonist use with women with PCOS, needs to consider side effects, and the potential need for long-term use in weight management, given the high risk for weight regain after discontinuation, and the lack of long-term safety data.

GRADE CONSIDERATIONS

Justifications:
Very few studies and small numbers in PCOS.
However, this is a high priority area for clinicians and women with PCOS.
The evidence to support the recommendation based on general population research is strong.

Subgroup considerations:
Recommendations will only apply to adult women with a higher weight not adolescents. There were no studies identified in adolescents and there is no evidence for these medications in the management of non-PCOS adolescents who are of a higher weight.

Implementation considerations:
Delivery of the medications (especially considering some are injectable), side effects and cost may affect acceptability of this intervention.
The cost of the medications may make it difficult to afford for some women both in the short-term and long-term.
Cost and regulation of these medications in different regions needs to be considered when implementing this recommendation, especially in women with moderate to severe excess weight whose biggest concern is weight management.

Monitoring and evaluation considerations:
There are known contraindications and side effects of these medications that need to be evaluated and monitored for if used for management of higher weight.
Post-marketing surveillance of some newer anti-obesity agents are required.
The role and the adverse effects of long-term therapy require more monitoring.

Research priorities:
There is a need for high-quality well-designed studies with metabolic, reproductive and psychological outcomes of high certainty comparing the anti-obesity medications to placebo in adolescents and women with PCOS.
Studies need to directly compare groups at the end of the intervention and also report on any adverse effects related to the medications.
The role and the adverse effects of long-term therapy require more research.

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1. Apovian CM, Aronne LJ, Bessesen DH, McDonnell ME, Murad MH, Pagotto U, et al. Pharmacological Management of Obesity: An Endocrine Society Clinical Practice Guideline. The Journal of Clinical Endocrinology & Metabolism. 2015;100(2):342-62.
2. Grunvald E, Shah R, Hernaez R, Chandar AK, Pickett-Blakely O, Teigen LM, Harindhanavudhi T, Sultan S, Singh S, Davitkov P; AGA Clinical Guidelines Committee. AGA Clinical Practice Guideline on Pharmacological Interventions for Adults With Obesity. Gastroenterology. 2022 Nov;163(5):1198-1225
3. Mead E, Atkinson G, Richter B, Metzendorf M-I, Baur L, Finer N, et al. Drug interventions for the treatment of obesity in children and adolescents. Cochrane Database of Systematic Reviews. 2016(11).

PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by ECR Lead: Simon Alesi

Other team members: Johanna Melin, Maria Forslund

Supervised, edited and supported by the Evidence Team (Aya Mousa, Jillian Tay)

GDG 4

Question 4.6.

Are anti-androgen pharmacological agents alone or in combination, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?

1. STUDY SELECTION

Table 1. PICO Criteria for Inclusion	
Question	Are anti-androgen pharmacological agents alone or in combination, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?
Clinical leads (key contacts)	Selma Witchel, Daniela Romualdi, and Alexia Pena Vargas
Allocation ranking	Level 2- updated systematic review

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits (language, year)
Inclusion	Females with PCOS (diagnosed by Rotterdam, NIH or AES) of any age, ethnicity and weight. Subgroups: adolescents (10-19y), adults, post-menopausal. Must be taking contraception.	Oral anti-androgen pharmacological agents (spironolactone, cyproterone acetate, finasteride, flutamide) alone or in combination with lifestyle, metformin, OCP, anti-obesity agents. All doses, duration of more than 6 months	Placebo or any other intervention (listed in intervention) or combinations of those listed in intervention	Androgenicity: Hirsutism- FG score (ethnicities), FAI, testosterone, SHBG, DHEAS, androstenedione, Irregular cycles Metabolic: insulin resistance HOMA, Clamp, OGTT Lipids: Chol LDL, HDL TG, CRP Psychological: Qol, depression Arthropometric: weight BMI, WHR Adverse effects: cycle irregularity, mood Liver function tests Hirsutism, insulin resistance, metabolic effects. Pregnancy with adverse outcomes Under virilisation of male births	Evidence based guidelines, systematic reviews, randomised controlled trials.	None
Exclusion	Females without PCOS.	Placebo, no intervention or any intervention other than an aromatase inhibitor.	Agent or combination used in the intervention.	None	Non-evidence-based guidelines, non-systematic reviews, any study lower than a RCT.	None

2. SEARCH STRATEGY

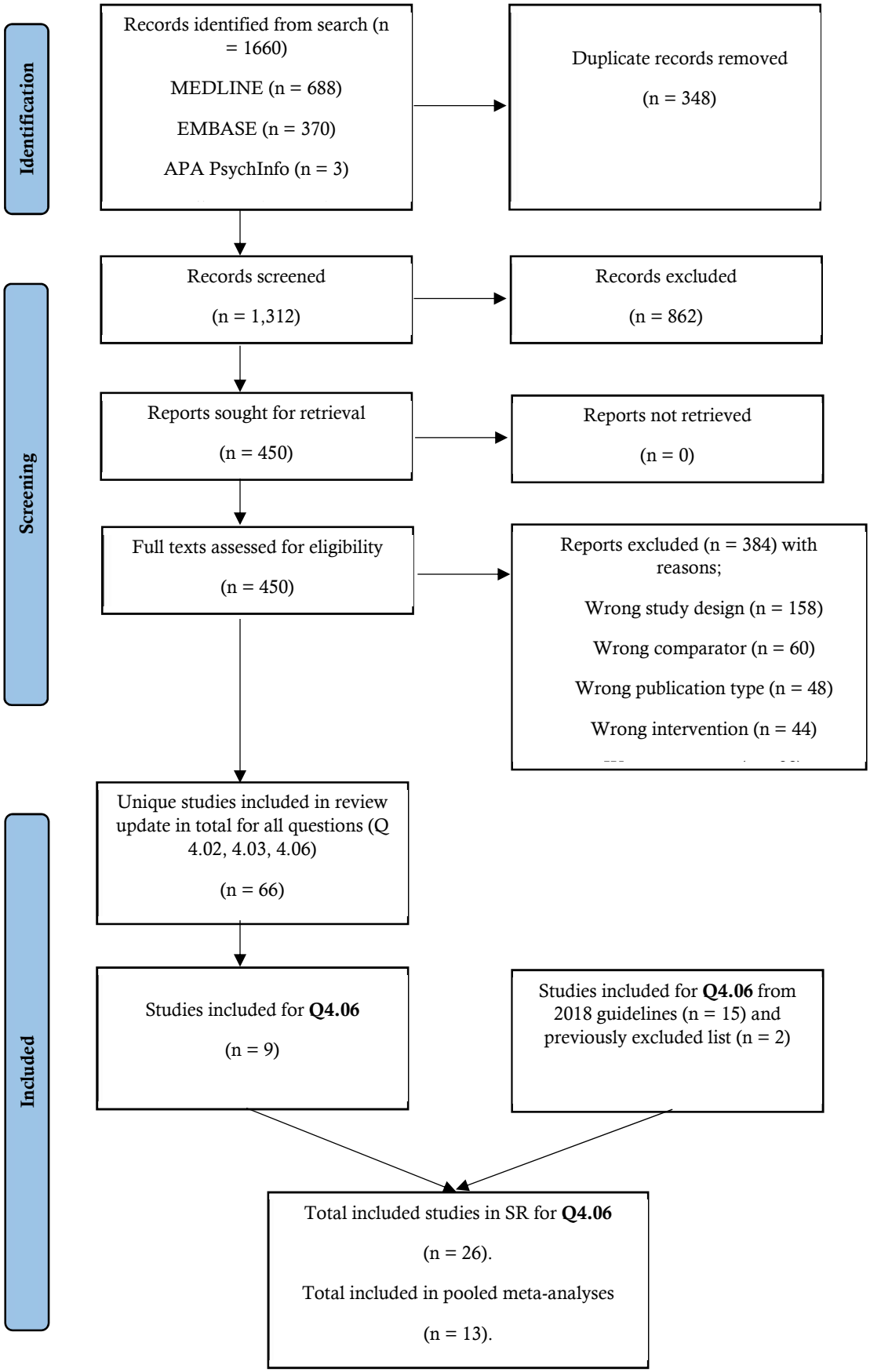
Search details	
Search strategy source: *[enter doi or 2018 technical report page number where search string was derived]*	
Evidence source	**Date of search**
Medline (Ovid)	8th July 2022
PsychInfo (Ovid)	8th July 2022
EMBASE (Ovid)	8th July 2022
All EBM (Ovid)	8th July 2022
CINAHL	8th July 2022
Initial search: Inception – January 2017; Updated search: 2017 – July 2022	

Questions addressed by this search *(add more rows as needed)*:		
GDG	**Q#**	**Question**
4	4.6	Are anti-androgen pharmacological agents alone or in combination, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?
4	4.2	Is the oral contraceptive pill alone or in combination effective for management of hormonal and clinical PCOS features in adolescents and adults with PCOS?
4	4.3	Is metformin alone or in combination, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?

Search strings used in OVID or other database/s	
OVID Medline, All EBM, PsychInfo, EMBASE (results= n?)	CINAHL
1 exp polycystic ovary syndrome/ 2 polycystic ovar*.mp. 3 poly-cystic ovar*.mp. 4 PCO*.mp. 5 (stein-leventhal or leventhal).mp. 6 anovulation/ 7 anovulat*.mp. 8 oligo-ovulat*.mp. 9 oligoovulat*.mp. 10 (ovar* adj5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*)).mp. 11 or/1-10 12 exp Contraceptives, Oral/ 13 ((Oral and contracept*) or OCP or COCP).tw. 14 exp Metformin/ 15 Metformin*.tw. 16 exp Androgen Antagonists/ 17 *Spironolactone/ 18 *Finasteride/ 19 (anti?androgen* or anti androgen or androgen antagonist* or spironolactone or cyproterone acetate or finasteride or flutamide).mp. 20 exp Anti-Obesity Agents/ 21 *Obesity/th [Therapy] 22 ((anti?obesity or anti obesity or weight loss) and (agent* or drug*)).mp. 23 (orlistat or sibutramine).mp.	**S26** S11 AND S25 **S25** S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 **S24** (inositol* or myo?inositol* or meso?inositol* or i-inositol* or epi?inositol* or chiro?inositol or l-chiro?inositol*) S23 (MH "Inositol+") **S22** (orlistat or sibutramine) **S21** ((anti?obesity or weight loss or weight-loss) and (agent* or drug*)) **S20** (MH "Antiobesity Agents+")

24 *Inositol/ 25 (inositol* or myo?inositol* or myo inositol* or meso?inositol* or meso inositol* or i-inositol* or epi?inositol* or epi inositol* or chiro?inositol* or chiro inositol* or l-chiro?inositol* or l-chiro inositol*).mp. 26 or/12-25 27 search$.tw. or meta-analysis.mp. or meta-analysis.pt. or review.pt. or di.xs. or associated.tw. 28 clinical trial.mp. or clinical trial.pt. or random.mp. or tu.xs. 29 27 or 28 30 11 and 26 and 29	**S19** (anti? androgen* or anti androgen or androgen antagonist* or spironolactone or cyproterone acetate or finasteride or flutamide) **S18** (MH "Finasteride") **S17** (MH "Spironolactone+") **S16** (MH "Androgen Antagonists+") S15 metformin* **S14** (MH "Metformin") **S13** ((Oral and contracept*) or OCP or COCP) **S12** (MH "Contraceptives, Oral+") **S11** S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 **S10** ovar* N5 sclerocystic or ovar* N5 polycystic or ovar* N5 polycystic or ovar* N5 degenerat* or ovar* N5 hyperandrogen* or ovar* N5 hyperandrogen* **S9** oligoovulat* **S8** oligo-ovulat* **S7** SU anovulation **S6** SU ovarian Cysts **S5** stein-leventhal or Leventhal **S4** PCO* **S3** poly-cystic ovar* **S2** polycystic ovar* **S1** SU polycystic ovary syndrome

3. SEARCH RESULTS: PRISMA flowchart



4. STUDY INCLUSION

Evidence processing: The literature search and screening were performed together in one Endnote library and Covidence project for anti-androgens, metformin, and COCP treatments in PCOS. Studies were selected by two reviewer/s in consultation with the evidence team/ key contact(s) using study selection and appraisal criteria (PICOs) established a priori. The articles were screened by title and abstract by two reviewers. When a decision could not be made based on title and abstract alone, full text was retrieved. Full-text studies were assessed in duplicate. Study appraisal was conducted by two reviewers independently with discussion to resolve any discrepancy.

Of the updated search and studies from previous guidelines and previously excluded list, **26 studies met the inclusion criteria for this question 4.6 on anti-androgens**, as detailed below.

4.1. Table of Included Studies
Alpañés M, Álvarez-Blasco F, Fernández-Durán E, Luque-Ramírez M, Escobar-Morreale HF. Combined oral contraceptives plus spironolactone compared with metformin in women with polycystic ovary syndrome: a one-year randomized clinical trial. European journal of endocrinology / European Federation of Endocrine Societies 2017;177(5):399-408. doi: 10.1530/EJE-17-0516.
Amiri M, Golsorkhtabaramiri M, Esmaeilzadeh S, Ghofrani F, Bijani A, Ghorbani L, Delavar MA. Effect of Metformin and Flutamide on Anthropometric Indices and Laboratory Tests in Obese/Overweight PCOS Women under Hypocaloric Diet. J Reprod Infertil 2014;15(4):205-13.
Burchall GF, Piva TJ, Ranasinha S, Teede HJ. Differential Effects on Haemostatic Markers by Metformin and the Contraceptive Pill: A Randomized Comparative Trial in PCOS. Thromb Haemost 2017;117(11):2053-62. doi: 10.1160/TH17-04-0248.
de Zegher F, Diaz M, Villarroya J, Cairo M, Lopez-Bermejo A, Villarroya F, Ibanez L. The relative deficit of GDF15 in adolescent girls with PCOS can be changed into an abundance that reduces liver fat. Sci Rep 2021;11(1):7018. doi: 10.1038/s41598-021-86317-9.
Diaz M, Gallego-Escuredo JM, Lopez-Bermejo A, de Zegher F, Villarroya F, Ibanez L. Low-Dose Spironolactone-Pioglitazone-Metformin Normalizes Circulating Fetuin-A Concentrations in Adolescent Girls with Polycystic Ovary Syndrome. Int J Endocrinol 2018;2018:4192940. doi: 10.1155/2018/4192940.
Falsetti L, De Fusco D, Eleftheriou G, Rosina B. Treatment of hirsutism by finasteride and flutamide in women with polycystic ovary syndrome. Gynecol Endocrinol 1997;11(4):251-7. doi: 10.3109/09513599709152542.
Falsetti L, Gambera A, Legrenzi L, Iacobello C, Bugari G. Comparison of finasteride versus flutamide in the treatment of hirsutism. Eur J Endocrinol 1999;141(4):361-7. doi: 10.1530/eje.0.1410361.
Gambineri A, Patton L, Vaccina A, Cacciari M, Morselli-Labate AM, Cavazza C, Pagotto U, Pasquali R. Treatment with flutamide, metformin, and their combination added to a hypocaloric diet in overweight-obese women with polycystic ovary syndrome: a randomized, 12-month, placebo-controlled study. J Clin Endocrinol Metab 2006;91(10):3970-80. doi: 10.1210/jc.2005-2250.
Gambineri, A.; Pelusi, C.; Genghini, S.; Morselli-Labate, A.M.; Cacciari, M.; Pagotto, U.; Pasquali, R. Effect of flutamide and metformin administered alone or in combination in dieting obese women with polycystic ovary syndrome. *Clin Endocrinol (Oxf)* 2004, *60*, 241-249, doi:10.1111/j.1365-2265.2004.01973.x.
Gambineri A, Pelusi C, Genghini S, Morselli-Labate AM, Cacciari M, Pagotto U, Pasquali R. Effect of flutamide and metformin administered alone or in combination in dieting obese women with polycystic ovary syndrome. Clin Endocrinol (Oxf) 2004;60(2):241-9. doi: 10.1111/j.1365-2265.2004.01973.x
Ganie MA, Khurana ML, Eunice M, Gupta N, Gulati M, Dwivedi SN, Ammini AC. Comparison of efficacy of spironolactone with metformin in the management of polycystic ovary syndrome: an open-labeled study. J Clin Endocrinol Metab 2004;89(6):2756-62. doi: 10.1210/jc.2003-031780.
Ganie MA, Khurana ML, Nisar S, Shah PA, Shah ZA, Kulshrestha B, Gupta N, Zargar MA, Wani TA, Mudasir S, et al. Improved efficacy of low-dose spironolactone and metformin combination than either drug alone in the management of women with polycystic ovary syndrome (PCOS): a six-month, open-label randomized study. J Clin Endocrinol Metab 2013;98(9):3599-607. doi: 10.1210/jc.2013-1040.
Hagag P, Steinschneider M, Weiss M. Role of the combination spironolactone-norgestimate-estrogen in Hirsute women with polycystic ovary syndrome. J Reprod Med 2014;59(9-10):455-63.
Ibanez L, de Zegher F. Ethinylestradiol-drospirenone, flutamide-metformin, or both for adolescents and women with hyperinsulinemic hyperandrogenism: opposite effects on adipocytokines and body adiposity. J Clin Endocrinol Metab 2004;89(4):1592-7. doi: 10.1210/jc.2003-031281.

Ibáñez L, del Río L, Díaz M, Sebastiani G, Pozo ÓJ, López-Bermejo A, de Zegher F. Normalizing Ovulation Rate by Preferential Reduction of Hepato-Visceral Fat in Adolescent Girls With Polycystic Ovary Syndrome. J Adolesc Health 2017;61(4):446-53. doi: 10.1016/j.jadohealth.2017.04.010.
Ibanez L, Diaz M, Garcia-Beltran C, Malpique R, Garde E, Lopez-Bermejo A, de Zegher F. Toward a Treatment Normalizing Ovulation Rate in Adolescent Girls With Polycystic Ovary Syndrome. J Endocr Soc 2020;4(5):bvaa032. doi: 10.1210/jendso/bvaa032.
Malpique R, Sanchez-Infantes D, Garcia-Beltran C, Taxeras SD, Lopez-Bermejo A, de Zegher F, Ibanez L. Towards a circulating marker of hepato-visceral fat excess: S100A4 in adolescent girls with polycystic ovary syndrome - Evidence from randomized clinical trials. Pediatr Obes 2019;14(5):e12500. doi: 10.1111/ijpo.12500.
Mazza A, Fruci B, Guzzi P, D'Orrico B, Malaguarnera R, Veltri P, Fava A, Belfiore A. In PCOS patients the addition of low-dose spironolactone induces a more marked reduction of clinical and biochemical hyperandrogenism than metformin alone. Nutr Metab Cardiovasc Dis 2014;24(2):132-9. doi: 10.1016/j.numecd.2013.04.016.
Mehrabian F, Ghasemi-Tehrani H, Mohamadkhani M, Moeinoddini M, Karimzadeh P. Comparison of the effects of metformin, flutamide plus oral contraceptives, and simvastatin on the metabolic consequences of polycystic ovary syndrome. J Res Med Sci 2016;21:7. doi: 10.4103/1735-1995.177354.
Meyer C, McGrath BP, Teede HJ. Effects of medical therapy on insulin resistance and the cardiovascular system in polycystic ovary syndrome. Diabetes Care 2007;30(3):471-8. doi: 10.2337/dc06-0618.
Moretti C, Guccione L, Di Giacinto P, Simonelli I, Exacoustos C, Toscano V, Motta C, De Leo V, Petraglia F, Lenzi A. Combined Oral Contraception and Bicalutamide in Polycystic Ovary Syndrome and Severe Hirsutism: A Double-Blind Randomized Controlled Trial. J Clin Endocrinol Metab 2018;103(3):824-38. doi: 10.1210/jc.2017-01186.
Spritzer PM, Lisboa KO, Mattiello S, Lhullier F. Spironolactone as a single agent for long-term therapy of hirsute patients. Clin Endocrinol (Oxf) 2000;52(5):587-94. doi: 10.1046/j.1365-2265.2000.00982.x.
Tartagni M, Schonauer LM, De Salvia MA, Cicinelli E, De Pergola G, D'Addario V. Comparison of Diane 35 and Diane 35 plus finasteride in the treatment of hirsutism. Fertil Steril 2000;73(4):718-23. doi: 10.1016/s0015-0282(99)00633-0.
Tartagni MV, Alrasheed H, Damiani GR, Montagnani M, De Salvia MA, De Pergola G, Tartagni M, Loverro G. Intermittent low-dose finasteride administration is effective for treatment of hirsutism in adolescent girls: a pilot study. J Pediatr Adolesc Gynecol 2014;27(3):161-5. doi: 10.1016/j.jpag.2013.09.010.
Tartagni M, Schonauer MM, Cicinelli E, Petruzzelli F, De Pergola G, De Salvia MA, Loverro G. Intermittent low-dose finasteride is as effective as daily administration for the treatment of hirsute women. Fertil Steril 2004;82(3):752-5. doi: 10.1016/j.fertnstert.2004.02.118.
Vieira CS, Martins WP, Fernandes JB, Soares GM, dos Reis RM, de Sa MF, Ferriani RA. The effects of 2 mg chlormadinone acetate/30 mcg ethinylestradiol, alone or combined with spironolactone, on cardiovascular risk markers in women with polycystic ovary syndrome. Contraception 2012;86(3):268-75. doi: 10.1016/j.contraception.2011.12.011.

4.2. Excluded studies (on full-text assessment)

Reference	Reason
Unknown. Effect of green tea pills and metformin versus placebo on the Nrf2-antioxidant system and proinflammatory cytokines, including IL-6 and TNF-a, in peripheral blood mononuclear cells of women with polycystic ovary syndrome: a single blind randomized clinica 2017.	Wrong publication type.
Effect of supplementation in treatment of women with polycystic ovary syndrome. Clinical trial of the effect of inofolic supplementation compared with metformin on parameters of mental health and oxidative stress in women with polycystic ovary syndrome 2017.	Wrong publication type.
Effect of inofolic supplementation in treatment of women with polycystic ovary syndrome. Clinical trial of the effect of inofolic supplementation compared with metformin on metabolic profiles and gene expression related to insulin and lipid in women with polycystic ovary syndrome 2017.	Full text not obtainable.
Comparison of oral contraceptives including Contrasmine, Etisterone and Desoceptive with Ovustop-L (LD) on clinical, biochemical and metabolic findings, and quality of life in women with polycystic ovary syndrome. A Randomized cross-over clinical trial to assess the effectiveness of oral contraceptives including Contrasmine, Etisterone and Desoceptive with Ovustop-L (LD) on clinical, biochemical and metabolic findings, and quality of life in women with polycystic o 2017.	Full text not obtainable.
The efficacy of Fennel infusion and cupping on ovarian failure. Comparison of ovarian cupping and fennel infusion with Metformin on oligomenorrhea and ovulation in women with polycystic ovarian syndrome: a clinical trial 2017.	Full text not obtainable.
Scientific Impact Paper No. 13: Metformin Therapy for the Management of Infertility in Women with Polycystic Ovary Syndrome. Obstetrician & Gynaecologist 2017, 19, 339-339, doi:10.1111/tog.12436.	Wrong study design.
Effect of using metformin on the incidence of gestational diabetes and preeclampsia in pregnant women with polycystic ovary. Effect of using metformin versus not using on the incidence of gestational diabetes and preeclampsia in pregnant women with polycystic ovary: A randomized clinical trial 2018.	Wrong publication type

?Effects of myo-inositol on induction of ovulation. Comparison the effects of myo-inositol plus clomiphene citrate with metformin plus clomiphene citrate on induction of ovulation among patients with polycystic ovarian syndrome. 2018.	Wrong publication type
New strategies to lose weight for women with polycystic ovary syndrome. Novel strategies in weight loss in women with polycystic ovary syndrome: does the gut microbiome play a role? 2018.	Wrong publication type
A study to compare the efficacy of two drugs on the success of assisted reproductive therapy in women with polycystic ovarian syndrome and undergoing treatment with IVF. Randomised Control Trial comparing the effects of Metformin to Myoinositol on ART outcome in women with PCOS undergoing IVF cycles 2018.	Wrong publication type
A study to compare the efficacy and adverse effects of metformin versus myoinositol plus d-chiroinositol combination therapy in polycystic ovarian syndrome. A prospective randomised comparative study of metformin versus myoinositol plus d-chiroinositol combination therapy in polycystic ovarian syndrome 2019.	Wrong publication type
Effect of combined electroacupuncture and medical therapy on insulin resistance in polycystic ovary syndrome patients. Combination of electroacupuncture and pharmacological treatment in improving insulin resistance (HOMA-IR) in polycystic ovary syndrome patients: a double-blind randomized clinical trial 2020.	Wrong study design
Study to find Effects of Chandraprabha Vati(Ayurvedic Medicine) in Polycystic Ovarian Syndrome Characterised by Small cysts in ovary with irregular,Scanty menses and excess/unwanted hairs on Face,Thighs,Abdomen etc. â??Randomized controlled clinical trial to study the efficacy OF Chandraprabha vati in PCOS.â?? 2020.	Wrong study design
A clinical trial to study the effect of exercise and metformin on mitochondrial health in patients with polycystic ovarian syndrome (PCOS). To assess the efficacy of moderate-intensity exercise training and metformin on mitophagy and mitochondrial phenotype in patients with polycystic ovarian syndrome (PCOS) 2020.	Wrong publication type
ffect of oral contraceptives on levels of adipokines, and adiposity indices in women with polycystic ovary syndrome. A randomized clinical trial to compare the effectiveness of oral contraceptives containing levonorgestrel, desogestrel, cyproterone acetate, and drospirenone on levels of adipokines, and adiposity indices in women with polycystic ovary syndrome. 2020.	Wrong publication type
Effect of treatment by OCP on infertility in PCOD patients. The randomized, single -blinded clinical trial comparing OCP effect before frozen embryo transfer versus gonadotropin â“ releasing hormone agonist injection on improving the outcome of pregnancy in infertile patients with hyper androgenic poly 2020.	Fulltext not obtainable
Expression of concern: Comparison of myo-inositol and metformin on mental health parameters and biomarkers of oxidative stress in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial The effects of fish oil omega-3 fatty acid supplementation on mental health parameters and metabolic status of patients with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. Journal of Psychosomatic Obstetrics & Gynecology 2020, 41, I-I, doi:10.1080/0167482X.2020.1842508	Wrong publication type
Evaluation of therapeutic effects of crocina (saffron tablets) in patients with polycystic ovary syndrome: a randomized double-blind clinical trial. 2021.	Wrong publication type
A clinical study in women suffering from polycystic ovary syndrome (PCOS) to test the drug LPRI-424 (dienogest/ethinyl estradiol) during 9 months of treatment. A multicentre, phase III, double-blind, randomised clinical trial to assess the efficacy and safety of LPRI-424 (dienogest 2.00 mg / ethinyl estradiol 0.02 mg) in the treatment of polycystic ovary syndrome (PCOS) versus placebo during 9 cycles 2021.	Wrong publication type
A clinical trial to study the effect of myoinositol based therapy in combination with metformin as compared to metformin alone in women with polycystic ovarian syndrome. A Randomized Controlled Trial comparing Myoinositol based therapy in combination with Metformin versus Metformin monotherapy on the clinical, metabolic and hormonal parameters in Obese reproductive age women with Polycystic Ovarian Syndrome 2021.	Wrong publication type
Efficacy of very low carbohydrate diet combined with metformin in overweight / obese PCOS patients on changing of clinical phenotype, gut microbiota and plasma metabolome after treatment: a randomized, controlled clinical trial. 2021.	Fulltext not obtainable
A Phase II, randomised, multi-centric, multi-national clinical trial to evaluate the efficacy, tolerability, and safety of a fixed dose combination of Spironolactone, Pioglitazone & Metformin (SPIOMET) for adolescent girls and young adult women (AYAs) with polycystic ovary syndrome (PCOS). 2021.	Wrong publication type
Investigation on the efficacy and safety of Ceylon cinnamon (Cinammomum zeylanicum) compared to metformin in ameliorating symptoms of Polycystic Ovary Syndrome (PCOS): A randomized controlled trial. Investigation on the Efficacy and Safety of Ceylon Cinnamon (Cinammomum zeylanicum) and Metformin in Ameliorating Polycystic Ovary Syndrome (PCOS): A Randomized Controlled Trial 2022.	Wrong comparator
Abdalla, M.A.; Deshmukh, H.; Atkin, S.; Sathyapalan, T. The potential role of incretin-based therapies for polycystic ovary syndrome: a narrative review of the current evidence. Therapeutic Advances in Endocrinology and Metabolism 2021, 12, doi:https://dx.doi.org/10.1177/2042018821989238.	Wrong study design
Abdalmageed, O.S.; Farghaly, T.A.; Abdelaleem, A.A.; Abdelmagied, A.E.; Ali, M.K.; Abbas, A.M. Impact of Metformin on IVF Outcomes in Overweight and Obese Women With Polycystic Ovary Syndrome: A Randomized Double-Blind Controlled Trial. Reproductive sciences (Thousand Oaks, Calif.) 2019, 26, 1336-1342, doi:https://dx.doi.org/10.1177/1933719118765985.	Wrong intervention

Acmaz, G.; Cınar, L.; Acmaz, B.; Aksoy, H.; Kafadar, Y.T.; Madendag, Y.; Ozdemir, F.; Sahin, E.; Muderris, I. The Effects of Oral Isotretinoin in Women with Acne and Polycystic Ovary Syndrome. BioMed research international 2019, 10.1155/2019/2513067, 1-5, doi:10.1155/2019/2513067.	Wrong study design
Advani, K.; Batra, M.; Tajpuriya, S.; Gupta, R.; Saraswat, A.; Nagar, H.D.; Makwana, L.; Kshirsagar, S.; Kaul, P.; Ghosh, A.K., et al. Efficacy of combination therapy of inositols, antioxidants and vitamins in obese and non-obese women with polycystic ovary syndrome: an observational study. Journal of Obstetrics & Gynaecology 2020, 40, 96-101, doi:10.1080/01443615.2019.1604644.	Wrong study design
Ahc, M. What Are the Roles of the Combined Oral Contraceptive Pill and Metformin in the Management of Polycystic Ovary Syndrome? OB/GYN Clinical Alert 2020, 36, N.PAG-N.PAG.	Wrong study design
Ainehchi, N.; Khaki, A.; Ouladsahebmadarek, E.; Hammadeh, M.; Farzadi, L.; Farshbaf-Khalili, A.; Asnaashari, S.; Khamnei, H.J.; Khaki, A.A.; Shokoohi, M. The effect of clomiphene citrate, herbal mixture, and herbal mixture along with clomiphene citrate on clinical and para-clinical parameters in infertile women with polycystic ovary syndrome: A randomized controlled clinical trial. Archives of Medical Science 2020, 16, 1304-1318, doi:https://dx.doi.org/10.5114/AOMS.2020.93271.	Wrong intervention
Akhtar, T.; Shaikh, F.; Basma; Ahmed, W.U.N.; Lashari, S.; Bhatti, N. Comparison of myoinositol versus combination of metformin and myoinositol in ovulation induction in polycystic ovarian syndrome. Pakistan Journal of Medical and Health Sciences 2021, 15, 1494-1496, doi:http://dx.doi.org/10.53350/pjmhs211561494.	Wrong outcome
Alalami, H.; Sathyapalan, T.; Atkin, S.L. Cardiovascular profile of pharmacological agents used for the management of polycystic ovary syndrome. Therapeutic Advances in Endocrinology and Metabolism 2019, 10, doi:http://dx.doi.org/10.1177/2042018818805674.	Wrong study design
Alalfy, M.; Rashwan, A.S.S.A.; Hussein, M.; Bakry, A.; Eid, A.; Eid, M.M. The Use of N-Acetyl Cysteine Versus Chromium Picolinate as an Adjuvant to Clomiphene Citrate and Metformin in PCOS Women to Improve Ovulation Induction and Insulin Resistance: A Pilot Randomized Controlled Trial. Current Women's Health Reviews 2022, 18, e241221192204, doi:https://dx.doi.org/10.2174/1573404817666210310164353.	Wrong comparator
Alhussain, F.; Alruthia, Y.; Al-Mandeel, H.; Bellahwal, A.; Alharbi, F.; Almogbel, Y.; Awwad, O.; Dala'een, R.; Alharbi, F.A. Metformin improves the depression symptoms of women with polycystic ovary syndrome in a lifestyle modification program. Patient Preference and Adherence 2020, 14, 737-746, doi:http://dx.doi.org/10.2147/PPA.S244273.	Wrong study design
Ali, D.-E.S.; Shah, M.; Ali, A.; Malik, M.O.; Rehman, F.; Badshah, H.; Ehtesham, E.; Vitale, S.G. Treatment with Metformin and Combination of Metformin Plus Pioglitazone on Serum Levels of IL-6 and IL-8 in Polycystic Ovary Syndrome: A Randomized Clinical Trial. Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme 2019, 51, 714-722, doi:https://dx.doi.org/10.1055/a-1018-9606.	Fulltext not obtainable
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Woodward, A.; Broom, D.; Harrop, D.; Lahart, I.; Carter, A.; Dalton, C.; Metwally, M.; Klonizakis, M. The effects of physical exercise on cardiometabolic outcomes in women with polycystic ovary syndrome not taking the oral contraceptive pill: a systematic review and meta-analysis. Journal of Diabetes and Metabolic Disorders 2019, 18, 597-612, doi:http://dx.doi.org/10.1007/s40200-019-00425-y.	Wrong intervention
Wu, Y.; Tu, M.; Huang, Y.; Liu, Y.; Zhang, D. Association of Metformin With Pregnancy Outcomes in Women With Polycystic Ovarian Syndrome Undergoing In Vitro Fertilization: A Systematic Review and Meta-analysis. JAMA network open 2020, 3, e2011995-e2011995, doi:10.1001/jamanetworkopen.2020.11995.	Wrong outcome
Xie, L.; Zhang, D.; Ma, H.; He, H.; Xia, Q.; Shen, W.; Chang, H.; Deng, Y.; Wu, Q.; Cong, J., et al. The Effect of Berberine on Reproduction and Metabolism in Women with Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis of Randomized Control Trials. Evidence-based Complementary & Alternative Medicine (eCAM) 2019, 10.1155/2019/7918631, 1-15, doi:10.1155/2019/7918631.	Wrong intervention
Xu, J.; Zuo, Y. [Efficacy of acupuncture as adjunctive treatment on infertility patients with polycystic ovary syndrome]. Zhongguo zhen jiu = Chinese acupuncture & moxibustion 2018, 38, 358-361, doi:https://dx.doi.org/10.13703/j.0255-2930.2018.04.004.	Wrong language
Xu, Q.; Xie, Q. Long-term effects of prenatal exposure to metformin on the health of children based on follow-up studies of randomized controlled trials: a systematic review and meta-analysis. Springer Nature: , <Blank>, 2019; Vol. 299, pp 1295-1303.	Wrong outcome
Xu, Z.; Meng, L.; Pan, C.; Chen, X.; Huang, X.; Yang, H. Does oral contraceptives pretreatment affect the pregnancy outcome in polycystic ovary syndrome women undergoing ART with GnRH agonist protocol? Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology 2019, 35, 124-127, doi:https://dx.doi.org/10.1080/09513590.2018.1500535.	Wrong study design
Yanbo, L.; Yupei, S.; Jiping, X.; Linlin, C.; Guang, Z.; Liu, Y.; Shao, Y.; Xie, J.; Chen, L.; Zhu, G. The efficacy and safety of metformin combined with simvastatin in the treatment of polycystic ovary syndrome: A meta-analysis and systematic review. Medicine 2021, 100, 1-8, doi:10.1097/MD.0000000000026622.	Wrong intervention
Yang, D.; Zhao, M.; Tan, J. [Effect of polycystic ovary syndrome treated with the periodic therapy of acupuncture]. Zhongguo zhen jiu = Chinese acupuncture & moxibustion 2017, 37, 825-829, doi:https://dx.doi.org/10.13703/j.0255-2930.2017.08.007.	Wrong language
Yang, J.; Liu, Y.; Huang, J.; Xu, J.; You, X.; Lin, Q.; Zhang, J.; Dun, J.; Huang, S. [Acupuncture and Chinese medicine of artificial cycle therapy for insulin resistance of polycystic ovary syndrome with phlegm damp type and its mechanism]. Zhongguo zhen jiu = Chinese acupuncture & moxibustion 2017, 37, 1163-1168, doi:https://dx.doi.org/10.13703/j.0255-2930.2017.11.007.	Wrong language
Yao, K.; Bian, C.; Zhao, X. Association of polycystic ovary syndrome with metabolic syndrome and gestational diabetes: Aggravated complication of pregnancy (Review). Experimental and Therapeutic Medicine 2017, 14, 1271-1276, doi:http://dx.doi.org/10.3892/etm.2017.4642.	Wrong study design
Yen, H.; Chang, Y.-T.; Yee, F.-J.; Huang, Y.-C. Metformin Therapy for Acne in Patients with Polycystic Ovary Syndrome: A Systematic Review and Meta-analysis. American journal of clinical dermatology 2021, 22, 11-23, doi:10.1007/s40257-020-00565-5.	Wrong outcome
Young, C.C.; Monge, M. Polycystic Ovary Syndrome in Primary Care: It Takes a Village. Journal for Nurse Practitioners 2019, 15, 694-695, doi:10.1016/j.nurpra.2019.05.008.	Wrong study design
Yousuf, S.D.; Ganie, M.A.; Jeelani, S.; Mudassar, S.; Shah, Z.A.; Zargar, M.A.; Amin, S.; Wani, I.A.; Rashid, F. Effect of six-month use of oral contraceptive pills on plasminogen activator inhibitor-1 & factor VIII among women with polycystic ovary syndrome: An observational pilot study. The Indian journal of medical research 2018, 148, S151-S155, doi:https://dx.doi.org/10.4103/ijmr.IJMR_1899_17.	Wrong study design
Zeng, L.; Yang, K. Effectiveness of myoinositol for polycystic ovary syndrome: a systematic review and meta-analysis. Endocrine 2018, 59, 30-38, doi:https://dx.doi.org/10.1007/s12020-017-1442-y.	Wrong intervention
Zhang, J.; Si, Q.; Li, J. Therapeutic effects of metformin and clomiphene in combination with lifestyle intervention on infertility in women with obese polycystic ovary syndrome. Pakistan journal of medical sciences 2017, 33, 8, doi:https://doi.org/10.12669/pjms.331.11764.	Wrong intervention
Zhang, J.; Su, M.; Xu, L.; Yang, Z.; Yin, W.; Nie, Y.; Qiao, X.; Cheng, R.; Ma, Y. [Efficacy and metabolic safety of long-term treatment with ethinyl oestradiol/cyproterone and desogestrel/ethinyl oestradiol tablets in women with	Wrong language

polycystic ovary syndrome]. Nan fang yi ke da xue xue bao = Journal of Southern Medical University 2018, 38, 917-922, doi:https://dx.doi.org/10.3969/j.issn.1673-4254.2018.08.03.	
Zhang, S.-W.; Zhou, J.; Gober, H.-J.; Leung, W.T.; Wang, L. Effect and mechanism of berberine against polycystic ovary syndrome. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 2021, 138, 111468, doi:https://dx.doi.org/10.1016/j.biopha.2021.111468.	Wrong study design
Zhang, Y.; Guo, X.; Ma, S.; Ma, H.; Li, H.; Wang, Y.; Qin, Z.; Wu, X.; Han, Y.; Han, Y. The Treatment with Complementary and Alternative Traditional Chinese Medicine for Menstrual Disorders with Polycystic Ovary Syndrome. Evidence-based Complementary & Alternative Medicine (eCAM) 2021, 10.1155/2021/6678398, 1-19, doi:10.1155/2021/6678398.	Wrong study design
Zhao, J.; Liu, X.; Zhang, W. The Effect of Metformin Therapy for Preventing Gestational Diabetes Mellitus in Women with Polycystic Ovary Syndrome: A Meta-Analysis. Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association 2020, 128, 199-205, doi:https://dx.doi.org/10.1055/a-0603-3394.	Fulltext not obtainable
Zhao, Y.X.; Wang, L.J.; Gong, F.Y.; Pan, H.; Miao, H.; Duan, L.; Yang, H.B.; Zhu, H.J. [Effects of orlistat and metformin on metabolism and gonadal function in overweight or obese patients with polycystic ovary syndrome]. Zhonghua nei ke za zhi 2021, 60, 1165-1168, doi:https://dx.doi.org/10.3760/cma.j.cn112138-20210302-00171.	Wrong language
Zhou, K.; Zhang, J.; Xu, L.; Lim, C.E.D. Chinese herbal medicine for subfertile women with polycystic ovarian syndrome. The Cochrane database of systematic reviews 2021, 6, CD007535, doi:https://dx.doi.org/10.1002/14651858.CD007535.pub4.	Wrong intervention
Zimmerman, L.D.; Setton, R.; Pereira, N.; Rosenwaks, Z. Contemporary Management of Polycystic Ovarian Syndrome. Clinical obstetrics and gynecology 2019, 62, 271-281, doi:https://dx.doi.org/10.1097/GRF.0000000000000449.	Wrong study design

GDG: 4

Clinical Question: 4.06. Are anti-androgen pharmacological agents alone or in combination, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS.

Key Contacts: Selma Witchel, Daniela Romualdi, Alexia Pena Vargas

3. STUDY CHARACTERISTICS TABLE FOR INCLUDED STUDIES

Author, year, country	Population/ PCOS criteria/ Setting	Study Design	Intervention N	Intervention description	Comparison N	Comparison description	Follow Up	Outcomes	Pooled in MA?	RoB
Alpanes 2017, Spain	Women with PCOS/ Androgen excess outpatient clinic	RCT	1: 18	**1:** 30 ug EE+ 150 ug DG + 100 mg spironolactone	**2**: 13	**2:** Metformin 850 mg b.i.d.	12 months	requency of menstrual dysfunction hirsutism score, BMI, waist circumference, serum total and free testosterone, androstenedione and DHEAS, OGTT, serum insulin and plasma glucose, HOMA, adverse effects	No	High
Amiri 2014, Iran	Overweight and obese infertile women with PCOS/ Fatemezahra Infertility and Reproductive Health Centre	RCT	1: 27 2: 27	**1:** 250mg FLU 2/day + 1 month HC pre-diet **2:** 500mg MET 3/day + 250mg FLU 2/day + 1 month HC pre-diet	3: 25 4: 26	**3:** 500mg MET 3/day + 1-month HC pre-diet. **4.** PLAC	6 months	BMI, WHR, Hirsutism, SHBG, Testosterone, DHEAS, fasting insulin, fasting glucose, OGTT, QUICKI, Total cholesterol, HDL, LDL, Triglycerides	Yes	Moderate*
Diri 2017, Turkey	Patients with PCOS/Department of Endocrinology Erciyes University Medical School	RCT	1: 16 2: 19	**1:** FIN 5mg/day **2:** FIN 5mg/day + MET	3: 17	**3:** MET 1700mg/day	12 months	BMI, Hirsutism, SHBG, Free testosterone, DHEAS, Androstenedione, HOMA-IR	No	High
Falsetti 1997, Italy* Falsetti 1999, Italy	Hirsute women with PCOS/ Department of Gynaecological Endocrinology of the University of Brescia	RCT	1: 22 1: 32	**1:** FIN 5mg once/day	2: 22 2: 32	**2:** FLU 250mg b.d.	6 months 12 months	Hirsutism, SHBG, Testosterone, free testosterone, DHEAS, Androstenedione, fasting insulin, GI severe.	Falsetti 1997 (No); Falsetti 1999 (Yes)	High*
Gambineri 2004, Italy Gambineri 2006, Italy**	Overweight women with PCOS/Division of endocrinology S. Orsola-Malpighi Hospital, Italy	RCT	1: 10 2: 10 1: 10 2: 10	**1:** FLU 250mg orally b.d. + hypocaloric diet **2:** MET 850mg orally b.d. + 250mg FLU 250mg orally twice/day + hypocaloric diet	3: 10 4: 10 3:20 4: 19	**3:** MET 850mg orally b.d. + hypocaloric diet **4:** PLAC + hypocaloric diet	12 months	Body weight, BMI, waist circumference, Hirsutism, frequency of menstruation, total testosterone, free-androgen index, androstenedione, DHEA-S, SHBG, fasting glucose, fasting insulin, QUICKI, ISI, LDL, HDL, Triglycerides Gambineri 2004 added: HOMA,	Gambineri 2004 (No); Gambineri 2006 (Yes)	Low*

Ganie 2004, India	Women with PCOS/Attending Endocrine and Metabolism Clinical of the All-India Institute of Medical Sciences between 2001 and 2002	RCT	1: 34	**1:** SPL 50mg b.d. + lifestyle advice	2: 35	**2:** MET 1000mg/day + lifestyle advice	6 months	BMI, WHR, Menstrual cyclicity, hirsutism, fasting blood glucose, HOMA, Testosterone	Yes	Moderate*
Ganie 2013, India	Women with PCOS/Tertiary care referral centre	RCT	1: 51 2: 62	**1:** SPL 50mg/day + diet counselling **2:** SPL 50mg/day + MET 1000mg/day + diet counselling	3: 56	**3:** MET 1000mg/day + diet counselling	6 months	Body weight, BMI, WHR, Menstrual cyclicity, Hirsutism, testosterone, fasting glucose, fasting insulin, HOMA-IR, QUICKI	Yes	Low*
Hagag 2014, Israel	Women with hirsutism due to PCOS/ University affiliated endocrinology clinic, Israel	RCT	1: 72 2: 70	**1:** 250ug NOR + 35ug EE [250ug NOR + 35ug EE] + 100mg SPL **2:** [2mg CPA + 35ug EE] + 10mg CPA added	3: 25	**3:** 250ug NOR + 35ug EE	12 months	Weight change, acne, Adverse events (Nausea, Breast tenderness, Nipple discharge, menorrhagia, headache, etc)	Yes	Moderate*
Ibanez 2004, Spain	Nonobese adolescents and adults with PCOS/Endocrinology Unit, Hospital Saint Joan de Deu, University of Barcelona	RCT	1: 16 2: 11	**1:** MET 850 mg + FLU 62.5 mg (adults) **2:** OCP + MET 850mg + FLU 62.5mg	3: 16 4: 11	**3:** EE 30 μg + 0.3 mg DRSP (adolescents) **4:** EE 30 μg + 0.3 mg DRSP (adults)	9 months	BMI, Hirsutism, Fasting glucose/insulin ratio, SHBG, Testosterone, TG, HDL, LDL	No	Moderate*
Ibanez 2020, Spain de Zegher 2021, Spain Malpique 2019, Spain** Ibanez 2017, Spain	Nonobese adolescents with PCOS/Endocrinology Unit, Hospital Saint Joan de Deu	RCT	1: 31 1: 29	**1:** SPL 50 mg/d + pioglitazone 7.5 mg/d + metformin 850 mg/d (SPIOMET).	2: 31 2: 29	**2:** EE 20μg –levonorgestrel 100 mg	12 months	BMI, hirsutism score, SHBG, TT, Androstenedione, insulin, HOMA, OGTT, TG, LDL, HDL, CRP, de Zegher: FAI, TT Ibanez 2017: Acne scores	No	Moderate

Clinical Question: 4.06. Are anti-androgen pharmacological agents alone or in combination, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS.

Key Contacts: Selma Witchel, Daniela Romualdi, Alexia Pena Vargas

Diaz 2018, Spain										
Mazza 2014, Italy	Overweight and obese women with PCOS/Endocrine Unit of University Magna Graecia of Catanzaro	RCT	1: 28	**1:** SPL 25mg/day + MET 1700mg/day + lifestyle modification (HCD: 1300kcal/d)	2: 28	**2:** MET 1700mg/day + lifestyle modification (HCD: 1300kcal/d)	6 months	Weight, BMI, Hirsutism, cholesterol, HDL, LDL, triglycerides, fasting glucose, fasting insulin, HOMA, total testosterone, SHBG, FAI, DHEAS	Yes	Low*
Mehrabian 2016, Iran	Women with PCOS/Midwifery clinic of Al-Zahra Hospital	RCT	1: 34	**1:** FLU 62.5mg + OCP (0.03mg EE + 0.15mg LVG)	2: 34	**2:** MET 1000mg/day	6 months	Waist circumference, triglycerides, fasting blood glucose, CRP, HDL, BMI,	Yes	Low*
Meyer 2007, Australia Burchall 2017, Australia	Overweight women with PCOS	RCT	1: 33 1: 16	**1:** 50mg SPL + low-dose OCP (EEµg + LVG)	2: 31 3: 36 2: 21 3: 23	**2:** High-dose OCP (35µg EE + 2mg CPA) **3:** MET 2000mg/day	6 months	Weight, BMI, OGTT, insulin, HOMA, testosterone, OGTT, Cholesterol, LDL, HDL, TG, CRP, TT, SHBG, FAI	Meyer (No); Burchall (Yes)	Moderate*
Moretti 2018, Italy	Women with PCOS/Unit of endocrinology, section of reproductive endocrinology, University of Rome	RCT	1: 28	**1:** OCP (EE 0.030mg + DRSP 2mg or CPA 2mg or dienogest 2mg) + BC 50mg	2: 24	**2:** OCP 0.030mg + DRSP 2mg or CPA 2mg or dienogest 2mg) + PLAC	12 months	Hirsutism, weight, BMI, total cholesterol, HDL, triglycerides, LDL, fasting glucose	Yes	Moderate*
Spritzer 2000, Brazil	Women with PCOS/Gynaecological Endocrinology Unit at Hospital	RCT	1: 10	**1:** 200mg/d SPL, 20d/month	2: 9	**2:** CPA 50mg/day, 20d/month + 35mg/d EE over the last 10 days of CPA	12 months	Hirsutism	No	Moderate*
Tartagni 2000, Italy	Women with PCOS/Outpatients in an academic research environment	RCT	1: 9	**1:** FIN + Diane-35 (CPA 2mg + EE 35µg)	2: 9	**2:** Diane-35 (CPA 2mg + EE 35µg)	6 months	Hirsutism, free testosterone, DHEAS, SHBG, Androstenedione	Yes	High*
Tartagni 2004, Italy	Women with hirsutism due to PCOS/Obstetrics and gynaecology outpatient clinic	RCT	1: 8	**1:** FIN 2.5mg/day	2: 8	**2:** FIN 2.5 mg every 3 days	10 months	Total testosterone, DHEAS, SHBG, androstenedione, BMI, Hirsutism	Yes	High*
Tartagni 2014, Italy	Women with hirsutism due to PCOS/Obstetrics	RCT	1: 7	**1:** FIN 2.5mg every 3 days	2: 7	**2:** Placebo	6 months	BMI, Hirsutism, SHBG, Testosterone, DHEAS, Androstenedione, GI-related adverse effects	No	High*

	and gynaecology outpatient clinic									
Vieira 2012, Brazil	Women with PCOS/University Hospital of Ribeirao Preto School of Medicine between 2007 and 2009	RCT	1: 20	**1:** OCP (2mg CMA + 30mcg EE) + SPL 100mg/day	2: 21	**2:** OCP (2mg CMA + EE 30mcg)	12 months	Weight, BMI, SHBG, FAI, Testosterone, free testosterone, fasting insulin, fasting glucose, total cholesterol, HDL, LDL, HOMA, CRP	Yes	Moderate*

BC, bicalutamide; BMI, body mass index; CPA, cyproterone acetate; CRP, c-reactive protein; DHEAS, dehydroepiandrosterone sulphate; EE, ethinylestradiol; FLU, flutamide; FIN, finasteride; HCL, hypocaloric diet; HDL, high density lipoprotein; IR, insulin resistance; LDL; low density lipoprotein; LVG, levonorgestrel; MET, metformin; MA, meta-analysis OGTT, oral glucose tolerance test; PLAC, placebo; PCOS, polycystic ovary syndrome; RCT, randomised controlled trial; RoB, risk of bias; SHBG, sex hormone binding globulin; SPL, spironolactone. *Risk of bias assessment derived from previous review from the guideline evidence team. ** No additional outcomes from Diaz and Malpique 2019, so nothing extracted.

4. FINDINGS

Comparisons Included:

- **Comparison 1**. Anti-androgen vs Placebo - ADOLESCENTS
- **Comparison 2.** Anti-androgen (daily) vs Anti-androgen (every 3 days)
- **Comparison 3.** Anti-androgen + lifestyle vs Placebo + lifestyle – ADULTS
- **Comparison 4.** Anti-androgen + lifestyle vs Anti-androgen + metformin + lifestyle
- **Comparison 5.** Anti-androgen vs metformin - ADULTS
- **Comparison 6.** Anti-androgen vs Anti-androgen + metformin – ADULTS
- **Comparison 7**. Anti-androgen vs COCP – ADULTS
- **Comparison 8**. Anti-androgen + metformin + Pioglitazone (SPIOMET) vs COCP – ADOLESCENTS
- **Comparison 9.** Anti-androgen + metformin vs COCP - ADOLESCENTS
- **Comparison 10**. Anti-androgen + metformin + COCP vs COCP - ADULTS
- **Comparison 11**. Anti-androgen + COCP vs COCP +/- placebo – ADULTS
- **Comparison 12.** Anti-androgen + COCP vs metformin – ADULTS
- **Comparison 13.** Anti-androgen + lifestyle vs metformin + lifestyle - ADULTS
- **Comparison 14.** Anti-androgen + metformin + lifestyle vs metformin + lifestyle - ADULTS

COMPARISON 1. Anti-androgen vs Placebo - ADOLESCENTS (6 MONTHS)

▪ EVIDENCE SUMMARY:

There was one study that compared a low-dose anti-androgen (finasteride) as compared to placebo in adolescent girls with PCOS. This study was of high risk (Tartagni, 2014) of bias and from Italy.

▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

In the mean difference estimates, it was highlighted that placebo was superior to the anti-androgen for reducing hirsutism as per the modified FG score. Certainty in the evidence was very low, as the single identified study was high risk of bias, with a very small sample size.

There were no differences in BMI, SHBG, testosterone, DHEAS, and androstenedione. The certainty of the evidence for these findings was very low due to high risk of bias and very small sample size.

Outcome or Subgroup	Studies	n	Effect Estimate; MD [95% CI], I-V, random	P-value	Favours	Certainty
Body mass index	1	14	0.50 kg/m^2 [-3.64, 4.64]	0.81	None	⊕◯◯◯ VERY LOW
Hirsutism	1	14	16.20 [11.99, 20.41]	<0.0001	Anti-androgen	⊕◯◯◯ VERY LOW
SHBG	1	14	0.00 µg/ml [-1.27, 1.27]	1.00	None	⊕◯◯◯ VERY LOW
Testosterone	1	14	0.30 ng/dl [-2.27, 2.87]	0.82	None	⊕◯◯◯ VERY LOW
DHEAS	1	14	0.60 µmol/l [0.07, 1.13]	0.03	Placebo	⊕◯◯◯ VERY LOW
Androstenedione	1	14	-0.10 ng/ml [-1.58, 1.38]	0.89	None	⊕◯◯◯ VERY LOW

OUTCOME 1.1 – 1.6: Body mass index, hirsutism, SHBG, testosterone, DHEAS, androstenedione
1.1.1.– 1.6.1. Individual Study Data Tables

OUTCOME: LISTED BELOW					**OUTCOME TYPE: Continuous**					
COMPARISON: Anti-androgen vs Placebo - ADOLESCENTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure) in intervention group	Sample size (n within this group)	Mean (specify if median) or median in control group	SD (or specify if other measure) in control group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
OUTCOME: BMI										
Tartagni 2014 (HRB)	Kg/m^2	Height and weight measurements; 6 months	24.4	4.1	7	23.9	3.8	7	Crude	N/A
OUTCOME: Hirsutism										

Tartagni 2014 (HRB)	Modified FG score	Ferriman-Gallaway score; 6 months	24.8	4.4	7	8.6	3.6	7	Crude	N/A
OUTCOME: SHBG										
Tartagni 2014 (HRB)	µg/ml	RIA assay; 6 months	1.9	1.4	7	1.9	1.0	7	Crude	N/A
OUTCOME: Testosterone										
Tartagni 2014 (HRB)	ng/dl	RIA assay; 6 months	75.1	2.5	7	74.8	2.4	7	Crude	N/A
OUTCOME: DHEAS										
Tartagni 2014 (HRB)	µmol/L	RIA assay; 6 months	5.1	0.4	7	4.5	0.6	7	Crude	N/A
OUTCOME: Androstenedione										
Tartagni 2014 (HRB)	Ng/ml	RIA assay; 6 months	3.6	1.6	7	3.7	1.2	7	Crude	N/A

COMPARISON 2. Anti-androgen (daily) vs Anti-androgen (every 3 days) – ADULTS (6 MONTHS – 12 MONTHS)

▪ EVIDENCE SUMMARY:

There were two RCTs that compared a daily anti-androgen and an anti-androgen given every 3 days (twice per week) in adult women with PCOS with 6- and 12-month follow-ups. Both studies had a high risk of bias (Falsetti 1999; Tartagni, 2004), and were conducted in Italy.

▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

In meta-analysis, a daily anti-androgen was superior to every 3-day regimen for hirsutism and androstenedione. Certainty in the evidence is very low for these outcomes, as both studies are high risk of bias with a small sample size.

There was no difference in SHBG, testosterone, DHEAS, BMI, fasting insulin and adverse events such as decreased libido and headache. The certainty of the evidence for these findings was very low reflective of the high risk of bias of both studies assessed and sample size.

Falsetti 1999 reported that two women (3.6%) dropped out of the study due to liver toxicity due to high transaminase levels potentially from the flutamide intervention.

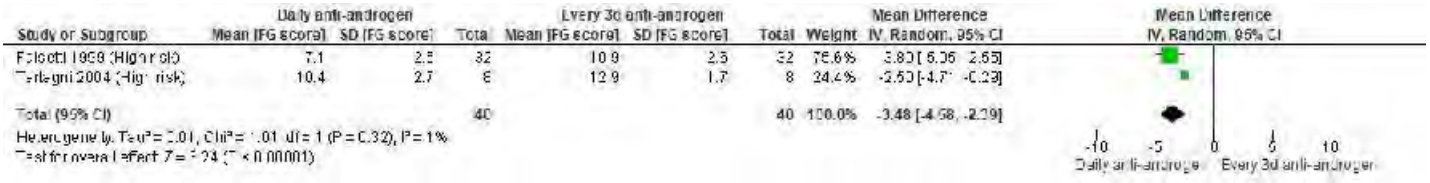
Outcome or Subgroup	Studies	n	Effect Estimate; MD [95% CI] or OR [95% CI], I-V, random	P-value	Favours	Certainty
Hirsutism	2	80	-3.48 [-4.58, -2.39]	<0.00001	Daily AA	⊕◯◯◯ VERY LOW
SHBG	2	80	0.29 nmol/l [-2.18, 2.76]	0.82	None	⊕◯◯◯ VERY LOW
Androstenedione	2	80	-0.30 ng/ml [-0.50, -0.10]	0.004	Daily AA	⊕◯◯◯ VERY LOW
Testosterone	2	80	-0.25 ng/ml [-0.73, 0.23]	0.30	None	⊕◯◯◯ VERY LOW
DHEAS	2	80	0.19 µg/ml [-0.79, 1.17]	0.71	None	⊕◯◯◯ VERY LOW
Body mass index	1	16	0.30 kg/m^2 [-3.67, 4.27]	0.88	None	⊕◯◯◯ VERY LOW
Fasting insulin	1	64	0.70 µU/ml [-0.17, 1.57]	0.11	None	⊕◯◯◯ VERY LOW
Dry skin	1	64	OR: 6.60 [2.21, 19.73]	0.0007	Every 3d AA	⊕◯◯◯ VERY LOW
Decreased libido	1	64	OR: 1.62 [0.41, 6.38]	0.49	None	⊕◯◯◯ VERY LOW
Headache	1	64	OR: 0.23 [0.02, 2.14]	0.19	None	⊕◯◯◯ VERY LOW

OUTCOME 2.1. Hirsutism

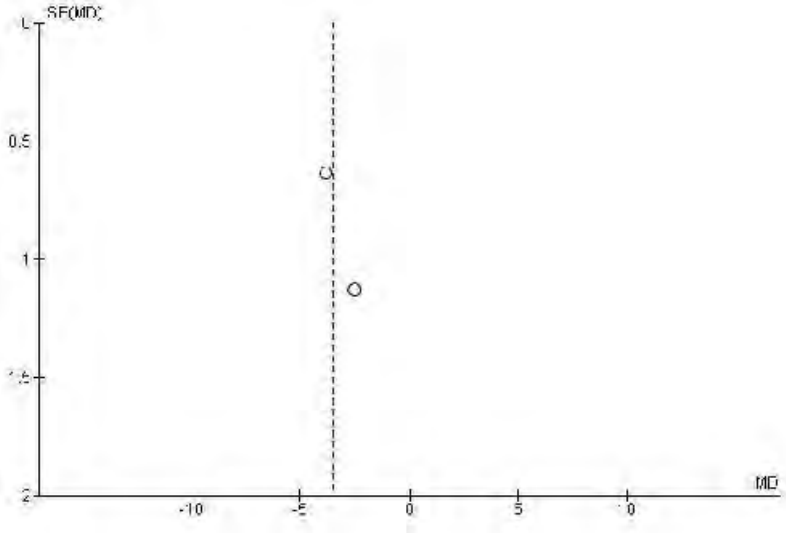
2.1.1 Individual Study Data Table

OUTCOME: Hirsutism					OUTCOME TYPE: Continuous					
COMPARISON: Anti-androgen (daily) vs Anti-androgen (every 3 days)										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Tartagni 2004 (HRB)	FG score	Ferriman-Gallaway score	10.4	2.7	8	12.9	1.7	8	Crude	N/A
Falsetti 1999 (HRB)	FG score	Ferriman-Gallaway score	7.1	2.5	32	10.9	2.6	32	Crude	N/A

2.1.2. Forest Plot of all included RCTs comparing Anti-androgen (daily) and Anti-androgen (every 3 days) for Hirsutism



2.1.3. Funnel plot for assessment of publication bias

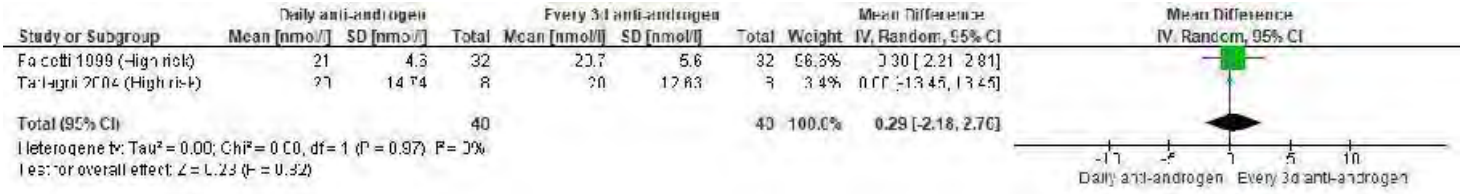


OUTCOME 2.2. SHBG

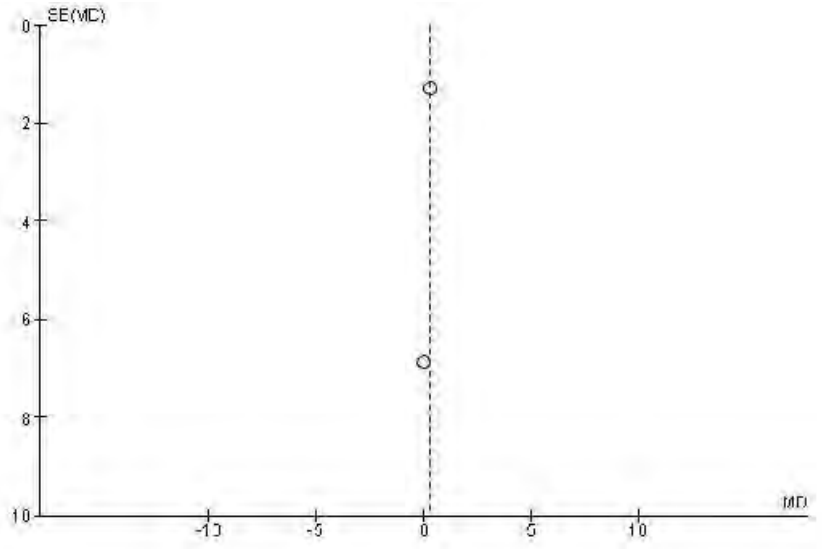
2.2.1 Individual Study Data Table

OUTCOME: SHBG					OUTCOME TYPE: Continuous					
COMPARISON: Anti-androgen (daily) vs Anti-androgen (every 3 days)										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Tartagni 2004 (HRB)	Nmol/l	RIA; 10 months	20	14.74	8	20	12.63	8	Crude	N/A
Falsetti 1999 (HRB)	Nmol/l	Immunoradiometric assay; 12 months	21.0	4.6	32	20.7	5.6	32	Crude	N/A

2.2.2. Forest Plot of all included RCTs comparing Anti-androgen (daily) and Anti-androgen (every 3 days) for SHBG



2.2.3. Funnel plot for assessment of publication bias

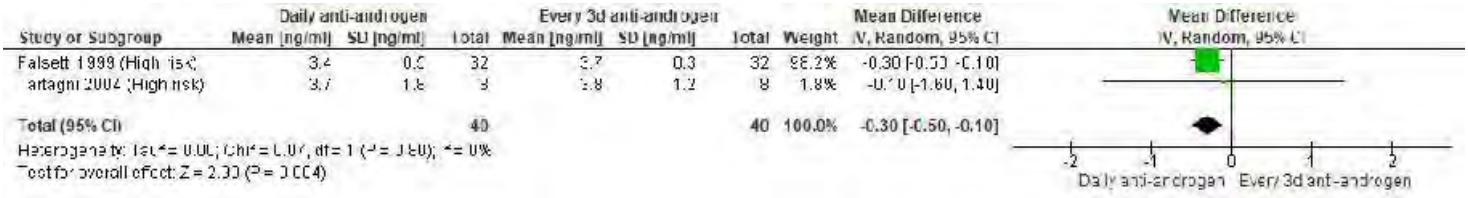


OUTCOME 2.3. Androstenedione

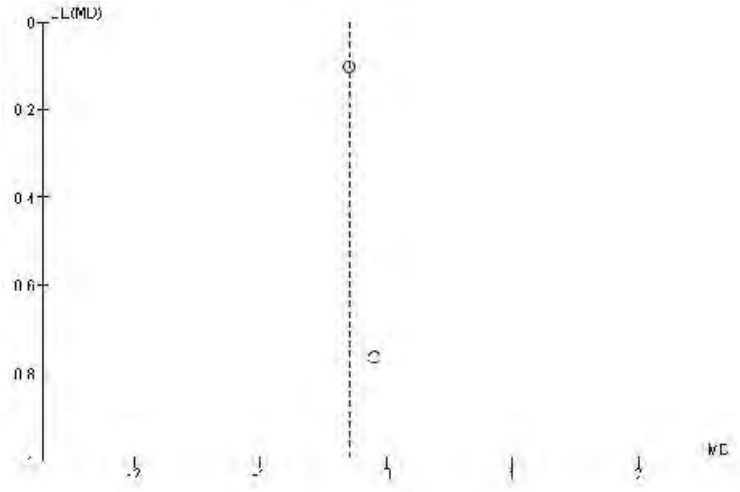
2.3.1 Individual Study Data Table

OUTCOME: Androstenedione					OUTCOME TYPE: Continuous					
COMPARISON: Anti-androgen (daily) vs Anti-androgen (every 3 days)										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Tartagni 2004 (HRB)	Ng/ml	Recombinant immunoassay; 10 months	3.7	1.8	8	3.8	1.2	8	Crude	N/A
Falsetti 1999 (HRB)	Ng/ml	RIA; 12 months	3.4	0.5	32	3.7	0.3	32	Crude	N/A

2.3.2. Forest Plot of all included RCTs comparing Anti-androgen (daily) and Anti-androgen (every 3 days) for Androstenedione



2.3.3. Funnel plot for assessment of publication bias

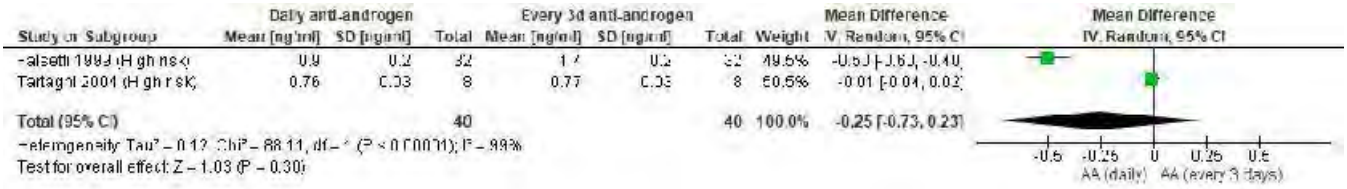


OUTCOME 2.4. Testosterone

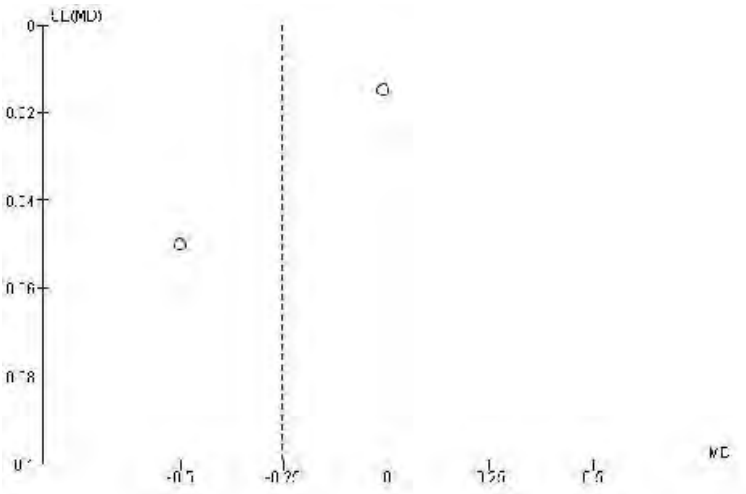
2.4.1 Individual Study Data Table

OUTCOME: Androstenedione					OUTCOME TYPE: Continuous					
COMPARISON: Anti-androgen (daily) vs Anti-androgen (every 3 days)										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Tartagni 2004 (HRB)	Ng/ml	Recombinant immunoassay ; 10 months	0.76	0.03	8	0.77	0.03	8	Crude	N/A
Falsetti 1999 (HRB)	Ng/ml	RIA; 12 months	0.9	0.2	32	1.4	0.2	32	Crude	N/A

2.4.2. Forest Plot of all included RCTs comparing Anti-androgen (daily) and Anti-androgen (every 3 days) for androstenedione



2.4.3. Funnel plot for assessment of publication bias

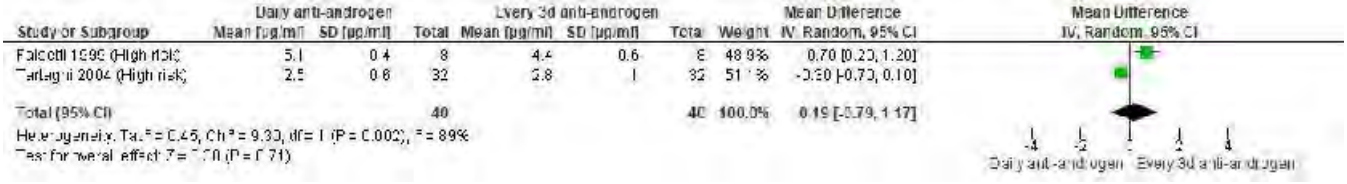


OUTCOME 2.5. DHEAS

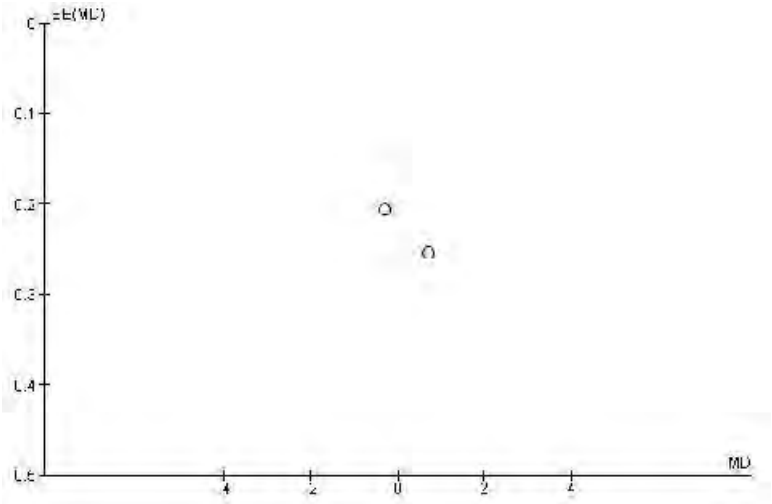
2.5.1 Individual Study Data Table

OUTCOME: Androstenedione					OUTCOME TYPE: Continuous					
COMPARISON: Anti-androgen (daily) vs Anti-androgen (every 3 days)										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Tartagni 2004 (HRB)	µg/ml	Recombinant immunoassay; 10 months	5.1	0.4	8	4.4	0.6	8	Crude	N/A
Falsetti 1999 (HRB)	µg/ml	RIA; 12 months	2.5	0.6	32	2.8	1.0	32	Crude	N/A

2.5.2. Forest Plot of all included RCTs comparing Anti-androgen (daily) and Anti-androgen (every 3 days) for DHEAS



2.5.3. Funnel plot for assessment of publication bias



OUTCOME 2.6. - 2.7: Body mass index, fasting insulin
2.6.1. – 2.7.1 Individual Study Data Tables

OUTCOME: LISTED BELOW					OUTCOME TYPE: Continuous					
COMPARISON: Anti-androgen (daily) vs Anti-androgen (every 3 days) - ADOLESCENTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
OUTCOME: BMI										
Tartagni 2004 (HRB)	Kg/m^2	Height and weight measurement; 10 months	24.2	4.1	8	23.9	4.0	8	Crude	N/A
OUTCOME: Fasting insulin										
Falsetti 1999 (HRB)	µU/ml	12 months	10.8	2.0	32	10.1	1.5	32	Crude	N/A

OUTCOME 2.8. - 2.10. Dry skin, decreased libido, headache
2.8.1. – 2.10.1 Individual Study Data Tables

OUTCOME: LISTED BELOW				OUTCOME TYPE: Dichotomous				
COMPARISON: Anti-androgen (daily) vs Anti-androgen (every 3 days)								
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	N events in intervention/ exposure group	N total in intervention/ exposure group	N events in control / comparison group	N total in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Outcome: Dry skin								
Falsetti 1999 (HRB)	Count	NR; 12 months	22	32	8	32	Crude	N/A
Outcome: Decreased libido								
Falsetti 1999	Count	NR; 12 months	6	32	4	32	Crude	N/A
Outcome: Headache								
Falsetti 1999	Count	NR; 12 months	1	32	4	32	Crude	N/A

COMPARISON 3. Anti-androgen + lifestyle vs Placebo + lifestyle – ADULTS (6 MONTHS – 12 MONTHS)

- **EVIDENCE SUMMARY:**

There were two studies that assessed the comparison between anti-androgen (flutamide) with lifestyle intervention and placebo with lifestyle intervention in adult women with PCOS with 6- and 12-month follow-ups, of which one had a moderate risk of bias (Amiri, 2014), and the other had a low risk of bias (Gambineri, 2006). Studies were conducted in Iran and Italy.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

Only three outcomes between the studies could be included in meta-analysis, with no specific intervention being superior. The certainty of the evidence ranged from low to very low due to risk of bias, small sample size, and was further downgraded as Amiri 2014 reported that the population was considered overweight, but the inclusion range was 19 to 35, thereby including lean women. Moreover, the exact BMIs of the population were not listed. It is noted that due to unit reporting leading to uncertainty, certain outcomes could not be pooled in meta-analysis, and instead, Gambineri 2006 was used for single study mean difference estimates. For the single study mean difference estimates, anti-androgen + lifestyle was superior for managing body weight, DHEAS, fasting insulin, LDL, triglyceride levels, frequency of menstruation, QUICKI, and insulin sensitivity index, as compared to the placebo + lifestyle intervention. The certainty of the evidence ranged from low to very low due to risk of bias and small sample.

There was no difference in outcomes such as BMI, hirsutism, SHBG, FAI, testosterone, and androstenedione. The certainty in the evidence of these findings ranged from very low to low reflective of the moderate risk of bias in Amiri 2014 and small sample size.

Outcome or Subgroup	Studies	n	Effect Estimate; MD [95% CI], I-V, random	P-value	Favours	Certainty
BMI	2	89	-3.08 kg/m^2 [-8.67, 2.50]	0.28	None	⊕◯◯◯ VERY LOW
Hirsutism	2	89	-0.93 [-3.37, 1.51]	0.45	None	⊕◯◯◯ VERY LOW
SHBG	2	89	9.72 nmol/l [-0.71, 20.14]	0.07	None	⊕⊕◯◯ LOW
Weight	1	36	-17.00 kg [-25.37, -8.63]	<0.0001	AA + LS	⊕⊕◯◯ LOW
FAI	1	36	-0.80 [-2.34, 0.74]	0.31	None	⊕◯◯◯ VERY LOW
Testosterone	1	36	0.05 ng/ml [-0.05, 0.15]	0.34	None	⊕⊕◯◯ LOW
DHEAS	1	36	-2.34 µg/ml [-4.06, -0.62]	0.008	AA + LS	⊕⊕◯◯ LOW
Androstenedione	1	36	-18.00 ng/ml [-74.86. 38.86]	0.53	None	⊕⊕◯◯ LOW
Fasting insulin	1	36	-4.00 µU/ml [-6.98, -1.02]	0.009	AA + LS	⊕⊕◯◯ LOW
HOMA	1	20	1.60 [-1.64, 4.84]	0.33	None	⊕⊕◯◯ LOW
Fasting glucose	1	36	0.00 mg/ml [-5.24, 5.24]	1.00	None	⊕⊕◯◯ LOW
QUICKI	1	36	0.04 [0.02, 0.06]	<0.00001	AA +LS	⊕⊕◯◯ LOW

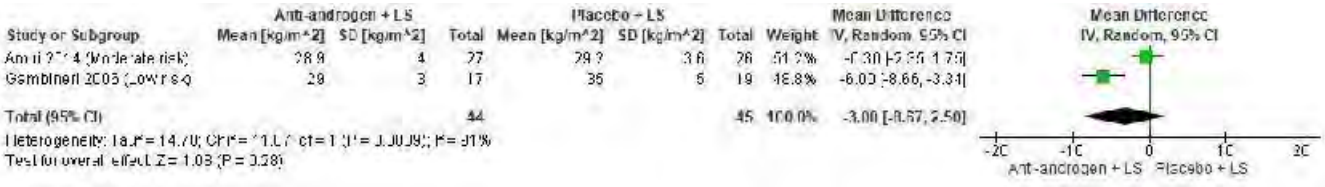
Insulin sensitivity index	1	36	5.10 [2.32, 7.88]	0.0003	AA + LS	⊕⊕◯◯ LOW
HDL	1	36	5.00 mg/dl [-1.54, 11.54]	0.13	None	⊕⊕◯◯ LOW
LDL	1	36	-21.00 mg/dl [-40.93, -1.07]	0.04	AA + LS	⊕⊕◯◯ LOW
Triglycerides	1	36	-50.00 mg/dl [-77.60, -22.40]	0.0004	AA + LS	⊕⊕◯◯ LOW
Frequency of menstruation	1	36	-0.80 [-1.54, -0.06]	0.03	AA + LS	⊕⊕◯◯ LOW

OUTCOME 3.1. Body mass index

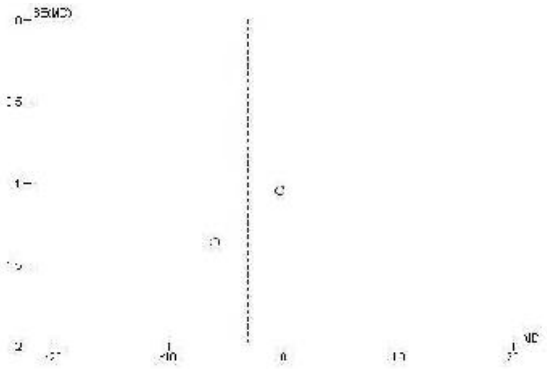
3.1.1. Individual Study Data Table

OUTCOME: BMI					OUTCOME TYPE: Continuous					
COMPARISON: Anti-androgen + LS vs Placebo + LS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Gambineri 2006	Kg/m^2	Height and weight measurements; 12 months	29	3	17	35	5	19	Crude	N/A
Amiri 2014	Kg/m^2	Height and weight measurements; 6 months	29.57	4	27	29.2	3.6	26	Crude	N/A

3.1.2. Forest Plot of all included RCTs comparing Anti-androgen + lifestyle and Placebo + lifestyle for BMI



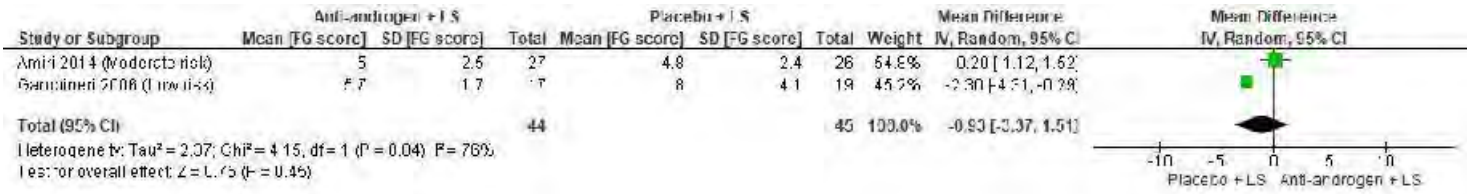
3.1.3. Funnel plot for assessment of publication bias



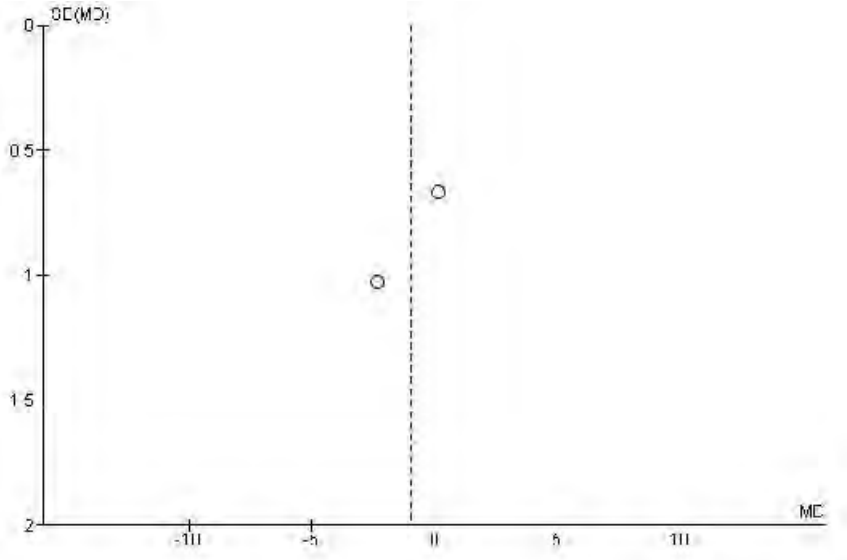
OUTCOME 3.2. Hirsutism
3.2.1. Individual Study Data Table

OUTCOME: Hirsutism					OUTCOME TYPE: Continuous					
COMPARISON: Anti-androgen + LS vs Placebo + LS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Gambineri 2006	FG score	Ferriman-Gallaway scoring; 12 months	5.7	1.7	17	8.0	4.1	19	Crude	N/A
Amiri 2014	FG score	Ferriman-Gallaway scoring; 6 months	5	2.5	27	4.8	2.4	26	Crude	N/A

3.2.1. Forest Plot of all included RCTs comparing Anti-androgen + lifestyle and Placebo + lifestyle for Hirsutism



3.2.2. Funnel plot for assessment of publication bias

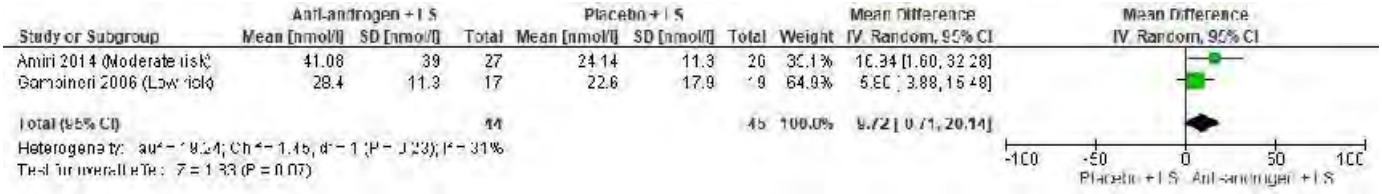


OUTCOME 3.3. SHBG

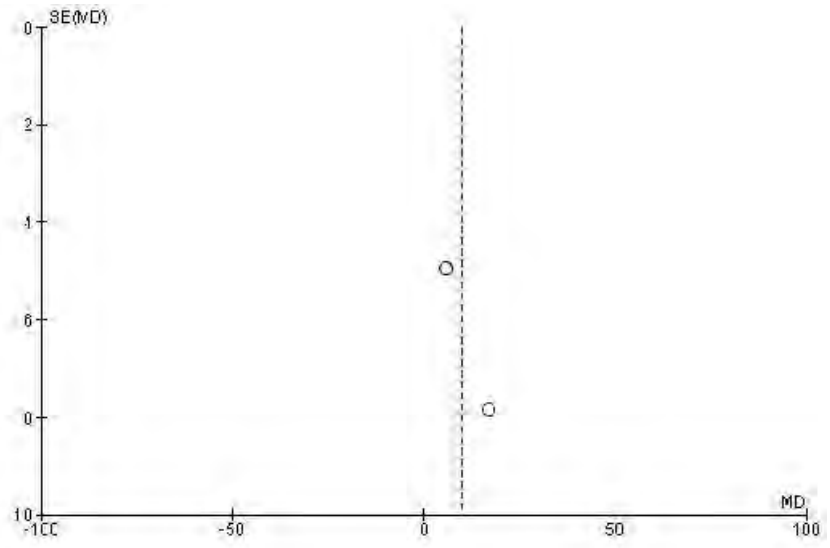
3.3.1. Individual Study Data Table

OUTCOME: SHBG					**OUTCOME TYPE: Continuous**					
COMPARISON: Anti-androgen + LS vs Placebo + LS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Gambineri 2006	Nmol/l	Hormone assays; 12 months	28.4	11.3	17	22.6	17.9	19	Crude	N/A
Amiri 2014	Nmol/l	6 months	41.08	39	27	24.14	11.3	26	Crude	N/A

3.3.2. Forest Plot of all included RCTs comparing Anti-androgen + lifestyle and Placebo + lifestyle for SHBG



3.3.3. Funnel plot for assessment of publication bias



OUTCOME 3.4 – 3.18: Weight, FAI, testosterone, DHEAS, androstenedione, fasting insulin, HOMA, fasting glucose, QUICKI, insulin sensitivity index, HDL, LDL, triglycerides, frequency of menstruation

3.4.1. – 3.18.1 Individual Study Data Tables

OUTCOME: LISTED BELOW					**OUTCOME TYPE: Continuous**					
COMPARISON: Anti-androgen + LS vs Placebo + LS - ADOLESCENTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
OUTCOME: Weight										
Gambineri 2006 (LRB)	kg	Weight measurement; 12 months	75	9	17	92	16	19	Crude	N/A
OUTCOME: FAI										
Gambineri 2006 (LRB)	Pg/ml	RIA; 12 months	2.4	2.1	17	3.2	2.6	19	Crude	N/A
OUTCOME: Testosterone										
Gambineri 2006 (LRB)	Ng/ml	RIA; 12 months	0.50	0.17	17	0.45	0.14	19	Crude	N/A
Amiri 2014 (MRB)#	Nmol/l	RIA; 6 months	0.55	0.2	27	0.95	0.2	26	Crude	N/A
OUTCOME: DHEAS										
Gambineri 2006 (LRB)	µg/ml	Hormone assays; 12 months	4.071	1.90	17	6.4136	3.26	19	Crude	N/A
Amiri 2014 (MRB)#	µmol/l	NR; 6 months	145.46	81	27	161.52	68.07	26	Crude	N/A
OUTCOME: Androstenedione										
Gambineri 2006 (LRB)	Ng/dl	Hormone assays; 12 months	224	80	17	242	94	19	Crude	N/A
OUTCOME: Fasting insulin										
Gambineri 2006 (LRB)	µU/ml	OGTT; 12 months	7	5	17	11	4	19	Crude	N/A
Amiri 2014 (MRB)#	Pmol/L	OGTT; 6 months	14.6	6.2	27	12.01	10.1	26	Crude	N/A
OUTCOME: HOMA										
Gambineri 2006 (LRB)	N/A	OGTT; 6 months	6.9	4.6	10	5.3	2.5	10	Crude	N/A
OUTCOME: Fasting glucose										
Gambineri 2006 (LRB)	Mg/ml	Glucose-oxidase method; 12 months	88	7	17	88	9	19	Crude	N/A
OUTCOME: QUICKI										
Gambineri 2006 (LRB)	N/A	OGTT; 12 months	0.38	0.03	17	0.34	0.02	19	Crude	N/A

OUTCOME: Insulin sensitivity index										
Gambineri 2006 (LRB)	N/A	OGTT; 12 months	10.2	5.5	17	5.1	2.1	19	Crude	N/A
OUTCOME: HDL										
Gambineri 2006 (LRB)	Mg/dL	Precipitation methods; 12 months	58	9	17	53	11	19	Crude	N/A
Amiri 2014 (MRB)#	Mmol/L	NR; 6 months	43	12.2	27	46.73	9.1	26	Crude	N/A
OUTCOME: LDL										
Gambineri 2006 (LRB)	Mg/dL	Precipitation methods; 12 months	88	28	17	109	33	19	Crude	N/A
Amiri 2014 (MRB)#	Mmol/L	NR; 6 months	105.8	32	27	99.12	23.7	26	Crude	N/A
OUTCOME: Triglycerides										
Gambineri 2006 (LRB)	Mg/dL	Precipitation methods; 12 months	63	19	17	113	58	19	Crude	N/A
Amiri 2014 (MRB)#	Mmol/L	NR; 6 months	133.6	72	27	128.6	76.4	26	Crude	N/A
OUTCOME: Frequency of menstruation										
Gambineri 2006 (LRB)	No. of cycles previous 6 months	Count; 12 months	5.0	1.4	17	5.8	0.7	19	Crude	N/A

Cannot perform meta-analysis due to uncertainty in units

COMPARISON 4. Anti-androgen + lifestyle vs Anti-androgen + metformin + lifestyle - ADULTS

(6 MONTHS – 12 MONTHS)

- **EVIDENCE SUMMARY:**

There were three RCTs that compared anti-androgen with lifestyle intervention with a combination therapy of anti-androgen and metformin with lifestyle intervention in adult women with PCOS with 6 to 12 months follow-up, of which two were low risk of bias (Gambineri, 2006; Ganie, 2013) and one was moderate (Amiri, 2014). Studies were conducted in India, Italy, and Iran.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

In meta-analysis, the combination therapy of an anti-androgen + metformin + lifestyle intervention was superior for fasting glucose compared to the anti-androgen + lifestyle intervention, with a moderate certainty of evidence. Conversely, the anti-androgen + lifestyle intervention was superior for triglycerides compared to the combination anti-androgen + metformin + lifestyle intervention, with a low certainty of evidence, due to the very small sample. In the single study mean difference estimates, the combination therapy of anti-androgen + metformin + lifestyle intervention was superior for WHR, with a high certainty of evidence.
There was no difference between other outcomes including BMI, hirsutism, SHBG, testosterone, fasting insulin, QUICKI in meta-analysis, with a certainty of evidence that ranged from very low to low mostly due to the risk of bias and inclusion of Amiri 2014 where it is uncertain whether the study included lean women. The certainty in the evidence of fasting insulin which was high. In the single study mean difference estimates, there was no difference in weight, total cholesterol, FAI, DHEAS, androstenedione, HDL, and HOMA-IR. Certainty in these finding ranged from very low to low due to risk of bias and sample sizes. Since the BMIs of the population of Amiri 2014 was uncertain, a sensitivity analysis was conducted to assess the influence of Amiri 2014 on several outcomes. When removing Amiri 2014 from BMI, hirsutism, SHBG, testosterone, and fasting glucose, they were still not statistically significant. Gambineri 2006 assessed tolerability to flutamide via liver function tests and reported that it was well-tolerated by all participants but did not report specific values.

Outcome or Subgroup	Studies	n	Effect Estimate; MD [95% CI], I-V, random	P-value	Favours	Certainty
BMI	3	204	-0.05 kg/m^2 [-1.21, 1.11]	0..94	None	⊕⊕◯◯ LOW
Hirsutism	3	204	-0.84 [-2.71, 1.03]	0.38	None	⊕◯◯◯ VERY LOW
SHBG	2	91	8.88 nmol/l [-7.01, 24.78]	0.27	None	⊕◯◯◯ VERY LOW
Testosterone	3	204	0.05 nmol/l [-0.15, 0.24]	0.64	None	⊕⊕◯◯ LOW
Fasting insulin	2	150	-0.18 µIU/ml [-1.94, 1.59]	0.84	None	⊕⊕⊕⊕ HIGH
Fasting glucose	3	204	3.81 mg/dl [1.35, 6.28]	0.002	AA + LS	⊕⊕⊕◯ MODERATE
QUICKI	2	150	0.00 [-0.03, 0.03]	0.79	None	⊕⊕◯◯ LOW
Weight	1	113	1.11 kg [-1.97, 4.19]	0.48	None	⊕⊕⊕◯ MODERATE
WHR	1	113	0.05 [0.03, 0.07]	<0.0001	AA + LS	⊕⊕⊕⊕ HIGH
Total cholesterol	1	54	-2.24 mg/dl [-26.00, 21.52]	0.85	None	⊕◯◯◯ VERY LOW
FAI	1	37	0.50 [-0.57, 1.57]	0.36	None	⊕⊕◯◯ LOW

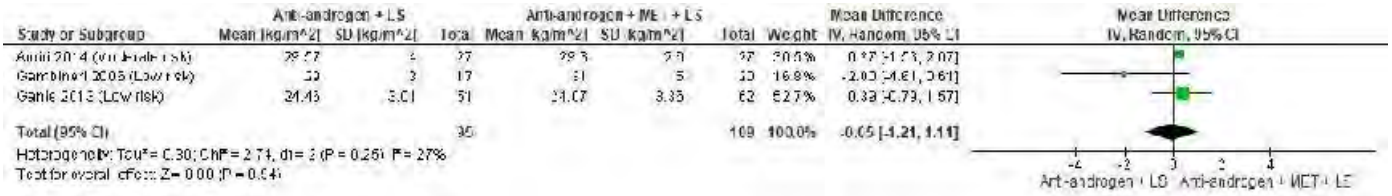
DHEAS	1	37	-0.20 µg/ml [-0.82, 0.42]	0.53	None	⊕⊕◯◯ LOW
Androstenedione	1	37	-34.00 ng/ml [-98.19, 30.19]	0.30	None	⊕⊕◯◯ LOW
Triglycerides	1	37	-19.00 mg/dl [-38.11, 0.11]	0.05	AA + LS	⊕⊕◯◯ LOW
HDL	1	37	1.00 mg/dl [-7.59, 9.59]	0.82	None	⊕⊕◯◯ LOW
HOMA-IR	1	113	0.60 [-0.04, 1.24]	0.06	None	⊕⊕⊕⊕ HIGH

OUTCOME 4.1. BMI

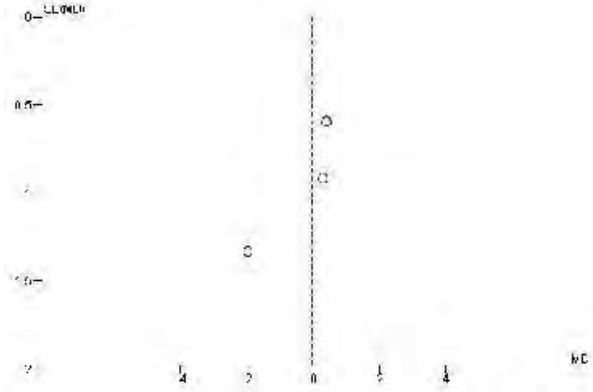
4.1.1. Individual Study Data Table

OUTCOME: BMI					**OUTCOME TYPE: Continuous**					
COMPARISON: Anti-androgen + LS vs Anti-androgen + MET + LS - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention group	Sample size (n within this group)	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Amiri 2014	Kg/m^2	Weight and height measurements; 6 months	29.57	4	27	29.3	2.6	27	Crude	N/A
Ganie 2013	Kg/m^2	Weight and height measurements; 6 months	24.46	3.01	51	24.07	3.36	62	Crude	N/A
Gambineri 2006	Kg/m^2	Weight and height measurements; 12 months	29	3	17	31	5	20	Crude	N/A

4.1.2. Forest Plot of all included RCTs comparing Anti-androgen + lifestyle and Anti-androgen + metformin + lifestyle for BMI



4.1.3. Funnel plot for assessment of publication bias

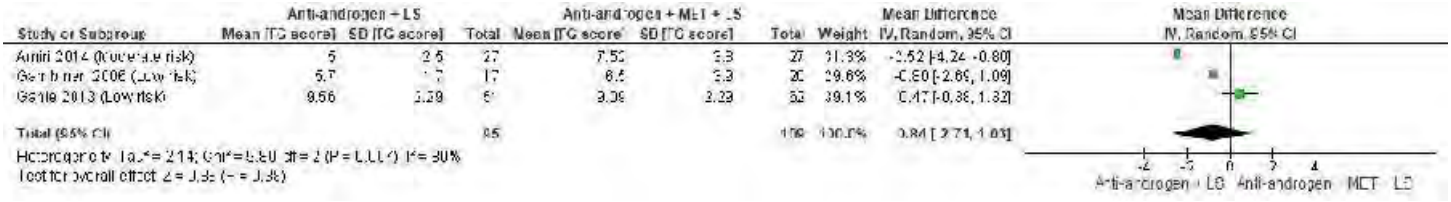


OUTCOME 4.2. Hirsutism

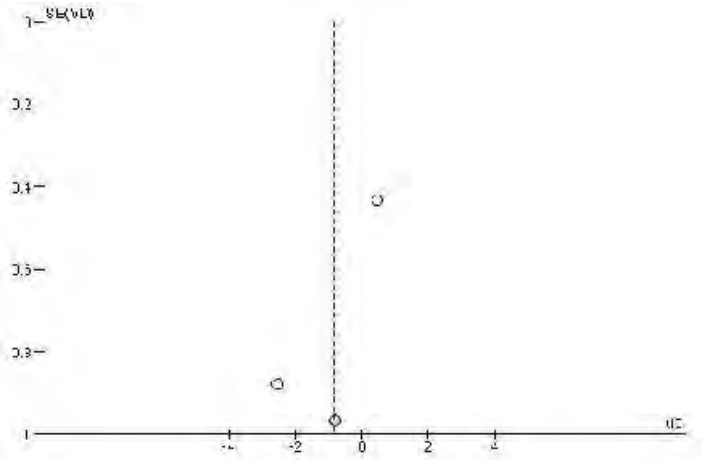
4.2.1. Individual Study Data Table

OUTCOME: Hirsutism					**OUTCOME TYPE: Continuous**					
COMPARISON: Anti-androgen + LS vs Anti-androgen + MET + LS - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Amiri 2014	FG score	Ferriman-Gallaway scoring; 6 months	5	2.5	27	7.52	3.8	27	Crude	N/A
Ganie 2013	Modified FG score	Modified Ferriman-Gallaway scoring system; 6 months	9.56	2.29	51	9.09	2.29	62	Crude	N/A
Gambineri 2006	FG score	Ferriman-Gallaway scoring; 12 months	5.7	1.7	17	6.5	3.9	20	Crude	N/A

4.2.2. Forest Plot of all included RCTs comparing Anti-androgen + lifestyle and Anti-androgen + metformin + lifestyle for hirsutism



4.2.3. Funnel plot for assessment of publication bias

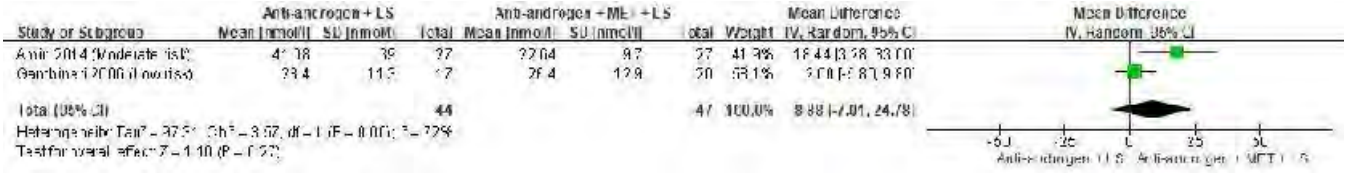


OUTCOME 4.3. SHBG

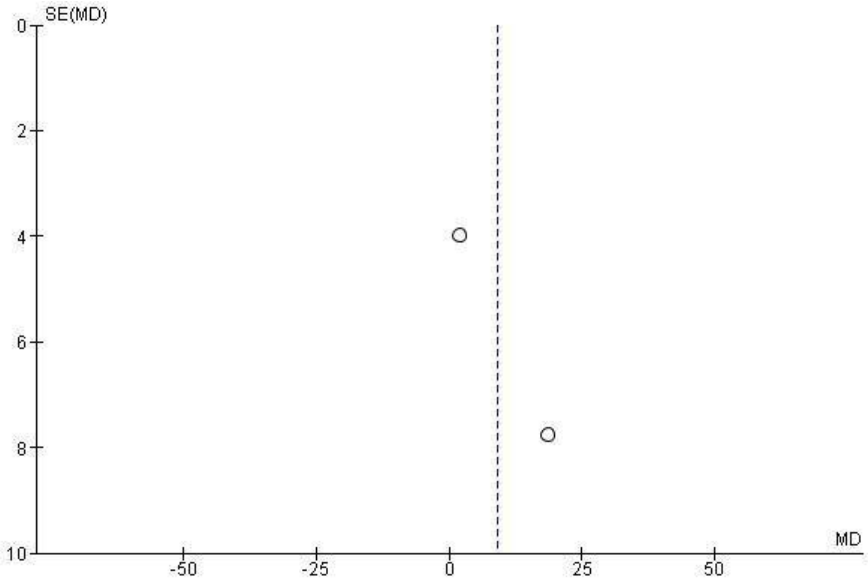
4.3.1. Individual Study Data Table

OUTCOME: SHBG					**OUTCOME TYPE: Continuous**					
COMPARISON: Anti-androgen + LS vs Anti-androgen + MET + LS - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Amiri 2014	Nmol/l	Hormone assays; 6 months	41.08	39	27	22.64	9.7	27	Crude	N/A
Gambineri 2006	Nmol/l	Hormone assays; 12 months	28.4	11.3	17	26.4	12.9	20	Crude	N/A

4.3.2 Forest Plot of all included RCTs comparing Anti-androgen + lifestyle and Anti-androgen + metformin + lifestyle for SHBG



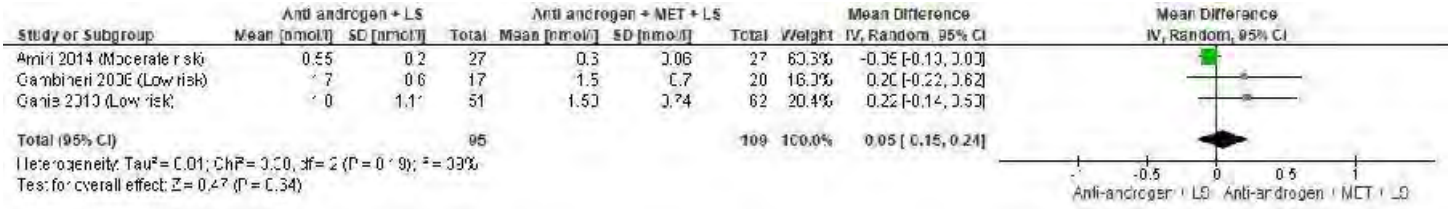
4.3.3. Funnel plot for assessment of publication bias



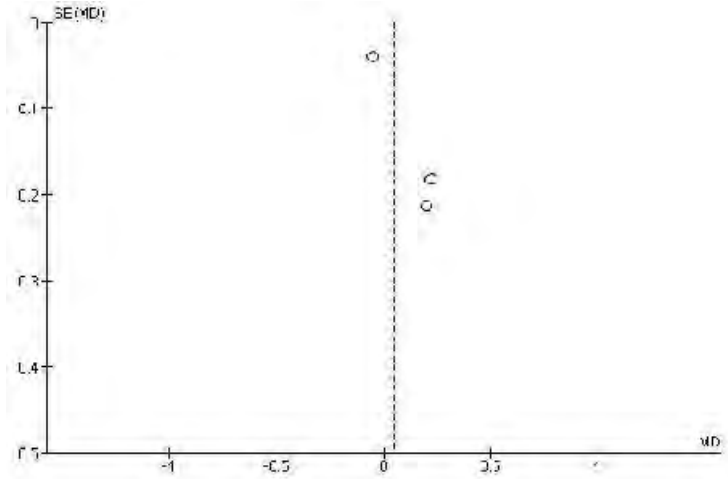
OUTCOME 4.4. Testosterone
4.4.1 Individual Study Data Table

OUTCOME: Testosterone					**OUTCOME TYPE: Continuous**					
COMPARISON: Anti-androgen + LS vs Anti-androgen + MET + LS - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Amiri 2014	Nmol/l	Hormone assays; 6 months	0.55	0.2	27	0.6	0.06	27	Crude	N/A
Ganie 2013	Nmol/l	RIA; 6 months	1.80	1.11	51	1.58	0.74	62	Crude	N/A
Gambineri 2006	Nmol/l	RIA; 12 months	1.70	0.6	17	1.5	0.70	20	Crude	N/A

4.4.2 Forest Plot of all included RCTs comparing Anti-androgen + lifestyle and Anti-androgen + metformin + lifestyle for testosterone



4.4.3. Funnel plot for assessment of publication bias



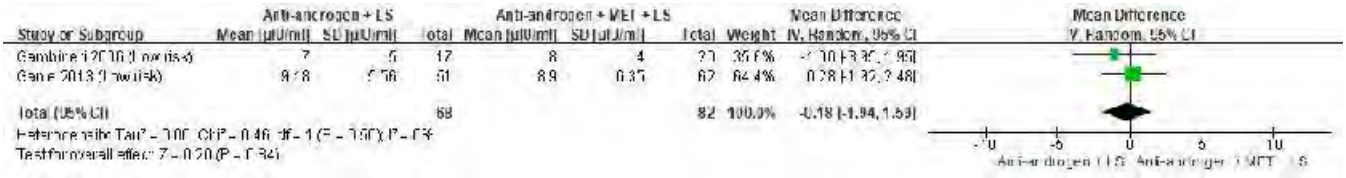
OUTCOME 4.5. Fasting insulin

4.5.1. Individual Study Data Table

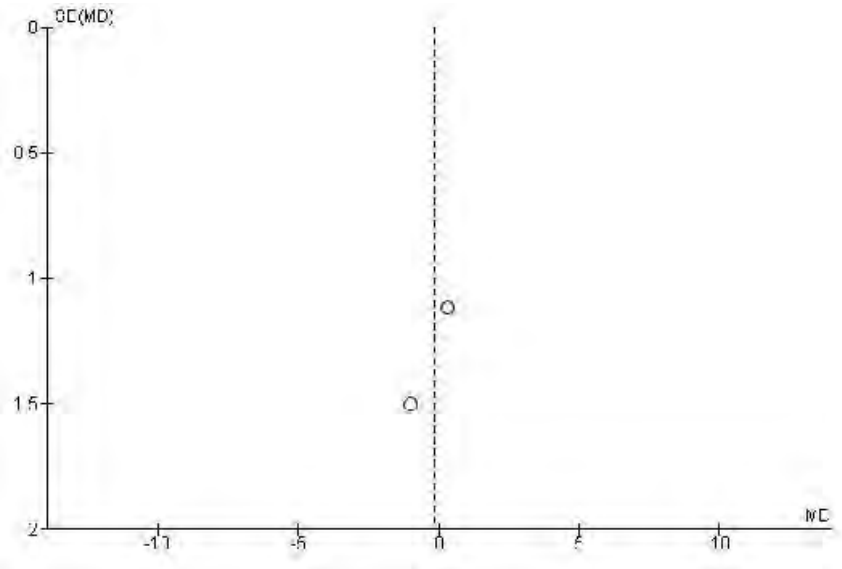
OUTCOME: Fasting insulin					**OUTCOME TYPE: Continuous**					
COMPARISON: Anti-androgen + LS vs Anti-androgen + MET + LS - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Amiri 2014#	pM/l	NR; 6 months	14.6	6.2	27	11.6	6.2	27	Crude	N/A
Ganie 2013	µIU/ml	Electroluminescence; 6 months	9.18	5.56	51	8.9	6.35	62	Crude	N/A
Gambineri 2006	µIU/ml	NR; 12 months	7	5	17	8	4	20	Crude	N/A

 # not including in meta-analysis due to uncertainty in units

4.5.2 Forest Plot of all included RCTs comparing Anti-androgen + lifestyle and Anti-androgen + metformin + lifestyle for fasting insulin



4.5.3 Funnel plot for assessment of publication bias

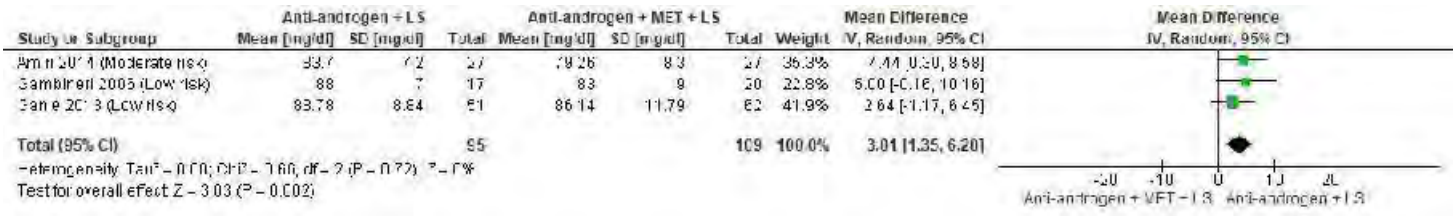


OUTCOME 4.6. Fasting glucose

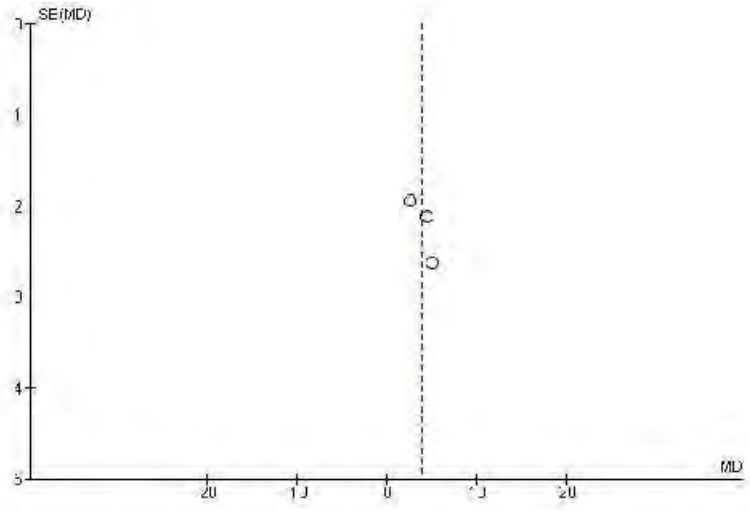
4.6.1 Individual Study Data Table

OUTCOME: Fasting glucose					**OUTCOME TYPE: Continuous**					
COMPARISON: Anti-androgen + LS vs Anti-androgen + MET + LS - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Amiri 2014	Mg/dL	Glucose-oxidase method; 6 months	83.7	7.2	27	79.26	8.3	27	Crude	N/A
Ganie 2013	Mg/dL	Glucose-oxidase method; 6 months	88.78	8.84	51	86.14	11.79	62	Crude	N/A
Gambineri 2006#	Mg/dL	Glucose-oxidase method 12 months	88	7	17	83	9	20	Crude	N/A

4.6.2 Forest Plot of all included RCTs comparing Anti-androgen + lifestyle and Anti-androgen + metformin + lifestyle for fasting glucose



4.6.3 Funnel plot for assessment of publication bias

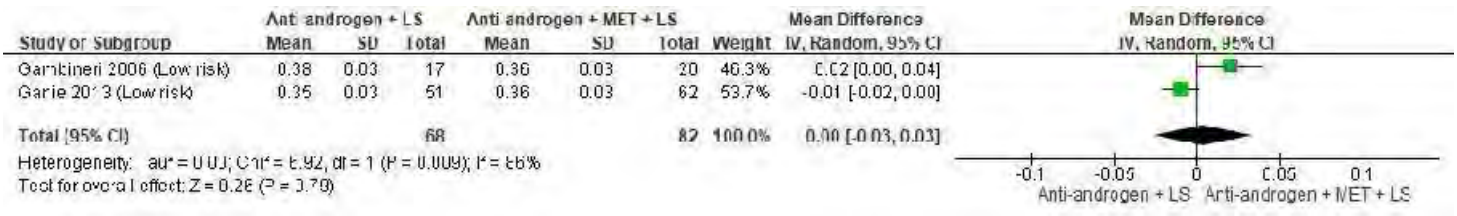


OUTCOME 4.7. QUICKI

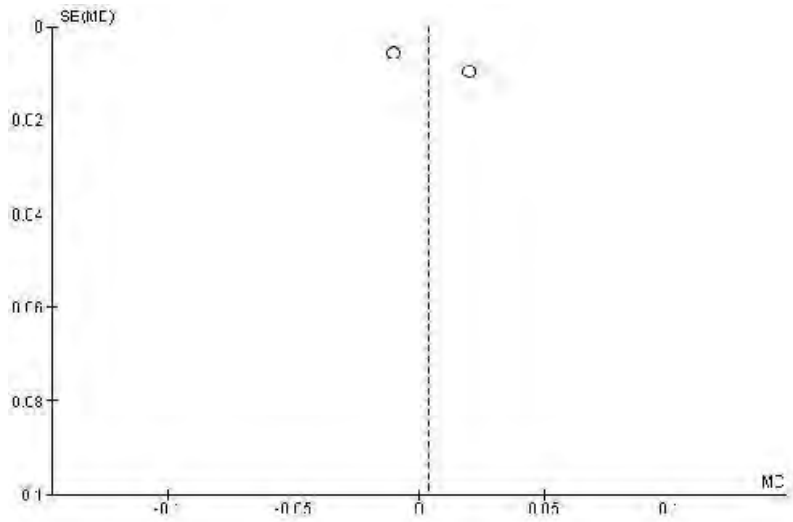
4.7.1 Individual Study Data Table

OUTCOME: QUICKI					**OUTCOME TYPE: Continuous**					
COMPARISON: Anti-androgen + LS vs Anti-androgen + MET + LS - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Ganie 2013 (LRB)	N/A	Formula (1/(log fasting insulin in µIU/ml + log glucose in mg/dL): 6 months	0.35	0.03	51	0.36	0.03	62	Crude	N/A
Gambineri 2006 (LRB)	N/A	Formula (1/(log fasting insulin in µIU/ml + log glucose in mg/dL); 12 months	0.38	0.03	17	0.36	0.03	20	Crude	N/A

4.7.2 Forest Plot of all included RCTs comparing Anti-androgen + lifestyle and Anti-androgen + metformin + lifestyle for QUICKI



4.7.3 Funnel plot for assessment of publication bias



OUTCOMES 4.8. – 4.18: Weight, WHR, total cholesterol, FAI, DHEAS, androstenedione, triglycerides, HDL, HOMA-IR, OGTT, frequency of menstruation

4.8.1 – 4.18.1 Individual Study Data Tables

OUTCOME: LISTED BELOW					**OUTCOME TYPE: Continuous**					
COMPARISON: Anti-androgen + LS vs Anti-androgen + MET + LS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention group	SD (or specify if other) in intervention group	Sample size (n within this group)	Mean (specify if median) or median in control /group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
OUTCOME: Weight										
Ganie 2013 (LRB)	kg	Weight measurements; 6 months	61.14	8.89	51	60.03	7.53	62	Crude	N/A
OUTCOME: WHR										
Ganie 2013 (LRB)	Cm	Measuring; 6 months	0.89	0.06	51	0.84	0.07	62	Crude	N/A
Amiri 2014 (MRB)*	Cm	Measuring; 6 months	0.8	0	27	0.83	0.04	27	Crude	N/A
OUTCOME: Total cholesterol										
Amiri 2014 (MRB)	Mg/dL	NR; 6 months	178.5	48	27	180.74	40.8	27	Crude	N/A
OUTCOME: FAI										
Gambineri 2006 (LRB)	Pg/ml	Formula (ratio between total T and SHBG); 12 months	2.4	2.1	17	1.9	0.9	20	Crude	N/A
OUTCOME: DHEAS										
Amiri 2014 (MRB)#	µmol/l	Hormone assays; 6 months	145.46	81	27	156.08	73.6	27	Crude	N/A
Gambineri 2006 (LRB)	µg/ml	Hormone assays; 12 months	1.5	0.7	17	1.7	1.2	20	Crude	N/A
OUTCOME: Androstenedione										
Gambineri 2006 (LRB)	Ng/dl	Hormone assays;12 months	224	80	17	258	118	20	Crude	N/A
OUTCOME: Triglycerides										
Amiri 2014 (MRB)#	Mmol/l	NR; 6 months	133.6	72	27	140.6	65.9	27	Crude	N/A
Gambineri 2006 (LRB)	Mg/dl	NR; 12 months	63	18	17	82	39	20	Crude	N/A
OUTCOME: HDL										
Amiri 2014 (MRB)#	Mmol/l	NR; 6 months	43	12.2	27	37.85	6	27	Crude	N/A
Gambineri 2006 (LRB)	Mg/dl	12 months	58	9	17	57	17	20	Crude	N/A

OUTCOME: HOMA-IR										
Ganie 2013 (LRB)	mIU*mmol/L^2	Using a formula; 6 months	2.56	1.90	51	1.96	1.47	62	Crude	N/A
Gambineri 2004 (LRB)##	N/A	Using a formula; 6 months	6.9	4.6	10	5.7	2.9	10	Crude	N/A
OUTCOME: OGTT										
Amiri 2014 (MRB)	Mg/dl	N/A; 6 months	102.56	20.1	27	107.22	25.9	27	Crude	N/A
OUTCOME: Frequency of menstruation										
Gambineri 2006 (LRB)	No. of menses in previous 6 months	12 months	5.0	1.4	17	5.8	0.7	20	Crude	N/A
Ganie 2013 (LRB)##	No. of cycles per year	6 months	10.35	2.8	51	10.86	3.20	62	Crude	N/A

*** Cannot run meta-analysis as SD was 0 in intervention group**

 # Did not run meta-analysis due to uncertainty in units. Have used the other study in the MD calculations above for this reason.

Did not run meta-analysis due to uncertainty in units. Have used the other study in the above MD calculations above for this reason.

COMPARISON 5. Anti-androgen vs MET - ADULTS (12 MONTHS)

(Also see in metformin question, 4.3)

- **EVIDENCE SUMMARY:**

There was one study that compared an anti-androgen (finasteride) and metformin, with no additive lifestyle intervention in adult women with PCOS with 6- and 12-month follow-ups. This study was a high risk of bias (Diri, 2017), and was conducted in Turkey.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

In single study mean difference estimates, anti-androgen intervention had higher SHBG levels, as compared to metformin, with a very low certainty of evidence reflective of the high risk of bias and very small sample size.

There was no difference between finasteride and metformin on BMI, hirsutism, free testosterone, DHEAS, androstenedione, and HOMA-IR. The certainty in the evidence for these findings were very low due to the only study identified being high risk of bias and the associated small sample size.

Outcome or Subgroup	Studies	n	Effect Estimate; MD [95% CI], I-V, random	P-value	Favours	Certainty
BMI	1	35	-0.20 kg/m^2 [-2.37, 1.97]	0.86	None	⊕◯◯◯ VERY LOW
Hirsutism	1	35	0.60 [-2.80, 4.00]	0.73	None	⊕◯◯◯ VERY LOW
SHBG	1	35	11.50 nmol/l [-0.08, 23.08]	0.05	AA	⊕◯◯◯ VERY LOW
Free testosterone	1	35	-0.30 pg/ml [-0.85, 0.25]	0.29	None	⊕◯◯◯ VERY LOW
DHEAS	1	35	-669.00 ng/ml [-1430.65, 92.65]	0.09	None	⊕◯◯◯ VERY LOW
Androstenedione	1	35	0.30 ng/ml [-0.13, 0.73]	0.17	None	⊕◯◯◯ VERY LOW
HOMA-IR	1	35	-0.20 [-0.88, 0.48]	0.56	None	⊕◯◯◯ VERY LOW

OUTCOME 5.1. – 5.7: BMI, hirsutism, SHBG, free testosterone, DHEAS, androstenedione, HOMA-IR
5.1.1. – 5.7.1 Individual Study Data Tables

OUTCOME: LISTED BELOW					**OUTCOME TYPE: Continuous**					
COMPARISON: Anti-androgen vs MET - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure) in intervention group	Sample size (n within this group)	Mean (specify if median) or median in control group	SD (or specify if other measure) in control group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
OUTCOME: BMI										
Diri 2017 (HRB)	Kg/m^2	Weight and height measurements; 12 months	26.7	2.2	16	26.9	4.2	19	Crude	N/A
OUTCOME: Hirsutism										

Diri 2017 (HRB)	Modified FG score	12 months	11.7	5.2	16	11.1	5.0	19	Crude	N/A
OUTCOME: SHBG										
Diri 2017 (HRB)	Nmol/ml	12 months	40.9	20	16	29.4	13.7	19	Crude	N/A
OUTCOME: Free testosterone										
Diri 2017 (HRB)	Pg/ml	12 months	2.1	0.5	16	2.4	1.1	19	Crude	N/A
OUTCOME: DHEAS										
Diri 2017 (HRB)	Ng/ml	12 months	2421	1098	16	3090	1199	19	Crude	N/A
OUTCOME: Androstenedione										
Diri 2017 (HRB)	Ng/mL	12 months	2.6	0.6	16	2.3	0.7	19	Crude	N/A
OUTCOME: HOMA-IR										
Diri 2017 (HRB)	N/A	12 months	1.2	0.7	16	1.4	1.3	19	Crude	N/A

COMPARISON 6. Anti-androgen vs Anti-androgen + MET - ADULTS (12 months)

(Also see in metformin question, 4.3)

- **EVIDENCE SUMMARY:**

There was one study that investigated anti-androgens with a combination of anti-androgens (finasteride) and metformin, with no additive lifestyle intervention in adult women with PCOS with 12 months follow-up. The single study identified was high risk of bias (Diri, 2017) and was conducted in Turkey.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

There was no difference in any outcome when comparing the anti-androgen with the combination therapy of anti-androgen + metformin. However, the certainty for every outcome was very low reflective of the high risk of bias and sample size.

Outcome or Subgroup	Studies	n	Effect Estimate; MD [95% CI], I-V, random	P-value	Favours	Certainty
BMI	1	33	0.10 kg/m^2 [-2.25, 2.45]	0.93	None	⊕◯◯◯ VERY LOW
Hirsutism	1	33	-0.40 [-4.05, 3.25]	0.83	None	⊕◯◯◯ VERY LOW
SHBG	1	33	-1.00 nmol/l [-14.72, 12.72]	0.89	None	⊕◯◯◯ VERY LOW
Free testosterone	1	33	0.10 pg/ml [-0.52, 0.72]	0.75	None	⊕◯◯◯ VERY LOW
DHEAS	1	33	-198 ng/ml [-941.98, 545.98]	0.60	None	⊕◯◯◯ VERY LOW
Androstenedione	1	33	0.30 ng/ml [-0.14, 0.74]	0.19	None	⊕◯◯◯ VERY LOW
HOMA-IR	1	33	-0.40 [-1.07, 0.27]	0.24	None	⊕◯◯◯ VERY LOW

OUTCOME 6.1. – 6.7: BMI, hirsutism, SHBG, free testosterone, DHEAS, androstenedione, HOMA-IR
6.1.1. – 6.7.1 Individual Study Data Tables

OUTCOME: LISTED BELOW					**OUTCOME TYPE: Continuous**					
COMPARISON: Anti-androgen vs MET - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
OUTCOME: BMI										
Diri 2017 (HRB)	Kg/m^2	Weight and height measurements; 12 months	26.7	2.2	16	26.6	4.4	17	Crude	N/A

OUTCOME: Hirsutism										
Diri 2017 (HRB)	Modified FG score	12 months	11.7	5.2	16	12.1	5.5	17	Crude	N/A
OUTCOME: SHBG										
Diri 2017 (HRB)	Nmol/ml	12 months	40.9	20.0	16	41.9	20.2	17	Crude	N/A
OUTCOME: Free testosterone										
Diri 2017 (HRB)	Pg/ml	12 months	2.1	0.5	16	2.0	1.2	17	Crude	N/A
OUTCOME: DHEAS										
Diri 2017 (HRB)	Ng/ml	12 months	2421	1098	16	2619	1081	17	Crude	N/A
OUTCOME: Androstenedione										
Diri 2017 (HRB)	Ng/mL	12 months	2.6	0.6	16	2.3	0.7	17	Crude	N/A
OUTCOME: HOMA-IR										
Diri 2017 (HRB)	N/A	12 months	1.2	0.7	16	1.6	1.2	17	Crude	N/A

COMPARISON 7. Anti-androgen vs COCP - ADULTS (12 months)

(Also see in COCP question, 4.02)

- **EVIDENCE SUMMARY:**

There was one study that investigated the comparison of an anti-androgen (spironolactone) and the COCP in adult women with PCOS with 12 months follow-up. The one identified study was a moderate risk of bias (Spritzer, 2000), and was from Brazil.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

There was only one outcome reported that was conducive to analysis. It was identified that hirsutism was higher in the spironolactone group compared to the COCP group after 12 months. The certainty for hirsutism was very low reflective of the moderate risk of bias and very low sample size.

Outcome or Subgroup	Studies	n	Effect Estimate; MD [95% CI], I-V, random	P-value	Favours	Certainty
Hirsutism	1	19	4.00 [1.21, 6.79]	0.005	AA	⊕◯◯◯ VERY LOW

OUTCOME 7.1. Hirsutism

7.1.1. Individual Study Data Table

OUTCOME: Hirsutism					**OUTCOME TYPE: Continuous**					
COMPARISON: Anti-androgen vs COCP - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention group	Sample size (n within this group)	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Spritzer 2000 (MRB)	FG score	12 months	16	3.2	10	12	3	9	Crude	N/A

COMPARISON 8. Spironolactone + MET + Pioglitazone (SPIOMET) vs COCP - ADULTS (12 months)

(Also see in COCP and metformin questions, 4.2, 4.3)

- **EVIDENCE SUMMARY:**

Five studies were identified that compared a combination therapy of spironolactone + metformin + pioglitazone (SPIOMET) compared to the combination oral contraceptive pill in adult women with PCOS with 12 months follow-up. All these studies were in the same population of women, and thus, Ibanez 2020 was considered the main publication due to the largest sample size and full outcome list. Therefore, there was nothing extracted from Malpique 2019 and Diaz 2018. FAI was reported as an extra outcome in deZegher 2021 and Acne scores from Ibanez 2017 and were hence extracted. These set of studies were assessed as moderate risk of bias (Ibanez, 2020), and were conducted in Spain.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

In the single study mean difference estimates, SPIOMET was superior for hirsutism, SHBG, fasting insulin, HOMA-IR, LDL, CRP, FAI, and ALT. Conversely, the SPIOMET group had higher androstenedione. The certainty in the evidence was low for all these outcomes reflective of the moderate risk of bias and small sample size. There were no differences in BMI, WC, testosterone, triglycerides, HDL, and AST levels. The certainty in the evidence was low reflecting the moderate risk of bias and sample size.

Outcome or Subgroup	Studies	n	Effect Estimate; MD [95% CI], I-V, random	P-value	Favours	Certainty
BMI	1	62	-1.00 kg/m^2 [-3.08, 1.08]	0.35	None	⊕⊕◯◯ LOW
Waist circumference	1	62	-4.00 cm [-8.38, 0.38]	0.07	None	⊕⊕◯◯ LOW
Hirsutism	1	62	-3.00 [-5.77, -0.23]	0.03	SPIOMET	⊕⊕◯◯ LOW
Acne	1	36	-0.30 [-3.07, 2.47]	0.83	None	⊕⊕◯◯ LOW
SHBG	1	62	-29.00 nmol/l [-39.56, -18.44]	<0.00001	SPIOMET	⊕⊕◯◯ LOW
Testosterone	1	62	-0.10 nmol/l [-0.38, 0.18]	0.49	None	⊕⊕◯◯ LOW
Androstenedione	1	62	1.00 nmol/l [0.29,1.71]	0.006	SPIOMET	⊕⊕◯◯ LOW
Fasting insulin	1	62	-62.00 pmol/l [-81.40, -42.60]	<0.00001	SPIOMET	⊕⊕◯◯ LOW
ALT	1	62	-0.09 µkat/L [-0.16, -0.02]	0.01	SPIOMET	⊕⊕◯◯ LOW
AST	1	62	0.00 [-0.06, 0.06]	1.00	None	⊕⊕◯◯ LOW
HOMA-IR	1	62	-1.80 [-2.42, -1.18]	<0.00001	SPIOMET	⊕⊕◯◯ LOW
Triglycerides	1	62	-0.08 mmol/l [-0.22, 0.06]	0.26	None	⊕⊕◯◯ LOW
LDL	1	62	-0.50 mmol/l [-0.78, -0.22]	0.0004	SPIOMET	⊕⊕◯◯ LOW
HDL	1	62	0.10 mmol/l [-0.18. 0.38]	0.48	None	⊕⊕◯◯ LOW
CRP	1	62	-18.10 mmol/l [-25, 75, -10.45]	<0.00001	SPIOMET	⊕⊕◯◯ LOW
FAI	1	58	-2.20 [-4.38, -0.02]	0.05	SPIOMET	⊕⊕◯◯ LOW

OUTCOME 8.1. – 8.13: BMI, waist circumference, hirsutism, SHBG, testosterone, androstenedione, fasting insulin, HOMA-IR, triglycerides, LDL, HDL, CRP, FAI

8.1.1. – 8.13.1 Individual Study Data Tables

OUTCOME: LISTED BELOW					**OUTCOME TYPE: Continuous**					
COMPARISON: Anti-androgen +MET + Pioglitazone (SPIOMET) vs COCP - ADOLESCENTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure) in intervention group	Sample size (n within this group)	Mean (specify if median) or median in control group	SD (or specify if other measure) in control group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
OUTCOME: BMI										
Ibanez 2020 (MRB)	Kg/m^2	12 months	23.9	3.897	31	24.9	4.45	31	Crude	N/A
OUTCOME: Waist circumference										
Ibanez 2020 (MRB)	cm	12 months	74	5.57	31	78	11.14	31	Crude	N/A
OUTCOME: Hirsutism										
Ibanez 2020 (MRB)	FG score	12 months	11	5.568	31	14	5.568	31	Crude	N/A
OUTCOME: Acne										
Ibanez 2017 (MRB)	LAS	12 months	1.0	4.24	18	1.3	4.24	18	Crude	N/A
OUTCOME: SHBG										
Ibanez 2020 (MRB)	Nmol/L	12 months	32	11.14	31	61	27.84	31	Crude	N/A
OUTCOME: Testosterone										
Ibanez 2020 (MRB)	Nmol/L	12 months	0.7	0.566	31	0.8	0.566	31	Crude	N/A
OUTCOME: Androstenedione										
Ibanez 2020 (MRB)	Nmol/L	12 months	3.5	1.697	31	2.5	1.114	31	Crude	N/A
OUTCOME: Fasting insulin										
Ibanez 2020 (MRB)	Pmol/L	12 months	42	38.97	31	104	38.97	31	Crude	N/A
OUTCOME: ALT										
Ibanez 2020 (MRB)	µkat/L	12 months	0.23	0.111	31	0.32	0.167	31	Crude	N/A
OUTCOME: AST										
Ibanez 2020 (MRB)	µkat/L	12 months	0.27	0.111	31	0.27	0.111	31	Crude	N/A
OUTCOME: HOMA-IR										
Ibanez 2020 (MRB)	N/A	12 months	1.2	0.557	31	3.0	1.67	31	Crude	N/A
OUTCOME: Triglycerides										
Ibanez 2020 (MRB)	Mmol/L	12 months	0.67	0.278	31	0.75	0.278	31	Crude	N/A
OUTCOME: LDL										
Ibanez 2020 (MRB)	Mmol/L	12 months	2.2	0.557	31	2.7	0.557	31	Crude	N/A

OUTCOME: HDL										
Ibanez 2020 (MRB)	Mmol/L	12 months	1.4	0.557	31	1.3	0.557	31	Crude	N/A
OUTCOME: CRP										
Ibanez 2020 (MRB)	Mmol/L	12 months	6.7	5.01	31	24.8	21.16	31	Crude	N/A
OUTCOME: FAI										
De Zegher 2021 (MRB)	Mmol/L	12 months	2.9	2.227	29	5.1	5.56	29	Crude	N/A

COMPARISON 9. Anti-androgen + MET vs COCP – ADOLESCENTS (9 months)

(Also see in COCP and metformin questions, 4.2, 4.3)

- **EVIDENCE SUMMARY:**

There was one RCT that investigated the combination therapy of an anti-androgen (specifically, flutamide) + metformin against the combined oral contraceptive in adolescent girls with PCOS with 9 months follow-up, of which was a moderate risk of bias (Ibanez, 2004). This study was conducted in Spain.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

In the single study mean difference estimates, the flutamide-metformin combination was superior for reducing SHBG, triglycerides, HDL, and LDL levels, as compared to the COCP. The certainty was very low, which was reflective of the moderate risk of bias and very small sample size.

There was no difference in BMI, hirsutism, fasting glucose/insulin ratio, and testosterone, with a very low certainty of the evidence, which was reflective of the moderate risk of bias and very small sample size.

Outcome or Subgroup	Studies	n	Effect Estimate; MD [95% CI], I-V, random	P-value	Favours	Certainty
BMI	1	32	-0.50 kg/m^2 [-2.03, 1.03]	0.52	None	⊕◯◯◯ VERY LOW
Hirsutism	1	32	-0.50 [-2.73, 1.73]	0.66	None	⊕◯◯◯ VERY LOW
Fasting glucose/ insulin ratio	1	32	2.40 [-0.93, 5.73]	0.16	None	⊕◯◯◯ VERY LOW
SHBG	1	32	-3.40 µg/dl [-4.21, -2.59]	<0.00001	AA + MET	⊕◯◯◯ VERY LOW
Testosterone	1	32	-5.00 ng/dl [-23.91, 16.91]	0.65	None	⊕◯◯◯ VERY LOW
Triglycerides	1	32	-44.00 mg/dl [-61.53, -26.47]	<0.00001	AA + MET	⊕◯◯◯ VERY LOW
HDL	1	32	-9.00 mg/dl [-17.77, -0.23]	0.04	AA + MET	⊕◯◯◯ VERY LOW
LDL	1	32	-26.00 mg/dl [-42.86, -9.14]	0.003	AA + MET	⊕◯◯◯ VERY LOW

OUTCOME 9.1. – 9.8: BMI, hirsutism, fasting glucose/insulin ratio, SHBG, testosterone, triglycerides, HDL, LDL

9.1.1 – 9.8.1 Individual Study Data Tables

OUTCOME: LISTED BELOW					**OUTCOME TYPE: Continuous**					
COMPARISON: Anti-androgen +MET vs COCP - ADOLESCENTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention group	SD (or specify if other measure) in intervention group	Sample size (n within this group)	Mean (specify if median) or median in control group	SD (or specify if other measure) in control group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
OUTCOME: BMI										
Ibanez 2004 (MRB)	Kg/m^2	9 months	22.0	2.4	16	22.5	2.0	16	Crude	N/A
OUTCOME: Hirsutism										

Ibanez 2004 (MRB)	FG score	9 months	10.4	3.6	16	10.9	2.8	16	Crude	N/A
OUTCOME: Fasting glucose/insulin ratio										
Ibanez 2004 (MRB)	N/A	9 months	10.0	6.0	16	7.6	3.2	16	Crude	N/A
OUTCOME: SHBG										
Ibanez 2004 (MRB)	µg/dl	9 months	1.1	0.4	16	4.5	1.6	16	Crude	N/A
OUTCOME: Testosterone										
Ibanez 2004 (MRB)	Ng/dl	9 months	61	20	16	66	40	16	Crude	N/A
OUTCOME: Triglycerides										
Ibanez 2004 (MRB)	Mg/dl	9 months	53	16	16	97	32	16	Crude	N/A
OUTCOME: HDL										
Ibanez 2004 (MRB)	Mg/dl	9 months	66	8	16	75	16	16	Crude	N/A
OUTCOME: LDL										
Ibanez 2004 (MRB)	Mg/dl	9 months	75	20	16	101	28	16	Crude	N/A

COMPARISON 10. Anti-androgen + MET + COCP vs COCP - ADULTS (9 months)

(Also see in COCP and metformin questions, 4.2, 4.3)

- **EVIDENCE SUMMARY:**

There was one RCT that investigated the combination therapy of an anti-androgen (specifically, flutamide) + metformin + COCP against the COCP alone in adult women with PCOS, of which was a moderate risk of bias (Ibanez, 2004). This study was conducted in Spain.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

In the single study mean difference estimates, the combination anti-androgen + metformin + COCP was superior in reducing SHBG as compared to the COCP alone with 9 months follow-up. There was a very low certainty in the evidence due to the moderate risk of bias and very small sample size.

There was no difference in BMI, hirsutism, fasting glucose/insulin ratio, testosterone, triglycerides, HDL, and LDL levels. There was very low certainty in the evidence due to the moderate risk of bias and very small sample size.

Outcome or Subgroup	Studies	n	Effect Estimate; MD [95% CI], I-V, random	P-value	Favours	Certainty
BMI	1	22	-0.30 kg/m^2 [-2.19, 1.59]	0.76	None	⊕◯◯◯ VERY LOW
Hirsutism	1	22	1.00 [-0.92, 2.92]	0.31	None	⊕◯◯◯ VERY LOW
Fasting glucose/insulin ratio	1	22	0.90 [-0.66, 2.46]	0.26	None	⊕◯◯◯ VERY LOW
SHBG	1	22	1.10 µg/dl [0.13, 2.07]	0.03	COCP	⊕◯◯◯ VERY LOW
Testosterone	1	22	1.00 ng/dl [-17.48, 19.48]	0.92	None	⊕◯◯◯ VERY LOW
Triglycerides	1	22	-8.00 mg/dl [-47.70, 31.70]	0.69	None	⊕◯◯◯ VERY LOW
HDL	1	22	0.00 mg/dl [-12.57, 12.57]	1.00	None	⊕◯◯◯ VERY LOW
LDL	1	22	-7.00 mg/dl [-25.06, 11.06]	0.45	None	⊕◯◯◯ VERY LOW

OUTCOME 10.1. – 10.8: BMI, hirsutism, fasting glucose/insulin ratio, SHBG, testosterone, triglycerides, HDL, LDL

10.1. – 10.8.1 Individual Study Data Tables

OUTCOME: LISTED BELOW					**OUTCOME TYPE: Continuous**					
COMPARISON: Anti-androgen + MET + COCP vs COCP - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention group	Sample size (n within this group)	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
OUTCOME: BMI										
Ibanez 2004 (MRB)	Kg/m^2	9 months	21.8	1.7	11	22.1	2.7	11	Crude	N/A
OUTCOME: Hirsutism										
Ibanez 2004 (MRB)	FG score	9 months	10.3	2.3	11	9.3	2.3	11	Crude	N/A
OUTCOME: Fasting glucose/insulin ratio										
Ibanez 2004 (MRB)	N/A	9 months	8.3	1.3	11	7.4	2.3	11	Crude	N/A
OUTCOME: SHBG										
Ibanez 2004 (MRB)	µg/dl	9 months	5.1	1.0	11	4.0	1.3	11	Crude	N/A
OUTCOME: Testosterone										
Ibanez 2004 (MRB)	Ng/dl	9 months	61	26.5	11	60	16.6	11	Crude	N/A
OUTCOME: Triglycerides										
Ibanez 2004 (MRB)	Mg/dl	9 months	107	36.5	11	115	56.4	11	Crude	N/A
OUTCOME: HDL										
Ibanez 2004 (MRB)	Mg/dl	9 months	77	13.3	11	77	16.6	11	Crude	N/A
OUTCOME: LDL										
Ibanez 2004 (MRB)	Mg/dl	9 months	93	23.2	11	100	19.9	11	Crude	N/A

COMPARISON 11. Anti-androgen + COCP vs COCP +/- placebo – ADULTS (6 – 12 MONTHS)

- **EVIDENCE SUMMARY:**

There were five RCTs that addressed the comparison of a combination therapy of an anti-androgen and combined oral contraceptive pill with the combined oral contraceptive with (in the case of Moretti, 2018) and without a placebo with 6 to 12 months follow-up. All the five studies were moderate risk of bias (Burchall, 2017; Hagag, 2014; Meyer, 2007; Tartagni, 2000; Vieira, 2012). Studies were conducted in Australia, Brazil, Italy, and Israel.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

In meta-analysis, the COCP alone was superior for total cholesterol, LDL, triglycerides, , as compared to the anti-androgen + COCP. The certainty in the evidence for these findings ranged from very low to low due to the risk of bias and/or small sample. In the single mean difference estimates, the COCP was superior for fasting insulin, HOMA-IR, and FAI, as compared to the AA + COCP. The certainty in the evidence for these outcomes was low due to the risk of bias and sample size.

In meta-analysis, there were no differences in weight, BMI, testosterone, SHBG, HDL, and adverse events such as breast tenderness, and nausea. The certainty in the evidence ranged from very low to low due risk of bias and sample size, except for BMI which was moderate due to only being downgraded due to the risk of bias. In the single study mean difference estimates, there were no difference in hirsutism, acne, fasting glucose, free testosterone, DHEAS, androstenedione, CRP, ALT, AST, and other adverse events (menorrhagia, premenstrual pelvic pain, metrorrhagia, hypercholesterolemia, hypertriglyceridemia, dysmenorrhea, menstrual spotting, and minor depressive state/mood reduction). The certainty in the evidence for all these findings ranged from very low to low due to the risk of bias and sample size.

Since Moretti 2018 had a placebo group in the comparison where the other studies did not, a sensitivity analysis was conducted to assess the influence of Moretti 2018 on all parameters where Moretti 2018 was included. Removing Moretti 2018 from the pooled analysis of weight, BMI, total cholesterol, HDL, adverse events (breast tenderness, nausea) had no effect on the significance attained. However, when removing Moretti from LDL and triglycerides, these outcomes were no longer significant.

Outcome or Subgroup	Studies	n	Effect Estimate; MD [95% CI], I-V, random; OR [95% CI], I-V, random	P-value	Favours	Certainty
Weight	2	93	5.57 kg [-0.67, 11.81]	0.08	None	⊕◯◯◯ VERY LOW
BMI	3	130	1.72 kg/m^2 [-0.29, 3.74]	0.09	None	⊕⊕⊕◯ MODERATE
Testosterone	2	78	0.10 nmol/l [-0.60, 0.79]	0.79	None	⊕◯◯◯ VERY LOW
SHBG	2	59	-38.37 nmol/l [-118.45, 41.72]	0.35	None	⊕◯◯◯ VERY LOW
Total cholesterol	2	93	20.81 mg/dl [7.81, 33.82]	0.002	AA + COCP	⊕⊕◯◯ LOW
HDL	2	93	1.44 mg/dl [-5.55, 8.42]	0.69	None	⊕⊕◯◯ LOW
LDL	2	93	15.12 mg/dl [3.20, 27.04]	0.01	AA + COCP	⊕⊕◯◯ LOW
Triglycerides	2	93	41.34 mg/dl [20.26, 62.42]	0.0001	AA + COCP	⊕⊕◯◯ LOW
Breast tenderness	2	149	OR: 0.73 [0.11, 5.00]	0.75	None	⊕◯◯◯ VERY LOW

Nausea	2	149	OR: 0.67 [0.12, 3.63]	0.64	None	⊕◯◯◯ VERY LOW
ALT	1	52	1.10 [-2.84, 5.04]	0.58	None	⊕⊕◯◯ LOW
AST	1	52	-0.60 [-3.27, 2.07]	0.66	None	⊕⊕◯◯ LOW
Hirsutism*	1	97	AA + OCP: mean: -57%, SD: 2.4%; OCP: mean: -68%, SD: 5.2%	NS	None	⊕⊕◯◯ LOW
Acne*	1	97	AA + OCP: mean: -78% SD: 13.6%; OCP: -68%, SD: 26%	NS	None	⊕⊕◯◯ LOW
Fasting insulin	1	41	3.50 µIU/ml [0.20, 6.80]	0.04	AA + COCP	⊕⊕◯◯ LOW
Fasting glucose	1	52	2.60 [-1.74, 6.94]	0.24	None	⊕⊕◯◯ LOW
HOMA-IR	1	42	0.70 [0.02, 1.38]	0.04	AA + COCP	⊕⊕◯◯ LOW
Free testosterone	1	18	-0.10 pg/ml [-0.47, 0.27]	0.60	None	⊕⊕◯◯ LOW
FAI	1	41	0.50 [0.01, 0.99]	0.04	AA + COCP	⊕⊕◯◯ LOW
DHEAS	1	18	-0.40 µg/ml [-1.23, 0.43]	0.34	None	⊕◯◯◯ VERY LOW
Androstenedione	1	18	0.10 ng/ml [-0.92, 1.12]	0.85	None	⊕◯◯◯ VERY LOW
LDL/HDL ratio*	1	97	AA + OCP: Mean: -5.1%, SD: 71.3%; OCP: -5.8%, SD: 35.5%	NS	None	⊕⊕◯◯ LOW
CRP	1	41	2.40 mg/l [-1.79, 6.59]	0.26	None	⊕⊕◯◯ LOW
Menorrhagia/ Heavy menstrual bleeding	1	52	OR: 2.67 [0.10, 68.70]	0.55	None	⊕⊕◯◯ LOW
Premenstrual pelvic pain**	1	97	AA + OCP: N events: 0, total: 72; OCP + P: N events: 0, total: 25	NS	None	⊕⊕◯◯ LOW
Metrorrhagia	1	52	OR: 2.67 [0.10, 68.70]	0.55	None	⊕⊕◯◯ LOW
Hypercholesterolemia	1	52	OR: 1.40 [0.47, 4.20]	0.55	None	⊕⊕◯◯ LOW
Hypertriglyceridemia	1	52	OR: 2.39 [0.42, 13.64]	0.33	None	⊕⊕◯◯ LOW
Dysmenorrhea	1	52	OR: 0.27 [0.01, 7.07]	0.44	None	⊕⊕◯◯ LOW
Menstrual spotting	1	52	OR: 1.67 [0.42, 6.58]	0.47	None	⊕⊕◯◯ LOW
Minor depressive state/ mood reduction	1	52	OR: 2.67 [0.10, 68.70]	0.55	None	⊕⊕◯◯ LOW

* reported as % change from baseline

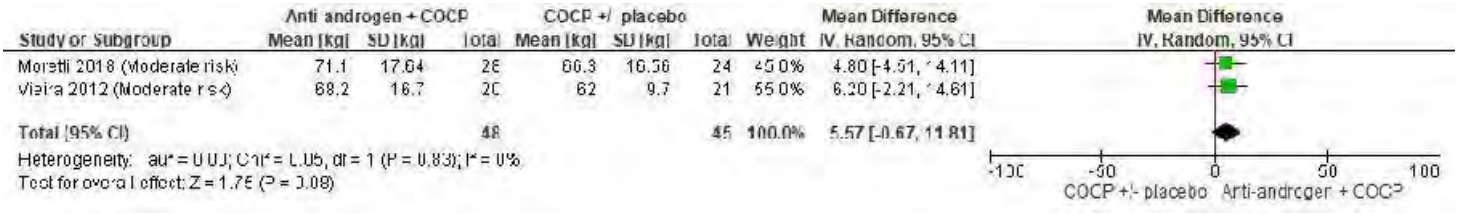
** no events in either intervention or control and thus cannot develop an OR.

OUTCOME 11.1. Weight
11.1.1. Individual Study Data Table

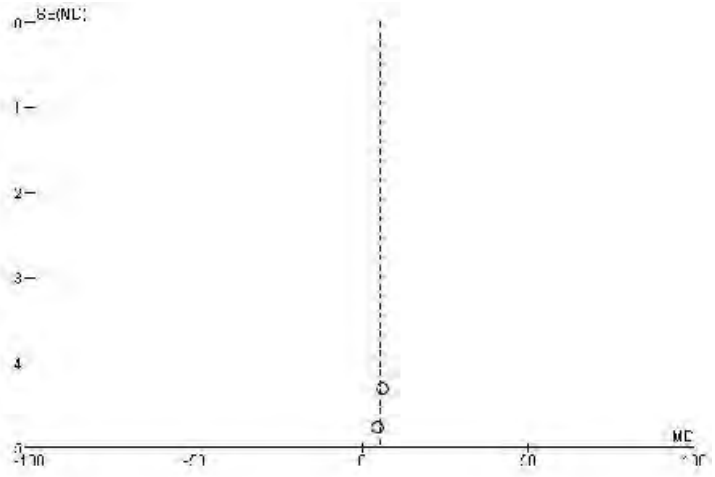
OUTCOME: Weight					**OUTCOME TYPE: Continuous**					
COMPARISON: Anti-androgen + COCP vs COCP +/- placebo - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Vieira 2012 (MRB)	Kg	12 months	68.2	16.7	20	62	9.7	21	Crude	N/A
Moretti 2018 (MRB)	Kg	12 months	71.1	17.64	28	66.3	16.56	24	Crude	N/A
Hagag 2014 (MRB)*	Kg	12 months	+1.3	5.7	72	+1.8	4.8	25	Crude	N/A

* weight change from baseline and hence cannot be used in meta-analysis

11.1.2. Forest Plot of all included RCTs comparing Anti-androgen + COCP and COCP +/- placebo for weight



11.1.3. Funnel plot for assessment of publication bias



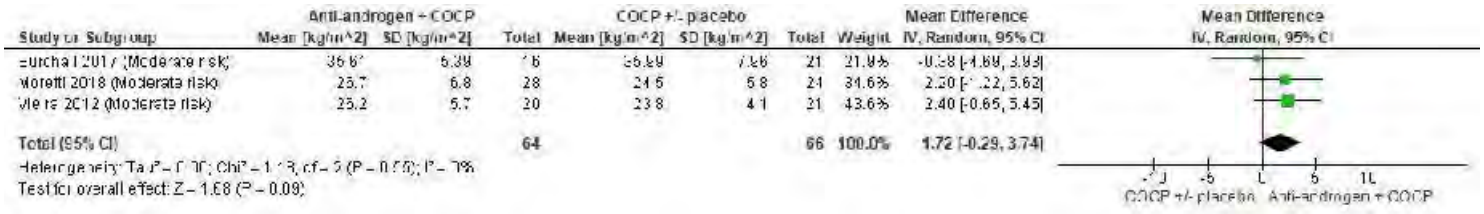
OUTCOME 11.2. BMI

11.2.1. Individual Study Data Table

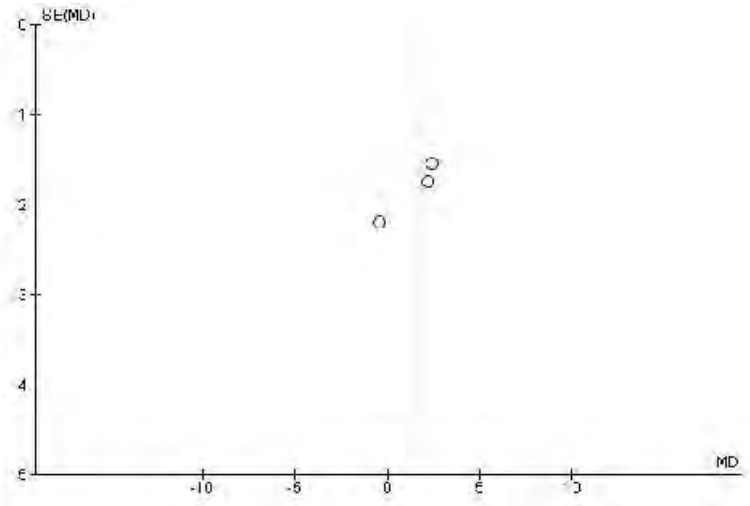
OUTCOME: BMI					**OUTCOME TYPE: Continuous**					
COMPARISON: Anti-androgen + COCP vs COCP +/- placebo - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention group	Sample size (n within this group)	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Burchall 2017 (MRB)	Kg/m^2	6 months	35.61	5.39	16	35.99	7.96	21	Crude	N/A
Moretti 2018 (MRB)	Kg/m^2	12 months	26.7	6.8	28	24.5	5.8	24	Crude	N/A
Vieira 2012 (MRB)	Kg/m^2	12 months	26.2	5.7	20	23.8	4.1	21	Crude	N/A
Meyer 2007 (MRB)*	Kg/m^2	6 months	-0.3	95% CI: -0.4, 0.9	33	+0.3	95% CI: -0.9, 0.3	31	Crude	N/A

***Cannot use in meta-analysis as only reported mean change, and as such have used Burchall 2017 which is a sub-study of Meyer 2007 in meta-analysis.**

11.2.2. Forest Plot of all included RCTs comparing Anti-androgen + COCP and COCP +/- placebo for BMI



11.2.3. Funnel plot for assessment of publication bias



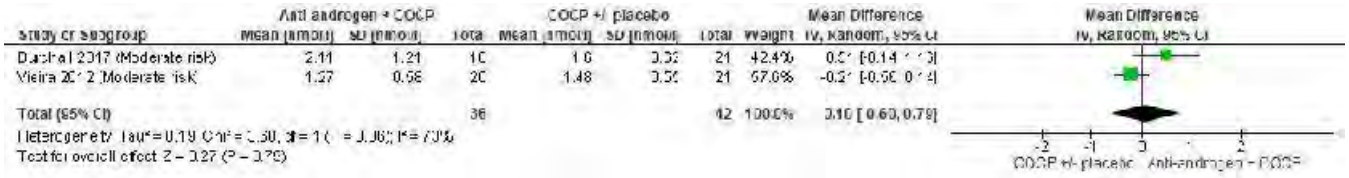
OUTCOME 11.3. Testosterone
11.3.1. Individual Study Data Table

OUTCOME: Testosterone					**OUTCOME TYPE: Continuous**					
COMPARISON: Anti-androgen + COCP vs COCP +/- placebo - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention group	SD (or specify if other measure) in intervention group	Sample size (n within this group)	Mean (specify if median) or median in control group	SD (or specify if other measure) in control group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Burchall 2017 (MRB)	Nmol/L	6 months	2.11	1.21	16	1.60	0.62	21	Crude	N/A
Vieira 2012 (MRB)	Nmol/L	12 months	1.27	0.58	20	1.48	0.55	21	Crude	N/A
Meyer 2007 (MRB)*	Nmol/L	6 months	-0.7	95% CI: -0.4, -1.2	33	-0.47	95% CI: -0.1, -0.8	31	Crude	N/A
Hagag 2014 (MRB)**	Pmol/L	12 months	-31%	30.55%	72	-43%	53%	25	Crude	N/A

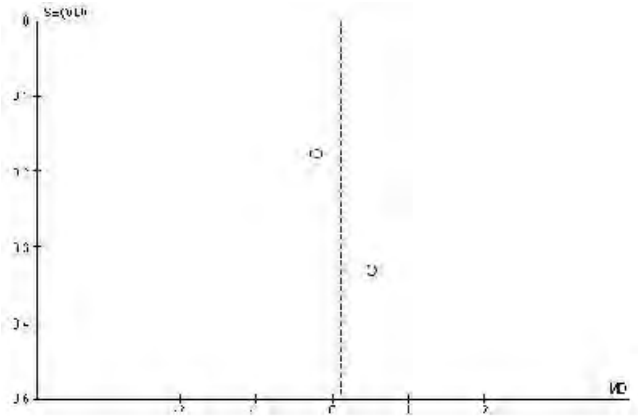
* Cannot use in meta-analysis as only reported mean change, and as such have used Burchall 2017 which is a sub-study of Meyer 2007 in meta-analysis.

**reported as % change from baseline (mean +/- SD)

11.3.2. Forest Plot of all included RCTs comparing Anti-androgen + COCP and COCP +/- placebo for testosterone



11.3.3. Funnel plot for assessment of publication bias



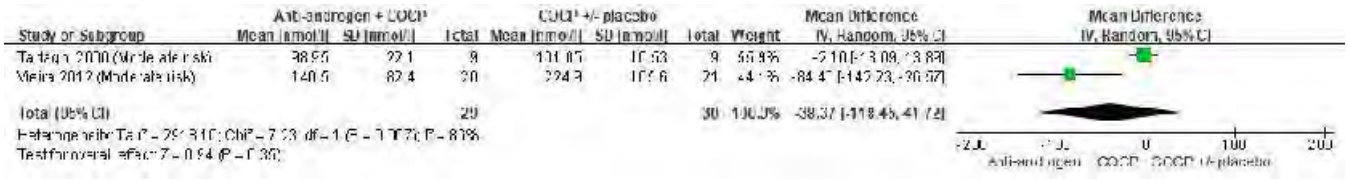
OUTCOME 11.4. SHBG

11.4.1. Individual Study Data Table

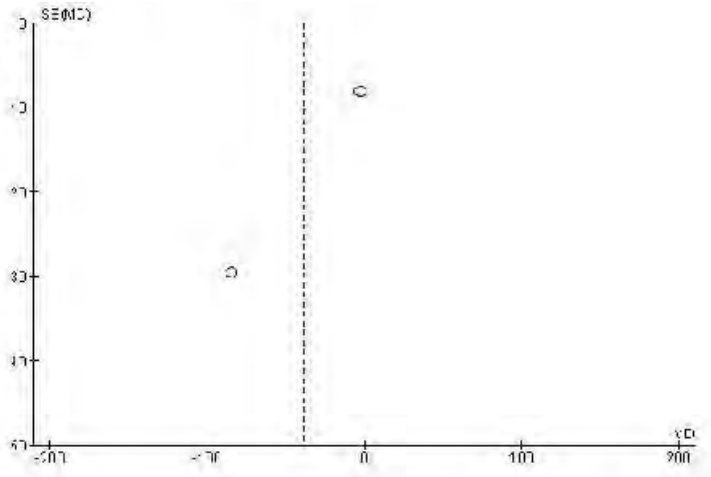
OUTCOME: SHBG					**OUTCOME TYPE: Continuous**					
COMPARISON: Anti-androgen + COCP vs COCP +/- placebo - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention group	SD (or specify if other measure) in intervention group	Sample size (n within this group)	Mean (specify if median) or median in control group	SD (or specify if other measure) in control group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Tartagni 2000 (HRB)	Nmol/L	6 months	98.95	22.10	9	101.05	10.53	9	Crude	N/A
Vieira 2012 (MRB)	Nmol/L	12 months	140.5	82.4	20	224.9	105.6	21	Crude	N/A
Meyer 2007 (MRB)*	Nmol/L	6 months	+44.7	95% CI: 29, 60	33	+115	95% CI: 87, 143	31	Crude	N/A

* Cannot use in meta-analysis as only reported mean change.

11.4.2. Forest Plot of all included RCTs comparing Anti-androgen + COCP and COCP +/- placebo for SHBG



11.4.3. Funnel plot for assessment of publication bias

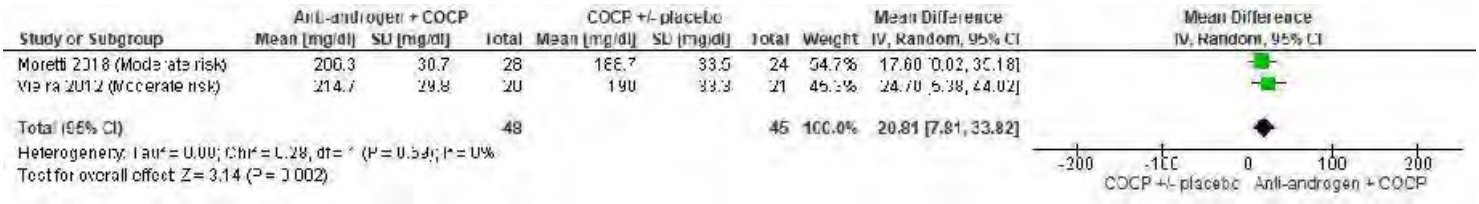


OUTCOME 11.5. Total cholesterol
11.5.1. Individual Study Data Table

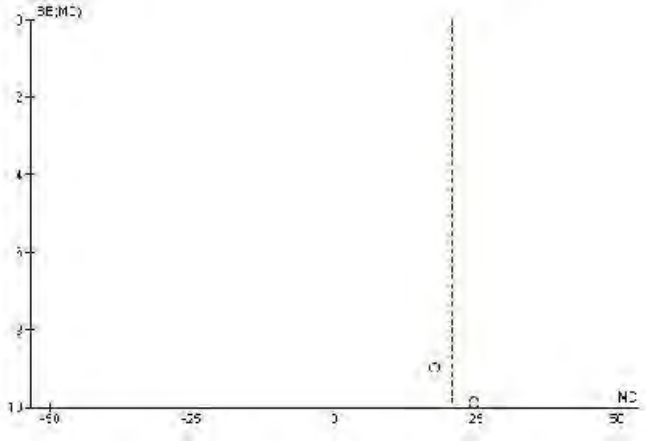
OUTCOME: Total cholesterol					**OUTCOME TYPE: Continuous**					
COMPARISON: Anti-androgen + COCP vs COCP +/- placebo - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention group	SD (or specify if other measure) in intervention group	Sample size (n within this group)	Mean (specify if median) or median in control group	SD (or specify if other measure) in control group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Vieira 2012 (MRB)	Mg/dL	12 months	214.7	29.8	20	190.0	33.3	21	Crude	N/A
Moretti 2018 (MRB)	Mg/dL	12 months	206.3	30.7	28	188.7	33.5	24	Crude	N/A
Meyer 2007 (MRB) *	Mmol/l	6 months	+0.19	95% CI: -0.1, 0.5	33	-0.12	95% CI: -0.2, 0.4	31	Crude	N/A

* Cannot use in meta-analysis as only reported mean change.

11.5.2. Forest Plot of all included RCTs comparing Anti-androgen + COCP and COCP +/- placebo for total cholesterol



11.5.3. Funnel plot for assessment of publication bias

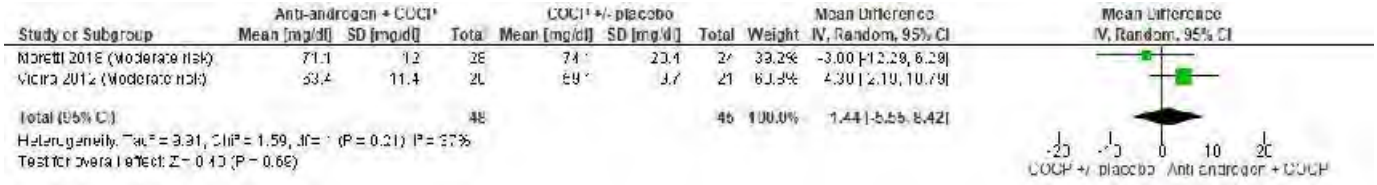


OUTCOME 11.6. HDL
11.6.1. Individual Study Data Table

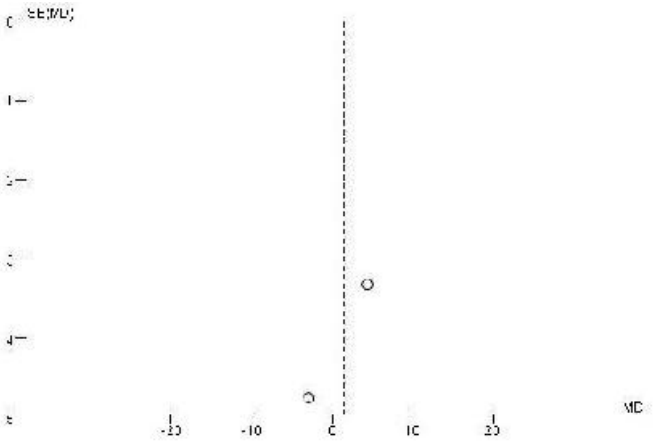
OUTCOME: HDL					**OUTCOME TYPE: Continuous**					
COMPARISON: Anti-androgen + COCP vs COCP +/- placebo - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention group	SD (or specify if other measure) in intervention group	Sample size (n within this group)	Mean (specify if median) or median in control group	SD (or specify if other measure) in control group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Vieira 2012 (MRB)	Mg/dL	12 months	63.4	11.4	20	59.1	9.7	21	Crude	N/A
Moretti 2018 (MRB)	Mg/dL	12 months	71.1	12	28	74.1	20.4	24	Crude	N/A
Meyer 2007 (MRB) *	Mmol/L	6 months	+0.01	95% CI: -0.1, 0.4	33	+0.10	95% CI: -0.1, 0.20	31	Crude	N/A

* Cannot use in meta-analysis as only reported mean change.

11.6.2. Forest Plot of all included RCTs comparing Anti-androgen + COCP and COCP +/- placebo for HDL



11.6.3. Funnel plot for assessment of publication bias

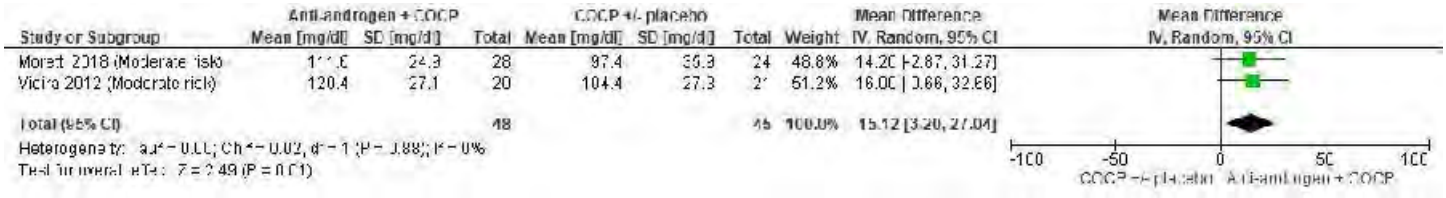


OUTCOME 11.7. LDL
11.7.1. Individual Study Data Table

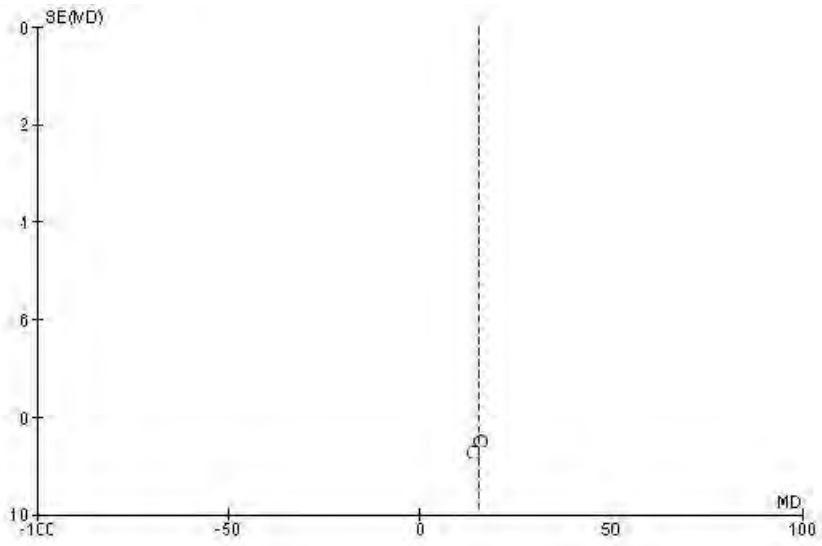
OUTCOME: LDL					**OUTCOME TYPE: Continuous**					
COMPARISON: Anti-androgen + COCP vs COCP +/- placebo - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention group	SD (or specify if other measure) in intervention group	Sample size (n within this group)	Mean (specify if median) or median in control group	SD (or specify if other measure) in control group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Vieira 2012 (MRB)	Mg/dL	12 months	120.4	27.1	20	104.4	27.3	21	Crude	N/A
Moretti 2018 (MRB)	Mg/dL	12 months	111.6	24.9	28	97.4	35.9	24	Crude	N/A
Meyer 2007 (MRB) *	Mmol/l	6 months	+0.06	95% CI: -0.3, 0.2	33	-0.40	95% CI: -0.1, -0.7	31	Crude	N/A

* Cannot use in meta-analysis as only reported mean change.

11.7.2. Forest Plot of all included RCTs comparing Anti-androgen + COCP and COCP +/- placebo for LDL



11.7.3. Funnel plot for assessment of publication bias

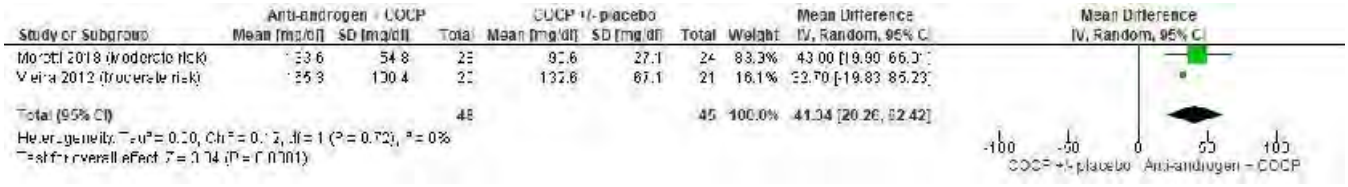


OUTCOME 11.8. Triglycerides
11.8.1. Individual Study Data Table

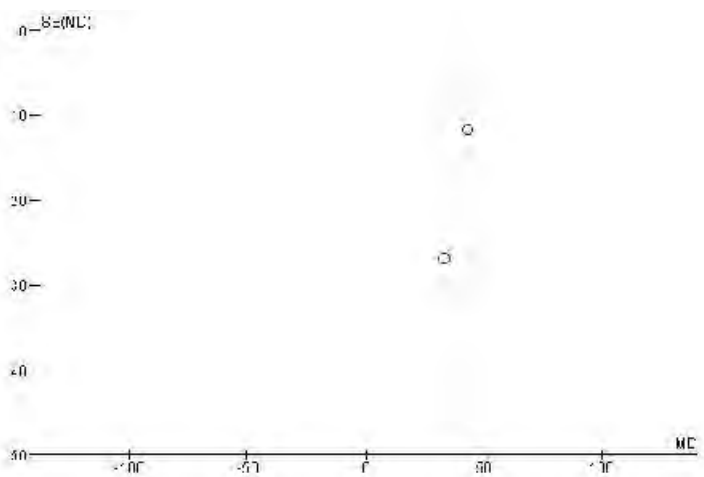
OUTCOME: Triglycerides					**OUTCOME TYPE: Continuous**					
COMPARISON: Anti-androgen + COCP vs COCP +/- placebo - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention group	SD (or specify if other measure) in intervention group	Sample size (n within this group)	Mean (specify if median) or median in control group	SD (or specify if other measure) in control group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Vieira 2012 (MRB)	Mg/dL	12 months	165.3	100.4	20	132.6	67.1	21	Crude	N/A
Moretti 2018 (MRB)	Mg/dL	12 months	133.6	54.8	28	90.6	27.1	24	Crude	N/A
Meyer 2007 (MRB)*	Mmol/L	6 months	+0.13	95% CI: -0.1, 0.3	33	+0.4	95% CI: 0.1, 0.7	31	Crude	N/A
Hagag 2014 (MRB)**	N/A	12 months	+32%	74.7%	72	+35%	29.5%	25	Crude	N/A

* Cannot use in meta-analysis as only reported mean change.
** reported as % change from baseline and hence cannot use in meta-analysis,

11.8.2. Forest Plot of all included RCTs comparing Anti-androgen + COCP and COCP +/- placebo for triglycerides



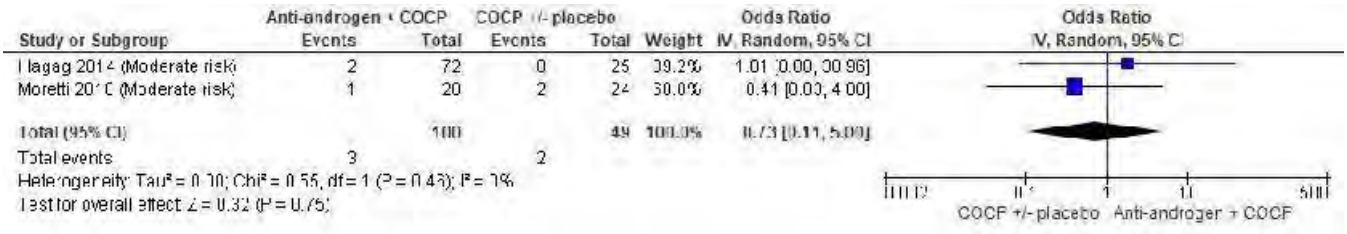
11.8.3. Funnel plot for assessment of publication bias



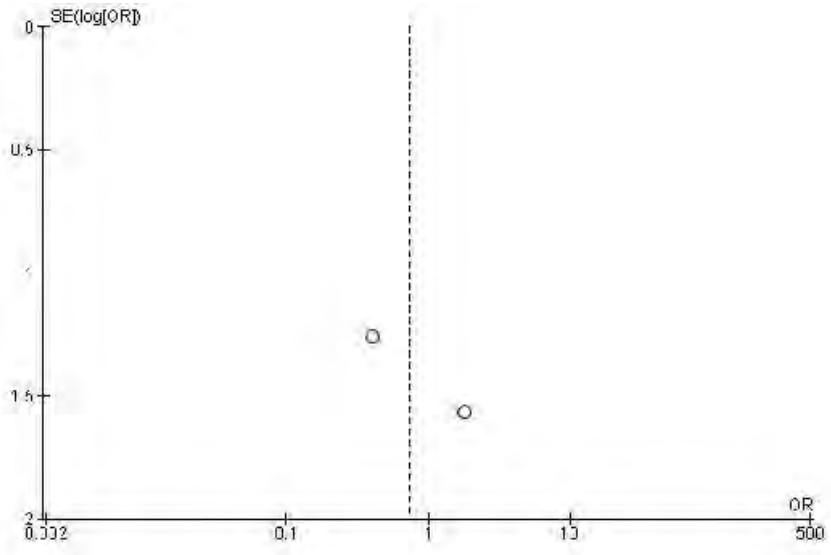
OUTCOME 11.9. Breast tenderness
11.9.1. Individual Study Data Table

OUTCOME: Breast tenderness				**OUTCOME TYPE: Dichotomous**				
COMPARISON: Anti-androgen + COCP vs COCP +/- placebo - ADULTS								
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention group	SD (or specify if other measure) in intervention group	Sample size (n within this group)	Mean (specify if median) or median in control group	SD (or specify if other measure) in control group	Sample size (n within this group)
Hagag 2014 (MRB)	Count	12 months	2	72	0	25	Crude	N/A
Moretti 2018 (MRB)	Count	General physical examination; 12 months	1	28	2	24	Crude	N/A

11.9.2. Forest Plot of all included RCTs comparing Anti-androgen + COCP and COCP +/- placebo for breast tenderness



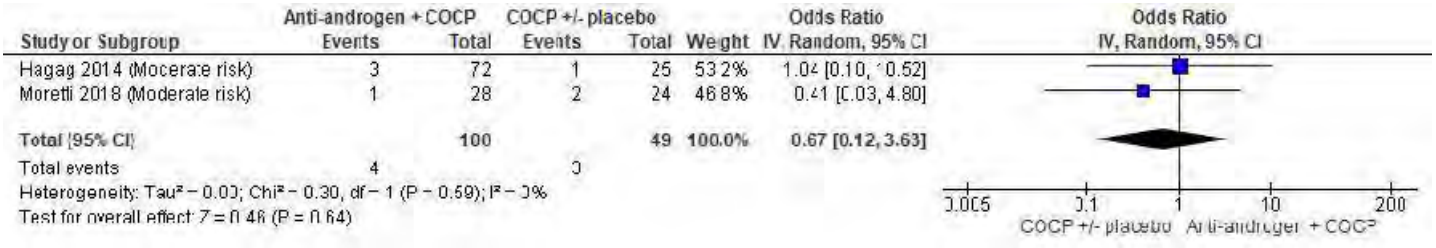
11.9.3. Funnel plot for assessment of publication bias



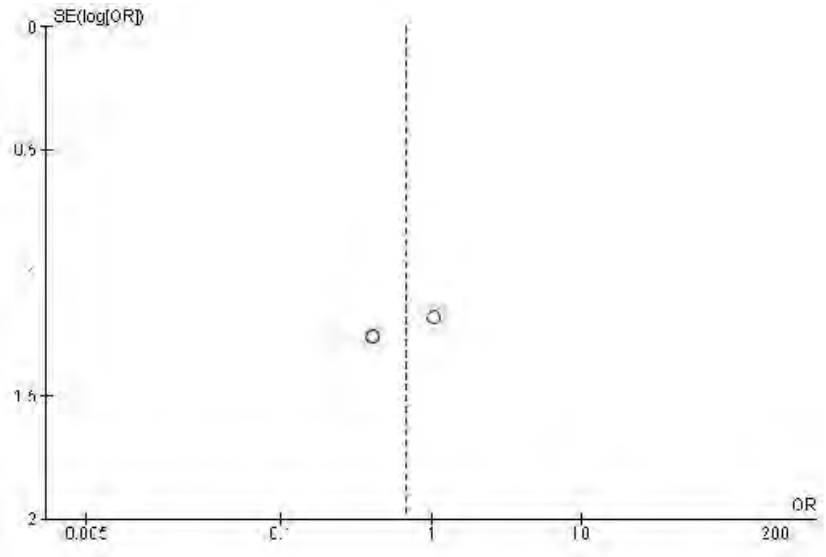
OUTCOME 11.10. Nausea
11.10.1. Individual Study Data Table

OUTCOME: Nausea				**OUTCOME TYPE: Dichotomous**				
COMPARISON: Anti-androgen + COCP vs COCP +/- placebo - ADULTS								
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention group	SD (or specify if other measure) in intervention group	Sample size (n within this group)	Mean (specify if median) in control group	SD (or specify if other measure) in control group	Sample size (n within this group)
Hagag 2014 (MRB)	Count	12 months	3	72	1	25	Crude	N/A
Moretti 2018 (MRB)	Count	General physical examination; 12 months	1	28	2	24	Crude	N/A

11.10.2. Forest Plot of all included RCTs comparing Anti-androgen + COCP and COCP +/- placebo for nausea



11.10.3. Funnel plot for assessment of publication bias



OUTCOME 11.11. – 11.21: Hirsutism, acne, fasting insulin, fasting glucose, HOMA-IR, free testosterone, FAI, DHEAS, androstenedione, LDL/HDL ratio, CRP

11.11.1. – 11.20.1 Individual Study Data Tables

OUTCOME: LISTED BELOW					**OUTCOME TYPE: Continuous**					
COMPARISON: Anti-androgen +COCP vs COCP +/- placebo - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention group	SD (or specify if other measure) in intervention group	Sample size (n within this group)	Mean (specify if median) in control group	SD (or specify if other measure) in control group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
OUTCOME: ALT										
Moretti 2018 (MRB)	NR	12 months	17.5	6.94	28	16.4	7.46	24	Crude	N/A
OUTCOME: AST										
Moretti 2018 (MRB)	NR	12 months	18.5	4.13	28	19.1	5.46	24	Crude	N/A
OUTCOME: Hirsutism										
Meyer 2007 (MRB)	FG score	6 months	-2.0	95% CI: -0.7, -3.4	33	-2.0	95% CI: -0.9, -3.2	31	Crude	N/A
Hagag 2014 (MRB)*	FG score	12 months	-57%	2.4%	72	-68%	5.2%	25	Crude	N/A
OUTCOME: Acne										
Hagag 2014*	Leeds Acne Scale score	LAS scoring system; 12 months	-78%	13.6%	72	-68%	26	25	Crude	N/A
OUTCOME: Fasting insulin										
Burchall 2017 (MRB)	mU/L	6 months	Median: 2.88	IQR: 2.36-3.14	16	Median: 2.88	IQR: 2.22-3.30	21	Crude	N/A
Meyer 2007 (MRB)	U/l	6 months	-1.67	95% CI: -2.3, 5.6	33	+1.15	95% CI: -4.2, 6.5	31	Crude	N/A
Vieira 2012 (MRB)	uIU/ml	12 months	9.6	5.9	20	6.1	4.8	21	Crude	N/A
OUTCOME: Fasting glucose										
Moretti 2018 (MRB)	-	12 months	80.3	6.7	28	77.7	8.9	24	Crude	N/A
OUTCOME: HOMA-IR										
Burchall 2017 (MRB)	N/A	6 months	Median: 1.27	IQR: 0.67 – 1.58	16	Median: 1.17	IQR: 0.54-0.63	21	Crude	N/A

Meyer 2007 (MRB)*	N/A	6 months	-0.22	95% CI: -1.14, 0.7	33	+0.10	95% CI: -1.3, 1.1	31	Crude	N/A
Vieira 2012 (MRB)	N/A	12 months	2.0	1.2	20	1.3	1.0	21	Crude	N/A
OUTCOME: Free testosterone										
Tartagni 2000 (HRB)	Pg/ml	6 months	1.2	0.4	9	1.3	0.4	9	Crude	N/A
Hagag 2014 (MRB)*	Pmol/L	12 months	-47%	73.82	72	-43%	533%	25	Crude	N/A
OUTCOME: FAI										
Vieira 2012 (MRB)	%	12 months	1.3	1.0	20	0.8	0.5	21	Crude	N/A
Meyer 2007 (MRB)*	N/A	6 months	-6.3	95% CI: -8.1, -4.4	33	-6.8	95% CI: -9.4, -4.2	31	Crude	N/A
OUTCOME: DHEAS										
Tartagni 2000 (HRB)	µg/mL	6 months	1.1	0.4	9	1.5	1.2	9	Crude	N/A
Meyer 2007 (MRB)*	µmol/L	6 months	-0.7	95% CI: -0.2, -1.1	33	-1.4	95% CI: -0.7, -2.1	31	Crude	N/A
Hagag 2014 (MRB)*	µmol/L	12 months	-29%	39.03%	72	-28%	20.5%	25	Crude	N/A
OUTCOME: Androstenedione										
Tartagni 2000 (HRB)	Ng/mL	6 months	1.5	1.1	9	1.4	1.1	9	Crude	N/A
Hagag 2014 (MRB)*	Nmol/L	12 months	-19%	42.4%	72	-17%	12%	25	Crude	N/A
OUTCOME: LDL/HDL ratio										
Hagag 2014 (MRB)*	N/A	12 months	-5.1%	71.3%	72	-5.8%	35.5%	25	Crude	N/A
OUTCOME: CRP										
Vieira 2012 (MRB)	Mg/l	12 months	7.4	8.8	20	5.0	3.8	21	Crude	N/A
Hagag 2014 (MRB)*	N/A	12 months	+83%	203.6%	72	+95%	140%	25	Crude	N/A

*reported as change from baseline and hence cannot run meta-analysis

OUTCOME 11.22. – 11.29: Menorrhagia/heavy menstrual bleeding, headache, breast lump, nipple discharge, breast pain, premenstrual pelvic pain, metrorrhagia, vaginal infections, vaginal dryness

11.21.1 – 11.29.1 Individual Study Data Tables

OUTCOME: Adverse events - LISTED BELOW				**OUTCOME TYPE: Dichotomous**				
COMPARISON: Anti-androgen + COCP vs COCP +/- placebo - ADULTS								
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention group	SD (or specify if other measure) in intervention group	Sample size (n within this group)	Mean (specify if median) in control group	SD (or specify if other measure) in control group	Sample size (n within this group)
Outcome: Menorrhagia/heavy menstrual bleeding								
Hagag 2014 (MRB)#	Count	12 months	0	72	0	25	Crude	N/A
Moretti 2018 (MRB)	Count	General physical examination; 12 months	1	28	0	24	Crude	N/A
Outcome: Premenstrual pelvic pain								
Hagag 2014 (MRB)	Count	12 months	0	72	0	25	Crude	N/A
Outcome: Metrorrhagia								
Moretti 2018 (MRB)	Count	General physical examination; 12 months	0	28	2	24	Crude	N/A
Outcome: Hypercholesterolemia								
Moretti 2018 (MRB)	Count	General physical examination; 12 months	14	28	10	24	Crude	N/A
Outcome: Hypertriglyceridemia								
Moretti 2018 (MRB)	Count	General physical examination; 12 months	5	28	2	24	Crude	N/A
Outcome: Dysmenorrhea								
Moretti 2018 (MRB)	Count	General physical examination; 12 months	0	28	1	24	Crude	N/A
Outcome: Menstrual spotting								
Moretti 2018 (MRB)	Count	General physical examination; 12 months	7	28	4	24	Crude	N/A
Outcome: Minor depressive state/mood reduction								
Hagag 2014	No. of	12 months	0	72	0	25	Crude	N/A

(MRB)#	cases							
Moretti 2018 (MRB)	No. of cases	General physical examination; 12 months	1	28	0	24	Crude	N/A

cannot run meta-analysis due to no counts.

COMPARISON 12. Anti-androgen + COCP vs MET - ADULTS (6 – 12 MONTHS)

- **EVIDENCE SUMMARY:**

There were four RCTs that investigated that addressed the comparison of a combination therapy of an anti-androgen + COCP against metformin in adult women with PCOS with 6 to 12 months follow-up. The studies were either low (Mehrabian, 2016), moderate (Burchall, 2017; Meyer, 2007), or high risk of bias (Alpanez, 2017) with 6 and 12 month follow-ups. The studies were conducted in Australia, Spain, and Iran.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

Due to the nature of the diversity in the way outcomes were reported, only BMI could be pooled in meta-analysis, which showed no effect with a moderate certainty of evidence only downgrading due to the inclusion of a moderate risk of bias study (Burchall, 2017). In the single study mean difference estimates, the combination anti-androgen + COCP was superior in free testosterone, androstenedione, DHEAS, CRP, and menstrual dysfunction. Conversely, metformin was superior for fasting glucose. The certainty of the evidence for these findings ranged from very low to low due to the risk of bias and sample size, except for CRP which was moderate only being downgraded due to the sample size.

There was no difference for BMI in meta-analysis, with a moderate certainty of evidence. In the single study mean difference estimates, fasting insulin HOMA-IR, testosterone, HDL, triglycerides, and adverse events such as abnormal glucose tolerance and dyslipidaemia. The certainty in the evidence for these outcomes ranged from very low to low due to the risk of bias and small sample size, except for triglycerides which was only downgraded due to the sample size.

Whilst Alpanez 2017 did not report specific liver function test results, it was reported that liver markers such as transaminases were checked routinely and remained unchanged throughout the study except in three women.

Outcome or Subgroup	Studies	n	Effect Estimate; MD [95% CI], I-V, OR [95% CI], random	P-value	Favours	Certainty
BMI	2	107	-0.07 kg/m^2 [-1.81, 1.67]	0.93	None	⊕⊕⊕◯ MODERATE
Hirsutism	1	46	4.6 [2.6, 6.7]	<0.0001	MET	⊕◯◯◯ VERY LOW
Fasting glucose	1	68	0.70 mmol/L [0.32, 1.07]	0.0003	AA + COCP	⊕⊕◯◯ LOW
Fasting insulin	1	39	AA + OCP: median: 2.88 mU/l, IQR: 2.36 – 3.14; MET: median: 2.37 mU/l, IQR: 2.10-3.23	>0.05	None	⊕◯◯◯ VERY LOW
HOMA-IR	1	39	AA + OCP: median: 1.27, IQR: 0.67 - 1.58; MET: median: 0.77, IQR: 0.40-1.53	>0.05	None	⊕◯◯◯ VERY LOW
Testosterone	1	39	0.01 nmol/l [-0.72, 0.74]	0.98	None	⊕◯◯◯ VERY LOW

Free testosterone	1	46	0.025 nmol/l [0.012, 0.039]	<0.0001	MET	⊕◯◯◯ VERY LOW
Androstenedione	1	46	5.5 nmol/l [1.8, 9.2]	0.0002	MET	⊕◯◯◯ VERY LOW
DHEAS	1	46	2.7 µmol/l [1.4, 4.0]	<0.0001	MET	⊕◯◯◯ VERY LOW
HDL	1	68	-0.00 mmol/l [-0.09, 0.08]	0.91	None	⊕⊕◯◯ LOW
Triglycerides	1	68	-0.06 mmol/l [-0.35, 0.23]	0.68	None	⊕⊕⊕◯ MODERATE
CRP	1	68	-0.23 mg/l [-0.42, -0.04]	0.02	AA + COCP	⊕⊕⊕◯ MODERATE
Menstrual dysfunction	1	46	OR: 0.06 [0.02, 0.23]	<0.0001	AA + COCP	⊕◯◯◯ VERY LOW
Abnormal glucose tolerance	1	46	OR: 1.7 [0.7, 4.4]	0.255	None	⊕◯◯◯ VERY LOW
Dyslipidaemia	1	46	OR: 0.6 [0.2, 1.8]	0.219	None	⊕◯◯◯ VERY LOW

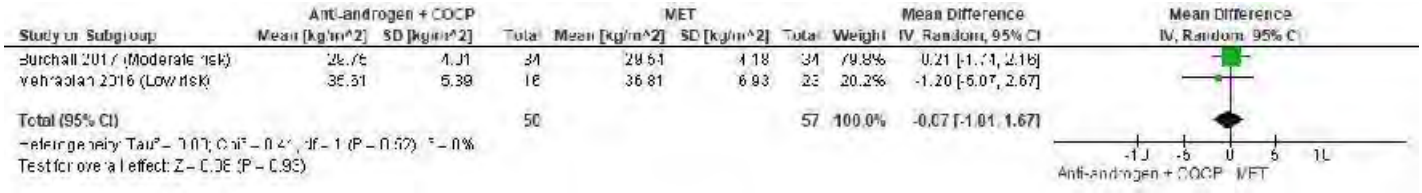
OUTCOME 12.1. BMI

12.1.1. Individual Study Data Table

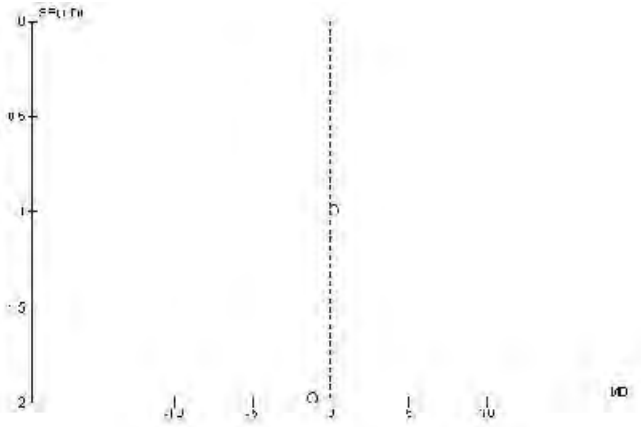
OUTCOME: BMI					OUTCOME TYPE: Continuous					
COMPARISON: Anti-androgen + COCP vs MET - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Mehrabian 2016 (LRB)	Kg/m^2	6 months	29.75	4.01	34	29.54	4.18	34	Crude	N/A
Burchall 2017 (MRB)	Kg/m^2	6 months	35.61	5.39	16	36.81	6.93	23	Crude	N/A
Meyer 2007 (MRB) *	Kg/m^2	6 months	-0.3	95% CI: -0.4, 0.9	33	-0.5	95% CI: -2.4, 4.0	36	Crude	N/A

* Cannot use in meta-analysis as only reported mean change, and as such have used Burchall 2017 which is a sub-study of Meyer 2007 in meta-analysis.

12.1.2. Forest Plot of all included RCTs comparing Anti-androgen + COCP and MET for BMI



12.1.3. Funnel plot for assessment of publication bias



OUTCOME 12.2 – 12.12: hirsutism, fasting glucose, fasting insulin, HOMA-IR, testosterone, free testosterone, androstenedione, DHEAS, HDL, triglycerides, CRP

12.2.1 – 12.12.1 Individual Study Data Tables

OUTCOME: LISTED BELOW					**OUTCOME TYPE: Continuous**					
COMPARISON: Anti-androgen +COCP vs MET - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention group	SD (or specify if other measure) in intervention group	Sample size (n within this group)	Mean (specify if median) in control group	SD (or specify if other measure) in control group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
OUTCOME: Hirsutism										
Alpanez 2017 (HRB)	FG score	6 months	MD: 4.6	95% CI: 2.6, 6.7	AA + OCP: 24			MET: 22	Crude	N/A
OUTCOME: Fasting glucose										
Mehrabian 2016 (LRB)	Mmol/L	6 months	5.005	0.73	34	4.31	0.854	34	Crude	N/A
OUTCOME: Fasting insulin										
Burchall 2017 (MRB)	mU/l	6 months	Median: 2.88	IQR: 2.36-3.14	16	Median: 2.37	IQR: 2.10-3.23	23	Crude	N/A
OUTCOME: HOMA-IR										
Burchall 2017 (MRB)	mU/l	6 months	Median: 1.27	IQR: 0.67-1.58	16	Median: 0.77	IQR: 0.40-1.53	23	Crude	N/A
OUTCOME: Testosterone										
Burchall 2017 (MRB)	Nmol/L	6 months	2.11	1.21	16	2.10	1.06	23	Crude	N/A
Alpanez 2017 (HRB)*	Nmol/l	12 months	MD: 1.1	95% CI: 0.4, 1.7	AA + OCP: 24			MET: 22	Crude	N/A
OUTCOME: Free testosterone										
Alpanez 2017 (HRB)	Nmol/l	12 months	MD: 0.025	95% CI: 0.012, 0.039	AA + OCP: 24			MET: 22	Crude	N/A
OUTCOME: Androstenedione										
Alpanez 2017 (HRB)	Nmol/l	12 months	MD: 5.5	95% CI: 1.8, 9.2	AA + OCP: 24			MET: 22	Crude	N/A
OUTCOME: DHEAS										
Alpanez 2017 (HRB)	Nmol/l	12 months	MD: 2.7	95% CI: 1.4, 4.0	AA + OCP: 24			MET: 22	Crude	N/A

OUTCOME: HDL										
Mehrabian 2016 (LRB)	Mmol/L	6 months	1.094	0.18	34	1.099	0.174	34	Crude	N/A
OUTCOME: Triglycerides										
Mehrabian 2016 (LRB)	Mmol/L	6 months	2.12	0.59	34	2.18	0.61	34	Crude	N/A
OUTCOME: CRP										
Mehrabian 2016 (LRB)	Mg/L	6 months	1.22	0.29	34	1.45	0.47	34	Crude	N/A

* Used Burchall 2017 in mean difference estimates, as cannot input due to reporting.

OUTCOME 12.13-12.16: Menstrual dysfunction, abnormal glucose tolerance, dyslipidaemia, hypertension

OUTCOME: Adverse events - LISTED BELOW				**OUTCOME TYPE: Dichotomous**				
COMPARISON: Anti-androgen + COCP vs COCP +/- placebo - ADULTS								
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention group	SD (or specify if other measure) in intervention group	Sample size (n within this group)	Mean (specify if median) in control group	SD (or specify if other measure) in control group	Sample size (n within this group)
Outcome: Menstrual dysfunction								
Alpanez 2017 (HRB)*	Odds ratio*	12 months	OR: 0.06	95% CI: 0.02, 0.23	AA + OCP: 24	MET: 22	Crude	N/A
Outcome: Abnormal glucose tolerance								
Alpanez 2017 (HRB)*	Odds ratio*	12 months	OR: 1.7	95% CI: 0.7, 4.4	AA + OCP: 24	MET: 22	Crude	N/A
Outcome: Dyslipidaemia								
Alpanez 2017 (HRB)*	Odds ratio*	12 months	OR: 0.6	95% CI: 0.2, 1.8	AA + OCP: 24	MET: 22	Crude	N/A

COMPARISON 13. Anti-androgen + lifestyle vs MET + lifestyle - ADULTS (6 – 12 MONTHS)

- **EVIDENCE SUMMARY:**

There were four RCTs that addressed the comparison of anti-androgen + lifestyle against metformin + lifestyle in adult women with PCOS with 6 – 12 months follow-up. Two studies were low risk of bias (Gambineri, 2006; Ganie 2013) and two were moderate risk of bias (Ganie, 2004; Amiri, 2014). The studies were conducted in India, Iran, and Italy.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

In meta-analysis, the anti-androgen + lifestyle was superior for frequency of menstruation, hirsutism, fasting insulin and fasting glucose-insulin ratio as compared to the metformin + lifestyle intervention. The certainty in the evidence ranged from very low, low, to moderate, mostly being downgraded due to the inclusion of Amiri 2014 where it is unclear whether lean women were included in the analysis. Conversely, the metformin + lifestyle intervention was superior for SHBG and HDL, with a very low and low certainty of evidence, respectively.

There was no difference in weight, BMI, WHR, testosterone, DHEAS, fasting glucose, and QUICKI in meta-analysis. The certainty of the evidence ranged from very low to low, except in the cases of WHR, testosterone, and QUICKI where there was only downgrading due to risk of bias or statistical heterogeneity. In the single study mean difference estimates, there was no difference in FAI, androstenedione, OGTT, HOMA, total cholesterol, LDL, and triglycerides, with the certainty of evidence ranging from very low to low reflective of the risk of bias and small sample sizes.

Since the BMIs of the population of Amiri 2014 was uncertain, a sensitivity analysis was conducted to assess the influence of Amiri 2014 on several outcomes. When removing Amiri 2014 from BMI and fasting glucose, the significance obtained remained unchanged. However, when removing Amiri 2014 from hirsutism and SHBG, they were no longer significant.

Outcome or Subgroup	Studies	n	Effect Estimate; MD [95% CI], I-V, random	P-value	Favours	Certainty
Weight	2	144	-5.64 kg [-19.33, 8.05]	0.42	None	⊕⊕◯◯ LOW
BMI	4	265	-0.79 kg/m^2 [-2.45, 0.87]	0.35	None	⊕◯◯◯ VERY LOW
WHR	2	176	0.02 [-0.00, 0.04]	0.11	None	⊕⊕⊕◯ MODERATE
Frequency of menstruation	2	176	0.79 cycles/year [0.05, 1.53]	0.04	AA + LS	⊕⊕⊕◯ MODERATE
Hirsutism	4	265	-1.59 [-3.06, -0.12]	0.03	AA + LS	⊕◯◯◯ VERY LOW
SHBG	2	89	7.70 nmol/l [0.75, 14.66]	0.03	AA + LS	⊕◯◯◯ VERY LOW
Testosterone	3	213	0.03 nmol/l [-0.21, 0.27]	0.81	None	⊕⊕⊕◯ MODERATE
DHEAS	2	106	-1.02 µmol/L [-3.27, 1.24]	0.38	None	⊕◯◯◯ VERY LOW
Fasting insulin	3	213	-2.11 µU/ml [-3.97, -0.26]	0.03	AA + LS	⊕⊕⊕◯ MODERATE
Fasting glucose	3	228	0.44 mg/dl [-2.14, 3.02]	0.74	None	⊕⊕◯◯ LOW

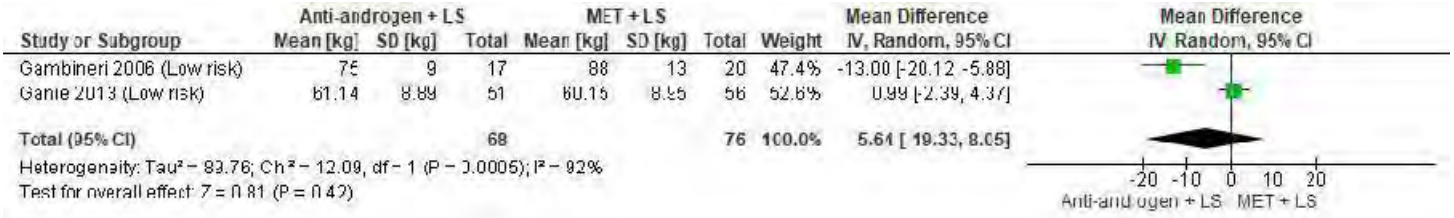
Fasting glucose-insulin ratio	2	176	-1.12 [-1.44, -0.79]	<0.00001	AA + LS	⊕⊕⊕◯ MODERATE
QUICKI	2	144	0.01 [-0.02, 0.04]	0.35	None	⊕⊕⊕◯ MODERATE
FAI	1	37	-0.60 [-1.99, 0.79]	0.40	None	⊕⊕◯◯ LOW
Androstenedione	1	37	-39.00 ng/dl [-123.43, -0.25]	0.37	None	⊕⊕◯◯ LOW
OGTT	1	52	-9.54 mg/dl [-23.70, 4.62]	0.19	None	⊕⊕◯◯ LOW
HOMA	1	69	2.72 [-0.28, 5.72]	0.08	None	⊕⊕◯◯ LOW
Total cholesterol	1	52	7.20 mmol/l [-13.06, 27.46]	0.49	None	⊕◯◯◯ VERY LOW
HDL	1	37	0.21 mmol/l [0.05, 0.37]	0.01	AA + LS	⊕⊕◯◯ LOW
LDL	1	37	-0.29 mmol/l [-0.83, 0.25]	0.29	None	⊕⊕◯◯ LOW
Triglycerides	1	37	-0.23 mmol/l [-0.51, 0.05]	0.10	None	⊕⊕◯◯ LOW

OUTCOME 13.1. Weight

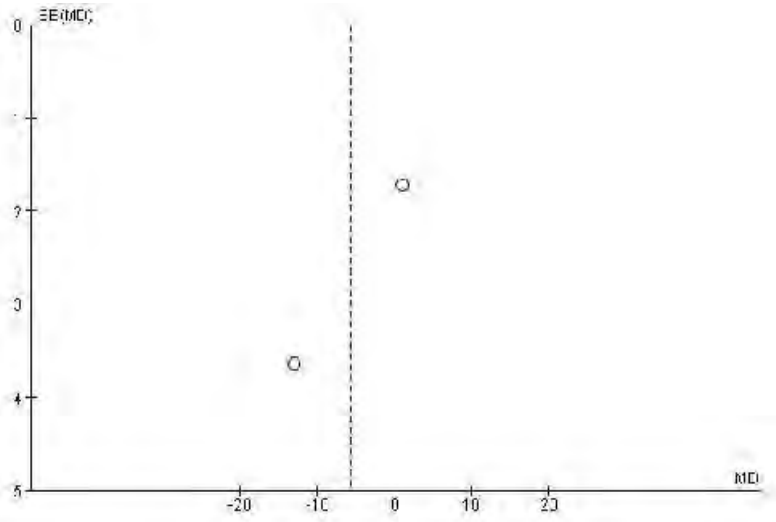
13.1.1. Individual Study Data Table

OUTCOME: Weight					OUTCOME TYPE: Continuous					
COMPARISON: Anti-androgen + LS vs MET + LS - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention group	SD (or specify if other measure) in intervention group	Sample size (n within this group)	Mean (specify if median) or median in control group	SD (or specify if other measure) in control group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Ganie 2013 (LRB)	Kg	6 months	61.14	8.89	51	60.15	8.95	56	Crude	N/A
Gambineri 2006 (LRB)	Kg	12 months	75	9	17	88	13	20	Crude	N/A

13.1.2. Forest Plot of all included RCTs comparing Anti-androgen + LS and MET + LS for weight



3.1.3. Funnel plot for assessment of publication bias

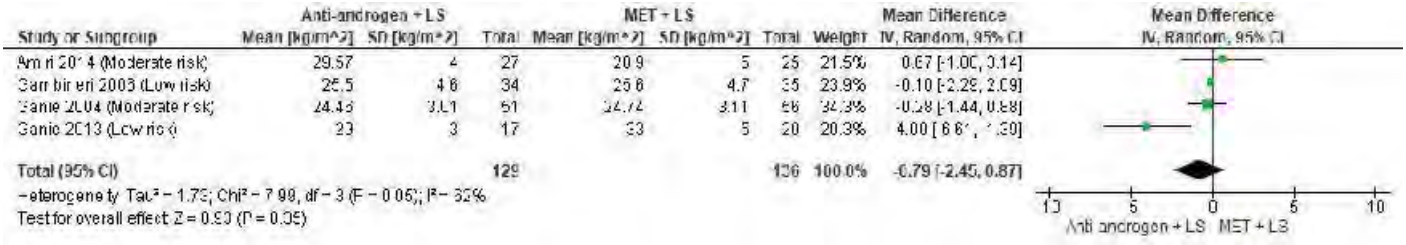


OUTCOME 13.2. BMI

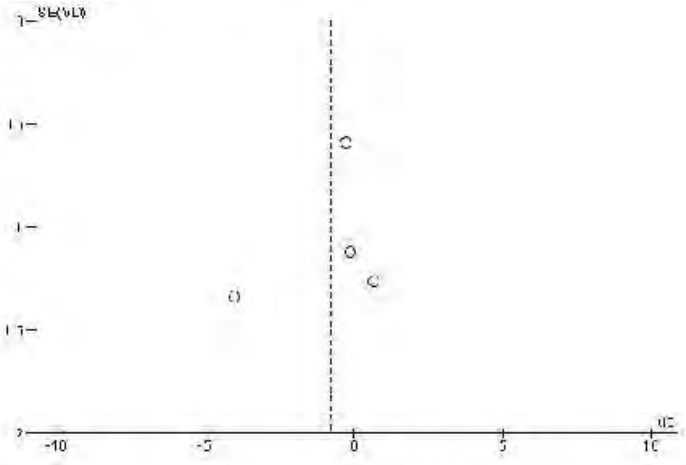
13.2.1. Individual Study Data Table

OUTCOME: BMI					OUTCOME TYPE: Continuous					
COMPARISON: Anti-androgen + LS vs MET + LS - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Amiri 2014 (MRB)	Kg/m^2	6 months	29.57	4	27	28.9	5	25	Crude	N/A
Ganie 2004 (MRB)	Kg/m^2	6 months	25.5	4.6	34	25.6	4.7	35	Crude	N/A
Ganie 2013 (LRB)	Kg/m^2	6 months	24.46	3.01	51	24.74	3.11	56	Crude	N/A
Gambineri 2006 (LRB)	Kg/m^2	12 months	29	3	17	33	5	20	Crude	N/A

13.2.2. Forest Plot of all included RCTs comparing Anti-androgen + LS and MET + LS for BMI



13.2.3. Funnel plot for assessment of publication bias

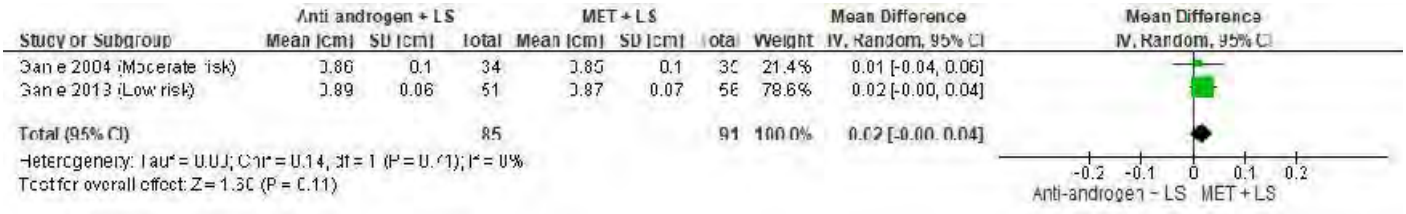


OUTCOME 13.3. WHR
12.1.1. Individual Study Data Table

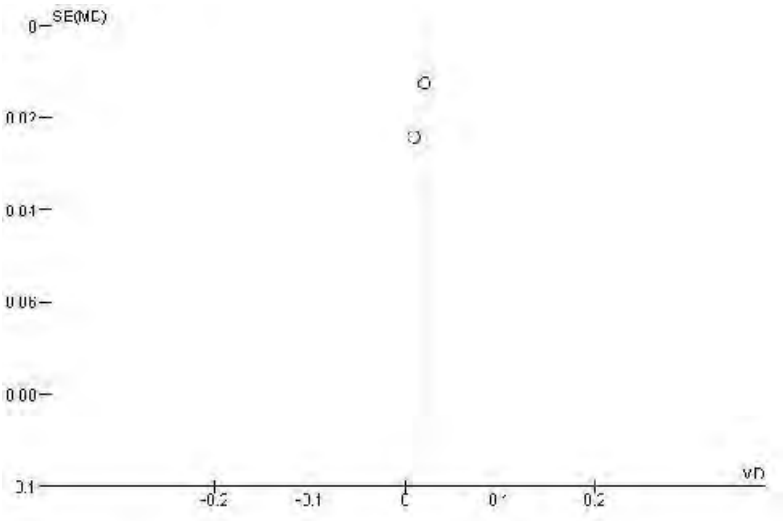
OUTCOME: WHR					OUTCOME TYPE: Continuous					
COMPARISON: Anti-androgen + LS vs MET + LS - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention / exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in exposure group	Sample size (n within this group)	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Amiri 2014 (MRB) #	N/A	6 months	0.8	0	27	0.8	0.1	25	Crude	N/A
Ganie 2004 (MRB)	N/A	6 months	0.86	0.1	34	0.85	0.1	35	Crude	N/A
Ganie 2013 (LRB)	N/A	6 months	0.89	0.06	51	0.87	0.07	56	Crude	N/A

cannot include in meta-analysis as SD is zero

13.3.1. Forest Plot of all included RCTs comparing Anti-androgen + LS and MET + LS for WHR



13.3.2. Funnel plot for assessment of publication bias

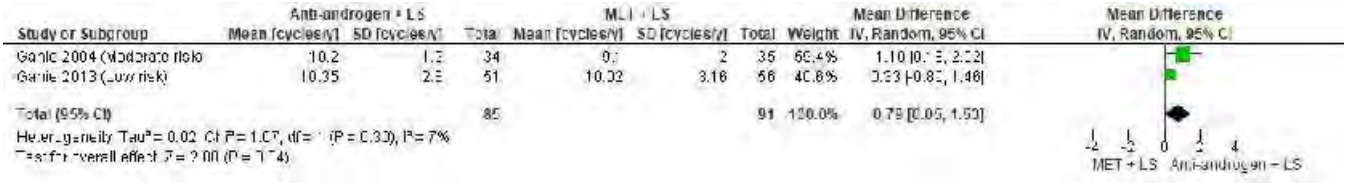


OUTCOME 13.4. Frequency of menstruation
13.4.1. Individual Study Data Table

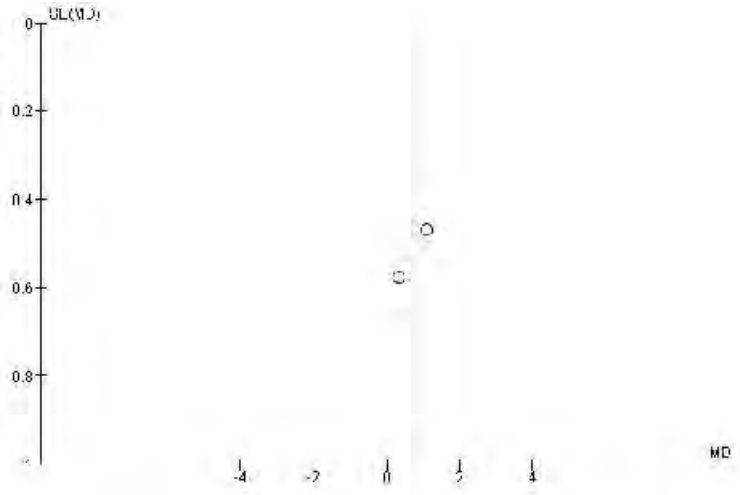
OUTCOME: Frequency of menstruation					**OUTCOME TYPE: Continuous**					
COMPARISON: Anti-androgen + LS vs MET + LS - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Ganie 2004 (MRB)	No. of cycles per year	6 months	10.2	1.9	34	9.1	2	35	Crude	N/A
Ganie 2013 (LRB)	No. of cycles per year	6 months	10.35	2.8	51	10.02	3.16	56	Crude	N/A
Gambineri 2006 (LRB)*	No. of cycles previous 6 months	12 months	5.0	1.4	17	4.6	1.8	20	Crude	N/A

* did not include in meta-analysis as different reporting.

3.4.2. Forest Plot of all included RCTs comparing Anti-androgen + LS and MET + LS for frequency of menstruation (cycles/year)



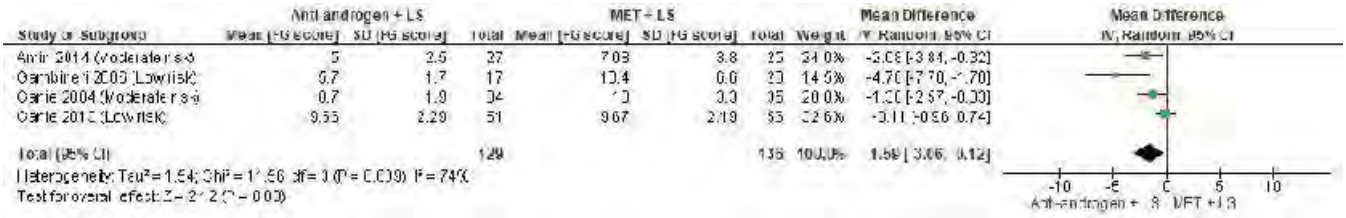
13.4.3. Funnel plot for assessment of publication bias



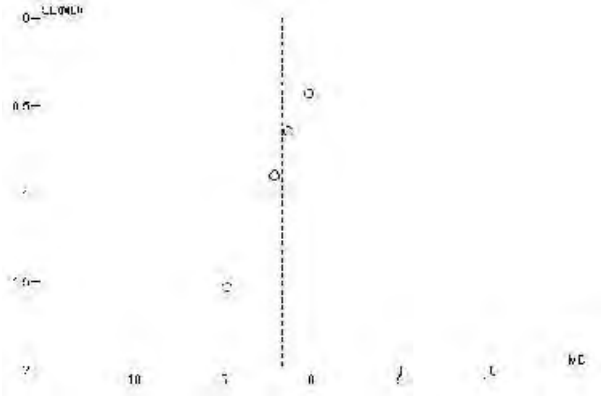
OUTCOME 13.5. Hirsutism
13.5.1. Individual Study Data Table

OUTCOME: Hirsutism					**OUTCOME TYPE: Continuous**					
COMPARISON: Anti-androgen + LS vs MET + LS - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Amiri 2014 (MRB)	FG score	6 months	5	2.5	27	7.08	3.8	25	Crude	N/A
Ganie 2004 (MRB)	FG score	6 months	8.7	1.9	34	10.0	3.3	35	Crude	N/A
Ganie 2013 (LRB)	FG score	6 months	9.56	2.29	51	9.67	2.19	56	Crude	N/A
Gambineri 2006 (LRB)	FG score	12 months	5.7	1.7	17	10.4	6.6	20	Crude	N/A

13.5.2. Forest Plot of all included RCTs comparing Anti-androgen + LS and MET + LS for hirsutism



13.5.3. Funnel plot for assessment of publication bias

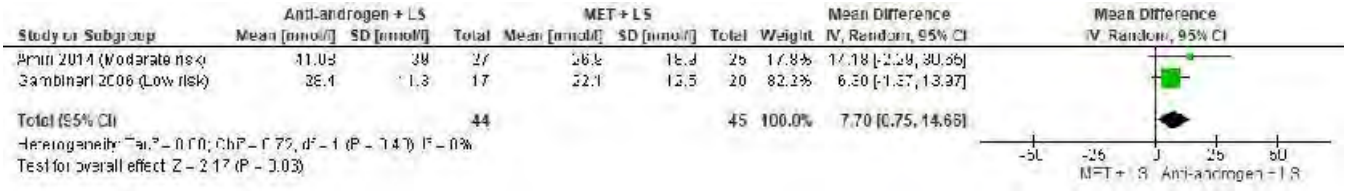


OUTCOME 13.6. SHBG

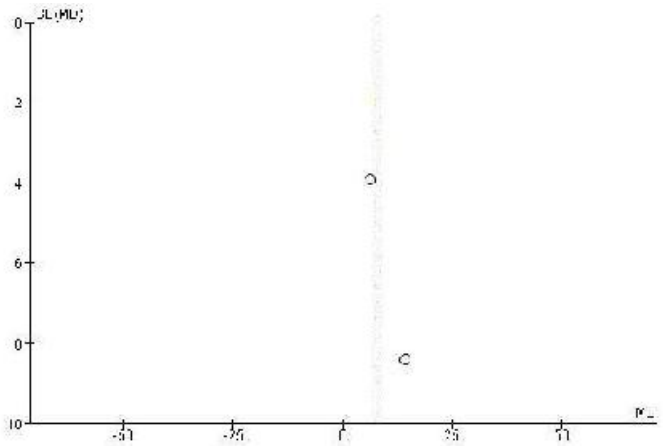
13.6.1. Individual Study Data Table

OUTCOME: SHBG					**OUTCOME TYPE: Continuous**					
COMPARISON: Anti-androgen + LS vs MET + LS - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Amiri 2014 (MRB)	Nmol/L	6 months	41.08	39	27	26.9	18.9	25	Crude	N/A
Gambineri 2006 (LRB)	Nmol/L	12 months	28.4	11.3	17	22.1	12.5	20	Crude	N/A

13.6.2. Forest Plot of all included RCTs comparing Anti-androgen + LS and MET + LS for SHBG



13.6.3. Funnel plot for assessment of publication bias



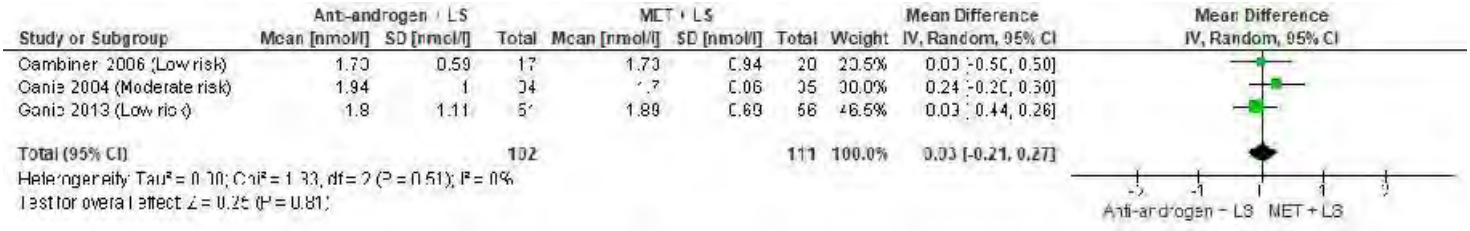
OUTCOME 13.7. Testosterone

13.7.1. Individual Study Data Table

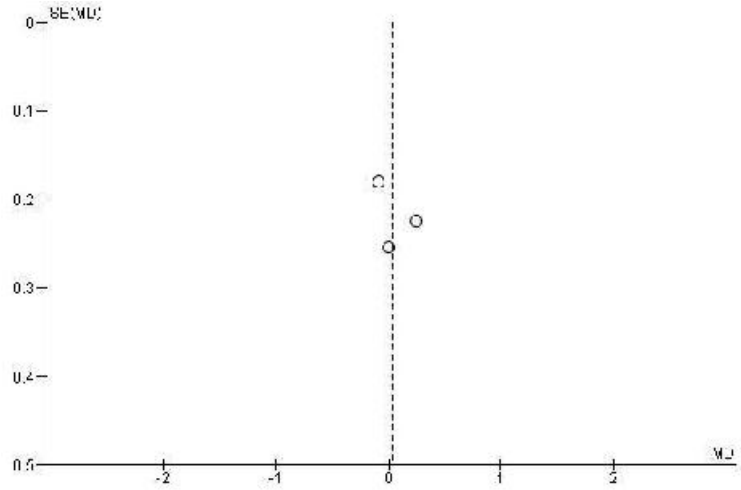
OUTCOME: Testosterone					**OUTCOME TYPE: Continuous**					
COMPARISON: Anti-androgen + LS vs MET + LS - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Amiri 2014 (MRB)#	Nmol/L	6 months	0.55	0.2	27	0.7	0.4	25	Crude	N/A
Ganie 2004 (MRB)	Nmol/L	6 months	1.94	1.0	34	1.7	0.86	35	Crude	N/A
Ganie 2013 (LRB)	Nmol/L	6 months	1.80	1.11	51	1.89	0.69	56	Crude	N/A
Gambineri 2006 (LRB)	Nmol/L	12 months	1.73	0.59	17	1.73	0.94	20	Crude	N/A

not included in meta analysis due to uncertainty in units

13.7.2. Forest Plot of all included RCTs comparing Anti-androgen + LS and MET + LS for testosterone



13.7.3. Funnel plot for assessment of publication bias

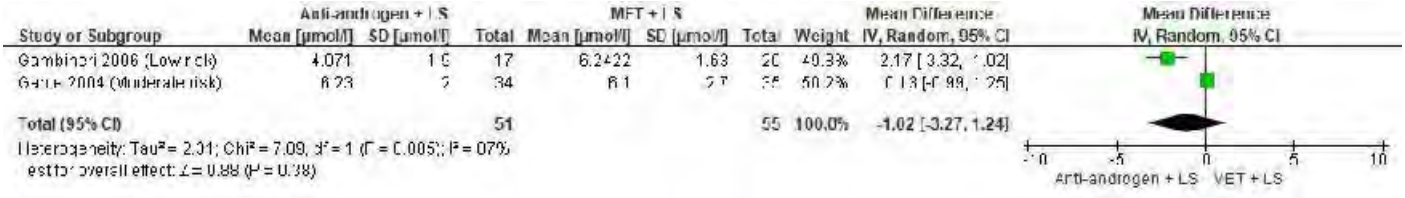


OUTCOME 13.8. DHEAS

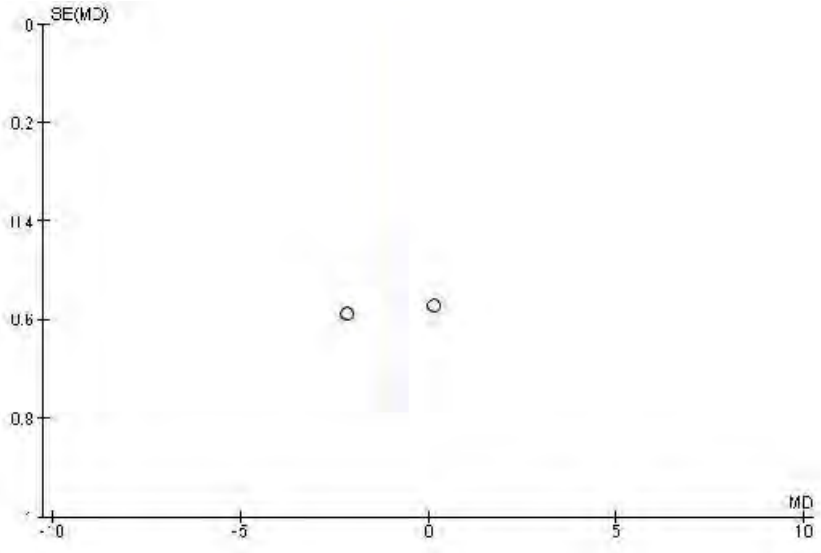
13.8.1. Individual Study Data Table

OUTCOME: DHEAS					**OUTCOME TYPE: Continuous**					
COMPARISON: Anti-androgen + LS vs MET + LS - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Amiri 2014 (MRB)#	µmol/L	6 months	145.46	81	27	222.5	129.1	25	Crude	N/A
Ganie 2004 (MRB)	µmol/L	6 months	6.23	2.0	34	6.1	2.7	35	Crude	N/A
Gambineri 2006 (LRB)	µmol/L	12 months	4.071	1.90	17	6.2422	1.63	20	Crude	N/A

13.8.2. Forest Plot of all included RCTs comparing Anti-androgen + LS and MET + LS for DHEAS



13.8.3. Funnel plot for assessment of publication bias

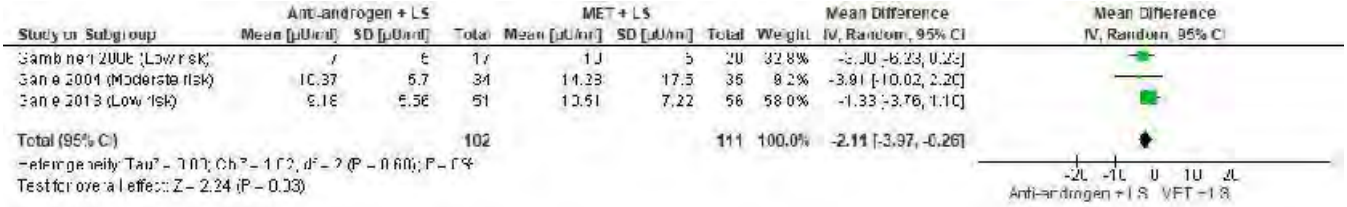


OUTCOME 13.9. Fasting insulin
13.9.1. Individual Study Data Table

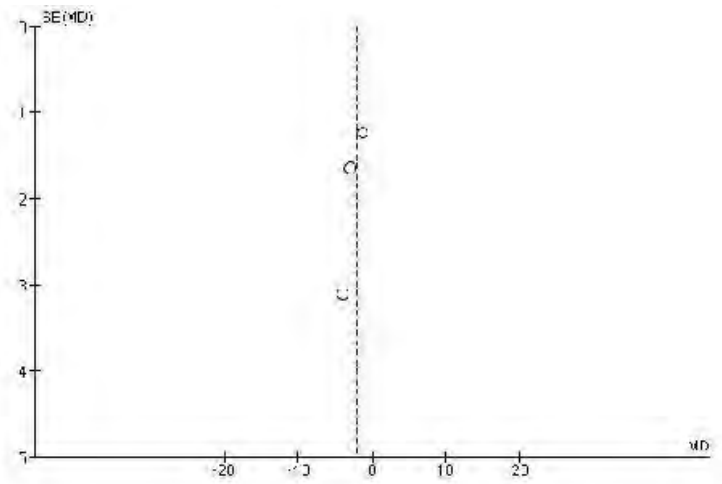
OUTCOME: Fasting insulin					**OUTCOME TYPE: Continuous**					
COMPARISON: Anti-androgen + LS vs MET + LS - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Amiri 2014 (MRB)#	Pmol/L	6 months	14.6	6.2	27	13.7	7.1	25	Crude	N/A
Ganie 2004 (MRB)	µU/ml	6 months	10.37	5.7	34	14.28	17.5	35	Crude	N/A
Ganie 2013 (LRB)	µU/ml	6 months	9.18	5.56	51	10.51	7.22	56	Crude	N/A
Gambineri 2006 (LRB)	µU/ml	12 months	7	5	17	10	5	20	Crude	N/A

not included in meta-analysis due to uncertainty in units

13.9.2. Forest Plot of all included RCTs comparing Anti-androgen + LS and MET + LS for fasting insulin



13.9.3. Funnel plot for assessment of publication bias

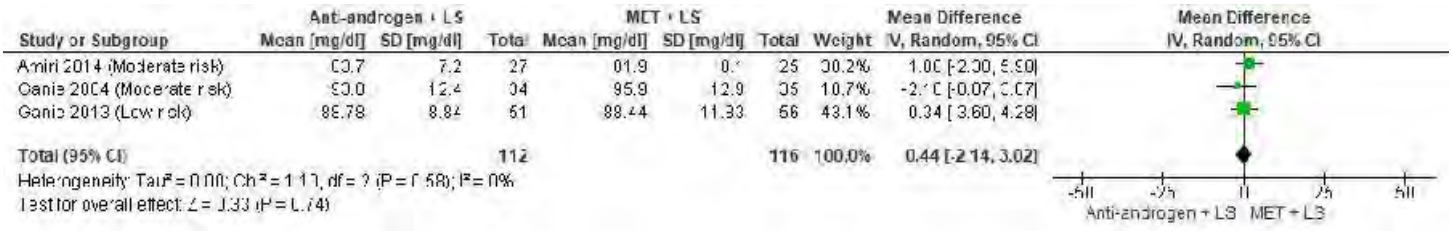


OUTCOME 13.10. Fasting glucose
13.10.1. Individual Study Data Table

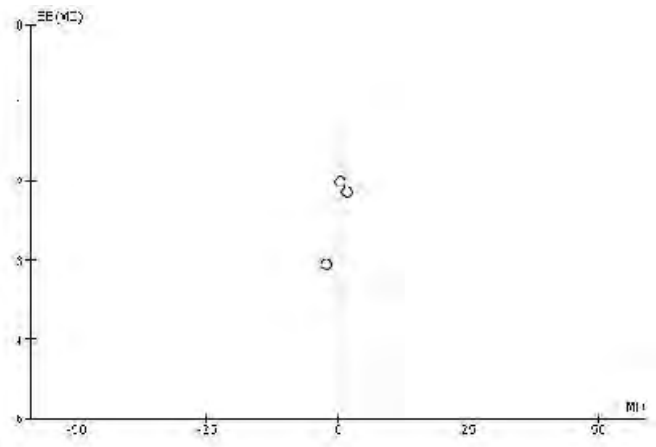
OUTCOME: Weight					OUTCOME TYPE: Continuous					
COMPARISON: Anti-androgen + LS vs MET + LS - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention group	Sample size (n within this group)	Mean (specify if median) or median in control group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Amiri 2014 (MRB)	Mg/dL	6 months	83.7	7.2	27	81.9	8.1	25	Crude	N/A
Ganie 2004 (MRB)	Mg/dL	6 months	93.8	12.4	34	95.9	12.9	35	Crude	N/A
Ganie 2013 (LRB)	Mg/dL	6 months	88.78	8.84	51	88.44	11.83	56	Crude	N/A
Gambineri 2006 (LRB)#	Mg/ml	12 months	88	7	17	91	9	20	Crude	N/A

did not include in meta-analysis due uncertainty in units

13.10.2. Forest Plot of all included RCTs comparing Anti-androgen + LS and MET + LS for fasting glucose



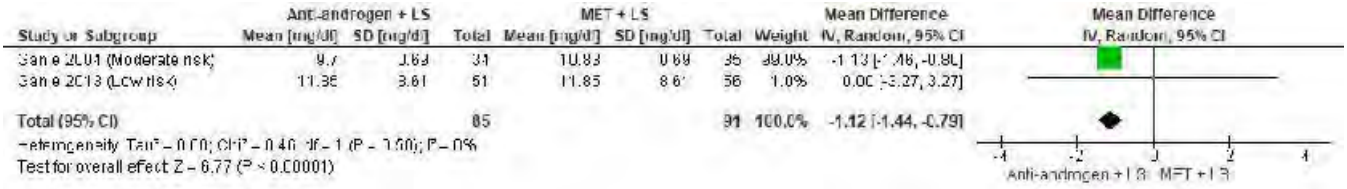
13.10.3. Funnel plot for assessment of publication bias



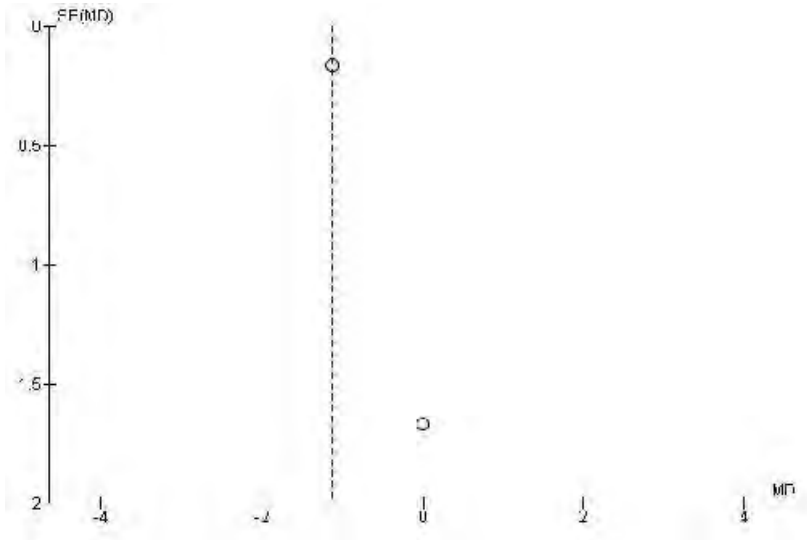
OUTCOME 13.11. Fasting glucose-insulin ratio
13.11.1. Individual Study Data Table

OUTCOME: Fasting glucose-insulin ratio					OUTCOME TYPE: Continuous					
COMPARISON: Anti-androgen + LS vs MET + LS - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Ganie 2004 (MRB)	Mg/dL	6 months	9.7	0.69	34	10.83	0.69	35	Crude	N/A
Ganie 2013 (LRB)	Mg/dL	6 months	11.85	8.61	51	11.85	8.61	56	Crude	N/A

13.11.2. Forest Plot of all included RCTs comparing Anti-androgen + LS and MET + LS for fasting glucose-insulin ratio



13.11.3. Funnel plot for assessment of publication bias

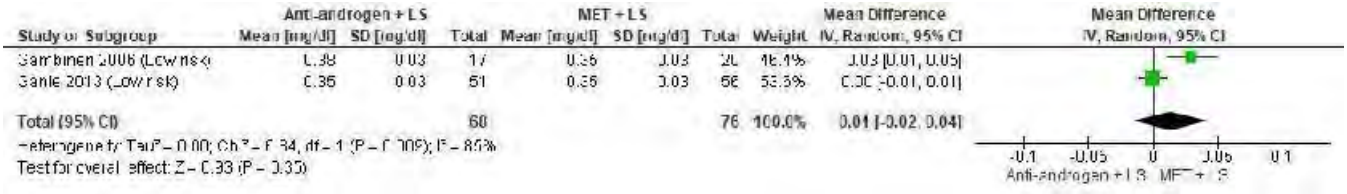


OUTCOME 13.12. QUICKI

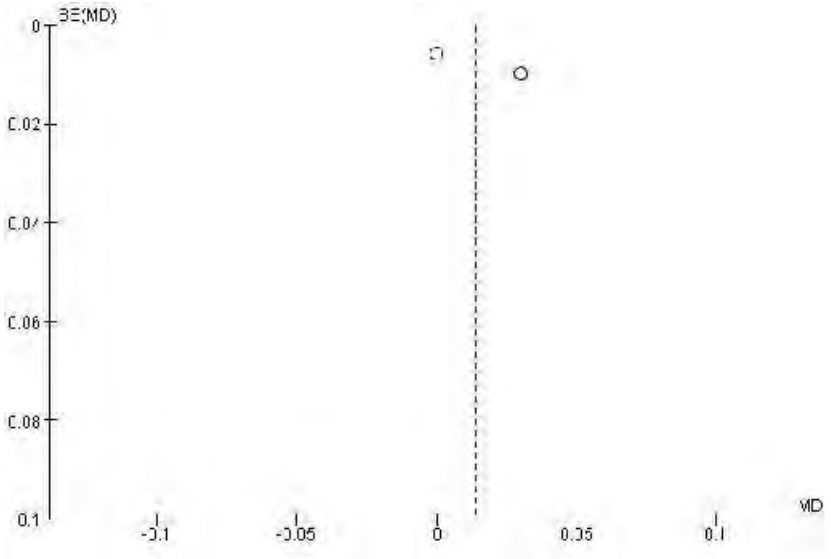
13.12.1. Individual Study Data Table

OUTCOME: QUICKI					OUTCOME TYPE: Continuous					
COMPARISON: Anti-androgen + LS vs MET + LS - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Gambineri 2006 (LRB)	Mg/dL	6 months	0.38	0.03	17	0.35	0.03	20	Crude	N/A
Ganie 2013 (LRB)	Mg/dL	6 months	0.35	0.03	51	0.35	0.03	56	Crude	N/A

13.12.2. Forest Plot of all included RCTs comparing Anti-androgen + LS and MET + LS for QUICKI



13.11.3. Funnel plot for assessment of publication bias



OUTCOME 13.13 – 13.20: FAI, androstenedione, OGTT, HOMA, total cholesterol, HDL, LDL, triglycerides
13.13.1. – 13.20.1 Individual Study Data Tables

OUTCOME: LISTED BELOW					OUTCOME TYPE: Continuous					
COMPARISON: Anti-androgen + LS vs MET + LS - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
OUTCOME: FAI										
Gambineri 2006 (LRB)	Pg/ml	12 months	2.4	2.1	17	3.0	2.2	20	Crude	N/A
OUTCOME: Androstenedione										
Gambineri 2006 (LRB)	Ng/dL	12 months	224	80	17	263	172	20	Crude	N/A
OUTCOME: OGTT										
Amiri 2014 (MRB)	Mg/dL	6 months	102.56	20.1	27	112.1	30.5	25	Crude	N/A
OUTCOME: HOMA										
Ganie 2004 (MRB)	N/A	6 months	5.27	8.81	34	2.55	1.44	35	Crude	N/A
OUTCOME: Total cholesterol										
Amiri 2014 (MRB)	Mmol/L	6 months	178.5	48	27	171.3	23.2	25	Crude	N/A
OUTCOME: HDL										
Amiri 2014 (MRB)#	Mmol/L	6 months	43	12.2	27	41.3	11.3	25	Crude	N/A
Gambineri 2006 (LRB)	Mmol/L	12 months	1.5022	0.23	17	1.295	0.26	20	Crude	N/A
OUTCOME: LDL										
Amiri 2014 (MRB)#	Mmol/L	6 months	105.8	32	27	100.74	19.7	25	Crude	N/A
Gambineri 2006 (LRB)	Mmol/L	12 months	2.27	0.72	17	2.56	0.96	20	Crude	N/A
OUTCOME: Triglycerides										
Amiri 2014 (MRB)#	Mmol/L	6 months	133.6	72	27	122.3	41.1	25	Crude	N/A
Gambineri 2006 (LRB)	Mmol/L	12 months	0.71	0.20	17	0.94	0.59	20	Crude	N/A

meta-analysis not run due to uncertainty in units

COMPARISON 14. Anti-androgen + MET + lifestyle vs MET + lifestyle - ADULTS (6 – 12 MONTHS)

▪ EVIDENCE SUMMARY:

There were four RCTs that addressed the comparison between a combination therapy of an anti-androgen + metformin + lifestyle against metformin + lifestyle in adult women with PCOS with 6-12 months follow-up. Three of the studies were low risk of bias (Gambineri, 2006; Ganie, 2013; Mazza, 2014) and one was moderate risk of bias (Amiri, 2014). The studies were conducted in India, Iran, and Italy.

▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

In meta-analysis, the anti-androgen + metformin + lifestyle intervention was superior for testosterone and fasting glucose, with a very low to low certainty of evidence. In the single study mean difference estimates, the anti-androgen + metformin + lifestyle intervention was superior for insulin sensitivity index, with a low certainty of evidence due to the very small sample size.

There was no difference in weight, BMI, WHR, hirsutism, SHBG, DHEAS, fasting insulin, HDL, LDL, triglycerides, and HOMA-IR in meta-analysis. The certainty in the evidence of these findings ranged from very low to low due to indirectness from being unsure of the population BMI in Amiri 2014, except for DHEAS, LDL, triglycerides that were moderate downgraded for inconsistency or sample size, and HOMA-IR being high. In the single study mean difference estimates, there was no difference in frequency of menstruation, FAI, androstenedione, fasting glucose-insulin ratio, QUICKI, OGTT, and total cholesterol, with a certainty of evidence low for androstenedione, QUICKI, and OGTT due to the risk of bias and/or small samples, except for FAI and total cholesterol that were moderate downgraded due to sample size, and QUICKI and frequency of menstruation being high.

Since the BMIs of the population of Amiri 2014 was uncertain, a sensitivity analysis was conducted to assess the influence of Amiri 2014 on several outcomes. When removing Amiri 2014 from BMI, hirsutism, SHBG, testosterone, the significance obtained remained unchanged. However, when removing Amiri 2014 from WHR, this outcome was then statistically significant, and fasting glucose was no longer statistically significant.

Outcome or Subgroup	Studies	n	Effect Estimate; MD [95% CI], I-V, random	P-value	Favours	Certainty
Weight	3	210	-0.92 kg [-7.30, 5.45]	0.78	None	⊕⊕◯◯ LOW
BMI	4	262	-0.20 kg/m^2 [-1.43, 1.02]	0.74	None	⊕⊕◯◯ LOW
WHR	2	170	-0.00 [-0.06, 0.06]	0.93	None	⊕◯◯◯ VERY LOW
Hirsutism	4	262	-0.58 [-1.86, 0.69]	0.37	None	⊕⊕◯◯ LOW
SHBG	3	144	-0.59 nmol/l [-4.52, 3.34]	0.77	None	⊕⊕◯◯ LOW
Testosterone	4	262	-0.29 nmol/l [-0.52, -0.06]	0.01	AA + MET + LS	⊕◯◯◯ VERY LOW
DHEAS	2	92	-0.24 µg/ml [-0.92, 0.45]	0.50	None	⊕⊕⊕◯ MODERATE
Fasting insulin	3	210	-1.22 µU/ml [-2.87, 0.43]	0.15	None	⊕⊕⊕⊕ HIGH
Fasting glucose	4	262	-2.93 mg/dl [-5.78, -0.09]	0.04	AA + MET + LS	⊕⊕◯◯ LOW

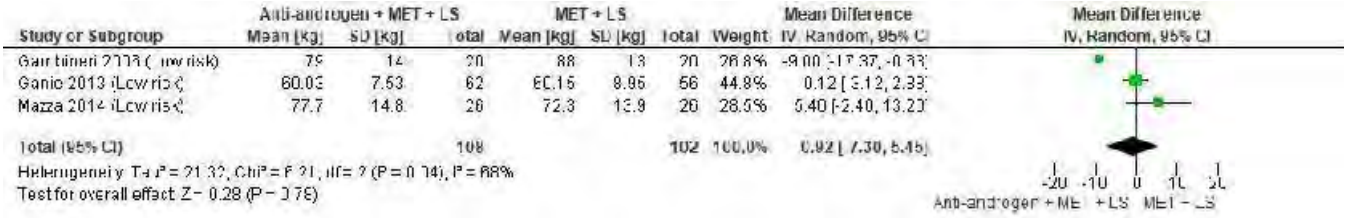
HDL	2	92	1.75 mg/dl [-7.72, 11.23]	0.72	None	⊕⊕◯◯ LOW
LDL	2	92	-8.24 mg/dl [-20.34, 3.86]	0.18	None	⊕⊕⊕◯ MODERATE
Triglycerides	2	92	-5.48 mg/dl [-24.06, 13.10]	0.56	None	⊕⊕⊕◯ MODERATE
HOMA-IR	2	170	-0.22 [-0.67, 0.23]	0.34	None	⊕⊕⊕⊕ HIGH
Frequency of menstruation (No. cycles/y)	1	118	0.84 cycles/year [-0.31, 1.99]	0.15	None	⊕⊕⊕⊕ HIGH
FAI	1	52	-2.10 [-4.47, 0.27]	0.08	None	⊕⊕⊕◯ MODERATE
Androstenedione	1	40	-5.00 ng/dl [-96.42, 86.42]	0.91	None	⊕⊕◯◯ LOW
Fasting glucose-insulin ratio	1	118	1.74 [-1.45, 4.93]	0.28	None	⊕⊕⊕⊕ HIGH
QUICKI	1	40	0.01 [-0.01, 0.03]	0.29	None	⊕⊕◯◯ LOW
OGTT	1	52	-4.88 mg/dl [-20.32, 10.56]	0.54	None	⊕⊕◯◯ LOW
Insulin sensitivity index	1	40	6.90 [2.96, 10.84]	0.0006	AA + MET + LS	⊕⊕◯◯ LOW
Total cholesterol	1	52	0.30 mg/dl [-16.76, 17.36]	0.97	None	⊕⊕⊕◯ MODERATE

OUTCOME 14.1. Weight

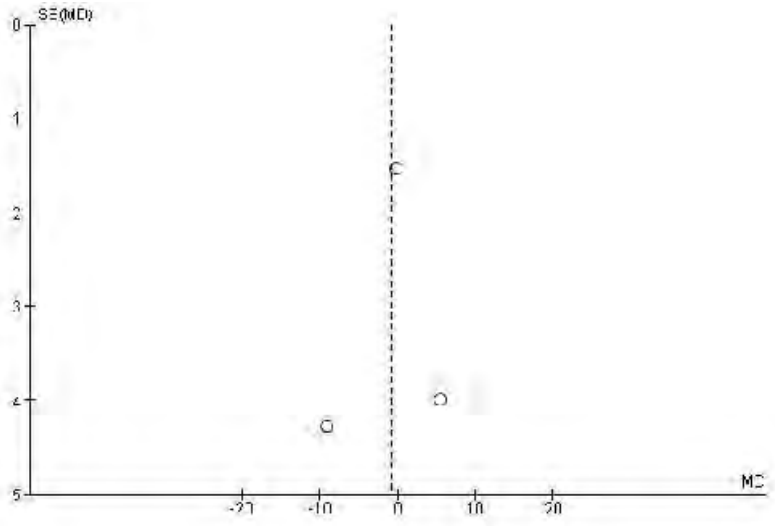
14.1.1. Individual Study Data Table

OUTCOME: Weight					**OUTCOME TYPE: Continuous**					
COMPARISON: Anti-androgen + MET + LS vs MET + LS - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Mazza 2014 (LRB)	kg	6 months	77.7	14.8	26	72.3	13.9	26	Crude	N/A
Ganie 2013 (LRB)	kg	6 months	60.03	7.53	62	60.15	8.95	56	Crude	N/A
Gambineri 2006 (LRB)	kg	12 months	79	14	20	88	13	20	Crude	N/A

14.1.2. Forest Plot of all included RCTs comparing Anti-androgen + LS and MET + LS for weight



14.1.3. Funnel plot for assessment of publication bias

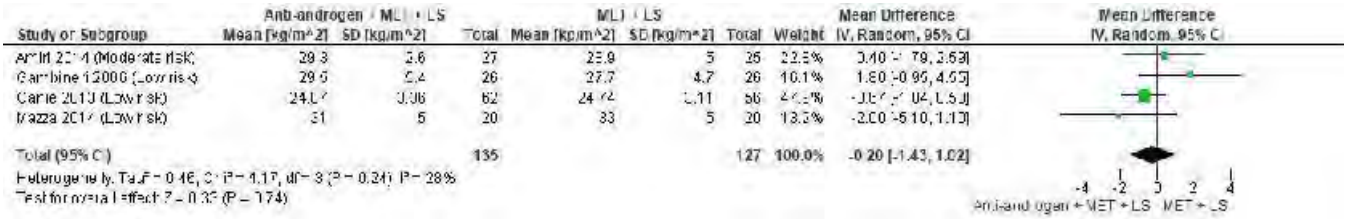


OUTCOME 14.2. BMI

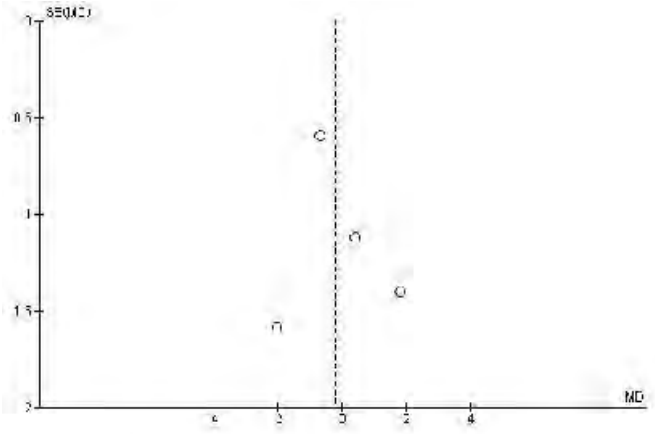
14.2.1. Individual Study Data Table

OUTCOME: BMI					OUTCOME TYPE: Continuous					
COMPARISON: Anti-androgen + MET + LS vs MET + LS - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Amiri 2014 (MRB)	Kg/m^2	6 months	29.3	2.6	27	28.9	5	25	Crude	N/A
Mazza 2014 (LRB)	Kg/m^2	6 months	29.5	5.4	26	27.7	4.7	26	Crude	N/A
Ganie 2013 (LRB)	Kg/m^2	6 months	24.07	3.36	62	24.74	3.11	56	Crude	N/A
Gambineri 2006 (LRB)	Kg/m^2	12 months	31	5	20	33	5	20	Crude	N/A

14.2.2. Forest Plot of all included RCTs comparing Anti-androgen + LS and MET + LS for BMI



14.2.3. Funnel plot for assessment of publication bias

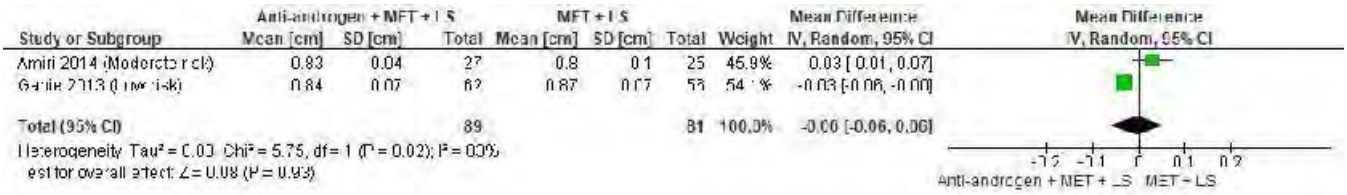


OUTCOME 14.3. WHR

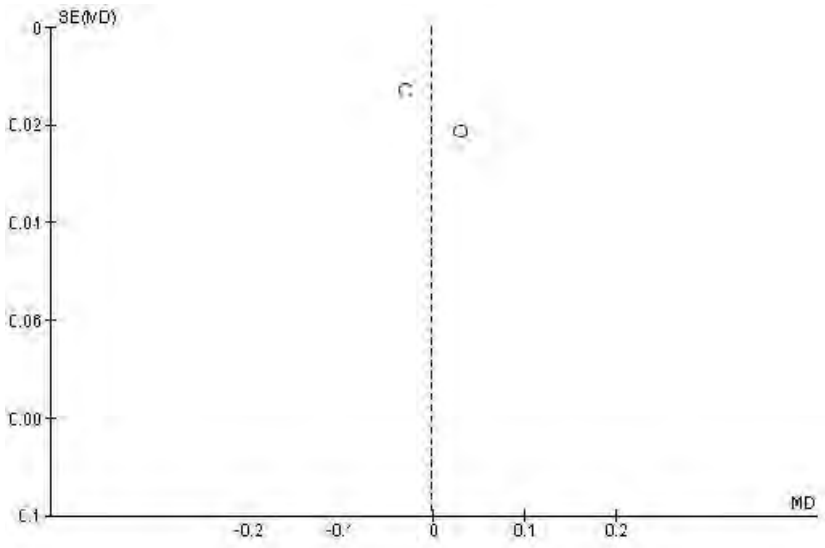
14.3.1. Individual Study Data Table

OUTCOME: WHR					OUTCOME TYPE: Continuous					
COMPARISON: Anti-androgen + MET + LS vs MET + LS - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Amiri 2014 (MRB)	Cm	6 months	0.83	0.04	27	0.8	0.1	25	Crude	N/A
Ganie 2013 (LRB)	cm	6 months	0.84	0.07	62	0.87	0.07	56	Crude	N/A

14.3.2. Forest Plot of all included RCTs comparing Anti-androgen + LS and MET + LS for WHR



14.3.3. Funnel plot for assessment of publication bias

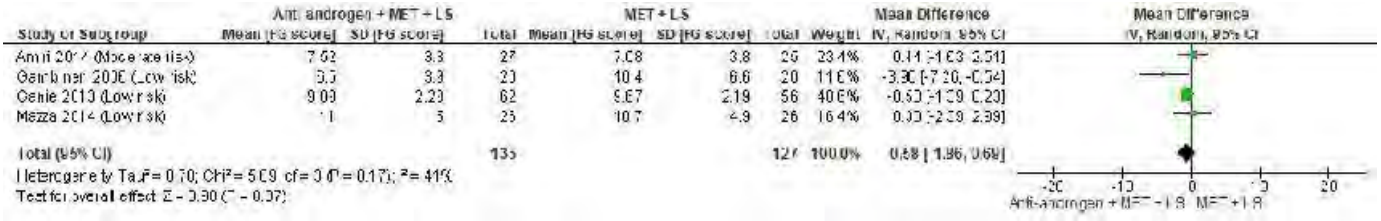


OUTCOME 14.4. Hirsutism

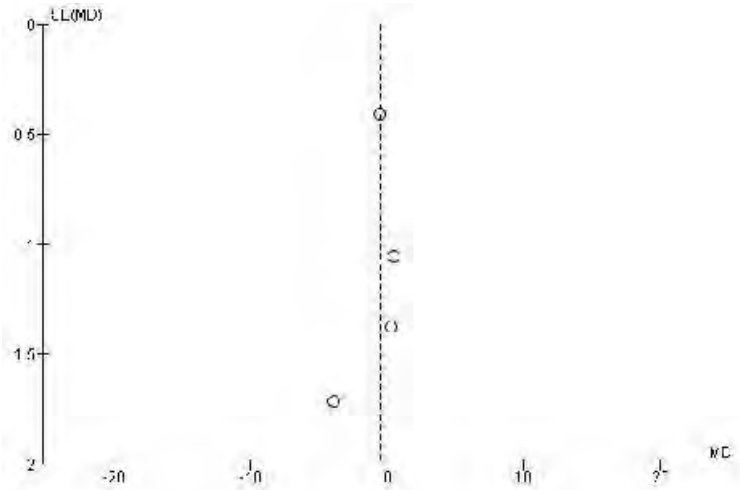
14.4.1. Individual Study Data Table

OUTCOME: Hirsutism					**OUTCOME TYPE: Continuous**					
COMPARISON: Anti-androgen + MET + LS vs MET + LS - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Amiri 2014 (MRB)	FG score	6 months	7.52	3.8	27	7.08	3.8	25	Crude	N/A
Mazza 2014 (LRB)	FG score	6 months	11.0	5.0	26	10.7	4.9	26	Crude	N/A
Ganie 2013 (LRB)	FG score	6 months	9.09	2.29	62	9.67	2.19	56	Crude	N/A
Gambineri 2006 (LRB)	FG score	12 months	6.5	3.9	20	10.4	6.6	20	Crude	N/A

14.4.2. Forest Plot of all included RCTs comparing Anti-androgen + LS and MET + LS for hirsutism



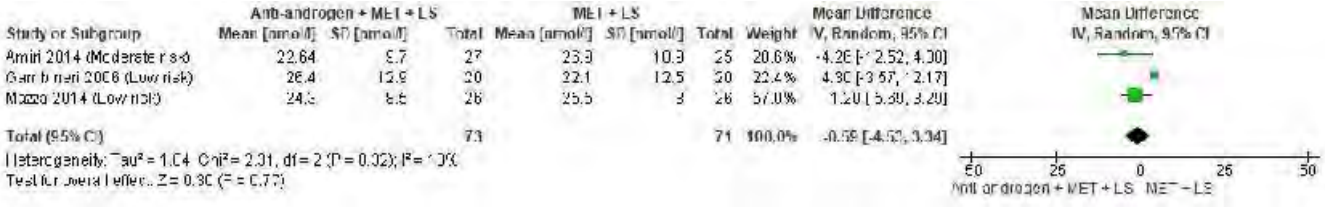
14.4.3. Funnel plot for assessment of publication bias



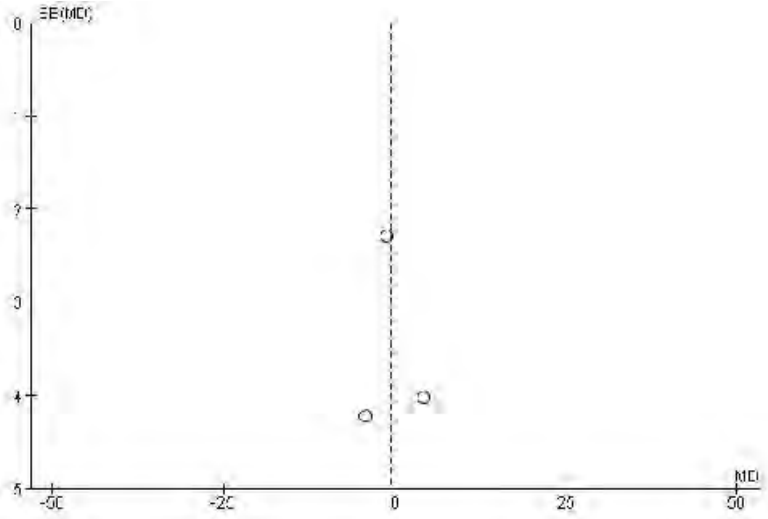
OUTCOME 14.5. SHBG
14.5.1. Individual Study Data Table

OUTCOME: SHBG					**OUTCOME TYPE: Continuous**					
COMPARISON: Anti-androgen + MET + LS vs MET + LS - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Amiri 2014 (MRB)	Nmol/L	6 months	22.64	9.7	27	26.9	18.9	25	Crude	N/A
Mazza 2014 (LRB)	Nmol/L	6 months	24.3	8.5	26	25.5	8.0	26	Crude	N/A
Gambineri 2006 (LRB)	Nmol/L	12 months	26.4	12.9	20	22.1	12.5	20	Crude	N/A

14.5.2. Forest Plot of all included RCTs comparing Anti-androgen + LS and MET + LS for SHBG



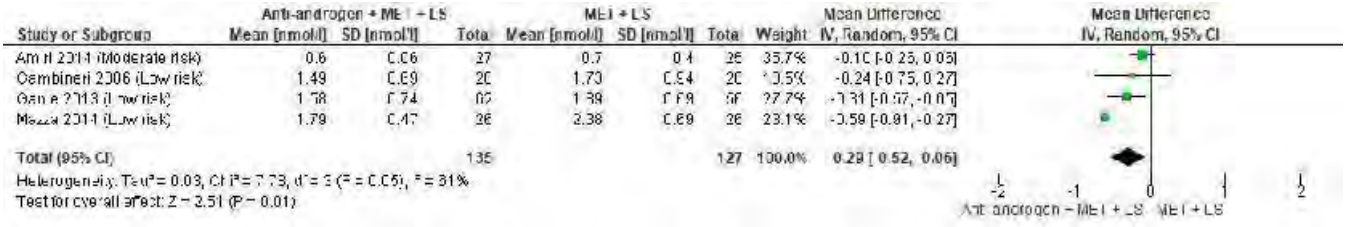
14.5.3. Funnel plot for assessment of publication bias



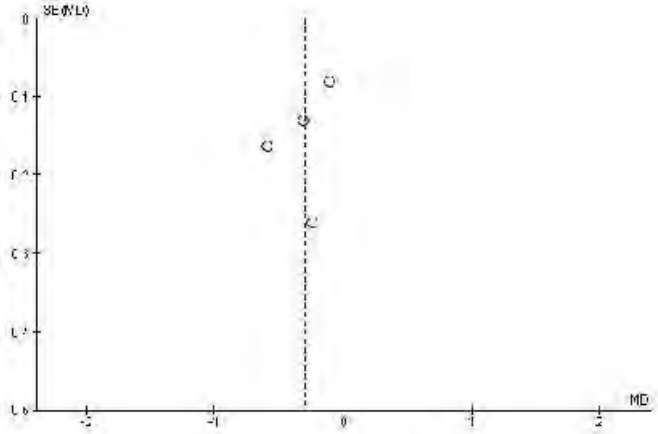
OUTCOME 14.6. Testosterone
14.6.1. Individual Study Data Table

OUTCOME: Testosterone					**OUTCOME TYPE: Continuous**					
COMPARISON: Anti-androgen + MET + LS vs MET + LS - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Amiri 2014 (MRB)	Nmol/L	6 months	0.6	0.06	27	0.7	0.4	25	Crude	N/A
Mazza 2014 (LRB)	Nmol/L	6 months	1.79	0.47	26	2.38	0.69	26	Crude	N/A
Ganie 2013 (LRB)	Nmol/L	6 months	1.58	0.74	62	1.89	0.69	56	Crude	N/A
Gambineri 2006 (LRB)	Nmol/L	12 months	1.49	0.69	20	1.73	0.94	20	Crude	N/A

14.6.2. Forest Plot of all included RCTs comparing Anti-androgen + LS and MET + LS for testosterone



14.6.3. Funnel plot for assessment of publication bias



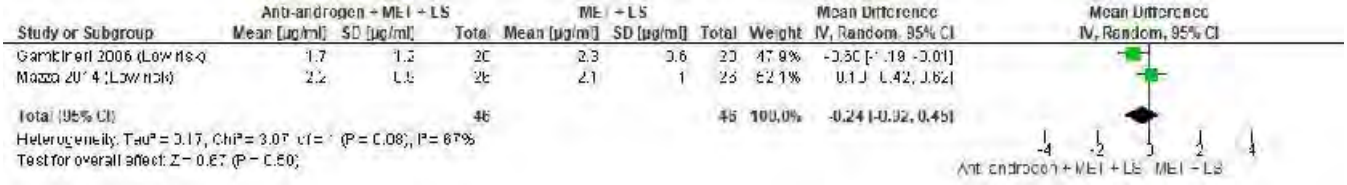
OUTCOME 14.7. DHEAS

14.7.1. Individual Study Data Table

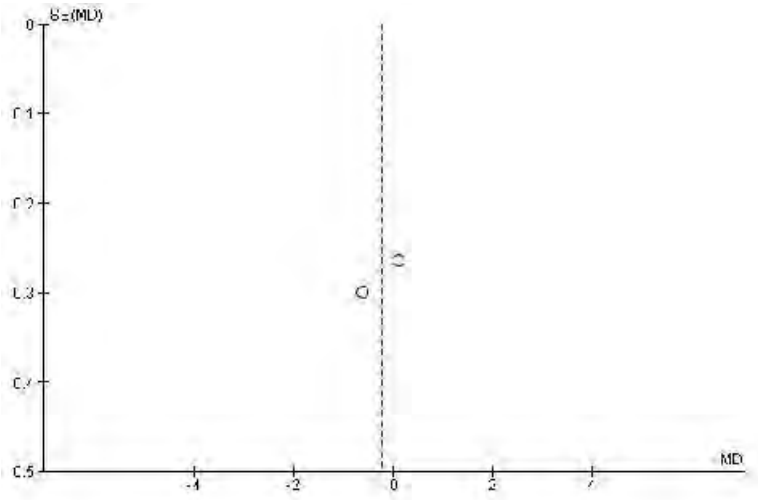
OUTCOME: DHEAS					OUTCOME TYPE: Continuous					
COMPARISON: Anti-androgen + MET + LS vs MET + LS - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Amiri 2014 (LRB)#	µmol/L	6 months	156.08	73.6	27	222.5	129.1	25	Crude	N/A
Mazza 2014 (LRB)	µg/ml	6 months	2.2	0.9	26	2.1	1.0	26	Crude	N/A
Gambineri 2006 (LRB)	µg/ml	12 months	1.7	1.2	20	2.3	0.6	20	Crude	N/A

not included in meta analysis due to uncertainty in units

14.7.2. Forest Plot of all included RCTs comparing Anti-androgen + LS and MET + LS for DHEAS



14.7.3. Funnel plot for assessment of publication bias

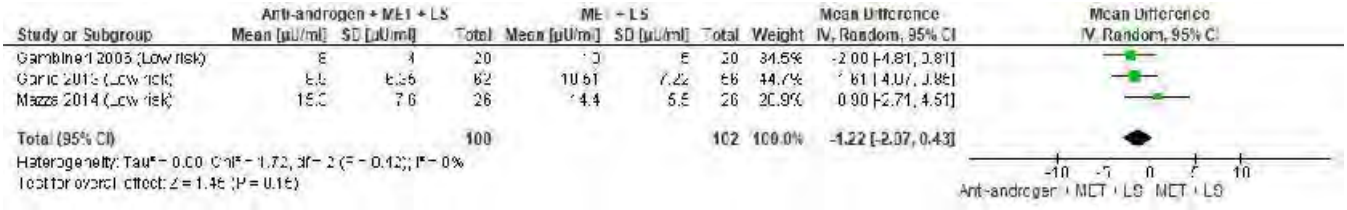


OUTCOME 14.8. Fasting insulin
14.8.1. Individual Study Data Table

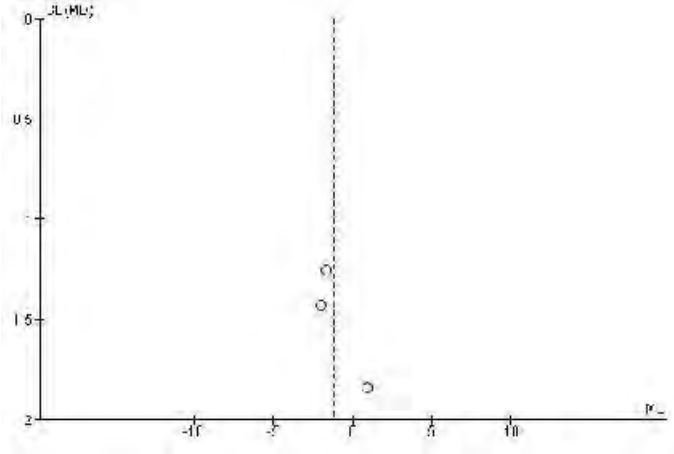
OUTCOME: Fasting insulin					OUTCOME TYPE: Continuous					
COMPARISON: Anti-androgen + MET + LS vs MET + LS - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention / exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Amiri 2014 (MRB)#	Pmol/l	6 months	11.6	6.2	27	13.7	7.1	25	Crude	N/A
Mazza 2014 (LRB)	µU/ml	6 months	15.3	7.6	26	14.4	5.5	26	Crude	N/A
Ganie 2013 (LRB)	µU/ml	6 months	8.9	6.35	62	10.51	7.22	56	Crude	N/A
Gambineri 2006 (LRB)	µU/ml	12 months	8	4	20	10	5	20	Crude	N/A

not included in meta analysis due to uncertainty in units

14.8.2. Forest Plot of all included RCTs comparing Anti-androgen + LS and MET + LS for fasting insulin



14.8.3. Funnel plot for assessment of publication bias

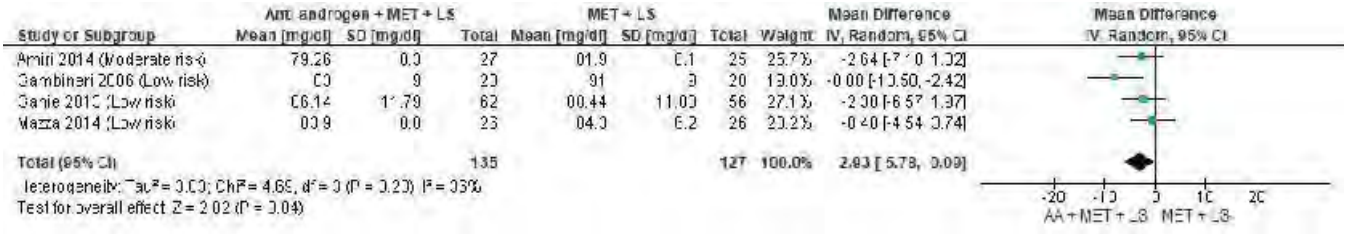


OUTCOME 14.9. Fasting glucose

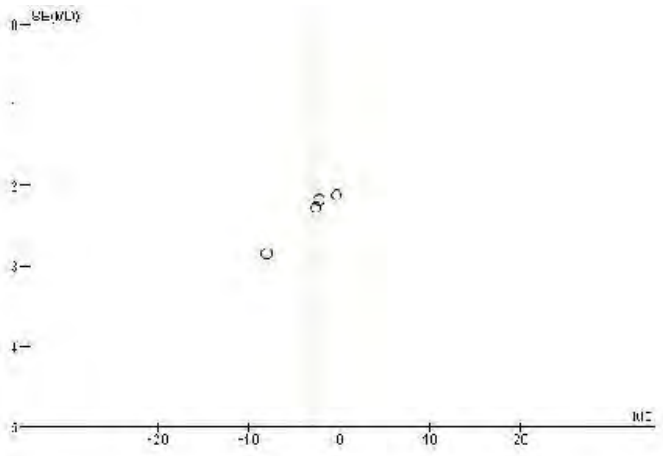
14.9.1. Individual Study Data Table

OUTCOME: Fasting glucose					OUTCOME TYPE: Continuous					
COMPARISON: Anti-androgen + MET + LS vs MET + LS - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention / exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Amiri 2014 (MRB)	Mg/dl	6 months	79.26	8.3	27	81.9	8.1	25	Crude	N/A
Mazza 2014 (LRB)	Mg/dl	6 months	83.9	8.8	26	84.3	6.2	26	Crude	N/A
Ganie 2013 (LRB)	Mg/dl	6 months	86.14	11.79	62	88.44	11.83	56	Crude	N/A
Gambineri 2006 (LRB)	Mg/dl	12 months	83	9	20	91	9	20	Crude	N/A

14.9.2. Forest Plot of all included RCTs comparing Anti-androgen + LS and MET + LS for fasting glucose



14.9.3. Funnel plot for assessment of publication bias

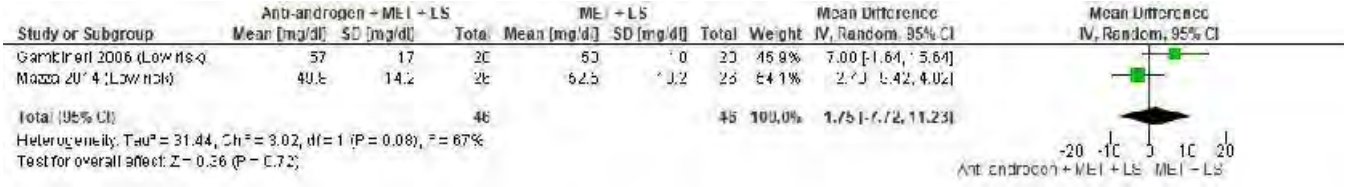


OUTCOME 14.10. HDL
14.10.1. Individual Study Data Table

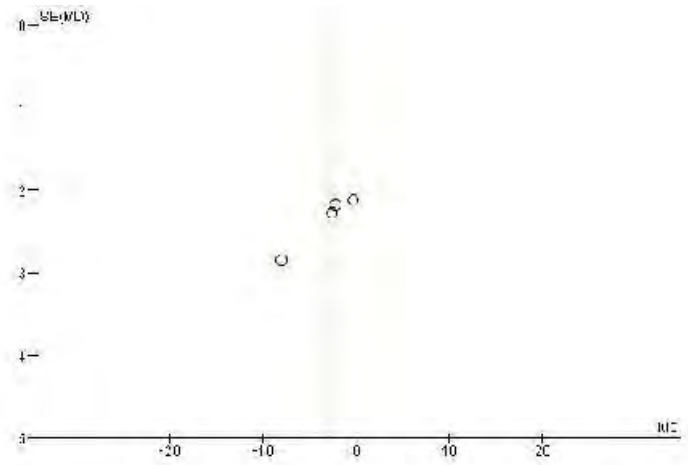
OUTCOME: HDL					OUTCOME TYPE: Continuous					
COMPARISON: Anti-androgen + MET + LS vs MET + LS - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Amiri 2014 (MRB)#	Mmol/L	6 months	37.85	6	27	41.3	11.3	25	Crude	N/A
Mazza 2014 (LRB)	Mg/dL	6 months	49.8	14.2	26	52.5	10.2	26	Crude	N/A
Gambineri 2006 (LRB)	Mg/dL	12 months	57	17	20	50	10	20	Crude	N/A

not included in meta analysis due to uncertainty in units

14.10.2. Forest Plot of all included RCTs comparing Anti-androgen + LS and MET + LS for HDL



14.10.3. Funnel plot for assessment of publication bias



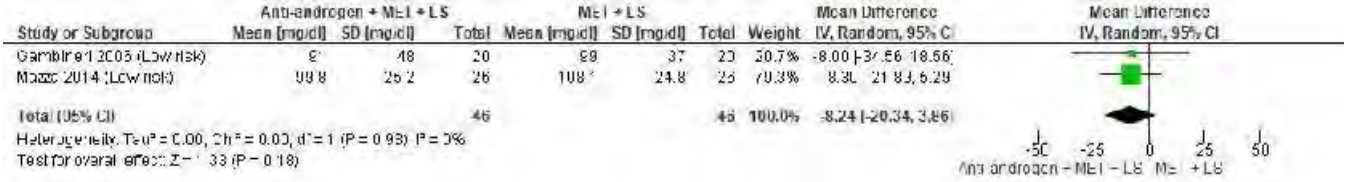
OUTCOME 14.11. LDL

14.11.1. Individual Study Data Table

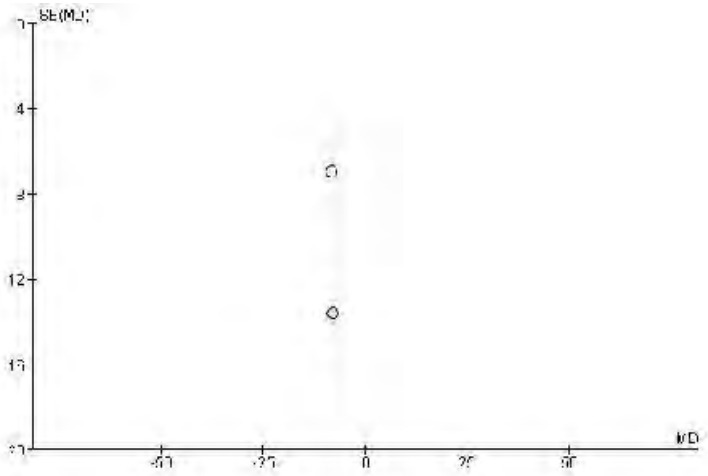
OUTCOME: Weight					OUTCOME TYPE: Continuous					
COMPARISON: Anti-androgen + MET + LS vs MET + LS - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Amiri 2014 (MRB)#	Mmol/L	6 months	121.04	81.2	27	100.74	19.7	25	Crude	N/A
Mazza 2014 (LRB)	Mg/dL	6 months	99.8	25.2	26	108.1	24.8	26	Crude	N/A
Gambineri 2006 (LRB)	Mg/dL	12 months	91	48	20	99	37	20	Crude	N/A

not included in meta analysis due to uncertainty in units

14.11.2. Forest Plot of all included RCTs comparing Anti-androgen + LS and MET + LS for LDL



14.11.3. Funnel plot for assessment of publication bias

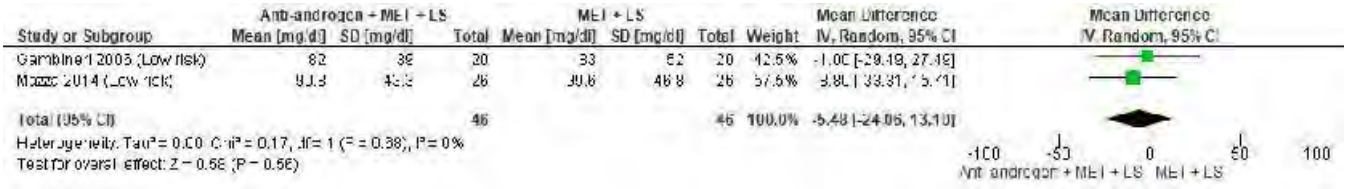


OUTCOME 14.12. Triglycerides
14.12.1. Individual Study Data Table

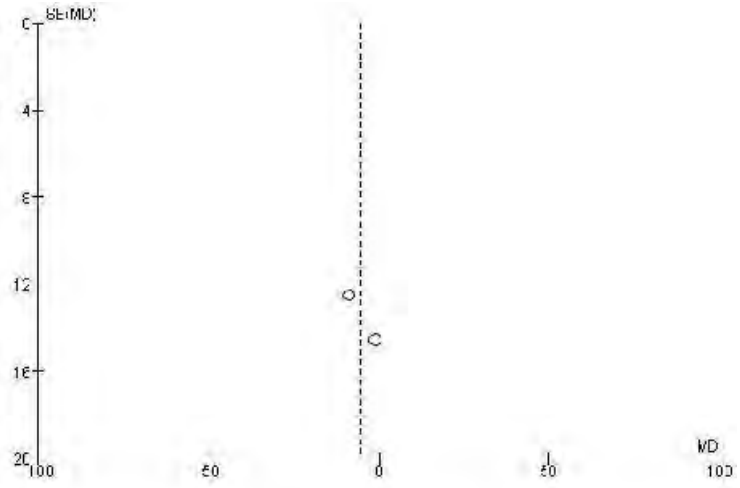
OUTCOME: Triglycerides					OUTCOME TYPE: Continuous					
COMPARISON: Anti-androgen + MET + LS vs MET + LS - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Amiri 2014 (MRB)#	Mmol/L	6 months	140.6	65.9	27	122.3	41.1	25	Crude	N/A
Mazza 2014 (LRB)	Mg/dL	6 months	90.8	43.3	26	99.6	46.8	26	Crude	N/A
Gambineri 2006 (LRB)	Mg/dL	12 months	82	39	20	83	52	20	Crude	N/A

not included in meta analysis due to uncertainty in units

14.12.2. Forest Plot of all included RCTs comparing Anti-androgen + LS and MET + LS for triglycerides



14.12.3. Funnel plot for assessment of publication bias

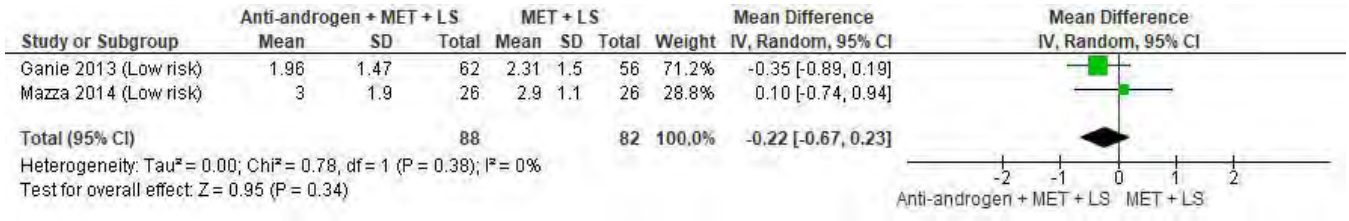


OUTCOME 14.14. HOMA-IR

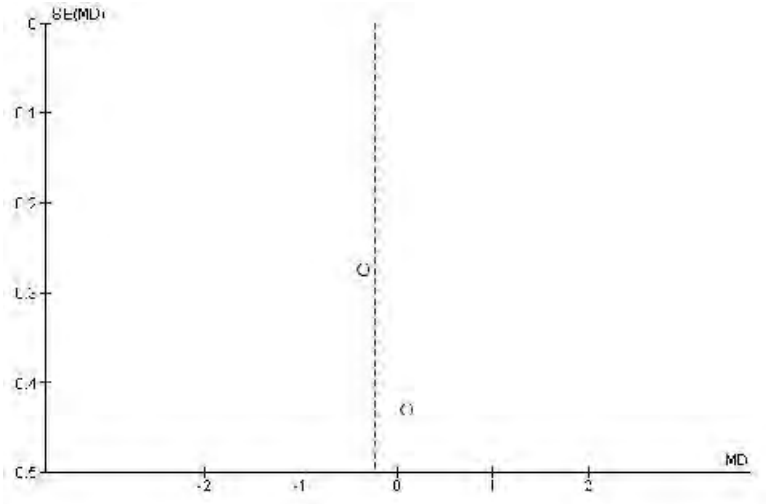
14.14.1. Individual Study Data Table

OUTCOME: HOMA-IR					OUTCOME TYPE: Continuous					
COMPARISON: Anti-androgen + MET + LS vs MET + LS - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Mazza 2014 (LRB)	N/A	6 months	3.0	1.9	26	2.9	1.1	26	Crude	N/A
Ganie 2013 (LRB)	N/A	6 months	1.96	1.47	62	2.31	1.5	56	Crude	N/A

14.14.2. Forest Plot of all included RCTs comparing Anti-androgen + LS and MET + LS for HOMA-IR



14.14.3. Funnel plot for assessment of publication bias



OUTCOME 14.15 - 14.22: Frequency of menstruation, FAI, androstenedione, fasting glucose-insulin ratio, QUICKI, OGTT, insulin sensitivity index, total cholesterol
14.15.1 – 14.22.1. Individual Study Data Tables

OUTCOME: LISTED BELOW					**OUTCOME TYPE: Continuous**					
COMPARISON: Anti-androgen + MET + LS vs MET + LS - ADULTS										
Author, year	Unit of outcome (e.g. g, mg)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
OUTCOME: Frequency of menstruation										
Ganie 2013 (LRB)	No. cycles/year	6 months	10.86	3.20	62	10.02	3.16	56	Crude	N/A
Gambineri 2006 (LRB)	No. of cycles previous 6 months	12 months	5.8	0.7	20	4.6	1.8	20	Crude	N/A
OUTCOME: FAI										
Mazza 2014 (LRB)	100*T/SHBG	6 months	8.2	3.6	26	10.3	5.0	26	Crude	N/A
Gambineri 2006 (LRB)#	Pg/ml	12 months	1.9	0.9	20	3.0	2.2	20	Crude	N/A
OUTCOME: Androstenedione										
Gambineri 2006 (LRB)	Ng/dL	12 months	258	118	20	263	172	20	Crude	N/A
OUTCOME: Fasting glucose-insulin ratio										
Ganie 2013 (LRB)	Mg/dL	6 months	13.59	9.04	62	11.85	8.61	56	Crude	N/A
OUTCOME: QUICKI										
Gambineri 2006 (LRB)	N/A	12 months	0.36	0.03	20	0.35	0.03	20	Crude	N/A
OUTCOME: OGTT										
Amiri 2014 (MRB)	Mg/dL	6 months	107.22	25.9	27	112.1	30.5	25	Crude	N/A
OUTCOME: Insulin sensitivity index										
Gambineri 2006	Mg/ml	12 months	11.9	8.6	20	5.0	2.6	20	Crude	N/A

(LRB)										
OUTCOME: Total cholesterol										
Amiri 2014 (MRB)#	Mmol/L	6 months	180.74	40.8	27	171.3	23.2	25	Crude	N/A
Mazza 2014 (LRB)	Mg/dL	6 months	165.2	34.6	26	164.9	27.8	26	Crude	N/A

did not run meta-analysis due to unit reporting or uncertainty with units.

5. GRADE ASSESSMENTS AND EVIDENCE PROFILE

COMPARISON 1: Anti-androgen vs placebo – ADOLESCENTS (6 months)											
	Quality assessment					No of participants					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**AA**	**PLAC**	**Effect, random, MD [95% CI]**	**Favours**	**Certainty**	**Importance**
Outcome: Body mass index											
1	RCT	Very serious[1]	Not applicable	Not applicable	Very Serious[2]	7	7	MD: 0.50 kg/m^2 [-3.64, 4.64]	None	⨁◯◯◯ VERY LOW	CRITICAL
Outcome: Hirsutism											
1	RCT	Very serious[1]	Not applicable	Not applicable	Very Serious[2]	7	7	MD: 16.20 [11.99, 20.41]	Anti-androgen	⨁◯◯◯ VERY LOW	CRITICAL
Outcome: SHBG											
1	RCT	Very serious[1]	Not applicable	Not applicable	Very Serious[2]	7	7	MD: 0.00 µg/ml [-1.27, 1.27]	None	⨁◯◯◯ VERY LOW	IMPORTANT
Outcome: Testosterone											
1	RCT	Very serious[1]	Not applicable	Not applicable	Very Serious[2]	7	7	MD: 0.30 ng/dl [-2.27, 2.87]	None	⨁◯◯◯ VERY LOW	IMPORTANT
Outcome: DHEAS											
1	RCT	Very serious[1]	Not applicable	Not applicable	Very Serious[2]	7	7	MD: 0.60 µmol/l [0.07, 1.13]	Anti-androgen	⨁◯◯◯ VERY LOW	IMPORTANT
Outcome: Androstenedione											
1	RCT	Very serious[1]	Not applicable	Not applicable	Very Serious[2]	7	7	MD: -0.10 ng/ml [-1.58, 1.38]	None	⨁◯◯◯ VERY LOW	IMPORTANT

1 Downgraded twice as the single study is high RoB

2 Downgraded twice due to the very small sample size/participants

COMPARISON 2: Anti-androgen (every day) vs Anti-androgen (every 3 days) – ADULTS (6 months to 12 months)											
	Quality assessment					No of participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Daily AA	Every 3d AA	Effect, random, MD or OR	Favours	Certainty	Importance
Outcome: Hirsutism											
2	RCT	Very serious[1]	No serious inconsistency	No serious	Serious imprecision[3]	40	40	MD: -3.48 [-4.58, -2.39]	Daily Anti-androgen	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Body mass index											
1	RCT	Very serious[5]	Not applicable	Not applicable	Very serious imprecision[3]	8	8	MD: 0.30 kg/m^2 [-3.67, 4.27]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: SHBG											
2	RCT	Very serious[1]	No serious inconsistency	Not applicable	Serious imprecision[3]	40	40	MD: 0.29 nmol/l [-2.18, 2.76]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Androstenedione											
2	RCT	Very serious[1]	No serious inconsistency	Not applicable	Very serious imprecision[3,4]	40	40	MD: -0.30 ng/ml [-0.50, -0.10]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Testosterone											
2	RCT	Very serious[1]	Very serious incosistency[2]	Not applicable	Serious imprecision[3]	40	40	MD: -0.25 ng/ml [-0.73, 0.23]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: DHEAS											
2	RCT	Very serious[1]	Very serious incosistency[2]	Not applicable	Serious imprecision[3]	40	40	MD: 0.19 µg/ml [-0.79, 1.17]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Fasting insulin											
1	RCT	Very serious[5]	Not applicable	Not applicable	Serious imprecision[3]	32	32	MD: 0.70 µU/ml [-0.17, 1.57]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Dry skin											
1	RCT	Very serious[5]	Not applicable	Not applicable	Serious imprecision[3]	32	32	OR: 6.60 [2.21, 19.73]	Daily Anti-androgen	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Decreased libido											
1	RCT	Very serious[5]	Not applicable	Not applicable	Serious imprecision[3]	32	32	OR: 1.62 [0.41, 6.38]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Headache											
1	RCT	Very serious[5]	Not applicable	Not applicable	Serious imprecision[3]	32	32	OR: 0.23 [0.02, 2.14]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT

1 Downgraded twice as both studies are high risk of bias

2 Downgraded twice due to no overlapping CIs, and statistically significant heterogeneity

3 Downgraded once due to small sample size or twice for very small sample size

4 Downgraded due to indirectness because of one study

5 Downgraded twice due to single study assessed is high RoB

COMPARISON 3: Anti-androgen + LS vs Placebo + LS – ADULTS (6 months to 12 months)											
	Quality assessment					No of participants					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**AA + LS**	**PLAC + LS**	**Effect, random**	**Favours**	**Certainty**	**Importance**
Outcome: BMI											
2[1]	RCT	No serious	Serious inconsistency[3]	Serious[7]	Serious imprecision[5]	44	45	MD: -3.08 kg/m^2 [-8.67, 2.50]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Hirsutism											
2[1]	RCT	No serious	Serious inconsistency[3]	Serious[7]	Serious imprecision[5]	44	45	MD: -0.93 [-3.37, 1.51]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Weight											
1[6]	RCT	No serious	Not applicable	Not applicable	Very serious imprecision[5]	17	19	MD: -17.00 kg [-25.37, -8.63]	AA + LS	⊕⊕◯◯ LOW	CRITICAL
Outcome: Frequency of menstruation											
1[6]	RCT	No serious	Not applicable	Not applicable	Very serious imprecision[5]	17	19	MD: -0.80 [-1.54, -0.06]	AA + LS	⊕⊕◯◯ LOW	CRITICAL
Outcome: SHBG											
2[1]	RCT	No serious	No serious inconsistency	Serious[7]	Serious imprecision[5]	44	45	MD: 9.72 nmol/l [-0.71, 20.14]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: FAI											
1[6]	RCT	No serious	Not applicable	Not applicable	Very serious imprecision[5]	17	19	MD: -0.80 [-2.34, 0.74]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Testosterone											
1[6]	RCT	No serious	Not applicable	Not applicable	Very serious imprecision[5]	17	19	MD: 0.05 ng/ml [-0.05, 0.15]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: DHEAS											
1[6]	RCT	No serious	Not applicable	Not applicable	Very serious imprecision[5]	17	19	MD: -2.34 µg/ml [-4.06, -0.62]	AA + LS	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Androstenedione											
1[6]	RCT	No serious	Not applicable	Not applicable	Very serious imprecision[5]	17	19	MD: -18.00 ng/ml [-74.86. 38.86]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Fasting insulin											
1[6]	RCT	No serious	Not applicable	Not applicable	Very serious imprecision[5]	17	19	MD: -4.00 µU/ml [-6.98, -1.02]	AA + LS	⊕⊕◯◯ LOW	IMPORTANT

Outcome: HOMA											
1[6]	RCT	No serious	Not applicable	Not applicable	Very serious imprecision[5]	17	19	MD: 1.60 [-1.64, 4.84]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Fasting glucose											
1[6]	RCT	No serious	Not applicable	Not applicable	Very serious imprecision[5]	17	19	MD: 0.00 mg/ml [-5.24, 5.24]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: QUICKI											
1[6]	RCT	No serious	Not applicable	Not applicable	Very serious imprecision[5]	17	19	MD: 0.04 [0.02, 0.06]	PLAC +LS	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Insulin sensitivity index											
1[6]	RCT	No serious	Not applicable	Not applicable	Very serious imprecision[5]	17	19	MD: 5.10 [2.32, 7.88]	PLAC +LS	⊕⊕◯◯ LOW	IMPORTANT
Outcome: HDL											
1[6]	RCT	No serious	Not applicable	Not applicable	Very serious imprecision[5]	17	19	MD: 5.00 mg/dl [-1.54, 11.54]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: LDL											
1[6]	RCT	No serious	Not applicable	Not applicable	Very serious imprecision[5]	17	19	MD: -21.00 mg/dl [-40.93, -1.07]	AA + LS	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Triglycerides											
1[6]	RCT	No serious	Not applicable	Not applicable	Very serious imprecision[5]	17	19	MD: -50.00 mg/dl [-77.60, -22.40]	AA + LS	⊕⊕◯◯ LOW	IMPORTANT

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1 Gambineri 2006, Amiri 2014

2 Not downgraded as evidence is either low or moderate risk, and the study with low risk has a weighting of 64.9%.

3 Downgraded once due to statistically significant heterogeneity

5 Downgraded once due to small sample size or twice for very small sample.

6 Gambineri 2006 (low risk of bias study).

7 Downgraded for indirectness as Amiri 2014 stated it was an overweight population, but the study has an inclusion of women with BMI 19 to 35 (not reporting BMIs), thus indicating this population could include lean women, whereas Gambineri 2006 is an overweight population with reported BMIs.

COMPARISON 4: Anti-androgen + LS vs Anti-androgen + MET + LS – ADULTS (6 months to 12 months)											
	Quality assessment					No of participants					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**AA + LS**	**AA + MET + LS**	**Effect, random**	**Favours**	**Certainty**	**Importance**
Outcome: BMI											
3	RCT	Serious[1]	No serious	Serious[7]	No serious	95	109	MD: -0.05 kg/m^2 [-1.21, 1.11]	No difference	⨁⨁◯◯ LOW	CRITICAL
Outcome: Hirsutism											
3	RCT	Serious[1]	Serious[2,3]	Serious[7]	No serious	95	109	MD: -0.84 [-2.71, 1.03]	No difference	⨁◯◯◯ VERY LOW	CRITICAL
Outcome: Weight											
1	RCT	No serious	Not applicable	Not applicable	Serious[6]	51	62	MD: 1.11 kg [-1.97, 4.19]	No difference	⨁⨁⨁◯ MODERATE	CRITICAL
Outcome: SHBG											
2	RCT	Serious[1]	Serious[3]	Serious[7]	Very serious[5,6]	44	47	MD: 8.88 nmol/l [-7.01, 24.78]	No difference	⨁◯◯◯ VERY LOW	IMPORTANT
Outcome: Testosterone											
3	RCT	Serious[1]	No serious	Serious[7]	No serious	95	109	MD: 0.05 nmol/l [-0.15, 0.24]	No difference	⨁⨁◯◯ LOW	IMPORTANT
Outcome: Fasting insulin											
2	RCT	No serious	No serious	No serious	No serious	68	82	MD: -0.18 µIU/ml [-1.94, 1.59]	No difference	⨁⨁⨁⨁ HIGH	IMPORTANT
Outcome: Fasting glucose											
3	RCT	Serious[1]	No serious	Serious[7]	No serious	95	109	MD: 3.81 mg/dl [1.35, 6.28]	AA + LS	⨁⨁◯◯ LOW	IMPORTANT
Outcome: QUICKI											
2	RCT	No serious	Very serious[2,3]	No serious	No serious	68	82	MD: 0.00 [-0.03, 0.03]	No difference	⨁⨁◯◯ LOW	IMPORTANT
Outcome: WHR											
1	RCT	No serious	Not applicable	Not applicable	No serious	51	62	MD: 0.05 [0.03, 0.07]	AA + LS	⨁⨁⨁⨁ HIGH	IMPORTANT
Outcome: Total cholesterol											
1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[5,6]	27	27	MD: -2.24 mg/dl [-26.00, 21.52]	No difference	⨁◯◯◯ VERY LOW	IMPORTANT
Outcome: FAI											

1	RCT	No serious	Not applicable	Not applicable	Very Serious[5]	17	20	MD: 0.50 [-0.57, 1.57]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: DHEAS											
1	RCT	No serious	Not applicable	Not applicable	Very Serious[5]	17	20	MD: -0.20 µg/ml [-0.82, 0.42]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Androstenedione											
1	RCT	No serious	Not applicable	Not applicable	Very serious[5,6]	17	20	MD: -34.00 ng/ml [-98.19, 30.19]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Triglycerides											
1	RCT	No serious	Not applicable	Not applicable	Very serious[5,6]	17	20	MD: -19.00 mg/dl [-38.11, 0.11]	AA + LS	⊕⊕◯◯ LOW	IMPORTANT
Outcome: HDL											
1	RCT	No serious	Not applicable	Not applicable	Very serious[5,6]	17	20	MD: 1.00 mg/dl [-7.59, 9.59]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: HOMA-IR											
1	RCT	No serious	Not applicable	Not applicable	No serious	51	62	MD: 0.60 [-0.04, 1.24]	No difference	⊕⊕⊕⊕ HIGH	IMPORTANT

1 Downgraded once as Amiri 2014 is moderate risk of bias and has sufficient weighting OR only identified study is moderate RoB

2 Downgraded once as one study or more has no overlapping CIs

3 Downgraded once due to statistical heterogeneity

5 Downgraded due to small sample size or very small sample size

6 Downgraded due to wide CIs

7 Downgraded for indirectness as Amiri 2014 stated it was an overweight population, but the study has an inclusion of women with BMI 19 to 35 (not reporting BMIs), thus indicating this population could include lean women, whereas Gambineri 2006 is an overweight population with reported BMIs.

COMPARISON 5: Anti-androgen vs MET – ADULTS (12 months) (also in metformin question, 4.3).											
	Quality assessment					No of participants					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Met**	**OCP**	**Effect, fixed**	**Favours**	**Certainty**	**Importance**
Outcome: BMI											
1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	16	19	MD: -0.20 kg/m^2 [-2.37, 1.97]	No difference	⨁◯◯◯ VERY LOW	CRITICAL
Outcome: Hirsutism											
1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	16	19	MD: 0.60 [-2.80, 4.00]	No difference	⨁◯◯◯ VERY LOW	CRITICAL
Outcome: SHBG											
1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	16	19	MD: 11.50 nmol/l [-0.08, 23.08]	MET	⨁◯◯◯ VERY LOW	IMPORTANT
Outcome: Free testosterone											
1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	16	19	MD: -0.30 pg/ml [-0.85, 0.25]	No difference	⨁◯◯◯ VERY LOW	IMPORTANT
Outcome: DHEAS											
1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	16	19	MD: -669.00 ng/ml [-1430.65, 92.65]	No difference	⨁◯◯◯ VERY LOW	IMPORTANT
Outcome: Androstenedione											
1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	16	19	MD: 0.30 ng/ml [-0.13, 0.73]	No difference	⨁◯◯◯ VERY LOW	IMPORTANT
Outcome: HOMA-IR											
1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	16	19	MD: -0.20 [-0.88, 0.48]	No difference	⨁◯◯◯ VERY LOW	IMPORTANT

1 Downgrading twice as only study assessed is high RoB

2 Downgrading twice as very small sample size

COMPARISON 6: Anti-androgen vs Anti-androgen + MET – ADULTS (12 months) (also in metformin question, 4.3).											
	Quality assessment					No of participants					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**AA**	**AA + MET**	**Effect, fixed**	**Favours**	**Certainty**	**Importance**
Outcome: BMI											
1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	16	17	MD: 0.10 kg/m^2 [-2.25, 2.45]	No difference	⨁◯◯◯ VERY LOW	CRITICAL
Outcome: Hirsutism											
1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	16	17	MD: -0.40 [-4.05, 3.25]	No difference	⨁◯◯◯ VERY LOW	CRITICAL
Outcome: SHBG											
1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	16	17	MD: -1.00 nmol/l [-14.72, 12.72]	No difference	⨁◯◯◯ VERY LOW	IMPORTANT
Outcome: Free testosterone											
1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	16	17	MD: 0.10 pg/ml [-0.52, 0.72]	No difference	⨁◯◯◯ VERY LOW	IMPORTANT
Outcome: DHEAS											
1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	16	17	MD: -198 ng/ml [-941.98, 545.98]	No difference	⨁◯◯◯ VERY LOW	IMPORTANT
Outcome: Androstenedione											
1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	16	17	MD: 0.30 ng/ml [-0.14, 0.74]	No difference	⨁◯◯◯ VERY LOW	IMPORTANT
Outcome: HOMA-IR											
1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[2]	16	17	MD: -0.40 [-1.07, 0.27]	No difference	⨁◯◯◯ VERY LOW	IMPORTANT

1 Downgrading twice as only study assessed is high RoB

2 Downgrading twice as very small sample size

COMPARISON 7: Anti-androgen vs COCP – ADULTS (12 months) **(also in COCP question, 4.2)**											
	Quality assessment					No of participants					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**AA**	**COCP**	**Effect, fixed**	**Favours**	**Certainty**	**Importance**
Outcome: Hirsutism											
1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	10	9	MD: 4.00 [1.21, 6.79]	Anti-androgen	⊕◯◯◯ VERY LOW	CRITICAL

1 Downgrading twice as only study assessed is high RoB

2 Downgrading twice for very small sample size

COMPARISON 8: Anti-androgen + Pioglitazone + MET (SPIOMET) vs COCP (12 months) – ADOLESCENTS (also in COCP and metformin questions, 4.2, 4.3).											
	Quality assessment					No of participants					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**SPIOMET**	**COCP**	**Effect, fixed**	**Favours**	**Certainty**	**Importance**
Outcome: BMI											
1	RCT	Serious[1]	Not applicable	Not applicable	Serious[2]	31	31	MD: -1.00 kg/m^2 [-3.08, 1.08]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Hirsutism											
1	RCT	Serious[1]	Not applicable	Not applicable	Serious[2]	31	31	MD: -3.00 [-5.77, -0.23]	SPIOMET	⊕⊕◯◯ LOW	CRITICAL
Outcome: ALT											
1	RCT	Serious[1]	Not applicable	Not applicable	Serious[2]	31	31	MD: -0.09 µkat/L [-0.16, -0.02]	SPIOMET	⊕⊕◯◯ LOW	CRITICAL
Outcome: AST											
1	RCT	Serious[1]	Not applicable	Not applicable	Serious[2]	31	31	MD: 0.00 [-0.06, 0.06]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Waist circumference											

1	RCT	Serious[1]	Not applicable	Not applicable	Serious[2]	31	31	MD: -4.00 cm [-8.38, 0.38]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: SHBG											
1	RCT	Serious[1]	Not applicable	Not applicable	Serious[2]	31	31	MD: -29.00 nmol/l [-39.56, -18.44]	SPIOMET	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Testosterone											
1	RCT	Serious[1]	Not applicable	Not applicable	Serious[2]	31	31	MD: -0.10 nmol/l [-0.38, 0.18]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Androstenedione											
1	RCT	Serious[1]	Not applicable	Not applicable	Serious[2]	31	31	MD: 1.00 nmol/l [0.29,1.71]	SPIOMET	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Fasting insulin											
1	RCT	Serious[1]	Not applicable	Not applicable	Serious[2]	31	31	MD: -62.00 pmol/l [-81.40, -42.60]	SPIOMET	⊕⊕◯◯ LOW	IMPORTANT
Outcome: HOMA-IR											
1	RCT	Serious[1]	Not applicable	Not applicable	Serious[2]	31	31	MD: -1.80 [-2.42, -1.18]	SPIOMET	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Triglycerides											
1	RCT	Serious[1]	Not applicable	Not applicable	Serious[2]	31	31	MD: -0.08 nmol/l [-0.22, 0.06]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: LDL											
1	RCT	Serious[1]	Not applicable	Not applicable	Serious[2]	31	31	MD: -0.50 mmol/l [-0.78, -0.22]	SPIOMET	⊕⊕◯◯ LOW	IMPORTANT
Outcome: HDL											
1	RCT	Serious[1]	Not applicable	Not applicable	Serious[2]	31	31	MD: 0.10 mmol/l [-0.18. 0.38]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: CRP											
1	RCT	Serious[1]	Not applicable	Serious[3]	Serious[2]	31	31	MD: -18.10 mmol/l [-25, 75, -10.45]	SPIOMET	⊕⊕◯◯ LOW	IMPORTANT
Outcome: FAI											
1	RCT	Serious[1]	Not applicable	Not applicable	Serious[2]	29	29	MD: -2.20 [-4.38, -0.02]	SPIOMET	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Acne											
1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	18	18	MD: -0.30 [-3.07, 2.46]	No difference	⊕⊕◯◯ LOW	IMPORTANT

1 Downgraded once as single study is moderate risk of bias

2 Downgraded once due sample size/participants

COMPARISON 9: Anti-androgen + MET vs COCP – ADOLESCENTS (9 months) (also in COCP and metformin questions, 4.2, 4.3)											
	Quality assessment					No of participants					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**AA + MET**	**COCP**	**Effect, random**	**Favours**	**Certainty**	**Importance**
Outcome: BMI											
1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	16	16	MD: -0.50 kg/m^2 [-2.03, 1.03]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Hirsutism											
1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	16	16	MD: -0.50 [-2.73, 1.73]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Fasting glucose/insulin ratio											
1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	16	16	MD: 2.40 [-0.93, 5.73]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: SHBG											
1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	16	16	MD: -3.40 µg/dl [-4.21, -2.59]	AA + MET	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Testosterone											
1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	16	16	MD: -5.00 ng/dl [-23.91, 16.91]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Triglycerides											
1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	16	16	MD: -44.00 mg/dl [-61.53, -26.47]	AA + MET	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: HDL											
1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	16	16	MD: -9.00 mg/dl [-17.77, -0.23]	AA + MET	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: LDL											
1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	16	16	MD: -26.00 mg/dl [-42.86, -9.14]	AA + MET	⊕◯◯◯ VERY LOW	IMPORTANT

1 Downgraded once as the single study is moderate RoB

2 Downgraded twice due to very low sample size

COMPARISON 10: Anti-androgen + MET + COCP vs COCP – ADULTS (9 months) (also in metformin and COCP questions, 4.2, 4.3).											
	Quality assessment					No of participants					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**AA + MET+ COCP**	**COCP**	**Effect, fixed**	**Favours**	**Certainty**	**Importance**
Outcome: BMI											
1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	11	11	MD: -0.30 kg/m^2 [-2.19, 1.59]	No difference	⨁◯◯◯ VERY LOW	CRITICAL
Outcome: Hirsutism											
1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	11	11	MD: 1.00 [-0.92, 2.92]	No difference	⨁◯◯◯ VERY LOW	CRITICAL
Outcome: Fasting glucose/insulin ratio											
1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	11	11	MD: 0.90 [-0.66, 2.46]	No difference	⨁◯◯◯ VERY LOW	IMPORTANT
Outcome: SHBG											
1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	11	11	MD: 1.10 µg/dl [0.13, 2.07]	COCP	⨁◯◯◯ VERY LOW	IMPORTANT
Outcome: Testosterone											
1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	11	11	MD: 1.00 ng/dl [-17.48, 19.48]	No difference	⨁◯◯◯ VERY LOW	IMPORTANT
Triglycerides											
1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	11	11	MD: -8.00 mg/dl [-47.70, 31.70]	No difference	⨁◯◯◯ VERY LOW	IMPORTANT
Outcome: HDL											
1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	11	11	MD: 0.00 mg/dl [-12.57, 12.57]	No difference	⨁◯◯◯ VERY LOW	IMPORTANT
Outcome: LDL											
1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	11	11	MD: -7.00 mg/dl [-25.06, 11.06]	No difference	⨁◯◯◯ VERY LOW	IMPORTANT

1 Downgraded once as the single study is moderate RoB

2 Downgraded twice due to very small sample size/participants

COMPARISON 11: Anti-androgen + COCP vs COCP +/- Placebo – ADULTS (6 months to 12 months)											
	Quality assessment					No of participants					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**AA + COCP**	**COCP +/- PLAC**	**Effect, fixed**	**Favours**	**Certainty**	**Importance**
Outcome: Weight											
2	RCT	Serious[1]	No serious	No serious	Very Serious[5,6]	48	45	MD: 5.57 kg [-0.67, 11.85]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: BMI											
3	RCT	Serious[1]	No serious	No serious	No serious	64	66	MD: 1.72 kg/m^2 [-0.29, 3.74]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: ALT											
1	RCT	Serious[1]	Not applicable	Not applicable	Serious[6]	28	24	MD: 1.10 [-2.84, 5.04]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: AST											
1	RCT	Serious[1]	Not applicable	Not applicable	Serious[6]	28	24	MD: -0.60 [-3.27, 2.07]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Hirsutism											
1	RCT	Serious[1]	Not applicable	Not applicable	Serious[6]	72	25	AA + OCP: mean: -57% SD: 2.4%; OCP: mean: -68%, SD: 5.2%	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Minor depressive state/mood reduction											
1	RCT	Serious[1]	Not applicable	Not applicable	Serious[6]	28	24	OR: 2.67 [0.10, 68.70]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Dysmenorrhea											
1	RCT	Serious[1]	Not applicable	Not applicable	Serious[6]	28	24	OR: 0.27 [0.01, 7.07]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Acne											
1	RCT	Serious[1]	Not applicable	Not applicable	Serious[6]	72	25	AA + OCP: mean: -78% SD: 13.6%; OCP: mean: -68%, SD: 26%	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Testosterone											
2	RCT	Serious[1]	Serious[3]	No serious	Serious[6]	36	42	MD: 0.10 nmol/l [-0.60, 0.79]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: SHBG											
2	RCT	Very serious[1]	Very serious[3,4]	No serious	Very Serious[5,6]	29	30	MD: -38.37 nmol/l[118.45, 41.72]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Total cholesterol											

2	RCT	Serious[1]	No serious	No serious	Serious[6]	48	45	MD: 20.81 mg/dl [7.81, 33.82]	AA + COCP	⊕⊕◯◯ LOW	IMPORTANT
Outcome: HDL											
2	RCT	Serious[1]	No serious	No serious	Serious[6]	48	45	MD: 1.44 mg/dl [-5.55, 8.42]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: LDL											
2	RCT	Serious[1]	No serious	No serious	Serious[6]	48	45	MD: 15.12 mg/dl [3.20, 27.04]	AA + COCP	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Triglycerides											
2	RCT	Serious[1]	No serious	No serious	Serious[6]	48	45	MD: 41.34 mg/dl [20.26, 62.42]	AA + COCP	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Breast tenderness											
2	RCT	Serious[1]	Serious[2]	Serious[7]	Serious[6]	100	49	OR: 0.73 [0.11, 5.00]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Nausea											
2	RCT	Serious[1]	No serious	Serious[7]	Serious[6]	100	49	OR: 0.67 [0.12, 3.63]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Fasting insulin											
1	RCT	Serious[1]	Not applicable	Not applicable	Serious[6]	20	21	MD: 3.50 µIU/ml [0.20, 6.80]	AA + COCP	⊕⊕◯◯ LOW	IMPORTANT
Fasting glucose											
1	RCT	Serious[1]	Not applicable	Not applicable	Serious[6]	28	24	MD: 2.60 [-1.74, 6.94]	No difference	⊕⊕◯◯ LOW	IMPORTANT
HOMA-IR											
1	RCT	Serious[1]	Not applicable	Not applicable	Serious[6]	20	21	MD: 0.70 [0.02, 1.38]	AA + COCP	⊕⊕◯◯ LOW	IMPORTANT
Free testosterone											
1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[6]	9	9	MD: -0.10 pg/ml [-0.47, 0.27]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
FAI											
1	RCT	Serious[1]	Not applicable	Not applicable	Serious[6]	20	21	MD: 0.50 [0.01, 0.99]	AA + COCP	⊕⊕◯◯ LOW	IMPORTANT
DHEAS											
1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[6]	9	9	MD: -0.40 µg/ml [-1.23, 0.43]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Androstenedione											
1	RCT	Very serious[1]	Not applicable	Not applicable	Very serious[6]	9	9	MD: 0.10 ng/ml [-0.92, 1.12]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
LDL/HDL ratio											
1	RCT	Serious[1]	Not applicable	Not applicable	Serious[6]	72	25	AA + OCP: mean: -5.1%, SD:	No difference	⊕⊕◯◯ LOW	IMPORTANT

								71.3%; OCP: -5.8%, SD: 35.5%			
CRP											
1	RCT	Serious[1]	Not applicable	Not applicable	Serious[6]	20	21	MD: 2.40 mg/l [-1.79, 6.59]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Acne											
1	RCT	Serious[1]	Not applicable	Not applicable	Serious[6]	72	25	AA + OCP: mean: -78%, SD: 13.6%; OCP: -68%, SD: 26%	No difference	⊕⊕◯◯ LOW	IMPORTANT
Menorrhagia/Heavy menstrual bleeding											
1	RCT	Serious[1]	Not applicable	Not applicable	Serious[6]	28	24	OR: 2.67 [0.10, 68.70]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Premenstrual pelvic pain											
1	RCT	Serious[1]	Not applicable	Not applicable	Serious[6]	72	25	AA + OCP: N events: 0, total: 72; OCP + P: N events: 0, total: 25	No difference	⊕⊕◯◯ LOW	IMPORTANT
Metrorrhagia											
1	RCT	Serious[1]	Not applicable	Not applicable	Serious[6]	28	24	OR: 2.67 [0.10, 68.70]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Hypercholesterolemia											
1	RCT	Serious[1]	Not applicable	Not applicable	Serious[6]	28	24	OR: 1.40 [0.47, 4.20]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Hypertriglyceridemia											
1	RCT	Serious[1]	Not applicable	Not applicable	Serious[6]	28	24	OR: 1.40 [0.47, 4.20]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Menstrual spotting											
1	RCT	Serious[1]	Not applicable	Not applicable	Serious[6]	28	24	OR: 1.67 [0.42, 6.58]	No difference	⊕⊕◯◯ LOW	IMPORTANT

1 Downgraded as at least one study is moderate RoB or very serious for at least one high RoB
2 Downgraded due to inconsistent direction of effect
3 Downgraded due to statistically significant ($p<0.05$) or high heterogeneity (>50%).
4 Downgraded due to no overlapping or at least one non-overlapping CI
5 Downgraded due to wide CIs
6 Downgraded once due to sample size (and when sample is not similar numbers between intervention and comparison group) and twice for very small sample
7 Downgraded due to indirectness as not systematic measurement of this outcome in Moretti 2018).

COMPARISON 12: Anti-androgen + COCP vs MET – ADULTS (6 months to 12 months)											
	Quality assessment					No of participants					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**AA + COCP**	**MET**	**Effect, fixed**	**Favours**	**Certainty**	**Importance**
Outcome: BMI											
2	RCT	Serious[1]	No serious	No serious	No serious	50	57	MD: -0.07 [-1.81, 1.67]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Hirsutism											
1	RCT	Very serious[1]	Not applicable	Not applicable	Serious[2]	24	22	MD: 4.6 [-2.6, 6.7]	MET	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Menstrual dysfunction											
1	RCT	Very serious[1]	Not applicable	Not applicable	Serious[2]	24	22	OR: 0.06 [0.02, 0.23]	AA + COCP	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Fasting glucose											
1	RCT	No serious	Not applicable	Not applicable	Serious[2]	34	34	MD: 0.70 nmol/L [0.32, 1.07]	AA + COCP	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Fasting insulin											
1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	16	23	AA + OCP: median: 2.88 mU/l, IQR: 2.36-3.14; MET: median: 2.37 mU/l, IQR: 2.10-3.23	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: HOMA-IR											
1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	16	23	AA + OCP: median: 1.27 IQR: 0.67-1.58; MET: median: 0.77, IQR: 0.40-1.53	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Testosterone											
1	RCT	Serious[1]	Not applicable	Not applicable	Very serious[2]	16	23	MD: 0.01 nmol/l [-0.72, 0.74]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Free testosterone											
1	RCT	Very serious[1]	Not applicable	Not applicable	Serious[2]	24	22	MD: 0.025 nmol/l [0.012, 0.039]	MET	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Androstenedione											
1	RCT	Very serious[1]	Not applicable	Not applicable	Serious[2]	24	22	MD: 5.5 nmol/l [1.8, 9.2]	MET	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: DHEAS											

1	RCT	Very serious[1]	Not applicable	Not applicable	Serious[2]	24	22	MD: 2.7 µmol/l [1.4, 4.0]	MET	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: HDL											
1	RCT	No serious	Not applicable	Not applicable	Serious[2]	34	34	MD: -0.00 mmol/l [-0.09, 0.08]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Triglycerides											
1	RCT	No serious	Not applicable	Not applicable	Serious[2]	34	34	MD: -0.06 mmol/l [-0.35, 0.23]	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
Outcome: CRP											
1	RCT	No serious	Not applicable	Not applicable	Serious[2]	34	34	MD: -0.23 mg/l [-0.42, -0.04]	AA + COCP	⊕⊕⊕◯ MODERATE	IMPORTANT
Outcome: Abnormal glucose tolerance											
1	RCT	Very serious[1]	Not applicable	Not applicable	Serious[2]	24	22	OR: 1.7 [0.7, 4.4]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Dyslipidemia											
1	RCT	Very serious[1]	Not applicable	Not applicable	Serious[2]	24	22	OR: 0.6 [0.2, 1.8]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT

1 Downgrade once if one or more studies have moderate RoB with significant weighting and very serious for at least one high RoB

2 Downgraded once for small sample size or twice for very small sample size.

COMPARISON 13: Anti-androgen + LS vs MET + LS - ADULTS (6 months to 12 months)											
	Quality assessment					No of participants					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**AA + LS**	**MET + LS**	**Effect, fixed**	**Favours**	**Certainty**	**Importance**
Outcome: Weight											
2	RCT	No serious	Serious[2]	No serious	Serious[5]	68	76	MD: -5.64 kg [-19.33, 8.05]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: BMI											
4	RCT	Serious[1]	Serious[3]	Serious[6]	No serious	129	136	MD: -0.79 kg/m^2 [-2.45, 0.87]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Hirsutism											
4	RCT	Serious[1]	Serious[3]	Serious[6]	No serious	129	136	MD: -1.59 [-3.06, -0.12]	AA + LS	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Frequency of menstruation											
2	RCT	Serious[1]	No serious	No serious	No serious	85	91	MD: 0.79 cycles/year [0.05, 1.53]	AA + LS	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: WHR											
2	RCT	Serious[1]	No serious	No serious	No serious	85	91	MD: 0.01 [-0.04, 0.06]	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
Outcome: SHBG											
2	RCT	Serious[1]	No serious	Serious[6]	Serious[4]	44	45	MD: 7.70 nmol/l [0.75, 14.66]	AA + LS	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Testosterone											
3	RCT	Serious[1]	No serious	No serious	No serious	102	111	MD: -0.01 nmol/l [-0.26, 0.24]	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
Outcome: DHEAS											
2	RCT	Serious[1]	Very serious[2,3]	No serious	No serious	51	55	MD: -1.02 µmol/l [-3.27, 1.24]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Fasting insulin											
3	RCT	Serious[1]	No serious	No serious	No serious	102	111	MD: -2.11 µU/ml [-3.97, -0.26]	AA + LS	⊕⊕⊕◯ MODERATE	IMPORTANT
Outcome: Fasting glucose											
3	RCT	Serious[1]	No serious	Serious[6]	No serious	112	116	MD: 0.44 mg/dl [-2.14, 3.02]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Fasting glucose-insulin ratio											
2	RCT	Serious[1]	No serious	No serious	No serious	85	91	MD: -1.12 [-1.44, -0.79]	AA + LS	⊕⊕⊕◯ MODERATE	IMPORTANT

Outcome: QUICKI											
2	RCT	No serious	Serious[3]	No serious	No serious	68	76	MD: 0.01 [-0.02, 0.04]	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
Outcome: FAI											
1	RCT	No serious	Not applicable	Not applicable	Very Serious[4]	17	20	MD: -0.60 [-1.99, 0.79]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Androstenedione											
1	RCT	No serious	Not applicable	Not applicable	Very Serious[4]	17	20	MD: -39.00 ng/dl [-123.43, 45.43]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: OGTT											
1	RCT	Serious[1]	Not applicable	Not applicable	Very Serious[4]	27	25	MD: -9.54 mg/dl [-23.70, 4.62]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: HOMA											
1	RCT	Serious[1]	Not applicable	Not applicable	Serious[4]	34	35	MD: 2.72 [-0.28, 5.72]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Total cholesterol											
1	RCT	Serious[1]	Not applicable	Not applicable	Very Serious[4,5]	27	25	MD: 7.20 mmol/l [-13.06, 27.46]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: HDL											
1	RCT	No serious	Not applicable	Not applicable	Very Serious[4]	17	20	MD: 0.21 mmol/l [0.05, 0.37]	AA + LS	⊕⊕◯◯ LOW	IMPORTANT
Outcome: LDL											
1	RCT	No serious	Not applicable	Not applicable	Very Serious[4]	17	20	MD: -0.29 mmol/l [-0.83, 0.25]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Triglycerides											
1	RCT	No serious	Not applicable	Not applicable	Very Serious[4]	17	20	MD: -0.23 mmol/l [-0.51, 0.05]	No difference	⊕⊕◯◯ LOW	IMPORTANT

1 One or more studies have moderate RoB with significant weighting

2 Downgraded for no overlapping CIs

3 Downgraded for statistically significant ($p<0.05$) or high heterogeneity (>50%).

4 Downgraded due to sample size/participants.

5 Downgraded due to wide CIs

6 Downgraded for indirectness as Amiri 2014 stated it was an overweight population, but the study has an inclusion of women with BMI 19 to 35 (not reporting BMIs), thus indicating this population could include lean women, whereas the other studies have clearly reported BMIs in overweight/obese individuals.

COMPARISON 14: Anti-androgen + MET + LS vs MET + LS – ADULTS (6 months to 12 months)											
	Quality assessment					No of participants					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**AA + MET + LS**	**MET + LS**	**Effect, fixed**	**Favours**	**Certainty**	**Importance**
Outcome: Weight											
3	RCT	No serious	Serious[2]	No serious	Serious[5]	108	102	MD: -0.92 kg [-7.30, 5.45]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: BMI											
4	RCT	Serious[1]	No serious	Serious[4]	No serious	135	127	MD: -0.20 kg/m^2 [-1.43, 1.02]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Hirsutism											
4	RCT	Serious[1]	No serious	Serious[4]	No serious	135	127	MD: -0.58 [-1.86, 0.69]	No difference	⊕⊕◯◯ LOW	CRITICAL
Frequency of menstruation (number of cycles per year)											
1	RCT	No serious	Not applicable	Not applicable	No serious	62	56	MD: -0.84 cycles/year [-0.31, 1.99]	No difference	⊕⊕⊕⊕ HIGH	CRITICAL
Outcome: WHR											
2	RCT	Serious[1]	Serious[2]	Serious[4]	No serious	89	81	MD: -0.00 [-0.06, 0.06]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: SHBG											
3	RCT	Serious[1]	No serious	Serious[4]	No serious	73	71	MD: -0.59 nmol/l [-4.53, 3.34]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Testosterone											
4	RCT	Serious[1]	Serious[2]	Serious[4]	No serious	135	127	MD: -0.29 nmol/l [-0.52, -0.06]	AA + MET + LS	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: DHEAS											
2	RCT	No serious	Serious[2]	No serious	No serious	46	46	MD: -0.24 µg/ml [-0.92, 0.45]	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
Outcome: Fasting insulin											
3	RCT	No serious	No serious	No serious	No serious	108	102	MD: -1.22 µU/ml [-2.87, 0.43]	No difference	⊕⊕⊕⊕ HIGH	IMPORTANT
Outcome: Fasting glucose											
4	RCT	Serious[1]	No serious	Serious[4]	No serious	135	127	MD: -2.93 mg/dl [-5.78, -0.09]	AA + MET + LS	⊕⊕◯◯ LOW	IMPORTANT
Outcome: HDL											
2	RCT	No serious	Serious[2]	No serious	Serious[6]	46	46	MD: 1.75 mg/dl [-7.72, 11.23]	No difference	⊕⊕◯◯ LOW	IMPORTANT

Outcome: LDL											
2	RCT	No serious	No serious	No serious	Serious[6]	46	46	MD: -8.24 mg/dl [-20.34, 3.86]	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
Outcome: Triglycerides											
2	RCT	No serious	No serious	No serious	Serious[6]	46	46	MD: -5.48 mg/dl [-24.06, 13.10]	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
HOMA-IR											
2	RCT	No serious	No serious	No serious	No serious	88	82	MD: -0.22 [-0.67, 0.23]	No difference	⊕⊕⊕⊕ HIGH	IMPORTANT
FAI											
1	RCT	No serious	Not applicable	Not applicable	Serious	26	26	MD: -2.10 [-4.47, 0.27]	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
Androstenedione											
1	RCT	No serious	Not applicable	Not applicable	Very Serious[6]	20	20	MD: -5.00 ng/dl [-96.42, 86.42]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Fasting glucose-insulin ratio											
1	RCT	No serious	Not applicable	Not applicable	No serious	62	56	MD: 1.74 [-1.45, 4.93]	No difference	⊕⊕⊕⊕ HIGH	IMPORTANT
QUICKI											
1	RCT	No serious	Not applicable	Not applicable	Very Serious[6]	20	20	MD: 0.01 [-0.01, 0.03]	No difference	⊕⊕◯◯ LOW	IMPORTANT
OGTT											
1	RCT	Serious[1]	Not applicable	Not applicable	Serious[6]	27	25	MD: -4.88 mg/dl [-20.32, 10.56]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Insulin sensitivity index											
1	RCT	No serious	Not applicable	Not applicable	Very Serious[6]	20	20	MD: 6.90 [2.96, 10.84]	AA + MET + LS	⊕⊕◯◯ LOW	IMPORTANT
Total cholesterol											
1	RCT	No serious	Not applicable	Not applicable	Serious[6]	26	26	MD: 0.30 mg/dl [-16.67, 17.36]	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT

1 One study has moderate RoB and has significant weighting

2 Downgraded for statistically significant or high heterogeneity (>50%)

3 Downgraded for no overlapping CIs

4 Downgraded for indirectness as Amiri 2014 stated it was an overweight population, but the study has an inclusion of women with BMI 19 to 35 (not reporting BMIs), thus indicating this population could include lean women, whereas the other studies have clearly reported BMIs in overweight/obese individuals.

5 Downgraded for wide CIs

6 Downgraded once for small sample and twice for very small sample

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 4

Question 4.6.

Are anti-androgen pharmacological agents alone or in combination, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?

BACKGROUND:

Treatment with anti-androgen drugs has been utilized to improve physical appearance, psychological health, and quality of life because these common clinical features adversely impact the health and well-being of women with PCOS (1, 2).

This sub-topic examines available data regarding the efficacy of anti-androgens in adolescents and adult women with PCOS. Available evidence was evaluated for all possible comparisons including monotherapy with anti-androgens and combination therapy involving other medications such as metformin, COCPs, and SPIOMET. For these comparisons, 24 studies were examined. Only eight studies were published after 2017; five of these studies were published by the same group, raising the possibility for inclusion of some subjects in several studies.

Women with PCOS often manifest metabolic features such as insulin resistance, hyperinsulinemia, dyslipidemia, and greater weight. Insulin resistance and hyperinsulinemia promote excessive ovarian and adrenal androgen secretion. One mechanism of action attributed to metformin is improved insulin sensitivity leading to decreased circulating androgen concentrations. Limited data suggest that hyperandrogenemia exacerbates insulin resistance and hyperinsulinemia (3).

Due to the growth cycle of hair, at least a 9–12 months course treatment is required in order to evaluate the effectiveness of the antiandrogen treatment in improving hirsutism and/or acne. To date, spironolactone, cyproterone acetate (CPA), finasteride and flutamide are the most thoroughly investigated and commonly used agents.

Assessment of the potential benefits and adverse consequences must be evaluated before prescribing any medications. Regarding this specific topic, the potential for adverse side effects for anti-androgens, COCPs, and/or metformin needs to be assessed. Anti-androgens are teratogens that interfere with virilization of a male fetus (4, 5). Hence, it is mandatory to use concomitant contraception with anti-androgens (especially monotherapy with anti-androgens) to avoid undervirilisation of a male fetus in the event of unplanned pregnancy. According to general population guidelines, absolute contraindications for COCP use include women with history of migraine with aura, deep vein thrombosis (DVT)/pulmonary emboli (PE), known thrombogenic mutations, multiple risk factors for arterial cardiovascular disease, history of ischemic heart disease or stroke, complicated valvular heart disease, breast cancer, neuropathy, severe cirrhosis and malignant liver tumours. In case of increased risk profile other methods like progestin only preparations (i.e. hormonal IUD) could be considered.

Metformin is an insulin sensitizer that is used to treat impaired glucose tolerance and PCOS symptoms in adolescents and women. Due to its low cost and availability, metformin is commonly used to treat adolescents and women with PCOS. Metformin has mild side effects of nausea, vomiting, diarrhoea, and flatulence. Metformin can be used alone or in combination with anti-androgens for PCOS.

GRADE EVIDENCE CERTAINTY	
Comparison	**GRADE for critical outcomes**
o **Comparison 1**. Anti-androgen vs Placebo - ADOLESCENTS	⨁◯◯◯ VERY LOW
o **Comparison 2.** Anti-androgen (daily) vs Anti-androgen (every 3 days)	⨁◯◯◯

	VERY LOW
o **Comparison 3.** Anti-androgen + lifestyle vs Placebo + lifestyle – ADULTS	⊕◯◯◯ VERY LOW
o **Comparison 4.** Anti-androgen + lifestyle vs Anti-androgen + metformin + lifestyle	⊕◯◯◯ VERY LOW
o **Comparison 5.** Anti-androgen vs metformin - ADULTS	⊕◯◯◯ VERY LOW
o **Comparison 6.** Anti-androgen vs Anti-androgen + metformin – ADULTS	⊕◯◯◯ VERY LOW
o **Comparison 7**. Anti-androgen vs COCP – ADULTS	⊕◯◯◯ VERY LOW
o **Comparison 8**. Anti-androgen + metformin + Pioglitazone (SPIOMET) vs COCP – ADOLESCENTS	⊕⊕◯◯ LOW
o **Comparison 9.** Anti-androgen + metformin vs COCP - ADOLESCENTS	⊕◯◯◯ VERY LOW
o **Comparison 10**. Anti-androgen + metformin + COCP vs COCP - ADULTS	⊕◯◯◯ VERY LOW
o **Comparison 11**. Anti-androgen + COCP vs COCP +/- placebo – ADULTS	⊕◯◯◯ VERY LOW
o **Comparison 12.** Anti-androgen + COCP vs metformin – ADULTS	⊕◯◯◯ VERY LOW
o **Comparison 13.** Anti-androgen + lifestyle vs metformin + lifestyle - ADULTS	⊕◯◯◯ VERY LOW
o **Comparison 14.** Anti-androgen + metformin + lifestyle vs metformin + lifestyle - ADULTS	⊕⊕◯◯ LOW

Evidence to Recommendations Framework

COMPARISONS (option versus other option)

Comparisons Included:
o Comparison 1. Anti-androgen vs Placebo - ADOLESCENTS
o Comparison 2. Anti-androgen (daily) vs Anti-androgen (every 3 days)
o Comparison 3. Anti-androgen + lifestyle vs Placebo + lifestyle – ADULTS
o Comparison 4. Anti-androgen + lifestyle vs Anti-androgen + metformin + lifestyle
o Comparison 5. Anti-androgen vs metformin - ADULTS
o Comparison 6. Anti-androgen vs Anti-androgen + metformin – ADULTS
o Comparison 7. Anti-androgen vs COCP – ADULTS
o Comparison 8. Anti-androgen + metformin + pioglitazone (SPIOMET) vs COCP – ADOLESCENTS
o Comparison 9. Anti-androgen + metformin vs COCP - ADOLESCENTS
o Comparison 10. Anti-androgen + metformin + COCP vs COCP - ADULTS
o Comparison 11. Anti-androgen + COCP vs COCP +/- placebo – ADULTS
o Comparison 12. Anti-androgen + COCP vs metformin – ADULTS
o Comparison 13. Anti-androgen + lifestyle vs metformin + lifestyle - ADULTS
o Comparison 14. Anti-androgen + metformin + lifestyle vs metformin + lifestyle - ADULTS

EVIDENCE-BASED RECOMMENDATION(S)

- **EBR:** In combination with effective contraception, antiandrogens should only be considered to treat hirsutism in women with PCOS, if there is a suboptimal response, after a minimum of six months of COCP and/or cosmetic therapy.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

- **CR:** Given the negative psychological impact of female pattern hair loss, anti-androgens in combination with COCP could be trialled, acknowledging the lack of evidence in the PCOS population.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

PRACTICE POINT(S)

- Whenever pregnancy is possible, health professionals must educate and counsel women and adolescents, parent/s or guardian/s, regarding the risks of incomplete development of external genital structures of male fetuses (undervirilization) when anti-androgens are used. To prevent this, women who can get pregnant should be strongly counselled to use effective contraception (e.g. Intrauterine device or COCPs).

Anti-androgens could be considered to treat hirsutism, in the presence of another effective form of contraception, for women with contraindications for COCP therapy or when COCPs are poorly tolerated.

- When prescribing antiandrogens, based on general population recommendations, health professionals should consider that:
  - Spironolactone at 25-100 mg / day appears to have lower risk of adverse effects.
  - Cyproterone acetate at doses ≥ 10 mg is not advised due to increased risks including for meningioma.
  - Finesteride has an increased risk of liver toxicity.
  - Flutamide and bicalutamide have an increased risk of severe liver toxicity.
  - The relatively limited evidence on anti-androgens in PCOS needs to be appreciated with small numbers of studies and limited numbers of participants.

GRADE CONSIDERATIONS

Justifications:

COMPARISON 1. Anti-androgen vs Placebo – ADOLESCENTS

One randomized control trial (RCT) was performed and published in 2014 (7). This study included 14 girls diagnosed with PCOS using Rotterdam criteria. The 14 patients were randomized to two treatment groups: 1) low dose finasteride (2.5 mg) every three days and 2) placebo. Outcome measures included BMI, gonadotropins, total testosterone, DHT, androstenedione, androstenediol glucuronide, SHBG, lipids, and liver function studies. The study lasted six months. The FG score was significantly lower at six months in the finasteride-treated group. As would be anticipated, androstanediol glucuronide and DHT concentrations were lower at 3 and 6 months. Finasteride-treated subjects reported positive subjective outcome of this study (excellent + good: finasteride treated = 13 and placebo = 0). Side effects were not reported – finasteride was “well tolerated” by subjects. Low quality data due to limited number of subjects. Hence, cannot make definitive recommendations in favor of an anti-androgen versus placebo.

Comparison 2. Anti-androgen (daily) vs Anti-androgen (every 3 days)

One RCT compared daily versus intermittent anti-androgens in adult women with PCOS with 6- and 12-month follow-ups. This study (8) had a high risk of bias. All subjects were 18 years of age and older in this study.

Tartagni et al (8) enrolled 38 women categorized as 38 with idiopathic hirsutism and 16 with PCOS. Subjects were randomized assigned to finasteride 2.5 mg daily or finasteride 2.5 mg every 3 days for 10 months. reported that daily finasteride was not superior to every 3-day finasteride. Outcome measures included BMI, gonadotropins, total testosterone, DHT, androstenedione, androstanediol glucuronide, SHBG, lipids, and liver function studies. The subjects reported good outcomes regardless of daily or intermittent treatment. As would be anticipated, androstanediol glucuronide and DHT concentrations were lower at the 5 month and 10-month timepoints. The authors concluded no superiority was demonstrated for either treatment.

Falsetti et al. (9) compared two different anti-androgens. This study also had a high risk of bias. In this study, women with PCOS were randomly assigned to receive either finasteride 5 mg daily or flutamide 250 mg twice daily for a total of 12 months. Both anti-androgen medications reduced the FG score at 12 months. Finasteride decreased FG score by 31% whereas flutamide decreased FG score by 60%. No hormone changes were observed with flutamide but two women had abnormal transaminase levels at 6 months. Subjects taking finasteride showed increased testosterone and decreased androstanediol glucuronide levels. The authors concluded that flutamide was more effective than finasteride. This study does not address the specified comparison.

Hence, only one RCT actually addressed this comparison. This RCT presents low quality data due to the limited number of subjects. Hence, no definitive recommendation in favor of a daily anti-androgen versus an intermittent anti-androgen (every 3 days) can be made.

Comparison 3. Anti-androgen + lifestyle vs Placebo + lifestyle – ADULTS

Two studies were available that assessed the comparison between anti-androgen (flutamide) with lifestyle intervention compared to placebo with lifestyle intervention in adult women with PCOS with 6- and 12-month

follow-ups. One study had a moderate risk of bias (10) and the other had a low risk of bias (11). Due to differences in units, meta-analyses could not be performed for some outcome measures.

BMI in Amiri (10) ranged between 19-35 kg/m^2 thus including both lean women and women of a higher weight. Amiri (10) stated that 117 women were recruited, 120 women were randomized, and 105 women completed the study. All subjects were started on a hypocaloric diet. One month later, subjects were randomized to four groups: 1) metformin (1500 mg daily); 2) flutamide (500 mg daily); 3) metformin (1500 mg daily) and flutamide (500 mg daily); and 4) placebo. Outcome measures included BMI, total testosterone, DHT, androstenedione, androstanediol glucuronide, SHBG, lipids, fasting blood glucose, fasting insulin, and liver function studies. No difference in outcomes was evident for BMI, hirsutism, SHBG, FAI, testosterone, and androstenedione.

Per Gambineri et al. (11), single study mean difference estimates, anti-androgen + lifestyle was superior for managing body weight, DHEAS, fasting insulin, LDL, triglyceride levels, frequency of menstruation, QUICKI, and insulin sensitivity index, as compared to the placebo + lifestyle intervention. The certainty of the evidence ranged from low to very low due to risk of bias and small sample. No differences in outcomes such as BMI, hirsutism, SHBG were evident. For this RCT, Gambineri et al (11) placed subjects on a hypocaloric diet for the first month and then on a hypocaloric diet plus placebo, metformin (850 mg, orally, twice a day), flutamide (250 mg, orally, twice a day), or metformin plus flutamide for the subsequent 12 months (20 subjects in each group). Forty women were included in their previous 2004 study. The Rotterdam criteria were used for the diagnosis of PCOS. Outcome measures included BMI, FG score, total T, androstenedione, DHEAS, SHBG, lipids, liver and renal function studies, an OGTT, and CT assessment of body fat. These authors concluded that "…flutamide significantly decreased visceral fat, glucose-stimulated glucose levels, and LDL cholesterol levels and improved insulin sensitivity, therefore favoring the achievement of a healthier metabolic profile, particularly in the long term. Moreover, after 12 months of treatment, we found that flutamide significantly increased the frequency of menstruation."

Reviewing the Forest Plots and prepared analyses and recognizing the limited number of subjects, no definitive recommendation can be made for this comparison, Anti-androgen + lifestyle vs Placebo + lifestyle.

Comparison 4. Anti-androgen + lifestyle vs Anti-androgen + metformin + lifestyle

Three RCTs are included in this comparison; two studies (10, 11) were included in Comparison 3. This comparison includes a third RCT by Ganie et al. (12). For this comparison, several outcomes are considered including hirsutism, lipids, androgen concentrations, and metabolic features (glucose and insulin).

No differences were apparent for BMI, hirsutism, total testosterone, fasting insulin, and QUICKI. However, certainty varied between very low to low due to small sample sizes and lack of details regarding BMI distribution in Amiri et al.(10). Since the BMIs of the population of Amiri 2014 was uncertain (10), a sensitivity analysis was conducted to assess the influence of Amiri 2014 (10) on several outcomes. When removing Amiri 2014 (10) from BMI, hirsutism, SHBG, testosterone, and fasting glucose, they were still not statistically significant. In the single study mean difference estimates, there was no difference in weight, total cholesterol, FAI, DHEAS, androstenedione, HDL, and HOMA-IR. Certainty in these findings ranged from very low to low due to risk of bias and sample sizes.

Fasting glucose was significantly lower for anti-androgen + metformin + lifestyle compared to anti-androgen + lifestyle (P=0.002). Thus, in meta-analysis, the combination therapy of an anti-androgen + metformin + lifestyle intervention was superior for lowering fasting glucose with a moderate certainty of evidence.
Conversely, the anti-androgen + lifestyle intervention was superior for triglycerides compared to the combination anti-androgen + metformin + lifestyle intervention, with a low certainty of evidence, due to the very small sample.

The certainty in the evidence that fasting insulin was similar was high in two studies (11, 12).

However, clinical care of women with PCOS is unlikely to depend on fasting glucose or triglyceride concentrations.

Comparison 5. Anti-androgen vs metformin - ADULTS

One RCT compared an anti-androgen (finasteride) and metformin without additive lifestyle intervention in adult women with PCOS with 6- and 12-month follow-ups. This study by Diri et al., (13) had high risk of bias. This study enrolled 70 patients with PCOS diagnosed by Rotterdam criteria but only 52 completed the study (13 failed to follow up, 2 stopped metformin, and 3 became pregnant). Subjects were randomized to three treatment groups: 1) finasteride 5 mg/day (n=16); 2 metformin 850 mg, bid (n=19); and 3) finasteride and metformin (n=17).

Fasting glucose concentrations improved in both finasteride and metformin groups, but were not different at 12 months. The finasteride group had higher SHBG concentrations at 12 months compared to the metformin group. The metformin group had lower estradiol concentrations. This is a single study with a small number of subjects and very low certainty.

Comparison 6. Anti-androgen vs Anti-androgen + metformin – ADULTS

Diri et al (13) was the only RCT that investigated anti-androgens with a combination of anti-androgens (finasteride) and metformin without additive lifestyle intervention in adult women with PCOS with 12 months follow-up. This study enrolled 70 patients with PCOS diagnosed by Rotterdam criteria but only 52 completed the study (13 failed to follow up, 2 stopped metformin, and 3 became pregnant). Subjects were randomized to three treatment groups: 1) finasteride 5 mg/day (n=16); 2 metformin 850 mg, bid (n=19); and 3) finasteride and metformin (n=17).

HOMA-IR and AUC-glucose were higher and estradiol concentrations were lower in the finasteride + metformin group compared to the finasteride group. This study was considered to be at high risk of bias and data were considered to be of very low level of certainty.

Comparison 7. Anti-androgen vs COCP – ADULTS

In the RCT (14), 46 hirsute women were separated randomly into two groups, stratified for polycystic ovary syndrome. One group (21 patients, 10 PCOS) received spironolactone only (200 mg/day) while the other group (23 patients, nine PCOS) received COCP consisting of CPA (50 mg/day) with ethinyl estradiol (35 microgram/day). Outcome measures included FG score, testosterone, androstenedione, and LH. FG score, testosterone, androstenedione, and LH concentrations decreased with COCP. This is a single study with a small number of subjects. Of note, it is unclear whether the subjects taking spironolactone alone were using an effective form of contraception.

Comparison 8. Anti-androgen + metformin + Pioglitazone (SPIOMET) vs COCP – ADOLESCENTS

In a series of studies, Ibáñez and colleagues (15, 16) have compared a specific regimen (SPIOMET: spironolactone 50 mg/day, pioglitazone 7.5 mg/day, and metformin 850 mg/day) with COCP (20 µg ethinylestradiol plus 100 mg levonorgestrel). This regimen consists of spironolactone + pioglitazone + metformin. She and colleagues hypothesize that hepatovisceral fat excess (central adiposity) attributed to restricted prenatal nutritional restriction followed by postnatal nutritional excess contributes to the development of PCOS.

Five studies were identified that compared a combination therapy of spironolactone + metformin + pioglitazone (SPIOMET) compared to COCP, the combination oral contraceptive pill in adult women with PCOS with 12 months follow-up. All these studies involved the same population of women. For this reason, Ibáñez et al. 2020 (16) was considered the main publication due to the largest sample size and full outcome list. Therefore, there was nothing extracted from Malpique 2019 (17) and Diaz 2018 (18). FAI was reported as an extra outcome in deZegher 2021 (19) and acne scores were from Ibáñez et al., 2017 (20) and were hence extracted. Given these multiple publications utilizing at least some common subjects raises concerns regarding high risk of bias.

The 2020 Ibáñez (16) publication in the Journal of the Endocrine Society includes data from an earlier study with this more recent study that includes 62 lean adolescents with PCOS. For this specific study, the primary endpoint was posttreatment ovulation rate; secondary outcomes included hirsutism score, fasting insulin, androgens, lipids, high-molecular-weight (HMW) adiponectin, C-reactive protein (CRP), carotid intima-media thickness (cIMT), body composition, and hepato-visceral fat. Subjects were treated for 12 months and subsequently followed for another 12 months.

Subjects treated with SPIOMET showed more ovulations post-therapy than those treated with COCP during the first 12 months after completion of this study. At 12 months, completion of medication, no differences were found for FG scores, testosterone, androstenedione, BMI Z-score, BMI, HOMA-IR, OGTT, lipids. SHBG levels were significantly higher in the COCP group at 12 months. Insulin (fasting and mean insulinemia Z score) was lower in the SPIOMET group. This combination of three medications has only been utilized by these investigators. Side effects/adverse events were not discussed. No data was available regarding benefits/risk among higher weight young women with PCOS. And, no longer term follow-up data (beyond 12 months) were reported.

No information regarding side effects is included. The certainty in the evidence was low for all these outcomes reflective of the moderate risk of bias and small sample size.

Comparison 9. Anti-androgen + metformin vs COCP - ADOLESCENTS

One RCT (15) investigated the combination therapy of an anti-androgen (specifically, flutamide)

+ metformin against the combined oral contraceptive in adolescent girls with PCOS for 9 months with follow-up. This study included 54 adolescent and young adult women. Subjects “not at risk for pregnancy” were enrolled in flutamide + metformin vs COCP study (n=32; mean age 14.6 ± 0.3 yr; range, 13–16 yr). For the OCP group, “appreciable decreases in hirsutism score and testosterone, as well as increments in SHBG and high-density lipoprotein (HDL) cholesterol” were noted. For the girls receiving flutamide + metformin monotherapy, testosterone, triglycerides, and lipids “reverted toward normal”. Side effects/adverse events were not discussed.

Young women at risk for pregnancy were treated with COCP and enrolled in a second sub-study with two groups: 1) COCP alone or 2) COCP + flutamide + metformin. This second sub-study is not included in this analysis and is considered in Comparison 10.

No definitive recommendations can be offered due to the small number of subjects with moderate risk of bias.

Comparison 10. Anti-androgen + metformin + COCP vs COCP - ADULTS + ADOLESCENTS

One RCT (15) investigated the combination therapy of an anti-androgen (specifically, flutamide) + metformin against the combined oral contraceptive in adolescent girls with PCOS for 9 months with follow-up. This study included 54 adolescent and young adult women. Young women at risk for pregnancy were treated with COCP and enrolled in a second sub-study with two groups: 1) COCP alone or 2) COCP + flutamide + metformin. For this sub-study (n=22; mean age 18.6 ± 0.3 yr; range, 17–21 yr), the specific study comparisons were monophasic OC (ethinylestradiol 30 µg + drospirenone 0.3 mg, 21 d/month) or COCP + anti-androgen + metformin (ethinylestradiol 30 µg + drospirenone 0.3 mg, 21 days, flutamide, 62.5 mg daily and metformin, 850 mg daily).

Subjects “not at risk for pregnancy” were enrolled in flutamide + metformin vs COCP study. For this sub-study, the specific study comparisons were anti-androgen + metformin (flutamide, 62.5 mg daily and metformin, 850 mg daily) or monophasic OC (ethinylestradiol 30 µg + drospirenone 0.3 mg, 21 d/month). This sub-study was considered in Comparison 9.

No differences in BMI, hirsutism, fasting glucose/insulin ratio, testosterone, triglycerides, HDL, or LDL levels were apparent. Side effects/adverse events were not discussed. There was a very low certainty in the evidence due to the moderate risk of bias and very small sample size.

Comparison 11. Anti-androgen + COCP vs COCP +/- placebo – ADULTS (6-12 months)

Five RCTs addressed the comparison of a combination therapy of an anti-androgen and combined oral contraceptive pill with the combined oral contraceptive with (in the case of Moretti, 2018 (21)) and without a placebo with 6 to 12 months follow-up. All the five studies were found to have a moderate risk of bias (22-26).

Moretti et al (21) was the only publication reporting outcome data with bicalutamide, an androgen receptor antagonist, in women with PCOS. The major outcome for this study was effects on hirsutism. Subjects were randomized to receive COCP (third generation: ethinylestradiol (0.030 mg) and a progestin with the same antiandrogen activity (chlormadinone acetate 2 mg, drospirenone 3 mg, or dienogest 2.5 mg) with or without oral bicalutamide 50 mg daily. Each group included 35 subjects. The combination of COCP and bicalutamide showed greater efficacy to decrease FG scores than COCP alone. No adverse events were reported.

Total cholesterol was lower in COCP ± placebo group (P=0.002), LDL cholesterol was lower in COCP ± placebo group (P-0.01), and triglycerides were lower in COCP ± placebo group (P=0.0001).

To summarize, no differences in weight, BMI, testosterone, SHBG, HDL, and adverse events such as breast tenderness, and nausea were noted. The certainty in the evidence ranged from very low to low due risk of bias and sample size, except for BMI which was moderate due to only being downgraded due to the risk of bias. In the single study mean difference estimates, there were no difference in hirsutism, acne, fasting glucose, free testosterone, DHEAS, androstenedione, CRP, ALT, AST, and other adverse events (menorrhagia, premenstrual pelvic pain, metrorrhagia, hypercholesterolemia, hypertriglyceridemia, dysmenorrhea, menstrual spotting, and minor depressive state/mood reduction). The certainty in the evidence for all these findings ranged from very low to low due to the risk of bias and sample size.

Comparison 12. Anti-androgen + COCP vs metformin – ADULTS

Four RCTs investigated that addressed the comparison of a combination therapy of an anti-androgen + COCP against metformin in adult women with PCOS with 6 to 12 months follow-up. The studies were either low (27) , moderate (22, 24), or high risk of bias (28) with 6- and 12-month follow-ups.

Due to the nature of the diversity in the way outcomes were reported, only BMI could be pooled in meta-analysis, which showed no effect with a moderate certainty of evidence only downgrading due to the inclusion of a moderate risk of bias study (22).

In the single study mean difference estimates, the combination anti-androgen + COCP was superior in free testosterone, androstenedione, DHEAS, CRP, and menstrual dysfunction. Conversely, metformin was superior for fasting glucose. The certainty of the evidence for these findings ranged from very low to low due to the risk of bias and sample size, except for CRP which was moderate only being downgraded due to the sample size.
There was no difference for BMI in meta-analysis, with a moderate certainty of evidence. In the single study mean difference estimates, fasting insulin HOMA-IR, testosterone, HDL, triglycerides, and adverse events such as abnormal glucose tolerance and dyslipidemia. The certainty in the evidence for these outcomes ranged from very low to low due to the risk of bias and small sample size, except for triglycerides, which was only downgraded due to the sample size.

Comparison 13. Anti-androgen + lifestyle vs metformin + lifestyle – ADULTS

Four RCTs addressed the comparison of anti-androgen + lifestyle versus metformin + lifestyle in adult women with PCOS with 6 – 12 months follow-up. Two studies were low risk of bias (11, 12) and two were moderate risk of bias (10, 29).
The
Amiri (10) stated that 117 women were recruited, 120 women were randomized, and 105 women completed the study. All subjects were started on a hypocaloric diet. One month later, subjects were randomized to four groups: 1) metformin (1500 mg daily); 2) flutamide (500 mg daily); 3) metformin (1500 mg daily) and flutamide (500 mg daily); and 4) placebo. Outcome measures included BMI, total testosterone, DHT, androstenedione, androstanediol glucuronide, SHBG, lipids, fasting blood glucose, fasting insulin, and liver function studies. BMI decreased. Hirsutism score decreased more in the flutamide group. Higher SHBG concentrations in the flutamide group.

Ganie (29) assessed menstrual frequency in two studies and reported more menses in the anti-androgen group.

For meta-analysis, hirsutism was improved with anti-androgen (P=0.03). SHBG was higher in the anti-androgen group (P=0.03). Fasting insulin was lower in the anti-androgen group (P=0.03). No apparent differences in testosterone, DHEAS, fasting glucose, QUICKI, androstenedione, HOMA-IR, or BMI.

Comparison 14. Anti-androgen + metformin + lifestyle vs metformin + lifestyle – ADULTS

Four RCTs addressed the comparison between a combination therapy of an antiandrogen + metformin + lifestyle against metformin + lifestyle in adult women with PCOS with 6-12 months follow-up. Three of the studies were low risk of bias (11, 12, 30) and one was moderate risk of bias (10) .

For meta-analysis, no differences in weight, BMI, WHR, hirsutism, SHBG, DHEAS, fasting insulin, HDL, LDL, triglycerides, and HOMA-IR were found. Testosterone and fasting insulin were lower in the anti-androgen + metformin + lifestyle group (P=0.01 and P=0.04, respectively).

Subgroup considerations:

Higher weight is a confounding factor in evaluating the effect of treatment on the metabolic assessment and other clinical parameters (e.g. menstrual irregularities).

Implementation considerations:

Potential barriers to implementation of the recommendations relate to the availability and costs of various COCP combinations, availability and costs of other medical interventions. One major limitation is how to encourage and obtain prolonged adherence to healthy lifestyle changes.

Monitoring and evaluation considerations:

- Assuring effective contraception when anti-androgens or other potentially teratogenic medications are utilized
- Assess risk for impaired glucose tolerance, diabetes, dyslipidemia recognizing that risks for these consequences are higher in individuals with high BMI or specific ethnic backgrounds.
- Assessment for risk for VTE by obtaining a thorough family history.

Research priorities:
Large scale population-based studies are required to validate comparisons that show potential differences.
Large scale comparative studies in particular in adolescents are required to determine the optimal COCP preparation in relation to specific progestins and estrogen doses.
Large scale comparative studies to determine optimal combination of therapies for specific phenotypes. Do optimal therapies differ for women with PCOS with much higher weight vs lean women?
Large scale studies comparing COCP and emerging anti-obesity medications plus the combination of COCP plus anti-obesity medications as weight is an important complaint in women with PCOS.
Comparison of efficacy of different antiandrogens agents
Comparison of efficacy of different treatment schedules
Assessment of optimal monitoring of adverse events
A better selection of study participants in order to make possible a tailored approach - BMI, age, different phenotypes and metabolic assessment should be taken into consideration for future research.

GRADE framework

GRADE DECIDE **Interactive Evidence to Decision Framework**

● DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

As detailed above, most comparisons were conditional recommendations to not recommend either option. Limited data due to few studies and sample number of subjects results in these conclusions. See above for details. All comparisons assessed within this subtopic are listed below. Nevertheless, not all comparisons will require a recommendation with a GRADE assessment in the final document. The comparison with SPIOMET should not be considered due to the limited outcome data and low level of certainty regarding the data. The importance of effective contraception when anti-androgens are used as monotherapy must be emphasized.

Panel discussion:

● UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Side effects and adverse events were not systematically reported but no major side effects were described and very few subjects withdrew from treatment due to side effects even with combinations

Metformin can cause mild GI side effects

COCP can cause mild side effects such as spotting and breast tenderness.

COCP are associated with risk for VTE

Spironolactone used as monotherapy can cause irregular menses and hyperkalemia

All anti-androgens are teratogens

● CERTAINTY OF THE EVIDENCE

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☒ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Overall certainty of evidence is low to very low.

● VALUES

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☐ Important uncertainty or variability	☒ Possibly important uncertainty or variability	☐ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Research evidence:

No research evidence was identified

Panel discussion:

Overall health care professionals and consumers share goals to promote weight loss, regular menses, fertility, and decreased androgen excess. Health professionals and consumers will likely value these revised recommendations.

Nevertheless, health care professionals and consumers may have different values and view main outcomes differently. Priorities for consumers include higher weight and difficulties losing weight, infertility, and hirsutism. And shared-decision making to individual therapeutic interventions will benefit all.

● BALANCE OF EFFECTS

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:

Individual preferences need to be considered.

● COSTS

How large are the resource requirements (costs)?

Judgement:

☒ Don't know	☐ Varies	☐ Large costs	☐ Moderate costs	☐ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:

No research evidence was identified

Panel discussion:

Costs for COCPs, anti-androgens, and metformin vary according to specific preparations, insurance and health care arrangements.

COCP availability might be an issue in some countries, i.e. cyproterone acetate is not available in all regions.

Using combinations of medications increases costs. Currently, evidence is limited regarding the benefits of multiple medications.

● CERTAINTY OF COST EVIDENCE

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

No research evidence was identified

Panel discussion:

Insufficient data is available to accurately answer this query.

● COST-EFFECTIVENESS

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

No research evidence was identified

Panel discussion:

No data are available regarding cost effectiveness on COCP, anti-androgens, and/or metformin for management of PCOS. No data are available specifically regarding lifestyle interventions. However, one presumes that weight loss and healthy lifestyle interventions likely improve general health and lower health care expenses. .

● EQUITY

What would be the impact on health equity?

Judgement:

☐ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☒ Probably increased	☐ Increased

Research evidence:

No research evidence was identified

Panel discussion:

Updated recommendations will likely benefit all individuals and have a positive impact on health equity.

● ACCEPTABILITY

Is the option acceptable to key stakeholders?

Judgement:

☐ Don't know	☒ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Key stakeholders include:

Health care system: COCP, metformin, and antiandrogens are not approved as specific treatments for PCOS by regulatory bodies. Currently, evidence-based and expert opinions favor the use of the medications for treatment of specific symptoms in individuals with PCOS.

Health care professionals are likely to find the recommendation acceptable (COCP and/or metformin) when targeting specific symptoms. Unsure of acceptability of combination treatments.

Patient acceptance (women) can vary if there are moral and ethical barriers to using COCP and/or if adherence issues exist when multiple combinations are proposed.

Patient acceptance (adolescent) can vary if parent/s and or guardian/s are concerned about specific therapies.

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PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by ECR Lead: Victoria Fitz

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Supervised, edited and supported by the Evidence Team (Aya Mousa, Jillian Tay)

GDG 4

Question 4.7.

In adolescents and adults with PCOS, is inositol alone or in combination with other therapies, effective for management of hormonal and clinical PCOS features, weight and reproductive outcomes**?**

CONTENTS

Table 1. PICO Criteria for Inclusion – Not to be adapted To be used by evidence team to decide which studies will be included when screening search results.	
Question	Q 4.7) In adolescents and adults with PCOS, is inositol alone or in combination with other therapies, effective for management of hormonal and clinical PCOS features, weight and reproductive outcomes?
Clinical leads (key contacts)	**Non-reproductive outcomes** **Dr Carolyn Ee** General practitioner Western Sydney University, Australia C.Ee@westernsydney.edu.au **Prof Selma Witchel** Paediatric endocrinologist Children's Hospital of Pittsburgh of UPMC, University of Pittsburg, USA witchelsf@upmc.edu **A/Prof Alexia Pena Vargas** Paediatric endocrinologist The Robinson Research Institute at the University of Adelaide, Australia alexia.pena@adelaide.edu.au **Prof Poli Mara Spritzer** Endocrinologist Universidade Federal do Rio Grande do Sul, Brazil spritzer@ufrgs.br **Reproductive outcomes** **Prof Rong Li** Obstetrician-gynaecologist Reproductive Medical Centre, Peking University Third Hospital, China roseli001@sina.com
Allocation ranking	Level 1- New systematic review

3. Selection criteria

In adolescents and adults with PCOS, is inositol alone or in combination with other therapies, effective for management of hormonal and clinical PCOS features, weight and reproductive outcomes

PICO	P	I	C	O	Study type	Limits
Inclusion	Females with PCOS (diagnosed by Rotterdam, NIH or AES) of any age, ethnicity and weight. Subgroups: adolescents (10-19y), adults (incl. peri-menopause), post-menopausal, overweight/obesity	Inositol (Myoinsotiol or D-Chiroinositol) alone or in combination, and combined with usual care, lifestyle, or any other interventions. Any dose and any duration.	Placebo or any other intervention (listed in intervention) or combinations of those listed in intervention. Comparisons should be meaningful to delineate the effects of inositol.	Androgenicity: Hirsutism- FG score (ethnicities), FAI, testosterone, SHBG, DHEAS, androstenedione, Irregular cycles Metabolic: insulin resistance HOMA, Clamp, OGTT Lipids: Chol LDL, HDL TG, CRP Psychological: Qol, depression Anthropometric: weight BMI, WHR, body composition Adverse effects: All Reproductive outcomes (for GDG 5): Live birth rate, pregnancy rate (biochemical or clinical ultrasound), ovulation, single and multiple pregnancies, miscarriage rate, other adverse events, quality of life, cost effectiveness.	Evidence based guidelines, systematic reviews, randomised controlled trials	English language. New search. No limit on date
Exclusion	Females without PCOS.		Agent or combination used in the intervention.			

2. SEARCH STRATEGY

Table 2.1. Search details	
Search strategy source: *[enter doi or 2018 technical report page number where search string was derived]*	
Evidence source	**Date of search**
Medline (Ovid)	8/5/2022
PsychInfo (Ovid)	8/5/2022
EMBASE (Ovid)	8/5/2022
All EBM (Ovid)	8/5/2022
CINAHL	8/4/2022
Any subsequent updates - enter database and date:	

Table 2.2. Questions addressed by this search *(add more rows as needed)*:		
GDG	Q#	Question
5	4.7	**In adolescents and adults with PCOS, is inositol alone or in combination with other therapies, effective for management of reproductive outcomes?**

Table 2.3. Search strings used in OVID or other database/s – *please save a screenshot of search results to submit alongside this template*

OVID Medline, All EBM, PsychInfo, EMBASE	CINAHL	Other?
Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present Ovid Nursing Database <1946 to July Week 5 2022> 1 exp inositol/ 24363 2 inositol*.tw. 39404 3 (mesoinositol or d-chiro-inositol).tw. 339 4 (myoinositol or myo-inositol).tw. 8348 5 1 or 2 or 3 or 4 48154 6 (inositol* or myo?inositol* or myo inositol* or meso?inositol* or meso inositol* or i-inositol* or epi?inositol* or epi inositol* or chiro?inositol* or chiro inositol* or l-chiro?inositol* or l-chiro inositol*).mp. 47314 7 5 or 6 49878 8 exp polycystic ovary syndrome/ 17425 9 polycystic ovar*.mp. 22975 10 poly-cystic ovar*.mp. 52 11 PCO*.mp. 36888 12 (stein-leventhal or leventhal).mp. 947 13 anovulation.mp. [mp=ti, bt, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy, dw] 4548 14 anovulat*.mp. 6924 15 oligo-ovulat*.mp. 110 16 oligoovulat*.mp. 61 17 (ovar* adj5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*)).mp. 23970	See attached PDF for CINAHL search strategy	

18 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 50850 19 7 and 18 347 20 limit 19 to english language 330 APA PsycInfo <1967 to July Week 4 2022> APA PsycInfo <1806 to 1966> APA PsycTests <1910 to July 2022> 1 exp inositol/ 0 2 inositol*.tw. 1631 3 (mesoinositol or d-chiro-inositol).tw. 0 4 (myoinositol or myo-inositol).tw. 722 5 (inositol* or myo?inositol* or myo inositol* or meso?inositol* or meso inositol* or i-inositol* or epi?inositol* or epi inositol* or chiro?inositol* or chiro inositol* or l-chiro?inositol* or l-chiro inositol*).mp. 1920 6 1 or 2 or 3 or 4 or 5 1920 7 exp polycystic ovary syndrome/ 0 8 polycystic ovar*.mp. 527 9 poly-cystic ovar*.mp. 1 10 PCO*.mp. 1138 11 (stein-leventhal or leventhal).mp. 369 12 anovulation.mp. [mp=ti, ab, hw, tc, id, ot, tm, mf, td] 78 13 anovulat*.mp. 161 14 oligo-ovulat*.mp. 0 15 oligoovulat*.mp. 0 16 (ovar* adj5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*)).mp. 546 17 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 1842 18 6 and 17 2 19 limit 18 to english language 2 EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016> EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012> EBM Reviews - Health Technology Assessment <4th Quarter 2016> EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016> EBM Reviews - ACP Journal Club <1991 to July 2022> EBM Reviews - Cochrane Central Register of Controlled Trials <July 2022> EBM Reviews - Cochrane Database of Systematic Reviews <2005 to August 3, 2022>		

EBM Reviews - Cochrane Clinical Answers <July 2022>

1 exp inositol/ 500
2 inositol*.tw. 782
3 (mesoinositol or d-chiro-inositol).tw. 103
4 (myoinositol or myo-inositol).tw. 503
5 (inositol* or myo?inositol* or myo inositol* or meso?inositol* or meso inositol* or i-inositol* or epi?inositol* or epi inositol* or chiro?inositol* or chiro inositol* or l-chiro?inositol* or l-chiro inositol*).mp. 1016
6 1 or 2 or 3 or 4 or 5 1113
7 exp polycystic ovary syndrome/ 1712
8 polycystic ovar*.mp. 4675
9 poly-cystic ovar*.mp. 136
10 PCO*.mp. 6256
11 (stein-leventhal or leventhal).mp. 99
12 anovulation.mp. [mp=ti, tx, kw, ab, hw, ct, ot, fx, sh] 820
13 anovulat*.mp. 1193
14 oligo-ovulat*.mp. 55
15 oligoovulat*.mp. 32
16 (ovar* adj5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*)).mp. 4868
17 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 8226
18 6 and 17 219
19 limit 18 to english language 213

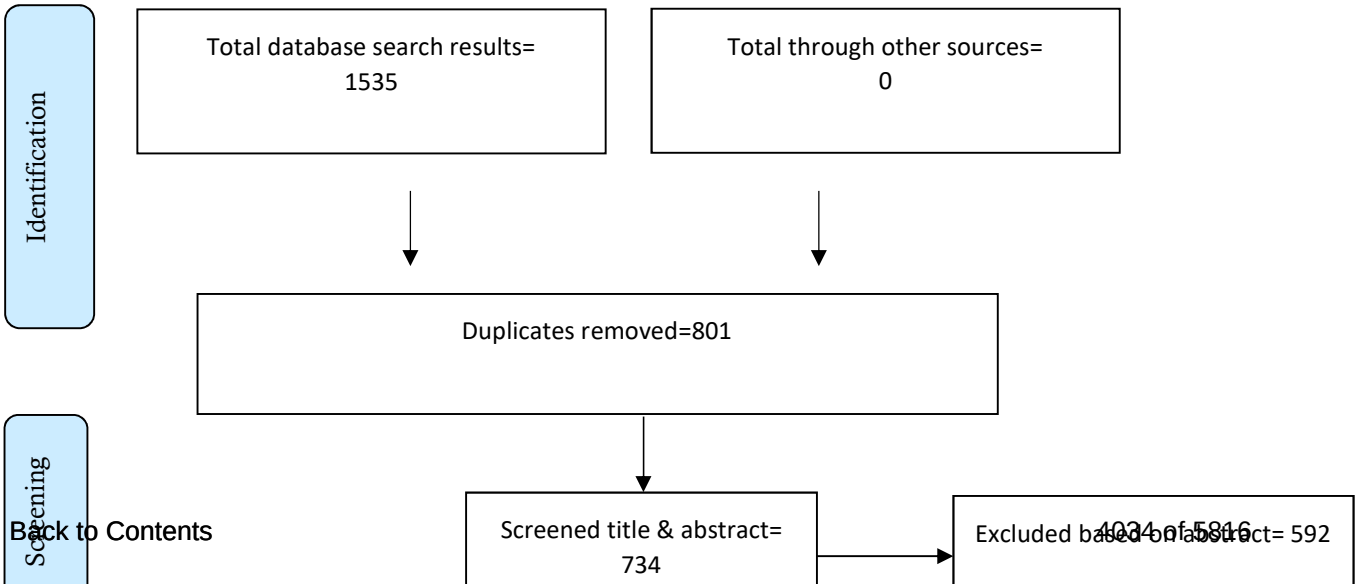
Embase Session Results

No.	Query	Results
#18	#10 AND #16 AND [english]/lim	588
#17	#10 AND #16	643
#16	#11 OR #12 OR #13 OR #14 OR #15	59,222
#15	'inositol*' OR 'myo?inositol*' OR 'myo inositol' OR 'meso?inositol*' OR 'meso inositol*' OR 'i-inositol*' OR 'epi inositol*' OR 'epi?inositol' OR 'chiro?inositol*' OR 'chiro inositol*' OR 'l-chiro?inositol*' OR 'l-chiro inositol*'	58,947
#14	'myoinositol':ab,ti	8,723
#13	'mesoinositol':ab,ti	177
		44,192

#12 **'inositol'**:ab,ti **15,281** **#11** **'inositol'**/exp **89,626** **#10** **#1** OR **#2** OR **#3** OR **#4** OR **#5** OR **#6** OR **#7** OR **#8** OR **#9** **38,902** **#9** **'ovar*'** NEAR/5 (**'sclerocystic'** OR **'polycystic'** OR **'poly-cystic'** OR **'degenerat*'** OR **'hyperandrogen*'** OR **'hyper-androgen*'**) **259** **#8** **'oligoovulat*'** **158** **#7** **'oligo-ovulat*'** **11,188** **#6** **'anovulat*'** **8,525** **#5** **'anovulation'** **64,932** **#4** **'pco*'** **207** **#3** **'poly-cystic ovar*'** **28,812** **#2** **'polycystic ovar*'** **34,486** **#1** **'polycystic ovary syndrome'**/exp		

Evidence processing: Studies were selected and appraised by 9 reviewer/s in consultation with the evidence team/ key contact using study selection and appraisal criteria (PICO above) established a priori. The articles were reviewed by title and abstract by 9 reviewers. When a decision could not be made based on title and abstract alone, full text was retrieved. In total, **36 studies met inclusion criteria for this review and 26 were included after integrity assessment.**

3. SEARCH RESULTS - PRISMA flowchart



4. STUDY INCLUSION

Table 4.1. Included Studies (full citation with doi)- add more rows as needed
Akbari Sene, Azadeh, Azam Tabatabaie, Hossein Nikniaz, Ahad Alizadeh, Kourosh Sheibani, Mona Mortezapour Alisaraie, Maryam Tabatabaie, Mahnaz Ashrafi, and Fatemehsadat Amjadi. 2019. "The Myo-Inositol Effect on the Oocyte Quality and Fertilization Rate among Women with Polycystic Ovary Syndrome Undergoing Assisted Reproductive Technology Cycles: A Randomized Clinical Trial." Archives of Gynecology & Obstetrics 299 (6): 1701–7. https://doi.org/10.1007/s00404-019-05111-1.
Angik, Riju, Shubhada S. Jajoo, C. Hariharan, and Amogh Chimote. 2017. "A Comparative Study of Metabolic and Hormonal Effects of Myoinositol vs. Metformin in Women with Polycystic Ovary Syndrome: A Randomised Controlled Trial." International Journal of Reproduction, Contraception, Obstetrics and Gynecology; Vol 4, No 1 (2015): January-February 2015. https://www.ijrcog.org/index.php/ijrcog/article/view/1838/1588.
Artini, P.G., O.M. Di Berardino, F. Papini, A.D. Genazzani, G. Simi, M. Ruggiero, and V. Cela. 2013. "Endocrine and Clinical Effects of Myo-Inositol Administration in Polycystic Ovary Syndrome. A Randomized Study." Gynecological Endocrinology 29 (4): 375–79. https://doi.org/10.3109/09513590.2012.743020.
Bahadur, Anupama, Hitanshi Arora, Anoosha K Ravi, Manisha Naithani, Yogesh Bahurupi, Jaya Chaturvedi, Megha Ajmani, and Rajlaxmi Mundhra. 2021. "Comparison of Clinical, Metabolic and Hormonal Effects of Metformin Versus Combined Therapy of Metformin With Myoinositol Plus D-Chiro-Inositol in Women With Polycystic Ovary Syndrome (PCOS): A Randomized Controlled Trial." Cureus 13 (6): e15510. https://doi.org/10.7759/cureus.15510.
Benelli, E., S. Del Ghianda, C. Di Cosmo, and M. Tonacchera. 2016. "A Combined Therapy with Myo-Inositol and D-Chiro-Inositol Improves Endocrine Parameters and Insulin Resistance in PCOS Young Overweight Women." International Journal of Endocrinology 2016 ((Benelli E., elena684@interfree.it; Del Ghianda S., scilladg@hotmail.it; Di Cosmo C., katiadicosmo@yahoo.it; Tonacchera M., mtonacchera@hotmail.com) Department of Clinical and Experimental Medicine, Section of Endocrinology, University Hospital of Pisa, V). https://doi.org/10.1155/2016/3204083.
Chirania, Kishan, Sujata Misra, and Sandhya Behera. 2017. "A Randomised Clinical Trial Comparing Myoinositol and Metformin in PCOS." International Journal of Reproduction, Contraception, Obstetrics and Gynecology; Vol 6, No 5 (2017): May 2017DO - 10.18203/2320-1770.Ijrcog20171563. https://www.ijrcog.org/index.php/ijrcog/article/view/2671.
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Donà, G., C. Sabbadin, C. Fiore, M. Bragadin, F.L. Giorgino, E. Ragazzi, G. Clari, L. Bordin, and D. Armanini. 2012. "Inositol Administration Reduces Oxidative Stress in Erythrocytes of Patients with Polycystic Ovary Syndrome." European Journal of Endocrinology 166 (4): 703–10. https://doi.org/10.1530/EJE-11-0840.
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Mendoza, N., M.P. Diaz-Ropero, M. Aragon, V. Maldonado, P. Llaneza, J. Lorente, R. Mendoza-Tesarik, J. Maldonado-Lobon, M. Olivares, and J. Fonolla. 2019. "Comparison of the Effect of Two Combinations of Myo-Inositol and D-Chiro-Inositol in Women with Polycystic Ovary Syndrome

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Studies Excluded After Integrity Check
Agrawal, A., R. Mahey, G. Kachhawa, R. Khadgawat, P. Vanamail, and A. Kriplani. 2019. "Comparison of Metformin plus Myoinositol vs Metformin Alone in PCOS Women Undergoing Ovulation Induction Cycles: Randomized Controlled Trial." Gynecological Endocrinology 35 (6): 511–14. https://doi.org/10.1080/09513590.2018.1549656.
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Roy SB. 2020. "A Study of the Effect of Metformin Versus Myo-Inositol in the Management of PCOS — A Randomised Controlled Trial" 118 (7): 40.
M. Jamilian et al., "Comparison of myo-inositol and metformin on clinical, metabolic and genetic parameters in polycystic ovary syndrome: A randomized controlled clinical trial.," Clin Endocrinol (Oxf), vol. 87, no. 2, pp. 194–200, 2017, doi: 10.1111/cen.13366.
Pkhaladze L, Russo M, Unfer V, Nordio M, Basciani S, and Khomasuridze A, "Treatment of lean PCOS teenagers: a follow-up comparison between Myo-Inositol and oral contraceptives," European review for medical and pharmacological sciences, vol. 25, no. 23, p. 7476, 2021, doi: 10.26355/eurrev20211227447.
M. Shokrpour et al., "Comparison of myo-inositol and metformin on glycemic control, lipid profiles, and gene expression related to insulin and lipid metabolism in women with polycystic ovary syndrome: a randomized controlled clinical trial.," Gynecol Endocrinol, vol. 35, no. 5, pp. 406–411, 2019, doi: 10.1080/09513590.2018.1540570.

Table 4.2. Excluded Studies (on full text assessment)- *add more rows as needed*

Reference	Reason
Agrawal 2015	No full text available, abstract only
Agrawal 2012	Wrong patient popultion
Akbarisene 2019	Abstract only
Akhtar 2021	Wrong comparator
Al-Mosawi 2021	Wrong patient population
AziziKutenaei 2021	Wrong Study Design
Bahadur 2018	Abstract Only
Cappelli 2013	Not in English
Carlomagno 2020	Abstract only
Cianci 2015	Wrong Intervention
Ciotta 2012	Abstract only
Ciotta 2012	Not in English
Cirillo 2018	Abstract Only
Colak 2020	Wrong study design
Colazingari 2013	Wrong comparator
DeLeo 2012	No fill text available
Deepti 2017	Wrong intervention
Formuso 2015	No full text available
Fruzzetti 2019	Wrong study design
Genazzani 2014	Wrong study design
Gennarelli 2020	Abstract only
Hoxha 2016	Abstract only
Immediata 2014	Abstract only
Isabella 2012	Duplicate
Isabella 2012	Wrong outcomes
Jamilian 2018	Wrong intervention
Janati 2022	Wrong outcomes
Januszewski 2019	Wrong study design
Jethaliya 2022	Wrong study design
Kitaya 2019	Wrong study design
Lesoine 2016	Wrong outcomes
Lisi 2012	Wrong patient population
Llaneza 2018	Abstract only
Mahey 2018	Abstract only
Mahey 2018	Abstract only
Malhotra 2019	Abstract only
Mendoza 2020	Wrong intervention
Minozzi 2011	Wrong study design
Montanino Oliva 2018	Wrong intervention
Moretti 2016	Abstract only
Morgante 2011	Wrong study design
Mazirudeen 2022	Abstract only
Nehra 2019	Abstract only
Nehra 2019	Abstract only

Nestler 2001	Abstract only
Noreen 2021	Abstract only
Oliva 2019	Wrong intervention
Obetzova 2016	Wrong intervention; abstract only
Ozay 2016	Wrong intervention
Ozay 2019	Wrong intervention
Pakhale 2022	Abstract only
Panico 2016	No full text available
Prabhakar 2021	Wrong comparator
Raissouni 2010	Abstract only
Rajasekaran 2020	Abstract only
Rajasekaran 2020	Abstract only
Rolland 2017	Wrong intervention
Salehpour 2016	Wrong study design
Schillaci 2012	Wrong patient population
Singh 2021	Wrong study design
Soldat – Stankovic 2021	Duplicate
Soldat – Stankovic 2021	Duplicate
Soufizadeh 2021	Wrong intervention
Stracquadanio 2017	Wrong intervention
Tabatabaie 2022	Wrong outcomes
Tilwani 2014	Abstract only
Troisi 2019	Wrong study design
Vartanyan 2-17	Wrong patient population
Wdowiak 2016	Wrong study design
Zacche 2009	Wrong study design
Zarazadeh 2022	Wrong study design
Zhang 2021	Wrong study design
Mahey 2018	Abstract only
Cheang 2008	Wrong study design (excluded during data extraction)
Rastegar 2021	Wrong intervention (excluded during data extraction)
21 remaining references were clinical trial registrations without associated author names	

5. DATA EXTRACTION TABLES

DICHOTOMOUS OUTCOMES –

i. D- chiro-inositol (DCI)

i. D-Chiro Inositol (DCI) v Placebo

OUTCOME: Ovulation							**OUTCOME TYPE:** Dichotomous			
		COMPARISON (if applicable): DCI v Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Iuorno et al. 2002	N of women who ovulated	Serum prog > 8.0ng/mL	6	-	10	2	-	10	crude	NA

ii. Myoinositol (MI) + DCI comparisons

ii. MI+DCI+FA v MI+FA

OUTCOME: Oligomenorrhoic patients			**OUTCOME TYPE:** Dichotomous
		COMPARISON (if applicable): MI + DCI + FA vs MI + FA	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Le Donne 2019 – 3mo	No definition of oligomenorrhoea was provided	count	2	-	12	9	-	10	Crude	NA
Le Donne 2019- 6 mo	No definition of oligomenorrhoea was provided	count	0	-	12	2	-	10	Crude	NA

iii. MI+DCI+Met vs Met

OUTCOME: Menstrual regularity					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): MYI+DCI+Metformin vs Metformin alone								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Bahadur 2021	%	Reported as menstrual irregularity	Rate=38.9%	NA (N=36 in this group)	Rate=63.9%	NA (N=36 in this group)	Crude	NA

iv. MI+DCI v MI+DCI

OUTCOME: Menses			**OUTCOME TYPE:** Dichotomous
		COMPARISON (if applicable): MI + DCI vs MI + DCI	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group N	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Nordio et al. 2019	count	Number of participants who had return of menses	1:3.5 = 0 2.5:1 = 0 5:1 = 1 20:1 = 3 40:1 = 5 80:1 = 4		n = 8 n = 7 n = 8 n = 8 n = 8 n = 8	0:1 = 0		n = 8	Crude	NA

OUTCOME: Pregnancy Rate (positive HCG among those who had embryo transfer)										
OUTCOME TYPE: Dichotomous										
		COMPARISON (if applicable): MI + DCI vs MI + DCI								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Mendoza 2019	Count	+HCG 2 weeks post retrieval	N = 17	-	25	6	-	19	Crude	NA

OUTCOME: Pregnancy Rate (positive HCG among all participants includes spontaneous pregnancies)										
OUTCOME TYPE: Dichotomous										
		COMPARISON (if applicable): MI + DCI vs MI + DCI								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

Mendoza 2019	Count	+HCG 2 weeks post retrieval	N = 19	-	30	N = 7	-	30	Crude	NA

OUTCOME: Live Birth Rate (among all participants includes IVF+spontaneous pregnancies)										
		COMPARISON (if applicable): MI + DCI vs MI + DCI								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Mendoza 2019	Count	+HCG 2 weeks post retrieval	N = 15	-	30	N = 4	-	30	Crude	NA

- Note the results in study have n=16 for live births in intervention group due to counting a twin delivery counted as 2 live births. Reduced count by 1 to correct for this.

iii. MI Comparisons

v. MI+FA vs FA alone

OUTCOME: Ovulation rate						**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): MI + FA v FA alone										
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention**	**Sample size**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Sample size**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

				/ exposure group			**comparison group**			
Pourghasem 2019	N of women with normal ovarian function	Mature follicle on TVU	31	-	50	24	-	50	Crude	NA

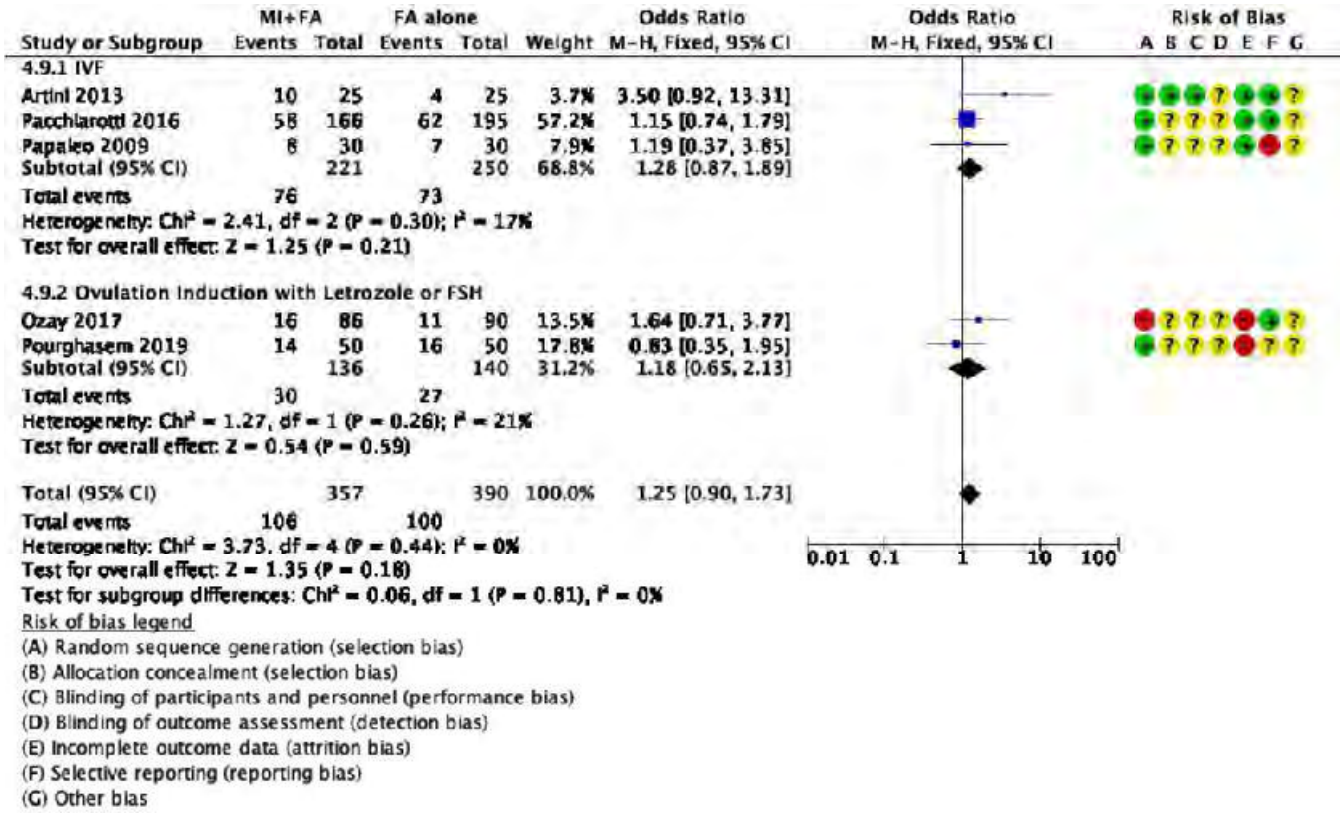
OUTCOME: Live birth rate				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): eg. MI+FA vs FA alone								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Artini et al 2013	%		32%	Not provided	12%	Not provided	Crude	

OUTCOME: Pregnancy rate – biochemical	**OUTCOME TYPE:** Dichotomous
COMPARISON (if applicable): Myo-Inositol + Folic Acid versus Folic Acid alone	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Papaleo 2009	Count	% defined as a small transitory increase in bHCG	n=1	9.1%	n=1	10%	Crude	NA

OUTCOME: Pregnancy rate – clinical				**OUTCOME TYPE:** Dichotomous					
COMPARISON (if applicable): Myo-Inositol + Folic Acid versus Folic Acid alone									
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**	**Co intervention**
Papaleo 2009	Count	Visualization of an embryo with cardiac activity at 6-7 weeks	n=8	26.6%	n=7	23.3%	Crude	NA	IVF
Pacchiarotti 2016	Count	%	n=58/166	36.7%	n=62/195	31%	Crude	NA	IVF

Artini et al 2013	%	US confirmed	40% (n=10)	Not provided	16% (n=4)	Not provided	Crude		IVF
Ozay et al 2017	%	US confirmed	18.6% (n=16/86)	Not provided	12.2% (n=11/90)	Not provided	Crude		COH + IUI
Pourghasem 2019	N	Gestational sac on US at 5 weeks N=50	14	-	16 N=50	-	Crude		Letrozole



a. Figure 1. MI+FA v FA alone: Clinical Pregnancy Rate

OUTCOME: Pregnancy rate (+HCG)	**OUTCOME TYPE:** Dichotomous	
COMPARISON (if applicable): Myo-Inositol + Folic Acid versus Folic Acid alone		

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?	Cointervention
Papaleo 2009	Count	% Total number of pregnancies including biochemical, SAB and clinical	n=11	37.9% (of 29 because 1 cycle was cancelled)	n=10	37.0% (of 27 because 3 cycles was cancelled)	Crude	NA	IVF
Artini et al 2013	%	Positive HCG	60% (n=15)	Not provided	32% (n=8)	Not provided	Crude		IVF
Akbari Sene 2019	%	Unclear if +hcg or clinical preg rate	40%	Not provided	35%	Not provided	Crude		IVF

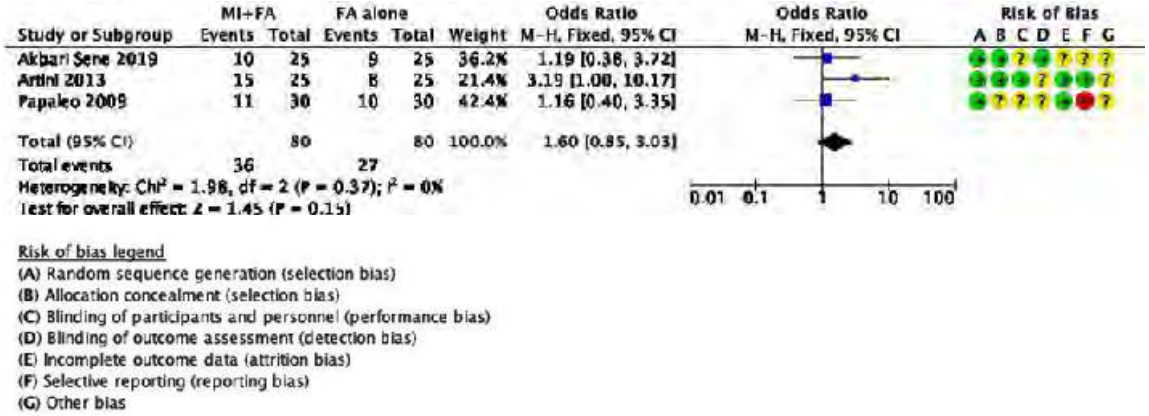


Figure 2. MI+FA v FA alone Pregnancy Rate (+HCG)

OUTCOME: Multiple Pregnancies				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Myo-Inositol + Folic Acid versus Folic Acid alone								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Pacchiarotti 2016	Count	%	n=36	20.0%	n=41	21.0%	Crude	NA
Ozay 2017	N		N= 2/16	Not provided	N=1/11	Not provided	Crude	na

**MA not done as this is comparing letrozole to IVF

OUTCOME: Miscarriages				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Myo-Inositol + Folic Acid versus Folic Acid alone								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Pacchiarotti 2016	Count	%	n=5	8.6%	n=24	38.7%	Crude	NA
Ozay 2017	%		12.5%	Not provided	18.2%	Not provided	Crude	NA

**MA not done as this is comparing letrozole to IVF

OUTCOME: N of singleton pregnancies				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): eg. MI+FA vs FA alone								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Ozay 2017	N		N=14/16	Not provided	N=10/11	Not provided	Crude	

vi. MI+Met v Met alone

OUTCOME: Resumption of spontaneous menstrual cycles					**OUTCOME TYPE: Dichotomous**					
		COMPARISON (if applicable): MI + Metformin v Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Chirania 2017	N	NR	16	NA	22	12	NA	28	Crude	NA

vii. MI v DCI

OUTCOME: biochemical pregnancies					**OUTCOME TYPE:** Dichotomous					
COMPARISON (if applicable): MI v DCI										
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Unfer 2011	count	Small and transitory increase in serum bHCG levels	3	-	43	2		41	Crude	NA

OUTCOME: Clinical pregnancies					**OUTCOME TYPE:** Dichotomous					
COMPARISON (if applicable): MI v DCI										
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Unfer 2011	count	Embryonic heart beat on ultrasound	15	-	43	5	-	41	Crude	NA

OUTCOME: Total pregnancies	**OUTCOME TYPE:** Dichotomous
COMPARISON (if applicable): MI v DCI	

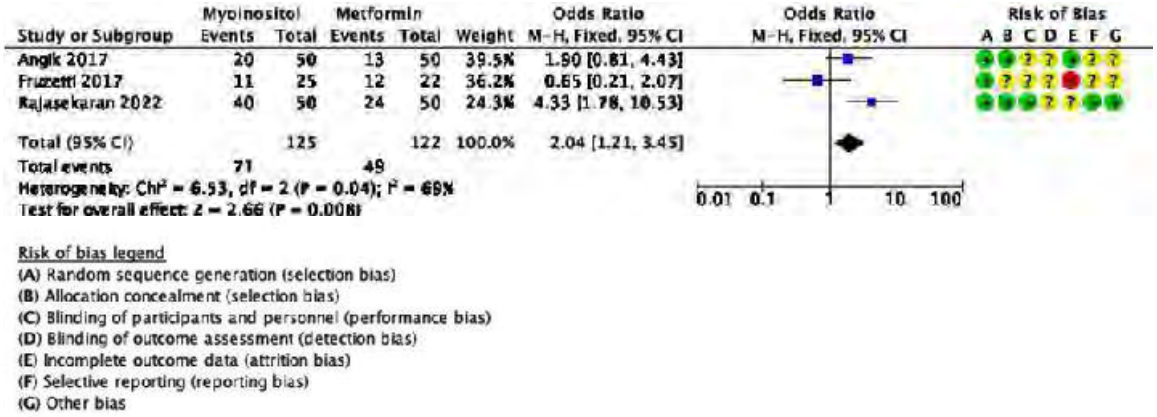
Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Unfer 2011	count	Unclear	22	-	43	10	-	41	Crude	NA

OUTCOME: Miscarriage rate					**OUTCOME TYPE:** Dichotomous					
COMPARISON (if applicable): MI v DCI										
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Unfer 2011	count	NR	4	-	43	3	-	41	Crude	NA

viii. MI v Metformin

OUTCOME: n women with regular menstrual cycles						**OUTCOME TYPE:** Dichotomous				
		COMPARISON (if applicable): MI v Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Angik 2017	N	NR	20	NA	50	13	NA	50	Crude	NA
Tagliaferri 2017	n	Number of cycles in 6 months	Median= 4	IQR= 2.75		Median= 6	IQR= 0		Crude	NA
Rajasekaran 2022	N	Not described	40		50	24		50	Crude	NA

Chirania 2017	N	Number without menstrual irregularity	22	NA	26	12	NA	28	Crude	NA
Fruzzetti et al. 2017	%	Menstrual cycle length was expressed as the average of days between cycles during the previous 6 months.		Normal: 44% (n=11) Improved, but not normal: 38% No changes: 18%	25		Normal: 53% (n=12) Improved, but not normal: 27% No changes: 20%	22	Crude	NA



a. Figure 3. MI v Met Resuming regular menses

OUTCOME: Ovulation rate					**OUTCOME TYPE:** Dichotomous					
COMPARISON (if applicable): MI vs Metformin										
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention /**	**Sample size**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in**	**Sample size**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

				exposure group			**control/ comparison group**			
Pourghasem 2019	N of women with normal ovarian function	Mature follicle on TVU	31	-	50	33	-	50	Crude	NA
Raffone et al. 2010	n (%)	Spontaneous ovarian activity - by weekly serum progesterone dosage, as well as transvaginal ultrasound scan documenting presence of follicular growth or luteal cyst.	39 (65%)	-	60	30 (50%)	-	60	Crude	NA

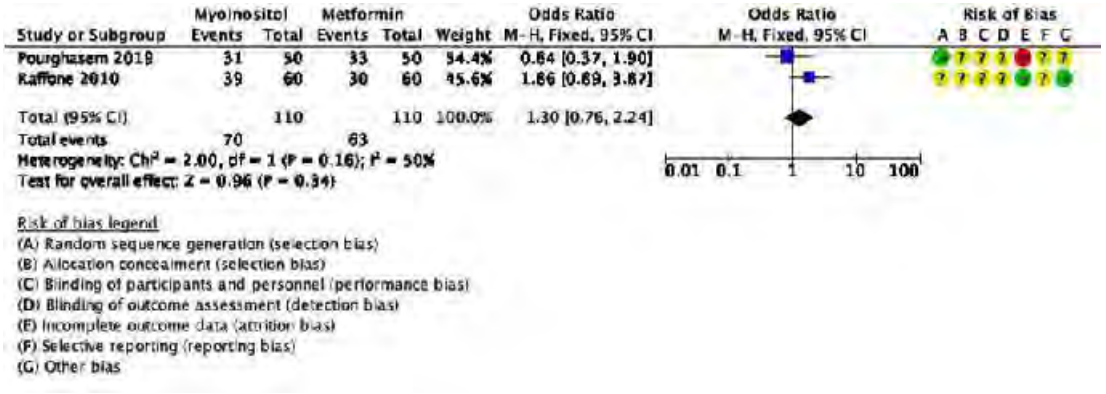
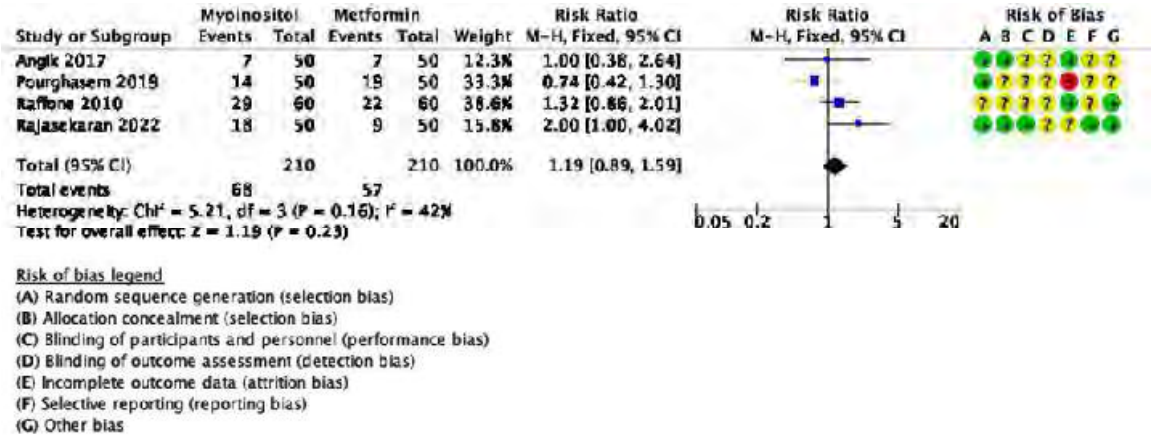


Figure MI v Met Ovulation Rate

OUTCOME: Clinical pregnancy rate						**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): MI vs Metformin										
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Pourghasem 2019	N	Gestational sac on US at 5 weeks	14	-	50	19	-	50	Crude	NA
Angik 2017	N	NR	7	NA	50	7		50		
Rajasekaran 2022	N	NR	18		50	9		50	Crude	NA
Raffone et al. 2010	n (%)	documented by positive β-hCG plasma level and fetal heart beat on ultrasound	29 (48.3%)		60	22 (36.6%)		60	Crude	NA



b. Figure 4. MI v Met Clinical pregnancy rate

OUTCOME: Pregnancy rate per IVF cycle						**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): MI vs Metformin										
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample Size**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Rajasekaran 2022	N (%)	Number of pregnancies from IVF/Total of IVF cycles	5		37	3		44	Crude	NA

OUTCOME: Miscarriage rate			**OUTCOME TYPE:** Dichotomous
		COMPARISON (if applicable): MI versus Metformin	

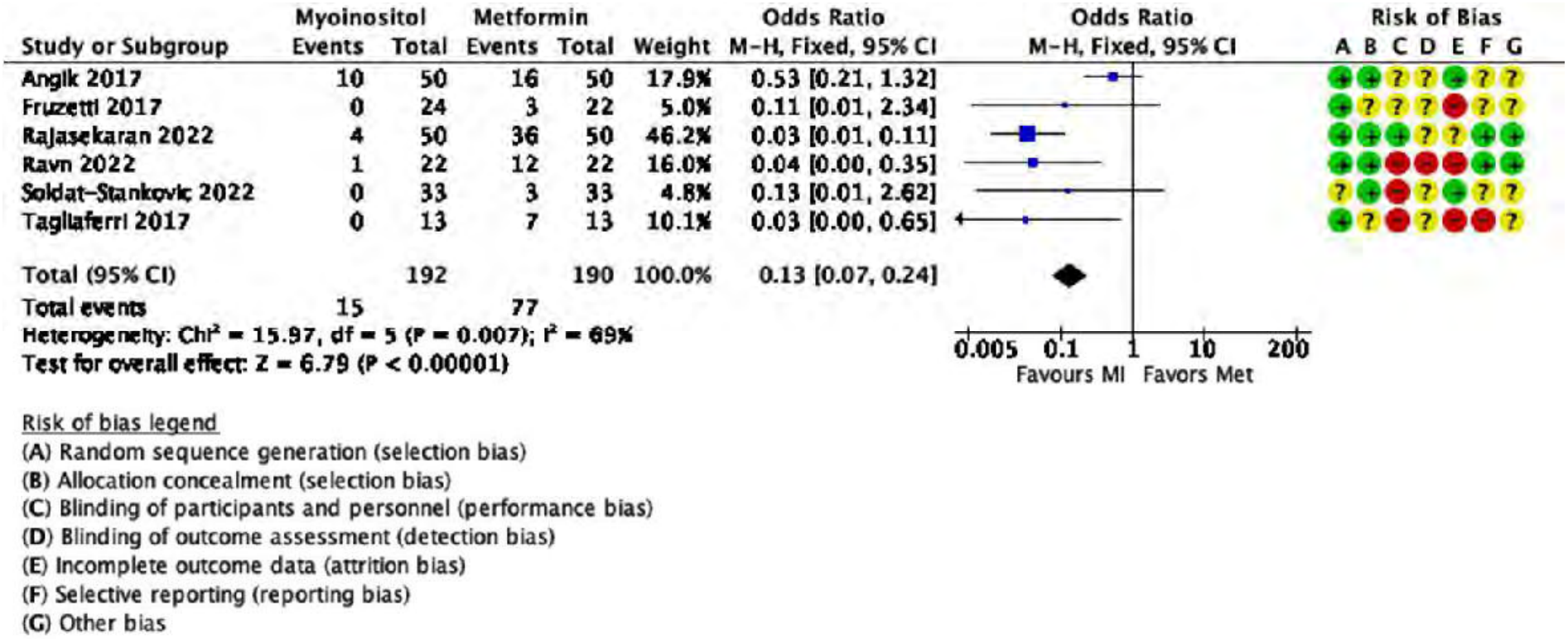
Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Raffone et al. 2010	n (%)	Pregnancy. Losss after confirmation of intrauterine pregnancy		6 (20.6%)	29		5 (22.7%)	22	Crude	NA

OUTCOME: lactic acidosis						**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): MI vs Metformin										
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Angik 2017	%	NR	0%	NA	50	2%		50		

OUTCOME: Generalised weakness						**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): MI vs Metformin										
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: SE, IQR or 95% CI) in**	**Sample size**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Sample size**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

				control/ comparison group			comparison group			
Angik 2017	%	NR	0%	NA	50	38%		50		

OUTCOME: GI Side effects						**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): MI vs Metformin										
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Angik 2017	% (nausea)	NR	2%	NA	50	32%		50		
Tagliaferri 2017	n	Reported incidents	N=0	NA	13	N=7	NA	13	Crude	NA
Rajasekaran 2022	N (%)		4		50	36		50	Crude	NA
Fruzzetti et al. 2017	n	diarrhoea and abdominal pain	0		24	3		22	Crude	
Soldat-Stankovic, 2022	Event	Clinical report	n=0	NA	33	Intolerable gastrointestinal disturbances that were not corrected by temporary reduction in dose n=3	NA	33	NA	NA
Ravn et al. 2022	n	GI side effects	1		22	12		23	Crude	



c. Figure 34. MI v Met GI Side Effects

OUTCOME: menorrhagia	**OUTCOME TYPE:** Dichotomous
COMPARISON (if applicable): MI vs Metformin	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Angik 2017	%	NR	14%	NA	50	0%		50		

ix. MI v Placebo

None

x. MI + Monacolin K v Inositol v Met

OUTCOME: Gastrointestinal side-effects						**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): MI + monacolin K vs Inositol vs Metformin										
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Leo 2013	rate	Not reported	N=2, 10%	Not reported	20	Inositol n=1, 5% Metformin: no numbers provided of rate of SE, just that n=2 'interrupted treatment' 'the women treated with metformin reported severe side effects like nausea and diarrhoea and	Inositol: Not reported Metformin: Not reported	Inositol=20 Metformin=20	Crude	NA

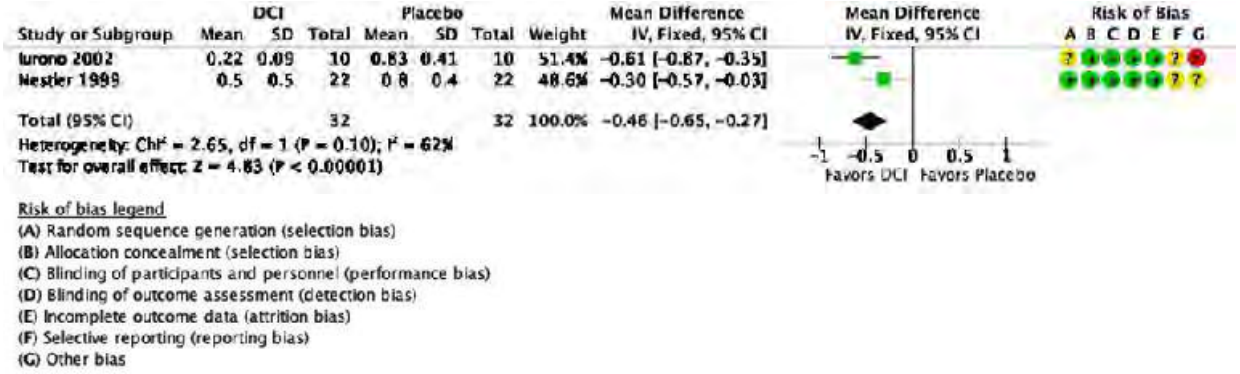
						two women interrupted treatment'				

CONTINUOUS OUTCOMES

iv. D-Chiro Inositol

xi. DCI v Placebo

OUTCOME: Testosterone free							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): DCI v Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Iuorno et al. 2002	ng/dL	NR	0.22	SE 0.03/SD 0.09	10	0.83	SE 0.13/SD 0.41	10	crude	NA
Nestler et al. 1999	Ng/dl	NR	0.5	0.5		0.8	0.4		crude	n/a



a. Figure 5. Free Testosterone DCI v Placebo

OUTCOME: Testosterone total							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): eg. DCI v Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Iuorno et al. 2002	ng/dL	NR	34	SE 4.3/SD 13.6	10	108	SE 7.5/SD23.72	10	crude	NA
Nestler et al. 1999	Ng/dl		61	33	22	79 (placebo B vitamin)	39	22	Crude	NA

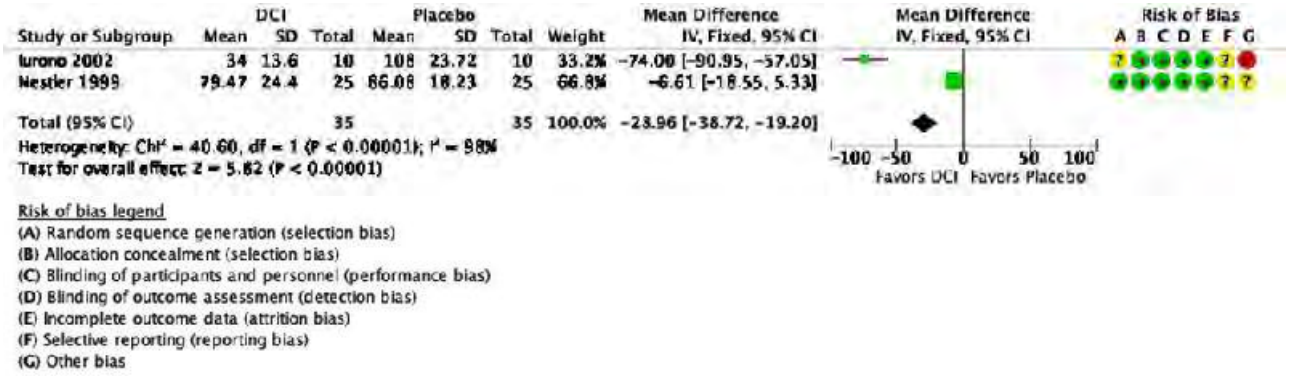
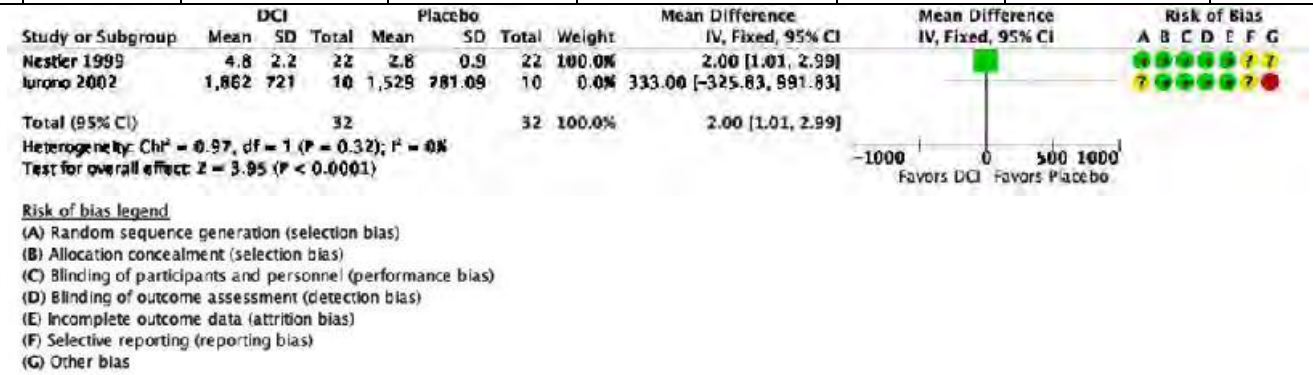


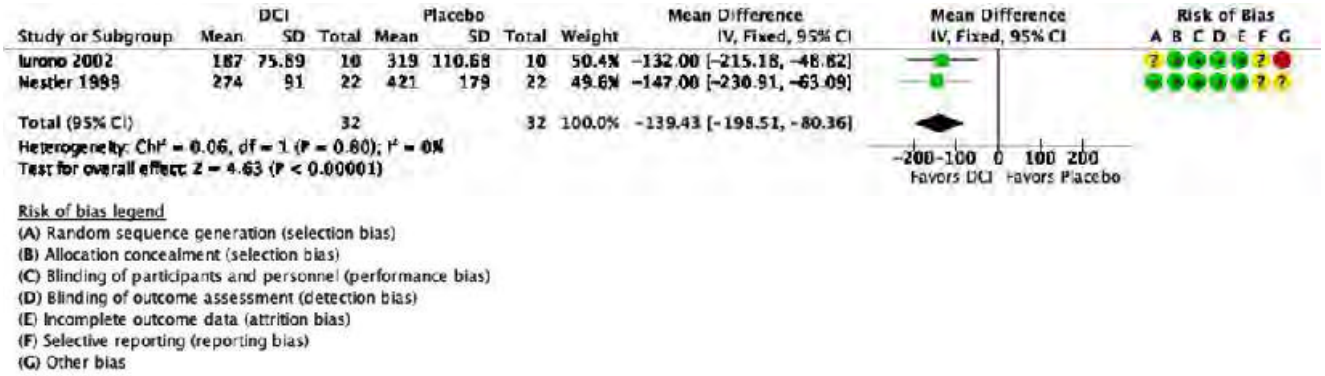
Figure 6. DCI v Placebo Total testosterone

OUTCOME: SHBG										**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable): DCI v Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Iuorno et al. 2002	Nmol/L	NR	196 (1862mcg/dL)	SE 24/SD 75.89 (720.995 mcg/dL)	10	161 (1529.5mcg/dL)	SE 26/ SD82.22 (781.09)	10	crude	NA
Nestler et al. 1999	µg/dl		4.8	2.2	22	2.8	0.9	22	crude	NA

OUTCOME: DHEAS										
OUTCOME TYPE: Continuous										
		COMPARISON (if applicable): DCI v Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Iuorno et al. 2002	ng/dL	NR	187	SE 24/SD 75.89	10	319	SE 35/SD 110.68	10	crude	NA
Nestler et al. 1999	µg/dl		274	91	22	421	179	22	crude	NA

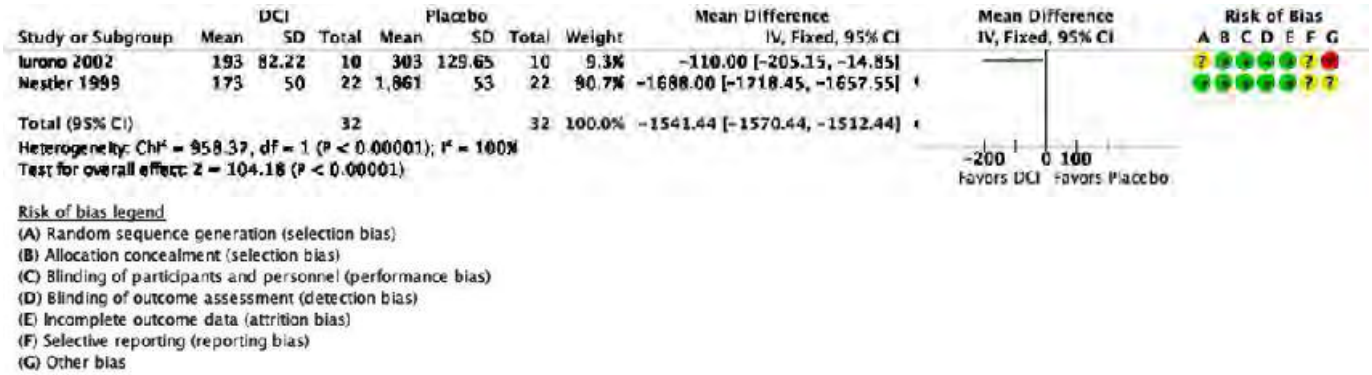


b. Figure 7. DCI v Placebo SHBG



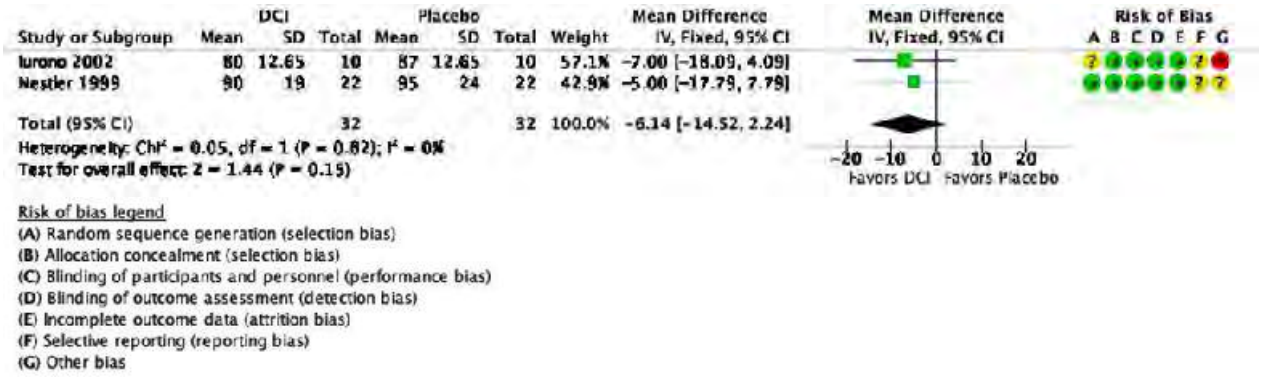
c. Figure 8. DCI v Placebo DHEAS

OUTCOME: Androstenedione										
OUTCOME TYPE: Continuous										
		COMPARISON (if applicable): DCI v Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Iuorno et al. 2002	ng/dL	NR	193	SE 26/SD 82.22	10	303	SE 41/SD129.65	10	crude	NA
Nestler et al. 1999	Ng/dl	NR	173	50	22	1861	53	22	Crude	NA



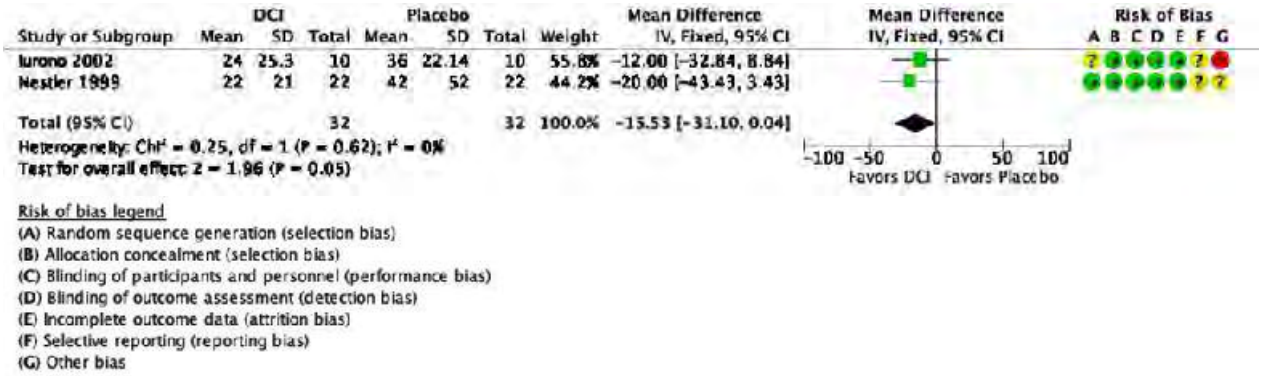
d. Figure 9. DCI v Placebo Androstendione

OUTCOME: Fasting glucose										
		COMPARISON (if applicable): DCI v Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Iuorno et al. 2002	mg/dL	NR	80	SE 4/ 12.65	10	87	SE 4/SD 12.65	10	crude	NA
Nestler et al. 1999	Mg/dl		90	19	22	95	24	22	crude	NA



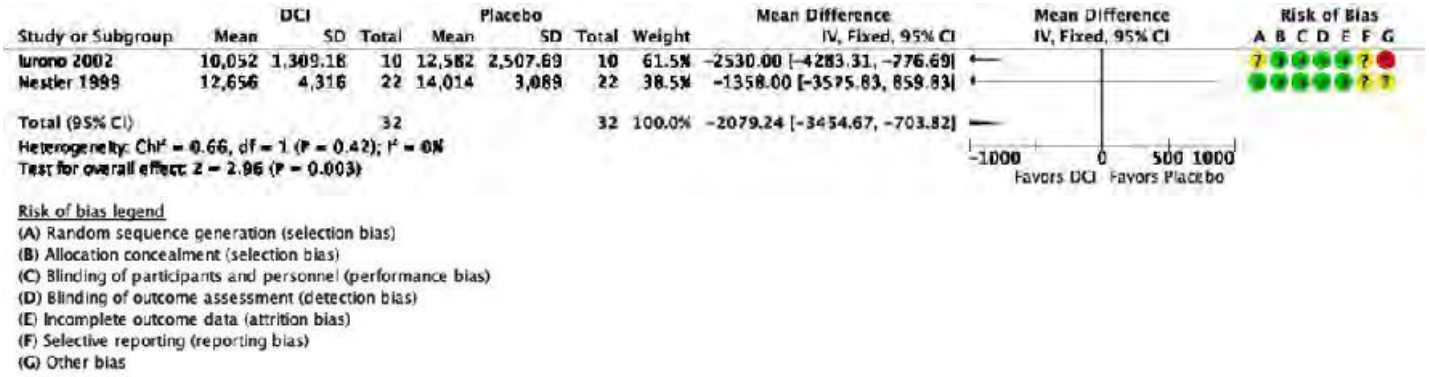
e. Figure 10. DCI v Placebo Fasting glucose

OUTCOME: Fasting insulin										
		COMPARISON (if applicable): DCI v Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Iuorno et al. 2002	µU/mL	Commercial kit	24	SE 8/ 25.30	10	36	SE 7/SD 22.14	10	crude	NA
Nestler et al. 1999	µU/ml		22	21	22	42	52	22	crude	NA



f. Figure 11. DCI v Placebo Fasting Insulin

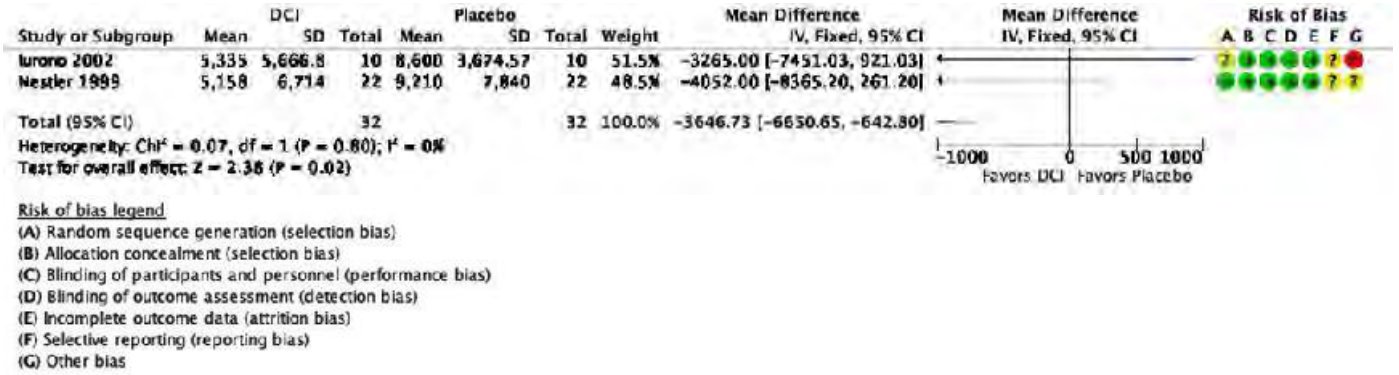
OUTCOME: AUCglucose										**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable): DCI v Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Iuorno et al. 2002	mg/dL/min	Not reported	10,052	SE 414/ SD1309.18	10	12,592	SE 793/SD2507.69	10	crude	NA
Nestler et al. 1999	mg/dl/min		12,656	4316	22	14,014	3089	22	crude	NA



g. Figure 12. DCI v Placebo – AUC Glucose

OUTCOME: AUCinsulin										**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable): DCI v Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Iuorno et al. 2002	µU/mL/min	Not reported	5,335	SE 1,792/ SD5666.8	10	8,600	SE 1,162/SD 3674.57	10	crude	NA

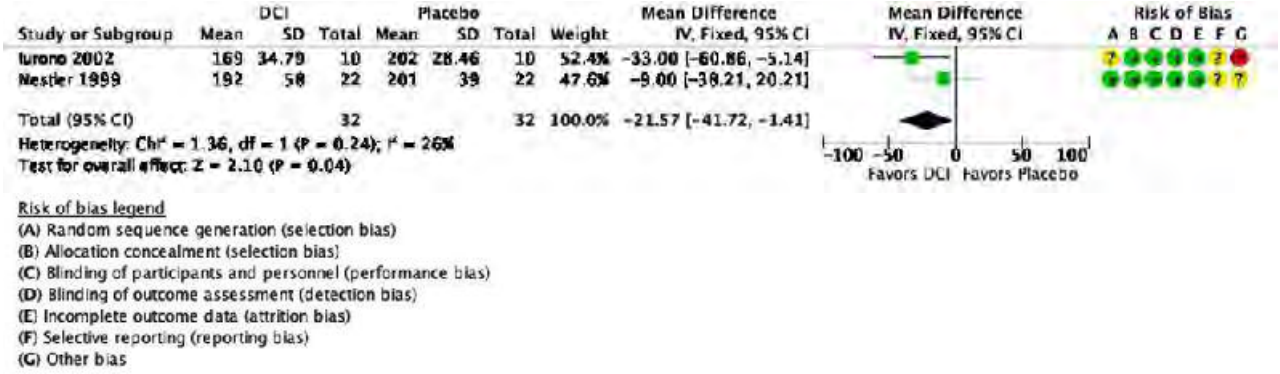
Nestler et al. 1999	µU/ml/min		5158	6714	22	9210	7840	22	crude	NA



h. Figure 13. DCI v Placebo AUC insulin

OUTCOME: Total cholesterol										**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable): DCI v Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

Iuorno et al. 2002	mg/dL	enzymatic colorimetric assays	169	SE 11/ 34.79	10	202	SE 9/SD 28.46	10	crude	NA
Nestler et al. 1999	Mg/dl		192	58	22	201	39	22	crude	NA



i. Figure 14. DCI v Placebo Total Cholesterol

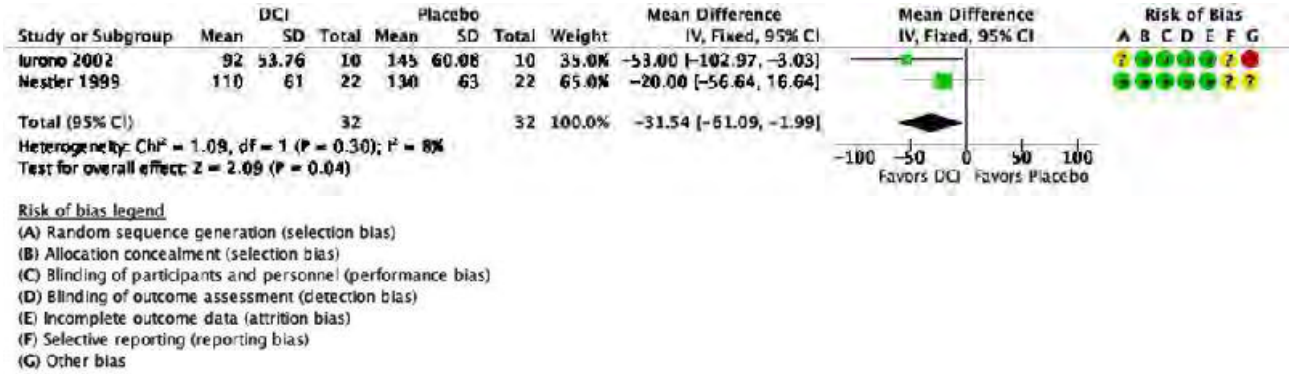
OUTCOME: LDL-C					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): DCI vs Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in**	**Mean (specify if median) or median in control /**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

				intervention / exposure group	**comparison group**	**comparison group**		
Nestler et al. 1999	Mg/dl		124	7	126	27	Crude	NA

OUTCOME: HDL-C					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): DCI vs Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Nestler et al. 1999	Mg/dl		38	8	38	8	Crude	NA

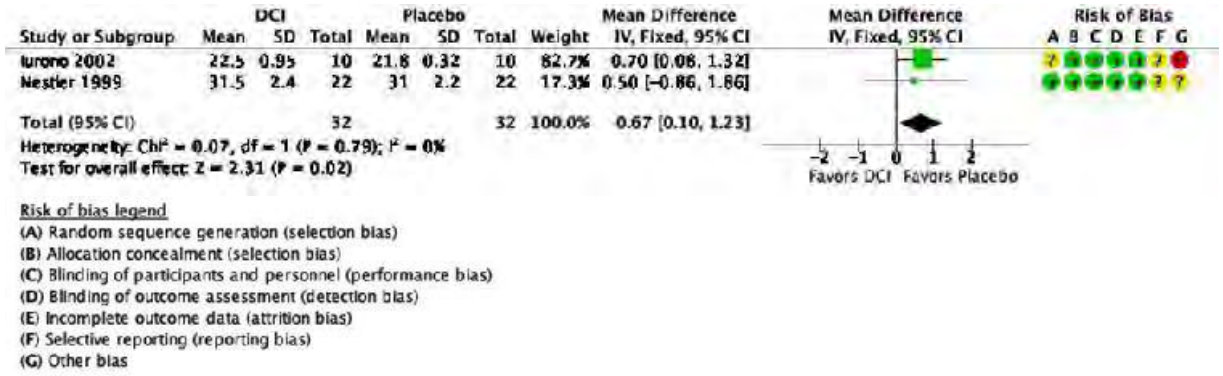
OUTCOME: Triglycerides			**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable): DCI v Placebo	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Iuorno et al. 2002	Mg/dL	enzymatic colorimetric assays	92	SE 17/SD 53.76	10	145	SE 19/SD 60.08	10	crude	NA
Nestler et al. 1999	Mg/dl		110	61	22	130	63	22	Crude	NA



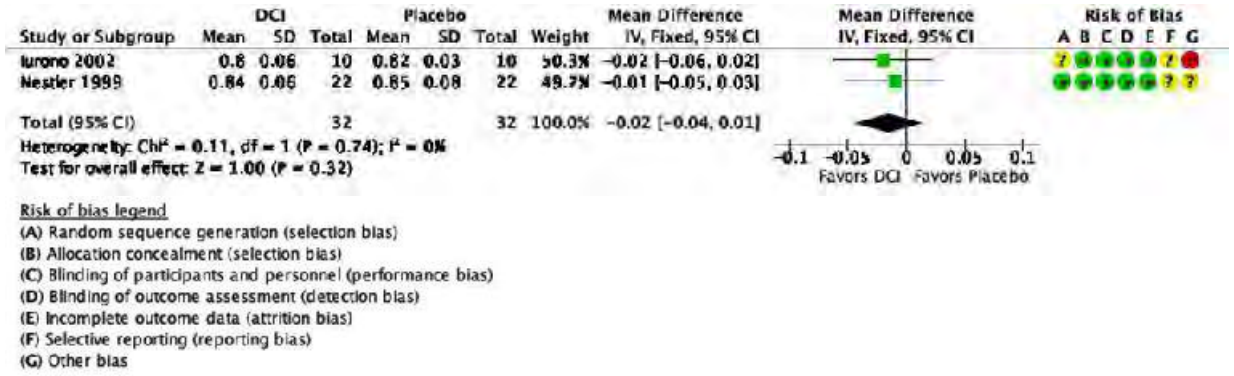
j. Figure 15. DCI v Placebo Triglycerides

OUTCOME: BMI						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable): DCI v Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Iuorno et al. 2002	Kg/m2	Not reported	22.5	SE 0.3 / SD 0.95	10	21.8	0.1/ SD 0.32	10	crude	NA
Nestler et al. 1999		Not reported	31.5	2.4	22	31.0	2.2	22	crude	NA



k. Figure 16. DCI v Placebo BMI

OUTCOME: WHR										**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable): DCI v Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Iuorno et al. 2002	Kg/m2	Not reported	0.8	SE 0.02/ SD 0.06	10	0.82	SE 0.01/SD 0.03	10	crude	NA
Nestler et al. 1999			0.84	0.06	22	0.85	0.08	22	crude	NA



l. Figure 17. DCI v Placebo WHR

OUTCOME: Progesterone				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): DCI vs Placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Nestler et al. 1999	Ng/ml		0.6	0.2	0.7	0.2	Crude	NA

v. Myoinositol (MI) + DCI comparisons

xii. MI+DCI+FA v MI+FA

OUTCOME: Hirsutism FG score				**OUTCOME TYPE:** Continuous						
		COMPARISON (if applicable): MI + DCI + FA vs MI + FA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

Le Donne 2019 6mo	NA	Ferriman-Gallwey score	5.2	3.4	12	7.8	5.1	10	Crude	NA

OUTCOME: BMI							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): MI + DCI + FA vs MI + FA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Le Donne 2019 – 3mo	Kg/m2		29.9	5.3	12	30.6	5.2	10	Crude	NA
Le Donne 2019 – 6mo	Kg/m2		28.2	5.4	12	29	4.4	10	Crude	NA

OUTCOME: Weight							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): MI + DCI + FA vs MI + FA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Le Donne 2019 – 3mo	Kg	NR	74.9	14.6	12	76.5	16.5	10	Crude	NA
Le Donne 2019 – 6 mo	Kg	NR	70.7	15.1	12	72.4	14.2	10	Crude	NA

OUTCOME: WHR										
		OUTCOME TYPE: Continuous								
		COMPARISON (if applicable): MI + DCI + FA vs MI + FA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Le Donne 2019 – 3 mo			0.84	0.06	12	0.79	0.1	10	Crude	NA
Le Donne 2019 – 6 mo			0.83	0.06	12	0.78	0.1	10	Crude	NA

OUTCOME: WC										
		OUTCOME TYPE: Continuous								
		COMPARISON (if applicable): MI + DCI + FA vs MI + FA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Le Donne 2019 – 3 mo	cm		87.2	12.1	12	86.5	13.2	10	Crude	NA
Le Donne 2019 – 6 mo	cm		83	10.4	12	81.7	12.1	10	Crude	NA

OUTCOME: Lean Mass										
		OUTCOME TYPE: Continuous								
		COMPARISON (if applicable): MI + DCI + FA vs MI + FA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Le Donne 2019 – 3 mo	Kg	BIO 101 instrument by Akern s.r.l (Pontassieve, Italy)	44.4	11.2	12	50.1	9	10	Crude	NA
Le Donne 2019 – 6mo	Kg	BIO 101 instrument by Akern s.r.l (Pontassieve, Italy)	45.8	9.3	12	50.9	9.3	10	Crude	NA

OUTCOME: Fat Mass						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable): MI + DCI + FA vs MI + FA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Le Donne 2019 – 3mo	Kg	BIO 101 instrument by Akern s.r.l (Pontassieve, Italy)	27.7	11	12	31.9	8.6	10	Crude	NA
Le Donne 2019 – 6 mo	Kg	BIO 101 instrument by Akern s.r.l (Pontassieve, Italy)	25.8	10.7	12	31.8	13.3	10	Crude	NA

OUTCOME: % Fat Mass						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable): MI + DCI + FA vs MI + FA								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Le Donne 2019 – 3 mo	%	BIO 101 instrument by Akern s.r.l	34.5	7.1	12	39.3	7.3	10	Crude	NA

		(Pontassieve, Italy)								
Le Donne 2019 – 6 mo	%	BIO 101 instrument by Akern s.r.l (Pontassieve, Italy)	32.8	7.9	12	36.6	7	10	Crude	NA

xiii. MI+DCI+FA v FA only

OUTCOME: Free Testosterone										
		COMPARISON (if applicable): MI + DCI + FA vs FA only								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Benelli 2016	ng/dL	Immune-enzymatic assay (Access Immunoassay System, free testosterone, Beckman Coulter, Brea, CA, USA)	0.62	0.15	n= 21	0.83	0.2	n= 25	Crude	NA

OUTCOME: SHBG						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable): MI + DCI + FA vs FA only								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Benelli 2016	nmol/L	Immunoassay (Access Immunoassay System, SHBG, Beckman Coulter, Brea, CA, USA).	35.85	24.3	n= 21	21.36	7.57	n= 25	Crude	NA

OUTCOME: DHEAS						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable): MI + DCI + FA vs FA only								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Benelli 2016	µg/dL	Conventional immunoassay (Access Immunoassay System, DHEAS, Beckman Coulter, Brea, CA, USA).	347.6	170.98	n= 21	315.83	145.59	n= 25	Crude	NA

OUTCOME: Androstenedione						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable): MI + DCI + FA vs FA only								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Benelli 2016	ng/mL	Immune-enzymatic assay (Access Immunoassay System, androstenedione, Beckman Coulter, Brea, CA, USA).	4.01	1.70	n= 21	3.12	2.23	n= 25	Crude	NA

OUTCOME: Fasting Glucose						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable): MI + DCI + FA vs FA only								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Benelli 2016	mg/dL		86	7.12	n= 21	84.73	8.3	n= 25	Crude	NA

OUTCOME: Fasting Insulin										**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable): MI + DCI + FA vs FA only								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Benelli 2016	µU/mL		10.74	5.46	n= 21	17.8	8.2	n= 25	Crude	NA

OUTCOME: HOMA										**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable): MI + DCI + FA vs FA only								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Benelli 2016			1.97	1.48	n= 21	2.8	1.4	n= 25	Crude	NA

3c. MI + DCI + Met v Met alone

OUTCOME: modified Ferriman Gallwey								**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): MYI+DCI+Metformin vs Metformin alone								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Bahadur 2021	score	Modified Ferriman-Gallwey score	4.86	2.70	5.47	3.22	Crude	NA

OUTCOME: Total testosterone				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): MYI+DCI+Metformin vs Metformin alone								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Bahadur 2021	Ng/dL	Day 2/3 of menstrual cycle	47.55	17.49	54.56	18.79	Crude	NA

OUTCOME: DHEAS				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): MYI+DCI+Metformin vs Metformin alone								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Bahadur 2021	µg/dL	Day 2/3 of menstrual cycle	188.62	97.81	191.37	88.96	Crude	NA

OUTCOME: Fasting glucose				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): MYI+DCI+Metformin vs Metformin alone								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Bahadur 2021	Mg/dL	Taken on day 2/3 of menstrual cycle	84.58	5.63	87.50	8.25	Crude	NA

OUTCOME: Fasting insulin					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): MYI+DCI+Metformin vs Metformin alone								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Bahadur 2021	mIU/L	Taken on day 2/3 of menstrual cycle	14.68	9.16	15.04	8.19	Crude	NA

OUTCOME: HOMA-IR					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): MYI+DCI+Metformin vs Metformin alone								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Bahadur 2021	Value	Taken on day 2/3 of menstrual cycle	3.08	2.05	3.23	1.73	Crude	NA

OUTCOME: Total cholesterol					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): MYI+DCI+Metformin vs Metformin alone								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Bahadur 2021	Mg/dL	Taken on day 2/3 of menstrual cycle	131.58	23.99	146.75	36.37	Crude	NA

OUTCOME: LDL					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): MYI+DCI+Metformin vs Metformin alone								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Bahadur 2021	Mg/dL	Taken on day 2/3 of menstrual cycle	85.89	19.84	106.16	22.78	Crude	NA

OUTCOME: HDL					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): MYI+DCI+Metformin vs Metformin alone								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Bahadur 2021	Mg/dL	Taken on day 2/3 of menstrual cycle	47.25	15.92	41.53	6.38	Crude	NA

OUTCOME: Triglycerides					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): MYI+DCI+Metformin vs Metformin alone								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Bahadur 2021	Mg/dL	Taken on day 2/3 of menstrual cycle	95.61	38.46	96.94	26.90	Crude	NA

OUTCOME: BMI	**OUTCOME TYPE:** Continuous

COMPARISON (if applicable): MYI+DCI+Metformin vs Metformin alone								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Bahadur 2021	Kg/m2	Overweight was defined using Asian BMI range of 23.0-26.9kg/m2. Obese was considered to be ³27kg/m2.	23.34	3.14	23.36	4.08	Crude	NA

OUTCOME: WHR				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): MYI+DCI+Metformin vs Metformin alone								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Bahadur 2021	Ratio	Not reported	0.85	0.05	0.85	0.08	Crude	NA

OUTCOME: WC				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): MYI+DCI+Metformin vs Metformin alone								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Bahadur 2021	cm	Not reported	82.81	8.20	81.11	12.68	Crude	NA

xiv. MI+DCI v MI

OUTCOME: Waist to hip ratio										
		COMPARISON (if applicable): eg. MI + DCI v MI								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Nordo and Proietti., 2012	ratio	Not reported. Only mention "calculated through standard equation."	0.87	0.04	12	0.87	0.02	24	Crude	NA

OUTCOME: BMI										
		COMPARISON (if applicable): eg. MI + DCI v MI								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Nordo and Proietti., 2012	kg/m2	Not reported. Only mention "calculated through standard equation."	26.9	2.4	12	27.3	2.1	24	Crude	NA

OUTCOME: Free testosterone			**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable): eg. MI + DCI v MI	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Nordo and Proietti., 2012	ng/dl	Not reported. In the morning, sex hormone binding globulin, serum steroids and lipid profile levels were measured.	3 months: 0.44 6 months: 0.23	3 months: 0.08 6 months: 0.02	26	3 months: 0.65 6 months: 0.24	3 months: 0.09 6 months: 0.03	24	Crude	NA

OUTCOME: Total testosterone										
		COMPARISON (if applicable): eg. MI + DCI v MI								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Nordo 2012	ng/dl	Not reported. In the morning, sex hormone binding globulin, serum steroids and lipid profile levels were measured.	3 months: 50.4 6 months: 32.7	3 months: 10.2 6 months: 10.0	26	3 months: 60.3 6 months: 40.1	3 months: 12.7 6 months: 9.	24	Crude	NA

OUTCOME: Androstenedione										
		COMPARISON (if applicable): eg. MI + DCI v MI								

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Nordo and Proietti., 2012	ng/dl	Not reported. In the morning, sex hormone binding globulin, serum steroids and lipid profile levels were measured.	3 months: 255 6 months: 194	3 months: 14 6 months: 15	26	3 months: 250 6 months: 198	3 months: 13 6 months: 19	24	Crude	NA

OUTCOME: DHEAS							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): eg. MI + DCI v MI								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Nordo and Proietti., 2012	µg/dl	Not reported	3 months: 278 6 months: 179	3 months: 32 6 months: 27	26	3 months: 320 6 months: 196	3 months: 31 6 months: 23	24	Crude	NA

OUTCOME: Sex hormone binding globulin (SHBG)							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): eg. MI + DCI v MI								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

Nordo and Proietti., 2012	nmol/L	Not reported Measured in the morning.	3 months: 180 6 months: 208	3 months: 17 6 months: 20	26	3 months: 160 6 months: 202	3 months: 24 6 months: 27	24	Crude	NA

OUTCOME: Glucose AUC						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable): eg. MI + DCI v MI								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Nordo and Proietti., 2012	mg/dl/min	Not reported. The incremental insulin ($AUC_{insulin}$) and glucose ($AUC_{glucose}$) areas under the curve (AUCs) were calculated by the trapezoidal method.	= 3 months: 12358 6 months: 10690	3 months: 515 6 months: 513	26	3 months: 16209 6 months: 11580	3 months: 447 6 months: 401	24	Crude	NA

OUTCOME: Fasting glucose						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable): eg. MI + DCI v MI								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

Nordo and Proietti., 2012	mg/dl	Not reported. Measured in the morning.	3 months: 85.9 6 months: 83.6	3 months: 7.2 6 months: 8.6	26	3 months: 93.2 6 months: 85.2	3 months: 10.9 6 months: 10.9	24	Crude	NA

OUTCOME: Fasting insulin						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable): eg. MI + DCI v MI								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Nordo and Proietti., 2012	µU/ml	Not reported. Measured in the morning.	3 months: 10.1 6 months: 9.2	3 months: 2.9 6 months: 2.1	26	3 months: 11.7 6 months: 9.6	3 months: 3.5 6 months: 1.9	24	Crude	NA

OUTCOME: HOMA index						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable): eg. MI + DCI v MI								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Nordo and Proietti., 2012		Not reported. The homeostasis model assessment (HOMA) was used as index of insulin resistance for each patient.	3 months: 1.82 6 months: 1.5	3 months: 0.12 6 months: 0.28	26	3 months: 2.2 6 months: 1.9	3 months: 1.3 6 months: 2.1	24	Crude	NA

xv. MI+DCI v Placebo

OUTCOME: Fasting glucose						**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Myo-inositol (MI) + D-Chiro-Inositol (DCI) versus Placebo										
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Khan et al. 2022	mg/dL	Not reported.	84.0	7.12	53	84.13	7.3	53	Crude	NA

xvi. MI+DCI v MI+DCI

OUTCOME: Free testosterone						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable): MI + DCI vs MI + DCI								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Mendoza 2019	No units		0.41	0.04	30	0.46	0.05	30	Crude	NA

OUTCOME: HOMA Index			**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable): MI + DCI vs MI + DCI	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Nordio et al. 2019	mU/ml	HOMA-IR	1:3.5 = 2.89 2.5:1 = 2.71 5:1 = 2.88 20:1 = 2.51 40:1 = 2.45 80:1 = 2.98	0.64 0.76 0.89 0.73 0.68 0.81	n = 8 n = 7 n = 8 n = 8 n = 8 n = 8	0:1 = 3.05	0.85	n = 8	Crude	NA
Mendoza et al. 2019		HOMA-IR	1.94	1.1	25	1.96	1.23	19	Crude	NA

OUTCOME: Basal Insulin / 3 months							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): MI + DCI vs MI + DCI								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Mendoza 2019	No units	Not reported	9.04	0.95	25	9.05	1.13	19	Crude	NA

OUTCOME: Glucose							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): MI + DCI vs MI + DCI								
Author, year	**Unit of outcome (e.g. g, mg, µg,**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control /**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

	mmol/L, etc.)					comparison group	comparison group			
Mendoza et al. 2019	Not provided		85.96	1.1	25	86.62	1.51	19	Crude	NA

vi. MI Comparisons

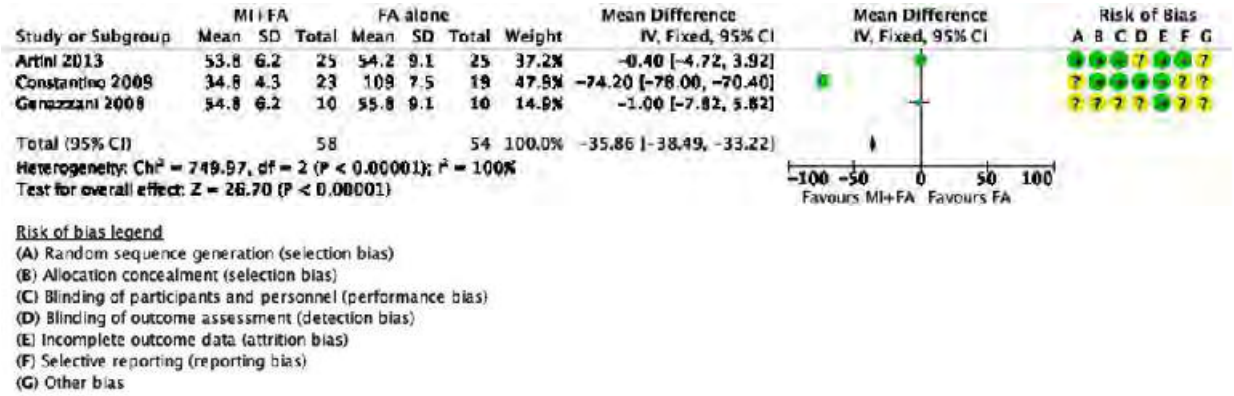
i. MI + FA v FA alone

3. **OUTCOME: Ferriman Gallway score**				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): eg. MI+FA vs FA alone								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Genazzani 2008		Not described	18	0.8	Not provided	Not provided	Crude	

OUTCOME: Free testosterone				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): eg. MI+FA vs FA alone								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in**	**Mean (specify if median) or median in control /**	**SD (or specify if other measure: SE, IQR or 95% CI)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

				intervention / exposure group	**comparison group**	**in control/ comparison group**		
Constantino 2009	ng/dl	Not described	0.24	0.03	0.85	0.13	Crude	

OUTCOME: Total testosterone				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): eg. MI+FA vs FA alone								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Artini 2013 (unsure if free or total)	Ng/dL	Not described	53.8	6.2	54.2	9.1	Crude	
Constantino 2009	ng/dl	Not described	34.8	4.3	109	7.5	Crude	
Genazzani 2008 (unsure if free or total)	ng/dl	radioimmunoassay	54.8	6.2	55.2	9.1	Crude	



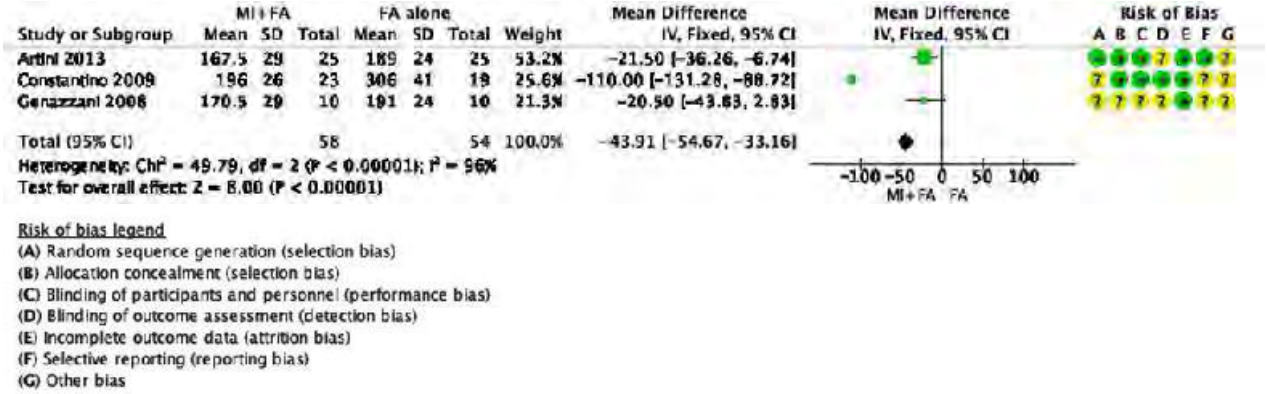
a. Figure 18. MI+FA v FA alone Total testosterone

OUTCOME: SHBG					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): eg. MI+FA vs FA alone								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Constantino 2009	Nmol/L	Not described	198	24	163	26	Crude	

OUTCOME: DHEAS				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): eg. MI+FA vs FA alone								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Constantino 2009	ug/dl	Not described	188	24	320	35	Crude	

OUTCOME: androstendione				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): eg. MI+FA vs FA alone								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

				/ exposure group		comparison group		
Artini 2013	Ng/100mL	Not described	167.5	29	189	24	Crude	
Constantino 2009	ng/dl	Not described	196	26	306	41	Crude	
Genazzani	ng/100ml	radioimmunoassay	170.5	29	191	24	Crude	

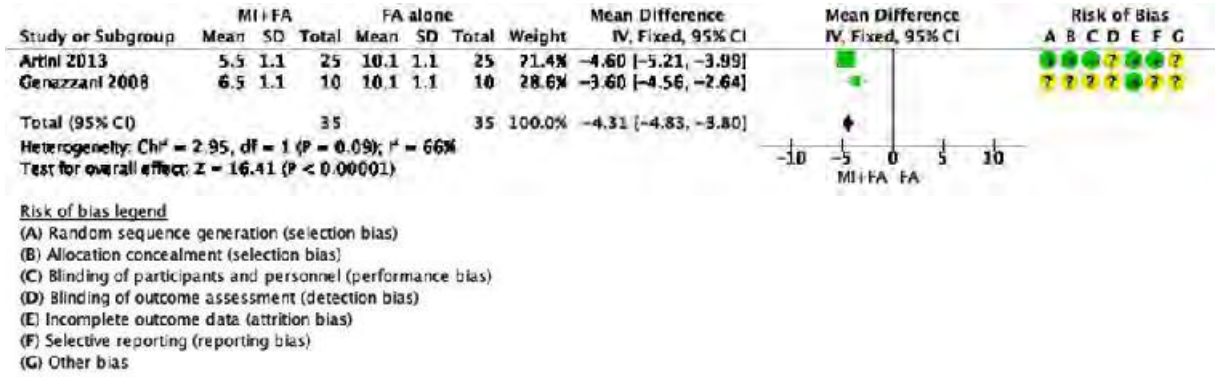


b. Figure 19. MI+FA v FA alone Androstenedione

OUTCOME: fasting glucose	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): eg. MI+FA vs FA alone	

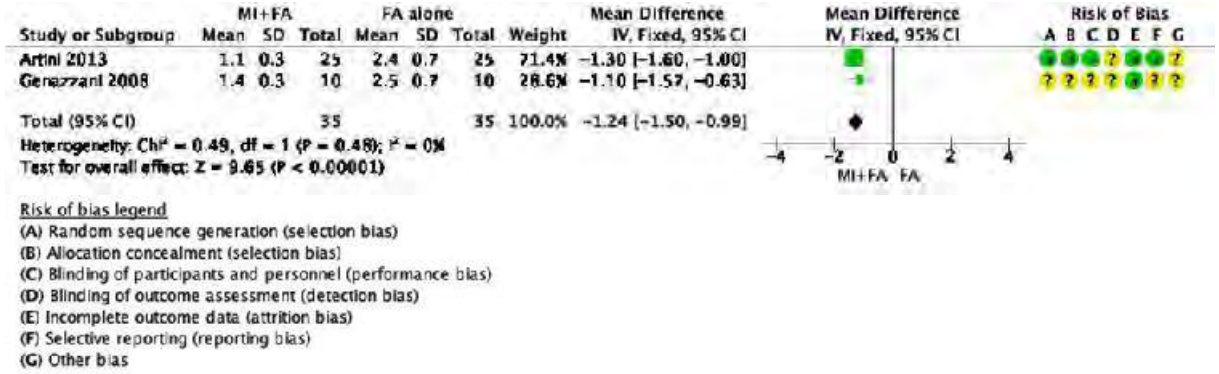
Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Gerli et al 2007	nmol/Liter	Glucose oxidase method	5.1	Not provided	5.0	Not provided	Crude	
Constantion 2009	mg/dl	Not described	81.6	4	88	4	Crude	

OUTCOME: fasting insulin				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): eg. MI+FA vs FA alone								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Gerli et al 2007	uU/mL	RIA	16.8	Not provided	17.3	Not provided	Crude	
Artini et al 2013	uU/mL	RIA	5.5	1.1	10.1	1.1	Crude	
Genazzani 2008	uU/mL	Immunoradiometric assay	6.5	1.1	11.3	1.1	Crude	



c. Figure 20. MI+FA v FA alone Fasting Insulin

OUTCOME: HOMA IR (fasting glucose *fasting insulin)/22.5					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): eg. MI+FA vs FA alone								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Artini et al 2013	(fasting glucose *fasting insulin)/22.5		1.1	0.3	2.4	0.7	Crude	
Genazzani 2008			1.4	0.3	2.5	0.7	Crude	



d. Figure 21. MI+FA v FA alone HOMA IR

OUTCOME: GTT insulin AUC – 75g OGTT					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): eg. MI+FA vs FA alone								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Artini et al 2013	None provided							Provided in a figure without discreet values – Fig 3
Constantino 2009	mcg/ml/min	None provided	5.535	1.792	9.1	1.162	Crude	

Genazzani 2008								Provided in Fig 2 without discreet values

OUTCOME: Total cholesterol				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): eg. MI+FA vs FA alone								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Constantino 2009	Mg/dl	Not provided	171	11	204	9	Crude	

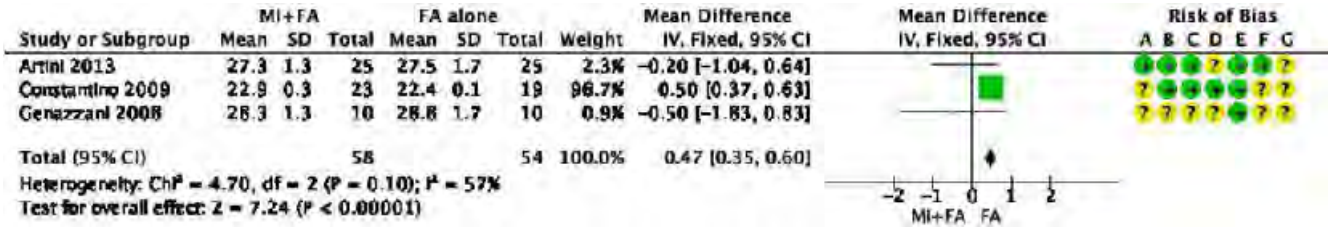
OUTCOME: GTT glucose AUC – 75g OGTT				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): eg. MI+FA vs FA alone								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

Constantino 2009	mg/ml/min	None provided	10.452	414	12.992	793	Crude	

OUTCOME: Triglycerides				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): eg. MI+FA vs FA alone								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Constantino 2009	mg/dl	Not provided	95	17	148	19	Crude	

OUTCOME: BMI				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): eg. MI+FA vs FA alone								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

Artini et al 2013	Kg/m^2		27.3	1.3	27.5	1.7	Crude	
Constantino 2009	Kg/m^2		22.9	0.3	22.4	0.1	Crude	
Genazzani 2008	Kg/m^2		28.3	1.3	28.8	1.7	Crude	



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

OUTCOME: WHR				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): eg. MI+FA vs FA alone								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in**	**Mean (specify if median) or median in control /**	**SD (or specify if other measure: SE, IQR or 95%**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

				intervention / exposure group	comparison group	CI) in control/ comparison group		
Constantino 2009	N/A		0.87	0.02	0.89	0.01	Crude	

e. Figure 22. MI+FA v FA alone, BMI

ii. MI+ Metformin v Metformin alone

OUTCOME: Fasting Insulin							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): eg. MI + Metformin v Metformin alone								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Chirania 2017	NR	NR	15.78	5.69	22	18.69	7.41	28	Crude	NA

OUTCOME: BMI			**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable): eg. MI + Metformin v Metformin alone	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Chirania 2017	NR	NR	25.62	4.02	22	25.14	2.67	28	Crude	NA

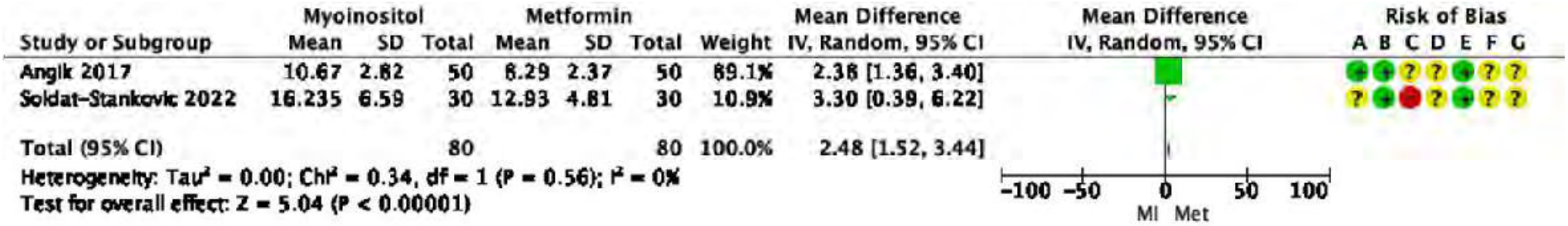
OUTCOME: Weight							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): eg. MI + Metformin v Metformin alone								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Chirania 2017	NR	NR	63.64	13.11	22	61.04	6.11	28	Crude	NA

iii. MI v Met

OUTCOME: mFG			**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable): MI v Metformin	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Angik 2017	NA	mFG	10.67	2.82	50	8.29	2.37	50	Crude	NA
Fruzzetti et al. 2017	mFG	%		No changes: 80% Slight improvement: 20% Worse: 0%	24		No changes: 76% Slight improvement: 12% Worse: 12%	22	Crude	NA
Ravn et al. 2022	FG			IQR 8 (3;12)	16		IQR 6 (2;12)	12		
Soldat-Stankovic 2022	Score	Ferriman-Gallwey	BMI ≤25 mean=15.00 BMI>25 mean=17.47 Calculated combined: 16.235	BMI ≤25 SD=5.84 BMI>25 SD=7.26 Calculated combined SD: 6.59	BMI ≤25 n=15 BMI>25 n=15 Calculated combined: 30	BMI ≤25 mean=12.93 BMI>25 mean=14.00 Calculated combined: 12.93	BMI ≤25 SD=4.60 BMI>25 SD=5.11 Calculated combined: 4.81	BMI ≤25 n=15 BMI>25 n=15 Calculated combined: 30	Crude	NA
Tagliaferri 2017	Score	Ferriman-Gallwey score The same two members of medical staff assessed FG-score at each visit, the mean between the two	Median= 11	IQR= 5.75		Median= 9.5	IQR= 5		Crude	NA

		considered for analysis.								



iv. Figure 11 Forest plot: MI v MET - FG score

OUTCOME: FAI				**OUTCOME TYPE:** Continuous					
COMPARISON (if applicable): MI vs Metformin									
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Sample size (n within this group)**	**Are these values adjusted or crude?**

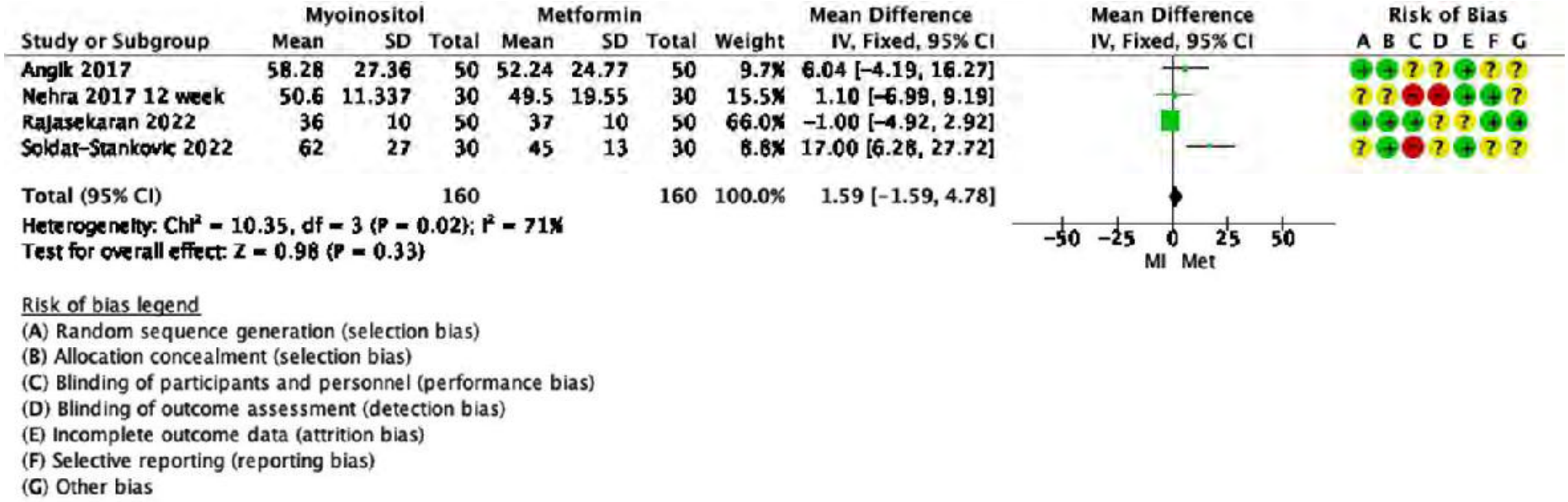
							comparison group		
Tagliaferri 2017	Ratio	Ratio of testosterone x 100/SHBG Testosterone and SHBG measurements needed for this calculation were performed with Electrochemiluminescence immunoassay (ECLIA) kits (Roche Diagnostics, Manheim, Germany).	Median= 5.3	IQR= 3		Median= 5.2	IQR= 1.5		Crude
Soldat-Stankovic, 2022	Index	Calculated using the formula 100xT (ng/dL)/28.84xSHBG (nmol/L)	BMI ≤25 mean=4.545 BMI>25 mean=8.45	BMI ≤25 SD=3.97 BMI>25 SD=9.59	BMI ≤25 n=15 BMI>25 n=15	BMI ≤25 mean=2.99 BMI>25 mean=5.38	BMI ≤25 SD=1.12 BMI>25 SD=3.46	BMI ≤25 n=15 BMI>25 n=15	Crude

OUTCOME: Free Testosterone							**OUTCOME TYPE:** Continuous		
		COMPARISON (if applicable): MI v Metformin							
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Ravn et al. 2022	nmol/L	Free testosterone was calculated		IQR 0.028 (0.025;0.045)	16		IQR 0.021 (0.017;0.028)	12	Crude	NA

		based on the Vermeulen equation with a standard albumin value of 4.3 g/dL								

OUTCOME: total testosterone							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): MI v Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Angik 2017	NR – also unclear if free or total testosterone. No SHBG so probably total	NR	58.28	27.36	50	52.24	24.77	50	Crude	NA
Mishra 2022	NR	NR	1.53	0.68	43	1.53	0.51	43		
Tagliaferri 2017	nmol/l (presumed total T)	Taken during early follicular phase of spontaneous or induced (medroxyprogesterone acetate 10mg/day for 7 days) menstrual cycles (day: 3±7) Performed with Electrochemiluminescence immunoassay (ECLIA) kits	Median= 1.4	IQR= 0.7		Median= 1.9	IQR= 0.8		Crude	NA

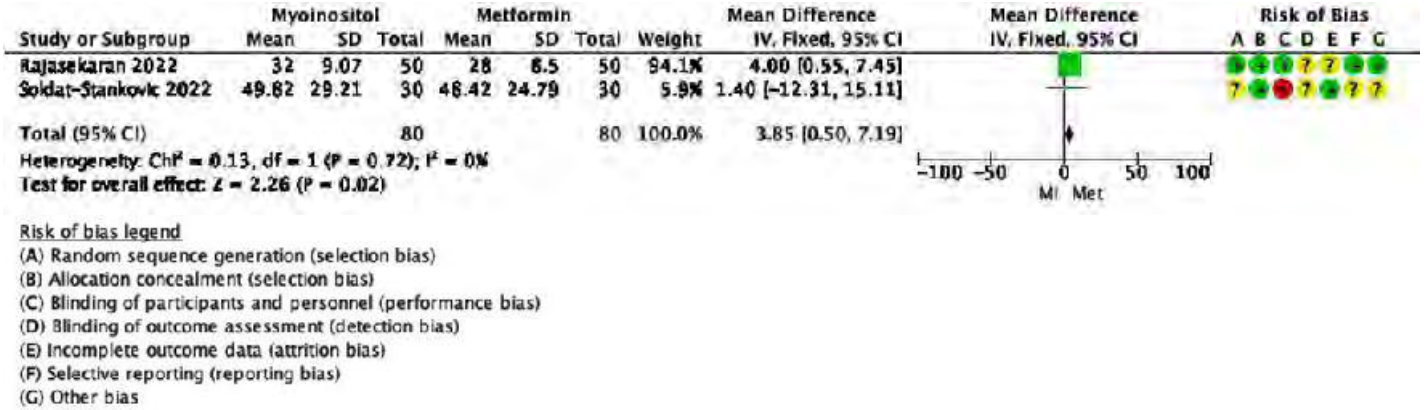
		(Roche Diagnostics, Manheim, Germany).								
Nehra 2017 (12 week measurement)	No units (presumed total T)	Not reported	50.06	SE 2.07 (SD = 11.337)		49.5	SE 3.57 (SD = 19.55)		Crude	NA
Rajasekaran 2022	ng/dL (presumed total T)	Not reported, obtained on CD 2-5	36	10		37	10		Crude	NA
Ravn et al. 2022	nmol/L	Plasma total testosterone was analyzed by liquid chromatography tandem mass spectrometry (Thermo Fischer Scientific, Waltham, MA, USA). CV was 3.3%.		IQR 1.2 (1.0;1.8)	16		IQR 1.2 (0.9;1.7)	12	Crude	NA
Soldat-Stankovic, 2022	ng/ml	Blood samples were collected after 12h of fasting during the early follicular phase (between the 3rd and 7th day) of the regular menstrual cycle, or at any time in case of severe oligo- or amenorrhoea.	BMI ≤25 mean=0.59 BMI>25 mean=0.65 Calculated combined mean: 0.62 = 62 ng/dL	BMI ≤25 SD=0.22 BMI>25 SD=0.32 Calculated combined SD: 0.27 = 27ng/dL	BMI ≤25 n=15 BMI>25 n=15 Calculated combined SS: 30	BMI ≤25 mean=0.49 BMI>25 mean=0.41 Calculated combined mean: 0.45 = 45 ng/dL	BMI ≤25 SD=0.14 BMI>25 SD=0.11 Calculated combined SD: 0.13 = 13 ng/dL	BMI ≤25 n=15 BMI>25 n=15 Calculated combined SS: 30	Crude	NA



a. Figure 23. MI v Met Total Testosterone

OUTCOME: SHBG					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): MI vs Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Tagliaferri 2017	nmol/l	Taken during early follicular phase of spontaneous or induced (medroxyprogesterone	Median= 25.1	IQR= 7.6	Median= 31.2	IQR= 4	Crude	NA

		acetate 10mg/day for 7 days) menstrual cycles (day: 3 ± 7) Performed with Electrochemiluminescence immunoassay (ECLIA) kits (Roche Diagnostics, Manheim, Germany).							
Rajasekaran 2022	nmol/L	Not reported, obtained on CD 2-5	32	9.7	28	8.5	Crude	NA	
Soldat-Stankovic, 2022	Nmol/l	Blood samples were collected after 12h of fasting during the early follicular phase (between the 3rd and 7th day) of the regular menstrual cycle, or at any time in case of severe oligo- or amenorrhoea.	BMI ≤25 mean=60.55 BMI>25 mean=39.09 Calculated combined mean =49.82	BMI ≤25 SD=35.67 BMI>25 SD=15.76 Calculated combined SD=29.21	BMI ≤25 n=15 BMI>25 n=15	BMI ≤25 mean=63.41 BMI>25 mean=33.43 Calculated combined mean = 48.42	BMI ≤25 SD=24.96 BMI>25 SD=12.99 Calculated combined SD=24.79	BMI ≤25 n=15 BMI>25 n=15	Crude NA
Ravn et al. 2022	nmol/L	Sex hormone binding globulin (SHBG) was analyzed by chemiluminescence in a sandwich assay (Immulite 2000 XPI, Siemens Healthineers, Erlangen, Germany). CV was 4.7%.		IQR 30 (14;37)	16		IQR 38 (29;44)	12	Crude NA



v. Figure 12 Forest plot: MI v Met - SHBG

OUTCOME: DHEAS										
OUTCOME TYPE: Continuous										
COMPARISON (if applicable): MI vs Metformin										
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Tagliaferri 2017	µmol/l	Taken during early follicular phase of spontaneous or induced (medroxyprogesterone acetate 10mg/day for 7 days) menstrual cycles (day: 3±7)	Median= 6.7	IQR= 1.8		Median= 6.8	IQR= 2.6		Crude	NA

		Performed with Electrochemiluminescence immunoassay (ECLIA) kits (Roche Diagnostics, Manheim, Germany).								
Soldat-Stankovic, 2022	µg/dl	Blood samples were collected after 12h of fasting during the early follicular phase (between the 3rd and 7th day) of the regular menstrual cycle, or at any time in case of severe oligo- or amenorrhoea.	BMI ≤25 mean=371.75 BMI>25 mean=377.39	BMI ≤25 SD=138.49 BMI>25 SD=179.21	BMI ≤25 n=15 BMI>25 n=15	BMI ≤25 mean=357.07 BMI>25 mean=393.15	BMI ≤25 SD=100.19 BMI>25 SD=122.06	BMI ≤25 n=15 BMI>25 n=15	Crude	NA

OUTCOME: Androstenedione				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): MI vs Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Tagliaferri 2017	nmol/l	Taken during early follicular phase of spontaneous or induced (medroxyprogesterone acetate 10mg/day for 7 days) menstrual cycles (day: 3±7). Performed with Electrochemiluminescence immunoassay (ECLIA) kits (Roche Diagnostics, Manheim, Germany).	Median= 8.2	IQR= 3.8	Median= 8.7	IQR= 5.1	Crude	NA

OUTCOME: Fasting Insulin						**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): MI vs Metformin										
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Angik 2017	NR	NR	17.03	15.41	50	14.58	9.8	50	Crude	NA
Chirania 2017	NR	NR	13.55	5.02	26	18.69	7.41	28		
Nehra 2017 (12 week measurement)	Not provided	NR	16.27	SE 1.27 (SD = 6.956)	30	16.09	SE 1.31 (SD = 7.175)	30	Crude	NA
Rajasekaran 2022	mIU/mL	NR	8.02	2.74		6.314	2.31		Crude	NA
Ravn et al. 2022	pmol/L	Serum insulin levels were analyzed by an electrochemiluminescence immunoassay (ECLIA) (Cobas e 801, Roche Diagnostics, Basel, Switzerland). Intra-assay coefficient of variation (CV) was 3.2–3.7% and inter-assay CV was 4.2–4.6%.		IQR 119 (78;219)	16		IQR 80 (65;121)	12	Crude	NA
Soldat-Stankovic, 2022	µIU/ml	Blood samples were collected after 12h of fasting during the early follicular phase (between the 3rd and 7th day) of the regular menstrual cycle, or at any time in case of	BMI ≤25 mean=9.21 BMI>25 mean=14.54	BMI ≤25 SD=3.40 BMI>25 SD=5.83	BMI ≤25 n=15 BMI>25 n=15	BMI ≤25 mean=8.69 BMI>25 mean=14.42	BMI ≤25 SD=2.61 BMI>25 SD=6.22	BMI ≤25 n=15 BMI>25 n=15	Crude	NA

		severe oligo- or amenorrhoea.	Calculated combined mean=11.875	Calculated combined SD=5.42		Calculated combined mean=11.555	Calculated combined SD=5.52			

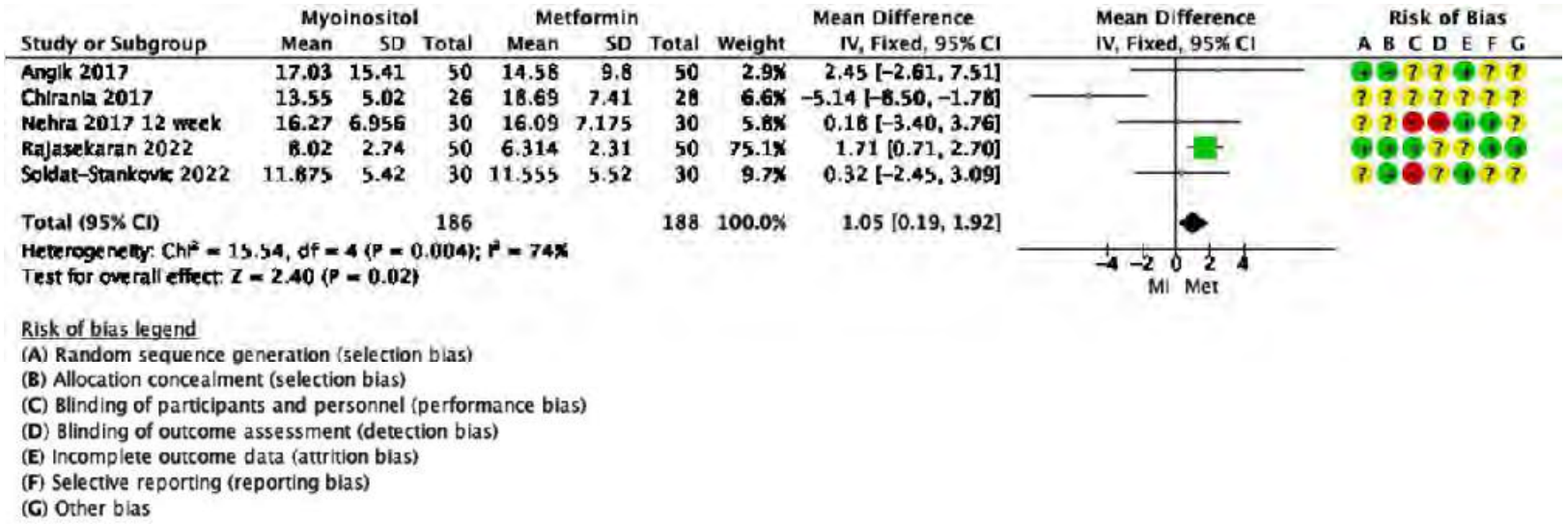
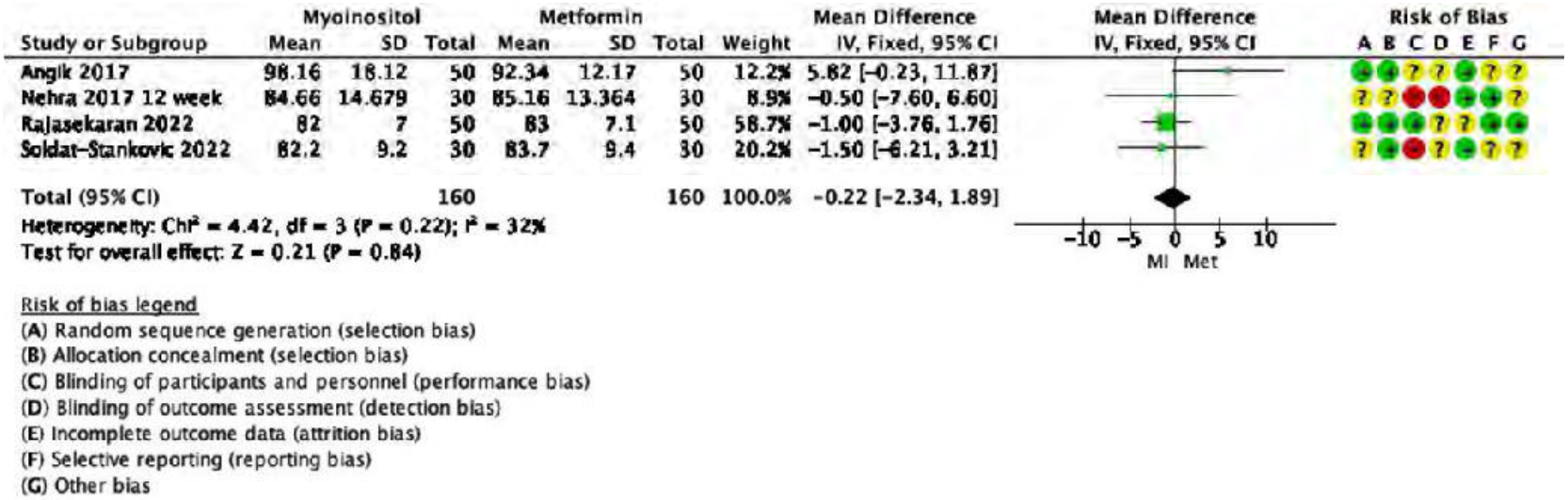


Figure 24. MI v Met Fasting Insulin

OUTCOME: fasting glucose										
		COMPARISON (if applicable): MI v Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Angik 2018	NR	NR	98.16	18.12	50	92.34	12.17	50		

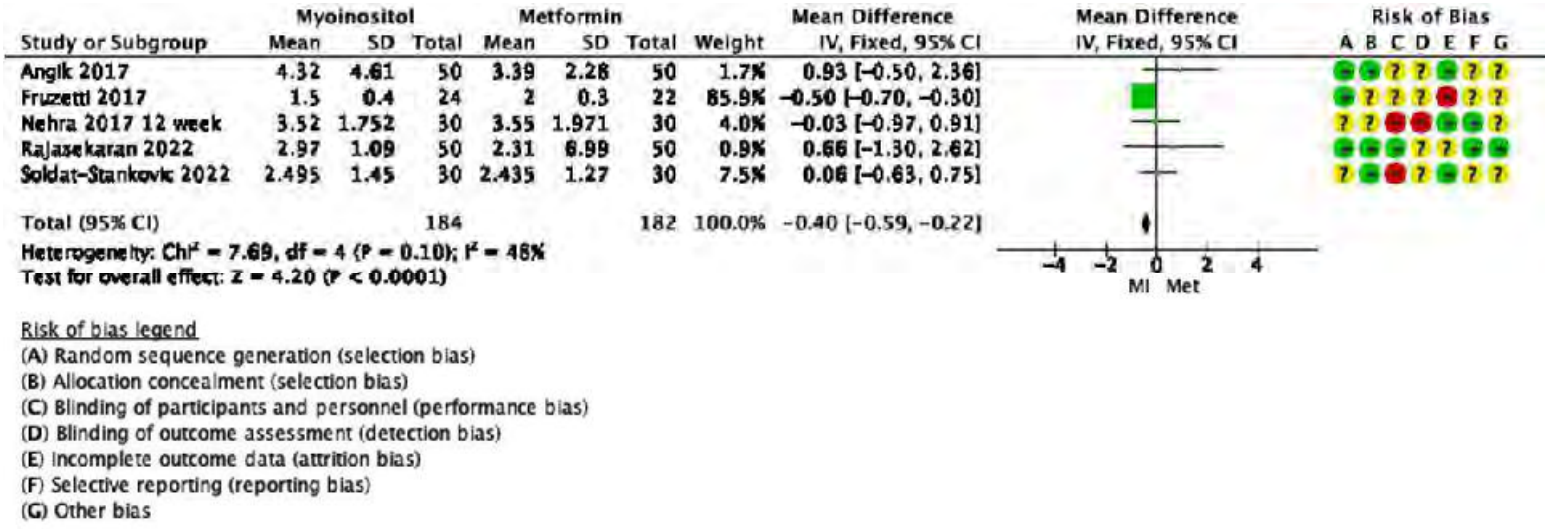
Nehra 2017 (12 week measurement)	Not provided	NR	84.66	SE 2.68 / SD 14.679		85.16	SE 2.44 / 13.364		Crude	NA
Rajasekaran 2022	mg/dL	NR	82	7		83	7.1		Crude	NA
Ravn et al. 2022	nmol/L	Fasting plasma glucose was analyzed by ultraviolet hexokinase analysis-based absorption photometry (Cobas 8000, Roche Diagnostics, Basel, Switzerland). CV was 2.4%.		IQR 5.4 (5.3;5.7)	16		IQR 5.2 (4.8;5.3)	12	Crude	NA
Soldat-Stankovic, 2022	Mmol/l	Blood samples were collected after 12h of fasting during the early follicular phase (between the 3rd and 7th day) of the regular menstrual cycle, or at any time in case of severe oligo- or amenorrhoea.	BMI ≤25 mean=4.31 BMI>25 mean=4.82 Calculated combined mean=4.565 = 82.2 mg/dl	BMI ≤25 SD=0.35 BMI>25 SD=0.68 Calculated combined SD=0.51=9.2 mg/dL	BMI ≤25 n=15 BMI>25 n=15	BMI ≤25 mean=4.45 BMI>25 mean=4.85 Calculated combined mean=4.65 = 83.7 mg/dL	BMI ≤25 SD=0.59 BMI>25 SD=0.35 Calculared combined SD=0.52= 9.4mg/dL	BMI ≤25 n=15 BMI>25 n=15	Crude	NA



a. Figure 25. MI v Met Fasting glucose

OUTCOME: HOMA-IR										
		COMPARISON (if applicable): MI v Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Angik 2017	NA	NR	4.32	4.61	50	3.39	2.28	50	Crude	NA
Nehra 2017 (12 week measurement)	No units	Not reported	3.52	SE 0.32 (sd = 1.752)		3.55	SE 0.36 (SD = 1.971)		Crude	NA
Rajasekaran 2022	No units	Not reported	2.97	1.09		2.31	6.99		Crude	NA

Fruzzetti et al. 2017			1.5 ± 0.4		24	2.0 ± 0.3		22	Crude	
Ravn et al. 2022	(pmol mmol L^{-2})			IQR 33.7 (27.1;49.6)	16		IQR 18.8 (14.3;29.6)	12	Crude	
Soldat-Stankovic, 2022	NA	Calculated using the formula [fasting insulin (mU/l) × fasting glucose (mmol/l)]/22.5	BMI ≤25 mean=1.79 BMI>25 mean=3.20 Calculated combined mean=2.495	BMI ≤25 SD=0.77 BMI>25 SD=1.65 Calculated combined SD=1.45	BMI ≤25 n=15 BMI>25 n=15	BMI ≤25 mean=1.76 BMI>25 mean=3.11 Calculated combined mean=2.435	BMI ≤25 SD=0.60 BMI>25 SD=1.41 Calculated combined SD=1.27	BMI ≤25 n=15 BMI>25 n=15	Crude	NA



b. Figure 26 MI v Met HOMA IR

OUTCOME: AUC glucose				**OUTCOME TYPE:** Continuous						
COMPARISON (if applicable): MI vs Metformin										
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size of this group (n)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size of this group (n)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Tagliaferri 2017	µIU/ml/180 min)	Taken during early follicular phase of spontaneous or induced (medroxyprogesterone acetate 10mg/day for 7 days) menstrual cycles (day: 3±7) OGTT – sampling 15 min before and 30, 60, 90, 120 and 180 minutes after oral ingestion of 75g glucose. Normal insulinaemic response to OGTT defined by threshold AUC value of 12,000 IU/ml/180 min.	Median= 18495	IQR= 2760.54		Median= 19350	IQR= 2567.82		Crude	NA
Soldat-Stankovic, 2022	NA	Analysed using the trapezoid formula for the assessment of glucose response to oral glucose load.	BMI ≤25 mean=12.21 BMI>25 mean=13.85	BMI ≤25 SD=2.82 BMI>25 SD=2.70	BMI ≤25 n=15 BMI>25 n=15	BMI ≤25 mean=12.06 BMI>25 mean=14.98	BMI ≤25 SD=2.88 BMI>25 SD=2.92	BMI ≤25 n=15 BMI>25 n=15	Crude	NA

OUTCOME: AUC insulin	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): MI vs Metformin	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Tagliaferri 2017	µIU/ml/180 min)	Taken during early follicular phase of spontaneous or induced (medroxyprogesterone acetate 10mg/day for 7 days) menstrual cycles (day: 3±7) OGTT – sampling 15 min before and 30, 60, 90, 120 and 180 minutes after oral ingestion of 75g glucose. Normal insulinaemic response to OGTT defined by threshold AUC value of 12,000 IU/ml/180 min.	Median= 12063	IQR= 6238.38		Median= 7690.5	IQR= 6048.15		Crude	NA
Fruzzetti et al. 2017	µU/mL x 180 min	Plasma samples for glucose and insulin concentrations were collected before and after 30, 60, 90, 120 and 180 minutes from a 75 g oral glucose administration. Insulin plasma concentrations were expressed as the area under the curve (AUC).	7392 ± 5277		24	8140 ± 2125		22	Crude	NA

		The AUC was calculated using the trapezoidal rule and was expressed as μU per ml x 180 minutes.								
Soldat-Stankovic, 2022	NA	Analysed using the trapezoid formula for the assessment of insulin response to oral glucose load.	BMI ≤25 mean=163.12 BMI>25 mean=189.49	BMI ≤25 SD=105.85 BMI>25 SD=65.79	BMI ≤25 n=15 BMI>25 n=15	BMI ≤25 mean=115.60 BMI>25 mean=176.79	BMI ≤25 SD=35.75 BMI>25 SD=80.87	BMI ≤25 n=15 BMI>25 n=15	Crude	NA

OUTCOME: QUICKI										
		OUTCOME TYPE: Continuous								
		COMPARISON (if applicable): MI vs Metformin								
Author, year	**Unit of outcome (e.g. g, mg, μg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Soldat-Stankovic, 2022	NA	Calculated using the formula [I/(log[fasting insulin (mU/l)] × log[fasting glucose (mg/dl)])]	BMI ≤25 mean=0.355 BMI>25 mean=0.33	BMI ≤25 SD=0.023 BMI>25 SD=0.021	BMI ≤25 n=15 BMI>25 n=15	BMI ≤25 mean=0.36 BMI>25 mean=0.33	BMI ≤25 SD=0.032 BMI>25 SD=0.022	BMI ≤25 n=15 BMI>25 n=15	Crude	NA

OUTCOME: 120min glucose from OGTT						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable): MI vs Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Soldat-Stankovic, 2022	Mmol/l	Serum glucose from blood samples collected at baseline (0 min) and 30, 60, 90 and 120 min after the oral consumption of 75g of glucose.	BMI ≤25 mean=5.12 BMI>25 mean=5.55 Calculated combined mean=5.335	BMI ≤25 SD=1.55 BMI>25 SD=1.54 Calculated combined SD=1.53	BMI ≤25 n=15 BMI>25 n=15	BMI ≤25 mean=5.34 BMI>25 mean=6.47 Calculated combined mean=5.905	BMI ≤25 SD=1.95 BMI>25 SD=1.66 Calculated combined SD=1.87	BMI ≤25 n=15 BMI>25 n=15	Crude	NA

OUTCOME: Matsuda index										
OUTCOME TYPE: Continuous										
		COMPARISON (if applicable): MI versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Fruzzetti et al. 2017			10.6 ± 3.4		24	9.6 ± 3.9		22	Crude	NA

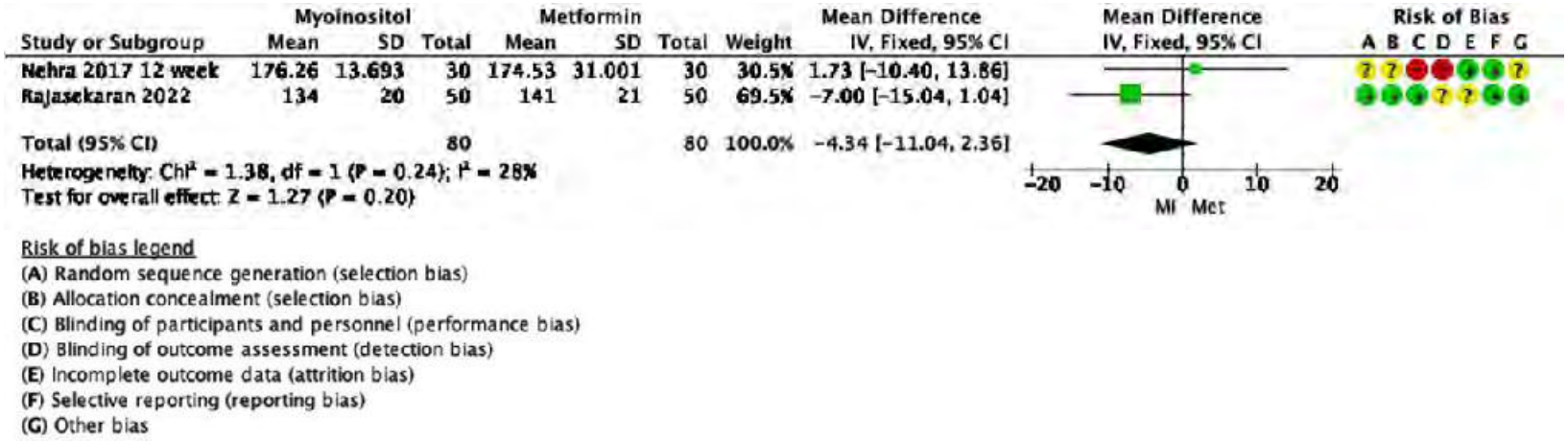
OUTCOME: 120min insulin from OGTT										
OUTCOME TYPE: Continuous										
		COMPARISON (if applicable): MI vs Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Soldat-Stankovic, 2022	µIU/ml	Serum insulin from blood samples collected at baseline (0 min) and 30, 60, 90 and 120 min after the oral	BMI ≤25 mean=79.24 BMI>25 mean=75.86	BMI ≤25 SD=61.66 BMI>25 SD=41.98	BMI ≤25 n=15 BMI>25 n=15	BMI ≤25 mean=57.13 BMI>25 mean=84.69	BMI ≤25 SD=36.21 BMI>25 SD=52.57	BMI ≤25 n=15 BMI>25 n=15	Crude	NA

		consumption of 75g of glucose.								

OUTCOME: Euglycemic hyperinsulinemic clamp (M)					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): MI vs Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Tagliaferri 2017	Mg/kg/min	Taken the day after OGTT was performed which was during the early follicular phase of spontaneous or induced (medroxyprogesterone acetate 10mg/day for 7 days) menstrual cycles (day: 3±7) Peripheral glucose utilisation - threshold value for insulin resistance set as 4.5mg/kg/min.	Median= 3.2	IQR= 1.43	Median= 3.86	IQR= 1.52	Crude	NA

OUTCOME: Total cholesterol					**OUTCOME TYPE:** Continuous					
COMPARISON (if applicable): MI vs Metformin										
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in**	**Sample size (n in this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/**	**Sample size (n in this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were**

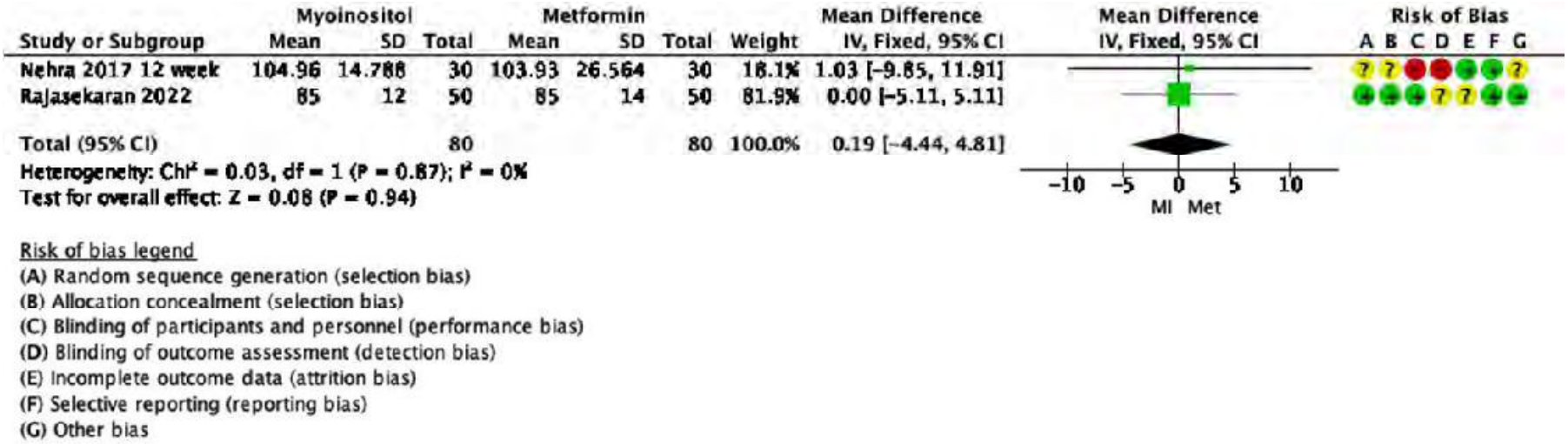
				intervention / exposure group			**comparison group**			**included in the model?**
Nehra 2017 (12 week measurement)	No units	Not reported	176.26	SE 2.50 (SD = 13.693)		174.53	SE 5.66(SD = 31.001)		Crude	NA
Rajasekaran 2022	mg/dL	Not reported	134	20		141	21		Crude	NA
Ravn et al. 2022	nmol/L	Plasma high-density lipoprotein (HDL) cholesterol, total cholesterol, and triglycerides were analyzed by enzymatic colorimetric analysis-based absorption photometry (Cobas 8000, Roche Diagnostics, Basel, Switzerland), and low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation. CVs were 1.3–2.3%.		IQR 4.7 (4.1;5.1)	16		IQR 4.8 (4.2;5.3)	12	Crude	NA



c. Figure 27. MI v Met Total Cholesterol

OUTCOME: LDL											
OUTCOME TYPE: Continuous											
COMPARISON (if applicable): MI vs Metformin											
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample Size (n in this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n in this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Nehra 2017 (12 week measurement)	No units	Not reported	104.96	SE 2.70 (SD = 14.788)		103.93	SE 4.85 (SD = 26.564)		Crude	NA
Rajasekaran 2022	mg/dL	Not reported	85	12		85	14		Crude	NA
Ravn et al. 2022	nmol/L	Plasma high-density lipoprotein (HDL) cholesterol, total cholesterol, and triglycerides were analyzed by enzymatic colorimetric		IQR 2.9 (2.5;3.1)	16		IQR 2.9 (2.6;3.3)	12	Crude	NA

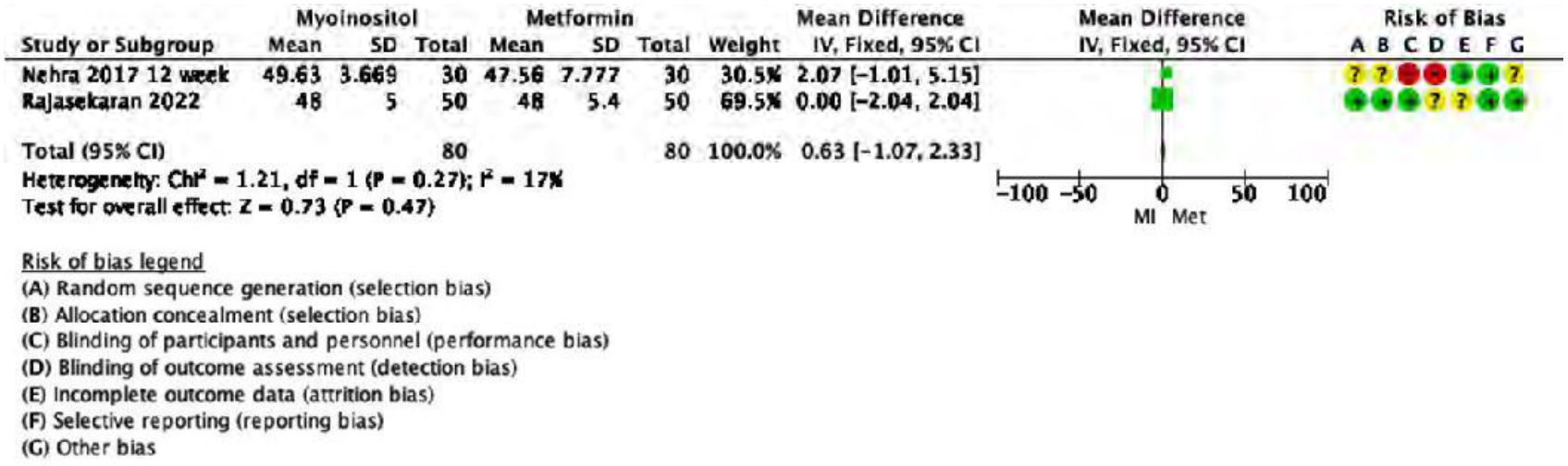
		analysis-based absorption photometry (Cobas 8000, Roche Diagnostics, Basel, Switzerland), and low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation. CVs were 1.3–2.3%.								



d. Figure 28. MI v Met LDL

OUTCOME: HDL	**OUTCOME TYPE:** Continuous
COMPARISON (if applicable): MI vs Metformin	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n in this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n in this group)	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Nehra 2017 (12 week measurement)	No units	Not reported	49.63	SE 0.67 / SD 3.669		47.56	SE 1.42/ SD 7.777		Crude	NA
Rajasekaran 2022	mg/dL	Not reported	48	5		48	5.4		Crude	NA
Ravn et al. 2022	nmol/L	Plasma high-density lipoprotein (HDL) cholesterol, total cholesterol, and triglycerides were analyzed by enzymatic colorimetric analysis-based absorption photometry (Cobas 8000, Roche Diagnostics, Basel, Switzerland), and low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation. CVs were 1.3–2.3%.		IQR 1.2 (1.1;1.3)	16		IQR 1.4 (1.2;1.6)	12	Crude	NA



e. Figure 29. MI v Met HDL

OUTCOME: TG				**OUTCOME TYPE:** Continuous						
COMPARISON (if applicable): MI vs Metformin										
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n in this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n in this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Nehra 2017 (12 week measurement)	No units	Not reported	126.43	SE 6.40/ SD 35.05		128.40	SE 8.24/SD45.132		Crude	NA
Ravn et al. 2022	nmol/L	Plasma high-density lipoprotein (HDL) cholesterol, total cholesterol, and triglycerides were analyzed by enzymatic colorimetric		IQR 1.3 (1.0;1.6)	16		IQR 1.0 (0.8;1.5)	12	Crude	NA

		analysis-based absorption photometry (Cobas 8000, Roche Diagnostics, Basel, Switzerland), and low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation. CVs were 1.3–2.3%.								

OUTCOME: QoL – RPH (role limitations due to physical health)						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable): MI versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Ravn et al. 2022		SF-36		IQR 100 (50;100)	14		IQR 100 (50;100)	12	Crude	NA

OUTCOME: QoL – REP (role limitations due to emotional problems)							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): MI versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Ravn et al. 2022		SF-36		IQR 100 (33;100)	14		IQR 100 (17;100)	12	Crude	NA

OUTCOME: QoL – energy / fatigue							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): MI versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Ravn et al. 2022		SF-36		IQR 53 (30;65)	14		IQR 48 (30;73)	12	Crude	NA

OUTCOME: QoL – emotional well-being							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): MI versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Ravn et al. 2022		SF-36		IQR 80 (52;84)	14		IQR 70 (52;84)	12	Crude	NA

OUTCOME: QoL – social functioning							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): MI versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Ravn et al. 2022		SF-36		IQR 69 (38;80)	14		IQR 64 (40;79)	12	Crude	NA

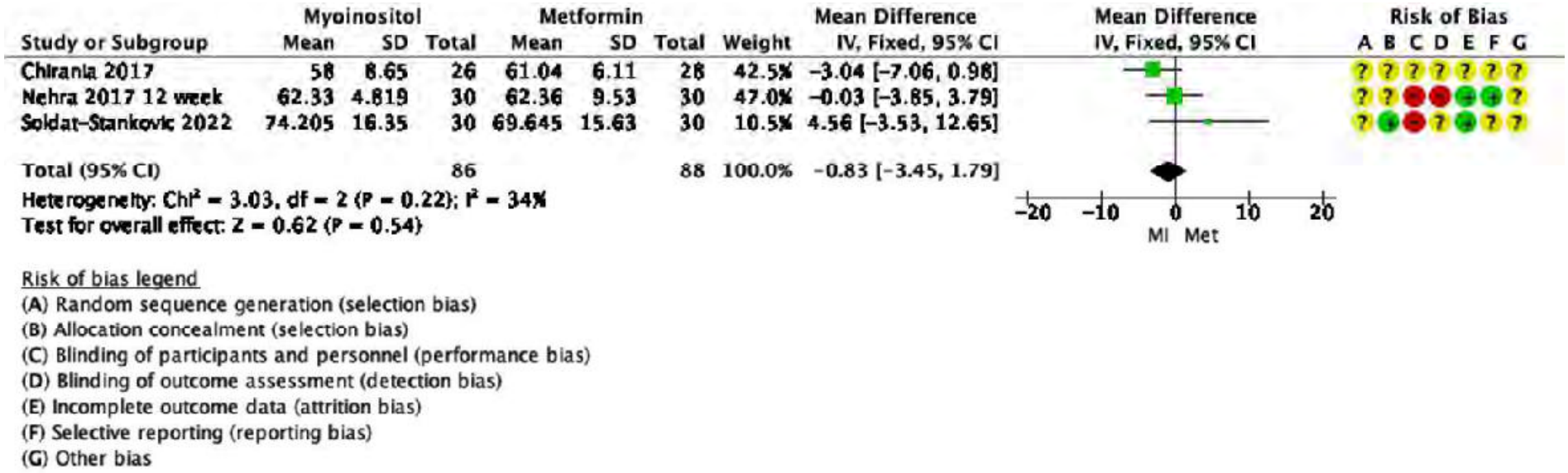
OUTCOME: QoL – pain							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): MI versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Ravn et al. 2022		SF-36		IQR 68 (55;90)	14		IQR 69 (68;90)	12	Crude	NA

OUTCOME: QoL – general health							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): MI versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Ravn et al. 2022		SF-36		IQR 63 (35;75)	14		IQR 68 (38;78)	12	Crude	NA

OUTCOME: Depression							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): MI versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Ravn et al. 2022	Score	MDI – Major Depression Inventory		IQR 10 (7;22)	14		IQR 15 (6;27)	12	Crude	NA

OUTCOME: Weight						**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): MI vs Metformin										
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Chirania 2017	NR	NR	58.0	8.65	26	61.04	6.11	28		
Nehra 2017 (12 week measurement)	Kg	NR	62.33	SE 0.88/SD 4.819		62.26	SE 1.74/SD 9.530		Crude	NA

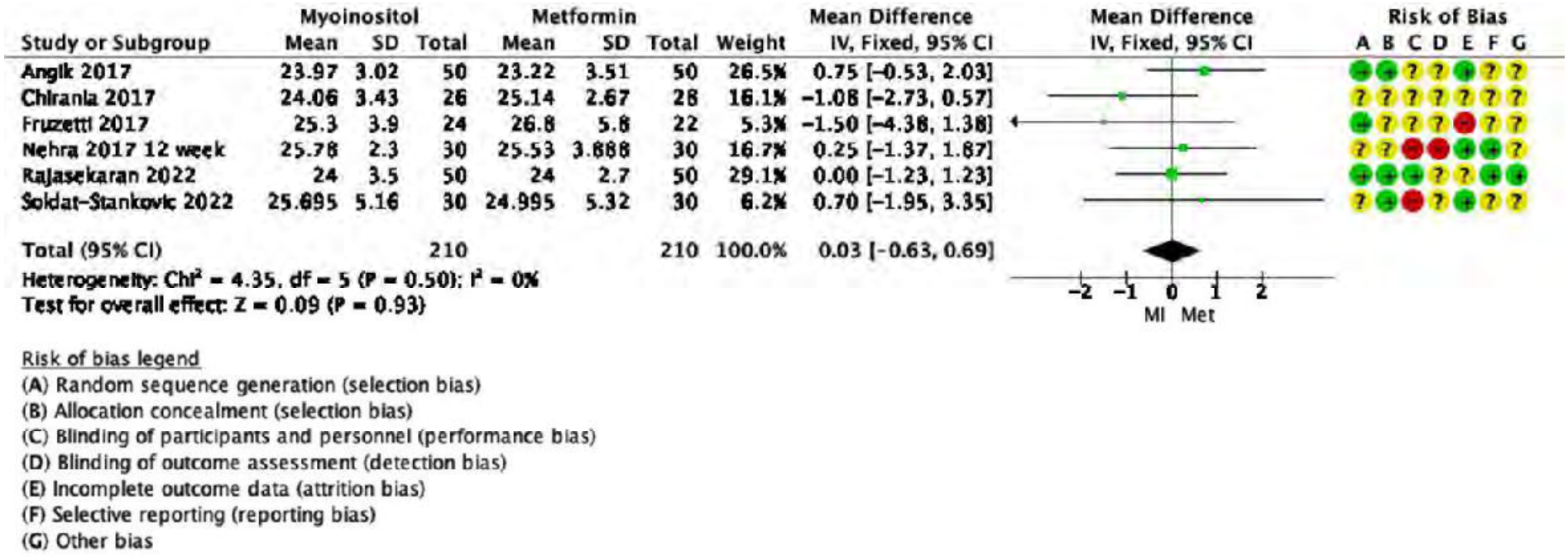
Ravn et al. 2022	Kg			IQR 94.4 (84.9;107.0)	16		IQR 93.7(81.7;106.8)	12	Crude	
Soldat-Stankovic, 2022	kg	Not described.	BMI ≤25 mean=61.60 BMI>25 mean=86.81 Calculated combined mean=74.205	BMI ≤25 SD=7.06 BMI>25 SD=12.78 Calculated combined SD=16.35	BMI ≤25 n=15 BMI>25 n=15	BMI ≤25 mean=57.07 BMI>25 mean=82.22 Calculated combined mean=69.645	BMI ≤25 SD=5.08 BMI>25 SD=11.89 Calculated combined SD=15.63	BMI ≤25 n=15 BMI>25 n=15	Crude	NA



f. Figure 30. MI v Met Weight (kg)

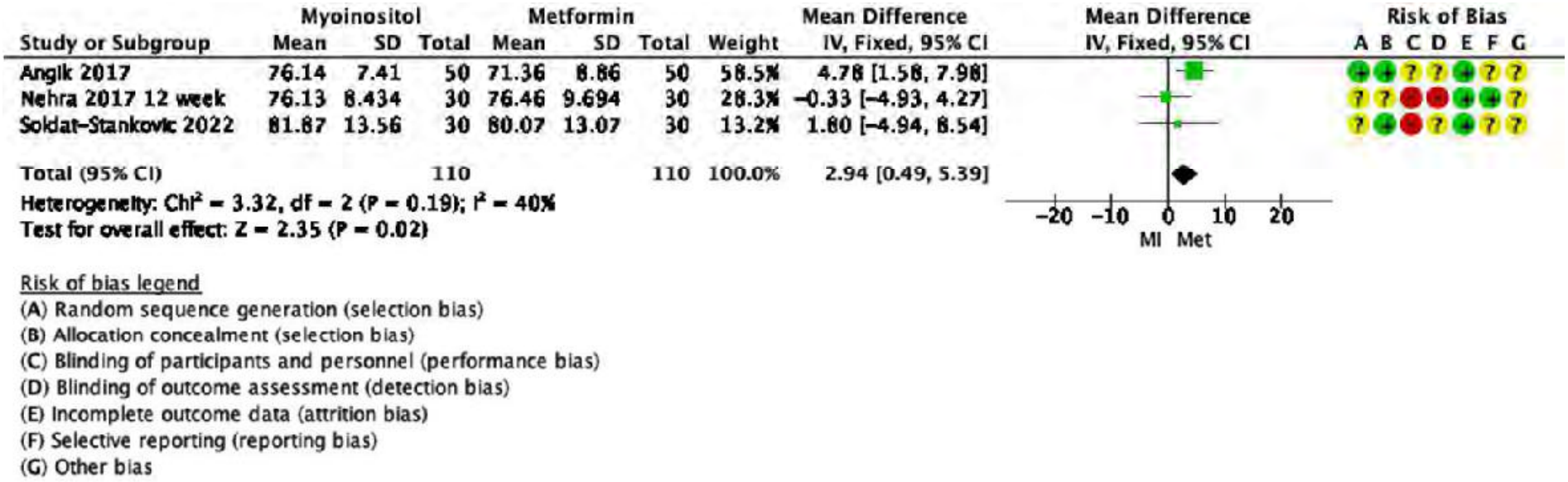
OUTCOME: BMI										
		COMPARISON (if applicable): MI v Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Angik 2017	NR	NR	23.97	3.02	50	23.22	3.51	50	Crude	NA
Chirania 2017	NR	NR	24.06	3.43	26	25.14	2.67	28	Crude	NA
Tagliaferri 2017	Kg/m2	Taken during early follicular phase of spontaneous or induced (medroxyprogesterone acetate 10mg/day for 7 days) menstrual cycles (day: 3±7) BMI>25kg/m2 overweight, BMI>30kg/m2 obese	Median= 31.2	IQR= 7.8		Median= 32.5	IQR= 7.9		Crude	NA
Nehra 2017 (12 week measurement)	Kg/m2		25.78	SE 0.42/SD 2.300		25.53	SE 0.71/ SD 3.888		Crude	NA
Rajasekaran 2022	Kg/m2		24	3.5		24	2.7		Crude	NA
Fruzzetti et al. 2017	Kg/m2		25.3 ± 3.9		24	26.8 ± 5.8		22	Crude	
Ravn et al. 2022	Kg/m2			IQR 34.5 (29.9;36.8)	16		IQR 32.8 (29.8;38.5)	12	Crude	
Soldat-Stankovic, 2022	Kg/m2	Calculated using the ratio of body weight (kg) and body height (m) squared	BMI ≤25 mean=21.67 BMI>25 mean=29.72	BMI ≤25 SD=2.46 BMI>25 SD=3.80	BMI ≤25 n=15 BMI>25 n=15	BMI ≤25 mean=20.61 BMI>25 mean=29.38	BMI ≤25 SD=1.79 BMI>25 SD=3.76	BMI ≤25 n=15 BMI>25 n=15	Crude	NA

			Calculated combined mean=25.695	Calculated combined SD=5.16		Calculated combined mean=24.995	Calculated combined SD=5.32			



g. Figure 31. MI v Met BMI

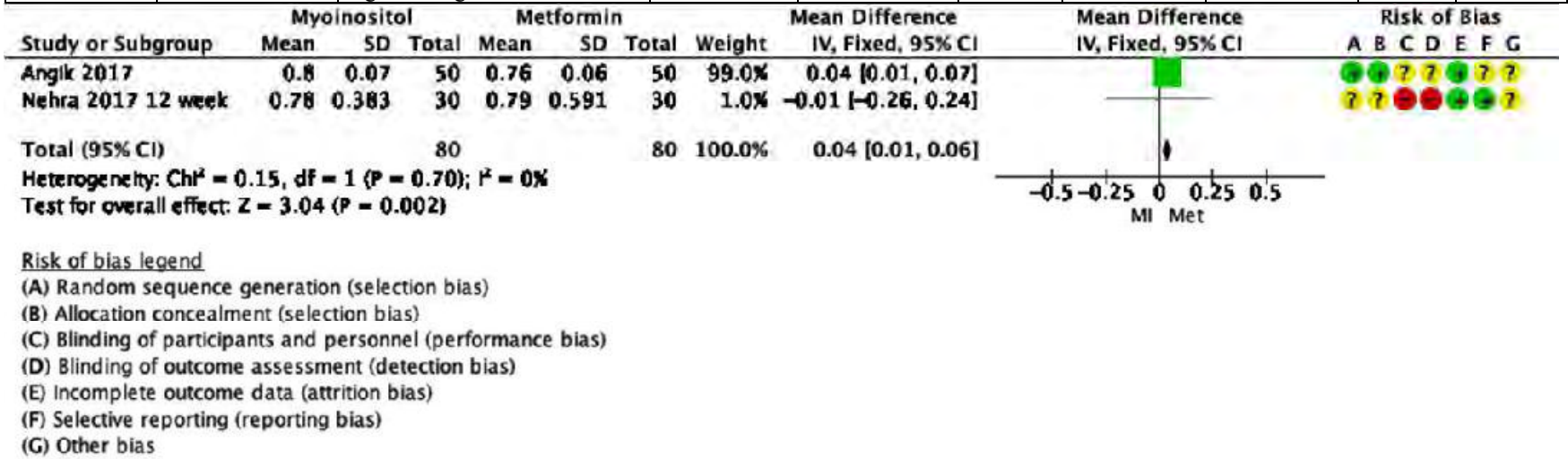
OUTCOME: Waist Circumfirence										
		COMPARISON (if applicable): MI v Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Angik 2017	NR	NR	76.14	7.41	50	71.36	8.86	50	Crude	NA
Nehra 2017 (12 week measurement)	cm	Waist circumference is measured with a tape midway between the lowest rib margin and the iliac crest in standing position	76.13	SE 1.54/ SD 8.434		76.46	SE 1.77/SD9.694		Crude	NA
Ravn et al. 2022	cm			IQR 100 (93;104)	16		IQR 100 (90;105)	12	Crude	
Soldat-Stankovic, 2022	cm	WC was measured at the midpoint between the lower border of the rib cage and the iliac crest by using a flexible centimeter tape.	BMI ≤25 mean=70.87 BMI>25 mean=92.87 Calculated combined mean=81.87	BMI ≤25 SD=7.77 BMI>25 SD=7.83 Calculated combined SD=13.56	BMI ≤25 n=15 BMI>25 n=15	BMI ≤25 mean=70.47 BMI>25 mean=89.67 Calculated combined mean=80.07	BMI ≤25 SD=7.34 BMI>25 SD=10.13 Calculated combined SD=13.07	BMI ≤25 n=15 BMI>25 n=15	Crude	NA



h. Figure 32. MI v Met Waist Circumference

OUTCOME: WHR										**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable): MI v Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Angik 2017	NR	NR	0.80	0.07	50	0.76	0.06	50	Crude	NA
Tagliaferri 2017	NR	Taken during early follicular phase of spontaneous or induced (medroxyprogesterone	Median= 0.85	IQR= 0.08		Median= 0.81	IQR= 0.12		Crude	NA

		acetate 10mg/day for 7 days) menstrual cycles (day: 3±7) Waist circumference – minimum value between iliac crest and lateral costal margin; hip circumference maximum value over buttocks. Cut off point for high WHR set at 0.80.								
Nehra 2017 (12 week measurement)	Waist circumference/Hip circumfirence	Waist circumference is measured with a tape midway between the lowest rib margin and the iliac crest in standing position. The hip circumference is measured over the widest part of gluteal region.	0.78	SE 0.007/SD 0.0383		0.79	SE 0.0108/ SD 0.591		Crude	NA



i. Figure 33. MI v Met Waist Hip Ratio

OUTCOME: Body fat mass							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): MI vs Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Soldat-Stankovic, 2022	kg	Body composition was estimated using bioelectrical impedance analysis (inBody 370, Biospace Co. Ltd, Seoul, South Korea).	BMI ≤25 mean=14.74 BMI>25 mean=33.53	BMI ≤25 SD=4.71 BMI>25 SD=9.70	BMI ≤25 n=15 BMI>25 n=15	BMI ≤25 mean=14.99 BMI>25 mean=31.13	BMI ≤25 SD=4.66 BMI>25 SD=7.92	BMI ≤25 n=15 BMI>25 n=15	Crude	NA

OUTCOME: Menstrual regularity							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): MI versus Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Fruzzetti et al. 2017	days		57 ± 50		24	54 ± 40		22	Crude	NA
Ravn et al. 2022	days			IQR 36 (32;60)	16		IQR 34 (28;37)	12	Crude	NA
Raffone et al. 2010	days from the first day of the menstrual cycle	Weekly serum progesterone dosage - progesterone levels higher than 8.0 ng/ml were considered significant for spontaneous ovulation.	14.8 (± 1.8)		60	16.7 (±2.5)		60	Crude	NA

vi. MI v Placebo

OUTCOME: Testosterone (assume free?)							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): MI vs placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Change score**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Dona 2012	Nmol/L	ECLIA	-0.35	0.24	18	-0.01	0.29	8	Crude	NA

OUTCOME: Androstenedione										**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable): MI vs placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Change score**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Change score**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Dona 2012	Nmol/L	Solid-phase competitive chemi-luminescent enzyme immunoassay	-3.96	2.16	18	0.28	0.39	8	Crude	NA

OUTCOME: Fasting glucose			**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable): MI vs placebo	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Change score	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Change score	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Dona 2012	Mmol/L	Enzymatically with glucose hexokinase kit	-0.14	0.31	18	0.06	0.13	8	Crude	NA

OUTCOME: Fasting insulin							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): MI vs placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Change score**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Change score**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Dona 2012	mIU/L	ECLIA	-2.33	2.61	1	0.76	0.13	8	Crude	NA

OUTCOME: HOMA-IR							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): MI vs placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Change score**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Change score**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Dona 2012	NA	ECLIA	-0.54	0.62	18	0.26	0.16	8	Crude	NA

OUTCOME: AUC glucose							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): MI vs placebo								

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Change score	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Change score	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Dona 2012	Mmol/L per min	As per glucose; 2 hr 75g OGTT	-13.42	65.52	18	17.06	28.64	8	Crude	NA

OUTCOME: AUC insulin							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): MI vs placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Change score**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Change score**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Dona 2012	mU/L per min	As per insulin; 2hr 75g OGTT	-1668.08	1388.52	18	347.38	314.98	8	Crude	NA

OUTCOME: Weight							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): MI vs placebo								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Change score**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Change score**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Dona 2012	Kg	NR	-1.83	1.86	18	0.25	0.71	8	Crude	NA

OUTCOME: BMI			**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable): MI vs placebo	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Change score	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Change score	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Dona 2012	Kg/m^2	NR	-0.69	0.69	18	0.09	0.27	8	Crude	NA

vii. MI + monacolin k v Inositol v Met

OUTCOME: Ferriman Gallwey score							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): MI + monacolin K vs Inositol vs Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Leo 2013	unit	Ferriman Gallwey score > 8 considered hirsute	Median=7	IQR=3.9	20	Inositol: Median=9 Metformin: Median=9	Inositol: IQR= 4 Metformin: IQR= 1	Inositol=20 Metformin=20	Crude	NA

Page Break

OUTCOME: Total testosterone							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): MI + monacolin K vs Inositol vs Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Leo 2013	Pg/ml	Not reported	Median=0.5	IQR=0.1	20	Inositol: Median=0.8 Metformin: Median=0.6	Inositol: IQR= 0.1 Metformin: IQR= 0.1	Inositol=20 Metformin=20	Crude	NA

OUTCOME: Free testosterone										**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable): MI + monacolin K vs Inositol vs Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Leo 2013	Pg/ml	Not reported	Median=0.6	IQR=0.1	20	Inositol: Median=1.1 Metformin: Median=0.8	Inositol: IQR= 0.3 Metformin: IQR= 0.1	Inositol=20 Metformin=20	Crude	NA

OUTCOME: SHBG										**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable): MI + monacolin K vs Inositol vs Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Leo 2013	nMol/L	Not reported	Median=96	IQR=10.8	20	Inositol: Median=50 Metformin: Median=85	Inositol: IQR= 2.7 Metformin: IQR= 5.6	Inositol=20 Metformin=20	Crude	NA

OUTCOME: Androstenedione			**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable): MI + monacolin K vs Inositol vs Metformin	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Leo 2013	Ng/ml	Not reported	Median=0.9	IQR=0.1	20	Inositol: Median=1.7 Metformin: Median=1.8	Inositol: IQR= 0.1 Metformin: IQR= 0.2	Inositol=20 Metformin=20	Crude	NA

OUTCOME: Fasting glucose							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): MI + monacolin K vs Inositol vs Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Leo 2013	Mg/dl	Not reported	Median=91	IQR=1.7	20	Inositol: Median=92 Metformin: Median=92.5	Inositol: IQR= 2.1 Metformin: IQR= 4.2	Inositol=20 Metformin=20	Crude	NA

OUTCOME: Fasting insulin							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): MI + monacolin K vs Inositol vs Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**

Leo 2013	mU/ml	Not reported	Median=10.2	IQR=1.1	20	Inositol: Median=11 Metformin: Median=15	Inositol: IQR= 0.6 Metformin: IQR= 0.7	Inositol=20 Metformin=20	Crude	NA

OUTCOME: HOMA							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): MI + monacolin K vs Inositol vs Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Leo 2013	Value	Product of fasting plasma insulin (mU/L) and glucose (mmol/L) concentrations divided by 22.5	Median=2.5	IQR=0.4	20	Inositol: Median=2.7 Metformin: Median=2.4	Inositol: IQR= 0.3 Metformin: IQR= 0.3	Inositol=20 Metformin=20	Crude	NA

OUTCOME: Total cholesterol							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): MI + monacolin K vs Inositol vs Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Leo 2013	Mg/dl	Not reported	Median=194	IQR=8.15	20	Inositol: Median=211.2 Metformin: Median=206	Inositol: IQR= 5.3 Metformin: IQR= 3.8	Inositol=20 Metformin=20	Crude	NA

OUTCOME: LDL						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable): MI + monacolin K vs Inositol vs Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Leo 2013	Mg/dl	Not reported	Median=96.5	IQR=7.3	20	Inositol: Median=174.4 Metformin: Median=198.5	Inositol: IQR= 7.1 Metformin: IQR= 5.8	Inositol=20 Metformin=20	Crude	NA

OUTCOME: HDL						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable): MI + monacolin K vs Inositol vs Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Leo 2013	Mg/dl	Not reported	Median=68.5	IQR=3.2	20	Inositol: Median=63.1 Metformin: Median=70	Inositol: IQR= 4.1 Metformin: IQR= 6.4	Inositol=20 Metformin=20	Crude	NA

OUTCOME: TG			**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable): MI + monacolin K vs Inositol vs Metformin	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	Mean (specify if median) in intervention/ exposure group	SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group	Sample size (n within this group)	Mean (specify if median) or median in control / comparison group	SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group	Sample size (n within this group)	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Leo 2013	Mg/dl	Not reported	Median=134.2	IQR=9.4	20	Inositol: Median=137.4 Metformin: Median=144.5	Inositol: IQR= 15.1 Metformin: IQR= 12	Inositol=20 Metformin=20	Crude	NA

OUTCOME: BMI							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): MI + monacolin K vs Inositol vs Metformin								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Leo 2013	Kg/m2	Not reported	Median=25.7	IQR=1.1	20	Inositol: Median=27.1 Metformin: Median=24	Inositol: IQR= 1 Metformin: IQR= 0.6	Inositol=20 Metformin=20	Crude	NA

4. STUDY CHARACTERISTICS AND QUALITY APPRAISAL

vii. DCI

viii. Iuorno 2002

Study ID	Iuorno 2002	
Study Citation	Iuorno et al., *Endocrine Practice*, 8:417-423, 2002	
Study Country	Venezuela	
BRIEF CHARACTERISTICS OF RCT		
Patient/population/ participants	Women with PCOS (18-40 years)	
PCOS diagnostic criteria	Defined by the presence of oligomenorrhea (≤6 menstrual periods during the previous year) and hyperandrogenism (high serum free testosterone levels or hirsutism).	
Presence of infertility	Not reported	
Presence of other condition/s	Not reported	
Medication History	*None of the women had taken any medications, including insulin-sensitizing agents or oral contraceptives, during the 2 months before the study.*	
N per group	*Allocated/randomised: 20 (10 DCI, 10 placebo)* *Analysed: 20 (10 DCI, 10 placebo)*	
Setting	Hospital de Clinicas, Caracas, Venezuela	
Intervention	*DCI 600mg daily*	
Comparison	*Placebo supplement daily*	
Co-interventions	*Women were instructed not to alter their usual eating habits, physical activity, or lifestyle during the study, and they were also advised to refrain from sexual intercourse or to use a barrier method of contraception.*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*BMI, total testosterone, free testosterone, fasting glucose, fasting insulin, total cholesterol*	
Follow up Duration	*6 – 8 weeks (follow-up was conducted during the follicular phase, determined by serum progesterone level < 2.5ng/mL).*	
Summary Result/s	*DCI improved glucose tolerance, reduces circulating insulin, decreases serum androgen concentrations and ameliorates other metabolite abnormalities associated with insulin resistance in lean women with PCOS.*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* *"we conducted the current study to determine whether the administration of D-chiro-inositol to lean women with the polycystic ovary syndrome would decrease serum androgens or improve ovulatory frequency (or both). In a randomized, double-blind study, 20 lean women with the polycystic ovary syndrome were given either D-chiro-inositol or placebo"*
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	*Partial –only diagnosis and use of medications*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Partial*
Inclusion criteria	Yes Partial No Not reported	Women with the polycystic ovary syndrome, as defined by the presence of oligomenorrhea (≤6 menstrual periods during the previous year) and hyperandrogenism (high serum free testosterone levels or hirsutism). Normal thyroid function and prolactin levels.
Exclusion criteria	Yes Partial No Not reported	*None of the women had taken any medications, including insulin-sensitizing agents or oral contraceptives, during the 2 months before the study.*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Not reported*
	Was allocation to intervention group concealed?	Yes Partial No Not reported	*Yes* *Intervention and placebo were packaged at the same time as the randomisation schedule was generated, and were labelled according to subject number.*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*Yes*
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*Yes*
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*Yes*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?** **Please also record reasons for withdrawal in each group**	X% treatment X% control/ comparison Not reported	*No dropouts/not reported*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Yes*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Not reported*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Yes, BMI and age were quite similar.*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Not reported*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*Possibly* *This study was supported by NIH SBIR grant R43HD35772 (Insmed Pharmaceuticals), NIH-NCRR M01 RR00065-37S1 (M.J.I.), R01HD35629 (J.E.N.), and Insmed Pharmaceuticals, Inc.* *There was no declaration of conflicts of interest or description of the role of the sponsor in the study.*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*No*

	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS		*Moderate RoB due to lack of reporting of randomisation sequence generation, and possible COI*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No – all outcomes had moderate risk of bias due to the nature of the study design.*	

ix.Nestler 1999

Study ID	Nestler 1999	
Study Citation	Nestler JE, Jakubowicz DJ, Reamer P, Gunn RD, Allan G. Ovulatory and metabolic effects of D-chiro-inositol in the polycystic ovary syndrome. New England Journal of Medicine. 1999 Apr 29;340(17):1314-20.	
Study Country	Venezuela	
BRIEF CHARACTERISTICS OF RCT		
Patient/population/ participants	Women with PCOS, 18 to 40 years of age	
PCOS diagnostic criteria	NR- Presence of oligomenorrhoea and hyperandrogenism.	
Presence of infertility	Not reported	
Presence of other condition/s	No	
Medication History	*No*	
N per group	*Allocated/randomised: 44 (22 DCI, 22 placebo)* *Assessed at end of study: 44 (22 DCI, 22 placebo)*	
Setting	Hospital de Clinicas Caracas in Caracas, Venezuela.	
Intervention	Oral administration of 1200 mg of D-chiro-inositol once daily for six to eight weeks	
Comparison	Placebo once daily for six to eight weeks	
Co-interventions	*No*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Ovulation* *Androgens* *Insulin resistance* *Lipid profile* *BMI* *WHR*	
Follow up Duration	*8 weeks*	
Summary Result/s	D-Chiro-inositol increases the action of insulin in patients with the polycystic ovary syndrome, thereby improving ovulatory function and decreasing serum androgen concentrations, blood pressure, and plasma triglyceride concentrations.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* Effects of D-chiroinositol on ovulation and ovarian production of androgens in women with the polycystic ovary syndrome.
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	*Partial*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Partial* Ultrasonography of the ovaries revealed polycystic ovaries in all the women, but this condition was not an inclusion criterion.
Inclusion criteria	Yes Partial No Not reported	Yes Obesity, defined as a body-mass index (the weight in kilograms divided by the square of the height in meters) of more than 28, normal results on thyroid-function tests, and normal serum prolactin concentrations. None of the women had diabetes mellitus, but 10 had impaired glucose tolerance, defined as a serum glucose concentration of at least 140 but less than 200 mg per deciliter (7.8 to 11.2 mmol per liter) two hours after the oral administration of 75 g of glucose. None had taken any medications for at least two months.
Exclusion criteria	Yes	*Not Reported*

		Partial No Not reported	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Yes* The randomization schedule was generated in blocks of four, and the drug and placebo were packaged at the same time and labelled according to subject number.
	Was allocation to intervention group concealed?	Yes Partial No Not reported	*Yes*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*Yes*
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*Yes*
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*Yes*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?** **Please also record reasons for withdrawal in each group**	X% treatment X% control/ comparison Not reported	*No drop outs*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Yes*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Not reported*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Yes*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*No*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*Not reported*
	Was the study sufficiently powered to detect any	Yes Partial	*Not Reported*

	differences between the groups?	No Not reported	
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

viii.MI+DCI

x.Le Donne 2019

Study ID	*Le Donne 2019*	
Study Citation	*Le Donne, M et al. "Effects of three treatment modalities (diet, myoinositol or myoinositol associated with D-chiro-inositol) on clinical and body composition outcomes in women with polycystic ovary syndrome." European review for medical and pharmacological sciences vol. 23,5 (2019): 2293-2301. doi:10.26355/eurrev_201903_17278*	
Study Country	*Italy*	
BRIEF CHARACTERISTICS OF RCT		
Patient/population/ participants	*Women with PCOS (Rotterdam criteria), age between 16 and 45 years; BMI ≥ 25kg/m^2*	
PCOS diagnostic criteria	*Rotterdam*	
Presence of infertility	*Not reported*	
Presence of other condition/s	*Overweight and obesity (BMI ≥ 25kg/m^2)*	
Medication History	*"no hormone therapy for less than 6 months " and "with commitment not to take any throughout the 6-month duration of the study"*	
N per group	*Allocated/randomised: 43 : Diet only (n=21), Diet + MI + FA (n=10), Diet + MI + DCI + FA (n=12)* *Assessed at end of study: 43 : Diet only (n=21), Diet + MI + FA (n=10), Diet + MI + DCI + FA (n=12)*	
Setting	*Department of Human Pathology in Adulthood and Childhood "G. Barresi", University of Messina, Messina, Italy*	
Intervention	*MI + FA; Lo.Li.Pharma (Rome, Italy), each sachet contains 2000 mg MI and 200 µg folic acid, 2 sachets daily*	
Comparison	*MI + DCI + FA; Lo.Li.Pharma (Rome, Italy), each softgel capsule contains 550 mg MI, 13.8 mg DCI, and 200 µg folic acid, 2 capsules daily*	
Co-interventions	*Diet (1200 Kcal) administered to all groups* • *according to Italian guidelines, Livelli di Assunzione di Riferimento di Nutrienti (LARN)39 and consisted of 25% fats, 15-18% proteins and the remaining portion glucids; low glycemic index (IG) foods were recommended.* *There was a third arm that received only the diet intervention. Details are not reported as there is no direct comparison between inositol and this group given inositol was combined with folic acid.*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Menstrual cycle, Ferriman-Gallwey score, BMI, waist circumference, hip circumference, WHR, and body composition by bioimpedentiometry - measured at baseline, 3 and 6 months.*	
Follow up Duration	*3 and 6 months*	
Summary Result/s	*MI + DCI (+ FA) in association with diet seems to accelerate the weight loss and the fat mass reduction with a slight increase of per- cent lean mass, and this treatment contributes significantly in restoring the regularity of the menstrual cycle.*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* *"The purpose of this study was to evaluate, in overweight/obese women with PCOS, which of three distinct treatment modalities*

			achieved the greatest clinical benefits in terms of clinical and body composition outcomes when administered for 6 months to three corresponding groups of patients."
Does the study have specified inclusion/exclusion criteria?		Yes Partial No Not reported	*Partial* ● *no exclusion criteria specified*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Partial* ● *Inclusion criteria: yes.* ● *Exclusion criteria: not specified.*
Inclusion criteria		Yes Partial No Not reported	*Yes* *Women with PCOS (Rotterdam criteria);* *age between 16 and 45 years;* *BMI ≥ 25kg/m2;* *no hormone therapy for less than 6 months;* *no concurrent medical disease and taking no medications or over-the-counter products at baseline with commitment not to take any throughout the 6-month duration of the study.*
Exclusion criteria		Yes Partial No Not reported	*Not reported*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Not reported*
	Was allocation to intervention group concealed?	Yes Partial No Not reported	*Not reported*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*Partial / unclear – the authors report that participants were blinded, however it is difficult to see how this transpired given one intervention is a sachet, another is a soft gel, and another is diet alone without a placebo.*
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*Not reported*
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes (all groups were on the same diet)*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?** **Please also record reasons for withdrawal in each group**	X% treatment X% control/ comparison Not reported	*No dropouts*

	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Yes*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Not reported – no trial registration or protocol available*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Yes* *"The three groups of women did not differ significantly for any index, including the frequency of irregular cycles."*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Yes* *Rate of oligomenorrhea and indices of body composition were reported in the results.*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No* *"The Authors declare that they have no conflict of interests."*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS		*Randomization method and allocation concealment not clear, no report of blinding for investigators and assessors, adherence to diet (self-reported?)*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*High*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

xi.Benelli 2016

Study ID	*Benelli 2016*
Study Citation	*Benelli, Elena et al. "A Combined Therapy with Myo-Inositol and D-Chiro-Inositol Improves Endocrine Parameters and Insulin Resistance in PCOS Young Overweight Women." International journal of endocrinology vol. 2016 (2016): 3204083. doi:10.1155/2016/3204083*
Study Country	*Italy*
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	*Women with PCOS, BMI > 30*
PCOS diagnostic criteria	*Rotterdam*
Presence of infertility	*Not reported*
Presence of other condition/s	*Obesity defined as: BMI > 30*
Medication History	*Not reported*
N per group	*Allocated/randomised: 46 (MI + DCI + FA= 21; FA only= 25)* *Assessed at end of study: 46 (MI + DCI + FA= 21; FA only= 25)*
Setting	*Department of Clinical and Experimental Medicine, University of Pisa, Italy*
Intervention	*MI + DCI combined treatment at the ratio of 40:1*.....Column Break..... *in soft gel capsule containing 550 mg of MI, 13.8 mg of DCI + 200 µg of folic acid (INOFOLIC® COMBI, LO.LI.PHARMA) 2x day*
Comparison	*200 µg of folic acid (INOFOLIC® COMBI, LO.LI.PHARMA) 2x day*
Co-interventions	*NR*
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Endocrine profile and insulin resistance*
Follow up Duration	*6 months*

Summary Result/s		*MI + DCI (+ FA) improved the endocrine and metabolic parameters in young women with PCOS and BMI > 30.*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT			
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	*Partial (no comparison reported in PICO)* *The goal of this study was to investigate if the therapy combining MI and DCI in the ratio of 40 : 1 could improve the endocrine profile and the insulin resistance of obese women with a PCOS diagnosis.*
Does the study have specified inclusion/exclusion criteria?		Yes Partial No Not reported	*Partial* *Both very vague, for example, "young women" but does not state age for inc/exc criteria*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Partial*
Inclusion criteria		Yes Partial No Not reported	*Yes* *Women with PCOS (Rotterdam criteria)* *Age not specified* *BMI > 30*
Exclusion criteria		Yes Partial No Not reported	*Diabetes* *Smokers* *Alcohol users*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Not reported* *"…they were randomly assigned to two groups"*
	Was allocation to intervention group concealed?	Yes Partial No Not reported	*Not reported*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*Not reported*
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?** **Please also record reasons for withdrawal in each group**	X% treatment X% control/ comparison Not reported	*No dropouts*

	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Yes*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Partial* *Note that Table 2 legend includes "P, progesterone; 17OHP, 17-OH-progesterone" but does not report those.* *Trial registration or protocol not reported.*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Yes* *"At baseline, patients in groups A and B did not differ significantly"*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Not reported*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No* *"The authors declare that there are no competing interests regarding the publication of this paper."*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS		*Randomization and blinding not reported, Inc/Exc criteria not conclusive (age? endocrine / menstrual / fertility issues?)*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*High*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

xii.Bahadur 2021

Study ID	Bahadur 2021
Study Citation	Bahadur, A. Arora, H. Ravi, A.K. Naithani, M. Bahurupi, Y. Chaturvedi, J. Ajmani, M. Mundhra, R. (2021). Comparison of clinical, metabolic and hormonal effects of metformin versus combined therapy of metformin with myoinositol plus D-chiro-inositol in women with polycystic ovary syndrome (PCOS): A randomized controlled trial. *Cureus,* 13(6): e15510
Study Country	India
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Newly diagnosed women with PCOS, aged 18-45
PCOS diagnostic criteria	Rotterdam
Presence of infertility	Not reported
Presence of other condition/s	Not reported
Medication History	*Those taking PCOS-related medications such as OCPs were not eligible.*
N per group	*Allocated/randomised: 77 (MYI+DCI+Metformin=39, Metformin alone=38)* *Assessed at end of study: 72 (MYI+DCI+Metformin=36, Metformin alone=36)*
Setting	*Obstetrics and Gynaecology department at medical institution, India*
Intervention	*Myoinositol 550mg +D-chiro-inositol 150mg +Metformin 500mg each dose, twice daily for 6 months* *Daily dose:* *MYO 1100mg + DCI 300mg + Metformin 1000mg*
Comparison	*Metformin 500mg each dose, twice daily for 6 months*

		Daily dose: *1000mg*	
Co-interventions		*None reported*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)		*Changes in clinical, metabolic and hormonal parameters:* *Clinical: Menstrual cyclicity, mFG score, global acne score, waist circumference, hip circumference, waist:hip ratio, BMI* *Metabolic and hormonal: lipid profile, fasting and postprandial blood sugar, fasting and postprandial insulin, LH/FSH ratio, serum testosterone, DHEAS, HOMA-IR index* *None identified as primary or secondary measures in publication but trials register specifies primary endpoint as post-prandial endogenous insulin levels.*	
Follow up Duration		*6 months*	
Summary Result/s		*Synergistic effect of metformin in combination with MYI+DCI in women with PCOS and insulin resistance in terms of improvement in cycle regularity, global acne score, LH levels, LH:FSH ratio, lipid profile including cholesterol, HDL and LDL levels and postprandial insulin.*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT			
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	*Partial* *Does not specify primary outcome measure in publication, although trials register shows primary outcome was specified as postprandial endogenous insulin levels.*
Does the study have specified inclusion/exclusion criteria?		Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Yes*
Inclusion criteria		Yes Partial No Not reported	*Yes* *Reproductive age 18-45 years old* *Newly diagnosed PCOS according to Rotterdam criteria* *Willing to participate in the study and follow up* *Provided written informed consent*
Exclusion criteria		Yes Partial No Not reported	*Yes* *Prescribed other PCOS-related drugs such as OCPs, deranged kidney or liver function tests, uncontrolled thyroid disorders, hyperprolactinaemia, known hypersensitivity to metformin or MYI+DCI, endocrinological disorders such as congenital adrenal hyperplasia, Cushing's syndrome or androgen-secreting tumours.*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Yes* *Computer-generated randomisation table*
	Was allocation to intervention group concealed?	Yes Partial No Not reported	*Not reported*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*No*
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*Not reported*
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*

DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?** **Please also record reasons for withdrawal in each group**	X% treatment X% control/ comparison Not reported	*MYI+DCI+Metformin=3/39 = 7.7%* *Metformin alone = 2/39 = 5.1%* *MYI+DCI+Metformin = 3 lost to follow up* *Metformin alone = 2 lost to follow up* *No reasons for withdrawal in each group were reported.*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Yes*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Partial* *Trials register shows primary outcome was postprandial endogenous insulin levels, which was not reported in publication.*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Yes*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Partial* *Outcomes not adjusted for age*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported* *The sample size is 77. Page 6/7 mentioned "The limitation of the study is that it has a small sample size." It is not clear whether this study was sufficiently powered.*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS		*Possible reporting bias. Primary outcome measure not clearly declared in publication. 20% dropout due to SEs from metformin commonly reported and yet very low dropout rates in this study.*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

xiii.Nordio 2012

Study ID	Nordio 2012
Study Citation	Nordio and Proietti., *European Review for Medical and Pharmacological Sciences* 16: 575-581, 2012
Study Country	Italy
BRIEF CHARACTERISTICS OF RCT	

Patient/population/ participants		*Women with PCOS (BMI > 27 kg/m2, mean age 28 years old, range 18-41)*	
PCOS diagnostic criteria		*Rotterdam*	
Presence of infertility		*Not reported*	
Presence of other condition/s		*No diabetes*	
Medication History		*Not reported*	
N per group		*Allocated/randomised: 50 (24 MI group, 26 MI+DCI group)* *Assessed at end of study: 36 (24 MI group, 12 MI+DCI group)*	
Setting		*Italy* *No information about outpatient or inpatient.*	
Intervention		*2 g of myo-inositol in powder (Inofolic® Lolipharma, Rome, Italy) twice a day for 6 months*	
Comparison		*550 mg of myo-inositol plus 13.8 mg of D-chiro-inositol in soft gel capsule (Inofolic® Combi, Lolipharma patent) twice a day for 6 months*	
Co-interventions		*The patients were asked not to change usual habits both for food, sport and lifestyle.*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)		*At pre-treatment blood pressure, weight and height were measured and waist to hip ratio (WHR) and BMI were calculated through standard equation. In the morning, sex hormone binding globulin, serum steroids and lipid profile levels were measured. All the patients underwent an oral glucose tolerance test (OGTT) and plasma glucose and insulin were measured after 20, 30, 60, 120 minutes.*	
Follow up Duration		*6 months*	
Summary Result/s		*At the end of the treatment, both MI and MI+DCI groups showed an improvement of the metabolic parameters and no significant differences were found. As expected, the combined supplementation with MI and DCI resulted to be more effective, compared to the MI group, after three months of treatment.*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT			
Does the study have a clearly focused question and/or PICO?		*Yes* *Partial* *No* *Not reported*	*Yes* *In this study we compared the effects of MI supplementation alone versus a combined MI and DCI therapy in reducing the metabolic syndrome risk as well as the improvement of the clinical features in PCOS overweight women.*
Does the study have specified inclusion/exclusion criteria?		*Yes* *Partial* *No* *Not reported*	*Partial* *Inclusion/ exclusion criteria not explicitly reported*
If there were specified inclusion/ exclusion criteria, were these appropriate?		*Yes* *Partial* *No* *Not reported*	*Partial*
Inclusion criteria		*Yes* *Partial* *No* *Not reported*	*Partial* *PCOS was diagnosed according to the criteria established by the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) in Rotterdam in 2003: (1) oligoanovulation, (2) hyperandrogenism (clinical or biochemical) and (3) presence of 12 or more follicles in each ovary measuring 2-9 mm in diameter, and/or increased ovarian volume (> 10 ml).*
Exclusion criteria		*Yes* *Partial* *No* *Not reported*	*Partial* *Diabetic subjects, smokers and alcohol users were excluded from the study.*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	*Yes* *Partial* *No* *Not reported*	*Not reported* *Randomisation method not reported or how the randomisation was performed*
	Was allocation to intervention group concealed?	*Yes* *Partial* *No* *Not reported*	*Not reported*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	*Yes* *Partial* *No* *Not reported*	*No* *Randomised controlled trial stated – no mention of blinding. Participants might be easy to guess which group they were allocated*

			as the dosage form of the two groups was different, one in powder and the other in soft gel capsule. However, we contacted the author by email and the author confirmed that participants and investigators were blinded to intervention groups.
	Were investigators and care providers blind to intervention group?	*Yes* *Partial* *No* *Not reported*	*Not reported.* *However, we contacted the author by email and the author confirmed that participants and investigators were blinded to intervention groups.*
	Aside from the experimental intervention, were the groups treated the same?	*Yes* *Partial* *No* *Not reported*	*Not reported*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	*Yes* *Partial* *No* *Not reported*	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	*Yes* *Partial* *No* *Not reported*	*Not reported*
	Were outcomes assessed objectively and independently?	*Yes* *Partial* *No* *Not reported*	*Not reported*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?** **Please also record reasons for withdrawal in each group**	*X% treatment X% control/ comparison* *Not reported*	*Anthropometrics* *MI Group* *0/24 = 0%* *MI+DCI Group* *14/26 = 53.84%*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	*Yes* *Partial* *No* *Not reported*	*Not reported*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	*Yes* *Partial* *No* *Not reported*	*Yes* *No protocol is available, but the outcomes reported in the methods are consistent with those reported in the results section.*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	*Yes* *Partial* *No* *Not reported*	*Yes* *Statistical analysis revealed no significant differences between groups at baseline (age, BMI, waist to hip ratio, hormonal and lipids profile levels)*
	If confounding was present, was it controlled for?	*Yes* *Partial* *No* *Not reported*	*Yes*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	*Yes* *Partial* *No* *Not reported*	*Not reported*
	Was the study sufficiently powered to detect any differences between the groups?	*Yes* *Partial* *No* *Not reported*	*Not reported* *No sample size calculation information was reported.*
	If statistical analysis was undertaken, was this appropriate?	*Yes* *Partial* *No* *Not reported*	*Yes* *To compare the two groups the unpaired t-test (parametric distribution) was used. The significance of differences between the pre- and posttreatment*

			measures (at first and third month) were analyzed using one-way ANOVAs. The source of the detected significances was determined by Bonferroni correction for repeated measures. p values less than 0.05 were considered statistically significant.
COMMENTS		*Lack of randomisation key reason for high RoB*	
What is the overall risk of bias?		*Low Moderate High Insufficient information*	*High*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No – all outcomes high risk of bias*	

xiv.Khan 2022

Study ID	*Khan 2022*	
Study Citation	Khan, RB. Sarosh, M. Answer, S. (2022). Role of myo-inositol and D-Chiro-inositol in improvement of endocrine and clinical parameters in teenage girls affected by PCOS: A prospective cohort study. *Pakistan Journal of Medical and Health Sciences* 16(1),21-24.	
Study Country	*Pakistan*	
BRIEF CHARACTERISTICS OF RCT		
Patient/population/ participants	*Women with PCOS (age 13-19 years old)*	
PCOS diagnostic criteria	*Not reported*	
Presence of infertility	*Not reported*	
Presence of other condition/s	*No*	
Medication History	*No*	
N per group	*Allocated/randomised: 106 (53 MI + DCI, 53 Placebo)* *Assessed at end of study: 106 (53 MI + DCI, 53 Placebo)*	
Setting	*Department of Gynaecology & Obstetrics, Avicenna Medical College and hospital, Lahore, Pakistan*	
Intervention	*MI + DCI (at the ratio of 40:1 (the physiologic ratio of two isomers in the body); Dose: 550 mg of MI, 13.8 mg of DCI, 200µg folic acid; twice a day; for 6 months*	
Comparison	*Placebo: Folic acid (200µg); twice a day; for 6 months*	
Co-interventions	*No*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Fasting glucose after 6 months of treatment*	
Follow up Duration	*6 months*	
Summary Result/s	*Combined therapy with MI plus DCI has promising results for treatment and improvement of clinical and lab parameters in teenage girls affected with PCOS compared to placebo.*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*PartialThe aim was to evaluate the effectiveness of Myo-inositol and D-chiro-Inositol combination therapy in improvement of Endocrine and clinical parameters in teenage girls affected by PCOS.*
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	*Partial*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Partial*
Inclusion criteria	Yes Partial No Not reported	*"106 eligible teen age girls, 13--19 years of age with PCOs were enrolled in the study after taking informed consent."* *Not report the criteria of PCOS used.*
Exclusion criteria	Yes Partial No Not reported	*"Patients with endocrine and metabolic disorders, Type I diabetes and thyroid disease were excluded."*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Not reported* *It only stated that "The participants were randomly assigned to two groups A and B."*
	Was allocation to intervention group concealed?	Yes Partial No Not reported	*Not reported*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*Not reported*
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?** **Please also record reasons for withdrawal in each group**	X% treatment X% control/ comparison Not reported	*MI + DCI = 0/53=0%* *Placebo=0/53=0%*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Yes* *No dropouts.*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Not reported* *No protocol and registered record reported in the article. This is difficult to determine if there isn't a protocol.*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Yes* *Baseline information is in Table 1.* *"Patients in group A and group B did not differ significantly."*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Not reported*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*Partial* *"Conflict of interest: Nil"* *Not reported the funding source.*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No	*Partial* *Potential confounders were identified and taken into account in the analysis*

		Not reported	
COMMENTS		*Lack of randomisation, concealment, blinding, and no report of funding source are key reason for high RoB*	
What is the overall risk of bias?		Low Moderate High Insufficient information	High
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		The overall risk of bias: High Some objective outcomes such as FBG at low risk of bias, other subjective outcomes such as hirsutism and acne high risk of bias, due to lack of information regarding how outcomes were recorded.	

3f. MI+DCI v MI+DCI

xv.Nordio 2019

Study ID	*Nordio 2019*	
Study Citation	*Nordio et al., European Review for Medical and Pharmacological Sciences 23:5512–5521, 2019*	
Study Country	*Italy*	
BRIEF CHARACTERISTICS OF RCT		
Patient/population/ participants	*Women with PCOS*	
PCOS diagnostic criteria	*Rotterdam*	
Presence of infertility	*Not reported*	
Presence of other condition/s	*No*	
Medication History	*No*	
N per group	*Allocated/randomised: 56 (DCI 0:1 alone = 8, MI/DCI 1:3.5 = 8, MI/DCI 2.5:1 = 8, MI/DCI 5:1 = 8, MI/DCI 20:1 = 8, MI/DCI 40:1 = 8, MI/DCI 80:1 = 8)* *Assessed at end of study: 55 (DCI 0:1 alone = 8, MI/DCI 1:3.5 = 8, MI/DCI 2.5:1 = 7, MI/DCI 5:1 = 8, MI/DCI 20:1 = 8, MI/DCI 40:1 = 8, MI/DCI 80:1 = 8)*	
Setting	*University teaching hospital with patients from gynecology/ endocrinology clinics, Glasgow, UK*	
Intervention	*Treated by oral route using the following formulations: DCI alone, and 1:3.5; 2.5:1; 5:1; 20:1; 40:1, 80:1 MI/DCI ratio. They received 2 g of inositols twice a day for 3 months.*	
Comparison		
Co-interventions	*After the enrolment, the patients were invited to avoid any change of usual habits both for food, physical activity and lifestyle.*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*The primary outcome was ovulation (defined by mid luteal progesterone. but do not report threshold level) the secondary outcome included the improvement of FSH, LH, Sex Hormone Binding Globulin (SHBG), 17-beta-Estradiol (E2), free testosterone, basal and postprandial insulin levels, as well as HOMA index, BMI and menses.*	
Follow up Duration	*3 months*	
Summary Result/s	*We found that the 40:1 MI/DCI ratio is the best for PCOS therapy aimed at restoring ovulation and normalizing important parameters in these patients. The other formulations were less effective. In particular, a decreased activity was observed when the 40:1 ratio was modified in favour of DCI.*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	*Yes* *Partial* *No* *Not reported*	*Partial* *The aim of this clinical trial was to evaluate the efficacy of seven different ratios between two inositols stereoisomers, myo-inositol (MI) and D-chiro-inositol (DCI), in the therapy of polycystic ovary syndrome (PCOS).*
Does the study have specified inclusion/exclusion criteria?	*Yes* *Partial* *No* *Not reported*	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	*Yes* *Partial* *No* *Not reported*	*Yes*
Inclusion criteria	*Yes* *Partial* *No*	*Yes*

		Not reported	*Inclusion criteria: age 18-45 years; PCOS diagnosed according to the Rotterdam ESHRE-ASRM consensus workshop group4 (PCOS diagnosed if 2 out of the 3 following conditions were met: a) oligo- or anovulation, b) clinical and/or biochemical signs of hyperandrogenism, and c) polycystic ovaries). Oligo-/anovulation or infertility > 1 year.*
Exclusion criteria		*Yes* *Partial* *No* *Not reported*	*Yes* *Exclusion criteria: presence of other pathologic or age-related conditions causing ovulatory dysfunction (such as hyperprolactinemia or hypothyroidism), androgen excess (such as adrenal hyperplasia or Cushing's syndrome) or poor ovarian reserve; the intake of other drugs that could potentially influence ovulation. Also, obese women (BMI > 29.9) were excluded, as well as women with partners with sperm abnormalities. In this way, we ruled out the concomitant factors that interfere with the possibility of becoming pregnant as potentially confounding variables. After the enrolment, the patients were invited to avoid any change of usual habits both for food, physical activity and lifestyle.*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	*Yes* *Partial* *No* *Not reported*	*Yes* *Randomized (using SAS® software), Interventional, Open-label.*
	Was allocation to intervention group concealed?	*Yes* *Partial* *No* *Not reported*	*No - "open label"*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	*Yes* *Partial* *No* *Not reported*	*No*
	Were investigators and care providers blind to intervention group?	*Yes* *Partial* *No* *Not reported*	*No*
	Aside from the experimental intervention, were the groups treated the same?	*Yes* *Partial* *No* *Not reported*	*Yes*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	*Yes* *Partial* *No* *Not reported*	*No*
	Were all outcomes measured in a standard, valid and reliable way?	*Yes* *Partial* *No* *Not reported*	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* *Partial* *No* *Not reported*	*Not reported*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?** **Please also record reasons for withdrawal in each group**	*X% treatment X% control/ comparison* *Not reported*	*DCI 0:1 alone = 0* *MI/DCI 1:3.5 = 0* *MI/DCI 2.5:1 = 1/8 = 12.5%* *MI/DCI 5:1 = 0* *MI/DCI 20:1 = 0* *MI/DCI 40:1 = 0* *MI/DCI 80:1 = 0* *All the fifty-six patients completed the study, except for one of the groups treated with 2.5:1 MI/DCI ratio, that withdrew for reasons not related to the clinical study.*
	Were all the subjects analysed in the groups to	*Yes* *Partial*	*Yes*

	which they were randomly allocated (ie intention to treat analysis)?	*No* *Not reported*	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	*Yes* *Partial* *No* *Not reported*	*Yes*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	*Yes* *Partial* *No* *Not reported*	*Yes* *The averages of patients' age and BMI at baseline did not display any significant difference among all the groups.*
	If confounding was present, was it controlled for?	*Yes* *Partial* *No* *Not reported*	*No*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	*Yes* *Partial* *No* *Not reported*	*No* *The Authors declare that they have no conflict of interests.*
	Was the study sufficiently powered to detect any differences between the groups?	*Yes* *Partial* *No* *Not reported*	*Not reported* *It is noteworthy that the difference between the effects due to the 40:1 treatment and those exerted by the other formulations was found **often** significant, especially when they were compared to the highest DCI dosages.*
	If statistical analysis was undertaken, was this appropriate?	*Yes* *Partial* *No* *Not reported*	*Yes* *Comparisons between the different times were performed using the one-way analysis of variance (ANOVA) and the post hoc Bonferroni adjustment. Comparisons in pairs between the different dosages were performed using the Chi-Square Test, while Student's t-test was used in order to compare quantitative variables between pairs of different dosages Statistical analyses were implemented at two-sided with a 0.05 significance level, using Stata version 8.2.*
COMMENTS		*Lack blinding key reason for moderate RoB*	
What is the overall risk of bias?		*Low Moderate High Insufficient information*	*Moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No – all outcomes moderate risk of bias*	

xvi.Mendoza 2019

Study ID	Mendoza 2019
Study Citation	Mendoza et al., *Gynaecological Endocrinology* 35:8, 695-7004, 2019
Study Country	Spain
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS undergoing IVF with ICSI (between 18 and 40 years)
PCOS diagnostic criteria	Rotterdam
Presence of infertility	Not reported (not explicitly reported but assumed given use of IVF)
Presence of other condition/s	
Medication History	*No*
N per group	*Allocated/randomised: 60 (30 study group, 30 control group)* *Assessed at end of study: 44 (25 study group, 19 control group)*
Setting	*Five clinical sites/ centers in Spain*
Intervention	*Oral soft gelatin capsules of 550 mg of MYO. 150 mg of DCI twice daily (3.6: 1) [Study group (SG)] over 12 weeks until the day of ovarian puncture.*
Comparison	*Oral soft gelatin capsules of 550 mg of MYO. 13.8 mg of DCI twice daily (40:1) [Control group (CG)] over 12 weeks until the day of ovarian puncture.*
Co-interventions	*Intake of other vitamins or antioxidants was not permitted during the study except for folic acid (400 mcg/ day), which was provided to all the patients.*

Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)			*The primary outcome was the pregnancy rate, and the secondary outcomes were oocyte maturation, embryo quality, testosterone levels and insulin sensitivity. Pregnancy was defined as a positive test at 2 weeks from ET. Oocyte maturation was defined by the percentage of metaphase II (MII) oocytes. Embryos were assessed according to ESHRE criteria [14]. Participants who conceived were followed at the clinical site for ultrasound evidence of a viable intrauterine pregnancy and were referred for obstetrical care.*
Follow up Duration			*12 weeks*
Summary Result/s			*The participants comprised 60 women with PCOS undergoing ICSI. At baseline, no differences were found between the two groups regarding age, BMI, HOMA-IR or testosterone levels. The pregnancy and live birth rates were significantly higher in the SG than in the CG (65.5 vs. 25.9 and 55.2 vs. 14.8, respectively) [risk ratio (RR) . 0.4; 95%CI (0.2, 0.79); p..003 and RR.0.27; 95%CI (0.10, 0.70); p..002 respectively]. The risk of ovarian hyperstimulation syndrome (OHSS) was lower in the SG (3.44 vs. 18.5%, p..07). The combination of MYO-DCI at high doses of DCI improves the pregnancy rates and reduces the risk of OHSS in women with PCOS undergoing ICSI.*
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT			
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	*Yes*
Does the study have specified inclusion/exclusion criteria?		Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Yes*
Inclusion criteria		Yes Partial No Not reported	*Inclusion criteria: women aged between 18 and 40 years with PCOS according to the Rotterdam criteria [13] with a body mass index (BMI) <30 who were undergoing ICSI and signed the informed consent document. All participants were required to have a normal uterine cavity. Before randomization, the patients were offered the possibility of doing inseminations or ICSI.*
Exclusion criteria		Yes Partial No Not reported	*Exclusion criteria: Contraindications for ICSI, adrenal hyperplasia, hyperprolactinemia, thyroid disease, severe endometriosis, poor responder and severe male factor.*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Yes* The volunteers were randomly assigned to one of two groups according to a randomization scheme generated by a computer program (SIGESMUVR).
	Was allocation to intervention group concealed?	Yes Partial No Not reported	*Yes* *Quadruple masking is described (Participant, care provider, investigator and outcomes assessor).*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*Yes* *This was a multicenter controlled, randomized, **double-blind** parallel group study*
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*Yes* *To maintain blinding, the investigator received a treatment allocation number for each subject from the IRT system.*
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*Yes*

	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?** **Please also record reasons for withdrawal in each group**	X% treatment X% control/ comparison Not reported	*Women with PCOS undergoing ICSI* *5/30 study group = 16.67% (2 for personal reasons, 2 spontaneous pregnancies after enrollment before IVF, 1 cancelled due to OHSS risk)* *11/30 control group = 36.67% (5 for personal reasons, 1 spontaneous pregnancy, 3 OHSS risk)*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Yes*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes* *Intention to treat analysis is the comparison of the treatment groups including all patients as originally allocated after randomization. We mainly present the per-protocol analysis for primary and secondary outcomes. However, to compare results, avoid possible bias in the primary outcome and increase the credibility of the results, an intention to treat analysis was also presented using R project 3.3.*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Partial* *At baseline, no differences were found between the two groups regarding age, BMI, HOMA-IR or testosterone levels. The pregnancy and live birth rates were significantly higher in the* *SG than in the CG (65.5 vs. 25.9 and 55.2 vs. 14.8, respectively) [risk ratio (RR) . 0.4; 95%CI (0.2, 0.79); p..003 and RR.0.27; 95%CI (0.10, 0.70); p..002 respectively]. The risk of ovarian hyperstimulation syndrome (OHSS) was lower in the SG (3.44 vs. 18.5%, p..07).*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Yes?* *Bivariate statistical tests for the personal variables were performed to determine the homogeneity of the women's characteristics between the treatment groups.*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*Yes* *Dıaz-Ropero MP, Maldonado-Lob on JA, Olivares M, Fonoll a J are workers of Biosearch Life, a company that produces DCI from carob fruit. The remaining authors declare that they have no competing interests.*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*No*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes* *Frequencies, percentages and chi-square tests were performed on qualitative variables. For quantitative variables, the mean, standard deviation (SD) and 95% confidence intervals were obtained, and the asymptotic ttest or bootstrap technique for the t-test was performed to compare groups. Additionally, statistical multivariate modeling was applied to check differences between groups regarding the evolution of parameters, which used multivariate linear mixed regression models and intra-subject random effect and was fitted with the patients' characteristics.*
COMMENTS		*Randomisation and blinding reasons for low RoB. Authors with possible conflict of interest key factor for moderate risk of bias*	

What is the overall risk of bias?	Low Moderate High Insufficient information	*Moderate – two authors work for a company that produces the intervention*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*No – all outcomes moderate risk of bias*	

ix.MI Comparisons

xvii.Akbari Sene 2019

Study ID		Akbari Sene 2019	
Study Citation		Akbari Sene et al, *Archives of Gynecology and Obstetrics*, 299:1701-1707, 2019	
Study Country		Iran	
BRIEF CHARACTERISTICS OF RCT			
Patient/population/ participants		Infertile women with PCOS referred to an IVF Center in Tehran, Iran	
PCOS diagnostic criteria		Rotterdam criteria	
Presence of infertility		Yes all patients	
Presence of other condition/s		Not reported	
Medication History		*No hormonal treatment x 3mo prior to study*	
N per group		*Allocated/randomised: 60 (1 month of: 30 placebo – folic acid 400mcg/day; 30 intervention – 400mcg FA +4g MI daily)*	
Setting		*University based IVF center in Tehran, Iran*	
Intervention		*(Inofolic, LOLI Pharma, Rome, Italy) Myo inositol 4g + 400mcg folic acid daily x 1 month prior to egg retrieval*	
Comparison		*400mcg folic acid daily x 1 month prior to egg retrieval*	
Co-interventions		*IVF done after treatment period of 1 month*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)		*Primary: Embryo quality, rate of mature oocytes, rate of fertilization* *Other: relative gene expression levels in mural granulosa cells,* ***cumulative pregnancy rate (only outcome of interest)***	
Follow up Duration		*Until IVF outcome*	
Summary Result/s		*The myoinostil treatment group had a higher percentage of mature oocytes, rate of fertilization and top quality embryos compared to placebo. Cumulative pregnancy rate was not different between the groups.*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT			
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	*Yes– The aim of our study was to evaluate the effect of myo-Inositol administration as an adjuvant on expression of some of the genes related to oocyte quality and oxidative stress parameters in the follicular fluid as well as oocyte maturation, fertilization rate and embryo quality in PCOS patients during ART cycle.*
Does the study have specified inclusion/exclusion criteria?		Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Yes*
Inclusion criteria		Yes Partial No Not reported	*Yes* - PCOS by Rotterdam criteria + candidate for IVF cycle, aged 20–35 years and with partner's normal semen analysis results (total volume > 1.5 cc, concentration > 15 million/ml and total motility > 40% as well as normal morphology > 4%, according to WHO 2010)
Exclusion criteria		Yes Partial No Not reported	Yes - excluded if they had other metabolic diseases such as diabetes, BMI above 35, had allergy to myo-Inositol or had received any hormonal medications for at least 3 months before the start of the study
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Yes – permuted block randomization*
	Was allocation to intervention group concealed?	Yes Partial No	*Yes*

		Not reported	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*Yes*
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*Not reported*
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*Yes*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Not reported*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?** **Please also record reasons for withdrawal in each group**	X% treatment X% control/ comparison Not reported	*83% (25/30) completed treatment and 83% (25/30) completed placebo treatment. Reason for drop out of 5 participants in each arm was not reported.*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Yes*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Not reported*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Yes*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Not reported*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*Not reported*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported (no power calculation provided)*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate*

Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*Yes – primary outcome was well defined, pregnancy rate was not well defined.*

xviii.Artini 2013

Study ID	Artini 2013	
Study Citation	Artini et al, *Gynecological Endocrinology*, 29:4, 375-379, 2013	
Study Country	Italy	
BRIEF CHARACTERISTICS OF RCT		
Patient/population/ participants	Women with PCOS with planned IVF treatment at a university based fertility clinic in Italy	
PCOS diagnostic criteria	(a) presence of micropolycystic ovaries at ultrasound, (b) mild to severe hirsutism and/or acne, (c) oligomenorrhea (menstrual cycle435 days) or amenorrhea, (d) absence of enzymatic adrenal deficiency and/or other endocrine disease, (e) normal PRL (Prolactin) levels (range 5–25ng/ml), (f) no hormonal treatment for at least six months before the study.	
Presence of infertility	All participants	
Presence of other condition/s	No	
Medication History	*No hormonal treatment for ≥6 months prior to study*	
N per group	*Allocated/randomised: 50 (12 weeks of: 25 placebo – folic acid 400mcg/day; 25 intervention – 400mcg FA +2g MI)*	
Setting	*University based Obgyn and fertility clinic*	
Intervention	*(Inofert, Italfarmaco, Milano Italy) Myo inositol 2g/day + 200mcg folic acid + additional 200mcg folic acid x 12 weeks*	
Comparison	*400mcg folic acid x 12weeks*	
Co-interventions	*IVF after completing 12 weeks of placebo or intervention*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*LH, FSH, PRL, E2, Testosterone, 17OHP, Androstendione, insulin (fasting), LH/FSH ratio, BMI, Glucose/insulin ratio, HOMA index, AUC insulin(2 hours after 75g OGTT), 30 min and 60 min 75g OGTT* *IVF outcomes: oocytes, top quality oocytes, fertilization rate, top quality embryos,* ***hcg positive, clinical pregnancy (pregnancy seen on US with + FHR),*** *delivery rate*	
Follow up Duration	*Until pregnancy resolution*	
Summary Result/s	*The myoinositol group had significantly lower fasting insulin and HOMA index as well as FSH/LH ratio at study completion. There was also a significantly higher rate of + hCG, clinical pregnancy and live birth in the myoinositol group.*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	**Yes** Partial No Not reported	*The aim of our study was to evaluate the effects of MYO administration on hormonal and clinical parameters in a group of PCOS patients undergoing IVF.*
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* - (a) presence of micropolycystic ovaries at ultrasound, (b) mild to severe hirsutism and/or acne, (c) oligomenorrhea (menstrual cycle435 days) or amenorrhea, (d) absence of enzymatic adrenal deficiency and/or other endocrine disease, (e) normal PRL (Prolactin) levels (range 5–25ng/ml), (f) no hormonal treatment for at least six months before the study.
Exclusion criteria	Yes Partial No Not reported	Yes – not meeting inclusion criteria
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Yes* *Computer generated randomization*
	Was allocation to intervention group concealed?	Yes Partial No Not reported	*Yes*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*Yes*
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*Yes*
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?** **Please also record reasons for withdrawal in each group**	X% treatment X% control/ comparison Not reported	*100% in both arms completed 12 weeks of treatment* *1/25 in treatment arm did not make it to retrieval due to OHSS (no IVF/pregnancy outcomes)* *4/25 in placebo arm did not make it to retrieval due to OHSS (no IVF/pregnancy outcomes)*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Yes*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Yes*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Not reported*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*Not reported*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported (no power calculation provided)*

	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Low*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No – low to moderate risk of bias due to lack of power calculation*	

xix.Constantino 2009

Study ID	Contantino 2009	
Study Citation	Constantino et al, *European Review for Medical and Pharmacological Sciences*, 13: 105-110, 2009	
Study Country	Italy	
BRIEF CHARACTERISTICS OF RCT		
Patient/population/ participants	Women 18-40yrs with PCOS	
PCOS diagnostic criteria	Oligomenorrhea (not defined), elevated free testosterone level and/or hirsutism and PCOS ovaries on ultrasound	
Presence of infertility	Not provided	
Presence of other condition/s	Impaired glucose tolerance (plasma glucose >140mg/dl and <200mg/dl after 75g 2 h OGTT)	
Medication History	*13/42 women were taking oral contraceptive or insulin sensitizers in the 2 months prior to study start*	
N per group	*Allocated/randomised: 42 (6 weeks of: 19 placebo – folic acid 400mcg/day; 23 intervention – 400mcg FA +4g MI daily)*	
Setting	*Not described*	
Intervention	*(Inofolic, LOLI Pharma, Rome, Italy) Myo inositol 4g + 400mcg folic acid daily x 6 weeks* *(methods describe 12-16 wk of treatment but then report measurements after 6 weeks)*	
Comparison	*400mcg folic acid daily x 6 weeks*	
Co-interventions	*None*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Blood pressure, BMI, WHR, T cholesterol, triglycerides, SBP, DBP, fasting. Insulin, fasting glucose, glucose AUC, insulin AUC, ISI comp, Testosterone total and free, androstendione, DHEAS, SHBG*	
Follow up Duration	*After 6-8 weeks of treatment*	
Summary Result/s	*Myoinostiol group had a greater reduction in triglycerides, total cholesterol, glucose AUC, insulin AUC, total and free testosterone after 6 weeks of treatment compared to placebo.*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Partial – The aim of our study was to investigate the metabolic and hormonal effects of myoinositol in PCOS patients.*
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	*Partial*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Partial – appropriate, but not clearly defined*
Inclusion criteria	Yes Partial No Not reported	*Yes* – Oligomenorrhea (not defined), elevated free testosterone level (value for elevated not provided) and/or hirsutism and PCOS ovaries on ultrasound (also not defined)
Exclusion criteria	Yes Partial No Not reported	Not reported
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Not reported*
	Was allocation to intervention group concealed?	Yes Partial No Not reported	*Yes*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*Yes*
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*Yes*
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*Yes*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Not reported*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?** **Please also record reasons for withdrawal in each group**	X% treatment X% control/ comparison Not reported	*100% in both arms completed 6 weeks of treatment* *No dropout was reported*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Yes*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Not reported*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Yes, there seems to be a difference in baseline total testosterone, but otherwise they appear similar*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Not reported*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*Not reported*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported (no power calculation provided)*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No	*Yes*

		Not reported	
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*High*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No – high risk of bias for all outcomes due to lack of power calculation, no reporting of method of randomization, insufficient description of inclusion criteria, no description of the population from which the patients were recruited*	

xx.Genazzani 2008

Study ID	Genazzani 2008	
Study Citation	Genazzani et al, *Gynecological Endocrinology*, 24:3, 139-144, 2008	
Study Country	Italy	
BRIEF CHARACTERISTICS OF RCT		
Patient/population/ participants	Women with PCOS recruited from the Gynecological Endocrinology Center at the University of Modena	
PCOS diagnostic criteria	a) presence of micropolycystic ovaries at ultrasound, b) mild to severe hirsutism and/or acne; c) oligomenorrhea or amenorrhea d) absence of enzymatic adrenal deficiency and/or other endocrine disease, e) normal PRL levels (range 5–25 ng/ml), f) no hormonal treatment for at least 6 months before the study	
Presence of infertility	Not provided	
Presence of other condition/s	All had normal insulin sensitivity at baseline (HOMA >4.5)	
Medication History	*No hormonal treatment x 6mo prior to study*	
N per group	*Allocated/randomised: 20(12 weeks of: 10 placebo – folic acid 200mcg/day; 10 intervention – 200mcg FA +2g MI daily)*	
Setting	*University based GYN endocrinology center in Italy*	
Intervention	*(Inofolic, LOLI Pharma, Rome, Italy) Myo inositol 2g + 200mcg folic acid daily x 12 weeks*	
Comparison	*200mcg folic acid daily x 12weeks*	
Co-interventions	*None*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*BMI, fasting Insulin, fasting glucose, glucose AUC, insulin AUC, Testosterone, androstenedione, farriman gallway score, prolactin, FSH, LH, 17 OHP, estradiol, progesterone, c-peptide*	
Follow up Duration	*After 12 weeks of treatment*	
Summary Result/s	*Myoinostiol group had a significantly lower fasting insulin level and HOMA index compared to placebo at the end of 12 weeks of treatment. There was also a reduction in the ferrman gallway score though not statistically significant.*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Partial – The aim of our study was to evaluate the effects of myoinositol administration on hormonal parameters in a group of oligomenorrheic/amenorrheic patients with PCOS*
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* a) presence of micropolycystic ovaries at ultrasound, b) mild to severe hirsutism and/or acne; c) oligomenorrhea or amenorrhea d) absence of enzymatic adrenal deficiency and/or other endocrine disease, e) normal PRL levels (range 5–25 ng/ml), f) no hormonal treatment for at least 6 months before the study
Exclusion criteria	Yes Partial No Not reported	Not reported
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Not reported*
	Was allocation to intervention group concealed?	Yes Partial No Not reported	*Not reported*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*Not reported*
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Not reported*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?** **Please also record reasons for withdrawal in each group**	X% treatment X% control/ comparison Not reported	*100% in both arms completed 12 weeks of treatment* *No dropout was reported*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Yes*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Not reported*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Yes*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Not reported*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*Not reported*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported (no power calculation provided)*

	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*High*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No – high risk of bias for all outcomes due to lack of power calculation, no reporting of method of randomization, or blinding.*	

xxi.Ozay 2017

Study ID		Ozay 2017	
Study Citation		Ozay et al, *Gynecological Endocrinology*, 33:7, 524-528, 2017	
Study Country		Turkey	
BRIEF CHARACTERISTICS OF RCT			
Patient/population/ participants		Women with infertility and PCOS age 18-35 with planned ovulation induction and IUI cycle at a university based fertility clinic in Turkey	
PCOS diagnostic criteria		Rotterdam criteria	
Presence of infertility		All participants	
Presence of other condition/s		Excluded smoking, hyperprolactinemia, hypogonadotropic hypogonadism, pregnancy, thyroid dyfunction, CAH, androgen secreting tumors and Cushing's Subgroup comparison of those with insulin resistance to without insulin resistance	
Medication History		*No hormonal treatment (OCPs or antiandrogens) for ≥6 months prior to study*	
N per group		*Allocated/randomised: 196 (12 weeks of: 98 placebo – folic acid 400mcg/day; 98 intervention – 400mcg FA +2g MI twice daily)*	
Setting		*University based Obgyn and fertility clinic in Turkey*	
Intervention		*(Inofolic, LOLI Pharma, Rome, Italy) Myo inositol 4g + 400mcg folic acid twice daily x 12 weeks*	
Comparison		*400mcg folic acid (unclear if 1 or 2x daily) x 12weeks*	
Co-interventions		*FSH + IUI after completing 12 weeks of placebo or intervention*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)		*Pregnancy outcomes: clinical pregnancy (pregnancy seen on US with + FHR), miscarriage rate, number of singleton. Pregnancies and number of multiple pregnancies*	
Follow up Duration		*Not specified*	
Summary Result/s		*The myoinositol group had significantly higher clinical pregnancy rate compared to placebo group after use of FSH and IUI (18.6% vs 12.2% p0.02). They had a lower miscarriage rate but this was not statistically significant (12.5% v. 18.2% p0.07). In the MI group 2/16 pregnancies were multiple gestation compared to 1/11 in the placebo group.*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT			
Does the study have a clearly focused question and/or PICO?		**Yes** Partial No Not reported	*The aim of our study was investigate the effect of MI on the pregnancy rate of patients with PCOS who undergo ovulation induction and IUI*
Does the study have specified inclusion/exclusion criteria?		Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Yes*
Inclusion criteria		Yes Partial No Not reported	*Yes – 2/3 of the following:* *oligomenorrhea(<6 cycles in the preceding year) and/or anovulation;* *clinical and/or biochemical hyperandrogenism; ≥12 2-9mm follicles/ ovary 2–9mm and/or increased ovarian volume(410mL)* *No use of hormonal meds in preceding 6 months*
Exclusion criteria		Yes Partial No Not reported	Yes – male infertility diagnosis, or other endocrine disorder (CAH, cushing's etc)
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No	*No* *Randomization was done according to protocol numbers (odd went into group 1 and even into group 2)*

		Not reported	
	Was allocation to intervention group concealed?	Yes Partial No Not reported	*Not reported*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*Not reported*
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Partial – unclear if the placebo was once or twice per day dosing*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?** **Please also record reasons for withdrawal in each group**	X% treatment X% control/ comparison Not reported	*100% in both arms completed 12 weeks of treatment* *9/98 in MI arm conceived spontaneously and therefore not undergo FSH/IUI intervention* *3/98 patients in MI arm had cancelled cycles and were not included in analysis* *8/98 patients in placebo arm had cancelled cycles*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*No – patients with cancelled cycles or spontaneous pregnancies were not included in the analysis*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Yes*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Not reported*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*Not reported*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported (no power calculation provided)*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS			

What is the overall risk of bias?	Low Moderate High Insufficient information	*High*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*No – high risk of bias due to lack of power calculation, method or randomization and failure to complete/report ITT analysis*	

xxii.Pacchiarotti 2016

Study ID	*Pacchiarotti 2016*	
Study Citation	*Pacchiarotti, Alessandro et al. "Effect of myo-inositol and melatonin versus myo-inositol, in a randomized controlled trial, for improving in vitro fertilization of patients with polycystic ovarian syndrome." Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology vol. 32,1 (2016): 69-73. doi:10.3109/09513590.2015.1101444*	
Study Country	*Italy*	
BRIEF CHARACTERISTICS OF RCT		
Patient/population/ participants	*Women with PCOS (Rotterdam criteria), between 27 and 38 years old, BMI of 20 to 26 kg/m2, and undergoing ICSI for the first time*	
PCOS diagnostic criteria	*Rotterdam*	
Presence of infertility	*Yes (primary and secondary infertility reported in Table 1).*	
Presence of other condition/s	*Not reported*	
Medication History	*Not reported*	
N per group	*Allocated/randomised: 569 recruited* ● *Folic acid alone: 211* ● *Myo-inositol + Folic acid:180* ● *Melatonin + Myo-inositol + Folic acid: 178* *Assessed at end of study: 526 (43 dropped out)* ● *Folic acid alone: 195 (16 dropped out; 9 low ovarian response, 7 excessive ovarian response)* ● *Myo-inositol + Folic acid:166 (14 dropped out; 8 low ovarian response, 6 excessive ovarian response)* ● *Melatonin + Myo-inositol + Folic acid: 165 (13 dropped out; 7 low ovarian response, 6 excessive ovarian response)*	
Setting	*Praxi Pro Vita IVF Center (Rome, Italy)*	
Intervention	*Myo-inositol (4000mg) + folic acid (400mcg) (Inofolic, Lo.Li.Pharma SRL, Rome Italy, twice daily)*	
Comparison	*Folic acid (400mcg) (Inofolic, Lo.Li.Pharma SRL, Rome Italy, twice daily)*	
Co-interventions	*All participants undergoing ICSI (for the first time).* *All the participating patients underwent a long down-regulation protocol with a gonadotropin-releasing hormone (GnRH) analogue (triptorelin, Decapeptyl; Ipsen, Milan, Italy) at 0.1 mg/ day on day 21 of their cycle. Moreover, they received a combined protocol at the beginning with 225 IU of acidic HMG (Menopur; Ferring, Milano, Italy) for the first 6 days starting from day 2 of the cycle, followed by 225 IU of less-acidic recombinant FSH (Puregon, MSD, Rome, Italy) until hCG administration.*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Primary: oocyte and embryo quality, clinical pregnancy and implantation rates.* *Secondary: gonadotropin IU administered, days of stimulation, serum estradiol (E2) levels and endometrial thickness on the day of human chorionic gonadotropin (hCG) administration.*	
Follow up Duration	*14 days after embryo transfer*	
Summary Result/s	*Myo-inositol and Melatonin behaved synergistically at ovarian level, improving ovarian response to gonadotropin stimulation, with the result to increase oocyte and embryo quality.*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Partial* *"This study was aimed at testing, in a significant number of PCOS patients, the synergistic effect of Myo-inositol and Metformin integrated in the common IVF protocols, on the main IVF outcomes."*
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	*Partial*

If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Partial*
Inclusion criteria		Yes Partial No Not reported	*Yes* *Women with PCOS, between 27 and 38 years old, with:* *(1) absence of tubal, uterine, genetics and male causes of infertility;* *(2) serum levels of FSH on day 3 of the ovarian cycle <512 IU/L;* *(3) Rotterdam criteria for PCOS;* *(4) normal uterine cavity (5) body mass index (BMI) of 20 to 26 kg/m2, and* *(6) first IVF treatment.*
Exclusion criteria		Yes Partial No Not reported	*Not reported*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Yes* *"Randomization was performed using a computer- based random assignment schedule for each patient and it was double-blinded."*
	Was allocation to intervention group concealed?	Yes Partial No Not reported	*Not reported*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*Partial* *"Randomization was performed using a computer- based random assignment schedule for each patient and it was double-blinded." – but it does not state who was double-blinded.*
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?** **Please also record reasons for withdrawal in each group**	X% treatment X% control/ comparison Not reported	*43 dropped out:* ● *Folic acid alone: 16 dropped out (9 low ovarian response, 7 excessive ovarian response) 195 of 211* ● *Myo-inositol + Folic acid: 14 dropped out (8 low ovarian response, 6 excessive ovarian response) 166 of 180* ● *Melatonin + Myo-inositol + Folic acid: 13 dropped out (7 low ovarian response, 6 excessive ovarian response) 165 of 178*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Yes*

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Yes* *"The differences among the three groups were not statistically significant"*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Not reported*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*Partial* *One of the authors reported being an employee of a pharmaceutical company: "Gianfranco Carlomagno is employee at Farmares SRL, Rome"* *Other authors reported no CoI* *Funding – not reported*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Yes* *"The statistical power calculation was based on a level of 0.05 with 80% power to detect a 20% difference with 50 evaluable patients per group. The sample size needed was estimated to be 214 (Confidence Interval 4; Confidence level 95%)."*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS		*"double-blinding" is not clear*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

xxiii.Papaleo 2009

Study ID	*Papaleo 2009*
Study Citation	*Papaleo, Enrico et al. "Myo-inositol may improve oocyte quality in intracytoplasmic sperm injection cycles. A prospective, controlled, randomized trial." Fertility and sterility vol. 91,5 (2009): 1750-4. doi:10.1016/j.fertnstert.2008.01.088*
Study Country	*Italy*
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	*Women with PCOS, aged <40 years old, undergoing ICSI*
PCOS diagnostic criteria	*Oligoamenorrhea (six or fewer menstrual cycles during a period of 1 year), hyperandrogenism (hirsutism, acne, or alopecia), or hyperandrogenemia (elevated levels of total or free T) and typical features of ovaries on ultrasound scan*
Presence of infertility	*Not reported, although the authors state: "All patients treated in our IVF department for a period of more than 12 months were asked to participate in the study"*
Presence of other condition/s	*Not reported*
Medication History	*Not reported*
N per group	*Allocated/randomised: 60 (30 myo-inositol + folic acid; 30 folic acid alone)* *Assessed at end of study: 60 (30 myo-inositol + folic acid; 30 folic acid alone)*
Setting	*IVF unit, Gynecologic-Obstetric Department, Istituto di Ricovera e Cura a Carattere Scientifico, San Raffaele Hospital, Vita-Salute University, Milan, Italy*
Intervention	*2 g myo-inositol twice a day combined + 400 µg folic acid (Inofolic, Lo.Li. Pharma, Rome, Italy)*
Comparison	*400 µg folic acid (Inofolic, Lo.Li. Pharma, Rome, Italy)*

Co-interventions		*Controlled Ovarian Hyperstimulation*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)		*Primary: number of morphologically mature oocytes retrieved, embryo quality, and pregnancy and implantation rates.* *Secondary total number of days of FSH stimulation, total dose of gonadotropin administered, E2 level on the day of hCG administration, fertilization rate per number of retrieved oocytes, embryo cleavage rate, live birth and miscarriage rates, cancellation rate, and incidence of moderate or severe ovarian hyperstimulation syndrome.*	
Follow up Duration		*Not reported – the longest outcome (spontaneous miscarriage) was classified as "the loss of the pregnancy between the fifth and twelfth weeks of gestation"*	
Summary Result/s		*In patients with PCOS, treatment with myo-inositol and folic acid, but not folic acid alone, reduces germinal vesicles and degenerated oocytes at ovum pick-up without compromising total number of retrieved oocytes*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT			
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	*Yes* *Investigate the effects of myo-inositol on ovarian function in women with PCOS undergoing ovulation induction for intracytoplasmic sperm injection (ICSI), treated within a randomized placebo-controlled trial.*
Does the study have specified inclusion/exclusion criteria?		Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Yes*
Inclusion criteria		Yes Partial No Not reported	*Yes* *Women aged <40 years, diagnosed with PCOS, undergoing ovulation induction for ICSI*
Exclusion criteria		Yes Partial No Not reported	*Yes* *Hyperinsulinemia, hyperprolactinemia, or hypothyroidism, or androgen excess, such as adrenal hyperplasia or Cushing syndrome.*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Yes* *Randomization table*
	Was allocation to intervention group concealed?	Yes Partial No Not reported	*Not reported*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*Not reported*
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*

	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?** **Please also record reasons for withdrawal in each group**	X% treatment X% control/ comparison Not reported	*There were no dropouts*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Yes*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*No* ● *"live birth" is one of the secondary outcomes mentioned in the Abstract (under "Main Outcome Measures") but it is not reported in the paper.* *No trial registration number or protocol.*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Yes* *No differences were found between the two groups in mean age, BMI, and duration of infertility. The causes of infertility also did not differ after randomization between the two groups.*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Not reported*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No* *The authors stated that they have "nothing to disclose"*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS		*See comment about "live birth" in reporting bias, plus blinding not reported*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*High*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

4b. MI + Metformin v Metformin alone

xxiv.Chirania 2017

Study ID	Chirania 2017
Study Citation	A randomised clinical trial comparing myoinositol and metformin in PCOS Chirania, Kishan; Misra, Sujata; Behera, Sandhya International Journal of Reproduction, Contraception, Obstetrics and Gynecology; Vol 6, No 5 (2017): May 2017DO - 10.18203/2320-1770.ijrcog20171563 2017;(): 2017
Study Country	India
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS (age not reported)

PCOS diagnostic criteria		Rotterdam	
Presence of infertility		Some participants had infertility but not all	
Presence of other condition/s		Lean or obese women were included	
Medication History		*No*	
N per group		*Allocated/randomised: This was very poorly reported. Final numbers were 26 MI, 28 Met and 22 MI + Met however the description of randomisation was "After randomisation each group comprised of 24 participants". Authors later reported "since patients already on treatment with either MI or met were also included in the study, the number of patients in each group slightly differed". This is hard to understand as there were fewer participants in the MI + Met group compared to the numbers randomised. It could be that 72 women were randomised and then a few more were added who were not randomised.* *Analysed: 72 (26 MI, 28 Met, 22 MI+ Met)*	
Setting		*Obstetric and gynaecology outpatient department in a medical college in India*	
Intervention		*Myo-inositol 1g/daily for 4 months*	
Comparison		*Metformin 1g daily for 4 months and* *MI + Metformin*	
Co-interventions		*Not reported*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)		*Primary: resumption in spontaneous menstrual cycles and pregnancy rate* *Secondary: anthropometric, metabolic*	
Follow up Duration		*4 months*	
Summary Result/s		*No between-group comparisons were reported. Both MI and MI + Met resulted in resumption in spontaneous menstrual cycles and pregnancies. Metformin alone did not result in resumption of spontaneous menstrual cycles.* *All three interventions reduced weight. MI and Met alone reduced BMI. MI + Met combination reduced fasting insulin.*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT			
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	*Partial* *Evaluate the effect of insulin sensitisers in improving clinical and hormonal alterations in cases of PCOS and improving the reproductive outcomes. Compare the effects of metformin and MI alone, with another group of patients taking a combination.*
Does the study have specified inclusion/exclusion criteria?		Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Partial* *Poorly described* *Unclear why some criteria were chosen eg AMH*
Inclusion criteria		Yes Partial No Not reported	*Rotterdam (oligomenorrhoea/amenorrhoea, with. Polycystic ovaries on US, with or without hyperandrogenism and/or obesity* *15-40* *"Patients who were already diagnosed with PCOS and on treatment with the drugs compared in this study"*
Exclusion criteria		Yes Partial No Not reported	*Partial* *Unclear why AMH is an exclusion* *Abnormal TSH, PRL, AMH* *Any chronic illness in the past or present – TB, thyroid disease, malabsorption* *Chemo/radio therapy in childhood*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Not reported* *Only reported as randomised. It is also unclear how this was implemented: "since patients already on treatment with either MI or met were also included in the study, the number of patients in each group slightly differed"*
	Was allocation to intervention	Yes Partial No	*Not reported*

	group concealed?	Not reported	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*Not reported*
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Not reported*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Not reported*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Not reported*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?** **Please also record reasons for withdrawal in each group**	X% treatment X% control/ comparison Not reported	*Not reported*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Not reported*

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Not reported* *This is difficult to determine if there isn't a protocol.*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Yes*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Not reported*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No* *The authors report no COI*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Partial* *A sample size calculation was performed but unclear if it is appropriate* *"* *It was an equivalence trial where the null hypothesis was that both myoinositol* *and metformin are equally effective in PCOS.* *The sample size was calculated based on the formula, n=Z2×(p)×(1-p)/Δ2* *n is the sample size.* *Z is confidence interval i.e., 1.96 for 95%* *Δ is confidence level i.e., 0.05 for ±5%* *P is the proportion of the population with the disease under study i.e, 5% which in decimal converts to 0.05.* *So, n= (1.96)2×(0.05)×(1-0.05)/(0.05)2 n = 72"*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Not reported*
COMMENTS		*Insufficient information to make a judgement on the risk of bias*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*Due to insufficient reporting it is not possible to make a judgement on the risk of bias.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No – all outcomes unclear ROB.*	

4c. MI v DCI

xxv.Unfer 2011

Study ID	Unfer 2011
Study Citation	*Myo*-inositol rather than D-*chiro*-inositol is able to improve oocyte quality in intracytoplasmic sperm injection cycles. A prospective, controlled, randomised trial. V.Unfer, G, Carlomagno, P. Rizzo, E. Raffone, S Roseff, Eur Rev Med Pharmacol Sci. 2011 Apr;15(4):452-7.
Study Country	Italy

BRIEF CHARACTERISTICS OF RCT			
Patient/population/ participants		Women with PCOS < 40 years that were diagnosed with euglycemia and attending an IVF clinic for ovulation induction for ICSI	
PCOS diagnostic criteria		Rotterdam	
Presence of infertility		Unclear if patients were diagnosed with infertility although criteria were that they had been visiting the IVF department for more than 12 months	
Presence of other condition/s		Nil reported	
Medication History		*No*	
N per group		*Allocated/randomised: 84 women (44 MI 2g twice a day, 41 DCI 0.6g always twice a day)* *Assessed at end of study: 84 women with, no reports of withdrawals from either group in the study*	
Setting		*IVF Clinic, Department of Obstetrics and Gynecology, University of Messina (Italy)*	
Intervention		*Pre-ICSI Myo-inositol 2g twice a day for 8 weeks*	
Comparison		*Pre-ICSI D-chiro inositol 0.6g twice a day for 8 weeks.*	
Co-interventions		*Controlled ovarian hyperstimulation (GnRH agonist then hCG then rFSH) and ICSI were performed after 8 weeks of MI or DCI*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)		*Pregnancy*	
Follow up Duration		*8 weeks + one cycle of ICSI*	
Summary Result/s		*No. of oocytes retrieved did not differ in both groups. No. of mature oocytes was significantly increased in MI group compared to DI group. MI treated group showed increase in average no. of top-quality embryos and total no. of pregnancies.*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT			
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	*Yes.* *The aim was to compare effects of myo-inositol and D-chiro-inositol on oocyte quality in euglycemic PCOS patients.*
Does the study have specified inclusion/exclusion criteria?		Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Yes* *Rotterdam criteria and age for inclusion criteria and insulin resistance/hyperglycaemia for exclusion criteria.*
Inclusion criteria		Yes Partial No Not reported	*Yes* *<40 years* *Euglycemic* *Undergoing fertility treatment at the IVF clinic*
Exclusion criteria		Yes Partial No Not reported	*Yes* *Insulin resistance* *Hyperglycaemia*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Not reported*
	Was allocation to intervention group concealed?	Yes Partial No Not reported	*Not reported*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*No*

	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*Not reported*
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Not reported*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?** **Please also record reasons for withdrawal in each group**	X% treatment X% control/ comparison Not reported	*Not reported, however assuming 0% dropped out.*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Yes*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Not reported* *This is difficult to determine if there isn't a protocol.*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Not reported*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Not reported*

OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*Not reported, not declared in paper*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS		*Lack of randomisation, insufficient information, unsure how they accounted for any confounders if there were any.*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*Insufficient information*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No – all outcomes unclear risk of bias*	

4d. MI v Metformin

xxvi.Angik 2017

Study ID	Angik 2017
Study Citation	A comparative study of metabolic and hormonal effects of myoinositol vs. metformin in women with polycystic ovary syndrome: a randomised controlled trial Angik, Riju; Jajoo, Shubhada S.; Hariharan, C.; Chimote, Amogh International Journal of Reproduction, Contraception, Obstetrics and Gynecology; Vol 4, No 1 (2015): January-February 2015 2017;(): 2017
Study Country	India
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS aged 15-40
PCOS diagnostic criteria	Rotterdam
Presence of infertility	Some participants had been diagnosed with infertility but notn all
Presence of other condition/s	Nil reported
Medication History	*No*
N per group	*Allocated/randomised: 100 (50 MI, 50 Met)* *Analysed: not explicitly reported but assume 100 (50 MI, 50 Met) as there was no reporting of dropouts/withdrawals. Note also that percentages were calculated with 50 as the denominator*
Setting	*Obstetrics and Gynaecology outpatient department at a medical college in a tertiary healthcare centre in India*
Intervention	*Myo-inositol 1g twice daily for 6 months*
Comparison	*Metformin 500mg twice daily for 6 months*
Co-interventions	*Not reported*
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Hormonal (mFG, Testosterone), metabolic (FBG, FINS, HOMA), anthropometric (BMI, WC, WHR), reproductive (menstrual regularity, pregnancy rate), AEs*
Follow up Duration	*6 months*
Summary Result/s	*Metformin was more effective than MI for WHR and HOMA-IR. There were no differences between groups for the other outcomes. This is based on the statistically significant*

		between-group differences reported in the manuscript. The authors reported that that there were within-group differences for FINS and HOMA-IR for MI but not for metformin. This is inconsistent with data reported in their table where HOMA-IR increased from 4.21 to 4.32 in the MI group and decreased from 3.5 to 3.39 in the Metformin group.
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT			
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	*Partial* *The aim was to compare the metabolic and hormonal effects in patients receiving myoinositol to those receiving metformin.*
Does the study have specified inclusion/exclusion criteria?		Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Partial* *Only Rotterdam and age for inclusion criteria*
Inclusion criteria		Yes Partial No Not reported	*15-40 years* *Rotterdam* *Attending the Outpatient department*
Exclusion criteria		Yes Partial No Not reported	*Yes* *Already on other drug treatment for PCOS e.g. OCP* *Kidney or liver dysfunction* *Thyroid disorders* *Known hypersensitivity to MI*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Yes* *Computer generated*
	Was allocation to intervention group concealed?	Yes Partial No Not reported	*Yes* *Sealed opaque consecutively numbered envelopes*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*Not reported*
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Not reported*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Not reported* *There was no reporting of how outcomes were collected or analysed*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Not reported*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?** **Please also record reasons for withdrawal in each group**	X% treatment X% control/ comparison Not reported	*Not reported, but assume 0% dropout as denominator for the percentages e.g. menstrual regularity was 50 in each group at 6 months*

	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Yes*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Not reported* *This is difficult to determine if there isn't a protocol.*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Not reported*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Not reported*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No* *Authors declare no COI*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS		*Unclear risk of bias. Although randomisation and allocation concealment were well described, other domains are poorly reported. There are also inconsistencies between the analysis and what was reported as the findings of the study which raises a red flag.*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*Insufficient information*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No – all outcomes unclear risk of bias.*	

xxvii.Chirania 2017

Study ID	Chirania 2017
Study Citation	A randomised clinical trial comparing myoinositol and metformin in PCOS Chirania, Kishan; Misra, Sujata; Behera, Sandhya International Journal of Reproduction, Contraception, Obstetrics and Gynecology; Vol 6, No 5 (2017): May 2017DO - 10.18203/2320-1770.ijrcog20171563 2017;(): 2017
Study Country	India
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS (age not reported)
PCOS diagnostic criteria	Rotterdam
Presence of infertility	Some participants had infertility but not all
Presence of other condition/s	Lean or obese women were included
Medication History	*No*
N per group	*Allocated/randomised: This was very poorly reported. Final numbers were 26 MI, 28 Met and 22 MI + Met however the description of randomisation was "After randomisation each group comprised of 24 participants". Authors later reported "since patients already on treatment with either MI or met were also included in the study, the number of patients in each group slightly differed". This is hard to understand as there were fewer participants in the MI + Met group compared to the numbers randomised. It could be that 72 women were randomised and then a few more were added who were not randomised.* *Analysed: 72 (26 MI, 28 Met, 22 MI+ Met)*
Setting	*Obstetric and gynaecology outpatient department in a medical college in India*
Intervention	*Myo-inositol 1g/daily for 4 months*
Comparison	*Metformin 1g daily for 4 months and* *MI + Metformin*

Co-interventions			*Not reported*
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)			*Primary: resumption in spontaneous menstrual cycles and pregnancy rate* *Secondary: anthropometric, metabolic*
Follow up Duration			*4 months*
Summary Result/s			*No between-group comparisons were reported. Both MI and MI + Met resulted in resumption in spontaneous menstrual cycles and pregnancies. Metformin alone did not result in resumption of spontaneous menstrual cycles.* *All three interventions reduced weight. MI and Met alone reduced BMI. MI + Met combination reduced fasting insulin.*
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT			
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	*Partial* *Evaluate the effect of insulin sensitisers in improving clinical and hormonal alterations in cases of PCOS and improving the reproductive outcomes. Compare the effects of metformin and MI alone, with another group of patients taking a combination.*
Does the study have specified inclusion/exclusion criteria?		Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Partial* *Poorly described* *Unclear why some criteria were chosen eg AMH*
Inclusion criteria		Yes Partial No Not reported	*Rotterdam (oligomenorrhoea/amenorrhoea, with. Polycystic ovaries on US, with or without hyperandrogenism and/or obesity* *15-40* *"Patients who were already diagnosed with PCOS and on treatment with the drugs compared in this study"*
Exclusion criteria		Yes Partial No Not reported	*Partial* *Unclear why AMH is an exclusion* *Abnormal TSH, PRL, AMH* *Any chronic illness in the past or present – TB, thyroid disease, malabsorption* *Chemo/radio therapy in childhood*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Not reported* *Only reported as randomised. It is also unclear how this was implemented: "since patients already on treatment with either MI or met were also included in the study, the number of patients in each group slightly differed"*
	Was allocation to intervention group concealed?	Yes Partial No Not reported	*Not reported*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*Not reported*
	Aside from the experimental intervention,	Yes Partial No	*Not reported*

	were the groups treated the same?	Not reported	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Not reported*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Not reported*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?** **Please also record reasons for withdrawal in each group**	X% treatment X% control/ comparison Not reported	*Not reported*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Not reported*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Not reported* *This is difficult to determine if there isn't a protocol.*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Yes*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Not reported*

OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No* *The authors report no COI*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Partial* *A sample size calculation was performed but unclear if it is appropriate* *"* *It was an equivalence trial where the null hypothesis was that both myoinositol and metformin are equally effective in PCOS.* *The sample size was calculated based on the formula, n=Z2×(p)×(1-p)/Δ2* *n is the sample size.* *Z is confidence interval i.e., 1.96 for 95%* *Δ is confidence level i.e., 0.05 for ±5%* *P is the proportion of the population with the disease under study i.e, 5% which in decimal converts to 0.05.* *So, n= (1.96)2×(0.05)×(1-0.05)/(0.05)2 n = 72"*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Not reported*
COMMENTS		*Insufficient information to make a judgement on the risk of bias*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*Due to insufficient reporting it is not possible to make a judgement on the risk of bias.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No – all outcomes unclear ROB.*	

xxviii.Nehra 2017

Study ID	Nehra 2017 + Nehra 2017 (2 separate manuscripts with different outcomes reported, same base population/study)
Study Citation	Nehra J, Kaushal J, Singhal, SR, Ghalaut VS. *International Journal of Pharmaceutical Sciences and Research*, Vol 8; 4 p 1664-1670, 2017 Nehra J, Kaushal J, Singhal, SR, Ghalaut VS. *International Journal of Pharmacy and Pharmaceutical Sciences*, Vol 9:4;144-148, 2017
Study Country	India
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women age 15-45 with PCOS by AES criteria who were seen at a Gynecology clinic at a single hospital in India
PCOS diagnostic criteria	Androgen Excess Society 2006 criteria
Presence of infertility	Not reported
Presence of other condition/s	None
Medication History	*Excluded those with any history of anti diabetic drug use, or estrogen or progesterone, or other treatment in the past 3 months*
N per group	*Allocated/randomised: 71(35 MI, 36 Met)* *Assessed at end of study: 60 (30 MI, 30 Met)*
Setting	*Outpatients attending Department of Pharmacology and Obstetrics and Gynecology at Pt BD Sharma PGIMS Rohtak, India*
Intervention	*Myoinositol, 1g each pill, two doses daily for 3 months i.e. 2g daily dose*
Comparison	*Metformin, 500 mg each dose, three doses daily for 3 months i.e. 1500mg daily dose*

Co-interventions		*None reported.*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)		*FSH, LH, insulin, glucose, glucose/insulin ratio, testosterone, HOMA-IR, FSH/LH ratio, total cholesterol, triglycerides, VLDL, LDL, HDL* *Weight, WHR, WC were reported in a separate manuscript (IJPPS 2017)*	
Follow up Duration		*24 weeks (outcomes were measured at 12 and 24 weeks of treatment)*	
Summary Result/s		*Both metformin and MI led to significant improvement in lipid profile with reduction of LDL, total cholesterol and triglycerides and increase in HDL. There was no significant difference when comparing metformin to MI. There were significant reductions in measures of insulin resistance from baseline to 24 week end point in both treatment groups, but the treatment were not compared to one another for these outcomes.* *Regarding weight and BMI, there were significant reductions in both the metformin and MI groups, but no significant difference between the two interventions. There was also not a significant change in waist circumference or WHR.*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT			
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	*Partial* *This study was done to compare the effect of MI versus Met on biochemical profile in women with PCOS.*
Does the study have specified inclusion/exclusion criteria?		Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Yes*
Inclusion criteria		Yes Partial No Not reported	*Yes* *Women with PCOS diagnosed according to AES criteria* *Age 15-45y*
Exclusion criteria		Yes Partial No Not reported	*Yes* *Women suffering from any neoplastic disease, hyperprolactinemia, Cushing's disease, Hypothyroidism / Hyperthyroidism, Pregnancy and nursing, Active liver disease, renal impairment, Established type 1 or type 2 diabetes mellitus, any history of drug intake- Anti diabetic (or) oestrogen and progesterone, history of any treatment taken in last 3 months, Smokers and alcoholic subjects, inability to come for regular follow ups.*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Partial* *"computer generated random numbers"*
	Was allocation to intervention group concealed?	Yes Partial No Not reported	*Not reported*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*No – described as open-label study*
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*No – described as open label study*
	Aside from the experimental intervention,	Yes Partial No	*Yes*

	were the groups treated the same?	Not reported	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*No – described as open label study*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Not reported* *No reporting of method of insulin, glucose, or hormone assay method*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?** **Please also record reasons for withdrawal in each group**	X% treatment X% control/ comparison Not reported	*MYI – 5 lost to follow up 14.3%* *Met – 6 lost to follow up 16.6%*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Yes*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Yes*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*No*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported* *Methods section states an adequate number of patients were screened and selected but no sample size calculation was reported.*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS		*No details of allocation concealment, open label study*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*High*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

xxix.Pourghasem 2019

Study ID	Pourghasem 2019
Study Citation	The effectiveness of inositol and metformin on infertile polycystic ovary syndrome women with resistant to letrozole. Pourghasem et al. Archives of Gynecology & Obstetrics 04// 2019;299(4):1193-1199

Study Country		Iran	
BRIEF CHARACTERISTICS OF RCT			
Patient/population/ participants		Women with PCOS and letrozole resistance	
PCOS diagnostic criteria		Rotterdam	
Presence of infertility		Yes	
Presence of other condition/s		Letrozole resistance, defined as no ovulation (no mature follicle on US) after 3 cycles (starting at 2.5mg, then 5mg and 7.5mg letrozole/daily from third day of menstrual cycle for 5 days). BMI categories (18.5-24.9; 25-29.9;30-24.9;35-39.9)	
Medication History		*No*	
N per group		*Allocated/randomised: 186 (62 folic acid only, 62 metformin + FA, 62 MI + FA)* *Assessed at end of study: 150 (50 FA only, 50 metformin + FA, 50 MI + FA)*	
Setting		*Infertility clinic in a University of Medical Sciences in Iran.*	
Intervention		*Myo-inositol (Amazing Nutrition, Jersey, USA) 2g + folic acid 200□g twice daily for 3 months*	
Comparison		1. *Metformin 1.5g daily (Apotex, Toronto, Canada) + folic acid 200□g daily for 3 months* 2. *Folic acid 200□g daily*	
Co-interventions		*Letrozole 7.5mg daily from third day of menstruation for 5 days in the third cycle (Also folic acid is essentially a co-intervention)*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)		*Ovulation (presence of mature follicle ≥17mm seen on TVU), pregnancy (presence of gestational sac on US 5 weeks after HCG injection).*	
Follow up Duration		*3 months*	
Summary Result/s		*No difference in pregnancy rates between the three groups*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT			
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	*Yes* *Compare the effects of inositol and metformin on ovarian function and pregnancy in women with PCOS with letrozole resistance*
Does the study have specified inclusion/exclusion criteria?		Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Yes*
Inclusion criteria		Yes Partial No Not reported	*Age 15-38* *Rotterdam criteria* *Infertility (unable to fall pregnant despite frequent unprotected intercourse for one year)* *Absence of tubal, anatomic and male factor infertility* *Intact uterine cavity* *Normal thyroid function*
Exclusion criteria		Yes Partial No Not reported	*Other endocrine disorders e.g. hyperprolactinemia* *No desire for cooperation*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Yes* *Random number table was used.*
	Was allocation to intervention group concealed?	Yes Partial No Not reported	*Not reported* *Only mentioned random number table*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*Yes* *Presume yes because folic acid is described as a placebo, and the study was described as single-blind. No other descriptions of blinding.*
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*Not reported*

	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*Not reported – unlikely as study was only single-blind*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?** **Please also record reasons for withdrawal in each group**	X% treatment X% control/ comparison Not reported	*FA only = 12/62 = 19.4%* *8 due to personal reasons, 4 fear of AEs and drug intolerance* *Metformin + FA = 12/62 = 19.4%* *9 due to personal reasons, 3 fear of AEs and drug intolerance* *MI + FA =12/62 = 19.4%* *7 due to personal reasons, 5 fear of AEs and drug intolerance*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Yes*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Not reported* *This is difficult to determine if there isn't a protocol.*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Yes*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Yes* *Post hoc analysis for duration of infertility and BMI*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No* *The authors report no COI*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Partial* *The authors report a sample size calculation was done but it was not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Partial* *Potential confounders were identified and taken into account in the analysis although this was post-hoc*
COMMENTS		*High – due to lack of allocation concealment, blinding, high dropout rate.*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*High*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No – all outcomes high risk of bias*	

xxx.Rajasekaran 2022

Study ID	Rajasekaran 2022
Study Citation	Rajasekaran K, Malhotra N, Mahey R, Khadgawat R, Kalaivani M. *Gynecological Endocrinology*, Vol 38: 2 ; 140-147, 2022
Study Country	India

BRIEF CHARACTERISTICS OF RCT			
Patient/population/ participants		*Women age 21-38 with PCOS who were undergoing their first IVF cycle*	
PCOS diagnostic criteria		Rotterdam	
Presence of infertility		Not explicitly stated but participants were attending an IVF and infertility clinic	
Presence of other condition/s		Excluded those with fibroids, history of ovarian drilling, known diabetes mellitus or those previously on hypoglycemic agents and those with disturbed liver or renal function	
Medication History		*Excluded those with any history of hypoglycemic agent use*	
N per group		*Allocated/randomised: 102(50 MI, 52 Met)* *Assessed at end of study: 100 (50 MI, 5 0 Met)*	
Setting		*Infertility and ART center of All India Institute of Medical Sciences (AIIMS) New Delhi*	
Intervention		*Pre-IVF Myoinositol, 2g each pill, two doses daily for at least 12 weeks i.e. 4g daily dose*	
Comparison		*Pre-IVF Metformin, 850 mg each dose, twice doses daily for 12 weeks i.e. 1700mg daily dose*	
Co-interventions		*IVF using a GnRH antagonist protocol after completion of MI or Met pre treatment x 12 weeks. Medications continued until day of oocyte retrieval*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)		*Menstrual regularity, BMI, LH, FSH, LH/FSH ratio, SHBG, testosterone, fasting glucose, postprandial glucose, fasting insulin, HOMA IR, total cholesterol, LDL, HDL, AMH, AFC, ovarian volume, GI side effects, OHSS incidence with IVF, clinical pregnancy rate (spontaneous + IVF), pregnancy rate per IVF cycle*	
Follow up Duration		*Followed through end of pregnancy*	
Summary Result/s		*Both metformin and MI led to significant improvements in lipid profile, BMI, serum testosterone reduction and rise in SHBG. Both were also found to result in improvement in measures of insulin resistance with reduction in fasting glucose, and insulin and HOMA IR. MI led to a larger proportion of women with regular cycles prior to IVF than metformin and a greater number of clinical pregnancies (both spontaneous and resulting from IVF). There was also less report of GI side effects with MI compared to Met.* *There was no difference in incidence of OHSS which was the primary outcome.*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT			
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	*Yes* *This study was done to compare the effect of MI versus Met pre treatment on the incidence of OHSS following IVF for women with PCOS*
Does the study have specified inclusion/exclusion criteria?		Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Yes*
Inclusion criteria		Yes Partial No Not reported	*Yes* *Women with PCOS diagnosed according to Rotterdam criteria* *Age 21-38y* *Presenting for first IVF cycle*
Exclusion criteria		Yes Partial No Not reported	*Yes* *Women with conditions unfavorable for implantation (fibroids distorting cavity and thin endometrium), prior ovarian drilling, known diabetes mellitus or previously on hypoglycemic agents and disturbed renal or liver function tests were excluded*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Yes* *Block randomization with varying size*
	Was allocation to intervention group concealed?	Yes Partial No Not reported	*Yes* *Sequentially numbered opaque sealed envelope (SNOSE) technique was used for allocation concealment*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No	*Yes*

		Not reported	
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*Yes*
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*Partial* *Allocation code was broken once the patients initiated the treatment cycle*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Partial* *No reporting of method of insulin, glucose, or hormone assay method*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?** **Please also record reasons for withdrawal in each group**	X% treatment X% control/ comparison Not reported	*MYI – 0 lost to follow up* *Met – 2 lost to follow up 3.8% ("due to personal reasons")*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Partial* *ITT and PP analysis for the primary outcome (OHSS)* *Pregnancy rate and other secondary outcomes were all per protocol subjects*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Partial* *MI group had a lower mean AMH, FSH and AFC at baseline, and a higher LH/FSH ratio. This was attributed to chance*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Yes* *Only for the primary outcome of OHSS they controlled for AMH, FSH, AFC and LH/FAH ratio*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Yes*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Low*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*Yes. Primary outcome analysed by intention to treat, but remaining outcomes analyzed by per protocol analysis so moderate risk of bias for other outcomes.*	

xxxi.Tagliaferri 2017

Study ID	Tagliaferri 2017	
Study Citation	Tagliaferri, V. Romualdi, D. Immediata, V. De Cicco, S. Di Florio, C. Lanzone, A. Guido, M. (2017). Metformin vs myoinositol: which is better in obese polycystic ovary syndrome patients? A randomized controlled crossover study. *Clinical Endocrinology*, 86, 725-730.	
Study Country	Italy	
BRIEF CHARACTERISTICS OF RCT		
Patient/population/ participants	Overweight/obese women with PCOS aged 18-35 years (mean age: 25·62 ± 4·7 years; mean BMI: 32·55 ± 5·67 kg/m2)	
PCOS diagnostic criteria	Rotterdam	
Presence of infertility	Not reported	
Presence of other condition/s	Overweight (BMI >25 kg/m^2) or Obese (BMI >30 kg/m^2)	
Medication History	*No use of drugs able to interfere with gluco-insulinaemic metabolism for at least three months prior to entering the study.*	
N per group	*Allocated/randomised: 34 (No other data on group numbers)* *Assessed at end of study: 26 (13 MYI, 13 Met)*	
Setting	*Outpatients attending Department of Obstetrics and Gynaecology at Catholic University of Sacred Heart, Rome, Italy*	
Intervention	*Myoinositol, 500 mg each pill, two oral pills each dose, two doses daily for 6 months i.e. 2g daily dose*	
Comparison	*Metformin, 850 mg each dose, two doses daily for 6 months i.e. 1700mg daily dose*	
Co-interventions	*None reported. Participants advised to continue their usual diet and lifestyle.*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*All measures apart from peripheral glucose utilisation were conducted early follicular phase of spontaneous or induced (medroxyprogesterone acetate 10mg/day for 7 days) menstrual cycles (day:3 ± 7)* *BMI, waist hip ratio, Ferriman-Gallwey score, Cycles in 6 months, FSH, LH, oestradiol, prolactin, testosterone, androstenedione, free androgen index, 17-hydroxyprogesterone, SHBG, dehydroepiandrosterone sulphate, anti-mullerian hormone, ovarian volume, total cholesterol, triglyceride, high-density lipoprotein, very low-density lipoprotein, low-density lipoprotein.* *AUC-Insulin, AUC-Glucose (OGTT for insulin and glucose sampling 15 min before and 30, 60, 90, 120 and 180 minutes after oral ingestion of 75g glucose).* *Day after OGTT:* *Peripheral glucose utilisation (M) via euglycaemic-hyperinsulinaemic clamp*	
Follow up Duration	*6 months*	
Summary Result/s	*Both MYI and metformin improved glyco-insulinaemic features in obese PCOS patients, but only metformin exerts a beneficial effect on endocrine features such as decreasing LH, oestradiol, androgens and anti-mullerian hormone levels, as well as clinical features such as body weight, menstrual pattern and Ferriman-Gallwey score.*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Partial* *(Primary outcome measure not reported in publication: 'To investigate which is the more effective between metformin ad myoinositol on hormonal, clinical and metabolic parameters in obese patients with PCOS.'* *However, in Clinical trials registration, primary outcome reported as 'number of cycles in 6 months', and only two other secondary outcome measures were reported which were 'glyco-insulinemic metabolism as measured by AUC post OGTT, and M value of euglycaemic hyperinsulinaemic clamp).*
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	*Partial* *Partially reported in publication, fully reported in clinical trials registration.*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No	*Yes*

		Not reported	
Inclusion criteria		Yes Partial No Not reported	*Yes* *Reported in publication:* *Women with PCOS diagnosed according to Rotterdam* *BMI >25 kg/m2* *Additionally reported in clinical trials registration:* *Age 18-35 years*
Exclusion criteria		Yes Partial No Not reported	*Yes* *Reported in publication:* *Pregnancy, nursing, significant liver or renal impairment, neoplasms, cardiovascular disease, other hormonal dysfunction (hypothalamic, pituitary, thyroidal or adrenal causes for clinical signs).* *Additionally reported in clinical trials registration:* *Unstable mental illness, diagnoses of diabetes mellitus or impaired glucose tolerance, use of drugs able to interfere with gluco-insulinaemic metabolism for at least three months prior to entering the study.*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Yes* *Simple randomisation with computer-generated random allocation sequence*
	Was allocation to intervention group concealed?	Yes Partial No Not reported	*Not reported*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*No*
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*Not reported*
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?** **Please also record reasons for withdrawal in each group**	X% treatment X% control/ comparison Not reported	*MYI - 1 pregnant, 1/34=2.9%* *Met - 7 dropped out (mild gastrointestinal side effects), 7/34=20.6%*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Not reported*

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*No* *Some important differences in details between Clinical trials registration details and publication.* *Even important outcomes reported in the method section of the publication were not reported in the results section.*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Partial* *'At baseline, the two groups were well matched in terms of clinical, endocrine and metabolic characteristics.'* *No p values provided to compare baseline characteristics, and no information regarding baseline differences according to variables such as age or time since diagnosis.*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*No*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No.* *Reported in the "Source of finding" and "Declaration of interest". None to declare.*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Partial* *Distribution of data was tested and Mann-Whitney U test was carried out since variables were not normally distributed.*
COMMENTS			*Possible selective outcome reporting bias. Primary outcome of menstrual cyclicity in clinical trials registration was not identified as primary measure in publication, and other secondary outcomes identified reported in publication had not been declared in the clinical trials registration.* *Doses of both metformin and MYI were different in clinical trials registration (1500mg daily dose for both) compared to described in publication (MYI 2g daily dose, metformin 1700mg daily dose).* *Publication does not clearly state those with existing diabetes or impaired glucose tolerance were excluded as was evident from clinical trials registration.*
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

4e. MI v Placebo

xxxii.Dona 2012

Study ID	Dona 2012
Study Citation	Inositol administration reduces oxidative stress in erythrocytes of patients with polycystic ovary syndrome Donà, G.; Sabbadin, C.; Fiore, C.; Bragadin, M.; Giorgino, F.L.; Ragazzi, E.; Clari, G.; Bordin, L.; Armanini, D. European Journal of Endocrinology 2012;166(4):703-710 2012
Study Country	Italy
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS 22-30 and normal BMI
PCOS diagnostic criteria	Rotterdam
Presence of infertility	Not reported

Presence of other condition/s		Obese (30 – 37 kg/m2) and morbid obese (above and equal to 37 kg/m2) No diabetes	
Medication History		*No*	
N per group		*Allocated/randomised: 26 (18 MI, 8 placebo)* *Analysed: 26 (18 MI, 8 placebo)*	
Setting		*Department of Medical and Surgical Sciences at a University in Italy*	
Intervention		*Myo-inositol 1.2g / day*	
Comparison		*Matched placebo powder*	
Co-interventions		*Subjects were instructed not to change their eating habits, activity level or lifestyle during the study.*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)		*Hormonal, metabolic, anthropometric*	
Follow up Duration		*3 months*	
Summary Result/s		*Within group improvement in weight, BMI, testosterone, androstenedione, insulin AUC and HOMA-IR in the MI group. Between-group differences for weight, BMI, testosterone, androstenedione, fasting inuslin, insulin AUC and HOMA-IR.*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT			
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	*Partial* *To evaluate any effects on clinical, hormonal and glucose metabolism parameters in PCOS patietns before and after 12 weeks of inositol (no comparison described).*
Does the study have specified inclusion/exclusion criteria?		Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Yes*
Inclusion criteria		Yes Partial No Not reported	*Rotterdam*
Exclusion criteria		Yes Partial No Not reported	*BMI >25 kg/m^2* *Pregnancy* *Diabetes* *Hyperprolactinemia* *Thyroid dysfunction* *Cushing's syndrome* *Late-onset adrenal hyperplasia* *Diabetes* *Taken oral contraceptives, anati-inflammatory drugs or hormonal drugs in previous 3 months*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Yes* *Computer-generated*
	Was allocation to intervention group concealed?	Yes Partial No Not reported	*Not reported*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*Yes*
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*Not reported*
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*

	Were outcome assessors blind to intervention group?	Yes Partial No Not reported	*Not reported*
DEDETECTION BIAS	**Were all outcomes measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?** **Please also record reasons for withdrawal in each group**	X% treatment X% control/ comparison Not reported	*0% in both groups*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Yes*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Not reported* *This is difficult to determine if there isn't a protocol.*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Yes*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Not reported*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No* *The authors declared no COI*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Low*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

4f. MI + monacolin K v Inositol v Met

xxxiii.Leo 2013

Study ID	Leo 2013 (referred to as Musacchio in Covidence)
Study Citation	Leo, V.D. Musacchio, M.C. Cappelli, V. Sabatino A.D. Tosti, C. Piomboni, P. (2013). A combined treatment with myo-inositol and monacolin K improve the androgen and lipid profiles of insulin-resistant PCOS patients. *J Metabolic Synd.2*:127
Study Country	Italy
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS and insulin resistance as evaluated by HOMA-index, aged 24-32 years
PCOS diagnostic criteria	Rotterdam

Presence of infertility		Not reported	
Presence of other condition/s		None. Other endocrinopathies were excluded.	
Medication History		*Not reported.*	
N per group		*Allocated and randomised: MI+monacolin K=20, inositol=20, metformin=20* *Analysed=No information*	
Setting		*Not reported.* *Presumed Obstetrics and gynaecology clinic at University of Siena, Italy (authors' affiliation).*	
Intervention		*Myo-inositol 1.5g + monacolin K 3g (AZELIP-ProgineFarmacuetici) each dose, two times daily for 6 months* *i.e. MI 3g + monacolin K 6g daily, for 6 months*	
Comparison		*Comparison 1: Galenic preparation containing inositol 1.5g each dose, two times daily for 6 months* *i.e. inositol 3g daily, for 6 months* *Comparison 2: Metformin 850 mg each dose, two times daily for 6 months* *Ie. Metformin 1700mg daily, for 6 months*	
Co-interventions		*Not reported*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)		*Physical examination: BMI, FG score* *Hormonal: FSH, LH, Total testosterone, Free testosterone, SHBG, Androstenedione* *Metabolic: fasting glucose, fasting insulin, HOMA* *Lipid: total cholesterol, LDL, HDL, triglycerides* *Other: Menstrual regularity, gastrointestinal side effects*	
Follow up Duration		*6 months*	
Summary Result/s		*All treatments improved patients' clinical, hormonal and metabolic profiles with a tendency towards better results using the combination of myo-inositol and monacolin K.*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT			
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	*Partial* *Primary outcome measure not specified in publication.*
Does the study have specified inclusion/exclusion criteria?		Yes Partial No Not reported	*Partial*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Yes*
Inclusion criteria		Yes Partial No Not reported	*Partial* *PCOS patients diagnosed according to Rotterdam* *Insulin resistance as defined by HOMA* *Provided informed consent*
Exclusion criteria		Yes Partial No Not reported	*Partial* *Participants excluded for other endocrinopathies*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Not reported* *'Randomly assigned' but no other information provided.*
	Was allocation to intervention group concealed?	Yes Partial No Not reported	*Not reported*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No	*Not reported*

		Not reported	
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*Not reported*
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Partial – yes for hormonal, lipid and metabolic outcomes. No information provided regarding BMI and FG-score assessments.*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?** **Please also record reasons for withdrawal in each group**	X% treatment X% control/ comparison Not reported	*Not reported* *It is reported that two women in the metformin group 'interrupted the treatment' due to side-effects, but it is unclear if they dropped out and if their data was included/excluded from final analysis.*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Not reported*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Not reported* *No protocol or trial register to compare publication against.*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Partial* *Baseline clinical, hormonal, metabolic and lipid profiles were comparable between the three study groups, but no information regarding age or time since diagnosis.*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Not reported*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*Not reported*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Partial* *Unclear how menstrual cycle data was analysed.*
COMMENTS		*Lack of clarity regarding primary outcome measure, possible selective outcome reporting and lack of information regarding method of randomisation, eligibility criteria and dropout information.*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

xxxiv. Fruzetti 2017

Study ID	Fruzzetti 2017
Study Citation	Franca Fruzzetti, Daria Perini, Marinella Russo, Fiorella Bucci & Angiolo Gadducci (2017) Comparison of two insulin sensitizers, metformin and myo-inositol, in women with polycystic ovary syndrome (PCOS), Gynecological Endocrinology, 33:1, 39-42, DOI: 10.1080/09513590.2016.1236078
Study Country	Italy
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS (18-28 y.o.), attending reproductive endocrinology clinic, affected by insulin resistance and/or hyperandrogenism, acne and/or hirsutism, and with no abnormal glucose response to the OGTT.
PCOS diagnostic criteria	Rotterdam
Presence of infertility	*Not reported*
Presence of other condition/s	Oligoamenorrhoea and clinical signs of hyperandrogenism. All women were affected by insulin resistance and/or hyperinsulinemia, acne and/or hirsutism, and with no abnormal glucose response to the OGTT.
Medication History	*No subject was using medication known to influence the endocrine and the metabolic profiles.*
N per group	*Allocated/randomised: 50 (25 metformin group, 25 myo-inositol group)* *Assessed at end of study: 46 (22 metformin group, 24 myo-inositol group)*
Setting	*Outpatient Clinic of Reproductive Endocrinology of the University of Pisa*
Intervention	*myo-inositol 4 g plus folic acid 400 mcg/daily*
Comparison	*metformin 1500 mg/daily (500 mg orally thrice daily)*
Co-interventions	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*HOMA-IR, AUC Insulin, Matsuda index, BMI, mF-G score, menstrual frequency, adverse events*
Follow up Duration	*6 months*
Summary Result/s	*Metformin and myo-inositol are equally effective in improving BMI, insulin sensitivity and menstrual cycle in PCOS patients.*
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT	

Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* *Women with PCOS, aged from 18 to 28 years, referred to the Outpatient Clinic of Reproductive Endocrinology of the University of Pisa for oligoamenorrhea and clinical signs of hyperandrogenism.*
Exclusion criteria	Yes Partial No Not reported	*Yes* *Subjects with hyperprolactinemia, hypo or hyper- thyroidism, congenital adrenal hyperplasia, Cushing's syndrome or androgen-secreting tumors were excluded from this study.*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS **Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Partial* *The allocation sequence of the treatments was decided by a third party (D.P. - one of the authors, Daria Perini) before the recruitment of patients by random-number tables.*
SELECTION BIAS **Was allocation to intervention group concealed?**	Yes Partial No Not reported	*Not reported*
PERFORMANCE BIAS **Were patients blind to intervention group?**	Yes Partial No Not reported	*Not reported*
PERFORMANCE BIAS **Were investigators and care providers blind to intervention group?**	Yes Partial No Not reported	*Not reported*
PERFORMANCE BIAS **Aside from the experimental intervention, were the groups treated the same?**	Yes Partial No Not reported	*Yes* *During the observation period, the patients did not modify their Mediterranean diet and did not follow a low-carbohydrate diet.*

DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?** **Please also record reasons for withdrawal in each group**	X% treatment X% control/ comparison Not reported	*Metformin group: 25 recruited, 22 treated (3 dropouts due to gastrointestinal symptoms – diarrhoea and abdominal pain) 12% dropout* *Myo-inositol group: 25 recruited, 24 treated (1 dropout due to poor compliance) 4% dropout*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Yes*
REPORT	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Not reported* *"The study protocol was approved by the Institutional Review Board of Pisa University."*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Yes*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Not reported*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*Partial* *Funding not reported.* *The authors reported no conflict of interest.*

	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Partial* *"in a post study power analysis the sample size of the study allowed us to identify an absolute difference between the groups in the frequency of normal cycles of 35% (with a rate of normal cycles of 45% in the control group and a power of 80%)."* *"Further randomized and properly sized studies are needed in order to confirm our data."*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

xxxv. Ravn 2022

Study ID	Ravn 2022
Study Citation	Ravn P, Gram F, Andersen MS, Glintborg D. Myoinositol vs. Metformin in Women with Polycystic Ovary Syndrome: A Randomized Controlled Clinical Trial. Metabolites. 2022; 12(12):1183. DOI:10.3390/metabo12121183
Study Country	Denmark
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Danish women (18-50 y.o.) with PCOS, not attempting pregnancy
PCOS diagnostic criteria	Rotterdam
Presence of infertility	*Not reported*
Presence of other condition/s	
Medication History	*Pausing was required for MET and oral contraceptive pills for at least one and three months, respectively, before study entry.*

	No woman was on MI before the study. *Use of barrier contraception or copper intrauterine device during the study was optional.*
N per group	*Allocated/randomised: 45 (23 metformin, 22 myo-inositol)* *Assessed at end of study: 28 (12 metformin, 16 myo-inositol)*
Setting	*PCOS outpatient clinic, Department of Gynecology and Obstetrics in collaboration with the Department of Endocrinology, Odense University Hospital (OUH), Denmark*
Intervention	*2 mg MI and 200 mg folic acid (Inofolic®, BiO4U Ltd., Dublin, Ireland), one dose twice daily.*
Comparison	*one tablet of Metformin 500 mg (Metformin, Actavis, TEVA, Tel Aviv, Israel) twice daily for two weeks followed by two tablets twice daily.*
Co-interventions	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*The primary study outcome was HOMA-IR.* *Secondary outcomes were fasting glucose, serum lipids, anthropometric measures (weight, BMI, waist, and hip circumference), Ferriman–Galwey (FG) score, cycle length, gonadothrophins, testosterone, anti-Müllerian hormone (AMH), and scores of QoL and depression as well as adverse effects.*
Follow up Duration	*6 months*
Summary Result/s	*HOMA-IR and weight were unchanged during MI whereas MET had beneficial effects on weight, fasting blood glucose, and HDL cholesterol.* *Cycle length decreased to a similar extent during MI and MET.* *Adverse effects were less frequent during MI vs. MET.*

ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* *Aim was to examine MI vs. MET monotherapy in Danish women with PCOS not attempting pregnancy in an open-label, six-month RCT.*

Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* *PCOS diagnosed according to the Rotterdam criteria and age 18–50 years*
Exclusion criteria	Yes Partial No Not reported	*Yes* *Other causes of oligomenorrhea and/or hirsutism including abnormal values of prolactin, thyroid stimulating hormone, or 17-hydroxy-progesterone, postmenopausal values of FSH (>25 IE/L), and type 1 or 2 diabetes mellitus.*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS – **Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Yes* *Randomization was conducted through the digital platform Research Electronic Data Capture (REDCap®) housed in The Unit for Good Clinical Practice, Odense Patient Explorative Network (OPEN) OUH.*
SELECTION BIAS – **Was allocation to intervention group concealed?**	Yes Partial No Not reported	*Yes* *RedCap*

PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*No* *Open label RCT*
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*No* *Open label RCT*
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes* *Study design included medical intervention without lifestyle intervention.*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*No* *Open label RCT*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*

ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?** **Please also record reasons for withdrawal in each group**	X% treatment X% control/ comparison Not reported	*Myo-inositol group: 6/22 (27.3% dropout)* *6 dropouts: 5 non-compliance, 1 adverse event (irregular menstruation – which was a change from amenorrhea, which was subjectively perceived as unwanted)* *Metformin group: 11/23 (47.8% dropout)* *11 dropouts: 2 non-compliance, 4 pregnancy, 2 adverse events (1 headache and 1 mood swing), 3 gastrointestinal adverse events*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Yes*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes* Clincial trial registration: EudraCT number: 2016-004506-34
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Yes*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Yes*

OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No* *The trial medication and trial registration fee were funded by BiO4U Ltd., Dublin, Ireland.* *The authors declare no conflict of interest. The funder had no role in the design of the study, in the collection, analyses, interpretation of data, in the writing of the manuscript, or in the decision to publish the results.*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Yes*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	*Low*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

xxxvi. Raffone 2010

Study ID	Raffone 2010
Study Citation	*Emanuela Raffone, Pietro Rizzo & Vincenzo Benedetto (2010) Insulin sensitiser agents alone and in co-treatment with r-FSH for ovulation induction in PCOS women, Gynecological Endocrinology, 26:4, 275-280, DOI: 10.3109/09513590903366996*
Study Country	Italy

BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	*Women with PCOS, aged <35 y.o., attending IVF Department for infertility that lasted for a period of more than 14–16 months*
PCOS diagnostic criteria	Rotterdam
Presence of infertility	*All patients attended our IVF Department for infertility that lasted for a period of more than 14–16 months.*
Presence of other condition/s	*Menstrual irregularities, chronic anovulation (ascertained by weekly plasma progesterone concentration below 2.5 ng/ml), and female infertility*
Medication History	
N per group	*Allocated/randomised: myo-inositol (n= 60), metformin (n= 60)* *Assessed at end of 6 months: myo-inositol (n=60), metformin (n= 60)*
Setting	*IVF Department, G. Martino Hospital, Messina, Italy*
Intervention	*4 g, myo-inositol + 400 µg folic acid (Inofolic®, Loli Pharma, Rome, Italy) as soluble powder, daily, continuously, until the end of the study or a positive pregnancy test*
Comparison	*Metformin 1500 mg/day (Glucophage®, Merck Pharma), orally, until the end of the study or a positive pregnancy test*
Co-interventions	*(after the initial 6 months) - if no pregnancy occurred, patients continuing insulin-sensitiser treatment underwent ovulation induction with recombinant FSH (Gonal-F1, Merk- Serono, SUI) for a maximum of three attempts.* *A very low-dose protocol (37.5 U/day) beginning from the day two of menstrual flow in a step up regime was selected.* *Urinary HCG (5000 UI Gonasi1 AMSA, Rome, Italy) was administrated until no more than two follicles of a diameter 417 mm were detected on ultrasound.*

Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Primary endpoint was to evaluate the restoration of spontaneous ovarian activity, by weekly serum progesterone dosage (progesterone levels higher than 8.0 ng/ml), as well as transvaginal ultrasound scan documenting presence of follicular growth or luteal cyst.* *Secondary endpoints were myo- or metformin- resistance (percentage of patient who did not restore spontaneous ovulation), pregnancy rate (documented by positive b-hCG plasma level and foetal heart beat on ultrasound scan) and abortion rate.*	
Follow up Duration	*6 months*	
Summary Result/s	*Both metformin and myo-inositol, can be considered as first line treatment for restoring normal menstrual cycles in most patients with PCOS, even if myo-inositol treatment seems to be more effective than metformin.*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* *This study was designed to test and compare the effects of metformin and myo-inositol on restoring spontaneous ovulation and menstrual cycles and increasing rate pregnancy in women with PCOS.*
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*A total of 120 women, aged <35 years, with PCOS, defined by Rotterdam Criteria, were enrolled.* *"All patients attended our IVF Department for infertility that lasted for a period of more than 14–16 months."*
Exclusion criteria	Yes	*Other medical condition causing ovulatory dysfunction:*

		Partial No Not reported	- ***Hyperprolactinemia or hypothyroidism, or androgen excess, adrenal hyperplasia or Cushing's syndrome, were excluded by hormonal tests.*** - ***Tubal defects: all women underwent assessment of tubal patency.*** - ***Semen parameters defects: all male partners were evaluated with two different sperm semen samples, without finding any defect.***
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Partial* *"Randomisation was performed with 'intention to treat' criteria."*
	Was allocation to intervention group concealed?	Yes Partial No Not reported	*Not reported*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*Not reported*
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*

DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?** **Please also record reasons for withdrawal in each group**	X% treatment X% control/ comparison Not reported	*Myo-inositol: 7/60 (10.9% dropout)* *Side effects (not specified) and loss of follow up* *Metformin: 4/60 (8.3% dropout)* *Loss of follow up*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Yes*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Not reported* *No trial registration number or protocol*

CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Yes*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Not reported*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No* *The authors report no conflicts of interest.*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Yes*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS		*No trial registration / protocol, no allocation, no randomization reported*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

xxxvii. Soldat Stankovic 2022

Study ID	Soldat-Stankovic 2022
Study Citation	Soldat-Stankovic, V. Popovic-Pejicic, S. Stankovic, S. Prtina, A. Malesevic, G. Bjekic-Macut, J. Livadas, S. Ognjanovic, S. Mastorakos, G. Micic, D. Macut, D. (2021) The effect of metformin and myoinositol on metabolic outcomes in women with polycystic ovary syndrome: role of body mass and adiponectin in a randomized controlled trial. Journal of Endocrinological Investigation, 45:583-595.
Study Country	Bosnia and Herzegovina
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS (age 18-40 eligible but age range/mean age of those randomised not provided)
PCOS diagnostic criteria	Rotterdam
Presence of infertility	Yes for some patients, no data available on how many cases in each group.
Presence of other condition/s	Non-obese (BMI ≤25 kg/m2) and overweight/obese (BMI>25 kg/m2) Irregular menstrual cycles, infertility, hirsutism or acne
Medication History	*No subjects had received oral contraceptives, glucocorticoids, antiandrogens or other hormonal agents within 3 months prior to initiation of the study.*
N per group	*Allocated/randomised: 66 randomised and allocated (metformin 33, MI+FA 33)* *Assessed at end of study: 60 (metformin n=30, non-obese n=15, overweight/obese n=15; MI+FA n=30, non-obese n=15, overweight/obese n=15)*
Setting	*University clinical centre, outpatient endocrinology clinic, Banja Luka, Bosnia and Herzegovina*
Intervention	*Myoinositol (2g) + folic acid (200mcg), twice daily for 6 months (i.e. Myoinositol (4g) + folic acid (400mcg) daily)*
Comparison	*Metformin, 500 mg three times daily for 6 months (i.e. 1500mg daily)*
Co-interventions	*None*

Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Primary outcomes: BMI, adiponectin levels, body composition, hormone profile and metabolism of glucose and insulin* *Secondary outcomes: Correlations of adiponectin with clinical and biochemical parameters, differences in clinical and biochemical parameters in groups of obese and non-obese women*	
Follow up Duration	*6 months*	
Summary Result/s	*Out study showed similar effects of metformin and MI+FA on BMI, body composition, hormonal profile, glucose and insulin metabolism and adiponectin level in PCOS patients.*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes	*The aim was to compare the effects of metformin to MI+FA and establish whether both can upregulate serum adiponectin levels in PCOS 'with respect to their BMI'*
Does the study have specified inclusion/exclusion criteria?	Partial	*Description of characteristics of the women participating in the study, but unclear if inclusion/exclusion criteria*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes	*Yes*
Inclusion criteria	Partial	*PCOS diagnosed according to Rotterdam* *Women aged 18-40* *No oral contraceptives, glucocorticoids, antiandrogens and other hormonal agents in 3 months prior to study initiation*
Exclusion criteria	Partial	*Thyroid dysfunction, hyperprolactinaemia, Cushing syndrome, non-classical congenital adrenal hyperplasia (NCAH) and androgen-secreting tumours* *Diabetes, hepatic, renal and cardiovascular disorders* *History of alcohol or drug abuse* *Breast or uterine cancer*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Not reported	*Not reported* *Stratification by BMI (≤25 kg/m2 and >25 kg/m2) and using random permuted blocks of size three. But not clear how the randomisation was done.*
	Was allocation to intervention group concealed?	Yes	*Yes*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*No*
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*No*
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No	*Yes*

		Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?** **Please also record reasons for withdrawal in each group**	X% treatment X% control/ comparison Not reported	*Metformin = 3/33 = 9.09%* *MI+FA = 3/33 = 9.09%* *Metformin = lost to follow up (n=0), discontinued due to adverse event (n=3)* *MI+FA = lost to follow up due to person reasons (n=2), discontinued due to pregnancy (n=1)*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Yes*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Not reported – no protocol available.*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Not reported*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Not reported*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*Not reported.* *'There was no specific funding for this study'.*

	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Yes*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS		*Lack of blinding and lack of published protocol key reasons for moderate RoB*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No – all outcomes at low risk of bias.*	

5. STUDY CHARACTERISTICS TABLES

x. D-Chiro Inositol v Placebo

Author, year, country	Population/ Setting	Study Design	Sample Size per group	Intervention/ exposure details	Comparison/ control details	Follow up Duration	Outcomes	Summary of findings	Other [add as needed]
Iuorno et al. 2002 United States of America	studied 20 lean women (body mass index, 20.0 to 24.4 kg/m2), 18 to 40 years of age, with the polycystic ovary syndrome, as defined by the presence of oligomenorrhea (≤6 menstrual periods during the previous year) and hyperandrogenism (high serum free testosterone levels or hirsutism). Although not a criterion for inclusion in the study or for diagnosis, all the women underwent pelvic ultrasonography at baseline and were found to have ovarian morphologic features consistent with the polycystic ovary syndrome (20). The women	Randomized double-blind RCT	Placebo = 10 DCI = 10	D-Chiro Inositol (600 mg/daily)	Placebo identical daily	6-8 weeks	BMI, Fasting insulin, Fasting glucose, total testosterone, free testosterone, AUCinsulin, AUCglucose	DCI improved glucose tolerance, reduces circulating insulin, decreases serum androgen concentrations and ameliorates other metabolite abnormalities associated with insulin resistance in lean women with PCOS.	

	were recruited from the Hospital de Clinicas Caracas in Caracas, Venezuela								
Nestler, 1999	Women with PCOS/Hospital	Parallel double blind RCT	DCI=22 Placebo=22	Oral administration of 1200 mg of D-chiro-inositol once daily for six to eight weeks	Placebo once daily for six to eight weeks	8 weeks	Ovulaiton (progesterone) Androgens FBG FI AUC-insulin and glucose Lipid profile BMI WHR	D-Chiro-inositol increases the action of insulin in patients with the polycystic ovary syndrome, thereby improving ovulatory function and decreasing serum androgen concentrations, blood pressure, and plasma triglyceride concentrations.	

*RCT = Randomized controlled trial

*LH = levothyroxine

*FSH = follicle stimulating hormone

*AUC = Area Under Curve

xi. Myoinositol (MI) + DCI Comparisons

a. MI + DCI + FA v MI + FA

Author, year, country	Population/ Setting	Study Design	Sample Size per group	Intervention/ exposure details	Comparison/ control details	Follow up Duration	Outcomes	Summary of findings	Other [add as needed]

Le Donne 2019	Women with PCOS (Rotterdam criteria), between 16 and 45 years; BMI ≥ 25kg/m2; no hormone therapy for less than 6 months; no concurrent medical disease; not taking medications or over-the-counter products at baseline with commitment not to take any throughout the 6-month duration of the study. Department of Human Pathology in Adulthood and Childhood "G. Barresi", University of Messina, Messina, Italy	RCT (patients were blind to the treatment)	MI + DCI + FA = 12 MI + FA = 10	MI + DCI + FA; 2x day for 6 months Manufactured by Lo.Li.Pharma (Rome, Italy), and each softgel capsule contains 550 mg MI, 13.8 mg DCI, and 200 µg folic acid.	MI + FA; 2x day. Manufactured by Lo.Li.Pharma (Rome, Italy), and each sachet contains 2000 mg MI and 200 µg folic acid.	Outcomes assessed at 3 months and 6 months	Menstrual cycle, Ferriman-Gallwey score, BMI, waist circumference, hip circumference, WHR, and body composition by bioimpedentiometry - measured at baseline, 3 and 6 months.	MI + DCI (+ FA) in association with diet seems to accelerate the weight loss and the fat mass reduction with a slight increase of per- cent lean mass, and this treatment contributes significantly in restoring the regularity of the menstrual cycle.	

b. MI+DCI+FA v FA only

Author, year, country	Population/ Setting	Study Design	Sample Size per group	Intervention/ exposure details	Comparison/ control details	Co-interventions	Follow up Duration	Outcomes	Summary of findings	Other [add as needed]
Benelli 2016	Women with PCOS (Rotterdam) and BMI > 30 Department of Clinical and Experimental Medicine, University of Pisa, Italy	RCT	MI + DCI + FA = 21 FA only = 25	MI + DCI combined treatment at the ratio of 40:1 in soft gel capsule containing 550 mg of MI, 13.8 mg of DCI + 200 µg of folic acid (INOFOLIC® COMBI, LO.LI.PHARMA) 2x day for 6 months	200 µg of folic acid (INOFOLIC® COMBI, LO.LI.PHARMA) 2x day for 6 months	None reported	6 months	Endocrine profile and insulin resistance	MI + DCI (+ FA) improved the endocrine and metabolic parameters in young women with PCOS and BMI > 30.	

c. MI + DCI + Met vs Met alone

Author, year, country	Population/ Setting	Study Design	Sample Size per group	Intervention/ exposure details	Comparison/ control details	Follow up Duration	Outcomes	Summary of findings	Other [add as needed]
Bahadur 2021	Newly diagnosed women with PCOS, aged 18-45; obstetrics and gynaecology department	Parallel non-blinded RCT	Myoinositol + D-chiro-inositol + metformin = 36 Metformin only = 36	Myoinositol 550mg + D-chiro-inositol 150mg + metformin 500g twice daily orally Total daily dosages: Myoinsotiol 1100mg + D-chiro-inositol 300mg + metformin 1000mg daily	Metformin 500mg twice daily i.e. 1000mg daily	6 months	Clinical: menstrual cyclicity, mFG score, waist circumference, waist:hip ratio, BMI. Metabolic and hormonal: lipids, fasting blood sugar, fasting insulin, serum testosterone, DHEAS and HOMA-IR index.	Synergistic effect of metformin in combination with MYI+DCI in women with PCOS and insulin resistance in terms of improvement in cycle regularity, global acne score, LH levels, LH:FSH ratio, lipid profile including cholesterol, HDL and LDL levels and postprandial insulin.	

d. MI+DCI v MI

Author, year, country	Population/ Setting	Study Design	Sample Size per group	Intervention/ exposure details	Comparison/ control details	Follow up Duration	Outcomes	Summary of findings	Other [add as needed]
Nordio 2012	Women with PCOS (BMI > 27 kg/m^2) mean age 28 years old, range 18 to 41.	RCT, parallel	MI = 24MI+DCI = 26	2 g of myo-inositol, twice daily	550 mg of myo-inositol plus 13.8 mg of D-chiro-inositol twice daily	6 months	Anthropomorphic (BMI, WHR), fasting insulin, insulin AUC, fasting glucose, glucose AUC, HOMA-IR, total testosterone, free testosterone, DHEAS, SHBG, androstenedione.	MI and MI+DCI groups showed an improvement of the metabolic parameters and no significant differences were found. As expected, the combined supplementation with MI and DCI resulted to be more effective,	

								compared to the MI group, after three months of treatment.	

e. MI + DCI v Placebo

Author, year, country	Population/ Setting	Study Design	Sample Size per group	Intervention/ exposure details	Comparison/ control details	Follow up Duration	Outcomes	Summary of findings	Other [add as needed]
Khan et al. 2022	Teenage girls with PCOS; Department of Obstetrics and Gynaecology Avicenna Hospital	Parallel Prospective Cohort Study	MI + DCI = 53 Placebo = 53	MI + DCI (550 mg of MI, 13.8 mg of DCI, 200µg folic acid) twice a day	Placebo (Folic acid) 200µg twice a day	6 months	Fasting glucose,	Combined therapy with MI plus DCI has promising results for treatment and improvement of clinical and lab parameters in teenage girls affected with PCOS compared to placebo.	

f. MI+DCI v MI+DCI

Author, year, country	Population/ Setting	Study Design	Sample Size per group	Intervention/ exposure details	Comparison/ control details	Follow up Duration	Outcomes	Summary of findings	Other [add as needed]
Nordio et al. 2019	Women with PCOS	RCT, open label	DCI 0:1 = 8 MI/DCI 1:3.5 = 8 MI/DCI 2.5:1 = 7 MI/DCI 5:1 = 8 MI/DCI 20:1 = 8 MI/DCI 40:1 = 8 MI/DCI 80:1 = 8	2g of inositols twice daily at different ratios		3 months	Ovulation (progesterone) FSH, LH, Sex Hormone Binding Globulin (SHBG), 17-beta-Estradiol (E2), free testosterone, basal and	40:1 MI/DCI ratio is the best for PCOS therapy aimed at restoring ovulation and normalizing important parameters	

							postprandial insulin levels, HOMA index, BMI, menses.		
Mendoza et al. 2019	Women with PCOS undergoing ICSI, 5 clinical sites/ centers	Multicentre controlled, randomised, double-blind, parallel group study	30 allocated to each Analyzed: Treatment: 25 Control: 19	550mg MYO + 150mg DCI twice daily (3.6:1)	550mg MYO + 13.8mg DCI twice daily (40:1)	3 months	Pregnancy rate, oocyte maturation, embryo quality, testosterone levels and insulin sensitivity	The combination of MYO-DCI at high doses of DCI improves the pregnancy rates and reduces the risk of OHSS in women with PCOS undergoing ICSI.	

xii. MI Comparisons

a. MI +FA v FA alone

Author, year, country	Population/ Setting	Study Design	Sample Size per group	Intervention / exposure details	Comparison/ control details	Follow up Duration	Outcomes	Summary of findings	Other [add as needed]	Co Intervention
Artini et al 2013	Women with PCOS presenting for planned IVF treatment at a university based fertility clinic in Italy	Parallel RCT (not clear if blinded)	Enrolled: MI+ FA = 25 FA alone = 25 Analyzed: MI+ FA = 25	MI+FA = 2g myoinositol + 400mcg Folic Acid	400mcg FA	12 weeks	LH, FSH, PRL, E2, Testosterone, 17OHP, Androstendione, insulin (fasting), LH/FSH ratio, BMI, Glucose/insulin ratio, HOMA index, AUC insulin(2 hours after 75g OGTT), 30 min and 60 min 75g OGTT IVF outcomes: oocytes, top quality oocytes, fertilization rate, top	The myoinositol group had significantly lower fasting insulin and HOMA index as well as FSH/LH ratio at study completion. There was also a significantly higher rate of + hCG, clinical pregnancy and live birth in the myoinositol group.		IVF

			FA alone = 25				quality embryos, hcg positive, clinical pregnancy (pregnancy seen on US with + FHR), delivery rate			
Ozay et al 2017	Women age 18-35 with PCOS and infertility planning to undergo ovulation induction and IUI	Parallel RCT blinding not specified	MI+FA = 98 vs FA alone = 98	MI+FA = 4g myoinositol + 400mcg Folic Acid BID	400mcg FA qD?	12 weeks	Pregnancy outcomes after FSH + IUI: clinical pregnancy (pregnancy seen on US with + FHR), miscarriage rate, number of singleton. Pregnancies and number of multiple pregnancies	The myoinositol group had significantly higher clinical pregnancy rate compared to placebo group after use of FSH and IUI (18.6% vs 12.2% p0.02). They had a lower miscarriage rate but this was not statistically significant (12.5% v. 18.2% p0.07). In the MI group 2/16 pregnancies were multiple gestation compared to 1/11 in the placebo group.	Treatment vs placebo was taken for 12 weeks then all patients underwent stimulation with rFSH followed by IUI, 9 patients in MI group conceived spontaneously prior to FSH/IUI and were not included in analysis. No patients in placebo group conceived spontaneously	FSH+IUI
Constantino 2009	Women age 18-40 with PCOS	Parallel double blind RCT	Enrolled and Analyzed: MI+FA = 23 vs FA alone = 19	MI+FA = 4g myoinositol + 400mcg Folic Acid qD	FA = 400mcg Folic Acid qD	6 weeks	Blood pressure, BMI, WHR, T cholesterol, triglycerides, SBP, DBP, fasting. Insulin, fasting glucose, glucose AUC, insulin AUC, ISI comp, Testosterone total and free, androstenedione, DHEAS, SHBG	Myoinostiol group had a greater reduction in triglycerides, total cholesterol, glucose AUC, insulin AUC, total and free testosterone after 6 weeks of treatment compared to placebo.		None
Genazzani 2008	Women with PCOS recruited from the Gynecological	RCT	Enrolled + Analyzed:	MI+FA = 2g myoinositol + 200mcg	FA = 200mcg folic acid qD	12 weeks	BMI, fasting Insulin, fasting glucose, glucose AUC, insulin AUC, Testosterone,	Myoinostiol group had a significantly lower fasting insulin level and HOMA index		None

	Endocrinology Center at the University of Modena		MI+FA = 10 vs FA alone = 10	folic acid qD			androstenedione, farriman gallway score, prolactin, FSH, LH, 17 OHP, estradiol, progesterone, c-peptide	compared to placebo at the end of 12 weeks of treatment. There was also a reduction in the ferriman gallway score though not statistically significant.		
Akbari Sene 2019	Women with infertility and PCOS who presented to an IVF center in Tehran	RCT	MI+ FA = 30 vs FA alone = 30	MI+FA = 4g myoinositol + 400mcg folic acid qD	FA = 400mcg folic acid qD	1 month prior to IVF treatment	Embryo quality, rate of mature oocytes, rate of fertilization, relative gene expression levels in mural granulosa cells, **cumulative pregnancy rate**	The myoinositol treatment group had a higher percentage of mature oocytes, rate of fertilization and top quality embryos compared to placebo. Cumulative pregnancy rate was not different between the groups.		IVF
Papaleo et al. 2009	Women with PCOS, aged <40 years old, undergoing ICSI IVF unit, Gynecologic-Obstetric Department, San Raffaele Hospital, Vita-Salute University, Milan, Italy	RCT	Myo-inositol + folic acid= 30 Folic acid alone= 30	2 g myo-inositol 2x day + 400 µg folic acid	400 µg folic acid	Not reported (up to 12 weeks of gestation?)	Primary: number of morphologically mature oocytes retrieved, embryo quality, and pregnancy and implantation rates. Secondary total number of days of FSH stimulation, total dose of gonadotropin administered, E2 level on the day of hCG administration, fertilization rate per number of retrieved oocytes, embryo cleavage rate, live birth and miscarriage rates, cancellation rate, and incidence of moderate or severe ovarian hyperstimulation syndrome.	In patients with PCOS, treatment with myo-inositol and folic acid, but not folic acid alone, reduces germinal vesicles and degenerated oocytes at ovum pick-up without compromising total number of retrieved oocytes		**IVF**
Pacchiarotti et al., 2016	Women with PCOS, between 27 and 38 years old, with: (1) absence of tubal, uterine, genetics and	Double-blind RCT	Myo-inositol + folic acid = 166	4000 mg myo-inositol + 400 mcg folic acid. Started treatment first	400 mcg folic acid	Followed until 5 weeks of gestation	Primary: oocyte and embryo quality, clinical pregnancy and implantation rates. Secondary: gonadotropin IU administered, days of	Myo-inositol and Melatonin behaved synergistically at ovarian level, improving ovarian response to gonadotropin stimulation,		**IVF**

	male causes of infertility; (2) serum levels of FSH on day 3 of the ovarian cycle <512 IU/L; (3) Rotterdam criteria for PCOS; (4) normal uterine cavity (5) body mass index (BMI) of 20 to 26 kg/m2, and (6) first IVF treatment. IVF Center (Rome, Italy)		Folic acid alone= 195 Myo-inositol + folic acid + Melatonin = 165	day of IVF cycle and continued until 14 days after embryo transfer			stimulation, serum estradiol (E2) levels and endometrial thickness on the day of human chorionic gonadotropin (hCG) administration.	with the result to increase oocyte and embryo quality.		
Pourghasem 2019	Women with PCOS and letrozole resistance	Parallel single-blind RCT	MI + FA = 50 FA alone = 50	Myoinositol 4g daily for 3 months + folic acid	Folic acid 400μg *daily for 3 months*	3 months	Pregnancy rate (primary), livebirth, ovulation	No differences between groups for pregnancy rate		Letrozole

b. MI + Metformin v Metformin Alone

Author, year, country	Population/ Setting	Study Design	Sample Size per group	Intervention/ exposure details	Comparison/ control details	Follow up Duration	Outcomes	Summary of findings	Other [add as needed]
Chirania 2017	Women with PCOS; Outpatient obstetrics and gynaecology dept in a medical college in India	Parallel 3-armed RCT (described as equivalence trial)	MI + Met = 22 Met=28	MI 1g daily for 4 months + Metformin 1g daily for 4 months	Metformin 1g daily for 4 months	4 months	Reproductive, metabolic, hormonal	*No between-group comparisons were reported. Both MI and MI + Met resulted in resumption in spontaneous menstrual cycles and pregnancies. However, pregnancy data is*	

								difficult to understand as it was reported as "infertility". Metformin alone did not result in resumption of spontaneous menstrual cycles. *All three interventions reduced weight. MI and Met alone reduced BMI. MI + Met combination reduced fasting insulin.*	

c. MI v DCI

Author, year, country	Population/ Setting	Study Design	Sample Size per group	Intervention/ exposure details	Comparison/ control details	Co-interventions	Follow up Duration	Outcomes	Summary of findings	Other [add as needed]
Unfer 2011	Women with PCOS <40 attending IVF clinic for ovulation induction and ICSI and without insulin resistance or hyperglycemia	Parallel RCT	MI=43 DCI=41	Pre-ICSI Myoinositol 4g daily for 8 weeks	Pre-ICSI D-Chiro-Inositol 1.2g daily for 8 weeks	ICSI following 8 weeks of DCI/MI	8 weeks plus one cycle of ICSI	Reproductive only	*No. of oocytes retrieved did not differ in both groups. No. of mature oocytes was significantly increased in MI group compared to DI group. MI treated group showed increase in average no. of top-quality embryos and total no. of pregnancies.*	

d. MI v Metformin

Author, year, country	Population/ Setting	Study Design	Sample Size per group	Intervention/ exposure details	Comparison/ control details	Follow up Duration	Outcomes	Summary of findings	Other [add as needed]
Pourghasem 2019	Women with PCOS and letrozole resistance; infertility clinic in University of Medical Sciences Iran	Parallel 3-armed RCT (Also compared against FA alone)	MI + FA = 50 Met + FA = 50	MI 2g + Folic Acid 200μg twice daily	Metformin 1.5g daily + Folic Acid 200μg *daily*	3 months	Ovulation, pregnancy	No difference in pregnancy rates across three groups	
Angik 2017	Women with PCOS 15-40 years; Outpatient obstetrics and gynaecology dept in tertiary healthcare centre, India	Parallel RCT	MI = 50 Met = 50	MI 2g daily for 6 months	Metformin 1g daily for 6 months	6 months	Hormonal, metabolic, anthropometric, reproductive, AEs	Metformin was more effective in lowering HOMA-IR and WHR	
Chirania 2017	Women with PCOS; Outpatient obstetrics and gynaecology dept in a medical college in India	Parallel 3-armed RCT (described as equivalence trial)	MI=26 Met=28	MI 1g daily for 4 months	Metformin 1g daily for 4 months	4 months	Reproductive, metabolic, hormonal	*No between-group comparisons were reported. Both MI and MI + Met resulted in resumption in spontaneous menstrual cycles and pregnancies. However, pregnancy data is difficult to understand as it was reported as "infertility". Metformin alone did not result in resumption of spontaneous menstrual cycles. All three interventions reduced weight. MI and Met*	

								alone reduced BMI. MI + Met combination reduced fasting insulin.	
Tagliaferri 2017	Overweight or obese women with PCOS; Outpatient department of obstetrics and gynaecology	Crossover RCT	Total randomised = 34 N per group not available for total randomised Total analysed = 26 Of which Myoinositol=13 Metformin=13	Myoinositol 2g daily	Metformin 1700mg daily	6 months	BMI, WHR, FG score, menstrual cyclicity, A, T, FAI, DHEAS, SHBG, AUC-insulin, AUC-glucose, peripheral insulin sensitivity (M), total cholesterol, triglyceride, HDL, LDL.	Both treatments improve glycol-insulinaemic features of obese PCOS patients, but only metformin exerts a beneficial effect on the endocrine and clinical features of the syndrome.	
Nehra 2017	Women age 15-45 with PCOS by AES criteria who were seen at a Gynecology clinic at a single hospital in India	Parallel RCT	Total randomized: 71 MI = 35 Met = 36 Total Analyzed MI = 30 Met = 30	Myoinositol 1g BID (2g daily)	Metformin 500mg TID (1500mg daily)	24 weeks (outcomes measured at 12 and 24 weeks)	FSH, LH, insulin, glucose, glucose/insulin ratio, testosterone, HOMA-IR, FSH/LH ratio, total cholesterol, triglycerides, VLDL, LDL, HDL, Weight, WHR, WC were reported in a separate manuscript (IJPPS 2017)	Both metformin and MI led to significant improvement in lipid profile with reduction of LDL, total cholesterol and triglycerides and increase in HDL. There was no significant difference when comparing metformin to MI. There were significant reductions in measures of insulin resistance from baseline to 24 week end point in both treatment groups, but the treatment were not compared to one another for these outcomes. Regarding weight and BMI, there were significant reductions in both the metformin and MI groups, but	Two separate papers, same study/population. Second paper reported only BMI, Weight, WHR

								no significant difference between the two interventions. There was also not a significant change in waist circumference or WHR.	
Rajasekaran 2022	Women age 21-38 with PCOS who were undergoing their first IVF cycle	Parallel double blind RCT	Total randomized: 102 MI = 50 Met = 52 Total analyzed: 100 MI = 50 Met = 50	Myoinositol 2g BID (4g daily)	Metformin 850mg BID (1700mg daily)	12 weeks treatment + outcome of IVF cycle until end of pregnancy	Menstrual regularity, BMI, LH, FSH, LH/FSH ratio, SHBG, testosterone, fasting glucose, postprandial glucose, fasting insulin, HOMA IR, total cholesterol, LDL, HDL, AMH, AFC, ovarian volume, GI side effects, OHSS incidence with IVF, clinical pregnancy rate, pregnancy rate per IVF cycle	Both metformin and MI led to significant improvements in lipid profile, BMI, serum testosterone reduction and rise in SHBG. Both were also found to result in improvement in measures of insulin resistance with reduction in fasting glucose, and insulin and HOMA IR. MI led to a larger proportion of women with regular cycles prior to IVF than metformin and a greater number of clinical pregnancies (both spontaneous and resulting from IVF). There was also less report of GI side effects with MI compared to Met. There was no difference in incidence of OHSS which was the primary outcome.	
Fruzzetti et al. 2017	Women with PCOS (Rotterdam), aged from 18-28 years,	3 arms: MI, MET, no PCOS	Myo-inositol (n= 24)	Myo-inositol 4 g	Metformin 1500 mg/daily	6 months	Metabolic and BMI, menstrual cycle,	Metformin and myo-inositol are equally effective in improving	In a post study power analysis, the sample size of the

	attending the Outpatient Clinic of Reproductive Endocrinology of the University of Pisa, Italy, for oligoamenorrhoea and clinical signs of hyperandrogenism.		Metformin (n= 22)	+ folic acid 400 mcg/daily	(500 mg orally 3x day)		hirsutism, acne, adverse events.	BMI, insulin sensitivity and menstrual cycle in PCOS patients.	study allowed us to identify an absolute difference between the groups in the frequency of normal cycles of 35% (with a rate of normal cycles of 45% in the control group and a power of 80%).
Ravn et al. 2022	Danish women with PCOS (Rotterdam) not attempting pregnancy, age 18–50 years. PCOS outpatient clinic, Department of Gynecology and Obstetrics in collaboration with the Department of Endocrinology, Odense University Hospital (OUH), Denmark.	Open label RCT	Myo-inositol (n= 16) Metformin (n= 12)	2 mg MI + 200 mg folic acid (Inofolic®, BiO4U Ltd., Dublin, Ireland) one dose twice daily.	Metformin: one tablet of 500mg (Metformin, Actavis, TEVA, Tel Aviv, Israel) 2xday for two weeks followed by two tablets twice daily.	6 months	The primary study outcome was HOMA-IR. Secondary outcomes were fasting glucose, serum lipids, anthropometric measures, FG score, cycle length, gonadothrophins, testosterone, AMH), and scores of QoL and depression as well as adverse effects.	HOMA-IR and weight were unchanged during MI whereas Metformin had beneficial effects on weight, fasting blood glucose, and HDL cholesterol. Cycle length decreased to a similar extent during MI and Metformin. Adverse effects were less frequent during MI vs. Metformin.	
Raffone et al. 2010	Women, aged <35 years, with PCOS (Rotterdam).		Myo-inositol (n= 60) Metformin (n= 60)	Myo-inositol 4g/day + folic acid 400 µg	Metformin 1500mg/day	6 months	Spontaneous ovarian activity, myo-inositol or metformin resistance, pregnancy	Both metformin and myo-inositol, can be considered first-line treatment in most patients with PCOS, for restoring normal menstrual cycles.	Furthermore, oral administration of myo-inositol is a simple and safe treatment that seems positively

	Attending IVF Department, G. Martino Hospital, Messina, Italy, for infertility that lasted for a period of more than 14-16 months.						(biochemical and clinical), and miscarriage rate.		correlated also to oocyte maturity, with the possibility in addition to increase spontaneous fertility.
Soldat-Stankovic, 2022, Bosnia and Herzegovina	Women with PCOS with irregular periods, infertility, hirsutism or acne, university outpatient endocrinology clinic	Parallel open-label randomised controlled trial	MI+FA=33 Metformin= 33	Myoinositol (4g) + Folic acid (400mcg) daily	Metformin 1500mg daily	6 months	Primary: BMI, adiponectin, body composition, hormonal profile, metabolism of glucose and insulin. Secondary: Correlations of adiponectin with clinical and biochemical parameters, ascertain differences in clinical and biochemical parameters in groups of obese and non-obese PCOS women	Metformin and MI+FA had similar effects on BMI, body composition, hormonal profile, metabolism of glucose and insulin and adiponectin level.	

e. MI v Placebo

Author, year, country	Population/ Setting	Study Design	Sample Size per group	Intervention/ exposure details	Comparison/ control details	Follow up Duration	Outcomes	Summary of findings	Other [add as needed]
Dona 2012	Women with lean PCOS; University in Italy	Parallel placebo-controlled RCT	MI = 18 Placebo = 8	Myo-inositol 1.2g daily for 12 weeks	Matched placebo powder for 12 weeks	3 months	Hormonal, metabolic, anthropometric	*Within group improvement in weight, BMI, testosterone, androstenedione, insulin AUC and HOMA-IR in the MI*	

								group. Between-group differences for weight, BMI, testosterone, androstenedione, fasting inuslin, insulin AUC and HOMA-IR.	

f. MI + monacolin K v Inositol v Met

Author, year, country	Population/ Setting	Study Design	Sample Size per group	Intervention/ exposure details	Comparison/ control details	Follow up Duration	Outcomes	Summary of findings	Other [add as needed]
Leo, 2013, Italy	Women with PCOS and insulin resistance	Parallel RCT	MI+moacolin K=20 Inositol=20 Metformin=20	MI 1.5 g + mocaolin K 3g (AZELIP-ProgineFarmaceutici), twice a day for 6 months i.e. MI 3g + moacolin K 6g daily for 6 months	Comparison 1: Inositol 1.5g each dose, twice a day for 6 months Ie. Inositol 35g daily for 6 months Comparison 2: Metformin 850mg each dose, twice a day for 6 months i.e. Metformin 1700mg daily for 6 months	6 months	FG score, free testosterone, total testosterone, SHBG, Androstenedione, fasting glucose, fasting insulin, HOMA, total cholesterol, LDL, HDL, TG, BMI, menstrual regularity, gastrointestinal side-effects	Combined treatment with moacolin K and MI is a valid and well tolerated alternative to metformin, improving PCOS-related symptoms and with minimal side-effects.	

GRADE ASSESSMENTS AND EVIDENCE PROFILE

COMPARISON: DCI vs Placebo												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	DCI	Placebo	Effect, fixed [95% CI]	Favours	Certainty	Importance
Outcome: Free testosterone												
2	RCT	No serious risk of bias	no serious inconsistency	no serious indirectness	Very serious[1]	none	32	32	MD -0.46 [-0.65, -0.27]	DCI	⊕⊕◯◯ LOW	CRITICAL
Outcome: HOMA-IR												
No studies reported on this outcome.												CRITICAL
Outcome: 2-hour glucose												
No studies reported on this outcome.												CRITICAL
Outcome: BMI												
2	RCT	No serious risk of bias	no serious inconsistency	no serious indirectness	Very serious[1]	none	32	32	MD 0.67 [0.10, 1.23]	Placebo	⊕⊕◯◯ LOW	CRITICAL
Outcome: QoL												
No studies reported on this outcome.												CRITICAL
Outcome: Total Testosterone												
2	RCT	No serious risk of bias	no serious inconsistency	no serious indirectness	Very serious[1]	none	32	32	MD -28.96 [-38.72, -19.20]	DCI	⊕⊕◯◯ LOW	IMPORTANT
Outcome: SHBG												
2	RCT	No serious risk of bias	no serious inconsistency	no serious indirectness	Very serious[1]	none	32	32	MD 2.00 [1.01,2.99]	Neither	⊕⊕◯◯ LOW	IMPORTANT
Outcome: DHEAS												
2	RCT	No serious risk of bias	no serious inconsistency	no serious indirectness	Very serious[1]	none	32	32	MD -139.43 [-198.51,-80.36]	DCI	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Androstendione												
2	RCT	No serious risk of bias	no serious inconsistency	no serious indirectness	Very serious[1]	none	32	32	MD -1541.44 [-1570.44,-1512.44]	DCI	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Fasting Glucose												
2	RCT	No serious risk of bias	no serious inconsistency	no serious indirectness	Very serious[1]	none	32	32	MD -6.14 [-14.52, 2.24]	Neither	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Fasting Insulin												
2	RCT	No serious risk of bias	no serious inconsistency	no serious indirectness	Very serious[1]	none	32	32	MD -15.53 [-31.10, 0.04]	Neither (p=0.05)	⊕⊕◯◯ LOW	IMPORTANT
Outcome: AUC Glucose												

2	RCT	No serious risk of bias	no serious inconsistency	no serious indirectness	Very serious[1]	none	32	32	MD -2079.24 [-3454.67, -703.82]	DCI	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Total Cholesterol												
2	RCT	No serious risk of bias	no serious inconsistency	no serious indirectness	Very serious[1]	none	32	32	MD -21.57 [-41.72, -1.41]	DCI	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Triglycerides												
2	RCT	No serious risk of bias	no serious inconsistency	no serious indirectness	Very serious[1]	none	32	32	MD -31.54 [-61.09, -1.99]	DCI	⊕⊕◯◯ LOW	IMPORTANT
Outcome: WHR												
2	RCT	No serious risk of bias	no serious inconsistency	no serious indirectness	Very serious[1]	none	32	32	MD -0.02 [-0.04, 0.01]	Neither	⊕⊕◯◯ LOW	IMPORTANT
Outcome: AUC Insulin												
2	RCT	No serious risk of bias	no serious inconsistency	no serious indirectness	Very serious[1]	none	32	32	MD -3646.73 [-6650.65, -642.8]	DCI	⊕⊕◯◯ LOW	IMPORTANT

[1] downgraded two levels due to very serious imprecision: very small sample size (64 participants).

COMPARISON: MI + FA vs FA												
	Quality assessment						No. participants					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**MI + FA**	**FA**	**Effect, fixed [95% CI]**	**Favours**	**Certainty**	**Importance**
Outcome: Free testosterone												
No studies reported on this outcome.												CRITICAL
Outcome: 2-hour glucose												
No studies reported on this outcome.												CRITICAL
Outcome: BMI												
3	RCT	Very Serious risk of bias[1]	no serious inconsistency	no serious indirectness	Serious imprecision[2]	none	58	54	MD 0.47 [0.35, 0.60]	FA	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: HOMA-IR												
2	RCT	Serious risk of bias[3]	no serious inconsistency	no serious indirectness	Very serious[4]	none	35	35	MD -1.24[-1.50,-0.99]	MI+FA	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: QoL												
No studies reported on this outcome.												CRITICAL
Outcome: Total Testosterone												
3	RCT	Very Serious risk of bias[1]	no serious inconsistency	no serious indirectness	Serious imprecision[2]	none	58	54	MD -35.86 [-38.49, -33.22]	MA+FA	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Clinical Pregnancy Rate												
5	RCT	Very Serious risk of bias[5]	no serious inconsistency	no serious indirectness	No serious imprecision	none	357	390	OR 1.25 [0.90, 1.73]	Neither (p=0.18)	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Pregnancy Rate (+ HCG)												
3	RCT	Serious risk of bias[6]	no serious inconsistency	no serious indirectness	Serious imprecision [7]	none	80	80	OR 1.60 [0.85, 3.03]	Neither (p=0.15)	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Androstendione												
3	RCT	Very Serious risk of bias[1]	no serious inconsistency	no serious indirectness	Serious imprecision[2]	none	58	54	MD -43.91 [-54.67,-33.16]	MI+FA	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Fasting Glucose												
2	RCT	No serious risk of bias	no serious inconsistency	no serious indirectness	Very serious[1]	none	32	32	MD -6.14 [-14.52, 2.24]	Neither	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Fasting Insulin												
2	RCT	Serious risk of bias[3]	no serious inconsistency	no serious indirectness	Very serious[4]	none	35	35	MD -4.31 [-4.83, -3.80]	MI+FA	⊕◯◯◯ VERY LOW	IMPORTANT

[1] downgraded two levels due to very serious risk of bias: Three studies contributed to this outcome. One of the three included studies is at unclear risk of bias for most domains, and one of the studies is at unclear risk for randomization.

[2] downgraded one level for serious imprecision: Small sample size (112 participants)

[3] downgraded one level due to serious risk of bias: One of the two included studies is at unclear risk of bias for most domains.

[4] downgraded two levels due to very serious imprecision: Very small sample size (70 participants).

[5] downgraded two levels due to very serious risk of bias: Five studies contributed to this outcome, four have unclear risk of bias in most domains, one has high risk of bias for randomization.

[6] downgraded one level for serious risk of bias: Three studies contributed to this outcome, one study has mostly unclear risk of bias across domains, and the other two studies have an unclear risk of bias in a blinding domain.

[7] downgraded one level for serious imprecision: small sample size for relatively rare events (160 participants).

COMPARISON: MI vs Metformin												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	MI	Metformin	Effect, fixed [95% CI]	Favours	Certainty	Importance
Outcome: Free testosterone												
1	RCT	Serious risk of bias[1]	NA	NA	Very serious imprecision[2]	none	16	12	Unable to calculate	Neither	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: 2-hour glucose												
1	RCT	Serious risk of bias[3]	NA	NA	Very serious imprecision[2]	none	30	30	MD -0.57 (-1.43, 0.29)	Neither (p=0.20)	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: BMI												
6	RCT	Very serious risk of bias[4]	Serious inconsistency[5]	no serious indirectness	No serious imprecision	none	210	210	MD 0.03 (-0.63, 0.69)	Neither (p=0.93)	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: HOMA-IR												
5	RCT	Very serious risk of bias[6]	no serious inconsistency	no serious indirectness	No serious imprecision	none	184	182	MD -0.40 [-0.59, -0.22]	MI	⊕⊕◯◯ LOW	CRITICAL
Outcome: QoL												
One study assessed physical functioning, emotional well-being, social functioning, pain, energy/fatigue and general health (n=26, high risk of bias). There were no between or within-group differences (Very low certainty).												CRITICAL
Outcome: FG score												
2	RCT	Serious risk of bias[7]	No serious inconsistency	No serious indirectness	Serious imprecision[8]	none	80	80	MD 2.48 [1.52, 3.44]	MET	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Total Testosterone												
4	RCT	Serious risk of bias[9]	no serious inconsistency	no serious indirectness	No serious imprecision	none	160	160	MD 1.59 [-1.59, 4.78]	Neither (p=0.33)	⊕⊕⊕◯ MODERATE	IMPORTANT
Outcome: SHBG												
2	RCT	Serious risk of bias[10]	No serious inconsistency	No serious indirectness	Serious imprecision[8]	none	80	80	MD 3.85 [0.50, 7.19]	MET	⊕⊕◯◯ LOW	
Outcome: Clinical Pregnancy Rate												
4	RCT	Serious risk of bias[11]	no serious inconsistency	no serious indirectness	No serious imprecision[12]	none	210	210	OR 1.19 [0.89, 1.59]	Neither (p=0.23)	⊕⊕⊕◯ MODERATE	IMPORTANT
Outcome: Miscarriage rate												
1	RCT	Serious risk of bias	NA	NA	Very serious imprecision	none	29	22	OR 0.89 [0.23, 3.39]	Neither (p=0.86)	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: GI Side effects												

6	RCT	Serious risk of bias[13]	no serious inconsistency	no serious indirectness	No serious imprecision	none	192	190	OR 0.13 [0.07, 0.24]	MI	⊕⊕⊕◯ MODERATE	IMPORTANT
Outcome: Regular menses												
3	RCT	Serious risk of bias [14]	no serious inconsistency	no serious indirectness	No serious imprecision	none	125	122	OR 2.04 [1.21, 3.45]	MI	⊕⊕⊕◯ MODERATE	IMPORTANT
Outcome: Ovulation												
2	RCT	Serious risk of bias [15]	no serious inconsistency	no serious indirectness	Serious imprecision[16]	none	110	110	OR 1.30 [0.76, 2.24]	Neither (p=0.34)	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Fasting Glucose												
4	RCT	Serious risk of bias[17]	no serious inconsistency	no serious indirectness	No serious imprecision	none	160	160	MD -0.29 [-2.35, 1.77]	Neither (P=0.84)	⊕⊕⊕◯ MODERATE	IMPORTANT
Outcome: Fasting Insulin												
5	RCT	Serious risk of bias[18]	no serious inconsistency	no serious indirectness	No serious imprecision	none	186	188	MD 1.05 [0.19, 1.92]	Met	⊕⊕◯◯ MODERATE	IMPORTANT
Outcome: LDL												
2	RCT	Serious risk of bias[19]	no serious inconsistency	no serious indirectness	Serious imprecision[20]	none	80	80	MD 0.19 [-4.44, 4.81]	Neither (p=0.94)	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Total Cholesterol												
2	RCT	Serious risk of bias[19]	no serious inconsistency	no serious indirectness	Serious imprecision[20]	none	80	80	MD -4.34 [-11.14, 2.36]	Neither (P=0.24)	⊕⊕◯◯ LOW	IMPORTANT
Outcome: HDL												
2	RCT	Serious risk of bias[19]	no serious inconsistency	no serious indirectness	Serious imprecision[20]	none	80	80	MD 0.63 [-1.07, 2.33]	Neither (p=0.47)	⊕⊕◯◯ LOW	IMPORTANT
Outcome: WHR												
2	RCT	Serious risk of bias[19]	no serious inconsistency	no serious indirectness	Serious imprecision[20]	none	80	80	MD 0.04 [0.01,0.06]	Met	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Weight *												
3	RCT	Serious risk of bias[21]	no serious inconsistency	no serious indirectness	Serious imprecision[22]	none	86	88	MD -0.83 [-3.45, 1.79]	Neither (p=0.54)	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Waist circumference												
3	RCT	Serious risk of bias[21]	no serious inconsistency	no serious indirectness	No serious imprecision	none	110	110	MD 2.94 [0.49, 5.39]	Met	⊕⊕⊕◯ MODERATE	IMPORTANT

[1]downgraded one level for serious risk of bias: high risk of bias for blinding and attrition

[2] downgraded two levels for very serious imprecision: single study

[3]downgraded one level for serious risk of bias: high risk of bias for blinding, unclear risk of bias for randomization, blinding of outcome assessors, incomplete outcome data and other bias.

[4]downgraded two levels for very serious risk of bias: Six studies that contribute to this outcome, one has unclear risk of bias in all domains including randomization and allocation concealment, another three studies having an unclear risk in one of the blinding domains, one study having a high risk of bias in both blinding domains, one study has high risk of bias for attrition bias. Half of studies are at unclear risk of bias for either randomization and/or allocation concealment.

[5]downgraded one level for serious inconsistency: point estimates vary

[6] downgraded two levels for very serious risk of bias: Five studies contributing to this outcome, the one with the greatest weight has unclear risk of bias for allocation concealment, blinding, selective outcome reporting and other bias and high risk of bias for attrition; four studies are at high or unclear risk of bias for blinding.

[7]downgraded one level for serious risk of bias: Two studies contributed to this outcome; randomization sequence was unclear in one study; blinding was unclear or high risk in both studies; selective outcome reporting and other bias were unclear in both studies.

[8]downgraded one level for serious imprecision: small sample size (160 participants)

[9]downgraded two levels for serious risk of bias: Four studies contributed to this outcome; two studies were at unclear risk of bias for randomization, one study for allocation concealment; two studies high risk for blinding; two studies unclear risk of bias for selective outcome reporting and three studies at unclear risk for other bias.

[10]downgraded one level for serious risk of bias: Two studies contributed to this outcome; one study was at high risk of bias due to lack of blinding.

[11] downgraded one level due to serious risk of bias: Four studies contribute to this outcome, all have unclear risk of bias in the blinding domain(s), and one study is at high risk of attrition bias.

[12] downgraded one level due to serious imprecision: Small sample size (420) given the relatively rare events of pregnancy.

[13]downgraded one level due to serious risk of bias: Six studies contribute to this outcome; three studies are at high risk of bias and two are unclear risk due to blinding of participants; all studies are at high or unclear risk of bias for blinding of outcome assessors; three studies are high risk of bias for attrition.

[14] downgraded one level due to serious risk of bias: Three studies contribute to this outcome, all three have unclear risk of bias in one or both of the blinding domains.

[15] downgraded one level due to serious risk of bias: Two studies contribute to this outcome, all three have unclear risk of bias in one or both of the blinding domains.

[16] downgraded one level for serious imprecision: small sample size (220 participants)

[17]downgraded one level due to serious risk of bias: Four studies contribute to this outcome; two are unclear risk of bias for randomization, one for allocation concealment; two are at high risk for blinding in one domain and one for blinding in one domain.

[18]downgraded one level due to serious risk of bias: Five studies contribute to this outcome; three are at unclear risk of bias for randomization, two for allocation concealment; two are high risk of bias due to blinding in one domain and one for blinding in another domain.

[19] downgraded one level due to serious risk of bias: Two studies contribute to this outcome. One study is at unclear risk of bias for randomization and allocation concealment, and at high risk of bias for both blinding domains.

[20] downgraded one level due to serious imprecision: Small sample size (160 participants).

[21]downgraded one level due to serious risk of bias: Three studies contribute to this outcome, all are at unclear risk of bias for randomization, two for allocation concealment; all are at high risk or unclear risk of bias for blinding in both domains.

[22]downgraded one level for serious imprecision: small sample size (174 participants).

COMPARISON: MI + DCI + FA v MI + FA – single trial Le Donne 2019 3 months												
	Quality assessment						**No. participants**					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**MI + DCI+FA**	**MI+FA**	**Effect, fixed [95% CI]**	**Favours**	**Certainty**	**Importance**
Outcome: Oligomenorrheic Patients												
1	RCT	serious[1]	NA	NA	very serious[1]	none	12	10	RR 0.19 [0.05, 0.67]	MI+DCI+FA	⨁◯◯◯ VERY LOW	-
Outcome: Weight												
1	RCT	serious[1]	NA	NA	very serious[1]	none	12	10	-1.60 [-14.75, 11.55]	Neither	⨁◯◯◯ VERY LOW	-
Outcome: BMI												
1	RCT	serious[1]	NA	NA	very serious[1]	none	12	10	-0.70 [-5.10, 3.70]	Neither	⨁◯◯◯ VERY LOW	-
Outcome: Waist Hip Ratio												
1	RCT	serious[1]	NA	NA	very serious[1]	none	12	10	0.05 [-0.02, 0.12]	Neither	⨁◯◯◯ VERY LOW	-
Outcome: Waist circumference												
1	RCT	serious[1]	NA	NA	very serious[1]	none	12	10	0.70 [-9.93, 11.33]	Neither	⨁◯◯◯ VERY LOW	-
Outcome: % Fat Mass												
1	RCT	serious[1]	NA	NA	very serious[1]	none	12	10	-4.80 [-10.85, 1.25]	Neither	⨁◯◯◯ VERY LOW	-

[1]downgraded one level for high risk of bias and two levels for very serious imprecision (single study, very small sample size)

[1]downgraded one level for high risk of bias and two levels for very serious imprecision (single study, very small sample size)

COMPARISON: MI + DCI + FA v MI + FA – single trial Le Donne 2019 6 months												
	Quality assessment						**No. participants**					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**MI + DCI+FA**	**MI+FA**	**Effect, fixed [95% CI]**	**Favours**	**Certainty**	**Importance**
Outcome: Oligomenorrheic Patients												
1	RCT	serious[1]	NA	NA	very serious[1]	none	12	10	RR 0.17 [0.01, 3.16]	MI+DCI+FA	⨁◯◯◯ VERY LOW	-
Outcome: Hirsutism (Ferriman Gallway Score)												
1	RCT	serious[1]	NA	NA	very serious[1]	none	12	10	-2.6 [-6.30, 1.10]	Neither	⨁◯◯◯ VERY LOW	-
Outcome: Weight												
1	RCT	serious[1]	NA	NA	very serious[1]	none	12	10	-1.70 [-13.97, 10.57]	Neither	⨁◯◯◯ VERY LOW	-
Outcome: BMI												
1	RCT	serious[1]	NA	NA	very serious[1]	none	12	10	-0.80 [-4.90, 3.30]	Neither	⨁◯◯◯ VERY LOW	-
Outcome: Waist Hip Ratio												
1	RCT	serious[1]	NA	NA	very serious[1]	none	12	10	0.05 [-0.02, 0.12]	Neither	⨁◯◯◯ VERY LOW	-
Outcome: Waist circumference												
1	RCT	serious[1]	NA	NA	very serious[1]	none	12	10	1.30 [-8.23, 10.83]	Neither	⨁◯◯◯ VERY LOW	-
Outcome: % Fat Mass												
1	RCT	serious[1]	NA	NA	very serious[1]	none	12	10	-3.80 [-10.03, 2.43]	Neither	⨁◯◯◯ VERY LOW	-

[1]downgraded one level for unclear/high risk of bias and two levels for very serious imprecision (single study, very small sample size)

COMPARISON: MI + DCI + FA v FA only – single trial Benelli 2016												
	Quality assessment						**No. participants**					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**MI + DCI+FA**	**FA Only**	**Effect, fixed [95% CI]**	**Favours**	**Certainty**	**Importance**
Outcome: Free Testosterone												
1	RCT	serious[1]	NA	NA	very serious[1]	none	21	25	-0.21 [-0.31, -0.11]	MI+DCI+FA	⨁◯◯◯ VERY LOW	-
Outcome: SHBG												
1	RCT	serious[1]	NA	NA	very serious[1]	none	21	25	14.49 [3.68, 25.30]	MI+DCI+FA	⨁◯◯◯ VERY LOW	-
Outcome: DHEAS												
1	RCT	serious[1]	NA	NA	very serious[1]	none	21	25	31.77 [-60.99, 124.53]	Neither	⨁◯◯◯ VERY LOW	-
Outcome: Androstenedione												
1	RCT	serious[1]	NA	NA	very serious[1]	none	21	25	0.89 [-0.25, 2.03]	Neither	⨁◯◯◯ VERY LOW	-
Outcome: Fasting Glucose												
1	RCT	serious[1]	NA	NA	very serious[1]	none	21	25	1.27 [-3.19, 5.73]	Neither	⨁◯◯◯ VERY LOW	-
Outcome: Fasting Insulin												
1	RCT	serious[1]	NA	NA	very serious[1]	none	21	25	-7.06 [-11.03, -3.09]	MI+DCI+FA	⨁◯◯◯ VERY LOW	-
Outcome: HOMA-IR												
1	RCT	serious[1]	NA	NA	very serious[1]	none	21	25	-0.83 [-1.67, 0.01]	Neither	⨁◯◯◯ VERY LOW	-

OMPARISON: MI + DCI + MET v MET only – single trial Bahadur 2021												
	Quality assessment						**No. participants**					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**MI + DCI+ MET**	**MET**	**Effect, fixed [95% CI]**	**Favours**	**Certainty**	**Importance**
Outcome: Menstrual Irregularity												
1	RCT	serious[1]	NA	NA	serious[1]	none	36	36	RR 0.61 [0.38, 0.98]	MI+DCI+Met	⊕⊕◯◯ LOW	-
Outcome: modified Ferriman Gallway Score												
1	RCT	serious[1]	NA	NA	serious[1]	none	36	36	-0.61 [-1.98, 0.76]	Neither	⊕⊕◯◯ LOW	-
Outcome: BMI												
1	RCT	serious[1]	NA	NA	serious[1]	none	36	36	-0.02 [-1.70, 1.66]	Neither	⊕⊕◯◯ LOW	-
Outcome: WHR												
1	RCT	serious[1]	NA	NA	serious[1]	none	36	36	0.00 [-0.03, 0.03]	Neither	⊕⊕◯◯ LOW	-
Outcome: WC												
1	RCT	serious[1]	NA	NA	serious[1]	none	36	36	1.70 [-3.23, 6.63]	Neither	⊕⊕◯◯ LOW	-
Outcome: Total Testosterone												
1	RCT	serious[1]	NA	NA	serious[1]	none	36	36	-7.01 [-15.40, 1.38]	Neither	⊕⊕◯◯ LOW	-
Outcome: DHEAS												
1	RCT	serious[1]	NA	NA	serious[1]	none	36	36	-2.75 [-45.94, 40.44]	Neither	⊕⊕◯◯ LOW	-
Outcome: Total Cholesterol												

1	RCT	serious[1]	NA	NA	serious[1]	none	36	36	-15.17 [-29.49, -0.85]	MI+DCI+Met	⊕⊕◯◯ LOW	-
Outcome: LDL												
1	RCT	serious[1]	NA	NA	serious[1]	none	36	36	-20.27 [-30.14, -10.40]	MI+DCI+Met	⊕⊕◯◯ LOW	-
Outcome: HDL												
1	RCT	serious[1]	NA	NA	serious[1]	none	36	36	5.72 [0.12, 11.32]	MI+DCI+Met	⊕⊕◯◯ LOW	-
Outcome: TG												
1	RCT	serious[1]	NA	NA	serious[1]	none	36	36	-1.33 [-16.66, 14.00]	Neither	⊕⊕◯◯ LOW	-
Outcome: Fasting Glucose												
1	RCT	serious[1]	NA	NA	serious[1]	none	36	36	-2.92 [-6.18, 0.34]	Neither	⊕⊕◯◯ LOW	-
Outcome: Fasting Insulin												
1	RCT	serious[1]	NA	NA	serious[1]	none	36	36	-0.36 [-4.37, 3.65]	Neither	⊕⊕◯◯ LOW	-
Outcome: HOMA-IR												
1	RCT	serious[1]	NA	NA	serious[1]	none	36	36	-0.15 [-1.03, 0.73]	Neither	⊕⊕◯◯ LOW	-

[1]downgraded one level for moderate risk of bias and one level for serious imprecision (single study, small sample size)

COMPARISON: MI + DCI v MI – single trial Nordo 2012 3 months												
	Quality assessment						**No. participants**					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**MI + DCI**	**MI**	**Effect, fixed [95% CI]**	**Favours**	**Certainty**	**Importance**
Outcome: Free Testosterone												
1	RCT	serious[1]	NA	NA	very serious[1]	none	26	24	-0.21 [-0.26, -0.16]	MI+DCI	⊕◯◯◯ VERY LOW	-
Outcome: Total Testosterone												
1	RCT	serious[1]	NA	NA	very serious[1]	none	26	24	-9.90 [-16.32, -3.48]	MI+DCI	⊕◯◯◯ VERY LOW	-
Outcome: Androstenedione												
1	RCT	serious[1]	NA	NA	very serious[1]	none	26	24	5.00 [-2.48, 12.48]	Neither	⊕◯◯◯ VERY LOW	-
Outcome: DHEAS												
1	RCT	serious[1]	NA	NA	very serious[1]	none	26	24	-42.00 [-59.47, -24.53]	MI+DCI	⊕◯◯◯ VERY LOW	-
Outcome: SHBG												
1	RCT	serious[1]	NA	NA	very serious[1]	none	26	24	20.00 [8.39, 31.61]	MI+DCI	⊕◯◯◯ VERY LOW	-
Outcome: Fasting Glucose												
1	RCT	serious[1]	NA	NA	very serious[1]	none	26	24	-7.30 [-12.46, -2.14]	MI+DCI	⊕◯◯◯ VERY LOW	-
Outcome: Fasting Insulin												
1	RCT	serious[1]	NA	NA	very serious[1]	none	26	24	-1.60 [-3.39, 0.19]	Neither	⊕◯◯◯ VERY LOW	-
Outcome: AUC Glucose												
1	RCT	serious[1]	NA	NA	very serious[1]	none	26	24	-3851.00 [-4117.77, -3584.23]	MI+DCI	⊕◯◯◯ VERY LOW	-

Outcome: HOMA-IR											
1	RCT	serious[1]	NA	NA	very serious[1]	none	26	24	-0.38 [-0.90, 0.14]	Neither	⊕◯◯◯ VERY LOW	-

[1]downgraded one level for high risk of bias and two levels for very serious imprecision (single study, very small sample size)

COMPARISON: MI + DCI v MI – single trial Nordo 2012 6 months												
	Quality assessment						**No. participants**					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**MI + DCI**	**MI**	**Effect, fixed [95% CI]**	**Favours**	**Certainty**	**Importance**
Outcome: WHR												
1	RCT	serious[1]	NA	NA	very serious[1]	none	12	24	0.00 [-0.02, 0.02]	Neither	⊕◯◯◯ VERY LOW	-
Outcome: BMI												
1	RCT	serious[1]	NA	NA	very serious[1]	none	12	24	-0.40 [-2.00, 1.20]	Neither	⊕◯◯◯ VERY LOW	-
Outcome: Free Testosterone												
1	RCT	serious[1]	NA	NA	very serious[1]	none	26	24	-0.01 [-0.02, 0.00]	Neither	⊕◯◯◯ VERY LOW	-
Outcome: Total Testosterone												
1	RCT	serious[1]	NA	NA	very serious[1]	none	26	24	-7.40 [-12.81, -1.99]	MI+DCI	⊕◯◯◯ VERY LOW	-
Outcome: Androstenedione												
1	RCT	serious[1]	NA	NA	very serious[1]	none	26	24	-4.00 [-13.54, 5.54]	Neither	⊕◯◯◯ VERY LOW	-
Outcome: DHEAS												
1	RCT	serious[1]	NA	NA	very serious[1]	none	26	24	-17.00 [-30.87, -3.13]	MI+DCI	⊕◯◯◯ VERY LOW	-
Outcome: SHBG												

1	RCT	serious[1]	NA	NA	very serious[1]	none	26	24	6.00 [-7.26, 19.26]	Neither	⨁◯◯◯ VERY LOW	-
Outcome: Fasting Glucose												
1	RCT	serious[1]	NA	NA	very serious[1]	none	26	24	-1.60 [-7.07, 3.87]	Neither	⨁◯◯◯ VERY LOW	-
Outcome: Fasting Insulin												
1	RCT	serious[1]	NA	NA	very serious[1]	none	26	24	-0.40 [-1.51, 0.71]	Neither	⨁◯◯◯ VERY LOW	-
Outcome: AUC Glucose												
1	RCT	serious[1]	NA	NA	very serious[1]	none	26	24	-890.00 [-1144.21, -635.79]	MI+DCI	⨁◯◯◯ VERY LOW	-
Outcome: HOMA-IR												
1	RCT	serious[1]	NA	NA	very serious[1]	none	26	24	-0.40 [-1.25, 0.45]	Neither	⨁◯◯◯ VERY LOW	-

[1]downgraded one level for high risk of bias and two levels for very serious imprecision (single study, very small sample size)

COMPARISON 8: MI + DCI v Placebo – Single Study Khan 2022												
	Quality assessment						**No. participants**					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**MI + DCI**	**Placebo**	**Effect, fixed [95% CI]**	**Favours**	**Certainty**	**Importance**
Outcome: Fasting Glucose												
1	RCT	serious[1]	NA	NA	serious[1]	none	53	53	-0.13 [-2.88, 2.62]	Neither	⨁⨁◯◯ LOW	-

[1]downgraded one level for unclear/high risk of bias and one level for serious imprecision (single study)

[1] downgraded one level for moderate-high risk of bias due to lack of blinding in one study and conflict of interest in the other study

COMPARISON 9: MI + DCI v MI+DCI												
	Quality assessment						No. participants					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**MI + DCI**	**MI+DCI control**	**Effect, fixed [95% CI]**	**Favours**	**Certainty**	**Importance**
Outcome: HOMA Index – Mendoza 2019 and Nordio 2019												
2	RCT	serious[1]	NA	Indirect[4]	serious[2]		77	38	Nordio -0.07 [-0.88, 0.74] Mendoza -0.02 [-0.67, 0.63]	Neither	⨁◯◯◯ VERY LOW	-
Outcome: Fasting Insulin - Mendoza 2019												
1	RCT	serious[3]	NA	Indirect[4]	serious[2]		30	30	-0.01 [-0.59, 0.57]	Neither	⨁◯◯◯ VERY LOW	-
Outcome: Fasting Glucose - Mendoza 2019												
1	RCT	serious[3]	NA	Indirect[4]	serious[2]		30	30	-0.66 [-1.40, 0.08]	Neither	⨁◯◯◯ VERY LOW	-
Outcome: Free Testosterone - Mendoza 2019												
1	RCT	serious[3]	NA	Indirect[4]	serious[2]		30	30	-0.05 [-0.08, -0.02]	MI+DCI intervention	⨁◯◯◯ VERY LOW	-
Outcome: Menses - Nordio 2019												
1	RCT	serious[3]	NA	Indirect[4]	serious[2]		8	8	NA	Neither	⨁◯◯◯ VERY LOW	-
Outcome: Pregnancy rate - Mendoza 2019												
1	RCT	serious[3]	NA	Indirect[4]	serious[2]		30	30	5.68 [1.84, 17.49]	MI+DCI intervention	⨁◯◯◯ VERY LOW	-
Outcome: Pregnancy Rate (IVF) - Mendoza 2019												
1	RCT	serious[3]	NA	Indirect[4]	serious[2]		30	30	4.60 [1.28, 16.58]	MI+DCI intervention	⨁◯◯◯ VERY LOW	-
Outcome: Live birth rate - Mendoza 2019												
1	RCT	serious[3]	NA	Indirect[4]	serious[2]		30	30	6.50 [1.82, 23.21]	MI+DCI intervention	⨁◯◯◯ VERY LOW	-

[2] downgraded due to small sample size in both studies

[3] downgraded one level for moderate-high risk of bias due to conflict of interest in the single study

[4] downgraded one level due to indirect comparison

COMPARISON: MI + Met v Met alone – Single Study Chirania 2017												
	Quality assessment						**No. participants**					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**MI + Met**	**Met**	**Effect, fixed [95% CI]**	**Favours**	**Certainty**	**Importance**
Outcome: BMI												
1	RCT	serious[1]	NA	NA	serious[1]	none	22	28	0.48 [-1.47, 2.43]	Neither	⊕⊕◯◯ LOW	-
Outcome: Weight												
1	RCT	serious[1]	NA	NA	serious[1]	none	22	28	2.60 [-3.33, 8.53]	Neither	⊕⊕◯◯ LOW	-
Outcome: Fasting Insulin												
1	RCT	serious[1]	NA	NA	serious[1]	none	22	28	-2.91 [-6.54, 0.72]	Neither	⊕⊕◯◯ LOW	-

[1] downgraded one level for unclear/high risk of bias and one level for serious imprecision (single study)

COMPARISON 11: MI v Placebo												
	Quality assessment						**No. participants**					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**MI**	**Placebo**	**Effect, fixed [95% CI]**	**Favours**	**Certainty**	**Importance**
Outcome: All outcomes												
1	RCT	serious[1]	NA	NA	serious[1]		18	8	NA	NA	⊕◯◯◯ VERY LOW	-

[1] downgraded one level for unclear/moderate risk of bias and two levels for serious imprecision (single study)

COMPARISON 12: MI + monacolin K v Inositol v Met													
	Quality assessment						No. participants						
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**MI + monacolin K**	**Metformin**	**Inositol**	**Effect, fixed [95% CI]**	**Favours**	**Certainty**	**Importance**
Outcome: All outcomes													
1	RCT	serious[1]	NA	NA	serious[1]	none	20	20	20	NA	NA	⨁⨁◯◯ LOW	-

[1]downgraded one level for moderate risk of bias and one level for serious imprecision (single study)

[1]downgraded two levels for unclear risk of bias and one level for serious imprecision (single study)

COMPARISON: MI v DCI – Single Study Unfer 2011												
	Quality assessment						**No. participants**					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**MI**	**Placebo**	**Effect, fixed [95% CI]**	**Favours**	**Certainty**	**Importance**
Outcome: Biochemical Pregnancy												
1	RCT	serious[1]	NA	NA	serious[1]		44	41	1.46 [0.23, 9.23]	NA	⊕⊕◯◯ LOW	-
Outcome: Clinical Pregnancy Rate												
1	RCT	serious[1]	NA	NA	serious[1]		44	41	3.86 [1.25, 11.89]	MI	⊕⊕◯◯ LOW	-
Outcome: Total Pregnancy Rate												
1	RCT	serious[1]	NA	NA	serious[1]		44	41	3.25 [1.28, 8.23]	MI	⊕⊕◯◯ LOW	-
Outcome: Miscarriage Rate												
1	RCT	serious[1]	NA	NA	serious[1]		44	41	1.30 [0.27, 6.20]	NA	⊕⊕◯◯ LOW	-

6. SRMA Summary of Results

Evidence Summary:

Total of 43 studies were included after full text review. Fourteen were excluded after integrity check. The remaining 29 studies were included in the systematic review and 19 in the meta-analysis. Ten studies were assessed to have high risk of bias while 16 had low or moderate risk and three had unclear risk of bias. All included studies were RCTs. The studies were heterogenous in intervention and comparator. Two studies compared DCI with placebo (Iuorno 2002, Nestler 1999). Three studies compared combinations of myoinositol (MI) + d-chiro-inositol (DCI) to folic acid (FA) or placebo (Le Donne 2019, Benelli 2016, Khan 2022) and one compared MI+DCI+Metformin to Metformin alone (Bahadur 2021). One study compared MI alone to MI+DCI (Nordio 2012). Two studies compared varying ratios of MI + DCI (Nordio 2019, Mendoza 2019). A single study compared MI to

DCI (Unfer 2011). Eight studies compared MI+FA to FA alone (Akbari Sene 2019, Artini 2013, Constantino 2009, Genazzani 2008, Ozay 2017, Pacchiarotti 2016, Papaleo 2009, Pourghasem 2019). One study compared MI+Metformin to Metformin alone (Chirania 2017) while ten compared MI alone or with folic acid to Metformin (Angik 2017, Chirania 2017, Nehra 2017, Pourghasem 2019, Rajasekaran 2022, Tagliaferri 2017, Fruzetti 2017, Ravn 2022, Raffone 2010, Soldat-Stankovic 2022). One study compared MI to placebo (Dona 2012) and one had three groups comparing MI+monacolin K to inositol and also to metformin alone (Leo 2013).

Meta-Analysis/Descriptive analysis Summary:

MI v Placebo

There is preliminary evidence from one trial with serious risk of bias with only 26 adult women that MI is more efficacious than placebo for weight, BMI, Testosterone, Androstenedione, fasting insulin, insulin AUC and HOMA-IR (very low certainty).

MI+FA v FA

Evidence suggests that MI + FA is superior to FA alone for insulin/HOMA-IR, and for total testosterone and androstenedione. However, FA alone was superior to MI + FA for BMI. Evidence from single trials suggest improvements in lipids and free testosterone but not for clinical hyperandrogenism. The populations were heterogeneous with some having impaired glucose tolerance, some populations with infertility and normal or unknown insulin sensitivity. There was no difference in pregnancy rate between groups though interventions for fertility were also heterogenous.

MI v Met

Pooled evidence suggests that MI has fewer GI adverse effects than metformin. Wide confidence intervals for other outcomes (TT, FBG, lipids and weight) limit the ability to conclude on equivalence for these outcomes. Metformin was superior to MI for FINS, WHR, WC, and Ferriman-Gallwey score. MI was superior to metformin in resumption of regular menses. A trend to lower BMI and HOMA-IR was observed with metformin in pooled analysis but there were no significant differences between groups. There is low certainty evidence from a single trial that adding MI + DCI to MET was better than MET alone for cycle regularity and lipids.

DCI v Placebo

Low certainty evidence suggests DCI improves free testosterone, total testosterone, androstenedione, DHEAS and lipids compared to placebo. There was no data on QoL, HOMA-IR or 2-hr Gluc. Placebo is superior to DCI for BMI (MD 0.67).

MI+DCI v MI alone

There were no differences between MI+DCI and MI alone for critical outcomes (HOMA-IR, BMI, FG score). There were improvements in some metabolic outcomes at 3 months but not at 6 months in one trial. There was no difference for hormonal and anthropometric outcomes.

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 4

Question 4.7.

In adolescents and adults with PCOS, is inositol alone or in combination with other therapies, effective for management of hormonal and clinical PCOS features, weight and reproductive outcomes**?**

BACKGROUND:

Women with PCOS are commonly treated with insulin sensitizing agents due to insulin resistance and hyperinsulinemia, common features of the syndrome both in women of healthy and of higher weight. Due to gastrointestinal side effects related to metformin and more serious adverse effects related to glitazones other medical options are needed in treating insulin resistance in women with PCOS.

Inositol is a nutrient supplement that acts as a second messenger in insulin and FSH signalling. There are nine stereo-isomers of inositol of which myo-inositol (MI) is the most abundant in the human body (1) . Myo-inositol promotes GLUT4 translocation to the plasma membrane for glucose uptake (2) and is also involved in FSH mediated pathways which regulate the proliferation and maturation of granulosa cells (3). Under the stimulus of insulin, MI is converted to D-chiro-inositol/DCI (4) , which stimulates glycogen production and facilitates additional uptake of glucose through mobilisation of GLUT4 transporters (5). It has been hypothesised that overproduction of insulin in PCOS enhances MI to DCI conversion which results in an increased DCI and decreased MI concentration in follicular fluid. In women without PCOS, ovarian MI:DCI ratio is 100:1 but in women with PCOS the ratio is 0.2:1 (6) . MI is also postulated to enhance aromatase synthesis in granulosa cells and therefore reducing androgen production (7) . It has been suggested that a 40:1 ratio of MI:DCI is physiological, and provision of inositol in this ratio has reverted PCOS phenotypes in mouse models (8).

GRADE evidence table

GRADE EVIDENCE CERTAINTY	
Comparison	**GRADE for critical outcomes**
o **Comparison 1:** MI v Placebo **Recommendation:** We are unable to make a recommendation on myoinositol 1.2g daily alone for premenopausal women with lean PCOS.	⨁◯◯◯ VERY LOW
o **Comparison 2.** MI + FA vs FA **Recommendation:** In premenopausal women with PCOS, myoinositol could be considered as an adjunct to folic acid for improving androgens, lipids and metabolic outcomes in women with PCOS. Myoinositol should not be recommended as an adjunct to folic acid for weight management.	⨁◯◯◯ VERY LOW
o **Comparison 3:** MI + MET v MET alone **Recommendation:** We are unable to make a recommendation on whether adding MI to MET is more useful than MET alone.	⨁⨁◯◯ LOW
o **Comparison 4.** MI vs Metformin **Recommendation:** MET should be recommended instead of MI for improving menstrual regularity central adiposity and insulin. We are unable to make a recommendation on hormonal outcomes and lipids.	⨁⨁◯◯ LOW
o **Comparison 5**. DCI vs Placebo **Recommendation:** In premenopausal women with PCOS, low dose DCI could be considered for improving biochemical hyperandrogenism but not for weight management.	⨁⨁◯◯ LOW
o **Comparison 6**. MI + DCI + FA v Placebo + FA **Recommendation:** We are unable to provide a recommendation on whether to use MI + DCI + FA.	⨁⨁◯◯ LOW
o **Comparison 7.** MI + DCI + FA v FA only – single trial **Recommendation:** We are unable to provide a recommendation on whether to use MI + DCI + FA.	⨁◯◯◯ VERY LOW
o **Comparison 8**. MI + DCI v MI – single trial **Recommendation:** We are unable to recommend a combination of MI + DCI for adolescents/women who are of above healthy weight (BMI >27) over MI alone.	⨁◯◯◯ VERY LOW
o **Comparison 9.** MI + DCI + diet + FA v MI + diet + FA – single trial **Recommendation:** We are unable to recommend a combination of MI + DCI for adolescents/women who are above healthy weight (BMI >27) over MI alone.	⨁◯◯◯ VERY LOW
o **Comparison 10.** MI + DCI + MET v MET alone – single trial	⨁⨁◯◯

Recommendation: We are unable to recommend MI + DCI + metformin over metformin alone for biochemical/clinical hyperandrogenism, metabolic outcomes, and weight in premenopausal women with PCOS.	LOW
o **Comparison 11.** MI + DCI v MI+DCI **Recommendation:** We are unable to make a recommendation about effectiveness of different ratios of MI:DCI in premenopausal women with PCOS.	⨁◯◯◯ VERY LOW

Critical outcomes: FT, HOMA-IR, 2hr glucose, BMI, QoL.

Evidence to Recommendations Framework

COMPARISONS

Myoinositol v Placebo
DCI vs placebo
Myoinositol vs Metformin
Myoinositol + folic acid vs folic acid

EVIDENCE-BASED RECOMMENDATION(S)

- **EBR:** Inositol (in any form) could be considered in women with PCOS based on individual preferences and values, given limited harm, potential for reduced biochemical hyperandrogenism and metabolic measures, with limited evidence for clinical benefits for ovulation, hirsutism, or excess weight.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

- **EBR:** Metformin should be considered over inositol for metabolic measures, hirsutism, cycle regulation and central adiposity, noting that metformin has more gastrointestinal side effects than inositol.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

PRACTICE POINT(S)
PP: Women taking inositol and other complementary therapies are encouraged to advise their health professional. PP: Specific types, doses or combinations of inositol cannot currently be recommended in adults and adolescents with PCOS, due to a lack of quality evidence. PP: Shared decision making should include discussion that regulatory status and quality control of inositol in any form (like other nutrient supplements) differs from those for pharmacological products and that dose and quality may vary. PP: Policy makers and health professionals have a responsibility to ensure women have access to unconflicted, evidence-based information to inform shared-decision making, whilst also acknowledging and respecting individual values and preferences, including for complementary therapies.
GRADE CONSIDERATIONS
Justifications: There is a strong consumer voice on the need to inform women on the efficacy, limited quality evidence and the concerns around misinformation surrounding these products, as well as considering the costs. Conflicts of interest may also present concerns in this field of research.
Subgroup considerations: Participants in this trial had a normal BMI No adolescents in the study Different types of inositol
Implementation considerations: Regulation of nutrient supplements varies around the globe, therefore the quality of nutrient supplements that are purchased by consumers may vary. There is a need for education in Health professionals and women about evidence-based approaches. There is a need for strategies to limit misinformation.
Monitoring and evaluation considerations: Monitor commercial conflicts of interest and the claims made by industry are evidence-based.
Research priorities: AEs should be included as outcomes. The impact on QoL and psychological outcomes should be evaluated. There is a strong consumer interest in these products and therefore independent funding bodies should fund large scale clinical trials that are adequately-powered.

GRADE framework

GRADE DECIDE **Interactive Evidence to Decision Framework**

● DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

High quality systematic review performed; extensive discussions occurred.

● UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Using agents without any evidence of clinical efficacy that come at cost.

● CERTAINTY OF THE EVIDENCE

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☒ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Certainty of the evidence was very low due to very serious imprecision and unclear/moderate risk of bias.

● VALUES

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☒ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☐ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Research evidence:

No research evidence was identified

Panel discussion:

It is acknowledged that there are many stakeholders with different values, perspectives and preferences and these were considered.

● BALANCE OF EFFECTS

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

Panel discussion:

Detailed systematic review.

● COSTS

How large are the resource requirements (costs)?

Judgement:

☐ Don't know	☐ Varies	☐ Large costs	☐ Moderate costs	☐ Negligible costs or savings	☒ Moderate savings	☐ Large savings

Research evidence:

No research evidence was sought

Panel discussion:

Metformin - 500 mg tablets for 3 months is approximately $12 (SD)

Myo-Inositol - a three month supply at a dose of 2000 mg daily can be purchased for approximately $65 (US).

● CERTAINTY OF COST EVIDENCE

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

No research evidence was sought

Panel discussion:

● COST-EFFECTIVENESS

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

No research evidence was found.

Panel discussion:

No evidence.

● EQUITY

What would be the impact on health equity?

Judgement:

☐ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☒ Probably increased	☐ Increased

Research evidence:

No research evidence was sought

Panel discussion:

Possibly increasing equity by reducing cost by not recommending agents with no clear clinical benefit.

● ACCEPTABILITY

Is the option acceptable to key stakeholders?

Judgement:

☐ Don't know	☒ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:

No research evidence was sought

Panel discussion:

It is acknowledged that there are many stakeholders with different values, perspectives and preferences and these were considered.

● FEASIBILITY

Is the option feasible to implement?

Judgement:

☐ Don't know	☒ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Challenges with education and regulations.

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PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by ECR Lead: Katrina Tan

Other team members: Thisara Coster

Supervised, edited and supported by the Evidence Team (Aya Mousa, Jillian Tay)

GDG 4

Question 4.8.

Is permanent hair reduction alone or in combination with other therapies, effective for management of hirsutism in adolescents and adults with PCOS?

1. SELECTION CRITERIA

Table 1. PICO Criteria for Inclusion – Not to be adapted To be used by evidence team to decide which studies will be included when screening search results.	
Question	Q 4.8) Is permanent hair reduction alone or in combination with other therapies, effective for the management of hirsutism in adolescents and adults with PCOS?
Clinical leads (key contacts)	**Dr Daniela Romauldi** Obstetrician-Gynaecologist Fondazione Policlinico Universitario Agostino Gemelli, Italy daniela.romualdi@policlinicogemelli.it **Prof Terhi Piltonen** Obstetrician-Gynaecologist, Reproductive endocrinologist Oulu University Hospital, University of Oulu, Finland terhi.piltonen@oulu.fi **A/Prof Jacqueline Boyle** Obstetrician-gynaecologist Monash University, Australia Jacqueline.Boyle@monash.edu
Allocation ranking	Level 1- New systematic review

	Participants (P)	**Intervention (I)**	**Comparison (C)**	**Outcomes (O)**	**Study type (S)**	**Limits** *(language, year)*
Inclusion	Hirsute females with PCOS (diagnosed by Rotterdam, NIH or AES) of any age, ethnicity and weight. Subgroups: adolescents (10-19y), adults, pregnancy, post-menopausal. Subgroups: Different skin colour; BMI informed by the most frequent presentation of the data.	Permanent mechanical hair removal (electrolysis, lasers and pulsed light devices) alone or in combination with other treatments	Each long-term mechanical hair removal method vs another, Placebo/no-hair removal, Other non-permanent or short-term hair removal method-epilation (shaving, chemical depilation, plucking, threading, waxing, and bleaching) alone or in combination with other pharmacological or non-pharmacological treatments (eg. Eflornithine hydrochloride topical cream, OCP alone or antiandrogens + OCP not associated with mechanical hair removal, Metformin or other metabolic treatments, associated or not with OCP-hormonal drugs)	FG-score/some other scoring/tricoscopic methods (hair shaft thickness, hair shaft colour, terminal vs. vellus hair ratio and hair density per cm2) for hirsutism evaluation. self-reported data on hirsutism QoL, safety (skin scars, skin spots), safety in pregnancy, cost	Systematic reviews Evidence-based guidelines Comparative cohort studies (can include cross sectional or case control if it compares PCOS and non- PCOS) RCTs	English Language
Exclusion	Females without PCOS. Non-Hirsute women					

2. SEARCH STRATEGY

Table 2.1. Search details	
Search strategy source: *[enter doi or 2018 technical report page number where search string was derived]*	
Evidence source	**Date of search**
Medline (Ovid)	**August 4th 2022**
EMBASE (Ovid)	**August 4th 2022**
EMCARE (Ovid)	**August 4th 2022**
CINAHL	**August 4th 2022**
Any subsequent updates - enter database and date:	

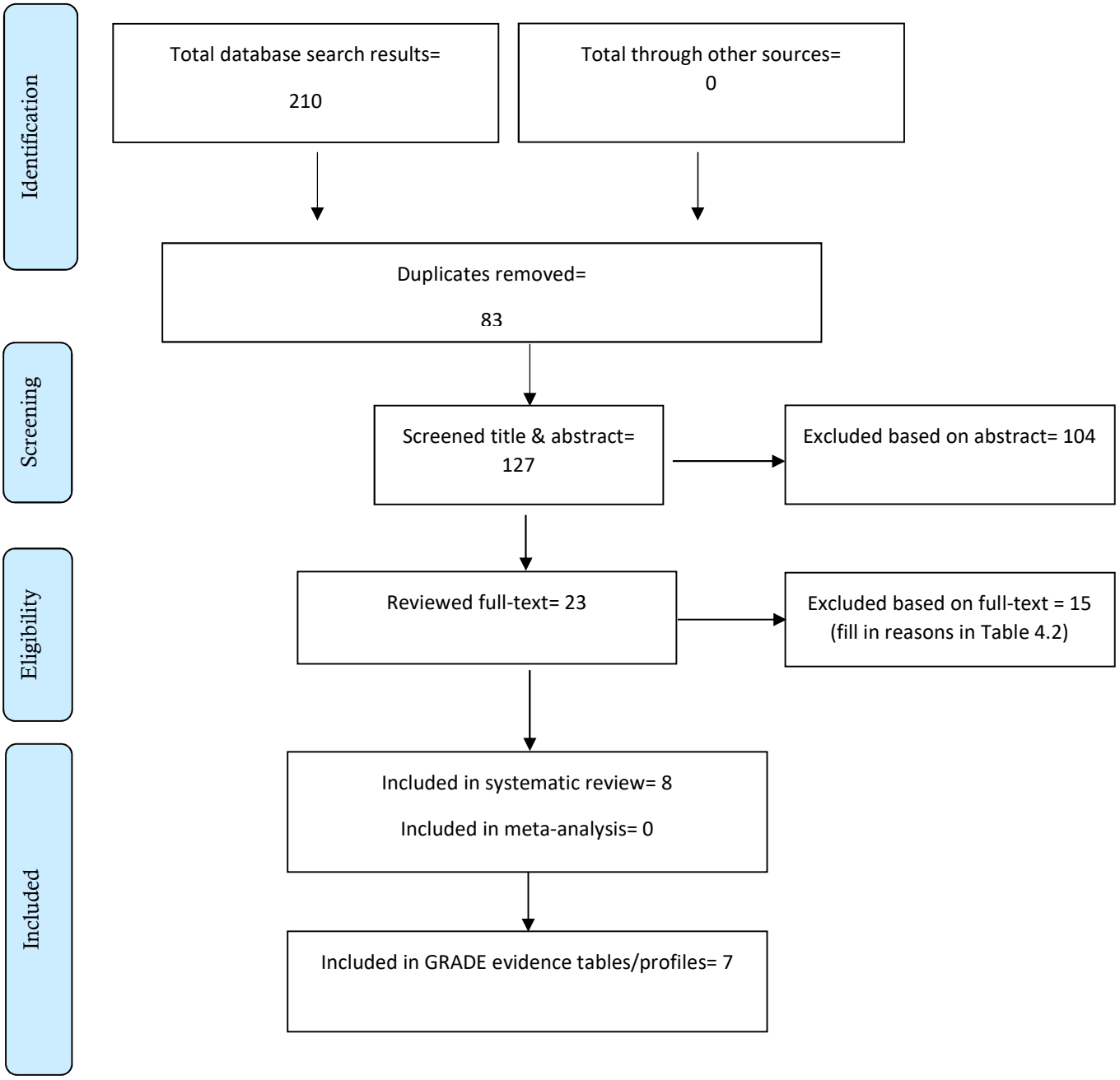
Table 2.2. Questions addressed by this search *(add more rows as needed)*:		
GDG	Q#	Question
1	4.8	Is mechanical hair removal alone or in combination with other therapies, effective for the management of hirsutism in adolescents and adults with PCOS?

Table 2.3. Search strings used in OVID or other database/s – *please save a screenshot of search results to submit alongside this template*		
OVID Medline, All EBM, PsychInfo, EMBASE (results= n?)	CINAHL?	Other?
Search 1 = PCOS 1. exp Polycystic Ovary Syndrome/ 2. polycystic ovar$.mp. 3. poly-cystic ovar$.mp. 4. PCO$.mp. 5. (stein-leventhal or leventhal).mp. 6. anovulation/ 7. anovulat$.mp. 8. oligo-ovulat$.mp. 9. oligoovulat$.mp. 10. (ovar$ adj5 (scelerocystic or polycystic or poly-cystic or degenerat$ or hyperandrogen$ or hyper-androgen$)).mp. **Search 2 = Conditions** 1. Exp hirsutism/ 2. hypertrichosis.ti,ab Combine with OR **Search 3 = Interventions** 3. Remov* adj5 hair.mp. 4. (Laser* adj5 (hair or hair-remov* or remov* or alexandrite or diode or ruby or YAG)).mp. 5. photoepilation.ti,ab 6. intense pulsed light.ti,ab 7. IPL.ti,ab 8. hair-follicl*.ti,ab 9. Hair follicl*.ti,ab 10. hair-removal.ti,ab	Same as described for OVID	No other search

11. Laser-surgery.ti,ab 12. Light-coagulation.ti,ab (N.B. in cinahl have to do light coagulation, light-coagulation nil search results) 13. Light adj5 (hair or remov* or laser) .ti,ab 14. Electrolysis adj5 hair.ti,ab Combine with OR Combine Search 1, Search 2 and Search 3 with AND		

Evidence processing: Studies were selected and appraised by 2 reviewer/s in consultation with the evidence team/ key contact using study selection and appraisal criteria (PICO above) established a priori. The articles were reviewed by title and abstract by 2 reviewers. When a decision could not be made based on title and abstract alone, full text was retrieved. **A total of 8 studies met inclusion criteria for this review.**

3. SEARCH RESULTS - PRISMA flowchart



4. STUDY INCLUSION

Table 4.1. Included Studies (full citation with doi)- *add more rows as needed*
Clayton, W. J.; Lipton, M.; Elford, J.; Rustin, M.; Sherr, L. (2005). A randomised controlled trial of laser treatment among hirsute women with polycystic ovary syndrome. British ournal of Dermatology, 2005;152(5):986-992. Doi: 0.1111/j.1365-2133.2005.06426.x
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Karn, D.; K C, S.; Timalsina, M.; Gyawali, P. (2014). Hormonal profile and efficacy of long pulse Nd-YAG laser in treatment of hirsutism. Journal of Nepal Health Research Council, 2014; 12(26):59-62. Doi: 10.33314/jnhrc.v0i0.440
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McGill, D. J.; Hutchison, C.; McKenzie, E.; McSherry, E.; Mackay, I. R. (2007). Laser hair removal in women with poilycystic ovary syndrome. Journal of plastic, reconstructive & aesthetic surgery: JPRAS 2007;60(4):426-31. doi :10.1016/j.bjps.2006.11.006
Nabi, N.; Bhat, Y. J.; Dar, U. K.; Hakeem, A.; Mir, S. A.; Shah, I. H.; Tilwani, M. R. (2022). Comparative study of the clinic-trichoscopic response to treatment of hirsutism with long pulsed (1064nm) Nd:YAG laser in idiopathic hirsutism and polycystic ovarian syndrome patients. Lasers in medical science 2022;37(1):545-553. Doi: 10.1007/s10103-021-03295-0
Pai, G. S.; Bhat, P. S.; Mallya, H.; Gold, M. (2011) Safety and efficacy of low-fluence, high-repetition rate versus high-fluence, low-repetition rate 810-nm diode laser for permanent hair removal A split-face comparison study. Journal of Cosmetic and Laser Therapy 2011;13(4):134-137. Doi: 10.3109/14764172.2011.594057
Rezvanian, H.; Adibi, N.; Siavash, M.; Kachuei, A.; Shojaee-Moradie, F.; Asilian, A.)2—0_. Increased insulin sensitivity by metformin enhances intense-pulsed-light-assisted hair removal in patients with polycystic ovary syndrome. Dermatology 2009;218(3):231-236. Doi: 10.1159/000187718

Table 4.2. Excluded Studies (on full text assessment)	
Reference	**Reason**
Moghetti et al. 2006	Wrong study design – Narrative review
Pasquali et al. 2014	Wrong study design – Narrative review/textbook chapter
Taylor et al. 2010	Wrong patient population – Cohort included patients with 'hyperandrogenism' some had PCOS, others had idiopathic/other, nil differentiation made specifically for patients with PCOS – results all grouped into one.
Grippaudo et al. 2009	Wrong patient population – cohort grouped PCOS & CAH patients into one, nil specific results for PCOS only or comparison between PCOS vs. CAH.
Rittmaster et al. 1999	Wrong study design – Narrative review
Escobar-Morreale et al. 2012	Wrong study design – Narrative review, consensus statement
Yildiz et al. 2008	Wrong study design – Narrative review
Harrison et al. 2010	Wrong study design – Narrative review
Vedak et al. 2022	Full text not published yet – unable to review full text
Roche et al. 2013	Wrong study design – narrative review
Pasquali et al. 2014, (treatment of hirsutism in PCOS)	Wrong study design – Narrative review
Lee et al. 2018	Wrong study design – Narrative review
Zainab et al. 2011	Wrong study design – Case report
Spritzer et al. 2016	Wrong study design – Narrative review of pathophysiology
Goodman et al. 2015	Wrong study design – Narrative review and guide

5. STUDY CHARACTERISTICS TABLE

Author, year, country	Population/ Setting	Study Design	Sample Size per group	Intervention/ exposure details	Comparison/ control details	Comparison/ control details	Follow up Duration	Outcomes	Summary of findings
Example et al. 2021	Women with PCOS and infertility; Fertility clinic	Parallel double blind RCT	Metformin= 59 Placebo=65	Metformin 500-2500g daily	Placebo identical daily		6 months	Pregnancy rate (primary), livebirth, ovulation	Metformin was more effective in achieving pregnancy and livebirth versus placebo
Clayton WJ, et al. 2005	Women with PCOS and facial hirsutism; Dermatology of dermatology	Single blinded RCT	Intervention group (high-fluence laser) = 51 Control (low-fluence laser)= 37	High Fluence Alexandrite laser (23.6 J cm^-2), 755nm pulse width 20ms spot size 12.5 (Apogee 6200; Cynosure, Chelmsford, MA, USA), 4-6 weekly for 6 months	Low fluence Alexandrite laser equivalent to ineffective/no laser (4.8 J cm ^-2), 755nm pulse width 20ms spot size 12.5 (Apogee 6200; Cynosure, Chelmsford, MA, USA), 4-6 weekly for 6 months		6 months	**1. Self-reported severity of facial hair** **2. Hair free period** **3. Depression & anxiety,** **4. quality of life** **5. time spent removing hair** **6. self-esteem**	Laser treatment reduces facial hirsutism severity and reduces time spend on hair removal. Laser treatment also alleviates depression and anxiety in women with PCOS.
Dorgham, N et al. 2021	Women with PCOS and facial hirsutism; "single centre" setting not otherwise specified	RCT	Group 1 (laser hair removal only): 50 women Group 2 (laser hair removal + metformin 500mg): 50 women Group 3 (laser hair removal + COCP Diane-35): 50 women	Laser & COCP (Diane-35). Assume once daily COCP. LightSheer DUET; Lumenis, Yokneam, Israel) was applied for hair removal for a total of six initially monthly sessions followed by two follow-up sessions at three and six months after the initial six sessions	Laser + 500mg Glucophage metformin hydrochloride – frequency of metformin not specified	Laser only	6 months	**1. DLQI** **2. HLQI** **3. Overall hirsutism - analog scale (subjectively assessed by treating physician)**	bination of hormonal treatment with laser hair removal can achieve greater hair reduction, significant improvements in patients' quality of life and better maintenance compared to combination of metformin + laser or laser alone
McGill DJ et al. 2007 (RCT)	Women with PCOS and facial hirsutism; University teaching hospital with patients from	RCT	31, split face	GentleLase Alexandrite laser; 755nm wavelength, 3 millisecond pulse duration	Lumina IPL, 650-1100nm filter - 6-weekly, total of 6 full treatments		6 months	**1. Hair counts completed prior and at 1,3- and 6-months following treatment** **2. Patient satisfaction questionnaires completed**	The alexandrite laser resulted in significantly longer hair-free intervals, larger reductions in hair

	gynecology/ endocrinology clinics, Glasgow, UK			6-weekly, total of 6 full treatments				**prior at 1,3- and 6-months following treatment** **3. Hair free intervals, defined as the time to first hair re-growth (as measured by patient) following each treatment**	counts and greater patient satisfaction than the IPL
Rezvanian,H et al. 2009	Women with PCOS and facial hirsutism; Dermatology clinic of St. Al-Zahra Hospital in Iran	Prospective RCT	Intervention (IPL/Metformin) = 35 Control (IPL only) = 35	IPL & Metformin IPL for 5 laser sessions at 45-day intervals 500mg Metformin TDS	IPL only for 5 laser sessions at 45-day intervals			**1. Reduction of hair count** **2. Reduction in hair width/thickness** **3. Degree of hair reduction (50% in hair count and 30% in hair diameter) as determined by dermatologists**	Hirsutism was significantly better controlled in participants who had combination IPL and metformin vs. IPL only. Patients satisfaction was also significantly better in IPL/Metformin group.
Karn, D et al. 2014	Women with PCOS and women without hyperandrogenism or US findings of PCOS (Controls), who presented to department of dermatology in Dhulikhel Hospital Kathmandu University Hospital, Dhulikhel, Nepal	Prospective cohort study	PCOS: 30 women Non-PCOS: 30 women	All patients received 1064nm longpulse Nd-YAG laser with 50 J/cm^2 energy and 50 msec pulse duration. Laser therapy was repeated every four weeks and number of settings was noted for substantial hair reduction.	Nil – all participants received the same treatment		Not reported, only reported number of sessions needed to reach 50% reduction in facial hirsutism, nil timeframe specified	Number of laser treatment sessions required to reach more than 50% reduction in hair count Method	Patients with PCOS require more laser treatment sessions compared to patients without PCOS to achieve at least 50% reduction in hair count
McGill, D.J. et al. (2) 2007	Women with PCOS and facial hirsutism who were referred to an outpatient department for laser hair removal	Prospective cohort study	60 women received the same intervention, nil comparison group	All participants treated with a 755nm GentleLase Alexandrite Laser (Candela Corp., Wayland, MD, USA). Initial patch test and then 6 treatments at 6 weekly intervals – then maintenance treatment as required	Nil – all participants received the same treatment		Patients followed up for maintenance laser treatments but unclear what this follow-up time period was over/when	**1. Hair counts** **2. Hair free interval** **3. Patient satisfaction**	Women with PCOS experience poorer than expected reduction in hair and HFI following laser treatment and more than 6 laser treatment sessions may have prolong HFI and overall patient satisfaction

Nabi, N et al. 2022	Women with PCOS-related hirsutism and idiopathic hirsutism who were seen in a non-specified outpatient dermatology department of an Indian hospital	Prospective cohort study	PCOS: 50 Controls (idiopathic hirsutism): 50	Nd: YAG laser with wavelength of 1064nm (Gentle YAGTM,Candela Corporation, Boston, USA). For a total of 6 sessions	Nil – all participants received the same treatment		3 months	**1. Efficacy of hair reduction** **2. Effect of laser on trichoscopic features**	Patients with PCOS-associated hirsutism have poorer response to Nd:YAG laser compared to patients with idiopathic hirsutism
Pai, GS et al. 2011	Women with PCOS and facial hirsutism who presented to a non-specified single-centre	Prospective cohort study	51 , split face	Low-fluence but high-repetition laser with Soprano® XL (Alma Lasers Ltd, Caesarea, Israel) in SHR mode using a technique of maintaining the handpiece in constant motion, with a fluence up to 10 J/cm^2, 10 Hz, and a 20-ms pulse duration as recommended by the manufacturers.	High fluence, single-pass Light- SheerTM (Lumenis, Inc., Santa Clara, CA, USA) using a conventional single-pass fluence to tolerance (25–35 J/cm^2), 2 Hz, and a 30-ms pulse duration (which was the pulse width found safest in our patient population based on past experiences on skin types IV and V).		Not reported. Only comment that subjects received 6 sessions with every 4-6 weeks. Nil other timeframe or total duration specified.	**1. Hair count** **2. Hair density** **3. Pain during treatment**	

6.1. FINDINGS

EVIDENCE SUMMARY:

Total of eight studies were included in the systematic review: four RCTs and four cohort studies. Meta-analysis was not performed due to significant heterogeneity of the types of permanent mechanical hair removal techniques used, and varying outcomes assessed across the studies. There were also significantly variable follow up durations, ranging from no follow-up or unspecified follow-up duration, to 3 or 6-months. Five studies had high risk of bias, the remaining three had moderate risk of bias, no studies were assessed to have low risk of bias. Overall, certainty of evidence in all 8 studies was rated low or very low due to imprecision, risk of bias, lack of meta-analysis, small sample numbers and single studies noted in outcome as per the GRADE evidence profile.

DESCRIPTIVE ANALYSIS SUMMARY:

No meta-analyses were performed due to non-consistent methods and outcomes across all eight studies. Overall, laser treatment was reported as an effective method of permanent hair removal technique for facial hirsutism. The combination of laser treatments with systemic hormonal agents such as metformin or the oral contraceptive pill seemed to better control hirsutism compared to laser treatment alone. Similar findings were noted when IPL treatments alone were compared to treatments in combination with metformin. No studies investigated whether the combination of IPL and systemic agents would lead to differing results when compared to the combination of laser and systemic agents, however one study reported laser treatments alone to be superior to IPL treatment alone.

Of the four studies that reported on psychological outcomes such as patient satisfaction, quality of life, depression and anxiety scores, treatment with permanent hair removal technique was found to improve all measures, more so when combined with systemic agents.

6.2. DATA EXTRACTION TABLES – DICHOTOMOUS OUTCOMES

OUTCOME: Reduction in Hair shaft thickness					**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Nd:YAG laser - PCOS vs. Non-PCOS									
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**P-value**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Nabi,N et al. 2022	N & %	Trichoscopy - Hair shaft thickness determined after comparing micrographs of trichoscopic images pre- and post- laser, unclear definition of 'reduction', by how much and who examined images	PCOS group N=15 (30%)	50	Idiopathic Hirs N=35 (70%)	50	<0.001	Crude	NA

OUTCOME: Reduction in Hair shaft colour					**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Nd:YAG laser - PCOS vs. Non-PCOS									
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**P-value**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Nabi,N et al. 2022	N & %	Trichoscopy - determined after comparing micrographs of trichoscopic images pre- and post- laser, unclear definition of 'decreased colour', or by how much and who examined images	PCOS group N=24 (48%)	50	Idiopathic Hirs N=31 (62%)	50	P=0.159	Crude	NA

OUTCOME: Reduction in terminal: vellus hair ratio					**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Nd:YAG laser - PCOS vs. Non-PCOS									
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**P-value**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Nabi,N et al. 2022	N & %	Calculated by the number of hairs counted in a $1*1cm^2$ cardboard window with the help of trichoscope	PCOS group N=23 (46%)	50	Idiopathic Hirs N=34(68%)	50	P=0.026	Crude	NA

OUTCOME: Reduction in hair density					**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Nd:YAG laser - PCOS vs. Non-PCOS									
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**P-value**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Nabi,N et al. 2022	N & %	Calculated by the number of hairs counted in a 1*1cm^2 cardboard window with the help of trichscope	PCOS group N=36 (72%)	50	Idiopathic Hirs N=27(54%)	50	P=0.044	Crude	NA

OUTCOME: Reduction by 50% in hair count & reduction 30% hair diameter					**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): IPL & Metformin vs. IPL alone									
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**P-value**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Rezvanian,H, 2009	%	Dermatology assessed (reduction of 50% in hair count & 30% in hair diameter) in the lower face areas, including the chin, upper lip, submental and preauricular areas if there was any unwanted hair.	IPL/metformin 59.9%	22	IPL only 23.3%	30	P=0.009	Crude	NA

N.B. Rezvanian,H et al 2009 – Improvement (%) measured immediately after treatment and at 6-month follow-up – only data at 6 month extracted

DATA EXTRACTION TABLES- CONTINUOUS OUTCOMES

OUTCOME: Reduction in overall facial hirsutism					**Outcome type:** Continuous				
COMPARISON (if applicable): High-fluence laser vs. Low-fluence laser									
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Group 1 - Mean (specify if median) in intervention/ exposure group**	**Group 1 -SD (or specify if other measure: IQR, SE or 95% CI) in exposure group**	**Group 2 - Mean (specify if median) or median in control / comparison group**	**Group 2 - SD (or specify if other measure: SE, IQR or 95% CI) in control group**	**p-value**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Clayton WJ et al. 2005	Numerical value	Self-reported via 10-point scale (1 = least severe, 10 = most severe) on survey created for this study	High-fluence laser Pre-laser mean =7.3 Post-laser mean = 3.6	Pre-laser SD =1.8 Post-laser SD= 2.8	Low-Fluence laser Pre-laser mean =7.1 Post-laser mean = 6.1	Pre-laser SD =1.9 Post-laser SD= 2.6	<0.05	Crude	NA

OUTCOME: Reduction in overall facial hirsutism					**Outcome type:** Continuous				
COMPARISON (if applicable): PCOS vs. Non-PCOS									
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Group 1 - Mean (specify if median) in intervention/ exposure group**	**Group 1 -SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Group 2 - Mean (specify if median) or median in control / comparison group**	**Group 2 - SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**p-value**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Nabi,N et al. 2022	Numerical value	4-point scale (poor <25% reduction, fair <25%-50%, good 50-75%, excellent >75%), unclear if physician or participant assessed	PCOS group Poor = 0 Fair = 32% Good = 20% Excellent = 48%		Idiopathic hirsutism group Poor = 0 Fair = 18% Good = 22% Excellent = 60%		P=0.0423	Crude	NA
Karn D et al. 2014	Number of Laser Sessions	Subjective physician assessment not reported if specific training provided: Until patient achieved 50% reduction in overall facial hirsutism	PCOS group 8.1	1.28	Non-PCOS group: 5.7	1.01	P<0.05	Crude	NA

N.B. Nabi,N 2022 – Hair reduction taken after each of the 6 sessions and at 3 follow-up – only data at 3 months extracted

OUTCOME: Reduction in overall facial hirsutism					**Outcome type:** Continuous				
COMPARISON (if applicable): Soprano XL laser vs. LightSheer laser									
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Group 1 - Mean (specify if median) in intervention/ exposure group**	**Group 1 -SD (or specify if other measure) in exposure group**	**Group 2 - Mean (specify if median) or median in control / comparison group**	**Group 2 - SD (or specify if other measure) in control group**	**p-value**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Pai GS et al. 2011	%	SIF-1 hair analysis system in predetermined square-shaped area (2x2 cm^2 area from the tip of the ear lobule to the jaw line)	Soprano XL Median = 90.5%	Soprano XL SD = 7	Lightsheer Median = 85%	LightSheer SD = 8.5	P<0.063	Crude	NA

OUTCOME: Reduction in hair count					**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): IPL vs. Alexandrite laser									
Author, year	**Unit of outcome (e.g. g, mg, µg.)**	**Method of measurement**	**Group 1 - Mean (specify if median) in intervention/ exposure group**	**Group 1 -SD (or specify if other measure: IQR, SE or 95% CI) in exposure group**	**Group 2 - Mean (specify if median) or median in control / comparison group**	**Group 2 - SD (or specify if other measure: SE, IQR or 95% CI) in control group**	**p-value**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
McGill,DJ 2007 (1) (split-face RCT)	n	Videomicroscope of pictures taken on the outer margin of the upper lip, the chin and neck from both the right and left side of the face - 1.04 cm^2 area in each area 3 independent experienced members of laser suite	IPL Pre = 37 6mo post = 28	IPL Pre SEM = 3 6mo post = 3	Alexandrite Pre = 37 6mo post =20	Alexandrite Pre SEM =3 6mo post = 2	IPL, p=0.004 vs. pre-rx Alexandrite, p<0.001 vs pre rx	Crude	NA
McGill,DJ 2007 (1) (split-face RCT)	%	Videomicroscope, as above.	IPL 27% decrease	NA	Alexandrite 46% decrease	NA	P<0.001	Crude	NA

OUTCOME: Reduction in hair count					**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): No comparison - all participants received Alexandrite laser									
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Group 1 - Mean (specify if median) in intervention/ exposure group**	**Group 1 - SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Group 2 - Mean (specify if median) or median in control / comparison group**	**Group 2 - SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**p-value**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
McGill,DJ 2007 (2 – cohort study)	%	Videomicroscope of pictures taken on the outer margin of the upper lip, the chin and neck from both the right and left side of the face - 1.04 cm^2 area in each area Counted by 3 laser nurse practitioners	31% decrease at 6 months	38% SD	Nil comparison		P=0.001	Crude	NA

OUTCOME: Reduction in hair count					**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): IPL & Metformin vs. IPL only									
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Group 1 - Mean (specify if median) in intervention/ exposure group**	**Group 1 - SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Group 2 - Mean (specify if median) or median in control / comparison group**	**Group 2 - SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**p-value**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Rezvanian,,H et al. 2009	n/cm^2	Count in 2 square areas of 1cm^2 in the chin area	IPL/metformin 22.14	IPL/metformin 10.52	IPL only 29.7	IPL only 14.67	P=0.044		

N.B. Rezvanian,H et al. 2009 recorded reduction in hair count at 0 months (immediately after 5 laser sessions) & at 6-month follow-up – only data from 6-month follow-up extracted

OUTCOME: Hair width/thickness					**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Soprano XL Laser vs. LightSheer Laser									
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Group 1 - Mean (specify if median) in intervention/ exposure group**	**Group 1 - SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Group 2 - Mean (specify if median) or median in control / comparison group**	**Group 2 - SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**p-value**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Pai GS et al. 2011	mm	Hair analysis system SIF-1 (Standardised machine and analysis program) in predetermined square-shaped area (2x2 cm^2 area from the tip of the ear lobule to the jaw line)	Soprano XL laser 0.02mm	NR	Lightsheer laser 0.05mm	NR	P<0.0005	Crude	NA

OUTCOME: Hair width/thickness					**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): IPL & Metformin vs. IPL alone									
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Group 1 - Mean (specify if median) in intervention/ exposure group**	**Group 1 - SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Group 2 - Mean (specify if median) or median in control / comparison group**	**Group 2 - SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**p-value**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Rezvanian, H, 2009	mm	Microscopy – diameter measured at its widest portion	IPL/Metformin Pre = 0.103 Post = 0.075	IPL/Metformin Pre = 0.035 Post = 0.069	IPL only Pre = 0.125 Post = 0.093	IPL only Pre=0.052 Post = 00496	Pre, p=0.12 Post, p=0.30	Crude	NA

N.B. Rezvanian,H et al. 2009 recorded hair thickness at 0 months (immediately after 5 laser sessions) & at 6-month follow-up – only data from 6-month follow-up extracted

OUTCOME: Time spent on hair removal					**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): High-fluence laser vs. low-fluence laser									
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Group 1 - Mean (specify if median) in intervention/ exposure group**	**Group 1 -** **SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Group 2 - Mean (specify if median) or median in control / comparison group**	**Group 2 - SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**p-value**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Clayton WJ et al. 2005	Mins	Self-reported, survey created for purpose of this study only	Pre-laser mean = 112 Post-laser mean = 21	Pre-laser SD = 135 Post-laser SD= 19	Pre-laser mean = 92 Post-laser mean = 56	Pre-laser SD = 88 Post-laser SD= 73	$F_{(1,80)} = 10.2$, $P \leq 0.05$	Crude	NA

OUTCOME: Hair free Intervals					**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): High-fluence laser vs. low-fluence laser									
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Group 1 - Mean (specify if median) in intervention/ exposure group**	**Group 1 - SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Group 2 - Mean (specify if median) or median in control / comparison group**	**Group 2 - SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**p-value**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Clayton WJ et al. 2005	Days	Self-reported, survey created for purpose of this study only	Pre-laser mean = 12.4 Post-laser mean = 24.4	Pre-laser SD = 13.4 Post-laser SD= 18.5	Pre-laser mean = 11.2 Post-laser mean = 5.9	Pre-laser SD = 9.5 Post-laser SD= 9.1	$F_{(1,79)} = 28.6$, $P < 0.01$	Crude	NA

OUTCOME: Hair free intervals					**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): IPL vs. Alexandrite laser									
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Group 1 - Mean (specify if median) in intervention/ exposure group**	**Group 1 - SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Group 2 - Mean (specify if median) or median in control / comparison group**	**Group 2 - SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**p-value**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
McGill,DJ 2007 – 1 (split-face RCT)	Weeks	Self-reported by participants defined as the time to first hair re-growth after each treatment	IPL Median =2	IPL Range = 0-10	Alexandrite Median =7	Alexandrite Range = 0-15	P<0.005	Crude	NA

N.B. McGill, DJ 2007 – 1 (split face RCT). HFI recorded after each 6 sessions – only data post last (6^{th}) session extracted

OUTCOME: Hair free intervals					**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): No comparison - all participants received Alexandrite laser									
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Group 1 - Mean (specify if median) in intervention/ exposure group**	**Group 1 - SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Group 2 - Mean (specify if median) or median in control / comparison group**	**Group 2 - SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**p-value**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
McGill,DJ 2007 – 2 (cohort study)	Weeks	Self-reported by participants defined as the time to first hair re-growth after each treatment	4.3	Unable to extract			NR	Crude	NA

N.B. McGill, DJ 2007 – 2 (cohort study). HFI recorded after 6, 8 and 10 sessions – only data post 10 session extracted

OUTCOME: Improvement in Visual analog scale					**OUTCOME TYPE:** Continuous						
COMPARISON (if applicable): LightSheer Laser only vs. LightSheer Laser & Metformin vs. LightSheer laser & COCP											
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Group 1 - Mean (specify if median) in intervention/ exposure group**	**Group 1 - SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Group 2 - Mean (specify if median) or median in control / comparison group**	**Group 2 - SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Group 3 - Mean (specify if median) or median in control / comparison group**	**Group 3 - SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**p-value**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Dorgham,N et al. 2021	Numerical value	Subjective assessment made by treating physician assessment on a 5-point scale, not specified if scale created for sole purpose of study or if an established scale - unclear if physicians received additional training (1 = worse, 2= no change, 3 = <30% improve, 4 = 30-60% improve, 5 = >60% improve)	Laser only 3 months = 3.2 6 months = 3	Laser only 3 months = 0.8 6 months = 0.6	Laser + Met 3 months = 3.3 6 months = 3.2	Laser + Met 3 months = 3.5 6 months = 0.4	Laser + COCP 3 months = 4.2 6 months = 4.2	Laser + COCP 3 months = 0.2 6 months = 0.6	Not reported	Crude	NA

N.B. Dorgham, N et al. 2021 recorded VAS immediately after the 6th session, and at 3- and 6-month follow-up – data for 3 and 6 months extracted

OUTCOME: Improvement in Visual analog scale					**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): IPL & Metformin vs. IPL only									
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Group 1 - Mean (specify if median) in intervention/ exposure group**	**Group 1 - SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Group 2 - Mean (specify if median) or median in control / comparison group**	**Group 2 - SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**p-value**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Rezvanian,H H et al. 2009	%	Self-reported scale made for this study, of 0-100%, to evaluate patient's impression of degree of improvement for her hirsutism	IPL/Metformin 52.95	IPL/Metformin 26.35	IPL only 34.13	IPL only 28.15	P=0.019	Crude	NA

N.B. Rezvanian,H et al 2009 recorded VAS immediately after 5th session and at 6-month follow-up – only data at 6 month extracted

OUTCOME: Reduction in hair density					**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Nd:YAG laser - PCOS vs. Non-PCOS									
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Group 1 - Mean (specify if median) in intervention/ exposure group**	**Group 1 - SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Group 2 - Mean (specify if median) or median in control / comparison group**	**Group 2 - SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**p-value**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Nabi,N et al. 2022	N & %	Trichoscopy - Measured in a 1x1cm^2 cardboard window with the help of trichoscope	PCOS group N=27 (54%)	50	Idiopathic Hirs N=36 (72%)	50	P=0.044	Crude	NA

OUTCOME: Depression scores					**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): High fluence laser vs. low fluence laser									
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Group 1 - Mean (specify if median) in intervention/ exposure group**	**Group 1 -SD (or specify if other measure: IQR, SE or 95% CI) in exposure group**	**Group 2 - Mean (specify if median) or median in control group**	**Group 2 - SD (or specify if other measure: SE, IQR or 95% CI) in control group**	**p-value**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Clayton WJ et al. 2005	Numerical value	Self-reported using established Hospital Anxiety and Depression Scale (HADS) – a 14-item scale, each item scored from 0-3, generating scores ranging 0-21. Normal (0-7), mild (8-10), moderate (11-14), severe (15-21)	Pre-laser mean = 6.7 Post-laser mean =3.6	Pre-laser SD = 4.5 Post-laser SD= 3.5	Pre-laser mean = 6.1 Post-laser mean = 5.4	Pre-laser SD = 3.7 Post-laser SD= 3.8	$F_{(1,83)} = 14.7$, $P < 0<0.05$	Crude	NA

OUTCOME: Anxiety scores					**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): High fluence laser vs. low fluence laser									
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Group 1 - Mean (specify if median) in intervention/ exposure group**	**Group 1 -SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Group 2 - Mean (specify if median) or median in control / comparison group**	**Group 2 - SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**p-value**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Clayton WJ et al. 2005	Numerical value	Self-reported using established Hospital Anxiety and Depression Scale (HADS) – a 14-item scale, each item scored from 0-3, generating scores ranging 0-21. Normal (0-7), mild (8-10), moderate (11-14), severe (15-21)	Pre-laser mean = 11.1 Post-laser mean = 8.2	Pre-laser SD = 3.5 Post-laser SD= 3.8	Pre-laser mean = 9.6 Post-laser mean =9.3	Pre-laser SD = 4.5 Post-laser SD= 4.9	$F(1,84) = 17.8$, $P < 0.05$	Crude	NA

OUTCOME: Psychological quality of life					**OUTCOME TYPE: Continuous**				
COMPARISON (if applicable: High fluence laser vs. low fluence laser									
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Group 1 - Mean (specify if median) in intervention/ exposure group**	**Group 1 - Mean (specify if median) in intervention/ exposure group**	**Group 1 -** **SD (or specify if other measure: IQR, SE or 95% CI) in exposure group**	**Group 2 - Mean (specify if median) or median in control group**	**p-value**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Clayton WJ et al. 2005	Numerical value	Self-report WHOQOL-BREF Psychological -	Pre-laser mean = 49.6 Post-laser mean = 61.2	Pre-laser SD = 18.8 Post-laser SD= 16.7	Pre-laser mean = 50.1 Post-laser mean = 51.5	Pre-laser SD = 20.6 Post-laser SD= 21.5	$F(1,84) = 0.0$, $P < 0.05$	Crude	NA
Clayton WJ et al. 2005	Numerical value	Self-report WHOQOL-BREF Social	Pre-laser mean = 49.5 Post-laser mean = 57.8	Pre-laser SD = 22.6 Post-laser SD= 24.0	Pre-laser mean = 49.3 Post-laser mean = 31.6	Pre-laser SD = 53.6 Post-laser SD= 27.2	>0.05	Crude	N/A
Clayton WJ et al. 2005	Numerical value	Self-report WHOQOL-BREF Physical	Pre-laser mean = 64.3 Post-laser mean = 70.6	Pre-laser SD = 19.9 Post-laser SD= 18.9	Pre-laser mean = 68.7 Post-laser mean = 67.9	Pre-laser SD = 19.3 Post-laser SD= 20.5	>0.05	Crude	N/A
Clayton WJ et al. 2005	Numerical value	Self-report WHOQOL-BREF Environmental	Pre-laser mean = 62.4 Post-laser mean = 65.6	Pre-laser SD = 13.7 Post-laser SD= 15.9	Pre-laser mean = 59.1 Post-laser mean = 60.6	Pre-laser SD = 16.8 Post-laser SD= 18.8	>0.05	Crude	N/A

OUTCOME: Psychological quality of life	**OUTCOME TYPE:** Continuous

COMPARISON (if applicable: LightSheer Laser only vs. LightSheer laser & Metformin vs. LightSheer Laser & COCP											
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Group 1 - Mean (specify if median) in intervention/ exposure group**	**Group 1 - Mean (specify if median) in intervention/ exposure group**	**Group 1 - SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Group 2 - Mean (specify if median) or median in control / comparison group**	**Group 3 - Mean (specify if median) or median in control / comparison group**	**Group 3 - SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**p-value**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Dorgham,N et al. 2021	Numerical value	Self-report HLQI	Group 1 (laser only) Pre = 14.7 3 months = 5 6 months = 6.5	Group 1 (laser only) Pre = 4.3 3 months = 1.5 6 months = 2.3	Group 2 (laser + metformin) Pre = 14.8 3 months = 4.6 6 months = 4.48	Group 2 (laser + metformin) Pre = 4.4 3 months = 1.2 6 months = 1.2	Group 3 (laser + COCP) Pre = 15.7 3 months = 1.9 6 months = 1.45	Group 3 (laser + COCP) Pre = 4.1 3 months = 0.8 6 months = 0.5	Pre p=0.913 Post at 3 and 6 month follow-up =0.001 for G3 vs. G2 and Vs G1, not G2 vs. G1	Crude	N/A
Dorgham,N et al. 2021	Numerical value	Self-report DLQI	Group 1 (laser only) Pre = 25 3 months = 5.2 6 months = 5.5	Group 1 (laser only) Pre = 0.4 3 months = 1.5 6 months = 2.5	Group 2 (laser + metformin) Pre = 24 3 months =4.3 6 months = 5.0	Group 2 (laser + metformin) Pre = 0.4 3 months = 1.5 6 months = 1.5	Group 3 (laser + COCP) Pre = 26 3 months = 1 6 months = 1.0	Group 3 (laser + COCP) Pre = 0.3 3 months = 0.4 6 months = 0.6	Pre, p=0.1 p =0.001 at 3- and 6-month follow-up on comparison between groups for G3 vs. G2 and Vs G1, p=0.05 G2 vs. G1	Crude	N/A

N.B. Dorgham et al, 2021. Reported HLQI & DLQI scores at 0,3,6 months - *pre* refers to scores at 0 months, prior to treatment

OUTCOME: Patient satisfaction					**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): High fluence laser vs. low fluence laser									
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Group 1 - Mean (specify if median) in intervention/ exposure group**	**Group 1 - SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Group 2 - Mean (specify if median) or median in control / comparison group**	**Group 2 - SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**P-value**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Clayton WJ et al. 2005	Numerical value	Self-reported by patient using standardised Rosenberg self-esteem scale	Pre-laser mean = 27.7 Post-laser mean = 30.9	Pre-laser SD = 5.4 Post-laser SD= 5.3	Pre-laser mean = 26.3 Post-laser mean = 28.7	Pre-laser SD = 5.7 Post-laser SD= 6.0	t = 10.2, P < 0.05	Crude	NA

OUTCOME: Patient satisfaction					**OUTCOME TYPE:** Continuous				
	COMPARISON (if applicable): IPL vs. Alexandrite Laser								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Group 1 - Mean (specify if median) in intervention/ exposure group**	**Group 1 - SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Group 2 - Mean (specify if median) or median in control / comparison group**	**Group 2 - SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**P-value**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
McGill, DJ et al. 2007 – 1 (split-face RCT)	Numerical value	Self-reported using linear analogue scale (0= very unhappy, 10 = very happy) -	IPL 3 months, median = 5.1	IPL 3 months, range= 0-10	Alexandrite 3 months, median = 7.8	Alexandrite 3 months, range = 0-10	P<0.001	Crude	NA

		unclear if scale created for purpose of this study only or if used a standardised LAS	6 months, median = 5.1	6 months, range = 0.4-9.6	6 months, median = 7.7	6 months, range = 1.3-9.8			

N.B. McGill et al 2007 – 1 (split-face RCT) reported LAS at 1,3,6 months follow-up - only data for 6 months extracted

OUTCOME: Patient satisfaction								**OUTCOME TYPE:** Continuous	
COMPARISON (if applicable): No comparison - all participants received Alexandrite laser									
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Group 1 - Mean (specify if median) in intervention/ exposure group**	**Group 1 -SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Group 2 - Mean (specify if median) or median in control / comparison group**	**Group 2 - SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**P-value**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
McGill, DJ et al. 2007 – (2-cohort study)	Numerical value	Self-reported using linear analogue scale (0= very unhappy, 10 = very happy - unclear if scale created for purpose of this study only or if used a standardised LAS	Mean 8.5, median 9.2	Nil SD, range 4.6-10			NR	Crude	NA

N.B. McGill et al 2007 – 2 reported overall LAS from post-treatment questionnaire for all patients, not broken into groups

OUTCOME: Pain during treatment					**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Soprano XL laser vs. LightSheer laser									
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Group 1 - Mean (specify if median) in intervention/ exposure group**	**Group 1 -** **SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Group 2 - Mean (specify if median) or median in control / comparison group**	**Group 2 - SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**P-value**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Pai, GS et al, 2011	Numerical value	Self-reported using linear analogue scale (0= no pain, 10 = unbearable pain - unclear if scale created for purpose of this study only or if used a standardised LAS	Soprano XL Median = 2	NR	LightSheer Median =6		P<0.0005	Crude	NA

7. GRADE ASSESSMENTS AND EVIDENCE PROFILE

COMPARISON 1: IPL plus metformin vs. IPL alone												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	IPL + Met	IPL	Effect, fixed [95% CI]	Favours	Certainty	Importance
Outcome: Reduction by 50% in hair count & reduction by 30% in hair diameter												
1	RCT	serious[1]	No serious inconsistency (only 1 study)	No serious indirectness	Serious (Single study & small sample sizes)	none	59.9%	23.3%	P=0.0009	IPL + Met (P=0.0009)	⊕⊕◯◯ LOW	CRITICAL
Outcome: Reduction in hair count												
1	RCT	serious[1]	No serious inconsistency (only 1 study)	No serious indirectness	Serious (Single study & small sample sizes)	none	22	30	End of study Mean (SD) IPL/Metformin 22.14 (SD 10.52) IPL only 29.7 (SD 14.67)	IPL + Met (p=0.044)	⊕⊕◯◯ LOW	CRITICAL
Outcome: Hair width/thickness												
1	RCT	serious[1]	No serious inconsistency (only 1 study)	No serious indirectness	Very Serious (Single study, small sample sizes & not statistically significant)	none	22	30	End of study (Mean & SD) IPL/Metformin 0.075 (SD 0.069) IPL only 0.093 (SD 0.0496)	IPL + Met (p=0.30)	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Improvement in Visual Analog Scale												
1	RCT	serious[1]	No serious inconsistency (only 1 study)	No serious indirectness	Serious (Single study & small sample sizes)	none	22	30	End of study (Mean & SD) IPL/Metformin 52.95 (SD 26.35) IPL only 34.13 (SD 28.15)	IPL + Met (p=0.019)	⊕⊕◯◯ LOW	CRITICAL

[1] **Downgraded once as the majority of evidence is at moderate or high risk of bias**

COMPARISON 2: High-fluence laser vs. low-fluence laser												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	High fluence	Low Fluence	Effect Estimate	Favours	Certainty	Importance
Outcome: Reduction in overall facial hirsutism												
1	RCT	serious[1]	NA	NA	serious[2]	none	44	31	ANCOVA $F_{(1,83)} = 24.5$, $P < 0.05$	High fluence laser ($p<0.05$)	⊕⊕◯◯ LOW	CRITICAL
Outcome: Time spent on hair removal												
1	RCT	serious[1]	NA	NA	serious[2]	none	44	31	$F_{(1,80)} = 10.2$, $P \leq 0.05$	High fluence laser ($p \leq 0.05$)	⊕⊕◯◯ LOW	CRITICAL
Outcome: Depression score												
1	RCT	serious[1]	NA	NA	serious[2]	none	44	31	$F_{(1,83)} = 14.7$, $P < 0<0.05$	High fluence laser ($p<0.05$)	⊕⊕◯◯ LOW	CRITICAL
Outcome: Anxiety score												
1	RCT	serious[1]	NA	NA	serious[2]	none	44	31	$F_{(1,84)} = 17.8$, $P < 0.05$	High fluence laser ($p<0.05$)	⊕⊕◯◯ LOW	CRITICAL
Outcome: Hair free intervals												
1	RCT	serious[1]	NA	NA	serious[2]	none	44	31	$F_{(1,79)} = 28.6$, $P < 0.01$	High fluence laser ($p<0.05$)	⊕⊕◯◯ LOW	CRITICAL
Outcome: WHO quality of life mean scores, psychological domain												
1	RCT	serious[1]	NA	NA	serious[2]	none	44	31	$F_{(1,84)} = 0.0$, $P < 0.05$	High fluence laser ($p<0.05$)	⊕⊕◯◯ LOW	CRITICAL
Outcome: WHO quality of life mean scores, social, physical, environmental domains												
1	RCT	serious[1]	NA	NA	serious[2]	none	44	31	$p>0.05$	None ($p>0.05$)	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Patient satisfaction												
1	RCT	serious[1]	NA	NA	serious[2]	none	44	31	$t = 10.2$, $P < 0.05$	High fluence laser ($p<0.05$)	⊕⊕◯◯ LOW	CRITICAL

[1] downgraded once for risk of bias

[2] Single study, small sample sizes, subjective self-assessment

COMPARISON 3: IPL vs. Alexandrite laser											
	Quality assessment						No. participants				
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Split face (n)**	**Effect, fixed [95% CI]**	**Favours**	**Certainty**	**Importance**
Outcome: Hair count											
1	RCT	Serious[1]	NA	NA	no serious imprecision	none	38	Mean hair count (SD) post mx IPL=28 (SD=3) Alexandrite=20(SD=2)	Alexandrite (p<0.001)	⊕⊕◯◯ LOW	CRITICAL
Outcome: Patient satisfaction Scores											
1	RCT	Serious[1]	NA	NA	no serious imprecision	none	38	Median LAS scores (range) at follow-up IPL = 5.1(0.4-9.6) Alexandrite = 7.7 (1.3-9.8)	Alexandrite (p≤ 0.002)	⊕⊕◯◯ LOW	CRITICAL
Outcome: Hair free interval											
1	RCT	Serious[1]	NA	NA	no serious imprecision	none	38	Median HFI (range) at follow-up IPL = 2 (0-10) Alexandrite = 7 (0-15)	Alexandrite (p<0.005)	⊕⊕◯◯ LOW	CRITICAL

[1] downgraded once for risk of bias

COMPARISON 4: LightSheer Laser only vs. LightSheer Laser & Metformin vs. LightSheer laser & COCP													
	Quality assessment						No. participants						
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Laser**	**Las + MET**	**Las + OCP**	**Effect, fixed [95% CI]**	**Favours**	**Certainty**	**Importance**
Outcome: Improvement in overall hirsutism – visual analog scale													
1	RCT	Serious[1]	NA	NA	No serious imprecision	none	50	50	50	Mean VAS (SD) at 6 months Laser only= 3 (SD=0.6) Laser+Met= 3.2 (SD=0.4) Laser + OCP= 4.2 (SD=0.6)	Laser + OCP	⊕⊕◯◯ LOW	CRITICAL
Outcome: HLQI													
1	RCT	Serious[1]	NA	NA	No serious imprecision	none	50	50	50	Mean HLQI (SD) at 6 months Laser only= 6.5 (SD=2.3) Laser+Met= 4.48 (SD=1.2) Laser + OCP= 1.45 (SD=0.5)	Laser + OCP	⊕⊕◯◯ LOW	CRITICAL
Outcome: DLQI													
1	RCT	Serious[1]	NA	NA	No serious imprecision	none	50	50	50	Mean DLQI (SD) at 6 months Laser only= 5.5 (SD=2.5) Laser+Met= 5.0 (SD=1.2) Laser + OCP= 1.0 (SD=0.6)	Laser + OCP	⊕⊕◯◯ LOW	CRITICAL

[1] downgraded once for risk of bias

COMPARISON 5: Soprano XL laser vs. LightSheer laser											
	Quality assessment						No. participants				
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Split face (n)**	**Effect, fixed [95% CI]**	**Favours**	**Certainty**	**Importance**
Outcome: Reduction in overall facial hirsutism											
1	Cohort study	serious[1]	NA	NA	serious[2]	none	42	Median (SD) Soprano XL 90% (SD=7) LightSheer 85% (SD = 8.5)	Soprano XL (P<0.063)	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Hair width/thickness											
1	Cohort study	serious[1]	NA	NA	serious[2]	none	42	Median Soprano XL = 0.02mm LightSheer=0.05mm	Soprano XL (p<0.0005)	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Pain during treatment											
1	Cohort study	serious[1]	NA	NA	serious[2]	none	42	Median Soprano XL =2 LightSheer=6	Soprano XL (p<0.0005)	⊕◯◯◯ VERY LOW	CRITICAL

[1] downgraded once for risk of bias

[2] median or mean reports, no other measures or nil SD reported

COMPARISON 6: Nd:YAG laser - PCOS vs. Non-PCOS												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	PCOS	Non-PCOS	Effect, fixed [95% CI]	Favours	Certainty	Importance
Outcome: Reduction in hair shaft thickness												
1	Cohort study	Serious[1]	NA	NA	no serious imprecision	none	15/50	35/50	P<0.001	Nd:YAG laser more effective in Non-PCOS patients	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Reduction in hair shaft colour												
1	Cohort study	Serious[1]	NA	NA	no serious imprecision	none	24/50	31/50	P=0.159	None	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Reduction in terminal : vellus hair ratio												
1	Cohort study	Serious[1]	NA	NA	no serious imprecision	none	23/50	34/50	P=0.026	Nd:YAG laser more effective in Non-PCOS patients	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Reduction in hair density per cm^2												
1	Cohort study	Serious[1]	NA	NA	no serious imprecision	none	23/50	34/50	P=0.044	Nd:YAG laser more effective in PCOS patients	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Reduction in overall facial hirsutism												
1	Cohort study	Serious[1]	NA	NA	serious[2]	none	NA	NA	P=0.0423	Nd:YAG laser more effective in PCOS patients	⊕◯◯◯ VERY LOW	CRITICAL

[1] downgraded once for risk of bias

[2] subjective assessment, not standardised

APPENDIX. QUALITY APPRAISAL TABLES

Randomised Controlled Trial #1	
Study ID	Clayton W.J. 2005
Study Citation	Clayton, W. J.; Lipton, M.; Elford, J.; Rustin, M.; Sherr, L. (2005). A randomised controlled trial of laser treatment among hirsute women with polycystic ovary syndrome. British ournal of Dermatology, 2005;152(5):986-992. Doi: 0.1111/j.1365-2133.2005.06426.x
Study Country	UK
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS aged 18 years and over
PCOS diagnostic criteria	Research team did not take part in establishing diagnosis, accepted PCOS diagnosis of specialist colleagues
Presence of infertility	*Not reported*
Presence of other condition/s	*Not reported*
Medication History	*Not reported*
N per group	*Allocated/randomised: 98* Intervention group (high-fluence laser): 51 Control (low-fluence laser): 37 *Assessed at end of study: 75* Intervention group (high-fluence laser): 44 Control (low-fluence laser): 31
Setting	*Department of Dermatology - Recruited from gynaecology, endocrinology and dermatology outpatient departments at a long teaching hospital and from PCOS patient support group called Verity*
Intervention	*High Fluence Alexandrite laser (23.6 J cm^-2), 755nm pulse width 20ms spot size 12.5 (Apogee 6200; Cynosure, Chelmsford, MA, USA), 4-6 weekly for 6 months*
Comparison	*Low fluence Alexandrite laser that was known to be relatively ineffective, but convincing to be used as a control (4.8 J cm ^-2), 755nm pulse width 20ms spot size 12.5 (Apogee 6200; Cynosure, Chelmsford, MA, USA), 4-6 weekly for 6 months*

Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	**Main outcomes:** **1. Self-reported severity of facial hair** **- Scale 1 (least severe) to 10 (most severe)** **2. Self-reported Hair free period (days)** **3. Anxiety and depression scores (measured with Hospital Anxiety and Depression Scale – HADS)** **4. Quality of life (WHOQOL-BREF), scored between 1-5, high scores – higher QoL** **- Psychological health** **- Social relationship** **- Environment** **- Physical health.** Others: **1. Self-esteem** **2. Time spent a week removing hair**	
Follow up Duration	*6 months*	
Summary Result/s	*Laser treatment reduces facial hirsutism severity and reduces time spend on hair removal. Laser treatment also alleviates depression and anxiety in women with PCOS.*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes –* *The study was designed to test the hypothesis that laser treatment would reduce the impact of facial hair and its associated psychological morbidity in women with facial hirsutism*
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	***Yes*** ***1. PCOS, diagnosed by other specialists (endocrinologists, gynaecologists, dermatologists) – not confirmed by researchers*** ***2. Facial hirsutism with dark hair and Fitzpatrick skin types I to pale V***

			3. Suitable for alexandrite laser (assessed by asking potential participants about skin and hair colour & visual examination by clinician)
Exclusion criteria		Yes Partial No Not reported	*Yes* ***1. White, blonde or ginger facial hair*** ***2. Fitzpatrick skin types medium V, dark V and VI*** ***3. Previous laser hair removal*** ***4. Insufficient English to complete questionnaires*** ***5. Age under 18 years***
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Partial* *Participants randomised by the treating physician using a random numbers table, not clear how the randomisation was done.*
	Was allocation to intervention group concealed?	Yes Partial No Not reported	*Yes*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*Yes*
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*Not reported*
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*

DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*No* *All questionnaires based on participant subjective perceptions.*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	*Intervention with high-fluence laser* *7/51 = 14%* *Control with low-fluence laser* *6/37 = 16%*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Yes*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*No* *Did not report on randomisation process*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Yes*

	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Not reported*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*Yes.* *First author and 4th author have a private hair removal practice* *Study was funded by Dermatrust*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*No*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS		*Inadequate method of randomisation, only participants were blinded, physicians assessing however it was inappropriate for physicians to be blinded as they needed to give the right intervention. Conflicts of interest*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Randomised Controlled Trial #2	
Study ID	Dorgham,N 2021
Study Citation	Dorgham, N.; Sharobim, A.; Haggag, H.; El-Kalioby, M.; Dorgham, D. (2021). Adding combined oral contraceptives or metformin to l aser treatment in polycystic ovarian syndrome hirsute patients. Journal of drugs in dermatology: JDD 2021;20(3)302-306. Doi: 10.36849/JDD.5652
Study Country	Cairo, Egypt
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS aged 18-40 years
PCOS diagnostic criteria	Rotterdam
Presence of infertility	*Not reported*
Presence of other condition/s	*Nil – participants with other dermatological and/or systemic diseases were ineligible for inclusion*
Medication History	*No*
N per group	*Allocated/randomised: 150* *Group 1 (laser hair removal only): 50 women* *Group 2 (laser hair removal + metformin 500mg): 50 women* *Group 3 (laser hair removal + COCP Diane-35): 50 women* *Assessed at end of study: 150* *Group 1 (laser hair removal only): 50 women* *Group 2 (laser hair removal + metformin 500mg): 50 women* *Group 3 (laser hair removal + COCP Diane-35): 50 women*
Setting	*Single centre, not otherwise specified*
Intervention	*Group 3: Laser + COCP Diane-35* *Frequency of COCP not specificized, assume daily* *LightSheer DUET; Lumenis, Yokneam, Israel) was applied for hair removal for a total of six initially monthly sessions followed by two follow-up sessions at three and six months after the initial six sessions*

Comparison #1	*Group 2: Laser + 500mg Glucophage metformin hydrochloride – frequency of metformin not specified*	
Comparison #2	*Group 1: Laser only*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	***1. DLQI*** ***2. HLQI*** ***3. Visual analogue scale (subjectively assessed by treating physician)*** ***- 1 = worse*** ***- 2 = no change*** ***- 3 = <30% improvement*** ***- 4 = 30-60% improvement*** ***- 5 = >60% improvement***	
Follow up Duration	*3 & 6 months*	
Summary Result/s	*Combining hormonal treatment with laser hair removal can achieve greater hair reduction, significant improvements in patients' quality of life and better maintenance as compared with when combining metformin with laser hair removal or conducting alone.*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* *The aim was to assess the impact of COCP or metformin to laser hair removal on the quality of life of women with PCOS with hirsutism*
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes	*Yes* ***1. Age 18-40***

		Partial No Not reported	***2. Confirmed PCOS diagnosis according to Rotterdam criteria*** ***3. Facial hirsutism assessed by Ferriman-Gallwey score***
Exclusion criteria		Yes Partial No Not reported	*Yes* ***1. Other dermatological and/or systemic diseases*** ***2. Patients with any contraindications to receiving laser or hormonal treatments (e.g. history of DVT)***
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Yes, an independent person created the allocation sequence using computer-generated random numbers. Allocation was concealed using sequentially numbered, opaque sealed envelopes kept by the attending nurse*
	Was allocation to intervention group concealed?	Yes Partial No Not reported	*Yes*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*No*
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*Not reported*
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*

DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Partial* *Self-reported DLQI and HLQI – standard, valid, and reliable* *Subjective VAS assessment – unclear if same clinician assessed all patients – hence 'partial'*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Partial* *Self-reported DLQI and HLQI – subjectively assessed based on participant perceptions* *Subjective VAS assessment – unclear if same clinician assessed all patients and not reported if clinicians were specifically trained.*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	*Not reported*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Yes*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*No* *Did not specify which clinician assessed VAS, if it was the same clinician or if this clinician had training to assess VAS*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Yes*

	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Not reported*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS		*Adequate randomisation method, but nil blinding for either patients or investigators, outcomes partially reported subjectively/objectively and not all outcomes measured in a standardised method*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*High*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*Yes* *VAS outcome was high risk* *DLQI/HDLQI was moderate risk*	

Randomised Controlled Trial #3	
Study ID	McGill, DJ 2007
Study Citation	McGill, D. J.; Hutchison, C.; McKenzie, E.; McSherry, E.; Mackay, I. R.(2007). A randomised, split-face comparison of facial hair removal with the alexandrite laser and intense pulsed light system. Lasers in surgery and medicine 2007;39(10):767-772. Doi: 10.1002/lsm.20584
Study Country	UK
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS and facial hirsutism, aged 16-69
PCOS diagnostic criteria	Researchers did not attempt to independently establish diagnosis – all patients diagnosed having PCOS prior to referral to study (through gynaecology or endocrinology clinics)
Presence of infertility	*Not reported*
Presence of other condition/s	*Recorded, but not disclosed in paper*
Medication History	*Recorded, but not disclosed in paper*
N per group	*Allocated/randomised: 31, split-face* *Assessed at end of study: 31, split-face*
Setting	*University teaching hospital with patients from gynecology/ endocrinology clinics, Glasgow, UK*
Intervention	*GentleLase Alexandrite laser; 755nm wavelength, 3 millisecond pulse duration* *6-weekly, total of 6 full treatments*
Comparison	*Lumina IPL, 650-1100nm filter - 6-weekly, total of 6 full treatments*
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	***1. Hair counts completed prior and at 1,3- and 6-months following treatment*** ***2. Patient satisfaction questionnaires completed prior at 1,3- and 6-months following treatment*** ***3. Hair free intervals, defined as the time to first hair re-growth (as measured by patient) following each treatment***
Follow up Duration	*1,3- and 6-months following treatment*

Summary Result/s	*The alexandrite laser resulted in significantly longer hair-free intervals, larger reductions in hair counts and greater patient satisfaction than the IPL*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* *The aim was to compare the efficacy of Alexandrite laser with Lumina IPL system on facial hirsutism in women with PCOS*
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* ***1. Diagnosis of PCOS*** ***2. Facial hirsutism comprising brown or black hair*** ***3. Fitzpatrick skin types I-V*** ***4. Age >16 years***
Exclusion criteria	Yes Partial No Not reported	*Yes* ***1. Idiopathic and non-facial hirsutism*** ***2. Patients with blonde, red, grey or white hair*** ***3. Patients aged younger than 16 years***
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS – **Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Yes* *Envelopes were made up randomising IPL treatment to either right or left and alexandrite treatment to the opposite side.* - ***Envelopes opened immediately prior to first treatment***
SELECTION BIAS – **Was allocation to intervention group concealed?**	Yes Partial	*Partial*

		No Not reported	- ***Participants initially received an envelope that randomly allocated which side of face would receive which treatment*** - ***Unable to continue concealment of allocation after this***
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*Not reported*
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes – same participants receiving both treatments*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*Yes* - ***Three experienced members of laser suite were blinded to treatment allocation and independently calculated hair counts from pictures to ensure accuracy***
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes* - ***Hair counts measured under video microscope by members of laser suite*** - ***Patient satisfaction measured on standardised questionnaire***
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Partial* - ***Hair counts measured relatively objectively as there were 3 independent assessors, although paper does not report whether 'experienced members of laser suite' were provided additional training as to video microscopy reading*** - ***Patient satisfaction is subjective***
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	*Not reported*

	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Yes*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Yes*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Not reported*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*Yes* *First author D.J.M disclosed potential financial conflict of interest*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS		*Unclear whether participants were blinded for their intervention. Assessors measuring hair counts were independent and blinded. Split-face and randomly allocated – same patients receiving both treatments so nil differences in patient characteristics.*	

What is the overall risk of bias?	Low Moderate High Insufficient information	*Moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*No*	

Randomised Controlled Trial #4	
Study ID	Rezvanian,H 2009
Study Citation	Rezvanian,H, H.; Adibi, N.; Siavash, M.; Kachuei, A.; Shojaee-Moradie, F.; Asilian, A.)2—0_. Increased insulin sensitivity by metformin enhances intense-pulsed-light-assisted hair removal in patients with polycystic ovary syndrome. Dermatology 2009;218(3):231-236. Doi: 10.1159/000187718
Study Country	UK
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	*Women with PCOS and facial hirsutism*
PCOS diagnostic criteria	Rotterdam
Presence of infertility	*Not reported*
Presence of other condition/s	*Not reported*
Medication History	*Not reported*
N per group	*Allocated/randomised: 70* *Intervention (IPL/Metformin) = 35* *Control (IPL only) = 35* *Assessed at end of study:52* *Intervention (IPL/Metformin) = 22* *Control (IPL only) = 30*
Setting	*Dermatology clinic of St. Al-Zahra Hospital in Iran*

Intervention	*IPL & Metformin* *IPL for 5 laser sessions at 45-day intervals* *500mg Metformin TDS*	
Comparison	*IPL only for 5 laser sessions at 45-day intervals*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	***1. Reduction of hair count*** ***- Self-assessed by patients who also assessed degree of improvement before and after treatment using Visual Analog Scale (0-100%)*** ***2. Reduction in hair width/thickness*** ***3. Degree of hair reduction (50% in hair count and 30% in hair diameter) as determined by dermatologists***	
Follow up Duration	*6 months*	
Summary Result/s	*Hirsutism was significantly better controlled in participants who had combination IPL and metformin vs. IPL only. Patients satisfaction was also significantly better in IPL/Metformin group.*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes* *Does laser hair removal treatment reduce severity of facial hirsutism and reduce psychological morbidity in women with PCOS?*
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	*Ye Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*Yes* ***1. Diagnosis of PCOS based on presence of at least two:*** ***- Oligoanovulation, clinical and/or biochemical signs of hyperandrogenisms and observation of polycystic ovaries on USS*** ***2. Hirsutism defined based on Ferriman-Gallwey score >8.***

Exclusion criteria		Yes Partial No Not reported	*Yes* ***1. Renal and liver dysfunction*** ***2. History of significant CCF*** ***3. Hx of significant alcohol abuse*** ***4. Hx of hyperprolactinemia, ovarian or adrenal tumours*** ***5. Hx of diabetes and congential renal hyperplasia*** ***6. Known Cushing's syndrome*** ***7. Participation in any hair removal program in previous 3 months***
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Partial* *Patients were divided into two groups based on random numbers table, but not clear how the randomisation was done.*
	Was allocation to intervention group concealed?	Yes Partial No Not reported	*Not reported*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*Not reported*
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No	*Not reported*

		Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes* *Self-assessment of patient perception for hirsutism improvement assessed on standardised questionnaire* *Hair counts/width assessed under videomicroscopy* *Degree of hair reduction assessed by dermatologist's consensus = not standard, not reliable/replicable*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*No* *Subjective participant self-assessment for degree of improvement* *Hair thickness assessed under microscopy, although not reported who counted/who measured and if they received additional training*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	*Intervention (IPL/Metformin) = 13/35 = 37.1%* *Control (IPL only) = 5/35 = 14.3%*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Yes*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*No* *Information regarding blinding and allocation not reported, not reported who assessed hair count, or how the dermatologist assessed degree of hair reduction overall.*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Yes*

	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Not reported*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*Not reported*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS		*Many missing fields re: method of randomisation, blinding & allocation, outcomes (particularly hair count measurement) not adequately reported*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*High*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

COHORT STUDIES

Cohort study #1		
Study ID	*Karn,D 2014*	
Study Citation	Karn, D.; K C, S.; Timalsina, M.; Gyawali, P. (2014). Hormonal profile and efficacy of long pulse Nd-YAG laser in treatment of hirsutism. Journal of Nepal Health Research Council, 2014; 12(26):59-62. Doi: 10.33314/jnhrc.v0i0.440	
Study Country	*Nepal*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women PCOS and women without hyperandrogenism or US findings of PCOS (controls)* *Age= Overall 27.9 ±9.6 years* *BMI= 63% of patients had BMI>25*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	*The number of participants that were:* ○ ***Screened = Not reported*** ○ ***Enrolled = 60*** ○ ***Allocated/randomised: PCOS= 30, controls= 30*** ○ ***Assessed (duration not specified): PCOS=30, controls= 30*** ○ ***Followed up = not reported***	
Setting	Department of dermatology, Dhulikhel Hospital Kathmandu University Hospital, Dhulikhel, Nepal.	
Intervention/ indicator	All patients received 1064nm longpulse Nd-YAG laser with 50 J/cm^2 energy and 50 msec pulse duration. Laser therapy was repeated every four weeks and number of settings was noted for substantial hair reduction.	
Comparison/ Control	*N/A*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	***1.*** **Number of laser treatment sessions required to reach more than 50% reduction in hair count** - ***Method of measurement to determine 50% reduction not specified***	
Inclusion criteria reported?	*Yes*	*PCOS based on having both and ultrasonographic findings "*had high androgen (total testosterone and dehydroepiandrosterone sulfate) or elevated LH: FSH ratio consistent with PCOS "Every patient underwent abdomino-pelvic ultrasound to meet the diagnosis of PCOS using Rotterdam's Criteria and adrenal tumor was ruled out among all
Exclusion criteria reported?	Yes Partial No	*Partial* - **USS to rule out adrenal tumour, nil other explicit exclusion criteria reported**

	Not reported	
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Partial* - Only inclusion criteria explicitly reported, partial exclusion criteria as noted above.
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	Duration of follow-up not reported, only reported on number of sessions needed to reach 50% reduction in facial hirsutism, timeframe not specified
Was matching performed?	Yes Partial No Not reported	*No*

Summary of Result/s		*Patients with PCOS require more laser treatment sessions compared to patients without PCOS to achieve at least 50% reduction in hair count*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	*Yes*	
	Was the exposed cohort truly representative?	Yes Partial No Not reported	*Method of participant recruitment not reported*
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	*Yes – all patients had hirsutism prior to start of study*
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No	*Method of measuring 'reduction in 50%' facial hirsutism not reported.*

		Not reported	
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Not reported*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	*0%*	*All participants included in final analysis*
	What percentage of the individuals were not included in the analysis?	*0*	*As above*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	No. Method of measuring hair reduction/baseline not reported, physician/person conducting laser not reported, timeframe of laser sessions not reported. Patient baseline characteristic not reported.
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	*Not reported – patient baseline characteristics not reported or compared*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*

	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS		Many fields not further reported in paper, would not be able to replicate study.	
What is the overall risk of bias?		*High*	*Nil specification of why 50% reduction in hair loss was the primary measure outcome, unclear where or how participants were recruited, unclear who assessed 50% reduction, against which measure and if they received specific training and if this was the same person assessing all participants*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Cohort study #2	
Study ID	*McGill DJ, 2007*
Study Citation	McGill, D. J.; Hutchison, C.; McKenzie, E.; McSherry, E.; Mackay, I. R. (2007). Laser hair removal in women with poilycystic ovary syndrome. Journal of plastic, reconstructive & aesthetic surgery: JPRAS 2007;60(4):426-31. doi :10.1016/j.bjps.2006.11.006
Study Country	*UK*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*60 women with PCOS* *Age = 24 years (range 17-72)* *BMI = Not reported*
PCOS diagnostic criteria	*PCOS diagnosis not established by researchers, diagnosis accepted from referring specialist colleagues*
N per group	*The number of participants that were:* ○ ***Screened = Not reported*** ○ ***Enrolled = 60*** ○ ***Allocated/randomised: NA*** ○ ***Assessed***

	- ***37/60 patients assessed for pre- and post-treatment hair counts*** - ***All 60 patients assessed for hair-free intervals*** ○ ***Followed up = 43/60 completed the post-treatment follow-up questionnaire***	
Setting	*New referrals to hospital department, not otherwise specified*	
Intervention/ indicator	All participants treated with a 755nm GentleLase Alexandrite Laser (Candela Corp., Wayland, MD, USA). Initial patch test and then 6 treatments at 6 weekly intervals – then maintenance treatment as required	
Comparison/ Control	*N/A*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	***1. Hair counts*** ***- Measured using videomicroscope, independently counted by 3 laser nurse practitioners with a 4th practitioner in the case of discrepancies*** ***2. Hair-free interval following each treatment*** ***- Self-reported measurements by patients of the time to new facial hair growth following treatment*** ***3. Patient Satisfaction questionnaires***	
Inclusion criteria reported?	*Yes*	***1. Diagnosis of PCOS (as diagnosed by other specialists)*** ***2. Facial hirsutism comprising brown or black hair*** ***3. Fitzpatrick skin types I-V*** ***4. Age >16***
Exclusion criteria reported?	Yes Partial No Not reported	*Yes* ***1. Idiopathic and non-facial hirsutism*** ***2. Patients with blonde, grey or white hair*** ***3. Patients under age of 16***
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*

If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?		Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Partial – patients followed up for maintenance laser treatments but unclear what this follow-up time period was*
Was matching performed?		Yes Partial No Not reported	*No – NA*
Summary of Result/s		*Women with PCOS experience poorer than expected reduction in hair and HFI following laser treatment and more than 6 laser treatment sessions may have prolong HFI and overall patient satisfaction*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	*NA*	*NA*
	Was the exposed cohort truly representative?	Yes Partial No Not reported	*Partial* *Severity of hirsutism not reported, only captured women with access to hospital outpatient setting of non-specified department.*
	Is it clear that the outcome of interest was not	Yes Partial	*Yes* *All patients prior to study commencement had hirsutism*

	present at the start of study?	No Not reported	
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes.*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*No*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes* □ **Hair counts** - ***Measured using videomicroscope, independently counted by 3 laser nurse practitioners with a 4th practitioner in the case of discrepancies*** □ **Hair-free interval following each treatment** - ***Self-reported measurements by patients of the time to new facial hair growth following treatment – standardised questionnaire designed for the purpose of this study*** □ **Patient Satisfaction questionnaires, *standardised survey designed for the purpose of this study***
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Partial – all outcomes assessed independently, however questionnaires for HFI and satisfaction were subjective*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	*Overall = 17 (28.3%)*	*17/60 patients lost to follow-up patient satisfaction survey*

	What percentage of the individuals were not included in the analysis?	*0*	*All patients included in the analysis*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Yes
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	*NA*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*Not reported*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Yes*
COMMENTS			
What is the overall risk of bias?		*Moderate*	*HFI and patient satisfaction were subjectively assessed*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*Yes:* *Low RoB for outcome re: reduction in hair count* *Moderate RoB for outcome re: HFI and patient satisfaction which were assessed on a survey designed only for this study and patients may not have accurately counted HFI/HFI counting may differ between patients*	

Cohort study #3		
Study ID	*Nabi,N 2022*	
Study Citation	Nabi, N.; Bhat, Y. J.; Dar, U. K.; Hakeem, A.; Mir, S. A.; Shah, I. H.; Tilwani, M. R. (2022). Comparative study of the clinic-trichoscopic response to treatment of hirsutism with long pulsed (1064nm) Nd:YAG laser in idiopathic hirsutism and polycystic ovarian syndrome patients. Lasers in medical science 2022;37(1):545-553. Doi: 10.1007/s10103-021-03295-0	
Study Country	*India*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with PCOS-related hirsutism and idiopathic hirsutism (controls)* *Age= PCOS: median 28.5± 9.72 years, controls: median 33.6±11.69 years* *BMI= not reported*	
PCOS diagnostic criteria	*Androgen Excess Society (AES)=PCOS Society guidelines (2006)*	
N per group	*The number of participants that were:* ○ ***Screened = Not reported*** ○ ***Enrolled = 100*** ○ ***Allocated/randomised: PCOS= 50, controls= 50*** ○ ***Assessed): PCOS= 50, controls= 50*** ○ ***Followed up = all participants***	
Setting	*Outpatient dermatology department in a non-specified hospital*	
Intervention/ indicator	Nd: YAG laser with wavelength of 1064nm (Gentle YAGTM,Candela Corporation, Boston, USA). For a total of 6 sessions	
Comparison/ Control	*N/A*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	***1. Efficacy of hair reduction – based on interval changes from trichoscopic images taken before each session and at follow-up of 3 months*** ***- Graded on a 4-point visual scale (poor -> excellent)*** ***- Poor = <25% reduction in hair from baseline*** ***- Fair <25-50% reduction in hair from baseline*** ***- Good <50-75% reduction in hair from baseline*** ***- Excellent >75% reduction in hair from baseline*** ***2. Effect of laser on trichoscopic features*** ***- Measured via tracheoscopy counted in a 1*1cm^2 cardboard window in a fixed area of the face (the chin)*** ***- Hair shaft thickness, hair shaft colour, terminal vs. vellus hair ratio, decrease density of hair per cm^2***	
Inclusion criteria reported?	*Yes*	***1. PCOS*** ***2. Facial hirsutism in patients presenting to outpatient department*** ***3. Age >18 years***

Exclusion criteria reported?	Yes Partial No Not reported	*Yes* ***1. Patients with fine, vellus hair (mFG score <8)*** ***2. Previous laser treatment to study area*** ***3. Gross hormongl dysfunction (not further defined0*** ***4. Chemical epilation of electrolysis within 6 weeks*** ***5. Associated photo-aggravated diseases*** ***6. Active skin infection*** ***7. History of keloid scarring*** ***8. Pregnancy/lactation*** ***9. Patients on immunosuppressants, oral hormonal treatment, anti-androgens, insulin sensitisers***
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No	*No – only followed up for 3 months even though full results from laser removal can be seen at 6 months, described in other comparative studies*

		Not reported	
Was matching performed?		Yes Partial No Not reported	*No*
Summary of Result/s		*Patients with PCOS-associated hirsutism have poorer response to Nd:YAG laser compared to patients with idiopathic hirsutism*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	*Yes*	
	Was the exposed cohort truly representative?	Yes Partial No Not reported	*No* *Only participants who attended this specific hospital and who were referred to a dermatology outpatient department were included, does not account for women with hirsutism who may never be referred to a dermatologist for management of hirsutism*
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	*Yes – all patients had hirsutism prior to study commencement*
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Partial* *4-point visual scale was assessed based on physician's subjective assessment, unclear if it was a single physician assessing this and whether they received specific training to assess.* *Also unclear who counted the number of hairs/assessed trichosocpic features and whether they received additional training as well.*

	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Partial – both outcomes measured in a valid way* - ***VAS = subjective based on physician assessment*** - ***Unclear how trichoscopic features measured***
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Not reported*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	*Not reported*	*Not reported*
	What percentage of the individuals were not included in the analysis?	*Not reported*	*As above*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Partial – did not report on who was assessing either outcome, if these were the same people for all patients.*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	*Not reported – participant baseline characteristics not recorded or compared*

OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	*Would not be able to replicate study based off of this paper.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Cohort study #4	
Study ID	*Pai, GS 2011*
Study Citation	Pai, G. S.; Bhat, P. S.; Mallya, H.; Gold, M. (2011) Safety and efficacy of low-fluence, high-repetition rate versus high-fluence, low-repetition rate 810-nm diode laser for permanent hair removal A split-face comparison study. Journal of Cosmetic and Laser Therapy 2011;13(4):134-137. Doi: 10.3109/14764172.2011.594057
Study Country	*USA*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with PCOS and facial hirsutism* *Age= 18 years +, not otherwise specified* *BMI= Not specified*
PCOS diagnostic criteria	*PCOS confirmed by ultrasonography*
N per group	*The number of participants that were:* ○ ***Screened = not reported*** ○ ***Enrolled = 51*** ○ ***Allocated/randomised: NA – split-face*** ○ ***Assessed = 42***

	○ ***Followed up = Not reported***	
Setting	*USA not otherwise specified*	
Intervention/ indicator	1 side of face: Low-fluence but high-repetition laser with Soprano® XL (Alma Lasers Ltd, Caesarea, Israel) in SHR mode using a technique of maintaining the handpiece in constant motion, with a fluence up to 10 J/cm^2, 10 Hz, and a 20-ms pulse duration as recommended by the manufacturers. Subjects treated 6 times at intervals of 4-6 weeks	
Comparison/ Control	Other side of face treated with high fluence, single-pass Light- SheerTM (Lumenis, Inc., Santa Clara, CA, USA) using a conventional single-pass fluence to tolerance (25–35 J/cm^2), 2 Hz, and a 30-ms pulse duration (which was the pulse width found safest in our patient population based on past experiences on skin types IV and V). Subjects treated 6 times at intervals of 4-6 weeks	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	**1. Hair count** **- Measured in 2x2cm area using hair analysis system SIF-1 for accuracy** **2. Hair density** **- Measured in 2x2cm area using hair analysis system SIF-1 for accuracy** **3. Pain during treatment** **- Measured subjectively by patients on a 0-10 visual analog scale (0=no pain, 10=unbearable pain)**	
Inclusion criteria reported?	*Yes*	*PCOS based ultrasonographic findings of polycystic ovaries*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes* ***1. Patients with obvious skin disease*** ***2. Patients with history of chronic skin disease other than moderate facial acne vulgaris, keloidal or hypertrophic scar tendency*** ***3. Skin types I,II,III and VI*** ***4. Severe photosensitivity*** ***5. Pregnant patients***
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*

Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*No – outcomes only assessed at the end of the 6th laser session, not followed-up to assess long-term effects "The subjects were treated six times at intervals of 4–6 weeks with each device to permit hair regrowth and mimic real-life laser hair removal." Nil further elaboration on follow-up or total duration of treatment*
Was matching performed?		Yes Partial No Not reported	*NA*
Summary of Result/s		*Low-fluence with high-repetition laser resulted in statistically insignificant increase in hair reduction compared to high-fluence laser but did show significant reduction in hair thickness and a low pain score*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	*NA*	*NA*
	Was the exposed cohort truly representative?	Yes Partial No Not reported	*No* *Participants recruited only included women with PCOS with ultrasonographic findings – nil biochemical markers reviewed or considered in the inclusion criteria*
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	*Yes – all participants had hirsutism prior to study commencement*
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA – split-faced study, same participants received both treatments*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes* - Baseline hair density and final hair counts after the sixth session were made within a predetermined square-shaped area (2x2 cm^2 area from the tip of the ear lobule to the jaw line) by using the hair analysis system SIF-1 for accuracy. Pain scores measured on a standardised visual analog scale (0-10)
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No	*Partial* Subjective pain scores reported by patients, not objective

		Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	*NA*	*Nil follow-up reported*
	What percentage of the individuals were not included in the analysis?	*17.65%*	*9 additional patients were enrolled but did not finish the protocol and were excluded from the results*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Partial* - ***Not reported who counted hair density***
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	*NA – split faced study, all participants received both treatments*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*Yes, Dr Gold speaks on behalf of Alma Lasers and Lumenis*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	*No blinding of either participants or assessors, and no follow-up. Results from after the 6th laser session analysed. Will never know if this is true in the longterm 3-6 months.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 4

Question 4.8.

Are mechanical laser and light therapies for hair reduction, alone or in combination with other therapies, effective for management of hirsutism in adolescents and adults with PCOS?

BACKGROUND:

Hirsutism, in particular facial hirsutism, is a distressing symptom of hyperandrogenism in women with PCOS at any age (see Chapter 1: Screening, diagnostic assessment, risk assessment and life-stage). Actually, excessive hair growth may display a negative impact on emotional wellbeing and QoL (see section 2 on emotional wellbeing). Cosmetic and COCP are considered first-line treatment for hirsutism in women, including in PCOS (1).

Several forms of mechanical hair removal are commonly used by women with PCOS with the aim to limit hirsutism including shaving, waxing, pharmacological topical treatments (eg. Eflornithine hydrochloride cream (2).

Selective thermolysis has revolutionised the approach to mechanical hair removal, as it was reported to be effective and safe. Different devices are commercially available: Intense Pulsed Light technology, long-pulsed ruby (694 nm), long-pulsed alexandrite (755 nm), diode (800–980 nm), and long-pulsed Nd:YAG (1064 nm) (3).

Laser hair removal is extensively practiced with advanced technology in clinics. Laser hair removal beams highly concentrated light onto hair follicles, with the pigment absorbing the light. The light energy is converted to heat, which destroys hair follicles, inhibiting or delaying future hair growth. Intense Pulsed Light (IPL) systems work on the same principles as lasers in that light energy is absorbed into particular target cells with colour (chromophores) in the skin. The light energy is again converted to heat energy, which causes damage to the specific target area. IPL systems are different to lasers in that they deliver many wavelengths (or colours) in each pulse of light instead of just one wavelength. The effectiveness differs based on the skin/hair colour, which introduces a degree of variability in the response to treatment, depending upon ethnicity and/or subjective characteristics (4).

Due to the high priority given to clinical hyperandrogenism outcomes during guideline development and revision, this clinical question was prioritised. A total of 8 studies (4 RCTs and 4 prospective cohort studies) on selective thermolysis techniques were selected based on appraisal criteria established a priori in the PICO question. We did not identify any specific evidence in adolescents with PCOS (age range of studies participants 16-79 years). No further studies on other forms of mechanical hair removal (shaving, waxing) were retrieved.

GRADE EVIDENCE CERTAINTY	
Comparison	**GRADE for critical outcomes**
o **Comparison 1:** IPL plus metformin vs. IPL alone	⊕○○○ VERY LOW
o **Comparison 2:** High-fluence laser vs. low-fluence laser (effectively placebo)	⊕○○○ VERY LOW
o **Comparison 3:** IPL vs. Alexandrite laser	⊕⊕○○ LOW
o **Comparison 4:** LightSheer Laser only vs. LightSheer Laser & Metformin vs. LightSheer laser & COCP	⊕⊕○○ LOW
o **Comparison 5:** Soprano XL laser vs. LightSheer laser	⊕⊕○○ LOW
o **Comparison 6:** Nd:YAG laser - PCOS vs. Non-PCOS	⊕⊕○○ LOW

Evidence to Recommendations Framework

COMPARISONS (option versus other option)

Laser (high fluence) vs no laser
Intense Pulse light plus metformin vs Intense Pulse Light alone
High Fluence laser vs Low Fluence laser
Intense Pulse Light vs. Alexandrite laser
Laser (HF)alone vs Laser (HF) plus metformin vs Laser (HF) plus COCP
Laser in PCOS vs laser in non PCOS

EVIDENCE-BASED RECOMMENDATION(S)

- **EBR:** Mechanical laser and light therapies should be considered for reducing facial hirsutism and for related depression, anxiety and quality of life in women with PCOS.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

- **EBR:** A greater number of laser treatment sessions may be required in women with PCOS, compared to women with idiopathic hirsutism, to achieve hair reduction.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

- **CR:** Adverse effects appear limited in the hands of experienced and suitably qualified providers, and women should be encouraged to seek hair reduction therapies from such providers.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

PRACTICE POINT(S)

- **PP:** Where laser hair removal is prescribed, the following need to be considered:
  - Wavelength and delivery of laser treatment varies by skin and hair colour
  - Laser is relatively ineffective in women with fair skin and blond, grey or white hair
  - The addition of COCP, with or without anti-androgens, to laser treatment may provide greater hair reduction and maintenance
  - Low and high fluence laser appear to have similar efficacy in reducing facial hair, while low fluence laser has reduced associated pain

- **PP:** Hair removal with Intense Pulse Light (IPL) could be considered, albeit benefits may be less pronounced compared to laser treatment. There is no evidence on home-based IPL kits.

- **PP:** Policy makers should consider funding this evidence-based effective therapy for women with PCOS to alleviate distressing symptoms of hirsutism, and related negative impact on quality of life, body image and psychological health.

GRADE CONSIDERATIONS

Justifications:
Based on three studies, women with PCOS may experience poorer than expected reduction in hirsutism compared with women who have idiopathic hirsutism (women without PCOS) after mechanical hair removal. Nevertheless, overall, the studies reported reduction of facial hair, less time spent on hair removal and improvement of depression, anxiety and psychological quality of life. We found a high heterogeneity in methods of treatment, treatment schedules and methods for efficacy assessment. Just one study reported data on pain during the procedure, documenting the worst pain VAS score in high fluence compared with low fluence laser. However, the undesirable effects, when reported, were mild and on balance, evidence was felt to probably favour laser use in hirsute PCOS women.

Subgroup considerations:
- Most studies excluded specific skin or hair colours
- Ethnicity/skin colour: Studies were conducted in the UK, India, Iran, Nepal. No subgroups based on skin colour were specifically identified. In one study white, blonde or ginger facial hair were considered exclusion criterion
- Pregnant women with PCOS: this was not addressed
- Adolescent and postmenopausal women: not specifically addressed

Implementation considerations:
Whilst the laser was most effective, it may not be applicable in all settings due to cost, availability of equipment and adequately qualified practitioners.
Policy makers will need to implement funding to support permanent hair reduction therapy for women with PCOS.
IPL whilst not as effective could be considered for treatment if more accessible and more affordable. The addition of other PCOS therapies may improve control of hirsutism and the woman's satisfaction

Monitoring and evaluation considerations:
Monitor equitable access to affordable services with appropriately qualified practitioners.
Patient satisfaction (including psychological aspects), hair free intervals following each treatment.
Adverse effects should be monitored.

Research priorities:
COCP alone or COCP + antiandrogens vs laser
Feasibility and efficacy of laser treatment of hirsutism in different age subgroups
Feasibility and efficacy of laser treatment of hirsutism in breastfeeding women
More clarity on best laser treatment by skin type (given the heterogeneity of skin types in the studies)
Evaluation of laser efficacy in general body areas other than face.
Adverse events and side effects should be reported.
Cost effectiveness of laser treatment

GRADE framework

GRADE DECIDE **Interactive Evidence to Decision Framework**

● DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

● UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

● CERTAINTY OF THE EVIDENCE

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☐ Very low	☒ Low	☐ Moderate	☐ High

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Individual outcomes and studies have low grades of evidence however taken together evidence is stronger.

● VALUES

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☐ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☒ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Research evidence:

No research evidence was identified

Panel discussion:

It is acknowledged that different stakeholders may value the outcome differently.

Facial hirsutism is considered one major concern for PCOS women.

● BALANCE OF EFFECTS

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:

Based on evidence

● COSTS

How large are the resource requirements (costs)?

Judgement:

☐ Don't know	☐ Varies	☐ Large costs	☒ Moderate costs	☐ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:

No research evidence was identified

Panel discussion:

Women currently pay for their own permanent hair reduction treatment. If implemented, the recommendation will shift some of those costs to other payers and if use is increased costs may be moderate to large including training and expanding the workforce.

● CERTAINTY OF COST EVIDENCE

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

No research evidence was identified

Panel discussion:

No evidence.

● COST-EFFECTIVENESS

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

No research evidence was identified

Panel discussion:

No data available

● EQUITY

What would be the impact on health equity?

Judgement:

☐ Don't know	☒ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☐ Probably increased	☐ Increased

Research evidence:

No research evidence was identified

Panel discussion:

No data available, but probably laser technology could be poorly accessible in some socio-economic environments or in countries with limited health resources.

High personal costs.

● ACCEPTABILITY

Is the option acceptable to key stakeholders?

Judgement:

☐ Don't know	☒ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

High value for women but challenging for funders.

● FEASIBILITY

Is the option feasible to implement?

Judgement:

☒ Don't know	☐ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Will need funding to implement.

REFERENCES:

1. Lizneva D, Gavrilova-Jordan L, Walker W, Azziz R. Androgen excess: Investigations and management. Best Pract Res Clin Obstet Gynaecol. 2016 Nov;37:98-118. doi: 10.1016/j.bpobgyn.2016.05.003. Epub 2016 May 19. PMID: 27387253.

2. Cahill D. PCOS. BMJ Clin Evid. 2009 Jan 15;2009:1408. PMID: 19445767; PMCID: PMC2907777.

3. Sadighha A, Mohaghegh Zahed G. Meta-analysis of hair removal laser trials. Lasers Med Sci. 2009 Jan;24(1):21-5. doi: 10.1007/s10103-007-0515-1. Epub 2007 Nov 20. PMID: 18027066.

4. Vaidya T, Hohman MH, Kumar D D. Laser Hair Removal. 2022 Aug 29. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–. PMID: 29939638.

PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by ECR Lead: Jamie Laura Benham

Other team members: Kathryn Corbett, Jennifer Yamamoto

Supervised, edited and supported by the Evidence Team (Aya Mousa, Jillian Tay)

GDG 4

Question 4.9.

In adults and adolescents with PCOS, is bariatric surgery effective for management of hormonal and clinical PCOS features and weight?

1. SELECTION CRITERIA

Table 1. PICO Criteria for Inclusion – Not to be adapted
To be used by evidence team to decide which studies will be included when screening search results.

Question	Q 4.9 In adults and adolescents with PCOS, is bariatric surgery effective for management of hormonal and clinical PCOS features and weight?
Clinical leads (key contacts)	**Non-reproductive outcomes** **Prof Terhi Piltonen** Obstetrician-Gynaecologist, Reproductive endocrinologist Oulu University Hospital, University of Oulu, Finland terhi.piltonen@oulu.fi **Prof Bulent Yildiz** Endocrinologist Hacettepe University, Turkey byildiz@hacettepe.edu.tr **A/Prof Jacqueline Boyle** Obstetrician-gynaecologist Monash University, Australia Jacqueline.Boyle@monash.edu **Prof Wendy Brown** Bariatric surgeon Monash University, Australia wendy.brown@monash.edu **Reproductive outcomes** **Prof Rong Li** Obstetrician-gynaecologist Reproductive Medical Centre, Peking University Third Hospital, China roseli001@sina.com
Allocation ranking	Level 1- New systematic review

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(language, year)*
Inclusion	Adults and adolescents with PCOS (NIH or Rotterdam criteria)	Bariatric surgery Metabolic surgery Gastric bypass Sleeve gastrectomy Gastric banding	No surgery Medical therapy	Menstrual cycles Hirsutism Total testosterone Free testosterone AMH SHBG BMI Adverse events Pregnancy outcomes Fertility outcomes (from GDG5): Live birth rate, pregnancy rate (biochemical or clinical ultrasound), ovulation, single and multiple pregnancies, miscarriage rate, other adverse events, quality of life, cost effectiveness. Weight Lipids (LDL, HDL, TG, cholesterol) Glucose Insulin Hba1c T2DM Hypertension	Systematic reviews Evidence-based guidelines Comparative cohort studies (can include cross sectional or case control if it compares PCOS and non-PCOS) RCTs	English language
Exclusion	Adults and adolescents without diagnosis of PCOS.	Placebo, no intervention.	Any intervention than those listed in the inclusion criteria.	None.	Non-evidence based guidelines, non-systematic reviews, case reports	None.

2. SEARCH STRATEGY

Table 2.1. Search details

Evidence source	Date of search
Medline (Ovid)	August 12, 2022
PsychInfo (Ovid)	August 12, 2022
EMBASE (Ovid)	August 12, 2022
All EBM (Ovid)	August 15, 2022
Cochrane (Reviews, Trials)	August 15, 2022
CINAHL	August 12, 2022

Table 2.2. Questions addressed by this search *(add more rows as needed)*:

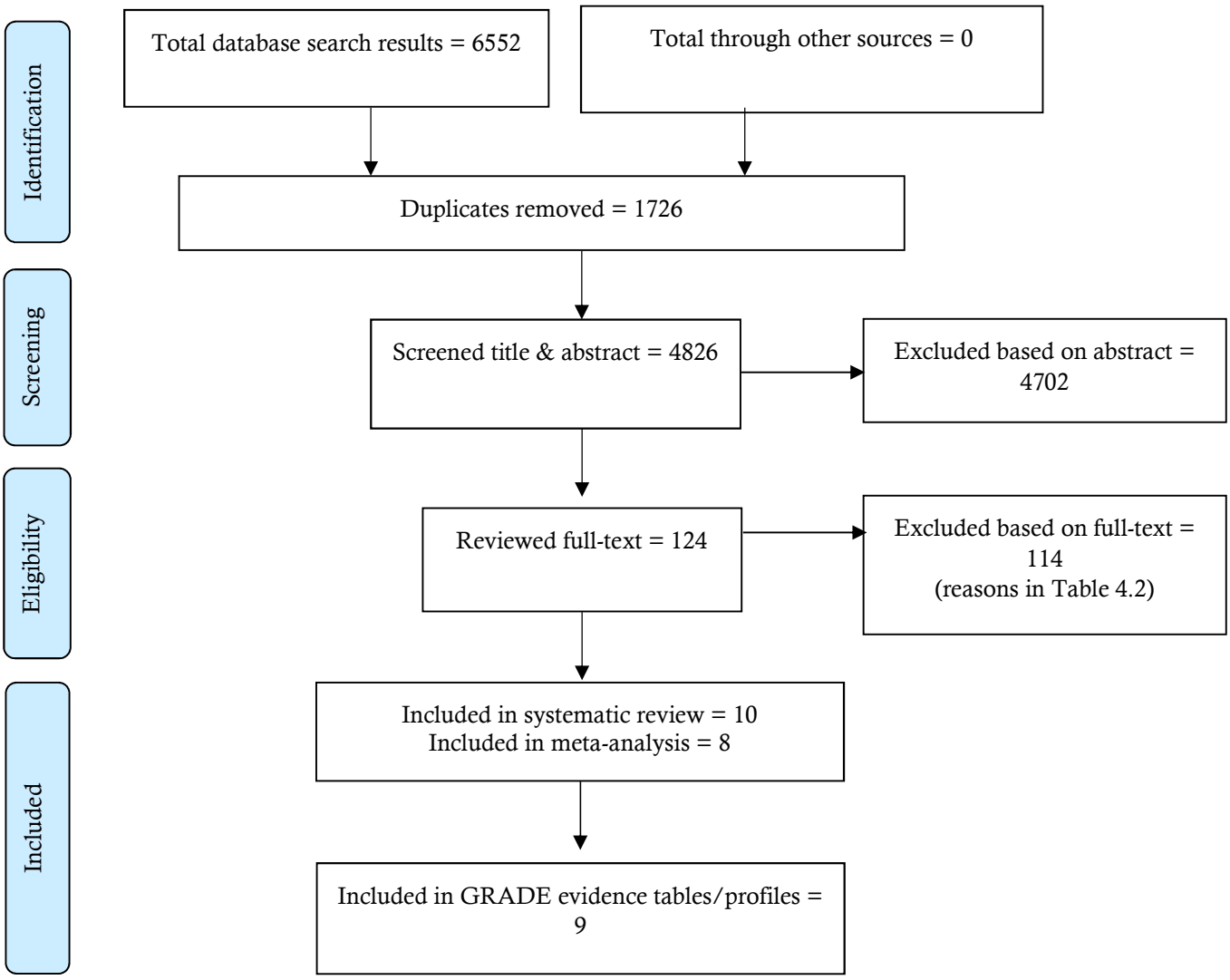
GDG	Q#	Question
4	9	In adults and adolescents with PCOS, is bariatric surgery effective for management of hormonal and clinical PCOS features and weight?

Table 2.3. Search strings used in OVID or other database/s

OVID Medline, All EBM, PsychInfo, EMBASE (results=6552)	CINAHL	Cochrane
1 polycystic ovary syndrome.tw. 2 pco*.tw. 3 stein-leventhal.tw. 4 anovulat*.tw. 5 oligoovulat*.tw. 6 polycyst*.tw. 7 sclerocyst*.tw. 8 Hyperandrogen*.tw. 9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 10 Laparoscop*.tw. 11 Gastroplast*.tw. 12 Gastric Bypass.tw. 13 Bariatric Surgery.tw. 14 surger*.tw. 15 Jejunoileal Bypass.tw. 16 Surgical Stapl*.tw. 17 Gastrect*.tw. 18 Biliary Tract Surgical Procedure*.tw. 19 Gastric Balloon.tw. 20 Biliopancreatic Diversion.tw. 21 Lipectom*.tw. 22 Gastroenterostom*.tw. 23 vagotom*.tw. 24 roux-en-y.tw. 25 lap-band.tw. 26 (gastr* adj3 (band* or imbrication* or plication* or sleeve or stapl* or resection* or reduction* or stimulation)).tw. 27 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 28 9 and 27	Same	Same

Evidence processing: Studies were selected and appraised by two reviewers in consultation with the evidence team/key contact using study selection and appraisal criteria (PICO above) established a priori. The articles were reviewed by title and abstract by 2 reviewers. When a decision could not be made based on title and abstract alone, full text was retrieved. Study appraisal was conducted by two reviewers independently and all conflicts were resolved by consensus. In total, 10 studies met the inclusion criteria for this review.

3. SEARCH RESULTS - PRISMA flowchart



4. STUDY INCLUSION

Table 4.1. Included Studies (full citation with doi)
Abiad, F., Khalife, D., Safadi, B., Alami, R., Awwad, J., Khalifeh, F., & Ghazeeri, G. (2018). The effect of bariatric surgery on inflammatory markers in women with polycystic ovarian syndrome. *Diabetes and Metabolic Syndrome: Clinical Research and Reviews*, 12(6), 999-1005. https://dx.doi.org/10.1016/j.dsx.2018.06.013
Ahmed, B., Ammori, B.J., Akhtar, K., Senapati, S., New, J.P., & Syed, A.A. (2022). Weight loss and metabolic outcomes in women with or without polycystic ovarian syndrome after Roux-en-Y gastric bypass: A case-matched study. *The Surgeon: Journal of the Royal Colleges of Surgeons of Edinburgh and Ireland*, 20(3), 137-141. https://dx.doi.org/10.1016/j.surge.2021.02.012
Benito, E., Gomez-Martin, J.M., Vega-Pinero, B., Priego, P., Galindo, J., Escobar-Morreale, H.F., & Botella-Carretero, J.I. (2020). Fertility and pregnancy outcomes in women with polycystic ovary syndrome following bariatric surgery. *Journal of Clinical Endocrinology and Metabolism*, 105(9), E3384-E3391. https://dx.doi.org/10.1210/clinem/dgaa439
Bhandari, S., Ganguly, I., Bhandari, M., Agarwal, P., Singh, A., Gupta, N., & Mishra, A. (2016). Effect of sleeve gastrectomy bariatric surgery-induced weight loss on serum AMH levels in reproductive aged women. *Gynecological Endocrinology*, 32(10), 799-802. https://dx.doi.org/10.3109/09513590.2016.1169267
Buyukkaba, M., Turgut, S., Ilhan, M. M., Ekinci, I., Yayllm, I., Zeybek, S. U., Turan, S., Tasan, E., & Karaman, O. (2021). Anti-Mullerian Hormone Levels Increase after Bariatric Surgery in Obese Female Patients with and Without Polycystic Ovary Syndrome. *Hormone and Metabolic Research,* 54(3), 194-198. https://dx.doi.org/10.1055/a-1756-4798
Cai, M., Gao, J., Du, L., Cheng, X., Zhou, D., Zhu, J., Qu, S., & Zhang, M. (2021). The Changes in Body Composition in Obese Patients with Polycystic Ovary Syndrome After Laparoscopic Sleeve Gastrectomy: A 12-Month Follow-Up. *Obesity Surgery*, 31(9), 4055-4063. https://dx.doi.org/10.1007/s11695-021-05496-6
Casals, G., Andreu, A., Barral, Y., Ventosa, S., Redondo, M., Torres, F., Ibarzabal, A., Manau, D., Carmona, F., Vidal, J., & Flores, L. (2021). Bariatric Surgery on Reproductive Outcomes: the Impact According to the Diagnosis of Polycystic Ovarian Syndrome and Surgical Procedures. *Obesity Surgery,* 31(6), 2590-2598. https://dx.doi.org/10.1007/s11695-021-05297-x
Chiofalo, F., Ciuoli, C., Formichi, C., Selmi, F., Forleo, R., Neri, O., Vuolo, G., Paffetti, P., & Pacini, F. (2017). Bariatric Surgery Reduces Serum Anti-mullerian Hormone Levels in Obese Women with and Without Polycystic Ovarian Syndrome. *Obesity Surgery*, 27(7), 1750-1754. https://dx.doi.org/10.1007/s11695-016-2528-y
Hu, L., Ma, L., Xia, X., Ying, T., Zhou, M., Zou, S., Yu, H., & Yin, J. (2022). Efficacy of Bariatric Surgery in the Treatment of Women with Obesity and Polycystic Ovary Syndrome. *The Journal of Clinical Endocrinology and Metabolism*, 107(8), e3217-e3229. https://dx.doi.org/10.1210/clinem/dgac294
Tatarchuk T., Todurov I., Anagnostis P., Tutchenko T., Pedachenko N., Glamazda M., Koseii N., & Regeda S. (2022). The Effect of Gastric Sleeve Resection on Menstrual Pattern and Ovulation in Premenopausal Women with Classes III-IV Obesity. *Obesity Surgery*, 32(3), 599-606. https://dx.doi.org/10.1007/s11695-021-05820-0

Table 4.2. Excluded Studies (on full text assessment)	
Reference	**Reason**
Abbas et al. 2014	Full text not available (abstract only)
Abhisheka et al. 2021	Full text not available (abstract only)
Aggarwal et al. 2019	Full text not available (abstract only)
Ahmed, A.S.M. 2003	Commentary/Editorial/Narrative Review
Ahmed, H.O. 2017	Not PCOS
Ahuja, A. 2016	Full text not available (abstract only)
Al Tubi et al. 2019	Full text not available (abstract only)

Alibhai et al. 2022	Study Protocol
Almehdi et al. 2017	Full text not available (abstract only)
Altamimi et al. 2020	Not PCOS
Arumalla et al. 2017	Full text not available (abstract only)
Balen et al. 2007	Not PCOS
Balen et al. 2016	Commentary/Editorial/Narrative Review
Bashian et al. 2018	Full text not available (abstract only)
Bazarah et al. 2021 (#2389)	Full text not available (abstract only)
Bazarah et al. 2021 (#2346)	Full text not available (abstract only)
Beydoun et al. 2020	Not PCOS
Brancatisano et al. 2008	Not PCOS
Butterworth et al. 2016	Not original research (guideline or SR)
Butterworth et al. 2015	Full text not available (abstract only)
Cai et al. 2021	Full text not available (abstract only)
Carr et al. 2011	Full text not available (abstract only)
Chang et al. 2021	Not original research (guideline or SR)
Chang et al. 2020	Full text not available (abstract only)
Chao et al. 2019	Full text not available (abstract only)
ChiCTR-IOR-17013169, 2017	Study Protocol
Christ et al. 2016	Full text not available (abstract only)
Christ et al. 2018	Not PCOS
Christinajoice et al. 2020	No comparator (no surgery or medical therapy)
Conway et al. 2014	Not original research (guideline or SR)
Costello et al. 2019	Not original research (guideline or SR)
Dai et al. 2021	No comparator (no surgery or medical therapy)
DiVincenzo et al. 2019	Commentary/Editorial/Narrative Review
Dilday et al. 2017	Full text not available (abstract only)
Dilday et al. 2019	Not PCOS
Dixon et al. 2002 (#4839)	Not PCOS
Dixon et al. 2002 (#4804)	Not PCOS
Dwivedee et al. 2010	Full text not available (abstract only)
Edison et al. 2016	Not PCOS
Eid et al. 2005	Not PCOS
Eid et al. 2014	No comparator (no surgery or medical therapy)
Escobar-Morreale et al. 2005	No comparator (no surgery or medical therapy)
Escobar-Morreale et al. 2017	Not original research (guideline or SR)
Ezzat et al. 2021	Not PCOS
Gao et al. 2018	Full text not available (abstract only)
Gao et al. 2019	Full text not available (abstract only)
Garvey et al. 2016 (#3179)	Not original research (guideline or SR)
Garvey et al. 2016 (#5654)	Not original research (guideline or SR)
George et al. 2013	Full text not available (abstract only)
Gomez-Meade et al. 2013	Not PCOS
Godman et al. 2010	Commentary/Editorial/Narrative Review
Gunay et al. 2011	Full text not available (abstract only)
ISRCTN16668711, 2020	Study Protocol

Jamal et al. 2012	No comparator (no surgery or medical therapy)
Jonsson et al. 2017	Commentary/Editorial/Narrative Review
Kjaer et al. 2016	Specified outcomes not reported
Kominiarek et al. 2017	Not original research (guideline or SR)
Koshy et al. 2012	Full text not available (abstract only)
Kosta et al. 2022	No comparator (no surgery or medical therapy)
Kunst et al. 2017	Full text not available (abstract only)
Kyriacou et al. 2014	Commentary/Editorial/Narrative Review
Lacey et al. 2021	Full text not available (abstract only)
Lee et al. 2020	Commentary/Editorial/Narrative Review
Lerner et al. 2011	Full text not available (abstract only)
Li et al. 2019	Not original research (guideline or SR)
Luk et al. 2014	Full text not available (abstract only)
Ma, C. 2019	Full text not available (abstract only)
Machado Junior et al. 2019	No comparator (no surgery or medical therapy)
Malik, S. 2016	Commentary/Editorial/Narrative Review
Mechanick et al. 2012	Not original research (guideline or SR)
Mechanick et al. 2008	Not original research (guideline or SR)
Menon et al. 2012	Full text not available (abstract only)
Menon et al. 2019	Full text not available (abstract only)
Mohan et al. 2012	Full text not available (abstract only)
Moran et al. 2012	Commentary/Editorial/Narrative Review
Morreale, H. F. E. 2008	Commentary/Editorial/Narrative Review
Moxthe et al. 2020	Not original research (guideline or SR)
Naeem Mohamed et al. 2020	Not PCOS
Nair et al. 2009	Full text not available (abstract only)
Nayak et al. 2019	Full text not available (abstract only)
Neff et al. 2014	Not PCOS
Nilsson-Condori et al. 2016	Full text not available (abstract only)
NTR7395, 2018	Study Protocol
Omarov et al. 2017	Full text not available (abstract only)
Pasquali et al. 2020	Wrong Intervention
Pivo et al. 2016	Full text not available (abstract only)
Plosker, S. 2014	Commentary/Editorial/Narrative Review
Pournaras et al. 2010	Commentary/Editorial/Narrative Review
Price et al. 2015	Full text not available (abstract only)
Rozanska-Waledziak et al. 2020	Not PCOS
Shekelle et al. 2008	Commentary/Editorial/Narrative Review
Silvestre Teruel et al. 2012	Full text not available (abstract only)
Singh et al. 2020	No comparator (no surgery or medical therapy)
Skubleny et al. 2015	Full text not available (abstract only)
Skubleny et al. 2016	Not original research (guideline or SR)
Stefater et al. 2013	Commentary/Editorial/Narrative Review
Stroh et al. 2008	Not English
Swanson et al. 2009	Full text not available (abstract only)
Talebpour, M. 2011	Full text not available (abstract only)
Talebpour et al. 2011	Full text not available (abstract only)
Teede et al. 2018	Not original research (guideline or SR)

Teitelman et al. 2006	Not PCOS
Tian et al. 2021	Not original research (guideline or SR)
Tolofari et al. 2013	Full text not available (abstract only)
Turkman et al. 2016	No comparator (no surgery or medical therapy)
Turkman et al. 2015	No comparator (no surgery or medical therapy)
Vasquez et al. 2019	Full text not available (abstract only)
Wang et al. 2015	Not PCOS
Wild et al. 2010	Not original research (guideline or SR)
Yheulon et al. 2019	Not PCOS
Yue et al. 2022	Not original research (guideline or SR)
Zhu et al. 2017	Full text not available (abstract only)
Zitsman et al. 2011	Not PCOS

5. STUDY CHARACTERISTICS TABLE

Author, year, country	Population/ Setting	Study Design	Sample Size per group	Intervention/ exposure details	Comparison/ control details	Follow up Duration	Outcomes	Summary of findings
Abiad et al., 2018, Lebanon	Females with PCOS and obesity; University hospital	Cohort	PCOS – 6 Non-PCOS - 16	Sleeve Gastrectomy	Females with obesity without PCOS	12 months	Anthropometric Metabolic	Both groups lost >30% body weight.
Ahmed et al., 2022, UK	Women with PCOS undergoing bariatric surgery; University Hospital	Cohort	PCOS - 30 Non-PCOS - 60	Roux-en-Y gastric bypass surgery	Women without PCOS undergoing bariatric surgery	24 months	% Total Weight Loss	Similar loss of total body weight between women with and without PCOS
Benito et al., 2022, Spain	Premenopausal women with PCOS; University Hospital	Cohort	PCOS – 49 Non-PCOS – 120	Bariatric surgery (RYGB, adjustable gastric banding, sleeve gastrectomy, revisional surgery)	Premenopausal women without PCOS	Up to 24 months	Anthropometric Metabolic Pregnancy	Pregnancy rates higher among PCOS than non-PCOS. Other outcomes similar.
Bhandari et al., 2022, India	Females with PCOS and obesity; University Hospital	Cohort	PCOS – 43 Non-PCOS - 32	Sleeve gastrectomy	Females with obesity without PCOS	6 months	AMH level Anthropometric Reproductive	AMH levels decreased in both groups post-surgery with no difference between groups
Buyukkaba et al., 2021, Turkey	Females with PCOS and obesity; University Hospital	Cohort	PCOS – 23 Non-PCOS - 47	Metabolic surgery - 62 laparoscopic sleeve gastrectomy, 8 Roux-en-Y gastric bypass	Females with obesity without PCOS	6 months	Body composition, metabolic health markers, AMH	AMH increased following bariatric surgery in women with and without PCOS with no significant difference between groups.
Cai et al., 2021, China	Females with PCOS and obesity; University Hospital	Cohort	PCOS – 83 Non-PCOS – 70	Laparoscopic sleeve gastrectomy	Females with obesity without PCOS	12 months	Anthropometric Metabolic	Both women with and without PCOS had improvements in body composition following LSG.
Casals et al., 2021, Spain	Women with PCOS; University Hospital	Cross-sectional	PCOS – 43 Non-PCOS - 165	Bariatric surgery	Women without PCOS	8+ years	Reproductive Anthropometric	Improvement in menstrual regularity with bariatric surgery.
Chiofalo et al., 2017, Italy	Women with obesity and PCOS; University Hospital	Cohort	PCOS – 29 Non-PCOS – 26	Bariatric surgery	Women with obesity without PCOS	12 months	AMH	AMH levels were reduced in both groups
Hu et al., 2022, China	Women with obesity and PCOS; University Hospital	Non-randomized trial	Bariatric surgery - 40 Medical therapy - 41	Laparoscopic sleeve gastrectomy	Metformin 2000 mg/day x 12 months + OCP 35 mg ethinyl-estradiol + 2 mg cyproterone acetate x 6 months	12 months	Anthropometric Metabolic	Greater reduction in BMI in the surgery group than the medical group, and improvement in signs and symptoms of PCOS associated with change in BMI
Tatarchuk et al., 2022, Ukraine	Premenopausal women with PCOS; Three metabolic surgery centres	Cohort	PCOS: Bariatric surgery – 33 Conservative - 27 Non-PCOS & surgery - 40	Gastric sleeve resection	Conservative management (no surgery or medical therapy) Non-PCOS	15 months	Anthropometric Metabolic Reproductive	Menstrual irregularity improved. Ovulation improved in more than half of these patients at 6–15 months. These effects were more evident in women with PCOS.

6. FINDINGS

Comparisons included:

Comparison 1. Bariatric Surgery vs Medical Therapy

Comparison 2. Bariatric Surgery vs Conservative Management

Comparison 3. Bariatric Surgery Among Individuals with PCOS vs. Non-PCOS

COMPARISON 1. Bariatric Surgery vs Medical Therapy

EVIDENCE SUMMARY:

One non-randomized trial (Hu et al, 2022) compared bariatric surgery (laparoscopic sleeve gastrectomy) to medical therapy (oral contraceptive pill and metformin). This study was conducted in Shanghai, China from September 2017 to July 2020. Eligible patients chose whether they wished to pursue surgical or medical therapy and were assigned to a group based on their intentions. Patients in the medical therapy group were prescribed six months of an oral contraceptive pill (35 mcg ethinyl-estradiol and 2 mg cyproterone acetate) and twelve months of metformin. Outcomes were evaluated at baseline and twelve months. Reported outcomes of relevance included adverse events, anthropometric outcomes (body weight, BMI), metabolic outcomes (fasting glucose, fasting insulin, lipids, hemoglobin A1C), total testosterone, and sex hormone binding globulin (SHBG). This study had a high risk of bias as it was non-randomized, and investigators were not blinded.

META-ANALYSIS/DESCRIPTIVE ANALYSIS SUMMARY:

It was not possible to perform a meta-analysis as only one study compared bariatric surgery to medical therapy in women with PCOS. The outcomes reported in this study are presented in the below table. The authors found that bariatric surgery compared with medical therapy led to improvements in metabolic outcomes (fasting glucose, fasting insulin, triglycerides, LDL-cholesterol, and hemoglobin A1C), anthropometric measures (body weight, BMI), as well as total testosterone and sex hormone binding globulin. These results are of low certainty given that they are derived from a single study with a high risk of bias and serious imprecision.

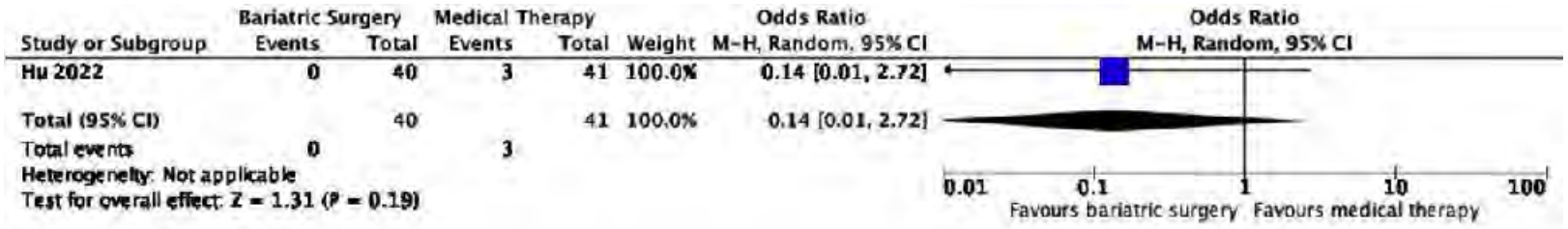
Outcome	Studies	n	Effect Estimate: OR [95%CI], M-H, random	P-Value	Favours	Certainty
Adverse events	1	81	0.14 [0.01, 2.72]	0.19	None	⊕◯◯◯ Very Low
Outcome	**Studies**	**n**	**Effect Estimate: Mean Difference [95%CI], M-H, random**	**P-Value**	**Favours**	**Certainty**
Fasting glucose	1	81	-0.80 [-1.00, -0.60]	<0.00001	Bariatric surgery	⊕◯◯◯ Very Low
Fasting insulin	1	81	-16.20 [-22.96, -9.44]	<0.00001	Bariatric surgery	⊕◯◯◯ Very Low
Total cholesterol	1	81	-0.30 [-0.76, 0.16]	0.20	None	⊕◯◯◯ Very Low
Triglycerides	1	81	-0.70 [-0.97, -0.43]	<0.00001	Bariatric surgery	⊕◯◯◯ Very Low
LDL-cholesterol	1	81	-0.30 [-0.37, -0.23]	<0.00001	Bariatric surgery	⊕◯◯◯ Very Low
HDL-cholesterol	1	81	0.00 [-0.11, 0.11]	1.00	None	⊕◯◯◯ Very Low
Hemoglobin A1C	1	81	-0.40 [-0.58, -0.22]	<0.0001	Bariatric surgery	⊕◯◯◯ Very Low
Body weight	1	81	-16.60 [-21.05, -12.15]	<0.00001	Bariatric surgery	⊕◯◯◯ Very Low
Body mass index	1	81	-6.40 [-7.66, -5.14]	<0.00001	Bariatric surgery	⊕◯◯◯ Very Low
Total testosterone	1	81	-0.70 [-1.07, -0.33]	0.0002	Bariatric surgery	⊕◯◯◯ Very Low
SHBG	1	81	39.60 [31.10, 48.10]	<0.00001	Bariatric surgery	⊕◯◯◯ Very Low

OUTCOME 1.1. Adverse Events

1.2.01. **Individual Study Data Table**

OUTCOME: Adverse events				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Bariatric surgery vs medical therapy								
Author, year	**Unit of outcome**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Hu et al., 2022	Count	Investigator	0	40	3	41	Crude	N/A

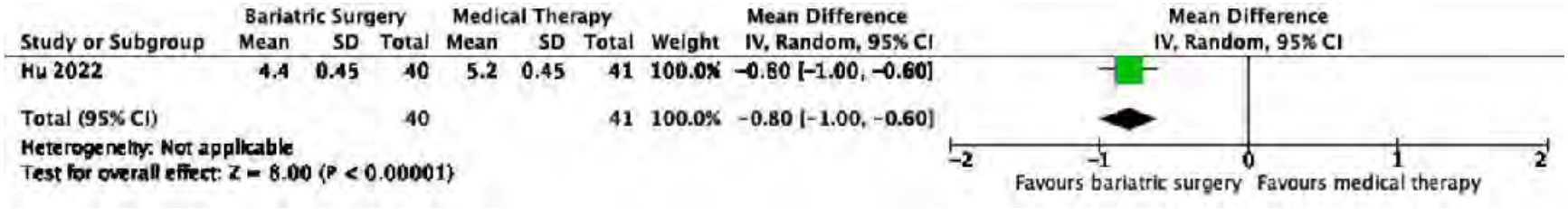
1.2.02. **Forest Plot for Included Non-Randomized Trial Comparing Bariatric Surgery with Metformin and OCP for Adverse Events**



OUTCOME 1.2. Fasting Glucose
1.2.1. Individual Study Data Table

OUTCOME: Fasting glucose										**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable): Bariatric surgery vs medical therapy								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Hu et al., 2022	mmol/L	Not specified	4.4 (median)	IQR 4.2-4.8	41	5.2 (median)	IQR 4.9-5.5	40	Crude	NA

1.2.2. Forest Plot for Included Non-Randomized Trial Comparing Bariatric Surgery with Metformin and OCP for Fasting Glucose

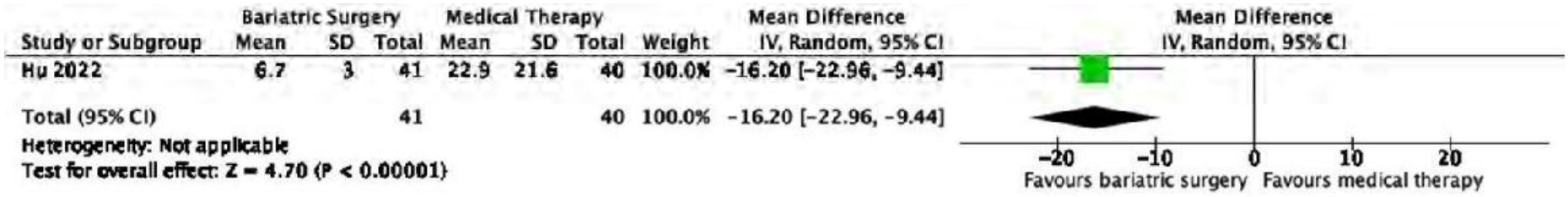


OUTCOME 1.3. Fasting Insulin

1.3.1. Individual Study Data Table

OUTCOME: Fasting insulin							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): Bariatric surgery vs medical therapy								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean difference (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Hu et al., 2022	µIU/mL	Not specified	6.7	IQR 4.7-8.9	41	22.9	IQR 15.0-36.4	40	Crude	NA

1.3.2. Forest Plot for Included Non-Randomized Trial Comparing Bariatric Surgery with Metformin and OCP for Fasting Insulin

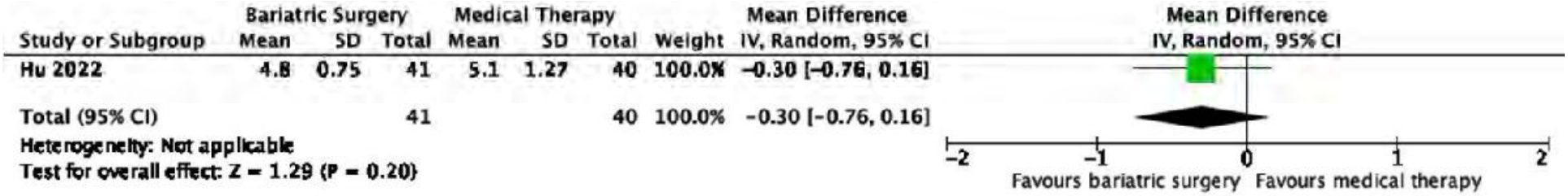


OUTCOME 1.4. Total Cholesterol
1.4.1. Individual Study Data Table

OUTCOME: Total cholesterol										
		COMPARISON (if applicable): Bariatric surgery vs medical therapy								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Hu et al., 2022	mmol/L	Not specified	4.8	IQR 4.1-5.1	41	5.1	IQR 4.3-6.0	40	Crude	NA

OUTCOME TYPE: Continuous

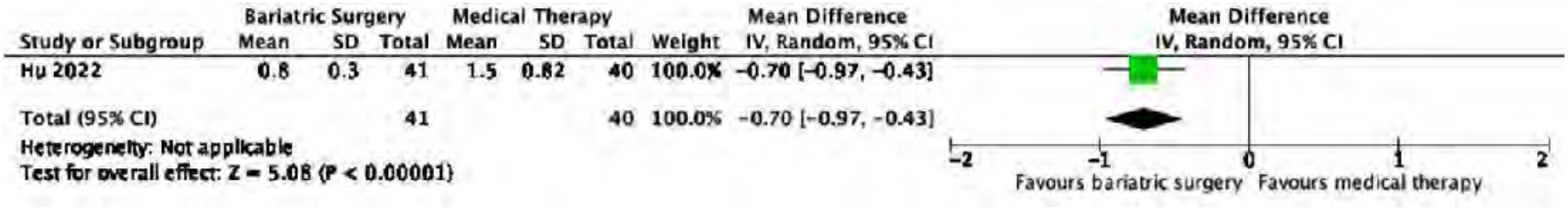
1.4.2. Forest Plot for Included Non-Randomized Trial Comparing Bariatric Surgery with Metformin and OCP for Total Cholesterol



OUTCOME 1.5. Triglycerides
1.5.1. Individual Study Table

OUTCOME: Triglycerides										**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable): Bariatric surgery vs medical therapy								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Hu et al., 2022	mmol/L	Not specified	0.8	IQR 0.6-1.00	41	1.5	IQR 0.9-2.0	40	Crude	NA

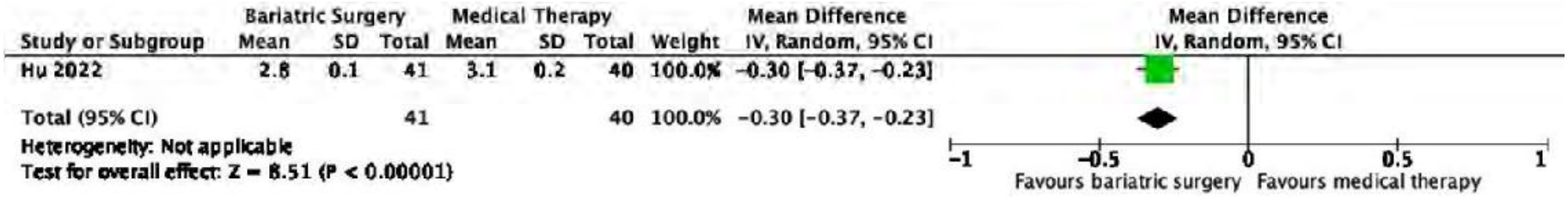
1.5.2. Forest Plot for Included Non-Randomized Trial Comparing Bariatric Surgery with Metformin and OCP for Triglycerides



OUTCOME 1.6. LDL-Cholesterol
1.6.1. Individual Study Data Table

OUTCOME: LDL-cholesterol										**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable): Bariatric surgery vs medical therapy								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Hu et al., 2022	mmol/L	Not specified	2.8	0.1	41	3.1	0.2	40	Crude	NA

1.6.2. Forest Plot for Included Non-Randomized Trial Comparing Bariatric Surgery with Metformin and OCP for LDL-Cholesterol

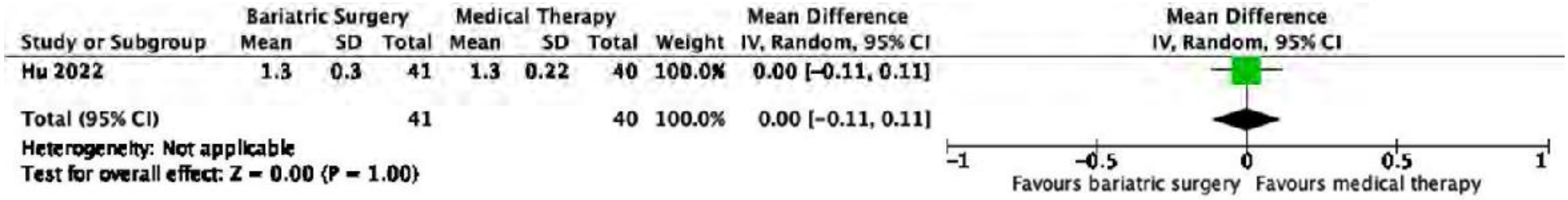


OUTCOME 1.7. HDL-Cholesterol

1.7.1. Individual Study Table

OUTCOME: HDL-cholesterol										**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable): Bariatric surgery vs medical therapy								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Hu et al., 2022	mmol/L	Not specified	1.3	IQR 1.1-1.5	41	1.3	IQR 1.1-1.4	40	Crude	NA

1.7.2. Forest Plot for Included Non-Randomized Trial Comparing Bariatric Surgery with Metformin and OCP for HDL-Cholesterol

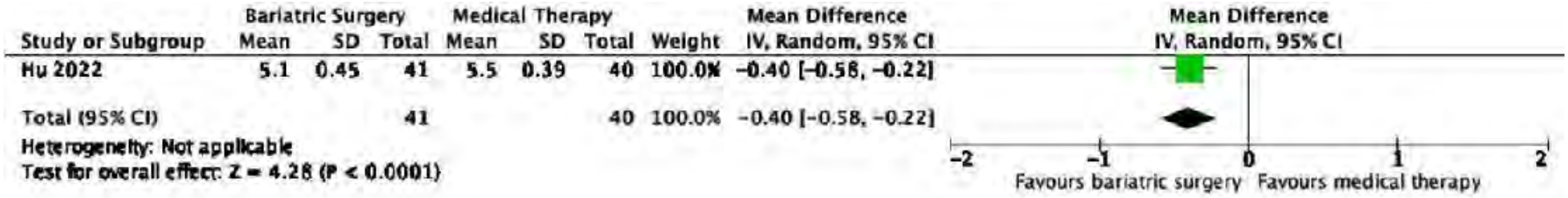


OUTCOME 1.8. Hemoglobin A1C

1.8.1. Individual Study Data Table

OUTCOME: Hemoglobin A1C							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): Bariatric surgery vs medical therapy								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean difference (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Hu et al., 2022	%	Not specified	5.1	IQR 4.9-5.5	41	5.5	IQR 5.2-5.7	40	Crude	NA

1.8.2. Forest Plot for Included Non-Randomized Trial Comparing Bariatric Surgery with Metformin and OCP for Hemoglobin A1C

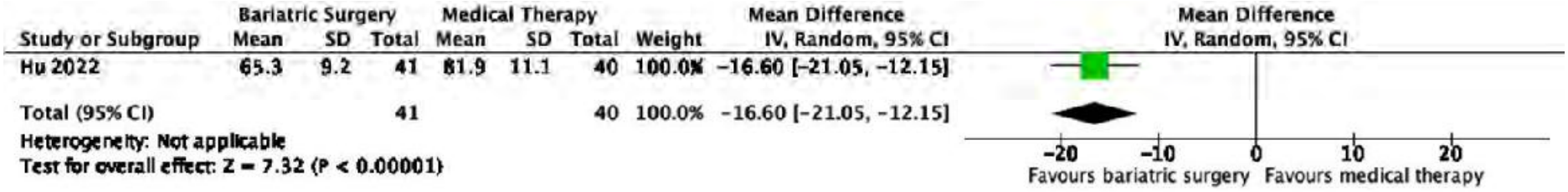


OUTCOME 1.9. Body Weight

1.9.1. Individual Study Data Table

OUTCOME: Body weight										
		COMPARISON (if applicable): Bariatric surgery vs medical therapy								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Hu et al., 2022	Kg	Investigator	65.3	9.2	41	81.9	11.1	40	Crude	NA

1.9.2. Forest Plot for Included Non-Randomized Trial Comparing Bariatric Surgery with Metformin and OCP for Body Weight

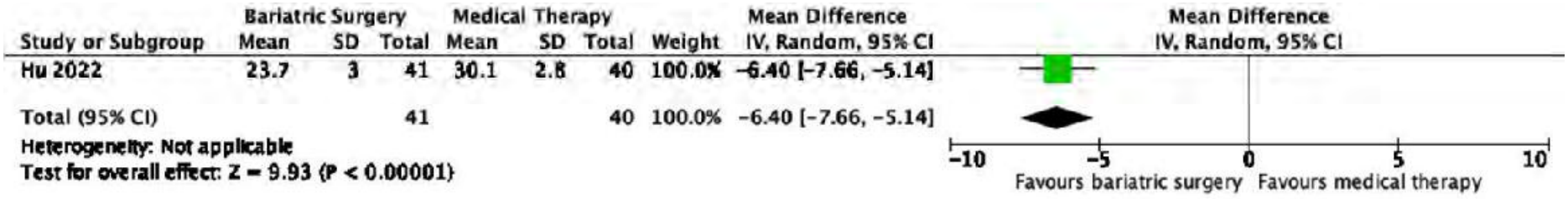


OUTCOME 1.10. Body Mass Index

1.10.1. Individual Study Data Table

OUTCOME: BMI										
		COMPARISON (if applicable): Bariatric surgery vs medical therapy								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Benito et al., 2020	kg/m2	Investigator	23.7	IQR 21.9-25.9	41	30.1	IQR 28.6-32.3	40	Crude	NA

1.10.2. Forest Plot for Included Non-Randomized Trial Comparing Bariatric Surgery with Metformin and OCP for BMI

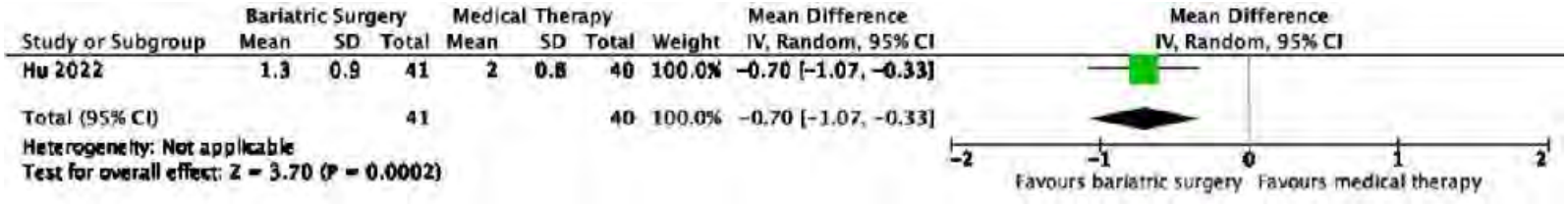


OUTCOME 1.11. Total Testosterone

1.11.1. Individual Study Data Table

OUTCOME: Total testosterone										**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable): Bariatric surgery vs medical therapy								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Hu et al., 2022	nmol/L	Not specified	1.3	IQR 1.0-2.0	41	2.0	IQR 1.5-2.6	40	Crude	NA

1.11.2. Forest Plot for Included Non-Randomized Trial Comparing Bariatric Surgery with Metformin and OCP for Total Testosterone

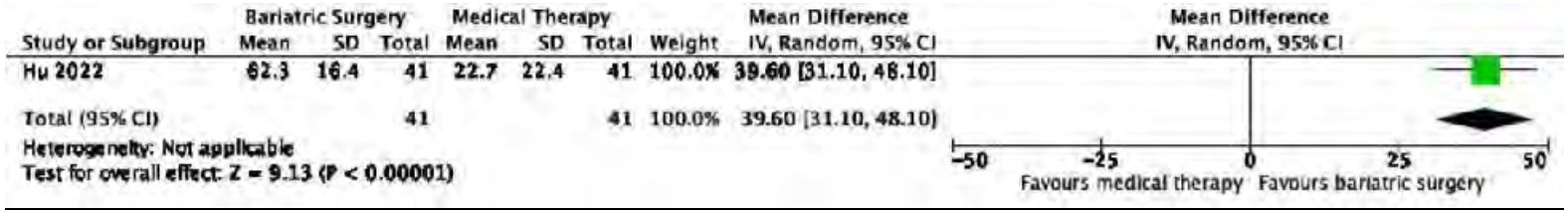


OUTCOME 1.12. Sex Hormone Binding Globulin

1.12.1. Individual Study Data Table

OUTCOME: SHBG										
		COMPARISON (if applicable): Bariatric surgery vs medical therapy								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Hu et al., 2022	nmol/L	Not specified	62.3	IQR 49.3-72.1	41	22.7	IQR 19.5-41.0	40	Crude	NA

1.12.2 Forest Plot for Included Non-Randomized Trial Comparing Bariatric Surgery with Metformin and OCP for SHBG



COMPARISON 2. Bariatric Surgery vs Conservative Management

EVIDENCE SUMMARY:

One prospective, non-randomized study (Tatarchuk et al, 2022) compared bariatric surgery (gastric sleeve resection) to conservative management in women with and without PCOS. This study was conducted in three metabolic surgery centres in Ukraine. Eligible patients chose whether they wished to pursue surgical or conservative management and were assigned to a group based on their intentions. Patients in the conservative management group did not receive bariatric surgery or medical therapy. Outcomes were evaluated at baseline and every three months until fifteen months. Reported outcomes of relevance included % total weight loss, intermenstrual length, and ovulation. This study had a high risk of bias as it was non-randomized, and investigators were not blinded.

META-ANALYSIS/DESCRIPTIVE ANALYSIS SUMMARY:

It was not possible to perform a meta-analysis as only one study compared bariatric surgery to conservative management in women with PCOS. The outcomes reported in this study are presented in the below table. The authors found that bariatric surgery compared with conservative management had improved ovulation, % total weight loss, and intermenstrual length among women with PCOS. These results are of low certainty given that they are derived from a single study with a high risk of bias and serious imprecision.

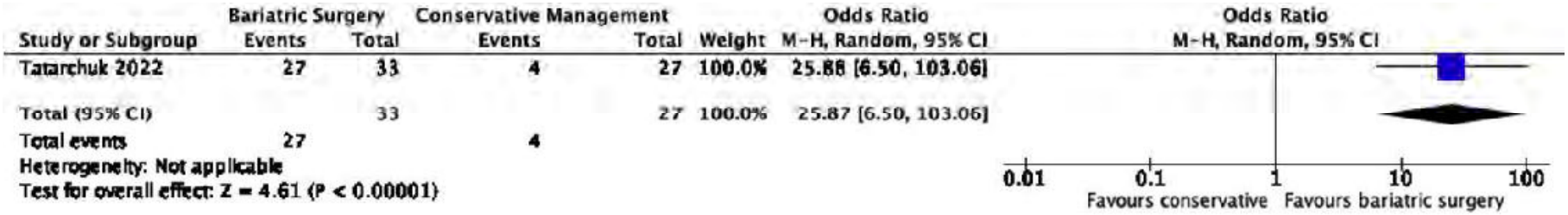
Outcome	Studies	n	Effect Estimate: OR [95%CI], M-H, random	P-Value	Favours	Certainty
Ovulation	1	60	25.87 [6.50, 103.06]	<0.00001	Bariatric Surgery	⊕◯◯◯ Very Low
Outcome	**Studies**	**n**	**Effect Estimate: Mean Difference [95%CI], M-H, random**	**P-Value**	**Favours**	**Certainty**
Intermenstrual Length	1	60	-43.00 [-46.28, -39.72]	<0.00001	Bariatric Surgery	⊕◯◯◯ Very Low
% Total Weight Loss	1	60	29.80 [29.07, 30.53]	<0.00001	Bariatric Surgery	⊕◯◯◯ Very Low

OUTCOME 2.1. Ovulation

2.1.1. Individual Study Table

OUTCOME: Ovulation					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Bariatric surgery vs conservative management								
Author, year	**Unit of outcome**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Tatarchuk et al., 2022	Count	Assessed by transvaginal ultrasound and serum progesterone concentrations >10 ng/ml on day 7 of the presumed ovulation	27	33	4	27	Crude	N/A

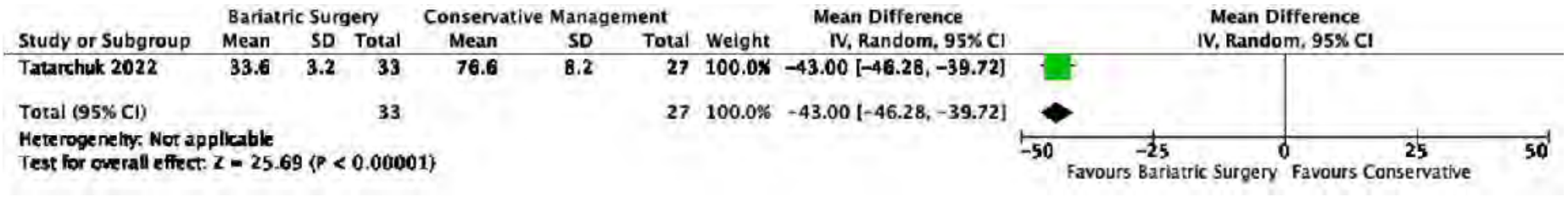
2.1.2. Forest Plot for Included Study Comparing Bariatric Surgery with Conservative Management for Ovulation



OUTCOME 2.2. Intermenstrual Length
2.2.1. Individual Study Data Table

OUTCOME: Intermenstrual length						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable): Bariatric surgery vs conservative management								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Tatarchuk et al., 2022	Days	Recorded in a standardized diary	33.6	3.2	33	76.6	8.2	27	Crude	NA

2.2.2. Forest Plot for Included Study Comparing Bariatric Surgery with Conservative Management for Intermenstrual Length

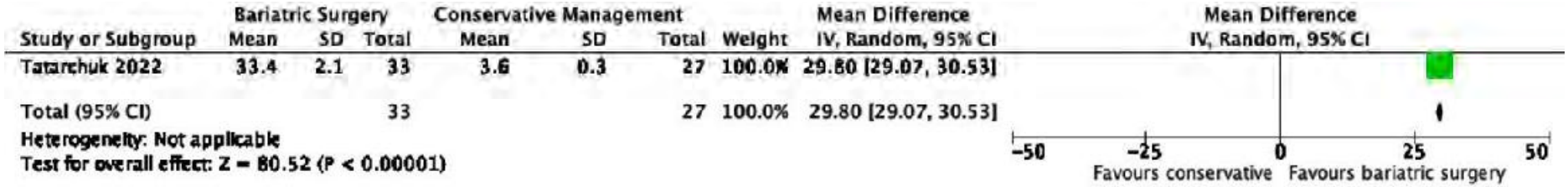


OUTCOME 2.3. % Total Weight Loss

2.3.1. Individual Study Data Table

OUTCOME: % Total Weight Loss						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable): Bariatric surgery vs conservative management								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Tatarchuk et al., 2022	%	Investigator	33.4	2.1	33	3.6	0.3	27	Crude	NA

2.3.2. Forest Plot for Included Study Comparing Bariatric Surgery with Conservative Management for % Total Weight Loss



COMPARISON 3. PCOS vs. Non-PCOS

EVIDENCE SUMMARY:

Nine studies compared the effect of bariatric surgery in women with and without PCOS. Eight of these studies were cohort studies (Abiad et al., 2018, Ahmed et al., 2022, Benito et al., 2020, Bhandari et al., 2016, Buyukkaba et al., 2021, Cai et al., 2021, Chiofalo et al., 2017, Tatarchuk et al., 2020) and one was a cross-sectional study (Casals et al., 2022). All studies were published between 2016 and 2022.

Six studies looked at reproductive outcomes within their surgical cohorts. One study (Benito et al., 2020) looked at the effect of bariatric surgery on reproductive and pregnancy outcomes in women with and without PCOS. Another study (Tatarchuk et al, 2020) examined the effect of bariatric surgery on reproductive outcomes (i.e., ovulation, intermenstrual length, and menstrual regularity) in women with and without PCOS. Three studies (Bhandari et al., 2016, Buyukkaba et al., 2021, Chiofalo et al., 2017) looked at the effect of bariatric surgery on anti-Mullerian hormone (AMH) levels in women with and without a diagnosis of PCOS. These studies are all at high risk of bias as they are surgical cohorts where investigators were not blinded to the outcomes.

Eight studies reported on non-reproductive outcomes (Abiad et al., 2018, Ahmed et al., 2022, Benito et al., 2020, Bhandari et al., 2016, Buyukkaba et al., 2021, Cai et al., 2021, Casals et al., 2022, Tatarchuk et al., 2020) including anthropometric, metabolic, and hormonal outcomes. The cross-sectional study by Casals et al., 2022 contacted female patients who had bariatric surgery at their centre between January 2005 and December 2010 with and without PCOS and conducted an interview to determine pregnancy and reproductive outcomes following surgery. They found there was an improvement in menstrual regularity among women with PCOS following bariatric surgery, but not in pregnancy outcomes. This study is at a high risk of bias due to non-response bias, and recall bias with self-reporting of outcomes. There was no data reported in any of the studies included in this comparison on prevalence of type 2 diabetes or hypertension, hirsutism, cost-effectiveness, or quality of life.

META-ANALYSIS/DESCRIPTIVE ANALYSIS SUMMARY:

It was not possible to perform a meta-analysis for the majority of the reproductive and pregnancy outcomes as only one study reported on each outcome for all but anti-Mullerian hormone. The outcomes reported are presented in the below table. The majority of results are of low certainty given that they are derived from a single or few studies with high risk of bias.

For the non-reproductive outcomes, two or more studies provided data on most of the outcomes of interest (as indicated in the table below) and therefore meta-analyses were performed. There is low certainty in the results of these meta-analyses due to high risk of bias in each of the included studies. The cross-sectional study (Casals et al., 2022) was excluded from all meta-analyses below due to an inability to compare outcomes across study designs.

Reproductive and Pregnancy Outcomes

Outcome	Studies	n	Effect Estimate: OR [95%CI], M-H, random	P-Value	Favours	Certainty
Regular Menstrual Cycles	1	75	3.36 [1.29,8.84]	0.01	PCOS	⊕◯◯◯ Very Low
Ovulation	1	73	4.07 [1.38, 12.00]	0.01	PCOS	⊕◯◯◯ Very Low
Live Birth Rate	1	169	1.83 [0.88, 3.79]	0.10	None	⊕◯◯◯ Very Low
Pregnancy Rate	1	169	2.07 [1.02, 4.18]	0.04	PCOS	⊕◯◯◯ Very Low
Multiple Gestations	1	44	0.50 [0.02, 13.11]	0.68	None	⊕◯◯◯ Very Low
Miscarriage Rate	1	50	2.47 [0.37, 16.32]	0.35	None	⊕◯◯◯ Very Low
Preterm Birth	1	44	5.57 [0.53, 58.69]	0.15	None	⊕◯◯◯ Very Low
Pre-eclampsia	1	44	3.47 [0.29, 41.53]	0.33	None	⊕◯◯◯ Very Low
Gestational Diabetes	1	44	0.78 [0.07, 9.34]	0.85	None	⊕◯◯◯ Very Low
Severe Iron Deficiency in Pregnancy	1	44	0.50 [0.02, 13.11]	0.68	None	⊕◯◯◯ Very Low
Placenta Previa	1	44	0.50 [0.02, 13.11]	0.68	None	⊕◯◯◯ Very Low
Caesarean Section	1	44	0.61 [0.13, 2.79]	0.53	None	⊕◯◯◯ Very Low
Labour Induction	1	44	0.29 [0.01, 6.45]	0.44	None	⊕◯◯◯ Very Low
Instrumental Delivery	1	44	1.67 [0.21, 13.10]	0.63	None	⊕◯◯◯ Very Low
Low Birth Weight	1	44	5.57 [0.53, 58.69]	0.15	None	⊕◯◯◯ Very Low
Chromosomal Abnormalities	1	44	0.50 [0.02, 13.11]	0.68	None	⊕◯◯◯ Very Low

Congenital Malformation	1	44	5.00 [0.19, 130.02]	0.33	None	⊕◯◯◯ Very Low
Neonatal Jaundice	1	44	1.63 [0.09, 27.84]	0.74	None	⊕◯◯◯ Very Low
Neonatal Hypoglycemia	1	44	0.50 [0.02, 13.11]	0.68	None	⊕◯◯◯ Very Low
Neonatal Hypotonia	1	44	5.00 [0.19, 130.02]	0.33	None	⊕◯◯◯ Very Low
NICU Admission	1	44	1.63 [0.09, 27.84]	0.74	None	⊕◯◯◯ Very Low
Outcome	**Studies**	**n**	**Effect Estimate: Mean Difference [95%CI], M-H, random**	**P-Value**	**Favours**	**Certainty**
Intermenstrual Length	1	73	-7.60 [-9.16, -6.04]	<0.00001	PCOS	⊕◯◯◯ Very Low
Anti-Mullerian Hormone	3	200	1.57 [-0.29, 3.42]	0.10	None	⊕◯◯◯ Very Low
Birth Weight	1	44	-392.00 [-759.64, -24.36]	0.04	Non-PCOS	⊕◯◯◯ Very Low
Apgar Score	1	44	-0.40 [-0.82, 0.02]	0.06	None	⊕◯◯◯ Very Low

Non-Reproductive Outcomes

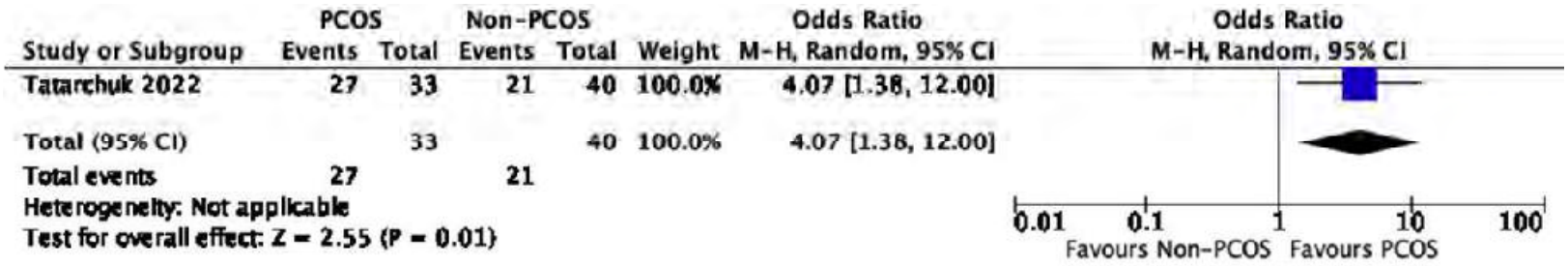
Outcome	Studies	n	Effect Estimate: OR [95%CI], M-H, random	P-Value	Favours	Certainty
Adverse Events	2	95	Not estimable		None	⊕◯◯◯ Very low
Outcome	**Studies**	**n**	**Effect Estimate: Mean Difference [95%CI], M-H, random**	**P-Value**	**Favours**	**Certainty**
Hemoglobin A1C	1	51	-0.20 [-0.52, 0.12]	0.22	None	⊕◯◯◯ Very Low
Fasting Glucose	3	242	-0.20 [-0.35, -0.06]	0.006	PCOS	⊕◯◯◯ Very Low
Fasting Insulin	3	242	1.30 [0.24, 2.35]	0.02	Non-PCOS	⊕◯◯◯ Very Low
Total Cholesterol	2	121	0.27 [-0.08, 0.62]	0.13	None	⊕◯◯◯ Very Low
LDL Cholesterol	3	143	0.01 [-0.61, 0.63]	0.98	None	⊕◯◯◯ Very Low
Triglycerides	3	143	0.03 [-0.22, 0.29]	0.81	None	⊕◯◯◯ Very Low
HDL Cholesterol	3	143	-0.06 [-0.16, 0.04]	0.21	None	⊕◯◯◯ Very Low
Body Weight	5	387	-3.30 [-6.97, 0.37]	0.15	None	⊕◯◯◯ Very Low
Body Mass Index	4	314	-1.19 [-2.28, -0.10]	0.03	PCOS	⊕◯◯◯ Very Low
% Total Weight Loss	2	148	4.29 [-4.13, 12.72]	0.32	None	⊕◯◯◯ Very Low
Total Testosterone	3	272	0.09 [-0.06, 0.23]	0.87	None	⊕◯◯◯ Very Low
Free Testosterone	2	220	1.09 [0.73, 1.45]	<0.0001	Non-PCOS	⊕◯◯◯ Very Low
Sex Hormone Binding Globulin	3	242	-26.06 [-64.31, 12.19]	0.18	None	⊕◯◯◯ Very Low

OUTCOME 3.1. Ovulation

3.1.1. Individual Study Data Table

OUTCOME: Ovulation					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Tatarchuk et al., 2022	Count	Investigator	27	33	21	40	Crude	N/A

3.1.2. Forest Plot for Included Study Comparing Bariatric Surgery in Women With and Without PCOS for Ovulation

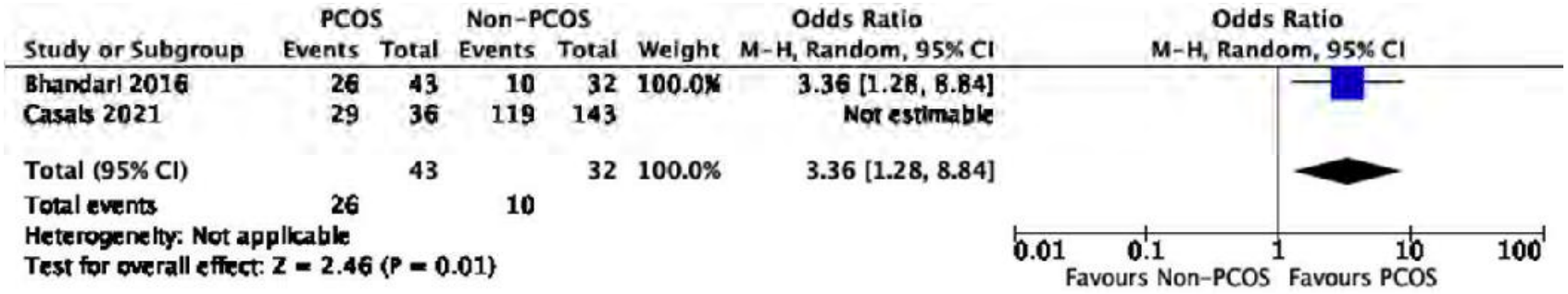


OUTCOME 3.2. Regular Menstrual Cycles

3.2.1. Individual Study Data Table

OUTCOME: Regular menstrual cycles				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Bhandari et al. 2016	Count	Investigator	26	43	10	32	Crude	N/A
Casals et al., 2021	Count	Investigator	29	43	119	165	Crude	N/A

3.2.2. Forest Plot for Included Studies Comparing Bariatric Surgery in Women With and Without PCOS for Regular Menstrual Cycles

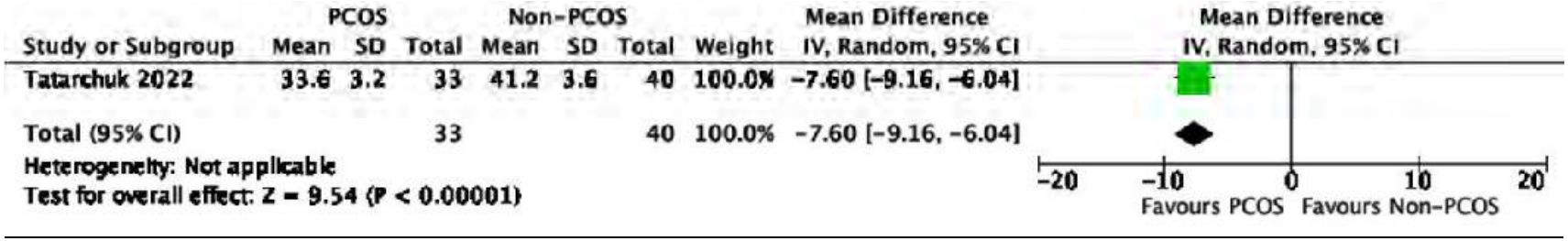


OUTCOME 3.3. Intermenstrual Length

3.3.1. Individual Study Data Table

OUTCOME: Intermenstrual length							**OUTCOME TYPE:** Continuous			
		COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Tatarchuk et al., 2022	Days	Investigator	33.6	3.2	33	41.2	3.6	40	Crude	NA

3.3.2. Forest Plot for Included Study Comparing Bariatric Surgery in Women With and Without PCOS for Intermenstrual Length

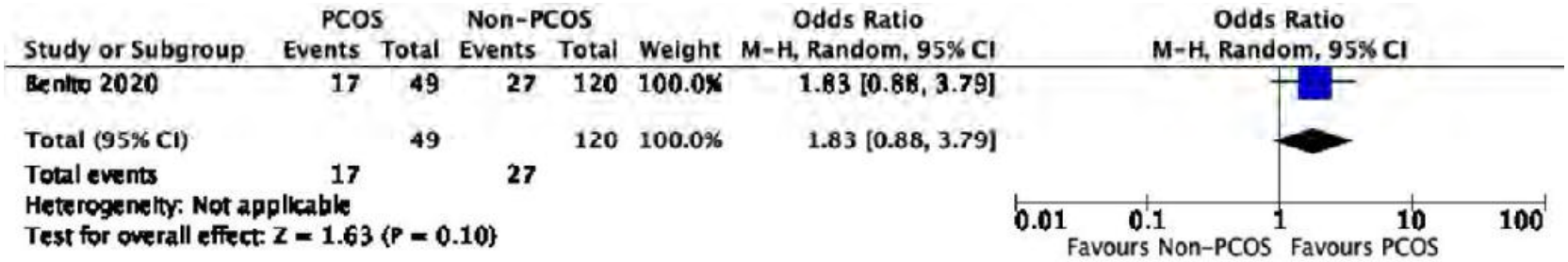


OUTCOME 3.4. Live Birth Rate

3.4.1. Individual Study Data Table

OUTCOME: Live birth rate				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Benito et al., 2020	Count	Investigator	17	49	27	120	Crude	N/A

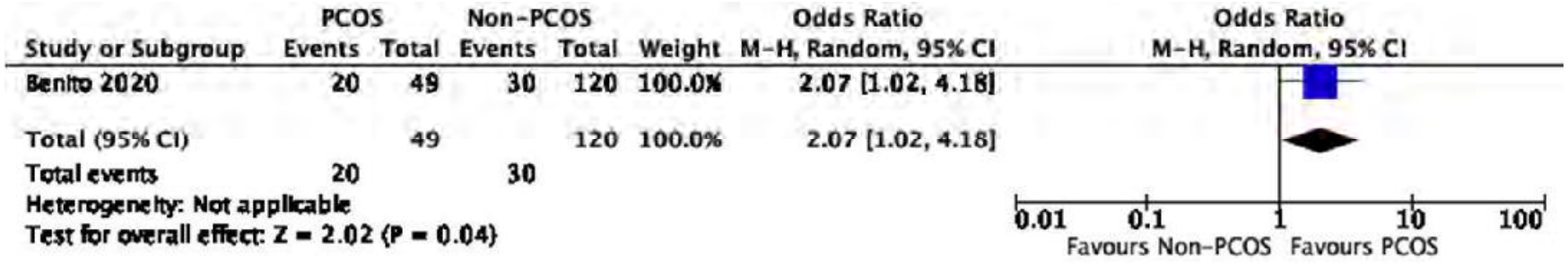
3.4.2. Forest Plot for Included Study Comparing Bariatric Surgery in Women With and Without PCOS for Live Birth Rate



OUTCOME 3.5. Pregnancy Rate
3.5.1. Individual Study Table

OUTCOME: Pregnancy rate				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Benito et al. 2020	Count	Investigator	20	49	30	120	Crude	N/A

3.5.2. Forest Plot for Included Study Comparing Bariatric Surgery in Women With and Without PCOS for Pregnancy Rate



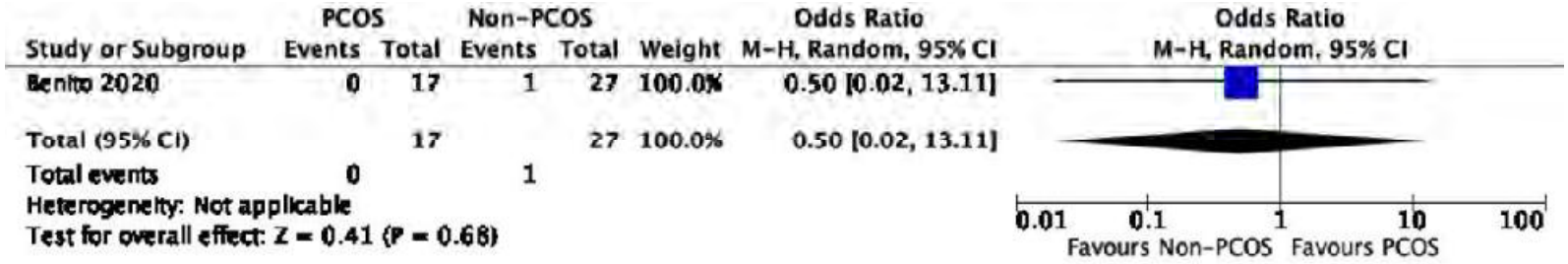
OUTCOME 3.6. Multiple Gestations

3.6.1. Individual Study Data Table

OUTCOME: Multiple gestations					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group***	**N events in control / comparison group**	**N total in control/ comparison group***	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Benito et al. 2020	Count	Investigator	0	17	1	27	Crude	N/A

*N total is the number of live births

3.6.2. Forest Plot for Included Study Comparing Bariatric Surgery in Women With and Without PCOS for Multiple Gestations



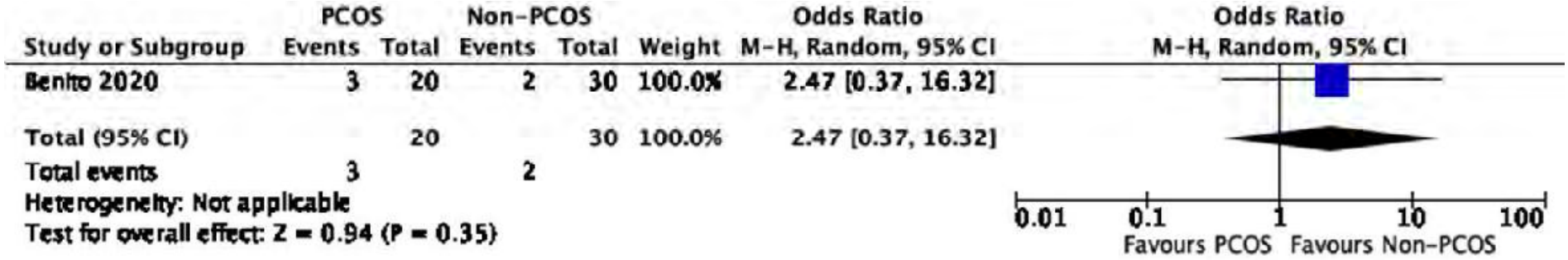
OUTCOME 3.7. Miscarriage Rate

3.7.1. Individual Study Data Table

OUTCOME: Miscarriage rate				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group***	**N events in control / comparison group**	**N total in control/ comparison group***	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Benito et al. 2020	Count	Investigator	3	20	2	30	Crude	N/A

*N total includes all pregnancies

3.7.2. Forest Plot for Included Study Comparing Bariatric Surgery in Women With and Without PCOS for Miscarriage Rate

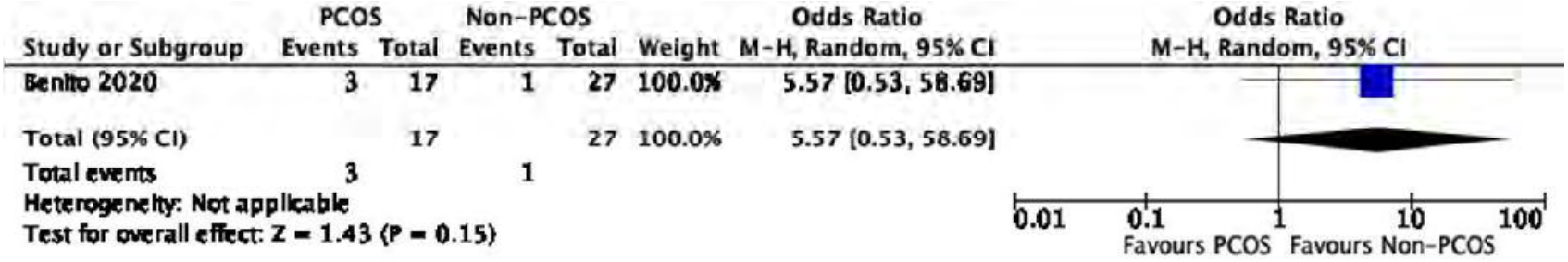


OUTCOME 3.8. Preterm Birth
3.8.1. Individual Study Data Table

OUTCOME: Preterm birth					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Benito et al. 2020	Count	Investigator	3	17	1	27	Crude	N/A

*N total is the number of live births

3.8.2. Forest Plot for Included Study Comparing Bariatric Surgery in Women With and Without PCOS for Preterm Birth



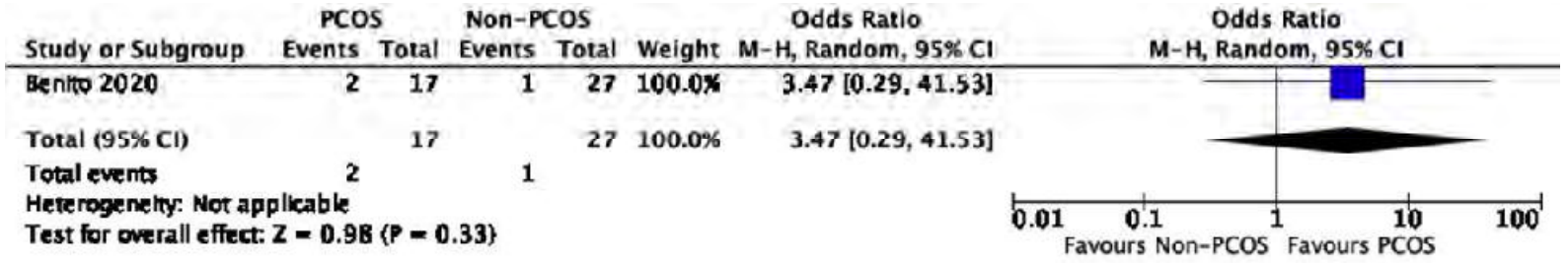
OUTCOME 3.9. Pre-eclampsia

3.9.1. Individual Study Data Table

OUTCOME: Pre-eclampsia					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Benito et al. 2020	Count	Investigator	2	17	1	27	Crude	N/A

*N total is the number of live births

3.9.2. Forest Plot for Included Study Comparing Bariatric Surgery in Women With and Without PCOS for Pre-Eclampsia

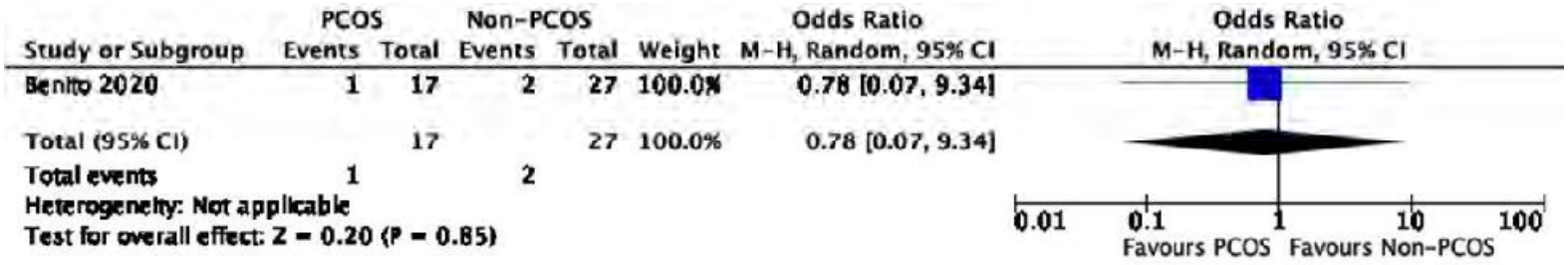


OUTCOME 3.10. Gestational Diabetes
3.10.1. Individual Study Data Table

OUTCOME: Gestational diabetes					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Benito et al. 2020	Count	Investigator	1	17	2	27	Crude	N/A

*N total is the number of live births

3.10.2. Forest Plot for Included Study Comparing Bariatric Surgery in Women With and Without PCOS for Gestational Diabetes



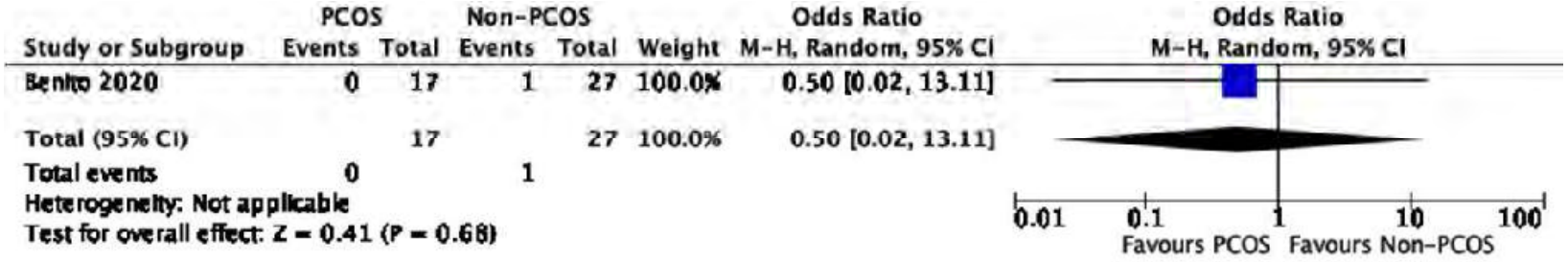
OUTCOME 3.11. Severe Iron Deficiency in Pregnancy

3.11.1. Individual Study Data Table

OUTCOME: Severe iron deficiency in pregnancy					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Benito et al. 2020	Count	Investigator	0	17	1	27	Crude	N/A

*N total is the number of live births

3.11.2. Forest Plot for Included Study Comparing Bariatric Surgery in Women With and Without PCOS for Severe Iron Deficiency in Pregnancy



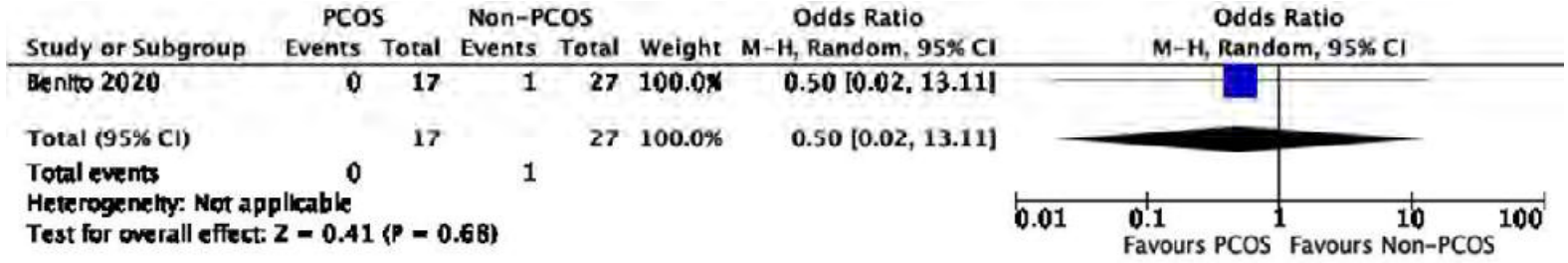
OUTCOME 3.12. Placenta Previa

3.12.1. Individual Study Data Table

OUTCOME: Placenta previa					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Benito et al. 2020	Count	Investigator	0	17	1	27	Crude	N/A

*N total is the number of live births

3.12.2. Forest Plot for Included Study Comparing Bariatric Surgery in Women With and Without PCOS for Placenta Previa

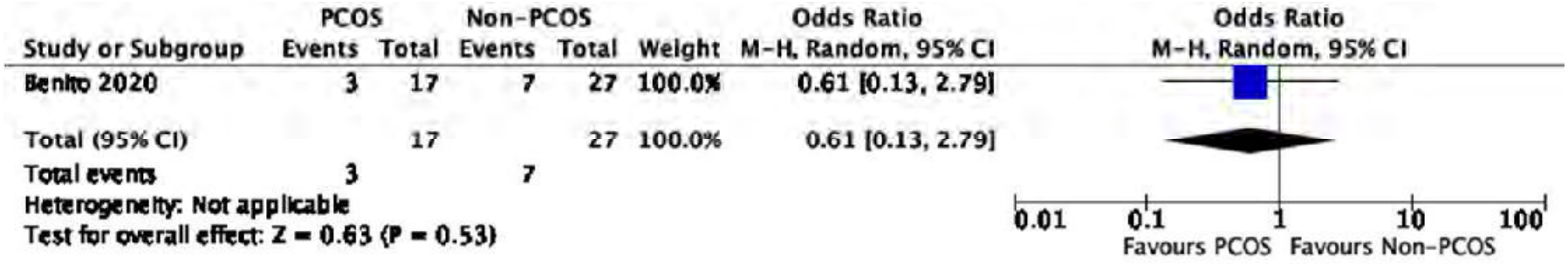


OUTCOME 3.13. Caesarean Section
3.13.1. Individual Study Data Table

OUTCOME: Caesarean section				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Benito et al. 2020	Count	Investigator	3	17	7	27	Crude	N/A

*N total is the number of live births

3.13.2. Forest Plot for Included Study Comparing Bariatric Surgery in Women With and Without PCOS for Caesarean Section



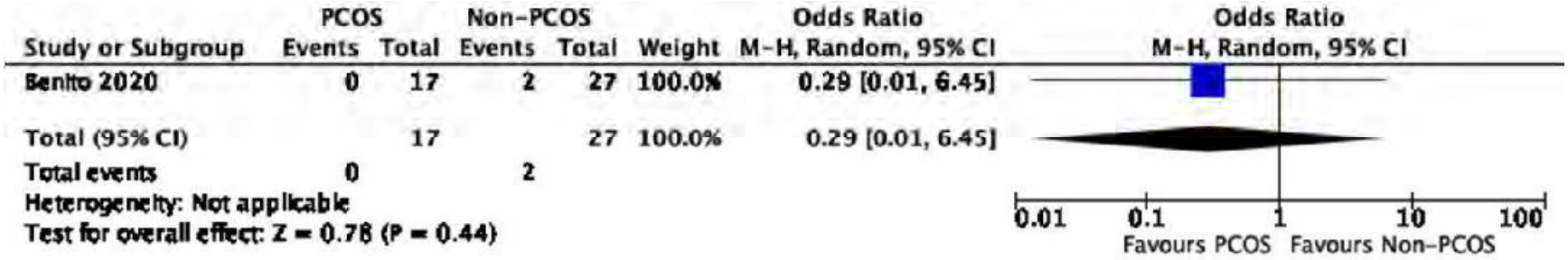
OUTCOME 3.14. Labour Induction

3.14.1. Individual Study Data Table

OUTCOME: Labour induction					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Benito et al. 2020	Count	Investigator	0	17	2	27	Crude	N/A

*N total is the number of live births

3.14.2. Forest Plot for Included Study Comparing Bariatric Surgery in Women With and Without PCOS for Labour Induction



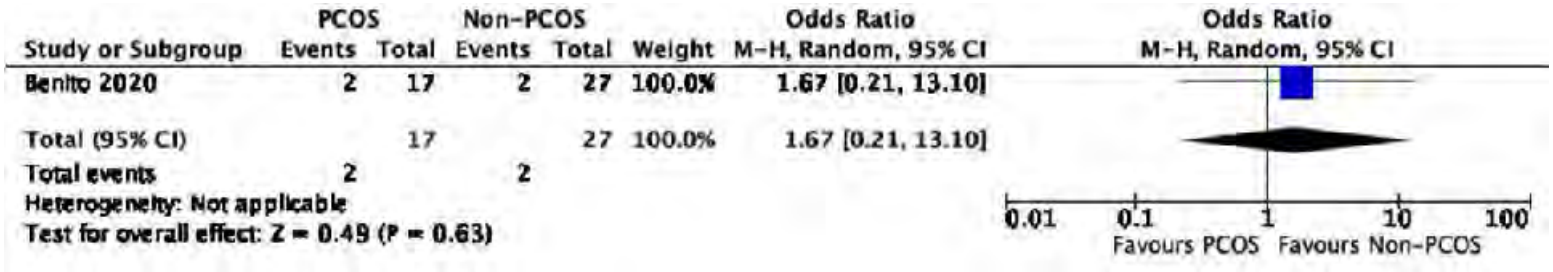
OUTCOME 3.15. Instrumental Delivery

3.15.1. Individual Study Data Table

OUTCOME: Instrumental delivery					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Benito et al. 2020	Count	Investigator	2	17	2	27	Crude	N/A

*N total is the number of live births

3.15.2. Forest Plot for Included Study Comparing Bariatric Surgery in Women With and Without PCOS for Instrumental Delivery



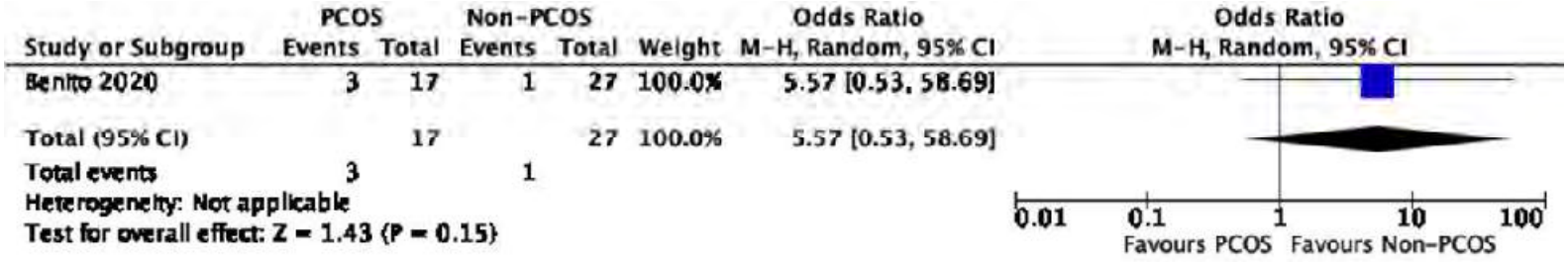
OUTCOME 3.16. Low Birth Weight

3.16.1. Individual Study Data Table

OUTCOME: Low birth weight				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Benito et al. 2020	Count	Investigator	3	17	1	27	Crude	N/A

*N total is the number of live births

3.16.2. Forest Plot for Included Study Comparing Bariatric Surgery in Women With and Without PCOS for Low Birth Weight



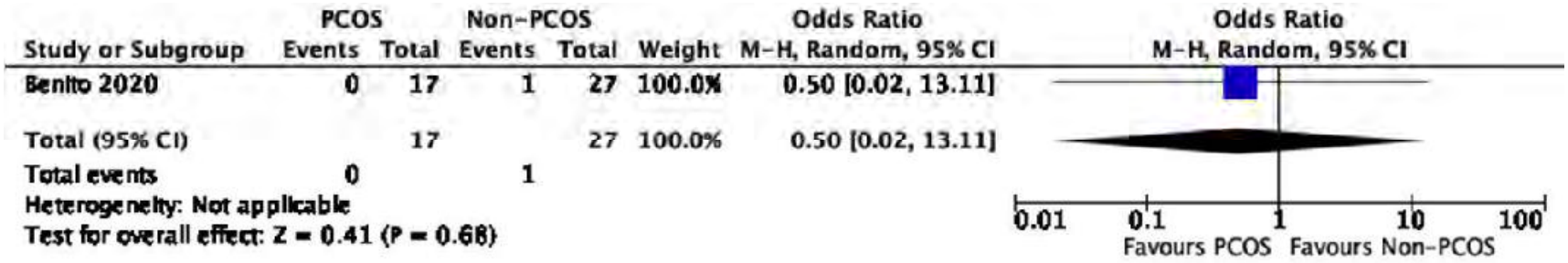
OUTCOME 3.17. Chromosomal Abnormalities

3.17.1. Individual Study Data Table

OUTCOME: Chromosomal abnormalities					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Benito et al. 2020	Count	Investigator	20	49	30	120	Crude	N/A

*N total is the number of live births

3.17.2. Forest Plot for Included Study Comparing Bariatric Surgery in Women With and Without PCOS for Chromosomal Abnormalities



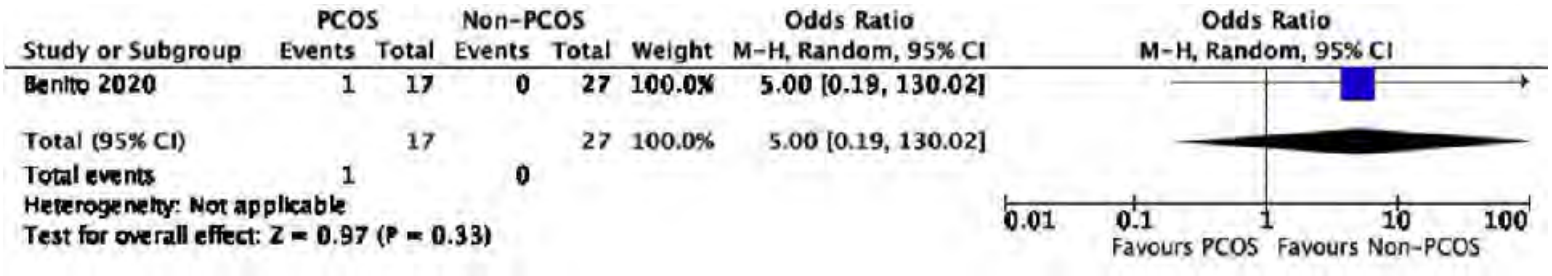
OUTCOME 3.18. Congenital Malformations

3.18.1. Individual Study Data Table

OUTCOME: Congenital malformations				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Benito et al. 2020	Count	Investigator	20	49	30	120	Crude	N/A

*N total is the number of live births

3.18.2. Forest Plot for Included Study Comparing Bariatric Surgery in Women With and Without PCOS for Congenital Malformations



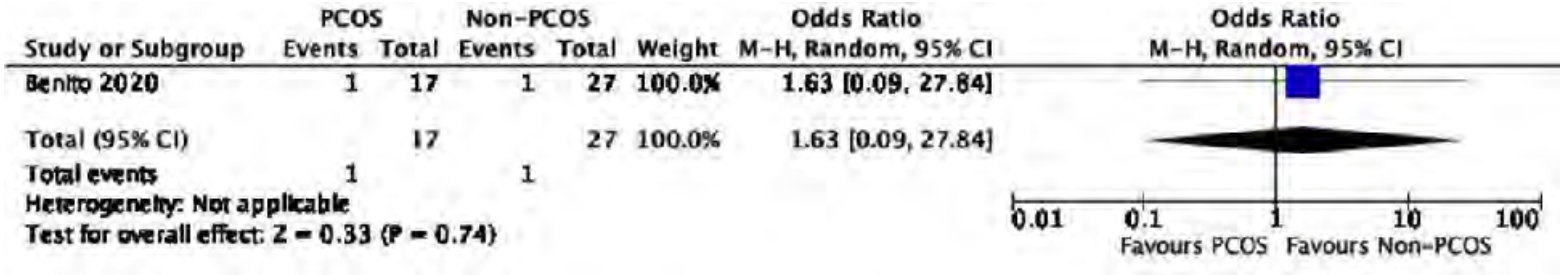
OUTCOME 3.19. Neonatal Jaundice

3.19.1. Individual Study Data Table

OUTCOME: Neonatal jaundice					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Benito et al. 2020	Count	Investigator	1	17	1	27	Crude	N/A

*N total is the number of live births

3.19.2. Forest Plot for Included Study Comparing Bariatric Surgery in Women With and Without PCOS for Neonatal Jaundice



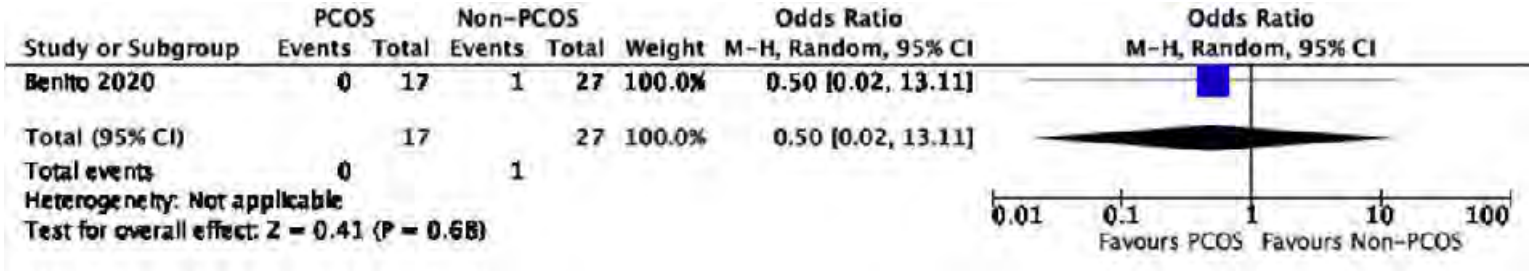
OUTCOME 3.20. Neonatal Hypoglycemia

3.20.1. Individual Study Data Table

OUTCOME: Neonatal hypoglycemia				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Benito et al. 2020	Count	Investigator	0	17	1	27	Crude	N/A

*N total is the number of live births

3.20.2. Forest Plot for Included Study Comparing Bariatric Surgery in Women With and Without PCOS for Neonatal Hypoglycemia



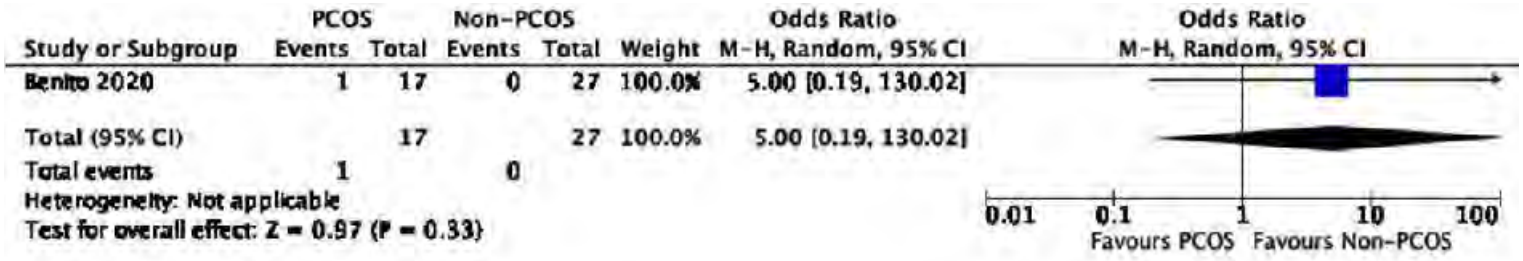
OUTCOME 3.21. Neonatal Hypotonia

3.21.1. Individual Study Data Table

OUTCOME: Neonatal hypotonia					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Benito et al. 2020	Count	Investigator	1	17	0	27	Crude	N/A

*N total is the number of live births

3.21.2. Forest Plot for Included Study Comparing Bariatric Surgery in Women With and Without PCOS for Neonatal Hypotonia



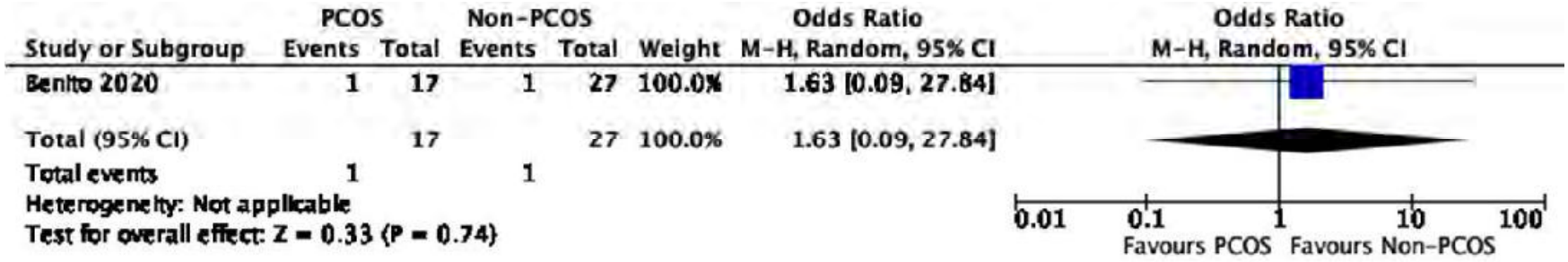
OUTCOME 3.22. Neonatal Intensive Care Unit Admission

3.22.1. Individual Study Data Table

OUTCOME: Neonatal intensive care unit admission					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Benito et al. 2020	Count	Investigator	1	17	1	27	Crude	N/A

*N total is the number of live births

3.22.2. Forest Plot for Included Study Comparing Bariatric Surgery in Women With and Without PCOS for NICU Admission



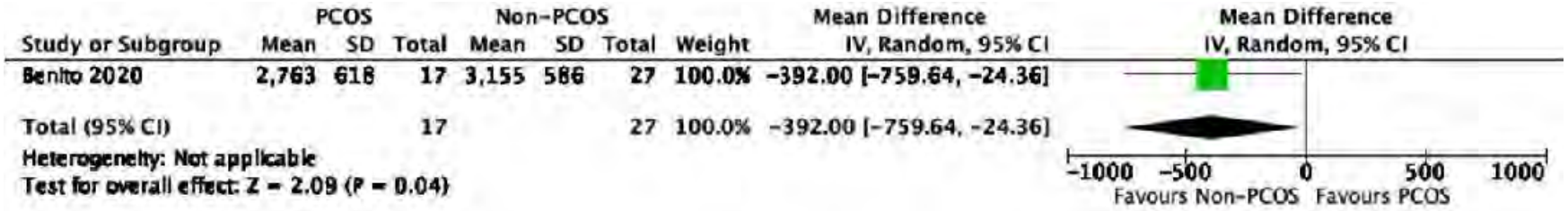
OUTCOME 3.23. Birth Weight

3.23.1. Individual Study Data Table

*Sample size is the total number of live births

OUTCOME: Birth Weight										
		OUTCOME TYPE: Continuous								
		COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Benito et al., 2020	g	Investigator	2763	618	17	3155	586	27	Crude	NA

3.23.2. Forest Plot for Included Study Comparing Bariatric Surgery in Women With and Without PCOS for Birth Weight

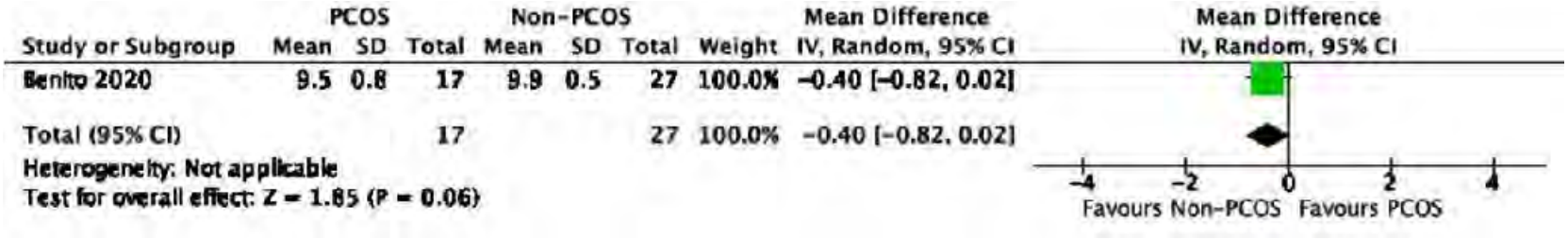


OUTCOME 3.24. Apgar Score

3.24.1. Individual Study Data Table

OUTCOME: Apgar Score										**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Benito et al., 2020	-	Investigator	9.5	0.8	17	9.89	0.5	27	Crude	NA

3.24.2. Forest Plot for Included Study Comparing Bariatric Surgery in Women With and Without PCOS for Apgar Score

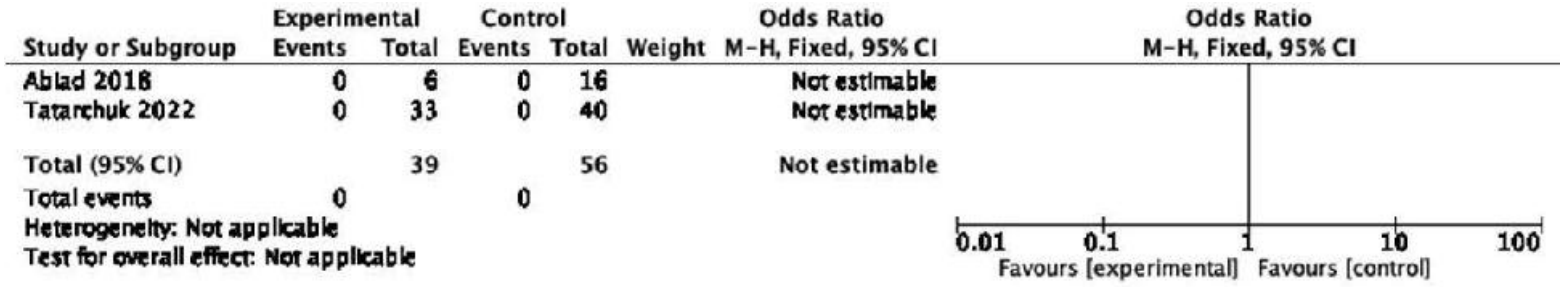


OUTCOME 3.25. Adverse Events

3.25.1. Individual Study Data Table

OUTCOME: Adverse events					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Abiad et al. 2018	Count	Investigator	0	6	0	16	Crude	N/A
Tatarchuk et al., 2022	Count	Investigator	0	33	0	40		

3.25.2. Forest Plot for Included Study Comparing Bariatric Surgery in Women With and Without PCOS for Adverse Events

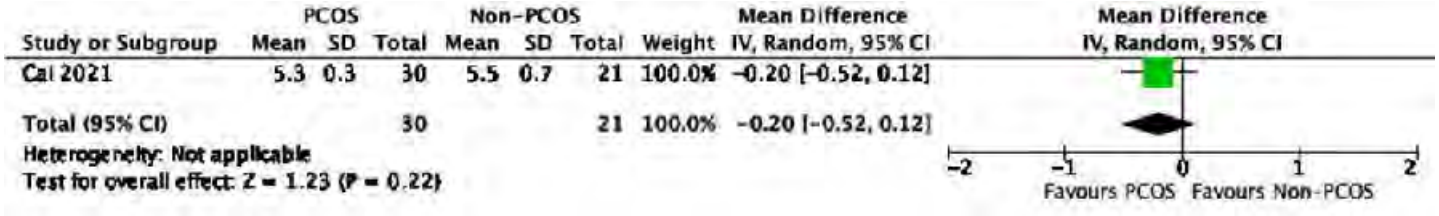


OUTCOME 3.26. Hemoglobin A1C

3.26.1. Individual Study Data Table

OUTCOME: Hemoglobin A1C										
		OUTCOME TYPE: Continuous								
		COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Cai et al., 2021	%	Investigator	5.3	0.3	30	5.5	0.7	21	Crude	NA

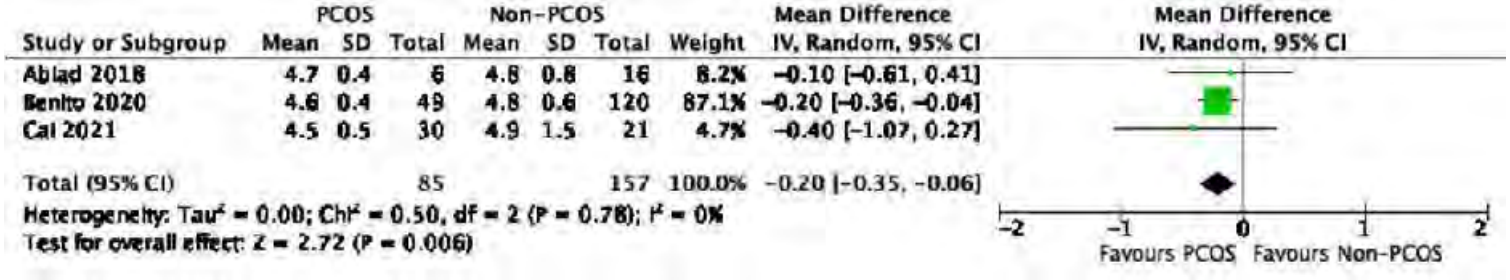
3.26.2. Forest Plot for Included Study Comparing Bariatric Surgery in Women With and Without PCOS for Hemoglobin A1C



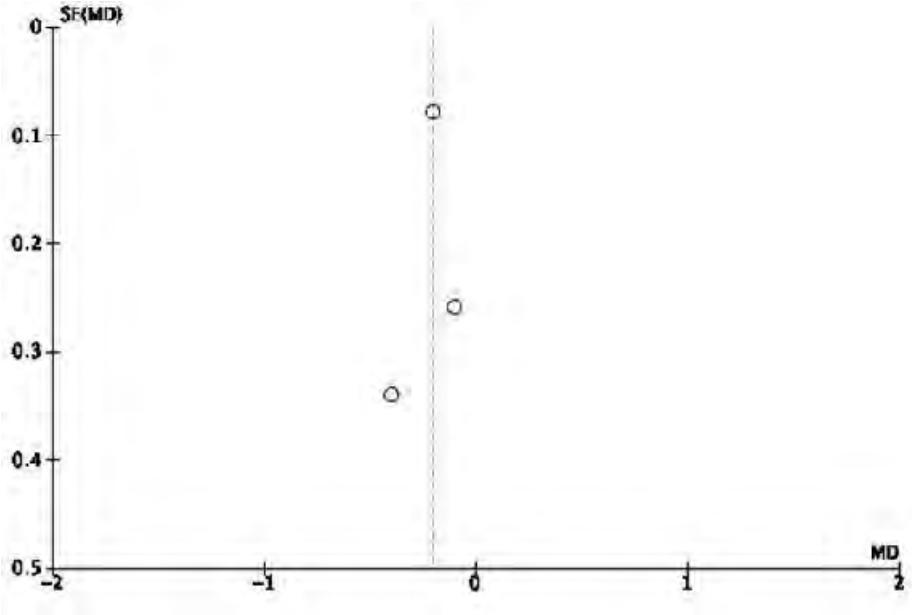
OUTCOME 3.27. Fasting Glucose
3.27.1. Individual Study Data Table

OUTCOME: Fasting glucose						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Abiad et al., 2018	mmol/L	Investigator	4.7	0.4	6	4.8	0.8	16	Crude	NA
Benito et al., 2020	mmol/L	Investigator	4.6	0.4	49	4.8	0.6	120	Crude	NA
Cai et al., 2021	mmol/L	Investigator	4.5	0.5	30	4.9	1.5	21	Crude	NA

3.27.2. Forest Plot for Included Study Comparing Bariatric Surgery in Women With and Without PCOS for Fasting Glucose



3.27.3. Funnel Plot for Assessment of Publication Bias



OUTCOME 3.28. Fasting Insulin

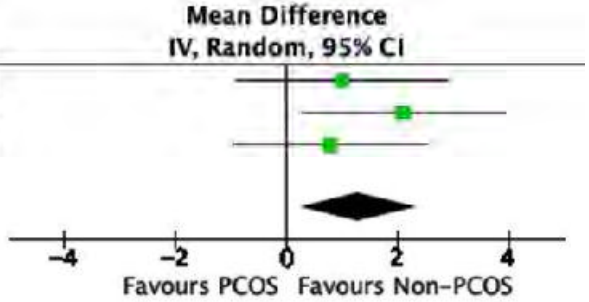
3.28.1. Individual Study Data Table

OUTCOME: Fasting insulin										**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Abiad et al., 2018	mU/L	Investigator	6.1	1.71	6	5.09	2.71	16	Crude	NA
Benito et al., 2020	pmol/L	Investigator	56	42	49	42	28	120	Crude	NA
Cai et al., 2021	mU/L	Investigator	7.2	3.2	30	6.4	3.1	21	Crude	NA

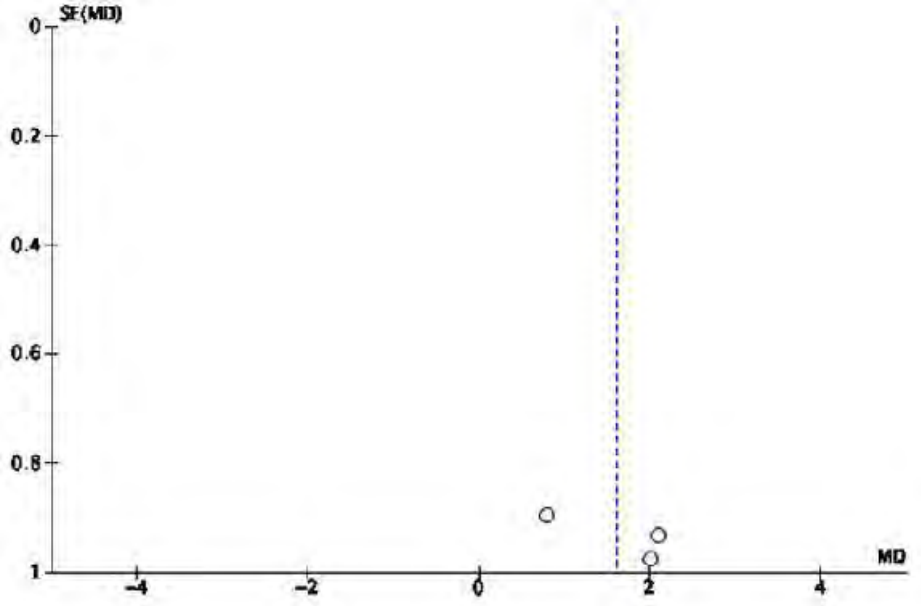
3.28.2. Forest Plot for Included Study Comparing Bariatric Surgery in Women With and Without PCOS for Fasting Insulin

Study or Subgroup	PCOS Mean	PCOS SD	PCOS Total	Non-PCOS Mean	Non-PCOS SD	Non-PCOS Total	Weight	Mean Difference IV, Random, 95% CI
Ablad 2018	6.1	1.71	6	5.09	2.71	16	30.5%	1.01 [-0.90, 2.92]
Benito 2020	8.1	6	49	6	4	120	33.3%	2.10 [0.27, 3.93]
Cai 2021	7.2	3.2	30	6.4	3.1	21	36.2%	0.80 [-0.95, 2.55]
Total (95% CI)			85			157	100.0%	1.30 [0.24, 2.35]

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.14$, $df = 2$ ($P = 0.57$); $I^2 = 0\%$
Test for overall effect: $Z = 2.41$ ($P = 0.02$)



3.28.3. Funnel Plot for Assessment of Publication Bias

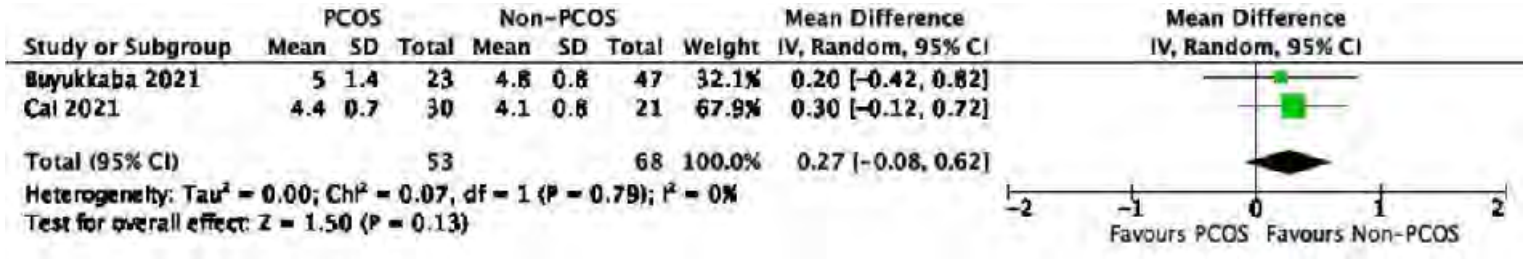


OUTCOME 3.29. Total Cholesterol

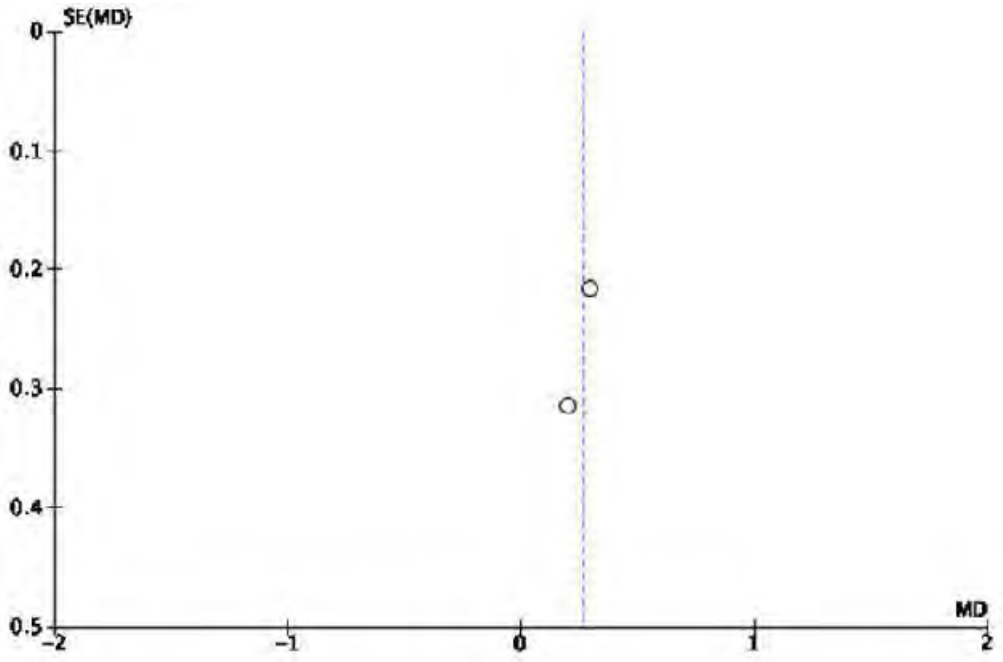
3.29.1. Individual Study Table Data

OUTCOME: Total cholesterol						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Buyukkaba et al., 2022	mmol/L	Investigator	5.0	1.4	23	4.8	0.8	47	Crude	NA
Cai et al., 2021	mmol/L	Investigator	4.4	0.7	30	4.1	0.8	21	Crude	NA

3.29.2. Forest Plot for Included Study Comparing Bariatric Surgery in Women With and Without PCOS for Total Cholesterol



3.29.3. Funnel Plot for Assessment of Publication Bias

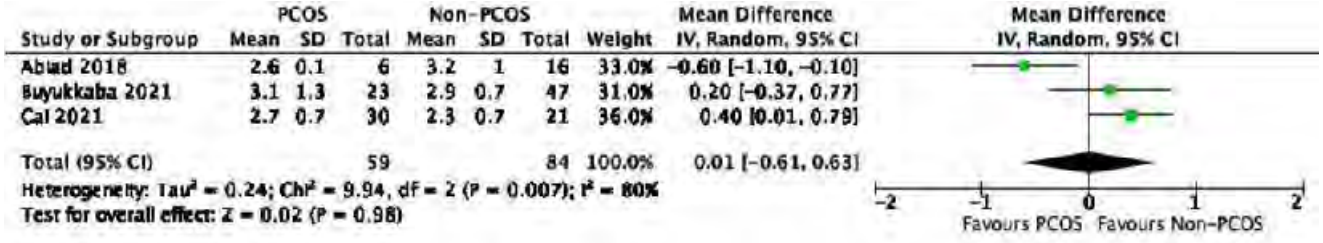


OUTCOME 3.30. LDL-Cholesterol

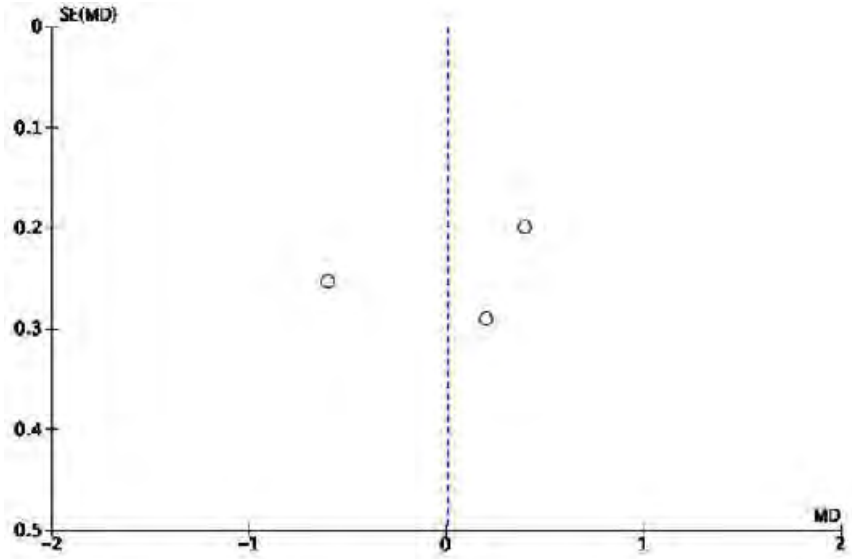
3.30.1. Individual Study Data Table

OUTCOME: LDL-cholesterol										
		COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Abiad et al., 2018	mmol/L	Investigator	2.6	0.1	6	3.2	1.0	16	Crude	NA
Buyukkaba et al., 2022	mmol/L	Investigator	3.1	1.3	23	2.9	0.7	47	Crude	NA
Cai et al., 2021	mmol/L	Investigator	2.7	0.7	30	2.3	0.7	21	Crude	NA

3.30.2. Forest Plot for Included Study Comparing Bariatric Surgery in Women With and Without PCOS for LDL-Cholesterol



3.30.3. Funnel Plot for Assessment of Publication Bias

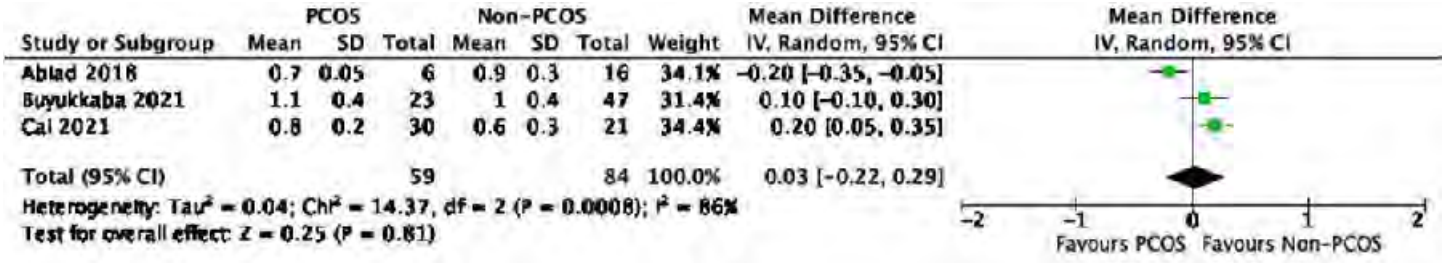


OUTCOME 3.31. Triglycerides

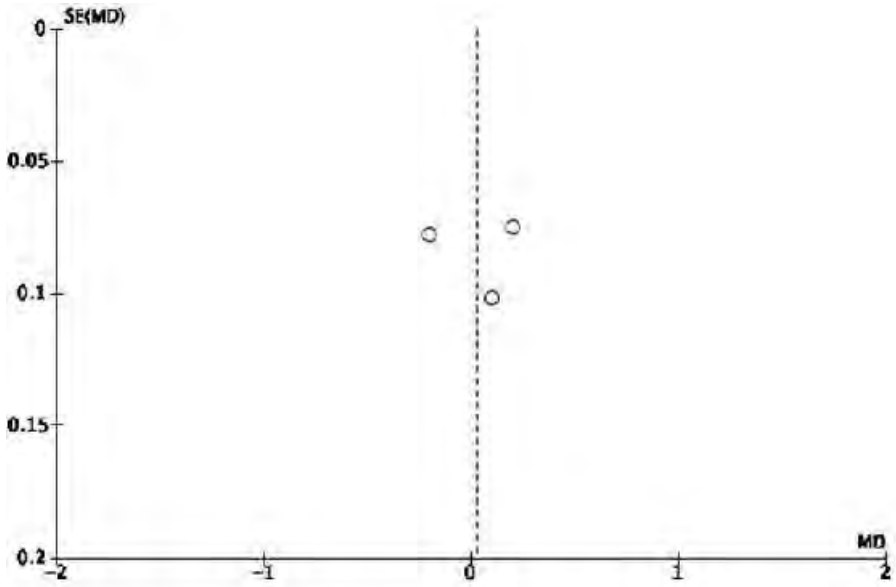
3.31.1. Individual Study Table Data

OUTCOME: Triglycerides										
		OUTCOME TYPE: Continuous								
		COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Abiad et al., 2018	mmol/L	Investigator	0.7	0.05	6	0.9	0.3	16	Crude	NA
Buyukkaba et al., 2022	mmol/L	Investigator	1.1	0.4	23	1.0	0.4	47	Crude	NA
Cai et al., 2021	mmol/L	Investigator	0.8	0.2	30	0.6	0.3	21	Crude	NA

3.31.2. Forest Plot for Included Study Comparing Bariatric Surgery in Women With and Without PCOS for Triglycerides



3.31.3. Funnel Plot for Assessment of Publication Bias

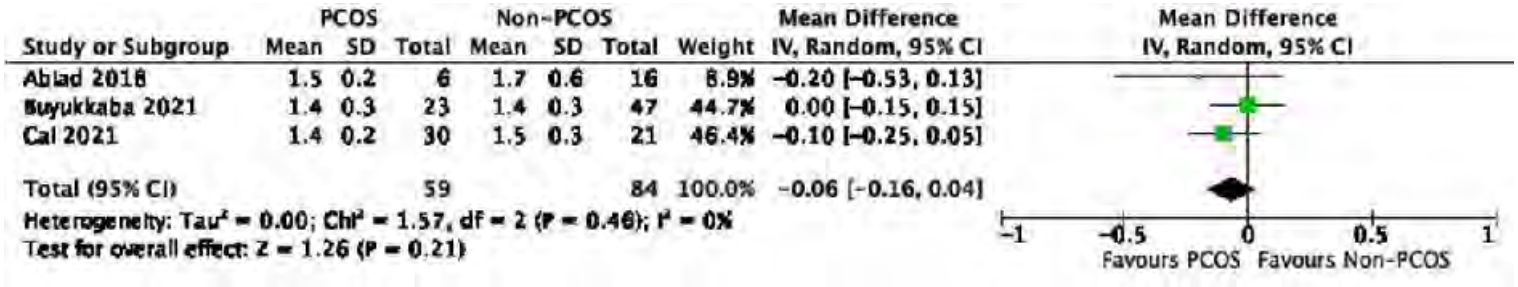


OUTCOME 3.32. HDL-Cholesterol

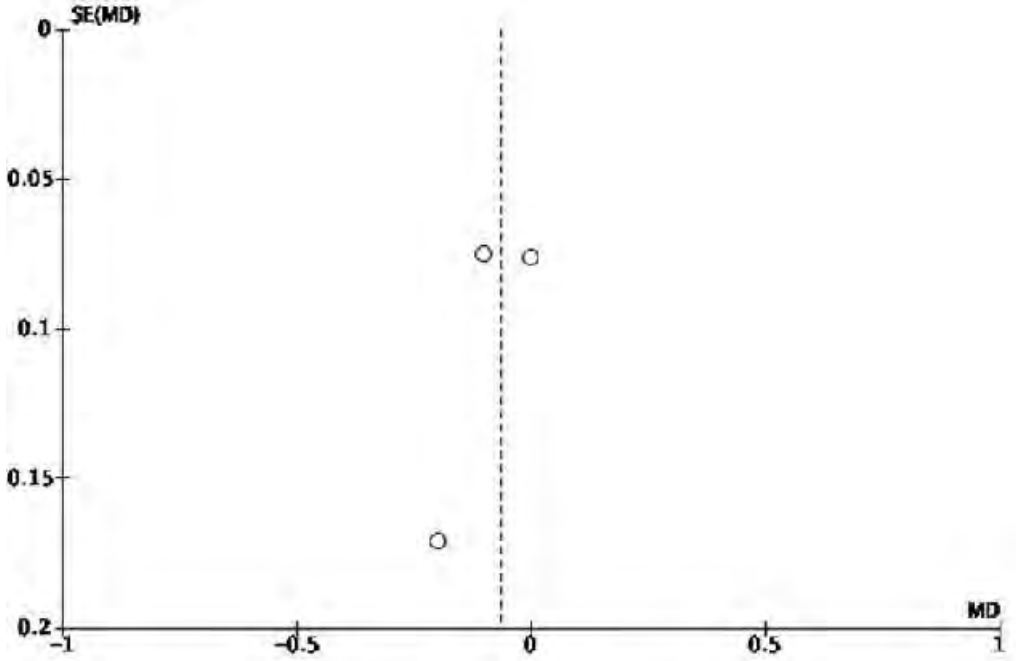
3.32.1. Individual Study Data Table

OUTCOME: HDL-cholesterol										**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Abiad et al., 2018	mmol/L	Investigator	1.5	0.2	6	1.7	0.6	16	Crude	NA
Buyukkaba et al., 2022	mg/dL	Investigator	1.4	0.3	23	1.4	0.3	47	Crude	NA
Cai et al., 2021	mmol/L	Investigator	1.4	0.2	30	1.5	0.3	21	Crude	NA

3.32.2. Forest Plot for Included Study Comparing Bariatric Surgery in Women With and Without PCOS for HDL-Cholesterol



3.32.3. Funnel Plot for Assessment of Publication Bias

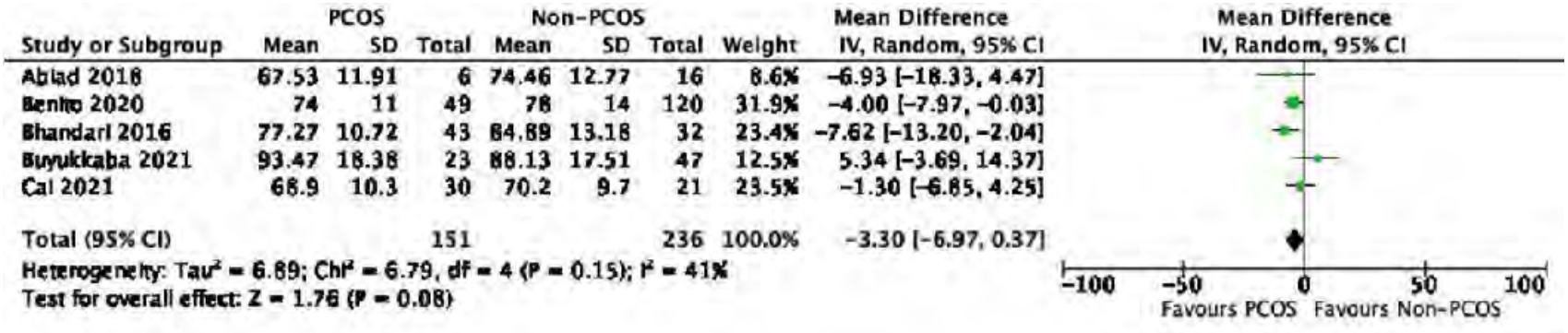


OUTCOME 3.33. Body Weight
3.33.1. Individual Study Data Table

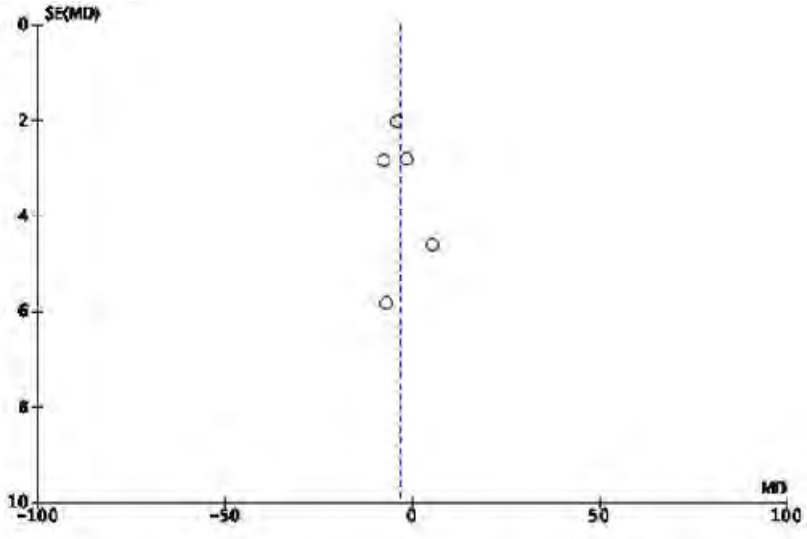
OUTCOME: Body weight										
		OUTCOME TYPE: Continuous								
		COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Abiad et al., 2018	kg	Investigator	67.53	11.91	6	74.46	12.77	16	Crude	NA
Benito et al., 2020	kg	Investigator	74	11	49	78	14	120	Crude	NA
Bhandari et al., 2016	kg	Investigator	77.27	10.72	43	84.89	13.18	32	Crude	NA
Buyukkaba et al., 2022	kg	Investigator	93.47	18.38	23	88.13	17.51	47	Crude	NA
Cai et al., 2021	Kg	Investigator	68.9	10.3	30	70.2	9.7	21	Crude	NA
Casals et al., 2021	Kg	Investigator	72.46	11.52	43	77.39	15.34	165	Crude	NA

*Casals et al., 2021 not included in the meta-analysis due to cross-sectional study design

3.33.2. Forest Plot for Included Study Comparing Bariatric Surgery in Women With and Without PCOS for Body Weight



3.33.3. Funnel Plot for Assessment of Publication Bias



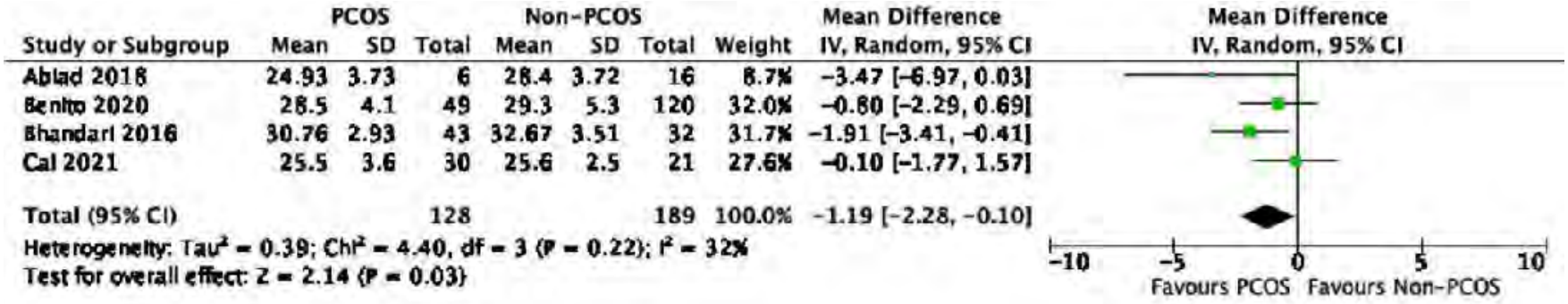
OUTCOME 3.34. Body Mass Index

3.34.1. Individual Study Data Table

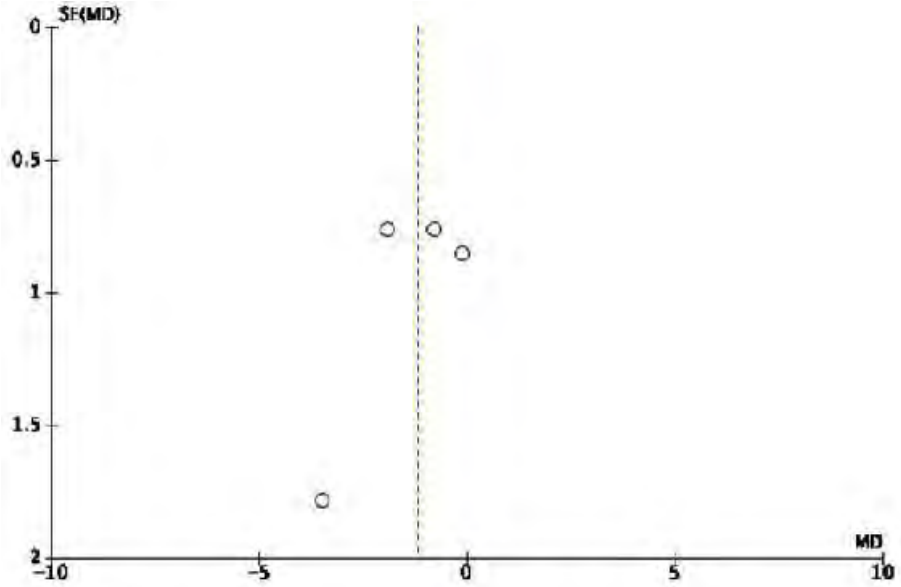
OUTCOME: BMI										**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Abiad et al., 2018	kg/m2	Investigator	24.93	3.73	6	28.40	3.72	16	Crude	NA
Benito et al., 2020	kg/m2	Investigator	28.5	4.1	49	29.3	5.3	120	Crude	NA
Bhandari et al., 2016	kg/m2	Investigator	30.76	2.93	43	32.67	3.51	32	Crude	NA
Cai et al., 2021	kg/m2	Investigator	25.5	3.6	30	25.6	2.5	21	Crude	NA
Casals et al., 2021	kg/m2	Investigator	27.73	4.34	43	29.19	5.23	165	Crude	NA

*Casals et al., 2021 not included in the meta-analysis due to cross-sectional study design

3.34.2. Forest Plot for Included Study Comparing Bariatric Surgery in Women With and Without PCOS for BMI



3.34.3. Funnel Plot for Assessment of Publication Bias

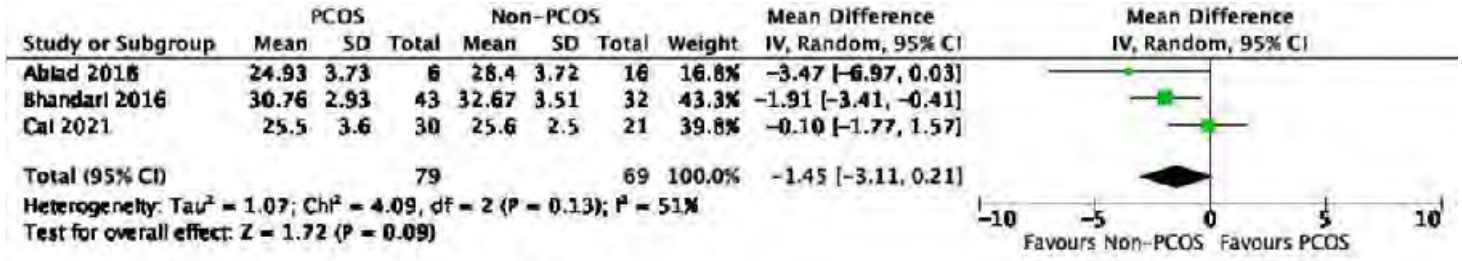


OUTCOME 3.35. % Total Weight Loss

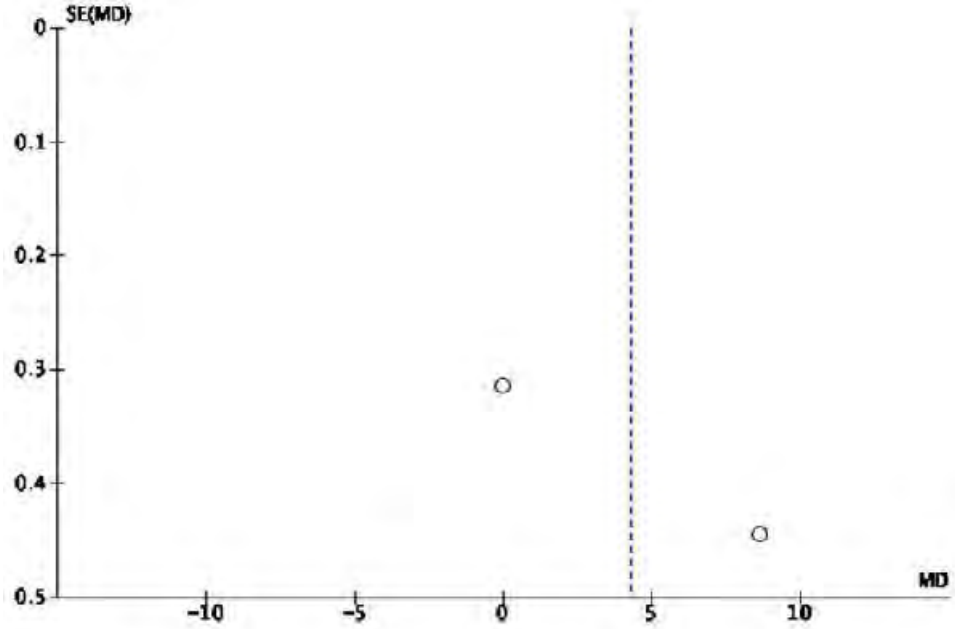
3.35.1. Individual Study Data Table

OUTCOME: % Total Weight Loss						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Ahmed et al., 2022	%	Investigator	32.6	1.3	24	32.6	1.2	51	Crude	NA
Tatarchuk et al., 2022	%	Investigator	33.4	2.1	33	24.8	1.6	40	Crude	NA

3.35.2. Forest Plot for Included Study Comparing Bariatric Surgery in Women With and Without PCOS for % Total Weight Loss



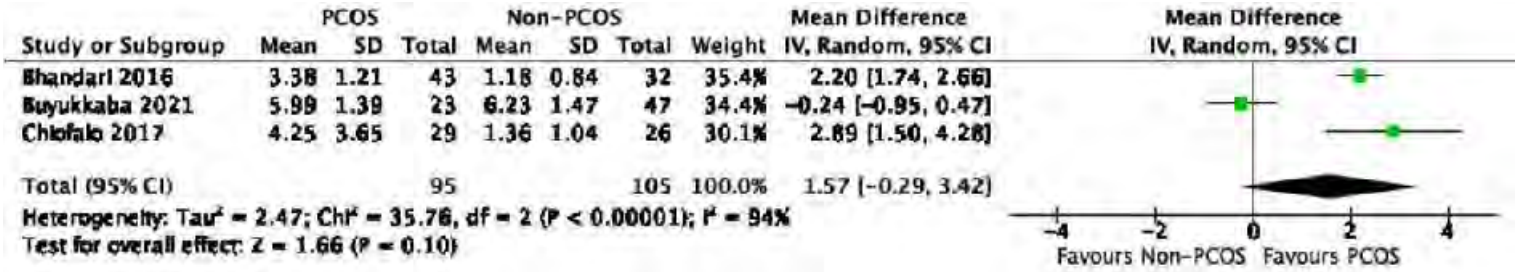
3.35.3. Funnel Plot for Assessment of Publication Bias



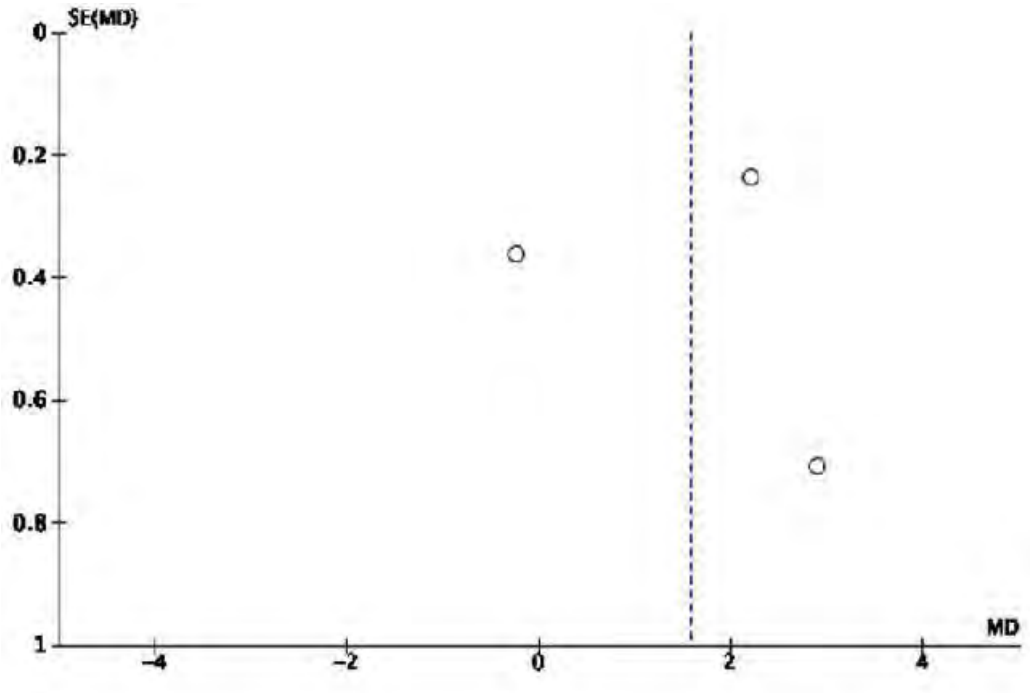
OUTCOME 3.36. Anti-Mullerian Hormone
3.36.1. Individual Study Data Table

OUTCOME: AMH										**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Bhandari et al., 2016	Not reported	Not reported	3.38	1.21	43	1.18	0.84	32	Crude	NA
Buyukkaba et al., 2021	ng/mL	ELISA	5.99	1.39	23	6.23	1.47	47	Crude	NA
Chiofalo et al., 2017	ng/mL	ELISA	4.25	3.65	29	1.36	1.04	26	Crude	NA

3.36.2. Forest Plot for Included Study Comparing Bariatric Surgery in Women With and Without PCOS for AMH



3.36.3. Funnel Plot for Assessment of Publication Bias

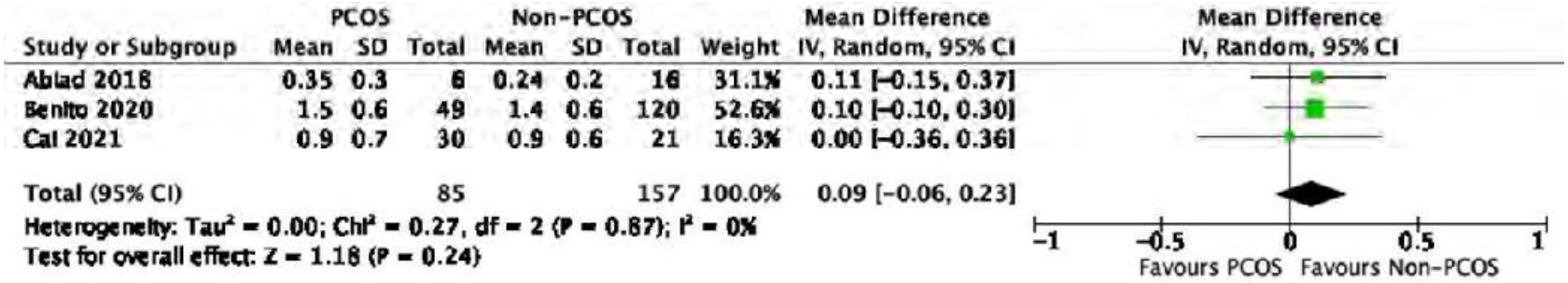


OUTCOME 3.37. Total Testosterone

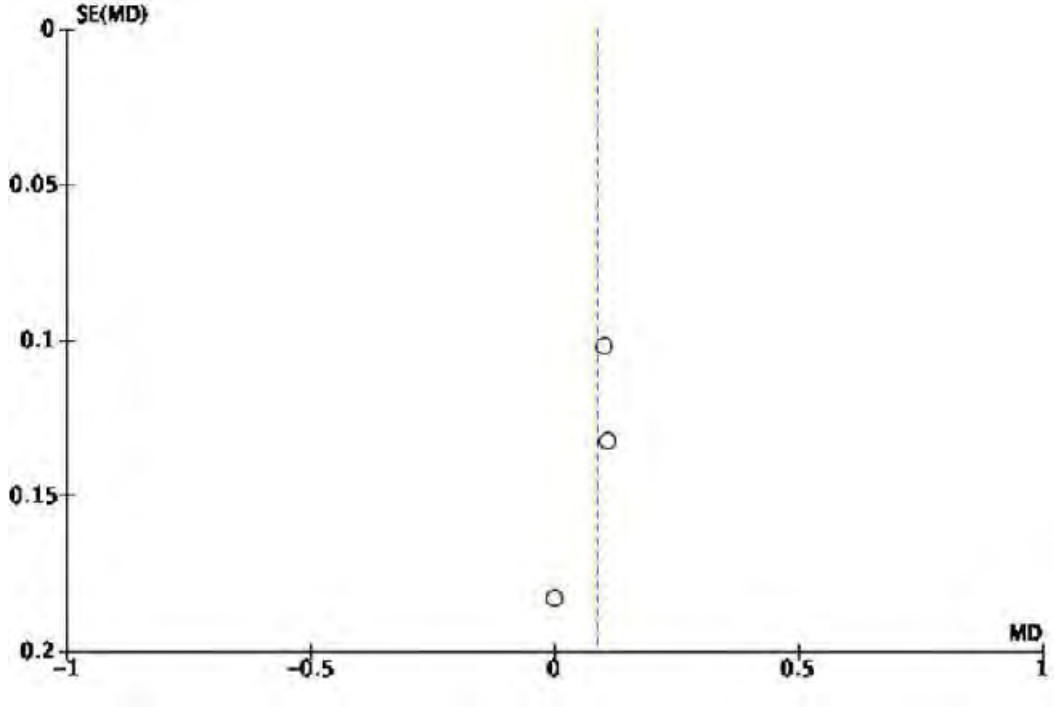
3.37.1. Individual Study Data Table

OUTCOME: Total testosterone										
		COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Abiad et al., 2018	ng/dL	Investigator	0.35	0.3	6	0.24	0.2	16	Crude	NA
Benito et al., 2020	nmol/L	Investigator	1.5	0.6	49	1.4	0.6	120	Crude	NA
Cai et al., 2021	nmol/L	Investigator	0.9	0.7	30	0.9	0.6	21	Crude	NA

3.37.2. Forest Plot for Included Study Comparing Bariatric Surgery in Women With and Without PCOS for Total Testosterone



3.37.3 Funnel Plot for Assessment of Publication Bias

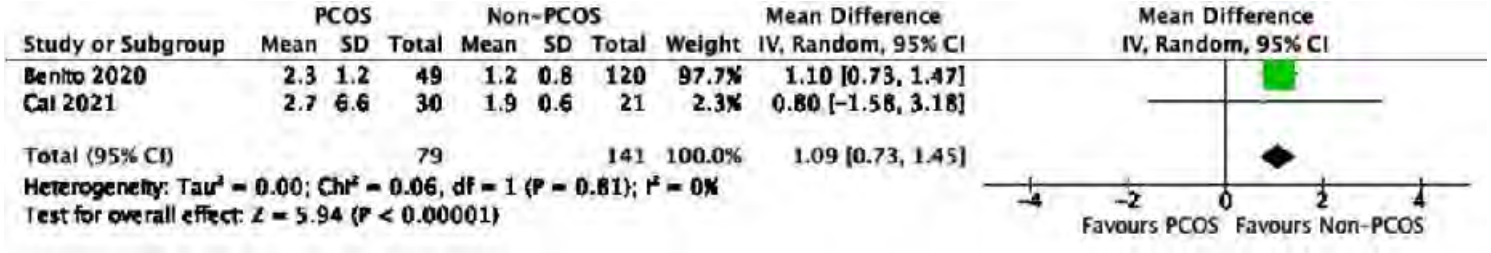


OUTCOME 3.38. Free Testosterone

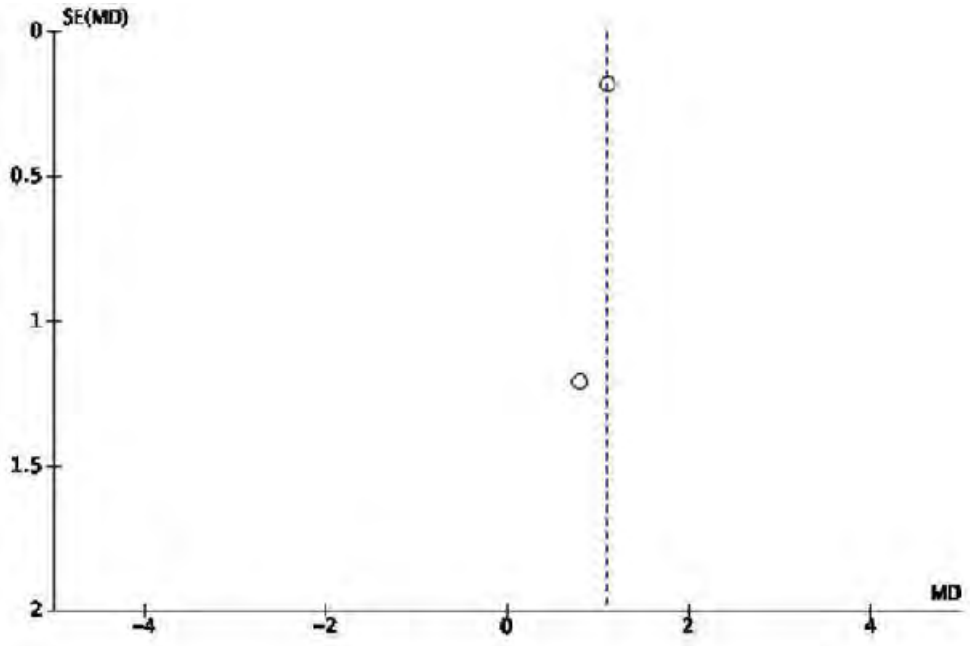
3.38.1. Individual Study Data Table

OUTCOME: Free testosterone						**OUTCOME TYPE:** Continuous				
		COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Benito et al., 2020	pmol/L	Investigator	23	12	49	12	8	120	Crude	NA
Cai et al., 2021	nmol/L	Investigator	2.7	6.6	30	1.9	0.6	21	Crude	NA

3.38.2. Forest Plot for Included Study Comparing Bariatric Surgery in Women With and Without PCOS for Free Testosterone



3.38.3. Funnel Plot for Assessment of Publication Bias

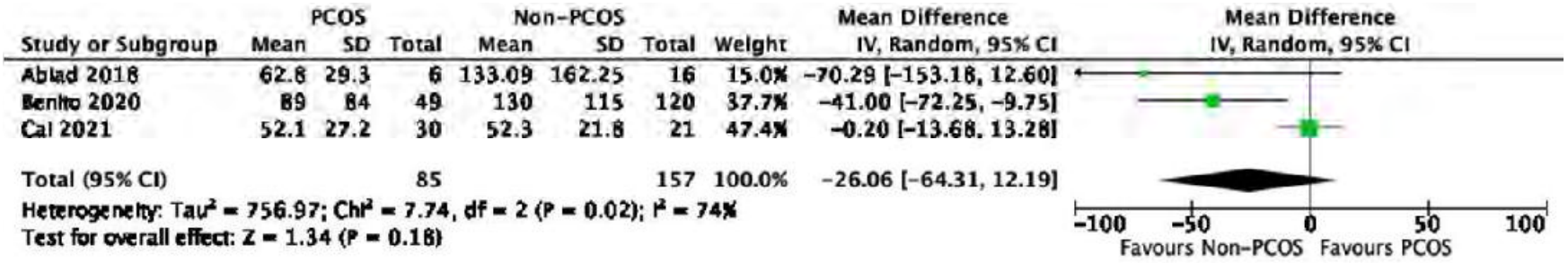


OUTCOME 3.39. Sex Hormone Binding Globulin

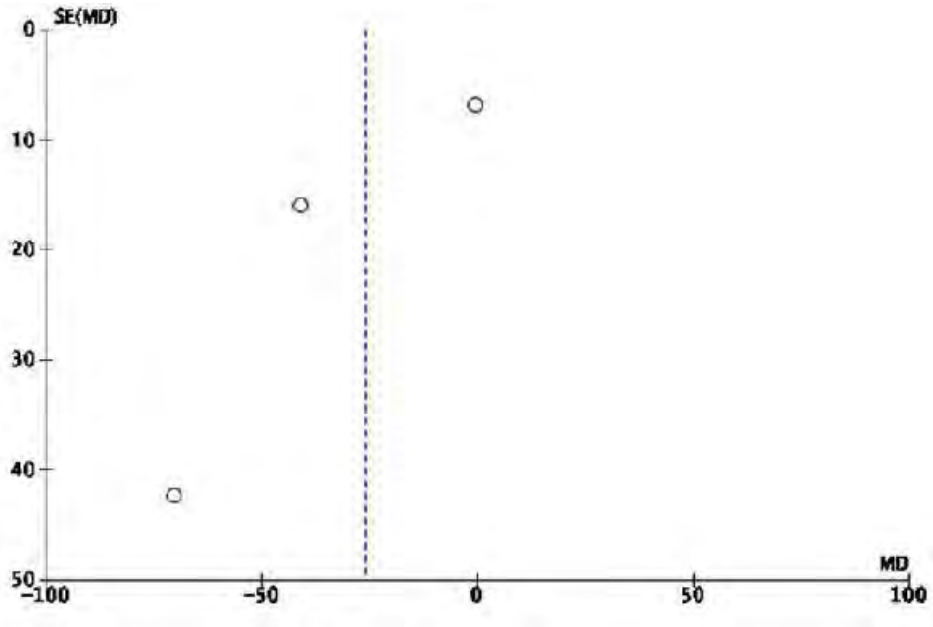
3.39.1. Individual Study Data Level

OUTCOME: SHBG										**OUTCOME TYPE:** Continuous
		COMPARISON (if applicable): PCOS vs non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Sample size (n within this group)**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Sample size (n within this group)**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Abiad et al., 2018	nmol/L	Investigator	62.8	29.3	6	133.09	162.25	16	Crude	NA
Benito et al., 2020	nmol/L	Investigator	89	84	49	130	115	120	Crude	NA
Cai et al., 2021	nmol/L	Investigator	52.1	27.2	30	52.3	21.8	21	Crude	NA

3.39.2. Forest Plot for Included Study Comparing Bariatric Surgery in Women With and Without PCOS for Free Testosterone



3.39.3. Funnel Plot for Assessment of Publication Bias



7. GRADE ASSESSMENTS AND EVIDENCE PROFILE

COMPARISON: Bariatric Surgery vs. Medical Therapy (Metformin + OCP)												
	Quality assessment						No. participants					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**BS**	**Met + OCP**	**Effect, fixed [95% CI]**	**Favours**	**Certainty**	**Importance**
Outcome: Adverse events												
1	NRT[2]	Serious[3]	None	No serious indirectness	Serious imprecision[4]	None	40	41	OR 0.14 [0.01, 2.72]	None	⨁◯◯◯ Very low	CRITICAL
Outcome: Fasting glucose												
1	NRT	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	40	41	MD -0.80 [-1.00, -0.60]	Bariatric surgery	⨁◯◯◯ Very low	CRITICAL
Outcome: Fasting insulin												
1	NRT	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	40	41	MD -16.20 [-22.96, -9.44]	Bariatric surgery	⨁◯◯◯ Very low	CRITICAL
Outcome: Total cholesterol												
1	NRT	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	40	41	MD -0.30 [-0.76, 0.16]	None	⨁◯◯◯ Very low	CRITICAL
Outcome: Triglycerides												
1	NRT	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	40	41	MD -0.70 [-0.97, -0.43]	Bariatric Surgery	⨁◯◯◯ Very low	CRITICAL
Outcome: LDL-cholesterol												
1	NRT	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	40	41	MD -0.30 [-0.37, -0.23]	Bariatric Surgery	⨁◯◯◯ Very low	CRITICAL
Outcome: HDL-cholesterol												
1	NRT	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	40	41	MD 0.00 [-0.11, 0.11]	None	⨁◯◯◯ Very low	CRITICAL
Outcome: Hemoglobin A1C												
1	NRT	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	40	41	MD -0.40 [-0.58, -0.22]	Bariatric Surgery	⨁◯◯◯ Very low	CRITICAL
Outcome: Body weight												

[2] NRT = Non-randomized trial

[3] Downgraded as the majority of evidence is at high risk of bias

[4] Downgraded once for all outcomes due to imprecision as based on one study

1	NRT	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	40	41	MD -16.60 [-21.05, -12.15]	Bariatric Surgery	⨁◯◯◯ Very low	CRITICAL
Outcome: Body mass index												
1	NRT	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	40	41	MD -6.40 [-7.66, -5.14]	Bariatric Surgery	⨁◯◯◯ Very low	CRITICAL
Outcome: Total testosterone												
1	NRT	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	40	41	MD -0.70 [-1.07, -0.33]	Bariatric Surgery	⨁◯◯◯ Very low	CRITICAL
Outcome: SHBG												
1	NRT	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	40	41	MD 39.60 [31.10, 48.10]	Bariatric Surgery	⨁◯◯◯ Very low	CRITICAL

COMPARISON: Bariatric Surgery vs. Conservative Management												
	Quality assessment						No. participants					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**BS**	**Conservative**	**Effect, fixed [95% CI]**	**Favours**	**Certainty**	**Importance**
Outcome: Ovulation												
1	Cohort	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	33	27	OR 25.87 [6.50, 103.06]	Bariatric Surgery	⨁◯◯◯ Very low	CRITICAL
Outcome: % Total Weight Loss												
1	Cohort	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	33	27	MD 29.80 [29.07, 30.53]	Bariatric surgery	⨁◯◯◯ Very low	CRITICAL
Outcome: Intermenstrual Length												
1	Cohort	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	33	27	MD -43.00 [-46.28, -39.72]	Bariatric surgery	⨁◯◯◯ Very low	CRITICAL

Downgraded as the majority of evidence is at high risk of bias

[2] Downgraded once for all outcomes due to imprecision as based on one study

COMPARISON: Bariatric Surgery in PCOS vs Non-PCOS												
	Quality assessment						No. participants					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**PCOS**	**Non-PCOS**	**Effect, fixed [95% CI]**	**Favours**	**Certainty**	**Importance**
Outcome: Regular Menstrual Cycles												
1	Cohort	Serious[1]	None	No serious indirectness	No serious imprecision	None	43	32	OR 3.36 [1.28, 8.84]	PCOS	⨁◯◯◯ Very low	CRITICAL
Outcome: Ovulation												
1	Cohort	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	33	40	OR 4.07 [1.38, 12.00]	PCOS	⨁◯◯◯ Very low	CRITICAL
Outcome: Live Birth Rate												
1	Cohort	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	49	120	OR 1.83 [0.88, 3.79]	None	⨁◯◯◯ Very low	CRITICAL
Outcome: Pregnancy Rate												
1	Cohort	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	49	120	OR 2.07 [1.02, 4.18]	PCOS	⨁◯◯◯ Very low	CRITICAL
Outcome: Multiple Gestations												
1	Cohort	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	17	27	OR 0.50 [0.02, 13.11]	None	⨁◯◯◯ Very low	CRITICAL
Outcome: Miscarriage Rate												
1	Cohort	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	20	30	OR 2.47 [0.37, 16.32]	None	⨁◯◯◯ Very low	CRITICAL
Outcome: Preterm Birth												
1	Cohort	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	17	27	OR 5.57 [0.53, 58.69]	None	⨁◯◯◯ Very low	CRITICAL
Outcome: Pre-Eclampsia												
1	Cohort	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	17	27	OR 3.47 [0.29, 41.53]	None	⨁◯◯◯ Very low	CRITICAL
Outcome: Gestational Diabetes												
1	Cohort	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	17	27	OR 0.78 [0.07, 9.34]	None	⨁◯◯◯ Very low	CRITICAL
Outcome: Severe Iron Deficiency in Pregnancy												
1	Cohort	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	17	27	OR 0.50 [0.02, 13.11]	None	⨁◯◯◯ Very low	CRITICAL
Outcome: Placenta Previa												

1	Cohort	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	17	27	OR 0.50 [0.02, 13.11]	None	⨁◯◯◯ Very low	CRITICAL
Outcome: Caesarean Section												
1	Cohort	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	17	27	OR 0.61 [0.13, 2.79]	None	⨁◯◯◯ Very low	CRITICAL
Outcome: Labour Induction												
1	Cohort	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	17	27	OR 0.29 [0.01, 6.45]	None	⨁◯◯◯ Very low	CRITICAL
Outcome: Instrumental Delivery												
1	Cohort	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	17	27	OR 1.67 [0.21, 13.10]	None	⨁◯◯◯ Very low	CRITICAL
Outcome: Low Birth Weight												
1	Cohort	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	17	27	OR 5.57 [0.53, 58.69]	None	⨁◯◯◯ Very low	CRITICAL
Outcome: Chromosomal Abnormalities												
1	Cohort	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	17	27	OR 0.50 [0.02, 13.11]	None	⨁◯◯◯ Very low	CRITICAL
Outcome: Congenital Malformation												
1	Cohort	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	17	27	OR 5.00 [0.19, 130.02]	None	⨁◯◯◯ Very low	CRITICAL
Outcome: Neonatal Jaundice												
1	Cohort	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	17	27	OR 1.63 [0.09, 27.84]	None	⨁◯◯◯ Very low	CRITICAL
Outcome: Neonatal Hypoglycemia												
1	Cohort	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	17	27	OR 0.50 [0.02, 13.11]	None	⨁◯◯◯ Very low	CRITICAL
Outcome: Neonatal Hypotonia												
1	Cohort	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	17	27	OR 5.00 [0.19, 130.02]	None	⨁◯◯◯ Very low	CRITICAL
Outcome: Neonatal Intensive Care Unit Admission												
1	Cohort	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	17	27	OR 1.63 [0.09, 27.84]	None	⨁◯◯◯ Very low	CRITICAL
Outcome: Intermenstrual Length												
1	Cohort	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	33	40	MD -7.60 [-9.16, -6.04]	PCOS	⨁◯◯◯ Very low	CRITICAL
Outcome: AMH												

3	Cohort	Serious[1]	None	No serious indirectness	No serious imprecision[2]	None	95	105	MD 1.57 [-0.29, 3.42]	None	⨁◯◯◯ Very low	CRITICAL
Outcome: Birth Weight												
1	Cohort	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	17	27	MD -392.00 [-759.64, -24.36]	Non-PCOS	⨁◯◯◯ Very low	CRITICAL
Outcome: Apgar Score												
1	Cohort	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	17	27	MD -0.40 [-0.82, 0.02]	None	⨁◯◯◯ Very low	CRITICAL
Outcome: Adverse Events												
2	Cohort	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	39	56	Not estimable	None	⨁◯◯◯ Very low	CRITICAL
Outcome: Hemoglobin A1C												
1	Cohort	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	30	21	MD -0.20 [-0.52, 0.12]	None	⨁◯◯◯ Very low	CRITICAL
Outcome: Fasting Glucose												
3	Cohort	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	85	157	MD -0.20 [-0.35, -0.06]	PCOS	⨁◯◯◯ Very low	CRITICAL
Outcome: Fasting Insulin												
3	Cohort	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	85	157	MD 1.30 [0.24, 2.35]	Non-PCOS	⨁◯◯◯ Very low	CRITICAL
Outcome: Total Cholesterol												
2	Cohort	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	53	68	MD 0.27 [-0.08, 0.62]	None	⨁◯◯◯ Very low	CRITICAL
Outcome: LDL Cholesterol												
3	Cohort	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	59	84	MD 0.01 [-0.61, 0.63]	None	⨁◯◯◯ Very low	CRITICAL
Outcome: Triglycerides												
3	Cohort	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	59	84	MD 0.03 [-0.22, 0.29]	None	⨁◯◯◯ Very low	CRITICAL
Outcome: HDL Cholesterol												
3	Cohort	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	59	84	MD -0.06 [-0.16, 0.04]	None	⨁◯◯◯ Very low	CRITICAL
Outcome: Body Weight												
5	Cohort	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	151	236	MD -3.30 [6.97, 0.37]	None	⨁◯◯◯ Very low	CRITICAL
Outcome: Body Mass Index												

4	Cohort	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	128	189	MD -1.19 [-2.28, -0.10]	PCOS	⨁◯◯◯ Very low	CRITICAL
Outcome: % Total Weight Loss												
2	Cohort	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	57	91	MD 4.29 [-4.13, 12.72]	None	⨁◯◯◯ Very low	CRITICAL
Outcome: Total Testosterone												
3	Cohort	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	85	157	MD 0.09 [-0.06, 0.23]	None	⨁◯◯◯ Very low	CRITICAL
Outcome: Free Testosterone												
2	Cohort	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	79	141	MD 1.09 [0.73, 1.45]	Non-PCOS	⨁◯◯◯ Very low	CRITICAL
Outcome: SHBG												
3	Cohort	Serious[1]	None	No serious indirectness	Serious imprecision[2]	None	85	157	MD -26.06 [-64.31, 12.19]	None	⨁◯◯◯ Very low	CRITICAL

Downgraded as the majority of evidence is at high risk of bias

[2] Downgraded once for all outcomes due to imprecision as based on one study and/or wide confidence interval

APPENDIX. STUDY CHARACTERISTICS AND QUALITY APPRAISAL

Study ID	Abiad 2018	
Study Citation	Abiad, F., Khalife, D., Safadi, B., Alami, R., Awwad, J., Khalifeh, F., & Ghazeeri, G. (2018). The effect of bariatric surgery on inflammatory markers in women with polycystic ovarian syndrome. *Diabetes and Metabolic Syndrome: Clinical Research and Reviews*, 12(6), 999-1005. https://dx.doi.org/10.1016/j.dsx.2018.06.013	
Study Country	Lebanon	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	Females with obesity and PCOS presenting to the bariatric surgery unit	
PCOS diagnostic criteria	Rotterdam	
N per group	PCOS – 6 Non-PCOS - 16	
Setting	University Hospital	
Intervention/ indicator	Sleeve gastrectomy	
Comparison/ Control	Females with obesity who did not have a diagnosis of PCOS presenting to the bariatric surgery unit	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Primary: Change in inflammatory markers (CRP and adiponectin) and anthropometric measurements after bariatric surgery Secondary: Rate of improvement in these parameters; correlation between change in CRP, adiponectin and metabolic profile after weight loss via sleeve gastrectomy	
Inclusion criteria reported?	Yes	Female Age 18-45 Eligible for sleeve gastrectomy surgery for management of obesity
Exclusion criteria reported?	Yes	Exclusion criteria were: pregnancy, BMI <40, Hx of cancer or liver disease, Hx of previous bariatric surgery, tying to conceive.
Does the study have a clearly focused question?	Yes Partial No Not reported	Yes
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Yes
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes
Were the outcomes measured appropriate?	Yes Partial No Not reported	Yes

Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Yes
Was matching performed?		Yes Partial No Not reported	No
Summary of Result/s		16 women without PCOS and 6 with PCOS underwent sleeve gastrectomy. At 12-months follow up, both groups lost >30% BW (36.28% PCOS and 33.04% non-PCOS).	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Yes
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	Yes
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes All anthropometrical measurements were made by the same trained staff.
	Were outcomes assessed objectively and independently?	Yes Yes Partial No Not reported	Yes
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**		3/19 were lost from the control group at 6 months; 0/6 from the PCOS group. It appears more were lost to follow up that are not reported according to the limitations but this is not clear.
	What percentage of the individuals were	Not reported	As above

	not included in the analysis?		
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported.
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported – No report of a power calculation and small sample size but significant differences were found
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		High	Few criteria have been fulfilled and the conclusions of the study are likely to be affected.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No All outcomes high risk of bias	

Study ID	Ahmed 2022	
Study Citation	Ahmed, B., Ammori, B.J., Akhtar, K., Senapati, S., New, J.P., & Syed, A.A. (2022). Weight loss and metabolic outcomes in women with or without polycystic ovarian syndrome after Roux-en-Y gastric bypass: A case-matched study. *The Surgeon: Journal of the Royal Colleges of Surgeons of Edinburgh and Ireland*, 20(3), 137-141. https://dx.doi.org/10.1016/j.surge.2021.02.012	
Study Country	UK	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	Women with PCOS undergoing gastric bypass surgery	
PCOS diagnostic criteria	Rotterdam	
N per group	PCOS - 30 Non-PCOS - 60	
Setting	University Hospital	
Intervention/ indicator	Roux-en-Y gastric bypass surgery	
Comparison/ Control	Women without PCOS undergoing gastric bypass surgery	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Primary: post-operative weight loss as measured by percent total weight loss or percent excess BMI loss at 12 and 24 months following gastric bypass Secondary: A1C, remission in DM, BP, remission in hypertension, OSA remission	
Inclusion criteria reported?	Yes	Patients who underwent primary RYGB
Exclusion criteria reported?	Yes	Patients who had single anastomosis gastric bypass or revisional surgery
Does the study have a clearly focused question?	Yes Partial No Not reported	Yes
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Yes

Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes
Were the outcomes measured appropriate?	Yes Partial No Not reported	Yes
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	Yes
Was matching performed?	Yes Partial No Not reported	Yes Age (+/- 5 years) Preoperative BMI (+/- 5 kg/m2) Presence of T2DM
Summary of Result/s	Women with and without PCOS had similar reduction in %TWL as well as improvement in A1C, resolution of OSA and improvement in blood pressure.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS – **Other than the exposure under investigation, were the groups selected from similar populations?**	Yes	Yes
SELECTION BIAS – **Was the exposed cohort truly representative?**	Yes Partial No Not reported	Yes
SELECTION BIAS – **Is it clear that the outcome of interest was not present at the start of study?**	Yes Partial No Not reported	Yes

PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	Yes
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Not reported. There is no information about how these data were collected.
	Were outcomes assessed objectively and independently?	Yes Yes Partial No Not reported	Yes
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**		83.3% follow up rate (does not specify difference in dropout rate between the groups) 6/30 lost to follow-up in 1st 12 months from PCOS group; 9/60 from non-PCOS.
	What percentage of the individuals were not included in the analysis?		20% in PCOS group, 15% in non-PCOS
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported.

CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported – No report of a power calculation and small sample size but significant differences were found
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		High	Few criteria have been fulfilled and the conclusions of the study are likely to be affected.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No All outcomes high risk of bias	

Study ID	Benito 2020
Study Citation	Benito, E., Gomez-Martin, J.M., Vega-Pinero, B., Priego, P., Galindo, J., Escobar-Morreale, H.F., & Botella-Carretero, J.I. (2020). Fertility and pregnancy outcomes in women with polycystic ovary syndrome following bariatric surgery. *Journal of Clinical Endocrinology and Metabolism*, 105(9), E3384-E3391. https://dx.doi.org/10.1210/clinem/dgaa439
Study Country	Spain
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	Premenopausal women with PCOS presenting for bariatric surgery
PCOS diagnostic criteria	NIH

N per group	PCOS - 49 Non-PCOS - 120	
Setting	University Hospital	
Intervention/ indicator	Bariatric surgery	
Comparison/ Control	Premenopausal women without PCOS presenting for bariatric surgery	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Fertility and pregnancy outcomes (investigator reported)	
Inclusion criteria reported?	Yes Partial No Not reported	Not reported.
Exclusion criteria reported?	Yes Partial No Not reported	Not reported.
Does the study have a clearly focused question?	Yes Partial No Not reported	Yes
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Yes
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Not reported
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Not reported
Were the outcomes measured appropriate?	Yes Partial No Not reported	Yes
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	Yes
Was matching performed?	Yes Partial No Not reported	No
Summary of Result/s	In women seeking fertility, pregnancy and live birth rates were higher among women with PCOS than without PCOS. The time to achieve the first pregnancy after surgery was similar between groups, as were maternal and neonatal complications.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Yes
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	Yes
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Partial Some outcomes were measured at sites outside of the original study centre, therefore it is not clear if these were standardized.
	Were outcomes assessed objectively and independently?	Yes Yes Partial No Not reported	Partial Some outcomes were measured at sites outside of the original study centre, therefore it is not clear if these were standardized.
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**		Full data for 49 women with PCOS and 120 women without PCOS.
	What percentage of the individuals were not included in the analysis?		Only women with complete data were included in the study and analysis.
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported.
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes

OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported – No report of a power calculation and small sample size but significant differences were found
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		High	Few criteria have been fulfilled and the conclusions of the study are likely to be affected.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No All outcomes high risk of bias	

Study ID	Bhandari 2016	
Study Citation	Bhandari, S., Ganguly, I., Bhandari, M., Agarwal, P., Singh, A., Gupta, N., & Mishra, A. (2016). Effect of sleeve gastrectomy bariatric surgery-induced weight loss on serum AMH levels in reproductive aged women. *Gynecological Endocrinology*, 32(10), 799-802. https://dx.doi.org/10.3109/09513590.2016.1169267	
Study Country	India	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	Females aged between 20 and 35 years with PCOS and BMI >35 kg/m2 undergoing sleeve gastrectomy	
PCOS diagnostic criteria	Rotterdam	
N per group	PCOS – 43 Non-PCOS - 32	
Setting	Tertiary Care Hospital	
Intervention/ indicator	Bariatric surgery (sleeve gastrectomy)	
Comparison/ Control	Females aged between 20 and 35 years and BMI >35 kg/m2 undergoing sleeve gastrectomy without PCOS	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Primary: change in AMH level Secondary: change in weight, BMI, and menstrual cycle regularity	
Inclusion criteria reported?	Yes Partial No Not reported	Yes. Surgery between 2012 and 2015 Age 20-35 Female BMI >35 Premenopausal with intact uterus and ovaries
Exclusion criteria reported?	Yes	Yes.

		Partial No Not reported	Hormonal treatment Fertility drugs Systemic disease (e.g., hypothyroidism, hyperprolactinemia) Did not report for follow up Had a surgical complication
Does the study have a clearly focused question?		Yes Partial No Not reported	Yes
Is a cohort study the appropriate design to answer this question?		Yes Partial No Not reported	Yes
Does the study have specified inclusion/ exclusion criteria?		Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Partial. Participants with surgical complications or who did not report for follow up were excluded from the study/analysis.
Were the outcomes measured appropriate?		Yes Partial No Not reported	Partial.
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	No. Only 6 months of follow-up
Was matching performed?		Yes Partial No Not reported	No
Summary of Result/s		There was a statistically significant change in AMH and normalization of menstrual irregularity with bariatric surgery in women with and without PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes Partial No Not reported	Partial. Unclear. No baseline demographics aside from age, BMI and weight.
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Yes
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes

PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	Yes
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Yes Partial No Not reported	Yes
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**		Not reported.
	What percentage of the individuals were not included in the analysis?		Outcomes were reported for all of the participants included in the study.
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported.
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported – No report of a power calculation and small sample size but significant differences were found
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			

What is the overall risk of bias?	High	Few criteria have been fulfilled and the conclusions of the study are likely to be affected.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?	No All outcomes high risk of bias	

Study ID	Buyukkaba 2021	
Study Citation	Buyukkaba, M., Turgut, S., Ilhan, M. M., Ekinci, I., Yayllm, I., Zeybek, S. U., Turan, S., Tasan, E., & Karaman, O. (2021). Anti-Mullerian Hormone Levels Increase after Bariatric Surgery in Obese Female Patients with and Without Polycystic Ovary Syndrome. *Hormone and Metabolic Research,* 54(3), 194-198. https://dx.doi.org/10.1055/a-1756-4798	
Study Country	Turkey	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	Females with obesity and PCOS of reproductive age	
PCOS diagnostic criteria	Rotterdam	
N per group	PCOS – 23 Bon-PCOS – 47	
Setting	University Hospital	
Intervention/ indicator	Metabolic surgery - 62 laparoscopic sleeve gastrectomy, 8 Roux-en-Y gastric bypass	
Comparison/ Control	Females with obesity of reproductive age without PCOS	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Primary: the effect of weight loss on AMH levels after bariatric surgery	
Inclusion criteria reported?	Yes Partial No Not reported	Yes. Age 18-39 Undergoing bariatric surgery
Exclusion criteria reported?	Yes Partial No Not reported	Yes. Hormonal replacement use Fertility treatment use (e.g., oral contraceptives) Systemic disease - overt DM, hypothyroidism Menopausal status
Does the study have a clearly focused question?	Yes Partial No Not reported	Yes This study aimed to investigate the effect of weight loss after bariatric surgery on AMH levels in morbidly obese female patients with and without PCOS in the reproductive age group.
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Yes
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes.
Were the outcomes measured appropriate?	Yes Partial No Not reported	Yes.

Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	No. Only 6 months of follow-up
Was matching performed?		Yes Partial No Not reported	No
Summary of Result/s		AMH increased following bariatric surgery in women with and without PCOS with no significant difference between groups.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes Partial No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No Small sample size
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFOR MANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	Yes
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Yes Partial No Not reported	Not reported
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**		22/92 participants did not complete the six-month follow up. They were excluded from the study.
	What percentage of the individuals were		Only individuals who completed the six-month follow-up were included in this study.

	not included in the analysis?		
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported.
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported – No report of a power calculation and small sample size but significant differences were found
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		High	Few criteria have been fulfilled and the conclusions of the study are likely to be affected.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No All outcomes high risk of bias	

Study ID	Cai 2021	
Study Citation	Cai, M., Gao, J., Du, L., Cheng, X., Zhou, D., Zhu, J., Qu, S., & Zhang, M. (2021). The Changes in Body Composition in Obese Patients with Polycystic Ovary Syndrome After Laparoscopic Sleeve Gastrectomy: A 12-Month Follow-Up. *Obesity Surgery*, 31(9), 4055-4063. https://dx.doi.org/10.1007/s11695-021-05496-6	
Study Country	China	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	Females with obesity and PCOS between the ages of 18 and 45 years who underwent LSG from May. 2013-Sept 202 at the Shanghai Tenth People's Hospital	
PCOS diagnostic criteria	Rotterdam	
N per group	PCOS – 83 Non-PCOS - 70	
Setting	University Hospital	
Intervention/ indicator	Laparoscopic sleeve gastrectomy	
Comparison/ Control	Females with obesity without PCOS between the ages of 18 and 45 years who underwent LSG from May. 2013-Sept 202 at the Shanghai Tenth People's Hospital	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Primary: Body composition Secondary: Metabolic outcomes	
Inclusion criteria reported?	Yes Partial No Not reported	Yes.
Exclusion criteria reported?	Yes Partial No Not reported	Yes. Age <18, Age >45, Secondary obesity due to endocrine disorders, severe hepatic, renal dysfunction, and/or heart failure, mental illnesses that caused ability to provide informed consent.
Does the study have a clearly focused question?	Yes Partial No Not reported	Yes - the aim was to investigate the effect of LSG on body fat distribution in premenopausal PCOS patients with obesity over a period of 12 months and explore the predictive factors for their body compositions after LSG
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Yes
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes.
Were the outcomes measured appropriate?	Yes Partial No Not reported	Yes.

Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	No. Due to attrition, very few were followed for an extended length of time.
Was matching performed?		Yes Partial No Not reported	No
Summary of Result/s		Both women with and without PCOS had improvements in body composition following LSG.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes Partial No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No Difficult to say. Attrition rate is high.
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFOR MANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	Yes
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Yes Partial No Not reported	Not reported
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**		At three months, only. 48/83 in the PCOS group and 26/70 in the non-PCOS group were seen in follow up. This number decreased at 6 and 12 months.
	What percentage of the individuals were		Only those that participated in the follow up visit were included in the analysis

	not included in the analysis?		
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported.
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported – No report of a power calculation and small sample size but significant differences were found
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		High	Few criteria have been fulfilled and the conclusions of the study are likely to be affected.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No All outcomes high risk of bias	

Study ID	Casals et al., 2021
Study Citation	Casals, G., Andreu, A., Barral, Y., Ventosa, S., Redondo, M., Torres, F., Ibarzabal, A., Manau, D., Carmona, F., Vidal, J., & Flores, L. (2021). Bariatric Surgery on Reproductive Outcomes: the Impact According to the Diagnosis of Polycystic Ovarian Syndrome and Surgical Procedures. *Obesity Surgery,* 31(6), 2590-2598. https://dx.doi.org/10.1007/s11695-021-05297-x
Study Country	Spain
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	Women with PCOS according to the 2003 Rotterdam criteria between the ages of 18-39 years who had bariatric surgery between January 2005 and December 2010
Control population	Women without PCOS according to the 2003 Rotterdam criteria between the ages of 18-39 years who had bariatric surgery between January 2005 and December 2010
PCOS diagnostic criteria	Rotterdam 2003
N per group	PCOS – 43 Non-PCOS - 165
Setting	University hospital

Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)		Reproductive outcomes (self-reported) - menstrual regularity, time to pregnancy, pregnancy, miscarriage, live birth Anthropometric outcomes (self-reported) - weight, BMI	
Does the study have a clearly focused question and/or PICO?		Yes Partial No Not reported	Yes
Inclusion criteria		Yes Partial No Not reported	Yes. Women age 18-39 who underwent bariatric surgery from Jan 2005 to Dec 2010
Exclusion criteria		Yes Partial No Not reported	Not reported.
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Partial. Only inclusion criteria reported
Is a cross sectional or case-control study the appropriate design to answer this question?		Yes Partial No Not reported	No.
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Yes.
Was matching performed?		Yes Partial No Not reported	No.
Summary Result/s		There was an improvement in menstrual regularity and some perinatal outcomes following bariatric surgery, but there was no change in fertility observed following bariatric surgery.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes Partial No Not reported	Yes
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
PERFOR MANCE BIAS	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes Partial No Not reported	Yes

DEDETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes Partial No Not reported	Partial. Participants in the phone interview were asked to recall these outcomes a variable amount of time after bariatric surgery
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Partial because of nature of study
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Partial because of nature of study
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	X% treatment X% control/ comparison Not reported	Not relevant to cross-sectional study
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	Not reported 217/298 women who had surgery during that time period responded to the phone survey - this data is not broken down by PCOS/non-PCOS
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Not reported
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		Low Moderate High Insufficient information	High
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No	

Study ID	Chiofalo 2017	
Study Citation	Chiofalo, F., Ciuoli, C., Formichi, C., Selmi, F., Forleo, R., Neri, O., Vuolo, G., Paffetti, P., & Pacini, F. (2017). Bariatric Surgery Reduces Serum Anti-mullerian Hormone Levels in Obese Women with and Without Polycystic Ovarian Syndrome. *Obesity Surgery*, 27(7), 1750-1754. https://dx.doi.org/10.1007/s11695-016-2528-y	
Study Country	Italy	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	Patients with obesity and PCOS between 18 and 39 years	
PCOS diagnostic criteria	Rotterdam	
N per group	PCOS – 29 Non-PCOS – 26	
Setting	University Hospital	
Intervention/ indicator	Bariatric Surgery	
Comparison/ Control	Patients with obesity between 18 and 39 years without PCOS	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Primary: AMH	
Inclusion criteria reported?	Yes Partial No Not reported	Yes.
Exclusion criteria reported?	Yes Partial No Not reported	Yes. Estro-progestin Metformin Inositol Hyperprolactinemia Cushing syndromoe Hypothyroidism 21-hydroxylase deficiency
Does the study have a clearly focused question?	Yes Partial No Not reported	Yes
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Yes

Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes.
Were the outcomes measured appropriate?	Yes Partial No Not reported	Yes.
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	Yes. 12 months
Was matching performed?	Yes Partial No Not reported	No
Summary of Result/s	After bariatric surgery, AMH levels were reduced in both groups (PCOS and non-PCOS)	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS – **Other than the exposure under investigation, were the groups selected from similar populations?**	Yes Partial No Not reported	Not reported
SELECTION BIAS – **Was the exposed cohort truly representative?**	Yes Partial No Not reported	Yes
SELECTION BIAS – **Is it clear that the outcome of interest was not present at the start of study?**	Yes Partial No Not reported	Yes

PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	Yes
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Yes Partial No Not reported	Not reported
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**		Not reported
	What percentage of the individuals were not included in the analysis?		Not reported
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported.

CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported – No report of a power calculation and small sample size but significant differences were found
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Partial. Unclear how sample was derived, and who was included in analysis.
COMMENTS			
What is the overall risk of bias?		High	Few criteria have been fulfilled and the conclusions of the study are likely to be affected.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No All outcomes high risk of bias	

Study ID	Hu 2022	
Study Citation	Hu, L., Ma, L., Xia, X., Ying, T., Zhou, M., Zou, S., Yu, H., & Yin, J. (2022). Efficacy of Bariatric Surgery in the Treatment of Women with Obesity and Polycystic Ovary Syndrome. *The Journal of Clinical Endocrinology and Metabolism*, 107(8), e3217-e3229. https://dx.doi.org/10.1210/clinem/dgac294	
Study Country	China	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	Women aged 18 to 40 years with BMI >27.5 kg/m2 and waist circumference >= 85 cm with PCOS	
PCOS diagnostic criteria	Chinese diagnostic criteria for PCOS based on the Rotterdam criteria	
N per group	Medical management – 40 Surgical management – 41	
Setting	University Hospital	
Intervention/ indicator	Laparoscopic sleeve gastrectomy	
Comparison/ Control	Medical management (Metformin x 12 months + OCP x first 6 months)	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Primary: Complete PCOS remission defined as regular menstrual cycles and/or spontaneous pregnancy in the last six months of the trial Secondary: Anthropometric and metabolic outcomes	
Inclusion criteria reported?	Yes Partial No Not reported	Yes.
Exclusion criteria reported?	Yes Partial No Not reported	Yes.
Does the study have a clearly focused question?	Yes Partial No Not reported	Yes
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial. A RCT would better answer the clinical question, but NRCT chosen to accommodate patient preference.
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes.
Were the outcomes measured appropriate?	Yes Partial No Not reported	Yes.

Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	Yes.
Was matching performed?		Yes Partial No Not reported	No
Summary of Result/s		BMI was lower in the surgical group than medical group and associated with remission of PCOS symptoms and signs.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes Partial No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Not reported
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFOR MANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	Yes
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Yes Partial No Not reported	Yes
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**		9 were not included in the analysis of 90 - 5 for medical management and 4 for LSG
	What percentage of the individuals were		As above.

	not included in the analysis?		
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported.
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported – No report of a power calculation but significant differences were found
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		High	Few criteria have been fulfilled and the conclusions of the study are likely to be affected.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No All outcomes high risk of bias	

Study ID	Tatarchuk 2022
Study Citation	Tatarchuk T., Todurov I., Anagnostis P., Tutchenko T., Pedachenko N., Glamazda M., Koseii N., & Regeda S. (2022). The Effect of Gastric Sleeve Resection on Menstrual Pattern and Ovulation in Premenopausal Women with Classes III-IV Obesity. *Obesity Surgery*, 32(3), 599-606. https://dx.doi.org/10.1007/s11695-021-05820-0
Study Country	Ukraine
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	Premenopausal women with PCOS who fulfilled the criteria for gastric sleeve resection
PCOS diagnostic criteria	Rotterdam criteria

N per group	Gastric sleeve resection – 33 Conservative - 27	
Setting	Three metabolic surgery centres	
Intervention/ indicator	Gastric sleeve resection	
Comparison/ Control	Conservative treatment (no surgery, no weight-reduction medication)	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Percentage of body weight loss Duration of inter menstrual interval Presence of ovulation	
Inclusion criteria reported?	Yes Partial No Not reported	Yes. Premenopausal women Age 26-44 years Stage III-IV obesity Met criteria for gastric sleeve resection (BMI >40, or BMI >35 with metabolic comorbidities, or a relapse of weight gain or failure of conservative treatment with lifestyle intervention)
Exclusion criteria reported?	Yes Partial No Not reported	Yes. Non-PCOS endocrine causes of ovulatory dysfunction Structural abnormalities of genitalia Endometriosis Use of levonorgestrel intrauterine device
Does the study have a clearly focused question?	Yes Partial No Not reported	Yes
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial. A RCT would better answer the clinical question, but this study design was chosen to accommodate patient preference.
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes.
Were the outcomes measured appropriate?	Yes Partial No Not reported	Yes.
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	Yes. 15 months

Was matching performed?		Yes Partial No Not reported	No
Summary of Result/s		Menstrual regularity and ovulation were improved in more than half of these patients at 6–15 months. The reproductive outcome changes were more evident in women with PCOS than without.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes Partial No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Partial. Small sample size.
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFOR MANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	Yes
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes
	Were outcomes assessed objectively and independently?	Yes Yes Partial No Not reported	Not reported
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**		Not reported
	What percentage of the individuals were		Not reported

	not included in the analysis?		
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Not reported.
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	No
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Not reported – No report of a power calculation but significant differences were found
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes
COMMENTS			
What is the overall risk of bias?		High	Few criteria have been fulfilled and the conclusions of the study are likely to be affected.
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?		No All outcomes high risk of bias	

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 4

Question 4.9.

In adults and adolescents with PCOS, is bariatric surgery effective for management of hormonal and clinical PCOS features and weight?

BACKGROUND:

Obesity is increasing in prevalence throughout the world (1). Depending on the dataset and ethnicity, 38-88% of women with PCOS are obese and have insulin resistance adversely affecting fertility and psychological health and increasing metabolic risks including type 2 diabetes mellitus and metabolic syndrome (2,3). Weight loss improves outcomes as previously outlined.

In class II (BMI 35-40 kg/m^2) and class III (≥40 kg/m2) obesity, lifestyle interventions are not durably effective, whereas bariatric/metabolic surgery has been demonstrated to provide substantial durable weight loss with accompanying improvement in health, well-being and longevity. (4)

The NICE guidelines (CG189) in the UK recommend surgery to aid weight loss for those with a class III obesity or class II obesity with other significant disease that would improve with weight loss (e.g. Type 2 diabetes or high blood pressure) when appropriate non-surgical measures have been tried (5) . Expedited referral for bariatric surgery assessment is recommended for those with class II or more obesity and a diagnosis of recent onset of Type 2 diabetes (i.e. in the last ten years) (5). They also recommend to consider referral for those with Class 1 obesity and recent onset of T2DM and to consider a lower threshold for referral in people of Asian backgrounds (5). Recent guidelines from the American Society for Metabolic and Bariatric Surgery and International Federation (ASMBS) for the Surgery of Obesity and Metabolic Disorders (IFSO) have lower thresholds recommending surgery for all those with a BMI $\geq$ 35kg/m2 and for surgery to be considered for those with a BMI between 30- 34.9 kg/m2 with associated metabolic co-morbidity (6). They also recommend adjusting thresholds for the Asian population such that those with a BMI $\geq$ 27.5kg/m2 are offered Bariatric/metabolic surgery (6).

Vertical Sleeve Gastrectomy (VSG)and Roux-en-Y gastric bypass (RYGB) are the most commonly performed type of weight loss surgery and are usually performed using minimally invasive surgical techniques. They are typically performed with low morbidity and mortality[3]. High quality RCTs of bariatric surgery versus medical management in DM2 show persistent benefits and superiority of weight loss and bariatric surgery in improvement or remission of diabetes, hypertension and dyslipidaemia (5-7).

The early onset of obesity in PCOS also sets challenges for weight managements as women at fertile age, pregnancies need to be taken into consideration when choosing the treatment modality. Women who undergo bariatric/metabolic surgery prior to pregnancy have improved ovulation and fertility and are less likely to experience comorbidities associated with obesity such as gestational diabetes and pregnancy induced hypertension. However, bariatric/metabolic surgery can cause nutrient deficiencies important for fetal development. This can contribute to an increased risk of adverse outcomes including perinatal mortality, pre-term birth and small for gestation age and this may vary with type of surgery (8,9).

Given the significant concerns of women with PCOS about weight, long term health and reproductive and pregnancy outcomes understanding the risks and benefits of metabolic and bariatric surgery is of importance for women and health professionals.

GRADE EVIDENCE CERTAINTY	
Comparison	**GRADE for critical outcomes**
o **Comparison 1.** Bariatric Surgery vs Medical Therapy	⨁◯◯◯ VERY LOW
o **Comparison 2**. Bariatric Surgery vs Conservative Management	⨁◯◯◯ VERY LOW
o **Comparison 3.** Bariatric Surgery Among Individuals with PCOS vs. Non-PCOS	⨁◯◯◯ VERY LOW

Evidence to Recommendations Framework

COMPARISONS (option versus other option)

1. **Bariatric Surgery compared with medical management**
2. **Bariatric Surgery vs Conservative Management**
3. **Bariatric Surgery PCOS vs non PCOS**

CONSENSUS RECOMMENDATION(S)

- **CR:** Bariatric/ metabolic surgery could be considered to improve weight loss, hypertension, diabetes (prevention and treatment), hirsutism, irregular menstrual cycles, ovulation and pregnancy rates in women with PCOS.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

- **CR:** Bariatric/ metabolic surgery in women with PCOS should be informed by general population guidelines.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

- **CR:** PCOS is a metabolic condition and could be considered an indication at a lower BMI threshold for bariatric/ metabolic surgery similarly to other metabolic conditions including diabetes.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

- **CR:** Women should be strongly counselled on the likelihood of rapid return of fertility and the need to commit to effective contraception, ideally prior to surgery. Even when pregnancy is desired, contraception should be

continued until a stable weight is achieved, usually after one year, to avoid significantly increased risk of growth restriction, prematurity, small for gestational age, pregnancy complications and prolonged hospitalisation of the infant.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

PRACTICE POINT

(Cannot find this section in the recommendation document LP- 21/02/2023)

GRADE CONSIDERATIONS

Justifications:

1. Bariatric Surgery compared with medical treatment

There was only one non-randomized and non-blinded trial undertaken in women with PCOS and BMI>27.5kg/m2 or WC >85 cm) in China that compared laparoscopic sleeve gastrectomy to medical therapy (oral contraceptive pill (35mcg EE/2 mgCPA) for 6 months and (and metformin 12 months).

Outcomes were assessed at twelve months and the main outcome was return of regular cycles or pregnancy which is not a recommended outcome within 12 months of surgery.

At 12 months post treatment women in the surgical group had a greater improvement in anthropometric measures (weight, BMI, waist circumference, hip circumference, W/H), hormonal measures (total testosterone, free androgen index), metabolic measures (fasting glucose, fasting insulin, triglycerides, LDL-cholesterol, and haemoglobin A1C),

There was no assessment of adverse outcomes for either group

2. Bariatric Surgery/metabolic (GSR) vs Conservative Management (no GSR) in women with and without PCOS

There was only one prospective non-randomised study comparing gastric sleeve resection (GSR) to conservative management in women (BMI >40 kg/m2 or >35 kg/m2 with comorbidity) with and without PCOS. Main outcome was ovulation and-menstrual regularity. Other measures included weight loss and HOMA-IR.

Total weight loss was greatest in the first 3-4 months post GSR for both women with and without PCOS and plateaued afterwards. The proportion of total weight loss was significantly greater for GSR compared to controls for women with and without PCOS.

3. Bariatric/metabolic Surgery PCOS vs non PCOS

Nine studies compared bariatric/metabolic surgery in women with PCOS compared to women without PCOS. Eight studies reported on non-reproductive outcomes including anthropometric, metabolic, and hormonal outcomes. None of these were randomised controlled trials. The majority were surgical cohorts, one was a non-randomised study and one a cross sectional study with self-reported symptoms years after surgery.

For the non-reproductive outcomes, two or more studies provided data on most of the outcomes of interest and therefore meta-analyses were performed. There is low certainty in the results of these meta-analyses due to high risk of bias in each of the included studies.

There were improvements in women with and without PCOS across weight loss and metabolic markers such as lipids.

For women with PCOS: There was more improvement post bariatric/metabolic surgery in fasting glucose and BMI.

There was no significant difference between women with and without PCOS post bariatric/metabolic surgery in total weight loss, total testosterone, sex hormone binding globulin, AMH, total cholesterol, LDL, triglycerides, HDL.

Subgroup considerations: Whilst some women in the studies had comorbidities (e.g. T2DM), data for the subgroups were either not reported by PCOS status or were reported by resolution.
Implementation considerations: Bariatric surgery is often underfunded by payers, leaving the financial burden to individual patients and can be difficult to access to women globally. Often access to these surgeries is inequitable. Some general population guidelines recommend alternative BMI categories for Asian populations in general but this has not been addressed for women with PCOS.
Monitoring and evaluation considerations: Monitoring in individual and patient cohorts long-term is critical, including pregnancy and child outcomes.
Research priorities: Further research on bariatric surgery in PCOS is a strong priority by ethnicity Bariatric surgery compared to anti-obesity medication in PCOS Differences in outcomes by type of bariatric/metabolic surgical procedures Pre-conception and pregnancy requirements post bariatric/metabolic surgery Cost effectiveness studies Individual and patient cohorts long-term is critical, including psychological, pregnancy and child outcomes.

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PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by ECR Lead: Mahnaz Bahri Khomami

Other team members: Somayeh Hashemi, Soulmaz Shorakae

Supervised, edited and supported by the Evidence Team (Aya Mousa, Jillian Tay)

GDG 4

Question 4.10.

Are women with PCOS at increased risk of adverse pregnancy outcomes?

2. SELECTION CRITERIA

Table 1. PICO Criteria for Inclusion – Not to be adapted
To be used by evidence team to decide which studies will be included when screening search results.

Question	Q 4.10) Are women with PCOS at increased risk of adverse pregnancy outcomes? CLINICAL PRACTICE POINT: Should women with PCOS undergo close (early or late) pregnancy monitoring for adverse pregnancy outcomes?
Clinical leads (key contacts)	**Prof Eszter Vanky** Obstetrician-Gynaecologist Norwegian University of Science and Technology, Norway eszter.vanky@ntnu.no **Prof Terhi Piltonen** Obstetrician-Gynaecologist, Reproductive endocrinologist Oulu University Hospital, University of Oulu, Finland terhi.piltonen@oulu.fi **Dr Daniela Romauldi** Obstetrician-Gynaecologist Fondazione Policlinico Universitario Agostino Gemelli, Italy daniela.romualdi@policlinicogemelli.it
Allocation ranking	Level 2- Update systematic review

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(language, year)*
Inclusion	Pregnant women with PCOS according to any criteria including the NIH, AES, ESHRE/ASRM No exclusion based on age, ethnicity, BMI, fertility status and parity.	N/A	Pregnant women without PCOS according to any criteria No exclusion based on age, ethnicity, BMI, fertility status and parity.	**Meta-Analysis** ***.Primary complications*** .Miscarriage .Spontaneous Preterm Labour, .Gestational Diabetes .Pregnancy Induced Hypertension .Preeclampsia .Eclampsia ***.Secondary complications*** .GWG/BMI .Birth Weight .Small for Gestational Age/Low Birth Weight/intrauterine growth restriction .Large for Gestational Age/Macrosomia .Instrumental delivery .Caesarean Section Perinatal depression	Observational studies including either cohort or case-control studies, RCTs (information among controls AND/OR prior to intervention among cases), systematic reviews/ meta-analysis (only references).	Studies published in English, human studies, original research articles
Exclusion		N/A			Narrative synthesis, Case report, Expert opinion.	Non-English language studies, Animal studies.

2. SEARCH STRATEGY

Table 2.1. Search details	
Search strategy source: *[enter doi or 2018 technical report page number where search string was derived]*	
Evidence source	Date of search *13 July 2022*
Medline (Ovid)	*YES*
PsychInfo (Ovid)	*NO*
EMBASE (Ovid)	*YES*
All EBM (Ovid)	*YES*
CINAHL	*NO*
Any subsequent updates - enter database and date:	

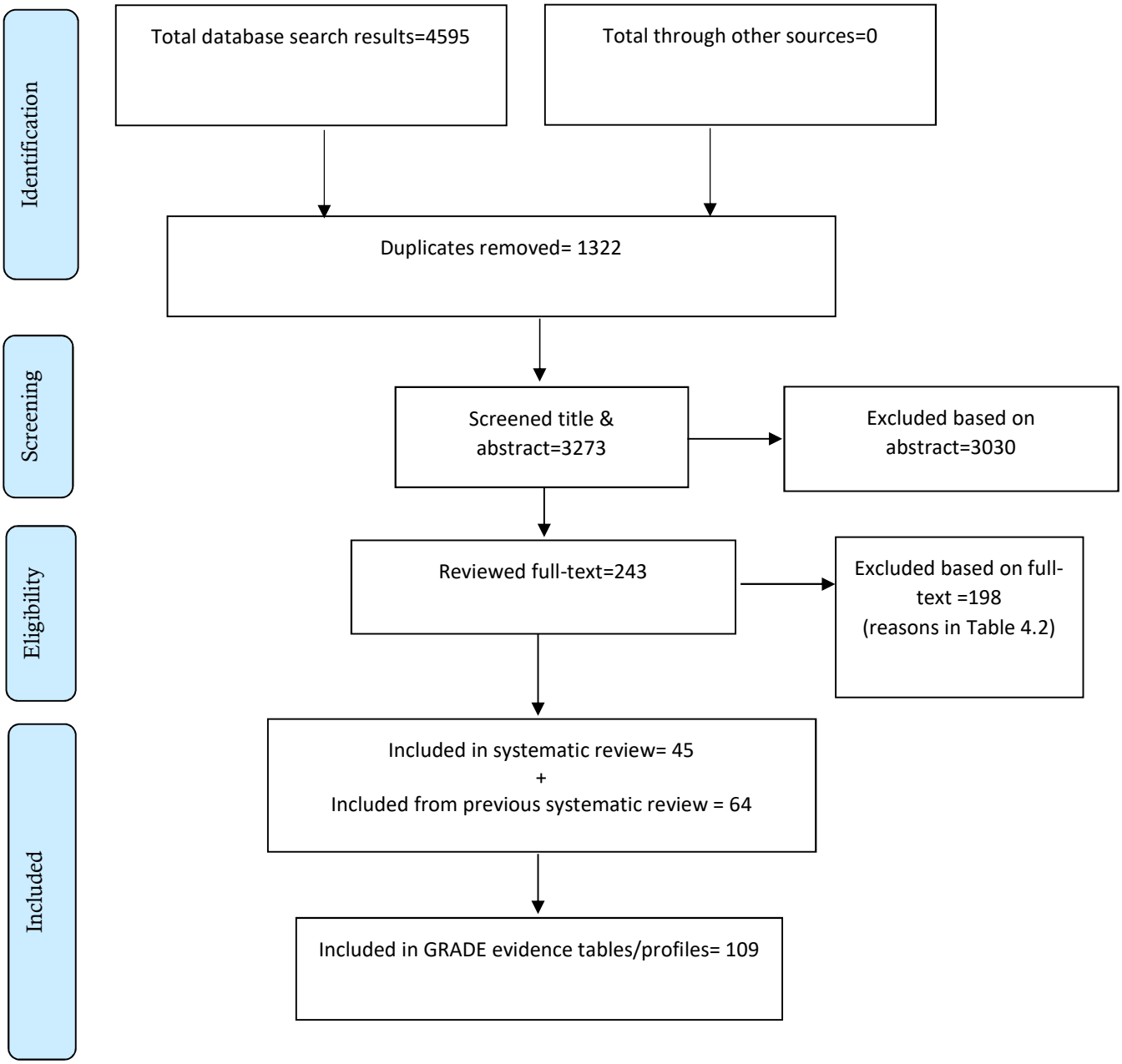
Table 2.2. Questions addressed by this search *(add more rows as needed)*:		
GDG	Q#4.11	Are women with PCOS at increased risk of adverse pregnancy outcomes?

Table 2.3. Search strings used in OVID or other database/s
OVID Medline, All EBM, PsychInfo, EMBASE (results= n?)
1. exp polycystic ovary syndrome/ 2. polycystic ovar*.mp. 3. poly-cystic ovar*.mp. 4. PCO*.mp. 5. (stein-leventhal or leventhal).mp. 6. exp anovulation/ 7. anovulat*.mp. 8. oligo-ovulat*.mp. 9. oligoovulat*.mp. 10. (ovar* adj5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*)).mp. 11. or/1-10 12. exp pregnancy/ 13. (pregnan* or gestation* or matern* or antenatal* or prenatal* or perinatal* or peripartu* or puerper* or intrapartum*).mp. 14. exp fetus/ 15. (fet* or infant* or birth).mp. 16. (pregnan* or gestation* or matern* or antenatal* or prenatal* or perinatal* or peripartu* or puerper* or intrapartum*).mp. 17. or/12-16 18. exp pregnancy complications/ 19. exp pregnancy outcome/ 20. exp obstetric labor complications/ 21. ((gestation* or pregnan*) adj2 (weight* or BMI* or hypertensi*)).mp. 22. ((birth or fet*) adj2 weight*).mp. 23. exp abortion, spontaneous/ 24. (((miscarriage or pregnancy) adj2 loss) or abortion).mp. 25. exp diabetes, gestational/ 26. (gestational diabet* or GDM).mp. 27. exp hypertension, pregnancy-induced/ 28. (preeclamp* or pre-eclamp* or eclamp*).mp. 29. exp pre-eclampsia/ 30. exp eclampsia/ 31. exp fetal membranes, premature rupture/ 32. exp infant, extremely premature/ 33. exp obstetric labor, premature/ 34. exp infant, premature/ 35. exp premature birth/ 36. ((preterm* or pre-term* or prematur* or pre-matur*) adj2 (birth or labor or labour or deliver*)).mp. 37. exp delivery, obstetric/

38. exp parturition/
39. exp labor, induced/
40. exp episiotomy/
41. exp obstetrical forceps/
42. exp vacuum extraction, obstetrical/
43. exp cesarean section/
44. (induc* or episiotomy or forceps or vacuum or C-section or c?esar*).mp.
45. exp fetal weight/
46. exp fetal growth retardation/
47. ('intrauterine growth retardation' or IUGR).mp.
48. exp birth weight/
49. exp fetal macrosomia/
50. macrosomia.mp.
51. ('large for gestational age' or LGA).mp 52. exp infant, small for gestational age/
53. ('small for gestational age' or SGA).mp.
54. exp infant, low birth weight/
55. ('low birth weight' or LBW).mp.
56. exp infant, very low birth weight/
57. exp infant, extremely low birth weight/
58. (depressi* or mood*).mp.
59. exp depression, postpartum/
60. or/18-59
61. 11 and 17 and 60
62. limit 61 to (english language and humans)
63. limit 62 to yr="2017 -Current"

Evidence processing: Studies were selected and appraised by 2 reviewer/s in consultation with the evidence team/ key contact using study selection and appraisal criteria (PICO above) established a priori. The articles were reviewed by title and abstract by 2 reviewers. When a decision could not be made based on title and abstract alone, full text was retrieved. **A total of *109* studies met inclusion criteria for this review.**

3. SEARCH RESULTS - PRISMA flowchart



4. STUDY INCLUSION

Table 4.1. Included Studies (full citation with doi)
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Wortsman, J.; de Angeles, S.; Futterweit, W.; et al. (1991): Gestational diabetes and neonatal macrosomia in the polycystic ovary syndrome. J Reprod Med 36, 9, 659-661, http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med3&AN=1774730
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Table 4.2. Excluded Studies (on full text assessment)- *add more rows as needed*

Reference	Reason
Sagle, 1988	Study groups were women with and without recurrent miscarriage
Braat, 1989	They reported pooled pregnancy outcomes. There were 24 pregnancies in PCOS patients and 188 in non-PCOS which included hypoandrogenic, normoandrogenic, corpus luteum deficiency and uncertain diagnosis. The outcomes have been only reported among hypoandrogenic women (174) not the whole 188.
Homburg, 1989	There was no comparison between women with and without PCOS; it was just a comparison between women with and without polycystic ovary morphology
Balen, 1993	There was no comparison between women with and without PCOS; it was just a comparison between women with and without polycystic ovary morphology
Naether, 1994	All participants had PCOS and androgen levels were assessed before and after laparoscopic electrocautery of the ovarian surface (LEOS) among
Lanzone, 1995	Missing/Unacceptable PCOS diagnostic criteria
Kumar, 1997	Systematic review and meta-analysis

Liddell, 1997	Study groups were women with and without recurrent miscarriage and polycystic ovary morphology
Anttila, 1998	There was no comparison between women with and without PCOS; it was just a comparison between women with and without polycystic ovary morphology
de Vries, 1998	Missing/Unacceptable PCOS diagnostic criteria
Hirahara, 1998	There was no comparison between women with and without PCOS; it was just a comparison between women with and without recurrent miscarriage
Radon, 1999	Missing/Unacceptable PCOS diagnostic criteria
Rai, 2000	There was no comparison between women with and without PCOS; it was just a comparison between women with and without polycystic ovary morphology
Glueck, 2003	None of outcomes of interest have been reported
Mulders, 2003	There was no comparison between women with and without PCOS; it was just a comparison between women with and without anovulatory infertility
Urman, 2004	Systematic review
Bjercke, 2005	None of outcomes of interest have been reported
Boomsma, 2006	Systematic review and meta-analysis
Lo, 2006	Missing/Unacceptable PCOS diagnostic criteria
Turner, 2006	No comparison with healthy controls
Vanky, 2006	No comparison with healthy controls
Boomsma, 2008	Systematic review and meta-analysis
Buckett, 2008	Study groups were based on various ART treatment received for the current pregnancy
Kashanian, 2008	Comparison between women with and without GDM
Koivunen, 2008	Missing/Unacceptable PCOS diagnostic criteria
Thomann, 2008	None of outcomes of interest have been reported
Beydoun, 2009	Missing/Unacceptable PCOS diagnostic criteria
Bolton, 2009	Missing/Unacceptable PCOS diagnostic criteria
Jammah, 2009	No comparison with healthy controls
Palomba, 2009	Systematic review and meta-analysis
Sugiura-Ogasawara, 2009	Study groups were women with and without recurrent miscarriage
Toulis, 2009	Systematic review and meta-analysis
Aali, 2010	There was no comparison between women with and without PCOS; it was just a comparison between women with and without Preeclampsia
Alshammari, 2010	Missing/Unacceptable PCOS diagnostic criteria
Sun, 2010	No comparison with healthy control
Vanky, 2010	No comparison with healthy controls
Azizia, 2011	Systematic review
Han, 2011	Outcomes have been reported per cycle of infertility treatment not per pregnancy
Kjerulff, 2011	Systematic review and meta-analysis
Roos, 2011	Missing/Unacceptable PCOS diagnostic criteria
Aziz, 2012	Study protocol
Carlsen, 2012	No comparison with healthy controls
Khan, 2012	Systematic review
Kosus 2012	None of outcomes of interest have been reported
Oteng-Ntim, 2012	Systematic review and meta-analysis
Palomba, 2012	None of outcomes of interest have been reported
Galazis, 2013	Systematic review and meta-analysis
Hong, 2013	There was no comparison between women with and without PCOS; it was just a comparison between women with and without recurrent miscarriage
Lautatzis, 2013	Systematic review
Qin, 2013	Systematic review and meta-analysis
Rogenhofer, 2013	There was no comparison between women with and without PCOS; it was just a comparison between women with and without recurrent miscarriage
Zheng, 2013	Systematic review and meta-analysis
Banu, 2014	Only recurrent miscarriage has been assessed not miscarriage
De Frene, 2014	No comparison with healthy controls
Gaafar, 2014	None of outcomes of interest have been reported
Hart, 2014	None of outcomes of interest have been reported
Joham, 2014	Only pooled miscarriage and stillbirth has been reported and there are no outcomes of interest reported separately.

Joham, 2014	Missing/Unacceptable PCOS diagnostic criteria
West, 2014	Only cumulative incidence was reported
Zhuo, 2014	Systematic review and meta-analysis
Doherty, 2015	Missing/Unacceptable PCOS diagnostic criteria
Feng, 2015	Systematic review and meta-analysis
Hart, 2015	Outcomes have been reported per number of PCOS/non-PCOS patients not per pregnancy in PCOS/non-PCOS
Huang, 2015	Systematic review and meta-analysis
Lovvik, 2015	Missing/Unacceptable PCOS diagnostic criteria
Palomba, 2015	Systematic review
Pan, 2015	Missing/Unacceptable PCOS diagnostic criteria
Brunisholz, 2016	There was no comparison between women with and without PCOS; it was just a comparison between women with and without prediabetes
Li, 2016	No comparison with healthy controls
Provost, 2016	Study groups were based on BMI categories not PCOS status.
Rodino, 2016	None of outcomes of interest have been reported
Szafarowska, 2016	None of outcomes of interest have been reported
Tan, 2016	Systematic review and meta-analysis
Yu, 2016	Systematic review and meta-analysis
Zeng, 2016	Systematic review and meta-analysis
BahriKhomami 2017	Missing/Unacceptable PCOS diagnostic criteria
Bond 2017	Missing/Unacceptable PCOS diagnostic criteria
Butts 2017	FT unavailable/conference abstract
Carbillon 2017	Missing/Unacceptable PCOS diagnostic criteria
Chappell 2017	FT unavailable/conference abstract
Choux 2017	Wrong patient population
Chowdhury 2017	FT unavailable/conference abstract
deGraaff 2017	Missing/Unacceptable PCOS diagnostic criteria
Evans-Hoeker 2017	FT unavailable/conference abstract
Finnbogadottir 2017	Missing/Unacceptable PCOS diagnostic criteria
Fang 2017	Wrong outcomes
Guo 2017	FT unavailable/conference abstract
Hodyl 2017	FT unavailable/conference abstract
Ingram 2017	Missing/Unacceptable PCOS diagnostic criteria
Kallak 2017	Missing/Unacceptable PCOS diagnostic criteria
Klevedal 2017	Missing/Unacceptable PCOS diagnostic criteria
Kurera 2017	FT unavailable/conference abstract
Legro 2017	FT unavailable/conference abstract
Li 2017	FT unavailable/conference abstract
Li 2017	No outcomes of interest per groups
Lovelock 2017	FT unavailable/conference abstract
McDonnell 2017	FT unavailable/conference abstract
Muchanga 2017	Missing/Unacceptable PCOS diagnostic criteria
Sadrzadeh 2017	Wrong study design
Stridsklev 2017	No outcomes of interest per groups
Tobiasz 2017	FT unavailable/conference abstract
VanHoorn 2017	FT unavailable/conference abstract
Weilnau 2017	Missing/Unacceptable PCOS diagnostic criteria
Wu 2017	No outcomes of interest per groups
Zhu 2017	Wrong patient population
Almasi-Hashiani 2018	No outcomes of interest per groups
Ashrafuzzaman 2018	Full text unavailable/Conference presentation
Benhalima 2018	Missing/Unacceptable PCOS diagnostic criteria
Bos-Mikich 2018	FT unavailable/conference abstract
Butts 2018	Duplicated information
Cherskov 2018	Missing/Unacceptable PCOS diagnostic criteria
Davies 2018	FT unavailable/conference abstract
Eisman 2018	FT unavailable/conference abstract
Fux-Otta 2018	No outcomes of interest per groups
Griffin 2018	FT unavailable/conference abstract

Khomami 2018	Wrong study design
Kouhkan 2018	Missing/Unacceptable PCOS diagnostic criteria
Li 2018	FT unavailable/conference abstract
Li 2018	FT unavailable/conference abstract
Li 2018	Missing/Unacceptable PCOS diagnostic criteria
Li 2018	No outcomes of interest per groups
LyttleSchumacher 2018	Wrong patient population
Koninger 2018	No outcomes of interest per groups
Parry 2018	FT unavailable/conference abstract
Rehman 2018	No outcomes of interest per groups
Ruan 2018	FT unavailable/conference abstract
Szafarowska 2018	Wrong study design
Tabibnejad 2018	No outcomes of interest per groups
Tannus 2018	No outcomes of interest per groups
Violante-Ortiz 2018	Missing/Unacceptable PCOS diagnostic criteria
Xu 2018	FT unavailable/conference abstract
Yang 2018	FT unavailable/conference abstract
Al-Dujaily 2019	No outcomes of interest per groups
Arffman 2019	Full text unavailable/Conference presentation
Basirat 2019	Missing/Unacceptable PCOS diagnostic criteria
Butts 2019	Duplicated information
D'Ambrosio 2019	FT unavailable/conference abstract
Emami 2019	FT unavailable/conference abstract
Hashem 2019	Wrong outcomes
Hussein 2019	Missing/Unacceptable PCOS diagnostic criteria
Jin 2019	Wrong study design
Komlosi 2019	FT unavailable/conference abstract
Kouhkan 2019	Missing/Unacceptable PCOS diagnostic criteria
Krysta 2019	FT unavailable/conference abstract
Lederer 2019	FT unavailable/conference abstract
Li 2019	Missing/Unacceptable PCOS diagnostic criteria
Li 2019	Wrong patient population
Musa 2019	Wrong study design
Peigne 2019	Wrong patient population
Piltonen 2019	Missing/Unacceptable PCOS diagnostic criteria
Sha 2019	Systematic review and meta-analysis
Steiner 2019	FT unavailable/conference abstract
Tabibnejad 2019	No outcomes of interest per groups
TadaionFar 2019	No outcomes of interest per groups
Thomas 2019	Missing/Unacceptable PCOS diagnostic criteria
Valdimarsdottir 2019	Missing/Unacceptable PCOS diagnostic criteria
Wadood 2019	No outcomes of interest per groups
Weedin 2019	FT unavailable/conference abstract
Xia 2019	No outcomes of interest per groups
Xu 2019	FT unavailable/conference abstract
AyparAkbag 2020	Wrong patient population
Barros 2020	Missing/Unacceptable PCOS diagnostic criteria
Bender 2020	FT unavailable/conference abstract
Bu 2020	Missing/Unacceptable PCOS diagnostic criteria
Chen 2020	Missing/Unacceptable PCOS diagnostic criteria
Christinajoice 2020	Missing/Unacceptable PCOS diagnostic criteria
Du 2020	Missing/Unacceptable PCOS diagnostic criteria
Engmann 2020	Wrong outcomes
Fabjan 2020	Wrong outcomes
Feferkorn 2020	FT unavailable/conference abstract
Firoozabadi 2020	Wrong comparator
Hajitarkhani 2020	FT unavailable/conference abstract
Li 2020	No outcomes of interest per groups
Liu 2020	Missing/Unacceptable PCOS diagnostic criteria

Liu 2020	Wrong comparator
Manoharan 2020	Missing/Unacceptable PCOS diagnostic criteria
Mills 2020	Missing/Unacceptable PCOS diagnostic criteria
Mills 2020	Missing/Unacceptable PCOS diagnostic criteria
Mills 2020	Missing/Unacceptable PCOS diagnostic criteria
Mills 2020	FT unavailable/conference abstract
Mochizuki 2020	FT unavailable/conference abstract
Nielsen 2020	Missing/Unacceptable PCOS diagnostic criteria
Oumeziane 2020	FT unavailable/conference abstract
Overgaard 2020	Missing/Unacceptable PCOS diagnostic criteria
Parker 2020	FT unavailable/conference abstract
Pearson 2020	FT unavailable/conference abstract
Perlman 2020	No outcomes of interest per groups
Robinson 2020	Missing/Unacceptable PCOS diagnostic criteria
Rouleau 2020	FT unavailable/conference abstract
Schmidt 2020	Missing/Unacceptable PCOS diagnostic criteria
Segers 2020	FT unavailable/conference abstract
Siffain 2020	FT unavailable/conference abstract
Siristatidis 2020	Wrong patient population
Steiner 2020	No outcomes of interest per groups
Valgeirsdottir 2020	FT unavailable/conference abstract
Yang 2020	Missing/Unacceptable PCOS diagnostic criteria
Zhang 2020	Missing/Unacceptable PCOS diagnostic criteria
Zhang 2020	FT unavailable/conference abstract
Afiat 2021	No outcomes of interest per groups
Alizadeh 2021	No outcomes of interest per groups
Alur-Gupta 2021	Missing/Unacceptable PCOS diagnostic criteria
Balen 2021	Wrong study design
Cai 2021	No outcomes of interest per groups
Coussa 2021	Missing/Unacceptable PCOS diagnostic criteria
Deshmukh 2021	FT unavailable/conference abstract
Dubey 2021	No outcomes of interest per groups
Emami 2021	FT unavailable/conference abstract
Epelboin 2021	FT unavailable/conference abstract
Gao 2021	Wrong comparator
Hajitarkhani 2021	No outcomes of interest per groups
Heidenberg 2021	FT unavailable/conference abstract
Huang 2021	FT unavailable/conference abstract
KabilKucur 2021	No outcomes of interest per groups
Kargasheh 2021	No outcomes of interest per groups
Khalifeh 2020	Missing/Unacceptable PCOS diagnostic criteria
Kheirollahi 2021	FT unavailable/conference abstract
Luo 2021	FT unavailable/conference abstract
Ma 2021	Systematic review and meta-analysis
Markantes 2021	FT unavailable/conference abstract
Minguez-Alarcon 2021	FT unavailable/conference abstract
Naigaonkar 2021	No outcomes of interest per groups
Nikbakht 2021	No outcomes of interest per groups
Ozer 2021	FT unavailable/conference abstract
Ozer 2021	FT unavailable/conference abstract
Pan 2021	Systematic review and meta-analysis
Parker 2021	FT unavailable/conference abstract
Raj 2021	Missing/Unacceptable PCOS diagnostic criteria
Robinson 2021	FT unavailable/conference abstract
Robinson 2021	Wrong study design
Rotem 2021	Missing/Unacceptable PCOS diagnostic criteria
Sarkar 2021	No outcomes of interest per groups
Tang 2021	Systematic review and meta-analysis
Vagios 2021	No outcomes of interest per groups
Valdimarsdottir 2021	FT unavailable/conference abstract

Valdimarsdottir 2021	Missing/Unacceptable PCOS diagnostic criteria
Valgeirsdottir 2021	Missing/Unacceptable PCOS diagnostic criteria
Valgeirsdottir 2021	Missing/Unacceptable PCOS diagnostic criteria
Valgeirsdottir 2021	Missing/Unacceptable PCOS diagnostic criteria
Vatannejad 2021	FT unavailable/conference abstract
Wang 2021	Missing/Unacceptable PCOS diagnostic criteria
Wang 2021	Missing/Unacceptable PCOS diagnostic criteria
Wesevich 2021	Missing/Unacceptable PCOS diagnostic criteria
Wu 2021	Wrong study design
Yang 2021	Missing/Unacceptable PCOS diagnostic criteria
Yaseen 2021	Missing/Unacceptable PCOS diagnostic criteria
Zhang 2021	Missing/Unacceptable PCOS diagnostic criteria
Belan 2022	Wrong study design
Bethel 2022	FT unavailable/conference abstract
Chatzakis 2022	Systematic review and meta-analysis
Chen 2022	Missing/Unacceptable PCOS diagnostic criteria
D'Alterio 2022	Wrong study design
Fornes 2022	Missing/Unacceptable PCOS diagnostic criteria
Kumari 2022	Missing/Unacceptable PCOS diagnostic criteria
Lewandowski 2022	No outcomes of interest per groups
Liu 2022	Wrong patient population
Mackens 2022	No outcomes of interest per groups
Molin 2022	Wrong comparator
Nabi 2022	Missing/Unacceptable PCOS diagnostic criteria
Pan 2022	Missing/Unacceptable PCOS diagnostic criteria
Qui 2022	Systematic review and meta-analysis
Sassin 2022	FT unavailable/conference abstract
Schoretsanitis 2022	Systematic review and meta-analysis
Souter 2022	Wrong outcomes
Stern 2022	Missing/Unacceptable PCOS diagnostic criteria
Thaller 2022	Missing/Unacceptable PCOS diagnostic criteria
Yan 2022	Systematic review and meta-analysis
Yu 2022	No outcomes of interest per groups
Zhang 2022	No outcomes of interest per groups
#206	Study protocol
#692	Study protocol
#693	Study protocol
#1473	Study protocol

5. FINDINGS

Comparison: Women with PCOS versus controls

Outcomes included:

Outcome 1. Miscarriage

Outcome 2. Gestational diabetes

Outcome 3. Pregnancy-induced/gestational hypertension

Outcome 4. Pre-eclampsia

Outcome 5. Eclampsia

Outcome 6. Preterm birth

Outcome 7. Low birth weight

Outcome 8. Small for gestational age

Outcome 9. Macrosomia

Outcome 10. Large for gestational age

Outcome 11. Intrauterine growth restriction

Outcome 12. Instrumental delivery/Induction of labour

Outcome 13. Caesarean Section

Outcome 14. Perinatal depression

Outcome 15. Gestational weight gain

Outcome 16. Birthweight

Outcome 17. Body mass index

- ## EVIDENCE SUMMARY:

Miscarriage

Forty-three studies were included in the meta-analysis for miscarriage in women with and without PCOS. Twenty-one studies were prospective cohort studies and twenty-two were retrospective cohort studies. Thirty studies had high risk of bias, seven had moderate risk of bias and the remaining six had low risk of bias.

One study reported miscarriage in women who continue taking metformin during pregnancy and one study (Benito 2020) reported miscarriage in pregnancies post bariatric surgery. These were excluded from meta-analysis on a sensitivity analysis. Six studies matched women on the basis of BMI and seven matched on the basis of age. Twenty-nine studies reported miscarriage in post ART pregnancies.

Gestational diabetes

Fifty-seven studies were included in the meta-analysis for gestational diabetes in women with and without PCOS. Twenty-two studies were prospective cohort studies and thirty-five were

retrospective cohort studies. Thirty-four studies had high risk of bias, fifteen had moderate risk of bias and the remaining eight had low risk of bias.

Five studies reported gestational diabetes in women who continue taking metformin during pregnancy and one study (Benito 2020) reported gestational diabetes in pregnancies post bariatric surgery. These were excluded from meta-analysis on a sensitivity analysis. Seven studies matched women on the basis of BMI and fourteen matched on the basis of age. Nine studies reported gestational diabetes in post ART pregnancies.

Pregnancy-induced hypertension

Forty studies were included in the meta-analysis for pregnancy-induced hypertension in women with and without PCOS. Seventeen studies were prospective cohort studies and twenty-three were retrospective cohort studies. Twenty-one studies had high risk of bias, nine had moderate risk of bias and the remaining ten had low risk of bias.

Three studies reported pregnancy-induced hypertension in women who continue taking metformin during pregnancy. These were excluded from meta-analysis on a sensitivity analysis. Seven studies matched women on the basis of BMI and twelve matched on the basis of age. Ten studies reported pregnancy-induced hypertension in post ART pregnancies.

Pre-eclampsia

Thirty-six studies were included in the meta-analysis for pre-eclampsia in women with and without PCOS. Eighteen studies were prospective cohort studies and eighteen were retrospective cohort studies. Nineteen studies had high risk of bias, eleven had moderate risk of bias and the remaining six had low risk of bias.

Two studies reported pre-eclampsia in women who continue taking metformin during pregnancy and one study (Benito 2020) reported pre-eclampsia in pregnancies post bariatric surgery. These were excluded from meta-analysis on a sensitivity analysis. Seven studies matched women on the basis of BMI and ten matched on the basis of age. Two studies reported pre-eclampsia in post ART pregnancies.

Eclampsia

Two studies reported eclampsia in women with and without PCOS. One study (Hu 2007) had no women affected by eclampsia; therefore one study (Wan 2015) with retrospective cohort design was included in the meta-analysis for eclampsia. The study had moderate risk of bias.

In this study women were not taking metformin during pregnancy. It matched women on the basis of age and reported eclampsia in post ART pregnancies.

Preterm birth

Fifty-five studies reported preterm birth in women with and without PCOS. One study (Dmitrovic 2011) had no infant born premature; therefore fifty-four studies were included in the meta-analysis. Twenty-one studies were prospective cohort studies and thirty-five were retrospective cohort

studies. Thirty-six studies had high risk of bias, nine had moderate risk of bias and the remaining nine had low risk of bias.

Four studies reported preterm birth in women who continue taking metformin during pregnancy and one study (Benito 2020) reported preterm birth in pregnancies post bariatric surgery. These were excluded from meta-analysis on a sensitivity analysis. Nine studies matched women on the basis of BMI and twelve matched on the basis of age. Fourteen studies reported preterm birth in post ART pregnancies.

Low birth weight

Fifteen studies were included in the meta-analysis for low birth weight in women with and without PCOS. Two studies were prospective cohort studies and thirteen were retrospective cohort studies. Ten studies had high risk of bias, four had moderate risk of bias and the remaining one had low risk of bias.

In these studies women were not taking metformin during pregnancy but one study (Benito 2020) reported low birth weight in pregnancies post bariatric surgery. This study was excluded from meta-analysis on a sensitivity analysis. There were no studies reporting low birth weight in BMI/age matched women. Seven studies reported low birth weight in post ART pregnancies.

Small for gestational age

Twenty-six studies reported small for gestational age in women with and without PCOS. One study (Dmitrovic 2011) had no infant born small for gestational age; therefore twenty-five were included in the meta-analysis for small for gestational age. Twelve studies were prospective cohort studies and thirteen were retrospective cohort studies. Fifteen studies had high risk of bias, six had moderate risk of bias and the remaining four had low risk of bias.

One study reported small for gestational age in women who continued taking metformin during pregnancy. This study was excluded from meta-analysis on a sensitivity analysis. Six studies matched women on the basis of BMI and six matched on the basis of age. Five studies reported small for gestational age in post ART pregnancies.

Macrosomia

Twenty-three studies were included in the meta-analysis for macrosomia in women with and without PCOS. Six studies were prospective cohort studies and seventeen were retrospective cohort studies. Sixteen studies had high risk of bias, four had moderate risk of bias and the remaining three had low risk of bias.

One study reported macrosomia in women who continue taking metformin during pregnancy. This study was excluded from meta-analysis on a sensitivity analysis. Two studies matched women on the basis of BMI and two matched on the basis of age. Six studies reported macrosomia in post ART pregnancies.

Large for gestational age

Twenty-five studies reported large for gestational age in women with and without PCOS. Two studies (Dmitrovic 2011 and Foroozanfard 2020) had no infant born large for gestational age; therefore twenty-three studies were included in the meta-analysis for large for gestational age.

Thirteen studies were prospective cohort studies and ten were retrospective cohort studies. Fourteen studies had high risk of bias, five had moderate risk of bias and the remaining four had low risk of bias.

One study reported large for gestational age in women who continued taking metformin during. This study was excluded from meta-analysis on a sensitivity analysis. Five studies matched women on the basis of BMI and five matched on the basis of age. Two studies reported large for gestational age in post ART pregnancies.

Intrauterine growth restriction

Twelve studies reported intrauterine growth restriction in women with and without PCOS. Two studies (Elkholi 2014 and Foroozanfard 2020) had no infant born large for gestational age; therefore ten studies were included in the meta-analysis for intrauterine growth restriction.

Four studies were prospective cohort studies and six were retrospective cohort studies. Five studies had high risk of bias, two had moderate risk of bias and the remaining three had low risk of bias.

In these studies women were not taking metformin during pregnancy. Three studies matched women on the basis of BMI and four matched on the basis of age. One study reported intrauterine growth restriction in post ART pregnancies.

Instrumental delivery

Ten studies were included in the meta-analysis for instrumental delivery in women with and without PCOS. Six studies were prospective cohort studies and four were retrospective cohort studies. Five studies had high risk of bias, two had moderate risk of bias and the remaining three had low risk of bias.

One study (Benito 2020) reported instrumental delivery in pregnancies post bariatric surgery. This study was excluded from meta-analysis on a sensitivity analysis. Four studies matched women on the basis of BMI and four matched on the basis of age. No studies reported instrumental delivery in post ART pregnancies.

Induction of labour

Eight studies were included in the meta-analysis for induction of labour in women with and without PCOS. Six studies were prospective cohort studies and two were retrospective cohort studies. Five studies had high risk of bias, two had moderate risk of bias and the remaining one had low risk of bias.

One study (Benito 2020) reported instrumental delivery in pregnancies post bariatric surgery. This study was excluded from meta-analysis on a sensitivity analysis. One study matched women on the basis of BMI and one matched on the basis of age. No studies reported instrumental delivery in post ART pregnancies.

Caesarean section

Thirty-seven studies were included in the meta-analysis for caesarean section in women with and without PCOS. Sixteen studies were prospective cohort studies and twenty-one were retrospective cohort studies. Twenty-three studies had high risk of bias, seven had moderate risk of bias and the remaining seven had low risk of bias.

One study reported miscarriage in women who continue taking metformin during pregnancy and one study (Benito 2020) reported caesarean section in pregnancies post bariatric surgery. These were excluded from meta-analysis on a sensitivity analysis. Six studies matched women on the basis of BMI and nine matched on the basis of age. Seven studies reported caesarean section in post ART pregnancies.

Perinatal depression

Only one retrospective cohort study with moderate risk of bias was included in the meta-analysis for perinatal depression in women with and without PCOS.

In this study women were not taking metformin during pregnancy. Women were not matched on the basis of BMI/age and were not recruited of post ART pregnancies.

Gestational weight gain

Sixteen studies were included in the meta-analysis for gestational weight gain in women with and without PCOS. Six studies were prospective cohort studies and ten were retrospective cohort studies. Eight studies had high risk of bias, five had moderate risk of bias and the remaining three had low risk of bias.

In these studies women were not taking metformin during pregnancy. Four studies matched women on the basis of BMI and seven matched on the basis of age. One study reported gestational weight gain in post ART pregnancies.

Birthweight

Forty-five studies were included in the meta-analysis for birthweight in women with and without PCOS. Eighteen studies were prospective cohort studies and twenty-seven were retrospective cohort studies. Twenty-six studies had high risk of bias, twelve had moderate risk of bias and the remaining seven had low risk of bias.

Four studies reported birthweight in women who continue taking metformin during pregnancy and one study (Benito 2020) reported birthweight in pregnancies post bariatric surgery. These were excluded from meta-analysis on a sensitivity analysis. Ten studies matched women on the basis of BMI and thirteen matched on the basis of age. Seven studies reported birthweight in post ART pregnancies.

Body mass index

Sixty-two studies were included in the meta-analysis for body mass index in women with and without PCOS. Twenty-one studies were prospective cohort studies and forty-one were retrospective cohort studies. Thirty-four studies had high risk of bias, eighteen had moderate risk of bias and the remaining ten had low risk of bias.

Three studies reported body mass index in women who continue taking metformin during pregnancy and one study (Benito 2020) reported body mass index in pregnancies post bariatric surgery. These were excluded from meta-analysis on a sensitivity analysis. Twelve studies matched women on the basis of BMI and sixteen matched on the basis of age. Seventeen studies reported body mass index in post ART pregnancies.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

On pooled and sensitivity meta-analyses, women with PCOS had significantly higher odds of miscarriage, gestational diabetes, gestational hypertension, pre-eclampsia, preterm birth, low birth weight, intrauterine growth restriction, and caesarean section; and also women with PCOS had significantly higher gestational weight gain, and body mass index but had significantly lower birthweight. Eclampsia, small for gestational age, macrosomia, large for gestational age, instrumental delivery and perinatal depression were similar in women with and without PCOS, on both pooled and sensitivity meta-analyses. Induction of labour was similar on pooled meta-analysis but higher in women with PCOS on sensitivity meta-analysis.

On subgroup analyses, in BMI matched studies significantly higher odds of miscarriage, gestational diabetes, gestational hypertension, pre-eclampsia, and caesarean section, and also significantly lower birthweight were retained in women with PCOS. Small for gestational age turned to be significantly higher in women with PCOS.

On subgroup analyses, in age matched studies significantly higher odds of miscarriage, gestational diabetes, gestational hypertension, pre-eclampsia, preterm birth, and caesarean section, and also significantly lower birthweight were retained in women with PCOS. Small for gestational age turned to be significantly higher in women with PCOS.

On subgroup analyses, in post ART pregnancies significantly higher odds of miscarriage, gestational diabetes, gestational hypertension, pre-eclampsia, preterm birth, low birth weight, and also significantly higher body mass index were retained in women with PCOS. Small for gestational age turned to be significantly higher in women with PCOS.

On subgroup analyses, in high quality studies significantly higher odds of miscarriage, gestational diabetes, gestational hypertension, pre-eclampsia, preterm birth, and caesarean section, and also significantly lower birthweight were retained in women with PCOS. Small for gestational age turned to be significantly higher in women with PCOS.

Outcome	N. studies	Effect size [95% CI]	P Value	I^2
Miscarriage	43	OR 1.50 [1.20, 1.87]	**<0.001**	83.2%
No metformin/bariatric surgery	41	OR 1.54 [1.23, 1.93]	**<0.001**	83.0%
BMI matched	6	OR 3.62 [2.47, 5.29]	**<0.001**	0.0%
Age matched	7	OR 3.51 [2.46, 5.02]	**<0.001**	0.0%
Post ART pregnancies	29	OR 1.25 [1.04, 1.50]	**0.016**	65.2%
High quality	6	OR 3.38 [2.03, 5.64]	**<0.001**	44.8%
Gestational diabetes	57	OR 2.35 [1.90, 2.90]	**<0.001**	82.0%
No metformin/bariatric surgery	51	OR 2.37 [1.92, 2.93]	**<0.001**	82.0%
BMI matched	7	OR 2.85 [1.41, 5.78]	**0.004**	60.5%
Age matched	14	OR 2.05 [1.27, 3.31]	**0.003**	52.4%

Post ART pregnancies	9	OR 1.70 [1.03, 2.80]	**0.037**	82.9%
High quality	8	OR 2.62 [1.13, 6.07]	**0.024**	87.1%
Pregnancy-induced hypertension	40	OR 2.20 [1.82, 2.67]	**<0.001**	52.1%
No metformin/bariatric surgery	37	OR 2.22 [1.83, 2.68]	**<0.001**	51.0%
BMI matched	7	OR 2.60 [1.59, 4.27]	**<0.001**	1.1%
Age matched	12	OR 2.54 [1.73, 3.73]	**<0.001**	0.0%
Post ART pregnancies	4	OR 1.84 [1.18, 2.85]	**0.007**	0.0%
High quality	10	OR 2.19 [1.44, 3.72]	**0.001**	38.8%
Pre-eclampsia	36	OR 2.28 [1.88, 2.77]	**<0.001**	24.7%
No metformin/bariatric surgery	34	OR 2.35 [1.93, 2.86]	**<0.001**	26.0%
BMI matched	7	OR 2.39 [1.14, 4.99]	**0.021**	39.5%
Age matched	10	OR 2.81 [1.47, 5.36]	**0.003**	48.7%
Post ART pregnancies	2	OR 3.06 [1.01, 9.25]	**0.047**	0.0%
High quality	6	OR 3.05 [1.20, 7.80]	**0.020**	51.3%
Eclampsia	1	OR 1.16 [0.44, 3.08]	0.766	.
No metformin/bariatric surgery	1	OR 1.16 [0.44, 3.08]	0.766	.
BMI matched	0	-	-	-
Age matched	1	OR 1.16 [0.44, 3.08]	0.766	.
Post ART pregnancies	1	OR 1.16 [0.44, 3.08]	0.766	.
High quality	0	-	-	-
Preterm birth	54	OR 1.54 [1.34, 1.76]	**<0.001**	66.5%
No metformin/bariatric surgery	49	OR 1.56 [1.36, 1.79]	**<0.001**	67.9%
BMI matched	8	OR 1.44 [0.86, 2.42]	0.169	30.9%
Age matched	11	OR 1.48 [1.03, 2.11]	**0.034**	14.6%
Post ART pregnancies	14	OR 1.46 [1.14, 1.87]	**0.003**	80.7%
High quality	9	OR 1.93 [1.19, 3.16]	**0.008**	50.9%
Low birth weight	15	OR 1.28 [1.04 ,1.59]	**0.022**	58.6%
No metformin/bariatric surgery	14	OR 1.27 [1.03, 1.57]	**0.028**	59.6%
BMI matched	0	-	-	-
Age matched	0	-	-	-
Post ART pregnancies	7	OR 1.37 [1.03, 1.81]	**0.029**	66.0%
High quality	1	OR 1.36 [0.58, 3.18]	0.485	.
Small for gestational age	25	OR 1.12 [0.89, 1.40]	0.345	50.8%
No metformin/bariatric surgery	24	OR 1.14 [0.90, 1.45]	0.268	51.9%
BMI matched	5	OR 2.75 [1.50, 5.04]	**0.001**	43.0%
Age matched	5	OR 2.75 [1.50, 5.04]	**0.001**	43.0%
Post ART pregnancies	1	OR 0.70 [0.51, 0.97]	**0.029**	0.0%
High quality	4	OR 2.20 [1.06, 4.54]	**0.034**	59.7%
Macrosomia	23	OR 1.14 [0.95, 1.37]	0.150	62.4%
No metformin/bariatric surgery	22	OR 1.17 [0.98, 1.41]	0.089	61.9%
BMI matched	2	OR 1.24 [0.34, 4.60]	0.743	0.0%
Age matched	2	OR 1.24 [0.34, 4.60]	0.743	0.0%
Post ART pregnancies	6	OR 1.16 [0.77, 1.75]	0.467	88.2%
High quality	2	OR 0.92 [0.55, 1.53]	0.735	0.0%
Large for gestational age	23	OR 1.12 [0.98, 1.28]	0.096	10.6%
No metformin/bariatric surgery	22	OR 1.13 [0.99, 1.29]	0.073	9.4%
BMI matched	5	OR 1.55 [1.00, 2.41]	0.052	0.0%
Age matched	5	OR 1.55 [1.00, 2.41]	0.052	0.0%
Post ART pregnancies	2	OR 1.54 [0.56, 4.19]	0.401	84.3%
High quality	6	OR 1.09 [0.81, 1.48]	0.571	8.4%
Intrauterine growth restriction	10	OR 1.77 [1.16, 2.69]	**0.008**	21.5%
No metformin/bariatric surgery	10	OR 1.77 [1.16, 2.69]	**0.008**	21.5%
BMI matched	3	OR 1.31 [0.55, 3.10]	0.545	0.0%
Age matched	4	OR 1.43 [0.69, 2.93]	0.336	0.0%

Post ART pregnancies	1	OR 1.74 [0.47, 6.43]	0.406	.
High quality	4	OR 2.21 [0.78, 6.24]	0.134	59.7%
Instrumental delivery	10	OR 1.18 [0.91, 1.53]	0.209	0.0%
No metformin/bariatric surgery	9	OR 1.17 [0.90, 1.52]	0.226	0.0%
BMI matched	4	OR 1.02 [0.58, 1.80]	0.940	8.2%
Age matched	4	OR 1.02 [0.58, 1.80]	0.940	8.2%
Post ART pregnancies	0	-	-	-
High quality	3	OR 0.84 [0.35, 2.04]	0.700	13.2%
Induction of labour	8	OR 1.62 [0.97, 2.70]	0.065	81.0%
No metformin/bariatric surgery	7	OR 1.69 [1.01, 2.85]	**0.047**	83.2%
BMI matched	1	OR 1.25 [0.56, 2.77]	0.583	.
Age matched	1	OR 1.25 [0.56, 2.77]	0.583	.
Post ART pregnancies	0	-	-	-
High quality	1	OR 1.25 [0.56, 2.77]	0.583	.
Caesarean section	37	OR 1.23 [1.06, 1.43]	**0.006**	63.5%
No metformin/bariatric surgery	35	OR 1.23 [1.06, 1.44]	**0.007**	65.0%
BMI matched	6	OR 1.57 [1.19, 2.07]	**0.001**	0.0%
Age matched	9	OR 1.57 [1.24, 2.00]	**<0.001**	4.1%
Post ART pregnancies	7	OR 0.96 [0.83, 1.12]	0.629	3.9%
High quality	7	OR 1.58 [1.19, 2.09]	**0.002**	0.0%
Perinatal depression	1	1.58 [0.87, 2.88]	0.131	.
No metformin/bariatric surgery	1	1.58 [0.87, 2.88]	0.131	.
BMI matched	0	-	-	-
Age matched	0	-	-	-
Post ART pregnancies	0	-	-	-
High quality	0	-	-	-
Gestational weight gain (kg)	16	WMD 0.96 [0.01, 1.90]	**0.048**	88.1%
No metformin/bariatric surgery	16	WMD 0.96 [0.01, 1.90]	**0.048**	88.1%
BMI matched	4	WMD 3.10 [-0.77, 6.98]	0.116	93.1%
Age matched	7	WMD 2.16 [-0.19, 4.50]	0.071	90.8%
Post ART pregnancies	1	WMD -1.10 [-2.53, 0.33]	0.132	.
High quality	3	WMD 3.24 [-0.72,7.20]	0.109	93.3%
Birthweight (g)	45	WMD -41.52 [-62.70, -20.34]	**0.005**	84.9%
No metformin/bariatric surgery	40	WMD -50.46 [-82.05, -18.88]	**0.002**	89.1%
BMI matched	10	WMD -106.03 [-187.56, -24.49]	**0.011**	54.0%
Age matched	13	WMD -115.40 [-187.59, -43.20]	**<0.001**	39.6%
Post ART pregnancies	7	WMD 13.44 [-35.21, 62.08]	0.588	65.6%
High quality	7	WMD -139.09 [-219.07, -59.11]	**0.001**	44.0%
Body mass index (kg/m^2)	62	WMD 1.88 [1.56, 2.20]	**<0.001**	95.0%
No metformin/bariatric surgery	58	WMD 1.81 [1.48, 2.13]	**<0.001**	95.1%
BMI matched	12	WMD 0.04 [-0.20, 0.27]	0.743	4.2%
Age matched	16	WMD 0.37 [0.01, 0.73]	0.046	39.0%
Post ART pregnancies	17	WMD 1.40 [1.05, 1.75]	**<0.001**	89.0%
High quality	10	WMD 0.41 [-0.6, 1.47]	0.443	92.7%

6. STUDY CHARACTERISTICS TABLE

Author, year, country	Population/ Setting	Study Design	Sample Size per group	Intervention/ exposure details	Comparison/ control details	Follow up Duration	Outcomes	Summary of findings	RoB
Diamant 1982, Israel	Women with and without PCOS / Note stated	Observational	PCOS: 70 Non-PCOS: 2071	Two or more of the following: hirsutism, oligomenorrhea, anovulation, elevated level of either serum Testosterone or urinary KS +PCOM	Anovulatory Non-PCOS/Non- PCOS with Spontaneous Pregnancy	NA	PE, BW, Instrumental delivery, CS	After induction of ovulation, in infertile women are accompanied by an increased incidence of PET. This was suggested as early as 20 yr ago by Stallworthy (1960). However, according to our results, the rate of PET differs significantly between the PC0 and A-NPCO patients. While the incidence of PET in A-NPCO group was only slightly elevated as compared to the normal control group, and even lower than in the control primipara group, PC0 women developed PET in more than 28% of the cases. This rate was almost 12 times higher than in the normal control group and more than 2.5 times higher than in the control primiparae.	High ROB
Levran 1990, Israel	Women with and without PCOS / Infertility treatment centre for PCOS, Outpatient clinic for Non-PCOS	Observational	PCOS: 76 Non-PCOS: 95	Anovulation with oligo/amenorrhea+obesity+hirsutism+PCOM	Normal menstrual pattern and spontaneous pregnancy	NA	GDM	GDM was higher in PCOS.	High ROB
Wortsman 1991, USA	Women with and without PCOS / e endocrine/gynaecology services	Observational	PCOS: 53 Non-PCOS: 2306	Menstrual irregularities, Hirsutism and/or infertility from ovulatory dysfunction and the presence of a biochemical profile showing serum LH levels≥25 mIU/m, LH/FSH ratio≥2 and/or elevated serum concentrations of the androgens testosterone, free testosterone, androstenedione and deydroepiandrosterone sufat+laparascopy or sonography	Non-PCOS	NA	GDM, BW, Macrosomia	GDM, BW and macrosomia were similar in PCOS and Non-PCOS.	High ROB
Urman 1992, Canada	Women with and with probably infertility treatment centre out PCOS /	Observational	PCOS: 4 Non-PCOS: 10	Hirsutism, oligoanovulation, LH/FSH>2, Hyperandrogenism	Non-PCOS and Infertility because of tubal factor	NA	Miscarriage	Miscarriage was similar in PCOS and Non-PCOS.	Low ROB
Homburg 1993, Israel	Women with and without PCOS / IVF centre	Observational	PCOS: 47 Non-PCOS: 38	PCOM+Anovulation+Infertility+Oligomenorrhea/hirsutism	tubal infertility, underwent IVF	NA	Miscarriage	Miscarriage was similar in PCOS and Non-PCOS.	Moderate ROB
Lesser 1997, USA	Women with and without PCOS / Infertility treatment at the reproductive endocrinology clinic of the	Observational	PCOS: 24 Non-PCOS: 45	Oligoanovulation AND clinical OR biochemical hyperandrogenism OR obesity OR hirsutism OR acantosis AND PCOM	Non-PCOS and Infertility unrelated to PCOS	NA	GWG, GDM	GWG and GDM were similar in PCOS and Non-PCOS.	High ROB

	University of Arizona Health Sciences Centre								
Urman 1997, Turkey	Women with and without PCOS / Infertility treatment centre	Observational	PCOS: 47 Non-PCOS: 100	Anovulation, oligoamenorrhea, hirsutism, luteinizing hormone /follicle-stimulating hormone ratio >2 and varying degrees of hyperandrogenism	Non-PCOS	NA	GWG, GDM, GH, PE, PTB, LBW and Macrosomia	GWG, PTB and macrosomia were similar in PCOS and Non-PCOS. GDM, GH, PE and LBW were higher in PCOS.	Moderate ROB for GDM, GH, PE, (Poor for GWG, PTB, LBW and Macrosomia)
Fridstrom 1999, Sweden	Women with and without PCOS / The IVF unit at Huddinge University Hospital	Observational	PCOS: 33 Non-PCOS: 66	Anovulation+PCOM	Non-PCOS and tubal damage infertility , endometriosis, unexplained infertility, or male infertility	NA	GWG, GDM, GH, PE, PTB, BW, CS	GWG, GDM, GH, PE, PTB, CS were similar in PCOS and Non-PCOS BW were lower in PCOS.	Low ROB for PTB, BW, CS (Moderate ROB for GWG, GDM, GH, PE)
Kashyap 2000, Canada	Women with and without PCOS / Infertility centre	Observational	PCOS: 22 Non-PCOS: 27	Irregular menstrual cycles, increased serum testosterone, and LH/FSH >2 or PCOM on US	Non-PCOS and Infertility due to tubal factor, unexplained, luteal phase deficiency and male factor.	NA	GH	GH was higher in PCOS	High ROB
Vollenhoven 2000, Australia	Women with and without PCOS / Infertility treatment centre (OI) for PCOS and antenatal care and delivery for Controls	Observational	PCOS: 60 Non-PCOS: 60	Infertile with Oligomenorrhea and or hirsutism, PCOM on US±LH/FSH≥3, Testosterone>3.5 nmol/L and or DHEAS> 7.5 nmol/L	Non-PCOS	NA	GDM, BW, Instrumental delivery	GDM, BW, Instrumental delivery were similar in PCOS and Non-PCOS.	Moderate R OB
Mikola 2001, Finland	Women with and without PCOS / The Department of Obstetrics and Gynaecology of Helsinki University Central Hospital	Observational	PCOS: 99 Non-PCOS: 737	(i) PCOM on US and ≥ 2 of the following: (ii) serum LH/FSH ratio >2; (iii) hyperandrogenemia or (iv) clinical picture of menstrual irregularities, hirsutism, or infertility from anovulation	Non-PCOS and all with normal US at 16-18 weeks of gestation.	NA	GDM, GH, PE, PTB, BW, Macrosomia, CS	GDM and PTB were higher in PCOS GH, PE, BW were similar in PCOS and Non-PCOS.	High ROB
Wang 2001, Australia	Women with and without PCOS / The Reproductive Medicine Unit, Department of Obstetrics and Gynaecology	Observational	PCOS: 373 Non-PCOS: 645	Testosterone>2.5 nmol/l or elevated androstenedione, SHBG<20 nmol/l, PCOM on US	Non-PCOS	NA	Miscarriage	GWG and GDM were similar in PCOS and Non-PCOS.	High ROB
Bjercke 2002, Norway	Women with and without PCOS / probably infertility treatment centre	Observational	PCOS: 52 Non-PCOS: 355	PCOM on ultrasonography+ ≥3 of the following: oligomenorrhea, amenorrhoea, hirsutism, hyperandrogenemia, elevated LH/FSH ratio >2 and chronic anovulation	Non-PCOS and Singleton pregnancies + ART pregnancies	NA	GDM, GH, PE, PTB, Instrumental delivery and CS	GDM, GH were higher in PCOS PE, PTB, Instrumental delivery and CS were similar in PCOS and Non-PCOS.	High ROB

Sir-Petermann 2002, Chile	Women with and without PCOS / Unit of Reproductive Medicine for PCOS, The antenatal care unit for Controls.	Observational	PCOS: 20 Non-PCOS: 26	Chronic oligo/amenorrhoea, clinical signs of hyperandrogenism with no virilization, clinical signs of hyperinsulinaemia (waist:hip ratio >0.85), serum testosterone >0.6 ng/ml and/or FAI >5.0, different grades of hyperinsulinaemia evaluated by an OGTT, and PCOM on US.	Non-PCOS and Regular menstrual cycles, No hirsutism and other manifestations of hyperandrogenism, No galactorrhoea, thyroid dysfunction and family history of DM. All were healthy and were not receiving any drug therapy.	NA	GDM	GDM was higher in PCOS.	Moderate R OB
Haakova 2003, Czech Republic	Women with and without PCOS / Department of Obstetrics and Gynaecology	Observational	PCOS: 66 Non-PCOS: 66	Rotterdam	Non-PCOS - those who had undergone US at the same department	NA	GWG, GDM, GH, PTB, BW, CS	GWG was higher in PCOS GDM, GH, PTB, BW, CS were similar in PCOS and Non-PCOS.	Low ROB
Turhan 200, Turkey	Women with and without PCOS / The outpatient clinic of the Department of Obstetrics and Gynecology of Fatih University Hospital	Observational	PCOS: 38 Non-PCOS: 136	Rotterdam	Non-PCOS - randomly selected	NA	GWG, GDM, GH, PE, PTB, IUGR, BW, Macrosomia, IOL, CS	GWG was higher in PCOS GDM, GH, PE, PTB, IUGR, BW, Macrosomia, IOL, CS were similar in PCOS and Non-PCOS.	High ROB
Glueck 2004, USA	Women with and without PCOS / The Jewish hospital for PCOS and a suburban community practice of obstetrics for Controls	Observational	PCOS: 122 Non-PCOS: 252	Rotterdam	Non-PCOS - Community healthy controls; Reglar menstrual cycles, no clinical signs of hyperandrogenism, had never been diagnosed with PCOS by Obstetricians	NA	GDM , PE, PTB	GDM, PE, PTB were similar in PCOS and Non-PCOS.	High ROB
Glueck 2004, USA	Women with and without PCOS / The Jewish hospital for PCOS and a suburban community practice of obstetrics for Controls	Observational	PCOS: 97 Non-PCOS: 252	Rotterdam	Non-PCOS- Healthy women not known to have PCOS, with ≥ 1 live birth, consecutively delivered in a suburban-urban community practice	NA	GDM, PE, PTB, BW, Macrosomia	GDM, PE, PTB, BW, Macrosomia were similar in PCOS and Non-PCOS.	High ROB
Weerakiet 2004, Thiland	Women with and without PCOS / Reproductive endocrinology and infertility unit	Observational	PCOS: 47 Non-PCOS: 264	Homburg (menstrula irregularity, clinical hyperandrogenism such as acne, seborrhea and hirsutism, and bilaterla PCOM on US	Non-PCOS and normal menstruation	NA	GWG, GDM, GH, PE, CS	GH,CS were higher in PCOS GWG, GDM, PE were similar in PCOS and Non-PCOS.	Moderate ROB

Sir-Petermann 2005, Chile	Women with and without PCOS / The Unit of Endocrinology and Reproductive Medicine seeking infertility treatment for PCOS and the prenatal care unit for controls	Observational	PCOS: 47 Non-PCOS: 108	Rotterdam	Non-PCOS - Normal pregnant, regular menstrual cycles, No hirsutism and other manifestations of hyperandrogenism, no drug therapy	NA	GWG, GDM, PTB, BW, SGA, LGA	GWG, GDM, SGA were higher in PCOS BW, LGA, PTB were similar in PCOS and Non-PCOS.	Moderate ROB
Al-Ojaimi 2006, Bahrain	Women with and without PCOS / Hospital laparoscopic drilling centre for PCOS and routine booking clinic at the same department and the same period of time	Observational	PCOS: 134 Non-PCOS: 479	Rotterdam	Non-PCOS - Normal menstrual cycles, no clinical signs of hyperandrogenism and were not receiving any drug therapy	NA	GWG, GDM, GH, PE, PTB, BW, LBW, Macrosomia	GDM, GH, PE were higher in PCOS GWG, PTB, BW, LBW, Macrosomia were similar in PCOS and Non-PCOS.	High ROB
Dokras 2006, USA	Women with and without PCOS / The infertility and in vitro fertilization (IVF) at the University of Iowa Hospitals and Clinics	Observational	PCOS: 46 Non-PCOS: 108	NIH	Non-PCOS	NA	Miscarriage, GDM, PTB, CS	GDM was higher in PCOS and obesity Miscarriage, PTB, CS were similar in PCOS and Non-PCOS.	Low ROB
Kovo 2006, Israel	Women with and without PCOS / Edith Wolfson Medical Center	Observational	PCOS: 33 Non-PCOS: 66	Rotterdam	Non-PCOS	NA	BMI, GDM, GH, PTB, BW, CS	GDM, GH were higher in PCOS. BMI, PTB, BW, CS were similar in PCOS and Non-PCOS.	Low ROB
Hu 2007, UK	Women with and without PCOS / The antenatal and gynaecology clinics at the Royal Free Hospital	Observational	PCOS: 22 Non-PCOS: 22	Rotterdam	Non-PCOS - healthy pregnant women with no PCOS symptoms	NA	GH, PE, EC, BW	GH, PE were higher in PCOS BW was lower in PCOS EC was similar in PCOS and Non-PCOS (n=0/group).	Low ROB
Palep-Singh 2007, UK	Women with and without PCOS / IVF/ICSI centre	Observational	PCOS: 324 Non-PCOS: 284	Rotterdam	Non-PCOS - Infertility due to tubal factor	NA	Miscarriage	Miscarriage was higher in PCOS	High ROB
Sir-Petermann 2007, Chile	Women with and without PCOS / The Unit of Endocrinology and Reproductive Medicine for PCOS and the antenatal care unit of the same hospital for Controls	Observational	PCOS: 48 Non-PCOS: 51	Rotterdam	Non-PCOS - Normal pregnant women with singleton pregnancies, had a history of regular menstrual cycles, No hirsutism and other manifestations of hyperandrogenism, No galactorrhoea and thyroid dysfunction. Healthy and not	NA	GDM, GH	GDM was higher in PCOS and obesity GH was similar in PCOS and Non-PCOS.	Moderate ROB

					receiving any drug therapy				
Beydoun 2009, USA	Women with and without PCOS / Analyses of existing records probably from an infertility treatment Centre	Observational	PCOS: 69 Non-PCOS: 69	NIH	Non-PCOS - underwent IVF/ICSI	NA	Miscarriage	Miscarriage was similar in PCOS and Non-PCOS.	High ROB
Gupta 2009, India	Women with and without PCOS / Suvidha Mother and Child Nursing Home	Observational	PCOS: 56 Non-PCOS: 56	Rotterdam	Non-PCOS - Those who had undergone US at the same department	NA	GDM, GH	GDM and GH were similar in PCOS and Non-PCOS.	Low ROB
Maliqueo 2009, Chile	Women with and without PCOS / The Unit of Endocrinology and Reproductive Medicine for PCOS (Women with PCOS who were seeking infertility treatment); the antenatal care unit of our hospital for Controls	Observational	PCOS: 30 Non-PCOS: 34	Rotterdam	Non-PCOS - Healthy women with a history of regular menstrual cycles, No hirsutism and other manifestations of hyperandrogenism, and No galactorrhea and thyroids function; not receiving any drug therapy.	NA	BMI, GWG, BW, SGA, LGA	BMI was higher in PCOS GWG, BW, SGA, LGA were similar in PCOS and Non-PCOS.	Moderate ROB
Falbo 2010, Italy	Women with and without PCOS / the Department of Obstetrics and Gynecology of the University	Observational	PCOS: 45 Non-PCOS: 42	Rotterdam	Non-PCOS	NA	BMI, GH, PE, BW	BW was lower in PCOS GH, PE were higher in PCOS and obesity BMI was similar in PCOS and Non-PCOS.	Low ROB
Li 2010, China	Women with and without PCOS / Beijing Obstetrics and Gynecology Hospital	Observational	PCOS: 34 Non-PCOS: 70	Rotterdam	Non-PCOS	NA	PE, PTB, BW, SGA, Macrosomia, LGA	PE, PTB, BW, SGA, Macrosomia, LGA were similar in PCOS and Non-PCOS.	Moderate ROB
Palomba 2010, Italy	Women with and without PCOS / Hospital (the Department of Obstetrics and Gynaecology)	Observational	PCOS: 97 Non-PCOS: 73	Rotterdam	Non-PCOS - Regular menstrual cycles (26–32days in length), no signs of clinical hyperandrogenism, normal range of serum androgens levels, no PCOM on transvaginal ultrasonography (TVUS), and no	NA	Miscarriage, GDM, GH, PE, PTB, SGA, LGA,	Miscarriage, GDM, GH, PE, PTB, SGA, LGA were higher in PCOS	Moderate ROB

					known male or tubal infertility factors				
Palomba 2010, Italy	Women with and without PCOS / Two academic Departments of Obstetrics and Gynaecology	Observational	PCOS: 73 Non-PCOS: 73	Rotterdam	Non-PCOS - Healthy primigravidas; regular menstrual cycles, no signs of clinical/ Biochemical hyperandrogenism, No PCOM	NA	Miscarriage, GDM, GH, PE, PTB, IUGR, SGA, LGA, Instrumental delivery, CS	Miscarriage, GDM, GH, PE, SGA, LGA, Instrumental delivery, CS were higher in PCOS and obesity PTB, IUGR were similar in PCOS and Non-PCOS.	Low ROB
De Leo 2011, Italy	Women with and without PCOS / The infertility and in vitro fertilization (IVF) unit for PCOS and Low-risk antenatal clinic for Controls;	Observational	PCOS: 98 Non-PCOS: 110	Rotterdam	Non-PCOS - healthy	NA	Miscarriage, GDM, GH, PE, PTB, BW	Miscarriage, GDM, GH, PTB were higher in PCOS PE, BW were similar in PCOS and Non-PCOS.	High ROB
Dmitrovic 2011, USA	Women with and without PCOS / Not stated for PCOS, Control group were volunteers recruited through advertisements or referrals	Observational	PCOS: 17 Non-PCOS: 17	chronic oligo/anovulation and the presence of hyperandrogenemia	Non-PCOS - Normal menstrual cycles before pregnancy and an absence of hirsutism and other manifestations of hyperandrogenism	NA	BMI, GDM, PTB, BW, SGA, LGA	BMI was higher in PCOS GDM, BW, PTB, SGA, LGA were similar in PCOS and Non-PCOS.	High ROB
Nejad 2011, Iran	Women with and without PCOS / Royan Infertility Research Centre	Observational	PCOS: 164 Non-PCOS: 161	Rotterdam	Non-PCOS - Infertility caused by tubal factor diagnosed by hysterosalpingogram and laparoscopy	NA	Miscarriage	Miscarriage was similar in PCOS and Non-PCOS.	High ROB
Nouh 2011, Egypt	Women with and without PCOS / The Obstetrics and Gynecology and Medical Biochemistry departments	Observational	PCOS: 40 Non-PCOS: 40	PCOM+clinical/biochemicl HA without oligoanovulation	Non-PCOS - Regular menstrual cycles, no clinical/biochemical signs of hyperandrogenism, no PCOM	NA	Miscarriage, GDM, GH, PE, PTB, SGA, LGA, CS	SGA, CS were higher in PCOS Miscarriage, GDM, GH, PE, PTB, and LGA were similar in PCOS and Non-PCOS.	Low ROB
Mehrabian 2012, Iran	Women with and without PCOS / Hospital	Observational	PCOS: 40 Non-PCOS: 40	NIH	Non-PCOS - singleton pregnancy, regular menstrual cycles; without hirsutism, other HA signs,	NA	BMI, GWG, BW	BW was lower in PCOS GWG was higher in PCOS BMI was similar in PCOS and Non-PCOS.	Low ROB

					galactorrhea, thyroid dysfunction, GDM, HTN and history of any chronic medication use				
Palomba 2012, Italy	Women with and without PCOS / Hospital (Women who were suffering from hyperandrogenism and/or ovulatory disorders and seeking pregnancy	Observational	PCOS: 42 Non-PCOS: 84	Rotterdam	Non-PCOS - Regular menstrual cycles before pregnancy, no signs of clinical hyperandrogenism, normal ranges of serum androgen levels, and no PCO morphologies on transvaginal ultrasonography	NA	BMI, GWG, GH, PE, PTB, BW, SGA, Macrosomia, LGA, IOL, Instrumental delivery, CS	GH, PE and CS were higher in PCOS and obesity BMI, GWG, PTB, BW, SGA, Macrosomia, LGA, IOL, Instrumental delivery were similar in PCOS and Non-PCOS.	Low ROB
Reyes-Munoz 2012, Mexico	Women with and without PCOS / Level three medical institution	Observational	PCOS: 52 Non-PCOS: 52	Rotterdam	Non-PCOS - Without a history of infertility and no PCOS and received prenatal care during the same period	NA	BMI, GWG, Miscarriage, GDM, PE, PTB, BW, SGA, LGA	GDM was higher in PCOS BMI, GWG, Miscarriage, PE, PTB, SGA, LGA, BW were similar in PCOS and Non-PCOS.	Moderate ROB
Yamamoto 2012, USA	Women with and without PCOS / Health care delivery system	Observational	PCOS: 908 Non-PCOS: 992	Rotterdam	Non-PCOS	NA	PTB	PTB was higher in PCOS	Moderate ROB
Boutzios 2013, Greece	Women with and without PCOS / Hospital (The 2nd Department of Obstetrics and Gynecology)	Observational	PCOS: 41 Non-PCOS: 110	NIH	Non-PCOS - Healthy controls (Regular menstrual cycles, normal plasma androgen levels, and no acne or hirsutism before conception	NA	BMI, BW, SGA, LGA	BMI, BW, SGA, LGA were similar in PCOS and Non-PCOS.	Moderate ROB
Wang 2013, China	Women with and without PCOS / The Obstetrics Department	Observational	PCOS: 144 Non-PCOS: 594	Rotterdam	Non-PCOS - selected by a computerized random number generator	NA	BMI, Miscarriage, GDM, GH, PTB, IUGR, LGA	Miscarriage, GDM, GH, PTB, IUGR were higher in PCOS BMI and LGA were similar in PCOS and Non-PCOS.	Moderate ROB
Ashrafi 2014, Iran	Women with and without PCOS / Reproductive biomedicine research centre	Observational	PCOS: 234 Non-PCOS: 468	Rotterdam	Non-PCOS - 1.Non-PCOS+ART / 2. Non-PCOS+ No infertility history	NA	BMI, GDM	BMI and GDM were higher in PCOS	High ROB

Elkholi 2014, Egypt	Women with and without PCOS / Infertility Clinic, Tanta University Hospitals	Observational	PCOS: 200 Non-PCOS: 200	Rotterdam	Non-PCOS - Pregnant patients attending the Outpatient Clinic	NA	BMI, Miscarriage, GDM, GH, PE, PTB, IUGR, BW, Macrosomia, CS	GDM, GH, PE, PTB were higher in PCOS BMI, Miscarriage, IUGR, BW, Macrosomia, CS were similar in PCOS and Non-PCOS.	Low ROB
Foroozanfard 2014, Iran	Women with and without PCOS / Shahbihkani Hospital	Observational	PCOS: 130 Non-PCOS: 131	Rotterdam	Non-PCOS	NA	BMI, GH, PE, PTB, BW, Macrosomia, CS	PE, GH were higher in PCOS BMI, PTB, CS, BW, Macrosomia were similar in PCOS and Non-PCOS.	Moderate ROB
Huang 2014, China	Women with and without PCOS / IVF/ICSI center of Tongji Hospital	Observational	PCOS: 128 Non-PCOS: 128	Rotterdam	Non-PCOS - Tubal factor infertility diagnosed by hysterosalpingography combined with laparoscopy undergoing IVF/ICSI at the same period of time	NA	Miscarriage	Miscarriage was similar in PCOS and Non-PCOS.	Moderate ROB
Lathi 2014, USA	Women with and without PCOS / Infertility treatment clinic	Observational	PCOS: 59 Non-PCOS: 287	Rotterdam	Non-PCOS	NA	BMI, Miscarriage	Miscarriage was higher in PCOS BMI was similar in PCOS and Non-PCOS	Moderate ROB
Li 2014, China	Women with and without PCOS / IVF centre	Observational	PCOS: 104 Non-PCOS: 751	Rotterdam	Non-PCOS - Isolated PCOM, With regular menstrual cycles; Without Hyperandrogenism	NA	Miscarriage	Miscarriage was higher in PCOS	High ROB
Liu 2014, China	Women with and without PCOS / IVF centre	Observational	PCOS: 301 Non-PCOS: 3591	Rotterdam	Non-PCOS - IVF due to tubal factor, male factor, endometriosis, and unexplained infertility	NA	Miscarriage	Miscarriage was similar in PCOS and Non-PCOS.	High ROB
Naver 2014, Denmark	Women with and without PCOS / The private fertility clinic	Observational	PCOS: 459 Non-PCOS: 5409	Rotterdam	Non-PCOS - based on ICD-10 from a birth cohort including all singleton deliveries from the year	NA	GDM, GH, PE, PTB, BW, SGA, LGA, IOL, CS	GDM, PE, PTB were higher in PCOS GH, BW, SGA, LGA, IOL, CS were similar in PCOS and Non-PCOS.	High ROB
Palomba 2014, Italy	Women with and without PCOS / The Academic Department of Obstetrics	Observational	PCOS: 150 Non-PCOS: 150	Rotterdam	Non-PCOS - Ruling out PCOS symptoms	NA	BMI, Miscarriage, GDM, GH,	BW was lower in PCOS Miscarriage, GDM, GH, PE, SGA were higher in PCOS	Low ROB

	and Gynaecology of the Pugliese-Ciaccio Hospital						PE, BW, SGA, LGA	BMI and LGA were similar in PCOS and Non-PCOS.	
Palomba 2014, Italy	Women with and without PCOS / The Academic Department of Obstetrics and Gynaecology of the Pugliese-Ciaccio Hospital	Observational	PCOS: 150 Non-PCOS: 150	Rotterdam	Non-PCOS - Ruling out PCOS symptoms	NA	BMI, Miscarriage, GDM, GH, PE, PTB, IUGR, BW, SGA, LGA, Instrumental delivery, CS	BW was lower in PCOS Miscarriage, GDM, GH, PE, SGA were higher in PCOS BMI, IUGR, PTB, LGA, Instrumental delivery and CS were similar in PCOS and Non-PCOS.	Low ROB
Zhang 2014, China	Women with and without PCOS / The Division of Reproductive Centre	Observational	PCOS: 27 Non-PCOS: 27	Rotterdam	Non-PCOS - Infertility due to male or tubal factor	NA	BMI, Miscarriage	BMI and Miscarriage were similar in PCOS and Non-PCOS.	High ROB
Kollmann 2015, Austria	Women with and without PCOS / The local perinatal database and the medical documentation system or patient file of the Medical University of Graz	Observational	PCOS: 177 Non-PCOS: 708	Rotterdam	Non-PCOS - Without pregestational diabetes or pregestational hypertension	NA	GDM, GH, PE, PTB, SGA, LGA, Instrumental delivery, CS	GDM, GH, Instrumental delivery, CS were higher in PCOS PE, PTB, SGA, LGA, were similar in PCOS and Non-PCOS.	Moderate ROB
Koster 2015, Netherlands	Women with and without PCOS / A subset of the CoPPer study (Complications of PCOS Pregnancy: Evaluating risk) for PCOS	Observational	PCOS: 73 Non-PCOS: 209	Rotterdam	Non-PCOS - Delivery at term, after an uncomplicated pregnancy, spontaneous onset of labour or benign indication for a primary CS	NA	GDM, GH, BW, SGA, LGA, IOL, CS	CS was lower in PCOS GDM, GH, IOL was higher in PCOS BW, SGA, LGA were similar in PCOS and Non-PCOS.	High ROB
Mumm 2015, Denmark	Women with and without PCOS / Odense University Hospital	Observational	PCOS: 157 Non-PCOS: 1037	Rotterdam	Non-PCOS - Retrospective from a community control from another city's registry, Non-PCOS/ hirsutism	NA	GDM, GH, PE, PTB, SGA, LGA, IOL, Instrumental delivery, CS	GDM, IOL was higher in PCOS GH, PE, PTB, SGA, LGA, Instrumental delivery, CS were similar in PCOS and Non-PCOS.	High ROB
Sawada 2015, Japan	Women with and without PCOS / Department of Obstetrics and Gynaecology	Observational	PCOS: 49 Non-PCOS: 49	1) cycle irregularities, 2) polycystic changes in the ovary on US and 3) endocrine anomalies (LH or hyperandrogenism)	Non-PCOS - Healthy pregnant women with normal pregnancies	NA	BMI, GDM, GH, PTB, IUGR, BW, CS	GDM was higher in PCOS BMI, BW, GH, PTB, IUGR, CS were similar in PCOS and Non-PCOS.	Low ROB
Wan 2015, China	Women with and without PCOS / Infertility and in vitro fertilization (IVF)	Observational	PCOS: 104 Non-PCOS: 751	Rotterdam	Non-PCOS - PCOM without HA and AnOvu	NA	BMI, GDM, GH, PE, EC, IUGR, BW	BMI, GDM, GH, PE, EC, IUGR, BW were similar in PCOS and Non-PCOS.	High ROB
Aktun 2016, Turkey	Women with and without PCOS / The Istanbul	Observational	PCOS: 150	Rotterdam	Non-PCOS	NA	BMI, GWG, GH, PE,	BMI, GWG was higher in PCOS	High ROB

	Medipol University Hospital		Non-PCOS: 160				Macrosomia, CS	GH, PE, Macrosomia, CS were similar in PCOS and Non-PCOS.	
Sterling 2016, Canada	Women with and without PCOS / The Centre for Reproductive Health (Infertility treatment)	Observational	PCOS: 71 Non-PCOS: 323	Rotterdam	Non-PCOS	NA	GDM, PTB, LBW, SGA, Macrosomia, LGA, CS	GDM, PTB, LGA were higher in PCOS LBW, SGA, Macrosomia, CS were similar in PCOS and Non-PCOS.	High ROB
Wang 2016, China	Women with and without PCOS / IVF/ICSI centre	Observational	PCOS: 2632 Non-PCOS: 28523	Rotterdam	PCOS: 2632 Non-PCOS: 28523	NA	BMI, Miscarriage	BMI was higher in PCOS Miscarriage was similar in PCOS and Non-PCOS.	High ROB
Wang 2016, China	Women with and without PCOS / The Center of Reproductive Medicine at the First Affiliated Hospital	Observational	PCOS: 119 Non-PCOS: 664	Rotterdam	Non-PCOS - No PCOS symptoms	NA	Miscarriage	Miscarriage was similar in PCOS and Non-PCOS.	High ROB
Xiao 2016, China	Women with and without PCOS / Women and Children's Medical Center	Observational	PCOS: 325 Non-PCOS: 2037	Rotterdam	Non-PCOS	NA	GDM, PTB, BW, LBW, SGA, Macrosomia, LGA, CS	GDM, PTB, LGA was higher in PCOS BW, SGA, LBW, Macrosomia, CS were similar in PCOS and Non-PCOS.	High ROB
Chen 2017, China	Women with and without PCOS / Reproductive Centre Department of the First Hospital	Observational	PCOS: 59 Non-PCOS: 120	Rotterdam	Non-PCOS - fallopian tube problems without PCOS, or treatment due to male infertility without PCOS	NA	Miscarriage	Miscarriage was similar in PCOS and Non-PCOS.	High ROB
deWilde 2017, Netherlands	Women with and without PCOS / PCOS: hospitals; Controls: December 2012 until December 2013 in 31 midwifery practices and six hospitals	Observational	PCOS: 188 Non-PCOS: 2889	Rotterdam	Non-PCOS - women enrolled at a booking appointment in the first trimester of their pregnancy	NA	GDM, GH, PE, PTB, SGA, LGA, IOL, CS	GDM, PE, IOL, PTB were higher in PCOS GH, CS SGA, LGA were similar in PCOS and Non-PCOS.	High ROB
Jonsdottir 2017, Denmark	Women with and without PCOS / Infertility centre	Observational	PCOS: 91 Non-PCOS: 300	Rotterdam	Non-PCOS	NA	BMI, GDM, PE, PTB, BW, LBW, SGA, IOL, CS	BMI , IOL,CS were lower in PCOS GDM, PE, PTB, BW, LBW, SGA, were similar in PCOS and Non-PCOS.	High ROB
Luo 2017, China	Women with and without PCOS / Centre of Reproductive Medicine, the First Affiliated Hospital of Sun Yat-sen University	Observational	PCOS: 67 Non-PCOS: 201	Rotterdam	Non-PCOS - undergoing PGD cycles due to chromosome translocation in either partner	NA	Miscarriage	Miscarriage was higher in PCOS	High ROB
Huang 2018, China	Women with and without PCOS / Infertility centre	Observational	PCOS: 146 Non-PCOS: 370	Rotterdam	Non-PCOS	NA	Miscarriage	Miscarriage was similar in PCOS and Non-PCOS.	High ROB

Kent 2018, USA	Women with and without PCOS / PCOS Infertility Centre; Controls from multiple university-affiliated hospitals	Observational	PCOS: 146 Non-PCOS: 176	Rotterdam with chronic anovulation	Non-PCOS - Unexplained Infertility	NA	GDM, PE	GDM and PE were similar in PCOS and Non-PCOS.	Moderate
Lai 2018, China	Women with and without PCOS / Infertility centre	Observational	PCOS: 22 Non-PCOS: 25	Rotterdam PCOS and tubal infertility	Non-PCOS - Tubal infertility	NA	Miscarriage	Miscarriage was similar in PCOS and Non-PCOS.	High ROB
Li 2018, China	Women with and without PCOS / Beijing Obstetrics and Gynecology Hospital, Capital Medical University	Observational	PCOS: 670 Non-PCOS: 6000	Rotterdam	Non-PCOS	NA	BMI, Miscarriage, GDM, GH, PTB, LBW, Macrosomia	BMI, GDM, GH, PTB were higher in PCOS Miscarriage, LBW, Macrosomia were similar in PCOS and Non-PCOS.	High ROB
March 2021, Australia	Women with and without PCOS / Community based	Observational	PCOS: 52 Non-PCOS: 514	Rotterdam	Non-PCOS	NA	Postnatal depression	Postnatal depression was higher in PCOS	Moderate ROB
Butts 2019, USA	Women with and without PCOS / infertility centre	Observational	PCOS: 607 Non-PCOS: 647	Rotterdam	Non-PCOS - Unexplained infertility	NA	Miscarriage	Miscarriage was higher in PCOS	High ROB
Schneider 2019, USA	Women with and without PCOS / setting unclear Keiser-Permanente data	Observational	PCOS: 809 Non-PCOS: 956	Rotterdam	Non-PCOS	NA	GH, PE	Hypertensive disorders were higher in PCOS	High ROB
Zheng 2019, China	Women with and without PCOS / Hospital	Observational	PCOS: 242 Non-PCOS: 324	Rotterdam	Non-PCOS	NA	BMI, GDM, GH, PE, PTB, BW, LBW, SGA , Macrosomia, LGA	BW was lower in PCOS PTB was higher in PCOS BMI, GDM, GH, PE, LBW, SGA, Macrosomia, LGA were similar in PCOS and Non-PCOS.	Low ROB
Benito 2020, Spain	Women with and without PCOS / Academic hospital	Observational	PCOS: 49 Non-PCOS: 120	Rotterdam - premenopausal women with infertility submitted to bariatric surgery	Non-PCOS - premenopausal women with infertility submitted to bariatric surgery	NA	BMI, Miscarriage, GDM, PE, PTB, BW, LBW, IOL, Instrumental, CS	BW was lower in PCOS BMI, Miscarriage, GDM, PE, PTB, LBW, IOL, Instrumental, CS were similar in PCOS and Non-PCOS.	High ROB
Chen 2020, China	Women with and without PCOS / Infertility centre	Observational	PCOS: 50 Non-PCOS: 50	Rotterdam	Non-PCOS - Regular menstrual cycles and normal ovulation without clinical and/or biochemical hyperandrogenism or polycystic ovary	NA	Miscarriage, PTB, BW, CS	Miscarriage, PTB, BW, CS were similar in PCOS and Non-PCOS.	High ROB
Elshewy 2020, China	Women with and without PCOS / Infertility centre	Observational	PCOS: 33 Non-PCOS: 35	Rotterdam (Anovulatory +PCOM)	Non-PCOS - Ovulatory non-PCOS	NA	Miscarriage	Miscarriage was similar in PCOS and Non-PCOS.	High ROB

Foroozanfard 2020, Iran	Women with and without PCOS / Infertility centre	Observational	PCOS: 40 Non-PCOS: 40	Rotterdam	Non-PCOS	NA	BMI, Miscarriage, GDM, GH, PE, PTB, CS	BMI, Miscarriage, GDM, GH, PE, PTB, CS were similar in PCOS and Non-PCOS.	High ROB
Liu 2020, China	Women with and without PCOS / Shenzhen Zhongshan Urology Hospital (SZUH)	Observational	PCOS: 666 Non-PCOS: 7012	Rotterdam	Non-PCOS + ART	NA	BMI, Miscarriage, GDM, GH, PTB, CS	Miscarriage, GH, PTB were higher in PCOS GDM, CS were similar in PCOS and Non-PCOS.	High ROB
Tobiasz 2020, USA	Women with and without PCOS / Hospital	Observational	PCOS: 28 Non-PCOS: 18	NIH	Non-PCOS	NA	BMI, PTB, IUGR, BW, CS	BMI, PTB, IUGR, BW, CS were similar in PCOS and Non-PCOS.	Moderate ROB
Abdulkhalikova 2021, Slovenia	Women with and without PCOS / IVF/ICSI centre	Observational	PCOS: 73 Non-PCOS: 196	Rotterdam - oligo- and/or anovulation, clinical and/or biochemical signs of hyperandrogenism and polycystic ovaries	Non-PCOS - participants who received IVF/ICSI	NA	GWG, GDM, GH, PE, PTB, BW, LBW, SGA, Macrosomia, CS	GWG, GDM, GH, PE, PTB, BW, LBW, SGA, Macrosomia, CS were similar in PCOS and Non-PCOS.	Low ROB
Cai 2021, China	Women with and without PCOS / Infertility centre	Observational	PCOS: 2357 Non-PCOS: 19463	Rotterdam	Non-PCOS	NA	BMI, Miscarriage, GDM	BMI, Miscarriage, GDM were higher in PCOS	Moderate ROB
Diboun 2021, Qatar	Women with and without PCOS / Research Center	Observational	PCOS: 16 Non-PCOS: 52	Qatar	Non-PCOS	NA	BW	BW was lower in PCOS	Moderate ROB
Feichtinger 2021, Austria	Women with and without PCOS / PCOS: 31 Non-PCOS: 36	Observational	PCOS: 31 Non-PCOS: 36	Rotterdam	Non-PCOS	NA	GDM	GDM was higher in PCOS	High ROB
Gongadashetti 2021, India	Women with and without PCOS / Infertility centre	Observational	PCOS: 43 Non-PCOS: 57	Rotterdam	Non-PCOS - Tubal infertility	NA	Miscarriage	Miscarriage was similar in PCOS and Non-PCOS.	High ROB
Hu 2021, China	Women with and without PCOS / Infertility centre	Observational	PCOS: 557 Non-PCOS: 3526	Rotterdam (Anovulatory +PCOM)	Non-PCOS - Non-hyperandrogenic	NA	GDM, PTB, BW, LBW, Macrosomia, CS	BW was higher in PCOS GDM, PTB, LBW, Macrosomia, CS were similar in PCOS and Non-PCOS.	High ROB
Jiang 2021, China	Women with and without PCOS / Infertility centre	Observational	PCOS: 100 Non-PCOS: 100	Rotterdam	Non-PCOS - Tubal infertility	NA	BMI, GDM, GH, PTB, LBW, Macrosomia, Instrumental delivery, CS	BMI was higher in PCOS GDM, GH, PTB, LBW, Macrosomia, Instrumental delivery, CS were similar in PCOS and Non-PCOS.	High ROB
Kaing 2021, USA	Women with and without PCOS / PCOS : Infertility Centre; Controls : Multiple university-affiliated hospitals	Observational	PCOS: 118 Non-PCOS: 146	Rotterdam with chronic anovulation	Non-PCOS - unexplained infertility	NA	BMI, BW	BMI was higher in PCOS BW was lower in PCOS	High ROB
Kollmann 2021, Austria	Women with and without PCOS / academic tertiary hospital	Observational	PCOS: 80 Non-PCOS: 420	Rotterdam	Non-PCOS	NA	BMI, GDM, GH, PE, IUGR, SGA, LGA	GDM were higher in PCOS BMI, GH, PE, IUGR, SGA, LGA were similar in PCOS and Non-PCOS.	Moderate ROB

Lin 2021, China	Women with and without PCOS / Infertility centre	Observational	PCOS: 1167 Non-PCOS: 9995	Rotterdam	Non-PCOS - tubal or male factor	NA	PTB, BW, LBW, Macrosomia, LGA	BW was lower in PCOS PTB, BW, LBW, were higher in PCOS Macrosomia, LGA were similar in PCOS and Non-PCOS.	High ROB
Liu 2021, China	Women with and without PCOS / Center for Reproductive Medicine, Shandong University	Observational	PCOS: 86 Non-PCOS: 60	Rotterdam	Non-PCOS - + ART	NA	BMI, Miscarriage	BMI, Miscarriage were higher in PCOS	High ROB
Mai 2021, China	Women with and without PCOS / Centre for Reproductive Medicine in Sun Yat-Sen Memorial Hospital	Observational	PCOS: 263 Non-PCOS: 526	Rotterdam	Non-PCOS - tubal factor infertility	NA	Miscarriage	Miscarriage was similar in PCOS and Non-PCOS.	High ROB
Pouya 2021, Turkey	Women with and without PCOS / university hospital infertility center	Observational	PCOS: 88 Non-PCOS: 90	Rotterdam	Non-PCOS	NA	Miscarriage	Miscarriage was similar in PCOS and Non-PCOS.	High ROB
Wang 2021, China	Women with and without PCOS / Dongyang Women and Children's Hospital	Observational	PCOS: 29 Non-PCOS: 116	Rotterdam	Non-PCOS	NA	BMI, GWG, BW, CS	BMI, GWG, BW, CS were similar in PCOS and Non-PCOS.	Moderate ROB
Wu 2021, China	Women with and without PCOS / Reproductive Medicine Center of The Sixth Affiliated Hospital of Sun Yat-sen University	Observational	PCOS: 1489 Non-PCOS: 1489	Rotterdam	Non-PCOS - tubal factor, incretion factor and immunity factor	NA	Miscarriage, PTB	Miscarriage, PTB were similar in PCOS and Non-PCOS.	Low ROB
Zhu 2021, China	Women with and without PCOS / Infertility centre	Observational	PCOS: 429 Non-PCOS: 890	Rotterdam	Non-PCOS - unexplained infertility and tubal factor infertility	NA	Miscarriage, GDM, GH, PTB, LBW	Miscarriage, GDM, GH, PTB, LBW were similar in PCOS and Non-PCOS.	High ROB
Liu 2022, China	Women with and without PCOS / Beijing Obstetrics and Gynaecology Hospital	Observational	PCOS: 1431 Non-PCOS: 6700	Rotterdam	Non-PCOS	NA	GDM, GH, PE, PTB, IUGR, Macrosomia	GDM, GH, PE, PTB, , Macrosomia were higher in PCOS IUGR was similar in PCOS and Non-PCOS.	High ROB
Ni 2022, China	Women with and without PCOS / Ninth People's Hospital	Observational	PCOS: 1376 Non-PCOS: 1376	Rotterdam	Non-PCOS - tubal factor or male infertility	NA	Miscarriage, PTB, LBW, Macrosomia	Miscarriage, PTB, LBW, Macrosomia were higher in PCOS	High ROB
Song 2022, China	Women with and without PCOS / Shandong University-affiliated Reproductive Hospital	Observational	PCOS: 115 Non-PCOS: 214	Rotterdam	Non-PCOS	NA	Miscarriage	Miscarriage was similar in PCOS and Non-PCOS.	High ROB
Stokkeland 2022, Norway, Sweden, Iceland	Women with and without PCOS / multiple centres in Sweden, Noway and Iceland	Observational	PCOS: 358 Non-PCOS: 258	Rotterdam	Non-PCOS - selected from the Training in Pregnancy (TRIP) study	NA	BMI, BW	BMI was higher in PCOS BW was similar in PCOS and Non-PCOS.	High ROB

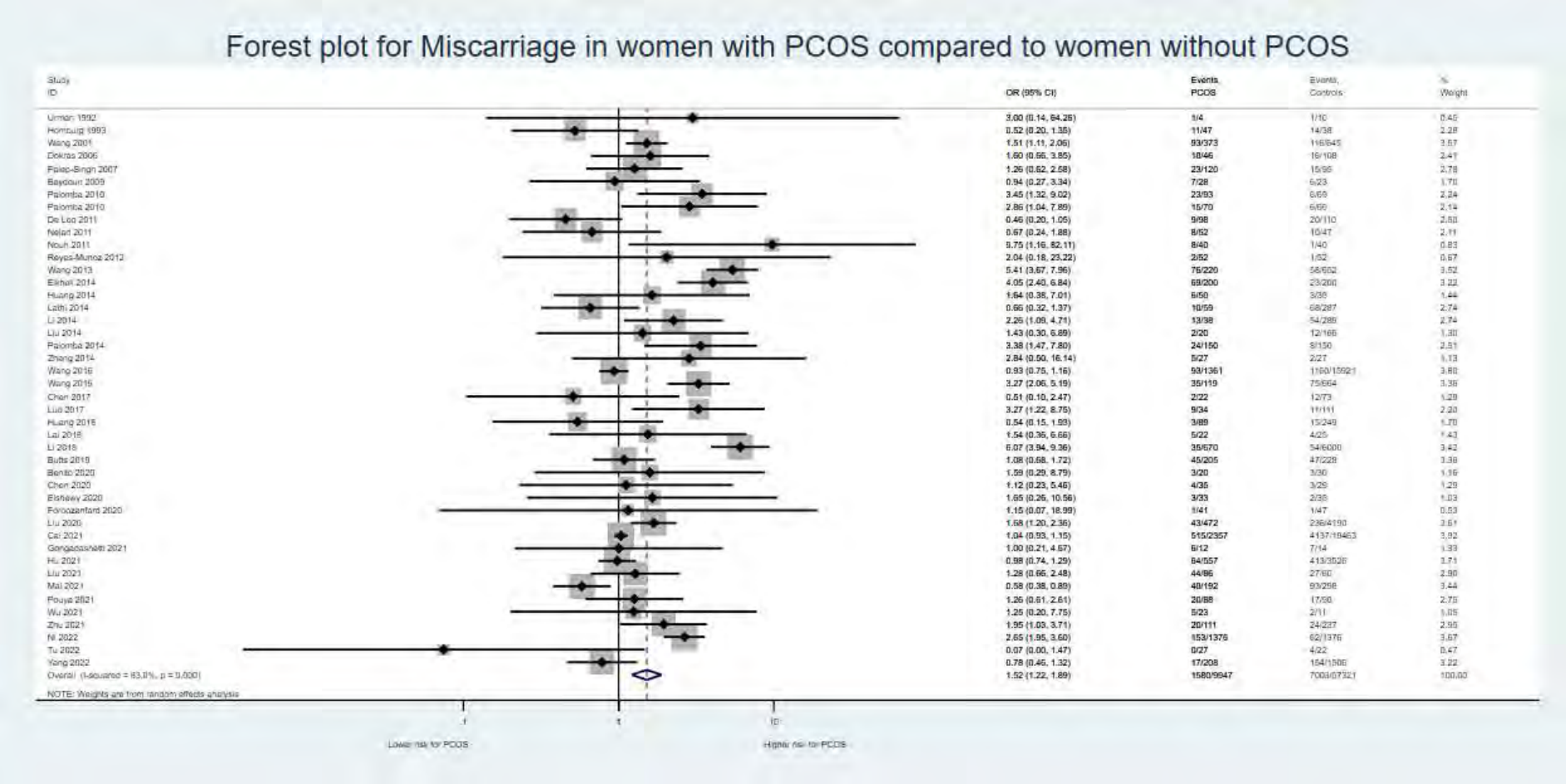
Tu 2022, China	Women with and without PCOS / Center for Reproductive Medicine, Women's Hospital	Observational	PCOS: 48 Non-PCOS: 48	Rotterdam	Non-PCOS - Tubal factor or male infertility	NA	Miscarriage, BW	Miscarriage was lower in PCOS BW was similar in PCOS and Non-PCOS.	High ROB
Wang 2022, China	Women with and without PCOS / Centre for Reproductive Medicine	Observational	PCOS: 1186 Non-PCOS: 5546	Rotterdam	Non-PCOS	NA	Miscarriage, GDM, PTB, CS	Miscarriage, GDM, PTB, CS were similar in PCOS and Non-PCOS.	High ROB
Yang 2022, China	Women with and without PCOS / Reproductive Medicine Center of Xiangya Hospital	Observational	PCOS: 450 Non-PCOS: 3165	Rotterdam	Non-PCOS	NA	Miscarriage	Miscarriage was similar in PCOS and Non-PCOS.	High ROB

Add abbreviations or important notes to footnotes

7. DATA EXTRACTION TABLES – DICHOTOMOUS OUTCOMES

OUTCOME: Miscarriage					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): PCOS vs. Non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Urman 1992	Count	-	1	4	1	10	Crude	NA
Homburg 1993	Count	-	11	47	14	38	Crude	NA
Wang 2001	Count	-	93	373	116	645	Crude	NA
Dokras 2006	Count	-	10	46	16	108	Crude	NA
Palep-Singh 2007	Count	-	23	120	15	95	Crude	NA
Beydoun 2009	Count	-	7	28	6	23	Crude	NA
Palomba 2010	Count	-	23	93	6	69	Crude	NA
Palomba 2010	Count	-	15	70	6	69	Crude	NA
De Leo 2011	Count	-	9	98	20	110	Crude	NA
Nejad 2011	Count	-	8	52	10	47	Crude	NA
Nouh 2011	Count	-	8	40	1	40	Crude	NA
Reyes-Munoz 2012	Count	-	2	52	1	52	Crude	NA
Wang 2013	Count	-	76	220	58	652	Crude	NA
Elkholi 2014	Count	-	69	200	23	200	Crude	NA
Huang 2014	Count	-	6	50	3	39	Crude	NA
Lathi 2014	Count	-	10	59	68	287	Crude	NA
Li 2014	Count	-	13	38	54	289	Crude	NA
Liu 2014	Count	-	2	20	12	166	Crude	NA
Palomba 2014	Count	-	24	150	8	150	Crude	NA

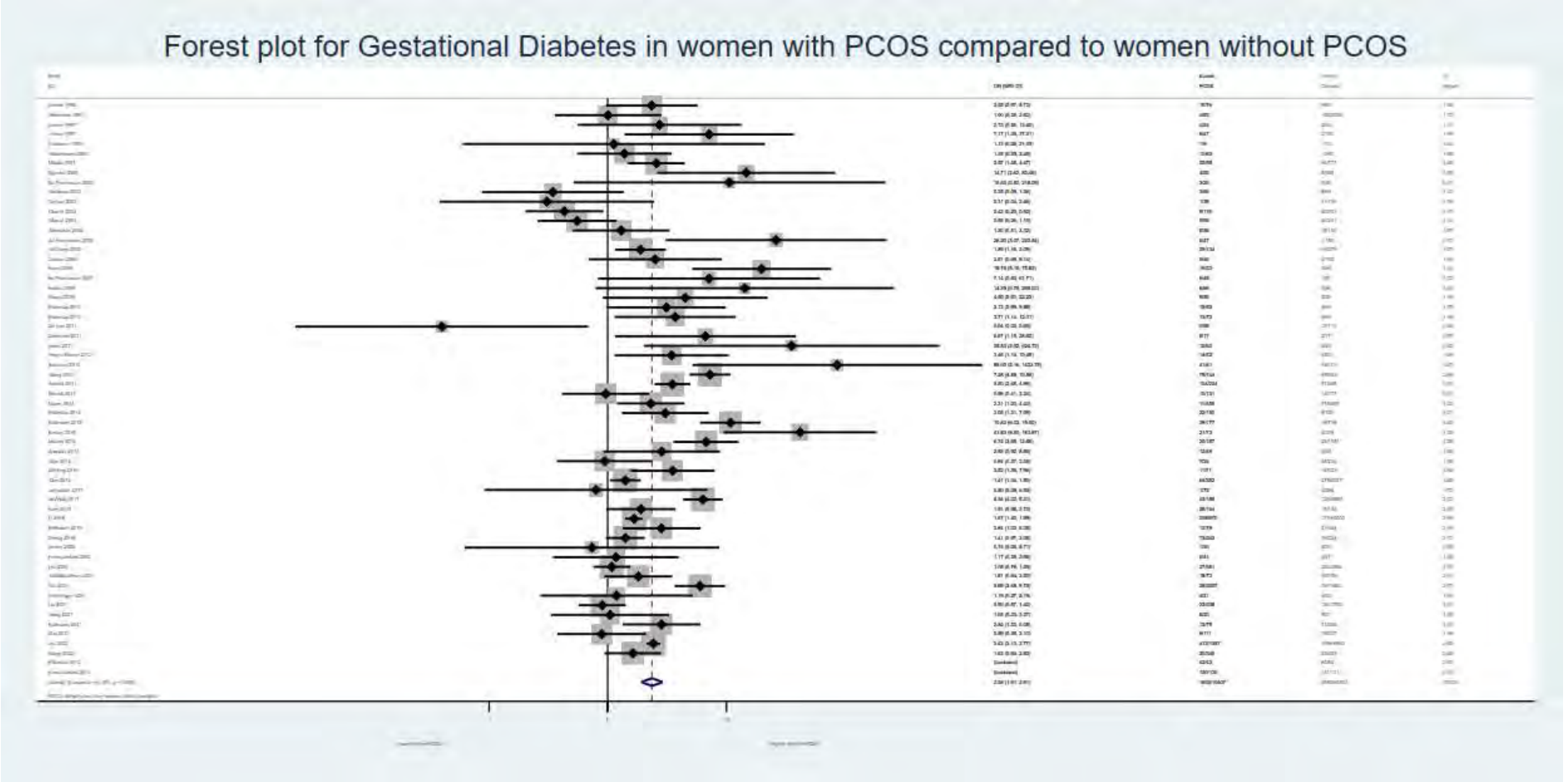
Palomba 2014	Count	-	24	150	8	150	Crude	NA
Zhang 2014	Count	-	5	27	2	27	Crude	NA
Wang 2016	Count	-	93	1361	1160	15921	Crude	NA
Wang 2016	Count	-	35	119	75	664	Crude	NA
Benito 2020	Count	-	3	20	3	30	Crude	NA
Butts 2019	Count	-	45	208	47	228	Crude	NA
Cai 2021	Count	-	515	2357	4137	19463	Crude	NA
Chen 2020	Count	-	4	35	3	29	Crude	NA
Chen 2017	Count	-	2	22	12	73	Crude	NA
Elshewy 2020	Count	-	3	33	2	35	Crude	NA
Foroozanfard 2020	Count	-	1	41	1	47	Crude	NA
Gongadashetti 2021	Count	-	6	12	7	14	Crude	NA
Huang 2018	Count	-	3	50	15	48	Crude	NA
Lai 2018	Count	-	5	22	4	25	Crude	NA
Liu 2020	Count	-	43	472	236	4190	Crude	NA
Liu 2021	Count	-	33	86	10	60	Crude	NA
Li 2018	Count	-	35	670	54	6000	Crude	NA
Luo 2017	Count	-	9	34	11	110	Crude	NA
Mai 2021	Count	-	40	192	93	298	Crude	NA
Ni 2022	Count	-	153	1376	62	1376	Crude	NA
Pouya 2021	Count	-	20	88	17	90	Crude	NA
Song 2022	Count	-	7	70	9	105	Crude	NA
Tu 2022	Count	-	0	48	4	48	Crude	NA
Wang 2022	Count	-	59	346	53	453	Crude	NA
Wu 2022	Count	-	5	23	2	11	Crude	NA
Yang 2022	Count	-	17	208	154	1506	Crude	NA
Zhu 2021	Count	-	20	111	24	237	Crude	NA


Forest plot for Miscarriage in women with PCOS compared to women without PCOS
Study ID
OR (95% CI)
Events, PCOS
Events, Controls
% Weight
Urman 1992
Homburg 1993
Wang 2001
Dokras 2006
Palep-Singh 2007
Baydoun 2009
Palomba 2010
Palomba 2010
De Leo 2011
Nelarl 2011
Nouh 2011
Reyes-Munoz 2012
Wang 2013
Elkhat 2014
Huang 2014
Lathi 2014
Li 2014
Liu 2014
Palomba 2014
Zhang 2014
Wang 2015
Wang 2015
Chen 2017
Luo 2017
Huang 2018
Lai 2018
Li 2018
Butts 2019
Benito 2020
Chen 2020
Elshaev 2020
Forouzantars 2020
Liu 2020
Cai 2021
Gongadasshetti 2021
Hu 2021
Liu 2021
Mai 2021
Pouya 2021
Wu 2021
Zhu 2021
Ni 2022
Tu 2022
Yang 2022
Overall (I-squared = 83.0%, p = 0.000)
3.00 (0.14, 64.26) 1/4 1/10 0.45
0.52 (0.20, 1.35) 11/47 14/38 2.28
1.51 (1.11, 2.06) 93/373 116/645 3.67
1.60 (0.66, 3.85) 10/46 16/108 2.47
1.26 (0.82, 2.58) 23/120 15/96 2.78
0.94 (0.27, 3.34) 7/28 6/23 1.70
3.45 (1.32, 9.02) 23/93 6/69 2.24
2.86 (1.04, 7.89) 15/70 6/69 2.14
0.46 (0.20, 1.05) 9/98 20/110 2.60
0.67 (0.24, 1.88) 8/52 10/47 2.11
9.75 (1.16, 82.11) 8/40 1/40 0.83
2.04 (0.18, 23.22) 2/52 1/52 0.67
5.41 (3.67, 7.96) 75/220 58/602 3.52
4.05 (2.40, 6.84) 69/200 23/200 3.22
1.64 (0.38, 7.01) 6/50 3/38 1.44
0.66 (0.32, 1.37) 10/59 68/287 2.74
2.25 (1.09, 4.71) 13/38 54/286 2.74
1.43 (0.30, 6.89) 2/20 12/166 1.30
3.38 (1.47, 7.80) 24/150 8/150 2.51
2.84 (0.50, 16.14) 5/27 2/27 1.13
0.93 (0.75, 1.16) 93/1361 1160/15921 3.80
3.27 (2.06, 5.19) 35/119 75/664 3.36
0.51 (0.10, 2.47) 2/22 12/73 1.29
3.27 (1.22, 8.75) 9/34 11/111 2.20
0.54 (0.15, 1.93) 3/89 15/249 1.70
1.54 (0.35, 6.66) 5/22 4/25 1.43
6.07 (3.94, 9.36) 35/670 54/6000 3.42
1.08 (0.68, 1.72) 45/205 47/228 3.38
1.59 (0.29, 8.79) 3/20 3/30 1.16
1.12 (0.23, 5.46) 4/35 3/29 1.29
1.65 (0.25, 10.56) 3/33 2/38 1.03
1.15 (0.07, 18.99) 1/41 1/47 0.53
1.58 (1.20, 2.36) 43/472 236/4190 3.61
1.04 (0.93, 1.15) 515/2357 4137/19463 3.92
1.00 (0.21, 4.67) 6/12 7/14 1.33
0.98 (0.74, 1.29) 84/557 413/3526 3.71
1.28 (0.66, 2.48) 44/86 27/60 2.90
0.58 (0.38, 0.89) 40/192 93/256 3.44
1.26 (0.61, 2.61) 20/88 17/50 2.75
1.25 (0.20, 7.75) 5/23 2/11 1.05
1.95 (1.03, 3.71) 20/111 24/237 2.95
2.65 (1.95, 3.60) 153/1376 62/1376 3.67
0.07 (0.00, 1.47) 0/27 4/22 0.47
0.78 (0.45, 1.32) 17/208 154/1508 3.22
1.52 (1.22, 1.89) 1580/9947 7004/97321 100.00
NOTE: Weights are from random effects analysis
.1
1
10
Lower risk for PCOS
Higher risk for PCOS

OUTCOME: Gestational diabetes			**OUTCOME TYPE:** Dichotomous					
COMPARISON (if applicable): PCOS vs. Non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Levran 1990	Count	OGTT at 28th week of gestation, based on O'Suullivan and Mahan Criteria	15	76	9	95	Crude	NA
Wortsman 1991	Count	a 50 g OGTT at 24-28 weeks of gestation. When 1-hr≥130 mg/dL, a further confirmatory test, based on the modified O'Suullivan's criteria: ≥2 of the followings: FBS≥100 mg/dl, 1 h OGTT≥180 mg/dl and 2 h OGTT≥160 mg/dl and 3 hr≥140 mg/dl	4	53	153	2036	Crude	NA
Lesser 1997	Count	a 50 g OGTT at 20-28 weeks of gestation. When 1 hour >135 mg/dL, a further confirmatory test, i.e., 3 hours 100 g OGTT and GDM was diagnosed based on NDDG criteria.	4	24	3	44	Crude	NA
Urman 1997	Count	a 50 g OGTT at 24-28 weeks of gestation. When ≥140 mg/dL, a further confirmatory test using 100 g OGTT and GDM was diagnosed based on NDDG criteria.	6	47	2	100	Crude	NA
Fridstrom 1999	Count	A 75 g OGTT with a 2-h value of ≥ 9 mmol/L	1	9	1	10	Crude	NA
Vollenhoven 2000	Count	a 75 g OGTT at 26-28 weeks of gestation; if 1-hr>8mmol/l, a 75 g fasting 2-hr OGTT which is considered abnormal if FBS≥5.5 mmol/l and or 2-hr ≥8 mmol/l	13	60	10	60	Crude	NA
Mikola 2001	Count	A 75 g OGTT, FBS>4.5, 1-hr>9.1, 2-hr>7.9 mmol/l; For capillary blood and venous plasma: FBS>4.8 1-hr>10.0, 2-hr>8.7 mmol/l	20	99	66	737	Crude	NA
Bjercke 2002	Count	a 75 g GTT. When 2h>11.1 mmol/L	4	52	2	355	Crude	NA
Sir-Petermann 2002	Count	FBS>126 mg/dl; 2 h OGTT>140 mg/dl after a 75 g OGTT were classified as having gestational diabetes mellitus.WHO criteria	3	20	0	26	Crude	NA
Haakova 2003	Count	A 75 g OGTT, FBS>5.5, 1-hr>8.8, 2-hr>7.7 mmol/l; Having two of them together would met the diagnosis of GDM.	3	66	8	66	Crude	NA
Turhan 2003	Count	a 50 g OGTT at 24-28 weeks of gestation. When >130 mg/dL, a further confirmatory test, i.e., 3 hours 100 g OGTT and if ≥2 of 4 following: FBS: 95; 1-hr: 180; 2-hr: 155; and 3-hr: 140 mg/dl	1	38	11	136	Crude	NA
Glueck 2004	Count	At 26-28th week of gestation, based on O'Suullivan and Mahan Criteria, ADA. PE: Based on ISSHP; SBP>140 or DBP>90 mmHg± proteinuria after 20 weeks.	9	119	40	251	Crude	NA
Glueck 2004	Count	-	9	95	40	251	Crude	NA
Weerakiet 2004	Count	a 100 g OGTT at 24-28 weeks of gestation. According to one-step method of the ADD: FBS≥95 mg/dl, 1-hr≥180 mg/dl, 2-hr≥155 mg/dl, 3-hr≥140 mg/dl.	8	36	18	100	Crude	NA

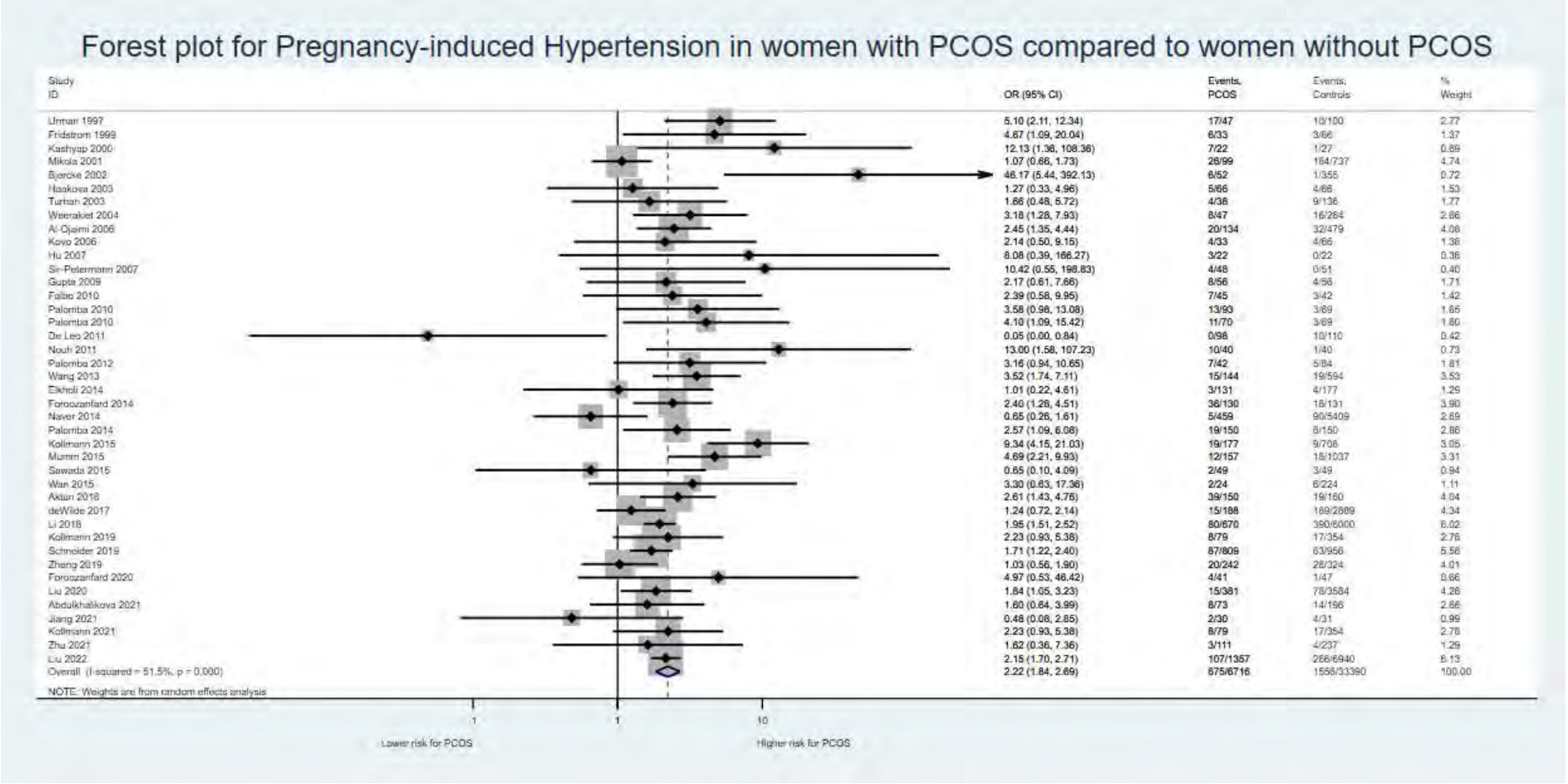
Sir-Petermann 2005	Count	a 75 g OGTT at 22-28 weeks of gestation. GDM was diagnosed based on WHO criteria	6	47	1	180	Crude	NA
Al-Ojaimi 2006	Count	a 50 g OGTT at 24 weeks of gestation. When 140 mg/dL, a further confirmatory test, i.e., 3 hours OGTT ≥2 of the following: FBS>95, 1-hr>180, 2-hr>155, 3-hr>140 mg/dl (5.3/10/8.6/7.8 mmol/l)	29	134	61	479	Crude	NA
Dokras 2006	Count		5	46	5	108	Crude	NA
Kovo 2006	Count	-	16	33	3	66	Crude	NA
Sir-Petermann 2007	Count	a 75 g OGTT at 22-28 weeks of gestation. GDM was diagnosed based on WHO criteria (FBS>126 mg/dl; 2-hr 140 mg/dl).	6	48	1	51	Crude	NA
Gupta 2009	Count	a 100 g OGTT . FBS>105 mg/dl; 1hrOGTT>190 mg/dl; 2hrOGTT>165 mg/dL; 3hrOGTT>145 mg/dL	8	56	2	56	Crude	NA
Palomba 2010	Count	WHO: Recognition of two abnormal values (FBS>105 mg/dl; 1hrOGTT>190 mg/dl; 2hrOGTT>165 mg/dL; 3hrOGTT>145 mg/dL) at 26 weeks of gestation	15	93	4	69	Crude	NA
Palomba 2010	Count	At 26 weeks of gestation; GDM was diagnosed based on ADA criteria.	13	70	4	69	Crude	NA
De Leo 2011	Count		0	98	12	110	Crude	NA
Dmitrovic 2011	Count	a 75 g OGTT at 6-10, 12-16, 24-28 and 34-38 weeks of gestation. When 130-140 mg/dL, a further confirmatory test, i.e., 3 hours 100 g OGTT and GDM was diagnosed based on WHO and ADA criteria.	10	17	2	17	Crude	NA
Nouh 2011	Count	-	12	40	0	40	Crude	NA
Reyes-Munoz 2012	Count	a 50 g OGTT at 14-24 weeks of gestation. When ≥130 mg/dL, a further confirmatory test, i.e., 3 hours 100 g OGTT and GDM was diagnosed based on ADA criteria i.e 2 of the following: FBS≥95 mg/dL, 1-hr≥180 mg/dL, 2-hr≥155 mg/dL and 3-hr≥140 mg/dL.	14	52	5	52	Crude	NA
Wang 2013	Count	a 75 g OGTT at 24-28 weeks of gestation. GDM was diagnosed with having 2 of the following: FBS≥5.1mmol/L, 1-hr≥10.0mmol/L, 2-hr≥8.5mmol/L. PIH: SBP>140 or DBP>90 mmHg.	79	144	85	594	Crude	NA
Ashrafi 2014	Count	a 50 g OGTT at 24-28 weeks of gestation. When 1-hr≥7.8 mmol/L or 140 mg/dL, a further confirmatory test 1-2 weeks later, with a 100 g 3-hr and GDM diagnosis based on ADA: ≥2 of the followings: FBS≥95 mg/dl, 1 h OGTT≥180 mg/dl and 2 h OGTT≥155 mg/dl and 3 hr≥140 mg/dl.	104	234	87	468	Crude	NA
Elkholi 2014	Count	a 50 g OGTT at 24 weeks of gestation. When ≥140 mg/dL, a further confirmatory test, i.e., 75 g OGTT and GDM was diagnosed based on the Fifth International Work Shop Conference on Gestational Diabetes. ≥2 of the followings: FBS≥95 mg/dl, 1 h OGTT≥180 mg/dl and 2 h OGTT≥155 mg/dl.	10	131	14	177	Crude	NA

Naver 2014	Count	FBS>10.0 mmol/l or a 75 g 2–hr oOGTT	11	459	57	5409	Crude	NA
Palomba 2014	Count	a 75 g OGTT, ADA criteria	22	150	8	150	Crude	NA
Palomba 2014	Count	a 75 g OGTT at 26 weeks of gestation	22	150	8	150	Crude	NA
Kollmann 2015	Count	A 75 g OGTT at 24-28 weeks of gestation. FBS>90, 1-hr>160, 2-hr>140 mg/dl (5/8.9/7.8 mmol/l)	39	177	18	708	Crude	NA
Koster 2015	Count	A 100 g OGTT, FBS>5.3, 1-hr>10, 2-hr>8.6, 3-hr>7.8 mmol/l.	21	73	2	209	Crude	NA
Mumm 2015	Count	2hr OGTT≥9.0 mmlo/L at 28-30 weeks of gestation (OGTT was only performed for women at high risk for GDM development not all)	20	157	22	1037	Crude	NA
Sawada 2015	Count	A 75 g OGTT, FBS>92, 1-hr>180, 2-hr>153 mg/dL.	12	49	5	49	Crude	NA
Wan 2015	Count	2-h 75 g OGTT using the WHO criteria	7	24	68	224	Crude	NA
Sterling 2016	Count	-	11	71	16	323	Crude	NA
Xiao 2016	Count	a 75 g OGTT at 24-28 weeks of gestation (IADPSG); FBS≥5.5 mmol/L, 1-hr≥10.0mmol/L, 2-hr ≥8.5 mmol/L	64	352	278	2037	Crude	NA
Jonsdottir 2017	Count	Plasma intravenous glucose level > 9.0 mmol/L after a 75-g 2-h oral glucose tolerance test.	1	72	5	288	Crude	NA
Kent 2018	Count	-	28	164	15	176	Crude	NA
Li 2018	Count	a 75 g OGTT 5.1/10/8.5	208	670	1274	6000	Crude	NA
Zheng 2019	Count	75g OGTT 5.1 / 10 / 8.5	73	242	76	324	Crude	NA
Benito 2020	Count	The Third International Workshop Conference on Gestational Diabetes Mellitus	1	20	2	30	Crude	NA
Foroozanfard 2020	Count	-	6	41	6	47	Crude	NA
Liu 2020	Count	at 24 weeks, 75g OGTT, 2HR > 10 mmol/L	37	381	324	3584	Crude	NA
Abdulkhalikova 2021	Count	The one-step 75 g oral glucose tolerance test (OGTT) according to the 2010 International Association of Diabetes and Pregnancy Study Groups Consensus	18	73	30	196	Crude	NA
Cai 2021	Count	a 75-g 2- hour oral glucose tolerance test	28	2357	39	19463	Crude	NA
Feichtinger 2021	Count	-	4	31	4	36	Crude	NA
Hu 2021	Count	The International Association of Diabetes and Pregnancy Study Groups	23	338	134	1783	Crude	NA
Jiang 2021	Count	-	8	30	8	31	Crude	NA
Kollmann 2021	Count	-	12	79	21	354	Crude	NA
Zhu 2021	Count	-	8	111	19	237	Crude	NA
Liu 2022	Count	75g OGTT. F=>5.1mmol/L or 1HR =>10mmol/L or 2HR=>8.5 mmol/L	412	1357	1056	6940	Crude	NA
Wang 2022	Count	-	30	346	25	453	Crude	NA


Forest plot for Gestational Diabetes in women with PCOS compared to women without PCOS

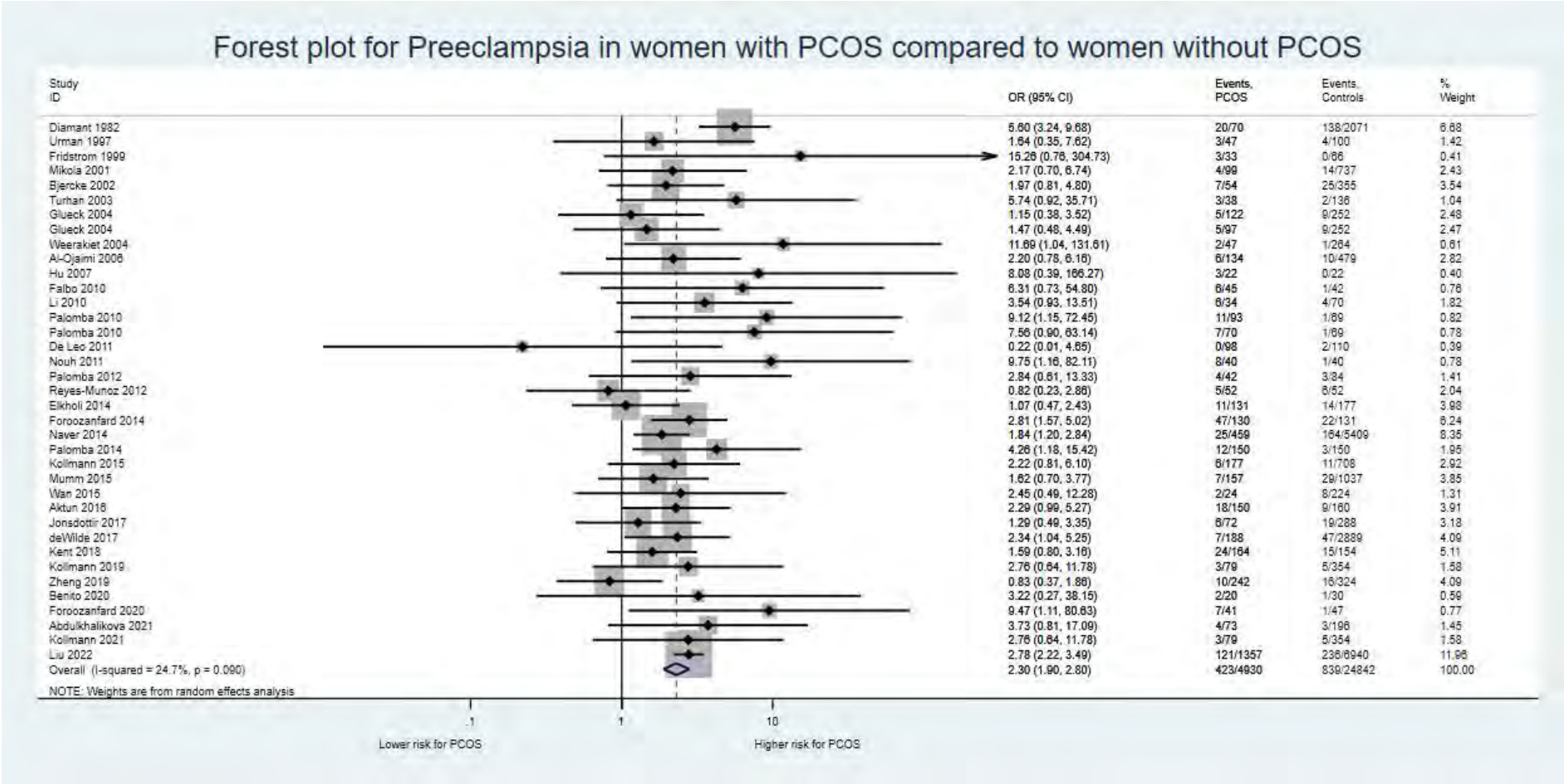
OUTCOME: Pregnancy-induced/Gestational hypertension					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): PCOS vs. Non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Urman 1997	Count	-	12	47	8	100	Crude	NA
Fridstrom 1999	Count	-	6	33	3	66	Crude	NA
Kashyap 2000	Count	-	7	22	1	27	Crude	NA
Mikola 2001	Count	-	26	99	184	737	Crude	NA
Bjercke 2002	Count	-	6	52	1	355	Crude	NA
Haakova 2003	Count	-	5	66	4	66	Crude	NA
Turhan 2003	Count	-	4	38	9	136	Crude	NA
Weerakiet 2004	Count	-	8	47	16	264	Crude	NA
Al-Ojaimi 2006	Count	-	20	134	32	479	Crude	NA
Kovo 2006	Count	-	4	33	4	66	Crude	NA
Hu 2007	Count	-	3	22	0	22	Crude	NA
Sir-Petermann 2007	Count	-	4	48	0	51	Crude	NA
Gupta 2009	Count	-	8	56	4	56	Crude	NA
Falbo 2010	Count	-	7	45	3	42	Crude	NA
Palomba 2010	Count	-	13	93	3	69	Crude	NA
Palomba 2010	Count	-	11	70	3	69	Crude	NA
De Leo 2011	Count	-	0	98	10	110	Crude	NA
Nouh 2011	Count	-	10	40	1	40	Crude	NA
Palomba 2012	Count	-	7	42	5	84	Crude	NA
Wang 2013	Count	-	15	144	19	594	Crude	NA
Elkholi 2014	Count	-	3	131	4	177	Crude	NA
Foroozanfard 2014	Count	-	36	130	18	131	Crude	NA
Naver 2014	Count	-	5	459	90	5409	Crude	NA
Palomba 2014	Count	-	19	150	8	150	Crude	NA
Palomba 2014	Count	-	19	150	8	150	Crude	NA
Kollmann 2015	Count	-	19	177	9	708	Crude	NA
Mumm 2015	Count	-	6	157	18	1037	Crude	NA
Sawada 2015	Count	-	2	49	3	49	Crude	NA
Wan 2015	Count	-	2	24	6	224	Crude	NA
Aktun 2016	Count	-	39	150	19	160	Crude	NA
Abdulkhalikova 2021	Count	-	8	73	14	196	Crude	NA
deWilde 2017	Count	-	15	188	189	2889	Crude	NA
Foroozanfard 2020	Count	-	5	41	1	47	Crude	NA

Jiang 2021	Count	-	2	30	4	31	Crude	NA
Kollmann 2021	Count	-	8	79	17	354	Crude	NA
Liu 2022	Count	-	107	1357	266	6940	Crude	NA
Liu 2020	Count	-	15	381	78	3584	Crude	NA
Li 2018	Count	-	80	670	390	6000	Crude	NA
Zheng 2019	Count	-	20	242	26	324	Crude	NA
Zhu 2021	Count	-	3	111	4	237	Crude	NA

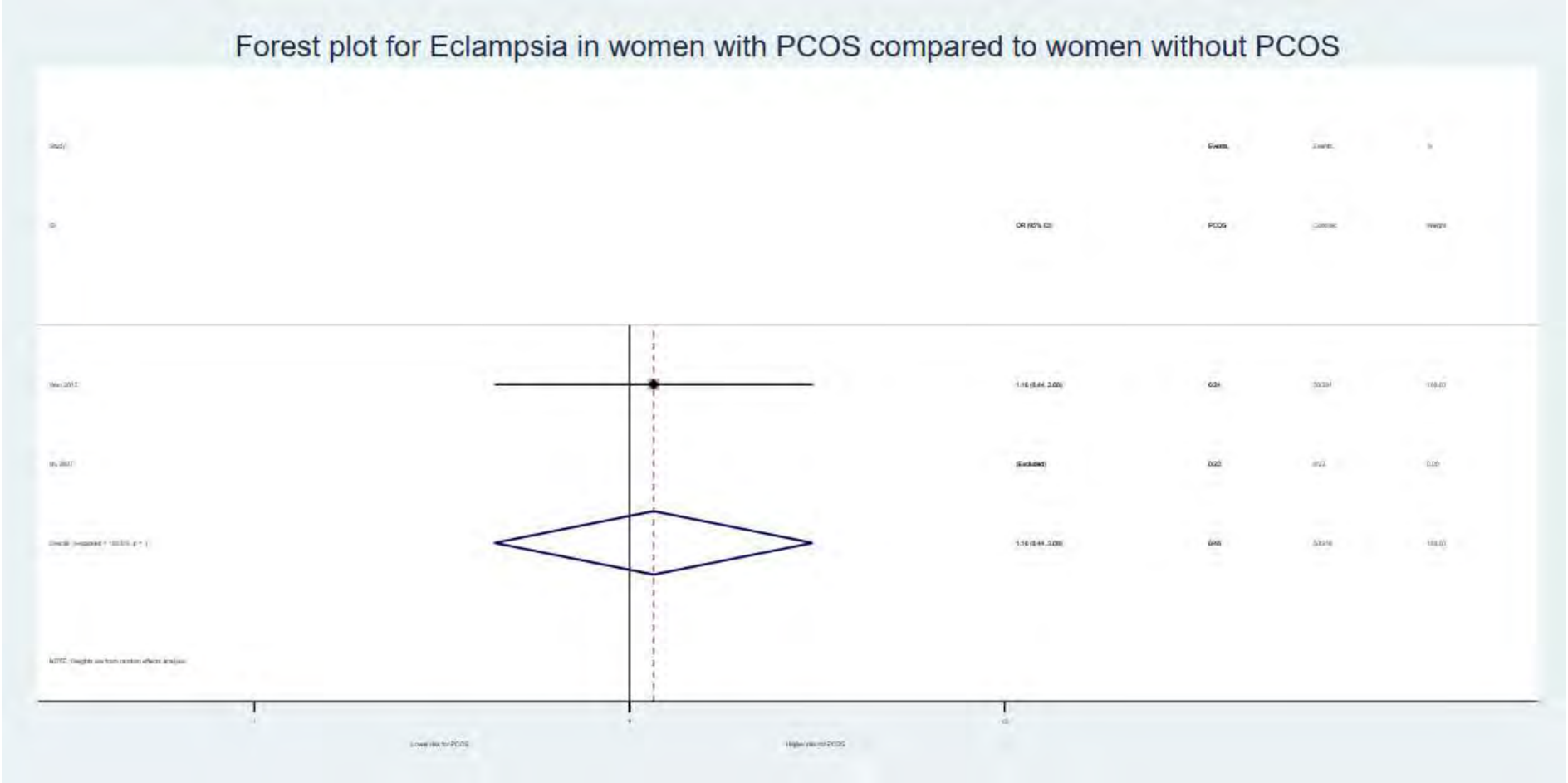


OUTCOME: Pre-eclampsia					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): PCOS vs. Non-PCOS								
Author, year	**Unit of outcome**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Diamant 1982	Count	According to the committee on terminology of the American college of obstetricians and gynaecologists	20	70	138	2071	Crude	NA
Urman 1997	Count	-	3	47	4	100	Crude	NA
Fridstrom 1999	Count	-	3	33	0	66	Crude	NA
Mikola 2001	Count	-	4	99	14	737	Crude	NA
Bjercke 2002	Count	-	7	52	25	355	Crude	NA
Turhan 2003	Count	-	3	38	2	136	Crude	NA
Glueck 2004	Count	-	5	122	9	252	Crude	NA
Weerakiet 2004	Count	-	2	47	1	264	Crude	NA
Al-Ojaimi 2006	Count	-	12	134	20	479	Crude	NA
Hu 2007	Count	-	3	22	0	22	Crude	NA
Falbo 2010	Count	-	6	45	1	42	Crude	NA
Li 2010	Count	-	6	34	4	70	Crude	NA
Palomba 2010	Count	-	9	93	1	69	Crude	NA
Palomba 2010	Count	-	7	70	1	69	Crude	NA
De Leo 2011	Count	-	0	98	2	110	Crude	NA
Nouh 2011	Count	-	8	40	1	40	Crude	NA
Palomba 2012	Count	-	4	42	3	84	Crude	NA
Reyes-Munoz 2012	Count	-	5	52	6	52	Crude	NA
Glueck 2004	Count	-	5	97	9	252	Crude	NA
Elkholi 2014	Count	-	11	131	14	177	Crude	NA
Foroozanfard 2014	Count	-	47	130	22	131	Crude	NA
Naver 2014	Count	-	25	459	164	5409	Crude	NA
Palomba 2014	Count	-	12	150	3	150	Crude	NA
Palomba 2014	Count	-	12	150	3	150	Crude	NA
Kollmann 2015	Count	-	6	177	11	708	Crude	NA
Mumm 2015	Count	-	14	157	29	1037	Crude	NA
Wan 2015	Count	-	2	24	8	224	Crude	NA
Aktun 2016	Count	-	18	150	9	160	Crude	NA
deWilde 2017	Count	-	7	188	47	2,889	Crude	NA
Jonsdottir 2017	Count	-	6	72	19	288	Crude	NA

Kent 2018	Count	-	24	164	15	176	Crude	NA
Benito 2020	Count	-	2	20	1	30	Crude	NA
Foroozanfard 2020	Count	-	7	41	1	47	Crude	NA
Abdulkhalikova 2021	Count	-	4	73	3	196	Crude	NA
Kollmann 2021	Count	-	3	79	5	354	Crude	NA
Liu 2022	Count	-	121	1357	236	6940	Crude	NA
Zheng 2019	Count	-	20	242	32	324	Crude	NA

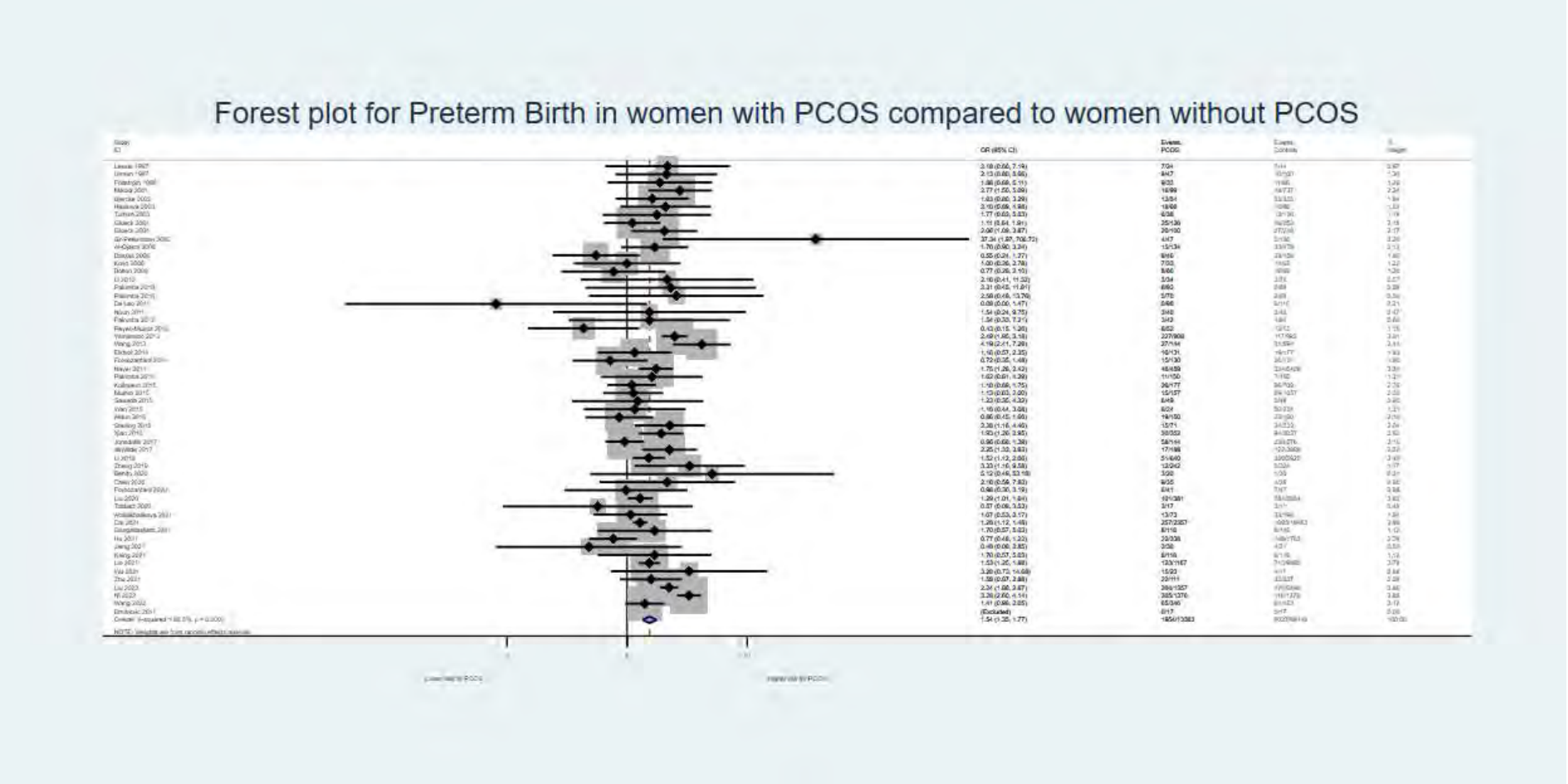


OUTCOME: Eclampsia				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): PCOS vs. Non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Hu 2007	Count	-	0	22	0	22	Crude	NA
Wan 2015	Count	-	6	24	50	224	Crude	NA

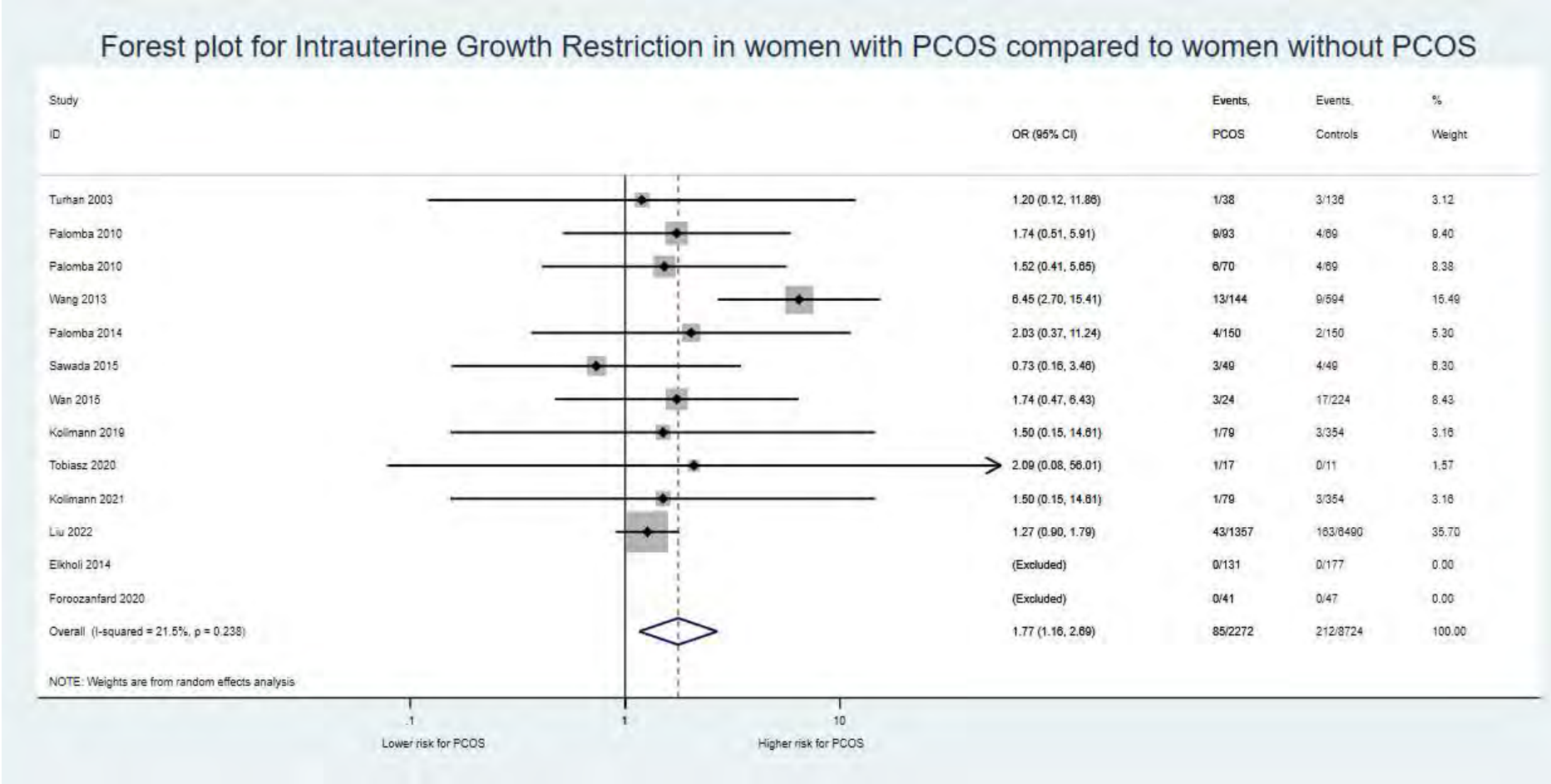

Forest plot for Eclampsia in women with PCOS compared to women without PCOS
Study
Events
ID
OR (95% CI)
PCOS
Weight
Wan 2017
1.16 (0.44, 3.08)
604
100.00
(Excluded)
0.00
1.16 (0.44, 3.08)
100.00
NOTE: Weights are from random effects analysis
Lower risk for PCOS
Higher risk for PCOS

OUTCOME: Preterm birth					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): PCOS vs. Non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Urman 1997	Count	-	9	47	10	100	Crude	NA
Fridstrom 1999	Count	-	9	33	11	66	Crude	NA
Mikola 2001	Count	-	16	99	48	737	Crude	NA
Bjercke 2002	Count	-	12	52	53	355	Crude	NA
Haakova 2003	Count	-	18	66	10	66	Crude	NA
Turhan 2003	Count	-	6	38	13	136	Crude	NA
Glueck 2004	Count	-	25	126	46	252	Crude	NA
Sir-Petermann 2005	Count	-	4	47	0	180	Crude	NA
Al-Ojaimi 2006	Count	-	15	134	33	479	Crude	NA
Dokras 2006	Count	-	9	46	33	108	Crude	NA
Kovo 2006	Count	-	7	33	14	66	Crude	NA
Li 2010	Count	-	3	34	3	70	Crude	NA
Palomba 2010	Count	-	6	93	2	69	Crude	NA
Palomba 2010	Count	-	5	70	2	69	Crude	NA
De Leo 2011	Count	-	0	98	6	110	Crude	NA
Dmitrovic 2011	Count	-	0	17	0	17	Crude	NA
Nouh 2011	Count	-	3	40	2	40	Crude	NA
Palomba 2012	Count	-	3	42	4	84	Crude	NA
Reyes-Munoz 2012	Count	-	6	52	12	52	Crude	NA
Yamamoto 2012	Count	-	227	908	117	992	Crude	NA
Wang 2013	Count	-	27	144	31	594	Crude	NA
Glueck 2004	Count	-	20	100	27	249	Crude	NA
Elkholi 2014	Count	-	16	131	19	177	Crude	NA
Foroozanfard 2014	Count	-	15	130	20	131	Crude	NA
Naver 2014	Count	-	46	459	324	5409	Crude	NA
Palomba 2014	Count	-	11	150	7	150	Crude	NA
Kollmann 2015	Count	-	26	174	96	708	Crude	NA
Mumm 2015	Count	-	15	157	89	1037	Crude	NA

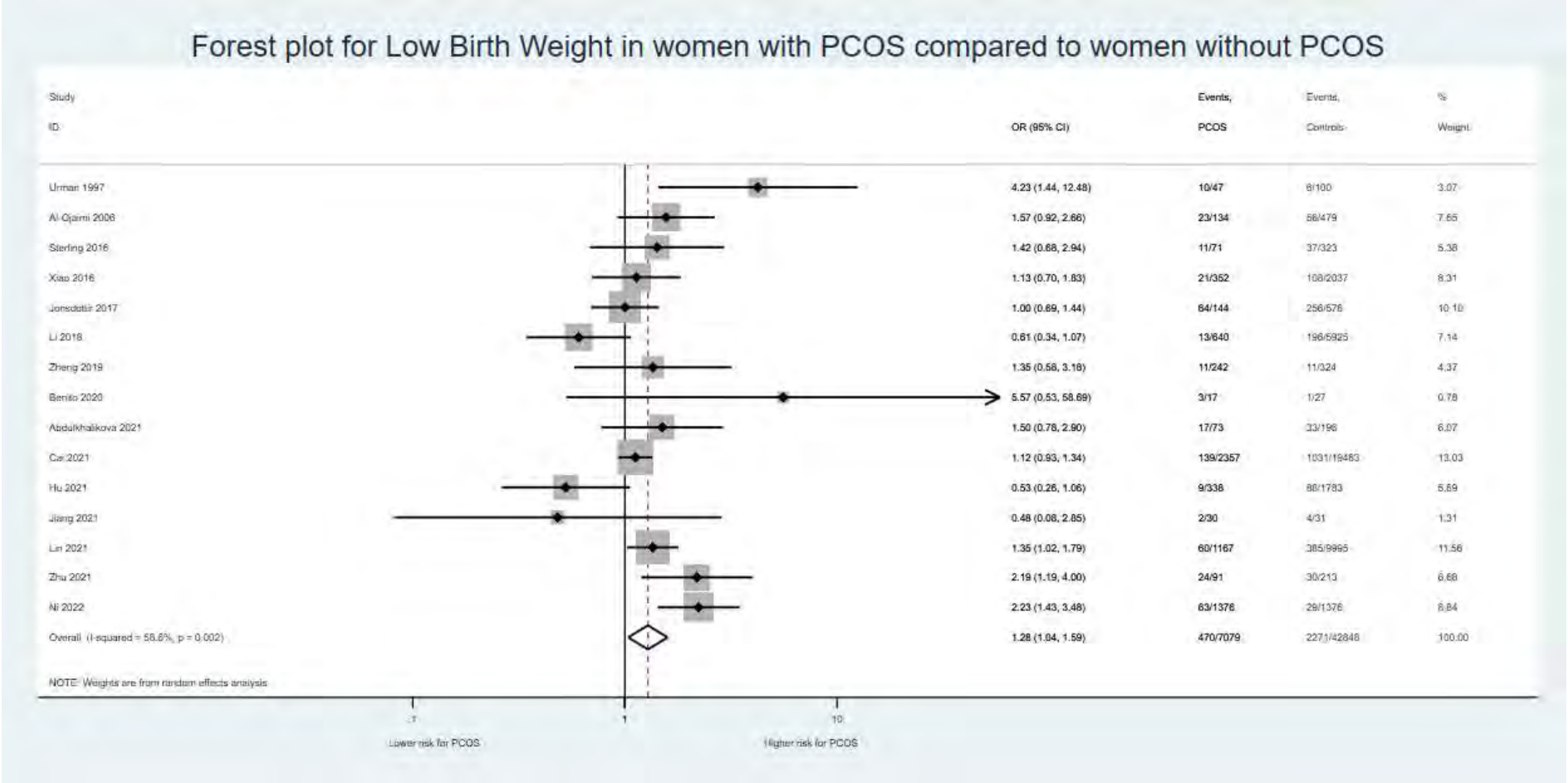
Sawada 2015	Count	-	6	49	5	49	Crude	NA
Aktun 2016	Count	-	19	150	23	160	Crude	NA
Sterling 2016	Count	-	15	71	34	323	Crude	NA
Xiao 2016	Count	-	30	352	94	2037	Crude	NA
Abdulkhalikova 2021	Count	-	13	73	33	196	Crude	NA
Benito 2020	Count	-	3	20	1	30	Crude	NA
Chen 2020	Count	-	9	35	4	29	Crude	NA
deWilde 2017	Count	-	17	188	122	2,889	Crude	NA
Foroozanfard 2020	Count	-	6	41	7	47	Crude	NA
Hu 2021	Count	-	22	338	148	1783	Crude	NA
Jiang 2021	Count	-	2	30	4	31	Crude	NA
Jonsdottir 2017	Count	-	43	72	135	288	Crude	NA
Lin 2021	Count	-	123	1167	713	9995	Crude	NA
Liu 2022	Count	-	204	1357	475	6490	Crude	NA
Liu 2020	Count	-	101	381	784	3584	Crude	NA
Li 2018	Count	-	51	635	320	5946	Crude	NA
Ni 2022	Count	-	305	1376	110	1376	Crude	NA
Tobiasz 2020	Count	-	3	28	3	18	Crude	NA
Wang 2022	Count	-	65	346	64	453	Crude	NA
Wu 2021	Count	-	15	23	4	11	Crude	NA
Zheng 2019	Count	-	24	242	10	324	Crude	NA
Zhu 2021	Count	-	22	111	32	237	Crude	NA


Forest plot for Preterm Birth in women with PCOS compared to women without PCOS

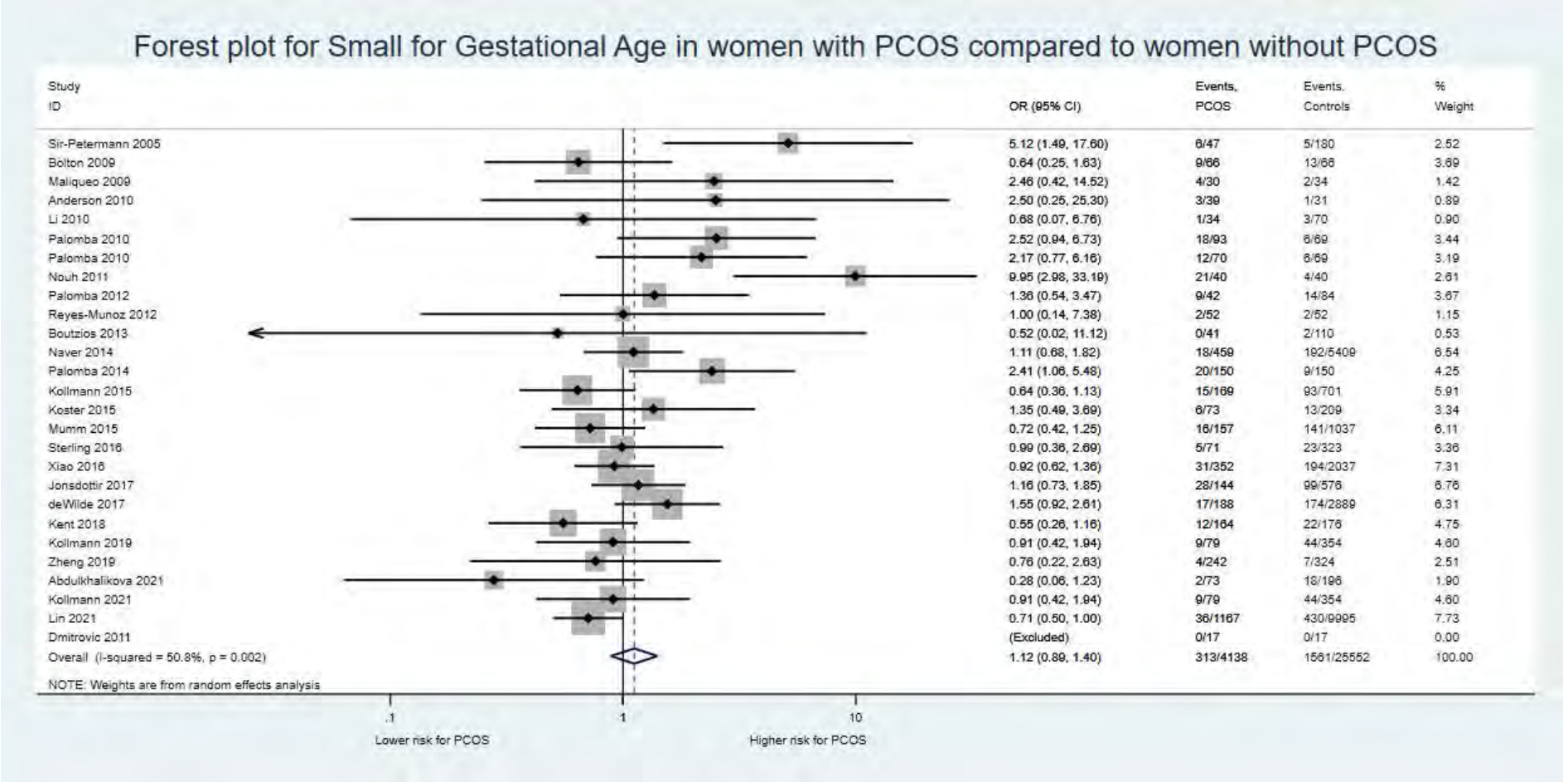
OUTCOME: Intrauterine growth restriction					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): PCOS vs. Non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Turhan 2003	Count	-	1	38	3	136	Crude	NA
Palomba 2010	Count	-	9	93	4	69	Crude	NA
Palomba 2010	Count	-	6	70	4	69	Crude	NA
Wang 2013	Count	-	13	144	9	594	Crude	NA
Elkholi 2014	Count	-	0	131	0	177	Crude	NA
Palomba 2014	Count	-	4	150	2	150	Crude	NA
Sawada 2015	Count	-	3	49	4	49	Crude	NA
Wan 2015	Count	-	3	24	17	206	Crude	NA
Kollmann 2021	Count	-	1	79	3	354	Crude	NA
Liu 2022	Count	-	43	1357	163	6490	Crude	NA
Tobiasz 2020	Count	-	1	28	0	18	Crude	NA


Forest plot for Intrauterine Growth Restriction in women with PCOS compared to women without PCOS
Study ID
OR (95% CI)
Events, PCOS
Events, Controls
% Weight
Turhan 2003 1.20 (0.12, 11.86) 1/38 3/136 3.12
Palomba 2010 1.74 (0.51, 5.91) 9/93 4/69 9.40
Palomba 2010 1.52 (0.41, 5.65) 6/70 4/69 8.38
Wang 2013 6.45 (2.70, 15.41) 13/144 9/594 15.49
Palomba 2014 2.03 (0.37, 11.24) 4/150 2/150 5.30
Sawada 2015 0.73 (0.16, 3.46) 3/49 4/49 6.30
Wan 2015 1.74 (0.47, 6.43) 3/24 17/224 8.43
Kollmann 2019 1.50 (0.15, 14.81) 1/79 3/354 3.16
Tobiasz 2020 2.09 (0.08, 56.01) 1/17 0/11 1.57
Kollmann 2021 1.50 (0.15, 14.81) 1/79 3/354 3.16
Liu 2022 1.27 (0.90, 1.79) 43/1357 163/8490 35.70
Elkholi 2014 (Excluded) 0/131 0/177 0.00
Foroozanfard 2020 (Excluded) 0/41 0/47 0.00
Overall (I-squared = 21.5%, p = 0.238) 1.77 (1.16, 2.69) 85/2272 212/8724 100.00
NOTE: Weights are from random effects analysis
.1
1
10
Lower risk for PCOS
Higher risk for PCOS

OUTCOME: Low birth weight					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): PCOS vs. Non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Urman 1997	Count	-	10	47	6	100	Crude	NA
Al-Ojaimi 2006	Count	-	23	134	56	479	Crude	NA
Sterling 2016	Count	-	11	71	37	323	Crude	NA
Xiao 2016	Count	-	21	352	108	2037	Crude	NA
Hu 2021	Count	-	2	338	88	1783	Crude	NA
Jiang 2021	Count	-	2	30	4	31	Crude	NA
Jonsdottir 2017	Count	-	64	144	256	576	Crude	NA
Lin 2021	Count	-	60	1167	385	9995	Crude	NA
Li 2018	Count	-	23	635	196	5946	Crude	NA
Ni 2022	Count	-	63	1376	29	1376	Crude	NA
Zheng 2019	Count	-	22	242	22	324	Crude	NA
Zhu 2021	Count	-	24	91	30	213	Crude	NA

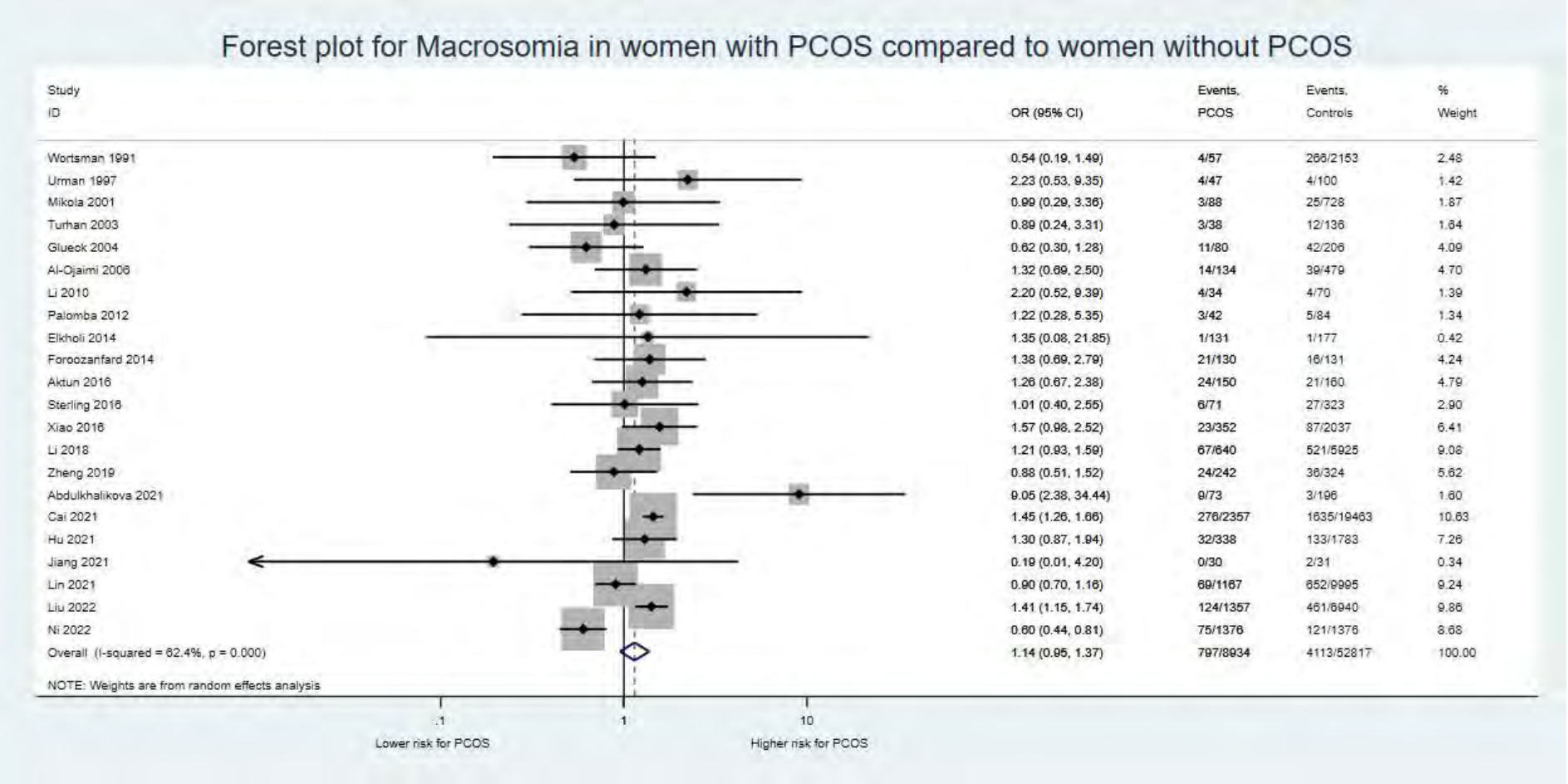

Forest plot for Low Birth Weight in women with PCOS compared to women without PCOS
Study ID
OR (95% CI)
Events, PCOS
Events, Controls
% Weight
Urman 1997 4.23 (1.44, 12.48) 10/47 8/100 3.07
Al-Qarmi 2008 1.57 (0.92, 2.66) 23/134 56/479 7.65
Sterling 2016 1.42 (0.68, 2.94) 11/71 37/323 5.38
Xiao 2016 1.13 (0.70, 1.83) 21/352 108/2037 8.31
Jonsdottir 2017 1.00 (0.69, 1.44) 64/144 256/576 10.10
Li 2018 0.61 (0.34, 1.07) 13/640 196/5925 7.14
Zheng 2019 1.35 (0.58, 3.18) 11/242 11/324 4.37
Benito 2020 5.57 (0.53, 58.69) 3/17 1/27 0.78
Abdulkhalikova 2021 1.50 (0.78, 2.90) 17/73 33/196 6.07
Cai 2021 1.12 (0.93, 1.34) 139/2357 1031/19483 13.03
Hu 2021 0.53 (0.26, 1.06) 9/338 88/1783 5.69
Jiang 2021 0.48 (0.08, 2.85) 2/30 4/31 1.31
Lin 2021 1.35 (1.02, 1.79) 60/1167 385/9995 11.56
Zhu 2021 2.19 (1.19, 4.00) 24/91 30/213 6.68
Ni 2022 2.23 (1.43, 3.48) 63/1376 29/1376 6.84
Overall (I-squared = 58.6%, p = 0.002) 1.28 (1.04, 1.59) 470/7079 2271/42846 100.00
NOTE: Weights are from random effects analysis
.1
1
10
Lower risk for PCOS
Higher risk for PCOS

OUTCOME: Small for gestational age					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): PCOS vs. Non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Sir-Petermann 2005	Count	-	6	47	5	180	Crude	NA
Maliqueo 2009	Count	-	4	30	2	34	Crude	NA
Li 2010	Count	-	1	34	3	70	Crude	NA
Palomba 2010	Count	-	18	93	6	69	Crude	NA
Palomba 2010	Count	-	12	70	6	69	Crude	NA
Dmitrovic 2011	Count	-	0	17	0	17	Crude	NA
Nouh 2011	Count	-	21	40	4	40	Crude	NA
Palomba 2012	Count	-	9	42	14	84	Crude	NA
Reyes-Munoz 2012	Count	-	2	52	2	52	Crude	NA
Boutzios 2013	Count	-	0	41	2	110	Crude	NA
Naver 2014	Count	-	18	459	192	5409	Crude	NA
Palomba 2014	Count	-	20	150	9	150	Crude	NA
Palomba 2014	Count	-	20	150	9	150	Crude	NA
Kollmann 2015	Count	-	15	169	93	701	Crude	NA
Koster 2015	Count	-	6	73	13	209	Crude	NA
Mumm 2015	Count	-	16	157	141	1037	Crude	NA
Sterling 2016	Count	-	5	71	23	323	Crude	NA
Xiao 2016	Count	-	31	352	194	2037	Crude	NA
deWilde 2017	Count	-	17	188	174	2,889	Crude	NA
Jonsdottir 2017	Count	-	28	144	99	576	Crude	NA
Kollmann 2021	Count	-	9	79	44	354	Crude	NA
Zheng 2019	Count	-	8	242	14	324	Crude	NA

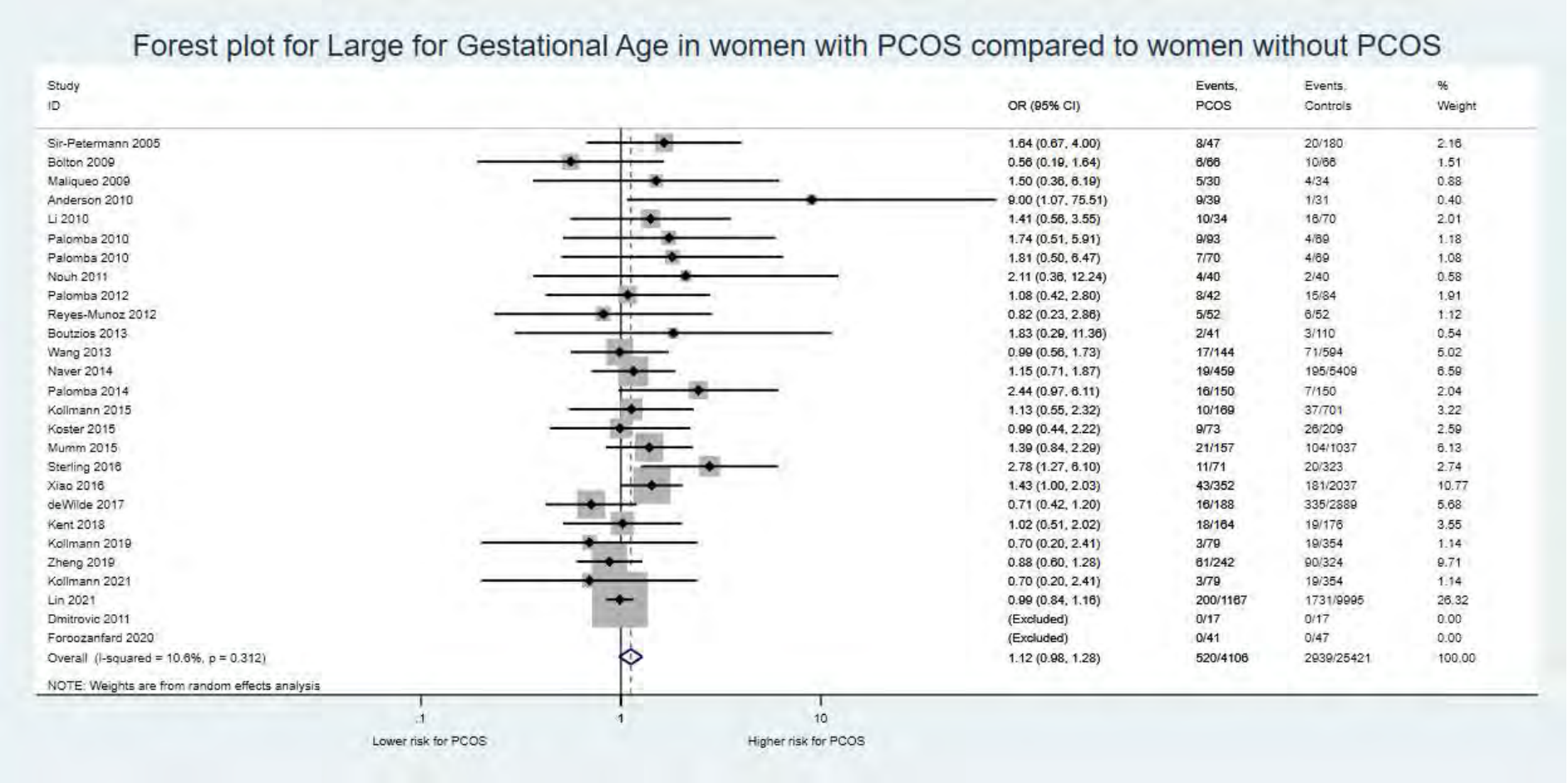


OUTCOME: Macrosomia	**OUTCOME TYPE:** Dichotomous
COMPARISON (if applicable): PCOS vs. Non-PCOS	

Author, year	Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)	Method of measurement	N events in intervention/ exposure group	N total in intervention/ exposure group	N events in control / comparison group	N total in control/ comparison group	Are these values adjusted or crude?	If adjusted, what variables were included in the model?
Wortsman 1991	Count	-	4	57	266	2153	Crude	NA
Urman 1997	Count	-	4	47	4	100	Crude	NA
Mikola 2001	Count	-	3	88	25	728	Crude	NA
Turhan 2003	Count	-	3	38	12	136	Crude	NA
Glueck 2004	Count	-	11	80	42	206	Crude	NA
Al-Ojaimi 2006	Count	-	14	134	39	479	Crude	NA
Li 2010	Count	-	4	34	4	70	Crude	NA
Palomba 2012	Count	-	3	42	5	84	Crude	NA
Elkholi 2014	Count	-	1	131	1	177	Crude	NA
Foroozanfard 2014	Count	-	21	130	16	131	Crude	NA
Aktun 2016	Count	-	24	150	21	160	Crude	NA
Sterling 2016	Count	-	6	71	27	323	Crude	NA
Xiao 2016	Count	-	23	352	87	2037	Crude	NA
Hu 2021	Count	-	32	338	133	1783	Crude	NA
Jiang 2021	Count	-	0	30	2	31	Crude	NA
Lin 2021	Count	-	69	1167	652	9995	Crude	NA
Liu 2022	Count	-	124	1357	461	6940	Crude	NA
Li 2018	Count	-	67	635	521	5946	Crude	NA
Ni 2022	Count	-	75	1376	121	1376	Crude	NA
Zheng 2019	Count	-	48	242	72	324	Crude	NA


Forest plot for Macrosomia in women with PCOS compared to women without PCOS
Study ID
OR (95% CI)
Events, PCOS
Events, Controls
% Weight
Wortsman 1991 0.54 (0.19, 1.49) 4/57 266/2153 2.48
Urman 1997 2.23 (0.53, 9.35) 4/47 4/100 1.42
Mikola 2001 0.99 (0.29, 3.36) 3/88 25/728 1.87
Turhan 2003 0.89 (0.24, 3.31) 3/38 12/136 1.64
Glueck 2004 0.62 (0.30, 1.28) 11/80 42/206 4.09
Al-Ojaimi 2006 1.32 (0.69, 2.50) 14/134 39/479 4.70
Li 2010 2.20 (0.52, 9.39) 4/34 4/70 1.39
Palomba 2012 1.22 (0.28, 5.35) 3/42 5/84 1.34
Elkholi 2014 1.35 (0.08, 21.85) 1/131 1/177 0.42
Foroozanfard 2014 1.38 (0.69, 2.79) 21/130 16/131 4.24
Aktun 2016 1.26 (0.67, 2.38) 24/150 21/160 4.79
Sterling 2016 1.01 (0.40, 2.55) 6/71 27/323 2.90
Xiao 2016 1.57 (0.98, 2.52) 23/352 87/2037 6.41
Li 2018 1.21 (0.93, 1.59) 67/640 521/5925 9.08
Zheng 2019 0.88 (0.51, 1.52) 24/242 36/324 5.62
Abdulkhalikova 2021 9.05 (2.38, 34.44) 9/73 3/196 1.60
Cai 2021 1.45 (1.26, 1.66) 276/2357 1635/19463 10.63
Hu 2021 1.30 (0.87, 1.94) 32/338 133/1783 7.26
Jiang 2021 0.19 (0.01, 4.20) 0/30 2/31 0.34
Lin 2021 0.90 (0.70, 1.16) 69/1167 652/9995 9.24
Liu 2022 1.41 (1.15, 1.74) 124/1357 461/6940 9.86
Ni 2022 0.60 (0.44, 0.81) 75/1376 121/1376 8.68
Overall (I-squared = 82.4%, p = 0.000) 1.14 (0.95, 1.37) 797/8934 4113/52817 100.00
NOTE: Weights are from random effects analysis
.1
1
10
Lower risk for PCOS
Higher risk for PCOS

OUTCOME: Large for gestational age					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): PCOS vs. Non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Sir-Petermann 2005	Count	-	8	47	20	180	Crude	NA
Maliqueo 2009	Count	-	5	30	4	34	Crude	NA
Li 2010	Count	-	10	34	16	70	Crude	NA
Palomba 2010	Count	-	9	93	4	69	Crude	NA
Palomba 2010	Count	-	7	70	4	69	Crude	NA
Dmitrovic 2011	Count	-	0	17	0	17	Crude	NA
Nouh 2011	Count	-	4	40	2	40	Crude	NA
Palomba 2012	Count	-	8	42	15	84	Crude	NA
Reyes-Munoz 2012	Count	-	5	52	6	52	Crude	NA
Boutzios 2013	Count	-	2	41	3	110	Crude	NA
Wang 2013	Count	-	17	144	71	594	Crude	NA
Naver 2014	Count	-	19	459	195	5409	Crude	NA
Palomba 2014	Count	-	16	150	7	150	Crude	NA
Palomba 2014	Count	-	16	150	7	150	Crude	NA
Kollmann 2015	Count	-	10	169	37	701	Crude	NA
Koster 2015	Count	-	9	73	26	209	Crude	NA
Mumm 2015	Count	-	21	157	104	1037	Crude	NA
Sterling 2016	Count	-	11	71	20	323	Crude	NA
Xiao 2016	Count	-	43	352	181	2037	Crude	NA
deWilde 2017	Count	-	16	188	335	2,889	Crude	NA
Kollmann 2021	Count	-	3	79	19	354	Crude	NA
Lin 2021	Count	-	200	1167	1731	9995	Crude	NA
Zheng 2019	Count	-	122	242	180	324	Crude	NA


Forest plot for Large for Gestational Age in women with PCOS compared to women without PCOS
Study ID
OR (95% CI)
Events, PCOS
Events, Controls
% Weight
Sir-Petermann 2005 1.64 (0.67, 4.00) 8/47 20/180 2.16
Bolton 2009 0.56 (0.19, 1.64) 6/66 10/66 1.51
Maliqueo 2009 1.50 (0.36, 6.19) 5/30 4/34 0.88
Anderson 2010 9.00 (1.07, 75.51) 9/39 1/31 0.40
Li 2010 1.41 (0.56, 3.55) 10/34 16/70 2.01
Palomba 2010 1.74 (0.51, 5.91) 9/93 4/69 1.18
Palomba 2010 1.81 (0.50, 6.47) 7/70 4/69 1.08
Nouh 2011 2.11 (0.36, 12.24) 4/40 2/40 0.58
Palomba 2012 1.08 (0.42, 2.80) 8/42 15/84 1.91
Reyes-Munoz 2012 0.82 (0.23, 2.86) 5/52 6/52 1.12
Boutzios 2013 1.83 (0.29, 11.36) 2/41 3/110 0.54
Wang 2013 0.99 (0.56, 1.73) 17/144 71/594 5.02
Naver 2014 1.15 (0.71, 1.87) 19/459 195/5409 6.59
Palomba 2014 2.44 (0.97, 6.11) 16/150 7/150 2.04
Kollmann 2015 1.13 (0.55, 2.32) 10/169 37/701 3.22
Koster 2015 0.99 (0.44, 2.22) 9/73 26/209 2.59
Mumm 2015 1.39 (0.84, 2.29) 21/157 104/1037 6.13
Sterling 2016 2.78 (1.27, 6.10) 11/71 20/323 2.74
Xiao 2016 1.43 (1.00, 2.03) 43/352 181/2037 10.77
deWilde 2017 0.71 (0.42, 1.20) 16/188 335/2889 5.68
Kent 2018 1.02 (0.51, 2.02) 18/164 19/176 3.55
Kollmann 2019 0.70 (0.20, 2.41) 3/79 19/354 1.14
Zheng 2019 0.88 (0.60, 1.28) 61/242 90/324 9.71
Kollmann 2021 0.70 (0.20, 2.41) 3/79 19/354 1.14
Lin 2021 0.99 (0.84, 1.16) 200/1167 1731/9995 26.32
Dmitrovic 2011 (Excluded) 0/17 0/17 0.00
Foroozanfard 2020 (Excluded) 0/41 0/47 0.00
Overall (I-squared = 10.6%, p = 0.312) 1.12 (0.98, 1.28) 520/4106 2939/25421 100.00
NOTE: Weights are from random effects analysis
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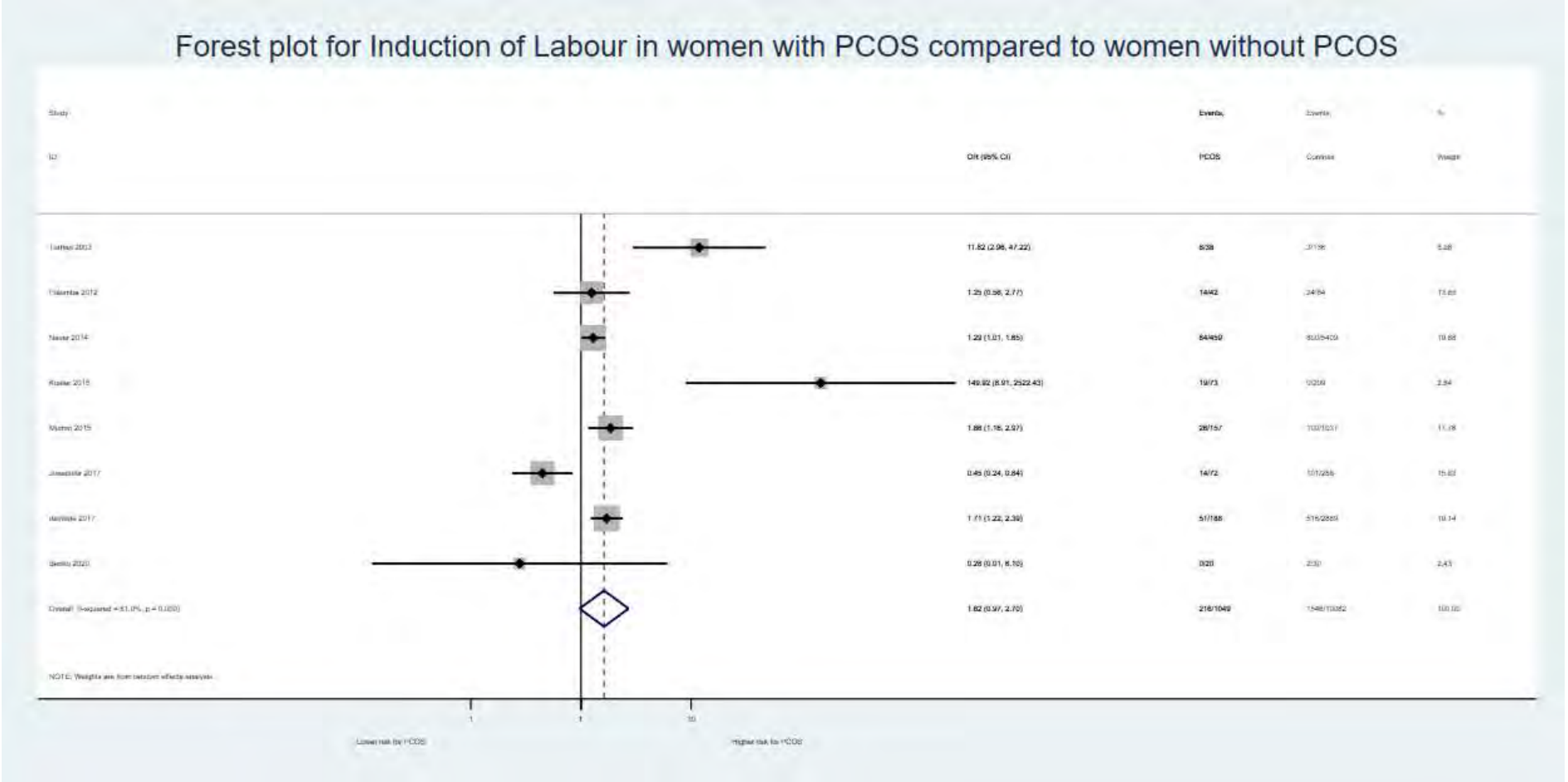
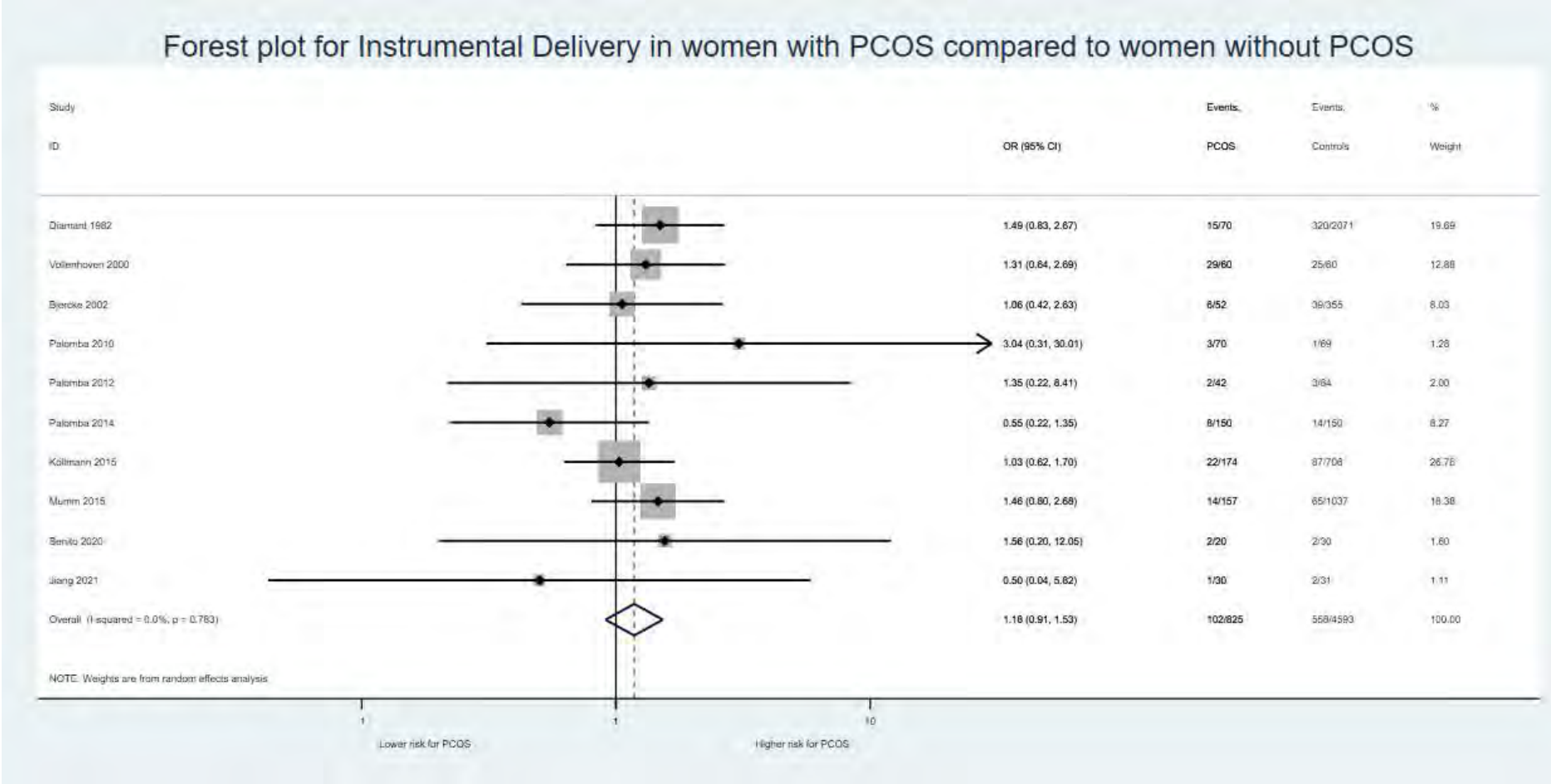
10
Lower risk for PCOS
Higher risk for PCOS

OUTCOME: Induction of labour					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): PCOS vs. Non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Turhan 2003	Count	-	8	38	3	136	Crude	NA
Palomba 2012	Count	-	14	42	24	84	Crude	NA
Naver 2014	Count	-	84	459	800	5409	Crude	NA
Koster 2015	Count	-	19	73	0	209	Crude	NA
Mumm 2015	Count	-	26	157	100	1037	Crude	NA
deWilde 2017	Count	-	51	188	516	2,889	Crude	NA
Jonsdottir 2017	Count	-	14	72	101	288	Crude	NA

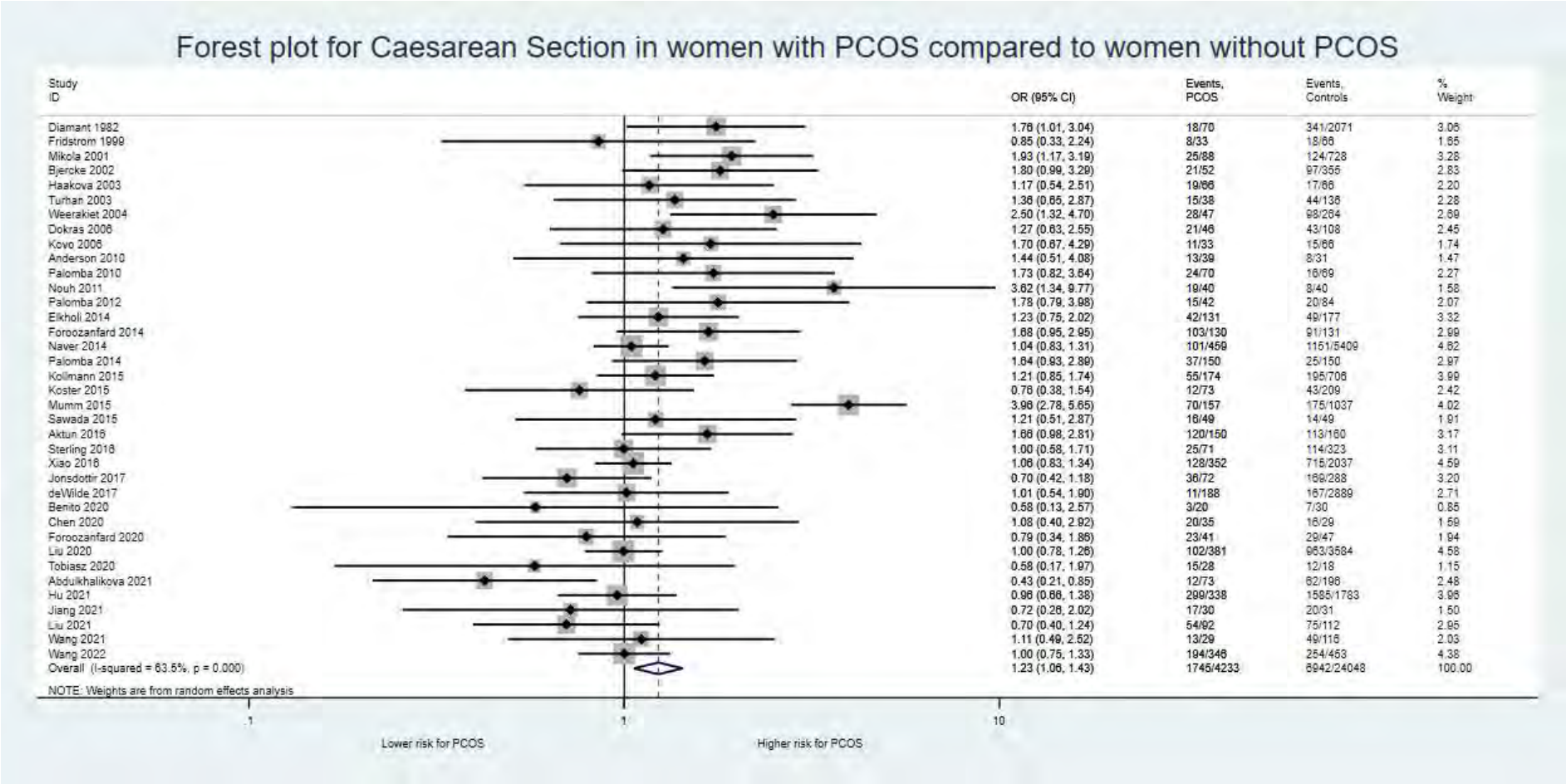

Forest plot for Induction of Labour in women with PCOS compared to women without PCOS
Study
ID
OR (95% CI)
Events
PCOS
Controls
Weight
11.82 (2.96, 47.22)
1.25 (0.56, 2.77)
1.23 (1.01, 1.85)
149.92 (8.91, 2522.43)
1.88 (1.16, 2.97)
0.45 (0.24, 0.84)
1.71 (1.22, 2.39)
0.28 (0.01, 6.10)
1.62 (0.97, 2.70)
218/1049
NOTE: Weights are from random effects analysis
1
10
Lower risk for PCOS
Higher risk for PCOS

OUTCOME: Instrumental delivery					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): PCOS vs. Non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Diamant 1982	Count	-	15	70	320	2071	Crude	NA
Vollenhoven 2000	Count	-	29	60	25	60	Crude	NA
Bjercke 2002	Count	-	6	52	39	355	Crude	NA
Turhan 2003	Count	-		38		136	Crude	NA
Palomba 2010	Count	-	3	70	1	69	Crude	NA
Palomba 2012	Count	-	2	42	3	84	Crude	NA
Palomba 2014	Count	-	8	150	14	150	Crude	NA
Kollmann 2015	Count	-	22	174	87	706	Crude	NA
Mumm 2015	Count	-	7	157	65	1037	Crude	NA
Jiang 2021	Count	-	1	30	2	31	Crude	NA

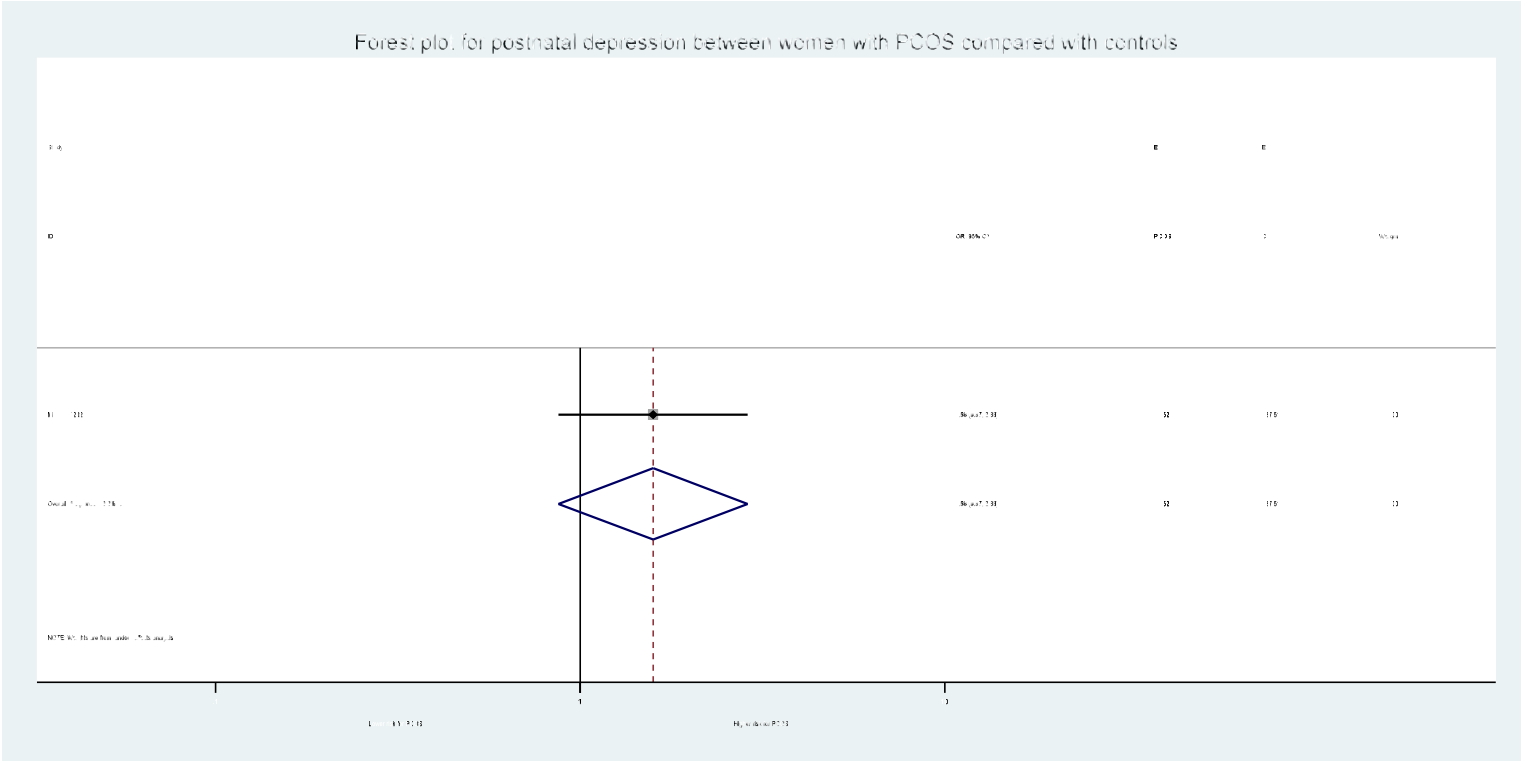

Forest plot for Instrumental Delivery in women with PCOS compared to women without PCOS
Study
ID
OR (95% CI)
Events, PCOS
Events, Controls
% Weight
Diamant 1982
1.49 (0.83, 2.67)
15/70
320/2071
19.69
Vollenhoven 2000
1.31 (0.64, 2.69)
29/60
25/60
12.88
Bjercke 2002
1.06 (0.42, 2.63)
6/52
39/355
8.03
Palomba 2010
3.04 (0.31, 30.01)
3/70
1/69
1.28
Palomba 2012
1.35 (0.22, 8.41)
2/42
3/84
2.00
Palomba 2014
0.55 (0.22, 1.35)
8/150
14/150
8.27
Köllmann 2015
1.03 (0.62, 1.70)
22/174
87/706
26.76
Mumm 2015
1.46 (0.80, 2.68)
14/157
65/1037
18.38
Benito 2020
1.56 (0.20, 12.05)
2/20
2/30
1.60
Jiang 2021
0.50 (0.04, 5.82)
1/30
2/31
1.11
Overall (I-squared = 0.0%, p = 0.783)
1.18 (0.91, 1.53)
102/825
558/4593
100.00
NOTE: Weights are from random effects analysis
1
1
10
Lower risk for PCOS
Higher risk for PCOS

OUTCOME: Caesarean section					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): PCOS vs. Non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Diamant 1982	Count	-	18	70	341	2071	Crude	NA
Fridstrom 1999	Count	-	8	33	19	66	Crude	NA
Mikola 2001	Count	-	25	88	124	728	Crude	NA
Bjercke 2002	Count	-	21	52	97	355	Crude	NA
Haakova 2003	Count	-	19	66	17	66	Crude	NA
Turhan 2003	Count	-	15	38	42	136	Crude	NA
Weerakiet 2004	Count	-	28	47	98	264	Crude	NA
Dokras 2006	Count	-	21	46	43	108	Crude	NA
Kovo 2006	Count	-	11	33	15	66	Crude	NA
Palomba 2010	Count	-	24	70	16	69	Crude	NA
Nouh 2011	Count	-	19	40	8	40	Crude	NA
Palomba 2012	Count	-	15	42	20	84	Crude	NA
Elkholi 2014	Count	-	42	131	49	177	Crude	NA
Foroozanfard 2014	Count	-	103	130	91	131	Crude	NA
Naver 2014	Count	-	101	459	1151	5409	Crude	NA
Palomba 2014	Count	-	37	150	25	150	Crude	NA
Kollmann 2015	Count	-	58	174	195	706	Crude	NA
Mumm 2015	Count	-	35	157	175	1037	Crude	NA
Sawada 2015	Count	-	16	49	14	49	Crude	NA
Aktun 2016	Count	-	120	150	113	160	Crude	NA
Sterling 2016	Count	-	25	71	114	323	Crude	NA
Xiao 2016	Count	-	128	352	715	2037	Crude	NA
Chen 2020	Count	-	20	35	16	29	Crude	NA
deWilde 2017	Count	-	11	188	167	2,889	Crude	NA
Foroozanfard 2020	Count	-	23	41	29	47	Crude	NA
Hu 2021	Count	-	299	338	1585	1783	Crude	NA
Jiang 2021	Count	-	17	30	20	31	Crude	NA
Jonsdottir 2017	Count	-	36	72	169	288	Crude	NA

Chen 2020	Count	-	20	35	16	29	Crude	NA
Liu 2020	Count	-	102	381	963	3584	Crude	NA
Tobiasz 2020	Count	-	15	28	12	18	Crude	NA
Wang 2021	Count	-	13	29	49	116	Crude	NA

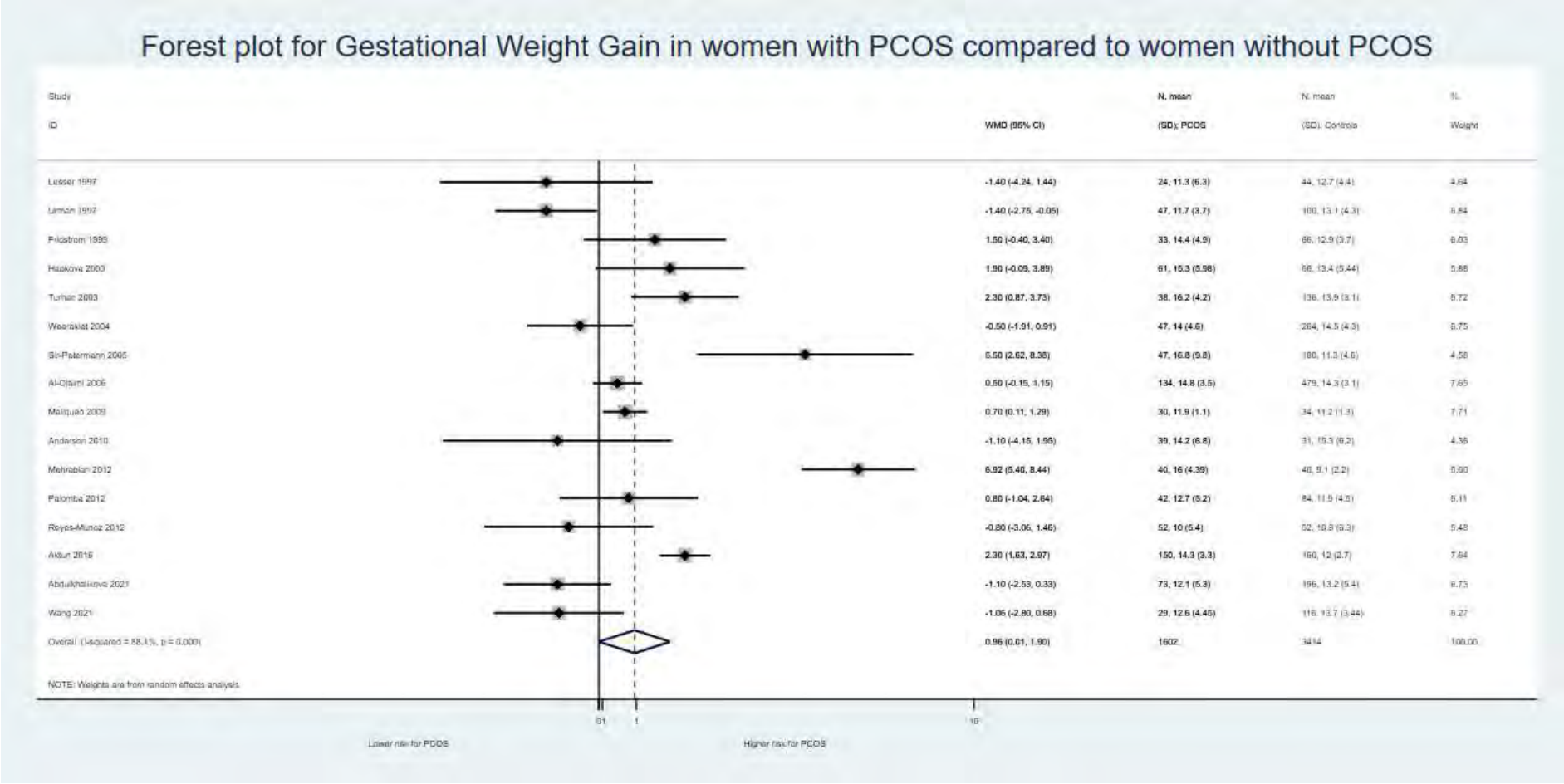


OUTCOME: Depression								
OUTCOME TYPE: Dichotomous								
COMPARISON (if applicable): PCOS vs. Non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
March 2021	Count	**All self-reported** a pregnancy of more than20 weeks were asked whether they had experienced depression when pregnant or postnatal (Cross-checked against another section of the structured inter-view concerning depression, in which women provided details of episodes, whether these were clinically diagnosed, and any treatment.);	19	52	137	514	Crude	NA



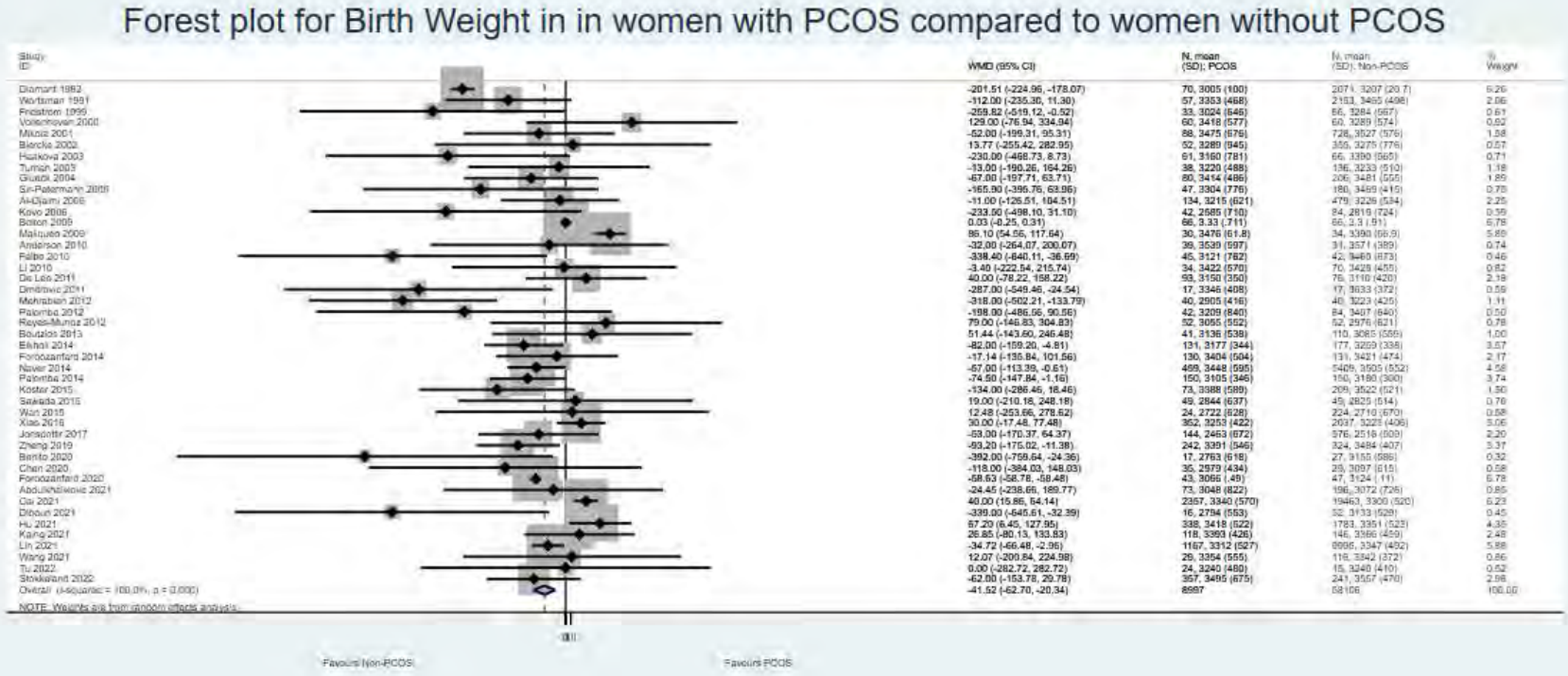
DATA EXTRACTION TABLES – CONTINUOUS OUTCOMES

OUTCOME: Gestational weight gain					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): PCOS vs. Non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Lesser 1997	Kg	-	11.3	6.3	12.7	4.4	Crude	NA
Urman 1997	Kg	-	11.7	3.7	13.1	4.3	Crude	NA
Fridstrom 1999	Kg	-	14.4	4.9	12.9	3.7	Crude	NA
Haakova 2003	Kg	-	15.3	5.98	13.4	5.44	Crude	NA
Turhan 2003	Kg	-	16.2	4.2	13.9	3.1	Crude	NA
Weerakiet 2004	Kg	-	14	4.6	14.5	4.3	Crude	NA
Sir-Petermann 2005	Kg	-	16.8	9.8	11.3	4.6	Crude	NA
Al-Ojaimi 2006	Kg	-	14.8	3.5	14.3	3.1	Crude	NA
Maliqueo 2009	Kg	-	11.9	1.1	11.2	1.3	Crude	NA
Mehrabian 2012	Kg	-	16.02	4.39	9.1	2.2	Crude	NA
Palomba 2012	Kg	-	12.7	5.2	11.9	4.5	Crude	NA
Reyes-Munoz 2012	Kg	-	10	5.4	10.8	6.3	Crude	NA
Aktun 2016	Kg	-	14.3	3.3	12	2.7	Crude	NA
Wang 2021	Kg	-	12.64	4.45	13.7	3.44	Crude	NA


Forest plot for Gestational Weight Gain in women with PCOS compared to women without PCOS
Study
ID
WMD (95% CI)
N, mean
(SD); PCOS
N, mean
(SD); Controls
%
Weight
Lesser 1997
-1.40 (-4.24, 1.44)
24, 11.3 (6.3)
44, 12.7 (4.4)
4.64
Limon 1997
-1.40 (-2.75, -0.05)
47, 11.7 (3.7)
100, 13.1 (4.3)
6.84
Pilstrom 1999
1.50 (-0.40, 3.40)
33, 14.4 (4.9)
66, 12.9 (3.7)
6.03
Hasikova 2003
1.90 (-0.09, 3.89)
61, 15.3 (5.98)
66, 13.4 (5.44)
5.88
Turhan 2003
2.30 (0.87, 3.73)
38, 16.2 (4.2)
136, 13.9 (3.1)
6.72
Wearnklat 2004
-0.50 (-1.91, 0.91)
47, 14 (4.6)
284, 14.5 (4.3)
6.75
Sir-Petermann 2005
5.50 (2.62, 8.38)
47, 16.8 (9.8)
180, 11.3 (4.6)
4.58
Al-Qjani 2006
0.50 (-0.15, 1.15)
134, 14.8 (3.5)
479, 14.3 (3.1)
7.65
Malquias 2009
0.70 (0.11, 1.29)
30, 11.9 (1.1)
34, 11.2 (1.3)
7.71
Anderson 2010
-1.10 (-4.15, 1.95)
39, 14.2 (6.8)
31, 15.3 (6.2)
4.36
Mehrabian 2012
6.92 (5.40, 8.44)
40, 16 (4.39)
40, 9.1 (2.2)
5.90
Palomba 2012
0.80 (-1.04, 2.64)
42, 12.7 (5.2)
84, 11.9 (4.5)
6.11
Reyes-Munoz 2012
-0.80 (-3.06, 1.46)
52, 10 (5.4)
52, 10.8 (6.3)
5.48
Aktun 2016
2.30 (1.63, 2.97)
150, 14.3 (3.3)
160, 12 (2.7)
7.84
Abdulkhalikova 2021
-1.10 (-2.53, 0.33)
73, 12.1 (5.3)
196, 13.2 (5.4)
6.73
Wang 2021
-1.05 (-2.80, 0.68)
29, 12.6 (4.45)
116, 13.7 (3.44)
6.27
Overall (I-squared = 88.1%, p = 0.000)
0.96 (0.01, 1.90)
1602
3414
100.00
NOTE: Weights are from random effects analysis
.01
1
10
Lower risk for PCOS
Higher risk for PCOS

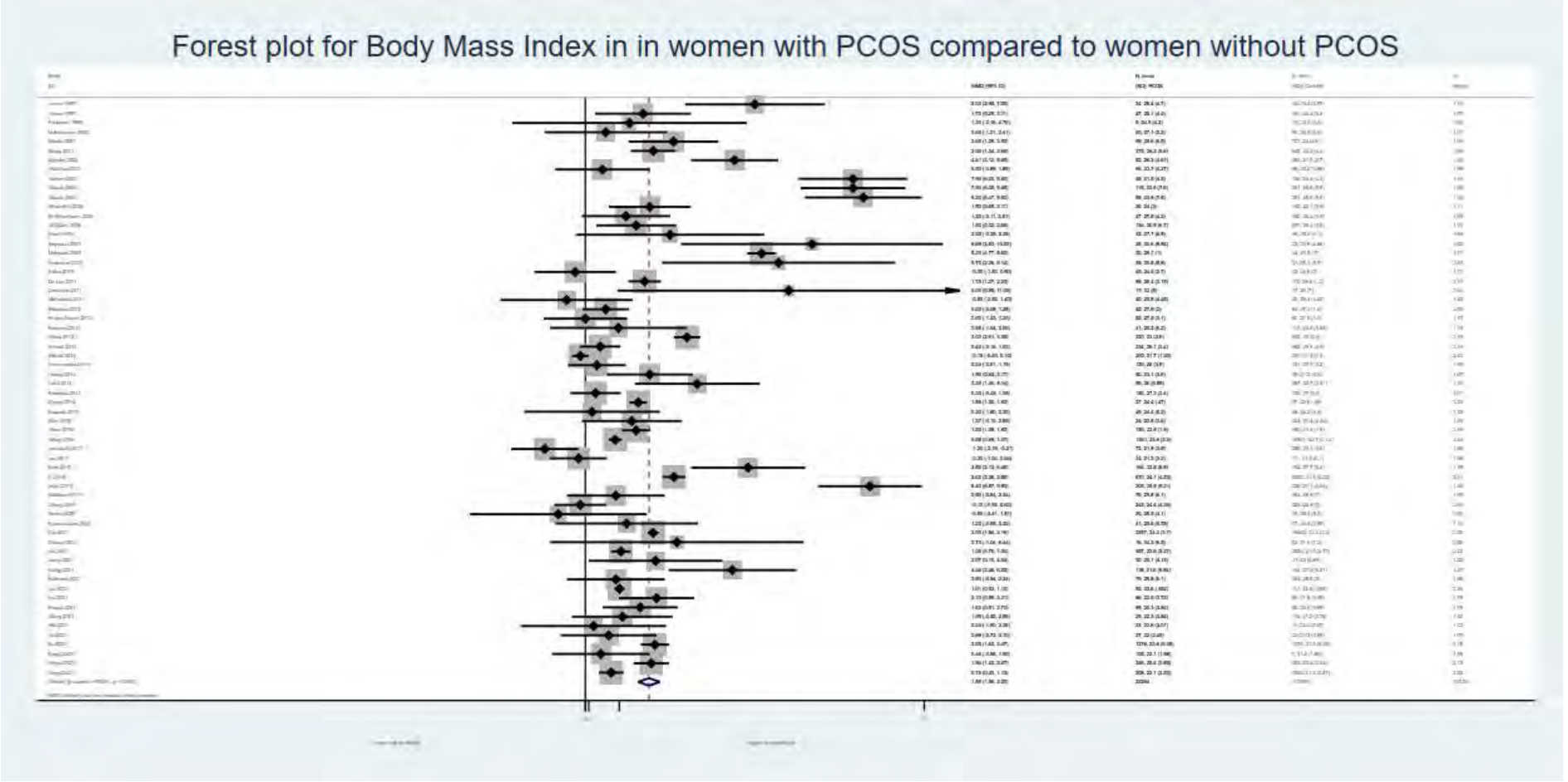
OUTCOME: Birth weight				**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): PCOS vs. Non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Diamant 1982	g	-	3005	100	3341.5	206.2	Crude	NA
Wortsman 1991	g	-	3353	468	3465	498	Crude	NA
Fridstrom 1999	g	-	3024.2727	605.36364	3284.0909	519.39394	Crude	NA
Vollenhoven 2000	g	-	3418	577	3289	574	Crude	NA
Mikola 2001	g	-	3475	676	3527	576	Crude	NA
Bjercke 2002	g	-	3288.7692	908.5	3275	776	Crude	NA
Haakova 2003	g	-	3160	781	3390	565	Crude	NA
Turhan 2003	g	-	3220	488	3233	510	Crude	NA
Glueck 2004	g	-	3414	486	3481	555	Crude	NA
Sir-Petermann 2005	g	-	3303.5	775.6	3469.4	414.6	Crude	NA
Al-Ojaimi 2006	g	-	3215	621	3226	534	Crude	NA
Kovo 2006	g	-	2585	709.5	2818.5	724	Crude	NA
Hu 2007	g	-	3270		3630		Crude	NA
Maliqueo 2009	g	-	3476.3	61.8	3390.2	66.9	Crude	NA
Falbo 2010	g	-	3121.4	762.1	3459.8	673.2	Crude	NA
Li 2010	g	-	3421.7	569.5	3425.1	455.3	Crude	NA
De Leo 2011	g	-	3150	350	3110	420	Crude	NA
Dmitrovic 2011	g	-	3346	408	3633	372	Crude	NA
Mehrabian 2012	g	-	2905.25	415.59	3223.25	425.02	Crude	NA
Palomba 2012	g	-	3209	840	3407	640	Crude	NA
Reyes-Munoz 2012	g	-	3055	552	2976	621	Crude	NA
Boutzios 2013	g	-	3136.31	537.9	3084.8724	549.31545	Crude	NA
Elkholi 2014	g	-	3176.2768	342.08475	3259.1243	334.15819	Crude	NA
Foroozanfard 2014	g	-	3404.23	504.1	3421.37	473.69	Crude	NA

Naver 2014	g	-	3448	595	3505	552	Crude	NA
Palomba 2014	g	-	3105.3	346.1	3179.8	300.4	Crude	NA
Palomba 2014	g	-	3105.3	346.1	3179.8	300.4	Crude	NA
Koster 2015	g	-	3388	589	3522	521	Crude	NA
Sawada 2015	g	-	2844	637	2825	514	Crude	NA
Wan 2015	g	-	2722	628	2709.5179	664.3125	Crude	NA
Xiao 2016	g	-	3253	422	3223	406	Crude	NA
Diboun 2021	g	-	2794.4	552.8	3133.4	528.6	Crude	NA
Hu 2021	g	-	3418.2	522.41	3351	522.89	Crude	NA
Jonsdottir 2017	g	-	2463	672	2516	509	Crude	NA
Kaing 2021	g	-	3392.85	425.78	3366	458.94	Crude	NA
Lin 2021	g	-	3,311.79	527.41	3,346.51	491.71	Crude	NA
Stokkeland 2022	g	-	3495	675	3557	470	Crude	NA
Tobiasz 2020	g	-	3275	396.2	3345	330	Crude	NA
Tu 2022	g	-	3250	480.0	3240	410.0	Crude	NA
Wang 2021	g	-	3353.79	554.57	3341.72	372.36	Crude	NA
Zheng 2019	g	-	3390.6	545.7	3483.8		Crude	NA


Forest plot for Birth Weight in in women with PCOS compared to women without PCOS
Study ID
WMD (95% CI)
N, mean (SD), PCOS
N, mean (SD), Non-PCOS
% Weight
Diamant 1982 -201.51 (-224.96, -178.07) 70, 3005 (100) 207, 3207 (207) 6.26
Wortsman 1991 -112.00 (-235.30, 11.30) 57, 3353 (468) 2193, 3465 (498) 2.06
Fridstrom 1999 -259.82 (-519.12, -0.52) 33, 3024 (646) 66, 3284 (567) 0.61
Vollenhoven 2000 129.00 (-76.94, 334.94) 60, 3418 (577) 60, 3289 (574) 0.92
Mikos 2001 -52.00 (-199.31, 95.31) 88, 3475 (676) 728, 3527 (576) 1.58
Blancke 2002 13.77 (-255.42, 282.95) 52, 3289 (945) 355, 3275 (776) 0.57
Hulkova 2003 -230.00 (-466.73, 8.73) 61, 3160 (781) 66, 3390 (665) 0.71
Turhan 2003 -13.00 (-190.26, 164.26) 38, 3220 (488) 136, 3233 (510) 1.18
Glueck 2004 -67.00 (-197.71, 63.71) 80, 3414 (486) 206, 3481 (555) 1.89
Sir-Petermark 2006 -165.90 (-395.76, 63.96) 47, 3304 (776) 180, 3469 (415) 0.78
Al-Djami 2006 -11.00 (-126.51, 104.51) 134, 3215 (621) 479, 3226 (584) 2.25
Kovo 2006 -233.50 (-498.10, 31.10) 42, 2585 (710) 84, 2819 (724) 0.59
Bolton 2006 0.03 (-0.25, 0.31) 66, 3.3 (.91) 66, 3.3 (.91) 6.78
Matsuura 2009 86.10 (54.56, 117.64) 30, 3476 (61.8) 34, 3390 (66.9) 5.89
Anderson 2010 -32.00 (-264.07, 200.07) 39, 3539 (597) 31, 3571 (389) 0.74
Falbo 2010 -338.40 (-840.11, -36.69) 45, 3121 (782) 42, 3460 (873) 0.46
Li 2010 -3.40 (-222.54, 215.74) 34, 3422 (570) 70, 3428 (455) 0.82
De Leo 2011 40.00 (-78.22, 158.22) 93, 3150 (350) 76, 3110 (420) 2.19
Dimitriou 2011 -287.00 (-549.46, -24.54) 17, 3346 (408) 17, 3633 (372) 0.59
Mehrabian 2012 -318.00 (-502.21, -133.79) 40, 2905 (416) 40, 3223 (425) 1.11
Palomba 2012 -198.00 (-486.66, 90.66) 42, 3209 (840) 84, 3407 (640) 0.50
Reyes-Muñoz 2012 79.00 (-146.83, 304.83) 52, 3055 (552) 52, 2976 (621) 0.78
Boutzios 2013 51.44 (-143.60, 246.48) 41, 3136 (539) 110, 3085 (555) 1.00
Elkholi 2014 -82.00 (-159.20, -4.81) 131, 3177 (344) 177, 3259 (338) 3.57
Forouzanfard 2014 -17.14 (-135.84, 101.56) 130, 3404 (504) 131, 3421 (474) 2.17
Naver 2014 -57.00 (-113.39, -0.61) 469, 3448 (595) 5409, 3505 (552) 4.56
Palomba 2014 -74.50 (-147.84, -1.16) 150, 3105 (346) 150, 3180 (300) 3.74
Koster 2015 -134.00 (-286.46, 18.46) 73, 3388 (589) 209, 3522 (521) 1.50
Sakeda 2015 19.00 (-210.18, 248.18) 49, 2844 (637) 49, 2825 (514) 0.76
Wan 2015 12.48 (-253.66, 278.62) 24, 2722 (628) 224, 2710 (670) 0.58
Xiao 2016 30.00 (-17.48, 77.48) 352, 3253 (422) 2037, 3223 (406) 5.06
Jonsdottir 2017 -59.00 (-170.37, 54.37) 144, 2463 (672) 376, 2518 (600) 2.20
Zheng 2019 -93.20 (-175.02, -11.38) 242, 3391 (546) 324, 3484 (407) 3.37
Benito 2020 -392.00 (-759.64, -24.36) 17, 2763 (618) 27, 3155 (586) 0.32
Chen 2020 -118.00 (-384.03, 148.03) 35, 2979 (434) 29, 3097 (615) 0.58
Forouzanfard 2020 -58.53 (-58.78, -58.48) 43, 3066 (.45) 47, 3124 (.11) 6.78
Abdulkhaleque 2021 -24.45 (-238.66, 189.77) 73, 3048 (822) 196, 3072 (726) 0.85
Cai 2021 40.00 (15.86, 64.14) 2357, 3340 (570) 19463, 3300 (520) 6.23
Dilbaz 2021 -339.00 (-645.61, -32.39) 16, 2794 (553) 52, 3133 (528) 0.45
Hu 2021 87.20 (6.45, 127.95) 338, 3418 (522) 1783, 3351 (523) 4.35
Kang 2021 26.85 (-80.13, 133.83) 118, 3393 (426) 146, 3366 (459) 2.48
Lin 2021 -34.72 (-66.48, -2.96) 1167, 3312 (527) 6996, 3347 (492) 5.88
Wang 2021 12.07 (-200.84, 224.98) 29, 3354 (555) 118, 3342 (372) 0.86
Tu 2022 0.00 (-282.72, 282.72) 24, 3240 (480) 15, 3240 (410) 0.52
Stokkeland 2022 -62.00 (-153.78, 29.78) 357, 3495 (675) 241, 3557 (470) 2.98
Overall (I-squared = 100.0%, p = 0.000) -41.52 (-62.70, -20.34) 8997 68106 100.00
NOTE: Weights are from random effects analysis
-1000
Favours Non-PCOS
Favours PCOS

OUTCOME: Body mass index					**OUTCOME TYPE:** Continuous			
COMPARISON (if applicable): PCOS vs. Non-PCOS								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**Mean (specify if median) in intervention/ exposure group**	**SD (or specify if other measure: IQR, SE or 95% CI) in intervention / exposure group**	**Mean (specify if median) or median in control / comparison group**	**SD (or specify if other measure: SE, IQR or 95% CI) in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were included in the model?**
Urman 1997	Kg/m^2	-	25.1	4.4	23.4	3.3	Crude	NA
Fridstrom 1999	Kg/m^2	-	24.5	4.2	23.2	3.4	Crude	NA
Vollenhoven 2000	Kg/m^2	-	27.1	5.2	26.5	4.9	Crude	NA
Mikola 2001	Kg/m^2	-	25.6	6.5	23	4.6	Crude	NA
Wang 2001	Kg/m^2	-	26.3	5.6	24.3	4.4	Crude	NA
Bjercke 2002	Kg/m^2	-	26.305769	4.4269231	21.9	2.7	Crude	NA
Haakova 2003	Kg/m^2	-	23.7	4.27	23.2	3.89	Crude	NA
Turhan 2003	Kg/m^2	-	31.5	4.5	23.6	4.3	Crude	NA
Glueck 2004	Kg/m^2	-	33.5	7.6	25.6	5.9	Crude	NA
Glueck 2004	Kg/m^2	-	33.8	7.8	25.6	5.9	Crude	NA
Weerakiet 2004	Kg/m^2	-	24	3	22.1	3.6	Crude	NA
Sir-Petermann 2005	Kg/m^2	-	27.5	4.2	26.3	3.5	Crude	NA
Al-Ojaimi 2006	Kg/m^2	-	30.9	6.7	29.4	3.6	Crude	NA
Kovo 2006	Kg/m^2	-	27.7	6.9	25.2	6.1	Crude	NA
Beydoun 2009	Kg/m^2	-	30.6	8.94	23.91	4.86	Crude	NA
Maliqueo 2009	Kg/m^2	-	29.1	1	23.9	0.7	Crude	NA
Falbo 2010	Kg/m^2	-	24.5	2.7	24.8	3	Crude	NA
De Leo 2011	Kg/m^2	-	28.35	2.15	26.6	1.2	Crude	NA
Dmitrovic 2011	Kg/m^2	-	32	8	26	7	Crude	NA
Mehrabian 2012	Kg/m^2	-	25.84	4.45	26.39	4.45	Crude	NA
Palomba 2012	Kg/m^2	-	27.9	2	27.3	1.5	Crude	NA
Reyes-Munoz 2012	Kg/m^2	-	27.5	3.1	27.5	3.3	Crude	NA
Boutzios 2013	Kg/m^2	-	25.2	6.2	24.223636	3.6254545	Crude	NA
Wang 2013	Kg/m^2	-	23	2.6	20	2.4	Crude	NA
Ashrafi 2014	Kg/m^2	-	26.1	3.4	25.6	4	Crude	NA

Elkholi 2014	Kg/m^2	-	31.7	1.25	31.85	1.3	Crude	NA
Foroozanfard 2014	Kg/m^2	-	28.01	3.8	27. 67	3.2	Crude	NA
Huang 2014	Kg/m^2	-	23.1	3.6	21.2	2.5	Crude	NA
Lathi 2014	Kg/m^2	-	26	6.99	22.7	3.91	Crude	NA
Palomba 2014	Kg/m^2	-	27.3	3.4	27	3.2	Crude	NA
Palomba 2014	Kg/m^2	-	27.3	3.4	27	3.2	Crude	NA
Zhang 2014	Kg/m^2	-	24.4	0.47	22.84	0.49	Crude	NA
Sawada 2015	Kg/m^2	-	24.4	5.2	24.2	4.9	Crude	NA
Wan 2015	Kg/m^2	-	22.8	3.6	21.426498	2.4468708	Crude	NA
Aktun 2016	Kg/m^2	-	22.9	1.9	21.4	1.9	Crude	NA
Wang 2016	Kg/m^2	-	23.6	3.5	22.72	3.12	Crude	NA
Butts 2019	Kg/m^2	-	35.5	9.21	27.1	6.64	Crude	NA
Cai 2021	Kg/m^2	-	24.3	3.7	22.3	3.2	Crude	NA
Foroozanfard 2020	Kg/m^2	-	24.9	5.64	24.34	3.99	Crude	NA
Hu 2021	Kg/m^2	-	22.56	3.27	21.51	2.77	Crude	NA
Jiang 2021	Kg/m^2	-	25.1	4.15	23.03	3.69	Crude	NA
Jonsdottir 2017	Kg/m^2	-	21.9	3.9	23.1	3.6	Crude	NA
Kaing 2021	Kg/m^2	-	31.61	8.94	27.27	6.01	Crude	NA
Kent 2018	Kg/m^2	-	32.5	8.8	27.7	6.4	Crude	NA
Kollmann 2021	Kg/m^2	-	29.8	6.1	28.9	5	Crude	NA
Liu 2021	Kg/m^2	-	23.58	0.3521	22.57	0.2591	Crude	NA
Liu 2021	Kg/m^2	-	23.91	3.73	21.81	3.09	Crude	NA
Li 2018	Kg/m^2	-	24.15	4.33	21.53	3.22	Crude	NA
Luo 2017	Kg/m^2	-	21.3	2.2	21.5	2.1	Crude	NA
Pouya 2021	Kg/m^2	-	25.26	3.84	23.3	3.7	Crude	NA
Stokkeland 2022	Kg/m^2	-	26.8	3.9	23.7	2	Crude	NA
Tobiasz 2020	Kg/m^2	-	33.9	4.2	31.9	4.9	Crude	NA
Wang 2021	Kg/m^2	-	22.32	3.84	21.23	2.78	Crude	NA
Wu 2021	Kg/m^2	-	22.65	3.01	22.41	2.97	Crude	NA
Zheng 2019	Kg/m^2	-	24.37	4.36	24.52	5	Crude	NA


Forest plot for Body Mass Index in in women with PCOS compared to women without PCOS

8. GRADE ASSESSMENTS AND EVIDENCE PROFILE

COMPARISON: Women with and without PCOS												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	PCOS	Non-PCOS	Effect, fixed [95% CI]	Favours	Certainty	Importance
Outcome: Miscarriage												
43	Observational	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1565/ 9877	6997/ 57252	OR 1.50 [1.20, 1.87]	PCOS	⊕⊕◯◯ Low	CRITICAL
Outcome: Gestational diabetes												
57	Observational	serious[1]	very serious[6]	no serious indirectness	no serious imprecision	none	1618/ 10165	4361/ 60219	OR 2.35 [1.90, 2.90]	PCOS	⊕⊕◯◯ Low	CRITICAL
Outcome: Pregnancy-induced/gestational hypertension												
40	Observational	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	664/ 6646	1553/ 33321	OR 2.20 [1.82, 2.67]	PCOS	⊕⊕⊕◯ Moderate	CRITICAL
Outcome: Pre-eclampsia												
36	Observational	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	416/ 4860	838/ 24773	OR 2.28 [1.88, 2.77]	PCOS	⊕⊕⊕◯ Moderate	CRITICAL
Outcome: Eclampsia												
1	Observational	serious[1]	very serious[2]	no serious indirectness	very serious[7]	none	6/ 46	50/ 246	OR 1.16 [0.44, 3.08]	No difference	⊕◯◯◯ Very low	CRITICAL
Outcome: Preterm birth												
54	Observational	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	1949/ 13313	6025/ 69079	OR 1.54 [1.34, 1.76]	PCOS	⊕⊕◯◯ Low	CRITICAL
Outcome: Low birth weight												
15	Observational	serious	no serious inconsistency	no serious indirectness	no serious imprecision	none	325/ 4627	1217/ 23183	OR 1.28 [1.04 ,1.59]	PCOS	⊕◯◯◯ Very low	IMPORTANT
Outcome: Small for gestational age												
24	Observational	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	266/ 2700	1049/ 14844	OR 1.12 [0.89, 1.40]	PCOS	⊕⊕◯◯ Low	IMPORTANT
Outcome: Macrosomia												

[5] **D**owngraded once as the majority of evidence is at moderate or high risk of bias or downgraded twice as majority of evidence is at very high risk of bias

[6] Downgraded once as I^2 is 50-75% or downgraded twice as I^2 is >75%

[7] Downgraded once due to imprecision as number of studies 5-9 / confidence intervals (CIs) wide (>2) or downgraded twice due to imprecision as number of studies < 5 and confidence intervals (CIs) wide (>2)

22	Observational	very serious[1]	very serious[2]	no serious indirectness	no serious imprecision	none	536/ 6045	2511/ 33633	OR 1.14 [0.95, 1.37]	No difference	⊕◯◯◯ Very low	IMPORTANT
Outcome: Large for gestational age												
25	Observational	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	561/ 3867	2987/ 24897	OR 1.12 [0.98, 1.28]	No difference	⊕⊕◯◯ Low	IMPORTANT
Outcome: Intrauterine growth restriction												
11	Observational	No serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	41/ 806	46/ 1822	OR 1.77 [1.16, 2.69]	PCOS	⊕⊕⊕◯ Moderate	IMPORTANT
Outcome: Instrumental delivery												
10	Observational	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	805/ 1517	4563/ 8570	OR 1.18 [0.91, 1.53]	No difference	⊕◯◯◯ Very low	IMPORTANT
Outcome: Induction of labour												
8	Observational	very serious[1]	very serious[2]	serious[8]	serious[3]	none	216/ 1029	1544/ 10052	OR 1.62 [0.97, 2.70]	PCOS	⊕◯◯◯ Very low	IMPORTANT
Outcome: Caesarean section												
37	Observational	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1425/ 3590	6492/ 23017	OR 1.23 [1.06, 1.43]	PCOS	⊕⊕◯◯ Low	IMPORTANT
Outcome: Perinatal depression												
1	Observational	serious[1]	very serious[2]	very serious[4]	very serious[3]	none	19/ 52	137/ 514	OR 1.58 [0.87, 2.88]	No difference	⊕◯◯◯ Very low	IMPORTANT
Outcome: Gestational weight gain												
16	Observational	serious[1]	very serious[2]	no serious indirectness	no serious imprecision	none	755	1765	WMD 0.96 [0.01, 1.90]	PCOS	⊕◯◯◯ Very low	IMPORTANT
Outcome: Birthweight												
45	Observational	serious[1]	very serious[2]	no serious indirectness	no serious imprecision	none	4940	28260	WMD -41.52 [-62.70, -20.34]	PCOS	⊕◯◯◯ Very low	IMPORTANT
Outcome: Body mass index												
62	Observational	serious[1]	very serious[2]	no serious indirectness	no serious imprecision	none	7777	38980	WMD 1.88 [1.56, 2.20]	PCOS	⊕◯◯◯ Very low	IMPORTANT

[8] Downgraded once as the majority of evidence did not include the outcome as an outcome of interest in PICO or downgraded twice as majority of evidence is secondary analyses of studies with aims other than pregnancy outcomes

APPENDIX. QUALITY APPRAISAL OF INCLUDED STUDIES

Study ID	Harborne 2005
Study Citation	Harborne et al., *J Clin Endocrinol Metab* 90:4593–4598, 2005
Study Country	UK
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS (age not reported)
PCOS diagnostic criteria	Rotterdam
Presence of infertility	*Not reported*
Presence of other condition/s	*Obese (30 – 37 kg/m2) and morbid obese (above and equal to 37 kg/m2)* *No diabetes*
Medication History	*No*
N per group	*Allocated/randomised: 83 (42 obese: 21 met 1500mg, 21 met 2550mg; 41 morbid obese: 21 met 1500mg, 20 met 2550mg)* *Assessed at end of study: 68 (35 obese: 18 met 1500mg, 17 met 2550mg; 33 morbid obese: 18 met 1500mg, 15 met 2550mg)*
Setting	*University teaching hospital with patients from gynecology/ endocrinology clinics, Glasgow, UK*
Intervention	*Metformin (Glucophage, Merck & Co., West Drayton, UK) dose was 850 mg, three times daily for 8 months*
Comparison	*Metformin (Glucophage, Merck & Co., West Drayton, UK) dose was 500 mg, three times daily for 8 months*
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Changes in body mass, circulating hormones, markers of inflammation, and lipid profiles after 4 months (T4) and 8 months (T8) of treatment*
Follow up Duration	*8 months*
Summary Result/s	*In the obese group, metformin xx was more effective in reducing xx compared with xx* *In the morbid obese group, metformin xx was effective in reducing BMI, but not …*
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT	

Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*The aim was to determine whether different doses of metformin (1500 or 2550 mg/ d) would have different effects on body weight, circulating hormones, markers of inflammation, and lipid profiles*
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Inclusion criteria	Yes Partial No Not reported	*The diagnosis of PCOS included at least two of the three features: - oligomenorrhea (fewer than eight cycles per year)/amenorrhea (fewer than two cycles per year), - polycystic ovaries determined by ultrasonography using the criteria of Adams et al. (12), - or an elevated free androgen index.*
Exclusion criteria	Yes Partial No Not reported	*Contraindications to metformin or its use within the previous 4 months or oral contraceptive use within the previous 2 months. None of the women had thyroid dysfunction, hyperprolactinemia, diabetes mellitus, or late-onset or congenital adrenal hyperplasia. Women taking medication known to affect weight loss, gonadal or adrenal function, or carbohydrate or lipid metabolism were also excluded.*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS – **Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	*Not reported* *Block randomisation based on dose and BMI, but not clear how the randomisation was done.*
SELECTION BIAS – **Was allocation to intervention group concealed?**	Yes Partial No Not reported	*Not reported*

PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	*No*
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	*Not reported*
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	*Obese women with PCOS* *Met 1500mg = 3/21 = 14.2%* *Met 2550mg = 4/21 = 19%* *Morbid obese women with PCOS* *Met 1500mg = 3/21 = 14.2%* *Met 2550mg = 5/20 = 25%*

	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	*Yes*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Not reported* *This is difficult to determine if there isn't a protocol.*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	*Partial* *Ages of the participants were not reported*
	If confounding was present, was it controlled for?	Yes Partial No Not reported	*Partial* *Outcomes not adjusted for age*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*Not reported*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	*Partial* *Potential confounders were identified and taken into account in the analysis*
COMMENTS		*Lack of randomisation and blinding key reason for high RoB*	

What is the overall risk of bias?	Low Moderate High Insufficient information	*High*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*No – all outcomes high risk of bias*	

CROSS-SECTIONAL or CASE-CONTROL STUDIES

Study ID	*Acmaz, 2013*	
Study Citation	*Açmaz, G., Albayrak, E., Acmaz, B., Başer, M., Soyak, M., Zararsız, G., & İpekMüderris, İ. (2013). Level of anxiety, depression, self-esteem, social anxiety, and quality of life among the women with polycystic ovary syndrome. The Scientific World Journal, 2013.*	
Study Country	*Turkey*	
CHARACTERISTICS AND EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*86 patients diagnosed with PCOS according to 2003 Rotterdam Criteria, had no physical disease but PCOS, did not receive any treatment (before the treatment) for PCOS and had at least primary school degree.*	
Control population	*47 healthy volunteer participants in reproductive age*	
PCOS diagnostic criteria	*Rotterdam 2003*	
N per group	*PCOS were classified according to the complaints at the time of polyclinic admission.* *- Infertility group (concern with having child)* *- Oligomenorrhea-hirsutism group (concerns with hirsutism)* *- Overweight-obesity group (concerns with losing weight and had a BMI 30 or more)*	
Setting	*Hospital*	
Outcomes (primary and other) with definition/tool (eg. self-reported, fasting etc.)	*Primary outcomes:* *- SF-36 Quality of Life Scale (Short-Form 36)* *Outcomes not relevant:* *- LSAS (Liebowitz' Social Anxiety Scale)* *- RSES (Rosenberg' Self-Esteem Scale)* *- Beck Anxiety Inventory (BAI)* *- Beck Depression Inventory (BDI)*	
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	*Yes*

Inclusion criteria	Yes Partial No Not reported	*Yes, no physical disease but PCOS, did not receive any treatment (before the treatment) for PCOS and had at least primary school degree.*
Exclusion criteria	Yes Partial No Not reported	*Yes, Those who had thyroid disorders, DM, Cushing' disease, positive malignancy, congenital adrenal hyperplasia, psychotic disorders and used antidepressants or steroidal hormone drugs and mood stabilizers were excluded. Patients with personality disorders assessed by SCID-I and SCID-II were not included.*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Is a cross sectional or case-control study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes, which design?*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Not relevant to this systematic review*
Was matching performed?	Yes Partial No Not reported	*Yes, age and BMI*
Summary Result/s	*Xx was associated with a, b, and c, independent of xx.*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Were the cases and controls taken from comparable populations?**	Yes Partial No Not reported	*Partial* *Control group using healthy volunteer participants in reproductive age, unknown whether also recruit at the hospital.*
	Was the case definition adequate and established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Was the control status established in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
PERFORMANCE BIAS	**Aside from the exposure/ intervention, were the groups treated the same?**	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	**Were measurements (for exposures or outcomes) carried out and calculated in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to case and control status?	Yes Partial No Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Partial because of nature of study*

	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	*Partial because of nature of study*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	X% treatment X% control/ comparison Not reported	*Not relevant to cross-sectional study*
	What percentage of the individuals were not included in the analysis?	X% treatment X% control/ comparison Not reported	*Not reported*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Not reported* *No protocol or PROSPERO*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	*Yes* *Demographic difference between group in marital status, number of children, obesity due to the aim of the study*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial	*Partial* *Some reported in median and percentiles without stating reasons.*

		No Not reported	
COMMENTS		*Unknown where they recruited healthy volunteer in control group*	
What is the overall risk of bias?		Low Moderate High Insufficient information	*Moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*Yes* *All outcomes moderate risk of bias except for primary outcome which had low risk of bias due to better attrition and more reliable measurement tool than remaining outcomes*	

COHORT STUDIES

Study ID	*Diamant 1982*
Study Citation	*Diamant, Y. Z.; Rimon, E.; Evron, S. (1982): High incidence of preeclamptic toxemia in patients with polycystic ovarian disease. Eur J Obstet Gynecol Reprod Biol 14, 3, 199-204*
Study Country	*Israel*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS* *Age= PCOS: 31 years, Non-PCOS: 27.2 years*
PCOS diagnostic criteria	*Two or more of the following: hirsutism, oligomenorrhea, anovulation, elevated level of either serum Testosterone or urinary KS +PCOM.*
N per group	***PCOS: 70*** ***Non-PCOS: 2071***
Setting	*Note stated; possibly all PCOS from infertility treatment centre and Non-PCOS partially from infertility treatment centre.*
Intervention/ indicator	N/A
Comparison/ Control	*Anovulatory Non- PCOS/Non- PCOS with Spontaneous Pregnancy*

Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*PE, BW, Instrumental delivery, CS*	
Inclusion criteria reported?	*Yes*	*All PCOS were anovulatory and conceived by OI*
Exclusion criteria reported?	Yes Partial No Not reported	*Not reported*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Partial - Only inclusion criteria reported*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial	*Yes*

		No Not reported	
Was matching performed?		Yes Partial No Not reported	*No*
Summary of Result/s		After induction of ovulation, in infertile women are accompanied by an increased incidence of PET. This was suggested as early as 20 yr ago by Stallworthy (1960). However, according to our results, the rate of PET differs significantly between the PC0 and A-NPCO patients. While the incidence of PET in A-NPCO group was only slightly elevated as compared to the normal control group, and even lower than in the control primipara group, PC0 women developed PET in more than 28% of the cases. This rate was almost 12 times higher than in the normal control group and more than 2.5 times higher than in the control primiparae.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	*Yes*	Not reported
	Was the exposed cohort truly representative?	Yes Partial No Not reported	*No* *Infertility treatment centre*
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	*Not reported*
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*

DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	Yes Partial No Not reported	Not reported
	What percentage of the individuals were not included in the analysis?	Yes Partial No Not reported	*Yes*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*

CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Partial one group of anovulatory non-PCOS women were age matched with anovulatory PCOS
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Levran 1990*	
Study Citation	*Levran, D.; Shoham, Z.; Habib, D.; et al. (1990): Glucose tolerance in pregnant women following treatment for sterility. Int J Fertil 35, 3, 157-159*	
Study Country	*Israel*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Anovulation with oligo/amenorrhea+obesity+hirsutism+PCOM*	
N per group	***PCOS: 76*** ***Non-PCOS: 95***	
Setting	*Infertility treatment centre for PCOS, Outpatient clinic for Non-PCOS*	
Intervention/ indicator	N/A	
Comparison/ Control	*Normal menstrual pattern and spontaneous pregnancy*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*GDM*	
Inclusion criteria reported?	*Yes*	*All husbands had a normal sperm count*
Exclusion criteria reported?	Yes Partial No Not reported	*Not reported*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*

Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Partial - Only inclusion criteria reported*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	Yes - *Age, weight, familial diabetic history and past medical history*
Summary of Result/s	GDM was higher in PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS – **Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	No
SELECTION BIAS – **Was the exposed cohort truly representative?**	Yes Partial No Not reported	*No* *Infertility treatment centre*

	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	*Not reported*
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were	0	

	not included in the analysis?		
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes Age, weight, familial diabetic history+past medical history were matched
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Wortsman 1991*	
Study Citation	*Wortsman, J.; de Angeles, S.; Futterweit, W.; et al. (1991): Gestational diabetes and neonatal macrosomia in the polycystic ovary syndrome. J Reprod Med 36, 9, 659-661*	
Study Country	*USA*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Menstrual irregularities, Hirsutism and/or infertility from ovulatory dysfunction and the presence of a biochemical profile showing serum LH levels≥25 mIU/m, LH/FSH ratio≥2 and/or elevated serum concentrations of the androgens testosterone, free testosterone, androstenedione and deydroepiandrosterone sufat+laparascopy or sonography*	
N per group	***PCOS: 53*** ***Non-PCOS: 2306***	
Setting	*The endocrine/gynaecology services*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*GDM, BW, Macrosomia*	
Inclusion criteria reported?	Not reported	
Exclusion criteria reported?	Yes Partial No Not reported	*Not reported*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial	*Yes*

		No Not reported	
Does the study have specified inclusion/ exclusion criteria?		Yes Partial No Not reported	*No*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Not reported
Were the outcomes measured appropriate?		Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Yes*
Was matching performed?		Yes Partial No Not reported	No
Summary of Result/s		GDM, BW and macrosomia were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Not reported

	Was the exposed cohort truly representative?	Yes Partial No Not reported	Yes
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION	**What percentage of the individuals**	0	

	recruited into each arm of the study were lost to follow up?		
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Not reported
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome*		*No*	

was low risk but rest were high)?	

Study ID	*Urman 1992*	
Study Citation	Urman, B.; Fluker, M. R.; Yuen, B. H.; et al. (1992): The outcome of in vitro fertilization and embryo transfer in women with polycystic ovary syndrome failing to conceive after ovulation induction with exogenous gonadotropins. Fertil Steril 57, 6, 1269-1273	
Study Country	*Canada*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Hirsutism, oligoanovulation, LH/FSH>2, Hyperandrogenism*	
N per group	***PCOS: 4*** ***Non-PCOS: 10***	
Setting	*Not stated but probably infertility treatment centre*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS and Infertility because of tubal factor*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Miscarriage*	
Inclusion criteria reported?	Not reported	
Exclusion criteria reported?	Yes Partial No Not reported	Partial - *Significant tubal or peritoneal factors*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*

Is a cohort study the appropriate design to answer this question?		Yes Partial No Not reported	*Yes*
Does the study have specified inclusion/ exclusion criteria?		Yes Partial No Not reported	Partial
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Not reported
Were the outcomes measured appropriate?		Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Yes*
Was matching performed?		Yes Partial No Not reported	Partial- Age matched
Summary of Result/s		Miscarriage was similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes

	Was the exposed cohort truly representative?	Yes Partial No Not reported	No
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION	**What percentage of the individuals**	0	

	recruited into each arm of the study were lost to follow up?		
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Partial- Age matched
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*Low*	
Did risk of bias differ by outcome *(eg. primary outcome*		*No*	

was low risk but rest were high)?	

Study ID	*Homburg 1993*	
Study Citation	*Homburg, R.; Berkowitz, D.; Levy, T.; et al. (1993): In vitro fertilization and embryo transfer for the treatment of infertility associated with polycystic ovary syndrome. Fertil Steril 60, 5, 858-863*	
Study Country	*Israel*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*PCOM+Anovulation+Infertility+Oligomenorrhea/hirsutism*	
N per group	***PCOS: 47*** ***Non-PCOS: 38***	
Setting	*IVF centre*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS and tubal infertility, underwent IVF*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Miscarriage*	
Inclusion criteria reported?	Yes Partial No Not reported	*Not reported*
Exclusion criteria reported?	Yes Partial No Not reported	*Not reported*
Does the study have a clearly focused question?	Yes Partial	*Yes*

	No Not reported	
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*No*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Not reported
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	Partial – Age matched
Summary of Result/s	Miscarriage was similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Not reported
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*Yes*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes	*Yes*

		Partial No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Partial – Age matched
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***

COMMENTS		
What is the overall risk of bias?	*Moderate*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*No*	

Study ID	*Lesser 1997*	
Study Citation	Lesser, K. B.; Garcia, F. A. (1997): Association between polycystic ovary syndrome and glucose intolerance during pregnancy. J Matern Fetal Med 6, 5, 303-307	
Study Country	*USA*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Oligoanovulation AND clinical OR biochemical hyperandrogenism OR obesity OR hirsutism OR acantosis AND PCOM*	
N per group	***PCOS: 24*** ***Non-PCOS: 45***	
Setting	*Infertility treatment at the reproductive endocrinology clinic of the University of Arizona Health Sciences Centre*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS and Infertility unrelated to PCOS*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*GWG, GDM*	
Inclusion criteria reported?	Not reported	
Exclusion criteria reported?	Yes Partial No	*Type 2 diabetes*

	Not reported	
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Partial
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Partial
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	No
Summary of Result/s	GWG and GDM were similar in PCOS and Non-PCOS.	

INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Not reported
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*

	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial	***Yes***

		No Not reported	
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Urman 1997*	
Study Citation	Urman, B.; Sarac, E.; Dogan, L.; et al. (1997): Pregnancy in infertile PCOD patients. Complications and outcome. J Reprod Med 42, 8, 501-505	
Study Country	*Turkey*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Anovulation, oligoamenorrhea, hirsutism, luteinizing hormone /follicle-stimulating hormone ratio >2 and varying degrees of hyperandrogenism*	
N per group	***PCOS: 47*** ***Non-PCOS: 100***	
Setting	*Infertility treatment centre*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*GWG, GDM, GH, PE, PTB, BW, LBW and Macrosomia*	
Inclusion criteria reported?	Not reported	

Exclusion criteria reported?	Yes Partial No Not reported	Yes - Multiple pregnancies, medical disease and previous history of infertility, PIH, GDM and perinatal mortality
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Partial
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial	Partial – Age was similar; GH and GDM were reported by BMI stratification.

		No Not reported	
Summary of Result/s		*GWG, PTB, BW and macrosomia* were similar in PCOS and Non-PCOS. GDM, GH, PE and LBW were higher in PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Not reported
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	Yes
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*

	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Partial- GH, PE and GDM were reported by BMI stratification.
	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*

OTHER BIAS	**Was the study sufficiently powered to detect any differences between the groups?**	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*Moderate*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*Yes* ***Poor*** *for GWG, PTB, BW, LBW and Macrosomia*	

Study ID	*Fridstrom 1999*
Study Citation	*Fridstrom, M.; Nisell, H.; Sjoblom, P.; et al. (1999): Are women with polycystic ovary syndrome at an increased risk of pregnancy-induced hypertension and/or preeclampsia? Hypertens 18, 1, 73-80*
Study Country	*Sweden*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Anovulation+PCOM*
N per group	***PCOS: 33*** ***Non-PCOS: 66***
Setting	*The IVF unit at Huddinge University Hospital*
Intervention/ indicator	N/A
Comparison/ Control	*Non-PCOS and tubal damage infertility , endometriosis, unexplained infertility, or male infertility*

Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*GWG, GDM, GH, PE, PTB, BW, CS*	
Inclusion criteria reported?	Yes Partial No Not reported	Yes - *Pregnant women with clomiphene resistant anovulatory infertility due to PCOS; No prior diagnosis of hypertension or diabetes.*
Exclusion criteria reported?	Yes Partial No Not reported	*No*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*

Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Yes*
Was matching performed?		Yes Partial No Not reported	No
Summary of Result/s		*GWG, GDM, GH, PE, PTB, CS* were similar in PCOS and Non-PCOS BW were lower in PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No	*Yes*

		Not reported	
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes – Age matched and BMI similar; stratification by singleton vs. multiple pregnancy for PTB, BM, CS

OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*Low for PTB, BW, CS*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*Yes* *Fair for GWG, GDM, GH, PE,*	

Study ID	*Kashyap 2000*
Study Citation	Kashyap, S.; Claman, P. (2000): Polycystic ovary disease and the risk of pregnancy-induced hypertension. J Reprod Med 45, 12, 991-994
Study Country	*Canada*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Irregular menstrual cycles, increased serum testosterone, and LH/FSH >2 or PCOM on US*

N per group	***PCOS: 22*** ***Non-PCOS: 27***	
Setting	*Infertility centre*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS and Infertility due to tubal factor, unexplained, luteal phase deficiency and male factor.*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*GH*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - Infertility, singletone pregnancies and live born infants, Pre-pregnancy HTN<140/90 mmHg; treated with Hmg*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes - Oligoovulation for Controls*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes

If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Were the outcomes measured appropriate?		Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Yes*
Was matching performed?		Yes Partial No Not reported	No
Summary of Result/s		GH was higher in PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes

PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Vollenhoven 2000*

Study Citation	Vollenhoven, B.; Clark, S.; Kovacs, G.; et al. (2000): Prevalence of gestational diabetes mellitus in polycystic ovarian syndrome (PCOS) patients pregnant after ovulation induction with gonadotrophins. Australian & New Zealand Journal of Obstetrics & Gynaecology 40, 1, 54-58	
Study Country	*Australia*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Infertile with Oligomenorrhea and or hirsutism, PCOM on US±LH/FSH≥3, Testosterone>3.5 nmol/L and or DHEAS> 7.5 nmol/L*	
N per group	***PCOS: 60*** ***Non-PCOS: 60***	
Setting	*Infertility treatment centre (OI) for PCOS and antenatal care and delivery for Controls*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*GDM, BW, Instrumental delivery*	
Inclusion criteria reported?	Yes Partial No Not reported	Not reported
Exclusion criteria reported?	Yes Partial No Not reported	Not reported
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*

Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Not reported
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Not reported
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	Yes, Age, BMI and ethnicity- matched
Summary of Result/s	*GDM, BW, Instrumental delivery* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS **Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Not reported

	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION	**What percentage of the individuals**	0	

	recruited into each arm of the study were lost to follow up?		
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes – Age, BMI and Ethnicity were matched
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*Moderate*	
Did risk of bias differ by outcome *(eg. primary outcome*		*No*	

was low risk but rest were high)?	

Study ID	*Mikola 2001*	
Study Citation	*Mikola, M.; Hiilesmaa, V.; Halttunen, M.; et al. (2001): Obstetric outcome in women with polycystic ovarian syndrome. Human Reproduction 16, 2, 226-229*	
Study Country	*Finland*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*(i) PCOM on US and ≥ 2 of the following: (ii) serum LH/FSH ratio >2; (iii) hyperandrogenemia or (iv) clinical picture of menstrual irregularities, hirsutism, or infertility from anovulation*	
N per group	***PCOS: 99*** ***Non-PCOS: 737***	
Setting	*The Department of Obstetrics and Gynaecology of Helsinki University Central Hospital*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS and all with normal US at 16-18 weeks of gestation.*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*GDM, GH, PE, PTB, BW, Macrosomia, CS*	
Inclusion criteria reported?	Yes Partial No Not reported	Not reported
Exclusion criteria reported?	Yes Partial No Not reported	Partial - *Miscarriage or abortion before 22 weeks for controls*

Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Partial
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Partial
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	No
Summary of Result/s	*GDM and PTB were higher in PCOS* *GH, PE, BW were* similar in PCOS and Non-PCOS.	

INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Not reported
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Yes
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*

	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial	***Yes***

		No Not reported	
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Wang 2001*	
Study Citation	*Wang, J. X.; Davies, M. J.; Norman, R. J. (2001): Polycystic ovarian syndrome and the risk of spontaneous abortion following assisted reproductive technology treatment. Human Reproduction 16, 12, 2606-2609*	
Study Country	*Australia*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Testosterone>2.5 nmol/l or elevated androstenedione, SHBG<20 nmol/l, PCOM on US*	
N per group	***PCOS: 373*** ***Non-PCOS: 645***	
Setting	*The Reproductive Medicine Unit, Department of Obstetrics and Gynaecology*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*GWG, Miscarriage*	
Inclusion criteria reported?	Yes Partial No	Partial - *All patients underwent ART. Three treatment modalities: IVF, gamete intraFallopian tube transfer (GIFT), and intracytoplasmic sperm injection*

	Not reported	
Exclusion criteria reported?	Yes Partial No Not reported	Not reported
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Partial
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Partial
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes	No

		Partial No Not reported	
Summary of Result/s		GWG and GDM were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Not reported
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	Partial
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*

	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No – No matching, PCOS were younger and had higher BMI.
	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*

OTHER BIAS	**Was the study sufficiently powered to detect any differences between the groups?**	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Bjercke 2002*
Study Citation	*Bjercke, S.; Dale, P. O.; Tanbo, T.; et al. (2002): Impact of insulin resistance on pregnancy complications and outcome in women with polycystic ovary syndrome. Gynecol Obstet Invest 54, 2, 94-98*
Study Country	*Norway*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*PCOM on ultrasonography+ ≥3 of the following: oligomenorrhea, amenorrhoea, hirsutism, hyperandrogenemia, elevated LH/FSH ratio >2 and chronic anovulation*
N per group	***PCOS: 52*** ***Non-PCOS: 355***
Setting	*Not stated; probably infertility treatment centre*
Intervention/ indicator	N/A

Comparison/ Control	*Non-PCOS and Singleton pregnancies + ART pregnancies*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*GDM, GH, PE, PTB, Instrumental delivery and CS*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - Singleton pregnancies, No DM2 prior to pregnancy in PCOS,*
Exclusion criteria reported?	Yes Partial No Not reported	Not reported
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	No- PCOS were younger and had higher BMI.
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Partial
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Partial
Were the outcomes measured appropriate?	Yes Partial	*Yes*

		No Not reported	
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Yes*
Was matching performed?		Yes Partial No Not reported	No
Summary of Result/s		*GDM, GH were higher in PCOS* *PE, PTB, Instrumental delivery and CS* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Not reported
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*

DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*

CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Sir-Petermann 2002*
Study Citation	*Sir-Petermann, T.; Maliqueo, M.; Angel, B.; et al. (2002): Maternal serum androgens in pregnant women with polycystic ovarian syndrome: possible implications in prenatal androgenization. Human Reproduction 17, 10, 2573-2579*
Study Country	*Chile*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	

Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Chronic oligo/amenorrhoea, clinical signs of hyperandrogenism with no virilization, clinical signs of hyperinsulinaemia (waist:hip ratio >0.85), serum testosterone >0.6 ng/ml and/or FAI >5.0, different grades of hyperinsulinaemia evaluated by an OGTT, and PCOM on US.*	
N per group	***PCOS: 20*** ***Non-PCOS: 26***	
Setting	*Unit of Reproductive Medicine for PCOS, The antenatal care unit for Controls.*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS and Regular menstrual cycles, No hirsutism and other manifestations of hyperandrogenism, No galactorrhoea, thyroid dysfunction and family history of DM. All were healthy and were not receiving any drug therapy.*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*GDM*	
Inclusion criteria reported?	Yes Partial No Not reported	Yes
Exclusion criteria reported?	Yes Partial No Not reported	Yes - *A normal LH:FSH ratio; Hyperprolactinaemia, androgen-secreting neoplasm, Cushing's syn-* *drome and attenuated 21-hydroxylase deficiency, thyroid* *disease*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial- Age and geographic area matched but BMI higher in PCOS

Does the study have specified inclusion/ exclusion criteria?		Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes
Were the outcomes measured appropriate?		Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Yes*
Was matching performed?		Yes Partial No Not reported	Partial- Age and geographic area matched but BMI higher in PCOS
Summary of Result/s		GDM was higher in PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Not reported
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre

	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were	0	

	not included in the analysis?		
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Partial
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*Moderate*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Haakova 2003*	
Study Citation	*Haakova, L.; Cibula, D.; Rezabek, K.; et al. (2003): Pregnancy outcome in women with PCOS and in controls matched by age and weight. Human Reproduction 18, 7, 1438-1441*	
Study Country	*Czech Republic*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	***PCOS: 66*** ***Non-PCOS: 66***	
Setting	*Department of Obstetrics and Gynecology*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - those who had undergone US at the same department*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*GWG, GDM, GH, PTB, BW, CS*	
Inclusion criteria reported?	Yes Partial No Not reported	Not reported
Exclusion criteria reported?	Yes Partial No Not reported	Not reported
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*

Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Not reported
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Not reported
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	Yes – Age and weight matched
Summary of Result/s	*GWG was higher in PCOS* *GDM, GH, PTB, BW, CS* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Not reported
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Yes
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes	*Yes*

		Partial No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***

COMMENTS		
What is the overall risk of bias?	*Low*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*No*	

Study ID	*Turhan 2003*	
Study Citation	*Turhan, N. O.; Seckin, N. C.; Aybar, F.; et al. (2003): Assessment of glucose tolerance and pregnancy outcome of polycystic ovary patients. Int J Gynaecol Obstet 81, 2, 163-168*	
Study Country	*Turkey*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	***PCOS: 38*** ***Non-PCOS: 136***	
Setting	*The outpatient clinic of the Department of Obstetrics and Gynecology of Fatih University Hospital*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - randomly selected*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*GWG, GDM, GH, PE, PTB, IUGR, BW, Macrosomia, IOL, CS*	
Inclusion criteria reported?	Yes Partial No Not reported	Partial - *All PCOS had PCOM and been screened for GDM*
Exclusion criteria reported?	Yes Partial	Not reported

	No Not reported	
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	No- Similar age but higher BMI in PCOS
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Partial
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Partial
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	No

Summary of Result/s		*GWG was higher in PCOS* *GDM, GH, PE, PTB, IUGR, BW, Macrosomia, IOL, CS* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Not reported
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Not reported
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Not reported
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No	*Yes*

		Not reported	
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*

	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Glueck 2004*
Study Citation	Glueck, C. J.; Goldenberg, N.; Pranikoff, J.; et al. (2004): Height, weight, and motor-social development during the first 18 months of life in 126 infants born to 109 mothers with polycystic ovary syndrome who conceived on and continued metformin through pregnancy. Human Reproduction 19, 6, 1323-1330.
Study Country	*USA*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam*
N per group	***PCOS: 122*** ***Non-PCOS: 252***
Setting	*The Jewish hospital for PCOS and a suburban community practice of obstetrics for Controls*
Intervention/ indicator	N/A
Comparison/ Control	*Non-PCOS - Community healthy controls; Reglar menstrual cycles, no clinical signs of hyperandrogenism, had never been diagnosed with PCOS by Obstetricians*
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*GDM , PE, PTB*

Inclusion criteria reported?	Yes Partial No Not reported	Partial - *100% of PCOS conceived on metformin, All were on diet*
Exclusion criteria reported?	Yes Partial No Not reported	Yes - *Creatinine>1.5 mg/dl, DM1, DM2 on pharmacological therapy, Pituitay insufficiency, persistant hyperprolactinaemia, congenital adrenal hyperplasia*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	No
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial	*Yes*

		No Not reported	
Was matching performed?		Yes Partial No Not reported	No
Summary of Result/s		*GDM, PE, PTB* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Not reported
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Partial
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*

	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No

OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Glueck 2004*
Study Citation	Glueck, C. J.; Bornovali, S.; Pranikoff, J.; et al. (2004): Metformin, pre-eclampsia, and pregnancy outcomes in women with polycystic ovary syndrome. Diabet Med 21, 8, 829-836
Study Country	*USA*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam*
N per group	***PCOS: 97*** ***Non-PCOS: 252***

Setting	**The Jewish hospital for PCOS and a suburban community practice of obstetrics for Controls**	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS- Healthy women not known to have PCOS, with ≥ 1 live birth, consecutively delivered in a suburban-urban community practice*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*GDM, PE, PTB, BW, Macrosomia*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes- All PCOS were on Metformin for getting pregnant and continued during pregnancy; received dietary advice; Preconception DM2 in PCOS 2/90 (2.2%) and in controls 1/252 (0.4%);*
Exclusion criteria reported?	Yes Partial No Not reported	Yes - *Serum creatinine > 1.5 mg/dl, Type 1 DM, pituitary insufficiency, persistent hyperprolactinaemia, and congenital adrenal hyperplasia*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	*No*
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No	Yes

		Not reported	
Were the outcomes measured appropriate?		Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Yes*
Was matching performed?		Yes Partial No Not reported	No
Summary of Result/s		*GDM, PE, PTB, BW, Macrosomia* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	No
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Not reported
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes

PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Weerakiet 2004*

Study Citation	Weerakiet, S.; Srisombut, C.; Rojanasakul, A.; et al. (2004): Prevalence of gestational diabetes mellitus and pregnancy outcomes in Asian women with polycystic ovary syndrome. Gynecological Endocrinology 19, 3, 134-140	
Study Country	*Thiland*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Homburg (menstrula irregularity, clinical hyperandrogenism such as acne, seborrhea and hirsutism, and bilaterla PCOM on US*	
N per group	***PCOS: 47*** ***Non-PCOS: 264***	
Setting	*Reproductive endocrinology and infertility unit*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS and normal menstruation*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*GWG, GDM, GH, PE, CS*	
Inclusion criteria reported?	Yes Partial No Not reported	Not reported
Exclusion criteria reported?	Yes Partial No Not reported	Yes - *Those who delivered elsewhere, did not receive antenatal care in the hospital or had miscarriage before 20 weeks of gestation*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*

Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial – Age matched, BMI higher in PCOS
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Partial
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Partial
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	Partial -Age matched, BMI higher in PCOS
Summary of Result/s	*GH,CS were higher in PCOS* *GWG, GDM, PE* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Not reported
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes	*Yes*

		Partial No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***

COMMENTS		
What is the overall risk of bias?	*Moderate*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*No*	

Study ID	*Sir-Petermann 2005*	
Study Citation	*Sir-Petermann, T.; Hitchsfeld, C.; Maliqueo, M.; et al. (2005): Birth weight in offspring of mothers with polycystic ovarian syndrome. Human Reproduction 20, 8, 2122-2126*	
Study Country	*Chile*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	***PCOS: 47*** ***Non-PCOS: 108***	
Setting	*The Unit of Endocrinology and Reproductive Medicine seeking infertility treatment for PCOS and the prenatal care unit for controls*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - Normal pregnant, regular menstrual cycles, No hirsutism and other manifestations of hyperandrogenism, no drug therapy*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*GWG, GDM, PTB, BW, SGA, LGA*	
Inclusion criteria reported?	Yes Partial No Not reported	Yes - *Singleton pregnancies; Non-smoking and non-alcohol or drug abusing; All PCOS were anovulatory, 6 month diet and exercise treatment program for PCOS; Normoglycaemic patients with and without clinical signs of hyperinsulinaemia (WHR .0.85), and with different grades of hyperinsulinaemia;*

Exclusion criteria reported?	Yes Partial No Not reported	Yes - *Smoking, Alcohol users, drug users; Hyperprolactinaemia, androgen-secreting neoplasm, Cushing's syndrome and attenuated 21-hydroxylase deficiency, thyroid disease*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes- Age, BMI and SES matched*
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial	*Yes- Age, BMI and SES matched*

		No Not reported	
Summary of Result/s		*GWG, GDM, SGA were higher in PCOS* *BW, LGA, PTB* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Not reported
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*

	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No
	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*

OTHER BIAS	**Was the study sufficiently powered to detect any differences between the groups?**	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*Moderate*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Al-Ojaimi 2006*
Study Citation	*Al-Ojaimi, E. H. (2006): Pregnancy outcomes after laparoscopic ovarian drilling in women with polycystic ovarian syndrome. Saudi Medical Journal 27, 4, 519-525*
Study Country	*Bahrain*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam*
N per group	***PCOS: 134*** ***Non-PCOS: 479***
Setting	*Hospital laparoscopic drilling centre for PCOS and routine booking clinic at the same department and the same period of time*
Intervention/ indicator	N/A

Comparison/ Control	*Non-PCOS - Normal menstrual cycles, no clinical signs of hyperandrogenism and were not receiving any drug therapy*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*GWG, GDM, GH, PE, PTB, BW, LBW, Macrosomia*	
Inclusion criteria reported?	Yes Partial No Not reported	Partial - *Laparascopic drilling for all PCOS*
Exclusion criteria reported?	Yes Partial No Not reported	Yes - *Medical diseases, multiple pregnancies, previous history of PIH, PE and GDM and whose pregnancies did not continue beyond 22 weeks of gestation. Those who delivered elsewhere or did not continue prenatal care at the hospital.*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial- Age similar, BMI higher in PCOS but stratification by BMI was performed
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Yes
Were the outcomes measured appropriate?	Yes Partial	*Yes*

		No Not reported	
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Yes*
Was matching performed?		Yes Partial No Not reported	No
Summary of Result/s		*GDM, GH, PE were higher in PCOS* *GWG, PTB, BW, LBW, Macrosomia* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Not reported
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- *Hospital laparoscopic drilling centre*
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*

DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*

CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Dokras 2006*
Study Citation	Dokras, A.; Baredziak, L.; Blaine, J.; et al. (2006): Obstetric outcomes after in vitro fertilization in obese and morbidly obese women. Obstet Gynecol 108, 1, 61-69
Study Country	*USA*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*

PCOS diagnostic criteria	*NIH*	
N per group	***PCOS: 46*** ***Non-PCOS: 108***	
Setting	*The infertility and in vitro fertilization (IVF) at the University of Iowa Hospitals and Clinics*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Miscarriage, GDM, PTB, CS*	
Inclusion criteria reported?	Yes Partial No Not reported	Partial - *First fresh conventional IVF or IVF with ICSI*
Exclusion criteria reported?	Yes Partial No Not reported	*Day 2 transfer cycles, cryopreserved embryo transfers, donor oocyte cycles, gamete intrafallopian transfer, and zygote intrafallopian transfer cycles, age≥38*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial – Similar age and limited to <38 years and BMI stratification
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Partial

If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?		Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Yes*
Was matching performed?		Yes Partial No Not reported	No
Summary of Result/s		*GDM was higher in PCOS and obesity* *Miscarriage, PTB, CS* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No	Yes

		Not reported	
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Similar age and limited to <38 years and BMI stratification
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*Low*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Kovo 2006*	
Study Citation	Kovo, M.; Weissman, A.; Gur, D.; et al. (2006): Neonatal outcome in polycystic ovarian syndrome patients treated with metformin during pregnancy. J Matern Fetal Neonatal Med 19, 7, 415-419.	
Study Country	*Israel*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	***PCOS: 33*** ***Non-PCOS: 66***	
Setting	*Edith Wolfson Medical Center*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*BMI, GDM, GH, PTB, BW, CS*	
Inclusion criteria reported?	Yes Partial No Not reported	Yes - Only those with glucose/insulin ration<4.5 (Insulin resistant); All PCOS were on Metformin 1-6 months prior to pregnancy till the end of first trimester
Exclusion criteria reported?	Yes Partial No Not reported	Yes - *Chronic diseases such as DM1&2, HTN, Renal disease, Epilepsy, those with chronic pharmacotherapy*
Does the study have a clearly focused question?	Yes Partial No Not reported	Yes

Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Yes
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	Yes - Age, mode of conception, number of foetuses and gestational age at delivery matched
Summary of Result/s	*GDM, GH were higher in PCOS.* *BMI, PTB, BW, CS* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre and all insulin resistant
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes	*Yes*

		Partial No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes - Age, mode of conception, number of foetuses and gestational age at delivery matched; BMI similar
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***

COMMENTS		
What is the overall risk of bias?	*Low*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*No*	

Study ID	*Hu 2007*	
Study Citation	Hu, S.; Leonard, A.; Seifalian, A.; et al. (2007): Vascular dysfunction during pregnancy in women with polycystic ovary syndrome. Human Reproduction 22, 6, 1532-1539.	
Study Country	*UK*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	***PCOS: 22*** ***Non-PCOS: 22***	
Setting	*The antenatal and gynaecology clinics at the Royal Free Hospital*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - healthy pregnant women with no PCOS symptoms*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*GH, PE, EC, BW*	
Inclusion criteria reported?	Yes Partial No Not reported	Yes - *Spontaneous singleton pregnancies*
Exclusion criteria reported?	Yes Partial	Yes - *Metformin treatment, gonadotrophin treatment, in vitro fertilization procedures, a history of diabetes, smoking, drug/alcohol abuse,chronic hypertension or respiratory, cardiovascular, renal or thyroid disease*

	No Not reported	
Does the study have a clearly focused question?	Yes Partial No Not reported	Yes
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Yes
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	Yes – Age, BMI at 11–13 week gestation, ethnicity and parity matched

Summary of Result/s		*GH, PE were higher in PCOS* *BW was lower in PCOS* *EC* was similar in PCOS and Non-PCOS (n=0/group).	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Yes
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a	Yes Partial	*Yes*

	standard, valid and reliable way?	No Not reported	
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes – Age, BMI at 11–13 week gestation, ethnicity and parity matched
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*

	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*Low*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Palep-Singh 2007*	
Study Citation	Palep-Singh, M.; Picton, H. M.; Vrotsou, K.; et al. (2007): South Asian women with polycystic ovary syndrome exhibit greater sensitivity to gonadotropin stimulation with reduced fertilization and ongoing pregnancy rates than their Caucasian counterparts. Eur J Obstet Gynecol Reprod Biol 134, 2, 202-207.	
Study Country	*UK*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	***PCOS: 324*** ***Non-PCOS: 284***	
Setting	*IVF/ICSI centre*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - Infertility due to tubal factor*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Miscarriage*	
Inclusion criteria reported?	Yes Partial No Not reported	Not reported
Exclusion criteria reported?	Yes Partial No Not reported	Not reported
Does the study have a clearly focused question?	Yes Partial No Not reported	Yes

Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial- stratification by ethnicity
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Not reported
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Not reported
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	No
Summary of Result/s	*Miscarriage was higher in PCOS*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes	*Yes*

		Partial No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Partial – Ethnicity was stratified, Age similar but BMI higher in PCOS
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***

COMMENTS		
What is the overall risk of bias?	*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*No*	

Study ID	*Sir-Petermann 2007*	
Study Citation	Sir-Petermann, T.; Echiburu, B.; Maliqueo, M. M.; et al. (2007): Serum adiponectin and lipid concentrations in pregnant women with polycystic ovary syndrome. Human Reproduction 22, 7, 1830-1836.	
Study Country	*Chile*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	***PCOS: 48*** ***Non-PCOS: 51***	
Setting	*The Unit of Endocrinology and Reproductive Medicine for PCOS and the antenatal care unit of the same hospital for Controls*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - Normal pregnant women with singleton pregnancies, had a history of regular menstrual cycles, No hirsutism and other manifestations of hyperandrogenism, No galactorrhoea and thyroid dysfunction. Healthy and not receiving any drug therapy*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*GDM, GH*	
Inclusion criteria reported?	Yes Partial No Not reported	Yes - Singleton pregnancies; All women with PCOS were anovulatory, All received diet and exercise program and 45/48 women were taking metformin but stopped using either with a positive pregnancy test or before 12 weeks of gestation. Non-smoking and non-alcohol or drug abusing. No preterm delivery in current pregnancy. Preconception inclusion criteria - chronic oligomenorrhoea or amenorrhoea, hirsutism, serum testosterone concentration >0.6 ng/ml and/or free androgen index >5.0,

		androstenedione concentration >3.0ng/ml and a characteristic ovarian pathology on ultrasound based on criteria described by Adams et al. Normoglycaemic patients with and without clinical signs of hyperinsulinaemia (waist-hip ratio>0.85) and different grades of hyperinsulaemia evaluated by OGTT were included
Exclusion criteria reported?	Yes Partial No Not reported	Yes - *Hyperprolactinaemia, androgen-secreting neoplasm, Cushing's syndrome and late-onset 21-hydroxylase deficiency and thyroid disease*
Does the study have a clearly focused question?	Yes Partial No Not reported	Yes
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Yes
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No	*Yes*

		Not reported	
Was matching performed?		Yes Partial No Not reported	Partial- similar age, and SES
Summary of Result/s		*GDM was higher in PCOS and obesity* GH was similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*

	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Partial- similar age, and SES but BMI higher in PCOS

OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*Moderate*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Beydoun 2009*
Study Citation	Beydoun, H. A.; Stadtmauer, L.; Zhao, Y.; et al. (2009): Impact of polycystic ovary syndrome on selected indicators of in vitro fertilization and intracytoplasmic sperm injection treatment success. J Womens Health (Larchmt) 18, 5, 717-723.
Study Country	*USA*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*NIH*
N per group	***PCOS: 69*** ***Non-PCOS: 69***
Setting	*Analyses of existing records probably from an infertility treatment Centre*
Intervention/ indicator	N/A

Comparison/ Control	*Non-PCOS - underwent IVF/ICSI*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Miscarriage*	
Inclusion criteria reported?	Yes Partial No Not reported	Partial - For PCOS: having at least 1 visit in the fertility centre, at least one IVF/ICSI cycle over the considered time. For Controls: an IVF=ICSI cycle at the fertility centre within the same time period
Exclusion criteria reported?	Yes Partial No Not reported	Yes - *Age<18 or>45 years, Only experiment type of treatment such as preimplantation genetic diagnosis (PGD), and testicular sperm aspiration (TESA), Unknown type of IVF/ICSI*
Does the study have a clearly focused question?	Yes Partial No Not reported	Yes
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial – Age and date of IVF/ICSI similar but BMI higher in PCOS
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Partial
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	No- Age and date of IVF/ICSI similar but BMI higher in PCOS
Summary of Result/s	*Miscarriage was* similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No- Age and date of IVF/ICSI similar but BMI higher in PCOS at treatment; not clear at those who conceived
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Gupta 2009*
Study Citation	Gupta, A.; Raina, K.; Kalkkar, T.; et al. (2009): Pregnancy outcome in women with the polycystic ovarian syndrome. JK Science 11, 2, 82-84
Study Country	*India*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam*
N per group	***PCOS: 56*** ***Non-PCOS: 56***
Setting	*Suvidha Mother and Child Nursing Home*
Intervention/ indicator	N/A

Comparison/ Control	*Non-PCOS - Those who had undergone US at the same department*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*GDM, GH*	
Inclusion criteria reported?	Yes Partial No Not reported	Not reported
Exclusion criteria reported?	Yes Partial No Not reported	Not reported
Does the study have a clearly focused question?	Yes Partial No Not reported	Yes
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Yes
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Partial - Age and weight matched groups
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Not reported
Were the outcomes measured appropriate?	Yes Partial No Not reported	Not reported
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	Yes - Age and weight matched groups
Summary of Result/s	GDM and GH were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Yes
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Age and weight matched
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*Low*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Maliqueo 2009*
Study Citation	Maliqueo, M.; Echiburu, B.; Crisosto, N.; et al. (2009): Metabolic parameters in cord blood of newborns of women with polycystic ovary syndrome. Fertil Steril 92, 1, 277-282
Study Country	*Chile*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam*
N per group	***PCOS: 30*** ***Non-PCOS: 34***
Setting	*The Unit of Endocrinology and Reproductive Medicine for PCOS (Women with PCOS who were seeking infertility treatment); the antenatal care unit of our hospital for Controls*

Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - Healthy women with a history of regular menstrual cycles, No hirsutism and other manifestations of hyperandrogenism, and No galactorrhea and thyroids function; not receiving any drug therapy.*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*BMI, GWG, BW, SGA, LGA*	
Inclusion criteria reported?	Yes Partial No Not reported	Yes - Women with PCOS were on a 6-month diet and exercise prior to pregnancy; All PCOS were anovulatory; Non smoking and non-alcohol- or non-drug-abusing PCOS and Controls
Exclusion criteria reported?	Yes Partial No Not reported	Yes - *Hyperprolactinemia, androgen-secreting neoplasm, Cushing's syndrome, and late-onset 21-hydroxylase deficiency and thyroid disease. GDM, PIH and PTB; Term and singleton pregnancies; Children with malformations or genetic disorders*
Does the study have a clearly focused question?	Yes Partial No Not reported	Yes
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial – Similar SES and age but higher BMI in PCOS.
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	No
Summary of Result/s	*BMI was higher in PCOS* *GWG, BW, SGA, LGA* were similar in PCOS and Non-PCOS.	

INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*Moderate*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Falbo 2010*
Study Citation	Falbo, A.; Rocca, M.; Russo, T.; et al. (2010): Changes in androgens and insulin sensitivity indexes throughout pregnancy in women with polycystic ovary syndrome (PCOS): Relationships with adverse outcomes. Journal of Ovarian Research 3 (1) (no pagination), 23.
Study Country	*Italy*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam*
N per group	***PCOS: 45*** ***Non-PCOS: 42***
Setting	*the Department of Obstetrics and Gynecology of the University*

Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*BMI, GH, PE, BW*	
Inclusion criteria reported?	Yes Partial No Not reported	Yes - All PCOS women were ovulatory; both groups were primigravidas
Exclusion criteria reported?	Yes Partial No Not reported	Yes - Age > 35 years, BMI>30 kg/m2, multiple pregnancies, GA>7 weeks by US, pre-malignancies or malignancies, medical conditions, smoking, drug/alcohol use, organic pelvic disease, uterine malformations, previous pelvic surgery, no compliance to our study-protocol, and current or previous (within the last six months) use of any hormonal and/or anti-diabetic and/or fertility drugs
Does the study have a clearly focused question?	Yes Partial No Not reported	Yes
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Yes
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	*Yes – Age and BMI matched*
Summary of Result/s	*BW was lower in PCOS* *GH, PE were higher in PCOS and obesity*	

		BMI was similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Yes
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*Low*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Li 2010*
Study Citation	Li, G.; Fan, L.; Zhang, L.; et al. (2010): Metabolic parameters and perinatal outcomes of gestational diabetes mellitus in women with polycystic ovary syndrome.[Erratum appears in J Perinat Med. 2010 May;38(3):343]. Journal of Perinatal Medicine 38, 2, 141-146.
Study Country	*China*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam*
N per group	***PCOS: 34*** ***Non-PCOS: 70***
Setting	*Beijing Obstetrics and Gynecology Hospital*

Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*PE, PTB, BW, SGA, Macrosomia, LGA*	
Inclusion criteria reported?	Yes Partial No Not reported	Yes - All PCOS and Controls had GDM with singleton pregnancies; All GDM women received medical nutrition therapy and individualized exercise guide.
Exclusion criteria reported?	Yes Partial No Not reported	Yes - Pre-pregnancy DM, HTN, cardiovascular disease, renal diseases or multiple pregnancies; Hyperprolactinemia, androgen-secreting neoplasm, Cushing's syndrome, and late-onset 21-hydroxylase deficiency, Thyroid disease.
Does the study have a clearly focused question?	Yes Partial No Not reported	Yes
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial – Age similar and all with GDM but BMI higher in PCOS
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	No
Summary of Result/s	*PE, PTB, BW, SGA, Macrosomia, LGA* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- had GDM
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Partial
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*Moderate*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Palomba 2010*
Study Citation	Palomba, S.; Falbo, A.; Russo, T.; et al. (2010): Pregnancy in women with polycystic ovary syndrome: the effect of different phenotypes and features on obstetric and neonatal outcomes. Fertil Steril 94, 5, 1805-1811
Study Country	*Italy*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam*
N per group	***PCOS: 97*** ***Non-PCOS: 73***
Setting	*Hospital (the Department of Obstetrics and Gynaecology)*

Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - Regular menstrual cycles (26–32days in length), no signs of clinical hyperandrogenism, normal range of serum androgens levels, no PCOM on transvaginal ultrasonography (TVUS), and no known male or tubal infertility factors*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Miscarriage, GDM, GH, PE, PTB, SGA, LGA, Instrumental delivery*	
Inclusion criteria reported?	Yes Partial No Not reported	Partial - Primigravidas
Exclusion criteria reported?	Yes Partial No Not reported	Yes - Age >35 years; BMI>30; multiple pregnancies; GA>7 weeks; premalignancies or malignancies; major medical conditions or other concurrent medical illnesses affecting the health status; smoking; drug/alcohol use; organic pelvic disease; previous pelvic surgery; patients who were not compliant; and current or previous (within the past 6 months) use of any hormonal or antidiabetic drugs; pevious treatments with fertility drugs; women who intended to start a diet or a specific program of physical activity
Does the study have a clearly focused question?	Yes Partial No Not reported	Yes
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Yes
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No	No

		Not reported	
Summary of Result/s		*Miscarriage, GDM, GH, PE, PTB, SGA, LGA were higher in PCOS* *Instrumental delivery was* similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Yes
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	

	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Partial – Similar age, BMI and WHR
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*Moderate*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Palomba 2010*
Study Citation	*Palomba, S.; Falbo, A.; Russo, T.; et al. (2010): Uterine blood flow in pregnant patients with polycystic ovary syndrome: relationships with clinical outcomes. Bjog 117, 6, 711-721.*
Study Country	*Italy*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam*

N per group	***PCOS: 73*** ***Non-PCOS: 73***	
Setting	*Two academic Departments of Obstetrics and Gynaecology*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - Healthy primigravidas; regular menstrual cycles, no signs of clinical/ Biochemical hyperandrogenism, No PCOM*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Miscarriage, GDM, GH, PE, PTB, IUGR, SGA, LGA, Instrumental delivery, CS*	
Inclusion criteria reported?	Yes Partial No Not reported	Yes - Primigravida; Ovulatory phenotypes of PCOS;
Exclusion criteria reported?	Yes Partial No Not reported	Yes - Non-ovulatory phenotypes of PCOS; Age >35; BMI > 30; multiple pregnancy; gestational age> 7 weeks; premalignancies or malignancies; medical conditions or other concurrent medical illnesses; smoking; drug/alcohol use; organic pelvic disease; uterine malformations; previous pelvic surgery; women noncompliant with our study protocol; and current or previous (within the last 6 months) use of any hormonal and/or antidiabetic drugs. Previous infertility treatments; Those who intended to start a diet or a specific program of physical activity.
Does the study have a clearly focused question?	Yes Partial No Not reported	Yes
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Yes- Age and BMI matched
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*

Was matching performed?		Yes Partial No Not reported	Yes- Age and BMI matched
Summary of Result/s		*Miscarriage, GDM, GH, PE, SGA, LGA, Instrumental delivery, CS were higher in PCOS and obesity* *PTB, IUGR* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Yes
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study**	0	

	were lost to follow up?		
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes- Age and BMI matched
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*Low*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*De Leo 2011*
Study Citation	*De Leo, V.; Musacchio, M. C.; Piomboni, P.; et al. (2011): The administration of metformin during pregnancy reduces polycystic ovary syndrome related gestational complications. Eur J Obstet Gynecol Reprod Biol 157, 1, 63-66.*
Study Country	*Italy*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	

Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	***PCOS: 98*** ***Non-PCOS: 110***	
Setting	*The infertility and in vitro fertilization (IVF) unit for PCOS and Low-risk antenatal clinic for Controls;*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - healthy*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Miscarriage, GDM, GH, PE, PTB, BW*	
Inclusion criteria reported?	Yes Partial No Not reported	Yes - *All PCOS patients with hyperinsulinemia, All treated with metformin 3-4 months prior to infertility treatment until 37 weeks of gestation,*
Exclusion criteria reported?	Yes Partial No Not reported	Not reported
Does the study have a clearly focused question?	Yes Partial No Not reported	Yes
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	No – *hyperinsulinemic PCOS but normal controls*
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*No*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*

Was matching performed?		Yes Partial No Not reported	No
Summary of Result/s		*Miscarriage, GDM, GH, PTB were higher in PCOS* *PE, BW* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	No
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- Hyperinsulinemic
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study**	0	

	were lost to follow up?		
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Dmitrovic 2011*	
Study Citation	*Dmitrovic, R.; Katcher, H. I.; Kunselman, A. R.; et al. (2011): Continuous glucose monitoring during pregnancy in women with polycystic ovary syndrome. Obstet Gynecol 118, 4, 878-885*	
Study Country	*USA*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*chronic oligo/anovulation and the presence of hyperandrogenemia*	
N per group	***PCOS: 17*** ***Non-PCOS: 17***	
Setting	*Not stated for PCOS, Control group were volunteers recruited through advertisements or referrals*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - Normal menstrual cycles before pregnancy and an absence of hirsutism and other manifestations of hyperandrogenism.*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*BMI, GDM, PTB, BW, SGA, LGA*	
Inclusion criteria reported?	Yes Partial No Not reported	Partial - Singleton pregnancies
Exclusion criteria reported?	Yes Partial No Not reported	Yes - DM2, family history of DM2,taking medication to treat DM2 such as metformin
Does the study have a clearly focused question?	Yes Partial No Not reported	Yes
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial - Singleton pregnancies and similar age but higher BMI in PCOS
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Partial

Were the outcomes measured appropriate?		Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Yes*
Was matching performed?		Yes Partial No Not reported	No
Summary of Result/s		*BMI was higher in PCOS* *GDM, BW, PTB, SGA, LGA* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	No
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Not reported
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*

	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	38%	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Partial
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Nejad 2011*

Study Citation	*Nejad, E. S.; Saedi, T.; Saedi, S.; et al. (2011): Comparison of in vitro fertilisation success in patients with polycystic ovary syndrome and tubal factor. Gynecological Endocrinology 27, 2, 117-120*	
Study Country	*Iran*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	***PCOS: 164*** ***Non-PCOS: 161***	
Setting	*Royan Infertility Research Centre*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - Infertility caused by tubal factor diagnosed by hysterosalpingogram and laparoscopy*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Miscarriage*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - Age 22-35 years, BMI 19–30 kg/m2, primary infertility and no history of systemic disease, also women who had not responded to the previous medical treatment or intrauterine insemination and were candidate for first treatment cycle of IVF.*
Exclusion criteria reported?	Yes Partial No Not reported	Yes - *Endometriosis*
Does the study have a clearly focused question?	Yes Partial No Not reported	Yes
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	No
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial	*Yes*

		No Not reported	
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Yes*
Was matching performed?		Yes Partial No Not reported	No
Summary of Result/s		*Miscarriage was* similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No	*Yes*

		Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Nouh 2011*

Study Citation	*Nouh, A. A.; Shalaby, S. M. (2011): The predictive value of uterine blood flow in detecting the risk of adverse pregnancy outcome in patients with polycystic ovary syndrome. Middle East Fertility Society Journal 16, 4, 284-290*	
Study Country	*Egypt*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*PCOM+clinical/biochemicl HA without oligoanovulation*	
N per group	***PCOS: 40*** ***Non-PCOS: 40***	
Setting	*The Obstetrics and Gynecology and Medical Biochemistry departments*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - Regular menstrual cycles, no clinical/biochemical signs of hyperandrogenism, no PCOM*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Miscarriage, GDM, GH, PE, PTB, SGA, LGA, CS*	
Inclusion criteria reported?	Yes Partial No Not reported	Yes - Ovulatory PCOS; All primigravidas
Exclusion criteria reported?	Yes Partial No Not reported	Yes - Age >35 years; BMI≥30 kg/m2, previous infertility treatments; multiple pregnancy; gestational age of >8 weeks; concurrent medical illnesses; smoking; drug use; organic pelvic disease; uterine malformations; previous pelvic surgery; current or previous (within the last 6 months) use of any hormonal and/or antidiabetic drugs.
Does the study have a clearly focused question?	Yes Partial No Not reported	Yes
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Yes- Age and BMI matched
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*

Were the outcomes measured appropriate?		Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Yes*
Was matching performed?		Yes Partial No Not reported	*Yes- Age and BMI matched*
Summary of Result/s		*SGA, CS were higher in PCOS* *Miscarriage, GDM, GH, PE, PTB, and LGA* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Yes
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*

	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*Low*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Mehrabian 2012*

Study Citation		
Study Country	*Iran*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*NIH*	
N per group	***PCOS: 40*** ***Non-PCOS: 40***	
Setting	*Hospital*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - singleton pregnancy, regular menstrual cycles; without hirsutism, other HA signs, galactorrhea, thyroid dysfunction,* *GDM, HTN and history of any chronic medication use*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*BMI, GWG, BW*	
Inclusion criteria reported?	Yes Partial No Not reported	Yes - *Mothers underwent elective CS*
Exclusion criteria reported?	Yes Partial No Not reported	Yes - *Hyperprolactinemia, androgen – secreting neoplasms, Cushing's syndrome and late-onset 21- hydroxylase deficiency and thyroid disease. Pre-term birth, malformation, genetic disorders*
Does the study have a clearly focused question?	Yes Partial No Not reported	Yes
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Yes- Age, BMI and SES matched
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No	*Yes*

		Not reported	
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Yes*
Was matching performed?		Yes Partial No Not reported	No
Summary of Result/s		*BW was lower in PCOS* *GWG was higher in PCOS* *BMI* was similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Yes
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial	*Yes*

		No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*Low*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Palomba 2012*

Study Citation	*Palomba, S.; Falbo, A.; Russo, T.; et al. (2012): The risk of a persistent glucose metabolism impairment after gestational diabetes mellitus is increased in patients with polycystic ovary syndrome. Diabetes Care 35, 4, 861-867*	
Study Country	*Italy*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	***PCOS: 42*** ***Non-PCOS: 84***	
Setting	*Hospital (Women who were suffering from hyperandrogenism and/or ovulatory disorders and seeking pregnancy*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - Regular menstrual cycles before pregnancy, no signs of clinical hyperandrogenism, normal ranges of serum androgen levels, and no PCO morphologies on transvaginal ultrasonography*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*BMI, GWG, GH, PE, PTB, BW, SGA, Macrosomia, LGA, IOL, Instrumental delivery, CS*	
Inclusion criteria reported?	Yes Partial No Not reported	Yes - *All participants (control and cases) were diagnosed with GDM*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes - Age >35 years, severe obesity, multiple pregnancies, a gestational age at the GDM diagnosis that was >28 or <24 weeks, medical conditions or other concurrent medical illnesses, a previous diagnosis of DM, cigarette smoking, drug/alcohol abuse, noncompliance with our study protocol, and a previous use of any antidiabetic drugs*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes- Age and BMI matched*
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*

Were the outcomes measured appropriate?		Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Yes*
Was matching performed?		Yes Partial No Not reported	*Yes- Age and BMI matched*
Summary of Result/s		*GH, PE and CS were higher in PCOS and obesity* *BMI, GWG, PTB, BW, SGA, Macrosomia, LGA, IOL, Instrumental delivery* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre + GDM
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*

	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	*Yes*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*Low*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Reyes-Munoz 2012*

Study Citation	*Reyes-Munoz, E.; Castellanos-Barroso, G.; Ramirez-Eugenio, B. Y.; et al. (2012): The risk of gestational diabetes mellitus among Mexican women with a history of infertility and polycystic ovary syndrome. Fertil Steril 97, 6, 1467-1471.*	
Study Country	*Mexico*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	***PCOS: 52*** ***Non-PCOS: 52***	
Setting	*Level three medical institution*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - Without a history of infertility and no PCOS and received prenatal care during the same period*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*BMI, GWG, Miscarriage, GDM, PE, PTB, BW, SGA, LGA*	
Inclusion criteria reported?	Yes Partial No Not reported	Yes -*Infertility for PCOS; Singleton pregnancies, ≤13 weeks of gestation, two-step screening for GDM, and prenatal care and resolution in the institute. If GDM was diagnosed, medical nutrition therapy, If did not work, Insulin therapy.*
Exclusion criteria reported?	Yes Partial No Not reported	Yes - FBS≥126 mg/dL at ≤13 weeks, pregestational DM and/or concomitant diseases, such as heart disease, kidney disease, chronic HTN, hypothyroidism, hyperthyroidism, asthma, epilepsy or autoimmune diseases.
Does the study have a clearly focused question?	Yes Partial No Not reported	Yes
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Yes- Age, BMI and parity were matched
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*

Were the outcomes measured appropriate?		Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Yes*
Was matching performed?		Yes Partial No Not reported	Yes- Age, BMI and parity were matched
Summary of Result/s		*GDM was higher in PCOS* *BMI, GWG, Miscarriage, PE, PTB, SGA, LGA, BW* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	No
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*

	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Partial – PCOS had infertility but non-PCOS did not have
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*Moderate*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Yamamoto 2012*

Study Citation	*Yamamoto, M.; Feigenbaum, S. L.; Crites, Y.; et al. (2012): Risk of preterm delivery in non-diabetic women with polycystic ovarian syndrome. Journal of Perinatology 32, 10, 770-776.*	
Study Country	*USA*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	***PCOS: 908*** ***Non-PCOS: 992***	
Setting	*Health care delivery system*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*PTB*	
Inclusion criteria reported?	Yes Partial No Not reported	Yes- Non-diabetic PCOS; Singleton pregnancies for both groups
Exclusion criteria reported?	Yes Partial No Not reported	Not reported
Does the study have a clearly focused question?	Yes Partial No Not reported	Yes
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial – Non-diabetics and singleton pregnancies but not report on age and BMI between the two groups
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*

Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Yes*
Was matching performed?		Yes Partial No Not reported	No
Summary of Result/s		*PTB was higher in PCOS*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Yes
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*

ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	*No*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*Moderate*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Boutzios 2013*
Study Citation	*Boutzios, G.; Livadas, S.; Piperi, C.; et al. (2013): Polycystic ovary syndrome offspring display increased oxidative stress markers comparable to gestational diabetes offspring. Fertil Steril 99, 3, 943-950*
Study Country	*Greece*

EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*NIH*	
N per group	***PCOS: 41*** ***Non-PCOS: 110***	
Setting	*Hospital (The 2nd Department of Obstetrics and Gynecology)*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - Healthy controls (Regular menstrual cycles, normal plasma androgen levels, and no acne or hirsutism before conception)*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*BMI, BW, SGA, LGA*	
Inclusion criteria reported?	Yes Partial No Not reported	Partial - *All had GDM,*
Exclusion criteria reported?	Yes Partial No Not reported	Yes - *Smoking, twin pregnancies, and pregnancy achieved through IVF techniques, concurrent medical complications known before or developed during pregnancy, such as diabetes mellitus type 1 or 2 and vascular and inflammatory diseases*
Does the study have a clearly focused question?	Yes Partial No Not reported	Yes
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial- Age and BMI were similar and multiple and post ART pregnancies excluded.
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No	*Yes*

		Not reported	
Was matching performed?		Yes Partial No Not reported	No
Summary of Result/s		*BMI, BW, SGA, LGA* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- all had GDM
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study**	0	

	were lost to follow up?		
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Partial
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*Moderate*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Wang 2013*
Study Citation	*Wang, Y.; Zhao, X.; Zhao, H.; et al. (2013): Risks for gestational diabetes mellitus and pregnancy-induced hypertension are increased in polycystic ovary syndrome. Biomed Res Int 2013, 182582*
Study Country	*China*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	

Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	***PCOS: 144*** ***Non-PCOS: 594***	
Setting	*The Obstetrics Department*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - selected by a computerized random number generator*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*BMI, Miscarriage, GDM, GH, PTB, IUGR, LGA*	
Inclusion criteria reported?	Yes Partial No Not reported	Partial - *Because the risk of DM is known to be increased in PCOS, preexisting DM was included. For those with GDM dietary guidance was provided; if not worked, Insulin therapy.*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes- Age>40 years, cardiomyopathy+cardiac insufficiency, active hepatitis, uncontrolled hyperthyroidism , active SLE, serious hematopathy, malignant tumors, serious trauma, smoking, drug/ alcohol use, organic pelvic disease, and pregnancy accompanied with acute abdominal disease; when over 50% of the data were incomplete;*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial- Age, BMI, SES, gravidity were similar
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Partial
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Partial
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*

Was matching performed?		Yes Partial No Not reported	No
Summary of Result/s		*Miscarriage, GDM, GH, PTB, IUGR were higher in PCOS* *BMI and LGA* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Yes
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Partial - DM2 was not excluded
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study**	0	

	were lost to follow up?		
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Partial
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes- Stratification based on conception method, age, BMI and GTT was done***
COMMENTS			
What is the overall risk of bias?		*Moderate*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Ashrafi 2014*	
Study Citation	*Ashrafi, M.; Sheikhan, F.; Arabipoor, A.; et al. (2014): Gestational diabetes mellitus risk factors in women with polycystic ovary syndrome (PCOS). Eur J Obstet Gynecol Reprod Biol 181, 195-199*	
Study Country	*Iran*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	***PCOS: 234*** ***Non-PCOS: 468***	
Setting	*Reproductive biomedicine research centre*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - 1.Non-PCOS+ART / 2. Non-PCOS+ No infertility history*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*BMI, GDM*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - Singleton pregnancies, ≤13 weeks of gestation, as well as two-step screening for GDM; ART treatment for groups 1 and 2 (PCOS and Non-PCOS*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes - Age≥40, BMI≥35 kg/m2, family history of diabetes in first degree relatives, pre-pregnancy DM, history of GDM, stillbirth, recurrent miscarriage, BW≥4 kg (macrosomia), parity>4, Cushing's syndrome, congenital adrenal hyperplasia, untreated (overt) hypothyroidism and hyperprolactinemia*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	No- Age and BMI higher in PCOS
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Partial

Were the outcomes measured appropriate?		Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Yes*
Was matching performed?		Yes Partial No Not reported	No
Summary of Result/s		BMI and GDM were *higher in PCOS*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*

	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Elkholi 2014*

Study Citation	*Elkholi, D. G. E. Y.; Nagy, H. M. (2014): The effects of adipocytokines on the endocrino-metabolic features and obstetric outcome in pregnant obese women with polycystic ovary syndrome. Middle East Fertility Society Journal 19, 4, 293-302.*	
Study Country	*Egypt*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	***PCOS: 200*** ***Non-PCOS: 200***	
Setting	*Infertility Clinic, Tanta University Hospitals*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - Pregnant patients attending the Outpatient Clinic*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*BMI, Miscarriage, GDM, GH, PE, PTB, IUGR, BW, Macrosomia, CS*	
Inclusion criteria reported?	Yes Partial No Not reported	*Partial - Obese (BMI≥30): 50% android obesity and 50% gynoid obesity*
Exclusion criteria reported?	Yes Partial No Not reported	Partial - *No kidney, liver or other endocrine diseases (pregestational diabetes mellitus, thyroid diseases and hyperprolactinemia), cardiovascular diseases, chronic hypertension and recent infections or inflammation.*
Does the study have a clearly focused question?	Yes Partial No Not reported	Yes
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Yes- Age, BMI and SES matched
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No	*Yes*

		Not reported	
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Yes*
Was matching performed?		Yes Partial No Not reported	Yes- Age, BMI and SES matched
Summary of Result/s		*GDM, GH, PE, PTB were higher in PCOS* *BMI, Miscarriage, IUGR, BW, Macrosomia, CS* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	No
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No	*Yes*

		Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes- Age, BMI and SES matched
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*Low*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Foroozanfard 2014*	
Study Citation	*Foroozanfard, F.; Moosavi, S. G.; Mansouri, F.; et al. (2014): Obstetric and Neonatal Outcome in PCOS with Gestational Diabetes Mellitus. J Family Reprod Health 8, 1, 7-12,*	
Study Country	*Iran*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	***PCOS: 130*** ***Non-PCOS: 131***	
Setting	*Shahbihkani Hospital*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*BMI, GH, PE, PTB, BW, Macrosomia, CS*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - GDM diagnosis, maternal age≤36 years and Iranian race*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes - Maternal age>36 years, a history of DM in a first-degree relative, pre-pregnancy weight>90 kg, parity>4, GDM in previous pregnancy, a previous abortion, a history of PTB or stillbirth, a recurrent abortion, smoking, neonate with a congenital malformation, a neonatal death, maternal disease (according to their health documentations and hormonal and sonography evidences), including congenital adrenal hyperplasia, malignant ovarian tumors, Cushing's syndrome, hypothyroidism, and hyperprolactinemia.*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial- Age, BMI and parity were similar
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes

If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Partial
Were the outcomes measured appropriate?		Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Yes*
Was matching performed?		Yes Partial No Not reported	No
Summary of Result/s		*PE, GH were higher in PCOS* *BMI, PTB, CS, BW, Macrosomia* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Yes
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*

	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Partial
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*Moderate*	
Did risk of bias differ by outcome *(eg. primary outcome*		*No*	

was low risk but rest were high)?	

Study ID	*Huang 2014*	
Study Citation	*Huang, K.; Dong, X.; Zhang, H.; et al. (2014): Effect of overweight/obesity on IVF-ET outcomes in chinese patients with polycystic ovary syndrome. International Journal of Clinical and Experimental Medicine 7, 12, 5872-5876,*	
Study Country	*China*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	***PCOS: 128*** ***Non-PCOS: 128***	
Setting	*IVF/ICSI center of Tongji Hospital*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - Tubal factor infertility diagnosed by hysterosalpingography combined with laparoscopy undergoing IVF/ICSI at the same period of time*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*BMI, Miscarriage*	
Inclusion criteria reported?	Yes Partial No Not reported	*Partial - Only the first cycle of IVF/ICSI of each patient*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes- Oocyte/sperm donation, in vitro maturation, preimplantation genetic diagnosis, testicular sperm aspiration, frozen embryo transfer, blastocyst transfer, patients with endometriosis/ metabolic diseases which may lead to abnormal BMI such as diabetes, and cycles not resulting in fresh embryo transfer.*
Does the study have a clearly focused question?	Yes Partial No Not reported	Yes
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial – Age matched but BMI higher in PCOS
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*

Were the outcomes measured appropriate?		Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Yes*
Was matching performed?		Yes Partial No Not reported	No- Age matched for infertile women; not for those who got pregnant later
Summary of Result/s		*Miscarriage was* similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*

	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes- BMI stratification***
COMMENTS			
What is the overall risk of bias?		*Moderate*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Lathi 2014*

Study Citation	*Lathi, R. B.; Dahan, M. H.; Reynolds-May, M. F.; et al. (2014): The role of serum testosterone in early pregnancy outcome: a comparison in women with and without polycystic ovary syndrome. J Obstet Gynaecol Can 36, 9, 811-816,*	
Study Country	*USA*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	***PCOS: 59*** ***Non-PCOS: 287***	
Setting	*Infertility treatment clinic*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*BMI, Miscarriage*	
Inclusion criteria reported?	Yes Partial No Not reported	*Not reported*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes -Thyroid dysfunction (TSH ≥ 2.5 mU/L), hyperprolactinemia on two samples (serum prolactin above the upper limit of normal for the assay used), ovarian or adrenal tumours, congenital adrenal hyperplasia, or hypothalamic amenorrhea. Uterine anomalies or intramural fibroids >3 cm in diameter; Women who conceived after oocyte donation or frozen embryo transfer and women with multiple gestations.*
Does the study have a clearly focused question?	Yes Partial No Not reported	Yes
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial – Age and BMI similar
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Partial
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*

Were the outcomes measured appropriate?		Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Yes*
Was matching performed?		Yes Partial No Not reported	No
Summary of Result/s		*Miscarriage was higher in PCOS* BMI was similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*

	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Partial – Age and BMI similar
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*Moderate*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Li 2014*

Study Citation	Li, H. W.; Lee, V. C.; Lau, E. Y.; et al. (2014): Cumulative live-birth rate in women with polycystic ovary syndrome or isolated polycystic ovaries undergoing in-vitro fertilisation treatment. J Assist Reprod Genet 31, 2, 205-211.	
Study Country	*China*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	***PCOS: 104*** ***Non-PCOS: 751***	
Setting	*IVF centre*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - Isolated PCOM, With regular menstrual cycles; Without Hyperandrogenism*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Miscarriage*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - Only women who were undergoing their first treatment cycle were included. None of the PCOS and Controls were treated with Metformin*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes - Cycles carried out for pre-implantation genetic diagnosis and those using donor oocytes; Those who still had frozen embryos not replaced by the time of study.*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial – Age matched but BMI higher in PCOS
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Partial
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No	Partial- Self-report by post/call

		Not reported	
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Yes*
Was matching performed?		Yes Partial No Not reported	Partial – Age matched
Summary of Result/s		*Miscarriage was higher in PCOS*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*No*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*

ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Liu 2014*
Study Citation	*Liu, L.; Tong, X.; Jiang, L.; et al. (2014): A comparison of the miscarriage rate between women with and without polycystic ovarian syndrome undergoing IVF treatment. Eur J Obstet Gynecol Reprod Biol 176, 178-182*
Study Country	*China*

EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	***PCOS: 301*** ***Non-PCOS: 3591***	
Setting	*IVF centre*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - IVF due to tubal factor, male factor, endometriosis, and unexplained infertility*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Miscarriage*	
Inclusion criteria reported?	Yes Partial No Not reported	Partial - Only the first pregnancy arising from IVF treatment
Exclusion criteria reported?	Yes Partial No Not reported	
Does the study have a clearly focused question?	Yes Partial No Not reported	
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No	*Yes*

		Not reported	
Was matching performed?		Yes Partial No Not reported	No
Summary of Result/s		*Miscarriage was* similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study**	0	

	were lost to follow up?		
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Partial- Age similar and BMI not reported
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Naver 2014*
Study Citation	*Naver, K. V.; Grinsted, J.; Larsen, S. O.; et al. (2014): Increased risk of preterm delivery and pre-eclampsia in women with polycystic ovary syndrome and hyperandrogenaemia. Bjog 121, 5, 575-581.*
Study Country	*Denmark*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	

Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	***PCOS: 459*** ***Non-PCOS: 5409***	
Setting	*The private fertility clinic*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - based on ICD-10 from a birth cohort including all singleton deliveries from the year*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*GDM, GH, PE, PTB, BW, SGA, LGA, IOL, CS*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - Singleton pregnancies*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes - Type–I or type–II diabetes prior to pregnancy*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Not reported -Age and BMI were not reported
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Partial
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*

Was matching performed?		Yes Partial No Not reported	No
Summary of Result/s		*GDM, PE, PTB were higher in PCOS* *GH, BW, SGA, LGA, IOL, CS* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	No
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Partial
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study**	0	

	were lost to follow up?		
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Palomba 2014*
Study Citation	Palomba, S.; Falbo, A.; Chiossi, G.; et al. (2014): Lipid profile in nonobese pregnant women with polycystic ovary syndrome: a prospective controlled clinical study. Steroids 88, 36-43.
Study Country	*Italy*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*

PCOS diagnostic criteria	*Rotterdam*	
N per group	***PCOS: 150*** ***Non-PCOS: 150***	
Setting	*The Academic Department of Obstetrics and Gynaecology of the Pugliese-Ciaccio Hospital*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - Ruling out PCOS symptoms*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*BMI, Miscarriage, GDM, GH, PE, BW, SGA, LGA*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - Primigravidas with PCOS and healthy controls at less than 7 weeks' gestation*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes - age>35, BMI>30 kg/m2, pre-malignancies or malignancies, major medical illnesses (including CVD, DM2,..), hematological disease (including anemia, thalassemia,..), smoking, drug or alcohol use, use of any metabolic and/or hormonal and/or other lipid altering drugs at the time of enrollment and/or in the preceding three months (only gonadotropins or CC for ovulation induction were permitted), multiple pregnancy, and non compliance to the study protocol.*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes- Age and BMI matched*
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*

Was matching performed?		Yes Partial No Not reported	*Yes- Age and BMI matched*
Summary of Result/s		*BW was lower in PCOS* *Miscarriage, GDM, GH, PE, SGA were higher in PCOS* *BMI* and *LGA* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Yes
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study**	0	

	were lost to follow up?		
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	*Yes- Age and BMI matched*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*Low*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Palomba 2014*	
Study Citation	Palomba, S.; Falbo, A.; Chiossi, G.; et al. (2014): Low-grade chronic inflammation in pregnant women with polycystic ovary syndrome: a prospective controlled clinical study. J Clin Endocrinol Metab 99, 8, 2942-2951.	
Study Country	*Italy*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	***PCOS: 150*** ***Non-PCOS: 150***	
Setting	*The Academic Department of Obstetrics and Gynaecology of the Pugliese-Ciaccio Hospital*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - Ruling out PCOS symptoms*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*BMI, Miscarriage, GDM, GH, PE, PTB, IUGR, BW, SGA, LGA, Instrumental delivery, CS*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - Primigravidas with PCOS and healthy controls at less than 7 weeks' gestation*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes - age>35, BMI>30 kg/m2, pre-malignancies or malignancies, major medical illnesses (including CVD, DM2,..), hematological disease (including anemia, thalassemia,..), smoking, drug or alcohol use, use of any metabolic and/or hormonal and/or other lipid altering drugs at the time of enrollment and/or in the preceding three months (only gonadotropins or CC for ovulation induction were permitted), multiple pregnancy, and non compliance to the study protocol.*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes- Age and BMI matched*
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes

If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?		Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Yes*
Was matching performed?		Yes Partial No Not reported	*Yes- Age and BMI matched*
Summary of Result/s		*BW was lower in PCOS* *Miscarriage, GDM, GH, PE, SGA were higher in PCOS* *BMI, IUGR,* PTB, *LGA, Instrumental delivery and CS* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Yes
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*

	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	*Yes- Age and BMI matched*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*Low*	
Did risk of bias differ by outcome *(eg. primary outcome*		*No*	

was low risk but rest were high)?	

Study ID	*Zhang 2014*	
Study Citation	*Zhang, C. M.; Zhao, Y.; Li, R.; et al. (2014): Metabolic heterogeneity of follicular amino acids in polycystic ovary syndrome is affected by obesity and related to pregnancy outcome. BMC Pregnancy Childbirth 14, 11.*	
Study Country	*China*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	***PCOS: 27*** ***Non-PCOS: 27***	
Setting	*The Division of Reproductive Centre*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - Infertility due to male or tubal factor*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*BMI, Miscarriage*	
Inclusion criteria reported?	Yes Partial No Not reported	*Partial - All patients received IVF*
Exclusion criteria reported?	Yes Partial No Not reported	*Partial - Any hormonal treatment or insulin-lowering agent during the last 3 months*
Does the study have a clearly focused question?	Yes Partial No Not reported	Yes
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial – Age and BMI similar at preconception but unclear in those who conceived
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes

If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?		Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Yes*
Was matching performed?		Yes Partial No Not reported	No
Summary of Result/s		BMI and Miscarriage were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a	Yes Partial	*Yes*

	standard, valid and reliable way?	No Not reported	
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Kollmann 2015*	
Study Citation	Kollmann, M.; Klaritsch, P.; Martins, W. P.; et al. (2015): Maternal and neonatal outcomes in pregnant women with PCOS: comparison of different diagnostic definitions. Human Reproduction 30, 10, 2396-2403.	
Study Country	*Austria*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	***PCOS: 177*** ***Non-PCOS: 708***	
Setting	*The local perinatal database and the medical documentation system or patient file of the Medical University of Graz*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS -Without pregestational diabetes or pregestational hypertension*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*GDM, GH, PE, PTB, SGA, LGA, Instrumental delivery, CS*	
Inclusion criteria reported?	Yes Partial No Not reported	*Primiparous with singletone pregnancies & giving birth to neonates ≥500 g. Pre-gestational Dm2: Full blown+Non-PCO PCOS: 29/84 Ovulatory PCOS: 5/14 Nonhyperandrogenic PCOS: 11/78 Controls:NA Pre-gestational HTN: Full blown+Non-PCO PCOS: 5/84 Ovulatory PCOS: 3/14 Nonhyperandrogenic PCOS: 4/78 Controls:NA*
Exclusion criteria reported?	Yes Partial No Not reported	*Miscarriage, Multiple pregnancy, Secondary pregnancy*
Does the study have a clearly focused question?	Yes Partial No Not reported	Yes
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial – Similar age but higher BMI in PCOS
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No	Yes

		Not reported	
Were the outcomes measured appropriate?		Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Yes*
Was matching performed?		Yes Partial No Not reported	No
Summary of Result/s		*GDM, GH, Instrumental delivery, CS were higher in PCOS* *PE, PTB, SGA, LGA,* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Yes
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*

	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Partial – Similar age but higher BMI in PCOS
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*Moderate*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Koster 2015*

Study Citation	Koster, M. P.; de Wilde, M. A.; Veltman-Verhulst, S. M.; et al. (2015): Placental characteristics in women with polycystic ovary syndrome. Human Reproduction 30, 12, 2829-2837	
Study Country	*Netherlands*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	***PCOS: 73*** ***Non-PCOS: 209***	
Setting	*A subset of the CoPPer study (Complications of PCOS Pregnancy: Evaluating risk) for PCOS*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - Delivery at term, after an uncomplicated pregnancy, spontaneous onset of labour or benign indication for a primary CS*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*GDM, GH, BW, SGA, LGA, IOL, CS*	
Inclusion criteria reported?	Yes Partial No Not reported	*Partial - Singleton neonate*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes -Women <18 years or >45 years, with a language barrier, with pre-existing DM*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial – Age similar but BMI unavailable in Non-PCOS
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No	*Yes*

		Not reported	
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Yes*
Was matching performed?		Yes Partial No Not reported	No
Summary of Result/s		*CS was lower in PCOS* *GDM, GH, IOL was higher in PCOS* *BW, SGA, LGA* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Yes
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial	*Yes*

		No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Partial – Age similar but BMI unavailable in Non-PCOS
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Mumm 2015*

Study Citation	Mumm, H.; Jensen, D. M.; Sorensen, J. A.; et al. (2015): Hyperandrogenism and phenotypes of polycystic ovary syndrome are not associated with differences in obstetric outcomes. Acta Obstetricia et Gynecologica Scandinavica 94, 2, 204-211.	
Study Country	*Denmark*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	***PCOS: 157*** ***Non-PCOS: 1037***	
Setting	*Odense University Hospital*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - Retrospective from a community control from another city's registry, Non-PCOS/ hirsutism*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*GDM, GH, PE, PTB, SGA, LGA, IOL, Instrumental delivery, CS*	
Inclusion criteria reported?	Yes Partial No Not reported	*Partial - The first singleton pregnancies*
Exclusion criteria reported?	Yes Partial No Not reported	*Partial - Not attending for the measurement of hormonal or metabolic parameters at time of evaluation, serious endocrine diseases, non-classic adrenogenital syndrome.*
Does the study have a clearly focused question?	Yes Partial No Not reported	Yes
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial – Age similar but BMI higher in PCOS
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Partial
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial	*Yes*

		No Not reported	
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Yes*
Was matching performed?		Yes Partial No Not reported	No
Summary of Result/s		*GDM, IOL was higher in PCOS* *GH, PE, PTB, SGA, LGA, Instrumental delivery, CS* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	No
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Yes
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial	*Yes*

		No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Sawada 2015*

Study Citation	Sawada, M.; Masuyama, H.; Hayata, K.; et al. (2015): Pregnancy complications and glucose intolerance in women with polycystic ovary syndrome. Endocr J 62, 11, 1017-1023.	
Study Country	*Japan*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*1) cycle irregularities, 2) polycystic changes in the ovary on US and 3) endocrine anomalies (LH or hyperandrogenism)*	
N per group	***PCOS: 49*** ***Non-PCOS: 49***	
Setting	*Department of Obstetrics and Gynaecology*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS* - Healthy pregnant women *with normal pregnancies*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*BMI, GDM, GH, PTB, IUGR, BW, CS*	
Inclusion criteria reported?	Yes Partial No Not reported	*Not reported*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes - Pre-existing renal disorders,* *DM or essential HTN or disease similar to PCOS, such as Cushing disease and congenital adrenal* *hyperplasia*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes*
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes- Age, gestational age, parity and BMI matched
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No	*Yes*

		Not reported	
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Yes*
Was matching performed?		Yes Partial No Not reported	Yes- Age, gestational age, parity and BMI matched
Summary of Result/s		*GDM was higher in PCOS* *BMI, BW, GH, PTB, IUGR, CS* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Yes
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No	*Yes*

		Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	*Yes*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*Low*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Wan 2015*

Study Citation	Wan, H. L.; Hui, P. W.; Li, H. W.; et al. (2015): Obstetric outcomes in women with polycystic ovary syndrome and isolated polycystic ovaries undergoing in vitro fertilization: a retrospective cohort analysis. J Matern Fetal Neonatal Med 28, 4, 475-478.	
Study Country	*China*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	***PCOS: 104*** ***Non-PCOS: 751***	
Setting	*Infertility and in vitro fertilization (IVF)*	
Intervention/ indicator	*N/A*	
Comparison/ Control	*Non-PCOS - PCOM without HA and AnOvu*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*BMI, GDM, GH, PE, EC, IUGR, BW*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - All women with the first IVF using conventional or ICSI method; Only an ongoing pregnancy at 12-week gestation*
Exclusion criteria reported?	Yes Partial No Not reported	Not reported
Does the study have a clearly focused question?	Yes Partial No Not reported	Yes
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial – Age matched and BMI similar for infertile women; not for those who conceived later
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Partial
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No	*Yes*

		Not reported	
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Yes*
Was matching performed?		Yes Partial No Not reported	Partial – Age matched and BMI similar at preconception not conception
Summary of Result/s		*BMI, GDM, GH, PE, EC, IUGR, BW* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*

ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Aktun 2016*
Study Citation	Aktun, H. L.; Yorgunlar, B.; Acet, M.; et al. (2016): The effects of polycystic ovary syndrome on gestational diabetes mellitus. Gynecological Endocrinology 32, 2, 139-142.
Study Country	*Turkey*

EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	***PCOS: 150*** ***Non-PCOS: 160***	
Setting	*The Istanbul Medipol University Hospital*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*BMI, GWG, GH, PE, Macrosomia, CS*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes- GDM diagnosis at 24-28 weeks. All GDM group on diet and if not regulated, insulin therapy.*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes - Age>35, multiple pregnancy, family history of diabetes, type 1 or type 2 diabetes, HTN, weight>90 kg prior to pregnancy, >4 previous deliveries, previous stillbirth, congenital malformations, habitual abortion, history of preterm delivery and presence of any systemic disease.*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	No – age higher in Non-PCOS and BMI higher in PCOS
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No	*Yes*

		Not reported	
Was matching performed?		Yes Partial No Not reported	No
Summary of Result/s		*BMI, GWG was higher in PCOS* *GH, PE, Macrosomia, CS* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- All had GDM
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each**	0	

	arm of the study were lost to follow up?		
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Sterling 2016*
Study Citation	Sterling, L.; Liu, J.; Okun, N.; et al. (2016): Pregnancy outcomes in women with polycystic ovary syndrome undergoing in vitro fertilization. Fertil Steril 105, 3, 791-797.e792.
Study Country	*Canada*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*

PCOS diagnostic criteria	*Rotterdam*	
N per group	***PCOS: 71*** ***Non-PCOS: 323***	
Setting	*The Centre for Reproductive Health (Infertility treatment)*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*GDM, PTB, LBW, SGA, Macrosomia, LGA, CS*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - IVF/ICSI/ET; Pre-existing medical conditions:* *Hypertension: 3 (4.2) in PCOS/6 (1.9) in Controls* *Diabetes: 1 (1.4) in PCOS/4 (1.2) in Controls* *Hypothyroidism: 11 (15.5) in PCOS/28 (8.7) in Controls*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes - Multiple pregnancies, medical comorbidities not associated with the metabolic syndrome (e.g., lupus, renal disease, malignancy, and uncontrolled hypothyroidism), drug or alcohol use, smokers, or vanishing twin and selective reduction; No subject contributed more than one pregnancy to the dataset.*
Does the study have a clearly focused question?	Yes Partial No Not reported	Yes
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial – Younger age in PCOS and similar BMI at preconception not conception
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial	No

		No Not reported	
Summary of Result/s		*GDM, PTB, LGA were higher in PCOS* *LBW, SGA, Macrosomia, CS* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	

	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Wang 2016*
Study Citation	Wang, F.; Dai, W.; Yang, X. H.; et al. (2016): Analyses of optimal body mass index for infertile patients with either polycystic or non-polycystic ovary syndrome during assisted reproductive treatment in China. Sci 6, 34538.
Study Country	*China*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam*

N per group	***PCOS: 2632*** ***Non-PCOS: 28523***	
Setting	*IVF/ICSI centre*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - participants who received IVF/ICSI*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*BMI, Miscarriage*	
Inclusion criteria reported?	Yes Partial No Not reported	*Partial - Those who received IVF/ICSI*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes - uterine malformation, endometriosis, donor sperms or donor oocytes, or pre-implantation genetic diagnosis, no oocytes due to poor ovarian response, a repeat cycle, a canceled cycle, no embryos for embryo transfer, hyperthyroidism and other endocrine-metabolic diseases*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	No- Lower age and higher BMI in PCOS; Not at conception
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	No

Summary of Result/s		*BMI was higher in PCOS* Miscarriage was similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were	0	

	not included in the analysis?		
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Wang 2016*
Study Citation	Wang, Q.; Luo, L.; Lei, Q.; et al. (2016): Low aneuploidy rate in early pregnancy loss abortuses from patients with polycystic ovary syndrome. Reproductive Biomedicine Online 33, 1, 85-92.
Study Country	*China*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam*
N per group	***PCOS: 119*** ***Non-PCOS: 664***
Setting	*The Center of Reproductive Medicine at the First Affiliated Hospital*

Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - No PCOS symptoms*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Miscarriage*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - All had tubal factor infertility; A total of 100 patients who had experienced spontaneous abortion of an intrauterine singleton clinical pregnancy*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes - Biochemical pregnancies, EPs, Multiple pregnancies, Abnormal karyotypes, history of spontaneous abortion, endometriosis, uterine adenomyosis, or both, evident endometrial abnormalities, malformation of the reproductive system and any other endocrine secretion diseases.*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	No- Age and BMI was not compared; preconception not pregnant
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	No
Summary of Result/s	Miscarriage was similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Xiao 2016*
Study Citation	Xiao, Q.; Cui, Y. Y.; Lu, J.; et al. (2016): Risk for Gestational Diabetes Mellitus and Adverse Birth Outcomes in Chinese Women with Polycystic Ovary Syndrome. Int 2016, 5787104.
Study Country	*China*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam*
N per group	***PCOS: 325*** ***Non-PCOS: 2037***
Setting	*Women and Children's Medical Center*
Intervention/ indicator	N/A

Comparison/ Control	*Non-PCOS*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*GDM, PTB, BW, LBW, SGA, Macrosomia, LGA, CS*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - Singleton pregnancies, <13 weeks of gestation at the first antenatal visit, and history of screening for GDM.*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes - Multiple pregnancies, history of preexisting diabetes, and missing delivery information*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	*No- Higher age and BMI in PCOS*
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	No
Summary of Result/s	*GDM, PTB, LGA was higher in PCOS* *BW, SGA, LBW, Macrosomia, CS* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Yes
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Chen 2017*
Study Citation	Chen, Y.; Ye, B.; Yang, X.; et al. (2017): Predicting the outcome of different protocols of in vitro fertilization with anti-Muullerian hormone levels in patients with polycystic ovary syndrome. Journal of International Medical Research 45, 3, 1138-1147.
Study Country	*China*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam*
N per group	***PCOS: 59*** ***Non-PCOS: 120***
Setting	*Reproductive Centre Department of the First Hospital*

Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - fallopian tube problems without PCOS, or treatment due to male infertility without PCOS*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Miscarriage*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - All IVF/ICSI*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes - >38 years, serum FSH levels >12 IU/L, a history of ovarian surgery, ovarian cyst or tumour, hydrosalpinx, endometriosis, and endocrine or systemic illnesses. In case of a positive Chlamydia test, women received routine antibiotics treatment. IVF was performed once the test became negative*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	No- Age and BMI similar at preconception group but not reported in those who got pregnant
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	No
Summary of Result/s	*Miscarriage was* similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*deWilde 2017*
Study Citation	de Wilde, M. A.; Lamain-de Ruiter, M.; Veltman-Verhulst, S. M.; et al. (2017): Increased rates of complications in singleton pregnancies of women previously diagnosed with polycystic ovary syndrome predominantly in the hyperandrogenic phenotype. Fertility & Sterility 108, 2, 333-340.
Study Country	*Netherlands*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam*
N per group	***PCOS: 188*** ***Non-PCOS: 2889***
Setting	*PCOS: hospitals; Controls: December 2012 until December 2013 in 31 midwifery practices and six hospitals*

Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - women enrolled at a booking appointment in the first trimester of their pregnancy*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*GDM, GH, PE, PTB, SGA, LGA, IOL, CS*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - Only singleton*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes – Pre-existing type 1 or type 2 diabetes, when their age was <18 or >45 years, or when there was a language barrier; multiple pregnancies*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	No – Younger age and higher BMI in PCOS (at preconception not pregnancy)
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	No
Summary of Result/s	*GDM, PE, IOL, PTB were higher in PCOS* *GH, CS SGA, LGA* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Jonsdottir 2017*
Study Citation	Jonsdottir, F.; Nilas, L.; Andreasen, K. R.; et al. (2017): Obstetrical complications in dichorionic twin pregnancies in women with polycystic ovary syndrome. Acta Obstetricia et Gynecologica Scandinavica 96, 12, 1453-1459.
Study Country	*Denmark*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam*
N per group	***PCOS: 91*** ***Non-PCOS: 300***
Setting	*Infertility centre*
Intervention/ indicator	N/A

Comparison/ Control	*Non-PCOS*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*BMI, GDM, PE, PTB, BW, LBW, SGA, IOL, CS*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - Women with a dichorionic twin pregnancy and delivery after gestational week 22*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes -Reduction of multiples to twins, unknown chorionicity, and intrauterine death of one twin*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Age similar but BMI different
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	No
Summary of Result/s	*BMI , IOL,CS were lower in PCOS* *GDM, PE, PTB, BW, LBW, SGA,* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	No
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Luo 2017*
Study Citation	Luo, L.; Gu, F.; Jie, H.; et al. (2017): Early miscarriage rate in lean polycystic ovary syndrome women after euploid embryo transfer - a matched-pair study. Reproductive Biomedicine Online 35, 5, 576-582.
Study Country	*China*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam*
N per group	***PCOS: 67*** ***Non-PCOS: 201***
Setting	*Centre of Reproductive Medicine, the First Affiliated Hospital of Sun Yat-sen University*

Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - undergoing PGD cycles due to chromosome translocation in either partner*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Miscarriage*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - PCOS+undergoing PGD due to chromosomal translocation in either partner + Lean*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes - Endometriosis, intrauterine adhesions or thin endometrium (endometrial thickness less than 8 mm on the day of progesterone initiation), uterine malformation or abnormal thyroid function*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	No- Age, BMI and embryo scores match at preconception but not for those who got pregnant
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	Not for those who got pregnant
Summary of Result/s	*Miscarriage was higher in PCOS*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No- Age, BMI and embryo scores match at preconception but not for those who got pregnant
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Huang 2018*
Study Citation	Huang, Q.; Niu, Y.; Xu, L.; et al. (2018): Relationship between a low ratio of serum estradiol to follicle number and fertility treatment outcomes: A retrospective cohort study of 516 cases. Medicine 97, 34, e12017.
Study Country	*China*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam*
N per group	***PCOS: 146*** ***Non-PCOS: 370***
Setting	*Infertility centre*
Intervention/ indicator	N/A

Comparison/ Control	*Non-PCOS*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Miscarriage*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - All IVF/ICSI; 20 to 44 years old; or 1 year duration of infertility 20 years*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes - Uterus does not have pregnancy function or they have serious physical illness which cannot afford pregnancy; or incomplete outpatient data*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	No
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	No
Summary of Result/s	*Miscarriage was* similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Kent 2018*
Study Citation	Kent, J.; Dodson, W. C.; Kunselman, A.; et al. (2018): Gestational Weight Gain in Women With Polycystic Ovary Syndrome: A Controlled Study. Journal of Clinical Endocrinology & Metabolism 103, 11, 4315-4323.
Study Country	*USA*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam with chronic anovulation*
N per group	***PCOS: 146*** ***Non-PCOS: 176***
Setting	*PCOS Infertility Centre; Controls from multiple university-affiliated hospitals*
Intervention/ indicator	N/A

Comparison/ Control	*Non-PCOS - Unexplained Infertility*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*GDM, PE*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - singleton live births, defined in both trials (PPCOS II and AMIGOS) as a pregnancy delivering $20 weeks' gestation*
Exclusion criteria reported?	Yes Partial No Not reported	*Not reported*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial - Age and BMI different but stratification for BMI performed
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*No- self-reported*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	No
Summary of Result/s	*GDM and PE* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	*Partial*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*Moderate*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Lai 2018*
Study Citation	Lai, Q.; Xiang, W.; Li, Q.; et al. (2018): Oxidative stress in granulosa cells contributes to poor oocyte quality and IVF-ET outcomes in women with polycystic ovary syndrome. Fronteras en Medicina 12, 5, 518-524.
Study Country	*China*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam PCOS and tubal infertility*
N per group	***PCOS: 22*** ***Non-PCOS: 25***
Setting	*Infertility centre*

Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - Tubal infertility*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Miscarriage*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - ≤ 35 years, body mass index (BMI) 18–25 kg/m2, and baseline follicle stimulating hormone < 10 IU/L.*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes - Presence of congenital uterine malformations, hydrosalpinx, ovarian cyst, endometrial tuberculosis, and other metabolic, hepatic, and cardiovascular disorders*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	*Partial - Age and BMI similar at preconception group but not reported in those who got pregnant*
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	No
Summary of Result/s	Miscarriage *was* similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	*Partial - Age and BMI similar at preconception group but not reported in those who got pregnant*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Li 2018*
Study Citation	Li, Y.; Ruan, X.; Wang, H.; et al. (2018): Comparing the risk of adverse pregnancy outcomes of Chinese patients with polycystic ovary syndrome with and without antiandrogenic pretreatment. Fertility & Sterility 109, 4, 720-727.
Study Country	*China*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam*
N per group	***PCOS: 670*** ***Non-PCOS: 6000***
Setting	*Beijing Obstetrics and Gynecology Hospital, Capital Medical University*
Intervention/ indicator	N/A

Comparison/ Control	*Non-PCOS*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*BMI, Miscarriage, GDM, GH, PTB, LBW, Macrosomia*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - PCOS (phenotype A, B, C) + pregnancy within 3 months of OI* *Non-PCOS - Age 20-40 Spontaneous pregnancy Singleton pregnancy*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes -Age <20 or > 40 years, multiple pregnancy, preexisting diabetes or impaired glucose tolerance and/or preexisting hypertension before pregnancy, use of antidiabetic agents such as metformin or myo-inositol before pregnancy, and a history of recurrent miscarriage and gynecological malignant tumors, neonatal malformation, cervical malfunction, thyroid dysfunction, systemic lupus erythematosus, smoking, excessive alcohol consumption, congenital malformations, intrauterine infection, or missing delivery information.*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	No- Younger age and higher BMI in PCOS
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	No
Summary of Result/s	*BMI, GDM, GH, PTB were higher in PCOS* *Miscarriage, LBW, Macrosomia* were similar in PCOS and Non-PCOS.	

INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No- Younger age and higher BMI in PCOS
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*March 2021*
Study Citation	March, W. A.; Whitrow, M. J.; Davies, M. J.; et al. (2018): Postnatal depression in a community-based study of women with polycystic ovary syndrome. Acta Obstetricia et Gynecologica Scandinavica 97, 7, 838-844.
Study Country	*Australia*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam*
N per group	***PCOS: 52*** ***Non-PCOS: 514***
Setting	*Community based*
Intervention/ indicator	N/A

Comparison/ Control	*Non-PCOS*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Postnatal depression*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - Around 30 years later, the 2199 eligible female births were traced. The 1984 (90.2%) women who were confirmed still to be living, without any severe impairment; parous*
Exclusion criteria reported?	Yes Partial No Not reported	*No*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial – Similar age but higher BMI in PCOS
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	No
Summary of Result/s	*Postnatal depression was higher in PCOS*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Yes
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Partial – Similar age but higher BMI in PCOS
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*Moderate*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Butts 2019*
Study Citation	Butts, S. F.; Seifer, D. B.; Koelper, N.; et al. (2019): Vitamin D Deficiency Is Associated With Poor Ovarian Stimulation Outcome in PCOS but Not Unexplained Infertility. J Clin Endocrinol Metab 104, 2, 369-378
Study Country	*USA*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam*
N per group	***PCOS: 607*** ***Non-PCOS: 647***
Setting	*infertility centre*
Intervention/ indicator	N/A

Comparison/ Control	*Non-PCOS - Unexplained infertility*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*BMI, Miscarriage*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - PCOS Group: ages 18 to 40 years; criteria were $1 patent fallopian tube and a normal uterine cavity, a male partner with a sperm concentration of $14 million per milliliter, with documented motility according to World Health Organization cutoff points, in at least one ejaculate during the previous year Non-PCOS Group: n 18 and 40 years of age with regular menses, had a normal uterine cavity with 1 patent fallopian tube, and had a male partner with a semen specimen of $5 million sperm/mL; unexplained infertility*
Exclusion criteria reported?	Yes Partial No Not reported	*No -*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	No - Younger age and higher BMI in PCOS
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	No
Summary of Result/s	*Miscarriage was higher in PCOS*	

INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No - Younger age and higher BMI in PCOS
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Schneider 2019*
Study Citation	Schneider, D.; Gonzalez, J. R.; Yamamoto, M.; et al. (2019): The Association of Polycystic Ovary Syndrome and Gestational Hypertensive Disorders in a Diverse Community-Based Cohort. Journal of pregnancy 2019, 9847057.
Study Country	*USA*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam*
N per group	***PCOS: 809*** ***Non-PCOS: 956***
Setting	*setting unclear Keiser-Permanente data*

Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS -*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*GH, PE*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - 16-44 years old; singleton; matched by delivery year*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes - Pre-existing hypertensive disorder*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	No – Higher age and BMI in PCOS
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	No
Summary of Result/s	*Hypertensive disorders were higher in PCOS*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No – Higher age and BMI in PCOS
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Zheng 2019*
Study Citation	Zheng, W.; Huang, W.; Tian, Z.; et al. (2019): Early pregnancy metabolic factors associated with gestational diabetes mellitus in normal-weight women with polycystic ovary syndrome: A two-phase cohort study. Diabetology and Metabolic Syndrome 11(1) (no pagination).
Study Country	*China*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam*
N per group	***PCOS: 242*** ***Non-PCOS: 324***
Setting	*Hospital*
Intervention/ indicator	N/A

Comparison/ Control	*Non-PCOS -*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*BMI, GDM, GH, PE, PTB, BW, LBW, SGA , Macrosomia, LGA*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes – recruited at gestational week 8–15;Women with singleton pregnancy, 18–45 years of age, a history of PCOS (or age and PPBMI-matched healthy controls) were enrolled in the study*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes - pre-existing chronic disease including diabetes, hypertension, liver, kidney, thyroid or cardiovascular disease were excluded*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Yes – Age and BMI matched
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	No
Summary of Result/s	*BW was lower in PCOS* *PTB was higher in PCOS* *BMI, GDM, GH, PE, LBW, SGA, Macrosomia, LGA* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Yes
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes – Age and BMI matched
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes- stratification by BMI categories was performed***
COMMENTS			
What is the overall risk of bias?		*Low*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Benito 2020*
Study Citation	Benito, E.; Gomez-Martin, J. M.; Vega-Pinero, B.; et al. (2020): Fertility and pregnancy outcomes in women with polycystic ovary syndrome following bariatric surgery. Journal of Clinical Endocrinology and Metabolism 105(9), E3384-E3391.
Study Country	*Spain*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam - premenopausal women with infertility submitted to bariatric surgery*
N per group	***PCOS: 49*** ***Non-PCOS: 120***
Setting	*Academic hospital*
Intervention/ indicator	N/A

Comparison/ Control	*Non-PCOS - premenopausal women with infertility submitted to bariatric surgery*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*BMI, Miscarriage, GDM, PE, PTB, BW, LBW, IOL, Instrumental, CS*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes* - premenopausal women with infertility submitted to bariatric surgery
Exclusion criteria reported?	Yes Partial No Not reported	*Yes - Uncertain diagnosis of being PCOS or normal*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial – Age and BMI similar at preconception after bariatric surgery but not reported for those who got pregnant
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	No
Summary of Result/s	*BW was lower in PCOS* *BMI, Miscarriage, GDM, PE, PTB, LBW, IOL, Instrumental, CS* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- post bariatric surgery population
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Chen 2020*
Study Citation	Chen, M.; Huang, X.; Liu, Y.; et al. (2020): Systematic oxidative stress is not associated with live birth rate in young non-obese patients with polycystic ovarian syndrome undergoing assisted reproduction cycles: A prospective cohort study. Eur J Obstet Gynecol Reprod Biol 253, 154-161.
Study Country	*China*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam*
N per group	***PCOS: 50*** ***Non-PCOS: 50***
Setting	*Infertility centre*

Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - Regular menstrual cycles and normal ovulation without clinical and/or biochemical hyperandrogenism or polycystic ovary*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Miscarriage, PTB, BW, CS*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - 20-35 years; BMI less than 28 kg/m2; IVF or ICSI cycle*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes – Individuals were excluded if they had endometriosis or any significant medical conditions.*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	*Partial – Age and BMI similar at preconception but not reported in those who got pregnant*
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	No
Summary of Result/s	*Miscarriage, PTB, BW, CS* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Elshewy 2020*
Study Citation	Elshewy, N.; Ji, D.; Zhang, Z.; et al. (2020): Association between mild stimulated IVF/M cycle and early embryo arrest in sub fertile women with/without PCOS. Reprod Biol Endocrinol 18, 1, 71.
Study Country	*China*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam (Anovulatory +PCOM)*
N per group	***PCOS: 33*** ***Non-PCOS: 35***
Setting	*Infertility centre*

Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - Ovulatory non-PCOS*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Miscarriage*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - aged < 35 years old, had normal basal FSH levels (< 10 mIU/mL) and a body mass index (BMI) range of 19–25 kg/m2. Patients with normal ovulatory or anovulatory cycles with any cause for infertility, including tubal factors, mild to moderate male factors, and unexplained infertility*
Exclusion criteria reported?	Yes Partial No Not reported	Not reported
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial – Age and BMI similar at preconception but not reported in those who got pregnant
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	No
Summary of Result/s	*Miscarriage was* similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Foroozanfard 2020*
Study Citation	Foroozanfard, F.; Asemi, Z.; Bazarganipour, F.; et al. (2020): Comparing pregnancy, childbirth, and neonatal outcomes in women with different phenotypes of polycystic ovary syndrome and healthy women: a prospective cohort study. Gynecological Endocrinology 36(1), 61-65.
Study Country	*Iran*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam*
N per group	***PCOS: 40*** ***Non-PCOS: 40***
Setting	*Infertility centre*
Intervention/ indicator	N/A

Comparison/ Control	*Non-PCOS -*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*BMI, Miscarriage, GDM, GH, PE, PTB, CS*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - 15–40 years of age, married, absence of non-classic adrenal hyperplasia, thyroid dysfunction, hyperprolactinemia, nonsmoking, no problems in speaking or understanding Iranian, first pregnancy, spontaneous pregnancy, no uterus malformations, no chronic diseases*
Exclusion criteria reported?	Yes Partial No Not reported	*Not reported*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial – Age and BMI were similar
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	No
Summary of Result/s	*BMI, Miscarriage, GDM, GH, PE, PTB, CS* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Partial
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Liu 2020*
Study Citation	Liu, S.; Mo, M.; Xiao, S.; et al. (2020): Pregnancy Outcomes of Women With Polycystic Ovary Syndrome for the First In Vitro Fertilization Treatment: A Retrospective Cohort Study With 7678 Patients. Frontiers in Endocrinology 11, 575337.
Study Country	*China*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam*
N per group	***PCOS: 666*** ***Non-PCOS: 7012***
Setting	*Shenzhen Zhongshan Urology Hospital (SZUH)*
Intervention/ indicator	N/A

Comparison/ Control	*Non-PCOS - Non-PCOS + ART*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*BMI, Miscarriage, GDM, GH, PTB, CS*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - ART*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes - HBV, HCV, HIV, and syphilis, aged > 38, treated with GnRH antagonist controlled ovarian hyperstimulation protocols, the cycles missing embryo information and clinical pregnancy data, patients suffering from a chromosomal abnormality, intrauterine death, a medical abortion, stillbirth, or ectopic pregnancy, nonclassic adrenal hyperplasia, thyroid dysfunction, hyperprolactinemia, type 2 diabetes mellitus or cardiovascular disease*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	No – Younger age and higher BMI in PCOS at preconception; not reported for those who got pregnant
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	No
Summary of Result/s	*Miscarriage, GH, PTB were higher in PCOS* *GDM, CS* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No – Younger age and higher BMI in PCOS at preconception; not reported for those who got pregnant
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Tobiasz 2020*
Study Citation	Tobiasz, A. M.; Duncan, J. R.; Detti, L.; et al. (2020): Lack of Fetal Insulin Resistance in Maternal Polycystic Ovary Syndrome. Reproductive Sciences 27, 6, 1253-1258
Study Country	*USA*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*NIH*
N per group	***PCOS: 28*** ***Non-PCOS: 18***
Setting	*Hospital*
Intervention/ indicator	N/A

Comparison/ Control	*Non-PCOS -*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*BMI, PTB, IUGR, BW, CS*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - presenting at labour/delivery singleton => 34 weeks 20 < BMI < 50*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes - multiple gestations, known foetal malformations, a BMI <20 or =50, and a diagnosis of gestational or pregestational diabetes.*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial – Age and BMI similar
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	No
Summary of Result/s	*BMI, PTB, IUGR, BW, CS* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Yes
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Partial – Age and BMI similar
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*Moderate*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Abdulkhalikova 2021*
Study Citation	Abdulkhalikova, D.; Korosec, S.; Blickstein, I.; et al. (2021): Perinatal outcome of in vitro fertilization pregnancies in women with polycystic ovary syndrome by pregravid BMI. Journal of Perinatal Medicine 49, 4, 514-519.
Study Country	*Slovenia*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam - oligo- and/or anovulation, clinical and/or biochemical signs of hyperandrogenism and polycystic ovaries*
N per group	***PCOS: 73*** ***Non-PCOS: 196***
Setting	*IVF/ICSI centre*

Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - participants who received IVF/ICSI*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*GWG, GDM, GH, PE, PTB, BW, LBW, SGA, Macrosomia, CS*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - Classical IVF or ICSI with single or double fresh embryo transfer were included into the study*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes - PCOS patients that either conceived spontaneously or with ovulation induction*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial - Age was similar but BMI not reported
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	No
Summary of Result/s	*GWG, GDM, GH, PE, PTB, BW, LBW, SGA, Macrosomia, CS* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Partial - Age was similar but BMI not reported
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes – Stratification by BMI was performed***
COMMENTS			
What is the overall risk of bias?		*Low*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Cai 2021*
Study Citation	Cai, H.; Mol, B. W.; Gordts, S.; et al. (2021): Early and late pregnancy loss in women with polycystic ovary syndrome undergoing IVF/ICSI treatment: a retrospective cohort analysis of 21 820 pregnancies. Bjog 128, 7, 1160-1169.
Study Country	*China*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam*
N per group	***PCOS: 2357*** ***Non-PCOS: 19463***
Setting	*Infertility centre*
Intervention/ indicator	N/A

Comparison/ Control	*Non-PCOS -*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*BMI, Miscarriage, GDM*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - A cohort of women with positive serum b-human chorionic gonadotropin (b-hCG) after embryo transfer*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes - Patients with other causes of hyperandrogenism and ovulation dysfunction (congenital adrenal hyperplasia, Cushing's syndrome and androgenic-secreting tumours), patients with recurrent pregnancy loss, uterine malformations, treatment with preimplantation genetic testing (PGT) and those involving donor sperms and oocytes.*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	No- Younger age and higher BMI in PCOS
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	No
Summary of Result/s	*BMI, Miscarriage, GDM were higher in PCOS*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No- Younger age and higher BMI in PCOS
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes – Stratification by age and BMI was performed***
COMMENTS			
What is the overall risk of bias?		*Moderate*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Diboun 2021*
Study Citation	Diboun, I.; Ramanjaneya, M.; Ahmed, L.; et al. (2021): Metabolomic Profiling of Pregnancies With Polycystic Ovary Syndrome Identifies a Unique Metabolic Signature and Potential Predictive Biomarkers of Low Birth Weight. Frontiers in Endocrinology 12, 638727.
Study Country	*Qatar*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*NIH*
N per group	***PCOS: 16*** ***Non-PCOS: 52***
Setting	*Research Center*
Intervention/ indicator	N/A

Comparison/ Control	*Non-PCOS -*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*BW*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - Obese but does not give the BMI cut-off* *All subjects had an oral glucose tolerance test to exclude diabetes*
Exclusion criteria reported?	Yes Partial No Not reported	Not reported
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial – Age and BMI were similar
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	No
Summary of Result/s	*BW was lower in PCOS*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Not reported
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Partial – Age and BMI similar
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*Moderate*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Feichtinger 2021*
Study Citation	Feichtinger, M.; Linder, T.; Rosicky, I.; et al. (2021): Maternal overweight vs. Polycystic ovary syndrome: Disentangling their impact on insulin action in pregnancy-a prospective study. Journal of Clinical Medicine 10(1), 1-7.
Study Country	*Austria*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam*
N per group	***PCOS: 31*** ***Non-PCOS: 36***
Setting	*Unclear*

Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS -*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*GDM*	
Inclusion criteria reported?	Yes Partial No Not reported	*Not reported*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes - acute and chronic illness, pre-existing diabetes mellitus, severe anaemia, HIV/hepatitis, decreased liver or kidney function, and alcohol abuse or abuse of other toxic substances; pre-existing diabetes*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial – Similar age but higher BMI in PCOS
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	No
Summary of Result/s	*GDM was higher in PCOS*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Not reported
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Partial – Similar age but higher BMI in PCOS
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Gongadashetti 2021*
Study Citation	Gongadashetti, K.; Gupta, P.; Dada, R.; et al. (2021): Follicular fluid oxidative stress biomarkers and art outcomes in PCOS women undergoing in vitro fertilization: A cross-sectional study. International Journal of Reproductive BioMedicine 19(5), 449-456.
Study Country	*India*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam*
N per group	***PCOS: 43*** ***Non-PCOS: 57***
Setting	*Infertility centre*

Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - Tubal infertility*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Miscarriage*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - All IVF/ICSI*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes - All women with endometriosis, male factor, unexplained infertility, and diminished ovarian reserve [follicle-stimulating hormone > 10 mIU/ml, Anti-Müllerian hormone < 1 ng/ml, and antral follicle counts (AFCs)*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial – Younger age and similar BMI
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	No
Summary of Result/s	*Miscarriage was* similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Partial – Younger age and similar BMI
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Hu 2021*
Study Citation	Hu, S.; Xu, B.; Long, R.; et al. (2021): The effect of polycystic ovary syndrome without hyperandrogenism on pregnancy-related outcomes: a retrospective cohort study. BJOG: An International Journal of Obstetrics and Gynaecology 128(6), 1003-1010.
Study Country	*China*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam (Anovulatory +PCOM)*
N per group	***PCOS: 557*** ***Non-PCOS: 3526***
Setting	*Infertility centre*
Intervention/ indicator	N/A

Comparison/ Control	*Non-PCOS - Non-hyperandrogenic*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*GDM, PTB, BW, LBW, Macrosomia, CS*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - All IVF/ICSI; only patients (≤40 years old) without hyperandrogenism*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes - (1) poor ovarian response; a history of hypertension, diabetes, hepatitis or chromosome abnormality; (3) a history of recurrent spontaneous termination of pregnancy; (4) a history of hypogonadotropic hypogonadism or congenital adrenal hyperplasia; (5) a history of uterine malformation, endometriosis or adenomyosis; (6) day 7 blastocyst transfer; or (7) use of gonadotropin-releasing hormone agonist in frozen–thawed cycles. Pregnancy and delivery information were recorded routinely, including both women who did and those who did not deliver at Tongji Hospital*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial- Younger age and higher BMI in PCOS at preconception
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	No
Summary of Result/s	*BW was higher in PCOS*	

		GDM, PTB, LBW, Macrosomia, CS were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Partial- Younger age and higher BMI in PCOS at preconception
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Jiang 2021*
Study Citation	Jiang, L.; Tian, L.; Yuan, J.; et al. (2021): Associations Between Sex Hormone Levels and Autistic Traits in Infertile Patients With Polycystic Ovary Syndrome and Their Offspring. Frontiers in Endocrinology 12, 789395.
Study Country	*China*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam*
N per group	***PCOS: 100*** ***Non-PCOS: 100***
Setting	*Infertility centre*
Intervention/ indicator	N/A

Comparison/ Control	*Non-PCOS - Tubal infertility*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*BMI, GDM, GH, PTB, LBW, Macrosomia, Instrumental delivery, CS*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - (1) age between 20 and 40 years old; (2) definite diagnosis issued by the hospital; (3) normal intelligence level and reading ability; and (4) voluntary participation in this study and signing of informed consent*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes - (1) serious physical or mental diseases; (2) pregnancy, lactation, or menopause; and (3) recent (within a month) use of contraceptives or other drugs that affect sex hormone levels*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	No – Younger age and higher BMI in PCOS
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	No
Summary of Result/s	*BMI was higher in PCOS* *GDM, GH, PTB, LBW, Macrosomia, Instrumental delivery, CS* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No – Younger age and higher BMI in PCOS
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Kaing 2021*
Study Citation	Kaing, A.; Jaswa, E. A.; Diamond, M. P.; et al. (2021): Highly elevated level of antimullerian hormone associated with preterm delivery in polycystic ovary syndrome patients who underwent ovulation induction. Fertil Steril 115, 2, 438-446.
Study Country	*USA*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam with chronic anovulation*
N per group	***PCOS: 118*** ***Non-PCOS: 146***
Setting	*PCOS : Infertility Centre; Controls : Multiple university-affiliated hospitals*
Intervention/ indicator	N/A

Comparison/ Control	*Non-PCOS - unexplained infertility*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*BMI, BW*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - 18 to 40 years of age, with a normal uterine cavity, at least one patent tube, and a partner with sperm concentration of at least 14 million/ml*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes - women with poorly controlled pre-gestational diabetes, uncontrolled essential hypertension, and prior known or suspected cervical or endometrial carcinoma; placental conditions, foetal growth restriction, multiple gestation, and hypertensive diseases of pregnancy*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	No- Younger age and higher BMI in PCOS
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	No
Summary of Result/s	*BMI was higher in PCOS* *BW was lower in PCOS*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	No
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No- Younger age and higher BMI in PCOS
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Kollmann 2021*
Study Citation	Kollmann, M.; Obermayer-Pietsch, B.; Lerchbaum, E.; et al. (2021): Article vitamin d concentrations at term do not differ in newborns and their mothers with and without polycystic ovary syndrome. Journal of Clinical Medicine 10(3), 1-9.
Study Country	*Austria*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam*
N per group	***PCOS: 80*** ***Non-PCOS: 420***
Setting	*academic tertiary hospital*
Intervention/ indicator	N/A

Comparison/ Control	*Non-PCOS -*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*BMI, GDM, GH, PE, IUGR, SGA, LGA*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - ongoing pregnancy ≥ 37 + 0 weeks of gestation were invited*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes - severe comorbidities (neurodegenerative, immune mediated, cardiovascular, or infectious disease), suspected abnormal placentation (placenta accreta, increta, or percreta), placenta previa, previous vertical uterine incision, a history of major abdominal surgery, or known fetal malformations*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Yes – Age and BMI were similar
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	No
Summary of Result/s	*GDM were higher in PCOS* *BMI, GH, PE, IUGR, SGA, LGA* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Yes
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Yes – Age and BMI were similar
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*Moderate*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Lin 2021*	
Study Citation	Lin, J.; Guo, H.; Wang, B.; et al. (2021): Neonatal outcomes in women with polycystic ovary syndrome after frozen-thawed embryo transfer. Fertil Steril 115, 2, 447-454.	
Study Country	*China*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	***PCOS: 1167*** ***Non-PCOS: 9995***	
Setting	*Infertility centre*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - tubal or male factor*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*PTB, BW, LBW, Macrosomia, LGA*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - singletons born to mothers with PCOS and singletons from mothers without PCOS*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes - congenital adrenal hyperplasia, androgen secreting tumours, and Cushing's syndrome; thyroid dysfunction, diabetes, hypertension, or tumours; congenital uterine malformations, unilateral oophorectomy, or chromosomal abnormalities*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	No – Younger age and higher BMI in PCOS
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial	*Yes*

		No Not reported	
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Yes*
Was matching performed?		Yes Partial No Not reported	No
Summary of Result/s		*BW was lower in PCOS* *PTB, BW, LBW, were higher in PCOS* *Macrosomia, LGA* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*

	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Liu 2021*

Study Citation	Liu, Y.; Yu, Z.; Zhao, S.; et al. (2021): Oxidative stress markers in the follicular fluid of patients with polycystic ovary syndrome correlate with a decrease in embryo quality. Journal of Assisted Reproduction and Genetics 38(2), 471-477.	
Study Country	*China*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	***PCOS: 86*** ***Non-PCOS: 60***	
Setting	*Center for Reproductive Medicine, Shandong University*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - + ART*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*BMI, Miscarriage*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - ART*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes -*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	No – Older ager and higher BMI in PCOS
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No	*Yes*

		Not reported	
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Yes*
Was matching performed?		Yes Partial No Not reported	No
Summary of Result/s		*BMI, Miscarriage were higher in PCOS*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*

ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No – Older ager and higher BMI in PCOS
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Mai 2021*
Study Citation	Mai, Z.; Liu, M.; Pan, P.; et al. (2021): Comparison of Cumulative Live Birth Rate Between Aged PCOS Women and Controls in IVF/ICSI Cycles. Frontiers in Endocrinology 12, 724333.
Study Country	*China*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	

Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	***PCOS: 263*** ***Non-PCOS: 526***	
Setting	*Centre for Reproductive Medicine in Sun Yat-Sen Memorial Hospital*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - tubal factor infertility*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Miscarriage*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - ART*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes - history of ovarian surgery, genital tumors, other endocrine disorders, endometriosis or uterine malformations were excluded.*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Yes – Age and BMI matched at preconception but not for those wo got pregnant
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*

Was matching performed?		Yes Partial No Not reported	No- Age and BMI matched at preconception but not for those wo got pregnant
Summary of Result/s		Miscarriage was similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	

	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Pouya 2021*
Study Citation	Pouya, K.; Sukur, Y. E.; Israfilova, G.; et al. (2021): hCG day progesterone level has no impact on the frozen thawed embryo transfer cycle outcome. Journal of Gynecology Obstetrics and Human Reproduction 50, 6, 102120.
Study Country	*Turkey*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam*

N per group	***PCOS: 88*** ***Non-PCOS: 90***	
Setting	*university hospital infertility center*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS -*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Miscarriage*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes – PCOS: Age 18-38; IVF-FET post artificial endometrial preparation with oestrogen and progesterone*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes - recurrent miscarriage, systemic diseases, history of recurrent implantation failure or presence of uterine anatomical abnormality. Missing Data s.*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial – Age and BMI were similar at preconception but not for those who got pregnant
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	No

Summary of Result/s		*Miscarriage was* similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Partial – Age and BMI were similar at preconception but not for those who got pregnant
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Wang 2021*
Study Citation	Wang, Y.; Guo, L.; Jiang, J.; et al. (2021): Development of 1-2 years offspring born to mothers with polycystic ovary syndrome. Journal of the College of Physicians and Surgeons Pakistan 31(10), 1186-1190.
Study Country	*China*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam*
N per group	***PCOS: 29*** ***Non-PCOS: 116***
Setting	*Dongyang Women and Children's Hospital*

Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS -*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*BMI, GWG, BW, CS*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes* - control mothers, the authors selected women of similar socio-economic level as the PCOS women, with a history of regular 28- to 32-day menstrual cycles, without hirsutism and other manifestations of hyperandrogenism
Exclusion criteria reported?	Yes Partial No Not reported	*Yes* – Children excluded if *were not born in a singleton pregnancy, less than 37-week gestational age, less than 2500-g birth weight or with missing data, and those with a history of birth asphyxia and congenital diseases*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial – Age and BMI were similar
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	Partial – SES matched
Summary of Result/s	*BMI, GWG, BW, CS* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Partial – Age and BMI were similar
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*Moderate*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Wu 2021*
Study Citation	Wu, Y.; Cai, M.; Liang, X.; et al. (2021): The prevalence of cervical insufficiency in Chinese women with polycystic ovary syndrome undergone ART treatment accompanied with negative prognosis: a retrospective study. J Obstet Gynaecol 41, 6, 888-892.
Study Country	*China*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam*
N per group	***PCOS: 1489*** ***Non-PCOS: 1489***
Setting	*Reproductive Medicine Center of The Sixth Affiliated Hospital of Sun Yat-sen University*
Intervention/ indicator	N/A

Comparison/ Control	*Non-PCOS - tubal factor, incretion factor and immunity factor*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Miscarriage, PTB*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes -*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes -*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	*Yes – A*ge, BMI, infertility duration, parity history matched
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	*Yes – A*ge, BMI, infertility duration, parity history matched
Summary of Result/s	*Miscarriage, PTB* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes	*Yes*

		Partial No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	*Yes – A*ge, BMI, infertility duration, parity history matched
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***

COMMENTS		
What is the overall risk of bias?	*Low*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*No*	

Study ID	*Zhu 2021*	
Study Citation	Zhu, J.; Zhang, J.; Yang, J.; et al. (2021): A comprehensive evaluation of progestin-primed ovarian stimulation protocol in patients with or without PCOS undergoing in vitro fertilization. Reproductive Biology 21, 4, 100540.	
Study Country	*China*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	***PCOS: 429*** ***Non-PCOS: 890***	
Setting	*Infertility centre*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - unexplained infertility and tubal factor infertility*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Miscarriage, GDM, GH, PTB, LBW*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - aged between 20–40 years*

Exclusion criteria reported?	Yes Partial No Not reported	*Yes - surgery including laparoscopic ovarian drilling, ovarian endometrioma stripping and unilateral oophorectomy; 4) congenital (septate uterus, duplex* *uterus, uterus bicornis and uterus unicornis) or acquired (intrauterine adhesion, submucosal myomas and adenomyosis) uterine anomalies; 5) recurrent spontaneous abortion for three or more times; 6) abnormal chromosomal karyotype in either of the partners; and 7) any other etiologies of hyperandrogenism hyperprolactinemia), and thyroid disease.*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial – Similar age but higher BMI in PCOS
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*

Was matching performed?		Yes Partial No Not reported	No
Summary of Result/s		*Miscarriage, GDM, GH, PTB, LBW* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*

	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Partial – Similar age but higher BMI in PCOS
	Were there any conflicts of interest in the writing or funding of this study?	Yes Partial No Not reported	*No*

OTHER BIAS	**Was the study sufficiently powered to detect any differences between the groups?**	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Liu 2022*
Study Citation	Liu, Q.; Wang, J.; Xu, Q.; et al. (2022): A retrospective cohort study of obstetric complications and birth outcomes in women with polycystic ovarian syndrome. J Obstet Gynaecol 42, 4, 574-579.
Study Country	*China*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam*
N per group	***PCOS: 1431*** ***Non-PCOS: 6700***
Setting	*Beijing Obstetrics and Gynaecology Hospital*
Intervention/ indicator	N/A
Comparison/ Control	*Non-PCOS -*

Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*GDM, GH, PE, PTB, IUGR, Macrosomia*	
Inclusion criteria reported?	Yes Partial No Not reported	Not reported
Exclusion criteria reported?	Yes Partial No Not reported	*Yes - stillbirth or miscarriage, triplet pregnancies and participants with spouses with infertility problems*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	No - Excluded stillbirth; younger age and higher BMI in PCOS
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*

Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Yes*
Was matching performed?		Yes Partial No Not reported	No
Summary of Result/s		*GDM, GH, PE, PTB, , Macrosomia were higher in PCOS* *IUGR* was similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	Yes
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No	*Yes*

		Not reported	
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No - Excluded stillbirth; younger age and higher BMI in PCOS

OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Ni 2022*
Study Citation	Ni, Z.; Mei, S.; You, S.; et al. (2022): Adverse Effects of Polycystic Ovarian Syndrome on Pregnancy Outcomes in Women With Frozen-Thawed Embryo Transfer: Propensity Score-Matched Study. Frontiers in Endocrinology 13, 878853.
Study Country	*China*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam*
N per group	***PCOS: 1376*** ***Non-PCOS: 1376***

Setting	*Ninth People's Hospital*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - tubal factor or male infertility*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Miscarriage, PTB, LBW, Macrosomia*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - ART*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes - congenital uterine malformations; severe cerebrovascular, liver, heart, or kidney diseases; gynecological cancers; metabolic or endocrine disorders (diabetes or pituitary adenomas); and autoimmune diseases, such as SLE or scleroderma*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial – Age matched but higher BMI at preconception not reported for those who got pregnant
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*

Were the outcomes measured appropriate?		Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Yes*
Was matching performed?		Yes Partial No Not reported	No
Summary of Result/s		*Miscarriage, PTB, LBW, Macrosomia were higher in PCOS*	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*

DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*

CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Song 2022*
Study Citation	Song, H.; Yu, Z.; Li, P.; et al. (2022): HOMA-IR for predicting clinical pregnancy rate during IVF. Gynecological Endocrinology 38(1), 33-38.
Study Country	*China*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*

PCOS diagnostic criteria	*Rotterdam*	
N per group	***PCOS: 115*** ***Non-PCOS: 214***	
Setting	*Shandong University-affiliated Reproductive Hospital*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS -*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Miscarriage*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - 21-40 age, ART*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes - endometriosis, abnormal intrauterine cavity, uterine abnormalities by ultrasound, a history of oophorectomy); (2) endocrine disorders (e.g. congenital adrenal hyperplasia, thyroid disease, and hyperprolactinemia); (3) a family history of diseases (e.g. diabetes, hypertension); (4) system diseases (e.g. abnormal liver or renal function); (5) recent treatment within 3months (e.g. glucocorticoids, oral contraceptive use); (6) a history of recurrent*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	No – Younger age and higher BMI in PCOS
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*

If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	No
Summary of Result/s	*Miscarriage was* similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS – **Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
SELECTION BIAS – **Was the exposed cohort truly representative?**	Yes Partial No Not reported	No- infertility treatment centre
SELECTION BIAS – **Is it clear that the outcome of interest was not present at the start of study?**	Yes Partial No Not reported	Yes

PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No – Younger age and higher BMI in PCOS
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Stokkeland 2022*

Study Citation	Stokkeland, L. M. T.; Giskeodegard, G. F.; Ryssdal, M.; et al. (2022): Changes in Serum Cytokines Throughout Pregnancy in Women With Polycystic Ovary Syndrome. J Clin Endocrinol Metab 107, 1, 39-52.	
Study Country	*Norway, Sweden, Iceland*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	***PCOS: 358*** ***Non-PCOS: 258***	
Setting	*attending multiple centres in Sweden, Noway and Iceland*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - selected from the Training in Pregnancy (TRIP) study*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*BMI, BW*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - selected from the placebo groups in PregMet and PregMet2*
Exclusion criteria reported?	Yes Partial No Not reported	*Yes - pre existing inflammatory conditions*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial	Partial – Similar age but higher BMI in PCOS

		No Not reported	
Does the study have specified inclusion/ exclusion criteria?		Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?		Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Yes*
Was matching performed?		Yes Partial No Not reported	No
Summary of Result/s		*BMI was higher in PCOS* *BW was* similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes

	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION	**What percentage of the individuals**	0	

	recruited into each arm of the study were lost to follow up?		
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome*		*No*	

was low risk but rest were high)?	

Study ID	*Tu 2022*	
Study Citation	Tu, M.; Wu, Y.; Wang, F.; et al. (2022): Effect of lncRNA MALAT1 on the Granulosa Cell Proliferation and Pregnancy Outcome in Patients With PCOS. Frontiers in Endocrinology 13, 825431.	
Study Country	*China*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	***PCOS: 48*** ***Non-PCOS: 48***	
Setting	*Center for Reproductive Medicine, Women's Hospital*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS - Tubal factor or male infertility*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Miscarriage, BW*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes - ART*
Exclusion criteria reported?	Yes Partial No Not reported	Not reported
Does the study have a clearly focused question?	Yes Partial	*Yes*

	No Not reported	
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial – Similar age and BMI
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	No
Summary of Result/s	*Miscarriage was lower in PCOS* *BW* was similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes
	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes	*Yes*

		Partial No Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Partial – Similar age and BMI
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***No***

COMMENTS		
What is the overall risk of bias?	*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*No*	

Study ID	*Wang 2022*	
Study Citation	Wang, Q.; Wang, H.; Li, P.; et al. (2022): Association of Polycystic Ovary Syndrome Phenotypes With Adverse Pregnancy Outcomes After In-Vitro Fertilization/Intracytoplasmic Sperm Injection. Frontiers in Endocrinology 13, 889029.	
Study Country	*China*	
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?		
Patient/population/ participants	*Women with and without PCOS*	
PCOS diagnostic criteria	*Rotterdam*	
N per group	***PCOS: 1186*** ***Non-PCOS: 5546***	
Setting	*Centre for Reproductive Medicine*	
Intervention/ indicator	N/A	
Comparison/ Control	*Non-PCOS -*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Miscarriage, GDM, PTB, CS*	
Inclusion criteria reported?	Yes Partial No Not reported	*Yes – ART*

Exclusion criteria reported?	Yes Partial No Not reported	*Yes - age >38 years old, serum FSH level >15 IU/L, diabetes, hypertension, abnormal parental karyotypes, severe intrauterine adhesion or uterine abnormality, chronic medical conditions that contraindicated pregnancy or with other endocrine dysfunction (such as Cushing's syndrome, primary hyperprolactinemia, thyroid dysfunction, congenital adrenal hyperplasia, androgen producing neoplasm), and history of recurrent spontaneous abortion (RSA) or unilateral oophorectomy.*
Does the study have a clearly focused question?	Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?	Yes Partial No Not reported	Partial – Similar age but higher BMI in PCOS
Does the study have specified inclusion/ exclusion criteria?	Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?	Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?	Yes Partial No Not reported	*Yes*
Was matching performed?	Yes Partial No Not reported	No
Summary of Result/s	*Miscarriage, GDM, PTB, CS* were similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS **Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes

	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*

CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	Partial – Similar age but higher BMI in PCOS
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Yang 2022*
Study Citation	Yang, T.; Yang, Y.; Zhang, Q.; et al. (2022): Homeostatic Model Assessment for Insulin Resistance Is Associated With Late Miscarriage in Non-Dyslipidemic Women Undergoing Fresh IVF/ICSI Embryo Transfer. Frontiers in Endocrinology 13, 880518.
Study Country	*China*
EXTERNAL VALIDITY – IS THIS STUDY AND ITS RESULTS GENERALIZABLE TO MY SYSTEMATIC REVIEW QUESTION?	
Patient/population/ participants	*Women with and without PCOS*
PCOS diagnostic criteria	*Rotterdam*
N per group	***PCOS: 450*** ***Non-PCOS: 3165***
Setting	*Reproductive Medicine Center of Xiangya Hospital*
Intervention/ indicator	N/A
Comparison/ Control	*Non-PCOS -*
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Miscarriage*

Inclusion criteria reported?		Yes Partial No Not reported	*Yes - Age 20-40; ART; normal lipid profile (Tg <1.7 mmol/l, TC <5.2mmol/l, LDL <3.4mmol/l and HDL>= 1.0 mmol/l)*
Exclusion criteria reported?		Yes Partial No Not reported	*Yes - diabetes mellitus or had a history of hypoglycemic and hypolipidemic medications within three months before the ART treatment;severe hydrosalpinx and did not receive tubal ligation or salpingectomy; severe adenomyosis; endometrial abnormalities such as endometrial polyps, endometrial hyperplasia, submucosal fibroids, intrauterine adhesions or chronic endometritis without management; genital tuberculosis; other severe systemic comorbidities, such as hypertension, prethrombotic conditions, autoimmune connective tissue diseases and malignant tumor*
Does the study have a clearly focused question?		Yes Partial No Not reported	*Yes*
Is a cohort study the appropriate design to answer this question?		Yes Partial No Not reported	Yes
Does the study have specified inclusion/ exclusion criteria?		Yes Partial No Not reported	*Yes*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	*Yes*
Were the outcomes measured appropriate?		Yes Partial No Not reported	*Yes*
Was there sufficient duration of follow-up for outcomes to occur?		Yes Partial No Not reported	*Yes*
Was matching performed?		Yes Partial No Not reported	No
Summary of Result/s		*Miscarriage was* similar in PCOS and Non-PCOS.	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Other than the exposure under investigation, were the groups selected from similar populations?**	Yes No Not reported	Yes

	Was the exposed cohort truly representative?	Yes Partial No Not reported	No- infertility treatment centre
	Is it clear that the outcome of interest was not present at the start of study?	Yes Partial No Not reported	Yes
PERFORMANCE BIAS	**Aside from the exposure, were the groups treated the same?**	Yes Partial No Not reported	*NA*
DEDETECTION BIAS	**Was exposure measured in a standard, valid and reliable way?**	Yes Partial No Not reported	*Yes*
	Were outcome assessors blind to the exposure?	Yes Partial No Not reported	*NA*
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	*Yes*
	Were outcomes assessed objectively and independently?	*Yes* Yes Partial No Not reported	*Yes*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study were lost to follow up?**	0	
	What percentage of the individuals were not included in the analysis?	0	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	*Yes*
CONFOUNDING	**Are the cohorts comparable on the basis of design or analysis?**	Yes Partial No Not reported	No

OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	*No*
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	*Not reported –* *No report of a power calculation but significant differences were found*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	***Yes***
COMMENTS			
What is the overall risk of bias?		*High*	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 4

Question 4.10.

Are women with PCOS at increased risk of adverse pregnancy outcomes?

BACKGROUND:

PCOS was originally considered as a condition impairing infertility with little attention paid to obstetric outcomes. However, well-known symptoms and related comorbidities associated with the condition, such as high BMI, metabolic disturbances, hyperandrogenism and infertility would all presume a higher risk of adverse pregnancy outcomes. The first reports on pregnancy complications in women with PCOS emerged in the 1980ies (1). Although publications from both clinical and register data on pregnancy outcomes have increased immensely since, guidelines are scarce on how to manage PCOS pregnancies and identify possible risk factors. During pregnancy, PCOS symptoms like irregular cycles, hyperandrogenism or polycystic ovarian morphology are difficult to detect, thus, the condition is seldom considered in everyday obstetric practice. During antenatal care, delivery and postpartum, there is little attention paid among patients and health personnel that PCOS-diagnosis may constitute a risk of poorer pregnancy outcomes.

There is a lack of quality evidence on pre-pregnancy management of women with PCOS.

The narrative review informing the 2018 International PCOS Guideline concluded that women with PCOS should undergo preconception lifestyle management to reduce weight. They should also be screened for hypertension and risk for diabetes before pregnancy. Emotional, mental health screening is probably useful.

Generalizability

Studies were conducted mostly at university hospitals, covering countries across North-America, South-America, Europe, Mid-East, Australia, China and India.

GRADE EVIDENCE CERTAINTY	
Comparison	**GRADE for critical outcomes**
o **Comparison 1:** Women with PCOS versus controls	⨁◯◯◯ VERY LOW

Evidence to Recommendations Framework

COMPARISONS (option versus other option)

Adverse pregnancy outcomes in women with PCOS vs. controls

EVIDENCE-BASED RECOMMENDATION(S)

- **EBR:** Women with PCOS have higher risk pregnancies, and health professionals should ensure that PCOS status is identified during antenatal care, and appropriate monitoring and support is provided.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

- **EBR:** Health professionals should recognise that pregnant women with PCOS, independent of age and BMI, have an increased risk of:
  - Excess gestational weight gain
  - Early miscarriage
  - Gestational diabetes
  - Hypertension in pregnancy and preeclampsia
  - Intrauterine growth restriction, small for gestational age babies and low birth weight
  - Preterm delivery
  - Caesarean section

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

- **EBR:** Assisted reproductive technology in women with PCOS should be considered as not conferring additional risk of miscarriage, preterm birth, impaired fetal growth and caesarean section, over that observed in women without PCOS.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

EBR: Women with PCOS should be considered as not having an increased risk of large for gestational age babies, macrosomia and instrumental delivery.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

PRACTICE POINT(S)

Early lifestyle intervention should be offered to pregnant women with PCOS, given the risk of higher prepregnancy weight, excess gestational weight gain and pregnancy complications.
Blood pressure measurement should be performed when planning pregnancy or seeking fertility treatment, given the high risk of hypertensive disorders in pregnancy and the associated comorbidities in women with PCOS.
An oral glucose tolerance test (OGTT) should be offered to all women with PCOS when planning pregnancy or seeking fertility treatment, given the high risk of hyperglycaemia and associated comorbidities in pregnancy. If not performed in the preconception phase, an OGTT should be offered at the first antenatal visit, and repeated at 24-28 weeks gestation.

GRADE CONSIDERATIONS

Justifications:
For the critical outcomes PHT, PE, GDM and preterm delivery certainty varies from moderate to low indicating higher risk in PCOS.
For the critical outcome eclampsia certainty is very low indicating no difference in PCOS vs controls.

Subgroup considerations:
Pregnancies after assisted reproductive technology may play a role in risk evaluation in PCOS-pregnancies.
Consideration of preconception BMI and GDM status may affect evaluation of pregnancy risks.
Potential risk associated with phenotype is not evaluated

Implementation considerations:
Very high priority for education to Health professionals and women.

Monitoring and evaluation considerations:
Monitoring the identification of PCOS status during antenatal care and if implementation of recommendation improves pregnancy outcomes in women with PCOS.
This includes dedicated fields in electronic medical records and pregnancy registries.

Research priorities:
Identify PCOS-status at the antenatal care and follow-up PCOS vs non- PCOS, registering predefined variables of adverse outcomes.
Exploring how phenotype, preconception body mass index, assisted reproductive technology affect adverse outcomes in addition to PCOS-status.
The potential impact of ethnicity on pregnancy outcomes in PCOS.
The role of prevention in pregnant women with PCOS.
Cost effectiveness of recommendation.

GRADE framework

GRADE DECIDE Interactive Evidence to Decision Framework

- **DESIRABLE EFFECTS**

How substantial are the desirable anticipated effects?

Judgement:

☒ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Many studies, robust evidence.

- **UNDESIRABLE EFFECTS**

How substantial are the undesirable anticipated effects?

Judgement:

☒ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Language is important and stigma should be avoided.

● CERTAINTY OF THE EVIDENCE

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☐ Very low	X☒ Low	☐ Moderate	☐ High

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Strong and robust evidence across the globe about general increase in pregnancy complications.

Evidence is rated low due to data coming from observational studies but this type of study design is appropriate for the question.

Six outcomes were predefined as critical.

Eclampsia is one of them. Only two studies and very few events. Graded as very low certainty.

The others were graded as low to moderate certainty.

● VALUES

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☐ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☐ Probably no important uncertainty or variability	☒ No important uncertainty or variability

Research evidence:

No research evidence was identified

Panel discussion:

No disagreements.

● BALANCE OF EFFECTS

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☒ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:

- **COSTS**

How large are the resource requirements (costs)?

Judgement:

☒ Don't know	☐ Varies	☐ Large costs	☐ Moderate costs	☐ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:

No research evidence was identified

Panel discussion:

Higher cost to screen for adverse outcomes in pregnancies of women with PCOS.

- **CERTAINTY OF COST EVIDENCE**

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

No research evidence was identified

Panel discussion:

- **COST-EFFECTIVENESS**

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

No research evidence was identified

Panel discussion:

No judgement could be made.

- **EQUITY**

What would be the impact on health equity?

Judgement:

☐ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☒ Probably increased	☐ Increased

Research evidence:

No research evidence was identified

Panel discussion:

Increased screening for pregnancy complications will increase equity.

- **ACCEPTABILITY**

Is the option acceptable to key stakeholders?

Judgement:

☐ Don't know	☒ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Funders may be against increased screening and increasing interventions.

More anxiety in relation to pregnancy, delivery and post-partum is also a potential scenario.

- **FEASIBILITY**

Is the option feasible to implement?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Funders may be against increased screening and increasing interventions.

REFERENCES:

1. Diamant YZ, Rimon E, Evron S. High incidence of preeclamptic toxemia in patients with polycystic ovarian disease. Eur J Obstet Gynecol Reprod Biol. 1982 Dec;14(3):199-204. doi: 10.1016/0028-2243(82)90097-1. PMID: 7160531.

PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by ECR Lead: Aya Mousa

Other team members: Jillian Tay

GDG 4

Question 4.11.

In women with PCOS in pregnancy, is metformin compared to placebo/standard care effective in reducing pregnancy complications and adverse neonatal outcomes?

3. SELECTION CRITERIA

Table 1. PICO Criteria for Inclusion – Not to be adapted To be used by evidence team to decide which studies will be included when screening search results.	
Question	Q 4.11) In women with PCOS in pregnancy, is metformin compared to placebo/standard care effective in reducing pregnancy complications and adverse neonatal outcomes?
Clinical leads (key contacts)	**Prof Eszter Vanky** Obstetrician-Gynaecologist Norwegian University of Science and Technology, Norway eszter.vanky@ntnu.no **Prof Rong Li** Obstetrician-gynaecologist Reproductive Medical Centre, Peking University Third Hospital, China roseli001@sina.com **Prof Terhi Piltonen** Obstetrician-Gynaecologist, Reproductive endocrinologist Oulu University Hospital, University of Oulu, Finland terhi.piltonen@oulu.fi **A/Prof Jacqueline Boyle** Obstetrician-gynaecologist Monash University, Australia Jacqueline.Boyle@monash.edu **Dr Aya Mousa** NHMRC Senior Research Fellow Monash University, Australia Aya.mousa@monash.edu
Allocation ranking	Level 1- New systematic review

	Participants (P)	**Intervention (I)**	**Comparison (C)**	**Outcomes (O)**	**Study type (S)**	**Limits** *(language, year)*
Inclusion	Pregnant women with PCOS (Rotterdam, NIH or AES criteria) of any age, ethnicity, socio-economic status, geographic area, co-morbidity, or gestational age	Metformin administered alone in any form and route, of any dosage and for any duration	Placebo, usual care, lifestyle intervention/s	Primary Maternal Outcomes: Glycaemic control (glucose, insulin, HbA1c); incidence of GDM or hyper/ hypoglycaemia; Pregnancy-induced hypertension and/or Pre-eclampsia; Miscarriage after gw 13; Preterm delivery gw 23- 36 Primary Neonatal Outcomes: hypoglycaemia, birthweight, birth length, head circumference and gestational age at delivery Apgar score, hyperbilirubinemia	Evidence based guidelines, systematic reviews, randomised controlled trials.	English language. New search Update of MiPS search from 2020
Exclusion	Studies in non-pregnant populations	Studies without a metformin therapy arm	Studies without a control or comparison arm	Studies without clinical outcomes (mechanistic studies)	Studies in non-pregnant populations	

2. SEARCH STRATEGY

Table 2.1. Search details

Search strategy source: *[enter doi or 2018 technical report page number where search string was derived]*

Evidence source	Date of search
Medline (Ovid)	7th July 2022
PsychInfo (Ovid)	N/A
EMBASE (Ovid)	7th July 2022
All EBM (Ovid)	7th July 2022
CINAHL	N/A

Any subsequent updates - enter database and date: Initial search was on 14/7/2020 and updated 7/7/2022 using the same string and databases with time limit '2020 to current' applied.

Table 2.2. Questions addressed by this search *(add more rows as needed)*:

GDG	Q#	Question
4	4.11	In women with PCOS in pregnancy, is metformin compared to placebo/standard care effective in reducing pregnancy complications and adverse neonatal outcomes?

Table 2.3. Search strings used in OVID or other database/s

OVID Medline, All EBM, PsychInfo, EMBASE (results= 4942)

1. metformin/
2. metformin.mp.
3. metformin hydrochloride.mp.
4. metformin HCL.mp.
5. hypoglycemic?.mp.
6. hypoglycaemic?.mp.
7. anti?diabetic?.mp.
8. antihyperglycemic?.mp.
9. antihyperglycaemic?.mp.
10. glucose?lowering.mp.
11. dimethylbiguanidine.mp.
12. dimethylguanylguanidine.mp.
13. glucophage.mp.
14. biguanide?.mp.
15. buformin.mp.
16. phenformin.mp.
17. sitagliptin.mp.
18. glumetza.mp.
19. carbophage.mp.
20. obimet.mp.
21. gluformin.mp.
22. dianben.mp.
23. diabex.mp.
24. diaformin.mp.
25. siofor.mp.
26. metfogamma.mp.
27. glifor.mp.
28. riomet.mp.
29. janumet.mp.
30. fortamet.mp.
31. obimet.mp.
32. pregnancy.mp.

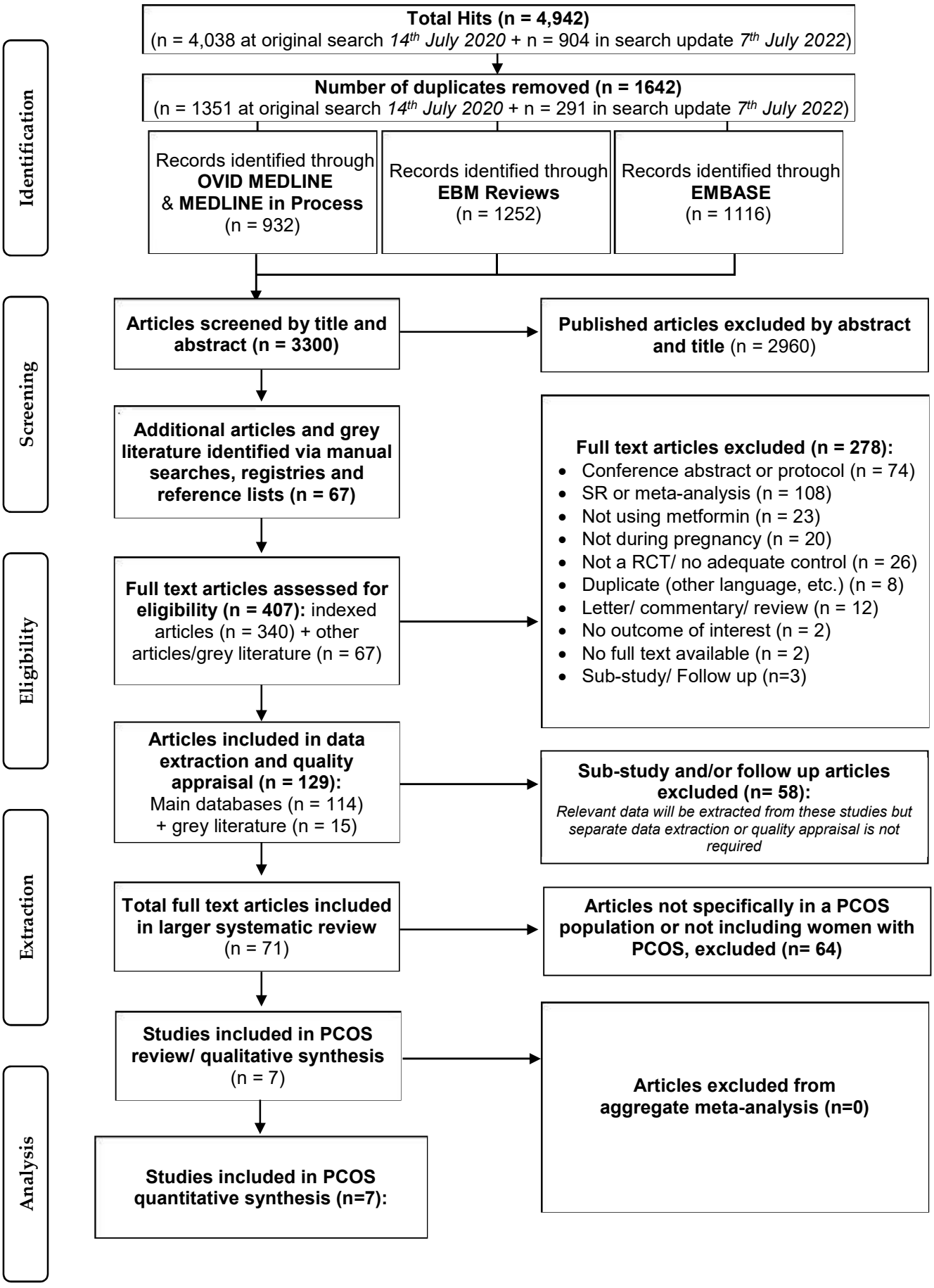
33. pregnan?.mp.
34. reproductive.mp.
35. maternal.mp.
36. neonatal.mp.
37. gestation?.mp.
38. infant.mp.
39. offspring.mp.
40. f?etal.mp.
41. neonat?.mp.
42. ?natal.mp.
43. gestational diabetes.mp.
44. GDM.mp.
45. or/1-44
46. randomi?ed controlled trial.pt.
47. controlled clinical trial.pt.
48. randomi?ed.ti,ab.
49. placebo.ti,ab.
50. clinical trials as topic.sh.
51. randomly.ti,ab.
52. trial.ti.
53. or/46-52
54. exp animals/ not exp humans/
55. 53 not 54
56. Meta-Analysis as Topic/
57. meta analy$.tw.
58. metaanaly$.tw.
59. Meta-Analysis/
60. (systematic adj (review$1 or overview$1)).tw.
61. exp Review Literature as Topic/
62. or/56-61
63. cochrane.ab.
64. embase.ab.
65. (psychlit or psyclit).ab.
66. (psychinfo or psycinfo).ab.
67. (cinahl or cinhal).ab.
68. science citation index.ab.
69. bids.ab.
70. cancerlit.ab.
71. or/63-70
72. reference list$.ab.
73. bibliograph$.ab.
74. hand-search$.ab.
75. relevant journals.ab.
76. manual search$.ab.
77. or/72-76
78. selection criteria.ab.
79. data extraction.ab.
80. 78 or 79
81. Review/
82. 80 and 81
83. Comment/
84. Letter/
85. Editorial/
86. animal/
87. human/
88. 86 not (86 and 87)

89. or/83-85,88
90. 62 or 71 or 77 or 82
91. 90 not 89
92. 53 or 91
93. 45 and 92
94. limit 93 to humans
95. or/1-31
96. or/32-44
97. 95 and 96
98. 92 and 97

limit 98 to humans

Evidence processing: Studies were selected and appraised by two reviewer/s in consultation with the evidence team/ key contact using study selection and appraisal criteria (PICO above) established a priori. The articles were reviewed by title and abstract by two reviewers. When a decision could not be made based on title and abstract alone, full text was retrieved. Full texts were screened for eligibility by two reviewers. **Seven studies met inclusion criteria for this review.**

3. SEARCH RESULTS - PRISMA flowchart



4. STUDY INCLUSION

Table 4.1. Included Studies (full citation with doi)

No.	First Author	Year	Full Citation
1.	Lovvik T.S.	2019	Løvvik TS, Carlsen SM, Salvesen Ø, et al. Use of metformin to treat pregnant women with polycystic ovary syndrome (PregMet2): a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2019;7(4):256-266. doi:10.1016/S2213-8587(19)30002-6
2.	Morin-Papunen, L.	2012	Morin-Papunen L, Rantala AS, Unkila-Kallio L, et al. Metformin improves pregnancy and live-birth rates in women with polycystic ovary syndrome (PCOS): a multicenter, double-blind, placebo-controlled randomized trial. *J Clin Endocrinol Metab*. 2012;97(5):1492-1500. doi:10.1210/jc.2011-3061
3.	Vanky E.	2004	Vanky E, Salvesen KA, Heimstad R, Fougner KJ, Romundstad P, Carlsen SM. Metformin reduces pregnancy complications without affecting androgen levels in pregnant polycystic ovary syndrome women: results of a randomized study. *Hum Reprod*. 2004;19(8):1734-1740. doi:10.1093/humrep/deh347.
4.	Vanky E.	2010	Vanky E, Stridsklev S, Heimstad R, et al. Metformin versus placebo from first trimester to delivery in polycystic ovary syndrome: a randomized, controlled multicenter study. *J Clin Endocrinol Metab*. 2010;95(12):E448-E455. doi:10.1210/jc.2010-0853
5.	Zolghadri J.	2008	Zolghadri J, Tavana Z, Kazerooni T, Soveid M, Taghieh M. Relationship between abnormal glucose tolerance test and history of previous recurrent miscarriages, and beneficial effect of metformin in these patients: a prospective clinical study. *Fertil Steril*. 2008;90(3):727-730. doi:10.1016/j.fertnstert.2007.06.079
6.	Begum	2009	Begum MR, Khanam NN, Quadir E, et al. Prevention of gestational diabetes mellitus by continuing metformin therapy throughout pregnancy in women with polycystic ovary syndrome. *J Obstet Gynaecol Res*. 2009;35(2):282-286. doi:10.1111/j.1447-0756.2008.00876.x
7.	Jamal, A.	2012	Jamal A, Milani F, Al-Yasin A. Evaluation of the effect of metformin and aspirin on utero placental circulation of pregnant women with PCOS. *Iran J Reprod Med*. 2012;10(3):265-270.

Table 4.2. Excluded Studies (on full text assessment)

This list is for studies excluded for this PCOS sub-analysis - see Appendix 1 for full list of 278 studies excluded from the main review

No.	First Author	Year	Title	Reason for Exclusion
1.	Balani J.	2017	Association between insulin resistance and preeclampsia in obese non-diabetic women receiving metformin	Substudy/ Follow up
2.	Barrett H.	2013	Maternal and neonatal circulating markers ofmetabolic and cardiovascular risk in themetformin in gestational diabetes (mig) trial.	Substudy/ Follow up
3.	Barrett H.	2013	Determinants of maternal triglycerides in women with gestational diabetes mellitus in themetformin in gestational diabetes (MiG) study.	Substudy/ Follow up
4.	Battin M.	2015	Blood pressure measurement at two years in offspring of women randomized to a trial of metformin for GDM: follow up data from the MiG trial	Substudy/ Follow up
5.	Carlsen S.	2012	Metformin's effect on first-year weight gain: a follow-up study.	Substudy/ Follow up
6.	Fougner K.	2008	Metformin has no major effects on glucose homeostasis in pregnant women with PCOS: results of a randomized double-blind study	Substudy/ Follow up
7.	Gatford K.	2013	Vitamin B12 and homocysteine status during pregnancy in the metformin in gestational diabetes trial: responses to maternal metformin compared with insulin treatment.	Substudy/ Follow up
8.	Greger H.	2020	Cognitive function in metformin exposed children, born to mothers with PCOS - Follow-up of an RCT.	Substudy/ Follow up
9.	Hanem L.	2018	Metformin Use in PCOS Pregnancies Increases the Risk of Offspring Overweight at 4 Years of Age: Follow-Up of Two RCTs.	Substudy/ Follow up
10.	Hanem L.	2019	Intrauterine metformin exposure and offspring cardiometabolic risk factors (PedMet study): a 5-10 year follow-up of the PregMet randomised controlled trial	Substudy/ Follow up
11.	Hassan J.	2012	Metformin prevents macrosomia and neonatal morbidity in gestational diabetes.	Substudy/ Follow up
12.	Helseth R.	2014	Maternal and fetal insulin levels at birth in women with polycystic ovary syndrome: data from a randomized controlled study on metformin	Substudy/ Follow up
13.	Hjorth-Hansen A.	2018	Fetal Growth and Birth Anthropometrics in Metformin-Exposed Offspring Born to Mothers With PCOS.	Substudy/ Follow up
14.	Huhtala Y.	2018	Amino acid profile in women with gestational diabetes mellitus treated with metformin or insulin.	Substudy/ Follow up
15.	Ijas H.	2015	A follow-up of a randomised study of metformin and insulin in gestational diabetes mellitus: growth and development of the children at the age of 18 months.	Substudy/ Follow up
16.	Panagiotopoulou O.	2020	Metformin use in obese mothers is associated with improved cardiovascular profile in the offspring.	Substudy/ Follow up
17.	Pellonpera, O.	2016	The effects of metformin treatment of gestational diabetes on maternal weight and glucose tolerance postpartum--a prospective follow-up study.	Substudy/ Follow up
18.	Ro T.	2012	Growth, body composition and metabolic profile of 8-year-old children exposed to metformin in utero.	Substudy/ Follow up
19.	Rowan J.	2018	Metformin in gestational diabetes: the offspring follow-up (MiG TOFU): body composition and metabolic outcomes at 7-9 years of age.	Substudy/ Follow up

20.	Rowan J.	2011	Metformin in gestational diabetes: the offspring follow-up (MiG TOFU): body composition at 2 years of age	Substudy/ Follow up
21.	Sales W.	2018	Effectiveness of Metformin in the Prevention of Gestational Diabetes Mellitus in Obese Pregnant Women.	Substudy/ Follow up
22.	Salvesen K.	2007	Metformin treatment in pregnant women with polycystic ovary syndrome--is reduced complication rate mediated by changes in the uteroplacental circulation?	Substudy/ Follow up
23.	Lovvik T.	2016	Cervical Length and Androgens in Pregnant Women With Polycystic Ovary Syndrome: Has Metformin Any Effect?	Substudy/ Follow up
24.	Silva J.	2010	Metformin compared with glyburide for the management of gestational diabetes	Substudy/ Follow up
25.	Stridsklev S.	2014	Midpregnancy Doppler ultrasound of the uterine artery in metformin- versus placebo-treated PCOS women: a randomized trial.	Substudy/ Follow up
26.	Tertti K.	2014	The degree of fetal metformin exposure does not influence fetal outcome in gestational diabetes mellitus	Substudy/ Follow up
27.	Tertti K.	2015	Neurodevelopment of Two-Year-Old Children Exposed to Metformin and Insulin in Gestational Diabetes Mellitus	Substudy/ Follow up
28.	Tertti K.	2016	Metformin Treatment Does Not Affect Testicular Size in Offspring Born to Mothers with Gestational Diabetes.	Substudy/ Follow up
29.	Underdal M.	2018	Does Metformin Treatment During Pregnancy Modify the Future Metabolic Profile in Women With PCOS?	Substudy/ Follow up
30.	Underdal M.	2019	Prolactin and breast increase during pregnancy in PCOS: linked to long-term metabolic health?	Substudy/ Follow up
31.	Vanky E.	2006	Beneficial effect of metformin on pregnancy outcome in women with polycystic ovary syndrome is not associated with major changes in C-reactive protein levels or indices of coagulation	Substudy/ Follow up
32.	Vanky E.	2012	Androgens and antimullerian hormone in mothers with polycystic ovary syndrome and their newborns	Substudy/ Follow up
33.	Vanky E.	2012	Breast size increment during pregnancy and breastfeeding in mothers with polycystic ovary syndrome: a follow-up study of a randomised controlled trial on metformin versus placebo	Substudy/ Follow up
34.	Vanky E.	2012	On the potential of metformin to prevent preterm delivery in women with polycystic ovary syndrome - an epi-analysis	Substudy/ Follow up
35.	Wouldes T.	2016	Neurodevelopmental outcome at 2 years in offspring of women randomised to metformin or insulin treatment for gestational diabetes	Substudy/ Follow up
36.	Chiswick	2016	Does metformin reduce excess birthweight in offspring of obese pregnant women? A randomised controlled trial of efficacy, exploration of mechanisms and evaluation of other pregnancy complications	Substudy/ Follow up
37.	Molina-Vega, M.	2022	Metformin action over gut microbiota is related to weight and glycemic control in gestational diabetes mellitus: a randomized trial	Substudy/ Follow up
38.	Nascimento, I.	2020	The impact of the use of metformine for obese pregnant women in prevention	Substudy/ Follow up
39.	Dienstmann, G.	2020	No effect of a low dose of metformin on the lipid profile, body mass index and weight gain in pregnant women with obesity: a randomized trial	Substudy/ Follow up
40.	Poprzeczny, A	2020	Effect of metformin in addition to an antenatal diet and lifestyle intervention on fetal growth and adiposity: the GRoW randomised trial	Substudy/ Follow up
41.	Paul, P.	2020	Follow-up of offspring and mothers with gestational diabetes treated with metformin or glibenclamide: a randomized controlled trial	Substudy/ Follow up
42.	Yang, L	2022	Metformin in obese pregnancy has no adverse effects on cardiovascular risk in early childhood	Substudy/ Follow up
43.	Panagiotopoulou O	2020	Metformin use in obese mothers is associated with improved cardiovascular profile in the offspring	Substudy/ Follow up
44.	Paavilainen, E	2021	Metformin versus insulin therapy for gestational diabetes: effects on offspring anthropometrics and metabolism at the age of 9 years: a follow-up study of two open-label, randomized controlled trials	Substudy/ Follow up
45.	Fu, J	2022	Gestational weight gain in women with type 2 diabetes and perinatal outcomes: a secondary analysis of the metformin in women with type 2 diabetes in pregnancy (MiTy) trial	Substudy/ Follow up
46.	Huhtala, M	2022	Comparison of glucose metabolism and anthropometry in women with previous gestational diabetes treated with metformin vs. insulin: 9-year follow-up of two randomized trials	Substudy/ Follow up
47.	Huhtala, M	2020	Metformin and insulin treatment of gestational diabetes: Effects on inflammatory markers and IGF-binding protein-1 - Secondary analysis of a randomized controlled trial	Substudy/ Follow up
48.	Huhtala, M.	2021	Cord serum metabolome and birth weight in patients with gestational diabetes treated with metformin, insulin, or diet alone	Substudy/ Follow up
49.	Huhtala, M.	2020	Serum lipids and their association with birth weight in metformin and insulin treated patients with gestational diabetes	Substudy/ Follow up
50.	Feig, D.	2022	Determinants of Small for Gestational Age in Women With Type 2 Diabetes in Pregnancy: who Should Receive Metformin?	Substudy/ Follow up
51.	Hanem, L.	2021	Maternal PCOS status and metformin in pregnancy: steroid hormones in 5-10 years old children from the PregMet randomized controlled study	Substudy/ Follow up
52.	Ryssdal, M.	2021	Y-012. Metformin changes serum cytokines in pregnant women with polycystic ovary syndrome	Substudy/ Follow up
53.	Grindheim, S.	2022	Metformin exposure, maternal PCOS status and fetal venous liver circulation: A randomized, placebo-controlled study	Substudy/ Follow up
54.	Andraelig, F	2020	Sustained Maternal Hyperandrogenism During PCOS Pregnancy Reduced by Metformin in Non-obese Women Carrying a Male Fetus	Substudy/ Follow up

55.	Trouva, A.	2022	Thyroid Status During Pregnancy in Women With Polycystic Ovary Syndrome and the Effect of Metformin	Substudy/ Follow up
56.	Fougner, S.	2021	No impact of gestational diabetes mellitus on pregnancy complications in women with PCOS, regardless of GDM criteria used	Substudy/ Follow up
57.	Molin, J	2022	Gestational weight gain, appetite regulating hormones, and metformin treatment in polycystic ovary syndrome: A longitudinal, placebo-controlled study	Substudy/ Follow up
58.	Greger, H.	2020	Cognitive function in metformin exposed children, born to mothers with PCOS - Follow-up of an RCT	Substudy/ Follow up
59.	Ainuddin J.	2015	Metformin versus insulin treatment in gestational diabetes in pregnancy in a developing country: a randomized control trial.	GDM population
60.	Ainuddin J.	2015	Metformin treatment in type 2 diabetes in pregnancy: an active controlled, parallel-group, randomized, open label study in patients with type 2 diabetes in pregnancy	T2D population
61.	Ashoush, S.	2016	Identification of metformin poor responders, requiring supplemental insulin, during randomization of metformin versus insulin for the control of gestational diabetes mellitus	GDM population
62.	Beyuo T.	2015	Metformin versus insulin in the management of pre-gestational diabetes mellitus in pregnancy and gestational diabetes mellitus at the Korle Bu Teaching Hospital: a randomized clinical trial.	GDM or T2DM
63.	Galal M.	2019	Metformin versus insulin in treatment of gestational diabetes mellitus: A randomized controlled trial.	GDM population
64.	George A.	2015	Comparison of neonatal outcomes in women with gestational diabetes with moderate hyperglycaemia on metformin or glibenclamide--a randomised controlled trial.	GDM population
65.	Ghomian N.	2019	The efficacy of metformin compared with insulin in regulating blood glucose levels during gestational diabetes mellitus: A randomized clinical trial	GDM population
66.	Hamadani A.	2017	Metformin versus insulin treatment in gestational diabetes in pregnancy and their effects on neonatal birthweight.	GDM population
67.	Hickman A.	2013	Metformin compared with insulin in the treatment of pregnant women with overt diabetes: a randomized controlled trial.	GDM or T2DM population
68.	Ibrahim M.	2014	The role of adding metformin in insulin-resistant diabetic pregnant women: a randomized controlled trial.	GDM or T2DM population
69.	Ijas H.	2011	Metformin should be considered in the treatment of gestational diabetes: a prospective randomised study.	GDM population
70.	Khan R.	2017	Comparison of metformin with insulin in the management of gestational diabetes.	GDM population
71.	Mesdaghinia, E.	2013	Comparison of newborn outcomes in women with gestational diabetes mellitus treated with metformin or insulin: A randomised blinded trial.	GDM population
72.	Moore L.	2007	Metformin and insulin in the management of gestational diabetes mellitus: preliminary results of a comparison.	GDM population
73.	Moore L.	2010	Metformin compared with glyburide in gestational diabetes: a randomized controlled trial.	GDM population
74.	Nachum Z.	2017	Glyburide Versus Metformin and Their Combination for the Treatment of Gestational Diabetes Mellitus: A Randomized Controlled Study.	GDM population
75.	Niromanesh S.	2012	Metformin compared with insulin in the management of gestational diabetes mellitus: a randomized clinical trial.	GDM population
76.	Refuerzo J.	2015	A pilot randomized, controlled trial of metformin versus insulin in women with type 2 diabetes mellitus during pregnancy	T2DM population
77.	Rowan J.	2008	Metformin versus insulin for the treatment of gestational diabetes.	GDM population
78.	Ruholamin S.	2014	Neonatal outcomes in women with gestational diabetes mellitus treated with metformin in compare with insulin: A randomized clinical trial	GDM population
79.	Siddique N.	2018	Comparison of mean birth weight of neonates born to females having gestational diabetes on metformin versus insulin.	GDM population
80.	Silva J.C.	2012	Perinatal impact of the use of metformin and glyburide for the treatment of gestational diabetes mellitus.	GDM population
81.	Spaulonci C.	2013	Randomized trial of metformin vs insulin in the management of gestational diabetes	GDM population
82.	Tertti K.	2013	Metformin vs. insulin in gestational diabetes. A randomized study characterizing metformin patients needing additional insulin	GDM population
83.	Waheed S.	2013	Efficacy of metformin versus insulin in the management of pregnancy with diabetes	Diabetes population
84.	Wasim T.	2019	Comparison of metformin and insulin for management of gestational diabetes mellitus: A randomized control trial	GDM population
85.	Zawiejska A.	2016	Short-term antidiabetic treatment with insulin or metformin has a similar impact on the components of metabolic syndrome in women with gestational diabetes mellitus requiring antidiabetic agents: results of a prospective, randomised study	GDM population
86.	Arshad	2017	Feto-maternal outcomes and glycemic control in metformin versus insulin treated gestational diabetes	GDM population
87.	Borg	2016	Metformin as opposed to insulin in the management of gestational diabetes.	GDM population
88.	Eid	2018	Is metformin a viable alternative to insulin in the treatment of gestational diabetes mellitus (GDM)? Comparison of maternal and neonatal outcomes.	GDM population
89.	Fenn	2015	Comparison of metformin with glyburide in gestational diabetes: a double blind randomised clinical trial.	GDM population
90.	Hague	2003	Contraindications to use of metformin - Metformin may be useful in gestational diabetes	GDM population

91.	Majeed	2015	To compare the efficacy of metformin with insulin in diabetes mellitus in terms of fetomaternal outcome.	GDM population
92.	Mohamed	2014	Oral hypoglycaemic as attractive alternative to insulin for the management of diabetes mellitus during pregnancy.	GDM population
93.	Najafian	2016	Investigation the effects of metformin versus insulin on neonatal and maternal outcomes in women with gestational diabetes mellitus: a randomized clinical trial	GDM population
94.	Pujara	2017	A comparative study of metformin and glyburide in gestational diabetes mellitus.	GDM population
95.	Riaz	2014	Comparison of metformin and insulin for the management of gestational diabetes.	GDM population
96.	Saleh	2016	Could metformin manage gestational diabetes mellitus instead of insulin?	GDM population
97.	Somani	2016	Treatment of gestational diabetes mellitus: insulin or metformin?	GDM population
98.	Hashaad, A.	2021	Neonatal outcomes in case of euglycemic control in gestational diabetes using insulin vs. metformin: Randomized controlled trial	GDM population
99.	Shuster, D.	2020	Pharmacodynamics of Glyburide, Metformin, and Glyburide/Metformin Combination Therapy in the Treatment of Gestational Diabetes Mellitus	GDM population
100.	Saraswat, D.	2022	Study on Evaluation of Metformin versus insulin Therapy in the Management of Gestational Diabetes	GDM population
101.	Tew, M.	2022	Metformin in gestational diabetes mellitus: a double-blind placebo-controlled randomized trial	GDM population
102.	Jiao, Y.	2022	Effects of metformin and insulin on gestational diabetes mellitus: a dual drugs therapy approach	GDM population
103.	Feig, D. S.	2020	Metformin in women with type 2 diabetes in pregnancy (MiTy): a multicentre, international, randomised, placebo-controlled trial	T2DM population
104.	Hantrakun, P.	2022	Effect of metformin on reducing platelet dysfunction in gestational diabetes mellitus: a randomized controlled trial	GDM population
105.	Sarwat, A.	2022	Comparison of Efficacy of Metformin and Insulin in management of Gestational Diabetes. An experience in Social Security Teaching Hospital, Ferozepur Road Lahore	GDM population
106.	Jahanshahi, M.	2020	Effects of metformin and insulin therapy regimens on postpartum oral glucose tolerance test results in pregnant women with gestational diabetes mellitus: a comparative study	GDM population
107.	Picon-Cesar, M.	2021	Metformin for gestational diabetes study: metformin vs insulin in gestational diabetes: glycemic control and obstetrical and perinatal outcomes: randomized prospective trial	GDM population
108.	Busarira, M.	2021	Impact of treatment with metformin in comparison with insulin in gestational diabetes in libyan population a randomized controlled study	GDM population
109.	Dasari, P.	2022	Comparison of metformin and insulin therapy for the treatment of gestational diabetes mellitus-a randomised controlled trial	GDM population
110.	Sadaf, J.	2021	Comparison of the fetal outcome between metformin and insulin in gestational diabetes mellitus	GDM population
111.	Cluver, C.	2022	Use of metformin to prolong gestation in preterm pre-eclampsia: randomised, double blind, placebo controlled trial	Population with preterm pre-eclampsia
112.	Mir, S.	2021	To Compare Metformin Vs Insulin in Gestational Diabetes in Terms of Neonatal Hypoglycaemia	GDM population
113.	Dodd, J.	2019	Effect of metformin in addition to dietary and lifestyle advice for pregnant women who are overweight or obese: the GRoW randomised, double-blind, placebo-controlled trial.	Obese population, not PCOS
114.	Nascimento I.	2020	Metformin for prevention of cesarean delivery and large-for-gestational-age newborns in non-diabetic obese pregnant women: a randomized clinical trial.	Obese population, not PCOS
115.	Brink H.S.	2018	Metformin in women at high risk of gestational diabetes mellitus	High risk population, not PCOS
116.	Dempsey, A.	2020	Metformin treatment vs a diabetes model of prenatal care in women with mild fasting hyperglycemia diagnosed in pregnancy: a feasibility study	Mild hyperglycemia; not PCOS
117.	Jamal A.	2010	The effect of metformin on uteroplacental circulation and pregnancy outcomes in pregnant women with polycystic ovary syndrome.	Not English
118.	Hong, J.	2021	Prophylactic metformin after antenatal corticosteroids (PROMAC): a double blind randomized controlled trial	GDM and non-GDM; not in PCOS
119.	Syngelaki, A.	2016	Metformin versus Placebo in Obese Pregnant Women without Diabetes Mellitus.	Includes PCOS but undefined (i.e. likely self-report)
120.	Chiswick, C.	2015	Effect of metformin on maternal and fetal outcomes in obese pregnant women (EMPOWaR): a randomised, double-blind, placebo-controlled trial.	Includes PCOS but undefined (i.e. likely self-report)
121.	Valdes, E.	2018	Metformin as a prophylactic treatment of gestational diabetes in pregnant patients with pregestational insulin resistance: A randomized study.	Includes PCOS but undefined and cannot differentiate effects in PCOS
122.	Perichart-Perera, O.	2022	Intensive Medical Nutrition Therapy Alone or with Added Metformin to Prevent Gestational Diabetes Mellitus among High-Risk Mexican Women: A Randomized Clinical Trial.	Includes PCOS but undefined and cannot differentiate effects in PCOS

5. STUDY CHARACTERISTICS TABLE

Author, year, country	Population/ Setting	Study Design	PCOS criteria	Sample Size per group (analysed)	Intervention/ exposure	Comparison/ control	Follow up Duration	Outcomes	Summary of findings	Risk of Bias
Jamal, 2012, Iran	Women with PCOS attending infertility outpatient clinic	RCT (single-blind)	> 8 subcapsular follicles 3-9 mm diameter and oligo-menorrhea or hirsutism or testosterone >2 nmol/L); all were taking metformin before study entry	N= 35 metformin; n= 35 aspirin; n=35 no intervention	Metformin 2000 mg/d	Aspirin (80 mg/d) ***OR*** No intervention	12 weeks GA to delivery	Uteroplacental circulation; GDM; PE; PTB; IUGR; birthweight (primary NR)	Reduced uteroplacental circulation with metformin or aspirin compared with placebo but no effects on other outcomes	High (all outcomes)
Begum, 2009, Bangladesh	Women with PCOS taking metformin + ovulation inducing agent attending infertility care centre	RCT (blinding NR)	Rotterdam 2003	N= 29 continued metformin through pregnancy N= 30 discontinued metformin at 8 wk GA	Continuation of metformin until delivery (1500-2500 m/d);+ ovulation induction 6-12 mo preconception	Discontinuation of metformin at 8 wk GA);+ ovulation induction 6-12 mo pre-conception	6-12 months pre-conception to delivery	GDM*; Abortion rate*; Live birth rate*; Congenital anomaly*; Condition of newborn at birth*; Birthweight; neonatal death; PTB; GA; birth asphyxia; LBW; macrosomia	GDM incidence, birth asphyxia and birthweight were lower and APGAR at 5 min higher with metformin use in pregnancy. No difference in abortion, LBW, GA, PTB, congenital anomalies. One neonatal death in controls.	High (all outcomes)
Lovvik, 2019, Norway	Women aged 18-45 with PCOS; at 6 to 12+6 weeks GA; singleton	DB, PC, RCT	Rotterdam 2003	N= 238 metformin N= 240 placebo (variable for different outcomes)	Metformin 1000 mg/d at week 1 then 2000 mg/d for the rest of pregnancy	Placebo	Median 10-11 weeks GA to delivery	Composite incidence of late miscarriage (week 13 - 22 + 6) and PTB (week 23 - 36 + 6)*. GDM preeclampsia, hypertension treatment with vaginal progesterone to prevent PTB, vaginal bleeding during pregnancy, admission to hospital; NICU admission + number of days, GWG, birthweight, length, head circumference, 5-min Apgar, cord pH, malformations.	In pregnant women with PCOS, metformin treatment from the late first trimester until delivery might reduce the risk of late miscarriage and preterm birth, but does not prevent gestational diabetes.	Low (primary outcomes) Moderate (secondary/ post-hoc outcomes)
Morin-Papunen, 2012, Finland	Women with PCOS and anovulatory infertility	DB, PC, RCT	Rotterdam 2003	During pregnancy: N= 79 metformin N= 56 placebo	Metformin 500 mg/d in wk 1, increased by 500 mg/d weekly steps up to 1500 mg/d in non-obese and 2000 mg/d in obese women; for max 9 months (or until GW 12). After 3 months, if no pregnancy, CC was added; if ovulating, CC continued with met or placebo for 4-6 cycles or until 12 GW; if no	Placebo	Preconception until 12 weeks GA	Early pregnancy loss (miscarriage)*; pregnancy rate and live birth rate	3 months metformin pre-treatment improves pregnancy rate in obese women, and live birth rate in obese and non-obese women, with anovulatory infertility	Low (primary outcomes) Moderate (secondary/ post-hoc outcomes)

					pregnancy, aromatase inhibitors or gonado-trophins were used. For male infertility, IVF/ICSI was used.					
Vanky, 2004, Norway	Women aged 18-40 with PCOS pre-pregnancy; GA 5-12 wk; singleton	DB, PC, RCT	Rotterdam 2003	N= 17 metformin N= 21 placebo	Metformin 850 mg/d at week 1 then 1700 mg/d for the rest of pregnancy	Placebo	5-12 weeks GA (mean 7-8.5 weeks) until delivery	DHEAS*, androstenedione*, testosterone*, SHBG*, free testosterone*, pregnancy outcomes and complications	Severe pregnancy complications occurred more frequently in the placebo group compared to metformin, with no change in androgens	Low (primary outcomes) Moderate (secondary/ post-hoc outcomes)
Vanky, 2010, Norway	Women aged 18-45 with PCOS pre-pregnancy; GA 5-12 wk; singleton	DB, PC, RCT	Rotterdam 2003	N= 135 metformin N= 135 placebo	Metformin 1000 mg/d at week 1 then 2000 mg/d for the rest of pregnancy	Placebo	Mean 10-11 weeks GA to delivery	Prevalence of PE, PTB and GDM and a composite of the three (1 or more)	Metformin treatment from first trimester to delivery did not reduce pregnancy complications in PCOS.	Low (primary outcomes) Moderate (secondary/ post-hoc outcomes)
Zolghadri, 2008, Iran	Women with PCOS + unexplained recurrent abortions (≥3 consecutive) with impaired GTT (75g OGTT 2h 140-200 mg/dl)	Prospective RCT	Chronic oligomenorrhea; clinical/ biochemical hyperandrogenism; >10 follicles 2-10mm diameter; increased ovarian stroma density; excluding other causes.	Of the 29 with recurrent abortions and impaired GTT; only 7 had PCOS. N=4 metformin, N=3 placebo	Metformin 1500 mg/d	Placebo	Preconception until delivery (timing preconception NR)	Normal ongoing pregnancies ≥14 weeks*, and absence or presence of anomaly in the baby after delivery *	Abortion rate decreased with metformin compared with placebo in women without PCOS but this was not significant in women with PCOS.	High (all outcomes)

* denotes primary outcomes defined in individual studies. DB, double-blind; GA, gestational age; GTT, glucose tolerance test; LBW, low birthweight; OGTT, oral glucose tolerance test; PC, placebo-controlled; PCOS, polycystic ovary syndrome; PTB, preterm birth; RCT, randomised controlled trial

6. FINDINGS

Comparisons included:

- **Comparison 1:** Metformin versus Placebo / or Control

Outcomes included:

- **Outcome 1.** GDM
- **Outcome 2.** Fasting glucose
- **Outcome 3.** Two-hour glucose
- **Outcome 4.** Hypertension in pregnancy
- **Outcome 5.** Pre-eclampsia
- **Outcome 6.** Preterm birth
- **Outcome 7.** Miscarriage
- **Outcome 8.** Gestational weight gain
- **Outcome 9.** Gestational age at delivery
- **Outcome 10.** Neonatal hypoglycaemia
- **Outcome 11.** Neonatal birthweight
- **Outcome 12.** Low birth weight
- **Outcome 13.** Macrosomia
- **Outcome 14.** Neonatal length
- **Outcome 15.** Neonatal head circumference
- **Outcome 16.** APGAR score
- **Outcome 17.** Neonatal icterus/ jaundice
- **Outcome 18.** Fetal malformations
- **Outcome 19.** Neonatal/ perinatal death
- **Outcome 20.** Asphyxia/ respiratory distress

COMPARISON 1: Metformin versus Placebo / or Control

▪ EVIDENCE SUMMARY:

Seven studies compared metformin versus placebo or control in pregnant women with PCOS, of which three had a high risk of bias and the remaining had a low risk for the primary outcomes (moderate risk for post-hoc or secondary outcomes). Only two of the seven RCTs were not placebo-controlled. For these two studies, one compared metformin with aspirin or no intervention, where only the no intervention comparator was used in this analysis (Jamal et al. 2012); and the other compared metformin continuation in pregnancy with discontinuation at 8 weeks gestation (Begum et al. 2009). Where applicable, sensitivity analyses were performed to exclude these two studies from the overall analysis to examine their impact on results.

▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

Pooled analysis showed that treatment with metformin resulted in a lower incidence of preterm birth (<37 weeks) and gestational age at delivery, less gestational weight gain, and larger neonatal head circumference, compared with placebo or control/no intervention. There were no differences in glycaemic measures including GDM, or in preeclampsia, neonatal anthropometry, or any measures of fetal well-being. Effects did not vary meaningfully in sensitivity analyses of only placebo-controlled RCTs. Certainty in the evidence was high for preterm birth and gestational age at delivery but low to moderate for the remaining outcomes, due mainly to downgrading for risk of bias (high or moderate risk of bias for studies or outcomes), inconsistency due to heterogeneity and/or varying estimates, and indirectness for some outcomes which used different cut-offs/criteria or tools to assess outcome measures.

Outcome or Subgroup	Studies	n	Effect Estimate; MD or OR [95% CI]	P	Favours	Certainty
Gestational diabetes (GDM)	6	990	0.76 [0.40, 1.44]	0.4	No difference	⊕⊕◯◯ LOW
Fasting glucose (24-36 wk) [mmol/L]	3	706	-0.03 [-0.20, 0.15]	0.8	No difference	⊕⊕◯◯ LOW
Two-hour post-OGTT glucose (24-36 wk) [mmol/L]	3	622	0.05 [-0.17, 0.27]	0.7	No difference	⊕⊕⊕◯ MODERATE
Hypertension in pregnancy	3	791	1.12 [0.62, 2.02]	0.7	No difference	⊕⊕◯◯ LOW
Pre-eclampsia	5	942	0.74 [0.36, 1.50]	0.4	No difference	⊕⊕◯◯ LOW
Preterm birth	6	1017	0.48 [0.28, 0.82]	**0.007**	**Metformin** (lower with MET)	⊕⊕⊕⊕ HIGH
Miscarriage	5	949	0.65 [0.32, 1.32]	0.2	No difference	⊕⊕◯◯ LOW
Gestational weight gain [kg]	3	700	-1.65 [-2.90, -0.40]	**0.01**	**Metformin** (lower with MET)	⊕⊕⊕◯ MODERATE
Gestational age at delivery [weeks]	5	953	0.31 [0.06, 0.56]*	**0.02**	**Metformin** (higher with MET)	⊕⊕⊕⊕ HIGH
Neonatal hypoglycaemia	3	777	1.28 [0.40, 4.05]	0.7	No difference	⊕⊕◯◯ LOW
Neonatal birthweight [g]	6	1005	40.92 [-72.23, 154.06]	0.5	No difference	⊕⊕◯◯ LOW
Low birth weight	5	940	0.88 [0.49, 1.57]	0.7	No difference	⊕⊕⊕◯ MODERATE
Macrosomia	5	940	1.00 [0.71, 1.40]	1.0	No difference	⊕⊕⊕◯ MODERATE
Neonatal length [cm]	3	770	0.33 [-0.13, 0.79]	0.2	No difference	⊕⊕⊕◯ MODERATE
Neonatal head circumference [cm]	3	775	0.47 [0.20, 0.74]	**0.0007**	**Metformin** (higher with MET)	⊕⊕⊕◯ MODERATE
APGAR score	5	908	-0.02 [-0.15, 0.11]	0.8	No difference	⊕⊕⊕◯ MODERATE
Neonatal icterus/ jaundice/ hyperbilirubinemia	3	778	0.78 [0.41, 1.48]	0.4	No difference	⊕⊕⊕◯ MODERATE
Fetal malformations	2	760	1.13 [0.38, 3.38]	0.8	No difference	⊕⊕◯◯ LOW
Neonatal/ perinatal death	3	816	1.01 [0.17, 5.87]	0.9	No difference	⊕⊕◯◯ LOW
Asphyxia/ respiratory distress	4	836	0.64 [0.33, 1.24]	0.2	No difference	⊕⊕◯◯ LOW

*uses fixed effect model

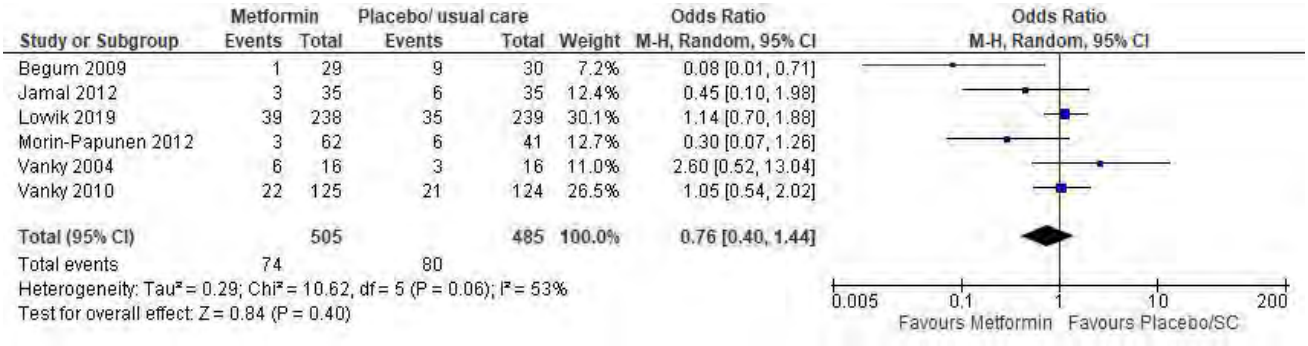
OUTCOME 1. Gestational diabetes mellitus

1.1 Individual Study Data Tables

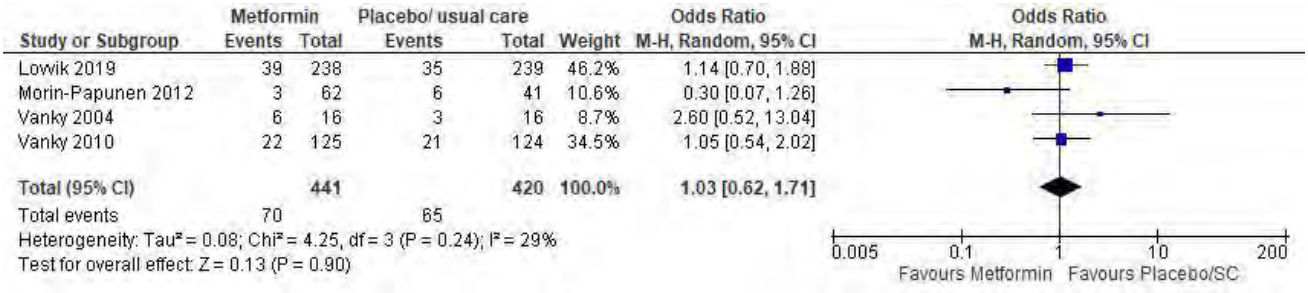
OUTCOME: GDM		**OUTCOME TYPE:** Dichotomous						
COMPARISON (if applicable): Metformin vs placebo or control								
Author, year	**Unit of outcome**	**Method of measurement**	**N events in MET group**	**N total in MET group**	**N events in control group**	**N total in control group**	**Are these values adjusted?**	**If adjusted, what variables were in the model?**
Begum 2008	Incidence/ count	Two hour post-prandial glucose (NFD)	1	29	9	30	No	NA
Jamal 2012	Incidence/ count	50g GCT ± 100g OGTT (NFD- no criteria)	3	35	6	35	No	NA
Lovvik 2019	Incidence/ count	75g OGTT – WHO 1998 at 24-28 wk GA	39	238	35	239	New GDM after inclusion	NA
Morin-Papunen	Incidence/ count	Criteria, timing NR	3	62	6	41	No	NA
Vanky 2004	Incidence/ count	75g OGTT- WHO 1998 at 32 wk GA	6	16	3	16	New GDM after inclusion	NA
Vanky 2010	Incidence/ count	75g OGTT- WHO 1998 at 32 wk GA	22	125	21	124	New GDM after inclusion	NA

NFD, not further defined

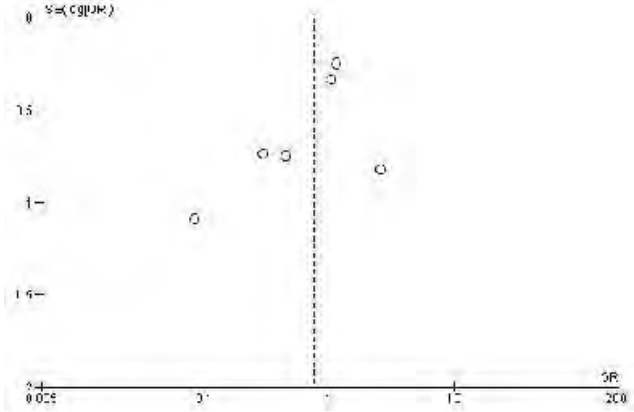
3.2. Forest plot for differences between metformin and placebo/ control in GDM incidence



3.3. SENSITIVITY ANALYSIS: Forest plot for differences between metformin and placebo only in GDM incidence



3.4. Funnel plot for assessment of publication bias



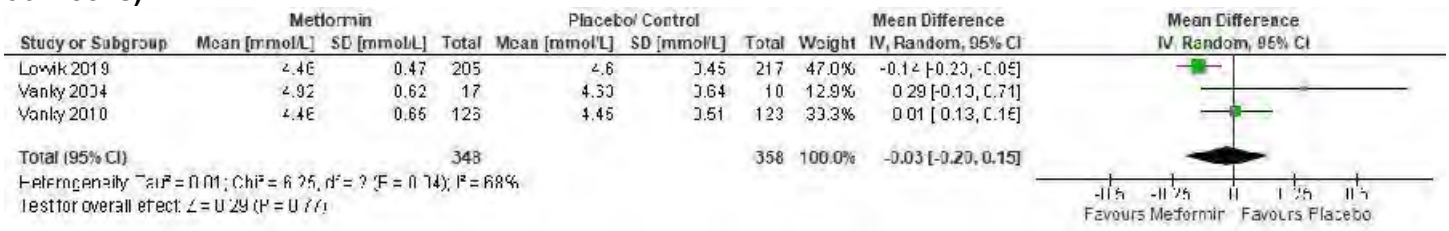
OUTCOME 2. Fasting glucose (24-36 wks)

2.1 Individual Study Data Tables

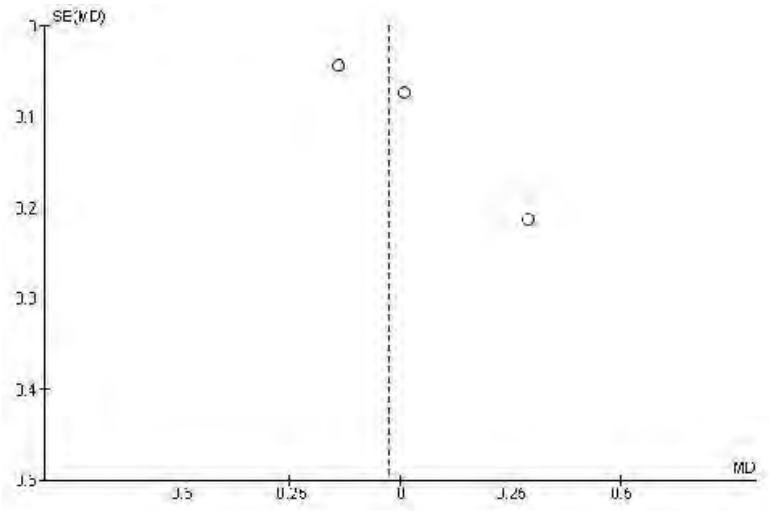
OUTCOME: Fasting blood glucose (24-36 wk)					**OUTCOME TYPE:** Continuous					
COMPARISON: Metformin vs placebo										
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L)**	**Method of measurement**	**Mean in MET group**	**SD in MET group**	**Sample Size MET**	**Mean in Placebo**	**SD in Placebo**	**Sample size Placebo**	**Are these values adjusted?**	**If adjusted, what variables were in the model?**
Lovvik 2019*	Mmol/L	28 wk	4.46	0.47	205	4.6	0.45	217	No	NA
Vanky 2004*	Mmol/L	32 wk (or 36 wk)	4.92	0.62	17	4.63	0.64	18	No	NA
Vanky 2010*	Mmol/L	32 wk (or 36 wk)	4.46	0.65	126	4.45	0.51	123	No	NA

*derived from individual patient data

2.2. Forest plot for differences between metformin and placebo in two-hour glucose post-OGTT (24-36 weeks)



2.3. Funnel plot for assessment of publication bias

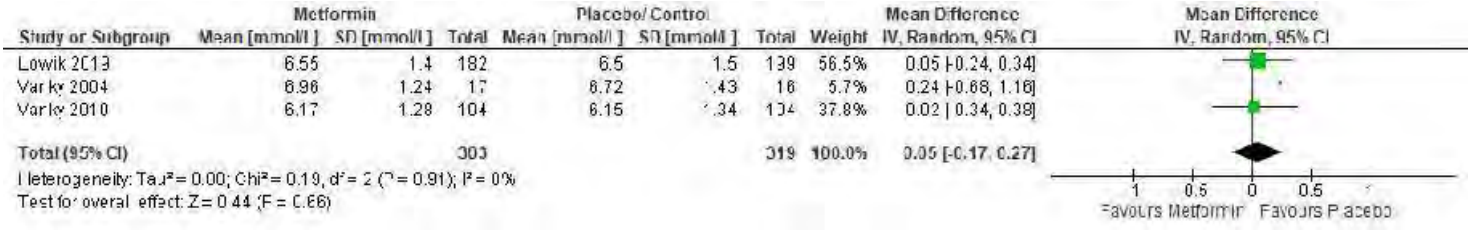


OUTCOME 3. Two-hour glucose post-OGTT (24-36 wks)

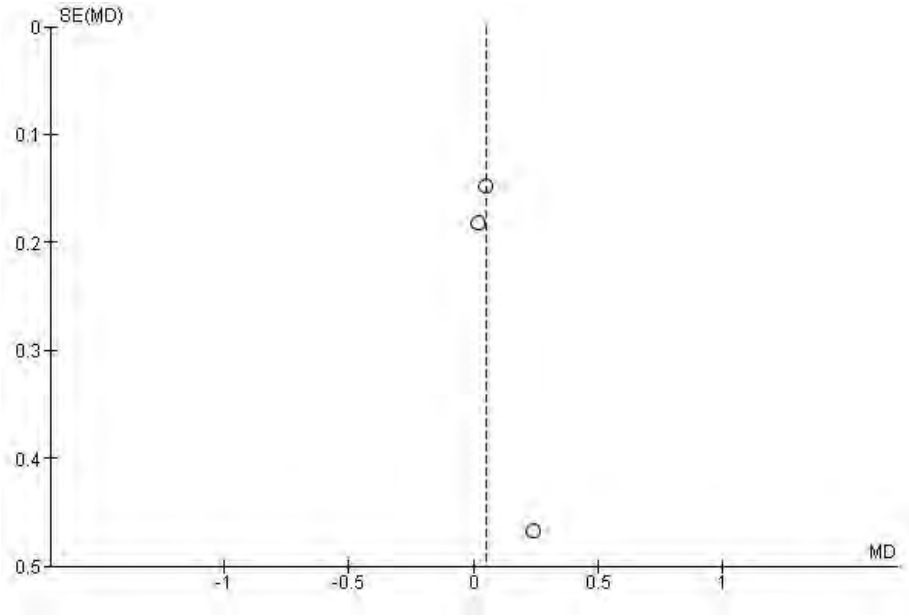
3.1 Individual Study Data Tables

OUTCOME: Two hour post-OGTT blood glucose (24-36 wk)					**OUTCOME TYPE:** Continuous					
COMPARISON (if applicable): Metformin vs placebo										
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L)**	**Method of measurement**	**Mean in MET group**	**SD in MET group**	**Sample Size MET**	**Mean in Placebo**	**SD in Placebo**	**Sample size Placebo**	**Are these values adjusted?**	**If adjusted, what variables were in the model?**
Lovvik 2019*	Mmol/L	28 weeks	6.55	1.4	182	6.5	1.5	199	No	NA
Vanky 2004*	Mmol/L	32 wk (or 36 wk)	6.96	1.24	17	6.72	1.43	16	No	NA
Vanky 2010*	Mmol/L	32 wk (or 36 wk)	6.17	1.28	104	6.15	1.34	104	No	NA

3.2. Forest plot for differences between metformin and placebo in two-hour glucose post-OGTT (24-36 weeks)



3.3. Funnel plot for assessment of publication bias

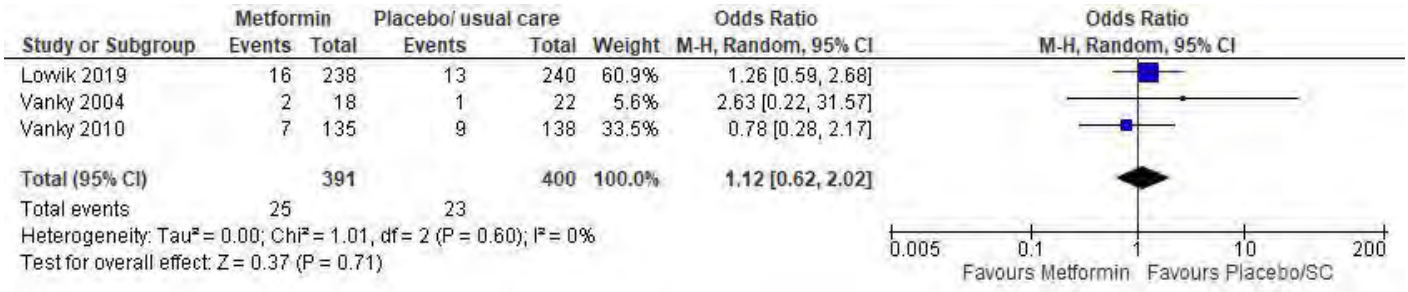


OUTCOME 4. Hypertension in Pregnancy

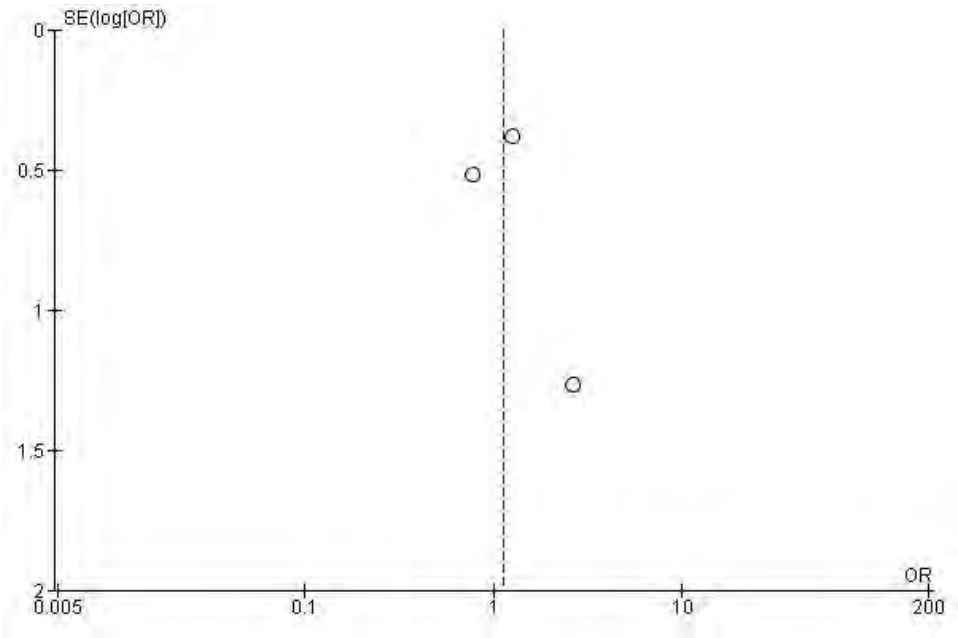
4.1. Individual Study Data Tables

OUTCOME: Hypertension in pregnancy					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Metformin vs placebo								
Author, year	**Unit of outcome (e.g. µg, mmol/L, etc.)**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted?**	**If adjusted, what variables were in the model?**
Lovvik 2019	Incidence/ count	Includes pre-existing HT	16	238	13	240	No	NA
Vanky 2004#	Incidence/ count	Includes pre-existing HT	2	18	1	22	No	NA
Vanky 2010#	Incidence/ count	Includes pre-existing HT	7	135	9	138	No	NA

4.2. Forest plot for differences between metformin and placebo in hypertension in pregnancy



4.3. Funnel plot for assessment of publication bias

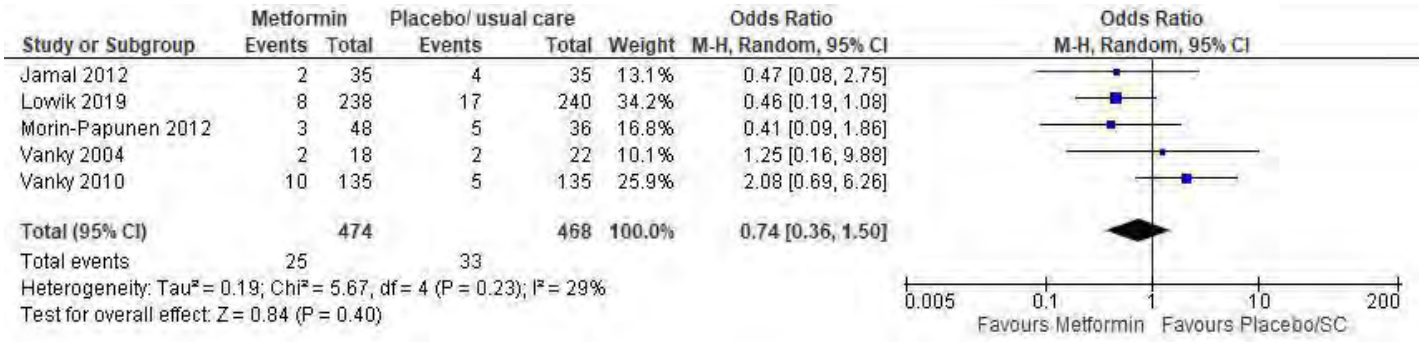


OUTCOME 5. Pre-eclampsia

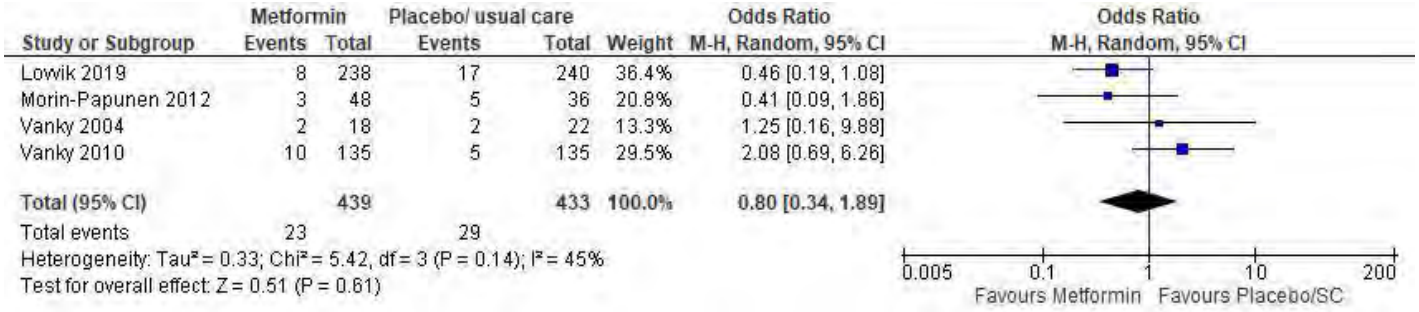
5.1. Individual Study Data Tables

OUTCOME: Pre-eclampsia					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Metformin vs placebo or control								
Author, year	**Unit of outcome**	**Method of measurement**	**N events in MET group**	**N total in MET group**	**N events in Placebo/ control group**	**N total in Placebo/ control group**	**Are these values adjusted?**	**If adjusted, what variables were in the model?**
Jamal 2012	Incidence/ count	BP ≥140/90 + albuminuria ≥0.3g/24h	2	35	4	35	No	NA
Lovvik 2019	Incidence/ count	All forms of PE, with or without pre-ex HT	8	238	17	240	No	NA
Morin- Papunen 2012*		NR	3	48	5	36	No	NA
Vanky 2004*		BP ≥140/90 + albuminuria ≥0.3g/24h on 2 occasions after GW 20	2	18	2	22	No	NA
Vanky 2010	Incidence/ count	BP ≥140/90 mmHg on 2 occasions after GW 20 + albuminuria of +2 or +1 on dipstick on 1 or 2 occasions, respectively	10	135	5	135	No	NA

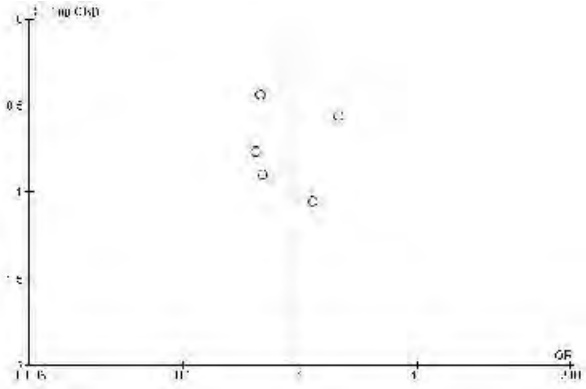
5.2. Forest plot for differences between metformin and placebo/ control in pre-eclampsia



5.3. SENSITIVITY ANALYSIS: Forest plot for differences between metformin and placebo only in pre-eclampsia



5.4. Funnel plot for assessment of publication bias



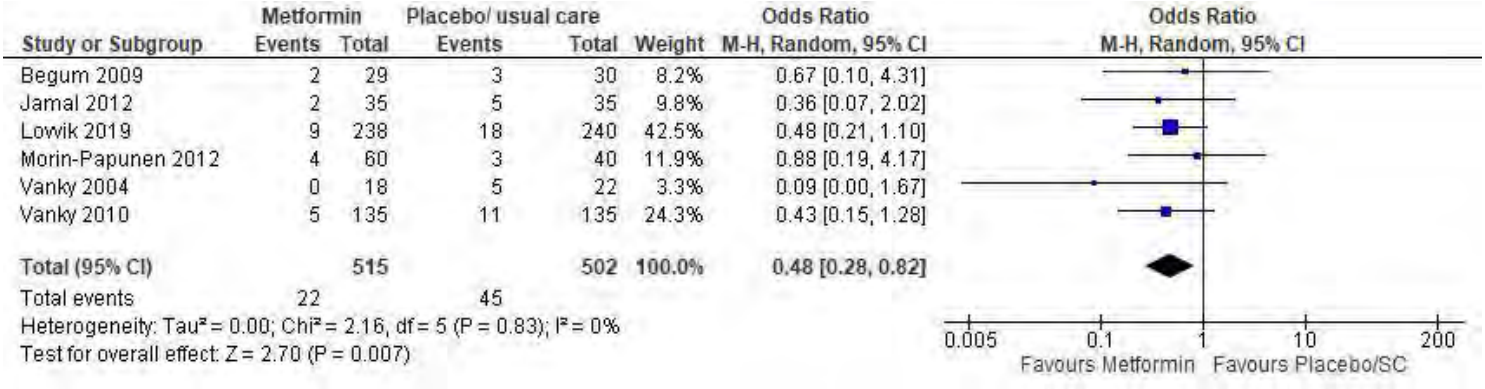
OUTCOME 6. Preterm birth

6.1. Individual Study Data Tables

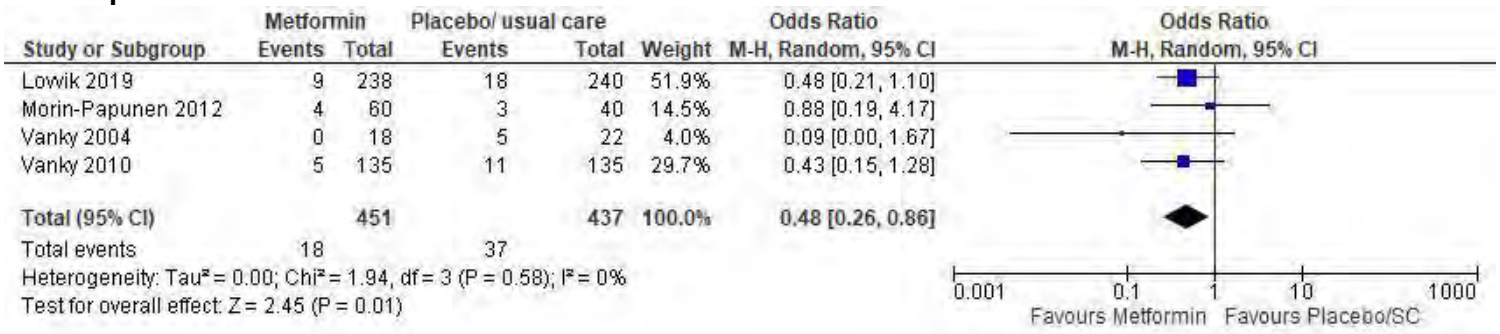
OUTCOME: Preterm birth					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Metformin vs placebo or control								
Author, year	**Unit of outcome**	**Method of measurement**	**N events in MET group**	**N total in MET group**	**N events in Placebo/ control group**	**N total in Placebo/ control group**	**Are these values adjusted?**	**If adjusted, what variables were in the model?**
Begum 2008	Incidence/ count	Definition not specified	2	29	3	30	No	NA
Jamal 2012	Incidence/ count	< 37 weeks GA on U/S	2	35	5	35	No	NA
Lovvik 2019	Incidence/ count	23< 37 weeks GA	9	238	18	240	No	NA
Morin-Papunen 2012#	Incidence/ count	<37 weeks	4	60	3	40	No	NA
Vanky 2004	Incidence/ count	22< 37 weeks	0	18	5	22	No	NA
Vanky 2010	Incidence/ count	< 37 weeks GA based on mid-pregnancy US scan	5	135	11	135	No	NA

#only includes dates from a subset of n=132 women who became pregnant

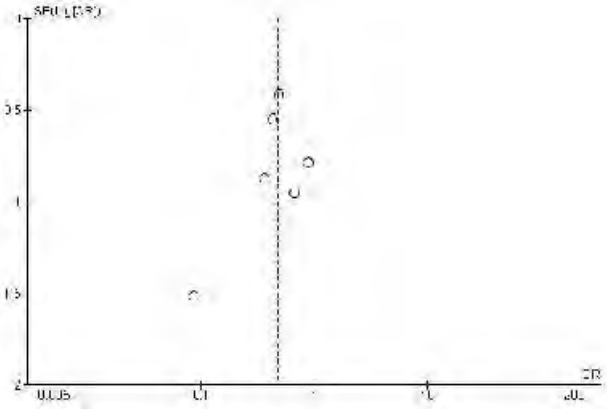
6.2. Forest plot for differences between metformin and placebo/ control in preterm birth



6.3. SENSITIVITY ANALYSIS: Forest plot for differences between metformin and placebo only in pre-eclampsia



6.4. Funnel plot for assessment of publication bias



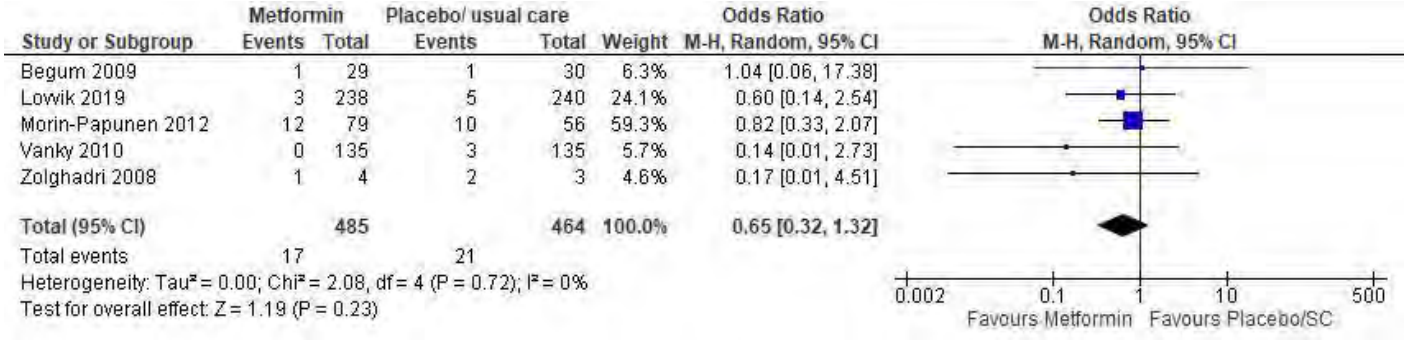
OUTCOME 7. Miscarriage/ spontaneous abortion

7.1. Individual Study Data Tables

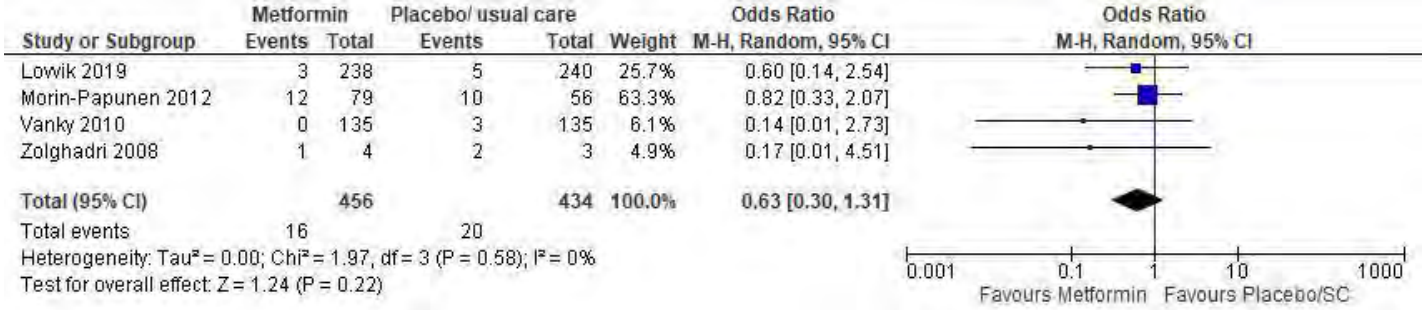
OUTCOME: Miscarriage/ spontaneous abortion			**OUTCOME TYPE:** Dichotomous					
COMPARISON (if applicable): Metformin vs placebo or control								
Author, year	**Unit of outcome**	**Method of measurement**	**N events in MET group**	**N total in MET group**	**N events in Placebo/ control group**	**N total in Placebo/ control group**	**Are these values adjusted?**	**If adjusted, what variables were in the model?**
Begum 2008	Incidence/ count	Definition not specified	1	29	1	30	No	NA
Lovvik 2019	Incidence/ count	Late miscarriage (13 wk - 22+6 wk)	3	238	5	240	No	NA
Morin-Papunen 2012	Incidence/ count	Up to 19 weeks GA	12	79	10	56	No	NA
Vanky 2010	Incidence/ count	Spontaneous abortion - conception to 22 weeks	0	135	3	135	No	NA
Zolghadri 2008	Incidence/ count	Definition not specified	1	4	2	3	No	NA

*derived from individual patient data; #only includes dates from a subset of n=132 women who became pregnant.

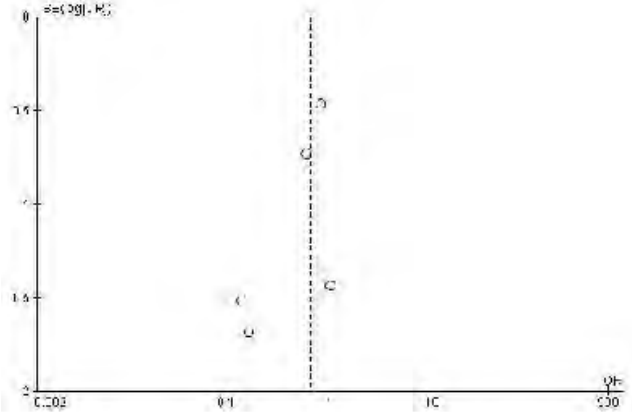
7.2. Forest plot for differences between metformin and placebo or control in miscarriage/ spontaneous abortion



7.3. SENSITIVITY ANALYSIS: Forest plot for differences between metformin and placebo only in miscarriage/ spontaneous abortion



7.4. Funnel plot for assessment of publication bias



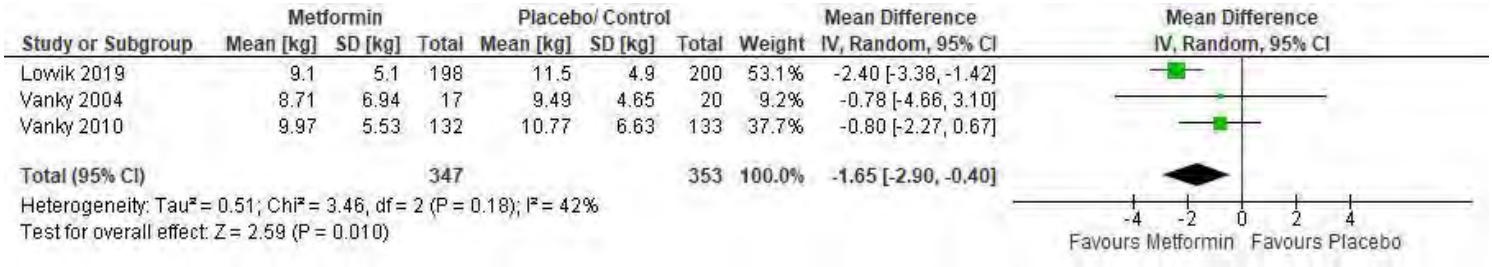
OUTCOME 8. Gestational Weight Gain

8.1. Individual Study Data Tables

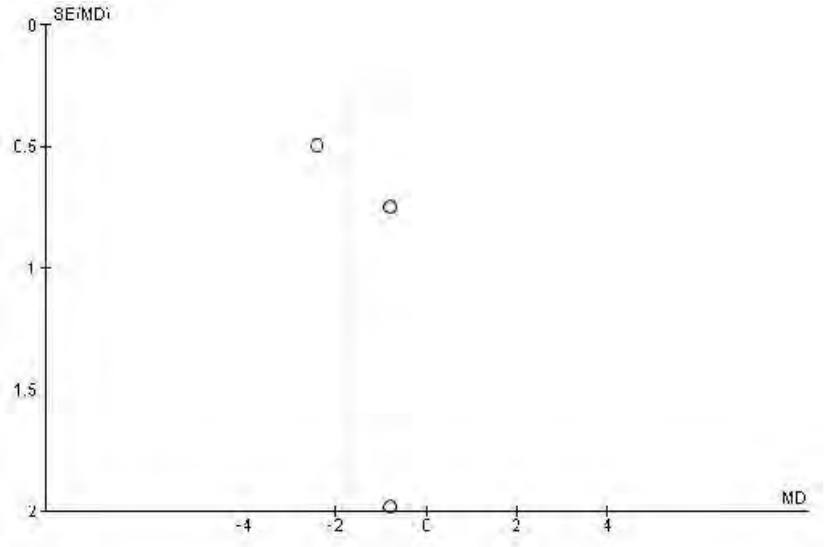
OUTCOME: Gestational weight gain					**OUTCOME TYPE:** Continuous					
COMPARISON (if applicable): Metformin vs placebo or control										
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L)**	**Method of measurement**	**Mean in intervention group**	**SD in intervention group**	**Sample size**	**Mean or median in control group**	**SD in control group**	**Sample size**	**Are these values adjusted?**	**If adjusted, what variables were in the model?**
Lovvik 2019	kg	Until week 36	9.1	5.1	198	11.5	4.9	200	No	NA
Vanky 2004*	kg	Until week 36	8.71	6.94	17	9.49	4.65	20	No	NA
Vanky 2010*	kg	Until week 36	9.97	5.53	132	10.77	6.63	133	No	NA

*derived from individual patient data

8.2. Forest plot for differences between metformin and placebo or control in gestational weight gain



8.3. Funnel plot for assessment of publication bias



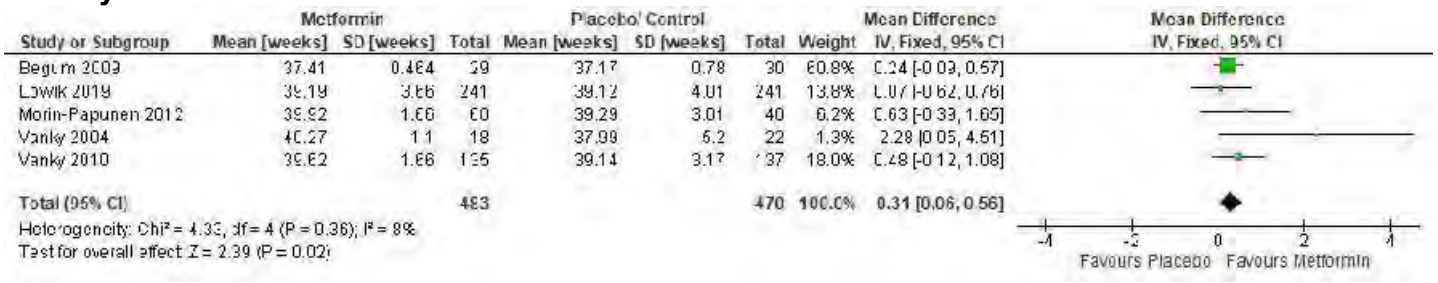
OUTCOME 9. Gestational Age at Delivery

9.1. Individual Study Data Tables

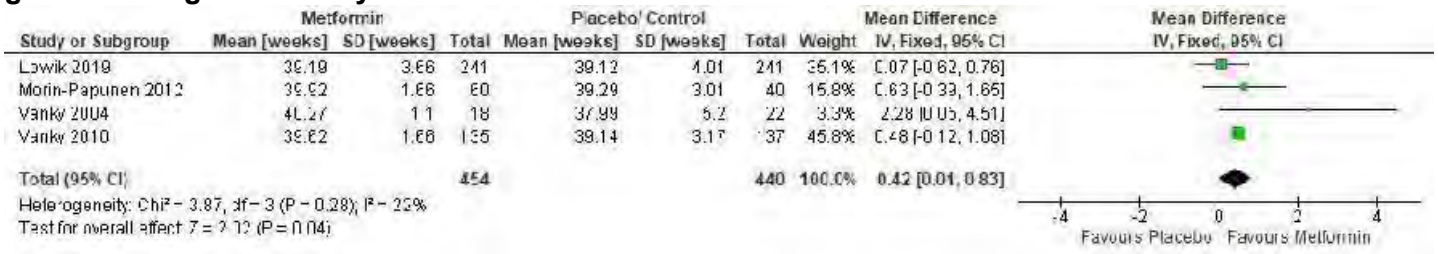
OUTCOME: Gestational Age at delivery					**OUTCOME TYPE:** Continuous					
COMPARISON (if applicable): Metformin vs placebo or control										
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L)**	**Method of measurement**	**Mean in intervention group**	**SD in intervention group**	**Sample size**	**Mean or median in control group**	**SD in control group**	**Sample size**	**Are these values adjusted?**	**If adjusted, what variables were in the model?**
Begum 2008	weeks	NA	37.41	0.464	29	37.17	0.780	30	No	NA
Lovvik 2019*	weeks	NA	39.19	3.66	241	39.12	4.01	241	No	NA
Morin-Papunen 2012*#	Weeks	NA	39.92	1.66	60	39.29	3.01	40	No	NA
Vanky 2004*	weeks	NA	40.27	1.1	18	37.99	5.2	22	No	NA
Vanky 2010*	weeks	NA	39.62	1.66	135	39.14	3.17	137	No	NA

*derived from individual patient data; #only includes dates from a subset of n=132 women who became pregnant.

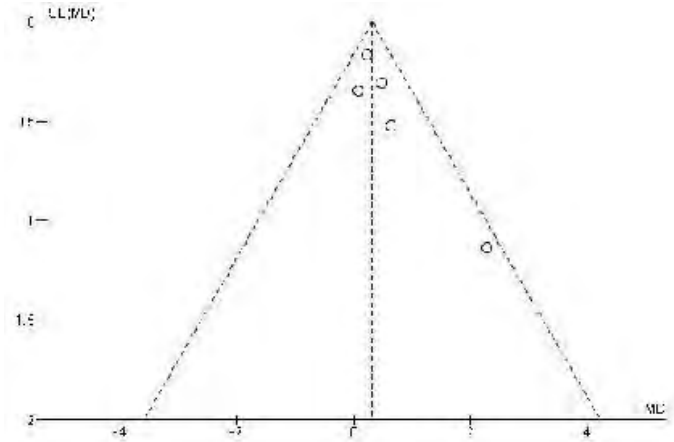
9.2. Forest plot for differences between metformin and placebo or control in gestational age at delivery



9.3. SENSITIVITY ANALYSIS: Forest plot for differences between metformin and placebo only in gestational age at delivery



7.4. Funnel plot for assessment of publication bias



OUTCOME 10. Neonatal hypoglycaemia

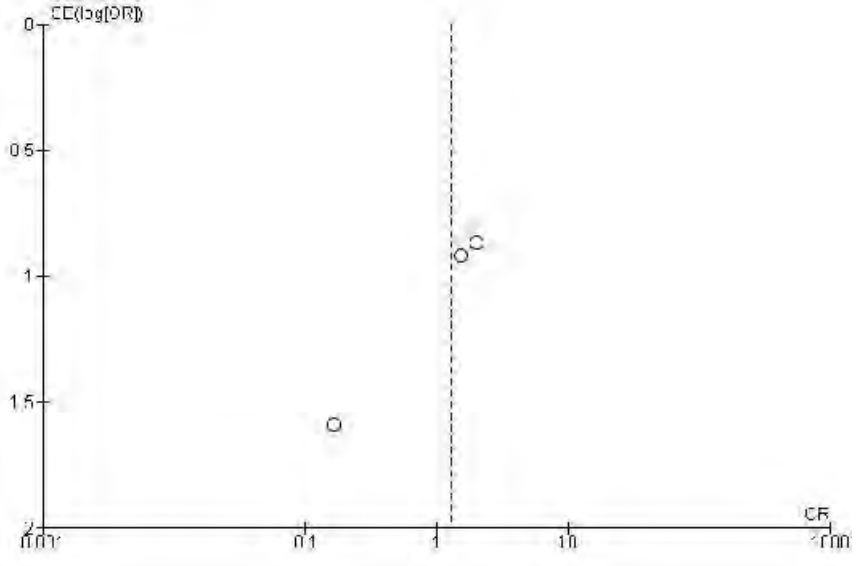
10.1. Individual Study Data Table

OUTCOME: Neonatal hypoglycaemia				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Metformin vs placebo or control								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted?**	**If adjusted, what variables were in the model?**
Lovvik 2019	Incidence/ count	Study-defined; NR	4	235	2	237	No	NA
Vanky 2004*	Incidence/ count	<2.6 mmol/L	0	18	2	17	No	NA
Vanky 2010	Incidence/ count	Study- defined; NR	3	135	2	135	No	NA

*derived from individual patient data

10.2. Forest plot for differences between metformin and placebo or control in neonatal hypoglycaemia

10.3. Funnel plot for assessment of publication bias



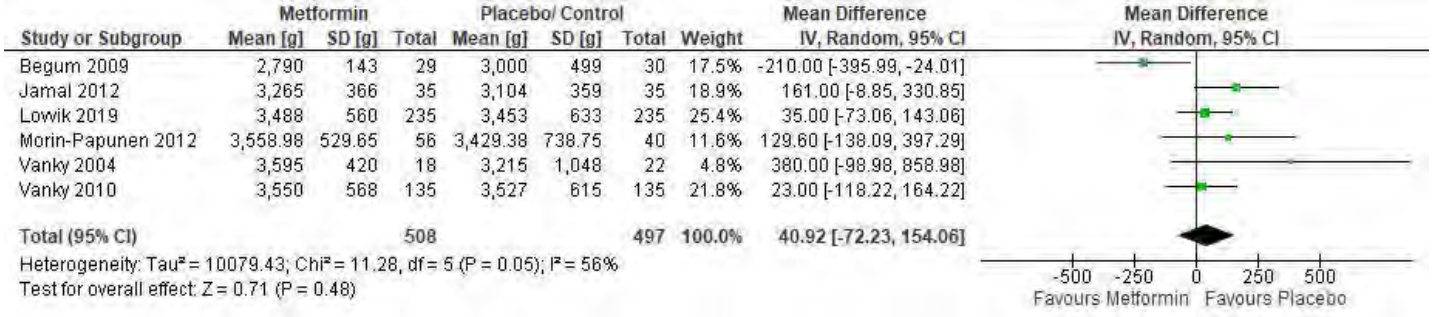
OUTCOME 11. Neonatal birthweight

11.1. Individual Study Data Table

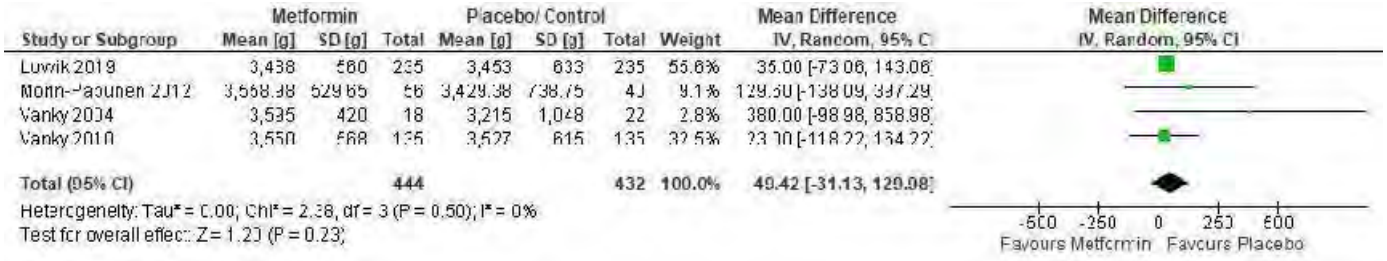
OUTCOME: Birthweight					**OUTCOME TYPE:** Continuous					
COMPARISON (if applicable): Metformin vs placebo or control										
Author, year	**Unit of outcome**	**Method of measurement**	**Mean in intervention group**	**SD in intervention group**	**Sample size**	**Mean or median in control group**	**SD in control group**	**Sample size**	**Are these values adjusted?**	**If adjusted, what variables were in the model?**
Begum 2008	g	NA	2790	143	29	3000	499	30	No	NA
Jamal 2012	g	NA	3265	366	35	3104	359	35	No	NA
Lovvik 2019	g	NA	3488	560	235	3453	633	235	No	NA
Morin-Papunen*#	g	NA	3558.98	529.65	56	3429.38	738.75	40	No	NA
Vanky 2004	g	NA	3595	420	18	3215	1048	22	No	NA
Vanky 2010	g	NA	3550	568	135	3527	615	135	No	NA

*derived from individual patient data; #only includes dates from a subset of n=132 women who became pregnant.

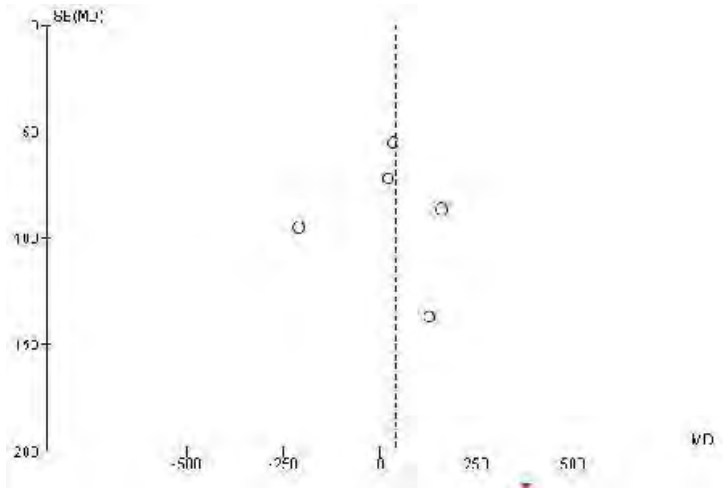
11.2. Forest plot for differences between metformin and placebo or control in neonatal birthweight



11.3. SENSITIVITY ANALYSIS: Forest plot for differences between metformin and placebo only in neonatal birthweight



11.4. Funnel plot for assessment of publication bias



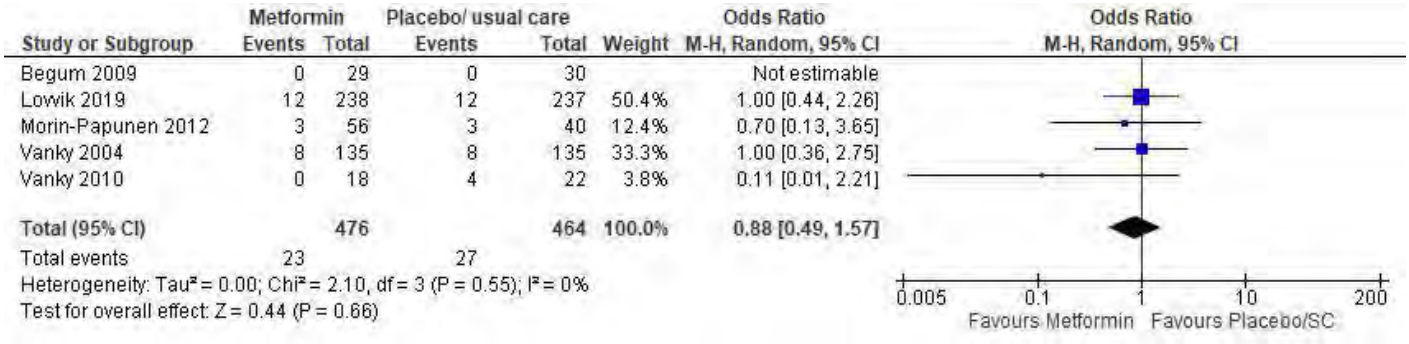
OUTCOME 12. Neonatal birthweight categorical – low birth weight

12.1. Individual Study Data Table

OUTCOME: Low birthweight								
OUTCOME TYPE: Dichotomous								
COMPARISON (if applicable): Metformin vs placebo or control								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted?**	**If adjusted, what variables were included in the model?**
Begum 2008	Incidence/ count	Definition not specified	0	29	0	30	No	NA
Lovvik 2019*	Incidence/ count	<2500g	12	238	12	237	No	NA
Morin-papunen*#	Incidence/ count	<2500g	3	56	3	40	No	NA
Vanky 2010	Incidence/ count	<2500g	8	135	8	135	No	NA
Vanky 2004*	Incidence/ count	<2500g	0	18	4	22	No	NA

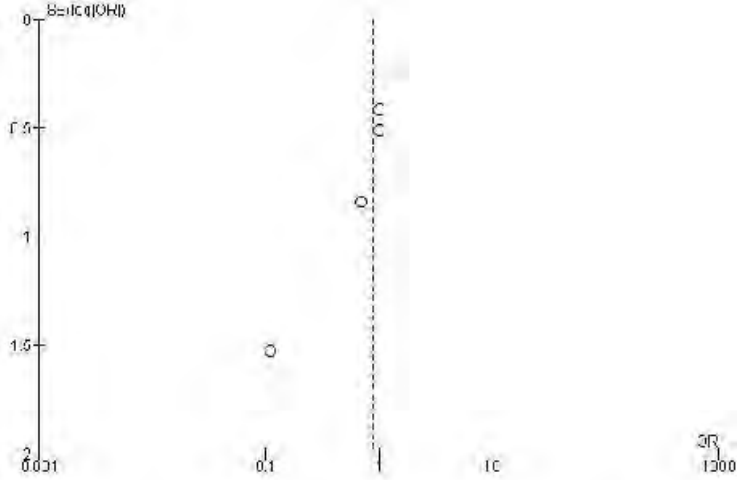
*derived from individual patient data; #only includes dates from a subset of n=132 women who became pregnant.

12.2. Forest plot for differences between metformin and placebo or control in low birthweight



12.3. SENSITIVITY ANALYSIS: Forest plot for differences between metformin and placebo only in low birthweight

12.4. Funnel plot for assessment of publication bias



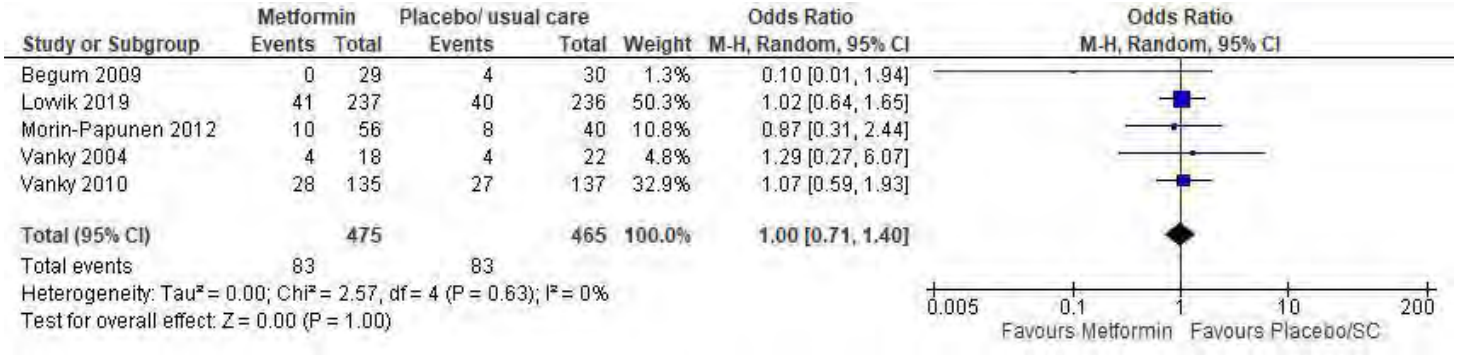
OUTCOME 13. Neonatal birthweight categorical – Macrosomia

13.1. Individual Study Data Table

OUTCOME: Macrosomia					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Metformin vs placebo or control								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted?**	**If adjusted, what variables were in the model?**
Begum 2008	Incidence/ count	Definition not specified	0	29	4	30	No	NA
Lovvik 2019*	Incidence/ count	>4000 g	41	237	40	236	No	NA
Morin-Papunen 2012*#	Incidence/ count	>4000 g	10	56	8	40	No	NA
Vanky 2004*	Incidence/ count	>4000 g	4	18	4	22	No	NA
Vanky 2010*	Incidence/ count	>4000 g	28	135	27	137	No	NA

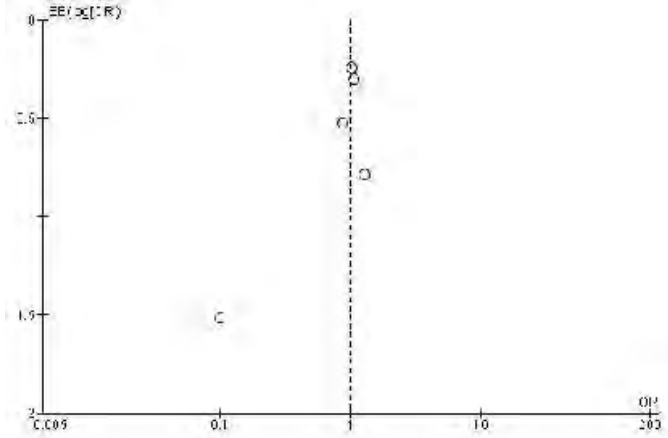
*derived from individual patient data; #only includes dates from a subset of n=132 women who became pregnant.

13.2. Forest plot for differences between metformin and placebo or control in macrosomia



13.3. SENSITIVITY ANALYSIS: Forest plot for differences between metformin and placebo only in macrosomia

13.4. Funnel plot for assessment of publication bias

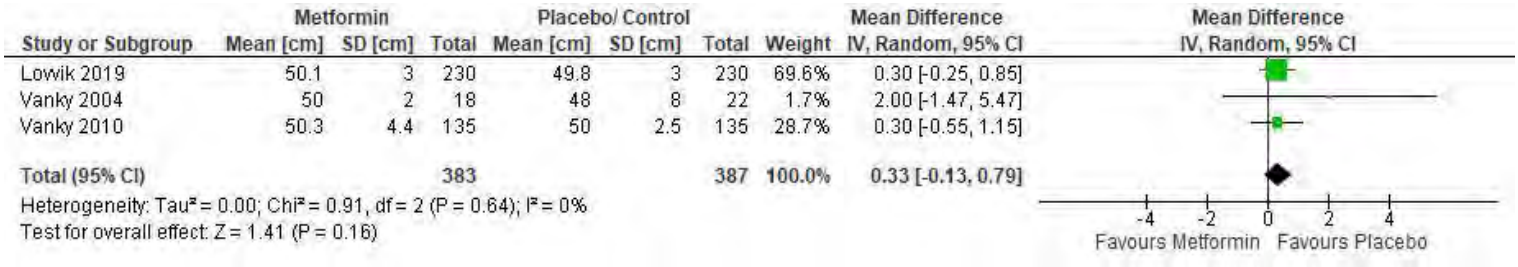


OUTCOME 14. Neonatal length

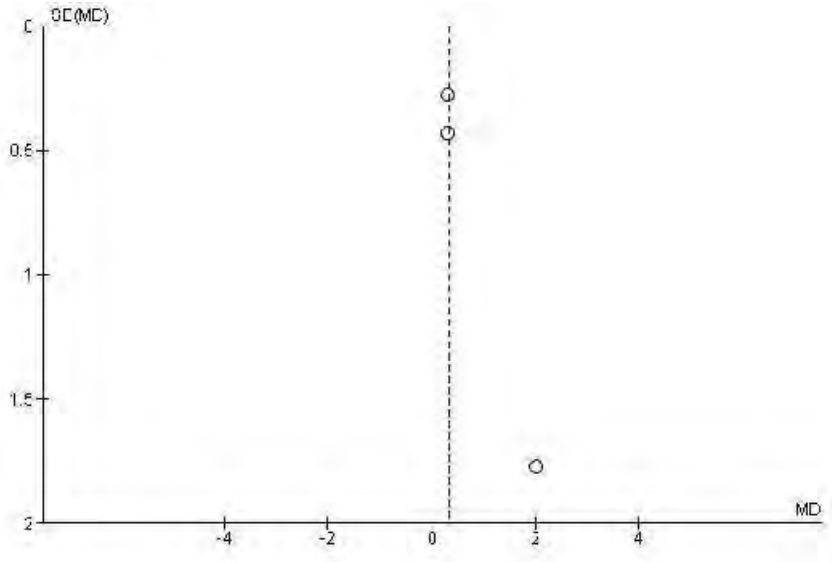
14.1. Individual Study Data Table

OUTCOME: Neonatal length					**OUTCOME TYPE:** Continuous					
COMPARISON (if applicable): Metformin vs placebo										
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L)**	**Method of measurement**	**Mean in intervention group**	**SD in intervention group**	**Sample size**	**Mean or median in control group**	**SD in control group**	**Sample size**	**Are these values adjusted?**	**If adjusted, what variables were in the model?**
Lovvik 2019	cm	NA	50.1	3.0	230	49.8	3.0	230	No	NA
Vanky 2004	cm	NA	50	2	18	48	8	22	No	NA
Vanky 2010	cm	NA	50.3	4.4	135	50.0	2.5	135	No	NA

14.2. Forest plot for differences between metformin and placebo in neonatal length



14.3. Funnel plot for assessment of publication bias

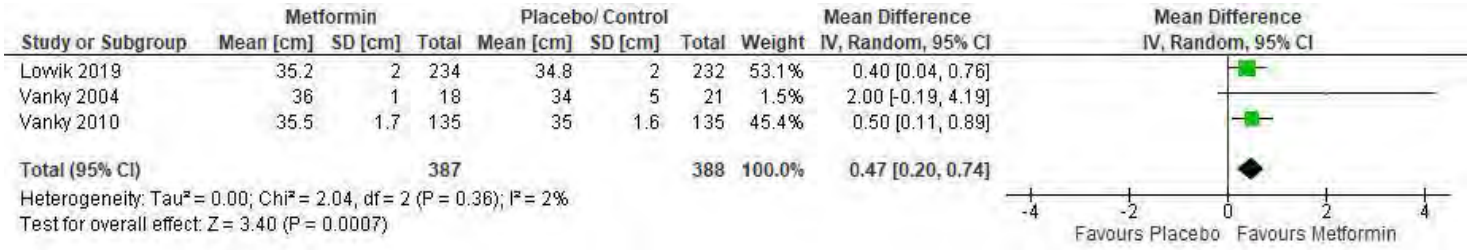


OUTCOME 15. Head Circumference

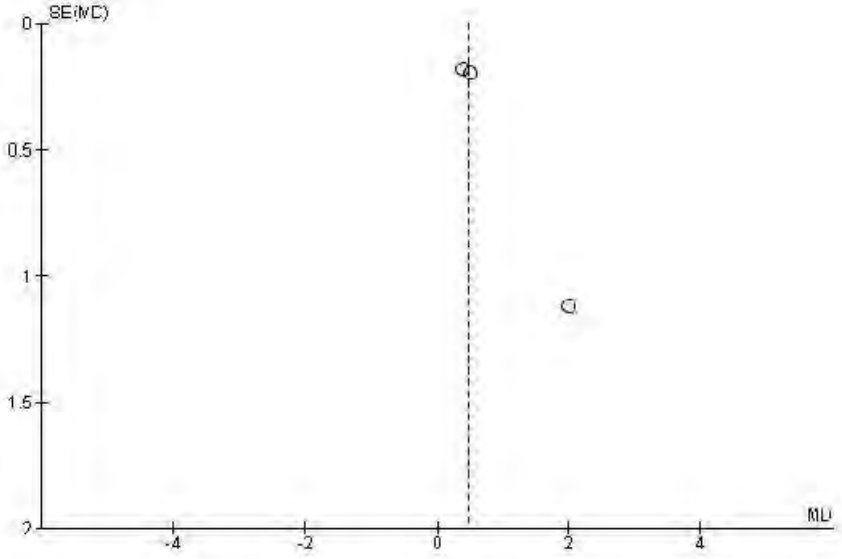
15.1. Individual Study Data Table

OUTCOME: Head circumference					**OUTCOME TYPE:** Continuous					
COMPARISON (if applicable): Metformin vs placebo										
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L)**	**Method of measurement**	**Mean in intervention group**	**SD in intervention group**	**Sample size**	**Mean or median in control group**	**SD in control group**	**Sample size**	**Are these values adjusted?**	**If adjusted, what variables were in the model?**
Lovvik 2019	cm	NA	35.2	2.0	234	34.8	2.0	232	No	NA
Vanky 2004	cm	NA	36	1	18	34	5	21	No	NA
Vanky 2010	cm	NA	35.5	1.7	135	35.0	1.6	135	No	NA

15.2. Forest plot for differences between metformin and placebo in head circumference



15.3. Funnel plot for assessment of publication bias

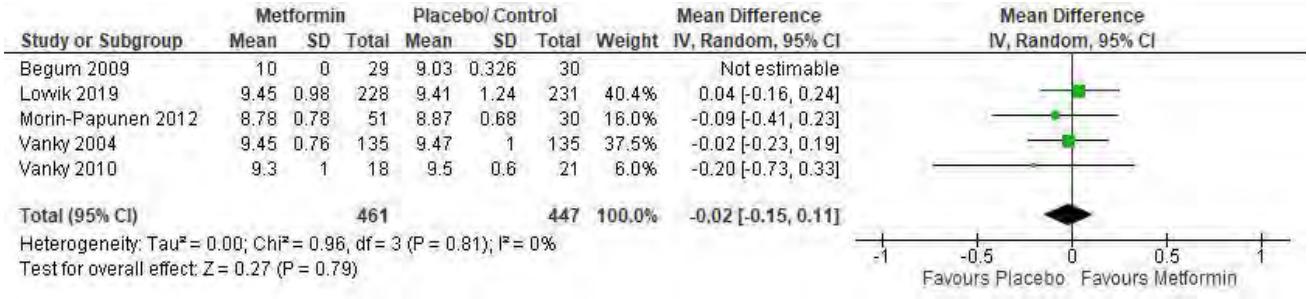


OUTCOME 16. APGAR score at 5 minutes

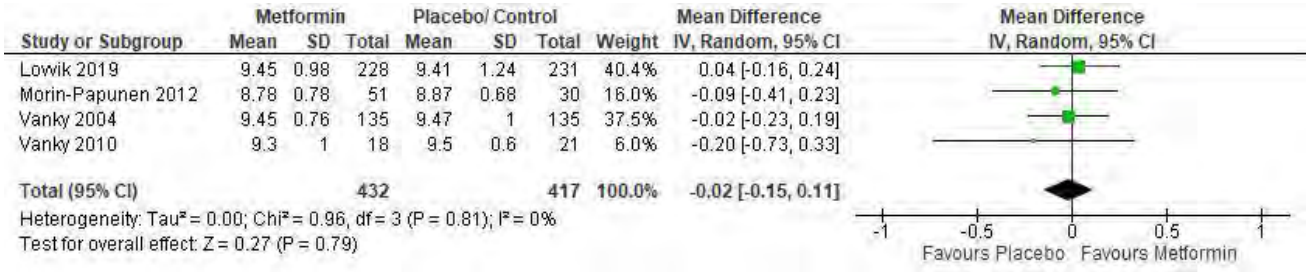
16.1. Individual Study Data Table

OUTCOME: APGAR at 5 min						**OUTCOME TYPE:** Continuous				
COMPARISON (if applicable): Metformin vs placebo or control										
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L)**	**Method of measurement**	**Mean in intervention group**	**SD in intervention group**	**Sample size**	**Mean or median in control group**	**SD in control group**	**Sample size**	**Are these values adjusted?**	**If adjusted, what variables were in the model?**
Begum 2008	Score	APGAR 5	10.00	00	29	9.03	0.326	30	No	NA
Lovvik 2019*	Score	APGAR 5	9.45	0.98	228	9.41	1.24	231	Live births only	NA
Morin-Papunen 2012*#	Score	APGAR 5	8.78	0.78	51	8.87	0.68	30	No	NA
Vanky 2010*	Score	APGAR 5	9.45	0.76	135	9.47	1.0	135	No	NA
Vanky 2004*	Score	APGAR 5	9.3	1.00	18	9.5	0.6	21	No	NA

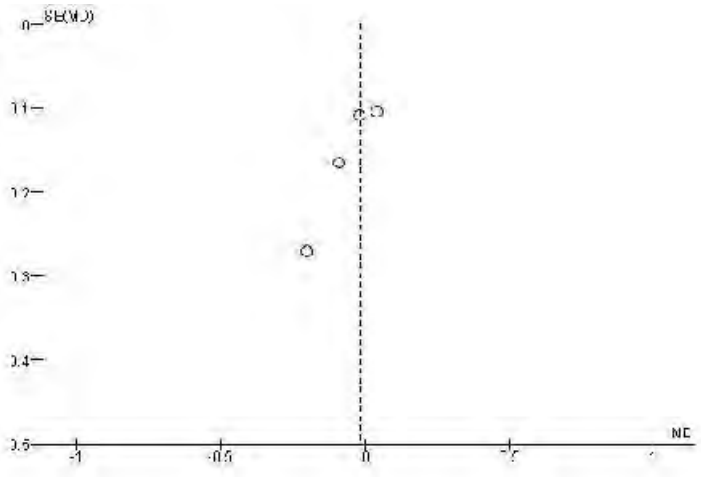
16.2. Forest plot for differences between metformin and placebo or control in APGAR score at 5 minutes



16.3. SENSITIVITY ANALYSIS: Forest plot for differences between metformin and placebo only in APGAR score at 5 minutes



16.4. Funnel plot for assessment of publication bias

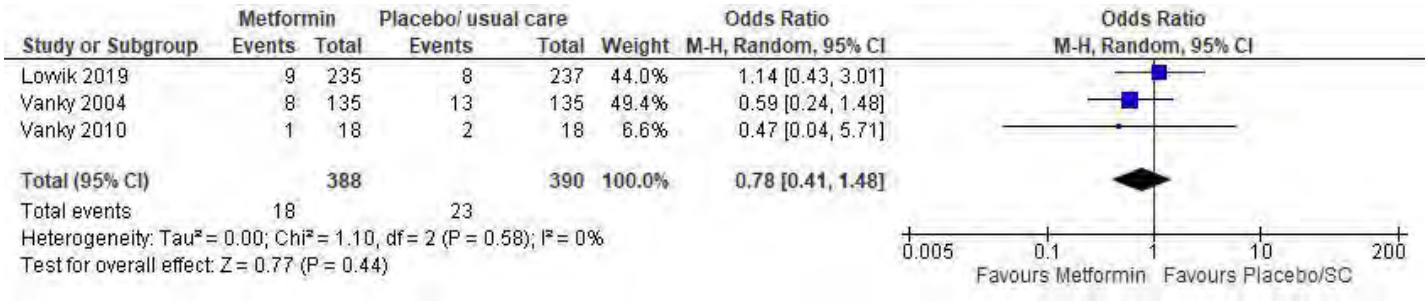


OUTCOME 17. Neonatal icterus/ jaundice

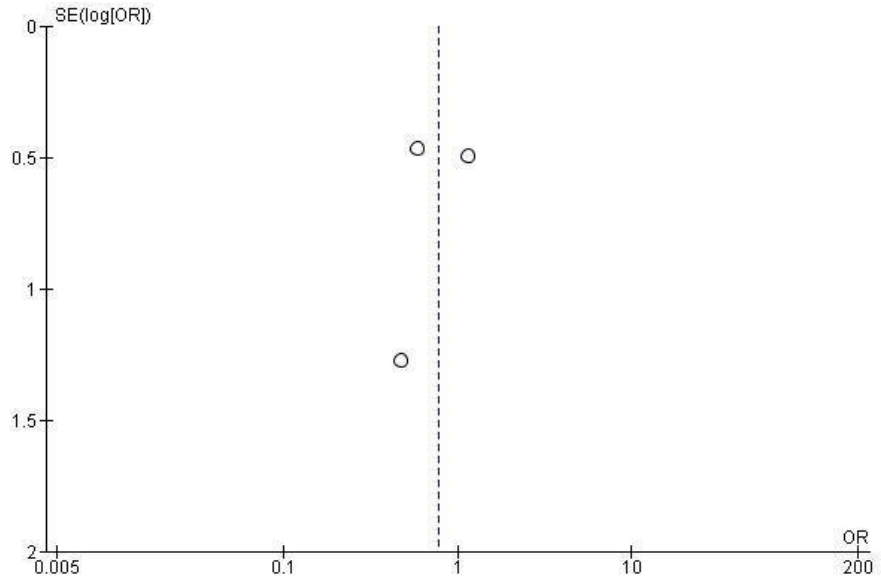
17.1. Individual Study Data Table

OUTCOME: Neonatal icterus/ jaundice					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Metformin vs placebo or control								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted?**	**If adjusted, what variables were included in the model?**
Lovvik 2019	Incidence/ count	NR	9	235	8	237	No	NA
Vanky 2010	Incidence/ count	NR	8	135	13	135	No	NA
Vanky 2004	Incidence/ count	NR	1	18	2	18	No	NA

17.2. Forest plot for differences between metformin and placebo in neonatal icterus/ jaundice



17.3. Funnel plot for assessment of publication bias

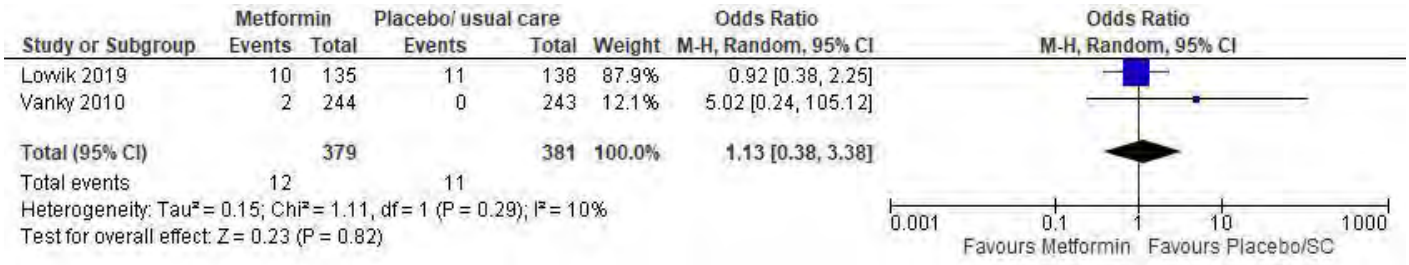


OUTCOME 18. Fetal malformations

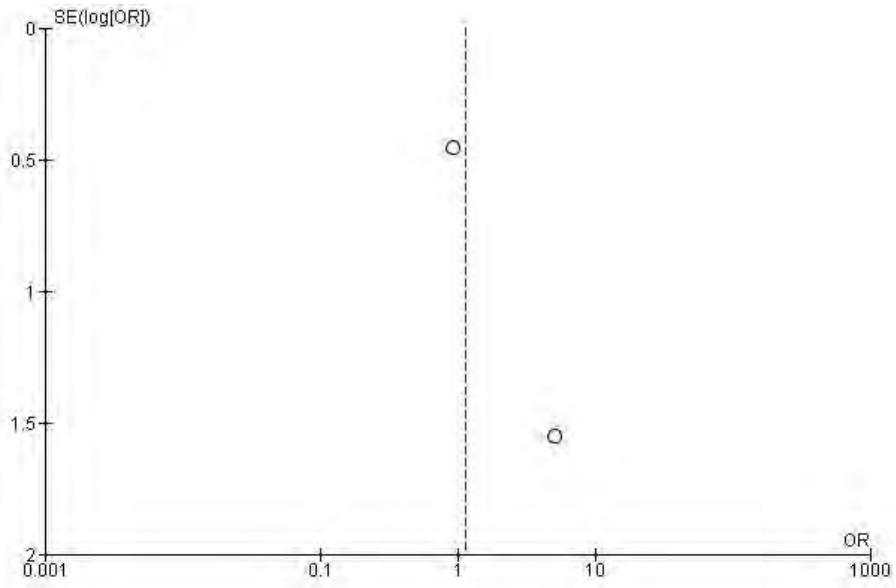
18.1. Individual Study Data Table

OUTCOME: Fetal malformations				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Metformin vs placebo or control								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted?**	**If adjusted, what variables were included in the model?**
Vanky 2010#	Incidence/ count	NA	10	135	11	138	No	NA
Lovvik 2019	Incidence/ count	NA	2	244	0	243	No	NA

18.2. Forest plot for differences between metformin and placebo in fetal malformations



18.3. Funnel plot for assessment of publication bias



OUTCOME 19. Neonatal/ perinatal death

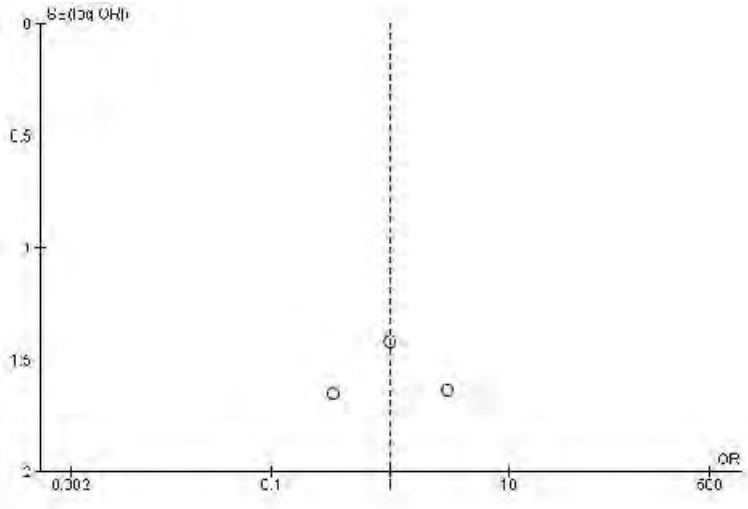
19.1. Individual Study Data Table

OUTCOME: Neonatal/ perinatal death					**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Metformin vs placebo or control								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted?**	**If adjusted, what variables were included in the model?**
Begum 2008	Incidence/ count	Post-birth death	0	29	1	30	No	NA
Lovvik 2019	Incidence/ count	Death at 22+wk or >500g until 4 wk post delivery	1	244	0	243	No	NA
Vanky 2010	Incidence / count	Infant/ perinatal death	1	135	1	135	No	NA

19.2. Forest plot for differences between metformin and placebo or control in neonatal death

19.3. SENSITIVITY ANALYSIS: Forest plot for differences between metformin and placebo only in neonatal death

19.4. Funnel plot for assessment of publication bias



OUTCOME 20. Neonatal birth asphyxia / respiratory distress

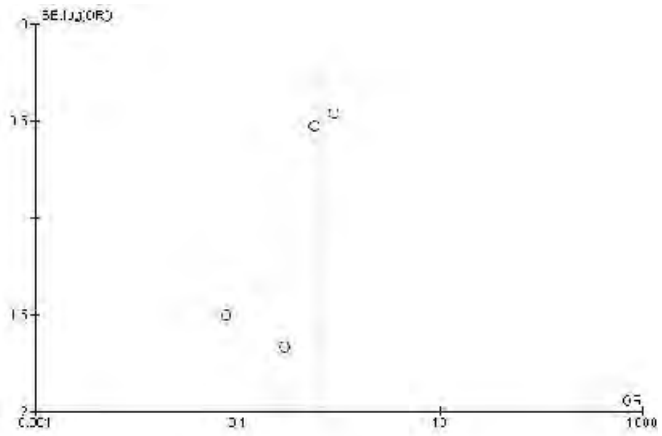
20.1. Individual Study Data Table

OUTCOME: Birth asphyxia/ RDS				**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Metformin vs placebo or control								
Author, year	**Unit of outcome (e.g. g, mg, µg, mmol/L, etc.)**	**Method of measurement**	**N events in intervention/ exposure group**	**N total in intervention/ exposure group**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted?**	**If adjusted, what variables were included in the model?**
Begum 2008	Incidence/ count	Definition not specified	0	29	5	30	No	NA
Lovvik 2019	Incidence/ count	Asphyxia	9	235	10	237	No	NA
Vanky 2004#	Incidence/ count	RDS	0	18	1	17	No	NA
Vanky 2010	Incidence/ count	Aspiration, respiratory failure	6	135	10	135	No	NA

20.2. Forest plot for differences between metformin and placebo or control in birth asphyxia/ respiratory distress

20.3. SENSITIVITY ANALYSIS: Forest plot for differences between metformin and placebo only in birth asphyxia/ respiratory distress

20.4. Funnel plot for assessment of publication bias



7. GRADE ASSESSMENTS AND EVIDENCE PROFILE

COMPARISON: Metformin v placebo / control												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Met	Placebo/ control	Effect, random [95% CI]	Favours	Certainty	Importance
Outcome: GDM incidence												
6	RCT	serious[1]	serious[2]	no serious indirectness[3,5]	no serious imprecision	none	74/ 505 (14.7%)	80/ 485 (16.5%)	OR 0.76 [0.40, 1.44]	No difference	⨁⨁◯◯ LOW	CRITICAL
Outcome: Fasting glucose												
3	RCT	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	348	358	MD -0.03 [-0.20, 0.15]	No difference	⨁⨁◯◯ LOW	CRITICAL
Outcome: Two-hour post-OGTT glucose												
3	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	303	319	MD 0.05 [-0.17, 0.27]	No difference	⨁⨁⨁◯ MODERATE	CRITICAL
Outcome: Hypertension in pregnancy												
3	RCT	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	25/ 391 (6.4%)	23/ 400 (5.8%)	OR 1.12 [0.62, 2.02]	No difference	⨁⨁◯◯ LOW	CRITICAL
Outcome: Pre-eclampsia												
5	RCT	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	25/ 474 (5.3%)	33/ 468 (7.1%)	OR 0.74 [0.36, 1.50]	No difference	⨁⨁◯◯ LOW	CRITICAL
Outcome: Preterm birth												
6	RCT	no serious risk of bias[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	22/ 515 (4.3%)	45/ 502 (9.0%)	OR 0.48 [0.28, 0.82]	**Metformin** (lower with MET)	⨁⨁⨁⨁ HIGH	CRITICAL
Outcome: Miscarriage												
5	RCT	serious[1]	no serious inconsistency	serious[3]	no serious imprecision	none	17/ 485 (3.5%)	21/ 464 (4.5%)	OR 0.65 [0.32, 1.32]	No difference	⨁⨁◯◯ LOW	CRITICAL
Outcome: Gestational weight gain												
3	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	347	353	MD -1.65 [-2.90, -0.40]	**Metformin** (lower with MET)	⨁⨁⨁◯ MODERATE	IMPORTANT
Outcome Gestational age at delivery												
5	RCT	no serious risk of bias[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	483	470	MD 0.31 [0.06, 0.56]*	**Metformin** (higher with MET)	⨁⨁⨁⨁ HIGH	CRITICAL
Outcome: Neonatal hypoglycaemia												
3	RCT	serious[1]	no serious inconsistency	serious[3]	no serious imprecision	none	7/ 388 (1.8%)	6/ 389 (1.5%)	OR 1.28 [0.40, 4.05]	No difference	⨁⨁◯◯ LOW	CRITICAL
Outcome: Neonatal birthweight												
6	RCT	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	508	497	MD 40.92 [-72.23, 154.06]	No difference	⨁⨁◯◯ LOW	CRITICAL
Outcome: Low birth weight												

5	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	23/ 447 (5.1%)	27/ 434 (6.2%)	OR 0.88 [0.49, 1.57]	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
Outcome: Macrosomia												
5	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	83/ 475 (17.5%)	79/ 435 (18.2%)	OR 1.00 [0.71, 1.40]	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT
Outcome: Neonatal length												
3	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	383	387	MD 0.33 [-0.13, 0.79]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Neonatal head circumference												
3	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	387	388	MD 0.47 [0.20, 0.74]	**Metformin** (higher with MET)	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: APGAR score												
5	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	461	447	MD -0.02 [-0.15, 0.11]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Neonatal icterus/ jaundice												
3	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	18/ 388 (4.6%)	23/ 390 (5.9%)	OR 0.78 [0.41, 1.48]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Fetal malformations												
2	RCT	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	12/ 379 (3.2%)	11/ 381 (2.9%)	OR 1.13 [0.38, 3.38]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Neonatal/ perinatal death												
3	RCT	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	2/ 379 (0.5%)	1/ 378 (0.3%)	OR 1.01 [0.17, 5.87]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Asphyxia/ respiratory distress												
4	RCT	serious[1]	no serious inconsistency	serious[3]	no serious imprecision	none	15/ 417 (3.6%)	26/ 419 (6.2%)	OR 0.64 [0.33, 1.24]	No difference	⊕⊕◯◯ LOW	IMPORTANT

[1] Downgraded once due to high or moderate risk of bias for some studies or outcomes
[2] Downgraded once for inconsistency due to variations in effect estimate directions and/or CIs, or heterogeneity as determined by the I^2 statistic
[3] Downgraded once for indirectness due to the use of different criteria and/or tools/ methods across included studies
[4] Downgraded once for including high risk studies, then upgraded once since the effect persisted in sensitivity analysis which included only the low risk of bias studies
[5] Upgraded once if the effect was not meaningfully changed when indirectness was addressed through sensitivity analysis
*fixed effect model used since the unit of age is measured consistently across studies

Appendix 1. Full List of Excluded Studies from Main Systematic Review Search

	Author	Year	Title	Reason for exclusion
1.	Singh I.	2001	Increased pregnancy rates with metformin and clomiphene citrate in non-obese patients with polycystic ovary syndrome: prospective randomized study	Conference Abstract
1.	Letonturier P.	2001	[Gestational diabetes: an alternative to insulin therapy?].	No full text available
2.	Lao T.	2001	A randomised controlled pilot study of the management of gestational impaired glucose tolerance.	Letter to Editor
3.	George S.S.	2003	Sequential treatment of metformin and clomiphene citrate in clomiphene-resistant women with polycystic ovary syndrome: a randomized, controlled trial	Not during pregnancy
4.	Palomba S.	2004	Metformin administration versus laparoscopic ovarian diathermy in clomiphene citrate-resistant women with polycystic ovary syndrome: a prospective parallel randomized double-blind placebo-controlled trial.	Not during pregnancy
5.	Glueck C.J.	2004	Height, weight, and motor-social development during the first 18 months of life in 126 infants born to 109 mothers with polycystic ovary syndrome who conceived on and continued metformin through pregnancy	Not randomised
6.	Palomba S.	2005	Prospective parallel randomized, double-blind, double-dummy controlled clinical trial comparing clomiphene citrate and metformin as the first-line treatment for ovulation induction in nonobese anovulatory women with polycystic ovary syndrome.	Not during pregnancy
7.	Moore L.E.	2005	A randomized trial of metformin compared to glyburide in the treatment of gestational diabetes.	Conference abstract
8.	Hwu Y.M.	2005	Ultra-short metformin pretreatment for clomiphene citrate-resistant polycystic ovary syndrome.	Not during pregnancy
9.	Vanky E.	2006	Metformin reduces pregnancy complications in PCOS women- could increased flow in the uterine arteries be an explanation? - Results of a prospective, randomized, double-blind study	Duplicate
10.	Moll E.	2006	Effect of clomifene citrate plus metformin and clomifene citrate plus placebo on induction of ovulation in women with newly diagnosed polycystic ovary syndrome: randomised double blind clinical trial.	Not during pregnancy
11.	Anonymous	2006	Metformin use during pregnancy does not increase the risk of major malformation	Letter/ Commentary
12.	Rowan J.	2007	A trial in progress: gestational diabetes. Treatment with metformin compared with insulin (the Metformin in Gestational Diabetes [MiG] trial).	
13.	Qublan, H.S.	2007	Dietary intervention versus metformin to improve the reproductive outcome in women with polycystic ovary syndrome. A prospective comparative study.	Not during pregnancy
14.	Ogunyemi D.	2007	Comparison of glyburide versus insulin in management of gestational diabetes mellitus	Letter to Editor; metformin not used
15.	Feig D.S.	2007	Oral antidiabetic agents in pregnancy and lactation: a paradigm shift?	Narrative review
16.	Carlsen S.M.	2007	Homocysteine levels are unaffected by metformin treatment in both nonpregnant and pregnant women with polycystic ovary syndrome.	No outcomes of interest
17.	Stridsklev S.	2008	Histopathological examination of pcos placentas - metformin or placebo in pregnancy	Conference Abstract
18.	Moore L.E.	2008	A randomized controlled trial of metformin and glyburide in gestational diabetes.	Conference abstract
19.	-	2008	Metformin (alone or with insulin) was as effective as insulin for preventing perinatal complications in gestational diabetes.	Duplicate of Xiong 2018 excluded study
20.	Zain M.M.	2009	Comparison of clomiphene citrate, metformin, or the combination of both for first-line ovulation induction, achievement of pregnancy, and live birth in Asian women with polycystic ovary syndrome: a randomized controlled trial	Not in pregnancy
21.	Wensel T.M.	2009	Role of metformin in the treatment of gestational diabetes	Review
22.	Johnson N.P.	2009	PCOSMIC-polycystic ovarian syndrome, metformin for infertility with clomiphene: a multi-centre double-blind randmised controlled trial	Conference abstract (and PCOSMIC was not performed during pregnancy)
23.	Rowan J.	2010	Glycemia and its relationship to outcomes in the metformin in gestational diabetes trial.	Observational assessment of baseline MiG data
24.	Martinez P.	2010	A randomized study comparing metformin and insulin in the treatment of gestational diabetes mellitus. Interim results.	Conference Abstract
25.	Irct 201011295272N	2010	The effect of metformine on the uteroplacental circulation in comparison with Aspirin in pregnant women with poly cystic ovary syndrome.	Protocol
26.	Carlsen S.M.	2010	Metformin influence on hormone levels at birth, in PCOS mothers and their newborns.	Sub-analysis of included trial
27.	Abu Hashim H.	2010	N-acetyl cysteine plus clomiphene citrate versus metformin and clomiphene citrate in treatment of clomiphene-resistant polycystic ovary syndrome: a randomized controlled trial	Not during pregnancy
28.	Li C.	2011	Prognostic value of total testosterone for pregnancy during treatment in patients with clomiphene-citrate-resistant polycystic ovary syndrome: a pilot study.	Not during pregnancy
29.	De Leo V.	2011	The administration of metformin during pregnancy reduces polycystic ovary syndrome related gestational complications.	Not randomised
30.	Davar R.	2011	Metformin-letrozole in comparison with Metformin-clomiphene citrate in clomiphene-resistance PCOS patients undergoing IUI.	Not during pregnancy/ metformin used in both groups
31.	Abu Hashim H.	2011	Combined metformin and clomiphene citrate versus laparoscopic ovarian diathermy for ovulation induction in clomiphene-resistant women with polycystic ovary syndrome: a randomized controlled trial	Not during pregnancy
32.	Vanky E.	2012	Breast size increment during pregnancy and breast feeding in PCOS mothers: A follow-up study of a randomized controlled trial on metformin vs. placebo	Conference abstract

33.	Vanky E.	2012	Breast size increment during pregnancy and breast feeding in PCOS mothers: A follow-up study of a randomized controlled trial on metformin vs. placebo	Conference abstract
34.	Vanky E.	2012	Metformin-effect on newborn head size, maternal and infant weight development: A follow-up study of an RCT on PCOS	Conference Abstract
35.	Navali N.	2012	Comparing therapeutic effects of Metformin and Pioglitazone in Polycystic ovary syndrome (PCOS).	Not during pregnancy
36.	Ghasemi N.	2012	Effectiveness of Metformin in treatment of infertility and recurrent pregnancy loss in polycystic ovarian syndrome	Conference Abstract
37.	Carlsen S.M.	2012	Metformin effect on newborn head size, maternal and infant weight gain: a follow-up study of an RCT on PCOS.	Conference Abstract
38.	Bahado-Singh R	2012	Fetal male gender and the benefits of treatment of mild gestational diabetes mellitus.	Not using metformin
39.	Ainuddin J.	2012	Metformin: A safe alternative to insulin therapy in gestational diabetes.	Conference Abstract
40.	Zinnat A.N.	2013	Can metformin be used in place of insulin for the treatment of GDM for low resource countries?	Conference abstract
41.	Mesdaghinia, E.	2013	Comparison of newborn outcomes in women with gestational diabetes mellitus treated with metformin or insulin: A randomised blinded trial.	Conference Abstract
42.	Hosseini M.A.	2013	Metformin treatment in different phenotypes of polycystic ovary syndrome.	Not during pregnancy
43.	Glueck C.J.	2013	Effects of metformin-diet intervention before and throughout pregnancy on obstetric and neonatal outcomes in patients with polycystic ovary syndrome	Not randomised
44.	Gatford K.L.	2013	Vitamin B<inf>12</inf> and homocysteine status during pregnancy in the metformin in gestational diabetes trial: Responses to maternal metformin compared with insulin treatment.	Duplicate
45.	Battin M.R.	2013	Neurodevelopmental outcome at 24-months in children following a randomized trial of metformin versus insulin treatment for gestational diabetes (mig trial).	
46.	Barrett H.L.	2013	Maternal and neonatal circulating markers of metabolic and cardiovascular risk in the metformin in gestational diabetes (MiG) trial: responses to maternal metformin versus insulin treatment.	
47.	Abd Elgafor I.	2013	Efficacy of combined metformin-letrozole in comparison with bilateral ovarian drilling in clomiphene-resistant infertile women with polycystic ovarian syndrome	Duplicate MiG Abstract
48.	Reyes-Munoz	2014	Medical nutrition therapy plus metformin for preventing gestational diabetes among high-risk women.	Conference abstract
49.	Coiner J.	2014	The treatment of diabetes in pregnancy; metformin vs glyburide and insulinebiomedical evidence of fetopathy	Conference Abstract and no outcomes of interest
50.	Christiansen SC	2014	The effect of exercise and metformin treatment on circulating free DNA in pregnancy.	No outcomes of interest
51.	Ardilouze J.L.	2014	Gestational diabetes mellitus: A randomized study comparing insulin therapy to a combination of half-maximal dosages of metformin and glyburide	Abstract / Poster EASD
52.	Ardilouze J.L.	2014	Gestational diabetes mellitus: The first prospective randomised study of metformine-glyburide vs insulin	Abstract Poster
53.	Ardilouze J.L.	2014	Gestational diabetes mellitus: A randomized study comparing insulin therapy to a combination of half maximal dosages of metformin and glyburide.	Conference Abstract
54.	Wali A.	2015	A phase-three, open-label randomized controlled trial to compare the efficacy of oral hypoglycemic agents with insulin in the treatment of gestational diabetes mellitus	Conference Poster
55.	Thom E.A.	2015	A randomised study of metformin versus insulin in gestational diabetes: early childhood outcomes	Mini Commentary
56.	Smith J.	2015	Metformin improved lipid profiles in women with gestational diabetes in the first six weeks postpartum	Conference Abstract
57.	Refuerzo J.S.	2015	The effects of metformin on weight loss in women with gestational diabetes: a pilot randomized, placebo-controlled trial.	Not during pregnancy
58.	Nachum Z.	2015	A comparison between two oral hypoglycemics: Glyburide and metformin and their combination for the treatment of gestational diabetes mellitus e a prospective randomized controlled study.	Conference Abstract
59.	Li S.S.	2015	Metformin and auxiliary acupuncture in the treatment of obese women infertility with polycystic ovary syndrome for 75 cases	Not during pregnancy
60.	De Bacco G.	2015	High rate of hypoglycemia in diabetic pregnant women on use of glyburide.	Conference Abstract
61.	Carroll D.M.	2015	In women with gestational diabetes requiring drug treatment, glibenclamide may be inferior to insulin and metformin: Metformin (plus insulin when required) performs better than insulin.	Commentary
62.	-	2015	Does maternal body mass index influence treatment effect in women with mild gestational diabetes?	Duplicate of Huhtala 2018 included study
63.	-	2015	Neurodevelopment of Two-Year-Old Children Exposed to Metformin and Insulin in Gestational Diabetes Mellitus.	Not using metformin
64.	Trouva A.	2016	Thyroid hormone function in pregnant women with polycystic ovary syndrome treated with metformin or placebo	Conference Abstract
65.	Tamer L.H	2016	Effect of metformin on the thyroid function in pregnant women with PCOS	Conference Abstract
66.	Steurer J.	2016	Metformin has no effect on median birth weight score in pregnant non-diabetic women with BMI >35	Full text not available
67.	Mumby C.	2016	Randomised controlled trial of metformin treatment versus standard diabetes antenatal care in women with mild fasting hyperglycaemia diagnosed in pregnancy: A pilot study.	Conference Abstract
68.	Huang W.	2016	Comparison of clomiphene citrate and letrozole for ovulation induction in women with polycystic ovary syndrome: A prospective randomized trial.	Conference Abstract
69.	Feig D.S.	2016	Metformin in women with type 2 diabetes in pregnancy (MiTy): a multi-center randomized controlled trial.	Protocol
70.	Dunne F.	2016	EMERGE: A randomized placebo controlled trial of early metformin in addition to usual care in the reduction of gestational diabetes mellitus effects.	Conference Abstract
71.	Balani J.	2016	Metformin versus Placebo in Obese Pregnant Women without Diabetes.	Letter to the Editor
72.	Wouldes T.	2017	Neurodevelopmental Outcome at 2 Years in Offspring of Women Randomised to Metformin or Insulin Treatment for Gestational Diabetes	Duplicate of Wouldes 2016
73.	Underdal M.O.	2017	Metabolic health in women with PCOS-5-11 years' followup after metformin or placebo in pregnancy	Conference Poster

74.	Singh N.	2017	Efficacy of metformin in improving glycaemic control & perinatal outcome in gestational diabetes mellitus: A non-randomized study	non-randomised
75.	Rezk M.	2017	Clomiphene citrate combined with metformin versus letrozole for induction of ovulation in clomiphene-resistant polycystic ovary syndrome: a randomized clinical trial.	Duplicate
76.	Reynolds R.M.	2017	Glibenclamide and metfoRmin versus stAndard care in gEstational diabeteS (GRACES): a feasibility open label randomised trial	No control group: Both groups receiving metformin
77.	Huhtala Y.M.	2017	Amino acid profile in metformin vs insulin treated women with gestational diabetes	Conference Abstract
78.	Hoffman C.B.	2017	Effect of metformin in the lipid profile of the obese pregnant women.	Conference Abstract
79.	Hjorth-Hansen A	2017	Head size and growth in utero and at birth in metformin exposed children born to mothers with PCOS-a randomized controlled trial	Conference Abstract
80.	Hanem L.G.E.	2017	Intrauterine metformin exposure influences offspring growth,-a 4-year follow-up of children born to mothers with polycystic ovary syndrome.	Conference Abstract of included study: Hanem 2018
81.	-	2017	Amino acid profile in metformin vs insulin treated women with gestational diabetes.	Conference Abstract
82.	Zhen X.M	2018	Longer-term outcomes in offspring of GDM mothers treated with metformin versus insulin	Review
83.	Xiong K.	2018	Clinical efficacy of metformin combined with clomiphene in patients with polycystic ovary syndrome and their effect on serum sex hormones	Not in pregnancy
84.	Tahseen S.	2018	Comparison of metformin versus insulin in females presenting with gestational diabetes during third trimester of pregnancy	Conference Abstract
85.	Souza M.	2018	Use of metformin for prevention of unfavorable obstetric outcomes in obese pregnant women	Conference Abstract
86.	Rezk M.	2018	Clomiphene citrate combined with metformin versus letrozole for induction of ovulation in clomiphene-resistant polycystic ovary syndrome: a randomized clinical trial	Not during pregnancy: for ovulation
87.	Lovvik T.S.	2018	Metformin treatment of pregnant women with polycystic ovary syndrome-a randomized, nordic multi-center trial.	Conference Abstract
88.	Huhtala Y.M.	2018	Inflammation markers and insulin like growth factor binding protein 1 in women with gestational diabetes treated with metformin or insulin	Conference abstract
89.	Hughes R.C	2018	Prediabetes in pregnancy, can early intervention improve outcomes? A feasibility study for a parallel randomised clinical trial.	No control group; metformin and insulin provided in both groups and early versus standard care assessed
90.	Ghomian N.	2018	The efficacy of metformin compared with insulin in regulating blood glucose levels during gestational diabetes mellitus: a randomized clinical trial.	Duplicate
91.	Gajardo F.M.	2018	Diet versus metformin plus diet for the treatment of mild gestational diabetes in obese patients.	Conference Abstract
92.	Dodd J.M.	2018	Metformin and dietary advice for pregnant women who are overweight or obese to promote gestational restriction of weight-the grow randomized trial.	Conference Abstract
93.	Dodd J.M.	2018	Metformin for women who are overweight or obese during pregnancy for improving maternal and infant outcomes	Conference Abstract
94.	Dienstmann G.	2018	Effect of metformin hydrochloride in the lipid profile and body mass index of obese pregnant women.	Conference Abstract
95.	Das V.	2018	Metformin vs insulin for management of gestational diabetes mellitus in developing nations: RCT.	Conference Abstract
96.	Anzolin G.	2018	Use of metformin prophylatic in gestacional diabetes mellitus	Letter/ Commentary
97.	-	2018	Amino acid profile in women with gestational diabetes mellitus treated with metformin or insulin	Conference Abstract
98.	-	2018	Clinical efficacy of metformin combined with clomiphene in patients with polycystic ovary syndrome and their effect on serum sex hormones.	Conference Abstract
99.	-	2018	Differing gestational diabetes pathophysiology uncovered by metabolic phenotyping of treatment groups in obese women across three time points in pregnancy.	Conference Abstract
100.	-	2018	Metformin treatment of pregnant women with polycystic ovary syndrome-a randomized, nordic multi-center trial.	Duplicate of Huhtala 2017 excluded abstract
101.	Rivera-Sanabria R	2019	Use of metformin for gestational diabetes treatment and its effects in placental nutrient transporters expression	Conference Abstract
102.	Panagio-topoulou O	2019	The influence of in utero exposure to metformin on body composition and cardiovascular phenotype in offspring; Metformin in obese non diabetic pregnant women (MOP) follow up	Conference Abstract
103.	Lillycrop K.A.	2019	Maternal gdm induces widespread changes in the infant's epigenome	Conference Abstract
104.	Jainchill A.L.	2019	Metformin for Improving Maternal and Infant Outcomes in Pregnant Women Who are Obese.	Review/ Opinion piece
105.	El Sharkwy I.	2019	l-Carnitine plus metformin in clomiphene-resistant obese PCOS women, reproductive and metabolic effects: a randomized clinical trial.	Not during pregnancy
106.	Dodd J.M.	2019	Metformin and dietary advice for pregnant women who are overweight or obese: the GROW randomised trial.	Conference Abstract
107.	Bogdanet D.	2019	Follow-up at 1 year and beyond of women with gestational diabetes treated with insulin and/or oral glucose-lowering agents: a core outcome set using a Delphi survey	Not RCT; Delphi, SR and Core outcomes set for follow up studies
108.	-	2019	The influence of in utero exposure to metformin on body composition and cardiovascular phenotype in offspring; Metformin in obese non diabetic pregnant women (MOP) follow up.	Duplicate of Tertti 2015 included study
109.	Chang C.	2020	66 the Impact of Bariatric Surgery Compared to Metformin Therapy on Pregnancy Outcomes in Patients with Polycystic Ovarian Syndrome	Conference Abstract; systematic review
110.	Casey B.M.	2020	Effect of Treatment of Mild Gestational Diabetes on Long-Term Maternal Outcomes.	Not using metformin

111.	Aiken, C.	2020	651: Comparative impact of pharmacological treatments for gestational diabetes on neonatal anthropometry: systematic review and meta-analysis. American Journal of Obstetrics and Gynecology, 222	Systematic Review
112.	Alqudah, A.	2018	Risk of pre-eclampsia in women taking metformin: a systematic review and meta-analysis. Diabetic Medicine, 35	Systematic Review
113.	Alwan, N.	2009	Treatments for gestational diabetes. Cochrane Database of Systematic Reviews	Systematic Review
114.	Alwan, N.	2011	Treatments for gestational diabetes. Cochrane Database of Systematic Reviews	Systematic Review
115.	Amin, M.	2015	Comparison of glyburide with metformin in treating gestational diabetes mellitus: a systematic review and meta-analysis. Clinical Drug Investigation	Systematic Review
116.	Balsells, M.	2015	Glibenclamide, metformin, and insulin for the treatment of gestational diabetes: a systematic review and meta-analysis. BMJ.	Systematic Review
117.	Bao, L. X.	2019	Metformin versus insulin for gestational diabetes: a systematic review and meta-analysis. Journal of Maternal Fetal and Neonatal Medicine.	Systematic Review
118.	Bennett, C. J.	2019	Attenuation of maternal weight gain impacts infant birthweight: systematic review and meta-analysis. Journal of Developmental Origins of Health and Disease, 10	Systematic Review
119.	Bidhendi Yarandi, R.	2019	Metformin therapy before conception versus throughout the pregnancy and risk of gestational diabetes mellitus in women with polycystic ovary syndrome: A systemic review, meta-analysis and meta-regression. Diabetology and Metabolic	Systematic Review
120.	Brown, J.	2017	Insulin or oral anti-iabetic agents? a cochrane systematic review. Journal of paediatrics and child health, 53	Systematic Review
121.	Brown, J.	2017	Insulin for the treatment of women with gestational diabetes. Cochrane Database of Systematic Reviews	Systematic Review
122.	Brown, J.	2017	Oral anti-diabetic pharmacological therapies for the treatment of women with gestational diabetes. Cochrane Database of Systematic Reviews	Systematic Review
123.	Butalia, S.	2017	Short- and long-term outcomes of metformin compared with insulin alone in pregnancy: a systematic review and meta-analysis. Diabetic Medicine, 34	Systematic Review
124.	Cassina, M.	2014	First-trimester exposure to metformin and risk of birth defects: a systematic review and meta-analysis. Human Reproduction Update, 20	Systematic Review
125.	Chatzakis, C.	2019	Prevention of gestational diabetes mellitus in overweight or obese pregnant women: A network meta-analysis. Diabetes Research & Clinical Practice, 158, 107924.	Systematic Review
126.	D'Ambrosio, V.	2019	Metformin reduces maternal weight gain in obese pregnant women: A systematic review and meta-analysis of two randomized controlled trials. Diabetes/Metabolism Research and Reviews, 35	Systematic Review
127.	Dhulkotia, J. S.	2010	Oral hypoglycemic agents vs insulin in management of gestational diabetes: a systematic review and metaanalysis. American Journal of Obstetrics & Gynecology, 203	Systematic Review
128.	Dodd, J. M.	2018	Metformin for women who are overweight or obese during pregnancy for improving maternal and infant outcomes. Cochrane Database of Systematic Reviews, 7, CD010564.	Systematic Review
129.	Doi, S. A. R.	2020	Metformin in pregnancy to avert gestational diabetes in women at high risk: Meta-analysis of randomized controlled trials. Obesity Reviews, 21	Systematic Review
130.	Eames, A. J.	2013	Metformin for women who are obese during pregnancy versus standard care for improving maternal and infant outcomes - a systematic review. Journal of paediatrics and child health, 2), 94.	Systematic Review
131.	Elmaraezy, A.	2017	Effect of metformin on maternal and neonatal outcomes in pregnant obese non-diabetic women: A meta-analysis. International Journal of Reproductive BioMedicine, 15	Systematic Review
132.	Farrar, D.	2017	Treatments for gestational diabetes: a systematic review and meta-analysis. BMJ Open, 7	Systematic Review
133.	Farrar, D.	2016	The identification and treatment of women with hyperglycaemia in pregnancy: an analysis of individual participant data, systematic reviews, meta-analyses and an economic evaluation. Health Technology Assessment	Systematic Review
134.	Feig, D.	2019	Meta-analysis suggests that metformin may reduce pre-eclampsia compared with insulin use during pregnancy. BMJ Evidence-Based Medicine, 24	Systematic Review
135.	Feig, D. M. D.	2009	Review: Oral drugs for gestational diabetes do not increase adverse maternal and neonatal outcomes more than insulin. ACP Journal Club, 150	Systematic Review
136.	Feng, L.	2015	Efficacy of metformin on pregnancy complications in women with polycystic ovary syndrome: a meta-analysis. Gynecological Endocrinology, 31	Systematic Review
137.	Feng, Y.	2017	Metformin - a potentially effective drug for gestational diabetes mellitus: a systematic review and meta-analysis. Journal of maternal-fetal & neonatal medicine, 30	Systematic Review
138.	Gilbert, C.	2006	Pregnancy outcome after first-trimester exposure to metformin: a meta-analysis. Fertility & Sterility, 86	Systematic Review
139.	Griffith, R.	2019	Interventions to prevent women developing gestational diabetes mellitus: An overview. Journal of paediatrics and child health, 55	Systematic Review
140.	Griffith, R. J.	2020	Interventions to prevent women from developing gestational diabetes mellitus: an overview of Cochrane Reviews. Cochrane Database of Systematic Reviews	Systematic Review
141.	Gui, J.	2013	Metformin vs insulin in the management of gestational diabetes: a meta-analysis. PLoS ONE [Electronic Resource], 8	Systematic Review
142.	Guo, L.	2019	Comparative Efficacy and Safety of Metformin, Glyburide, and Insulin in Treating Gestational Diabetes Mellitus: A Meta-Analysis. Journal of diabetes research, 2019, 9804708.	Systematic Review
143.	Gutzin, S. J.	2003	The safety of oral hypoglycemic agents in the first trimester of pregnancy: a meta-analysis. Canadian Journal of Clinical Pharmacology, 10	Systematic Review
144.	Horvath, K.	2010	Effects of treatment in women with gestational diabetes mellitus: Systematic review and meta-analysis. BMJ	Systematic Review

145.	Imam, A. A.	2012	Can we prescribe oral hypoglycemic agents safely for treatment of gestational diabetes mellitus	Systematic Review
146.	Jiang, Y. F.	2015	Comparative efficacy and safety of OADs in management of GDM: network meta-analysis of randomized controlled trials. Journal of Clinical Endocrinology & Metabolism, 100	Systematic Review
147.	Kalafat, E.	2018	Metformin for prevention of hypertensive disorders of pregnancy in women with gestational diabetes or obesity: systematic review and meta-analysis of randomized trials. Ultrasound in Obstetrics & Gynecology, 52	Systematic Review
148.	Khin, M. O.	2013	Effectiveness of metformin in gestational diabetes: Systematic review and meta-analysis. Diabetologia, 1), S504.	Systematic Review
149.	Kitwitee, P.	2015	Metformin for the treatment of gestational diabetes: An updated meta-analysis. Diabetes Research & Clinical Practice, 109	Systematic Review
150.	Kolding, L.	2020	Drug exposure during pregnancy and fetal cardiac function- A systematic review. Journal of Perinatal Medicine, 48	Systematic Review
151.	Lautatzis, M. E.	2013	Efficacy and safety of metformin during pregnancy in women with gestational diabetes mellitus or polycystic ovary syndrome: a systematic review. Metabolism: Clinical & Experimental, 62	Systematic Review
152.	Li, G.	2015	Effect comparison of metformin with insulin treatment for gestational diabetes: a meta-analysis based on RCTs. Archives of Gynecology & Obstetrics, 292	Systematic Review
153.	Liang, H. L.	2017	Comparative efficacy and safety of oral antidiabetic drugs and insulin in treating gestational diabetes mellitus: An updated PRISMA-compliant network meta-analysis. Medicine, 96	Systematic Review
154.	Liew, A..	2018	Metformin vs insulin for treatment of gestational diabetes: A systematic review and meta-analysis of randomised controlled trials. Diabetic Medicine, 35	Systematic Review
155.	Madhuvrata, P.	2015	Prevention of gestational diabetes in pregnant women with risk factors for gestational diabetes: a systematic review and meta-analysis of randomised trials. Obstetric Medicine, 8	Systematic Review
156.	Martis, R.	2018	Treatments for women with gestational diabetes mellitus: an overview of Cochrane systematic reviews. Cochrane Database of Systematic Reviews	Systematic Review
157.	Mateus, J.	2020	890: Best gestational diabetes therapy to reduce adverse maternal outcomes. A network meta-analysis. American Journal of Obstetrics and Gynecology, 222	Systematic Review
158.	Mateus, J.	2020	1124: Glyburide is the least effective gestational diabetes therapy to improve neonatal outcomes. A network Meta-analysis. American Journal of Obstetrics and Gynecology, 222	Systematic Review
159.	Medley, N.	2018	Interventions during pregnancy to prevent preterm birth: an overview of Cochrane systematic reviews. Cochrane Database of Systematic Reviews	Systematic Review
160.	Nascimento, IB	2018	Evaluation of Preeclampsia Results after Use of Metformin in Gestation: Systematic Review and Meta-analysis. Revista Brasileira de Ginecologia e Obstetricia, 40	Systematic Review
161.	Nascimento, IB	2018	Avaliacao dos resultados da pre-eclampsia apos o uso da metformina na gestacao: revisao sistematica e metanalise, Evaluation of Preeclampsia Results after Use of Metformin in Gestation: Systematic Review and Meta-analysis.	Systematic Review
162.	Nicholson, W.	2009	Benefits and risks of oral diabetes agents compared with insulin in women with gestational diabetes: a systematic review. Obstetrics & Gynecology, 113	Systematic Review
163.	Oostdam, N.	2011	Interventions for preventing gestational diabetes mellitus: A systematic review and meta-analysis. Journal of Women's Health, 20	Systematic Review
164.	Panchaud, A.	2019	#48 Use of metformin during pregnancy and risk of major congenital malformations: Preliminary findings of a systematic review and meta-analysis. Reproductive Toxicology, 88, 149.	Systematic Review
165.	Poolsup, N.	2014	Efficacy and safety of oral antidiabetic drugs in comparison to insulin in treating gestational diabetes mellitus: a meta-analysis. PLoS ONE [Electronic Resource], 9	Systematic Review
166.	Singh, K. P.	2015	Metformin for the management of gestational diabetes mellitus. Australian & New Zealand Journal of Obstetrics & Gynaecology, 55	Systematic Review
167.	Su, D. F.	2014	Metformin vs insulin in the management of gestational diabetes: a systematic review and meta-analysis. Diabetes Research & Clinical Practice, 104	Systematic Review
168.	Tan, X.	2016	Effect of metformin treatment during pregnancy on women with PCOS: a systematic review and meta-analysis. Clinical & Investigative Medicine - Medecine Clinique et Experimentale, 39	Systematic Review
169.	Tarry-Adkins, JL	2019	Neonatal, infant, and childhood growth following metformin versus insulin treatment for gestational diabetes: A systematic review and meta-analysis. PLoS Medicine / Public Library of Science, 16	Systematic Review
170.	Tarry-Adkins, JL	2020	Comparative impact of pharmacological treatments for gestational diabetes on neonatal anthropometry independent of maternal glycaemic control: A systematic review and meta-analysis. PLoS medicine, 17	Systematic Review
171.	Tieu, J.	2009	Oral anti-diabetic agents for women with pre-existing diabetes mellitus/impaired glucose tolerance or previous gestational diabetes mellitus. Cochrane Database of Systematic Reviews,	Systematic Review
172.	Tieu, J.	2010	Oral anti-diabetic agents for women with pre-existing diabetes mellitus/impaired glucose tolerance or previous gestational diabetes mellitus. Cochrane Database of Systematic Reviews	Systematic Review
173.	Tieu, J.	2017	Oral anti-diabetic agents for women with established diabetes/impaired glucose tolerance or previous gestational diabetes planning pregnancy, or pregnant women with pre-existing diabetes. Cochrane Database of Systematic Reviews	Systematic Review
174.	Tieu, J.	2010	Oral anti-diabetic agents for women with pre-existing diabetes mellitus/impaired glucose tolerance or previous gestational diabetes mellitus - A Cochrane review. Journal of paediatrics and child health, 46	Systematic Review
175.	van Weelden, W	2018	Long-Term Effects of Oral Antidiabetic Drugs During Pregnancy on Offspring: A Systematic Review and Meta-analysis of Follow-up Studies of RCTs. Diabetes Therapy, 9	Systematic Review
176.	Varrey, A.	2013	Metformin versus insulin in gestational diabetes: A meta-analysis. Reproductive sciences, 1), 311A.	Systematic Review

177.	Xu, Q. & Xie, Q.	2019	Long-term effects of prenatal exposure to metformin on the health of children based on follow-up studies of randomized controlled trials: a systematic review and meta-analysis. Archives of Gynecology & Obstetrics, 299	Systematic Review
178.	Zeng, X. L.	2016	Effects of metformin on pregnancy outcomes in women with polycystic ovary syndrome: A meta-analysis. Medicine, 95	Systematic Review
179.	Zhao, J.	2020	The Effect of Metformin Therapy for Preventing Gestational Diabetes Mellitus in Women with Polycystic Ovary Syndrome: A Meta-Analysis. Experimental and Clinical Endocrinology and Diabetes, 128	Systematic Review
180.	Zhao, L. P.	2015	Metformin versus insulin for gestational diabetes mellitus: a meta-analysis. British Journal of Clinical Pharmacology, 80	Systematic Review
181.	Zhen, X. M.	2018	Metformin versus insulin for gestational diabetes: The reporting of ethnicity and a meta-analysis combining English and Chinese literatures. Obesity Medicine, 11, 48-58.	Systematic Review
182.	Zheng, J.	2013	The efficacy of metformin in pregnant women with polycystic ovary syndrome: a meta-analysis of clinical trials. Journal of Endocrinological Investigation, 36	Systematic Review
183.	Zhu, B.	2016	Metformin versus insulin in gestational diabetes mellitus: a meta-analysis of randomized clinical trials. Irish Journal of Medical Science, 185	Systematic Review
184.	Zhuo, Z.	2014	Effect of metformin intervention during pregnancy on the gestational diabetes mellitus in women with polycystic ovary syndrome: a systematic review and meta-analysis. Journal of diabetes research, 2014, 381231.	Systematic Review
185.	Abebe	2017	Comparison of Two Screening Strategies for Gestational Diabetes (GDM2) Trial: Design and rationale	Protocol
186.	Anjalakshi	2007	A prospective study comparing insulin and glibenclamide in gestational diabetes mellitus in Asian Indian women.	not using metformin
187.	Ashrafi	2014	Gestational diabetes mellitus risk factors in women with PCOS.	Cross-sectional
188.	Ashrafi	2017	Gestational Diabetes Mellitus and Metabolic Disorder among different phenotypes of PCOS	Cross-sectional
189.	Balaji	2005	Insulin aspart - Safe during pregnancy	Conference abstract
190.	Bancroft	2000	A randomised controlled pilot study of the management of gestational impaired glucose tolerance.	not using metformin
191.	Behrashi	2016	Comparison of glibenclamide and insulin on neonatal outcomes in pregnant women with gestational diabetes.	not using metformin
192.	Biesty	2018	Planned birth at or near term for improving health outcomes for pregnant women with gestational diabetes and their infants.	Systematic review
193.	Buchanan	2002	Preservation of pancreatic beta-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women.	not using metformin
194.	Bung	1993	Therapeutic exercise for insulin-requiring gestational diabetics: effects on the fetus — results of a randomized prospective longitudinal study	not using metformin
195.	Clark	2009	Do postal reminders increase postpartum screening of diabetes mellitus in women with gestational diabetes mellitus? A randomized controlled trial.	not using metformin
196.	Coetzee	1984	Oral hypoglycaemics in the first trimester and fetal outcome.	not RCT
197.	Culliney	2016	Regimens of fetal surveillance of suspected large-for-gestational-age fetuses for improving health outcomes	SR
198.	East	2014	Antenatal breast milk expression by women with diabetes for improving infant outcomes	SR
199.	Ehrlich	2014	Post-partum weight loss and glucose metabolism in women with gestational diabetes: the DEBI Study	not using metformin
200.	Ekpebegh	2007	A 10-year retrospective analysis of pregnancy outcome in pregestational type 2 diabetes: comparison of insulin and oral glucose-lowering agents	not RCT
201.	Ferrara	2011	A pregnancy and postpartum lifestyle intervention in women with gestational diabetes mellitus reduces diabetes risk factors	not using metformin
202.	Ford	1997	Preliminary report of a randomised trial of dietary advice in women with mild abnormalities of glucose tolerance in pregnancy.	personal communication
203.	Gargaun	2003	Pregnancy outcome in women with polycystic exposed to metformin	Conference abstract
204.	Gillen	2004	Advice that includes food sources of unsaturated fat supports future risk management of gestational diabetes mellitus.	not using metformin
205.	Glueck	2008	Prevention of gestational diabetes by metformin plus diet in patients with PCOS.	not RCT
206.	Glueck	2004	Metformin, pre-eclampsia, and pregnancy outcomes in women with PCOS	not RCT
207.	Glueck	2002	pregnancy outcomes among women with PCOS treated with metformin	not RCT
208.	Glueck	2001	Continuing metformin throughout pregnancy in women with polycystic ovary syndrome appears to safely reduce first-trimester spontaneous abortion: a pilot study	not RCT
209.	Glueck	2002	Metformin therapy throughout pregnancy reduces the development of gestational diabetes in women with polycystic ovary syndrome.	not RCT
210.	Hellmuth	2000	Oral hypoglycaemic agents in 118 diabetic pregnancies	not RCT
211.	Hu	2012	Tianjin Gestational Diabetes Mellitus Prevention Program: study design, methods, and 1-year interim report on the feasibility of lifestyle intervention program	not using metformin; prior GDM
212.	Hutchinson	2008	A comparison of glyburide/metformin and insulin for gestational diabetes.	Conference abstract
213.	Infanti	2014	Reasons for participation and non-participation in a diabetes prevention trial among women with prior gestational diabetes mellitus (GDM)	not using metformin (lifestyle vs standard care)
214.	Jakubowicz	2002	Effects of metformin on early pregnancy loss in the polycystic ovary syndrome	not RCT
215.	Jefferys	2013	Deflation of gastric band balloon in pregnancy for improving outcomes.	Systematic review
216.	Keely	2008	Prevalence of metabolic markers of insulin resistance in offspring of gestational diabetes pregnancies	not using metformin

217.	Keely	2010	Screening for type 2 diabetes following gestational diabetes. Family phisicians and patients perspective;	not using metformin
218.	Kestila	2007	Continuous glucose monitoring versus self-monitoring of blood glucose in the treatment of gestational diabetes mellitus	no control group (metformin used in both groups)
219.	Khattab	2011	Can metformin reduce the incidence of gestational diabetes mellitus in pregnant women with PCOS? Prospective cohort study	not RCT
220.	Khattab	2006	Metformin reduces abortion in pregnant women with polycystic ovary syndrome	not RCT
221.	Kolu	2016	Effectiveness and Cost-Effectiveness of a Cluster-Randomized Prenatal Lifestyle Counseling Trial: A Seven-Year Follow-Up	not using metformin
222.	Langer	1989	Management of women with one abnormal oral glucose tolerance test value reduces adverse outcome in pregnancy.	not using metformin
223.	Luoto	2010	Prevention of gestational diabetes: design of a cluster-randomized controlled trial and one-year follow-up	protocol
224.	Moore	2004	Metformin (M) vs. insulin (I) in A2 diabetes: a randomized clinical trial.	Conference abstract
225.	Murguia	2016	Pregnancy-Associated Hypertension in Glucose Intolerant Pregnancy and Subsequent Metabolic Syndrome	not RCT
226.	Myers	2014	Metformin treatment vs a diabetes model of antenatal care in women with mild fasting hyperglycaemia diagnosed in pregnancy: a pilot study.	Protocol registration
227.	Nawaz	2008	Does continuous metformin throughout pregnancy improve pregnancy outcomes in women with polycystic ovarian syndrome?	not RCT
228.	Niklas	2014	A web-based lifestyle intervention for women with recent gestational diabetes mellitus: a randomized controlled trial.	not using metformin
229.	Notelovitz	1971	Sulphonylurea therapy in the treatment of the pregnant diabetes	not using metformin
230.	Peacock	2015	A Randomised Controlled Trial to Delay or Prevent Type 2 Diabetes after Gestational Diabetes: Walking for Exercise and Nutrition to Prevent Diabetes for You	Not during pregnancy; postpartum study
231.	Perez-Ferre	2015	Diabetes mellitus and abnormal glucose tolerance development after gestational diabetes: A three-year, prospective, randomized, clinicalbased, Mediterranean lifestyle interventional study with parallel groups	not using metformin
232.	Piacquadio	1991	Effects of in-utero exposure to oral hypoglycaemic drugs	not RCT
233.	Rai	2009	Metformin - a convenient alternative to insulin for Indian women with diabetes in pregnancy.	not RCT
234.	Rono	2014	Prevention of gestational diabetes through lifestyle intervention: study design and methods of a Finnish randomized controlled multicenter trial (RADIEL).	Protocol; not using metformin
235.	Ryan	2001	Glyburide was as safe and effective as insulin in gestational diabetes,	not using metformin
236.	Yang	2003	Postpartum glucose intolerance in Chinese women with gestational diabetes	not using metformin
237.	NA	2021	Prevention of Pre-eclampsia Using Metformin: a Randomized Control Trial	Conference Abstract or Protocol;
238.	NA	2020	Metformin Versus Standard of Care Treatment in Pregnant Women With Prediabetes	Conference Abstract or Protocol
239.	Rastegar, F.	2021	Comparison of Effect of Metformin Versus Combination of Folic Acid/Myo-inositol in Infertile Women with Poly Cystic Ovary Syndrome Undergoing in Vitro Fertilization: A Randomized Clinical Trial	Not during pregnancy
240.	NA	2021	The effect of the metformin in preventing of the preeclampsia	Conference Abstract or Protocol
241.	NA	2020	Preventing gestational diabetes and pregnancy hypertensive disorders in obese pregnant women in resource-poor settings	Conference Abstract or Protocol
242.	NA	2021	A randomized, open-label trial to evaluate metformin to prevention preterm pre-eclampsia in Chinese overweight pregnancies	Conference Abstract or Protocol
243.	NA	2021	Role of Metformin in treatment of preclampsia	Conference Abstract or Protocol
244.	NA	2020	MeDiGes Study: Metformine Use in Gestational Diabetes	Conference Abstract or Protocol
245.	Sammor, H. M.	2020	Mode of delivery in gestational diabetes controlled by metformin versus insulin: randomized controlled trial	Conference Abstract or Protocol
246.	NA	2022	A Randomized Double Blinded Controlled Trial of Using Metformin to Prevent Preterm Birth in Twin Pregnancy	Conference Abstract or Protocol
247.	NA	2020	Efficacy and safety evaluation of metformin combined with insulin for gestational diabetes mellitus: a multicenter randomized open-label clinical trial	Conference Abstract or Protocol;
248.	Doi, S. A. R.	2020	Metformin in pregnancy to avert gestational diabetes in women at high risk: Meta-analysis of randomized controlled trials	SR or meta-analysis
249.	Ouyang, H.	2021	Effects of Different Glucose-Lowering Measures on Maternal and Infant Outcomes in Pregnant Women with Gestational Diabetes: A Network Meta-analysis	SR or meta-analysis
250.	Yu, D. Q.	2021	Glycemic control and neonatal outcomes in women with gestational diabetes mellitus treated using glyburide, metformin, or insulin: a pairwise and network meta-analysis	SR or meta-analysis
251.	Musa, O. A. H.	2021	Metformin is comparable to insulin for pharmacotherapy in gestational diabetes mellitus: A network meta-analysis evaluating 6046 women	SR or meta-analysis
252.	Li, C.	2022	Comparison of the effectiveness and safety of insulin and oral hypoglycemic drugs in the treatment of gestational diabetes mellitus: a meta-analysis of 26 randomized controlled trials	SR or meta-analysis

253.	Zhu, D.	2022	Effects of metformin on pregnancy outcome, metabolic profile, and sex hormone levels in women with polycystic ovary syndrome and their offspring: a systematic review and meta-analysis	SR or meta-analysis
254.	Zhao, Q.	2022	Efficacy and safety of metformin in pregnant women with polycystic ovary syndrome: a systematic review with meta-analysis of randomized and non-randomized controlled trials	SR or meta-analysis
255.	Zhao, J.	2020	The Effect of Metformin Therapy for Preventing Gestational Diabetes Mellitus in Women with Polycystic Ovary Syndrome: A Meta-Analysis	SR or meta-analysis
256.	Wang, X.	2021	Comparison of Insulin, Metformin, and Glyburide on Perinatal Complications of Gestational Diabetes Mellitus: A Systematic Review and Meta-Analysis	SR or meta-analysis
257.	Tarry-Adkins	2021	Impact of metformin treatment during pregnancy on maternal outcomes: a systematic review/meta-analysis	SR or meta-analysis
258.	Tarry-Adkins	2020	Comparative impact of pharmacological treatments for gestational diabetes on neonatal anthropometry independent of maternal glycaemic control: A systematic review and meta-analysis	SR or meta-analysis
259.	Raperport, C.	2021	Effects of metformin treatment on pregnancy outcomes in patients with polycystic ovary syndrome	SR or meta-analysis
260.	Pascual-Morena	2021	Physical Exercise vs. Metformin to Improve Delivery- and Newborn-Related Outcomes Among Pregnant Women With Overweight: A Network Meta-Analysis	SR or meta-analysis
261.	Mateus, J	2020	890: Best gestational diabetes therapy to reduce adverse maternal outcomes. A network meta-analysis	SR or meta-analysis
262.	Pascual-Morena	2021	Exercise versus metformin to improve pregnancy outcomes among overweight pregnant women: A systematic review and network meta-analysis	SR or meta-analysis
263.	Oliveira, M. M.	2022	Metformin versus glyburide in treatment and control of gestational diabetes mellitus: a systematic review with meta-analysis	SR or meta-analysis
264.	Nascimento, IB	2020	Evaluation on the use of metformin in non-diabetic obese pregnant women: Systematic review and metanalysis	SR or meta-analysis
265.	Mateus, J.	2020	1124: Glyburide is the least effective gestational diabetes therapy to improve neonatal outcomes. A network Meta-analysis	SR or meta-analysis
266.	Lin, J.	2022	Comparative efficacy and safety of glyburide, metformin, and insulin in treatment of gestational diabetes mellitus	SR or meta-analysis
267.	Kolding, L.	2020	Drug exposure during pregnancy and fetal cardiac function- A systematic review	SR or meta-analysis
268.	Herath, M. P.	2021	Gestational diabetes mellitus and infant adiposity at birth: A systematic review and meta-analysis of therapeutic interventions	SR or meta-analysis
269.	Griffith, R. J.	2020	Interventions to prevent women from developing gestational diabetes mellitus: an overview of Cochrane Reviews	SR or meta-analysis
270.	He, K.	2022	The efficacy and safety of metformin alone or as an add-on therapy to insulin in pregnancy with GDM or T2DM: A systematic review and meta-analysis of 21 randomized controlled trials	SR or meta-analysis
271.	Chang, C.	2021	The Impact of Bariatric Surgery Compared to Metformin Therapy on Pregnancy Outcomes in Patients with Polycystic Ovarian Syndrome: a Systematic Review and Meta-analysis	SR or meta-analysis
272.	Cao, Q.	2021	Gestational metformin administration in women with polycystic ovary syndrome: A systematic review and meta-analysis of randomized control studies	SR or meta-analysis
273.	Bidhendi Yarandi, R.	2021	Effectiveness of antidiabetic agents for treatment of gestational diabetes: A methodological quality assessment of meta-analyses and network meta-analysis	SR or meta-analysis
274.	Alshamsi, R.	2021	Evaluation of safety and efficacy of oral antidiabetic medication in gestational diabetes: A systematic review	SR or meta-analysis
275.	Bao, L. X	2021	Metformin versus insulin for gestational diabetes: a systematic review and meta-analysis	SR or meta-analysis
276.	Anness, A. R	2021	Effect of metformin on biomarkers of placental- mediated disease: A systematic review and meta-analysis	SR or meta-analysis
277.	Aiken, C.	2020	651: Comparative impact of pharmacological treatments for gestational diabetes on neonatal anthropometry: systematic review and meta-analysis	SR or meta-analysis

APPENDIX 2. QUALITY APPRAISAL OF RANDOMISED CONTROLLED TRIALS

Study ID	Begum 2008	
Study Citation	Begum MR, Khanam NN, Quadir E, et al. Prevention of gestational diabetes mellitus by continuing metformin therapy throughout pregnancy in women with polycystic ovary syndrome. *J Obstet Gynaecol Res*. 2009;35(2):282-286. doi:10.1111/j.1447-0756.2008.00876.x	
Study Country	Bangladesh	
BRIEF CHARACTERISTICS OF RCT		
Patient/population/ participants	Women with PCOS and CC resistance and insulin resistance who conceived while taking metformin	
PCOS diagnostic criteria	Rotterdam criteria	
Presence of infertility	Yes, no ovulation with 150 mg CC daily for 5 days (D3-D7) for 2 consecutive cycles (defined as CC resistant)	
Presence of other condition/s	Insulin resistance defined by HOMA-IR but non-diabetic	
Medication History	Not reported	
N per group	Allocated/ randomised: 59 (attrition not reported) Assessed at end of study: 59 (attrition not reported)	
Setting	Infertility Care Centre	
Intervention	**Continuation of Metformin until delivery** at a dose of 1500 mg daily for BMI ≤29; 2000 mg daily for BMI 30-32 and 2500 mg daily for BMI >32 (ovulation induction agents + metformin were provided for 6-12 months preconception until pregnancy)	
Comparison	**Discontinuation of Metformin at 8 weeks gestation** (ovulation induction agents + metformin were provided for 6-12 months preconception until pregnancy)	
Outcomes (primary and other) with definition (e.g. self-reported, fasting etc.)	**Primary**: GDM; Abortion rate; Live birth rate; Congenital anomaly; Condition of newborn at birth. **Other**: Birthweight; neonatal death; preterm birth; gestational age; birth asphyxia; low birthweight; macrosomia	
Follow up Duration	Preconception to delivery	
Summary Result/s	GDM incidence, birth asphyxia were lower in women continuing metformin (significance not clear). Birthweight was lower and APGAR at 5 min higher with continuing metformin use in pregnancy, statistically significant ($p<0.05$) No difference in abortion, low birthweight, gestational age, preterm labour or congenital anomalies. One neonatal death in controls- significance not clear.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	Partial- Describes aim to determine whether metformin reduces GDM but primary outcomes include a range of outcomes not specific to GDM
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	No explicit criteria reported

If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Not reported
Inclusion criteria		Yes Partial No Not reported	Partial- Non-diabetic on OGTT, CC-resistant, insulin resistant (HOMA; cut-off not specified), with PCOS using Rotterdam.
Exclusion criteria		Yes Partial No Not reported	Not reported
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	States patients were divided by lottery method but no further detail provided (i.e., by whom, how?)
	Was allocation to intervention group concealed?	Yes Partial No Not reported	Not reported but likely not since the controls did not take placebo
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	Not reported but likely not since the controls did not take placebo
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	Not reported
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	Not clear from the paper, as not double-blinded or controlled with placebo
DETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Two hour postprandial sugar used to determine GDM with no further information on cut-off/ criteria; whether this was during OGTT or post-meal, etc. Other measures not described at all.
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Not reported
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	Attrition not reported

	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	Attrition not reported and no mention of ITT
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	No- Difficult to determine since there is no protocol. Would likely be 'No' because for example it is reported that there were no differences in baseline characteristics but then in Table 1, there is a statistically significant difference in age between groups. Also pre-eclampsia mentioned in discussion but no data or results provided for this outcome.
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	Partial- Metformin group was older and had lower LH at baseline
	If confounding was present, was it controlled for?	Yes Partial No Not reported	No- No Adjustment for age differences
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	Not reported
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	No- no power calculation or protocol
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Partial- potential confounders were not taken into account in the analysis; no protocol with predetermined primary outcomes
COMMENTS		Lack of blinding and no placebo control are key reasons for high RoB; also cannot determine conflicts of interest or attrition; poor analysis and reporting of study methods and results, groups not balanced at baseline, and no explicit criteria for exclusion, criteria for diagnoses (eg.GDM) or detail around randomization methods	
What is the overall risk of bias?		Low Moderate High Insufficient information	High due to the above
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		No – all outcomes high risk of bias	

Study ID	Jamal 2012	
Study Citation	Jamal A, Milani F, Al-Yasin A. Evaluation of the effect of metformin and aspirin on utero placental circulation of pregnant women with PCOS. Iran J Reprod Med, 2012. 10 (3); 265-270.	
Study Country	Iran	
BRIEF CHARACTERISTICS OF RCT		
Patient/population/ participants	Women with PCOS attending infertility clinic	
PCOS diagnostic criteria	More than 8 subcapsular follicles of 3-9mm diameter and oligomenorrhea (> 35 days or hirsutism or testosterone >2 nmol/L) and all women took metformin before study entry.	
Presence of infertility	Not reported but assumed as patients were attending infertility clinic	
Presence of other condition/s	Not reported	
Medication History	Not reported; except patients were taking 1mg folate, one multivitamin tablet and one ferrous sulfate tablet	
N per group	Allocated/ randomised: 105; Assessed at end of study: 105 (no patients discontinued or lost to follow up or excluded according to CONSORT; all zero)	
Setting	Infertility outpatient clinic at University Hospital	
Intervention	**Metformin** (two tablets twice daily, 2000 mg) until the end of pregnancy	
Comparison	**Aspirin** (one tablet 80 mg daily) or **No intervention** until the end of pregnancy	
Outcomes (primary and other) with definition (e.g. self-reported, fasting etc.)	Uteroplacental circulation and pregnancy complications (unclear which is primary), including GDM, PE, preterm labour and IUGR	
Follow up Duration	6-12 weeks until delivery	
Summary Result/s	Mean uterine pulsatility index reduced in all groups but was more pronounced in metformin and aspirin groups than controls. No differences in any pregnancy complications assessed (GDM, PE, PTB, IUGR, birthweight)	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	Only inclusion criteria reported
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	Only inclusion criteria reported
Inclusion criteria	Yes Partial No Not reported	Diagnosis of PCOS before the pregnancy; age 18-40 years; gestational age 6-12 weeks; single viable fetus; and no history of diabetes or hypertension.

Exclusion criteria		Yes Partial No Not reported	Not reported
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Not reported
	Was allocation to intervention group concealed?	Yes Partial No Not reported	Single blinded- not sure which side- no mention of how concealment was achieved if done (except for ultrasound exams)
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	Single blinded- not sure which side
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	Single blinded- not sure which side
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	No, some women received insulin, some diet controlled GDM, not stratified analysis
DETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	Examiner was blinded to group status during ultrasound examinations
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	GDM criteria not specified
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Only noted for ultrasound- unclear about other measures
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	0% treatment 0% control/ comparison Not reported	Apparent perfect retention- all zero for drop outs, exclusions or loss to follow up
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	Apparent perfect retention- all zero for drop outs, exclusions or loss to follow up
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	No - Difficult to determine since there is no protocol. Would likely be 'No' because for example it is reported that there were no differences in baseline characteristics with reference to Figure 1, but this does not state any baseline characteristic data.

CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	Cannot be determined, says in the text that groups were homogenous for BMI, age and gravidity and refers to Figure 1, which is a CONSORT with no baseline data!
	If confounding was present, was it controlled for?	Yes Partial No Not reported	No- No stratified analysis for different GDM treatments or adjustment for insulin use or any other potentially confounding/ effect modifying variable
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	Not reported
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	No- no power calculation or protocol, unlikely powered for GDM and adverse outcomes and not clear for uterine artery pulsatility
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Partial- potential confounders were not taken into account in the analysis; no protocol with predetermined primary outcomes
COMMENTS		Lack of blinding and no placebo control are key reasons for high RoB; also cannot determine conflicts of interest; perfect attrition seems unlikely; lacking analysis and study methods, unclear if groups were balanced at baseline, and no explicit criteria for exclusion or detail around randomization or allocation concealment methods	
What is the overall risk of bias?		Low Moderate High Insufficient information	High due to the above
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		No – all outcomes high risk of bias	

Study ID	Zolghadri 2008	
Study Citation	Zolghadri J, Tavana Z, Kazerooni T, Soveid M, Taghieh M. Relationship between abnormal glucose tolerance test and history of previous recurrent miscarriages, and beneficial effect of metformin in these patients: a prospective clinical study. *Fertil Steril*. 2008;90(3):727-730. doi:10.1016/j.fertnstert.2007.06.079	
Study Country	Iran	
BRIEF CHARACTERISTICS OF RCT		
Patient/population/ participants	Women with history of recurrent spontaneous abortion and women with a history of normal full term pregnancy, with and without PCOS	
PCOS diagnostic criteria	Chronic oligomenorrhea (≤6 menses/ year); clinical and biochemical hyperandrogenism (hirsutism, severe acne, high levels of total or free testosterone, androstenedione and DHEAS); exclusion of hypothyroidism, hyperprolactinemia, and congenital adrenal hyperplasia; ancillary criteria: presence of >10follicles of 2-10mm diameter and increased density of ovarian stroma in transvaginal sonography.	
Presence of infertility	Included women with history of unexplained recurrent spontaneous abortions (RSA): ≥3 consecutive abortions with normal karyotype, hormonal assay (thyroid function + PRL), hysterosalpingogram or hysteroscopy, anticardiolipin antibodies, lupus anticoagulant, PT and PTT.	
Presence of other condition/s	PCOS or no PCOS	
Medication History	Not reported	
N per group	Allocated/ randomised: **Step 1:** 164 RSA and 74 normal allocated. **Step 2:** 29 RSA women included as PCOS (n=7) or non-PCOS (n= 22) and divided into 4 groups. Assessed at end of study: **Step 1:** 162 RSA (2 excluded due to DM)+ 74 normal. **Step 2:** No drop outs reported.(n=29 total; 7 with PCOS)	
Setting	University affiliated hospital	
Intervention	**Metformin** (1500 mg daily) before conception until the end of pregnancy	
Comparison	**Placebo** before conception until the end of pregnancy	
Outcomes (primary and other) with definition (e.g. self-reported, fasting etc.)	Normal ongoing pregnancies ≥14 weeks, and absence or presence of anomaly in the baby after delivery.	
Follow up Duration	Preconception to delivery	
Summary Result/s	Abortion rate decreased with metformin compared with placebo in women without PCOS but this was not significant in women with PCOS.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	Partial- Unclear if GTT was an inclusion criteria, also unclear what inclusions/exclusions applied for normal pregnancies

If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	No exclusion except for PCOS diagnosis
Inclusion criteria	Yes Partial No Not reported	Partial- Women with history of unexplained recurrent spontaneous abortions (RSA): ≥3 consecutive abortions with normal karyotype, hormonal assay (thyroid function + PRL), hysterosalpingogram or hysteroscopy, anticardiolipin antibodies, lupus anticoagulant, PT and PTT. Women with at least 2 normal full term pregnancies.
Exclusion criteria	Yes Partial No Not reported	Not reported; except for PCOS criteria to exclude other causes
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Yes- Computer randomization method
	Was allocation to intervention group concealed?	Yes Partial No Not reported	Partial- Medication were given in a double-blind manner- unclear how this was achieved
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	Yes- assumed from the double-blind terminology
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	Yes- assumed from the double-blind terminology
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	Not reported- unclear if women received any treatment for abnormal GTT
DETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Not reported- unclear how sugars were assessed or hormones etc. for PCOS diagnosis
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Not reported

ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	0% treatment 0% control/ comparison Not reported	No loss to follow up in group of 29 PCOS of interest to this analysis
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	Partial- Not for Step 1, 2 were excluded; for Step 2 which is of interest here, no loss to follow up.
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	No - Difficult to determine since there is no protocol, but one of the outcomes - fetal anomaly- was not reported in any results despite being prespecified.
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	Patient group had more abnormal GTTs than controls. Only age described in relation to step 2 for PCOS comparisons, no other prognostic baseline variables reported such as BMI, etc.
	If confounding was present, was it controlled for?	Yes Partial No Not reported	No- No stratified analysis for different GDM treatments or adjustment for insulin/medication use or any other potentially confounding/ effect modifying variable; sample size was too small for this anyway
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	Not reported
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	No- no power calculation or protocol, unlikely powered given the very small sample size
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Partial- potential confounders were not taken into account in the analysis; no protocol with predetermined primary outcomes; small sample size of only 7 with PCOS
COMMENTS		Cannot determine conflicts of interest; lacking proper analysis and very small sample size, unclear population differences and if groups were balanced at baseline, and no explicit criteria for exclusion or detail around randomization or allocation concealment methods	
What is the overall risk of bias?		Low Moderate High Insufficient information	High due to the above
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		No – all outcomes high risk of bias	

Study ID	Vanky 2004	
Study Citation	Vanky E, Salvesen KA, Heimstad R, Fougner KJ, Romundstad P, Carlsen SM. Metformin reduces pregnancy complications without affecting androgen levels in pregnant polycystic ovary syndrome women: results of a randomized study. *Hum Reprod*. 2004;19(8):1734-1740. doi:10.1093/humrep/deh347.	
Study Country	Norway	
BRIEF CHARACTERISTICS OF RCT		
Patient/population/ participants	Women with PCOS	
PCOS diagnostic criteria	Rotterdam 2003	
Presence of infertility	Assumed for some based on setting for recruitment (infertility outpatient clinic). Also, 10 had IVF/ICSI and 4 received CC	
Presence of other condition/s	Not reported except as per exclusion criteria	
Medication History	Metformin at conception; 1 tablet folate daily + 1 multivitamin; CC at conception (n=4); IVF/ICSI at conception (n=10); no other medication reported.	
N per group	Allocated/ randomised: 40 Assessed at end of study: 38	
Setting	Gynaecological and infertility outpatient clinic at University affiliated hospital	
Intervention	**Metformin** (425mg capsules) at 5-12 weeks until delivery- once daily for Week 1 (850mg) then twice daily for the rest of pregnancy (1700 mg)	
Comparison	**Placebo** at 5-12 weeks until the end of pregnancy	
Outcomes (primary and other) with definition (e.g. self-reported, fasting etc.)	**Primary**: DHEAS, androstenedione, testosterone, SHBG, free testosterone. **Secondary**: pregnancy outcomes and complications	
Follow up Duration	5-12 weeks until delivery (some used metformin preconception and had ≥2 day washout)	
Summary Result/s	Severe pregnancy complications occurred more frequently in the placebo group compared to metformin, with no change in androgens.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No Not reported	
Inclusion criteria	Yes Partial No	The inclusion criteria for the study were: (i) diagnosis of PCOS

		Not reported	before the actual pregnancy, (ii) age 18–40 years, (iii) gestational age between 5 and 12 weeks, and a singleton viable fetus judged by ultrasonography.
Exclusion criteria		Yes Partial No Not reported	The exclusion criteria were known liver disease, creatinine >130 mmol/l, known alcohol abuse, previously known diabetes mellitus, fasting plasma glucose >5.6 mmol/l, treatment with oral glucocorticoids or use of drugs known to interfere with metformin.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Yes- Randomization was performed with sealed envelopes. The envelopes were ordered in a random manner and given a randomization number by a pharmacist who did not belong to the research group. Randomization was performed in blocks of 10 and women were stratified according to whether or not they used metformin at conception.
	Was allocation to intervention group concealed?	Yes Partial No Not reported	As above
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	Yes
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	Yes
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	Yes- All participants received individual, verbal and written, diet and lifestyle counselling at inclusion. All patients were followed up and treated during pregnancy according to standard antenatal care.
DETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	Yes- A blinded evaluation of all maternal and infant diagnoses was performed by one of the authors
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes- assays reported, criteria reported for GDM and OGTT methods defined.
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Not reported- unclear where blood analyses were performed and by whom
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	0% treatment 0% control/ comparison Not reported	No loss to follow up in group of 29 PCOS of interest to this analysis

	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	Partial- Not for Step 1, 2 were excluded; for Step 2 which is of interest here, no loss to follow up.
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Partial - Difficult to determine since there is no protocol, but primary and secondary outcomes outlined clearly in the paper
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	
	If confounding was present, was it controlled for?	Yes Partial No Not reported	Not applicable for study design and balanced randomisation
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	Not clearly stated
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	For the primary outcome but sample size is small for other outcomes
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Partial- no protocol with predetermined primary outcomes; small sample size
COMMENTS		Clearly reported and includes key relevant details. Minor issues only including not being powered for individual pregnancy complications and reporting this as a composite of severe complications	
What is the overall risk of bias?		Low Moderate High Insufficient information	Overall low risk of bias. Moderate risk for pregnancy complications due to being underpowered and no clear protocol or indication of statistical significance of individual complications; also the drop outs were included in the analysis? unclear how this was achieved or why given they withdrew 2 weeks into the study and did not take the study medication
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		Hormones- low risk of bias Secondary outcomes/ pregnancy complications: moderate risk of bias	

Study ID	Vanky 2010	
Study Citation	Vanky E, Stridsklev S, Heimstad R, et al. Metformin versus placebo from first trimester to delivery in polycystic ovary syndrome: a randomized, controlled multicenter study. *J Clin Endocrinol Metab*. 2010;95(12):E448-E455. doi:10.1210/jc.2010-0853	
Study Country	Norway	
BRIEF CHARACTERISTICS OF RCT		
Patient/population/ participants	Women with PCOS	
PCOS diagnostic criteria	Rotterdam 2003; based on documentation before the actual pregnancy, all diagnosed by a gynaecologist.	
Presence of infertility	Assumed since 13.3 and 15.9% undergoing IVF/ICSI and 29.6 and 22.5 receiving CC treatment at baseline.	
Presence of other condition/s	GDM at inclusion in 7.4 and 9.4% of metformin and placebo groups. Other conditions not reported outside of those mentioned in exclusion criteria.	
Medication History	Metformin at conception; Women who used metformin at conception and in early pregnancy had a washout period of at least 7 d before inclusion in the study. Patients were advised to take 0.8 mg folate daily and one daily multivitamin tablet. Other concomitant medication collected but not reported in main paper.	
N per group	Allocated/ randomised: 274 pregnancies in 258 women (1 excluded after randomization due to 21-hydroxylase deficiency) Assessed at end of study: 270 (3 LFTU and 1 with deficiency as above)	
Setting	11 study centres: three university hospitals, seven local hospitals, and one gynaecological specialist practice.	
Intervention	**Metformin** (500 mg oral tables): one tablet twice daily during the first week (1000mg) and two tablets twice daily (2000 mg) for the rest of the study period.	
Comparison	**Placebo** - matching in the same form as above	
Outcomes (primary and other) with definition (e.g. self-reported, fasting etc.)	**Primary**: prevalence of PE, PTB and GDM and a composite of the three (≥1) **Secondary**: Weight, BP, HR, mode and length of delivery. SAE, including fatal events to mother or baby, life-threatening conditions or events requiring prolonged hospitalisation.	
Follow up Duration	First trimester to delivery	
Summary Result/s	Metformin treatment from first trimester to delivery did not reduce pregnancy complications in PCOS.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	To test the hypothesis that metformin use in PCOS pregnancy reduces preeclampsia, preterm delivery, and/or GDM.
Does the study have specified inclusion/exclusion criteria?	Yes Partial No Not reported	Yes- below
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes Partial No	Yes- below

		Not reported	
Inclusion criteria		Yes Partial No Not reported	1) PCOS diagnosed according to the Rotterdam criteria (4), 2) age 18 – 45 yr, 3) gestational age between 5 and 12 wk, and 4) a singleton viable fetus shown on ultrasonography.
Exclusion criteria		Yes Partial No Not reported	Alanine aminotransferase >90 IU/L, serum creatinine >1.70 mg/dl, known alcohol abuse, previously diagnosed diabetes or fasting serum glucose >126 mg/dl at the time point of inclusion, treatment with oral glucocorticoids, or use of drugs known to interfere with metformin.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Yes- Randomization was performed at the Trondheim University Hospital Pharmacy in blocks of 10 (five metformin and five placebo) and stratified according to metformin use at conception. The method was random drawing of an envelope (ordered in groups of 10: five metformin and five placebo) by two pharmacy employees, one executing the drawing and the other monitoring the drawing.
	Was allocation to intervention group concealed?	Yes Partial No Not reported	The enrolling doctor at the study centres faxed patient details to the university pharmacy. The participants were allotted to placebo or metformin, and the study medication was subsequently mailed to the participants. The participants and care providers were blinded for treatment allocation.
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	Yes- The participants and care providers were blinded for treatment allocation.
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	Yes- The participants and care providers were blinded for treatment allocation.
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	Yes- All participants received written and individual verbal counselling on diet and lifestyle at inclusion. All patients were advised to take 0.8 mg folate daily and one daily multivitamin tablet
DETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	Yes- One of the authors (R.H.) evaluated and quality checked (blinded) all outcomes and diagnoses. Assumed since all analyses were conducted before the randomization code was broken.
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Partial- Methods used for laboratory or on site analysis of glucose were not specified (assay/ CV/ equipment) to assess reliability
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Yes- One of the authors (R.H.) evaluated and quality checked (blinded) all outcomes and diagnoses.
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	0.7% treatment 2.2% control/ comparison Not reported	1 from metformin and 3 from placebo LFTU/ excluded

	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	Yes – ITT for most participants except LFTU for spontaneous abortion
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	
	If confounding was present, was it controlled for?	Yes Partial No Not reported	Yes- although to note, small effects may have been masked by tight and thorough pregnancy follow-up and lifestyle intervention provided to all women
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	Power calculation required 152 women in each group but only 135 were analysed. Possibly underpowered for some outcomes.
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	
COMMENTS		Clearly reported and includes key relevant details. Minor issues only including not being powered for individual pregnancy complications and reporting this as a composite of severe complications	
What is the overall risk of bias?		Low Moderate High Insufficient information	Overall low risk of bias. Moderate for post-hoc or secondary outcomes which were not adjusted for multiple testing.
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		Primary outcomes- all low risk of bias Post-hoc analyses or non-primary outcomes- moderate risk of bias	

Study ID	Lovvik 2019	
Study Citation	Løvvik TS, Carlsen SM, Salvesen Ø, et al. Use of metformin to treat pregnant women with polycystic ovary syndrome (PregMet2): a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol. 2019;7(4):256-266. doi:10.1016/S2213-8587(19)30002-6	
Study Country	Norway, Sweden and Iceland	
BRIEF CHARACTERISTICS OF RCT		
Patient/population/ participants	Women with PCOS	
PCOS diagnostic criteria	Rotterdam 2003	
Presence of infertility	Not explicitly reported but can be derived from mode of conception, with ~43% having ovulation induction medication, IVF/ICSI or gonadotrophin releasing hormone analogues.	
Presence of other condition/s	Yes but not reported in the main study: only that 267 (55%) of the participants suffered from one or more chronic conditions or had a history of bariatric surgery.	
Medication History	Metformin use at conception; other medication collected but not reported in primary study	
N per group	Allocated/ randomised: 487 Assessed at end of study: 478 included in ITT analysis	
Setting	14 hospitals in Norway, Sweden, and Iceland.	
Intervention	**Metformin** oral tablets; 500 mg twice daily (1000 mg/ day)during the first week of treatment, with the dose increased to 1000 mg twice daily (2000 mg/day) from week 2 until delivery.	
Comparison	**Placebo** from enrolment until delivery	
Outcomes (primary and other) with definition (e.g. self-reported, fasting etc.)	**Primary**: composite incidence of late miscarriage (between week 13 and week 22 and 6 days) and preterm birth (between week 23 and week 36 and 6 days), including spontaneous birth, induced vaginal deliveries, and operative deliveries for medical indications **Secondary**: GDM (WHO 1999); preeclampsia (any form) and hypertension (including pre-existing), treatment with vaginal progesterone to prevent imminent preterm delivery, vaginal bleeding during pregnancy, admission to hospital of patients during pregnancy, except for delivery and postpartum; admission to NICU and the total number of days in NICU per baby. **Tertiary**: weight gain in pregnancy (inclusion- 36wk, excluding participants with delivery < 36 wk or those without weight at 36wk). Neonatal birthweight, birth length, head circumference, 5-minute Apgar score, and umbilical cord pH, malformations (listed separately as adverse events).	
Follow up Duration	Enrolment (6-12+6 gestational weeks; Median 10-11 weeks gestation) to delivery	
Summary Result/s	In pregnant women with PCOS, metformin treatment from the late first trimester until delivery might reduce the risk of late miscarriage and preterm birth, but does not prevent gestational diabetes.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	To test the hypothesis that metformin prevents late miscarriage and preterm birth in pregnant women with PCOS
Does the study have specified inclusion/exclusion criteria?	Yes Partial No	Yes- below

		Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	Yes- below
Inclusion criteria		Yes Partial No Not reported	Patients were eligible for inclusion if they had an established diagnosis of PCOS according to the Rotterdam 2003, were aged 18–45 years, were pregnant by any mode of conception with a singleton viable fetus (determined by ultrasound) between gestational week 6 and week 12 plus 6 days, had a minimum of 7 days washout of metformin (if used before inclusion), and were able to communicate in a Scandinavian language or English. If there was no certain PCOS diagnosis before inclusion, anamnestic data were gathered and medical files were checked to confirm the diagnosis.
Exclusion criteria		Yes Partial No Not reported	Patients were excluded if they had diabetes, known liver or kidney failure, conditions that could induce tissue hypoxia (ie, emphysema, severe asthma, or heart failure), known hypersensitivity to metformin, known alcohol or drug misuse, were using drugs known to interfere with metformin, were breastfeeding, or were unsuitable for participation for other reasons.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Yes- randomly assigned women (1:1) to receive metformin or placebo via computer-generated random numbers. Randomisation was in blocks of ten for each country and centre; the first block had a random size between one and ten to assure masking. Randomisation of treatment packages was computer generated and was done before inclusion by personnel not involved in the trial. At inclusion, the local principal investigator logged on to a website and was given a randomisation number from one of the medication packages.
	Was allocation to intervention group concealed?	Yes Partial No Not reported	Yes - Placebo tablets and metformin tablets were identical and allocated in a blinded fashion as above.
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	Yes - Placebo tablets and metformin tablets were identical.
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	Yes- the local principal investigator logged on to a website and was given a randomisation number from one of the medication packages.
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	Yes- All women received diet and lifestyle advice according to national guidelines. No dietary supplements were recommended while the women participated in the study, with the exception of 0·4 mg folic acid and one multivitamin tablet per day.
DETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	Yes- In addition to masking of participants and study personnel, obstetricians not involved in the care or treatment of participants assessed the study outcomes, a statistician masked to the treatment allocation did the

			statistical analyses, and the design of tables and figures were planned before the results were known
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Partial- detailed outcome measures reported in protocol in suppl material except for biochemical measures (e.g. glucose); no mention of assays/kits used, CV%, laboratory, etc.
	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Partial - unclear where blood analyses were performed and by whom
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	2.5% treatment 1.2% control/ comparison Not reported	6 of the 244 metformin and 3 of the 243 placebo participants excluded from the ITT analysis as below
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	Yes – ITT conducted with most participants included except where there were protocol violations/ accidental inclusions or missing data/ evaluation could not be performed
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	Protocol outlines all primary and secondary outcomes and reported clearly in the paper
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	Partial- groups were similar except for the combined Asian group when south and east Asian were compared together across groups
	If confounding was present, was it controlled for?	Yes Partial No Not reported	Not applicable for study design and balanced randomisation
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	ISP reports personal fees for teaching and for being part of a review board panel from Gedeon Richter and Bayer, outside the current study. All other authors declare no competing interests.
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	No- sample size reduced to 500 despite sample size calculation of 1000 determined due to feasibility issues. Although IPD was conducted to increase power, this was still below the n=1000 required and was likely insufficient power to detect significant differences for some outcomes.
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes- except for sample size issues as above
COMMENTS		Clearly reported and includes key relevant details. Minor issues only including not being powered but this isreported transparently and attempts to validate results through IPD	
What is the overall risk of bias?		Low Moderate	Overall low risk of bias for this study- post hoc analyses would be moderate risk of bias.

	High Insufficient information	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	All prespecified outcomes low risk of bias. Post-hoc analyses moderate risk of bias	

Study ID	Morin Papunen 2015	
Study Citation	Morin-Papunen L, Rantala AS, Unkila-Kallio L, et al. Metformin improves pregnancy and live-birth rates in women with polycystic ovary syndrome (PCOS): a multicenter, double-blind, placebo-controlled randomized trial. *J Clin Endocrinol Metab*. 2012;97(5):1492-1500. doi:10.1210/jc.2011-3061.	
Study Country	Finland	
BRIEF CHARACTERISTICS OF RCT		
Patient/population/ participants	Women with anovulatory infertility and PCOS	
PCOS diagnostic criteria	Rotterdam 2003	
Presence of infertility	Anovulatory infertility for at least 6 months but all had patent tubes on sonosalpingography	
Presence of other condition/s	Male factor infertility, but normal tubal patency. No other conditions listed outside of exclusion criteria below.	
Medication History	Washout of infertility treatments for at least 3 months. No other medications mentioned.	
N per group	Allocated/ randomised: 320 Assessed at end of study: 320 (61 LFTU or discontinued but included in ITT)	
Setting	All University hospitals of Finland (5 sites)	
Intervention	**Metformin** oral tablets: 500 mg once daily during the first week, with the dose increased by one tablet/day in weekly steps up to 3 tablets daily in non-obese women and 4 tablets daily in obese women: (1000 mg/day in week 2; 1500 mg/day in week 3; 2000 mg/day in week 4) for up to 9 months maximum (or if pregnancy was achieved, until gestational week 12). After 3 months, if no pregnancy occurred, CC was added; if ovulation occurred CC continued with met or placebo for 4-6 cycles or until 12 weeks gestation; if pregnancy did not occur, aromatase inhibitors or gonadotrophins were used. For male infertility, IVF/ICSI was used.	
Comparison	**Placebo** in the same process as above	
Outcomes (primary and other) with definition (e.g. self-reported, fasting etc.)	**Primary**: decrease in early pregnancy loss. **Secondary**: improve pregnancy rates and live birth rates	
Follow up Duration	Preconception for 9 months or until gestational week 12 if pregnancy is achieved	
Summary Result/s	3 months pre-treatment with metformin is particularly beneficial for obese women in terms of improving pregnancy rate with similar benefits for live birth rate in both obese and non-obese women with anovulatory infertility	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes Partial No Not reported	To assess whether metformin decreases early pregnancy loss, and the second one was to clarify whether it improves pregnancy rates (PR) and livebirth rates (LBR) in women with anovulatory infertility and PCOS.

Does the study have specified inclusion/exclusion criteria?		Yes Partial No Not reported	
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes Partial No Not reported	
Inclusion criteria		Yes Partial No Not reported	Eligible participants were women aged 18 –39 yr at entry, with a body mass index (BMI) greater than 19 kg/m and diagnosed with PCOS according to Rotterdam criteria (19). All the subjects had polycystic ovaries at ultrasound according to ESHRE/ASRM, and a large majority had oligo-amenorrhea, 44.7% had hyperandrogenism or hirsutism or both. The women had suffered from anovulatory infertility for at least 6 months and a washout period of at least 3 months since the last infertility treatment was required.
Exclusion criteria		Yes Partial No Not reported	Exclusion criteria were type 2 diabetes mellitus, active liver disease (alanine aminotransferase >100 IU/liter), history of cardiac or renal failure, hormone medication, alcohol use, and regular smoking.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes Partial No Not reported	Yes- Randomization (after simple randomization procedures) was performed by the hospital pharmacy with 1:1 allocation in random blocks of 10 using two computer-generated lists, one for the nonobese and one for the obese women.
	Was allocation to intervention group concealed?	Yes Partial No Not reported	Yes- Metformin and placebo tablets were provided by Leiras (Turku, Finland) and prepacked in opaque identical containers of 100 tablets and consecutively numbered for each woman according to the randomization schedule. Each woman was assigned a number and received the tablets in the corresponding container.
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes Partial No Not reported	Yes- Randomization codes remained blinded until the database lock had taken place. The patients and all study site personnel were blinded to the study drug codes.
	Were investigators and care providers blind to intervention group?	Yes Partial No Not reported	Yes- Randomization codes remained blinded until the database lock had taken place. The patients and all study site personnel were blinded to the study drug codes.
	Aside from the experimental intervention, were the groups treated the same?	Yes Partial No Not reported	No- some women received CC, others received AI or GnRH or IVF/ICSI.
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes Partial No Not reported	Yes- assumed so since all personnel were blinded until database lock had taken place
	Were all outcomes measured in a standard, valid and reliable way?	Yes Partial No Not reported	Yes- assays reported, criteria reported for GDM and OGTT methods defined.

	Were outcomes assessed objectively and independently?	Yes Partial No Not reported	Not reported- unclear where blood analyses were performed and by whom
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	17% treatment 21% control/ comparison Not reported	27 and 34 LFTU/ discontinued in metformin and placebo groups respectively. Included in ITT analysis
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes Partial No Not reported	ITT was performed where data were available
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes Partial No Not reported	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial No Not reported	Different treatments may affect pregnancy outcomes for the purpose of this review/ analysis. Different doses in obese and non-obese groups
	If confounding was present, was it controlled for?	Yes Partial No Not reported	Weight loss should have been used as a time-dependent covariate in the intent-to-treat analysis as this may have been the key influence on the results
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes Partial No Not reported	
	Was the study sufficiently powered to detect any differences between the groups?	Yes Partial No Not reported	150 needed for each group, 160 included in ITT
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Yes, but although exclusion of IVF/ICSI was performed for most of the primary analyses, other ovulation induction meds including CC and GnRH/AI were not excluded to examine the effects on results
COMMENTS		Clearly reported and includes key relevant details. Issues for the present analysis are outside the aims of this study - since we are interested in pregnancy outcomes and the study itself was designed to assess pregnancy rate/ LBR	
What is the overall risk of bias?		Low Moderate High Insufficient information	Overall low risk of bias for the study and primary outcomes. Moderate risk of bias for pregnancy complications outside of miscarriage/ LBR/ PR, due to different baseline treatments within groups. Most outcomes will need to be derived from IPD, not from the main published paper.
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		Primary and pre-specified outcomes - low risk of bias Other pregnancy complications- moderate risk of bias	

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 4

Question 4.11.

In women with PCOS in pregnancy, is metformin compared to placebo/standard care effective in reducing pregnancy complications and adverse neonatal outcomes?

BACKGROUND:

Metformin is an oral medication commonly used to treat type 2 diabetes mellitus. It is commonly available and affordable worldwide. Metformin has glucose-lowering properties by reducing hepatic gluconeogenesis, increasing insulin sensitivity, and enhancing uptake of peripheral glucose (1) Metformin is actively transported through cell membranes mainly by organic cation transporters (2). The drug was first introduced in 1980's, to treat diabetes in pregnancy (3). In PCOS, the related insulin resistance has promoted the use of metformin. During the last two decades, metformin has been used to facilitate weight management, improve fertility and regular menstrual cycles in affected women, and also aiming to reduce the risk for early miscarriage and pregnancy complications.

Pregnancy in women with PCOS is associated with a strong early mobilization of inflammatory and other serum cytokines persisting throughout pregnancy, indicating a more activated immune status. These findings provide a new insight to the connection between PCOS and pregnancy complications (4). During pregnancy, renal metformin clearance is increased, and serum concentration drops to about 70% compared to a non-pregnant state (5, 6). Metformin crosses the placenta, and consequently, the fetus is exposed to therapeutic concentrations (7). Dosages and treatment protocols (immediate vs. extended release) are diverging, 500-2500 mg daily being most often reported. Common practices also vary regarding the start of the drug therapy (prior pregnancy or early pregnancy) and the time of cessation (pregnancy test positive, throughout the pregnancy). Side effects are mostly mild, transient gastrointestinal symptoms and potential reduction on vitamin B-12 levels. Teratogenicity is not reported (8), however, lately there has been more concern on long-term metabolic effects of metformin on offspring health (9, 10).

Methodological quality/risk of bias

Only RCTs (n=7) were included. Risk of bias for the included studies varied. Studies on preterm delivery and gestational age were rated as of low risk of bias. Studies focusing on GDM, glucose homeostasis, PE, hypertension, miscarriage, and gestational weight gain were rated as high risk of bias and should be interpreted with caution. The bias was often related to underpowered study set-up. Studies on neonatal outcomes were rated as high risk of bias and should be interpreted with caution. The most common reasons for the ratings assigned include: 1) allocation to the intervention group was not blinded (two studies); 2) power calculations were not reported; 3) insufficient number of patients in the trials, and 4) a lack of conflict-of-interest statements. These methodological issues may have an impact on the direction of bias and reliability of the findings.

Generalizability

Studies were conducted at university hospitals, infertility clinics in hospitals and laboratories covering countries across the world; Norway, Finland, Iran and Bangladesh.

GRADE EVIDENCE CERTAINTY	
Comparison	**GRADE for critical outcomes**
Comparison 1. Metformin versus placebo/ control	⊕⊕◯◯ LOW

Evidence to Recommendations Framework

COMPARISONS (option versus other option)

Metformin vs. placebo/ standard care

EVIDENCE-BASED RECOMMENDATION(S)

EBR: Metformin could be considered in some circumstances (e.g. risk for preterm birth), to reduce preterm delivery and limit excess gestational weight gain, in pregnant women with PCOS.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

- **EBR:** Healthcare professionals should be aware that metformin in pregnant women with PCOS has not been shown to prevent:
  - Gestational diabetes
  - Late miscarriage (12 weeks+1 day to 21 weeks +6 days gestational age)
  - Hypertension in pregnancy
  - Pre-eclampsia
  - Macrosomia or birthweight ≥ 4000 g

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☒ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

PRACTICE POINT(S)

Women should be counselled that the consequences of metformin exposure on long-term offspring health remain unclear and there is a suggestion of increased childhood weight, although causality is not certain.

Side effects of metformin are mostly mild, transient gastrointestinal symptoms and are not worse in pregnancy.

GRADE CONSIDERATIONS

Justifications:
Two critical (associated) outcomes (preterm birth and gestational age) had high certainty.
One important outcome (gestational weight gain) had moderate certainty.

Subgroup considerations:
The studies did not focus on women with high risk of preterm delivery (previous late miscarriage, preterm delivery, smokers, cervical conization) – theoretically they may benefit more from metformin therapy, but it is not investigated.
Grouping according to pre-pregnancy weight may be beneficial to the analysis of gestational weight gain
Further, there is a need to examine whether metformin may assist in glycaemic control (alongside diet/lifestyle) among women with PCOS and an established GDM diagnosis (i.e. for treatment rather than for prevention).

Implementation considerations:
Potential side-effects of the drug should be considered.

Monitoring and evaluation considerations:
Long-term effects of metformin-exposure during pregnancy on the next generation's metabolic and neuropsychological health. Monitoring the implementation of the recommendation in clinical practice and evaluate the change in health outcomes.

Research priorities:
Understanding the mechanisms of metformin action in pregnancy
Timing, dosing, duration and subgroups that benefits most from metformin in pregnancy
To follow up the potential long-term the next generation health effects of metformin-exposure in utero

GRADE framework

GRADE DECIDE **Interactive Evidence to Decision Framework**

- **DESIRABLE EFFECTS**

How substantial are the desirable anticipated effects?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Metformin may have positive effect, no effect or negative effect on the outcomes we review

Is a larger head circumference good or bad?

Is less weight gain in pregnancy good or bad?

A “no difference” for a drug vs placebo in pregnancy – would result in no treatment

Long-term safety is not evaluated and considered here

Do we have an indication that pre-pregnancy start for metformin is beneficial?

For 2 studies the initiation was prior pregnancy and one at week 2.

Do we have an indication of women “at risk” that should be prioritized for treatment?

Comment on when to stop metformin use during pregnancy.

- **UNDESIRABLE EFFECTS**

How substantial are the undesirable anticipated effects?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Still unclear on balance of effects.

- **CERTAINTY OF THE EVIDENCE**

What is the overall certainty of the evidence of effects?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☒ Probably favours other options	☒ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

EBR: Health professionals should be aware that metformin use in pregnant women with PCOS reduces preterm delivery and gestational weight gain. (Moderate to high certainty)

EBR: Health professionals should not use metformin in pregnant women with PCOS to prevent gestational diabetes. (Low certainty)

EBR: Health professionals should be aware that there is inadequate evidence to support the use of metformin in pregnant women with PCOS to prevent:

- Hypertension in pregnancy or pre-eclampsia (Low certainty)
- Late miscarriage (12+1 to 21+6 gestational age) (Low certainty)
- Macrosomia or birthweight ≥ 4000 g (Moderate certainty)

Long-term safety evidence is not reviewed

- **VALUES**

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☐ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☒ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Research evidence:

No research evidence was identified

Panel discussion:

Preterm delivery/gestational age: no important uncertainty or variability

Miscarriage, birthweight, length, low birth weight, macrosomia: no important uncertainty or variability

Gestational weight gain, head circumference: probably no important uncertainty or variability

- **BALANCE OF EFFECTS**

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:

As the other option is placebo - metformin should not be used if it has not more desirable effect than placebo

Probably certain subgroups (high risk of preterm delivery) would benefit.

- **COSTS**

How large are the resource requirements (costs)?

Judgement:

☐ Don't know	☐ Varies	☐ Large costs	☐ Moderate costs	☒ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:

No research evidence was identified

Panel discussion:

Recommend to not routine use metformin, and metformin is cheap.

- **CERTAINTY OF COST EVIDENCE**

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

No research evidence was identified

Panel discussion:

- **COST-EFFECTIVENESS**

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

No research evidence was identified

Panel discussion:

Prevention of preterm birth is associated with cost savings.

- **EQUITY**

What would be the impact on health equity?

Judgement:

☐ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☒ Probably increased	☐ Increased

Research evidence:

No research evidence was identified

Panel discussion:

Metformin is cheap and available.

- **ACCEPTABILITY**

Is the option acceptable to key stakeholders?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

- **FEASIBILITY**

Is the option feasible to implement?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☐ Probably Yes	☒ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Recommendations are cautious but appropriate with evidence.

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GUIDELINE DEVELOPMENT GROUP 5

Assessment and treatment of infertility

Clinical Questions	
Q 5.1.	In women with PCOS with infertility, what are the preconception risk factors associated with poor/negative fertility outcomes?
Q 5.2.	Should women with PCOS and infertility due to anovulation alone with normal semen analysis undergo tubal patency testing prior to starting ovulation induction with timed intercourse or IUI treatment?
Q 5.3.	In women with PCOS, are aromatase inhibitors effective for improving fertility outcomes?
Q 5.4.	In women with PCOS, is clomiphene citrate effective for improving fertility outcomes? In women with PCOS, is metformin effective for improving fertility outcomes? In women with PCOS and a BMI<30-32, what is the effectiveness of metformin compared to clomiphene citrate for improving fertility outcomes?
Q 5.5	In women with PCOS, are gonadotrophins effective for improving fertility outcomes?
Q 5.6	In women with PCOS, is ovarian surgery effective for improving fertility outcomes?
Q 5.7	In women with PCOS, is stimulated IVF/ICSI effective for improving fertility outcomes?
Q 5.7.1.	In women with PCOS undergoing IVF/ICSI treatment, is the GnRH antagonist protocol or GnRH agonist long protocol the most effective for improving fertility outcomes?
Q 5.7.2.	In women with PCOS undergoing GnRH antagonist IVF/ICSI treatment, is the use of hCG trigger or GnRH agonist trigger the most effective for improving fertility outcomes?
Q 5.7.3.	In women with PCOS undergoing (controlled) ovarian (hyper) stimulation for IVF/ICSI, does the choice of FSH effect fertility outcomes?
Q 5.7.4.	In women with PCOS undergoing (controlled) ovarian (hyper) stimulation for IVF/ICSI, is exogenous LH treatment during IVF/ICSI effective for improving fertility outcomes?

Q 5.7.5.	In women with PCOS undergoing (controlled) ovarian (hyper) stimulation for IVF/ICSI, is adjuvant metformin effective for improving fertility outcomes?
Q 5.7.6.	In women with PCOS, is In Vitro Maturation (IVM) effective for improving fertility outcomes?
Q 5.8.	In women with PCOS, is inositol alone or in combination with other therapies, effective for management of reproductive outcomes? (fertility outcomes only)
Q 5.9.	In women with PCOS, are anti-obesity pharmacological agents alone or in combination, effective for management of reproductive outcomes? (fertility outcomes only)
Appendix	GDG 5 Methodology Appendix (applicable to all GDG 5 questions, except Q 5.1, Q 5.2, Q 5.8 and Q 5.9)

PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by ECR Lead: Thisara Coster

(meta-analysis by Aya Mousa)

Other team members: Katrina Tan, Lane Carrandi, Demelash Handiso, Rejoy Benjamin, Tamadher Al-Shaali, Darren Rajit, Yanan Hu, Loyal Pattuwage

Supervised, edited and supported by the Evidence Team (Aya Mousa, Jillian Tay)

GDG 5

Question 5.1.

In women with PCOS with infertility, what are the preconception risk factors associated with poor/negative fertility outcomes?

1. STUDY SELECTION

Table 1. PICO Criteria for Inclusion	
Question	**In women with PCOS with infertility, what are the preconception risk factors associated with poor/negative fertility outcomes?**
Clinical leads (key contacts)	**Prof Helena J Teede**
Allocation ranking	**Level 1 – new systematic review**

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(language, year)*
Inclusion	Women with PCOS (Rotterdam, AES, NIH)	None, ovulation induction, any other form of fertility treatment (e.g. metformin, IVF etc.)	None	Preconception or pre-fertility treatment maternal factors associated with 1) Natural conception 2) positive fertility treatment measures (e.g. Live birth rate, pregnancy rate (biochemical or clinical ultrasound) 3) fertility treatment related adverse events (e.g. OHSS, miscarriage) Factors may include: Screening or assessment Metabolic health measures, BMI (as per WHO parameters appropriate for geographic region), weight, WHR, WC, BP, lipids, glucose Medications"/ drugs; Alcohol, smoking, recreational drug use, medications, vaccination, Mental health: Mental health measures, QOL, emotional and psychosocial wellbeing, eating disorders, anxiety, depression, body image. Document only valid measures. Illness: medial chronic illness Other assessments - vitamin D levels	Evidence based guidelines, Systematic reviews, health technology assessments, randomised controlled trials (RCTs), cohort/observational studies	English language. Human studies
Exclusion	Women without infertility			Gene expression studies		

SEARCH STRATEGY

Search details	
Search strategy source:	
Evidence source	**Date of search**
Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to August 22, 2022>	23/08/2022
Embase Classic+Embase <1947 to 2022 August 22>	23/08/2022
Any subsequent updates - enter database and date: not applicable	

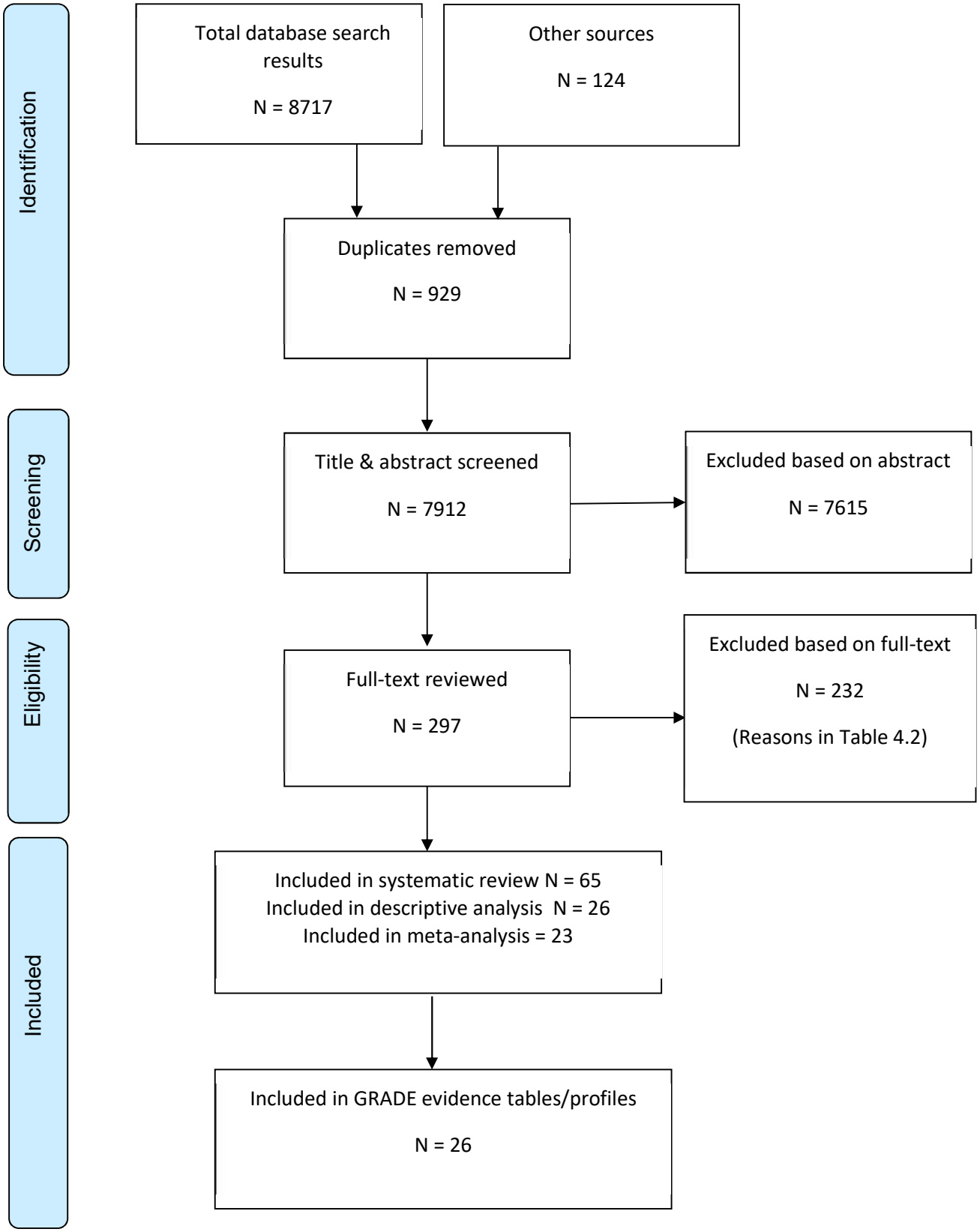
Questions addressed by this search:		
GDG	Q#	Question
5	5.1.	In women with PCOS with infertility, what are the preconception risk factors associated with poor/negative fertility outcomes?

Search strategy	
OVID Medline, All EBMs (including Cochrane dataset for SRs), EMBASE	**CINAHL Plus**
1 exp polycystic ovary syndrome/ 16990 2 polycystic ovar$.mp. 22551 3 "poly cystic ovar$".mp. 52 4 PCO$.mp. 36312 5 (stein?leventhal or leventhal).mp. 916 6 anovulation/ 2267 7 anovulat$.mp. 6776 8 oligoovulat$.mp. 61 9 "oligo ovulat$".mp. 108 10 (ovar$ adj5 (sclerocystic or polycystic or "poly cystic" or degenerat$ or hyperandrogen$ or "hyper androgen$")).mp. 23539 11 or/1-10 49911 12 fertility/ 43362 13 fertility agents/ 380 14 fertility agents, female/ 3103 15 fertil$.mp. 244098 16 infertility/ 16251 17 infertility, female/ 30495 18 infert$.mp. 104792 19 pregnancy complications/ 96246 20 pregnancy/ 958687 21 pregnancy outcome/ 56146 22 pregnancy rate/ 12927 23 pregnant women/ 12768 24 or/12-23 1192586 25 exp Reproductive Techniques, Assisted/ 77753 26 Ectogenesis/ 419 27 ((in vitro or invitro) adj (fertili?ation or maturation)).mp. 31110 28 (intracytoplasm* sperm inject* or ICSI).mp. 12691	exp polycystic ovary syndrome/ 33702 2 polycystic ovar$.mp. 28943 3 "poly cystic ovar$".mp. 205 4 PCO$.mp. 53850 5 (stein?leventhal or leventhal).mp. 1514 6 anovulation/ 6707 7 anovulat$.mp. 11181 8 oligoovulat$.mp. 123 9 "oligo ovulat$".mp. 155 10 (ovar$ adj5 (sclerocystic or polycystic or "poly cystic" or degenerat$ or hyperandrogen$ or "hyper androgen$")).mp. 38432 11 or/1-10 78818 12 fertility/ 71217 13 fertility agents/ 1345 14 fertility agents, female/ 1345 15 fertil$.mp. 322047 16 infertility/ 49694 17 infertility, female/ 20644 18 infert$.mp. 161357 19 pregnancy complications/ 17891 20 pregnancy/ 790754 21 pregnancy outcome/ 73742 22 pregnancy rate/ 37069 23 pregnant women/ 94328 24 or/12-23 1227205 25 exp Reproductive Techniques, Assisted/ 132229 26 Ectogenesis/ 196 27 ((in vitro or invitro) adj (fertili?ation or maturation)).mp. 50278 28 (intracytoplasm* sperm inject* or ICSI).mp. 29482 29 ((controlled or ovar*) adj (hyper or stimulat*)).mp. 13541 30 (IVF or IVM).mp. 55106

29 ((controlled or ovar*) adj (hyper or stimulat*)).mp. 7610 30 (IVF or IVM).mp. 30763 31 (zygote intrafallopian transfer* or zygote intra fallopian transfer* or ZIFT).mp. 268 32 (embryo transfer* or ET).mp. 565582 33 or/25-32 636452 34 search$.tw. or "meta analysis".mp. or "meta analysis".pt. or "metaanalysis".tw. or review.pt. or di.xs. or associated.tw. 10174568 35 clinical trial.mp. or clinical trial.pt. or random.mp. or tu.xs. 5869302 36 34 or 35 13776027 37 11 and 24 and 36 7890 38 11 and 33 and 36 3421 39 37 or 38 8555 40 11 and 24 11243 41 11 and 33 4731 42 40 or 41 12380 43 42 not 39 3825 44 limit 43 to (english language and humans and yr="1990 -Current") 1487 45 limit 44 to yr="2000 -Current" 1241	31 (zygote intrafallopian transfer* or zygote intra fallopian transfer* or ZIFT).mp. 209 32 (embryo transfer* or ET).mp. 3653271 33 or/25-32 3764507 34 exp methodology/ or search.tw. or review.pt. 9636588 35 random*.tw. or clinical trial.mp. or exp health care quality/ 6124312 36 34 or 35 12442966 37 11 and 24 and 36 10390 38 11 and 33 and 36 9027 39 37 or 38 13475 40 11 and 24 19544 41 11 and 33 17972 42 40 or 41 27649 43 42 not 39 14174 44 limit 43 to (english language and humans and yr="1990 -Current")7986 45 limit 44 to yr="2000 -Current" 6733

Evidence processing: Studies were selected and appraised by five reviewers using study selection and appraisal criteria (PICO above) established a priori. The articles were reviewed by title and abstract by three reviewers. When a decision could not be made based on title and abstract alone, full text was retrieved. **A total of 65 studies met inclusion criteria for this review**.

2. SEARCH RESULTS - PRISMA flowchart



3. STUDY INCLUSION

4.1.1 Included studies

1. Abu-Fakher B, Al-Quobaili F, Alhalabi M. Follicular fluid antimullerian hormone (AMH) does not predict IVF outcomes in polycystic ovary syndrome patients. Middle East Fertility Society Journal. 2013;18(2):110-4.
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48. McCormick B, Thomas M, Maxwell R, Williams D, Aubuchon M. Effects of polycystic ovarian syndrome on in vitro fertilization-embryo transfer outcomes are influenced by body mass index. Fertility & Sterility. 2008;90(6):2304-9.
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50. Mostinckx L, Segers I, Belva F, Buyl R, Santos-Ribeiro S, Blockeel C, et al. Obstetric and neonatal outcome of ART in patients with polycystic ovary syndrome: IVM of oocytes versus controlled ovarian stimulation. Human Reproduction. 2019;34(8):1595-607.
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64. Zhao Y, Ruan X, Mueck AO. Letrozole combined with low dose highly purified HMG for ovulation induction in clomiphene citrate-resistant infertile Chinese women with polycystic ovary syndrome: a prospective study. Gynecological Endocrinology. 2017;33(6):462-6.
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4.2 Excluded Studies (on full text assessment)	
Reference	Reason
1. Abd Elgafor et al. 2013	Risk factors not analysed against fertility outcomes
2. Abu Hashim et al. 2011	Integrity check exclusion
3. Abdalmageed, et al. 2019	No preconception risk factors
4. Abdellah et al. 2011	Risk factors not analysed against fertility outcomes
5. Abu Hashim et al. 2010	Risk factors not analysed against fertility outcomes
6. Abu Hashim et al. 2010	Risk factors not analysed against fertility outcomes
7. Abu Hashim et al. 2011	Risk factors not analysed against fertility outcomes
8. Abu Hashim et al. 2011	Risk factors not analysed against fertility outcomes
9. Abu Hashim et al. 2012	Risk factors not analysed against fertility outcomes
10. Abu Hashim et al. 2015	SR and no analysis of risk factors vs. fertility outcomes
11. Aflatoonian et al. 2020	No preconception risk factors
12. Al-Mosawi RH et al. 2021	Commentary
13. Ali Al-Dahhan NA et al. 2021	No fertility outcomes
14. Alizzi, F. J. Et al. 2018	No preconception risk factors
15. Almasi-Hashiani et al. 2018	No preconception risk factors
16. Amer et al. 2009	Risk factors not analysed against fertility outcomes
17. Amer, et al. 2017	No preconception risk factors analysed
18. Arslan E, et al. 2019	No fertility outcomes
19. Ashrafi et al. 2005	No preconception risk factors
20. Atay et al. 2006	Risk factors not analysed against fertility outcomes
21. Atwa et al. 2021	No preconception risk factors analysed
22. Ayaz et al. 2013	No preconception risk factors
23. Ayaz et al. 2013	No preconception risk factors
24. Aziz M et al. 2012	Protocol paper. NOTE: Also checked references and did not find any relevant papers

25. Badawy A et al. 2008	No preconception risk factors
26. Badawy et al. 2009	Risk factors not analysed against fertility outcomes
27. Bahceci et al. 2005	Risk factors not analysed against fertility outcomes
28. Banerjee Ray et al. 2012	Risk factors not analysed against fertility outcomes
29. Bansal et al. 2021	No preconception risk factors analysed
30. Bayar et al. 2006	Risk factors not analysed against fertility outcomes
31. Bayram et al. 2004	No preconception risk factors
32. Begum et al. 2009	Risk factors not analysed against fertility outcomes
33. Begum et al. 2013	Risk factors not analysed against fertility outcomes
34. Belli SH et al. 2004	No fertility outcomes
35. Beydoun HA, 2009	No preconception risk factors
36. Bokal EV et al. 2006	No preconception risk factors
37. Bongrani A et al.2019	Risk factors not analysed against fertility outcomes
38. Bousmpoula A, et al. 2018	No fertility outcomes
39. Brown et al. 2016	Not the study design of interest – SR
40. Celik C et al. 2013	No relevant outcomes
41. Chang CL et al. 2014	No relevant outcomes
42. Cordeiro FB et a. 2015	No fertility outcomes
43. Costello et al. 2006	Not the study design of interest – SR & meta analysis
44. Dabkowska-Huc A et al. 2013	No relevant outcomes
45. Das M et al. 2008	No fertility outcomes
46. De Leo V, et al. 1999	No preconception risk factors
47. Debras E 2019	No preconception risk factors
48. Dehbashi et al. 2009	Risk factors not analysed against fertility outcomes
49. Dikmen E et al. 2011	No fertility outcomes
50. Doldi N et al. 2006	No preconception risk factors
51. Eftekhar M et al. 2019	No preconception risk factors
52. Elgafor IA et al. 2013	No preconception risk factors
53. Elsedeek et al. 2011	Integrity check exclusion
54. Engmann et al. 2008	Unable to locate/access full text
55. Eskandari Z et al. 2016	Data not relevant
56. Farquhar et al. 2012	Not the study design of interest - SR
57. Farquhar et al. 2002	No preconception risk factors
58. Farquhar et al. 2004	No preconception risk factors or fertility outcomes
59. Fedorcsák et al. 2003	Participant risk factors not analysed against fertility outcomes
60. Fleming R et al. 2002	No preconception risk factors
61. Foroozanfard F, et al. 2011	No preconception risk factors
62. Franik et al. 2014	Not the study design of interest - SR
63. Gaafar TM, et al. 2014	No fertility outcomes
64. Garruti G et al. 2011	No outcomes
65. George SS et al. 2003	No preconception risk factors
66. Gupta A et al. 2009	Unable to locate/access full text
67. Haakova L et al. 2003	No preconception risk factors in PCOS group. Groups were matched for age and BMI
68. Hafed NN et al. 2019	No preconception risk factors
69. Hamed et al. 2010	Participant risk factors not analysed against fertility outcomes
70. Haydardedeoglu et al. 2012	Participant risk factors not analysed against fertility outcomes
71. Hoeger KM et al. 2004	No preconception risk factors
72. Homburg et al. 2012	Risk factors not analysed against fertility outcomes
73. Huang et al. 2015	SR, not study design of interest
74. Hwang et al. 2004	Risk factors not analysed against fertility outcomes
75. Ibragimov B et al. 2020	Unable to locate/access full text
76. Ibrahim et al. 2017	Does not analyse risk factors to fertility

77. Jacob SL et al. 2017	No fertility outcomes
78. Jacob, S. L. et al. 2016	No preconception risk factors
79. Jafarabadi et al. 2018	Reason unstated
80. Jahromi BN et al. 2016	No fertility outcomes
81. Jakubowicz DJ, et al. 2002	No preconception risk factors
82. Jensterle M et al. 2008	No fertility outcomes
83. Jeon YE et al. 2013	No fertility outcomes
84. Jia R et al. 2022	No fertility outcomes
85. Jiang et al. 2019	No preconception risk factors
86. Joham AE et al. 2014	No preconception risk factors
87. Joseph-Horne R et al. 2002	No fertility outcomes
88. Kabil Kucur S et al. 2021	Grouped fertility outcomes of PCOS and non-PCOS women
89. Kahyaoglu I et al. 2014	Preconception risk factors not analysed against outcomes of interest
90. Kamath et al. 2010	Does not analyse risk factors to fertility
91. Kanamarlapudi V et al. 2016	Fertility outcome no reported
92. Kandil et al. 2018	No preconception risk factors
93. Kar et al. 2012	Does not analyse risk factors to fertility
94. Kar S et al. 2015	Unable to locate/access full text
95. Karimzadeh 2010_Met vs Met+CC	Does not analyse risk factors to fertility
96. Khmil M et al. 2020	Fertility outcome no reported
97. Khurana A et al. 2022	Fertility outcome no reported
98. Kjotrod et al. 2004	Does not analyse risk factors to fertility
99. Kocak M et al. 2007	no preconception risk factors
100. Koninger A et al. 2014	Fertility outcome no reported
101. Kuang H et al. 2015	No preconception risk factors
102. Kulmann MIR et al. 2016	Unable to locate/access full text
103. Kumar HKVS et al. 2008	Unable to locate/access full text
104. Kurabayashi et al. 2006	Wrong study population - analysed males and females in one cohort; nil differentiation for PCOS alone
105. Kurabayashi T et al. 2004	Exclude
106. Kurzawa et al.2008	No relevant outcome/ analysis
107. Lainas et al. 2007	No relevant outcome/ analysis
108. Lainas et al.201	No relevant outcome/ analysis
109. Laven JSE et al. 2004	Insufficient data for extraction
110. Lawal OI et al. 2020	No fertility outcomes
111. Ledee-Bataille N et al. 2001	No preconception risk factors
112. Lee H et al. 2009	No fertility outcomes
113. Lee H et al. 2015	Poster presentation(not article)
114. Legro RS et al. 2007	Unable to locate/access full text
115. Leonhardt H et al. 2012	No relevant outcome
116. Leonhardt H et al. 2011	Exclude no outcomes
117. Lewandowski KC et al. 2006	No outcomes
118. Li H et al. 2022	No preconception risk factors
119. Li J et al. 2022	Exclude
120. Li J et al. 2015	No outcome and risk factors
121. Li Y et al. 2017	No outcome and risk factors
122. Li Z et al. 2018	Unable to locate/access full text
123. Lin AW et al. 2014	Review
124. Lin S et al. 2008	Unable to locate/access full text
125. Lin XF et al. 2015	Exclude
126. Lindheim SR, et al. 2000	No outcome and risk factors
127. Liu F et al. 2021	No outcome and risk factors

128. Liu KE et al. 2006	Unable to locate/access full text
129. Liu L et al. 2020	Outcome variables not reported
130. Liu L et al. 2019	Outcomes and risk factors not reported
131. Liu YD et al. 2017	Outcomes and risk factors not reported
132. Liu et al. 2017	No preconception risk factors
133. Lo JC, 2006	No preconception risk factors
134. Lopez et al. 2004	No relevant outcome/ analysis
135. Lv P-P et al. 2020	No fertility outcomes
136. Ma C. et al. 2020	Unable to locate/access full text
137. Mackens S et al. 2020	No risk factors
138. Macut D, et al. 2002	No outcome and risk factors
139. Madani T et a. 2006	Unable to locate/access full text
140. Maged et al. 2015	No relevant outcome/ analysis
141. Mai Z et al. 2021	Fertility outcomes not assessed against LBR; only analysed diagnosis of PCOS w LBR
142. Manteghi G et al. 2021	Unable to locate/access full text
143. Mantzoros CS et al. 2000	Exclude
144. Marquard K et al. 2009	Unable to locate/access full text
145. Mellembakken JR et al. 2011	No fertility outcome
146. Merk K et al. 2019	Unable to locate/access full text
147. Misso et al.2012	No relevant outcome/ analysis
148. Mokhtar et al. 2015	No relevant outcome/ analysis
149. Moll et al. 2007	No relevant outcome/ analysis
150. Morley et al. 2017	No relevant outcome/ analysis
151. Mukherjee et al. 2010	No relevant outcome/ analysis
152. Nahuis et al. 2011	no preconception risk factors
153. Najafi et al. 2020	Unable to locate/access full text
154. Nazik et al. 2012	No relevant outcome/ analysis
155. Ng EHY et al. 2001	No preconception risk factors
156. Nikbakht R et al. 2021	Does not stratify fertility outcomes between PCOS and non-PCOS groups using baseline preconception risk factors
157. Njoku C et al 2022	Exclude - no fertility outcomes
158. Omokanye LO et al 2017	Unable to locate/access full text
159. Onalan et al. 2005	No relevant outcome/ analysis
160. Pabuccu R et al. 2019	Unable to locate/access full text
161. Palep-Singh M et al. 2007	No relevant outcome/ analysis
162. Palmoba et al. 2004	No relevant outcome/ analysis
163. Palmoba et al. 2009	No relevant outcome/ analysis
164. Palomba et al. 2005	No relevant outcome/ analysis
165. Palomba et al. 2011	No relevant outcome/ analysis
166. Palomba et al. 2013	No relevant outcome/ analysis
167. Palomba Set al. 2011	No preconception risk factors
168. Palomba S et al. 2005	No preconception risk factors
169. Palomba S et al. 2005	No preconception risk factors
170. Palomba et al. 2009	No preconception risk factors
171. Pourghasem et al. 2019	No fertility outcomes
172. Pundir et al. 2012	No relevant outcome/ analysis
173. Qin Y et al. 2011	Women with PCOS excluded from study
174. Qublan HS et al. 2009	No preconception risk factors
175. Rausch ME, et al. 2009	Unable to locate/access full text
176. Rausch ME et al. 2010	Unable to locate/access full text
177. Rees DA et al. 2016	No relevant outcome/ analysis
178. Rezaee Z et al. 2012	No fertility outcomes

179. Rezk M et al. 2016	No fertility outcomes
180. Rezk, M. et al. 2018	No preconception risk factors
181. Roy et al. 2012	No relevant outcome/ analysis
182. Roy et al. 2009	No preconception risk factors
183. Sahin Y et al. 2004	No preconception risk factors
184. Sahmay S et al. 2013	Exclude
185. Sayed GA et al. 2020	Exclude
186. Selcuk S et al. 2016	No risk factors
187. Selim et al. 2012	No relevant outcome/ analysis
188. Sharif et al. 2022	No preconception risk factors
189. Sharma et al. 2006	Unable to locate/access full text
190. Shi et al. 2020	No preconception risk factors
191. Shokeir T, et al. 2008	Unable to locate/access full text
192. Sohrabvand F, et al. 2006	No preconception risk factors
193. Sun B et al. 2020	Groups not clearly defined
194. Sun Z et al. 2019	No fertility outcomes
195. Sunj M et al. 2014	No preconception risk factors
196. Tang et al. 2006	No relevant outcome/ analysis
197. Tang T et al. 2006	No preconception risk factors
198. Tasdemir S et al. 2004	No preconception risk factors
199. Tehraninejad et al. 2010	No relevant outcome/ analysis
200. Tian X et al. 2014	Exclude
201. Tokmak A et al. 2017	Unable to locate/access full text
202. Trenkic M et al. 2016	No English version available
203. Tso et al. 2014	No relevant outcome/ analysis
204. Tu Y et al. 2020	Exclude
205. Turkcapar et al. 2013	No relevant outcome/ analysis
206. Vagios S et al. 2021	No relevant outcome/ analysis
207. Valgeirsdottir H et al. 2019	No risk factors
208. Van Dam EWCM, et al. 2004	I can't find the outcome
209. van Wely M, et al. 2004	no preconception risk factors
210. van Wely et al 2004	No preconception risk factors
211. Vandermolen DT et al. 2001	No preconception risk factors
212. Vidales LM et al. 2017	Unable to locate/access full text
213. Wang Q et al. 2022	STRATIFIES STUDY OUTCOMES BY PHENOTYPE
214. Wang et al. 2020	No preconception risk factors
215. Wang et al. 2019	No preconception risk factors
216. Wei D et al. 2018	STRATIFIES FERTILITY OUTCOME BY PEAK ESTRADIOL LEVELES
217. Wei D et al. 2018	STRATIFIED FERTILITY OUTCOMES BY BASELINE GLUCOSE LEVELS - exclude
218. West S et al. 2014	Women included were not diagnosed with PCOS
219. Wu XK, et al. 2000	Does not stratify fertility outcomes by any preconception risk factor
220. Xi WY,et al. 2012	Stratified fertility outcomes by olig. vs amen. women
221. Xita N et al. 2007	No relevant outcome/ analysis
222. Yadav et al. 2017	No preconception risk factors
223. Yang H et al. 2020	Stratified fertility outcomes by follicular output rate
224. Yarali H et al. 2002	No preconception risk factors
225. Yilmaz N et al. 2013	Unable to locate/access full text
226. Yurci A et al. 2022	Does not stratify fertility outcomes by any preconception risk factor
227. Zafar et al. 2021	No reason stated
228. Zainul et al. 2006	Unable to locate/access full text
229. Zeinalzadeh et al. 2010	No relevant outcome/ analysis

230. Zhang C et al. 2021	Reports of fertility outcomes by preconception risk do not separate PCOS and non-PCOS
231. Zhang C et al. 2022	Unable to locate/access full text
232. Zhang HY et al. 2013	Unable to locate/access full text

5. STUDY CHARACTERISTICS TABLE FOR INCLUDED STUDIES

First Author/ Year/ Country	Design	Population	Setting	PCOS criteria	Total randomized/ recruited	Total analysed	Patient Age (years)	Baseline characteristics mentioned	Intervention/ Treatment A	Intervention/ Treatment B
Abu-Fakher B, 2013 Syria	Prospective case-control study	Infertile PCOS patients	NR	Rotterdam criteria 2003, the association of at least two of the three criteria	PCOS 43 Control 20	PCOS 33 Control 20	PCOS 29.2 ± 5.2 Control 29.2 ± 6.2	BMI, sAMH, FF AMH,	IVF/ICSI	IVF/ICSI
Akpınar F, 2014 Turkey	Cohort study	PCOS patients that met the following criteria: BMI of 18.5-35 kg m-2; undergoing ovarian stimulation using the mid-luteal long GnRH agonist protocol or the flexible GnRH antagonist protocol; and age ≤35 years. Normal weight (BMI: 18.5-24.9 kg m-2 [group 1]) Overweight (BMI: 25-29.9kg m-2 [group 2]) Obese (BMI: 30-34.9 kg m-2 [group3])	NR	N/A	Normal weight (Group 1): 109 Overweight (Group 2): 84 Obese (Group 3): 79	Normal weight (Group 1): 109 Overweight (Group 2): 84 Obese (Group 3): 79	Normal weight (Group 1): 28.1±4.6 Overweight (Group 2): 29.0±3.9 Obese (Group 3): 29.2±4.2	Hormonal profile (FSH, LH, E2), Antral follicle count etc.	GnRH agonist	GnRH agonist
Al Safi WG, 2021 Iraq	Cohort study	Women with PCOS. Group 1 (Normal ratio): 1/2 LH/FSH ratio Group 2 (High ratio): 2/1 or 3/1 LH/FSH ratio	Fertility center	N/A	Normal ratio: 37 High ratio: 10	Normal ratio: 37 High ratio: 10	Normal ratio: 27.3 ± 3.6 High ratio: 29.9 ± 3.1	BMI, Age, Hormonal profile,	ICSI	ICSI
Al-Azemi M, 2004 Kuwait	Cohort study	Women with PCOS. Normal weight women (BMI 18–24) Overweight women (BMI 25–29) Obese women (BMI 30–34) Grossly obese women (BMI >=35)	Combined infertility clinic at Maternity Hospital	PCOS is defined as the detection of polycystic ovaries by US (enlarged ovaries with more than 10 cysts, 2–8 mm in diameter, scattered either around or through an echodense, thickened central stroma) plus presence of 1+ of clinical symptoms (oligo/amenorrhoea, obesity and hyperandrogenism [acne, hir- sutism]) or biochemical findings (high luteinising hormone [LH], hyperandrogenism)	270	270 Patients according to BMI: <18: 2 18-24: 62 25-29:100 30-34: 72 >=35: 34	<20: 4 (1.5) 20–29: 126 (46.7) 30–39: 125 (46.6) >40: 15 (5.6)	Ethnicity, weight, height, BMI	All patients underwent ovulation induction	
Aleyasian A, 2011 Iran	Cohort study	PCOS patients (based on Rotterdam criteria) who were candidates for assisted reproductive techniques. All patients were aged less than 35 years with normal prolactin and thyroid hormone levels and normal male spermogram.	Hospital	According to the Rotterdam criteria, we accepted the presence of two of the three following characteristics for inclusion in the study: 1) oligomenorrhea/amenorrhea, 2) clinical (hirsutism) or biochemical findings of hyperandrogenism, and 3) polycystic ovaries on transvaginal sonography	60	60 (N=48 non-pregnant and N=12 pregnant)	Mean +-SD = 29.25+-5.16	Age, BMI, infertility duration, serum levels (AMH, FSH, LH, E2, free testosterone, testerone, inhibin B, MIS)	Controlled ovarian hyperstimulation (COH) with gonadotropin/GnRH-agonist long protocol.	N/a
Arabzadeh S, 2010 Iran	Case-control	2 groups: women with and without PCOS Women with PCOS (N=26): infertile, 21 to 37 years of age and with body mass index (BMI) ranging between 17 kg/m2 and 32 kg/m2 Women without PCOS (N=42): infertile (due	IVF/ET clinic	According to the Rotterdam criteria, the diagnosis of PCOS was based on the association of at least two of the following three criteria: 1) ovulatory disturbance, mainly oligomenorrhea or amenorrhea; 2) hyperandrogenism, as	68	68	women with PCOS, 21 to 37 years women without, 24-42 years [no mean age reported]	BMI (kg/m^2): women with PCOS = 27 (17-32) women without = 27 (21-35)	IVF/ET treatment	N/a

		to sperm or tubal abnormalities, endometriosis or unexplained) normo-ovulatory women 24 to 42 years of age, both ovaries were present, menstrual cycle length was between 25 and 35 days, there were no current or past diseases affecting the ovaries or gonadotropin or sex steroid secretion, there were no clinical signs of hyperandrogenism, FSH levels were ≤10 mIU/mL on day 3 of the cycle, BMI ranged between 21 kg/m2 and 35 kg/m2		defined either by hirsutism, seborrhea, and/or testosterone > 0.7 ng/mL and/or androstenedione > 2.2 ng/mL, as measured on day 3 of the cycle; 3) more than 12 follicles in the 2- to 9-mm range in each ovary at US and/or ovarian volume higher than 10 mL.						
Bailey A, 2014	Cohort study	79 women younger than 40 years old who started a fresh, autologous IVF cycle with or without ICSI	IVF practice	2003 Rotterdam	79 women (101 cycles)	79 women (101 cycles)	Average age was similar across groups Lean group BMI 18.7-24.9 kg/m2 (N=51): 32.0 (3.5) Overweight group BMI 25-29.9 kg/m2 (N=19): 32.6 (2.9) Obese group BMI of ≥30 kg/m2 (N=31): 32.4 (3.2)	BMI, age	IVF cycle	N/A
Bakir VL, 2019	Retrospecti ve cohort study	230 women with PCOS	Hospital Gynecology outpatient clinic	Rotterdam Criteria,	230	230	Mean 26.7 years	BMI, total cholesterol, HDL, LDL, insulin resistane, impaired OGTT/DM	Nil intervention/ Treatment - was retrospective analysis of database	N/A
Berker,B	Cohort study	52 women, failed 3 x ovulatory cycles after ovulation induction with gonadotrophins	Not specified	Revised Rotterdam ESHRE/ASRM criteria	52 women	52 women, 94 follicular fluid samples	Homocysteine groups: Low, 29.4 ± 3.1, average 29.1 ± 3.7, high 30.1 ± 3.3	Homocysteine (Hcy) levels in follicular fluid	GnRH agonist / rFSH	N/A
Bousmpoul a A, 2019/ Greece	Case-control study	comprised women enrolled in the in vitro fertilization (IVF) program; specifically, 70 women (35 lean, BMI <25 kg/m2 and 35 overweight, BMI >25 kg/m2) with diagnosed PCOS		hyperandrogenism, menstrual irregularity, and polycystic ovary morphology, according to the Rotterdam consensus criteria	70	70		Age, BMI,		
Cakiroglu,T 2016	Case control study	292 total women, 146 with PCOS and 146 without PCOS (matched for age and BMI)	Assisted reproductive unit of Kocaeli University School of Medicine, Kocaeli, Turkey	ROtterdam (ESHRE/ASRM consensus, 2004)	292	292	Normal weight cases: 29.3 ± 3.5; Normal weight control: 29.5 ± 3.2, Obese cases: 30.4 ± 3.4; Obese controls: 30.7 ± 3.8	WCC, neutrophil count, inflammatory markers	IVF/ ICSI	NA
Catak Z, 2019, Turkey	case-control study	20 infertile women with PCOS and 20 control women diagnosed as poor ovarian responders stimulated with a GnRH	VF center, Firat University Hospital, Turkey	Rotterdam criteria	20 infertile women with PCOS and 20 control	20 infertile women with PCOS and 20 control	cases: 30.96±2.93; control: 35.6±2.88	BMI, Infertility duration; FSD days	NA	NA

Chen R, 2018 China	Cohort study	less than 35 years	Shanghai First Maternity and Infant Hospital	Rotterdam criteria	398	Normal weight= 260 Overweight/ Obese = 138	less than 35 years a	Age, BMI, Hormone kevels	Gonadotrophin	Gonadotrophin
Fedorcsak, 2001 Norway	Cohort study	Women with PCOS recieving ovarian stimulation for IVF or ICSI. Based on CIGMA test, 26 women were insulin resistant (CIGMA score>4) and 30 women had normal insulin sensitivity.	NR	The prescence of polycystic ovaries on vaginal ultrasound scan (at least 10 follicles between 2 and 8mm in diameter) and at lease 2 of the following criteria: Oligo/amenorrhoea, hirtuism or hyperandrogenism.	56	56	Non-insulin resistant (Median 31 yrs (range 25-28)) Insulin resistant (Median 30 yrs (range 23-28))	Hormone concentrations, age, BMI	IVF/ ICSI	IVF/ ICSI
Feng Y, 2022 China	Cohort study	Women aged 22–35 years, and undergoing IVF were recruited for this study. Of these, 32 had been diagnosed with PCOS and 32 were age- and BMI-matched controls	NR	Rotterdam criteria	64	64	22-35	NR	Gonadotropin releasing hormone antagonist protocol	Gonadotropin releasing hormone antagonist protocol
Gupta A, India	Descriptive study	pregnant women with polycystic ovary syndrome was carried out in a tertiary care hospital	hospital	Rotterdam's criteria	135	135	mean age was 26.8 year	BMI, age	NA	NA
Guido M, 2003 Italy	Cohort study	Women with PCOS, aged between 25 and 45 years, who underwent ovulation induction with recombinant FSH for timed intercourse	NR	Clinical finding of amenorrhea or oligomenorrhea and hirsutism, and presence of chronic anovulation; plasma androgen concentrations at the upper limits of or above the normal range (androstenedione 2.0–8.5 nmol/l, testosterone 0.6–2.0 nmol/l); the presence of ovaries that were bilaterally of normal volume or enlarged, with 10 cortical follicles (< 6 mm in diameter) and a hyperechoic stroma (ovarian stromal area/total ovarian area ratio of > 0.34) at the time of ultrasonography15. A normal LH/FSH ratio was not considered an exclusion criterion.	33	33	Younger PCOS patients (< 35 years old): 20 Older PCOS patients (>35 years old): 13	BMI, Hormonal parameters	Ovulation induction	
Hashimoto DM, 2003	comparative study	102 Brazilian women ageing between 18 and 32 years (x = 25.5, ± 3.9 yrs.) and 31 Austrian women also ranging in age between 18 to 32 years (x = 23.8, ± 4.7 yrs.) were enrolled in the present study	The study was carried out between 1999 and 2001 in two Departments of Gynecology in São Paulo Brazil (Hospital das Clinicas, Hospital Pérola Byington,) and	ultrasound plus one additional	133	133	5, ± 3.9 yrs and 8, ± 4.7 yrs	BMI	BMI(Weight)	NA
Hassani F, 2019, Iran	case-control	20 subjects were assigned to control (fertile women with male infertility history) group, 20 subjects with PCOS were insulin resistant	Royan Institute		60	60	age>36 years	BMI & age	rFSH	rFSH

		(IR) and 20 subjects with PCOS were insulin sensitive (IS)								
Ho VNA, 2018	retrospective study	women had to have PCOS diagnosed according to the Rotterdam criteria and be aged 18–42 years, and were undergoing IVM	IVF center in Ho Chi Minh City,	Rotterdam criteria	921	921	18–42 years	BMI & age	NA	NA
Huang Q, 2018	retroprective study	Women with PCOS, 20 to 44 years old, undergoing a long gonadotrophin releasing hormone receptor agonist (GnRH-a) protocol for COH	Hospital	Rotterdam criteria	516	516	22-44 years	ratio of serium estadiol to follicle number	GnRH-agonist protocol	
Hwang Yi, 2016	Retrospective cohort study	307 women with PCOS and 364 with tubal factor infertility	IVF database of Cheil General Hospital and Women's Healthcare Center, Dankook University College of Medicine	diagnosed according to the Rotterdam 2003 criteria	671	671	PCOS patients: 33.5 ± 2.7, Controls: 33.8 ± 2.7	Age	NA	NA
Inal HA, 2016, Turkey	prospective cross-sectional study	a total of 120 primary infertile women	Reproductive endocrinology department, Women's Health Research and Education Hospital		120	120	Non-PCOS - BMI <25 kg/m2: 30.30 ± 3.97/ PCOS - BMI <25 kg/m2: 29.40 ± 3.70/ Non-PCOS - BMI ≥25 kg/m2: 31.57 ± 4.04/ PCOS - BMI ≥25 kg/m2: 29.97 ± 3.66	BMI and age	IVF	IVF
Inal ZO, 2018	prospective sequential cross-sectional study	women with primary infertility	reproductive endocrinology department of Konya Research and Education Hospital.	Rotterdam criteria	160	160	27.63±4.10	BMI	IVF	IVF
Janati S, 2021 Iran	Cross sectional study	Women with PCOS, 20-45 years old	Hospital	NR	90	90 women, 740 oocyte samples	20-45 years	Age, BMI	ART	
Nikolai Jaschke	Retrospective cohort study	59 reproductive age women (21–43 years) who presented for in vitro fertilization (IVF) between 2014 and 2016	Not specified	Rotterdam criteria	Of the 59 women included in our study, 16 were stratifed to the PCOS group according to the Rotterdam criteria. The remaining 43 women were assigned to the control group.	59 women, 16 stratified to PCOS group according to Rotterdam criteria, 43 control group	21 - 43 years	Age, BMI	4 in the PCOS group (25%) with an agonist protocol. In the control group, 17 (40%) were treated with an agonist	12 women (75%) in the PCOS group were treated using an antagonist protocol and 26 in the control group (60%) with an

										antagonist -protocol
Jin Y, 2019	Case control study	Fifty-six infertile women with PCOS and 51 infertile women with tubal blockage (who served as controls) were recruited into this case-control pilot study	Referred to IVF department of nons-specified hospital	Rotterdam's Criteria	107	107	20-45 years of age	DEHP (Di(2-ethylhexyl) phthalate)	NA	NA
Kalra 2013 USA	Case control	Total of 44,286 IVF cycles from 2004–2006 Tubal factor infertility (controls) N=27,870 PCOS (cases) N=16,416	IVF clinic	Not reported	44286	44286	Control: 35.5 +- 4.3 (19.3–50.4) Case: 33.5 +- 4.4 (19.7–50.0) P <.001	Age, race, parity	IVF	Na
Kamardi S, 2021, Indonesia.	Retrospecti ve case–control	Data from 170 patients under the age of 38 years old and who had undergone ICSI were collected	Royal IVF Clinic, Bali Royal Hospital, Indonesia.	Rotterdam	170	170	under the age of 38 years	BMI(weight)	BMI(weight gain)	FSH (rFSH, Gonal F, Serono) based on age and follicle size and Ovulation stimulation
Kolibianaki s, 2003	Cohort study	110 patients were evaluated	Reproductive Medicine of the Dutch-Speaking Brussels Free University were included in the study.	ultrasound	110	110	mean age of patients was 30.6 ± 0.4 years	combinant FSH (rFSH) and gonadotrophin releasing hormone (GnRH) & BMI	Ovarian stimulation and type of ART	
Kudesia, 2018/US	retrospectiv e cohort	women who initiated their first autologous IVF cycle with conventional insemination or intracytoplasmic sperm injection	fertility treatment centers	ultrasound	51,198 cycles included	45,950 women reached oocyte retrieval	Underweight: 34.4+=4.47/ Normal: 35.34+- 4.52/ Overweight: 35.76 +- 4.59/ Obese: 35.63 +- 4.64	Age, BMI, basline hormone levels	IVF	IVF
Lai Q, 2018/ China	retrospectiv e study	77	Reproduction Center, Tongji Hospital, Wuhan, China	Rotterdam criteria	77	77		FSH and LH (IU/L)		
Li Y, 2018/ China	retrospectiv e study	PCOS women who accepted their first fresh IVF/ICSI cycles at the IVF center	IVF center of Sun Yat-sen Memorial Hospital, Sun Yat-sen University	Rotterdam diagnostic criteria	188	188			age, obesity	
Lin J, 2019/ China	retrospectiv e cohort study	Patients diagnosed as having PCOS according to the Rotterdam criteria who were aged ≥20 and < 35 years old who were undergoing their first FET cycles	Department of Assisted Reproduction of the Ninth People's Hospital of Shanghai JiaoTong University School of Medicine	Rotterdam criteria	1680	1680	aged ≥20 and < 35 years	BMI		

Lujan ME/2010/Canada	follow up study	Women had not used hormonal contraception, fertility medications, insulin sensitizers or antiepileptic drugs in the three months prior to enrollment		PCOS was defined by the 2003 international consensusguidelines	16	16	mean age of the women was 28.7±1.1(range, 18 – 35) years			
Luo L, 2016/ China	cohort study	40 pregnant women were included.	First Affiliated Hospital of Sun Yat-sen University	Rotterdam criteria	40	40	BMI			
Shari Mackens/ 2020/ Russia	retrospective cohort study	320	tertiary referral hospital	Rotterdam criteria	320	320	NA	Age, BMI, previously failed OS cycles (%), CLBR(%)	IVM	NA
Tahereh Madani, M.D./2010-2011/ Iran	prospective study	96	Department of Endocrinology and Female Infertility, Reproductive Biomedicine Research Center, Royan Institute for Reproductive Biomedicine, ACECR, Tehran, Iran	referred to Royan Research Center with history of infertility, irregular menstruation or hirsutism between 2005 to 2006.	96	First cycle there were 96, second cycle only 69 were willing to participate	between 18-37	Age, BMI	Flutamide tab 250 mg, started on day 3 till end of menstrual cycles Clomiphene Citrate 50mg was given to both groups, started on day 3 to day 7 of their menstrual cycles for two consecutive cycles.	Group B received placebo. Clomiphene Citrate 50 mg given to both groups, started on day 3 to day 7 of menstrual cycles for two consecutive cycles.
Nalini Mahajan/2019/India	prospective study	410	fertility center, Department of Reproductive Medicine, Mother and Child	Rotterdam criteria (2004) + ppl of indian origin	367	367	The mean age of patients in the PCOS, PCOM, and control group was 33.66 ± 3.56, 24.07 ± 1.91, and 30.74 ± 3.72 years, respectively	Age, BMI	306 went through controlled ovarian stimulation (OS) for ICSI	NR
Ahmad Mahran / 2013 / Egypt	prospective cohort observational study.	60	The study was conducted at the Fertility Unit, Derby, United Kingdom.	Age between 18 and 39 years, body mass index (BMI) of 35 kg/m2 or less, anovulatory infertility, and a diagnosis of PCOS based on Rotterdam	60	60	between 18 and 39 years	Age, BMI	Patients received CC as per standard protocol	NR
McCormick, 2008/ UK	longitudinal, anonymized research database	Women age 15– 44 years with a diagnosis of PCOS defined by the Read code classification	Clinical Practice Research Database (CPRD),	Read code classification & 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10)	9068	9068	15– 44			

Mostinckx / 2019 / Belgium	retrospective observational study	1036	NR	Rotterdam criteria	1036	393	between 18 and 36 years	Age, BMI	20 weeks after IVM	COS
Muharam / 2022 / Indonesia	retrospective cohort study	238	fertility clinic	Rotterdam criteria	238	238	aged 24–41 years	Age, BMI	NR	NR
Müberra Namlı Kalem / 2016 / Turkey	cohort study	653	private IVF clinic	Rotterdam criteria	653	653	562 patients were under the age of 35 years and 91 patients were above the age of 35 years.	Age, BMI	NR	NR
Niu, 2017, China	case-control	90	Hospital	Rotterdam criteria	90	90	Control (N=30): 29.4 +-3.7 PCOS non-metabolic syndrome (MS): 30.2+-3.9 PCOS MS: 30.6+-3.5	Metabolic syndrome	IVF or ICSI	
Oberg / 2019 / Sweden	RCT	Overweight/obese women with PCOS	Hospital	Rotterdam	68	57 at 4-months and 47 at 12-months	Intervention (n=34): 31 +-5.1 Control / minimal intervention (n=34): 29.9 +-5.7	BMI	Behavioural modification intervention	Minimal interventio n
Palomba, 2012/ Italy	Retrospective cohort	PCOS diagnosed according to well-recognised diagnostic criteria	Academic Department of Obstetrics and Gynaecology of the University Magna Graecia of Catanzaro, Italy.		378	378	Metformin: 33 (8; 21–43)/ Control: 35 (9; 22–42)	BMI, Age, Hormonal profile	IVF	IVF
Provost / 2015 / USA	Retrospective cohort study	239127	NR	NR	239127	239127	NR	Age, BMI	NR	NR
Shalom-Paz, 2011/ CanadA	Retrospective, cohort study	One hundred thirteen women with polycystic ovaries	Tertiary IVF unit.	Rotterdam criteria	116	116		BMI		
Sheng Y, 2017/ Canada	prospective, observational study	Women with PCOS. BMI categories: underweight, <18.5 kg/m2; normal, 19–23.9 kg/m2; overweight, 24–27.9 kg/m2; and obese, ≥28 kg/m2	Hospital	NR	801	774	27.9 ± 3.1	BMI, Age	rFSH	
Wang, 2013/ China	retrospective cohort analysis	women who achieved clinical pregnancies after IVF-ET in the Clinical Center for Reproductive Medicine,	Clinical Center for Reproductive Medicine, First Affiliated Hospital of Nanjing Medical University	Rotterdam criteria	5339 women who had clinical pregnancies after in vitro fertilization treatment (PCOS, 205 women; non-PCOS	PCOS (n =114) and without PCOS (n =3189)		30.2 +/-3.9 with PCOS; Without PCOS: 30.5 +/-4.1	NR	NR

Wang, 2001	Prospective cohort study	1018 infertile women, 373 with PCOS & 645 without PCOS	Reproductive medicine unit, department of O&G, university of Adelaid	Increased concentration of serum testosterone (>2.5nmol/l) or elevated androstenedione, together with a low concentration of sex hormone binding globulin (SHBG), in addition to characteristic ovarian morphology on ultrasoun (presence of 8+ peripheral cysts <10mm in demater w increased stroma in one or both ovaries).	1018	1018	PCOS group: 31.4 +/- 3.8; NOn-PCOS: 32.7 +/- 4.3	BMI	Cohort was treated in this department from 1987-1999, using treatment modalities including IVF, ICSI (intracytoplasmic sperm injection), gamete intraFallopian tuibe transfer - treatment protocols not descirbed in this paper	
Yang W, 2018/ China	retrospectiv e study	Patients with PCOS between 20 and 35 years of age who were undergoing their first IVF cycle were included.	Department of Obstetrics and Gynecology, Peking University	Rotterdam 2003 criteria	583	583	20 and 35 years	Age, BMI, basline hormone levels		
Zhang CM, 2014/ China	a prospective study	63 PCOS patients and 48 controls	Division of Reproductive Center, Peking University Third Hospital.	2003 Rotterdam criteria	63 PCOS patients and 48 controls	63 PCOS patients and 48 controls		BMI, Age, Hormonal profile	IVF	IVF
Zhao 2017 China	prospective , single-arm and single-center trial	200 infertile outpatients with PCOS and CC-resistance and who need ovulation induction and intercourse guidance	hospital	Rotterdam (2004)	200	200 patients (395 cycles)	30.01 ± 4.11	BMI, age	IVF	N/a
Zhou H, 2020/ China	Retrospecti vely	PCOS women who received IVF/ICSI-ET for the first time	Department of Reproductive Medicine, Second Clinical Hospital, Hebei Medical University	2003 Rotterdam consensus criteria	1782 women were included in the analysis: 42 were underweight, 742 were overweight, 198 were obese, and 800 were normal weight.	1782 women were included in the analysis: 42 were underweight, 742 were overweight, 198 were obese, and 800 were normal weight.	≤35 years	Age, duration of infertiltiy, basline hormone levels	IVF/ ICSI	IVF/ ICSI

6. FINDINGS

Comparisons included:

- **Comparison 1:** Lean versus Overweight/ obese PCOS
- **Subgroups:** Sub-grouped by fertility treatment for most outcomes (where possible)
- **Comparison 2:** Younger versus older PCOS

COMPARISON 1: Lean vs Overweight/obese PCOS

▪ EVIDENCE SUMMARY:

A total of 20 studies reported on preconception BMI and/or obesity status as a risk factor or determinant of fertility outcomes in PCOS. Studies ranged from observational to randomised trial designs and included various fertility treatments including ovulation induction medications such as metformin or clomiphene citrate, gonadotrophins including GnRH or rFSH, as well as IVF. Most studies had moderate or low risk of bias and included large sample sizes with varied BMI cut-offs. For the purpose of this analysis, individuals with a BMI of 18.5 – 24.9 kg/m^2 and those classified with as lean or normal weight (as defined by individual studies) were classified as the lean/ normal weight group, whereas individuals with a BMI >25 kg/m^2 were classified as the overweight/ obese group (with no upper limit).

▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

Women with PCOS in the lean/ normal weight category for BMI (18.5 - 24.9 kg/m^2) had a higher pregnancy rate than those in the overweight/ obese category (≥25 kg/m^2), although this did not reach statistical significance when examining studies explicitly stating a clinical pregnancy rate as the outcome. These groups also had a higher live birth rate and ovulation rate per patient and per cycle and lower miscarriage rate per patient compared to the overweight/ obese BMI category group. Certainty in the evidence was very low to low for most outcomes, largely due to the observational nature of the studies, as well as being downgraded for risk of bias (many studies had moderate or high risk) and inconsistency (high and/or significant heterogeneity).

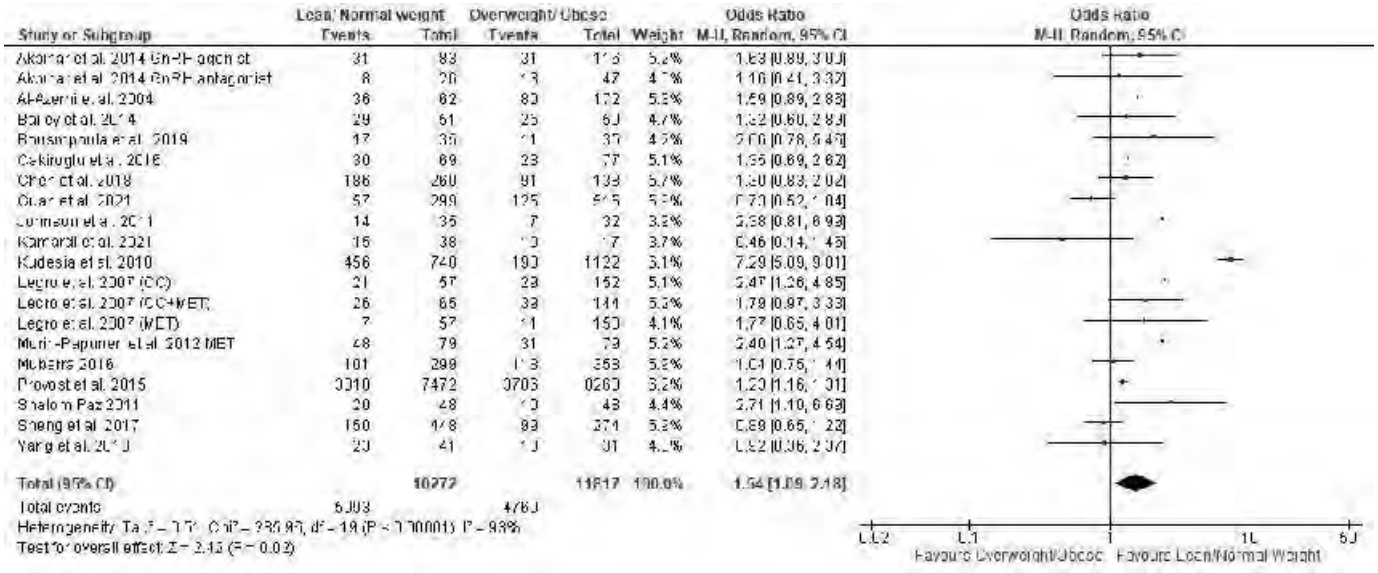
Outcome	Studies	N	Effect size [95% CI]	P	Favours	I²	Certainty
Pregnancy Rate per patient	20	22089	1.54 [1.09, 2.18]	0.02	Lean/ normal weight (higher in lean normal weight)	93% (p<0.05)	⊕◯◯◯ VERY LOW
Clinical pregnancy rate per patient	14	5621	1.58 [0.91, 2.74]	0.1	No difference	94% (p<0.05)	⊕◯◯◯ VERY LOW
Biochemical pregnancy rate (or not reported) per patient	6	16468	1.35 [1.11, 1.62]	0.002	Lean/ normal weight (higher in lean normal weight)	16% (NS)	⊕⊕◯◯ LOW
Live birth rate per patient	16	20878	1.39 [1.17, 1.65]	0.0002	Lean/ normal weight (higher in lean normal weight)	56% (p=0.004)	⊕◯◯◯ VERY LOW
Ovulation rate- all	4	3190	2.06 [1.62, 2.62]	<0.00001	Lean/ normal weight (higher in lean normal weight)	42% (NS)	NA
Ovulation rate- per patient	1	268	5.14 [1.97, 13.43]	0.0008	Lean/ normal weight (higher in lean normal weight)	NA	⊕◯◯◯ VERY LOW
Ovulation rate- per cycle	1 (3 groups)	2922	1.95 [1.64, 2.32]	<0.00001	Lean/ normal weight (higher in lean normal weight)	0% (NS)	⊕⊕⊕◯ MODERATE
OHSS	7	2255	1.44 [0.73, 2.84]	0.3	No difference	50% (p=0.06)	⊕◯◯◯ VERY LOW
Miscarriage rate	11	18978	0.64 [0.59, 0.71]	<0.00001	Lean/ normal weight (lower in lean normal weight)	0% (NS)	⊕⊕◯◯ LOW

OUTCOME 1. Pregnancy Rate per patient

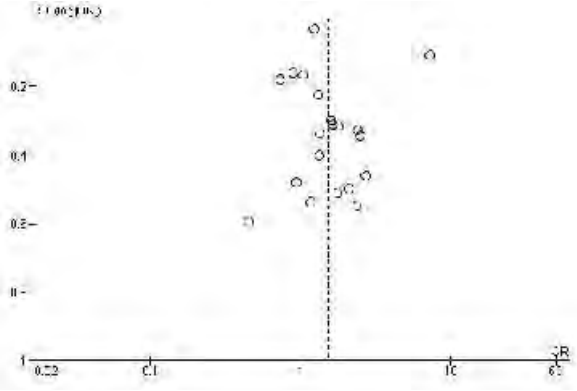
1.1. Individual Study Data Tables

OUTCOME: Pregnancy Rate		Outcome type: Dichotomous			
Comparison: Lean/normal weight versus overweight/obese					
Author, year	Fertility treatment	N events in lean PCOS	N total in lean PCOS	N events in overweight/ obese PCOS	N total in overweight/ obese PCOS
Akpinar, 2014 (MRB)	GnRH agonist	31	83	31	116
Akpinar, 2014 (MRB)	GnRH antagonist	8	26	13	47
Al-Azemi, 2004 (MRB)	OI	36	62	80	172
Bailey, 2014 (LRB)	IVF +/- ICSI	29	51	25	50
Bousmpoula A, 2019 (MRB)	IVF	17	35	11	35
Cakiroglu 2016 (MRB)	IVF	30	69	28	77
Chen, 2018 (MRB)	Gonadotrophins	186	260	91	138
Guan 2011 (HRB)	OI + IUI	57	299	125	515
Johnson 2010 (MRB)	MET	14	35	7	32
Kamardi S, 2021 (HRB)	rFSH	15	38	10	17
Kudesia R (MRB)	IVF	456	748	198	1122
Legro 2007 (LRB)	MET	7	57	11	150
Legro 2007 (LRB)	CC	21	57	29	152
Legro 2007 (LRB)	MET + CC	26	65	39	144
Morin- Papunen 2012 (LRB)	MET	48	79	31	79
Muberra 2016 (LRB)	Gonadotrophins	101	299	118	358
Provost, 2015 (LRB)	IVF	3818	7472	3786	8260
Shalom-paz 2011 (MRB)	IVM	20	48	10	48
Sheng, 2017 (MRB)	IVF	150	448	99	274
Yang, 2018 (LRB)	IVF	23	41	18	31

1.2. Forest plot for lean/ normal weight versus overweight/obese PCOS for pregnancy rate per patient

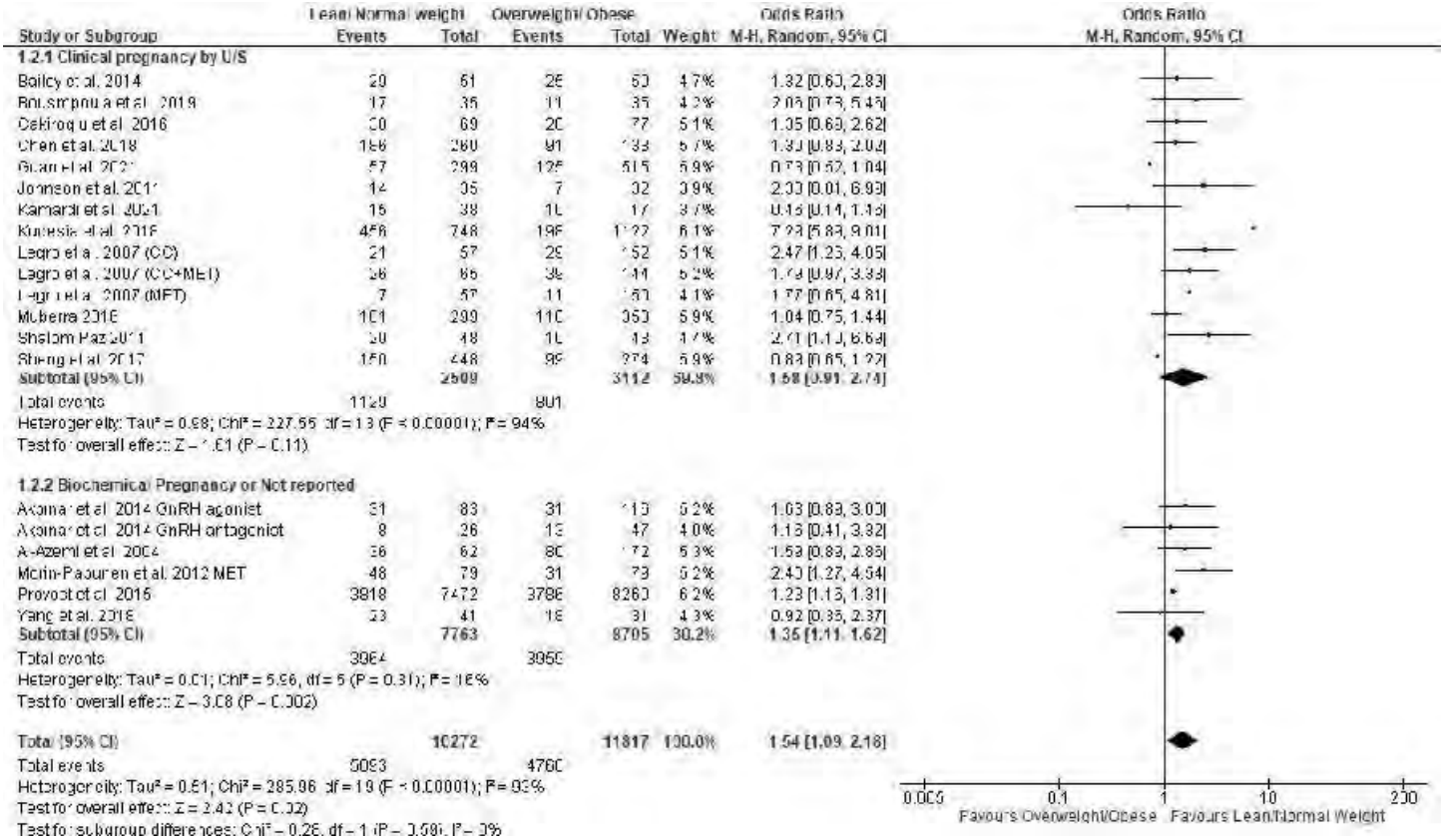


1.3. **Funnel plot for assessment of publication bias**

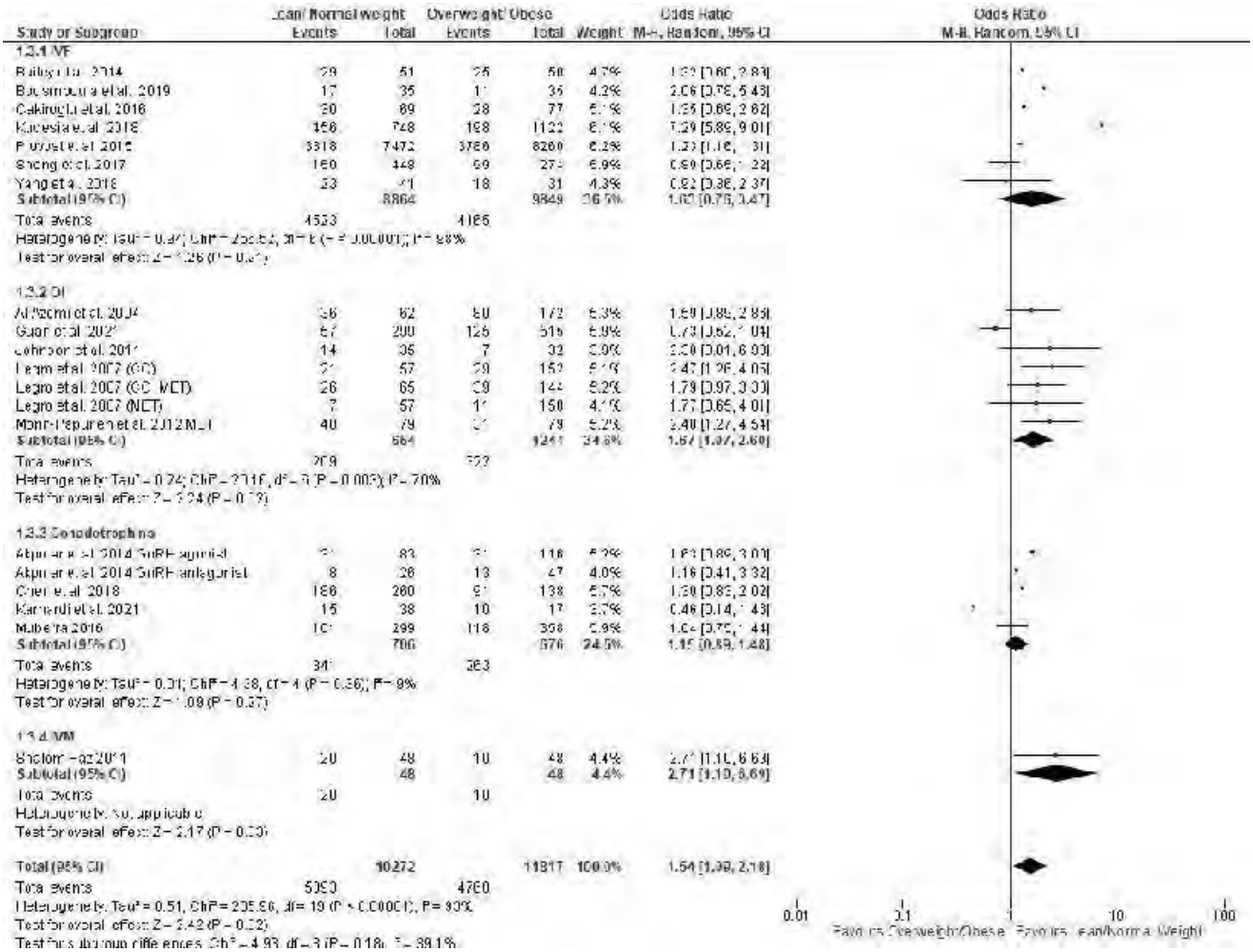


1.4. **Subgroup analyses:**

1.4.1. Pregnancy rate sub-grouped by clinical versus biochemical pregnancy (or not reported)



1.4.2. Pregnancy rate per patient sub-grouped by fertility treatment

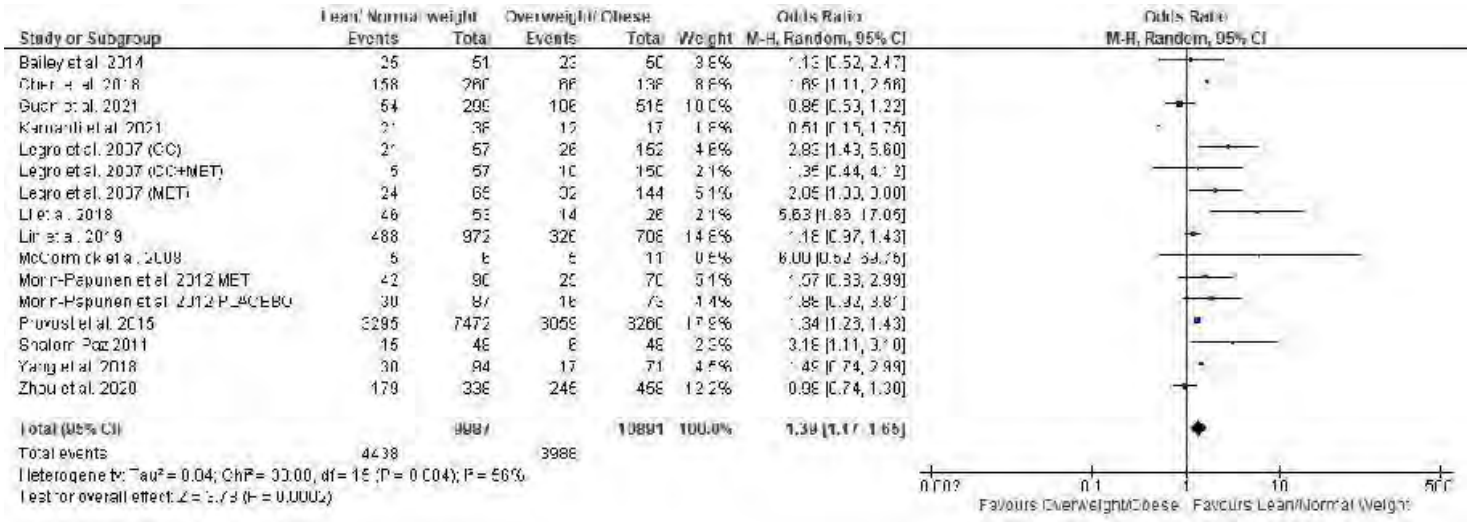


OUTCOME 2. Live Birth Rate

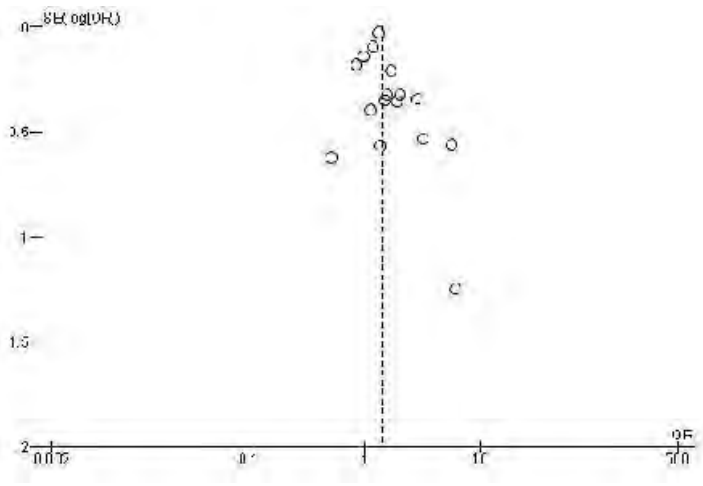
2.1. Individual Study Data Table

OUTCOME: Live birth rate		Outcome type: Dichotomous			
Comparison: Lean/normal weight versus overweight/obese					
Author, year	Fertility treatment	N events in lean PCOS	N total in lean PCOS	N events in overweight/ obese PCOS	N total in overweight/ obese PCOS
Bailey 2014 (LRB)	IVF	25	51	23	50
Chen R, 2018 (MRB)	Gonadotrophin	158	260	66	138
Guan, 2021 (HRB)	OI + IUI	54	299	106	515
Kamardi S, 2021 (HRB)	rFSH	21	38	12	17
Legro, 2007 (LRB)	CC	21	57	26	152
Legro, 2007 (LRB)	MET	5	57	10	150
Legro, 2007 (LRB)	CC +MET	24	65	32	144
Li Y, 2018 (MRB)	IVF	46	53	14	26
Lin J, 2019 (LRB)	IVF	488	972	326	708
McCormick B, 2008 (MRB)	IVF	5	6	5	11
Morin-papunen (LRB)	MET	42	90	25	70
Morin-Papunen placebo (LRB)	Placebo	30	87	16	73
Provost 2015 (LRB)	IVF	3295	7472	3059	8260
Shalom Paz, 2011 (MRB)	IVM	15	48	6	48
Yang W, 2018 (LRB)	IVF	30	94	17	71
Zhou H, 2020 (MRB)	IVF/ ICSI-ET	179	338	245	458

2.2. Forest plot for lean/ normal weight versus overweight/obese PCOS for live birth rate

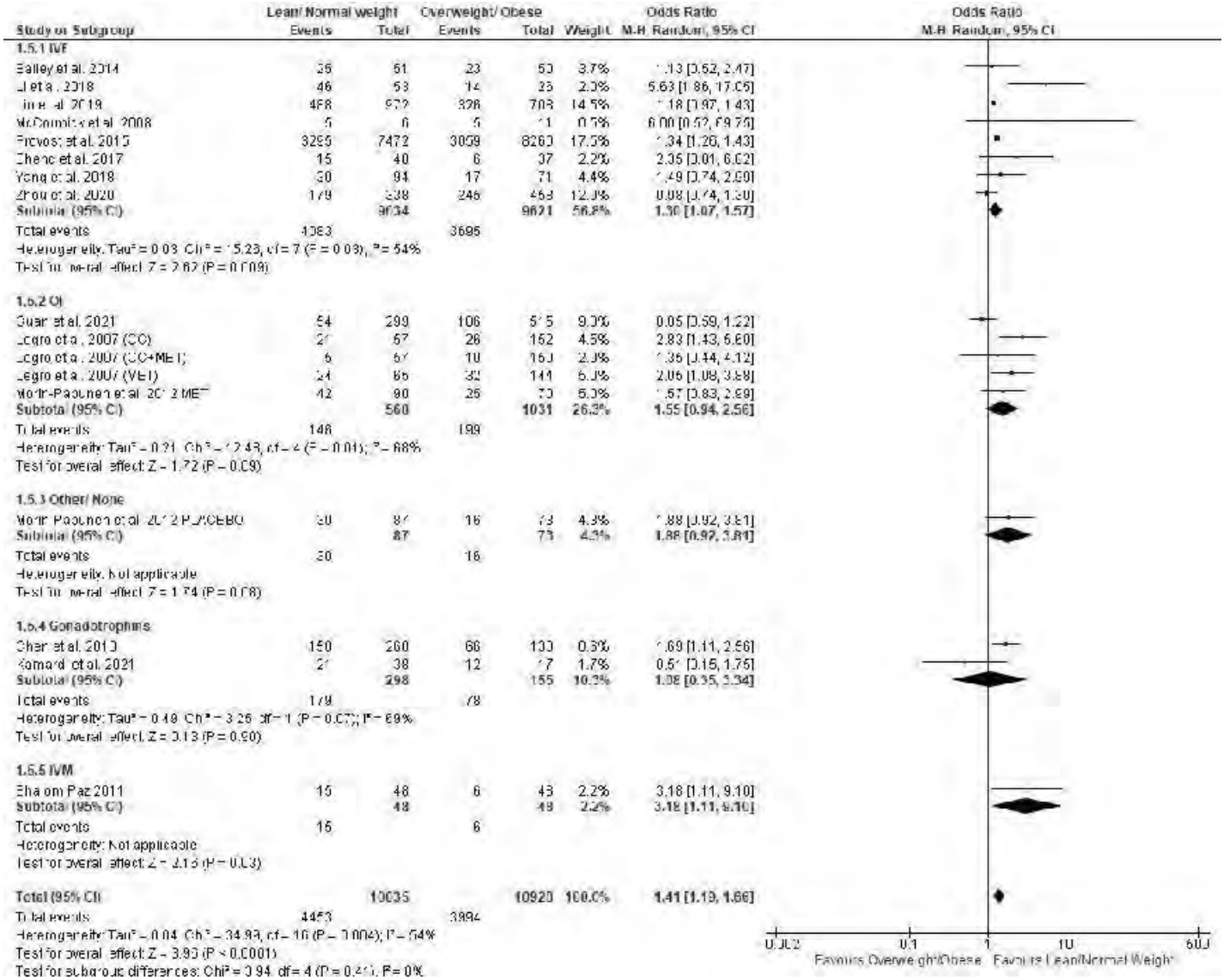


2.3. Funnel plot for assessment of publication bias



2.4. Subgroup Analysis:

2.4.1. Live birth rate sub-grouped by fertility treatment

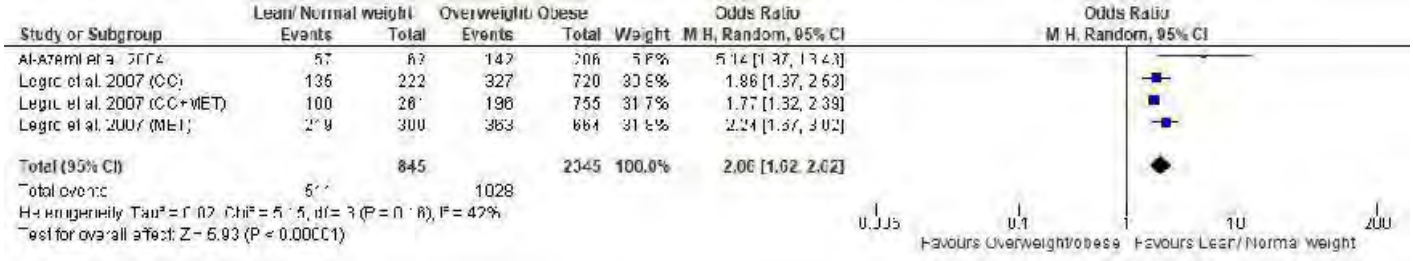


OUTCOME 3. Ovulation Rate

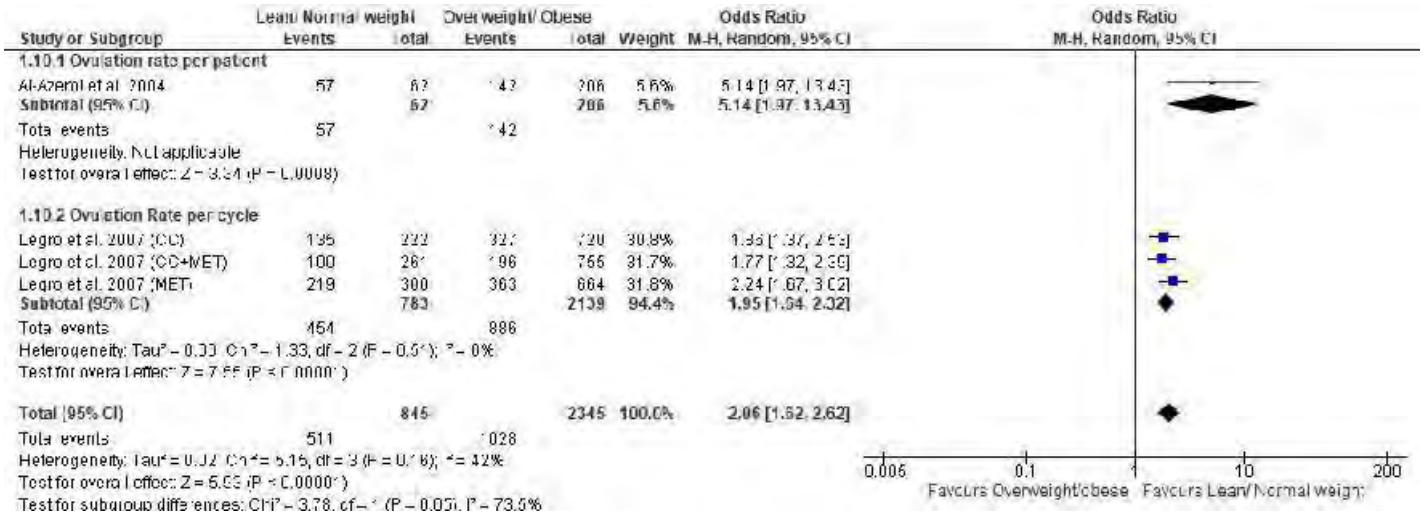
3.1. Individual Study Data Table

OUTCOME: Ovulation Rate		Outcome type: Dichotomous			
Comparison: Lean/normal weight versus overweight/obese					
Author, year	Fertility treatment	N events in lean PCOS	N total in lean PCOS	N events in overweight/ obese PCOS	N total in overweight/ obese PCOS
Al Azemi (MRB)	OI	57	62	142	206
Legro 2007 (LRB)	CC	135	222	327	720
Legro 2007 (LRB)	MET	100	261	196	755
Legro 2007 (LRB)	MET + CC	219	300	363	664

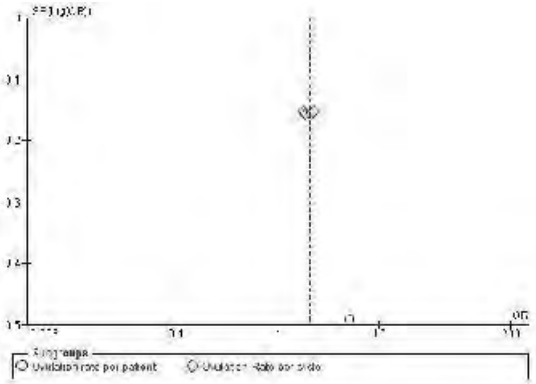
3.2. Forest plot for lean/ normal weight versus overweight/obese PCOS for ovulation rate – all



3.3. Forest plot for lean/ normal weight versus overweight/obese PCOS for ovulation rate per patient and per cycle subgroups



3.4. Funnel plot for assessment of publication bias

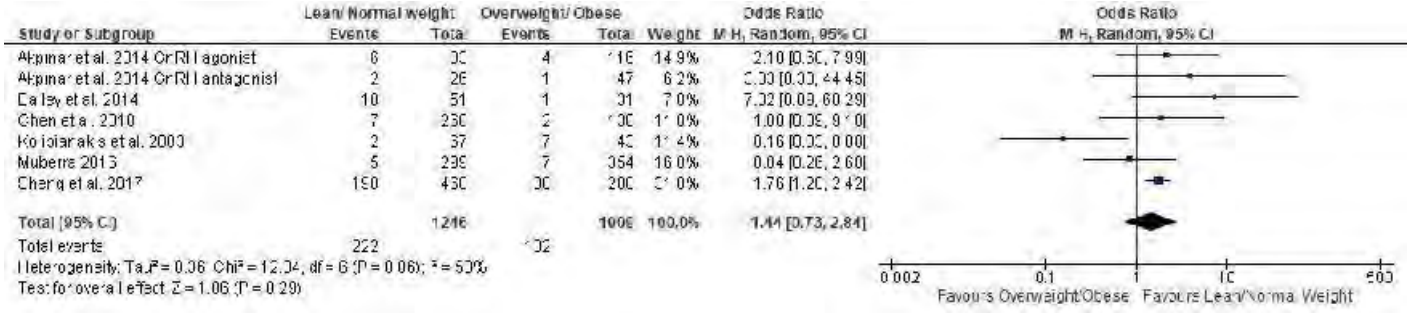


All studies used ovulation induction medication and therefore, there is no subgroup by fertility treatment for this outcome

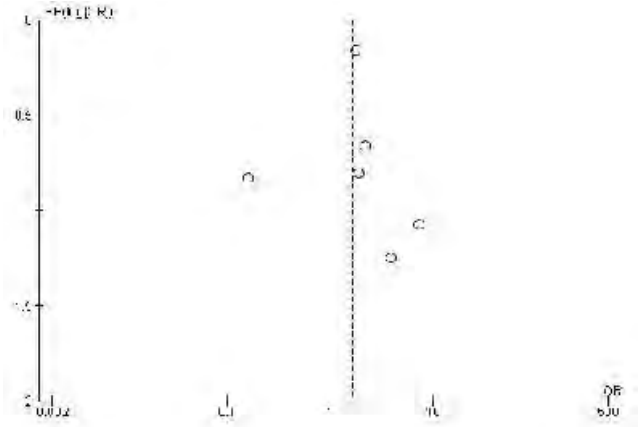
OUTCOME 4. OHSS
Individual Study Data Table

OUTCOME: OHSS		**Outcome type: Dichotomous**			
Comparison: Lean/normal weight versus overweight/obese					
Author, year	**Fertility treatment**	**N events in lean PCOS**	**N total in lean PCOS**	**N events in overweight/ obese PCOS**	**N total in overweight/ obese PCOS**
Akpinar 2014 (MRB)	GnRH Agonist	6	83	4	116
Akpinar 2014 (MRB)	GnRH antagonist	2	26	1	47
Bailey, 2018 (LRB)	IVF	10	51	1	31
Chen, 2018 (MRB)	Gonadotrophins	7	260	2	138
Kolbianakis 2003 (MRB)	GnRH + FSH	2	67	7	43
Muberra 2016 (LRB)	Gonadotrophins	5	299	7	354
Sheng 2017 (MRB)	IVF	190	460	80	280

3.1. Forest plot for lean/ normal weight versus overweight/obese PCOS for OHSS

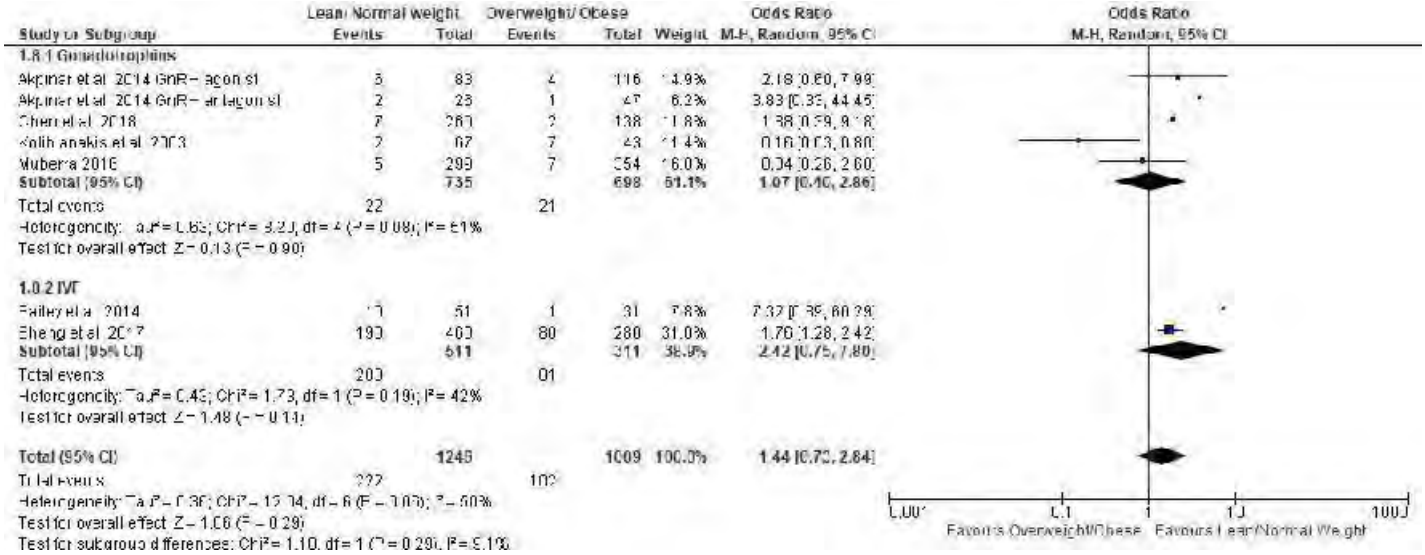


3.2. Funnel plot for assessment of publication bias



4.4. Subgroup Analysis:

4.4.1. Forest plot for lean/ normal weight vs overweight/obese PCOS in OHSS, sub-grouped by fertility treatment

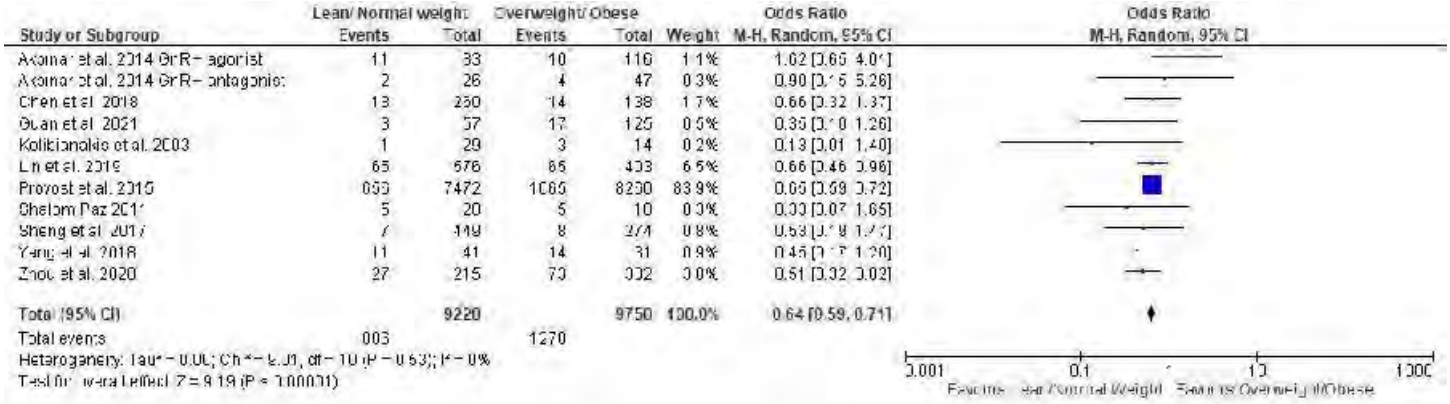


OUTCOME 5. Miscarriage rate per patient

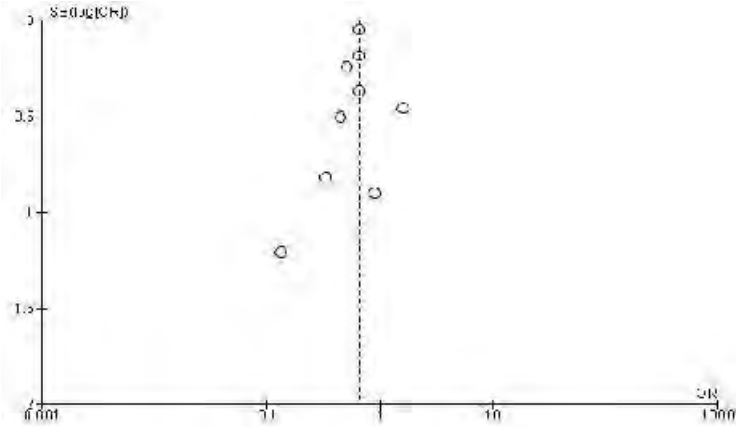
5.1. Individual Study Data Table

OUTCOME: Miscarriage rate per patient		Outcome type: Dichotomous			
Comparison: Lean/normal weight versus overweight/obese					
Author, year	**Fertility treatment**	**N events in lean PCOS**	**N total in lean PCOS**	**N events in overweight/ obese PCOS**	**N total in overweight/ obese PCOS**
Akpınar, 2014 (MRB)	GnRH Agonist	11	83	10	116
Akpınar, 2014 (MRB)	GnRH antagonist	2	26	4	47
Chen, 2018 (MRB)	Gonadotrophin	18	260	14	138
Guan, 2021 (HRB)	OI + IUI	3	57	17	125
Kolibianakis E, 2003	GnRH + FSH	1	29	3	14
Lin 2019 (LRB)	IVF	65	576	65	403
Provost 2015 (LRB)	IVF	656	7472	1065	8260
Shalom Paz 2011 (MRB)	IVM	5	20	5	10
Sheng 2017 (MRB)	IVF	7	449	8	274
Yang 2018 (LRB)	IVF	11	41	14	31
Zhou 2020 (MRB)	IVF/ ICSI-ET	27	215	73	332

5.2. Forest plot for lean/ normal weight versus overweight/obese PCOS for miscarriage rate per patient

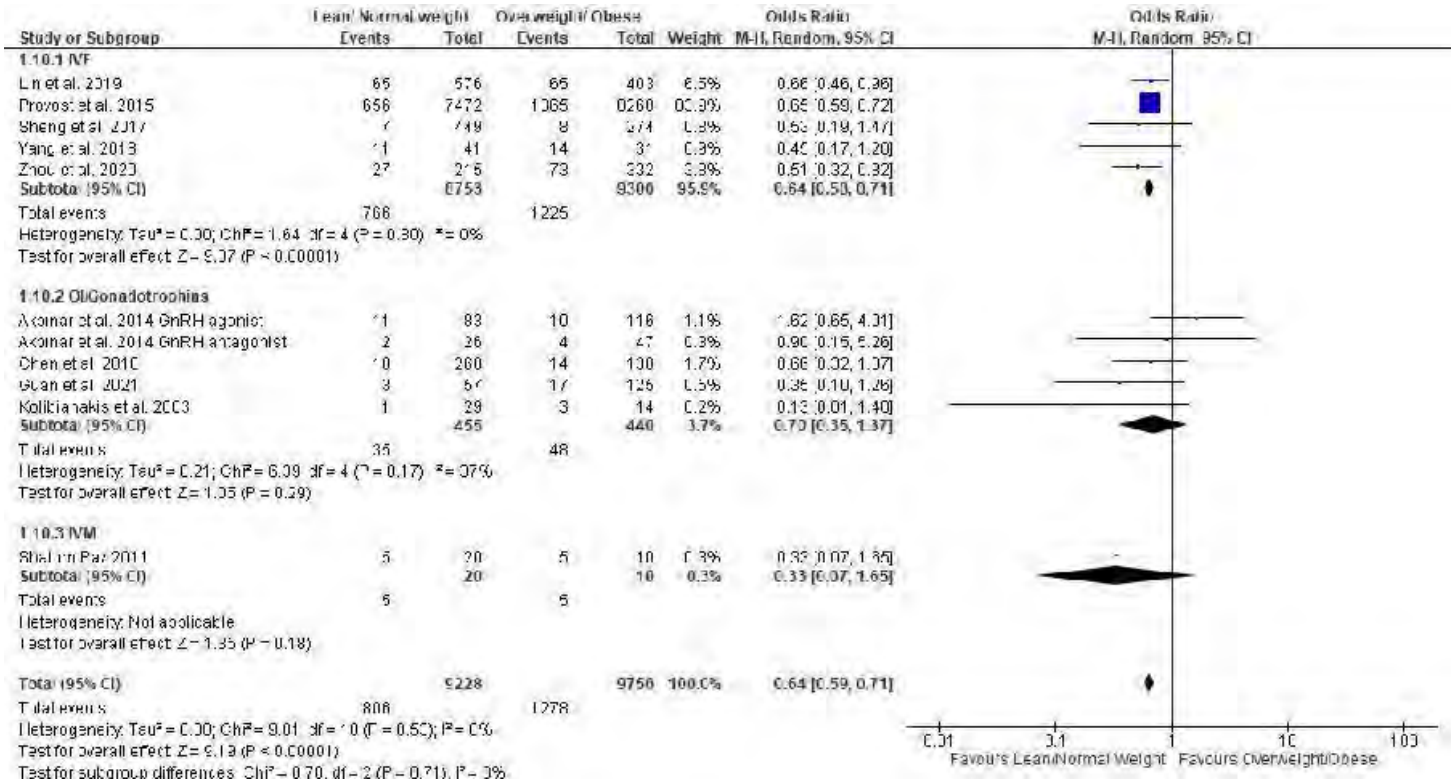


5.3. Funnel plot for assessment of publication bias



5.4. Subgroup analysis:

5.4.1. Forest plot for lean/ normal weight vs overweight/obese PCOS in miscarriage rate per patient, sub-grouped by fertility treatment



COMPARISON 2: Older versus Younger PCOS Age Groups

▪ EVIDENCE SUMMARY:

Few studies (n=6 identified) examined age in relation to fertility outcomes in PCOS. However, variations in analysis methods, age groupings and data reported meant it was not possible to pool these studies in meta-analysis for most outcomes. Three studies were in IVF treatment and two studies (the ones pooled in meta-analysis) were using gonadotrophin protocols. All five studies identified were of moderate to low risk of bias and were of observational design.

▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

Data could only be pooled for two studies for the outcomes of clinical pregnancy rate and OHSS. Both these outcomes were not significantly different between women aged <35 years compared to women aged 35 years and over. Studies not pooled in the analysis also found no differences by age in most outcomes, however, Kalra et al. (2013) reported a decline in pregnancy rate in women with PCOS undergoing IVF aged between 40 and 45, reducing from 24.4% at age 40 to 13.3% at age 44. Live birth rates also decreased from 17.8% at age 40 to 6.7% at age 44. In contrast, miscarriage rates increased from 24.3% at age 40 to 50% at age 44 in the same cohort. Certainty of the evidence was low to very low due mainly to risk of bias (mostly moderate risk) and imprecision (small number of studies and/or small sample sizes).

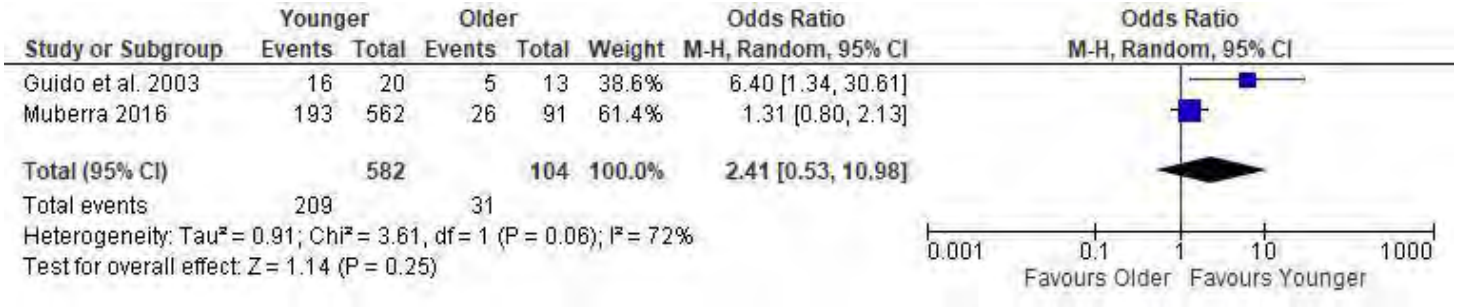
Outcome	Studies	N	Effect size [95% CI]	P	Favours	I^2	Certainty
Clinical pregnancy rate per patient	2	686	2.41 [0.53, 10.98]	0.3	No difference	72% (p=0.06)	⊕◯◯◯ VERY LOW
OHSS per patient	2	686	0.96 [0.24, 3.84]	0.9	No difference	0% (NS)	⊕⊕◯◯ LOW
Ovulation rate per cycle	1	80	1.71 [0.36, 8.18]	0.5	No difference	NA	⊕◯◯◯ VERY LOW
Multiple pregnancy rate per patient	1	653	0.95 [0.52, 1.76]	0.9	No difference	NA	⊕⊕◯◯ LOW
Miscarriage rate per patient	2	1093	Not estimable	NA	No difference	NA	⊕◯◯◯ VERY LOW

OUTCOME 1. Clinical pregnancy per patient

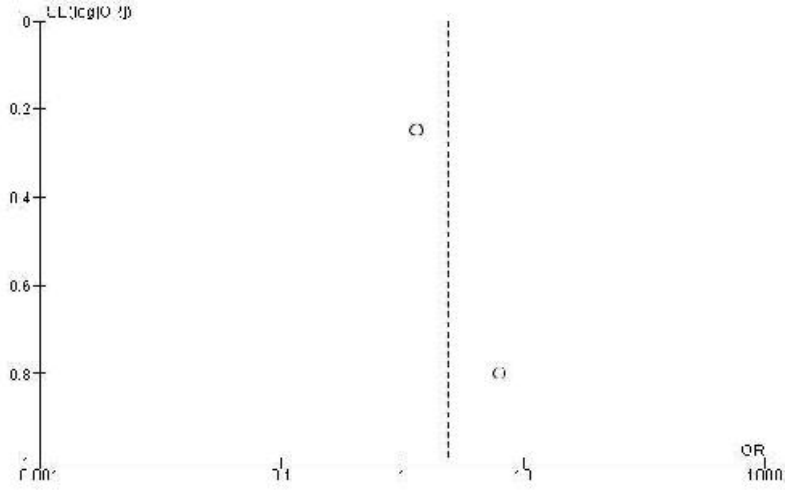
1.1. Individual Study Data Table

OUTCOME: Clinical pregnancy rate per patient		Outcome type: Dichotomous			
Comparison: Younger versus older PCOS age groups					
Author, year	**Fertility treatment**	**N events in younger PCOS**	**N total in younger PCOS**	**N events in older PCOS**	**N total in older PCOS**
Guido 2003 (MRB)	Gonadotrophin	16	20	5	13
Muberra 2016 (LRB)	Gonadotrophin	193	562	26	91
Kalra 2013 (MRB)	IVF	NR	NR	Age 40 (n=375): 24.4% Age 41 (n=295): 21.2% Age 42 (n=205): 22.7% Age 43 (n=115): 10.1% Age 44 (n=47): 13.3% Age 45 (n=20): 0% Age >=46 (n=7): 0%	1064
Cakiroglu 2016 (MRB)	IVF	OR= 1 (95% CI 0.8-1.1)	146	OR= 0.09 (95% CI 0.8-0.9)	146
Inal 2019 (MRB)	IVF	Mean age 27.41±3.54 in clinical pregnancy group	96	Mean age 28.85±4.85 in no clinical pregnancy group	64

1.2. Forest plot for younger versus older PCOS age groups for clinical pregnancy rate per patient



1.3. Funnel plot for assessment of publication bias

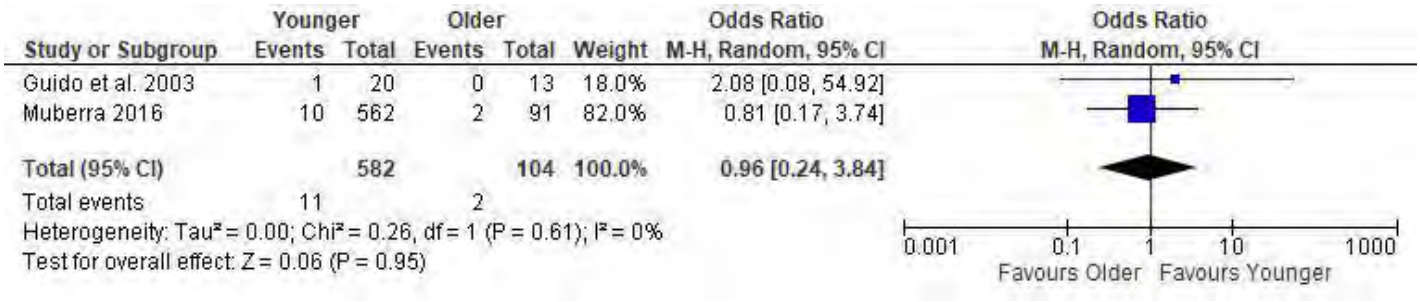


OUTCOME 2. OHSS per patient

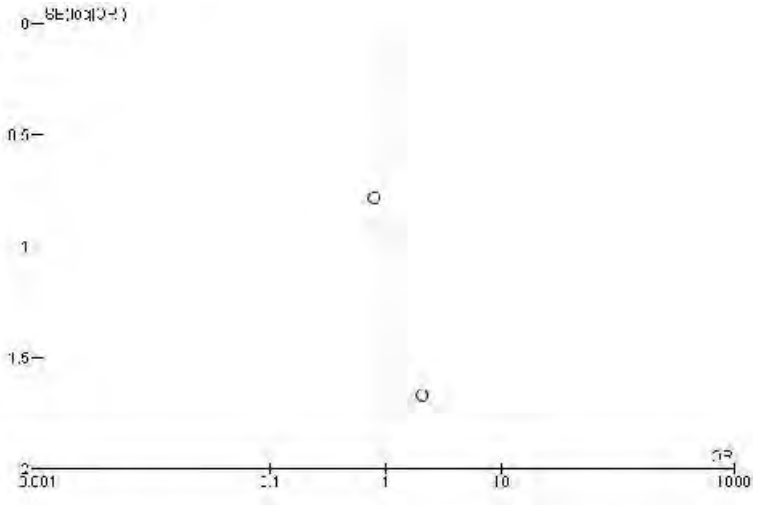
2.1. Individual Study Data Table

OUTCOME: OHSS per patient		Outcome type: Dichotomous			
Comparison: Younger versus older PCOS age groups					
Author, year	Fertility treatment	N events in younger PCOS	N total in younger PCOS	N events in older PCOS	N total in older PCOS
Guido 2003 (MRB)	Gonadotrophin	1	20	0	13
Muberra 2016 (LRB)	Gonadotrophin	10	562	2	91

2.2. Forest plot for younger versus older PCOS age groups for OHSS per patient



2.3. Funnel plot for assessment of publication bias



OUTCOME 3. Ovulation rate per cycle
3.1. Individual Study Data Table

OUTCOME: Ovulation rate per cycle		**Outcome type: Dichotomous**			
Comparison: Younger versus older PCOS age groups					
Author, year	**Fertility treatment**	**N events in younger PCOS**	**N total in younger PCOS**	**N events in older PCOS**	**N total in older PCOS**
Guido 2003 (MRB)	Gonadotrophin	41	44	32	36

OUTCOME 4. Multiple pregnancy rate per patient
4.1. Individual Study Data Table

OUTCOME: Multiple pregnancy rate per patient		**Outcome type: Dichotomous**			
Comparison: Younger versus older PCOS age groups					
Author, year	**Fertility treatment**	**N events in younger PCOS**	**N total in younger PCOS**	**N events in older PCOS**	**N total in older PCOS**
Muberra 2016 (LRB)	Gonadotrophin	83	562	14	91

OUTCOME 5. Miscarriage rate per patient
5.1. Individual Study Data Table

OUTCOME: Clinical pregnancy rate per patient		**Outcome type: Dichotomous**			
Comparison: Younger versus older PCOS age groups					
Author, year	**Fertility treatment**	**N events in younger PCOS**	**N total in younger PCOS**	**N events in older PCOS**	**N total in older PCOS**
Kalra 2013 (MRB)	IVF	NR	NR	Age 40 (n=375): 24.3% Age 41 (n=295): 34.2% Age 42 (n=205): 41.3% Age 43 (n=115): 60% Age 44 (n=47): 50% Age 45 (n=20): 0% Age >=46 (n=7): 0%	1064
Luo 2017 (MRB)	IVF	Mean age 30.2 ± 5.2 years in miscarriage group	9	Mean age 31.0 ± 4.4 years in no miscarriage group	20

7. GRADE ASSESSMENTS AND EVIDENCE PROFILE

COMPARISON 1: Lean/ normal weight versus overweight/ obese PCOS												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Lean	O/O	Effect Estimate: MD (95% CI)	Favours	Certainty	Importance
Outcome: Pregnancy rate per patient												
20	Obs + RCTs	serious[1]	serious[2]	no serious indirectness	no serious imprecision	Obs study downgrade[3]	5093/ 10272	4760/ 11817	1.59 [1.07, 2.35]	Lean/ normal weight (higher in lean/ normal weight)	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Clinical pregnancy rate per patient												
14	Obs + RCTs	serious[1]	serious[2]	no serious indirectness	no serious imprecision	Obs study downgrade[3]	1129/ 2509	801/ 3112	1.66 [0.87, 3.15]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Biochemical (or unreported) pregnancy rate per patient												
6	Obs + RCTs	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	Obs study downgrade[3]	3964/ 7763	3959/ 8705	1.35 [1.11, 1.62]	Lean/ normal weight (higher in lean/ normal weight)	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Live birth rate per patient												
16	Obs + RCTs	serious[1]	serious[2]	no serious indirectness	no serious imprecision	Obs study downgrade[3]	4438/ 9987	3988/ 10891	1.39 [1.17, 1.65]	Lean/ normal weight (higher in lean/ normal weight)	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Ovulation rate- per patient												
1	Obs	serious[1]	not applicable	not applicable	serious[4]	Obs study downgrade[3]	57/ 62	142/ 206	5.14 [1.97, 13.43]	Lean/ normal weight (higher in lean/ normal weight)	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Ovulation rate- per cycle												
1	RCT	no serious risk of bias	not applicable	not applicable	serious[4]	none	454/ 783	886/ 2139	1.95 [1.64, 2.32]	Lean/ normal weight (higher in lean/ normal weight)	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: OHSS												
7	Obs + RCTs	serious[1]	serious[2]	no serious indirectness	no serious imprecision	Obs study downgrade[3]	222/ 1246	102/ 1009	1.61 [0.72, 3.58]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Miscarriage rate per patient												
11	Obs+ RCTs	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	Obs study downgrade[3]	806/ 9228	1278/ 9750	0.64 [0.59, 0.71]	Lean/ normal weight (lower in lean/ normal weight)	⊕⊕◯◯ LOW	IMPORTANT

[1] Downgraded once for risk of bias due to the inclusion of some studies with high or moderate risk of bias
[2] Downgraded once for inconsistency due to high and/or statistically significant heterogeneity (I^2) or varied CIs
[3] Downgraded once since the evidence is derived from lower levels of evidence (observational studies)
[4] Downgraded once for imprecision due to the evidence being derived from a single study and/or a small sample size

COMPARISON 2: Younger versus older PCOS age groups												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Younger	Older	Effect Estimate: MD (95% CI)	Favours	Certainty	Importance
Outcome: Clinical pregnancy rate per patient												
5 (2 in MA)	Obs	serious[1]	serious[2]	no serious indirectness	no serious imprecision	Obs study downgrade[3]	209/ 582	31/ 104	2.41 [0.53, 10.98]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: OHSS per patient												
2	Obs	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	Obs study downgrade[3]	11/ 582	2/ 104	0.96 [0.24, 3.84]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Ovulation rate- per cycle												
1	Obs	no serious risk of bias	not applicable	not applicable	very serious[4]	Obs study downgrade[3]	41/ 44	32/ 36	1.71 [0.36, 8.18]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Multiple pregnancy rate per patient												
1	Obs	no serious risk of bias	not applicable	not applicable	serious[4]	Obs study downgrade[3]	83/ 562	14/ 91	0.95 [0.52, 1.76]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Miscarriage rate per patient												
2	Obs	serious[1]	not applicable	not applicable	serious[4]	Obs study downgrade[3]	NA	NA	Not estimable	No difference	⊕◯◯◯ VERY LOW	IMPORTANT

[1] Downgraded once for risk of bias due to the inclusion of studies with high or moderate risk of bias
[2] Downgraded once for inconsistency due to high and/or statistically significant heterogeneity (I^2) or varied CIs
[3] Downgraded once since the evidence is derived from lower levels of evidence (observational studies)
[4] Downgraded once for imprecision due to the evidence being derived from a single study or twice because it is a single study with a small sample size
MA= mete analysis; Obs= observational study

APPENDIX. Risk of bias assessment table

Study	Design	Selection bias		Performance bias	Detection bias		Attrition bias	Reporting bias	Confounding		Other bias	ROB score
		Comparable populations	Case and controls defined/ representative	Groups treated the same	Outcome assessors blinded	Outcomes measured reliably	Dropouts reported	Free of selective reporting	Groups similar at baseline	Adequate statistical analysis	Funding/ COI reported	
Abu-Fakher B, Al-Quobaili F, Alhalabi M. Follicular fluid antimullerian hormone (AMH) does not predict IVF outcomes in polycystic ovary syndrome patients. Middle East Fertility Society Journal. 2013;18(2):110-4.	Prospective case-control study	No	yes	yes	NR	yes	yes	NR	yes	yes	No	Medium
Akpınar F, Demir B, Dilbaz S, Kaplanoğlu İ, Dilbaz B. Obesity is not associated with the poor pregnancy outcome following intracytoplasmic sperm injection in women with polycystic ovary syndrome. Journal of the Turkish-German Gynecological Association. 2014;15(3):144-8.	Cohort study	yes	yes	yes	NR	yes	NR	NR	yes	yes	no	Medium
Al Safi WG, Hassan MF. Pregnancy rate in women with pcos with high lh/fsh ratio undergoing icsi. Latin American Journal of Pharmacy. 2021;40(Special Issue):336-40.	Cohort study	yes	yes	yes	NR	yes	yes	yes	yes	yes	no	Medium
Al-Azemi M, Omu FE, Omu AE. The effect of obesity on the outcome of infertility management in women with polycystic ovary syndrome. Archives of Gynecology and Obstetrics. 2004;270(4):205-10.	Cohort study	yes	yes	yes	NR	yes	NR	yes	yes	yes	no	Medium
Aleyasin A, Aghahoseini M, Mokhtar S, Fallahi P. Anti-mullerian hormone as a predictive factor in assisted reproductive technique of polycystic ovary syndrome patients. Acta Medica Iranica. 2011;49(11):715-20.	Cohort study	No	yes	yes	NR	yes	yes	NR	yes	yes	No	Low
Arabzadeh S, Hossein G, Rashidi BH, Hosseini MA, Zeraati H. Comparing serum basal and follicular fluid levels of anti-Mullerian hormone as a predictor of in vitro fertilization outcomes in patients with and without polycystic ovary syndrome. Annals of Saudi Medicine. 2010;30(6):442-7.	Case-control	yes	yes	yes	NR	yes	NR	NR	yes	yes	no	Medium
Bailey AP, Hawkins LK, Missmer SA, Correia KF, Yanushpolsky EH. Effect of body mass index on in vitro fertilization outcomes in women with polycystic ovary syndrome. American Journal of Obstetrics & Gynecology. 2014;211(2):163.e1-6.	Cohort study	yes	yes	yes	NR	yes	NR	NR	yes	yes	no	Low
Bakir VL, Karahan G. Evaluation of obesity and metabolic status in polycystic ovary syndrome in fertile and infertile groups. Zeynep Kamil Tip Bulteni. 2019;50(2):44-8.	Retrospective cohort study	yes	yes	yes	NR	yes	NR	NR	yes	yes	no	Medium
Berker B, Kaya C, Aytac R, Satiroglu H. Homocysteine concentrations in follicular fluid are associated with poor oocyte and embryo qualities in polycystic ovary syndrome patients undergoing assisted reproduction. Human Reproduction. 2009;24(9):2293-302.	Cohort study	yes	yes	yes	NR	yes	NR	NR	yes	yes	no	Medium
Beydoun HA, Stadtmauer L, Beydoun MA, Russell H, Zhao Y, Oehninger S. Polycystic ovary syndrome, body mass index and outcomes of assisted reproductive technologies. Reproductive Biomedicine Online. 2009;18(6):856-63.	Cohort study	yes	yes	yes	NR	yes	NR	NR	yes	yes	no	Medium

Bousmpoula A, Benidis E, Demeridou S, Kapeta-Kourkouli R, Chasiakou A, Chasiakou S, et al. Serum and follicular fluid irisin levels in women with polycystic ovaries undergoing ovarian stimulation: correlation with insulin resistance and lipoprotein lipid profiles. Gynecological Endocrinology. 2019;35(9):803-6.	Case control study	yes	yes	yes	partially	yes	no	no	Yes	yes	yes	Medium
Cakiroglu Y, Vural F, Vural B. The inflammatory markers in polycystic ovary syndrome: association with obesity and IVF outcomes. Journal of Endocrinological Investigation. 2016;39(8):899-907.	Case control study	Yes	no	Yes	NR	Yes	NR	Yes	Yes	no	Yes	Medium
Catak Z, Yavuzkir S, Kocdemir E, Ugur K, Yardim M, Sahin I, et al. NUCB2/nesfatin-1 in the blood and follicular fluid in patients with polycystic ovary syndrome and poor ovarian response. Journal of Reproduction and Infertility. 2019;20(4):225-30.	case-control study	yes	yes	yes	N/A	partial	no	parial	partial	yes	no	Medium
Chen M, Huang X, Liu Y, Lei S, Wu Y, Chen Z, et al. Systematic oxidative stress is not associated with live birth rate in young non-obese patients with polycystic ovarian syndrome undergoing assisted reproduction cycles: A prospective cohort study. European Journal of Obstetrics & Gynecology & Reproductive Biology. 2020;253:154-61.	prospective cohort study	yes	yes	yes	N/A		No	no	yes	yes	no	Medium
Chen R, Chen S, Liu M, He H, Xu H, Liu H, et al. Pregnancy outcomes of PCOS overweight/obese patients after controlled ovarian stimulation with the GnRH antagonist protocol and frozen embryo transfer. Reproductive Biology & Endocrinology. 2018;16(1):36.	Cohort study	yes	yes	yes	N/A	yes	yes	yes	yes	yes	no	Medium
Debras E, Fernandez H, Neveu ME, Deffieux X, Capmas P. Ovarian drilling in polycystic ovary syndrome: Long term pregnancy rate. European Journal of Obstetrics and Gynecology and Reproductive Biology: X. 2019;4 (no pagination).	Retrospective, observational, multicenter study	yes	N/A	yes	N/A	yes	yes	No	yes	No	no	High
Fedorcsak P, Dale PO, Storeng R, Tanbo T, Abyholm T. The impact of obesity and insulin resistance on the outcome of IVF or ICSI in women with polycystic ovarian syndrome. Human Reproduction. 2001;16(6):1086-91.	Cohort study	yes	yes	yes	N/A	yes	yes	yes	yes	yes	yes	High
Feng Y, Qi J, Xue X, Li X, Liao Y, Sun Y, et al. Follicular free fatty acid metabolic signatures and their effects on oocyte competence in non-obese PCOS patients. Reproduction. 2022;164(1):1-8.	Cohort study	Cannot locate full text for RoB assessment										
Gaafar TM, Hanna MOF, Hammady MR, Amr HM, Osman OM, Nasef A, et al. Evaluation of cytokines in follicular fluid and their effect on fertilization and pregnancy outcome. Immunological Investigations. 2014;43(6):572-84.	cohort study	yes	yes	yes	no	yes	no	no	no	no	yes	medium
Guan HJ, Pan LQ, Song H, Tang HY, Tang LS. Predictors of pregnancy after intrauterine insemination in women with polycystic ovary syndrome. Journal of International Medical Research. 2021;49(5):3000605211018600.	Descriptive study	no	no	no	no	yes	no	no	yes	yes	yes	High
Guido M, Belosi C, Selvaggi L, Lattanzi F, Apa R, Fulghesu AM, et al. The effect of age on the ovarian response to gonadotropin and on pregnancy rate in polycystic ovary syndrome. Gynecological Endocrinology. 2003;17(3):215-21.	Cohort study	yes	no	no	no	yes	no	no	no	Partial	No	Medium

Hashimoto DM, Schmid J, Martins FM, Fonseca AM, Andrade LH, Kirchengast S, et al. The impact of the weight status on subjective symptomatology of the Polycystic Ovary Syndrome: a cross-cultural comparison between Brazilian and Austrian women. Anthropologischer Anzeiger. 2003;61(3):297-310.	Comaprative study	n/a	n/a	n/a	no	no	n/a	no	yes	partial	no	High
Hassani F, Oryan S, Eftekhari-Yazdi P, Bazrgar M, Moini A, Nasiri N, et al. Association between the number of retrieved mature oocytes and insulin resistance or sensitivity in infertile women with polycystic ovary syndrome. International Journal of Fertility and Sterility. 2019;12(4):310-5.	case-control	yes	no	yes	no	yes	no	yes	yes	partially	no	Medium
Ho VNA, Pham TD, Le AH, Ho TM, Vuong LN. Live birth rate after human chorionic gonadotropin priming in vitro maturation in women with polycystic ovary syndrome. Journal of ovarian research. 2018;11(1) (no pagination).	retrospective study	yes	yes	yes	NR	yes	NR	NR	yes	yes	no	Medium
Huang Q, Niu Y, Xu L, Chen B, Zhang Y, Song LJ, et al. Relationship between a low ratio of serum estradiol to follicle number and fertility treatment outcomes A retrospective cohort study of 516 cases. Medicine (United States). 2018;97(34) (no pagination).	retroprective study	yes	yes	yes	no	yes	no	yes	yes	yes	no	Medium
Hwang YI, Cha SW, Song IO, Yang KM, Min EG, Kim HO. Fertility of patients with polycystic ovary syndrome undergoing in vitro fertilization by age. International Journal of Gynaecology & Obstetrics. 2016;135(1):91-5.	Retrospective cohort study	yes	yes	yes	NR	yes	NR	NR	yes	yes	yes	Medium
Inal HA, Yilmaz N, Gorkem U, Oruc AS, Timur H. The impact of follicular fluid adiponectin and ghrelin levels based on BMI on IVF outcomes in PCOS. Journal of Endocrinological Investigation. 2016;39(4):431-7.	prospective cross-sectional study	yes	no	yes	no	yes	no	no	yes	partially	yes	medium
Inal ZO, Inal HA, Erdem S. The effect of serum and follicular fluid secreted frizzle-related protein-5 on in vitro fertilization outcomes in patients with polycystic ovary syndrome. Molecular Biology Reports. 2018;45(6):2037-44.	prospective sequential cross-sectional study	Yes	N/A	Yes	N/A	Yes	N/A	N/A	Yes	Yes	yes	Medium
Janati S, Behmanesh MA, Najafzadehvarzi H, Akhundzade Z, Poormoosavi SM. Follicular Fluid Zinc Level and Oocyte Maturity and Embryo Quality in Women with Polycystic Ovary Syndrome. International Journal of Fertility & Sterility. 2021;15(3):197-201.	Cross sectional study	yes	n/a	yes	n/a	yes	n/a	no	yes	partial	yes	Medium
Jaschke N, Lunger F, Wildt L, Seeber B. Beta endorphin in serum and follicular fluid of PCOS- and non-PCOS women. Archives of Gynecology & Obstetrics. 2018;298(1):217-22.	Retrospective cohort study	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	Low
Jeon YE, Lee KE, Jung JA, Yim SY, Kim H, Seo SK, et al. Kisspeptin, leptin, and retinol-binding protein 4 in women with polycystic ovary syndrome. Gynecologic and Obstetric Investigation. 2013;75(4):268-74.	Cannot locate full text for RoB assessment											
Jin Y, Zhang Q, Pan JX, Wang FF, Qu F. The effects of di(2-ethylhexyl) phthalate exposure in women with polycystic ovary syndrome undergoing in vitro fertilization. Journal of International Medical Research. 2019;47(12):6278-93.	Case control study	yes	no	yes	n/a	yes	no	yes	yes	yes	yes	Medium

Kalra SK, Ratcliffe SJ, Dokras A. Is the fertile window extended in women with polycystic ovary syndrome? Utilizing the Society for Assisted Reproductive Technology registry to assess the impact of reproductive aging on live-birth rate. Fertility & Sterility. 2013;100(1):208-13	Case control	yes	yes	yes	NR	yes	NR	NR	yes	yes	no	Medium
Kamardi S, Surya IHW, Mahendra INB, Adnyana IP, Suardika A, Tondohusodo N, et al. Impact of body mass index on intracytoplasmic sperm injection in women with polycystic ovary syndrome. Zygote. 2021;29(3):229-33.	Retrospective case–control	yes	no	yes	n/a	yes	yes	n/a	yes	partially	yes	Medium
Kolibianakis E, Zikopoulos K, Albano C, Camus M, Tournaye H, Van Steirteghem A, et al. Reproductive outcome of polycystic ovarian syndrome patients treated with GnRH antagonists and recombinant FSH for IVF/ICSI. Reproductive Biomedicine Online. 2003;7(3):313-8.	Cohort study	Yes	Yes	Yes		Yes	Yes	Yes	Yes	Yes	Yes	Medium
Kudesia R, Wu H, Hunter Cohn K, Tan L, Lee JA, Copperman AB, et al. The effect of female body mass index on in vitro fertilization cycle outcomes: a multi-center analysis. Journal of Assisted Reproduction & Genetics. 2018;35(11):2013-23.	retrospective cohort	Yes	Yes	Yes	No	Yes	N/A	Yes	No	Yes	yes	Medium
Lai Q, Xiang W, Li Q, Zhang H, Li Y, Zhu G, et al. Oxidative stress in granulosa cells contributes to poor oocyte quality and IVF-ET outcomes in women with polycystic ovary syndrome. Frontiers of medicine. 2018;12(5):518-24.	cohort study	yes	yes	yes	NR	yes	NR	NR	yes	yes	no	Medium
Li Y, Lin H, Pan P, Yang D, Zhang Q. Impact of Central Obesity on Women with Polycystic Ovary Syndrome Undergoing in Vitro Fertilization. BioResearch Open Access. 2018;7(1):116-22.	retrospective study	Yes	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Yes	yes	Medium
Lin J, Huang J, Wang N, Kuang Y, Cai R. Effects of pre-pregnancy body mass index on pregnancy and perinatal outcomes in women with PCOS undergoing frozen embryo transfer. BMC Pregnancy and Childbirth. 2019;19(1) (no pagination).	retrospective cohort	Yes	Yes	Yes	NR	Yes	NR	Yes	Yes	Yes	Yes	Low
Lo JC, Feigenbaum SL, Escobar GJ, Yang J, Crites YM, Ferrara A. Increased prevalence of gestational diabetes mellitus among women with diagnosed polycystic ovary syndrome: a population-based study. Diabetes Care. 2006;29(8):1915-7	Prospective follow-up study	yes	no	yes	n/a	yes	no	no	yes	yes	no	Medium
Lujan ME, Kepley AL, Chizen DR, Lehotay DC, Pierson RA, Lujan ME, et al. Development of morphologically dominant follicles is associated with fewer metabolic disturbances in amenorrheic women with polycystic ovary syndrome: a pilot study. Ultrasound in Obstetrics & Gynecology. 2010;36(6):759-66.	follow up study	yes	no	yes	no	yes	no	no	yes	no	no	High
Luo L, Wang Q, Chen M, Yuan G, Wang Z, Zhou C. IGF-1 and IGFBP-1 in peripheral blood and decidua of early miscarriages with euploid embryos: comparison between women with and without PCOS. Gynecological Endocrinology. 2016;32(7):538-42.	cohort study	yes	yes	yes	no	yes	no	no	yes	yes	yes	medium
Mackens S, Pareyn S, Drakopoulos P, Deckers T, Mostinckx L, Blockeel C, et al. Outcome of in-vitro oocyte maturation in patients with PCOS: does phenotype have an impact? Human Reproduction. 2020;35(10):2272-9.	retrospective cohort study	yes	n/a	no	no	yes	yes	yes	yes	yes	yes	High

Macut D, Micic D, Parapid B, Cvijovic G, Sumarac M, Kendereski A, et al. Age and body mass related changes of cardiovascular risk factors in women with polycystic ovary syndrome. Vojnosanitetski Pregled. 2002;Military-medical and pharmaceutical review. 59(6):593-9.	Cross-sectional study	Yes	N/A	Yes	N/A	Yes	N/A	N/A	Yes	Yes	No	Medium
Madani T, Irani S, Ashrafi M, Alsadat Nabavi M. The Effect of Flutamide on Ovulation Induction in PCOS Patients. International Journal of Fertility & Sterility. 2012;6(1):65-9.	RCT	Yes	Yes	Yes	Yes	Yes	No	N/A	Yes	Yes	Yes	Medium
Mahajan N, Kaur J. Establishing an Anti-Mullerian hormone cutoff for diagnosis of polycystic ovarian syndrome in women of reproductive age-bearing Indian ethnicity using the automated Anti-Mullerian hormone assay. Journal of Human Reproductive Sciences. 2019;12(2):104-13.	Prospective cohort	Yes	Yes	Yes	N/A	Yes	Yes	N/A	Yes	Yes	Yes	Low
Mahran A, Abdelmeged A, El-Adawy AR, Eissa MK, Shaw RW, Amer SA. The predictive value of circulating anti-mullerian hormone in women with polycystic ovarian syndrome receiving clomiphene citrate: a prospective observational study. Journal of Clinical Endocrinology & Metabolism. 2013;98(10):4170-5.	Prospective cohort	Yes	Yes	Yes	N/A	Yes	N/A	Yes	Yes	Yes	Yes	Low
McCormick B, Thomas M, Maxwell R, Williams D, Aubuchon M. Effects of polycystic ovarian syndrome on in vitro fertilization-embryo transfer outcomes are influenced by body mass index. Fertility & Sterility. 2008;90(6):2304-9.	Retrospective cohort	Yes	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Yes	No	Medium
Mostinckx L, Segers I, Belva F, Buyl R, Santos-Ribeiro S, Blockeel C, et al. Obstetric and neonatal outcome of ART in patients with polycystic ovary syndrome: IVM of oocytes versus controlled ovarian stimulation. Human Reproduction. 2019;34(8):1595-607.	Retrospective cohort	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Medium
Muharam R, Prasetyo YD, Prabowo KA, Putri YI, Maidarti M, Hestiantoro A. IVF outcome with a high level of AMH: a focus on PCOS versus non-PCOS. BMC Women's Health. 2022;22(1):172.	Retrospective cohort	Yes	Yes	Yes	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Low
Namlı Kalem M, Kalem Z, Sarı T, Ateş C, Gürgan T. Effect of body mass index and age on in vitro fertilization in polycystic ovary syndrome. Journal of the Turkish-German Gynecological Association. 2016;17(2):83-90.	Retrospective cohort	Yes	N/A	Yes	NR	Yes	NR	Yes	N/A	Yes	Yes	Low
Niu Z, Ye Y, Xia L, Feng Y, Zhang A. Follicular fluid cytokine composition and oocyte quality of polycystic ovary syndrome patients with metabolic syndrome undergoing in vitro fertilization. Cytokine. 2017;91:180-6.	Case-control	Yes	Yes	Yes	NR	Yes	NR	Yes	Yes	Yes	Yes	Low
Oberg E, Gidlof S, Jakson I, Mitsell M, Tollet Egnell P, Hirschberg AL. Improved menstrual function in obese women with polycystic ovary syndrome after behavioural modification intervention-A randomized controlled trial. Clinical Endocrinology. 2019;90(3):468-78	RCT	Cannot locate full text for RoB assessment										
Palomba S, Falbo A, Russo T, Di Cello A, Morelli M, Orio F, et al. Metformin administration in patients with polycystic ovary syndrome who receive gonadotropins for in vitro fertilization cycles: 10-year experience in a large infertile population. Gynecological Endocrinology. 2012;28(2):81-6.	Retrospective cohort	Yes	Yes	Yes	NR	Yes	NR	Yes	Yes	Yes	Yes	Low

Provost MP, Acharya KS, Acharya CR, Yeh JS, Steward RG, Eaton JL, et al. Pregnancy outcomes decline with increasing body mass index: analysis of 239,127 fresh autologous in vitro fertilization cycles from the 2008-2010 Society for Assisted Reproductive Technology registry. Fertility & Sterility. 2016;105(3):663-9.	Retrospective cohort	Yes	Yes	Yes	NR	Yes	NR	Yes	Yes	Yes	Yes	Low
Shalom-Paz E, Marzal A, Wiser A, Almog B, Reinblatt S, Tulandi T, et al. Effects of different body mass indices on in vitro maturation in women with polycystic ovaries. Fertility & Sterility. 2011;96(2):336-9.	Retrospective cohort	Yes	Yes	Yes	NR	Yes	NR	Yes	Yes	Yes	No	Medium
Sheng Y, Lu G, Liu J, Liang X, Ma Y, Zhang X, et al. Effect of body mass index on the outcomes of controlled ovarian hyperstimulation in Chinese women with polycystic ovary syndrome: a multicenter, prospective, observational study. Journal of Assisted Reproduction and Genetics. 2017;34(1):61-70.	Prospective cohort	Yes	Yes	Yes		Yes	Yes	Yes	Yes	Yes	Yes	Low
Wang J, Wei Y, Diao F, Cui Y, Mao Y, Wang W, et al. The association between polycystic ovary syndrome and ectopic pregnancy after in vitro fertilization and embryo transfer. American Journal of Obstetrics & Gynecology. 2013;209(2):139.e1-9.	Retrospective Cohort Study	Yes	Yes	Yes	No	Yes	N/A	Yes	No	Yes	No	Low
Wang JX, Davies MJ, Norman RJ. Polycystic ovarian syndrome and the risk of spontaneous abortion following assisted reproductive technology treatment. Human Reproduction. 2001;16(12):2606-9.	Retrospective Cohort Study	Yes	Yes	Yes	No	Yes	N/A	Yes	No	Yes	No	Low
Yang W, Yang R, Lin M, Yang Y, Song X, Zhang J, et al. Body mass index and basal androstenedione are independent risk factors for miscarriage in polycystic ovary syndrome. Reproductive Biology & Endocrinology. 2018;16(1):119.	Retrospective Cohort Study	Yes	Yes	Yes	No	Yes	N/A	Yes	No	Yes	No	Low
Zhang CM, Zhao Y, Li R, Yu Y, Yan LY, Li L, et al. Metabolic heterogeneity of follicular amino acids in polycystic ovary syndrome is affected by obesity and related to pregnancy outcome. BMC Pregnancy & Childbirth. 2014;14:11.	Prospective Cohort Study	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes	Yes	Low
Zhao Y, Ruan X, Mueck AO. Letrozole combined with low dose highly purified HMG for ovulation induction in clomiphene citrate-resistant infertile Chinese women with polycystic ovary syndrome: a prospective study. Gynecological Endocrinology. 2017;33(6):462-6.	Prospective Study	Cannot locate full text for RoB assessment										
Zhou H, Zhang D, Luo Z, Yang A, Cui N, Hao G, et al. Association between Body Mass Index and Reproductive Outcome in Women with Polycystic Ovary Syndrome Receiving IVF/ICSI-ET. BioMed Research International. 2020:1-7.	Retrospective Cohort Study	Yes	No	Yes	No	Yes	No	Yes	No	Yes	Yes	Medium

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 5

Question 5.1.

In women with PCOS with infertility, what are the preconception risk factors associated with poor/negative fertility outcomes?

BACKGROUND

NARRATIVE REVIEW

Prevalence and problem

Polycystic ovary syndrome is a common heterogeneous endocrine disorder of uncertain aetiology, although genetics is indicated due to the increase in prevalence between first degree relatives and sisters and epigenetic impact from lifestyle and environmental exposure (1-3). PCOS has lifelong psychological and mental health implications and early diagnosis is crucial to optimise health. Women with PCOS suffer from greater body dissatisfaction and higher rates of eating disorders. They are also at increased risk of mood, anxiety, depression, and eating disorders which may affect libido and sexual relationships, impacting fertility (4-7).

Lifestyle factors especially obesity and being overweight exacerbate the condition; hence prevention of weight gain from adolescence is very important. The condition often results in several health complications, including menstrual dysfunction, infertility and metabolic syndrome disorders such as type 2 diabetes and cardiovascular disease. The endometrium of women with PCOS is further compromised by obesity and may improve with weight loss (8, 9).

The risk of infertility is increased in PCOS and pregnancy complications are higher including gestational diabetes. Preconception care is defined as “a set of interventions that aim to identify and modify biomedical, behavioural, and social risks to a woman's health or pregnancy outcome through prevention and management, emphasizing those factors that must be acted on before conception or early in pregnancy to have maximal impact”. As women with PCOS often require infertility treatment, both the requirement for and the opportunity for preconception care is increased. Preconception care should be considered in the context or routine recommendations and PCOS specific considerations.

Modifiable risk factors that may impact fertility: These include Body Mass Index <18 or >25, smoking status, alcohol consumption, pre-existing medical conditions such as diabetes and epilepsy, prescribed and recreational drug use, untreated sexually transmitted infections, nutritional status, supplementation requirements with folate, vitamin D, coeliac disease and dental health (10-15). These should be optimised as part of routine preconception care.

Pregnancy and fertility complications: Women with PCOS are at an increased risk of pregnancy complications including gestational diabetes, preterm birth, pre-eclampsia, miscarriage, longer time to conception and poor embryo development, reduced embryo implantation rates, increased risk of ovarian hyperstimulation syndrome (16) all exacerbated by obesity.

Mental health: Anxiety and depression coexist with PCOS, although it is unclear if this is a direct consequence of PCOS or due to associated psychological stressors such as obesity, hirsutism, body image issues and infertility (17). All women with PCOS should be screened for anxiety and depression. Body image and eating disorders should be considered and explored, irrespective of BMI (5, 7, 18). All can impact relationship health and sexual intimacy for fertility as well as impacting fertility treatment compliance or leading women to prematurely “drop out of treatment” due to the stress and demands of treatment (19). Mental health care supports treatment adherence, relationship health and quality of life.

GRADE EVIDENCE CERTAINTY	
Comparison	**GRADE for critical outcomes**
Comparison 1. Lean/ normal weight versus overweight/ obese PCOS	⊕◯◯◯ VERY LOW
Comparison 2. Younger versus older PCOS age groups	⊕◯◯◯ VERY LOW

Evidence to Recommendations Framework

COMPARISONS (option versus other option)

Not relevant

EVIDENCE-BASED RECOMMENDATION(S)

EBR: Women with PCOS should be counseled on the adverse impact of excess weight on clinical pregnancy, miscarriage and live birth rates following infertility treatment.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

RECOMMENDATION

CR: Consistent with routine preconception care, in women with PCOS planning pregnancy, weight, blood pressure, smoking, alcohol, diet and nutritional status, folate supplementation (higher dose in those with BMI >30), exercise, sleep and mental, emotional and sexual health should be considered and optimised to improve reproductive and pregnancy outcomes and overall health.

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

See also sections: Lifestyle; Assessment and Management of Emotional Wellbeing; and Cardiometabolic risk

PRACTICE POINT(S)

A reproductive life plan and age appropriate education on optimising reproductive health, is recommended in adolescents and women with PCOS, including including healthy lifestyle, prevention of excess weight gain, and optimising preconception risk factors.

- Healthcare professionals are encouraged to seek permission and if given, to assess weight and body mass index and initiate a dialogue on the importance of weight and lifestyle on women's health before pregnancy. This requires caution to avoid weight stigma and needs to consider the cultural, social and environmental determinants of health (see 3.6).

- Chronic conditions such as diabetes, high blood pressure, anxiety, depression and other mental health conditions, should be optimally managed and women should be counselled regarding related risks of adverse pregnancy outcomes.

GRADE CONSIDERATIONS

Justifications:

These recommendations are guided by WHO and FIGO and the evidence on weight associations (20).

Subgroup considerations:

Subgroups by infertility treatment in relation to the impact of weight, there were no significant differences between the groups.

Implementation considerations:

Optimise provider awareness and counselling skills on weight and health impacts in PCOS in relation to fertility.

Monitoring and evaluation considerations:

Preconception risk factors could be better identified and monitored in PCOS

PCOS status should be better captured and recorded in infertility and pregnancy to optimise monitoring and evaluation of preconception risk factor and infertility and pregnancy outcomes.

Research priorities:

Individual patient data meta-analysis of preconception risk factors in women with PCOS and impact on fertility outcomes.

Greater data on ethnic and geographical variations in PCOS reproductive outcomes and fertility treatment responses is needed.

The impact of age on fertility and fertility treatment outcomes in women with PCOS.
The cumulative weight gain over the reproductive life course and the impact of this on fertility and pregnancy outcomes.

The impact of underweight on fertility outcomes in women with PCOS.

GRADE framework

GRADE DECIDE **Interactive Evidence to Decision Framework**

● DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Clearly recommended and beneficial in all women and even more so in high risk women with PCOS.

● UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Undesirable impacts not anticipated.

● CERTAINTY OF THE EVIDENCE

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☐ Very low	☒ Low	☐ Moderate	☐ High

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Evidence certainty high in general population but lower in PCOS specifically. Stronger evidence for weight.

● VALUES

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☐ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☐ Probably no important uncertainty or variability	☒ No important uncertainty or variability

Research evidence:

No research evidence was identified

Panel discussion:

● BALANCE OF EFFECTS

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:

Impressed by the consistent evidence around the impact of weight and strongly felt that this needed to be considered.

● CERTAINTY OF COST EVIDENCE

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

No research evidence was identified

Panel discussion:

● COST-EFFECTIVENESS

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

No research evidence was identified

Panel discussion:

● EQUITY

What would be the impact on health equity?

Judgement:

☐ Don't know	☒ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☐ Probably increased	☐ Increased

Research evidence:

No research evidence was identified

Panel discussion:

- **ACCEPTABILITY**

Is the option acceptable to key stakeholders?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Concerns about stigma and body image / eating disorders need to be considered.

- **FEASIBILITY**

Is the option feasible to implement?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Consider skills gaps

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2. Balen, A.H., et al., Polycystic ovary syndrome: the spectrum of the disorder in 1741 patients. Hum Reprod, 1995. 10(8): p. 2107-11.
3. Symonds, M.E., et al., Nutritional programming of the metabolic syndrome. Nat Rev Endocrinol, 2009. 5(11): p. 604-10.
4. Coker, E. and R. Lahoud, Polycystic Ovarian Syndrome and Eating Disorder Quality of Life: A Pilot Study. Journal of Fertilization: In Vitro - IVF-Worldwide, Reproductive Medicine, Genetics & Stem Cell Biology, 2016. 04(01).
5. Dokras, A., et al., Increased prevalence of anxiety symptoms in women with polycystic ovary syndrome: systematic review and meta-analysis. Fertil Steril, 2012. 97(1): p. 225-30
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9. Ujvari, D., et al., Lifestyle intervention up-regulates gene and protein levels of molecules involved in insulin signaling in the endometrium of overweight/obese women with polycystic ovary syndrome. Hum Reprod, 2014. 29(7): p. 1526-35.

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11. Legro, R.S., et al., Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab, 2013. 98(12): p. 4565-92.

12. Moran, L.J., et al., Lifestyle changes in women with polycystic ovary syndrome. Cochrane Database Syst Rev, 2011(7): p. CD007506.

13. Saccone, G., et al., Celiac disease and obstetric complications: a systematic review and metaanalysis. Am J Obstet Gynecol, 2016. 214 (2): p. 225-234.

14. Teede, H.J., et al., Longitudinal weight gain in women identified with polycystic ovary syndrome: results of an observational study in young women. Obesity (Silver Spring), 2013. 21(8): p. 1526-32.

15. Tay, C.T., et al. "Negative associations of ideal family size achievement with hypertension, obesity and maternal age in women with and without polycystic ovary syndrome." *Clinical Endocrinology* 97.2 (2022): 217-226.

16. Practice Committee of American Society for Reproductive Medicine, Ovarian hyperstimulation syndrome. Fertil Steril, 2008. 90 (5 Suppl): p. S188-93.

17. Legro, R.S., et al., Benefit of Delayed Fertility Therapy With Preconception Weight Loss Over Immediate Therapy in Obese Women With PCOS. J Clin Endocrinol Metab, 2016. 101 (7): p. 2658-66.

18. Tay, C.T., et al. "Increased prevalence of eating disorders, low self-esteem, and psychological distress in women with polycystic ovary syndrome: a community-based cohort study." *Fertility and sterility* 112.2 (2019): 353-361.

19. Domar, A.D., et al., Burden of care is the primary reason why insured women terminate in vitro fertilization treatment. Fertil Steril, 2018. 109 (6): p. 1121-1126.

20. Jacob, C.M., et al., Prevention of noncommunicable diseases by interventions in the preconception period: A FIGO position paper for action by healthcare practitioners. Int J Gynaecol Obstet, 2020. 151 Suppl 1 (Suppl 1): p. 6-15

PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by the Evidence Team: Aya Mousa, Jillian Tay
Other team members: Loyal Pattuwage

GDG 5

Question 5.2.

Should women with PCOS and infertility due to anovulation alone with normal semen analysis undergo tubal patency testing prior to starting ovulation induction with timed intercourse or IUI treatment?

1. STUDY SELECTION

Table 1. PICO Criteria for Inclusion	
Question	Should women with PCOS and infertility due to anovulation alone with normal semen analysis undergo tubal patency testing prior to starting ovulation induction with timed intercourse or IUI treatment?
Clinical leads (key contacts)	Ho Manh Tuong; Lisa Bedson
Allocation ranking	Systematic review Level 2 (updated)

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(language, year)*
Inclusion	Females with PCOS (diagnosed by Rotterdam, NIH or AEPCOS) of any age, ethnicity and weight AND normal semen analysis for male factor Note: subgroups by phenotypes	Fallopian tubal patency testing prior to starting ovulation induction. Methods of tubal testing include: Hysterosalpingography (HSG), ultrasound hyterography or sonohysterography (HyCoSy) or dye perturbation at laparoscopy.	No fallopian tubal patency testing prior to starting ovulation induction.	Live birth rate, pregnancy rate (biochemical or clinical ultrasound), miscarriage rate, OHSS rate, other adverse events, quality of life, cost effectiveness.	Evidence-based guidelines, systemic reviews of RCTs, RCTs	English Human
Exclusion	Women without diagnosis of PCOS.	No intervention or any intervention not listed above	None	None	Observational studies, non-evidence based guidelines, abstracts, protocols	None

2. SEARCH STRATEGY

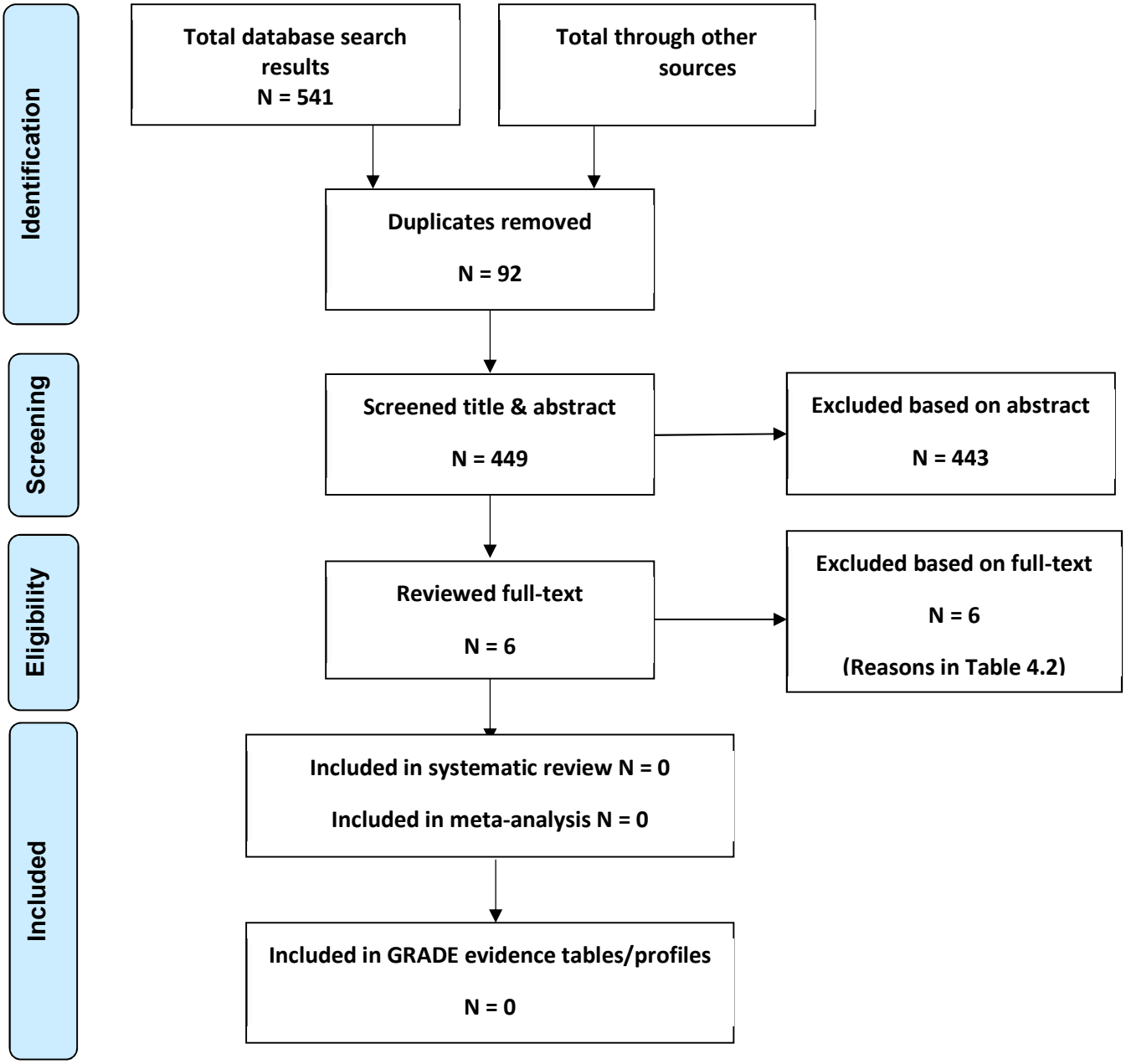
Table 2.1. Search details	
Search strategy source: *New search*	
Evidence source	**Date of search**
Medline (Ovid)	1990 until 2022 August 30
PsychInfo (Ovid)	1990 until 2022 August 30
EMBASE (Ovid)	1990 until 2022 August 30
All EBM (Ovid)	1990 until 2022 August 30
CINAHL	1990 until 2022 August 30
Any subsequent updates - enter database and date: Not applicable	

Table 2.2. Questions addressed by this search	
5.1.4	Should women with PCOS and infertility due to anovulation alone with normal semen analysis undergo tubal patency testing prior to starting ovulation induction with timed intercourse or IUI treatment?

OVID Medline, All EBM, PsychInfo, EMBASE	CINAHL
1 exp polycystic ovary syndrome/	S1 (MM "Polycystic Ovary Syndrome")
2 polycystic ovar*.mp.	S2 TX polycystic ovar*
3 poly-cystic ovar*.mp.	S3 TX poly-cystic ovar*
4 PCO*.mp.	S4 TX PCO*
5 (stein-leventhal or leventhal).mp.	S5 TX (stein-leventhal or leventhal)
6 anovulation/	S6 (MM "Anovulation")
7 anovulat*.mp.	S7 TX anovulat*
8 oligo-ovulat*.mp.	S8 TX oligo-ovulat*
9 oligoovulat*.mp.	S9 TX oligoovulat*
10 (ovar* adj5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper-androgen*)).mp.	S10 TX (ovar* N5 (sclerocystic or polycystic or poly-cystic or degenerat* or hyperandrogen* or hyper- androgen*))
11 or/1-10	S11 S1ORS2ORS3ORS4ORS5OR S6ORS7ORS8ORS9ORS10
12 exp fallopian tube diseases/ or pelvic inflammatory disease/ or salpingitis/	S12 (MH "Fallopian Tube Diseases+/DI/US") OR (MM "Fallopian Tube Patency Tests")
13 exp Fallopian Tubes/	S13 (MH "Pelvic Inflammatory Disease+")
14 ((tubal or tube or tubes or peritubal) adj3 (patent or patency or pathology or infertil* or subfertil* or factor* or disten* or occlusion* or occluded or damage* or adhesion* or lesion* or blockage* or blocked or block or disease* or obstruct* or fibrosis or fibrotic)).tw.	S14 TX ((tubal or tube or tubes or peritubal) N3 (patent or patency or pathology or infertil* or subfertil* or factor* or disten* or occlusion* or occluded or damage* or adhesion* or lesion* or blockage* or blocked or block or disease* or obstruct* or fibrosis or fibrotic))
15 (fallopian* adj3 (patent or patency or patholog* or infertil* or subfertil* or factor* or disten* or occlusion* or occluded or damage* or adhesion* or lesion* or blockage* or blocked or block or disease* or obstruct* or fibrosis or fibrotic)).tw.	S15 TX (fallopian* N3 (patent or patency or patholog* or infertil* or subfertil* or factor* or disten* or occlusion* or occluded or damage* or adhesion* or lesion* or blockage* or blocked or block or disease* or obstruct* or fibrosis or fibrotic))
16 (oviduct* adj3 (patent or patency or patholog* or infertil* or subfertil* or factor* or disten* or occlusion* or occluded or damage* or adhesion* or lesion* or blockage* or blocked or block or disease* or obstruct* or fibrosis or fibrotic)).tw.	S16 TX (oviduct* N3 (patent or patency or patholog* or infertil* or subfertil* or factor* or disten* or occlusion* or occluded or damage* or adhesion* or lesion* or blockage* or blocked or block or disease* or obstruct* or fibrosis or fibrotic))
17 ((salpinges or salpinx) adj3 (patent or patency or patholog* or infertil* or subfertil* or factor* or disten* or occlusion* or occluded or damage* or adhesion* or lesion* or blockage* or blocked or block or disease* or obstruct* or fibrosis or fibrotic)).tw.	S17 TX ((salpinges or salpinx) N3 (patent or patency or patholog* or infertil* or subfertil* or factor* or disten* or occlusion* or occluded or damage* or adhesion* or lesion* or blockage* or blocked or block or disease* or obstruct* or fibrosis or fibrotic))
18 Salpingitis.tw.	S18 TX Salpingitis
19 (Hydrosalpin* or pyosalpin* or h?ematosalpin*).tw.	S19 TX Hydrosalpin* or pyosalpin* or h? ematosalpin*
	S20 TX Endosalping*

20 Endosalping*.tw. 21 or/12-20 22 exp Laparoscopy/ 23 hysterolaparoscop*.tw. 24 (Laparoscop* and (fallopian* or chromopertubation or diagnos* or sensitivity or specificity or patency or patent or dye or methylene or LSC)).tw. 25 (laparoscop* adj10 predictive value).tw. 26 (laparoscop* adj10 receiver operating characteristic).tw. 13 27 (Laparoscop* and likelihood ratio*).tw. 28 (LSC and fallopian*).tw. 4 29 (minilaparoscop$ and (fallopian* or diagnos*)).tw. 30 (microlaparoscop$ and (fallopian* or diagnos*)).tw. 31 mini-laparoscop*.tw. 32 micro-laparoscop*.tw. 33 or/22-32 34 Hysterosalpingography/ 35 Hysterosalpingo-Contrast Sonography.af. 36 HyCoSy.af. 37 HyFoSy.af. 38 or/34-37 39 (hysterosalpingo* or salpingogra* or salpingoscop*).tw. 40 (hydrolaparoscop* or fertiloscop*).tw. 41 (sonohysterosalping* or SonoVue*).tw. 42 (HSG or HSSG or MRHSG).tw. 43 (HyCoSy or HyCoUs).tw. 44 hysteroscop*.tw. 45 hystero-laparoscop*.tw. 46 foam sonogra*.tw. 47 HyFoSy.tw. 48 exp Magnetic Resonance Imaging/ or exp Magnetic Resonance Spectroscopy/ 49 or/39-48 50 33 or 38 or 49 51 21 and 50 52 Fallopian Tube Patency Tests/ or Fallopian Tube Diseases/dg 53 51 or 52 54 11 and 53 55 limit 54 to (english language and humans and yr="1990 -Current")	S21 S12ORS13ORS14ORS15OR S16ORS17ORS18ORS19OR S20 S22 (MH "Surgery, Laparoscopic+") OR (MM "Laparoscopy") S23 TX hysterolaparoscop* S24 TX (Laparoscop* and (fallopian* or chromopertubation or diagnos* or sensitivity or specificity or patency or patent or dye or methylene or LSC)) S25 TX laparoscop* N10 predictive value S26 TX laparoscop* N10 receiver operating characteristic S27 TX Laparoscop* and likelihood ratio* S28 TX LSC and fallopian* S29 TX (minilaparoscop* and (fallopian* or diagnos*)) S30 TX (microlaparoscop* and (fallopian* or diagnos*)) S31 TX mini-laparoscop* OR TX micro- laparoscop* S32 S22ORS23ORS24ORS25OR S26ORS27ORS28ORS29ORS30 OR S31 S33 (MM "Hysterosalpingography") S34 (MM "Enhancement of Contrast Effect") OR "Hysterosalpingo Contrast Sonography" S35 TX hycosy OR TX hyfosy S36 S33 OR S34 OR S35 S37 TX (hysterosalpingo* or salpingogra* r salpingoscop*) OR TX (hydrolaparoscop* or fertiloscop*) OR TX (sonohysterosalping* or SonoVue*) OR TX (HSG or HSSG or MRHSG) OR TX (HyCoSy or HyCoUs) OR TX hysteroscop* OR TX hystero-laparoscop* OR TX foam sonogra* OR TX HyFoSy S38 (MH "Magnetic Resonance Imaging+") S39 (MH "Magnetic Resonance Spectroscopy+") S40 S37 OR S38 OR S39 S41 S32 OR S36 OR S40 S42 S21 AND S41 S43 S11 AND S42 S44 S11 AND S42

3. SEARCH RESULTS - PRISMA flowchart



4. STUDY INCLUSION

Table 4.1. Included Studies (full citation with doi)-
None

Table 4.2. Excluded Studies (on full text assessment)-

Title	Author/Year	Journal	Volume/Pages	Notes
ACR Appropriateness Criteria Female Infertility	Wall 2020	Journal of the American College of Radiology	17(5 Supplement): S113-S124	Exclusion reason: Wrong study design;
ACR Appropriateness Criteria Infertility	Wall 2015	Ultrasound Quarterly	31(1): 37-44	Exclusion reason: Wrong study design;
Comparison of sonohysterography to hysterosalpingogram for tubal patency assessment in a multicenter fertility treatment trial among women with polycystic ovary syndrome	Wall 2018	Journal of Assisted Reproduction & Genetics	35: 2173-2180	Exclusion reason: Wrong comparator;
Hysterosalpingography and laparoscopy in diagnosis of the Fallopian tubes obstruction in infertile women	Brankovic 2013	Giornale Italiano di Ostetricia e Ginecologia	35(1): 148-149	Exclusion reason: non english;
The position of diagnostic laparoscopy in current fertility practice	Bosteels 2007	Human Reproduction Update	13: 477-85	Exclusion reason: Wrong study design;
Utility of sonohysterography for tubal patency assessment in the pregnancy in polycystic ovary syndrome II trial	Christianson 2015	Fertility and Sterility	e98-e99	Exclusion reason: Wrong comparator;

Evidence processing: The search and screening for this question was a separate process to the rest of Guideline Development Group 5 (which all underwent a single search/ screening). Studies were selected and appraised by 1 reviewer/s in consultation with the evidence team/ key contact using study selection and appraisal criteria (PICO above) established a priori. The articles were reviewed by title and abstract by 1 reviewer. When a decision could not be made based on title and abstract alone, full text was retrieved. **No studies met inclusion criteria for this review.** Therefore, the available evidence has been reviewed narratively

5. FINDINGS

See PART 2 for this question.

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 5

Question 5.2.

Should women with PCOS and infertility due to anovulation alone with normal semen analysis undergo tubal patency testing prior to starting ovulation induction with timed intercourse or IUI treatment?

BACKGROUND

Prevalence and problem

One of the leading causes of female infertility is tubal pathology. It has been estimated that it affects around 30% of infertile women. The diagnostic assessment of infertile women often includes tubal testing by hysterosalpingography, ultrasound (Saline infusion sonohysterography, Hysterosalpingo-Contrast Sonography, [Hysterosalpingo-Foam Sonography]) or laparoscopy.

Clinical gap and need for guidance

PCOS is the most frequent cause of anovulation in infertile women. Ovulation induction is the most common treatment. There is little information about the prevalence of tubal pathology or for the need of intrauterine insemination with normal semen analysis in infertile women with PCOS.

Summary of key information

There is no evidence to support that tubal disease is more frequent in PCOS women (1). Therefore, it would be suitable to perform hysterosalpingography prior to IUI or timed intercourse in women with PCOS and the following clinical risk factors, independent of PCOS, consistent with usual infertility care.

Risk factors for Infertility associated with tubal pathology:

1) Women with PCOS and a history of previous abdominal septic surgery like peritonitis or any pelvic surgical procedure.

2) Women with PCOS with a history of Sexual Transmitted Infection or Pelvic Inflammatory Disease or have a positive serum test for sexually transmitted infection might be considered at risk of an etiologic factor that potentially disrupt fallopian tube function.
3) PCOS associated with endometriosis.

In large studies including a study with 1002 women with PCOS, 33 had tubal abnormalities (3%) with 97% having at least one patent fallopian tube or a normal uterine cavity (2) and other studies also show 3-5% abnormality (3).

In women with PCOS undergoing hysterosalpingography, in 185 women (85.2%) had bilateral tubal patency and 32 (14.7%) had unilateral patency. Seventeen patients underwent laparoscopy with six having both tubes patent and nine having one tube patent (4).

In a large cohort of women with PCOS (N= 619) with at least one patent fallopian tube confirmed by tubal patency test, who were then randomized to up to 5 cycles of letrozole or clomiphene citrate, there was no significant difference in clinical pregnancy rate between women who had tubal patency confirmed by HSG versus Saline infusion sonohysterography (OR 1.14, 95% CI 0.77, 1.67, P = 0.52) (4).
Finally, a multicentre, prospective, comparative study with a randomized design (N=1026), showed that hystero contrast sonography produces similar tubal pathology findings in a majority of infertile couples and, where they differ, a difference in findings does not lead to substantial difference in pregnancy outcome, while hystero contrast sonography is associated with significantly less pain (5). The authors suggested that [Hysterosalpingo-Foam Sonography can be preferred as first-choice tubal patency test during fertility work-up. In case of suspected tubal pathology or inconclusive results, further testing can be done (5).

Recommendations Framework

CONSENSUS RECOMMENDATION

CR: In women with PCOS and infertility due to anovulation alone with normal semen analysis, the risks, benefits, costs and timing and techniques of tubal patency testing in relation to the cost and complexity of the treatment, should be considered on an individual basis, depending on personal history and population prevalence, prior to starting ovulation induction with timed intercourse or IUI insemination.

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

CONSIDERATIONS

Justifications:

See background on broad evidence, no evidence found specifically for this PICO on evidence search

Subgroup considerations:

NA

Implementation considerations:

NA as recommendation is for discussion on risks vs benefits

Monitoring and evaluation considerations:

NA

Research priorities:

Define whether tubal patency test should be done during infertile work-up to identify the optimal timing and method of assessing tubal patency in women with PCOS and infertility due to anovulation alone with normal semen analysis, considering cost effectiveness and quality of life implications for the woman or the couple.

Equity:

NA

Acceptability

Likely acceptable as advice is for discussion on risk vs benefits

FEASIBILITY

NA

REFERENCES:

1. Broeze, K.A., et al., Are patient characteristics associated with the accuracy of hysterosalpingography in diagnosing tubal pathology? An individual patient data meta-analysis. Hum Reprod Update, 2011. 17(3): p. 293-300.
2. Legro, R.S., et al., Letrozole versus clomiphene citratefor infertility in the polycystic ovary syndrome. N Engl J Med, 2014. 371(2): p. 119-29.
3. McGovern, P.G., et al., Utility of screening for other causes of infertility in women with “known” polycystic ovary syndrome. Fertility and Sterility, 2007. 87(2): p. 442-444.
4. Christianson, M.S., et al., Comparison of sonohysterography to hysterosalpingogram for tubal patency assessment in a multicenter fertility treatment trial among women with polycystic ovary syndrome. J Assist Reprod Genet, 2018. 35(12): p. 2173-2180.
5. van Welie, N., et al., Can hysterosalpingo-foam sonography replace hysterosalpingography as first-choice tubal patency test? A randomized non-inferiority trial. Hum Reprod, 2022. 37(5): p. 969-979.

PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by the Evidence Team: Aya Mousa, Jillian Tay

Other team members: Loyal Pattuwage, Jennifer Tamblyn, Loriana Soma

GDG 5

Question 5.3.

In women with PCOS, are aromatase inhibitors effective for improving fertility outcomes?

1. STUDY SELECTION

Table 1. PICO Criteria for Inclusion	
Question	In women with PCOS, are aromatase inhibitors effective for improving fertility outcomes?
Clinical leads (key contacts)	Rick Legro
Allocation ranking	Level 2- updated systematic review (with update of integrity check for all pre-2017 studies)

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(language, year)*
Inclusion	Women of any age, ethnicity and weight with PCOS diagnosed by Rotterdam, NIH or AIS and 1) at least one patent tube 2) normal sperm AND 3) have never been treated or been exposed to treatment for infertility (therapy naïve) OR 4) have been treated or exposed to treatment OR 5) have been treated or exposed to clomiphene citrate and ovulate but don't conceive (clomid failure) OR 6) have been treated or exposed to clomid and don't ovulate (clomid resistant). Also specifically identifying the 4 phenotypes where possible.	Any type, dose and frequency of aromatase inhibitor.	Placebo, no intervention, other infertility treatment interventions (ie. another type of aromatase inhibitor, metformin, clomiphene citrate, gonadotrophins, ovarian surgery) including aromatase inhibitors in combination with other infertility treatment intervention(s).	Live birth rate, pregnancy rate (biochemical or clinical ultrasound), ovulation, single and multiple pregnancies, miscarriage rate, other adverse events, quality of life, cost effectiveness.	Evidence based guidelines, systematic reviews, health technology assessments, randomised controlled trials (RCTs).	None
Exclusion	Women without diagnosis of PCOS.	Placebo, no intervention or any intervention other than an aromatase inhibitor.	Any intervention other than those listed in the inclusion criteria.	None	Nonevidence based guidelines, non-systematic reviews, any study lower than a RCT.	None

2. SEARCH STRATEGY

The search and screening for all GDG 5 questions were done together. Details can be found in the GDG 5 Methodology Appendix, including for:

- Databases
- Search Dates
- Search String(s)
- PRISMA flowchart
- Full list of included studies
- Full list of excluded studies with reasons for exclusion

Evidence processing: The literature search and screening were performed together in one Endnote library and Covidence project for all non-IVF, IVF and IVM fertility treatments in PCOS. Studies were selected by one reviewer/s in consultation with the evidence team/ key contact(s) using study selection and appraisal criteria (PICOs) established a priori. The articles were screened by title and abstract by one reviewer. When a decision could not be made based on title and abstract alone, full text was retrieved. Study appraisal was conducted by two reviewers independently with discussion to resolve any discrepancy. In total, 102 unique studies met inclusion criteria across all non-IVF, IVF and IVF questions, of which 57 were included in the guideline update following the integrity check (refer to methodology appendix of guidelines for details).

Integrity Assessment: Of these eligible 102 studies, 14 studies met the inclusion criteria for this particular question (Q.5.3) on aromatase inhibitors, as detailed below.

Table of Included Studies
Atay, V., Cam, C., Muhcu, M., Cam, M., & Karateke, A. (2006). Comparison of letrozole and clomiphene citrate in women with polycystic ovaries undergoing ovarian stimulation. *Journal of international medical research*, *34*(1), 73-76.
Amer SA, Smith J, Mahran A, Fox P, Fakis A. Double-blind randomized controlled trial of letrozole versus clomiphene citrate in subfertile women with polycystic ovarian syndrome. Hum Reprod. 2017 Aug 1;32(8):1631-1638. doi: 10.1093/humrep/dex227. PMID: 28854590; PMCID: PMC5850470.
Bansal S, Goyal M, Sharma C, Shekhar S. Letrozole versus clomiphene citrate for ovulation induction in anovulatory women with polycystic ovarian syndrome: A randomized controlled trial. Int J Gynaecol Obstet. 2021 Mar;152(3):345-350. doi: 10.1002/ijgo.13375. Epub 2020 Oct 14. PMID: 32920843.
Bayar U, Basaran M, Kiran S, Coskun A, Gezer S. Use of an aromatase inhibitor in patients with polycystic ovary syndrome: a prospective randomized trial. Fertil Steril. 2006 Nov;86(5):1447-51. doi: 10.1016/j.fertnstert.2006.04.026. PMID: 17070196.
Begum, M. R., J. Ferdous, et al. (2009). "Comparison of efficacy of aromatase inhibitor and clomiphene citrate in induction of ovulation in polycystic ovarian syndrome." Fertility & Sterility 92(3): 853-7.
Ganesh A, Goswami SK, Chattopadhyay R, Chaudhury K, Chakravarty B. Comparison of letrozole with continuous gonadotropins and clomiphene-gonadotropin combination for ovulation induction in 1387 PCOS women after clomiphene citrate failure: a randomized prospective clinical trial. J Assist Reprod Genet. 2009 Jan;26(1):19-24. doi: 10.1007/s10815-008-9284-4.
Legro, R. S., R. G. Brzyski, et al. (2014). "Letrozole versus clomiphene for infertility in the polycystic ovary syndrome." New England Journal of Medicine 371(2): 119-129.
Liu, C., G. Feng, W. Huang, Q. Wang, S. Yang, J. Tan, J. Fu and D. Liu (2017). "Comparison of clomiphene citrate and letrozole for ovulation induction in women with polycystic ovary syndrome: a prospective randomized trial." Gynecol Endocrinol 33(11): 872-876.
Nazik, H., & Kumtepe, Y. (2012). Comparison of efficacy of letrozole and clomiphene citrate in ovulation induction for women with polycystic ovarian syndrome. *HealthMED*, *6*(3), 879-83.
Pourghasem S, Bazarganipour F, Taghavi SA, Kutenaee MA. The effectiveness of inositol and metformin on infertile polycystic ovary syndrome women with resistant to letrozole. Arch Gynecol Obstet. 2019 Apr;299(4):1193-1199. doi: 10.1007/s00404-019-05064-5. Epub 2019 Feb 5. PMID: 30847561.
Ray Banerjee P, Ray A, Chakraborti PS. Comparison of efficacy of letrozole and clomiphene citrate in ovulation induction in Indian women with polycystic ovarian syndrome Archives Gynecology and Obstetrics (2012) 285:873–877

Roy KK, Baruah J, Singla S, Sharma JB, Singh N, Jain SK, Goyal M. A prospective randomized trial comparing the efficacy of Letrozole and Clomiphene citrate in induction of ovulation in polycystic ovarian syndrome. J Hum Reprod Sci. 2012 Jan;5(1):20-5. doi: 10.4103/0974-1208.97789. PMID: 22870010; PMCID: PMC3409915.
Sohrabvand F, Ansari Sh, Bagheri M. Efficacy of combined metformin-letrozole in comparison with metformin-clomiphene citrate in clomiphene-resistant infertile women with polycystic ovarian disease. Hum Reprod. 2006 Jun;21(6):1432-5. doi: 10.1093/humrep/del020.
Zeinalzadeh, M., Z. Basirat and M. Esmailpour (2010). "Efficacy of letrozole in ovulation induction compared to that of clomiphene citrate in patients with polycystic ovarian syndrome." J Reprod Med 55(1-2): 36-40.

3. STUDY CHARACTERISTICS TABLE FOR INCLUDED STUDIES

Author, year, country	Population/ PCOS criteria/ Setting/ CC sensitivity	Study Design	Intervention N	Intervention description	Comparison N	Comparison description	Follow Up	Outcomes	Pooled in MA?	RoB
Amer 2017, UK	Women aged 18 – 39 years with BMI ≤ 35 kg/m2 and PCOS by Rotterdam, proven patency, CC sensitivity NR	Double blind RCT	79 randomised and analysed Age: 28.3 (4.4) BMI: 27.5 (23.4 - 32.2)	letrozole 2.5 mg/d for 5 days from day 2-4 doubled in the second cycle if no ovulation	80 randomised and analysed Age: 28.1 (4.2) BMI: 27.7 (23.0 - 31.0)	50 mg CC daily for 5 days from day 2-4, double in second cycle if no ovulation. CCR with max dose or no conception after 6 cycles were crossed-over to LET group after 6-week washout	NR	**Primary:** clinical pregnancy (by US gestational sac) rate per participant on primary treatment (before the cross-over). **Secondary:** ovulation, live birth, pregnancy by ovulating participant, pregnancy by strata, mono-ovulation, endometrial development (thickness and grades), pregnancy outcome and pregnancy complications. Other outcomes included pregnancy and live birth rates on secondary and overall (primary and secondary) treatments.	Yes	Low
Atay 2006, Turkey	Women with primary infertility and PCOS with no other known cause of infertility (criteria NR, CC sensitivity NR); history of oligo/amenorrhoea, ovaries with ≥10 cysts 2-10mm diameter + hyperechogenic stroma	RCT	51 randomised and analysed Age: 27.1 ± 0.9 BMI: 26.1 ± 1.9	2.5 mg letrozole daily for 5 days from day 3 of the menstrual cycle	55 randomised and analysed Age: 26.2 ± 1.1 BMI: 25.8 ± 1.8	100 mg CC daily for 5 days from day 3 of the menstrual cycle	Data suggests 1 treatment cycle for each patient	number of mature follicles, endometrial thickness (mm), day of hCG administration, ovulation rate, pregnancy rate, multiple pregnancies	Yes	High
Banerjee Ray, 2012, India	infertile women aged 20 - 35 with PCOS by Rotterdam; CC sensitivity NR; no CC for previous 2 months; Hospital	Comparative phase III open-label RCT	69 randomised and analysed (132 cycles) Age: 28 (19 - 35) BMI: 28.8 (23.2 - 34.6)	Letrozole 2.5mg day 3-7 of menstrual cycle	78 randomised and analysed (156 cycles) Age: 29 (20 - 35) BMI: 28.5 (24.2 - 33.6)	CC 100mg	NR	**Primary:** ovulation rate, average follicular diameter on day 16, number of mature follicles produced by cycle, mean estradiol level on the day of hCG administration, mean endometrial thickness, pregnancy rate **Secondary:** miscarriage rate, live birth rate	Yes	High

Bansal 2021, India	18–35 years with anovulatory infertility; PCOS by Rotterdam; Tertiary care teaching institute	RCT; not double-blinded	45 randomised, 41 analysed Age: 27.1±0.9 BMI: 26.1±1.91	LET, 2.5mg daily (5days)	45 randomised, 39 analysed Age: 26.2±1.1 BMI: 25.8±1.77	CC, 50 mg daily (5days)	3 cycles	**Primary**: ET. **Secondary**: Ovulation rate (free fluid in pouch of Douglas + collapsed follicle on transvaginal US and/or day 21 progesterone of ≥3 ng/mL), monofollicular development, pregnancy rate (detection of urinary hCG >7 days of missed period and/or detection of gestational sac by US), and time to pregnancy assessment.	Yes	High
Bayar 2006, Turkey	**Therapy naïve** women with anovulatory PCOS by Rotterdam; University outpatient clinic	RCT	40 randomised; 38 analysed Age: 32.2 ± 3.9 BMI: NR	2.5 mg/d letrozole, on days 3 to 7 of menstrual cycle	40 randomised; 36 analysed Age: 30.6 ± 4.0 BMI: NR	100 mg/d CC, administered on days 3 to 7 of the menstrual cycle	1-5 cycles	Ovulation rate by cycle, pregnancy rate by cycle, delivery rate by cycle, miscarriage rate, multiple pregnancy rate, endometrial thickness on the day of hCG (mm), N of follicles sized > 15 mm in diameter on the day of hCG, E2 level on the day of hCG (pg/mL), E2 per follicle sized > 15 mm in diameter on the day of hCG (pg/mL)	Yes	Low
Begum 2009, Bangladesh	CCR women with PCOS by Rotterdam who failed to ovulate by 100 mg of CC/day for 5 days in 2 consecutive cycles; private infertility care setting	Non-blinded RCT	32 Age: 25.5 ± 4.0 BMI: 22.7 ± 2.8	7.5 mg of letrozole daily for 5 days starting from day 3 of the cycle	32 Age: 26.1 ± 3.6 BMI: 23.6 ± 3.2	150 mg of CC daily for 5 days starting from day 3 of the cycle	NR	**Primary:** ovulation and pregnancy rate **Secondary:** follicular development by day 16 (mm), serum E2 on day of hCG (pg/mL), endometrial development by day 16 (mm), serum progesterone on day 21 (ng/mL), multiple pregnancies, OHSS cases.	Yes	Mod
Ganesh, 2009, India	Women with PCOS by Rotterdam who had previously failed to conceive or ovulate with CC and undergoing IUI; tertiary infertility care unit	Single blind RCT	**LET:** 372 analysed Age: 30.3 ± 4.9	**LET**: letrozole, 5 mg/day orally given for 5 days from cycle days 3 - 7	**CC + FSH:** 669 analysed Age: 30.4 ± 5.2 BMI: 24.8 ± 4.1	**CC + FSH:** clomiphene citrate, 100 mg/day orally given for 5 days from cycle days 3 - 7 + 75 or 100 IU rFSH during cycle days 3 and 8	NR	**Primary**: ovulation rate, cancellation rate, miscarriage rate and clinical pregnancy rate **Secondary**: OHSS rate and multiple pregnancy rate.	No	Mod*

			BMI: 24.5 ± 3.8		**FSH**: 346 analysed Age: 30.8 ± 4.6 BMI: 24.1 ± 3.4	**FSH**: rFSH 75IU/100IU from day 2 until the day of hCG administration				
Legro 2014, USA	Women with PCOS by Rotterdam; CC sensitivity NR	Multi-centre double blind RCT	374 (1352 cycles) Age: 29 ± 5 BMI: 35 ± 10	5 mg/day progestin for 10 days to induce bleed, then letrozole (2.5 mg daily) was given from cycle day 3 for 5 days. Maximum dose 7.5 mg/d of letrozole given for 5 days.	376 (1425 cycles) Age: 28 ± 4 BMI: 35 ± 9	5 mg/day progestin for 10 days to induce bleed, then CC (50 mg daily) was given from cycle day 3 for 5 days. Dose was increased in subsequent cycles for nonresponse or poor ovulatory response. Maximum dose of CC 150 mg/d given for 5 days.	Up to 5 cycles	Live birth, ovulation rate, clinical pregnancy rate, miscarriage rate, multiple pregnancy rate	Yes	Low
Liu, 2017, China	Infertile women aged 20-35, BMI≤35; normal patency; PCOS by Rotterdam; Hospital outpatient dept.; CC sensitivity mixed (some CCR)	RCT; blinding NR	**LET**: 67 randomised, 62 analysed; Age: 27.0 ± 3.0 BMI: 20.8 (19.1, 22.3) **LET + MET**: 67 randomised, 57analysed Age: 27.2 ± 3.3 BMI: 21.6 (19.2, 23.6)	**LET**: letrozole 5mg/d (5days) **LET + MET**: letrozole 5mg/d (5 days) + MET 1000–1500 mg/d	**CC**: 67 randomised, 63 analysed; Age: 26.8 ± 3.1 BMI: 21.1 (19.9, 22.8) **CC + MET**: 67 randomised, 58 analysed Age: 27.2 ± 2.8 BMI: 21.4 (19.8, 23.6)	**CC**: CC 50mg/d (5 days) **CC + MET**: CC, 50 mg daily (5days) + MET 1000–1500 mg/d	2 cycles	Ovulation rate, clinical pregnancy rate, and pregnancy outcome (abortion, premature delivery, and live birth)	Yes	High
Nazik 2012, Turkey	Infertile women with PCOS by Rotterdam; LET group CCR; CC group Treatment	Partly randomised trial	31 randomised and analysed (40 cycles)	Letrozole 2.5mg/day from day 3 -7	33 randomised and analysed (40 cycles)	All patients with oligomenorrhoea given 6 days of medroxyprogest-erone acetate to induce	NR	**Primary Outcomes:** ovulation rate and pregnancy rate **Secondary Outcomes:** ovarian hyperstimulation syndrome rate, miscarriage	Yes	High

	naïve; infertility polyclinic of University		Age: 25.6 ± 4.5 BMI: 24.7 ± 3.6		Age: 27.8 ± 6.2 BMI: 24.9 ± 4.8	withdrawal bleed, then CC 100mg/day from day 3-7		rate, multiple pregnancy rate, number of follicles on day of hCG (≥ 17 mm), E2 (pg/mL) on hCG day, endometrial thickness (mm), other side effects		
Pourghasem, 2019, Iran	Infertile women aged 15–38 years old; PCOS by Rotterdam; infertility clinic of University; Letrozole resistant (no ovulation at 7.5 mg letrozole)	RCT; not double-blind	**LET + folic acid**: 62 randomised, 50 analysed	Letrozole 7.5 mg per day from the third day of menstruation for 5 days; + folic acid 200 µg	**LET + MET + folic acid**: 62 randomised, 50 analysed; **LET + Inositol + folic acid:** 62 randomised, 50 analysed	**LET + MET + folic acid:** Letrozole 7.5 mg/d + Metformin 1500 mg/d + 200 µg folic acid **LET + Inositol + folic acid:** Letrozole 7.5 mg/d + Inositol 2g + 200 µg folic acid twice daily for 3 months.	3 cycles	Primary outcomes were ovarian function (presence or absence of a mature follicle ≥17 mm seen by transvaginal US) during 12–16 menstrual cycles; and clinical pregnancy (presence of gestational sac on US 5 weeks after HCG injection).	Yes	High
Roy 2012, India	Women aged 20 - 35 with infertility for > 1 year, normal fertility tests (patency, semen, hormone) BMI < 28, and anovulatory PCOS by Rotterdam; CC sensitivity **NR**; Tertiary care hospital	RCT	104 randomised; 98 analysed (294 cycles) Age: 26.1 ± 1.8 BMI: 25.8 ± 2.1	2.5 mg/d letrozole, increasing up to 5 mg/d, from Day 3-7 (5 days) after a 5-day course of 10 mg/ d medroxyprogesterone acetate to induce bleed	108 randomised; 106 analysed (318 cycles) Age: 26.5 ± 1.3 BMI: 25.4 ± 1.6	50 mg/d CC, increasing up to 100 mg/d, from Day 3-7 (5 days) after a 5-day course of 10 mg/ d medroxyprogesterone acetate to induce bleed	3 months	Mean number of follicles, endometrial thickness, ovulatory cycle rate, conception rate, pregnancy outcome, miscarriage rate, multiple pregnancies and OHSS rate	Yes	Low
Sohrabvand, 2006, Iran	**CCF** women (failed to become pregnant after 3 courses of 150 mg CC) with PCOS; Hospital infertility clinic	Single - blind RCT	30 randomised and analysed Age: 28.2 ± 3.1	metformin 500 mg x 3/d for 6 - 8 weeks. If pregnancy did not occur, 2.5 mg letrozole from cycle days 3 - 7 was given orally.	30 randomised and 29 analysed Age: 29.6 ± 3.5	metformin 500 mg x 3/d for 6 - 8 weeks. If pregnancy did not occur, 100 mg CC from cycle days 3 - 7 was given orally.	2 cycles	Endometrial thickness on day of hCG administration (cm), N of follicles > 18 mm in diameter, Mean total estradiol level on day of hCG administration (pM/L), mean estradiol level by mature follicle (pM/l), regular menses after metformin, adverse effects of metformin,	Yes	Mod*

			BMI: 30.0 ± 4.8		BMI: 30.2 ± 3.9			live birth rate, clinical pregnancy rate, miscarriage rate		
Zeinalzadeh 2010, Iran	Women with primary infertility, documented PCOS by ultrasound, oligomenorrhea, and an increased LH/ FSH ratio (>3), age < 35 years, < 5 years infertility and BMI between 19 and 26. CC sensitivity **NR**	RCT	50 randomised and analysed Age: 23.8±3.6 BMI: 19-26	5 mg/d letrozole within days 3-7 of menstrual cycle for 5 days	57 randomised and analysed Age: 23.1±3.6 BMI: 19-26	100 mg of CC daily within days 3-7 of menstrual cycle for 5 days	NR	Ovulation rate, pregnancy rate, number of follicles > 17mm, OHSS rate, multiple pregnancy rate, endometrial thickness.	Yes	High

CC, clomiphene citrate; CCR, clomiphene citrate resistant (to ovulate); CCF, clomiphene citrate failure (to become pregnant); LET, letrozole; MET, metformin; NR; not reported; OHSS, ovarian hyperstimulation syndrome; IUI, intrauterine insemination; hCG, human chorionic gonadotrophin; LH, luteinizing hormone; FSH, follicle stimulating hormone; MA, meta-analysis; RoB, risk of bias. All age data is in years and BMI is in kg/m^2. *Risk of bias assessment derived from reliable systematic review (e.g. Cochrane or previous review from the guideline evidence team).

4. FINDINGS

Comparisons Included:

- **Comparison 1.** Letrozole vs Clomiphene Citrate
- **Comparison 2.** Letrozole + Metformin vs Clomiphene Citrate + Metformin
- **Comparison 3.** Letrozole vs Letrozole + Metformin
- **Comparison 4.** Letrozole vs Clomiphene Citrate + rFSH vs continuous rFSH
- **Comparison 5.** Letrozole + Metformin vs Clomiphene Citrate
- **Comparison 6.** Letrozole vs Clomiphene Citrate + Metformin

COMPARISON 1. Letrozole vs Clomiphene Citrate

▪ EVIDENCE SUMMARY:

Eleven RCTs compared letrozole with clomiphene citrate, of which six had a high risk of bias (Atay, 2006; Nazik, 2012; Ray, 2012; Zeinalzadeh, 2010; Bansal, 2021; Liu, 2017), one had a moderate risk of bias (Begum, 2009), and four had a low risk of bias (Legro, 2014; Roy, 2012; Amer, 2017; Bayar, 2006). Studies were conducted in the UK, USA, Iran, India, Bangladesh and China.

▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

In meta-analysis, letrozole was superior to clomiphene citrate for ovulation rate (per patient and per cycle); pregnancy rate and clinical pregnancy rate per patient; and live birth rate per patient. Certainty in the evidence is high for live birth rate, and moderate for pregnancy rate, clinical pregnancy rate and ovulation rate, downgraded once for serious risk of bias since the majority of studies included had high to moderate risk of bias.

There were no differences between letrozole and clomiphene citrate for other outcomes including live birth rate per pregnancy, multiple pregnancy rate (per patient or pregnancy); and miscarriage rate (per patient or pregnancy). Certainty in these findings ranged from low to very low due to risk of bias, serious imprecision and serious inconsistency, except for multiple pregnancy rate per patient which was moderate due to 3 of the 5 studies having a high risk of bias. There was no evidence of statistical heterogeneity or publication bias for any of the outcomes.

Outcome or Subgroup	Studies	n	Effect Estimate; OR [95% CI], M-H, random	P	Favours	Certainty
Live birth rate- per patient	6	1449	1.78 [1.40, 2.26]	<0.00001	LET (live birth is higher with LET)	⊕⊕⊕⊕ HIGH
Live birth rate- per pregnancy	4	319	1.43 [0.62, 3.29]	0.4	None	⊕⊕◯◯ LOW
Clinical pregnancy rate- per patient†	8	1668	1.87 [1.50, 2.33]	<0.00001	LET (clinical pregnancy is higher with LET)	⊕⊕⊕◯ MODERATE
Pregnancy rate- per patient*	11	1870	1.83 [1.49, 2.26]	<0.00001	LET (pregnancy is higher with LET)	⊕⊕⊕◯ MODERATE
Ovulation Rate- per patient	8	1697	1.93 [1.35, 2.76]	0.0003	LET (ovulation per patient is higher with LET)	⊕⊕⊕◯ MODERATE
Ovulation Rate- per cycle	1	280	2.32 [1.41, 3.82]	0.0009	LET (ovulation per cycle is higher with LET)	⊕◯◯◯ VERY LOW
Multiple Pregnancy Rate- per patient	7	1394	1.20 [0.48, 2.99]	0.7	None	⊕◯◯◯ VERY LOW
Multiple pregnancy rate- per pregnancy	5	318	0.38 [0.14, 1.04]	0.06	None	⊕⊕◯◯ LOW
Miscarriage rate- per patient	8	1511	0.92 [0.44, 1.91]	0.8	None	⊕◯◯◯ VERY LOW
Miscarriage rate- per pregnancy	6	353	1.00 [0.60, 1.67]	0.9	None	⊕⊕◯◯ LOW

*includes biochemical (or undefined pregnancy rate) as reported in each study; †clinical pregnancy rate is confirmed by ultrasound detection of gestational sac/ fetal heart activity

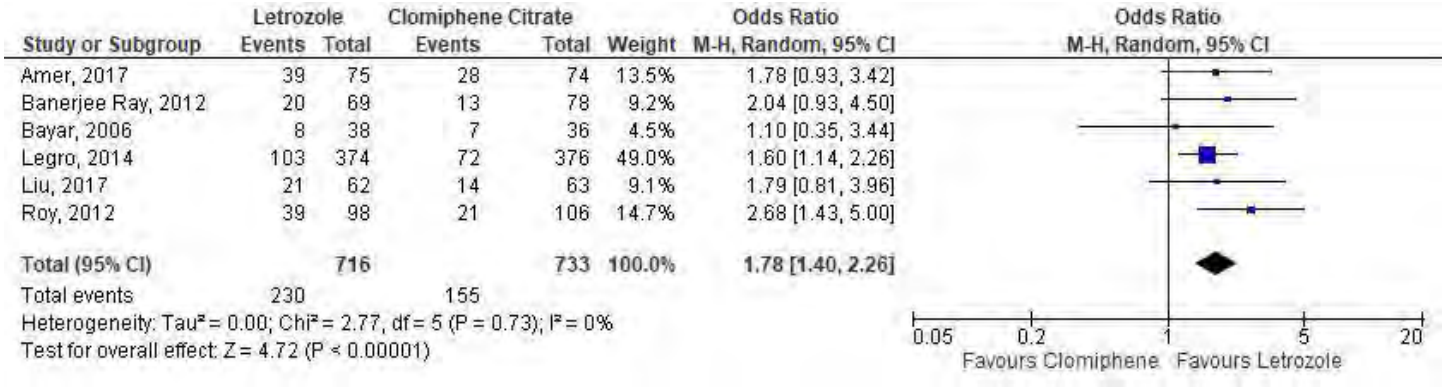
OUTCOME 1.1. Live birth rate – per patient

OUTCOME: Live birth rate - per patient					**OUTCOME TYPE:** Dichotomous				
COMPARISON: Letrozole vs. Clomiphene Citrate									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (LET)**	**N total in intervention/ exposure group (LET)**	**N events in control / comparison group (CC)**	**N total in control/ comparison group (CC)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Amer 2017 (LRB)	NR	Count	Investigator	39	75	28	74	Crude	NA
Banerjee Ray 2012 (HRB)	NR	Count	Investigator	20	69	13	78	Crude	NA
Bayar 2006 (LRB)	TN	Count	Investigator	8	38	7	36	Crude	NA
Legro 2014 (LRB)	NR	Count	Investigator	103	374	72	376	Crude	NA
Liu 2017 (HRB)	Mixed	Count	Investigator	21	62	14	63	Crude	NA
Roy 2012 (LRB)	NR	Count	Investigator	39	98	21	106	Crude	NA

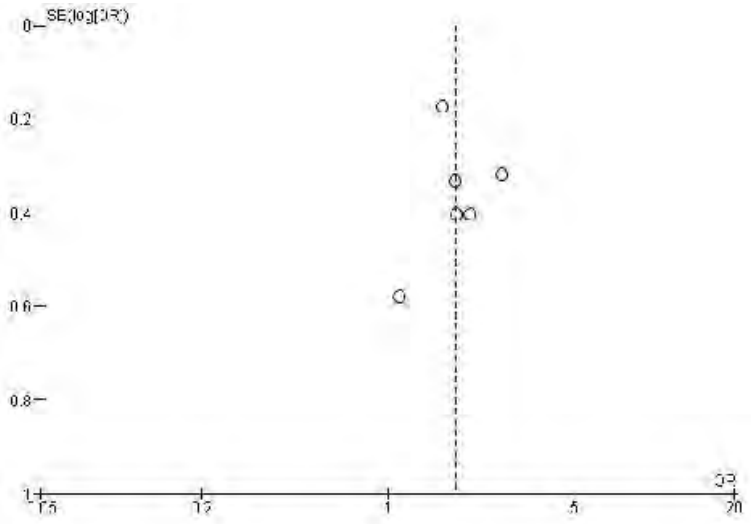
1.1.1. Individual Study Data Table

CCR, Clomiphene citrate resistant; **TN**, therapy naïve; **NR**, not reported; **Mixed**, includes some clomiphene citrate resistant/failure and/or therapy naïve and/or not reported.

1.1.2. Forest Plot of all included RCTs comparing Letrozole and Clomiphene Citrate for live birth rate – per patient

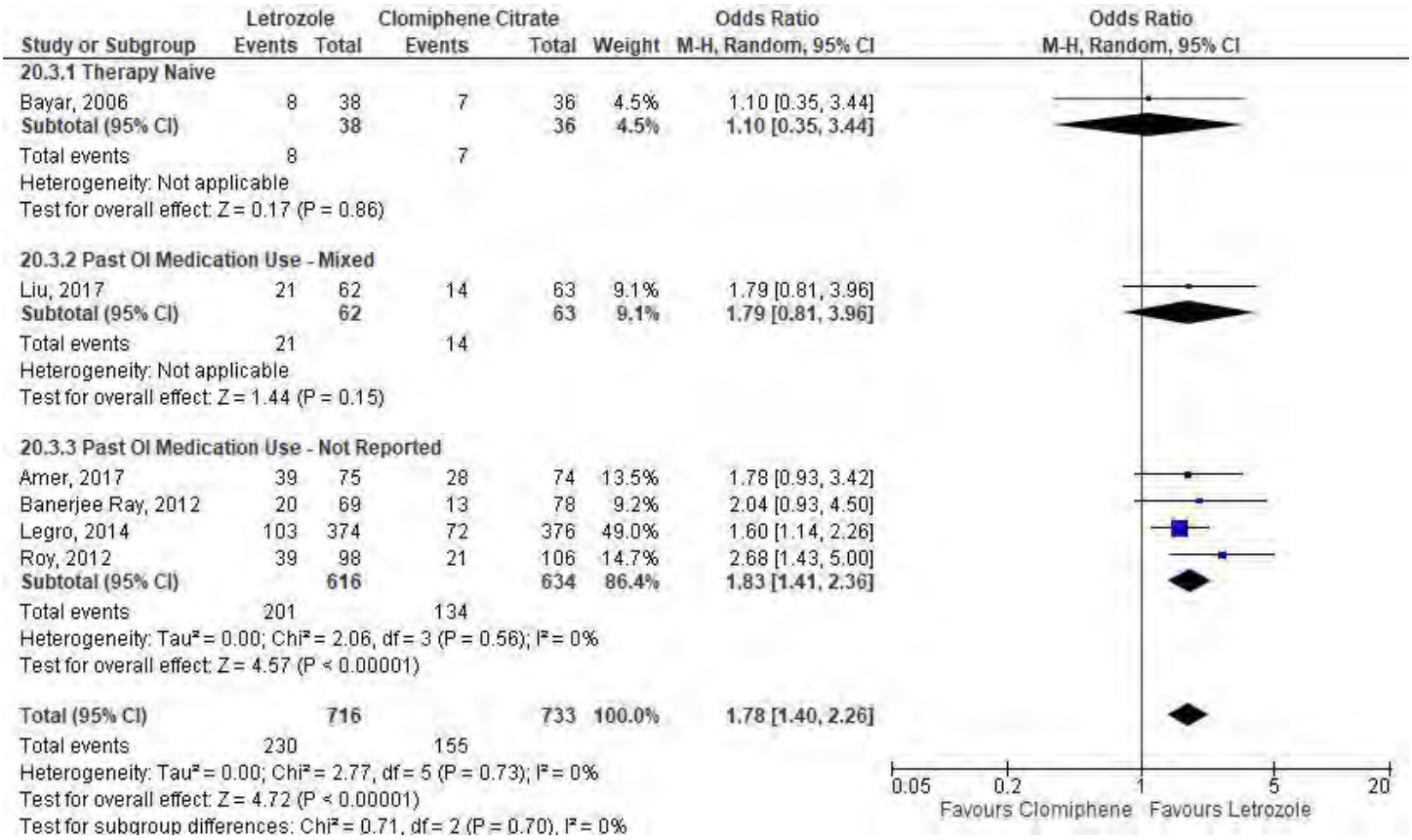


1.1.3. Funnel plot for assessment of publication bias

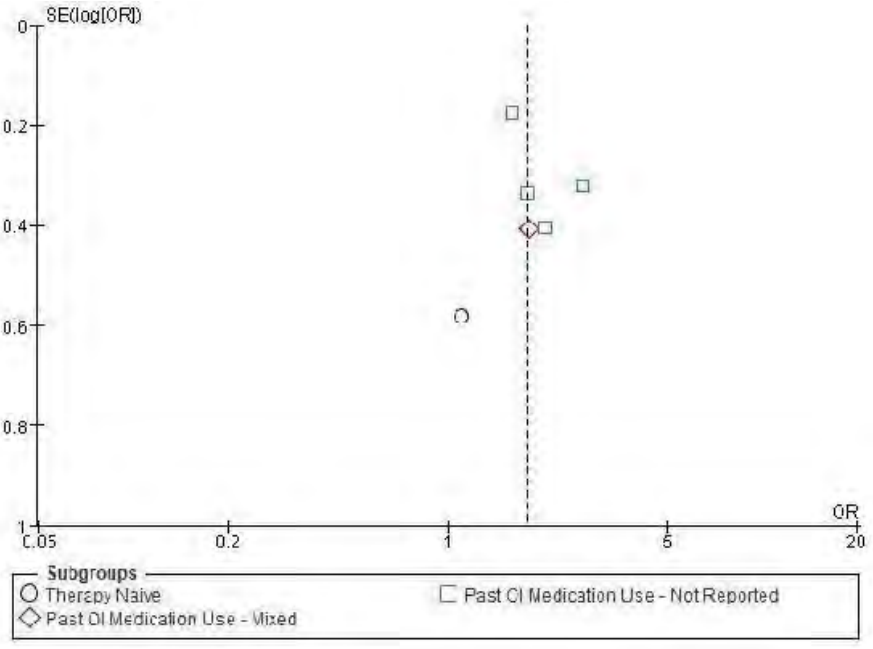


1.1.4. Subgroup analysis: Live birth rate- per patient

1.1.4.1. Forest Plot of all included RCTs comparing Letrozole and Clomiphene Citrate for live birth rate- per patient, sub-grouped by past ovulation induction (OI) medication use



1.1.4.2. Funnel plot for assessment of publication bias for subgroup analysis



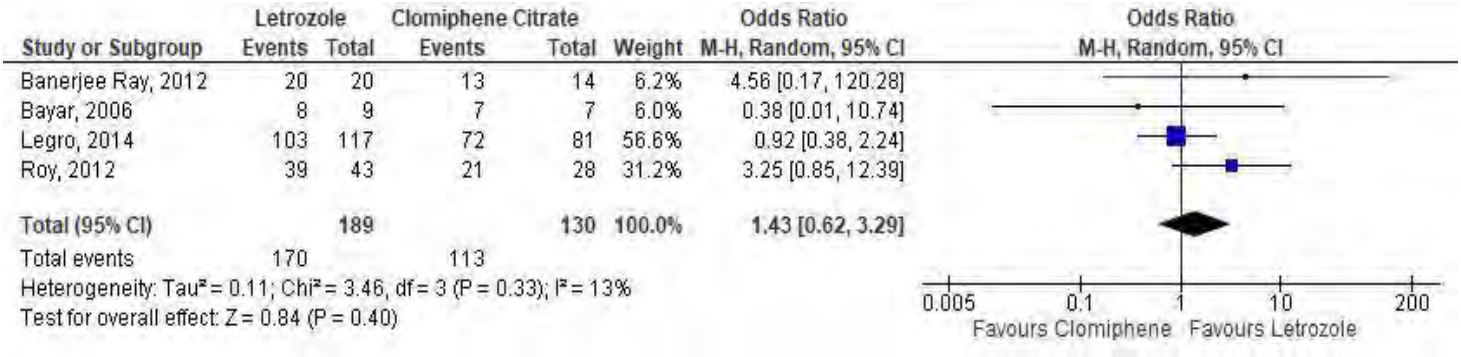
OUTCOME 1.2. Live birth rate – per pregnancy

1.2.1. Individual Study Data Table

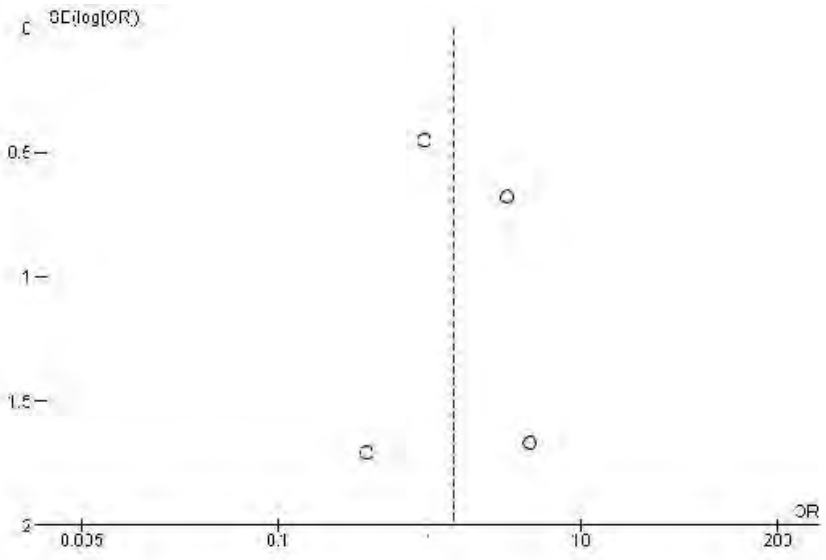
OUTCOME: Live birth rate - per pregnancy						**OUTCOME TYPE:** Dichotomous			
COMPARISON: Letrozole vs. Clomiphene Citrate									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (LET)**	**N total in intervention/ exposure group (LET)**	**N events in control / comparison group (CC)**	**N total in control/ comparison group (CC)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Banerjee Ray 2012 (HRB)	NR	Count	Investigator	20	20	13	14	Crude	NA
Bayar 2006 (LRB)	TN	Count	Investigator	8	9	7	7	Crude	NA
Legro 2014 (LRB)	NR	Count	Investigator	103	117	72	81	Crude	NA
Roy 2012 (LRB)	NR	Count	Investigator	39	43	21	28	Crude	NA

CCR, Clomiphene citrate resistant; **TN**, therapy naïve; **NR**, not reported; **Mixed**, includes some clomiphene citrate resistant/failure and/or therapy naïve and/or not reported.

1.2.2. Forest Plot of all included RCTs comparing Letrozole and Clomiphene Citrate for live birth rate – per pregnancy



1.2.3. Funnel plot for assessment of publication bias



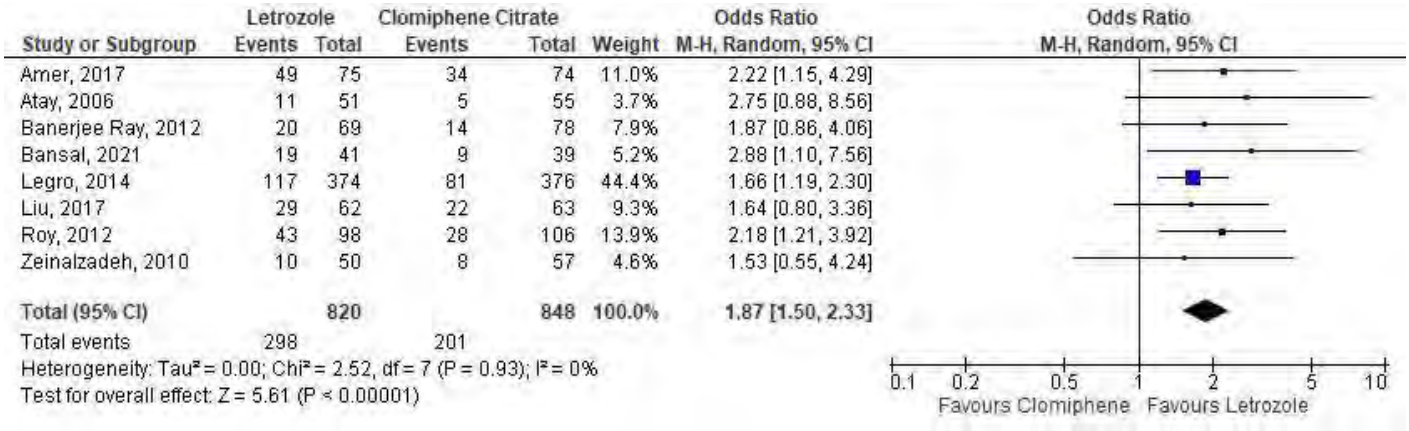
OUTCOME 1.3. Clinical pregnancy rate – per patient (confirmed by gestational sac/ fetal heart activity on ultrasonography)

1.3.1. Individual Study Data Table

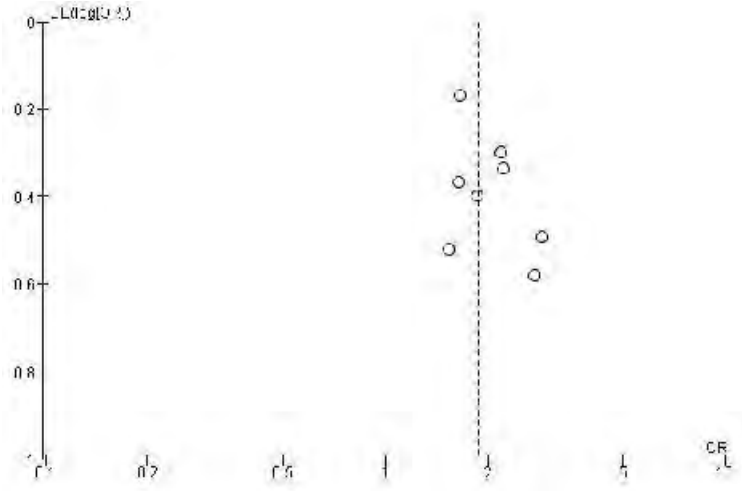
OUTCOME: Pregnancy rate - per patient				**OUTCOME TYPE:** Dichotomous					
COMPARISON: Letrozole vs. Clomiphene Citrate									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (LET)**	**N total in intervention/ exposure group (LET)**	**N events in control / comparison group (CC)**	**N total in control/ comparison group (CC)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Amer 2017 (LRB)	NR	Count	Investigator	49	75	34	74	Crude	NA
Atay 2006 (HRB)	NR	Count	Investigator	11	51	5	55	Crude	NA
Banerjee Ray 2012 (HRB)	NR	Count	Investigator	20	69	14	78	Crude	NA
Bansal 2021 (HRB)	NR	Count	Investigator	19	41	9	39	Crude	NA
Legro 2014 (LRB)	NR	Count	Investigator	117	374	81	376	Crude	NA
Liu 2017 (HRB)	Mixed	Count	Investigator	29	62	22	63	Crude	NA
Roy 2012 (LRB)	NR	Count	Investigator	43	98	28	106	Crude	NA
Zeinalzadeh 2010 (HRB)	NR	Count	Investigator	10	50	8	57	Crude	NA

NR, not reported; **Mixed**, includes clomiphene citrate resistant/failure and therapy naïve and/or not reported; **OI**, ovulation induction

1.3.2. Forest Plot of all included RCTs comparing Letrozole and Clomiphene Citrate for clinical pregnancy rate- per patient (confirmed by gestational sac/ fetal heart activity)

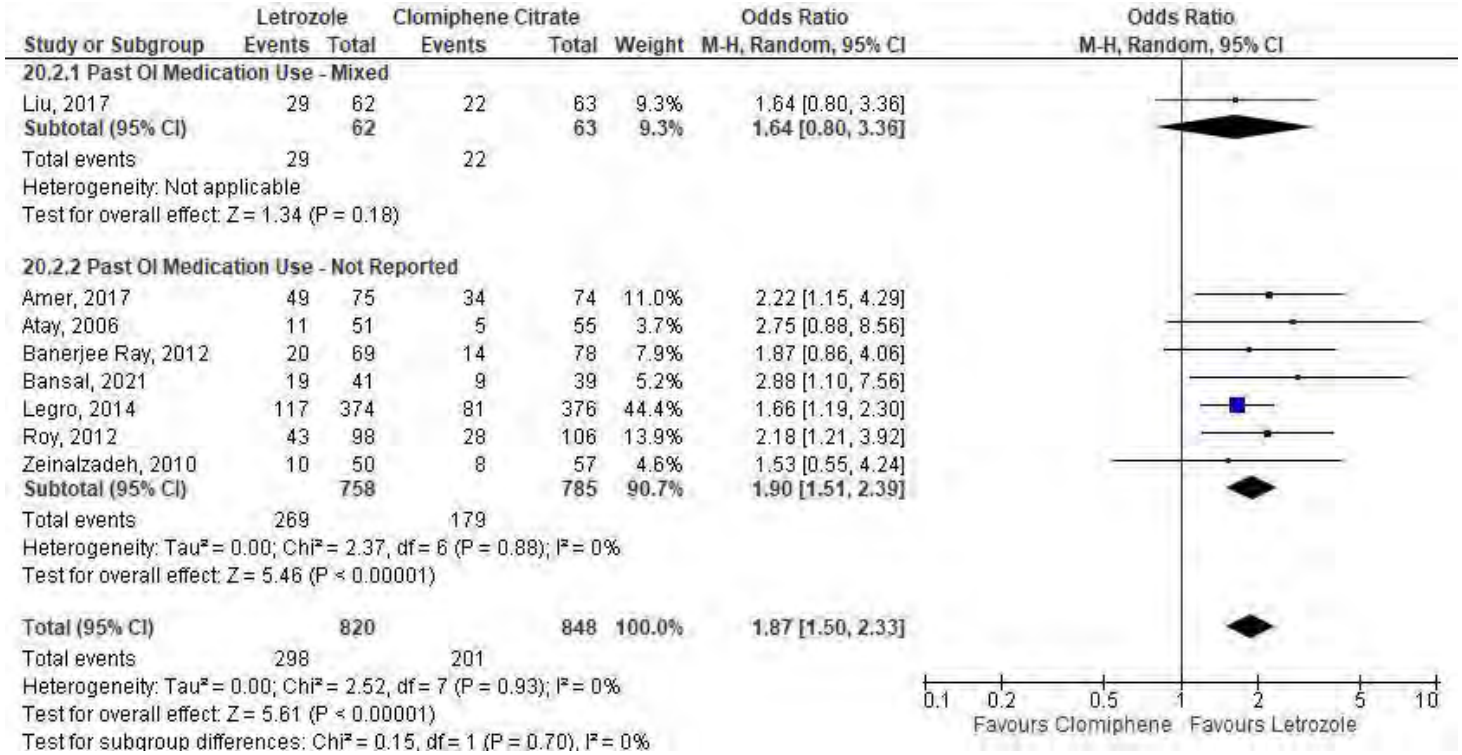


1.3.3. Funnel plot for assessment of publication bias

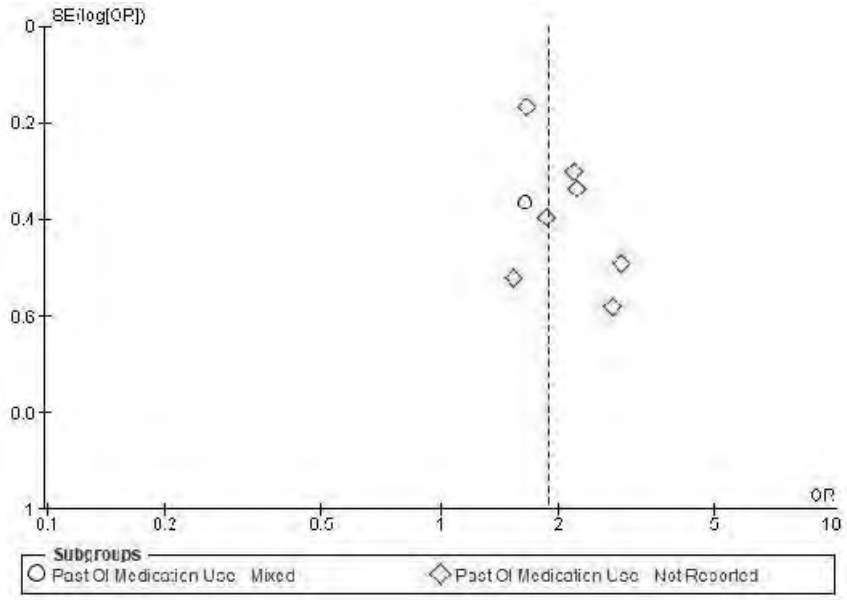


1.3.4. SUBGROUP ANALYSIS: Clinical pregnancy rate-per patient

1.3.4.1. Forest Plot of all included RCTs comparing Letrozole and Clomiphene Citrate for clinical pregnancy rate- per patient, sub-grouped by past ovulation induction (OI) medication use



1.3.4.2. Funnel plot for assessment of publication bias for subgroup analysis



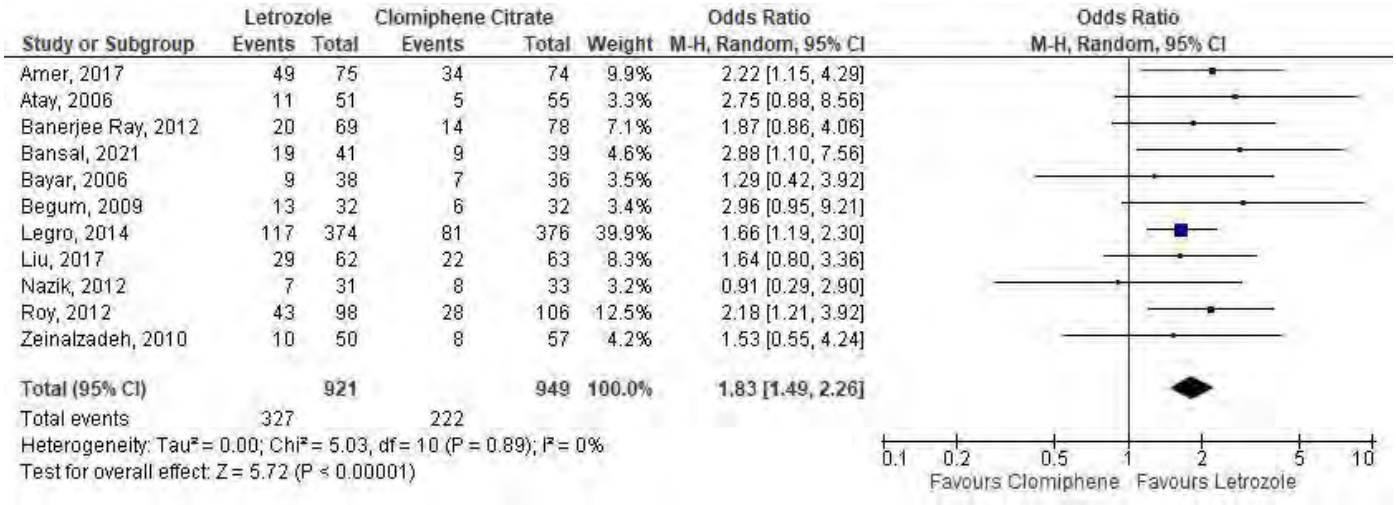
OUTCOME 1.4. Pregnancy rate – per patient

1.4.1. Individual Study Data Table

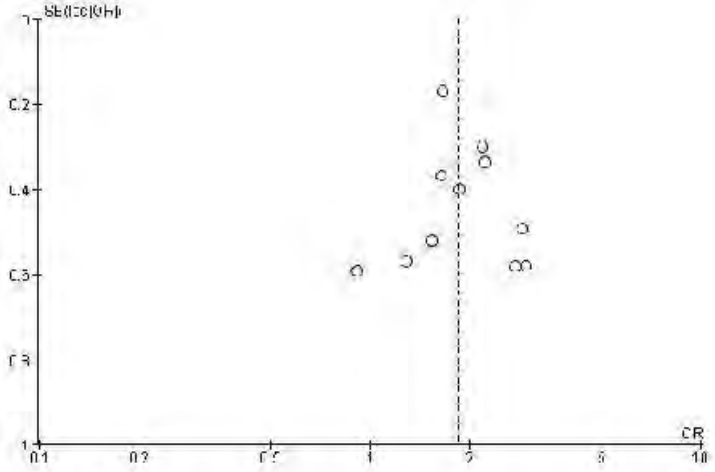
OUTCOME: Pregnancy rate - per patient				OUTCOME TYPE: Dichotomous					
COMPARISON: Letrozole vs. Clomiphene Citrate									
Author, year	Past OI Med Use	Unit of outcome (e.g. g, mg)	Method of measurement	N events in intervention/ exposure group (LET)	N total in intervention/ exposure group (LET)	N events in control / comparison group (CC)	N total in control/ comparison group (CC)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Amer 2017 (LRB)	NR	Count	Investigator	49	75	34	74	Crude	NA
Atay 2006 (HRB)	NR	Count	Investigator	11	51	5	55	Crude	NA
Banerjee Ray 2012 (HRB)	NR	Count	Investigator	20	69	14	78	Crude	NA
Bansal 2021 (HRB)	NR	Count	Investigator	19	41	9	39	Crude	NA
Bayar 2006 (LRB)	TN	Count	Investigator	9	38	7	36	Crude	NA
Begum 2009 (MRB)	CCR	Count	Investigator	13	32	6	32	Crude	NA
Legro 2014 (LRB)	NR	Count	Investigator	117	374	81	376	Crude	NA
Liu 2017 (HRB)	Mixed	Count	Investigator	29	62	22	63	Crude	NA
Nazik 2012 (HRB)	Mixed	Count	Investigator	7	31	8	33	Crude	NA
Roy 2012 (LRB)	NR	Count	Investigator	43	98	28	106	Crude	NA
Zeinalzadeh 2010 (HRB)	NR	Count	Investigator	10	50	8	57	Crude	NA

CCR, Clomiphene citrate resistant; **TN**, therapy naïve; **NR**, not reported; **Mixed**, includes some clomiphene citrate resistant/failure and/or therapy naïve and/or not reported.

1.4.2. Forest Plot of all included RCTs comparing Letrozole and Clomiphene Citrate for pregnancy rate- per patient

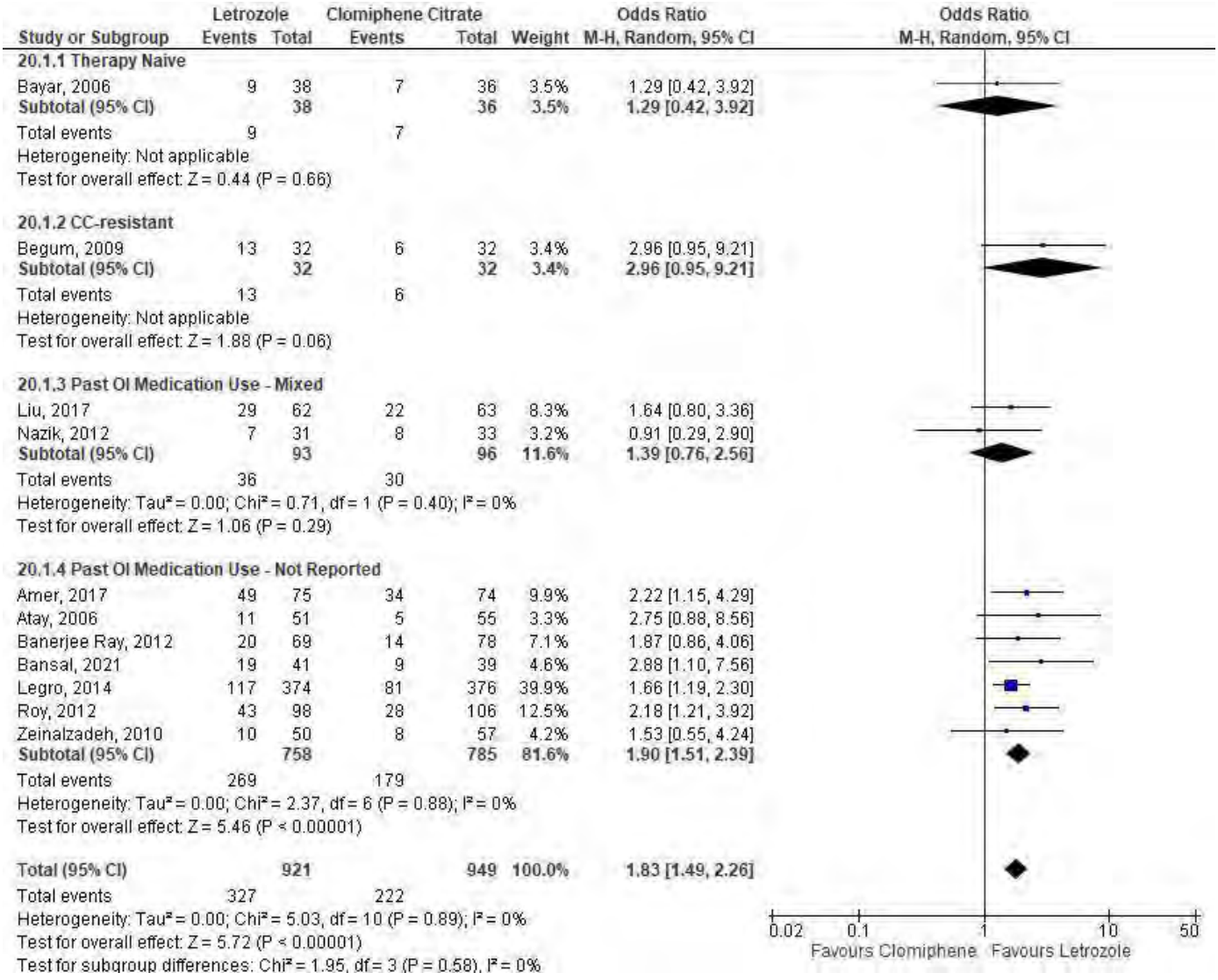


1.4.3. Funnel plot for assessment of publication bias

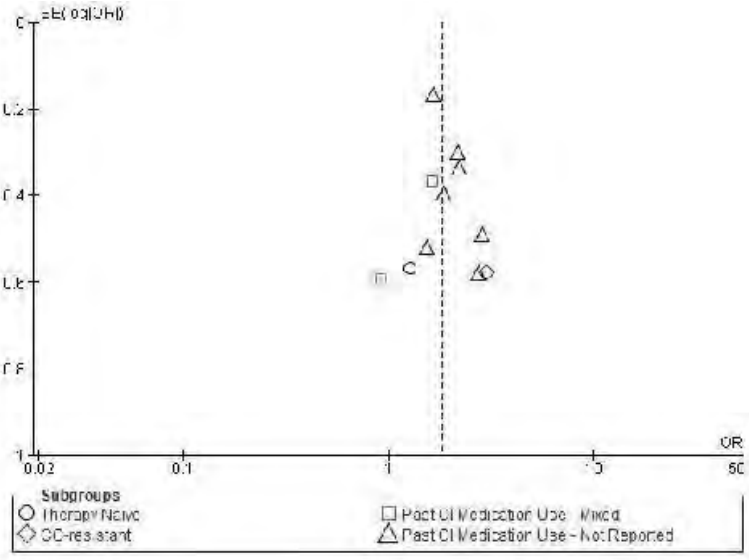


1.4.4. SUBGROUP ANALYSIS: Pregnancy rate-per patient

1.4.4.1. Forest Plot of all included RCTs comparing Letrozole and Clomiphene Citrate for pregnancy rate- per patient, sub-grouped by past ovulation induction (OI) medication use



1.4.4.2. Funnel plot for assessment of publication bias- subgroup analysis: pregnancy rate-per patient



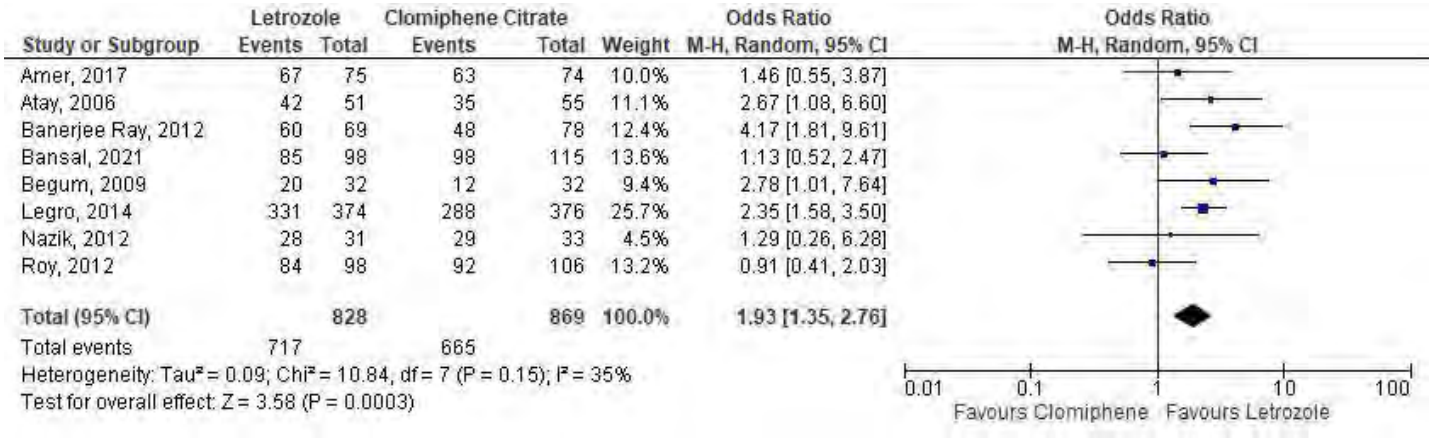
OUTCOME 1.5. Ovulation rate- per patient

1.5.1. Individual Study Data Table

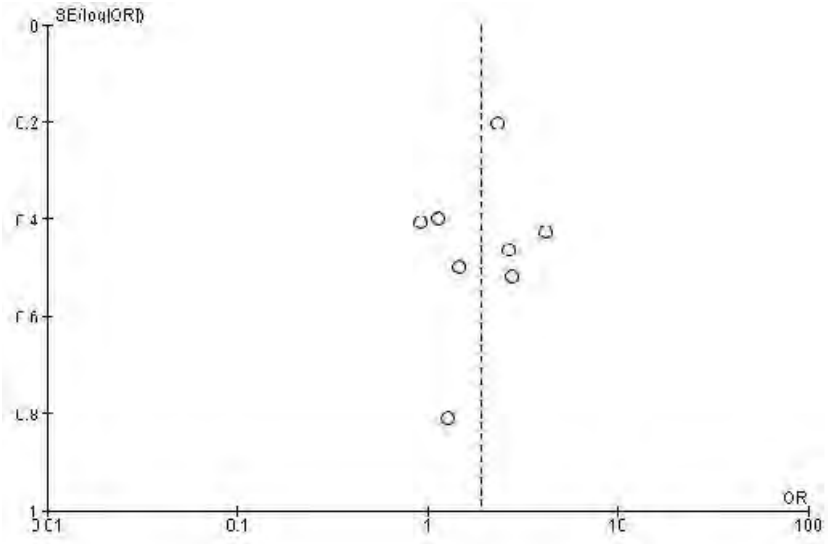
OUTCOME: Ovulation rate - per patient					**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Letrozole vs. Clomiphene Citrate									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (LET)**	**N total in intervention/ exposure group (LET)**	**N events in control / comparison group (CC)**	**N total in control/ comparison group (CC)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Amer 2017 (LRB)	NR	Count	Investigator	67	75	63	74	Crude	NA
Atay 2006 (HRB)	NR	Count	Investigator	42	51	35	55	Crude	NA
Banerjee Ray 2012 (HRB)	NR	Count	Investigator	60	69	48	78	Crude	NA
Bansal 2021 (LRB)	NR	Count	Investigator	85	98	98	115	Crude	NA
Begum 2009 (MRB)	CCR	Count	Investigator	20	32	12	32	crude	NA
Legro 2014 (LRB)	NR	Count	Investigator	331	374	288	376	Crude	NA
Nazik 2012 (HRB)	Mixed	Count	Investigator	28	31	29	33	Crude	NA
Roy 2012 (LRB)	NR	Count	Investigator	84	98	92	106	Crude	NA

CCR, Clomiphene citrate resistant; **TN**, therapy naïve; **NR**, not reported; **Mixed**, includes clomiphene citrate resistant/failure and therapy naïve and/or not reported; **OI**, ovulation induction

1.5.2. Forest Plot of all included RCTs comparing Letrozole and Clomiphene Citrate for ovulation rate- per patient

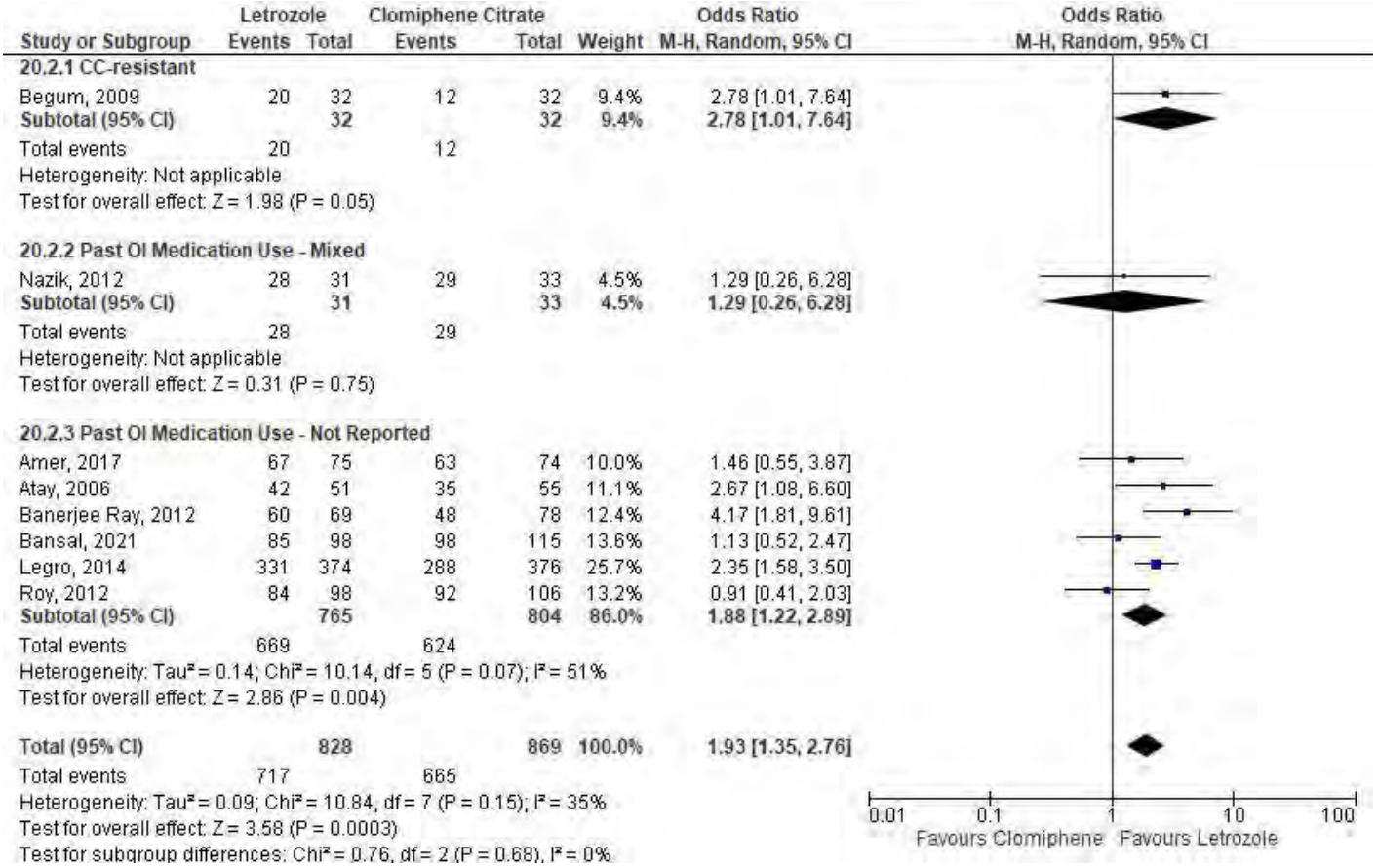


1.5.3. Funnel plot for assessment of publication bias

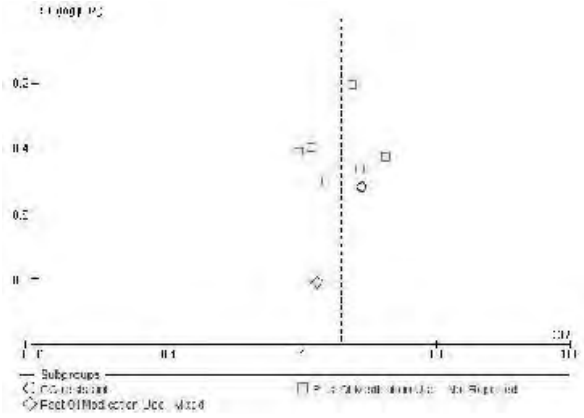


1.5.4. SUBGROUP ANALYSIS: Ovulation rate- per patient

1.5.4.1. Forest Plot of all included RCTs comparing Letrozole and Clomiphene Citrate for ovulation rate- per patient, sub-grouped by past ovulation induction (OI) medication use



1.5.4.2. Funnel plot for assessment of publication bias- subgroup analysis: ovulation rate - per patient



OUTCOME 1.6. Ovulation rate- per cycle

1.6.1. Individual Study Data Table

OUTCOME: Ovulation rate per cycle					OUTCOME TYPE: Dichotomous				
COMPARISON: Clomiphene Citrate vs Letrozole									
Author, year	Past OI Med Use	Unit of outcome (e.g. g, mg)	Method of measurement	N events in intervention/ exposure group (LET)	N total in intervention/ exposure group (LET)	N events in intervention/ exposure group (CC)	N total in intervention/ exposure group (CC)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Liu 2017 (HRB)	Mixed	Count	Investigator	93	130	78	150	Crude	NA

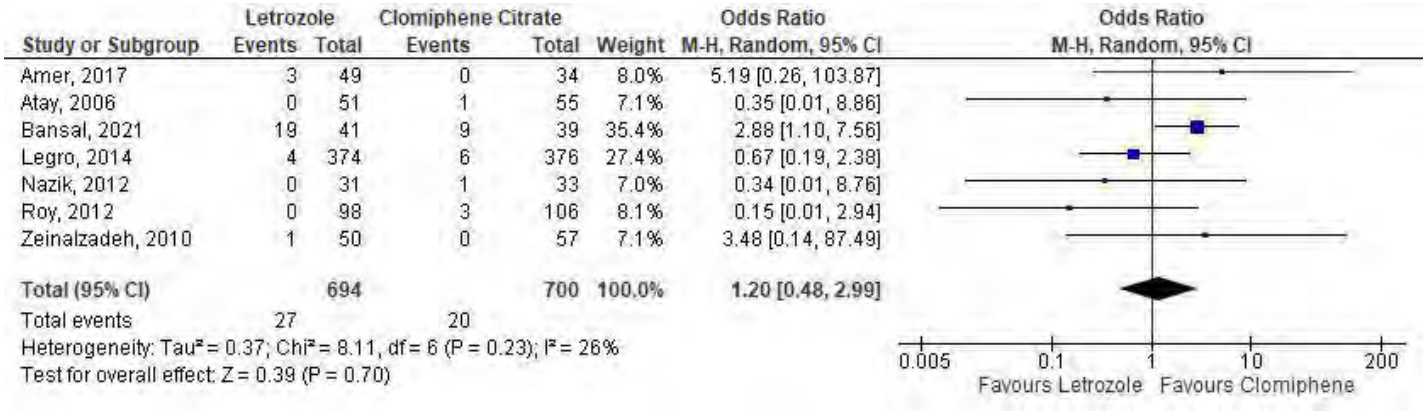
OUTCOME 1.7. Multiple pregnancy rate – per patient

1.7.1. Individual Study Data Table

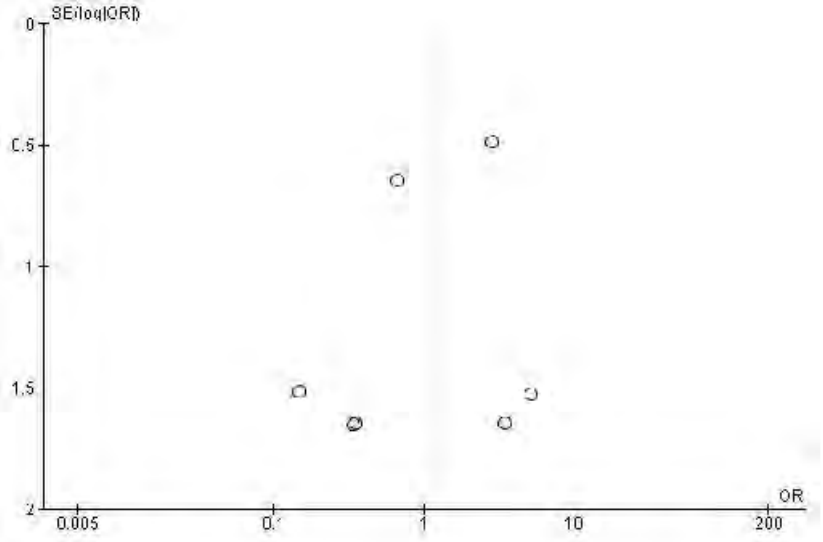
OUTCOME: Multiple pregnancy rate per patient					**OUTCOME TYPE:** Dichotomous				
COMPARISON (if applicable): Letrozole vs. Clomiphene Citrate									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (LET)**	**N total in intervention/ exposure group (LET)**	**N events in control / comparison group (CC)**	**N total in control/ comparison group (CC)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Amer 2017 (LRB)	NR	Count	Investigator	3	49	0	34	Crude	NA
Atay 2006 (HRB)	NR	Count	Investigator	0	51	1	55	Crude	NA
Bansal 2021 (HRB)	NR	Count	Investigator	19	41	9	39	Crude	NA
Legro 2014 (LRB)	NR	Count	Investigator	4	374	6	376	Crude	NA
Nazik 2012 (HRB)	Mixed	Count	Investigator	0	31	1	33	Crude	NA
Roy 2012 (LRB)	NR	Count	Investigator	0	98	3	106	Crude	NA
Zeinalzadeh 2010 (HRB)	NR	Count	Investigator	1	50	0	57	Crude	NA

CCR, Clomiphene citrate resistant; **TN**, therapy naïve; **NR**, not reported; **Mixed**, includes some clomiphene citrate resistant/failure and/or therapy naïve and/or not reported.

1.7.2. Forest Plot of all included RCTs comparing Letrozole and Clomiphene Citrate for multiple pregnancy rate – per patient



1.7.3. Funnel plot for assessment of publication bias



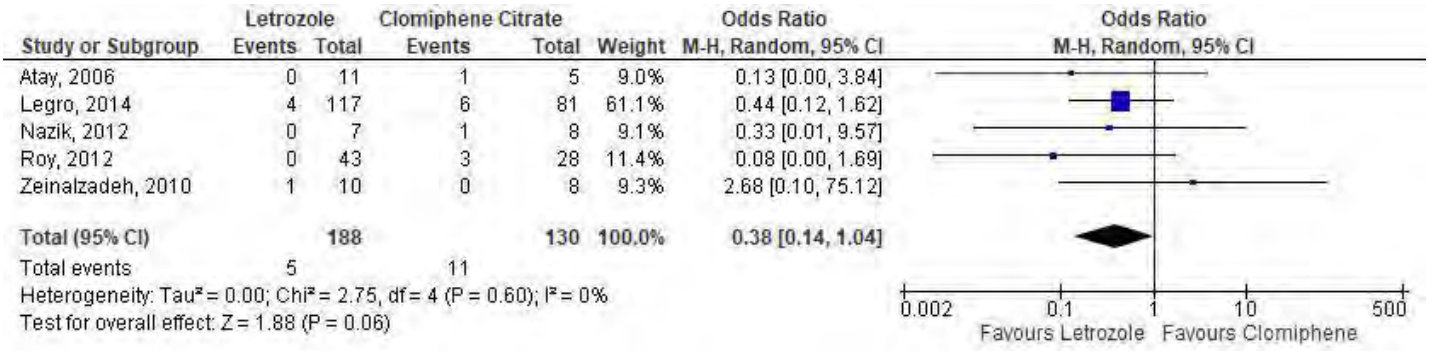
OUTCOME 1.8. Multiple pregnancy rate – per pregnancy

1.8.1. Individual Study Data Table

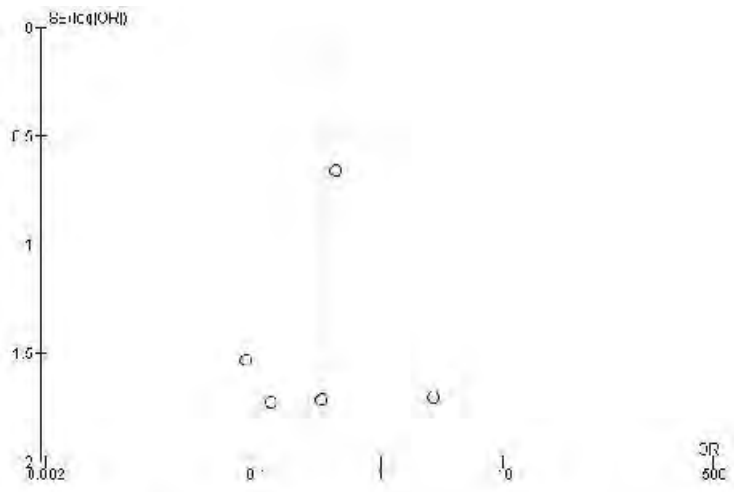
OUTCOME: Multiple pregnancy rate per pregnancy						**OUTCOME TYPE:** Dichotomous			
COMPARISON (if applicable): Letrozole vs. Clomiphene Citrate									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (LET)**	**N total in intervention/ exposure group (LET)**	**N events in control / comparison group (CC)**	**N total in control/ comparison group (CC)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Atay 2006 (HRB)	NR	Count	Investigator	0	11	1	5	Crude	NA
Legro 2014 (LRB)	NR	Count	Investigator	4	117	6	81	Crude	NA
Nazik 2012 (HRB)	Mixed	Count	Investigator	0	7	1	8	Crude	NA
Roy 2012 (LRB)	NR	Count	Investigator	0	43	3	28	Crude	NA
Zeinalzadeh 2010 (HRB)	NR	Count	Investigator	1	10	0	8	Crude	NA

CCR, Clomiphene citrate resistant; **TN**, therapy naïve; **NR**, not reported; **Mixed**, includes some clomiphene citrate resistant/failure and/or therapy naïve and/or not reported.

1.8.2. Forest Plot of all included RCTs comparing Letrozole and Clomiphene Citrate for multiple pregnancy rate – per pregnancy



1.8.3. Funnel plot for assessment of publication bias



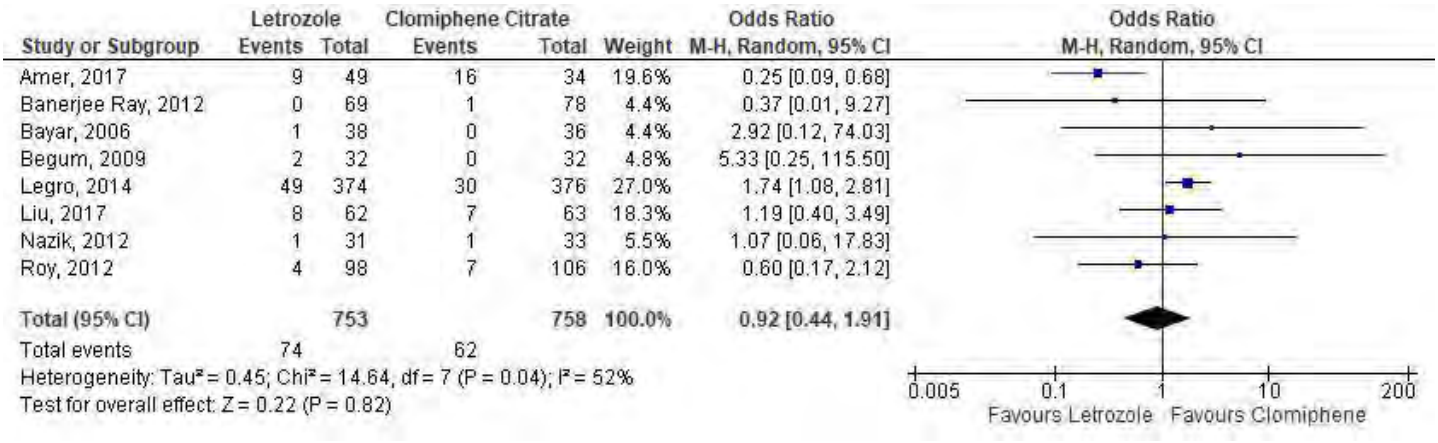
OUTCOME 1.9. Miscarriage rate – per patient

1.9.1. Individual Study Data Table

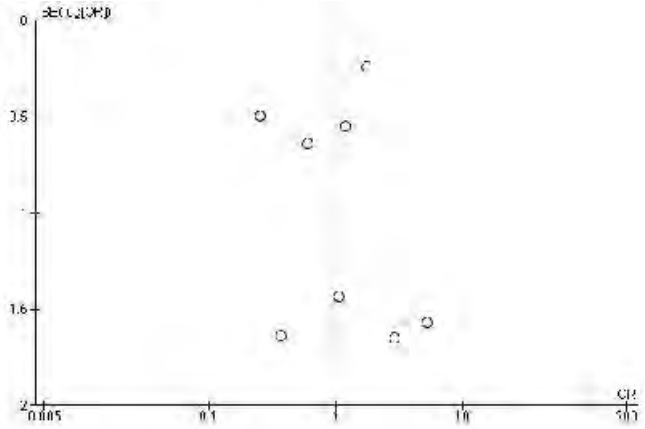
OUTCOME: Miscarriage rate per patient						**OUTCOME TYPE:** Dichotomous			
COMPARISON: Letrozole vs. Clomiphene Citrate									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (LET)**	**N total in intervention/ exposure group (LET)**	**N events in control / comparison group (CC)**	**N total in control/ comparison group (CC)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Amer 2017 (LRB)	NR	Count	Investigator	9	49	16	34	Crude	NA
Banerjee Ray 2012 (HRB)	NR	Count	Investigator	0	69	1	78	Crude	NA
Bayar 2006 (LRB)	TN	Count	Investigator	1	38	0	36	Crude	NA
Begum 2009 (MRB)	CCR	Count	Investigator	2	32	0	32	Crude	NA
Legro 2014 (LRB)	NR	Count	Investigator	49	374	30	376	Crude	NA
Liu 2017 (HRB)	Mixed	Count	Investigator	8	62	7	63	Crude	NA
Nazik 2012 (HRB)	Mixed	Count	Investigator	1	31	1	33	Crude	NA
Roy 2012 (LRB)	NR	Count	Investigator	4	98	7	106	Crude	NA

CCR, Clomiphene citrate resistant; **TN**, therapy naïve; **NR**, not reported; **Mixed**, includes some clomiphene citrate resistant/failure and/or therapy naïve and/or not reported.

1.9.2. Forest Plot of all included RCTs comparing Letrozole and Clomiphene Citrate for miscarriage rate – per patient



1.9.3. Funnel plot for assessment of publication bias



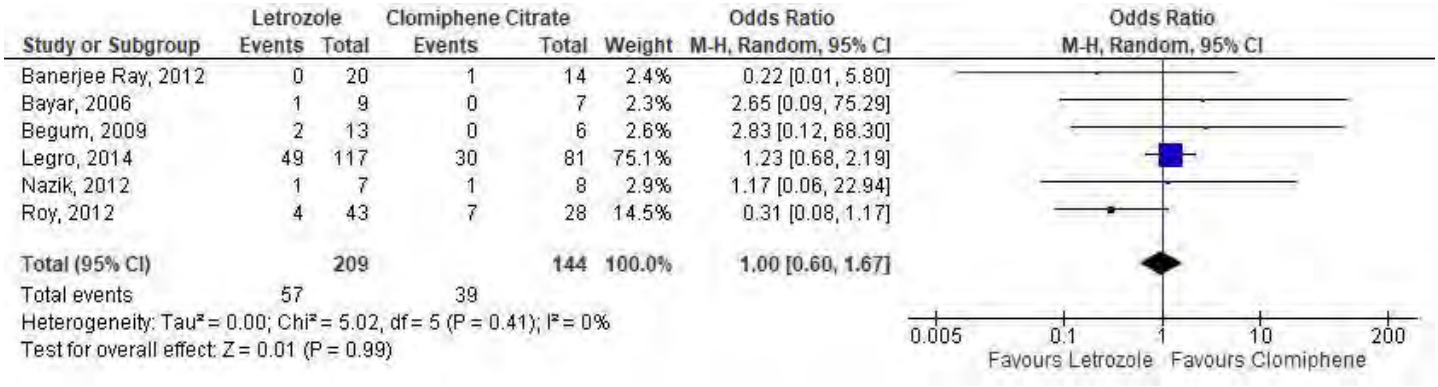
OUTCOME 1.10. Miscarriage rate – per pregnancy

1.10.1. Individual Study Data Table

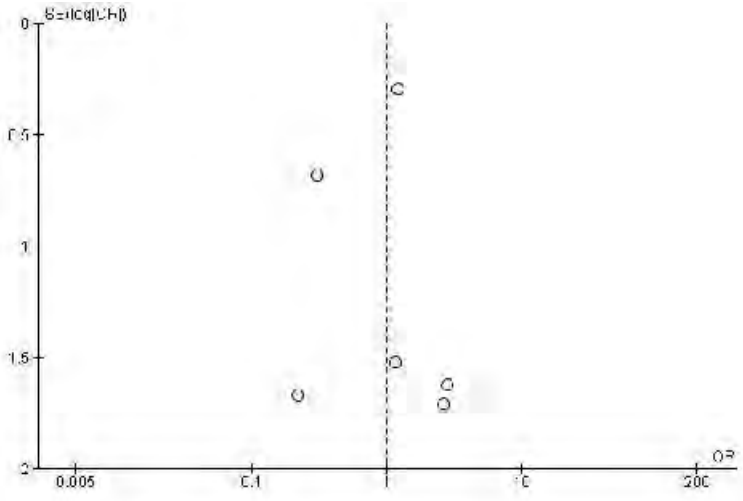
OUTCOME: Miscarriage rate - per pregnancy								**OUTCOME TYPE:** Dichotomous	
COMPARISON: Letrozole vs. Clomiphene Citrate									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (LET)**	**N total in intervention/ exposure group (LET)**	**N events in control / comparison group (CC)**	**N total in control/ comparison group (CC)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Banerjee Ray 2012 (HRB)	NR	count	Investigator	0	20	1	14	Crude	NA
Bayar 2006 (LRB)	TN	Count	Investigator	1	9	0	7	Crude	NA
Begum 2009 (MRB)	CCR	Count	Investigator	2	13	0	6	Crude	NA
Legro 2014 (LRB)	NR	Count	Investigator	49	117	30	81	Crude	NA
Nazik 2012 (HRB)	Mixed	count	Investigator	1	7	1	8	Crude	NA
Roy 2012 (LRB)	NR	Count	Investigator	4	43	7	28	Crude	NA

CCR, Clomiphene citrate resistant; **TN**, therapy naïve; **NR**, not reported; **Mixed**, includes some clomiphene citrate resistant/failure and/or therapy naïve and/or not reported.

1.10.2. Forest Plot of all included RCTs comparing Letrozole and Clomiphene Citrate for miscarriage rate – per pregnancy



1.10.3. Funnel plot for assessment of publication bias



COMPARISON 2. Letrozole + Metformin vs Clomiphene Citrate + Metformin

▪ EVIDENCE SUMMARY:

Two studies compared letrozole + metformin with clomiphene citrate + metformin (Liu, et al. 2017; Sohrabvand, et al. 2006), with relevant outcomes including ovulation rate per cycle and pregnancy and miscarriage rate per patient. Liu et al. (2017) additionally assessed live birth rate per patient, whereas Sohrabvand et al. (2006) reported full term pregnancy per patient. Both studies were moderate (Sohrabvand, et al. 2006) or high (Liu, et al. 2017) risk of bias due to lack of blinding of participants and insufficient information around allocation concealment.

▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

Meta-analysis of these two studies was performed for ovulation rate per cycle and pregnancy and miscarriage rate per patient, with results in the table below. Ovulation and pregnancy rates per patient were greater with letrozole + metformin compared with clomiphene citrate + metformin with odds ratios of 2.02 and 1.90, respectively. Miscarriage rates per patient did not differ between groups. Certainty of the evidence for these three outcomes was low, downgraded once due to high/ moderate risk of bias and once for serious imprecision (small n and wide confidence intervals).

The study by Liu et al. (2017) additionally assessed live birth rate per patient, showing no difference between letrozole + metformin versus clomiphene citrate + metformin groups. Sohrabvand et al. (2006) assessed full term pregnancy per patient and found that letrozole + metformin was more effective than clomiphene citrate + metformin for this outcome, with borderline statistical significance (10 versus 3 full term pregnancies per group, respectively, p=0.045).These results for both these outcomes are of very low certainty given that they are derived from only single studies with moderate to high risk of bias.

Outcome or Subgroup	Studies	n	Effect Estimate; OR [95% CI], M-H, random	P	Favours	Certainty
Live birth rate- per patient	1	115	1.30 [0.60, 2.81]	0.5	None	⊕○○○ VERY LOW
Clinical pregnancy rate- per patient†	2	174	1.90 [1.01, 3.58]	0.0486	**LET + MET** (clinical pregnancy is higher with LET + MET)	⊕⊕○○ LOW
Ovulation rate- per cycle	2	369 (cycles)	2.02 [1.24, 3.30]	0.005	**LET + MET** (ovulation per cycle is higher with LET + MET)	⊕⊕○○ LOW
Miscarriage rate- per patient	2	174	0.98 [0.12, 7.89]	0.9	None	⊕⊕○○ LOW
Full term pregnancy- per patient	1	59	4.74 [1.15, 19.55]	0.03	**LET + MET** (full term pregnancy is higher with LET + MET)	⊕○○○ VERY LOW

†clinical pregnancy rate is confirmed by ultrasound detection of gestational sac/ fetal heart activity

OUTCOME 2.1. Live birth rate – per person

2.1.1. Individual Study Data Table

OUTCOME: Live birth rate – per person						**OUTCOME TYPE:** Dichotomous			
COMPARISON: Letrozole + Metformin vs. **Clomiphene Citrate + Metformin**									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in intervention group (LET + MET)**	**N total in intervention group (LET + MET)**	**N events in control / comparison group (CC+ MET)**	**N total in control/ comparison group (CC +MET)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Liu 2017	Mixed	Count	Investigator	21	57	18	58	Crude	NA

Mixed, includes some clomiphene citrate resistant/failure and/or therapy naïve and/or not reported.

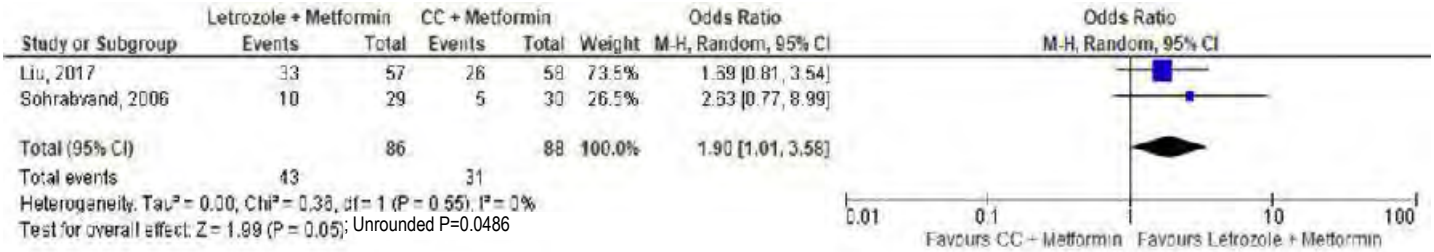
OUTCOME 2.2. Clinical pregnancy rate – per patient

2.2.1. Individual Study Data Table

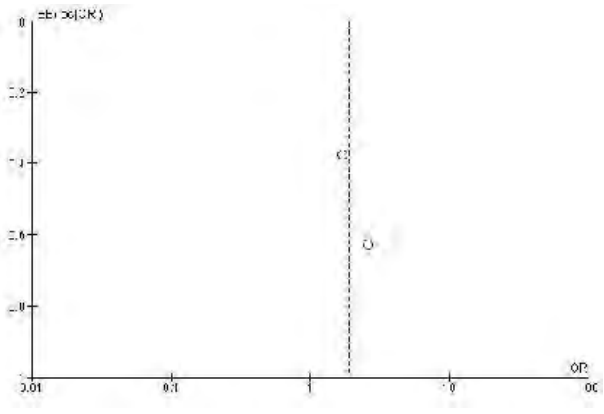
OUTCOME: Clinical pregnancy rate - per patient						**OUTCOME TYPE:** Dichotomous			
COMPARISON: (Letrozole + Metformin) vs. (Clomiphene Citrate + Metformin)									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (LET + MET)**	**N total in intervention/ exposure group (LET + MET)**	**N events in control / comparison group (CC + MET)**	**N total in control/ comparison group (CC+ MET)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Liu 2017	Mixed	Count	Investigator	33	57	26	58	Crude	NA
Sohrabvand 2006	CCF	Count	Investigator	10	29	5	30	Crude	NA

CCF, Clomiphene citrate failure; **Mixed**, includes some clomiphene citrate resistant/failure and/or therapy naïve and/or not reported.

2.2.2. Forest Plot of all included RCTs comparing Letrozole + Metformin and Clomiphene Citrate + Metformin for clinical pregnancy rate – per patient



2.2.3. Funnel plot for assessment of publication bias



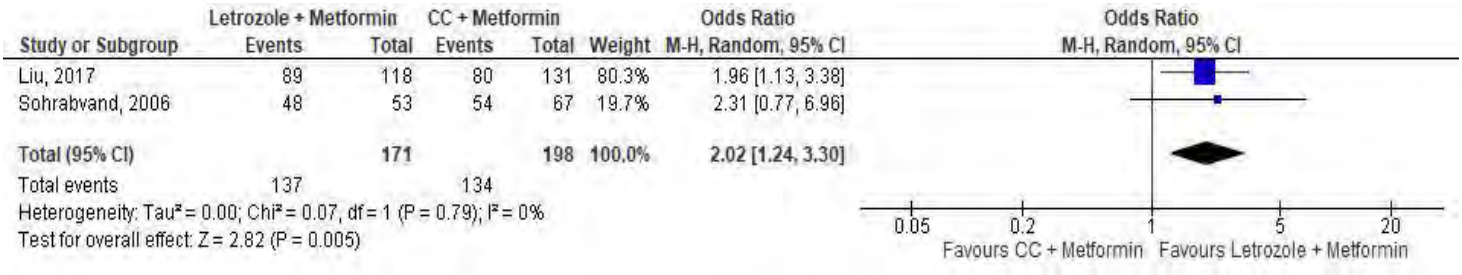
OUTCOME 2.3. Ovulation rate – per cycle

2.3.1. Individual Study Data Table

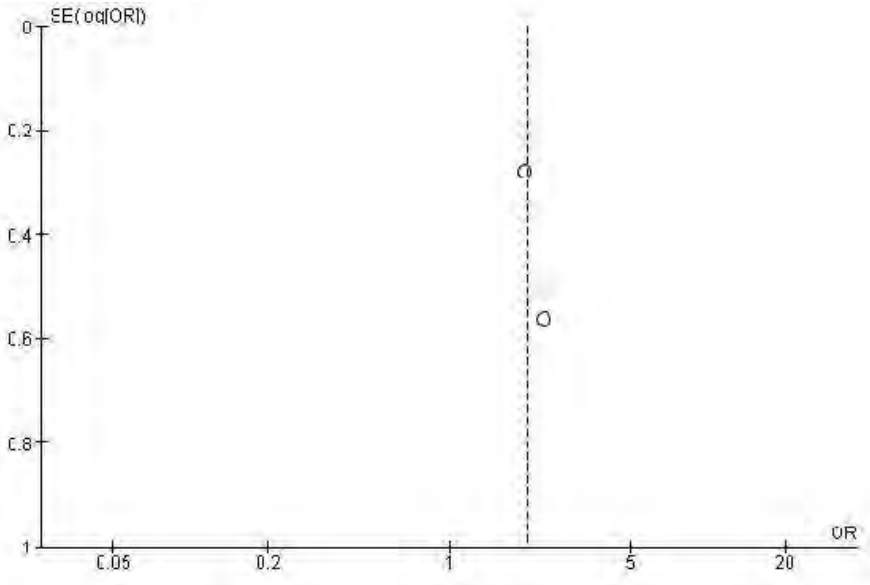
OUTCOME: Ovulation rate - per cycle						**OUTCOME TYPE:** Dichotomous			
COMPARISON: (Letrozole + Metformin) vs. (Clomiphene Citrate + Metformin)									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (LET + MET)**	**N total in intervention/ exposure group (LET + MET)**	**N events in control / comparison group (CC + MET)**	**N total in control/ comparison group (CC + MET)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Liu 2017	Mixed	Count	Investigator	89	118	80	131	Crude	NA
Sohrabvand 2006	CCF	Count	Investigator	48	53 (cycles)	54	67 (cycles)	Crude	NA

CCF, Clomiphene citrate failure; **Mixed**, includes some clomiphene citrate resistant/failure and/or therapy naïve and/or not reported.

2.3.2. Forest Plot of all included RCTs comparing Letrozole + Metformin and Clomiphene Citrate + Metformin for ovulation rate – per cycle



2.3.4. Funnel plot for assessment of publication bias



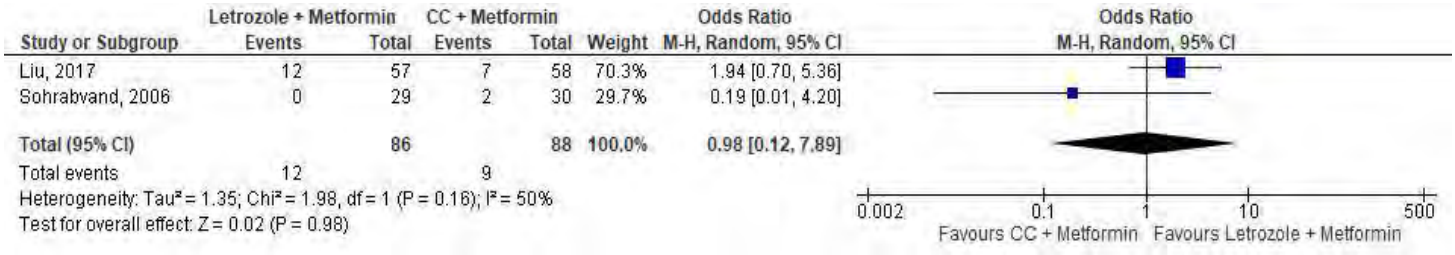
OUTCOME 2.4. Miscarriage rate – per patient

2.4.1. Individual Study Data Table

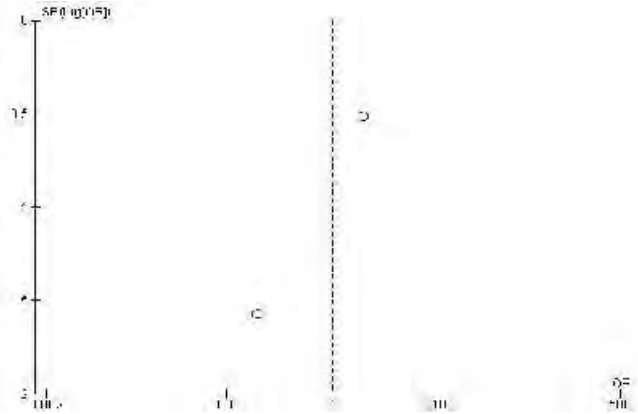
OUTCOME: Miscarriage rate - per person					**OUTCOME TYPE:** Dichotomous				
COMPARISON: (Letrozole + Metformin) vs. (Clomiphene Citrate + Metformin)									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (LET + MET)**	**N total in intervention/ exposure group (LET + MET)**	**N events in control / comparison group (CC + MET)**	**N total in control/ comparison group (CC + MET)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Liu 2017	Mixed	Count	Investigator	12	57	7	58	Crude	NA
Sohrabvand 2006	CCF	Count	Investigator	0	29	2	30	Crude	NA

CCF, Clomiphene citrate failure; **Mixed**, includes some clomiphene citrate resistant/failure and/or therapy naïve and/or not reported.

2.4.2. Forest Plot of all included RCTs comparing Letrozole + Metformin and Clomiphene Citrate + Metformin for miscarriage rate – per patient



2.4.3. Funnel plot for assessment of publication bias



OUTCOME 2.5. Full-term pregnancy – per person

2.5.1. Individual Study Data Table

OUTCOME: Full term pregnancy– per person					**OUTCOME TYPE:** Dichotomous				
COMPARISON: Letrozole + Metformin vs. **Clomiphene Citrate + Metformin**									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in intervention group (LET + MET)**	**N total in intervention group (LET + MET)**	**N events in control / comparison group (CC+ MET)**	**N total in control/ comparison group (CC +MET)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Sohrabvand 2006	CCF	Count	Investigator	10	29	3	30	Crude	NA

CCF, Clomiphene citrate failure

COMPARISON 3. Letrozole vs Letrozole + Metformin

▪ EVIDENCE SUMMARY:

Only two studies compared letrozole alone or combined with metformin. One of the studies performed in Iran (Pourghasem, et al. 2019) provided folic acid 200 µg daily (as a placebo) to both the letrozole and letrozole + metformin groups. Reported outcomes of relevance were clinical pregnancy rate per patient and live birth rate per patient. Both studies had a high risk of bias due to issues around lack of blinding and insufficient information about randomisation or allocation concealment. The study by Liu et al. (2017) was conducted in China and had a high dropout rate of 15% in the letrozole + metformin group, with 7.5% drop outs in the letrozole group.

▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

Meta-analysis was only possible for the outcome of clinical pregnancy rate per person, with two studies pooled for this analysis (Liu, et al. 2017; Pourghasem, et al. 2019), showing no difference between letrozole alone or combined with metformin for this outcome. There is very low certainty in this result due to very serious risk of bias, with serious imprecision and serious indirectness.

For the outcomes of ovulation rate per cycle and live birth rate and miscarriage rate per patient, only one study was available. This study by Liu et al. (2017) was conducted in China in 119 women with PCOS (for this comparison) aged 20-35, with a BMI ≤35 kg/m^2 and showed no difference in live birth rate between letrozole alone versus letrozole + metformin (36.8% vs. 33.9%). Ovulation rate per cycle was higher in the letrozole + metformin group than letrozole alone, but this was not significant (89/118 cycles vs 93/130 cycles, $p > .05$). Similarly, miscarriage/ abortion rate per patient was slightly higher in the letrozole + metformin than in the letrozole group, but the difference was not statistically significant (21.1% vs 12.9%, $p > .05$). These results are of very low certainty given that they are derived from a single study with a high risk of bias.

Outcome or Subgroup	Studies	n	Effect Estimate; OR [95% CI], M-H, random	P	Favours	Certainty
Live birth rate- per patient	1	119	0.88 [0.41, 1.86]	0.7	None	⊕◯◯◯ VERY LOW
Clinical pregnancy rate- per patient	2	219	0.69 [0.40, 1.19]	0.2	None	⊕◯◯◯ VERY LOW
Ovulation rate per cycle	1	248	0.82 [0.46, 1.44]	0.5	None	⊕◯◯◯ VERY LOW
Miscarriage rate- per person	1	119	0.56 [0.21, 1.48]	0.2	None	⊕◯◯◯ VERY LOW

OUTCOME 3.1. Live birth rate – per patient

3.1.1. Individual Study Data Table

OUTCOME: Live birth rate – per person					OUTCOME TYPE: Dichotomous				
COMPARISON: Letrozole vs. Letrozole + Metformin									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events intervention group (LET)**	**N total in intervention group (LET)**	**N events in control / comparison group (LET + MET)**	**N total in control/ comparison group (LET + MET)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Liu 2017 (HRB)	Mixed	Count	Investigator	21	62	21	57	Crude	NA

Mixed, includes some clomiphene citrate resistant/failure and/or therapy naïve and/or not reported.

OUTCOME 3.2. Clinical Pregnancy rate – per person

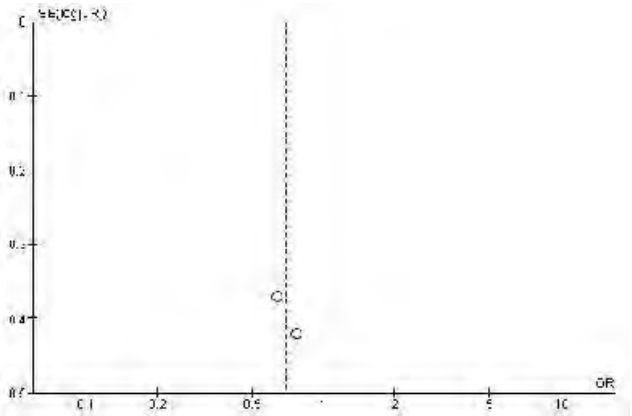
3.2.1. Individual Study Data Table

OUTCOME: Clinical pregnancy rate – per person					OUTCOME TYPE: Dichotomous				
COMPARISON: Letrozole vs. Letrozole + Metformin									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in intervention group (LET)**	**N total in intervention group (LET)**	**N events in control / comparison group (LET + MET)**	**N total in control/ comparison group (LET + MET)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Liu 2017	Mixed	Count	Investigator	29	62	33	57	Crude	NA
Pourghasem 2019	LR	Count	Investigator	16	50	19	50	Crude	NA

LR, letrozole resistant; **Mixed**, includes some clomiphene citrate resistant/failure and/or therapy naïve and/or not reported.

3.2.2. Forest Plot of all included RCTs comparing Letrozole and Letrozole + Metformin for pregnancy rate – per patient

3.2.3. Funnel plot for assessment of publication bias



OUTCOME 3.3. Ovulation rate – per cycle

3.3.1. Individual Study Data Table

OUTCOME: Ovulation rate – per cycle					**OUTCOME TYPE:** Dichotomous				
COMPARISON: Letrozole vs. Letrozole + Metformin									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events intervention group (LET)**	**N total in intervention group (LET)**	**N events in control / comparison group (LET + MET)**	**N total in control/ comparison group (LET + MET)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Liu 2017 (HRB)	Mixed	Count	Investigator	93	130	89	118	Crude	NA

Mixed, includes some clomiphene citrate resistant/failure and/or therapy naïve and/or not reported.

OUTCOME 3.4. Miscarriage rate – per patient

3.4.1. Individual Study Data Table

OUTCOME: Miscarriage rate – per person					**OUTCOME TYPE:** Dichotomous				
COMPARISON: Letrozole vs. Letrozole + Metformin									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events intervention group (LET)**	**N total in intervention group (LET)**	**N events in control / comparison group (LET + MET)**	**N total in control/ comparison group (LET + MET)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Liu 2017 (HRB)	Mixed	Count	Investigator	8	62	12	57	Crude	NA

Mixed, includes some clomiphene citrate resistant/failure and/or therapy naïve and/or not reported.

COMPARISON 4. Letrozole vs Clomiphene Citrate + rFSH (cycle days 3 to 8)

▪ EVIDENCE SUMMARY:

A single study (Ganesh, et al. 2009) in India compared letrozole with clomiphene citrate + gonadotropins (rFSH) in 1387 women with PCOS who had previously failed to conceive or ovulate with CC and were undergoing IUI. Outcomes assessed included clinical pregnancy, ovulation rate, and miscarriage rate per patient. The study was judged as having a moderate risk of bias due to the single-blind design.

▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

Combined clomiphene citrate and FSH was less effective than letrozole in achieving clinical pregnancy or ovulation per patient in this study, with odds ratios of 0.55 and 0.35, respectively. There were no differences between clomiphene citrate + FSH compared with letrozole for miscarriage rates per patient. Certainty in these results is moderate given the narrow confidence intervals and large sample size, downgraded once due to risk of bias given its single-blind design.

OUTCOME 14.1 – 14.3: Clinical pregnancy rate-per patient; ovulation rate- per patient, miscarriage rate-per pregnancy

Outcome or Subgroup	Studies	n	Effect Estimate; OR [95% CI], M-H, random	P	Favours	Certainty
Clinical pregnancy rate- per patient†	1	1041	1.82 [1.32, 2.52]	0.0003	**LET** (clinical pregnancy is lower with CC+ FSH)	⊕⊕⊕◯ Moderate
Ovulation rate - per patient	1	1041	2.90 [2.16, 3.89]	<0.00001	**LET** (ovulation rate is lower with CC + FSH)	⊕⊕⊕◯ Moderate
Miscarriage rate- per pregnancy	1	183	0.80 [0.36, 1.80]	0.6	None	⊕⊕⊕◯ Moderate

†clinical pregnancy rate is confirmed by ultrasound detection of gestational sac/ fetal heart activity

14.1.1 - 14.4.3. Individual Study Data Tables

OUTCOME: LISTED BELOW						**OUTCOME TYPE:** Dichotomous			
COMPARISON: Letrozole vs Clomiphene Citrate + FSH									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in intervention / exposure group (LET)**	**N total in intervention / exposure group (LET)**	**N events in control / comparison group (CC +FSH)**	**N total in control/ comparison group (CC +FSH)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
OUTCOME: Clinical pregnancy rate – per patient						**OUTCOME TYPE:** Dichotomous			
Ganesh 2009 (MRB)	CCR/ CCF	Count	Investigator	87				Crude	NA
OUTCOME: Ovulation rate – per patient						**OUTCOME TYPE:** Dichotomous			
Ganesh 2009 (MRB)	CCR/ CCF	Count	Investigator	295		381		Crude	NA
OUTCOME: Miscarriage rate – per pregnancy						**OUTCOME TYPE:** Dichotomous			
Ganesh 2009 (MRB)	CCR/ CCF	Count	Investigator	12		16		Crude	NA

CCR/CCF, clomiphene citrate-resistant or failure

COMPARISON 5: Letrozole + Metformin versus Clomiphene Citrate

- **EVIDENCE SUMMARY:**

One study compared letrozole + metformin with clomiphene citrate (Liu, et al. 2017), with relevant outcomes including live birth, clinical pregnancy and miscarriage rate per patient, and ovulation rate per cycle. This study, by Liu et al. (2017) was conducted in China with 120 participants and had a high risk of bias due to lack of blinding of participants and insufficient information around allocation concealment.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

Letrozole + metformin was more effective than metformin for clinical pregnancy rate and ovulation rate per cycle. There were no differences between metformin + letrozole versus clomiphene citrate for the outcomes of live birth or miscarriage rate per patient. Given that these results are from a single, relatively small, high-risk of bias study, certainty in the evidence is very low for all outcomes.

Outcome or Subgroup	Studies	n	Effect Estimate; OR [95% CI], M-H, random	P	Favours	Certainty
Live birth rate- per patient	1	120	2.04 [0.92, 4.55]	0.08	None	⊕◯◯◯ VERY LOW
Clinical pregnancy rate- per patient†	1	120	2.56 [1.22, 5.36]	0.01	**LET + MET** (clinical pregnancy is higher with LET + MET)	⊕◯◯◯ VERY LOW
Ovulation rate - per cycle	1	268	2.83 [1.67, 4.80]	0.0001	**LET + MET** (ovulation per cycle is higher with LET + MET)	⊕◯◯◯ VERY LOW
Miscarriage rate- per patient	1	120	2.13 [0.78, 5.87]	0.1	None	⊕◯◯◯ VERY LOW

OUTCOME 5.1 – 5.4: Live birth rate- per patient, clinical pregnancy rate-per patient; ovulation rate- per cycle, miscarriage rate-per patient

5.1.1 - 5.4.1. Individual Study Data Tables

OUTCOME: LISTED BELOW						**OUTCOME TYPE:** Dichotomous			
COMPARISON: Letrozole + Metformin vs Clomiphene Citrate									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in control / comparison group (LET + MET)**	**N total in control/ comparison group (LET+ MET)**	**N events in control / comparison group (CC)**	**N total in control/ comparison group (CC)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
OUTCOME: Live birth rate – per patient									
Liu 2017 (HRB)	Mixed	Count	Investigator	21		14		Crude	NA
OUTCOME: Clinical pregnancy rate – per patient						**OUTCOME TYPE:** Dichotomous			
Liu 2017 (HRB)	Mixed	Count	Investigator	33		22		Crude	NA
OUTCOME: Ovulation rate – per cycle						**OUTCOME TYPE:** Dichotomous			
Liu 2017 (HRB)	Mixed	Count	Investigator	89		78		Crude	NA
OUTCOME: Miscarriage rate – per patient						**OUTCOME TYPE:** Dichotomous			
Liu 2017 (HRB)	Mixed	Count	Investigator	12		7		Crude	NA

COMPARISON 6: Letrozole versus Clomiphene Citrate + Metformin

▪ EVIDENCE SUMMARY:

One study compared letrozole with clomiphene citrate + metformin (Liu, et al. 2017), with relevant outcomes including live birth, clinical pregnancy and miscarriage rate per patient, and ovulation rate per cycle. This study, by Liu et al. (2017) was conducted in China with 120 participants and had a high risk of bias due to lack of blinding of participants and insufficient information around allocation concealment.

▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

There were no differences between letrozole versus clomiphene citrate + metformin for any of the outcomes. Certainty in these results is very low due to being derived from a single, relatively small, high-risk of bias study.

Outcome or Subgroup	Studies	n	Effect Estimate; OR [95% CI], M-H, random	P-value	Favours	Certainty
Live birth rate- per patient	1	120	1.14 [0.53, 2.45]	0.7	None	⊕◯◯◯ VERY LOW
Clinical pregnancy rate- per patient†	1	120	1.08 [0.53, 2.22]	0.8	None	⊕◯◯◯ VERY LOW
Ovulation rate - per cycle	1	261	1.60 [0.95, 2.69]	0.07	None	⊕◯◯◯ VERY LOW
Miscarriage rate- per patient	1	120	1.08 [0.37, 3.19]	0.9	None	⊕◯◯◯ VERY LOW

OUTCOME 11.1 – 11.4: Live birth rate- per patient, clinical pregnancy rate-per patient; ovulation rate- per cycle, miscarriage rate-per patient

6.1.1 - 6.4.1. Individual Study Data Tables

OUTCOME: LISTED BELOW						**OUTCOME TYPE:** Dichotomous			
COMPARISON: Letrozole vs Clomiphene Citrate + Metformin versus									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in intervention / exposure group (LET)**	**N total in intervention / exposure group (LET)**	**N events in control / comparison group (CC +MET)**	**N total in control/ comparison group (CC +MET)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
OUTCOME: Live birth rate – per patient									
Liu 2017 (HRB)	Mixed	Count	Investigator	21		18		Crude	NA
OUTCOME: Clinical pregnancy rate – per patient						**OUTCOME TYPE:** Dichotomous			
Liu 2017 (HRB)	Mixed	Count	Investigator	29		26		Crude	NA
OUTCOME: Ovulation rate – per cycle						**OUTCOME TYPE:** Dichotomous			
Liu 2017 (HRB)	Mixed	Count	Investigator	93		80		Crude	NA
OUTCOME: Miscarriage rate – per patient						**OUTCOME TYPE:** Dichotomous			
Liu 2017 (HRB)	Mixed	Count	Investigator	8		7		Crude	NA

5. GRADE ASSESSMENTS AND EVIDENCE PROFILE

COMPARISON 1: Letrozole vs. Clomiphene Citrate												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	LET	CC	Effect, random OR [95% CI]	Favours	Certainty	Importance
Outcome: Live birth rate - per patient												
6	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	230/ 716 (32.1%)	155/ 733 (21.1%)	1.78 [1.40, 2.26]	**LET** (live birth rate is higher with LET)	⊕⊕⊕⊕ HIGH	CRITICAL
Outcome: Clinical pregnancy rate- per patient												
8	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	298/ 820 (36.3%)	201/ 848 (23.7%)	1.87 [1.50, 2.33]	**LET** (clinical pregnancy is higher with LET)	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Multiple pregnancy rate - per patient												
7	RCT	serious[1]	serious[2]	no serious indirectness	serious[3]	none	27/ 694 (3.9%)	20/ 700 (2.9%)	1.20 [0.48, 2.99]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Live birth rate - per pregnancy												
4	RCT	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	170/ 189 (89.9%)	113/ 130 (86.9%)	1.43 [0.62, 3.29]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Pregnancy rate- per patient												
11	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	327/ 921 (35.5%)	222/ 949 (23.4%)	1.83 [1.49, 2.26]	**LET** (pregnancy rate is higher with LET)	⊕⊕⊕◯ MODERATE	IMPORTANT
Outcome: Ovulation rate - per patient												
8	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	717/ 828 (86.6%)	605/ 869 (69.6%)	1.93 [1.35, 2.76]	**LET** (ovulation per patient is higher with LET)	⊕⊕⊕◯ MODERATE	IMPORTANT
Outcome: Ovulation rate - per cycle												
1	RCT	serious[1]	not applicable	not applicable	very serious[4]	none	93/130 (71.5%)	78/150 (52%)	2.32 [1.41, 3.82]	**LET** (ovulation per cycle is higher with LET)	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Multiple pregnancy rate - per pregnancy												
5	RCT	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	5/ 188 (2.7%)	11/ 130 (8.5%)	0.38 [0.14, 1.04]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Miscarriage rate - per patient												
8	RCT	serious[1]	serious[2]	no serious indirectness	serious[3]	none	74/ 753 (9.8%)	62/ 758 (8.2%)	0.92 [0.44, 1.91]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Miscarriage rate - per pregnancy												

6	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	57/ 209 (27.3%)	39/ 144 (27.1%)	1.00 [0.60, 1.67]	No difference	⨁⨁◯◯ LOW	IMPORTANT

[1] Downgraded once due to the majority of studies (half or more) having high or moderate risk of bias
[2] Downgraded once due to inconsistency of direction of effect and/ or variations in effect estimates/ CIs
[3] Downgraded once for imprecision due to wide CIs in more than one study
[4] Downgraded twice due to the evidence being derived from a single small high risk of bias study

COMPARISON 2: Letrozole + Metformin vs. Clomiphene Citrate + Metformin												
	Quality assessment						**No. participants**					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**LET + MET**	**CC + MET**	**Effect, random, OR [95% CI]**	**Favours**	**Certainty**	**Importance**
Outcome: Live birth rate- per patient												
1	RCT	very serious[5]	Not applicable	Not applicable	serious imprecision[6]	none	21 / 57 (36.8%)	18 / 58 (31.0%)	1.30 [0.60, 2.81]	No difference	⨁◯◯◯ VERY LOW	CRITICAL
Outcome: Clinical Pregnancy rate- per patient												
2	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious imprecision[4]	none	43 / 86 (50.0%)	31 / 88 (35.2%)	1.90 [1.01, 3.58]	**LET + MET** (clinical pregnancy is higher with LET + MET)	⨁⨁◯◯ LOW	CRITICAL
Outcome: Ovulation rate- per cycle												
2	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious imprecision[4]	none	137 / 171 (80.1%)	134 / 198 (67.7%)	2.02 [1.24, 3.30]	**LET + MET** (ovulation per cycle is higher with LET + MET)	⨁⨁◯◯ LOW	IMPORTANT
Outcome: Miscarriage rate- per patient												
2	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious imprecision[4]	none	12 / 86 (14.0%)	9 / 88 (10.2%)	0.98 [0.12, 7.89]	No difference	⨁⨁◯◯ LOW	IMPORTANT
Outcome: Full term pregnancy												
1	RCT	serious[1]	Not applicable	Not applicable	very serious imprecision[6]	none	10 / 29 (34.5%)	3 / 30 (10.0%)	4.05 [1.96, 16.94]	**LET + MET** (full term pregnancy is higher with LET + MET)	⨁◯◯◯ VERY LOW	IMPORTANT

Downgraded once as the majority of evidence (half or more) is at moderate or high risk of bias
[2] Downgraded once due to varied confidence intervals
[3] Downgraded once due to varied effect estimates and inconsistent direction of effect
[4] Downgraded once due to imprecision as confidence intervals (CIs) were wide
[5] Downgraded twice due to having a single high risk of bias study
[6] Downgraded once due to having a small number of studies/ participants or twice for having a very small number of participants

COMPARISON 3: Letrozole vs. Letrozole + Metformin												
	Quality assessment						No. participants					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**LET**	**LET + MET**	**Effect, random OR, [95% CI]**	**Favours**	**Certainty**	**Importance**
Outcome: Live birth rate - per patient												
1	RCT	very serious[1]	Not applicable	Not applicable	serious[3]	none	21/62 (36.8%)	21/57 (33.9%)	0.88 [0.41, 1.86]	No difference	⨁◯◯◯ VERY LOW	CRITICAL
Outcome: Clinical Pregnancy rate - per patient												
2	RCT	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	45/112 (40.2%)	52/107 (48.6%)	0.69 [0.40, 1.19]	No difference	⨁◯◯◯ VERY LOW	CRITICAL
Outcome: Ovulation rate - per cycle												
1	RCT	very serious[1]	Not applicable	Not applicable	serious[3]	none	93/130 (71.5%)	89/118 (75.4%)	0.82 [0.46, 1.44]	No difference	⨁◯◯◯ VERY LOW	IMPORTANT
Outcome: Miscarriage rate – per patient												
1	RCT	very serious[1]	Not applicable	Not applicable	serious[3]	none	8/62 (12.9%)	12/57 (21.1%)	0.56 [0.21, 1.48]	No difference	⨁◯◯◯ VERY LOW	IMPORTANT

[1] Downgraded twice due to both studies having high risk of bias or the single study reporting a given outcome having high risk of bias
[2] Downgraded once due to imprecision given the small number of studies and/or participants
[3] Downgraded once due to indirectness since one study included adolescents and provided folic acid whereas the other was in adults and did not provide folic acid

COMPARISON 4: Letrozole versus Clomiphene Citrate + gonadotropins (FSH)												
	Quality assessment						No. participants					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**LET**	**CC + FSH**	**Effect, random , OR [95% CI]**	**Favours**	**Certainty**	**Importance**
Outcome: Clinical pregnancy rate- per patient												
1	RCT	serious[1]	not applicable	not applicable	no serious imprecision	none	87/ 372 (23.4%)	96/ 669 (14.3%)	1.82 [1.32, 2.52]	**LET** (clinical pregnancy is lower with CC + FSH)	⨁⨁⨁◯ MODERATE	CRITICAL
Outcome: Ovulation rate - per patient												
1	RCT	serious[1]	not applicable	not applicable	no serious imprecision	none	295/ 372 (79.3%)	381/ 669 (57.0%)	2.90 [2.16, 3.89]	**LET** (ovulation rate is lower with CC + FSH)	⨁⨁⨁◯ MODERATE	IMPORTANT
Outcome: Miscarriage rate - per pregnancy												
1	RCT	serious[1]	not applicable	not applicable	no serious imprecision	none	12/ 87 (13.8%)	16/ 96 (16.7%)	0.80 [0.36, 1.80]	No difference	⨁⨁⨁◯ MODERATE	IMPORTANT

[1]Downgraded once for risk of bias (despite being a single study, imprecision was not downgraded given the large sample size)

COMPARISON 5: Letrozole + Metformin vs Clomiphene Citrate												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	LET + MET	CC	Effect, random , OR [95% CI]	Favours	Certainty	Importance
Outcome: Live birth rate - per patient												
1	RCT	very serious[1]	not applicable	not applicable	serious[2]	none	21/57 (36.8%)	14/63 (22%)	2.04 [0.92, 4.55]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Clinical pregnancy rate- per patient												
1	RCT	very serious[1]	not applicable	not applicable	serious[2]	none	33/57 (57.9%)	22/63 (34.9%)	2.56 [1.22, 5.36]	LET + MET (clinical pregnancy is higher with LET + MET)	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Ovulation rate - per cycle												
1	RCT	very serious[1]	not applicable	not applicable	serious[2]	none	89/118 (75.4%)	78/150 (52.0%)	2.83 [1.67, 4.80]	LET + MET (ovulation per cycle is higher with LET + MET)	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Miscarriage rate - per patient												
1	RCT	very serious[1]	not applicable	not applicable	serious[2]	none	12/57 (21.1%)	7/63 (11.1%)	2.13 [0.78, 5.87]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT

[1] Downgraded twice due to the evidence being derived from a single high risk of bias study
[2] Downgraded once due to having a small number of studies/ participants

[1] Downgraded twice due to the evidence being derived from a single high risk of bias study

COMPARISON 6: Letrozole vs Clomiphene Citrate + Metformin												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	LET	CC + MET	Effect, random , OR [95% CI]	Favours	Certainty	Importance
Outcome: Live birth rate - per patient												
1	RCT	very serious[1]	not applicable	not applicable	serious[2]	none	21/62 (33.9%)	18/58 (31.0%)	1.14 [0.53, 2.45]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Clinical pregnancy rate- per patient												
1	RCT	very serious[1]	not applicable	not applicable	serious[2]	none	29/62 (46.8%)	26/58 (44.8%)	1.08 [0.53, 2.22]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Ovulation rate - per cycle												
1	RCT	very serious[1]	not applicable	not applicable	serious[2]	none	93/130 (71.5%)	80/131 (61.1%)	1.60 [0.95, 2.69]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Miscarriage rate - per patient												
1	RCT	very serious[1]	not applicable	not applicable	serious[2]	none	8/62 (12.9%)	7/58 (12.1%)	1.08 [0.37, 3.19]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT

[2] Downgraded once due to having a small number of studies/ participants

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 5

Question 5.3.

In women with PCOS, are aromatase inhibitors effective for improving fertility outcomes?

BACKGROUND

Aromatase inhibitors are oral ovulation-inducing drugs that were first proposed as new ovulation-inducing agents in anovulatory women (with an inadequate response to clomiphene citrate) in 2001 (1). The most commonly used aromatase inhibitor in ovulation induction is letrozole (2). Anastrazole is likely less effective than letrozole, given its proven inferiority to clomiphene citrate in industry sponsored studies (3).

The enzyme aromatase is a member of the cytochrome P450 hemoprotein containing enzyme complex super family and catalyses the conversion of androgens to oestrogens, specifically the conversion of testosterone and androstenedione to oestradiol and estrone respectively in the ovary, and likely in other areas including adipose tissue and the hypothalamus. The exact mechanism of aromatase inhibition inducing ovulation is unknown. However, it is generally accepted that aromatase inhibitors inhibit oestrogen biosynthesis, thereby releasing the hypothalamus/pituitary axis from oestrogenic negative feedback and increasing the secretion of FSH by the pituitary (4). This is analogous to the proposed mechanism of clomiphene citrate as a selective oestrogen receptor modulator (SERM). As a result, the ovary receives increased FSH stimulation, allowing for greater follicular growth and development and development of an ovulatory follicle(s) from the antral follicle pool.

The main incentives for the proposal of aromatase inhibitors as ovulation induction agents were to improve pregnancy rates with first line treatments as well as avoid some of the adverse effects of clomiphene citrate including the effects on the endometrium and cervical mucus (5) and the increased risk of multiple pregnancy (6). Clomiphene citrate resistance, defined as failure to ovulation in response to ovulation induction is common and may affect over 25% of women with anovulation treated with clomiphene citrate (7) and clomiphene citrate failure, defined as failure to conceive after ovulation an even larger percentage of women (8). Although there have been data from smaller studies to suggest higher rates of monofollicular ovulation and a thicker endometrium in the luteal phase after ovulation induction with letrozole (6), larger trials to date have not confirmed these findings or the hope for a significantly lower multiple pregnancy rate (9).

Letrozole is typically administered on days 3–7 of the menstrual cycle at doses of 2.5–7.5 mg per day in 2.5mg increments (10). Adverse effects include gastrointestinal disturbances, asthenia, hot flushes, headache and back pain (11). While hot flushes are significantly less common with letrozole and clomiphene, fatigue and dizziness are more common (12). Letrozole has also been given concurrently with clomiphene citrate with one small study reporting improved ovulation versus letrozole alone (13). However, there are limited studies with combination therapy with an aromatase inhibitor.

The potential teratogenic effect of letrozole for infertility treatment was first raised at an American Society for Reproductive Medicine meeting in 2005 where an oral abstract presentation suggested that the use of letrozole for infertility treatment might be associated with a higher risk of congenital cardiac and bone malformations in newborns (14). These results were never confirmed in a peer-reviewed journal but led to a series of black box warnings in various countries to avoid use as an infertility agent. However multiple subsequent case series anomaly (15-19) as well as large multi-centre randomized clinical trials (12, 20) failed to note an increased congenital anomaly rate with letrozole nor significant differences between letrozole and clomiphene citrate with all prevalence of anomalies with letrozole or clomiphene citrate ***under*** 5% (the expected anomaly rate in this population is 5-8% (21). A recent meta-analysis and systematic review documented this low anomaly rate with letrozole and found it comparable with anomaly rates with pregnancies conceived from clomiphene, natural conception or other treatment agents (22).

A network meta-analysis performed in 2017 and updated in 2022 (23, 24) after retracted and ineligible studies were removed supported letrozole as the first line treatment for anovulatory infertility in PCOS. No first line oral therapy was associated with a difference in multiple pregnancy rate.

GRADE EVIDENCE CERTAINTY	
Comparison	**GRADE for critical outcomes**
Comparison 1. Letrozole vs Clomiphene citrate	⊕⊕⊕⊕ HIGH
Comparison 2. Letrozole + Metformin vs Clomiphene citrate + Metformin	⊕◯◯◯ VERY LOW
Comparison 3. Letrozole vs Letrozole + Metformin	⊕◯◯◯ VERY LOW
Comparison 4. Letrozole vs Clomiphene citrate + rFSH vs continuous rFSH	⊕⊕⊕◯ MODERATE
Comparison 5. Letrozole + Metformin vs Clomiphene citrate	⊕◯◯◯ VERY LOW
Comparison 6. Letrozole vs Clomiphene citrate + Metformin	⊕◯◯◯ VERY LOW

COMPARISONS (option versus other option)
COMPARISON 1. Letrozole vs Clomiphene citrate
COMPARISON 2. Letrozole + Metformin vs Clomiphene citrate + Metformin
COMPARISON 3. Letrozole vs Letrozole + Metformin
COMPARISON 4. Letrozole vs Clomiphene citrate + rFSH (cycle days 3 to 8) vs rFSH (cycle days 2 to trigger)
COMPARISON 5: Letrozole + Metformin versus Clomiphene citrate
COMPARISON 6: Letrozole versus Clomiphene citrate + Metformin

Recommendations Framework

EVIDENCE-BASED RECOMMENDATION(S)

EBR: Letrozole should be the first line pharmacological treatment for ovulation induction in infertile anovulatory women with PCOS, with no other infertility factors.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

PRACTICE POINT(S)

The use of letrozole is still off label in many countries.

Where it is not allowed, clinicians should use other ovulation induction agents.

Letrozole should not be given where there is any possibility of a pre-existing pregnancy, though there is no evidence for increased teratogenicity compared to other ovulation induction agents.

RESEARCH RECOMMENDATION

Further adequately powered, well designed, conducted and reported RCTs are needed to compare letrozole versus letrozole combined with metformin, in women with PCOS with anovulatory infertility (preferably therapy naive) and no other infertility factors for reproductive outcomes.

GRADE CONSIDERATIONS

Justifications:

This recommendation was based on the following totality of evidence:

1. International Evidence Based Guidelines 2022 updated evidence summaries on the clinical questions for Aromatase Inhibitors (AIs), metformin (MET) / clomiphene citrate (CC), gonadotrophins (Gns) and laparoscopic ovarian surgery (LOS), but especially the comparisons of:

- Letrozole Vs CC (favours Letrozole)
- CC Vs MET (favours CC)
- Gn’s Vs CC (favours Gn’s in terms of efficacy)

2. Cochrane review on Aromatase Inhibitors 2022 update (incorporated an integrity check list) (25) : especially the comparisons of

- Letrozole Vs CC (favours Letrozole)
- Letrozole V CC with other Ovulation Induction (OI) agents as adjuvants such as MET and Gn's (favours Letrozole)

3. Rui et al BMJ 2022 systematic review and network meta-analysis (incorporated an integrity check list): Letrozole 1st line OI agent (23, 24)

The justification for recommending letrozole as first line therapy is the replication of a similar magnitude of benefit vs clomiphene citrate in multiple studies with a cumulative large sample size (relative to other studies in PCOS or reproductive medicine). There is also a consistency about the benefit across all surrogate outcomes including improved ovulation and clinical pregnancy rates as well as the primary clinical outcome of live birth rates per patient. This is also supported by network meta-analysis comparing the main agents.

Subgroup considerations:

There are insufficient data to recommend whether patients who are drug naïve or clomiphene citrate resistant have varying pregnancy or live birth rates with letrozole therapy. There is evidence of an increased ovulation rate with letrozole in patients with clomiphene citrate resistance compared to those patients taking clomiphene.

Implementation considerations:

Letrozole is available widely as a generic drug and is used extensively for the treatment of breast cancer. The primary concern about implementation of letrozole as first line therapy for anovulatory infertility in women with PCOS are unwarranted concerns about increased teratogenicity based on one published abstract. Sharing the data from published studies and the meta-analysis with countries that have a black box warning may lead to a change of policy. Where it is forbidden, then clomiphene citrate should be the first line therapy.

Monitoring and evaluation considerations:

There should be ongoing monitoring of patients for adverse effects and infants for any teratogenicity in all studies conducted with aromatase inhibitors. These should be reported in any published papers.

Research priorities:

In descending order:

1. Establishing the ideal number of cycles of ovulation induction with letrozole before moving on to other treatments
2. Validation of prediction models to select first line ovulation induction agents and dose
3. Studying combination therapies of aromatase inhibitors with other inexpensive and widely available medications with different mechanisms of action such as metformin, inositol and clomiphene citrate would be helpful
4. Best therapies for drug naïve vs drug resistant/ drug failure patients is another research consideration.

GRADE framework

GRADE DECIDE Interactive Evidence to Decision Framework

EVIDENCE-BASED RECOMMENDATION(S)
Letrozole should be considered the first line pharmacological treatment for ovulation induction in infertile anovulatory women with polycystic ovary syndrome, with no other infertility factors.

- **DESIRABLE EFFECTS**

How substantial are the desirable anticipated effects?

Judgement:

☒ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Clear definitive evidence for first line

- **UNDESIRABLE EFFECTS**

How substantial are the undesirable anticipated effects?

Judgement:

☒ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

While fatigue and dizziness and hot flashes differ between clomiphene citrate and letrozole, it is difficult to assess which side effect profile is more acceptable. Generally, dropout rates are higher in groups taking metformin compared to clomiphene citrate most likely due to GI side effects.

- **CERTAINTY OF THE EVIDENCE**

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☐ Very low	☐ Low	☒ Moderate	☒ High

Moderate to high for the key comparisons that informed this recommendation

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Based on extensive evidence synthesis

- **VALUES**

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☐ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☐ Probably no important uncertainty or variability	☒ No important uncertainty or variability

Research evidence:

No research evidence was identified

Panel discussion:

Good evidence, no uncertainty

- **BALANCE OF EFFECTS**

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☒ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:

- **COSTS**

How large are the resource requirements (costs)?

Judgement:

☐ Don't know	☐ Varies	☐ Large costs	☐ Moderate costs	☐ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:

No research evidence was identified

Panel discussion:

Cost of drugs and monitoring comparable; higher efficiency of letrozole would result in savings.

- **CERTAINTY OF COST EVIDENCE**

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

Cost effectiveness systematic review is done across PCOS. Please reference the overarching section on cost

Panel discussion:

- **COST-EFFECTIVENESS**

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

Cost effectiveness systematic review is done across PCOS. Please reference the overarching section on cost.

Panel discussion:

- **EQUITY**

What would be the impact on health equity?

Judgement:

☐ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☒ Probably increased	☐ Increased

Research evidence:

No research evidence was identified

Panel discussion:

- **ACCEPTABILITY**

Is the option acceptable to key stakeholders?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☐ Probably Yes	☒ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Are key stakeholders likely to find the recommendation acceptable, given the relative importance they attach to the desirable and undesirable consequences of implementing the recommendation; the timing of the benefits, harms and costs; and their moral values? This includes considering patients' values and preferences.

- **FEASIBILITY**

Is the option feasible to implement?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☐ Probably Yes	☒ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Limited ability to prescribe depending on regulatory approval

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PART 1

EVIDENCE SUMMARY AND GRADE

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Other team members: Loyal Pattuwage

GDG 5

Question 5.4.

In women with PCOS, is clomiphene citrate effective for improving fertility outcomes? In women with PCOS, is metformin effective for improving fertility outcomes? In women with PCOS and a BMI<30-32, what is the effectiveness of metformin compared to clomiphene citrate for improving fertility outcomes?

1. STUDY SELECTION

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(language, year)*
Q.5.4.1. Clomiphene Citrate						
Inclusion	Women of any age, ethnicity and weight with PCOS diagnosed by Rotterdam, NIH or AEPCOS and 1) at least one patent tube 2) normal sperm AND 3) have never been treated or been exposed to treatment for infertility (therapy naïve) OR 4) have been treated or exposed to treatment OR 5) have been treated or exposed to clomiphene citrate and ovulate but don't conceive (clomid failure) OR 6) have been treated or exposed to clomid and don't ovulate (clomid resistant). Subgroup by BMI. Also specifically identifying the 4 phenotypes where possible.	Any type, dose and frequency of clomiphene citrate.	Placebo, no intervention, other infertility treatment interventions (ie. aromatase inhibitor, metformin, gonadotrophins, ovarian surgery) including clomiphene cirate in combination with other infertility treatment intervention(s).	Live birth rate, pregnancy rate (biochemical or clinical ultrasound), ovulation, single and multiple pregnancies, miscarriage rate, other adverse events, quality of life, cost effectiveness.	Evidence based guidelines, systematic reviews, health technology assessments, randomised controlled trials (RCTs).	2017-current, combined with studies from previous guideline
Exclusion	Women without diagnosis of PCOS.	Placebo, no intervention or any intervention other than clomiphene citrate.	Any intervention other than those listed in the inclusion criteria.	None	Non-evidence based guidelines, non-systematic reviews, any study lower than a RCT.	None
Q.5.4.2. & Q.5.4.3. Metformin						
Inclusion	Women of any age, ethnicity and weight with PCOS diagnosed by Rotterdam, NIH or AIS and 1) at least one patent tube 2) normal sperm AND 3) have never been treated or been exposed to treatment for infertility (therapy naïve) OR 4) have been treated or exposed to treatment OR 5) have been treated or exposed to clomiphene citrate and ovulate but don't conceive (clomid failure) OR 6) have been treated or exposed to clomid and don't ovulate (clomid resistant). Subgroup by BMI. Also specifically identifying the 4 phenotypes where possible.	At least 1000mg of any type of metformin at any frequency including slow release and standard release.	Placebo, no intervention, other infertility treatment interventions (ie. clomiphene citrate, aromatase inhibitors, gonadotrophin, ovarian surgery) including metformin in combination with other infertility treatment intervention(s).	Live birth rate, pregnancy rate (biochemical or clinical ultrasound), ovulation, single and multiple pregnancies, miscarriage rate, other adverse events, quality of life, cost effectiveness.	Evidence based guidelines, systematic reviews, health technology assessments, randomised controlled trials (RCTs).	2017-current, combined with studies from previous guideline
Exclusion	Women without diagnosis of PCOS.	Placebo, no intervention or any intervention other than metformin.	Any type, dose and frequency of metformin alone.	None	Non-EB guidelines, non-systematic reviews, any study lower than a RCT.	None

2. SEARCH STRATEGY

The search and screening for all GDG 5 questions were done together. Details can be found in the GDG 5 Methodology Appendix, including for:

- Databases
- Search Dates
- Search String(s)
- PRISMA flowchart
- Full list of included studies

- Full list of excluded studies with reasons for exclusion

Evidence processing: The literature search and screening were performed together in one Endnote library and Covidence project for all non-IVF, IVF and IVM fertility treatments in PCOS. Studies were selected by one reviewer/s in consultation with the evidence team/ key contact(s) using study selection and appraisal criteria (PICOs) established a priori. The articles were screened by title and abstract by one reviewer. When a decision could not be made based on title and abstract alone, full text was retrieved. Study appraisal was conducted by two reviewers independently with discussion to resolve any discrepancy. In total, 102 unique studies met inclusion criteria across all non-IVF, IVF and IVF questions, of which 57 were included in the guideline update following the integrity check (refer to methodology appendix for details).

Integrity Assessment: Of these eligible 57 studies, 34 studies met the inclusion criteria for this particular set of questions (Q.5.4.1, Q.5.4.2, Q.5.4.3) on clomiphene citrate, metformin, and metformin in women with PCOS and BMI<30-32, as detailed below.

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3. STUDY CHARACTERISTICS TABLE FOR INCLUDED STUDIES

Author, year, country	Population/ PCOS criteria/ Setting/ CC sensitivity	Study Design	Intervention N, Age, BMI	Intervention Description	Comparison N, Age, BMI	Comparison description	Follow up	Outcomes	Poole d in MA?	RoB
Amer 2009, UK	Women with BMI ≤32 kg/m^2 anovulatory infertility ≥1 year associated with PCOS (PCOS diagnosed by; at least two of: clinical (oligo/ amenorrhoea and/or hyperandrogenaemia), biochemical [LH ≥ 10 IU/l, LH/FSH ratio ≥2, T >2.6 nmol/l or FAI >5] and/or polycystic ovaries on U/S; Reproductive Medicine Centre; CCR	RCT	LOD: 36 Age: 28.1 ± 4.3 BMI: 26.2 ± 3.9	Monopolar electrocautery probe was used to penetrate the ovarian capsule making four punctures per ovary at a power setting of 30 W applied for 5 s per puncture If the patient did not ovulate as evidenced by the low progesterone levels or lack of menstruation, CC would be started 6–8 weeks after surgery	CC: 36 Age: 29.1 ± 4.8 BMI: 26.1 ± 3.5	Incremental doses starting with a daily dose of 50 up to 150 mg on Days 2–6 of a menstrual period or after a progestogen withdrawal bleed using medroxy-progesterone acetate. Continued for 6 cycles and if still anovulatory after the maximum dose of CC or failed to conceive after six ovulatory cycles, surgery was offered.	Up to 12 months after surgery	Primary: cumulative pregnancy rate at 12 months Secondary: ovulation, miscarriage, multiple pregnancy and live birth rates Conception was diagnosed with a positive urinary pregnancy test taken 1 week after a missed period, then transvaginal ultrasound scan at 7 weeks of gestation	No	Mod – no blinding
Amer 2017, UK	Women aged 18 – 39 years with BMI ≤ 35 kg/m2 and PCOS by Rotterdam, proven patency, CC sensitivity NR	Double blind RCT	79 randomised and analysed Age: 28.3 (4.4) BMI: 27.5 (23.4 - 32.2)	letrozole 2.5 mg/d for 5 days from day 2-4 doubled in the second cycle if no ovulation	80 randomised and analysed Age: 28.1 (4.2) BMI: 27.7 (23.0 - 31.0)	50 mg CC daily for 5 days from day 2-4, double in second cycle if no ovulation. CCR with max dose or no conception after 6 cycles were crossed-over to LET group after 6-week washout	NR	Primary: clinical pregnancy (by US gestational sac) rate per participant on primary treatment (before the cross-over). Secondary: ovulation, live birth, pregnancy by ovulating participant, pregnancy by strata, mono-ovulation, endometrial development (thickness and grades), pregnancy outcome and pregnancy complications. Other outcomes included pregnancy and live birth rates on secondary and overall (primary and secondary) treatments.	Yes	Low
Atay 2006, Turkey	Women with primary infertility and PCOS with no other known cause of	RCT	51 randomised and analysed	2.5 mg letrozole daily for 5 days from	55 randomised and analysed	100 mg CC daily for 5 days from day 3 of the menstrual cycle	Data suggests 1	number of mature follicles, endometrial thickness (mm), day of	Yes	High

	infertility (criteria NR, CC sensitivity NR); history of oligo/amenorrhoea, ovaries with ≥10 cysts 2-10mm diameter + hyperechogenic stroma		Age: 27.1 ± 0.9 BMI: 26.1 ± 1.9	day 3 of the menstrual cycle	Age: 26.2 ± 1.1 BMI: 25.8 ± 1.8		treatment cycle for each patient	hCG administration, ovulation rate, pregnancy rate, multiple pregnancies		
Bansal 2021, India	18–35 years with anovulatory infertility; PCOS by Rotterdam; Tertiary care teaching institute	RCT; not double-blinded	45 randomised, 41 analysed Age: 27.1±0.9 BMI: 26.1±1.91	LET, 2.5mg daily (5days)	45 randomised, 39 analysed Age: 26.2±1.1 BMI: 25.8±1.77	CC, 50 mg daily (5days)	3 cycles	Primary: ET. Secondary: Ovulation rate (free fluid in pouch of Douglas + collapsed follicle on transvaginal US and/or day 21 progesterone of ≥3 ng/mL), monofollicular development, pregnancy rate (detection of urinary hCG >7 days of missed period and/or detection of gestational sac by US), and time to pregnancy assessment.	Yes	High
Bayar 2006, Turkey	Therapy naïve women with anovulatory PCOS by Rotterdam; University outpatient clinic	RCT	40 randomised; 38 analysed Age: 32.2 ± 3.9 BMI: NR	2.5 mg/d letrozole, on days 3 to 7 of menstrual cycle	40 randomised; 36 analysed Age: 30.6 ± 4.0 BMI: NR	100 mg/d CC, administered on days 3 to 7 of the menstrual cycle	1-5 cycles	Ovulation rate by cycle, pregnancy rate by cycle, delivery rate by cycle, miscarriage rate, multiple pregnancy rate, endometrial thickness on the day of hCG (mm), N of follicles sized > 15 mm in diameter on the day of hCG, E2 level on the day of hCG (pg/mL), E2 per follicle sized > 15 mm in diameter on the day of hCG (pg/mL)	Yes	Low
Begum 2009 Bangladesh	CCR women with PCOS by Rotterdam who failed to ovulate by 100 mg of CC/day for 5 days in 2 consecutive cycles; private infertility care setting	Non-blinded RCT	32 Age: 25.5 ± 4.0 BMI: 22.7 ± 2.8	7.5 mg of letrozole daily for 5 days starting from day 3 of the cycle	32 Age: 26.1 ± 3.6 BMI: 23.6 ± 3.2	150 mg of CC daily for 5 days starting from day 3 of the cycle	NR	Primary: ovulation and pregnancy rate Secondary: follicular development by day 16 (mm), serum E2 on day of hCG (pg/mL), endometrial development by day 16 (mm), serum progesterone on day 21 (ng/mL), multiple pregnancies, OHSS cases.	Yes	Mod
Begum 2013, Bangladesh	PCOS patients diagnosed with Rotterdam criteria; Outpatient department of a teaching hospital; CCR	RCT (3 groups)	MET + CC: 55 Age: 26.96±4.05 BMI: 27.71±3.61	MET + CC 500 mg metformin 3x daily (1500 mg) for 4 weeks then the same dose was continued for another 6 months along with scheduled CC 150	rFSH: 55 Age: 27.15±4.20 BMI: 28.98±3.19	75 IU rFSH every alternate day starting from D3 of the cycle (then daily if necessary after first monitoring on D12) till maturity of follicles or maximum 15 doses of rFSH.	6 cycles	Primary: Clinical pregnancy, live-birth rate Secondary: ovulation, spontaneous abortion, ectopic pregnancy, multiple pregnancies, congenital anomaly and other adverse perinatal or obstetric complications.	No	High Unblinded Missing details on randomisation, dropouts, blinding etc.

			MET + rFSH: 55 Age: 26.84±5.13 BMI: 28.36±4.54	mg daily for 5 days (D3–D7 of the cycle). MET + rFSH 500 mg metformin 3x daily (1500 mg) for 4 weeks, then same dose was continued for 6 months with 75 IU rFSH every alternate day from D3 of the cycle (then daily if needed after first monitoring on D12) till maturity of follicles or maximum 15 doses of rFSH.				Unclear on how pregnancy was tested: "Treatment was terminated:…(iv) after positive pregnancy test."		
De Leo 1999, Italy	Women with CCR/CCF and PCOS (chronic oligomenorrhoea or amenorrhoea and hyperandrogenemia); University department	RCT	10 Age: 28.0 ± 4.0 BMI: 27.7±3.1	Started with FSH (75 IU then increased to 5 ampoules/day) alone for two cycles and then for a month with metformin, then underwent a third cycle of combined metformin and FSH stimulation	10 Age: 29.5±2.9 BMI: 26.9±4.8	Metformin (1500 mg) for a month before undergoing ovarian stimulation with combined metformin and FSH for one cycle	2-4 cycles	Primary: number of FSH ampoules, days of treatment, E2 level on the day of hCG, number of follicles > 15mm, number of hyperstimulation, number of cycles with hCG withheld Secondary: Number of pregnancies (NR if clinical or biochemical)	No	High – unblinded, small
Fleming 2002, UK BMI ≥30 kg/m2	Obese PCOS (oligomenorrhoea < 8 cycles/year, exclusion of other endocrinopathy, US finding of PCO); age <35 years; infertility outpatient clinics; CC sensitivity NR	Double-blind RCT	N=45 Age: 28.6 ± 5.8 BMI: 34.2 ± 8.6	MET 850 mg 2/d	N=47 Age: 29.2 ± 5.6 BMI: 35.0 ± 8.2	Placebo	12-16 wks	Ovulation: by twice-weekly serum oestradiol. Where oestradiol > 300 pmol/L, LH and progesterone (> 8 nmol/L in ≥ 2 successive samples defined ovulation) were determined; Reproductive hormones, anthropometry, metabolic markers Others: ovarian US, biochemical pregnancy, adverse effects	Yes	Mod due to attrition*
Ganesh 2009, India	Women with PCOS by Rotterdam who had previously failed to conceive or ovulate with CC and undergoing IUI (CCR and	Single blind RCT	LET: 372 analysed Age: 30.3 ± 4.9	LET: letrozole, 5 mg/day orally given for 5 days from cycle days 3 - 7	CC + FSH: 669 analysed Age: 30.4 ± 5.2 BMI: 24.8 ± 4.1	CC + FSH: clomiphene citrate, 100 mg/day orally given for 5 days from cycle days 3 - 7 + 75	NR	Primary: ovulation rate, cancellation rate, miscarriage rate and clinical pregnancy rate Secondary: OHSS rate and multiple pregnancy rate.	Yes	Mod*

	CCF); tertiary infertility care unit		BMI: 24.5 ± 3.8		FSH: 346 analysed Age: 30.8 ± 4.6 BMI: 24.1 ± 3.4	or 100 IU rFSH during cycle days 3 and 8 FSH: rFSH 75IU/100IU from day 2 until the day of hCG administration				
George 2003, India	CCR women with PCOS based on oligomenorrhoea and hyperandrogenism, along with either biochemical abnormalities of a raised LH/FSH ratio or LH or ultrasound features of polycystic ovary; setting: Medical clinic at a medical school	RCT	MET: 30 Age: 25.1±3 BMI: 25.5 ± 3.7	MET: 1500 mg/day in three divided doses for 6 months	hMG: 30 Age: 26. ± 2.9 BMI: 24.6 ± 2.6	hMG: starting at 75 units 5 days after a spontaneous or induced cycle increased by increments of 75 units every 7±10 days	NR	Pregnancy rate (NR if clinical or biochemical)	No	Mod- unblinded (not possible); high drop outs
Ghanem 2012, Egypt Based on clinical registry entry: Egypt	PCOS women aged 18-38; Diagnosis of PCOS based on Rotterdam criteria; The women had not undergone a similar treatment protocol before; CCR	RCT	CC-HP uFSH: 87 Age: 24.8±4.7 BMI: 33.3±5.4 (CC-Clomiphene Citrate; HP: highly purified; uFSH: urinary FSH)	CC 100 mg daily doses for 5 days plus intramuscular (IM) injection of 37.5 IU/day HP uFSH from the 3rd to the 13th cycle day. Subsequent increments of uFSH by 37.5 IU/day were made according to response	HP uFSH: 87 Age: 24.7±4.3 BMI: 33.2±5.7	Highly purified (HP uFSH) only in the same daily doses and for the same duration. Subsequent increments of uFSH by 37.5 IU/day were made according to response	NR (? 1 cycle)	Primary: ovulation rate Secondary: clinical pregnancy rates, number of follicles, endometrial thickness, and gonadotropins consumption. Clinical pregnancy was defined by intrauterine gestational sac observed by an ultrasound scan 2 weeks after a positive pregnancy test in urine or blood	Yes	Mod- single blind
Hoeger 2004, USA	PCOS (oligomenorrhoea with < 6 menses/yr and hyperandrogenism), BMI > 25, normal TSH, prolactin and FSH concentrations; CC sensitivity NR; Academic medical centre	Double-blind RCT	MET: 9 Age: 29.5 ± 6.4 BMI: 37.1 ± 4.9 MET + L/S: 9 Age: 30.4 ± 5.4	MET 850 mg 2/d MET 850 mg 2/d + Lifestyle modification programme to reduce calorie intake by 500-1000 kcal/d	Placebo: 9 Age: 27.1 ± 4.5 BMI: 37.1 ± 4.6 Placebo + L/S: 11 Age: 27.1 ± 4.3 BMI: 40.0 ± 7.4	Placebo alone Lifestyle modification programme alone to reduce calorie intake by 500-1000 kcal/d	24 months	Ovulation; Anthropometric: weight, BMI, hirsutism Hormones: total testosterone, SHBG, FAI, AUC glucose, AUC insulin, fasting glucose, fasting insulin; Others: menstrual pattern; (pregnancy not an outcome of interest)	No	Mod*

			BMI: 41.7 ± 6.2							
Homburg 2012, Europe and South America	PCOS by Rotterdam; Therapy naïve	Multi-centre RCT	CC: Randomised: 143; Analysed/ received CC: 123 Age: 29.4±4 BMI: 25.7±6.0	The starting dose of CC was 50 mg/day (oral) for 5 days from Day 4 of a spontaneous or progestin-induced menstruation, rising by 50 mg/day up to 150 mg in subsequent cycles if ovulation was not achieved	FSH: Randomised: 159; Analysed/ received FSH:132 Age: 29.8±3.8 BMI: 25.1±5.2	Recombinant human FSH was given s.c. in a low-dose protocol starting with 50 IU on cycle day 4, with weekly increments of 25 IU as necessary to induce a follicular response	NR	Primary: clinical pregnancy rate	Yes	Mod
Johnson 2010, New Zealand BMI >32 and ≤ 32 kg/m^2	PCOS by Rotterdam; 14 to 20% of patients had past treatment with CC; excluding those with fertility treatment history using CC for >5 months.	Double-blind RCT	>32 BMI MET: 32 Age: 29.5±4.3 ≤32 BMI MET: 35 Age: 28.9±4.4	MET 500 mg 3/d (increasing dose over 2 weeks) CC 50 mg from day 2-6 (increasing up to 150 mg over 3 months if no evidence of ovulation)	>32 BMI Placebo (stand. care): 33 Age: 29.2±4.2 ≤32 BMI CC (stand. Care): 36 Age: 28.2±4.0 MET + CC: 35 Age: 29.2±4.7	Placebo MET+CC: MET as above + CC 50 mg from day 2-6 (increasing up to 150 mg over 3 months if no evidence of ovulation)	3 months or until pregnanc y	Primary outcomes were clinical pregnancy (intrauterine gestation sac) and live birth Secondary outcomes were ovulation, miscarriage, ectopic pregnancy or multiple pregnancy	Yes	Mod
Kar 2015, India	Treatment naïve Asian Indian women with PCOS by Rotterdam, gynaecology outpatient clinic	Double-blind RCT	CC: 32 Age: 25.8 ± 3.0 BMI: 26.5 ± 3.7	CC: 50-150 mg/d.	MET: 24 Age: 25.2 ± 3.47 BMI: 24.5 ± 5.0 CC + MET: 24 Age: 26.62 ± 3.54 BMI: 27.2 ± 3.7	MET: 1700 mg/d. CC + MET: CC 50-150 mg/d plus metformin 1700 mg/d	6 months, or until pregnant or until resistant to CC	Primary: live birth rate Secondary: ovulation rate, clinical pregnancy rate, early pregnancy loss rate	Yes	Mod*
Kocak 2002, Turkey	CC-resistant, primary infertile PCOS based on oligomenorrhea (<6 cycles in last year) + hirsutism, hyperandrogenism,or presence of multiple subcapsular follicles; Infertility clinic of a tertiary referral center	Double-blind RCT	MET + CC: 27 Age: 26.2 ± 3.7 BMI: 31.91± 5.38	MET: Metformin 850 mg, twice daily + CC (100 mg/day) on cycle days 3-7 of the second cycle	Placebo + CC: 28 Age: 27.1 ± 4.5 BMI: 30.8 ± 4.4	Placebo + CC (100 mg/day) on cycle days 3-7 of the second cycle	2 cycles	Insulin, T, DHEAS, FSH, LH, body mass index (BMI), waist-to-hip ratio, endometrial thickness, cervical score, ovulation, and clinical pregnancy rates (confirmed transvaginal US)	Yes	Mod (random-isation method unclear, no SS calc, 1 drop out); no BL diff

Kjotrod 2011, Denmark, Finland, Norway, Sweden BMI <28	Women PCOS by Rotterdam; Most had previously unsuccessful CC treatment (CCR/ CCF/ mixed); aged <38 years and with a BMI of <28 kg/m^2, who were scheduled to undergo a first or second cycle of IVF or ICSI; infertility treatment centres	Double-blind RCT	MET: 74 Age: 29.6 ± 3.4 BMI: 24.0± 2.7	MET: 2000 mg/day metformin	Placebo: 75 Age: 29.5 ± 3.8 BMI: 23.6±2.8	Placebo	≥ 12 weeks prior to and during long protocol IVF or ICSI and until the day of pregnanc y testing	The primary outcome measure was clinical pregnancy rate. Secondary outcome measures included spontaneous pregnancy rates during the pretreatment period, and the live birth rate	Yes	Mod
Legro 2007, USA BMI mixed, majority >30 kg/m^2	Women with PCOS (oligomenorrhoea < 8 menses/year), biochemical hyperandrogenism; normal uterine cavity, proven patency, normal semen; 40% therapy naïve	Multi-centre double-blind RCT	MET: 208 Age: 28.1 ± 4.0 BMI: 35.6 ± 8.5	MET: 2 extended-release metformin 500 mg	CC: 208 Age: 27.9 ± 4.0 BMI: 36.0 ± 8.9 MET + CC: 209 Age: 28.3 ± 4.0 BMI: 34.2 ± 8.4	CC: CC 50 mg + placebo on day 3-7 of cycle, increased by 50mg (or placebo tablet) for women with poor response to max 150mg (or 3 placebo tablets) Metformin + CC: metformin 500mg 2/d + 50 mg CC increased as above	up to 6 cycles or 30 weeks	Primary: Live birth rate. Secondary: rate of pregnancy loss, singleton birth and ovulation; clinical pregnancy rate	Yes	Low
Legro 2014, USA	Women with PCOS by Rotterdam; CC sensitivity NR	Multi-centre double blind RCT	LET: 374 (1352 cycles) Age: 29 ± 5 BMI: 35 ± 10	5 mg/day progestin for 10 days to induce bleed, then letrozole (2.5 mg daily) was given from cycle day 3 for 5 days. Maximum dose 7.5 mg/d of letrozole given for 5 days.	CC: 376 (1425 cycles) Age: 28 ± 4 BMI: 35 ± 9	5 mg/day progestin for 10 days to induce bleed, then CC (50 mg daily) was given from cycle day 3 for 5 days. Dose was increased in subsequent cycles for nonresponse or poor ovulatory response. Maximum dose of CC 150 mg/d given for 5 days.	Up to 5 cycles	Live birth, ovulation rate, clinical pregnancy rate, miscarriage rate, multiple pregnancy rate	Yes	Low
Liu, 2017, China	Infertile women aged 20-35, BMI≤35; normal patency; PCOS by Rotterdam; Hospital outpatient dept.;	RCT; blinding NR	LET: 67 randomised, 62 analysed;	LET: letrozole 5mg/d (5days)	CC: 67 randomised, 63 analysed; Age: 26.8 ± 3.1	CC: CC 50mg/d (5 days) CC + MET: CC, 50 mg daily (5days) +	2 cycles	Ovulation rate, clinical pregnancy rate, and pregnant outcome (abortion, premature delivery, and live birth)	Yes	High

BMI ≤35 kg/m^2	CC sensitivity mixed (some CCR)		Age: 27.0 ± 3.0 BMI: 20.8 (19.1, 22.3) LET + MET: 67 randomised, 57analysed Age: 27.2 ± 3.3 BMI: 21.6 (19.2, 23.6)	LET + MET: letrozole 5mg/d (5 days) + MET 1000–1500 mg/d	BMI: 21.1 (19.9, 22.8) CC + MET: 67 randomised, 58 analysed Age: 27.2 ± 2.8 BMI: 21.4 (19.8, 23.6)	MET 1000–1500 mg/d				
Lopez 2004, Spain	PCOS by Rotterdam; Therapy naïve; single centre.	RCT (crossover if unsuccessful)	CC= 38 (104 cycles) Age: 29 (23-38) Median (range) BMI: 22.3±1.9	CC daily dose of 50 mg for 5 days, from on day 5 after spontaneous or induced uterine bleeding, increased by 50mg from next cycle if ovulation not achieved until 150mg max.	FSH= 38 (91 cycles) Age: 30 (22-39) Median (range) BMI: 21.9±1.9	Recombinant FSH commencing at 75 IU daily on day 3 after spontaneous or induced menses with dose increments of 37.5 IU daily every 7 days if there was no evidence of ovarian response	Up to 3-6 cycles	Primary: cumulative pregnancy (before crossover) Secondary: cycle cancellation rate, ovulation rate per cycle, cumulative ovulation rate, clinical pregnancy rate per cycle, incidence of OHSS, cumulative live birth rate, and multiple birth rate	Partial	High
Morin-Papunen 2012, Finland BMI ≥27 or <27 kg/m^2	PCOS by Rotterdam with anovulatory infertility for at least 6 months and 3 months washout since the last infertility treatment (CC sensitivity not specified; likely mixed). Age range 18-39 years.	Multi-centre double-blind RCT	MET: 160 Age: 28.4 ± 3.9 BMI: 27.1 ± 6.3	MET: Metformin 500 mg 1/d for 1 week, then 1 extra tablet/d upto to 1.5 g in non-obese and 2 g/d in obese women; if no pregnancy= CC added after 3 months and AI or gonadotropins after 4-6 months/cycles	Placebo: 160 Age: 27.9 ± 4.1 BMI: 27.4 ± 6.2	Placebo	3-9 months or until 12 weeks pregnancy	Primary: Pregnancy (biochemical; positive pregnancy test) and live birth rate Other: miscarriage rate, pregnancy complications; Anthropometric: WHR, waist (cm), hirsutism score, BMI, ovarian volume	Yes	Low
Nazik 2012, Turkey	Infertile women with PCOS by Rotterdam; LET group CCR; CC group Treatment naïve; infertility polyclinic of University	Partly randomised trial	LET: 31 randomised and analysed (40 cycles) Age: 25.6 ± 4.5	Letrozole 2.5mg/day from day 3 -7	CC: 33 randomised and analysed (40 cycles) Age: 27.8 ± 6.2 BMI: 24.9 ± 4.8	All patients with oligomenorrhoea given 6 days of medroxyprogest-erone acetate to induce withdrawal bleed, then CC	NR	Primary Outcomes: ovulation rate and biochemical pregnancy rate Secondary Outcomes: ovarian hyperstimulation syndrome rate, miscarriage rate, multiple pregnancy rate, number of follicles on day of hCG (≥ 17 mm), E2 (pg/mL) on hCG	Yes	High

			BMI: 24.7 ± 3.6			100mg/day from day 3-7		day, endometrial thickness (mm), other side effects		
Ng 2001, Hong Kong	Chinese women with PCOS (irregular cycles of ≤ 21 days or ≥ 35 days and variation of > 4 days, anovulation with mid-luteal progesterone <16 nmol/L whilst taking CC 100 mg for 5 d over 3 cycles (CCR), exclusion of other endocrinopathy, PCO by US, age < 40, day 2 FSH < 10, bilateral patent tubes, normal semen; University obstetric dept.	Double-blind RCT	N=9 (9 cycles) Age: 30.4 ± 2.1 BMI: 25.5 ± 4.6	metformin 500 mg 3/d CC 100 mg for 5 d was given after 3 months if there was no ovulation	N= 9 (9 cycles) Age: 31.2 ± 2.6 BMI: 23.5 ± 4.4	Placebo CC 100 mg for 5 d was given after 3 months if there was no ovulation	3 months + extra cycle for those who do not ovulate	Ovulation: by serum progesterone (> 16 nmol/L) weekly Live births, clinical pregnancy confirmed by pelvic US Anthropometric: BMI Reproductive hormones: total testosterone, androstenedione, DHEA, SHBG, FSH, LH Metabolic markers: fasting glucose, fasting insulin, 120-min glucose levels after GTT, fasting leptin, HDL, LDL, triglycerides	Yes	Mod*
Pourghasem , 2019, Iran	Infertile women aged 15–38 years old; PCOS by Rotterdam; infertility clinic of University; Letrozole resistant (no ovulation at 7.5 mg letrozole)	RCT; not double-blind	LET + folic acid: 62 randomised, 50 analysed	Letrozole 7.5 mg per day from the third day of menstruation for 5 days; + folic acid 200 µg	LET + MET + folic acid: 62 randomised, 50 analysed; LET + Inositol + folic acid: 62 randomised, 50 analysed	LET + MET + folic acid: Letrozole 7.5 mg/d + Metformin 1500 mg/d + 200 µg folic acid LET + Inositol + folic acid: Letrozole 7.5 mg/d + Inositol 2g + 200 µg folic acid twice daily for 3 months.	3 cycles	Primary outcomes were ovarian function (presence or absence of a mature follicle ≥17 mm seen by transvaginal US) during 12–16 menstrual cycles; and clinical pregnancy (presence of gestational sac on US 5 weeks after HCG injection).	Yes	High
Qublan 2009, Jordan	CC-resistant women with PCOS by Rotterdam, undergoing IVF; tubal patency and normal sperm	Single-blinded RCT	MET: 34	850 mg of metformin 2/d + IVF Age: 34.6 ± 4.3 BMI: 32.2 (27–39)	Placebo: 32	Placebo + IVF Age: 33.8 ± 3.9 BMI: 31.9 (26–38)	1 month before IVF until day of pregnancy test. If pregnant, continued metformin for 12 wks.	Clinical pregnancy rates; implantation rates; hormones including FSH, LH, testosterone (T), androstenedione (A), 17-hydroxyprogesterone (17-OHP), oestradiol (E2) and dehydroepiandrosterone sulphate (DHEAS)	Yes	Mod
Roy 2012, India	Women aged 20 - 35 with infertility for > 1 year, normal fertility tests	RCT	LET: 104 randomised;	2.5 mg/d letrozole, increasing up to 5 mg/d, from Day 3-7	CC: 108 randomised; 106	50 mg/d CC, increasing up to 100 mg/d, from Day 3-7 (5	3 months	Mean number of follicles, endometrial thickness, ovulatory cycle rate, clinical pregnancy/	Yes	Low

	(patency, semen, hormone) BMI < 28, and anovulatory PCOS by Rotterdam; CC sensitivity NR; Tertiary care hospital		98 analysed (294 cycles) Age: 26.1 ± 1.8 BMI: 25.8 ± 2.1	(5 days) after a 5-day course of 10 mg/ d medroxyprogesterone acetate to induce bleed	analysed (318 cycles) Age: 26.5 ± 1.3 BMI: 25.4 ± 1.6	days) after a 5-day course of 10 mg/ d medroxyprogesterone acetate to induce bleed		conception rate, pregnancy outcome, miscarriage rate, multiple pregnancies and OHSS rate		
Sahin 2004, Turkey	Women with primary infertility and PCOS; PCO on USS (≥ 10 cysts 2-10 mm), oligomenorrhoea (> 35 d) or amenorrhoea (no period > 6 months), hyperandrogenism participants received no medication known to affect pituitary-ovarian function or carbohydrate metabolism for min 12 wks	RCT	CC: 10 Median (range) Age: 24.5 (19–28) BMI: 25.7 (23.1–35.7)	CC 100 mg daily for 5 d from day 5 of the cycle. Ovulation was triggered by administration of 10,000 IU hCG	MET + CC: 11 Median (range) Age: 27 (21–31) BMI: 30.4 (24.6–33.9)	Met + CC: Metformin 850 mg twice daily + CC 100 mg daily for 5 d from day 5 of the cycle. Ovulation was triggered by administration of 10,000 IU hCG, at which point metformin was terminated and repeated in the next cycle	3 months, pregnancy or maximum of 6 CC cycles	Clinical pregnancy (gestational sac on US and fetal heart motion), insulin resistance, ovarian androgen production, and clomiphene-induced ovulation		High* No blinding?-NR
Siebert 2009, South Africa	PCOS based on Rotterdam criteria; Couples with history of infertility at least 18 months; academic hospital; CC sensitivity status: NR	Unblinded RCT	MET + CC: 52 Age: BMI: 30.48 (26.55-34.05) Median (IQR)	metformin 850 mg twice daily, CC 50-150 mg day 4-8 for 4 cycles + lifestyle modification	CC: 55 Age: BMI: 30.71 (24.05–34.48) Median (IQR)	Starting dose of 50 mg day 4–8 and increase with increments of 50 mg to a maximum of 150 mg if no response was achieved	6 weeks before and throughout ovulation induction with CC	Primary: ovulation success NR pregnancy rates		High*
Sohrabvand 2006, Iran	CCF women (failed to become pregnant after 3 courses of 150 mg CC) with PCOS; Hospital infertility clinic	Single - blind RCT	30 randomised and analysed Age: 28.2 ± 3.1 BMI: 30.0 ± 4.8	MET + LET: 500 mg x 3/d for 6 - 8 weeks. If pregnancy did not occur, 2.5 mg letrozole from cycle days 3 - 7 was given orally.	30 randomised and 29 analysed Age: 29.6 ± 3.5 BMI: 30.2 ± 3.9	MET + CC: 500 mg x 3/d for 6 - 8 weeks. If pregnancy did not occur, 100 mg CC from cycle days 3 - 7 was given orally.	2 cycles	Endometrial thickness on day of hCG administration, N of follicles > 18 mm in diameter, Mean total estradiol level on day of hCG administration, mean estradiol level by mature follicle, regular menses after metformin, adverse effects of metformin, live births, clinical pregnancy rate, miscarriage	Yes	Mod*
Tang 2006b, UK BMI>30	Obese women with PCOS (PCO on USS > 10 cysts 2-8 mm diameter), oligomenorrhoea (cycle length > 35 d) or	Multi-centre RCT	MET: 69 Age: 29.7±3.7	Metformin (850 mg) twice daily + Dietary advice for 500kcal reduction	Placebo: 74 Age: 29.8±3.8 BMI: 38.9±9.5	Placebo + Dietary advice for 500kcal reduction	6 months	The primary outcome measures were: (i) change in menstrual cycle; (ii) change in anthropometric measurements; and (iii) changes in the endocrine parameters, insulin		Mod*

	amenorrhoea (no period in 6 months); Age 18-39 years; BMI > 30; normal semen; min 1 tubal patency; infertility clinics; Mixed but most therapy naïve due to BMI		BMI: 37.6±5.0					sensitivity and lipid profile. The main secondary outcome measure was pregnancy rate (assuming clinical since monthly US scans were used)		
Vandermolen 2001, USA	Women with PCOS and CCR/ anovulatory in response to a 5-day course of CC, 150 mg/day; Clinical Research Center	Multi-centre RCT	MET: 11 Age: 29 ± 1.2 BMI: 37.6 ± 4.3	MET: 500 mg three times daily, for 7 weeks CC treatment was begun at 50 mg daily for 5 days.	Placebo: 15 Age: 30 ± 1.0 BMI: 38.4 ± 2.2	Placebo CC treatment was begun at 50 mg daily for 5 days.	7 weeks; or 6 ovulatory cycles, fell pregnant, or anovulatory with 150 mg of CC	Ovulatory rates, Clinical pregnancy rate (gestational sac on US), and hormonal variables while attempting ovulation induction with CC.	Yes	High*
Zeinalzadeh 2010, Iran	Women with primary infertility, documented PCOS by ultrasound, oligomenorrhea, and an increased LH/ FSH ratio (>3), age < 35 years, < 5 years infertility and BMI between 19 and 26; CC sensitivity NR; Infertility centre.	RCT	50 randomised and analysed Age: 23.8±3.6 BMI: 19-26	LET: 5 mg/d letrozole within days 3-7 of menstrual cycle for 5 days	57 randomised and analysed Age: 23.1±3.6 BMI: 19-26	CC: 100 mg of CC daily within days 3-7 of menstrual cycle for 5 days	NR	Ovulation rate, clinical pregnancy rate, number of follicles > 17mm, OHSS rate, multiple pregnancy rate, endometrial thickness.	Yes	High

CC, clomiphene citrate; CCR, clomiphene citrate resistant (to ovulate); CCF, clomiphene citrate failure (to become pregnant); LET, letrozole; MET, metformin; NR; not reported; OHSS, ovarian hyperstimulation syndrome; IUI, intrauterine insemination; hCG, human chorionic gonadotrophin; LH, luteinizing hormone; FSH, follicle stimulating hormone; MA, meta-analysis; RoB, risk of bias. All age data is in years and BMI is in kg/m^2. *Risk of bias assessment derived from checklists/ summaries of previous systematic reviews (Morley et al. Cochrane Database Syst Rev. 2017 Nov; 2017(11): CD003053; and Franik et al. Cochrane Database Syst Rev. 2018; 2018(5): CD010287).

4. FINDINGS

Comparisons Included:

- **Comparison 1.** Metformin vs Placebo
- **Comparison 2.** Metformin vs Clomiphene Citrate
- **Comparison 3.** Metformin + Clomiphene Citrate vs Metformin
- **Comparison 4.** Metformin + Letrozole vs Letrozole
- **Comparison 5.** Metformin + Letrozole vs Metformin + Clomiphene Citrate
- **Comparison 6.** Metformin vs gonadotropins (hMG)
- **Comparison 7.** Metformin + gonadotropins vs gonadotropins

- **Comparison 8.** Clomiphene Citrate vs Metformin + Clomiphene Citrate
- **Comparison 9.** Clomiphene Citrate vs Letrozole
- **Comparison 10.** Clomiphene Citrate vs Metformin + Letrozole
- **Comparison 11.** Clomiphene Citrate + Metformin vs Letrozole
- **Comparison 12.** Clomiphene Citrate vs gonadotropins
- **Comparison 13.** Clomiphene Citrate + gonadotropins vs Clomiphene Citrate
- **Comparison 14.** Clomiphene Citrate + gonadotropins vs Letrozole
- **Comparison 15.** Clomiphene Citrate + gonadotropins vs Metformin
- **Comparison 16.** Clomiphene Citrate vs Laparoscopic ovarian drilling (LOD)

COMPARISON 1. Metformin versus Placebo

- **EVIDENCE SUMMARY:**

A total of seven studies compared metformin with placebo for fertility outcomes in PCOS. Studies were conducted in the UK, Europe (Norway, Finland, Sweden, Denmark), China, New Zealand and Jordan. Six of the studies had a moderate risk of bias and one had a low risk. Two studies were specifically in women with clomiphene citrate-resistant PCOS, and three had a mixed population (the remaining two did not report ovulation induction medication use in their populations).

- **META-ANALYSIS SUMMARY:**

All outcomes assessed were amenable to meta-analysis except for multiple pregnancy rate per patient which was only reported in a single study. Metformin was superior to placebo for improving live birth, clinical pregnancy and overall pregnancy rates, with ORs >1.8 and moderate certainty in the evidence for all. Downgrading was due to risk of bias since most of the studies (half or more) in these three analyses were of moderate risk of bias. No differences between metformin and placebo were identified for ovulation rate per patient, miscarriage rate or multiple pregnancy rates per patient or pregnancy. Evidence for these outcomes was of low certainty due to small sample sizes, wide confidence intervals and risk of bias.

Summary Table for meta-analysis results:

Outcome or Subgroup	Studies	n	Effect Estimate; OR [95% CI], M-H, random	P	Favours	Certainty
Live birth rate - per patient	4	552	1.84 [1.27, 2.66]	0.001	MET (live birth rate is higher with metformin)	⊕⊕⊕◯ MODERATE
Clinical pregnancy rate - per patient†	5	443	1.93 [1.19, 3.10]	0.007	MET (clinical pregnancy rate is higher with metformin)	⊕⊕⊕◯ MODERATE
Pregnancy rate - per patient*	7	805	1.89 [1.37, 2.61]	0.0001	MET (pregnancy rate is higher with metformin)	⊕⊕⊕◯ MODERATE
Ovulation rate - per patient	2	112	2.34 [0.99, 5.53]	0.05	None	⊕⊕◯◯ LOW
Multiple pregnancy rate – per patient	1	66	0.34 [0.09, 1.25]	0.1	None	⊕⊕◯◯ LOW
Multiple pregnancy rate - per pregnancy	3	112	0.61 [0.13, 2.91]	0.5	None	⊕⊕◯◯ LOW
Miscarriage rate - per pregnancy	5	250	0.48 [0.14, 1.62]	0.2	None	⊕⊕◯◯ LOW

*includes clinical, biochemical (or undefined pregnancy rate) as reported in each study; †clinical pregnancy rate is confirmed by ultrasound detection of gestational sac/ fetal heart activity

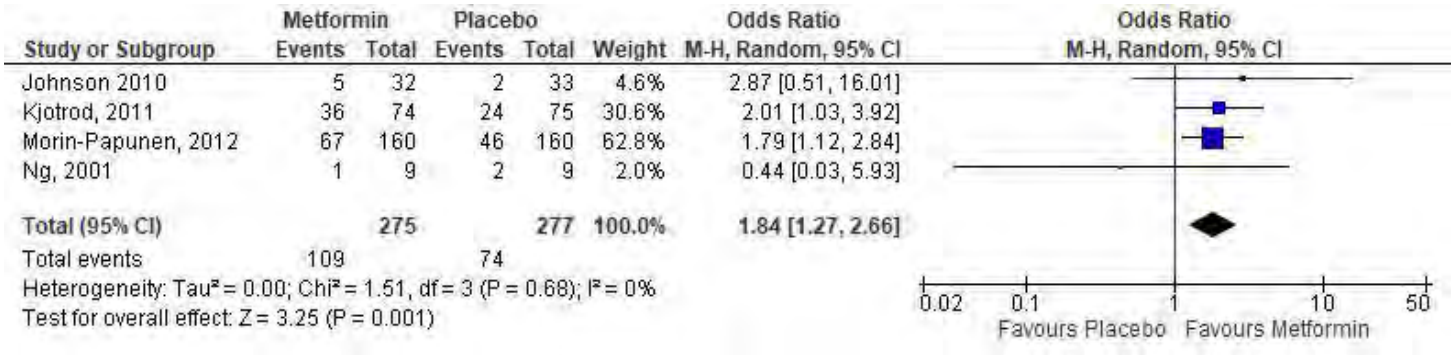
OUTCOME 1.1. Live birth rate- per patient

1.1.1. Individual Study Data Table

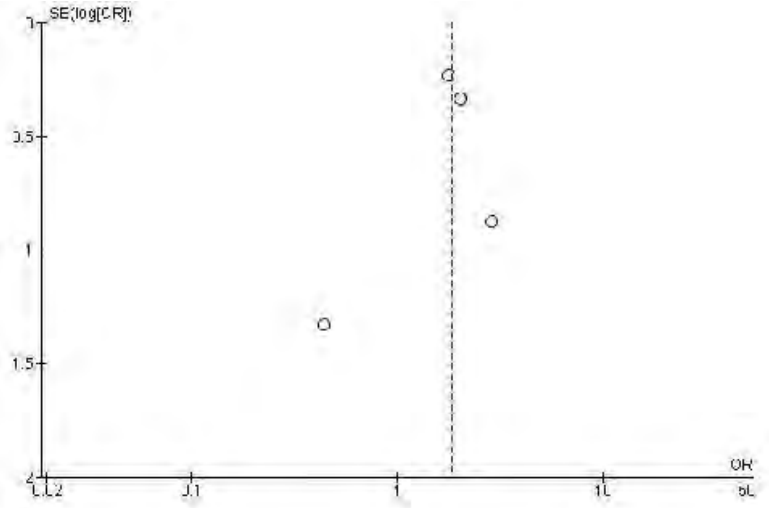
OUTCOME: Live birth rate per person					OUTCOME TYPE: Dichotomous				
COMPARISON: Metformin vs. placebo									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (MET)**	**N total in intervention/ exposure group (MET)**	**N events in control / comparison group (Placebo)**	**N total in control/ comparison group (Placebo)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Johnson 2010 (MRB)	Mixed	Count	Investigator	5	32	2	33	Crude	NA
Kjotrod (MRB)	Mixed	Count	Investigator	36	74	24	75	Crude	NA
Morin-Papunen 2012 (LRB)	NR	Count	Investigator	33	160	16	160	Crude	NA
Ng 2001 (MRB)	CCR	Count	Investigator	1	9	2	9	Crude	NA

CCR, Clomiphene citrate resistant; **TN**, therapy naïve; **NR**, not reported; **Mixed**, includes clomiphene citrate resistant/failure and therapy naïve and/or not reported; **OI**, ovulation induction

1.1.2. Forest Plot of all included RCTs comparing Metformin and Placebo for live birth rate- per patient

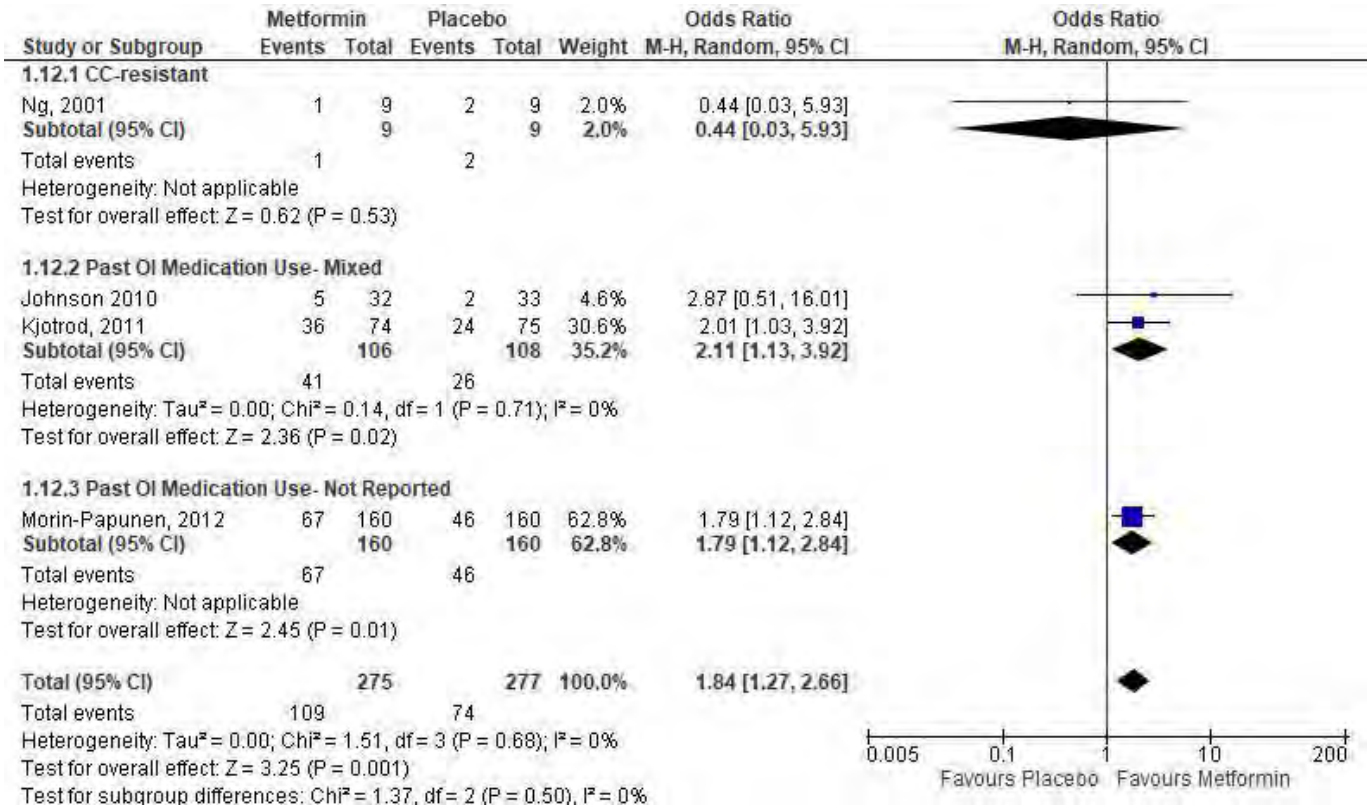


1.1.3. Funnel plot for assessment of publication bias

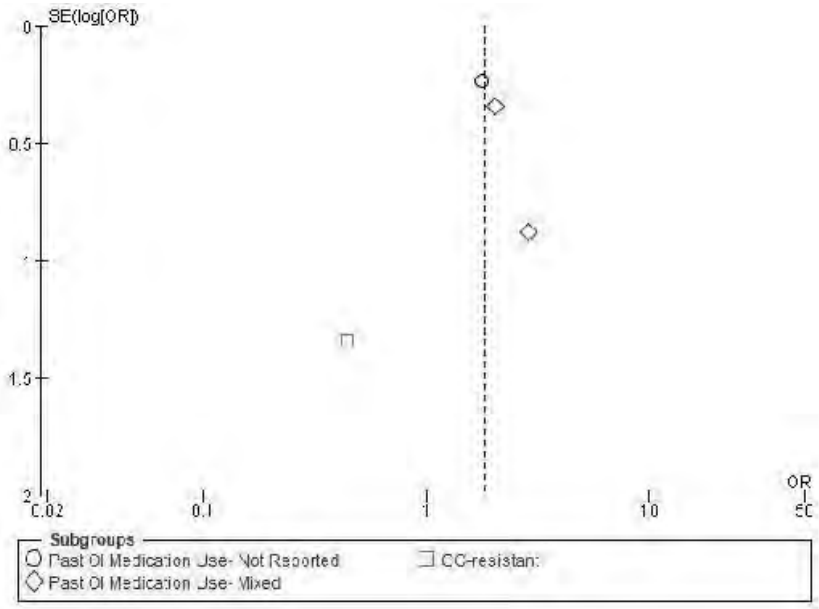


1.1.4. SUBGROUP ANALYSIS: Live birth rate – per patient

1.1.4.1. Forest plot of all included RCTs comparing Metformin and Placebo for live birth rate- per patient, sub-grouped by past ovulation induction (OI) medication use



1.1.4.2. Funnel plot for assessment of publication bias- subgroup analysis: live birth rate- per patient



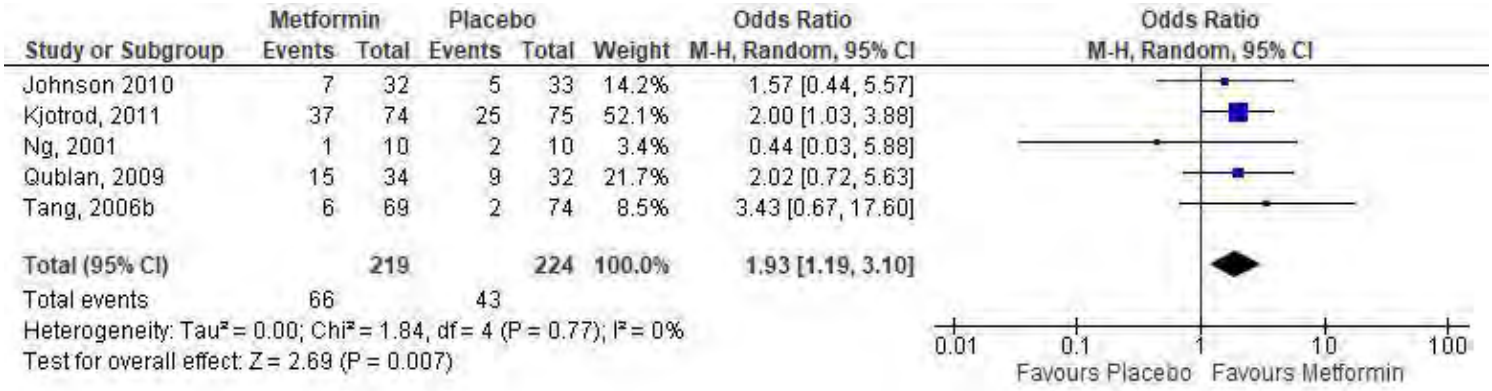
OUTCOME 1.2. Clinical pregnancy rate- per patient

1.2.1. Individual Study Data Table

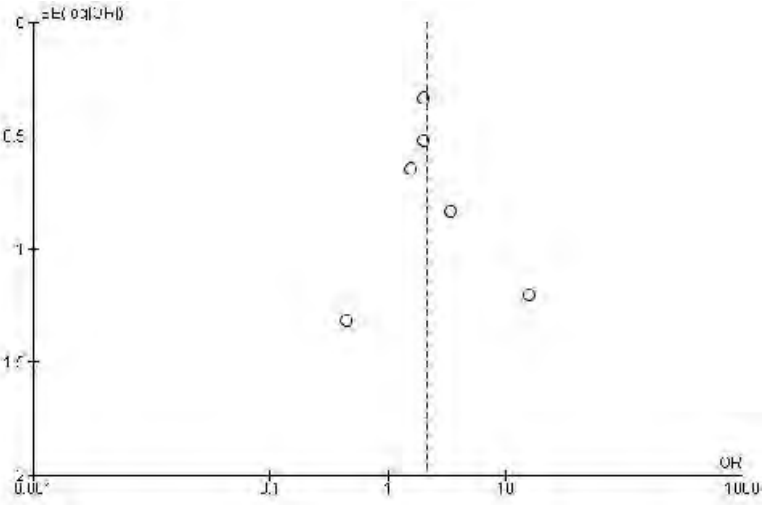
OUTCOME: Clinical pregnancy rate per patient				**OUTCOME TYPE:** Dichotomous					
COMPARISON (if applicable): Metformin vs. placebo									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in intervention/ exposure group (MET)**	**N total in intervention/ exposure group (MET)**	**N events in control / comparison group (Placebo)**	**N total in control/ comparison group (Placebo)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Johnson 2010 (MRB)	Mixed	Count	Investigator	7	32	5	33	Crude	NA
Kjotrod 2011 (MRB)	Mixed	Count	Investigator	37	74	25	75	Crude	NA
Ng 2001(MRB)	CCR	Count	Investigator	1	10	2	10	Crude	NA
Qublan 2009 (MRB)	CCR	Count	Investigator	15	34	9	32	Crude	NA
Tang 2006b (MRB)	Mixed	Count	Investigator	6	69	2	74	Crude	NA

CCR, Clomiphene citrate resistant; **Mixed**, includes clomiphene citrate resistant/failure and therapy naïve and/or not reported; **OI**, ovulation induction

1.2.2. Forest Plot of all included RCTs comparing Metformin and Placebo for clinical pregnancy rate- per patient

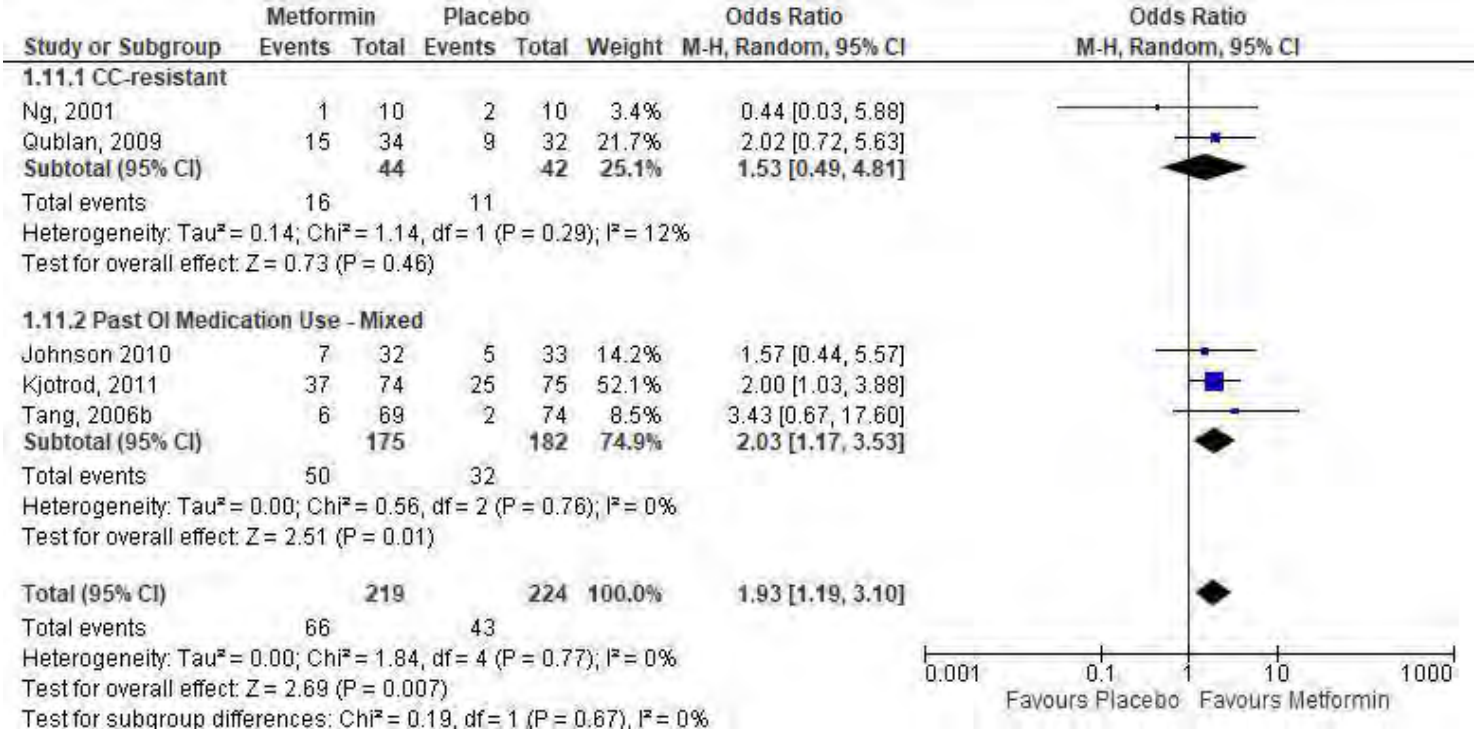


1.2.3. Funnel plot for assessment of publication bias

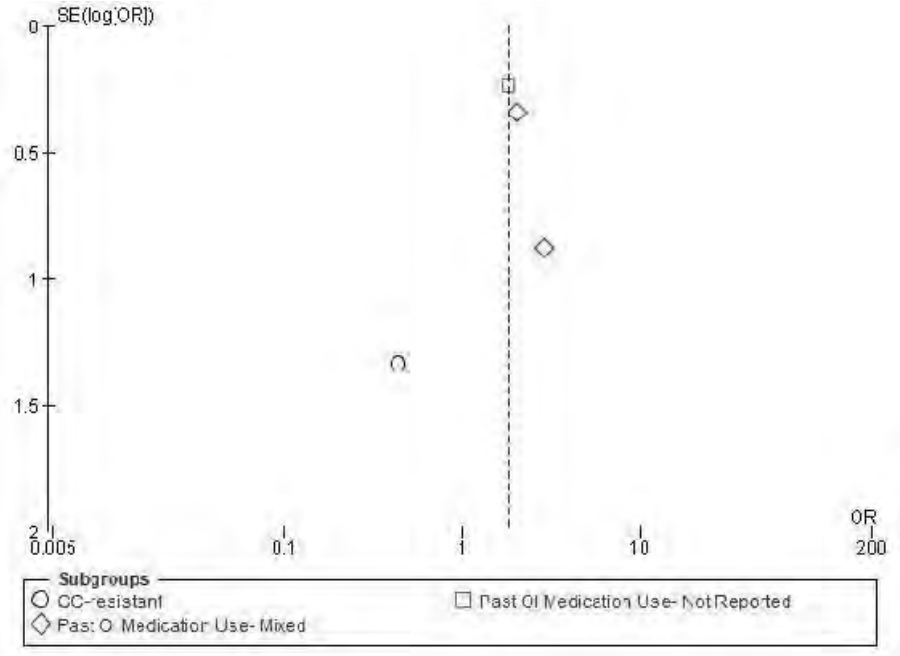


1.2.4. SUBGROUP ANALYSIS: Clinical pregnancy rate – per patient

1.2.4.1. Forest Plot of all included RCTs comparing Metformin and Placebo for clinical pregnancy rate- per patient, sub-grouped by past ovulation induction (OI) medication use



1.2.4.2. Funnel plot for assessment of publication bias- subgroup analysis: clinical pregnancy rate- per patient



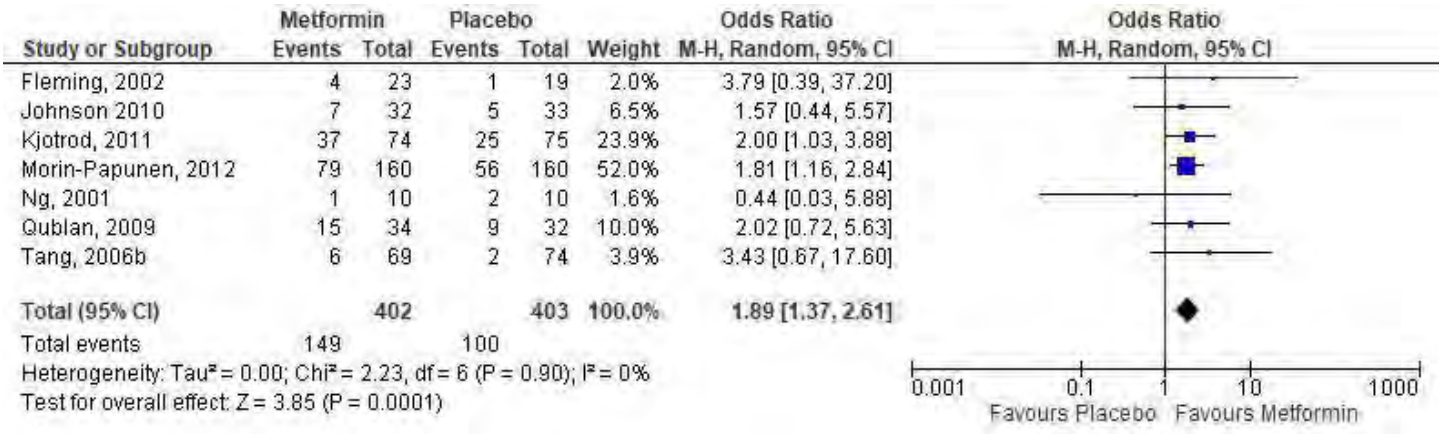
OUTCOME 1.3. Pregnancy rate- per patient

1.3.1. Individual Study Data Table

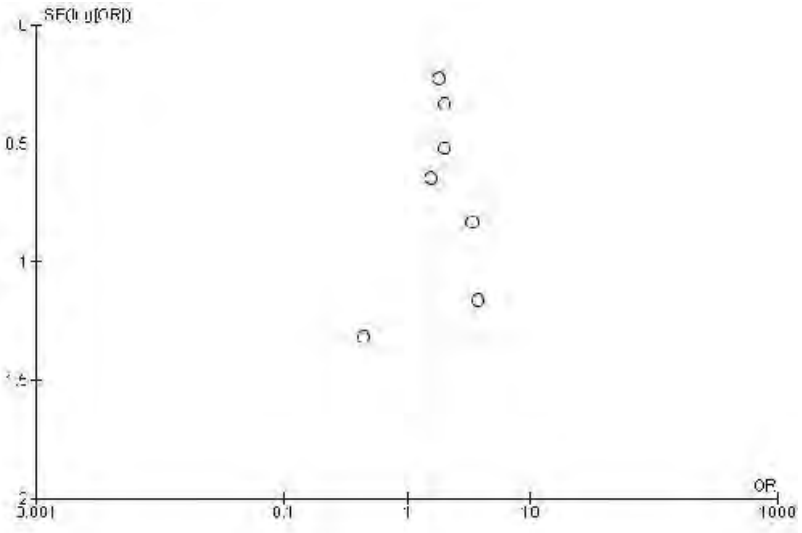
OUTCOME: Pregnancy rate per person				**OUTCOME TYPE:** Dichotomous					
COMPARISON: Metformin vs. placebo									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in intervention/ exposure group (MET)**	**N total in intervention/ exposure group (MET)**	**N events in control / comparison group (Placebo)**	**N total in control/ comparison group (Placebo)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Fleming 2002 (MRB)	NR	Count	Investigator	4	23	1	19	Crude	NA
Johnson 2010 (MRB)	Mixed	Count	Investigator	7	32	5	33	Crude	NA
Kjotrod 2011 (MRB)	Mixed	Count	Investigator	37	74	25	75	Crude	NA
Morin-Papunen 2012 (LRB)	NR	Count	Investigator	79	160	56	160	Crude	NA
Ng 2001 (MRB)	CCR	Count	Investigator	1	10	2	10	Crude	NA
Qublan 2009 (MRB)	CCR	Count	Investigator	15	34	9	32	Crude	NA
Tang 2006b (MRB)	Mixed	Count	Investigator	6	69	2	74	Crude	NA

CCR, Clomiphene citrate resistant; **NR**, not reported; **Mixed**, includes clomiphene citrate resistant/failure and therapy naïve and/or not reported; **OI**, ovulation induction

1.3.2. Forest Plot of all included RCTs comparing Metformin and Placebo for pregnancy rate- per patient

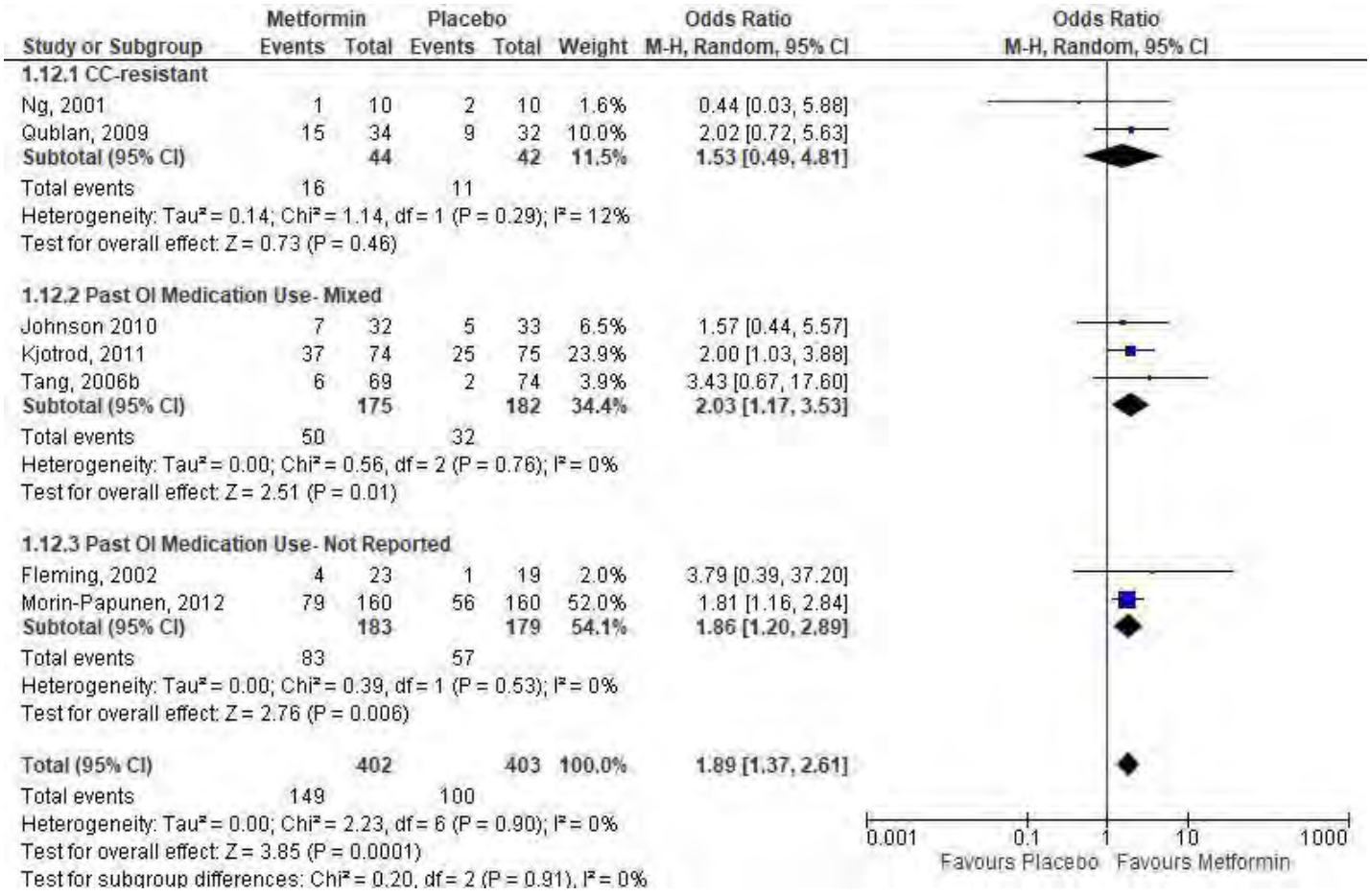


1.3.3. Funnel plot for assessment of publication bias

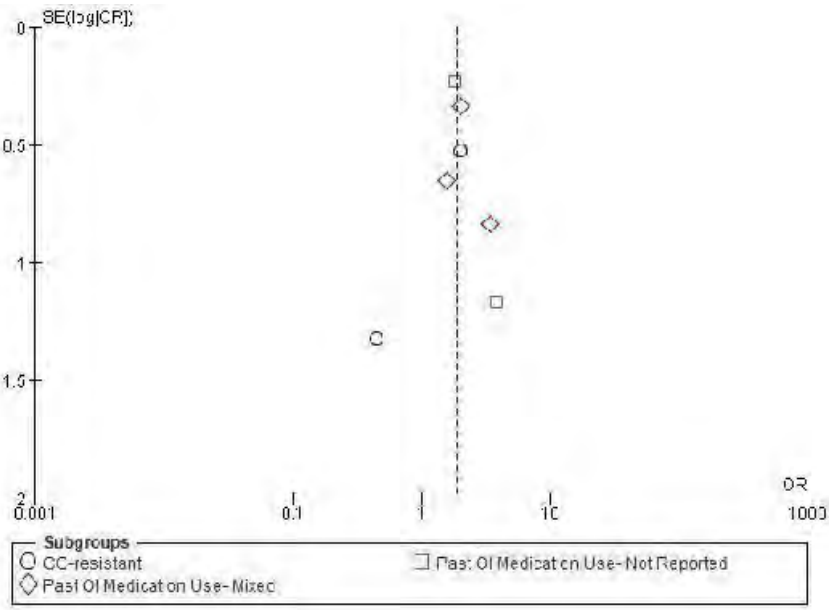


1.3.4. SUBGROUP ANALYSIS: Pregnancy rate- per patient

1.3.4.1. Forest Plot of all included RCTs comparing Metformin and Placebo for pregnancy rate- per patient, sub-grouped by past ovulation induction (OI) medication use



1.3.4.2. Funnel plot for assessment of publication bias- subgroup analysis: pregnancy rate- per patient



OUTCOME 1.4. Ovulation rate- per patient

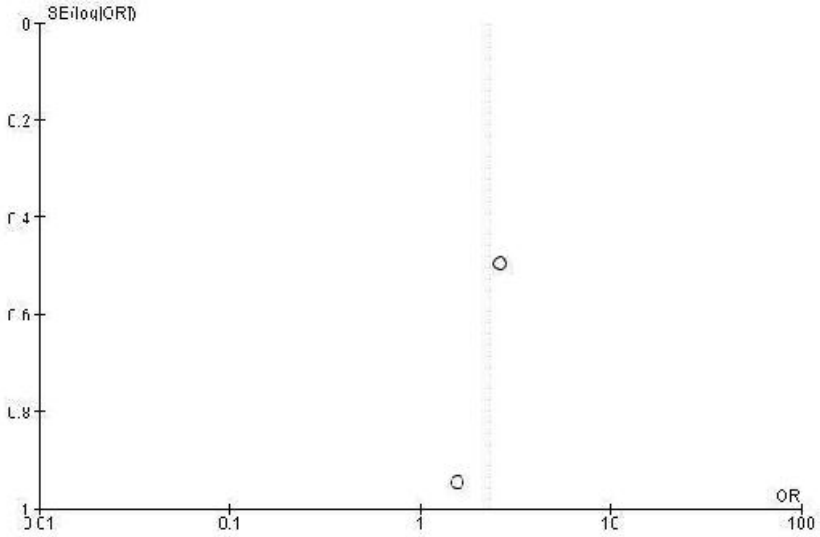
1.4.1. Individual Study Data Table

OUTCOME: Ovulation rate – per patient					**OUTCOME TYPE:** Dichotomous				
COMPARISON: Metformin vs. placebo									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention / exposure group (MET)**	**N total in intervention / exposure group (MET)**	**N events in control / comparison group (Placebo)**	**N total in control/ comparison group (Placebo)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Fleming 2002 (MRB)	NR	Count	Investigator	37	45	30	47	Crude	NA
Ng 2001 (MRB)	CCR	Count	Investigator	4	10	3	10	Crude	NA

CCR, Clomiphene citrate resistant; **NR**, not reported; **Mixed**, includes clomiphene citrate resistant/failure and therapy naïve and/or not reported; **OI**, ovulation induction

1.4.2. Forest Plot of all included RCTs comparing Metformin and Placebo for ovulation rate- per patient

1.4.3. Funnel plot for assessment of publication bias



OUTCOME 1.5. Multiple pregnancy rate- per patient

1.5.1. Individual Study Data Table

CCR, Clomiphene citrate resistant; **OI**, ovulation induction]

OUTCOME: Multiple pregnancy rate - per patient				**OUTCOME TYPE:** Dichotomous					
COMPARISON: Metformin vs. placebo									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (MET)**	**N total in intervention/ exposure group (MET)**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Qublan 2009 (MRB)	CCR	Count	Investigator	4	34	9	32	Crude	NA

OUTCOME 1.6. Multiple pregnancy rate- per pregnancy

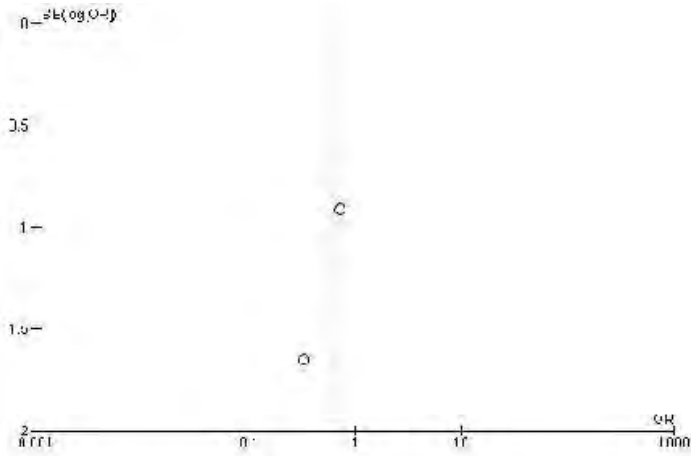
1.6.1. Individual Study Data Table

OUTCOME: Multiple pregnancy rate - per pregnancy				**OUTCOME TYPE:** Dichotomous					
COMPARISON: Metformin vs. placebo									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (MET)**	**N total in intervention/ exposure group (MET)**	**N events in control / comparison group**	**N total in control/ comparison group**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Johnson 2010 (MRB)	Mixed	Count	Investigator	0	32	1	33	Crude	NA
Kjotrod 2011 (MRB)	Mixed	Count	Investigator	0	15	0	8	Crude	NA
Qublan 2009 (MRB)	CCR	Count	Investigator	4	15	3	9	Crude	NA

CCR, Clomiphene citrate resistant; **NR**, not reported; **Mixed**, includes clomiphene citrate resistant/failure and therapy naïve and/or not reported; **OI**, ovulation induction

1.6.2. Forest Plot of all included RCTs comparing Metformin and Placebo for multiple pregnancy rate- per pregnancy

1.6.3. Funnel Plot for Assessment of Publication Bias

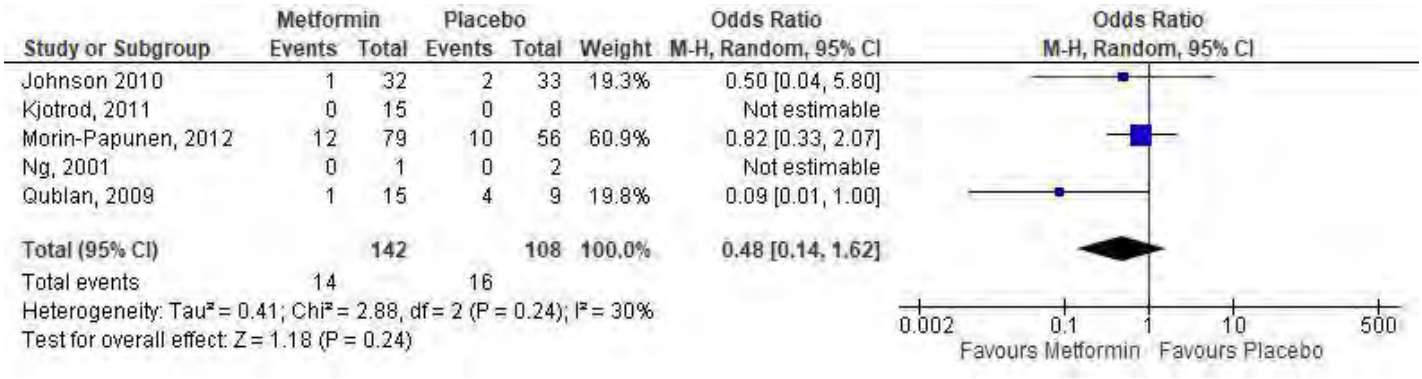


OUTCOME 1.7. Miscarriage rate – per pregnancy

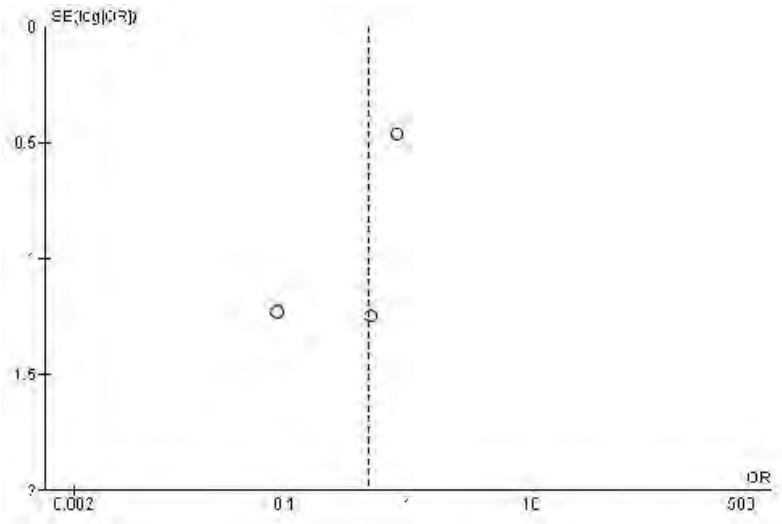
OUTCOME: Miscarriage rate - per pregnancy						OUTCOME TYPE: Dichotomous			
COMPARISON: Metformin vs. placebo									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (MET)**	**N total in intervention/ exposure group (MET)**	**N events in control / comparison group Placebo**	**N total in control/ comparison group Placebo**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Johnson 2010 (MRB)	Mixed	Count	Investigator	1	32	2	33	Crude	NA
Kjotrod 2011 (MRB)	Mixed	Count	Investigator	0	15	0	8	Crude	NA
Morin-Papunen 2012 (LRB)	NR	Count	Investigator	12	79	10	56	Crude	NA
Ng 2001 (MRB)	CCR	Count	Investigator	0	1	0	1	Crude	NA
Qublan 2009	CCR	Count	Investigator	1	15	4	9	Crude	NA

CCR, Clomiphene citrate resistant; **NR**, not reported; **Mixed**, includes clomiphene citrate resistant/failure and therapy naïve and/or not reported; **OI**, ovulation induction

1.5.2. Forest Plot of all included RCTs comparing Metformin and Placebo for miscarriage rate- per pregnancy



1.5.3. Funnel Plot for Assessment of Publication Bias



COMPARISON 2. Metformin vs Clomiphene Citrate

- **EVIDENCE SUMMARY:**

Only three included studies compared metformin with clomiphene citrate, two of which included women with a BMI<30-32 kg/m^2 (Johnson et al. 2010; Kar et al. 2015), while the remaining study included women with a mean BMI ≥30-32 kg/m^2 (Legro et al. 2007). One of the studies (Johnson et al. 2010) had a moderate risk of bias and the other (Legro et al. 2007) had a low risk of bias. Both studies included participants with a mixed history of past ovulation induction medication use, with the study by Legro et al. 2007 being of a relatively large sample size (n>400). The third study by Kar et al. 2015 had a moderate risk of bias and included therapy naïve women with PCOS.

- **META-ANALYSIS SUMMARY:**

In meta-analysis, there were no differences between metformin and clomiphene citrate for live birth, clinical pregnancy, multiple pregnancy or ovulation rates per patient. In a single study, ovulation rate per cycle was significantly lower with metformin compared with clomiphene citrate (OR= 0.43) and miscarriage rate per patient was significantly higher with metformin in meta-analysis of three studies (OR= 2.44). In subgroup analysis by BMI, clomiphene citrate was more effective than metformin for achieving live birth rate and clinical pregnancy rates among women with a BMI ≥30-32 kg/m^2. This result was derived from a single study, however, and should be interpreted with caution. Certainty in the evidence was low for live birth, clinical pregnancy, and ovulation rate per cycle while the remaining outcomes were of moderate certainty (refer table below), with main reasons for downgrading the evidence including risk of bias and imprecision due to small sample sizes or single studies for some outcomes.

Summary Table for meta-analysis results:

Outcome or Subgroup	Studies	n	Effect Estimate; OR [95% CI], M-H, random	P	Favours	Certainty
Live birth rate- per patient	3	544	0.61 [0.21, 1.73]	0.35	None	⊕⊕◯◯ LOW
Clinical pregnancy rate- per patient†	3	544	0.88 [0.24, 3.21]	0.8	None	⊕⊕◯◯ LOW
Ovulation Rate- per patient	1	56	1.30 [0.44, 3.82]	0.6	None	⊕⊕⊕◯ MODERATE
Ovulation Rate- per cycle	1	1961	0.43 [0.35, 0.51]	<0.00001	**CC** (ovulation per cycle is lower with metformin)	⊕⊕◯◯ LOW
Multiple pregnancy rate- per patient	1	71	1.03 [0.06, 17.13]	0.9	None	⊕⊕⊕◯ MODERATE
Miscarriage rate- per patient	3	181	2.44 [1.03, 5.82]	0.04	**CC** (miscarriage is higher with metformin)	⊕⊕⊕◯ MODERATE

†clinical pregnancy rate is confirmed by ultrasound detection of gestational sac/ fetal heart activity

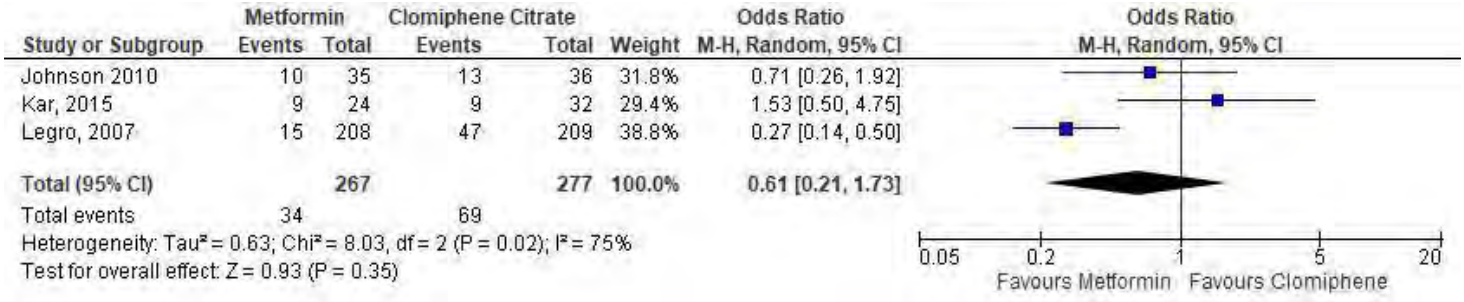
OUTCOME 2.1. Live birth rate- per patient

2.1.1. Individual Study Data Table

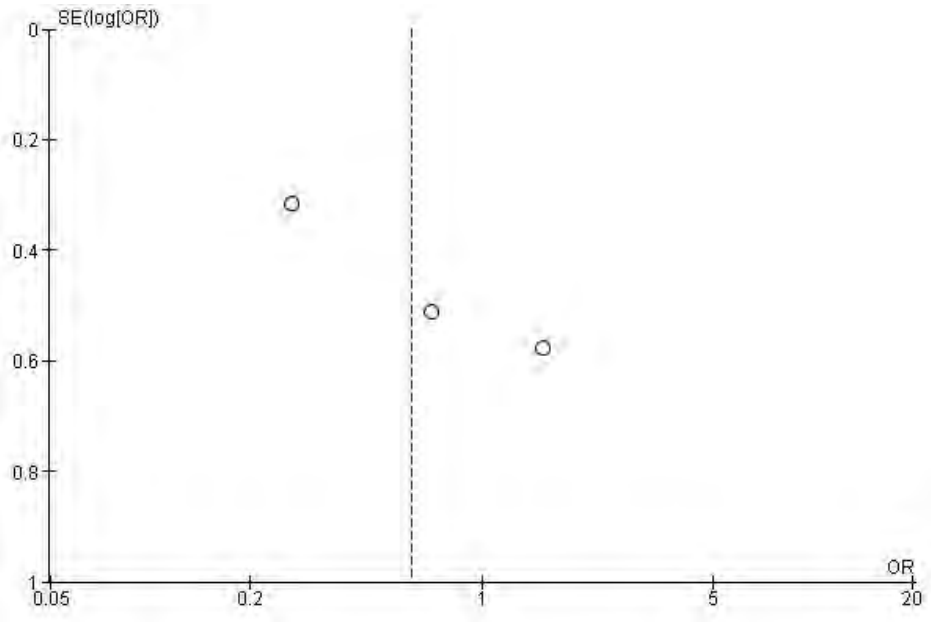
OUTCOME: Live birth rate per patient						**OUTCOME TYPE:** Dichotomous			
COMPARISON: Metformin vs CC									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in control / comparison group (MET)**	**N total in control/ comparison group (MET)**	**N events in intervention/ exposure group (CC)**	**N total in intervention/ exposure group (CC)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Johnson 2010 (MRB)	Mixed	Count	Investigator	10	35	13	36	Crude	NA
Kar 2015 (MRB)	TN	Count	Investigator	9	24	9	32	Crude	NA
Legro 2007 (LRB)	Mixed	Count	Investigator	15	208	47	209	Crude	NA

TN, therapy naïve; **Mixed**, includes clomiphene citrate resistant/failure and therapy naïve and/or not reported; **OI**, ovulation induction

2.1.2. Forest Plot of all included RCTs comparing Metformin and Clomiphene Citrate for live birth rate- per patient

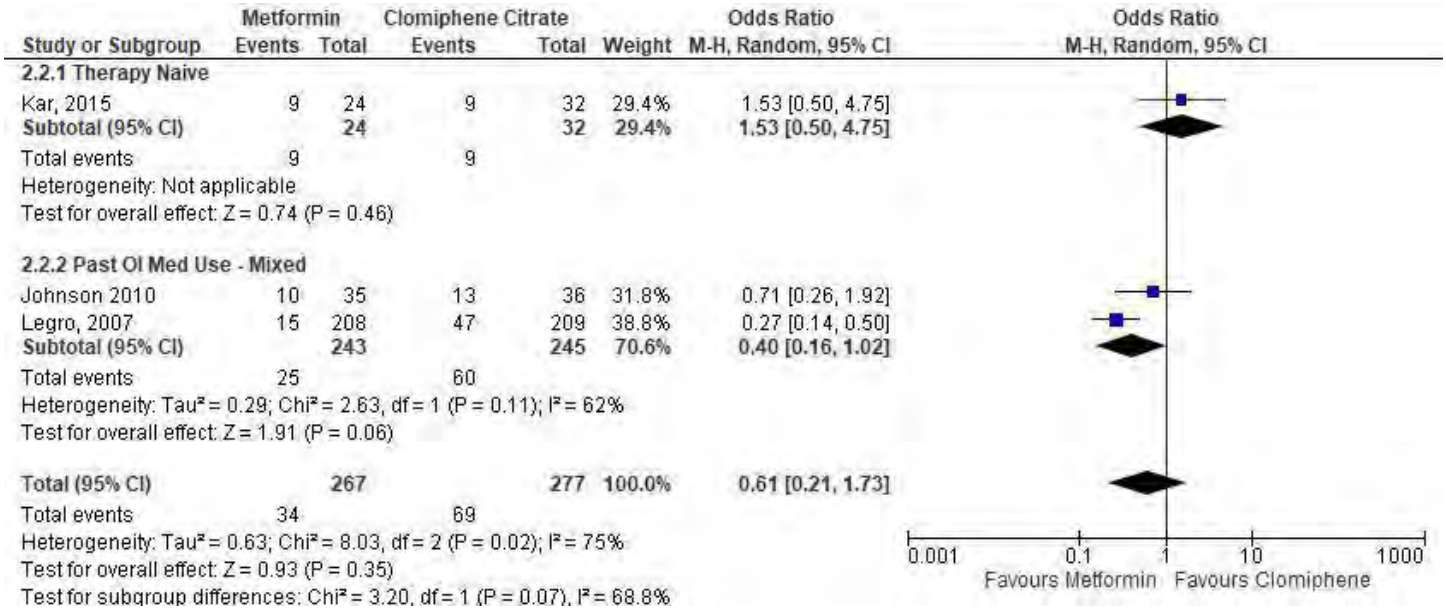


2.1.3. Funnel plot assessment for publication bias

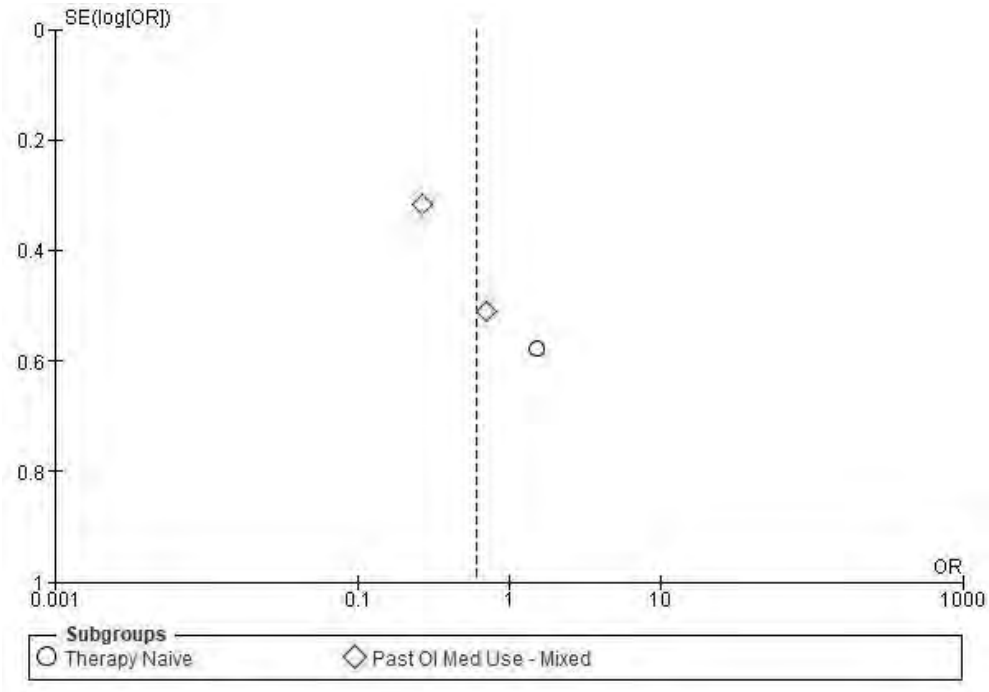


2.1.4. SUBGROUP ANALYSIS: Live birth rate – per patient

2.1.4.1. Forest Plot of all included RCTs comparing Metformin and Clomiphene Citrate for live birth rate- per patient, sub-grouped by past ovulation induction (OI) medication use

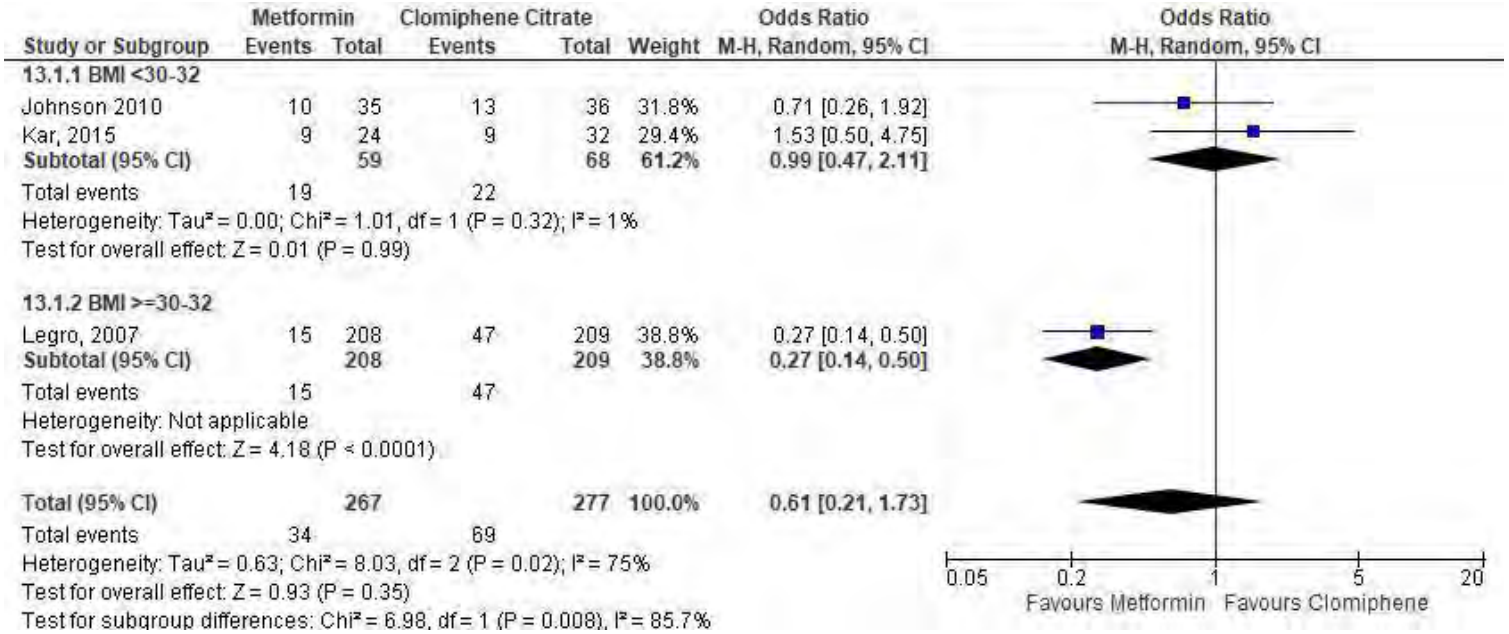


2.1.4.2. Funnel plot for assessment of publication bias: subgroup analysis: live birth rate- per patient



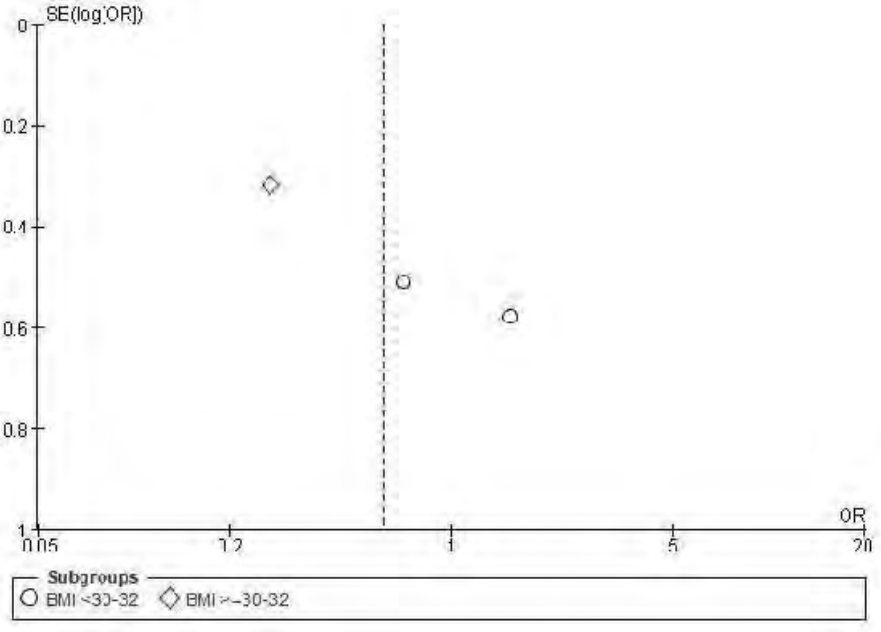
2.1.5. SUBGROUP ANALYSIS: Live birth rate – per patient

2.1.5.1. Forest Plot of all included RCTs comparing Metformin and Clomiphene Citrate for live birth rate- per patient, sub-grouped by BMI



Note: The above can also be considered subgrouped by risk of bias since Johnson and Kar were moderate risk and Legro was low risk

2.1.5.2. Funnel plot for assessment of publication bias: subgroup analysis: live birth rate- per patient



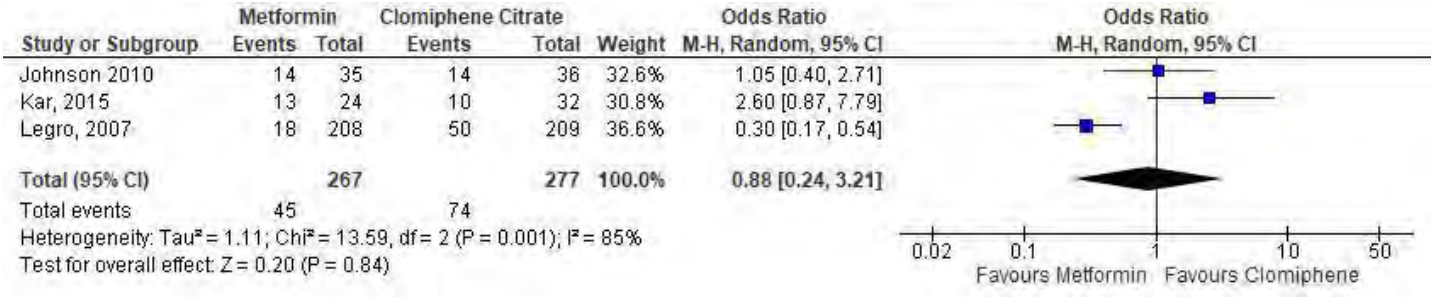
OUTCOME 2.2. Clinical pregnancy rate – per patient

OUTCOME: Clinical pregnancy rate per patient				**OUTCOME TYPE:** Dichotomous					
COMPARISON: Metformin vs Clomiphene Citrate									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in control / comparison group (MET)**	**N total in control/ comparison group (MET)**	**N events in intervention/ exposure group (CC)**	**N total in intervention/ exposure group (CC)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Johnson 2010 (MRB)	Mixed	Count	Investigator	14	35	14	36	Crude	NA
Kar 2015 (MRB)	TN	Count	Investigator	13	24	10	32	Crude	NA
Legro 2007 (LRB)	Mixed	Count	Investigator	18	208	50	209	Crude	NA

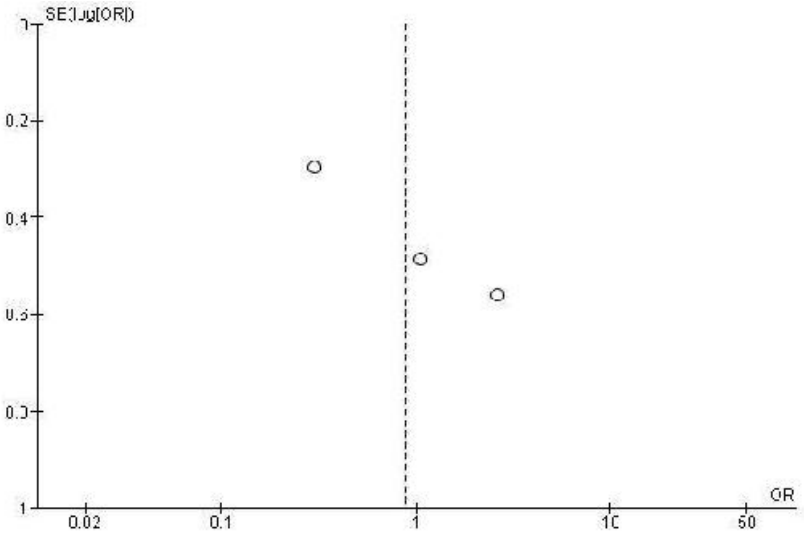
2.2.1. Individual Study Data Table

TN, therapy naïve; Mixed, includes clomiphene citrate resistant/failure and therapy naïve and/or not reported; **OI**, ovulation induction

2.2.2. Forest plot of all included RCTs comparing Metformin and Clomiphene Citrate for clinical pregnancy rate - per patient

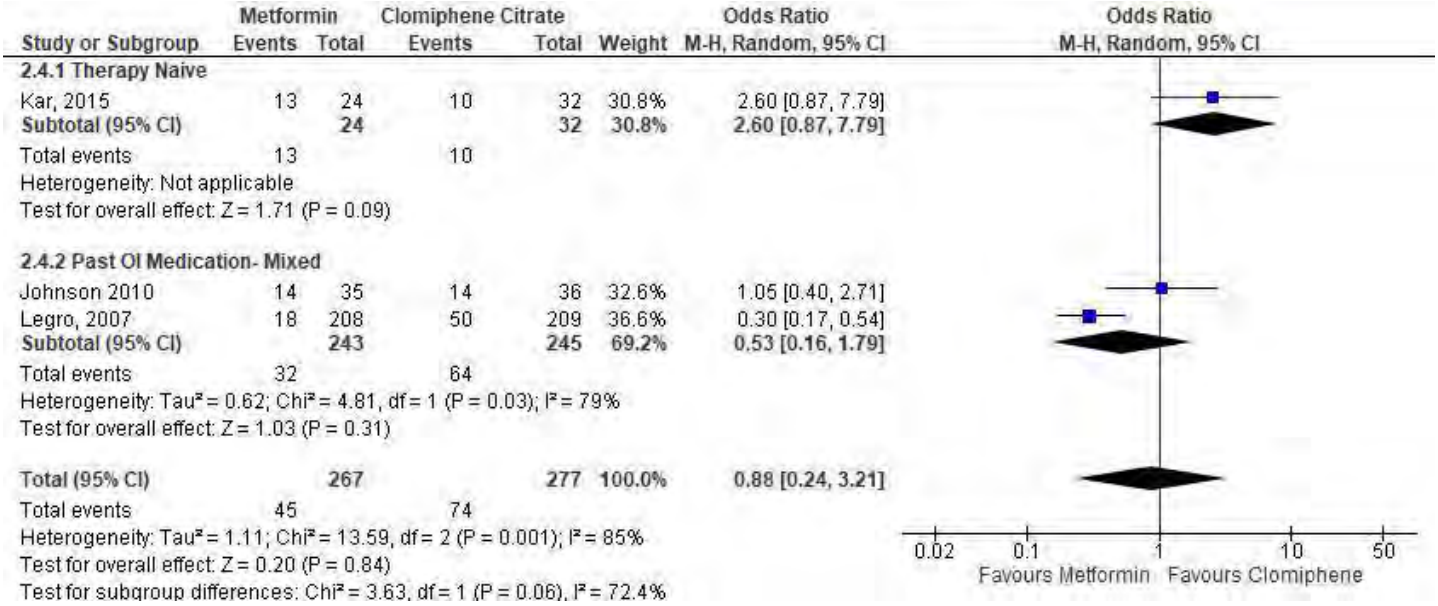


2.2.3. Funnel plot for assessment of publication bias

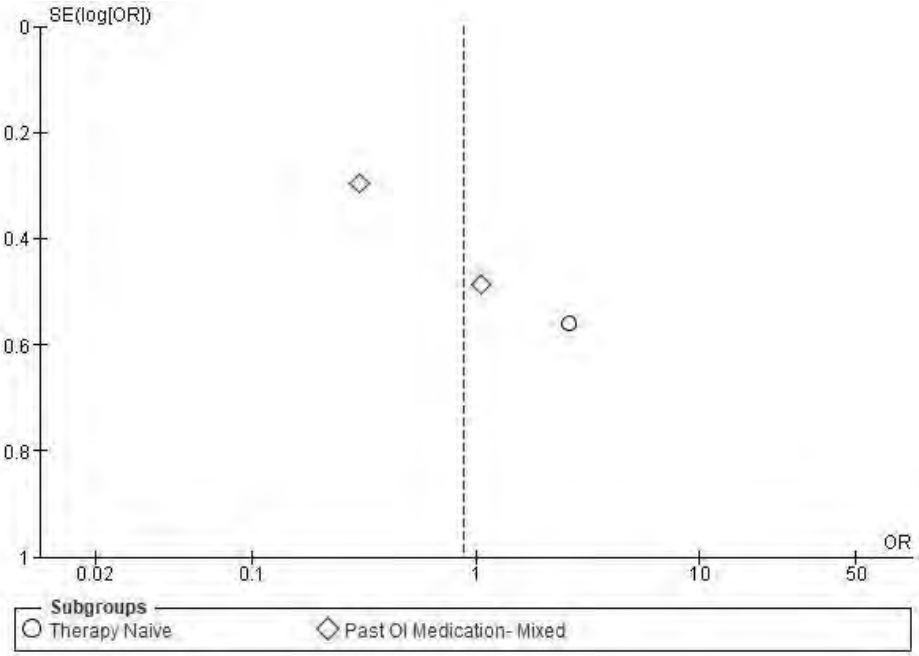


2.2.4.SUBGROUP ANALYSIS: Clinical pregnancy rate – per patient

2.2.4.1. Forest Plot of all included RCTs comparing Metformin and Clomiphene Citrate for clinical pregnancy rate- per patient, sub-grouped by past ovulation induction (OI) medication use

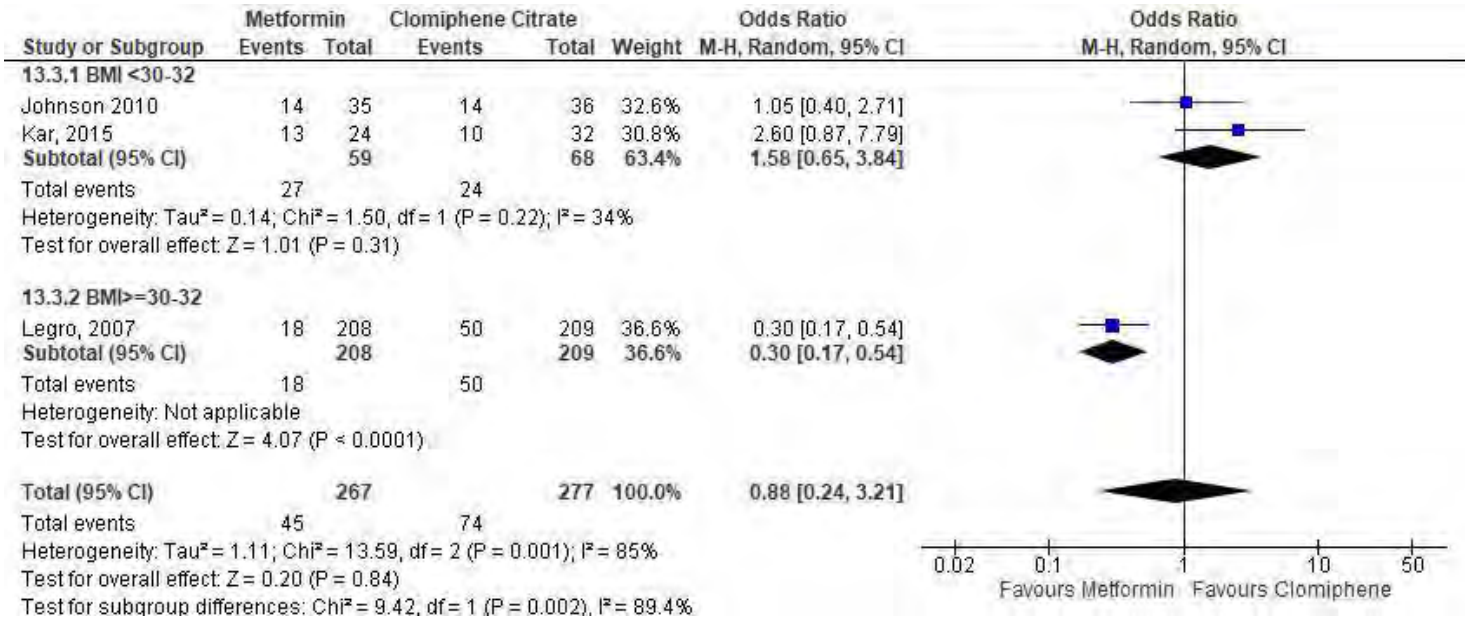


2.2.4.2. Funnel plot for assessment of publication bias: subgroup analysis: clinical pregnancy rate - per patient



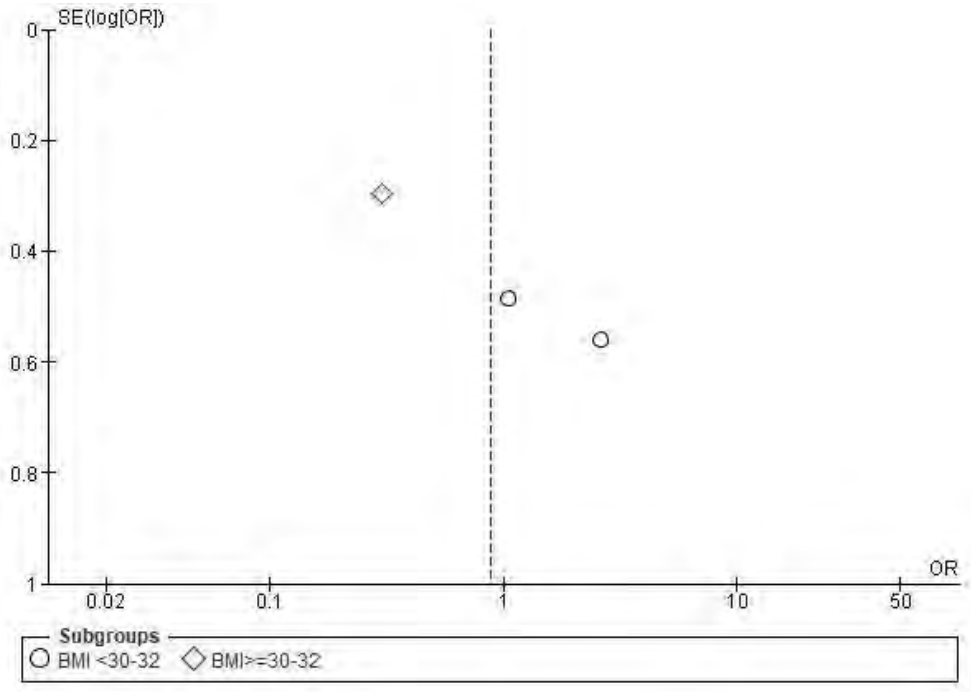
2.2.5. SUBGROUP ANALYSIS: Clinical pregnancy rate – per patient

2.2.5.1. Forest Plot of all included RCTs comparing Metformin and Clomiphene Citrate for clinical pregnancy rate- per patient, sub-grouped by BMI



Note: The above can also be considered subgrouped by risk of bias since Johnson and Kar were moderate risk and Legro was low risk

2.2.5.2. Funnel plot for assessment of publication bias: subgroup analysis: clinical pregnancy rate - per patient



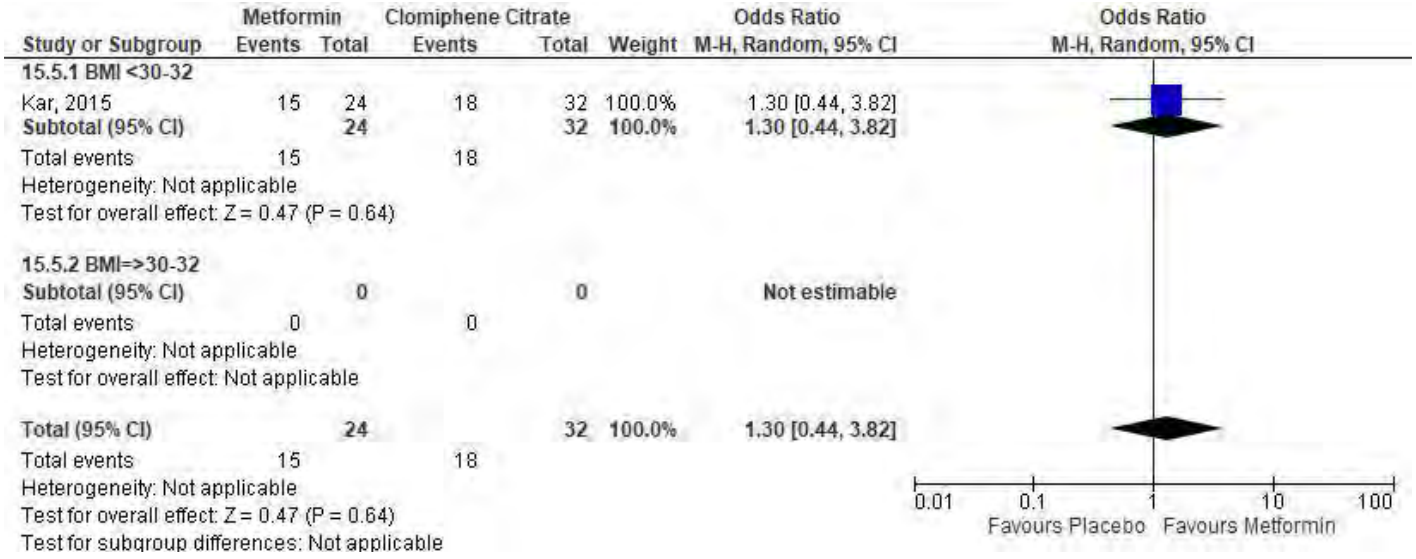
OUTCOME 2.3. Ovulation rate - per patient

2.3.1. Individual Study Data Table

OUTCOME: Ovulation rate per patient					**OUTCOME TYPE:** Dichotomous				
COMPARISON: Metformin vs Clomiphene Citrate									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in control / comparison group (MET)**	**N total in control/ comparison group (MET)**	**N events in intervention/ exposure group (CC)**	**N total in intervention/ exposure group (CC)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Kar 2015 (MRB)	TN	Count	Investigator	15	24	18	32	Crude	NA

TN, therapy naive; **OI**, ovulation induction

2.3.2. SUBGROUP ANALYSIS: Forest Plot of all included RCTs comparing Metformin and Clomiphene Citrate for ovulation rate- per patient, sub-grouped by BMI



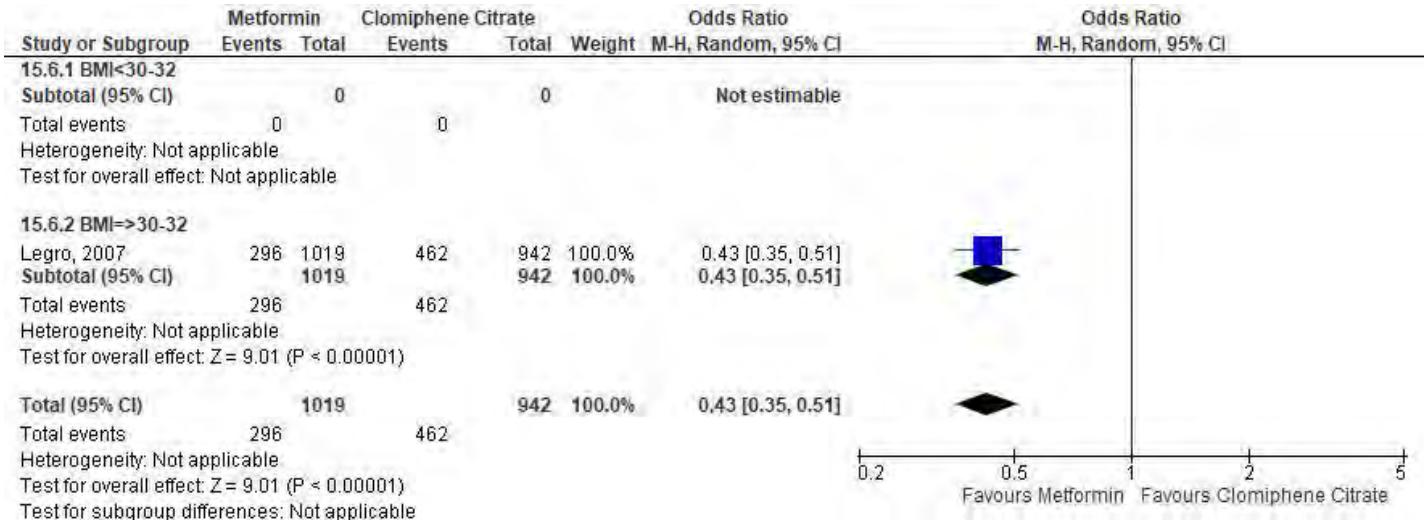
OUTCOME 2.4. Ovulation rate - per cycle

2.4.1. Individual Study Data Table

OUTCOME: Ovulation rate per cycle					**OUTCOME TYPE:** Dichotomous				
COMPARISON: Metformin vs Clomiphene Citrate									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in control / comparison group (MET)**	**N total in control/ comparison group (MET)**	**N events in intervention/ exposure group (CC)**	**N total in intervention/ exposure group (CC)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Legro 2007 (LRB)	Mixed	Count	Investigator	296	1019	462	942	Crude	NA

Mixed, includes clomiphene citrate resistant/failure and therapy naïve and/or not reported; **OI**, ovulation induction

2.4.2. SUBGROUP ANALYSIS: Forest Plot of all included RCTs comparing Metformin and Clomiphene Citrate for ovulation rate - per cycle, sub-grouped by BMI



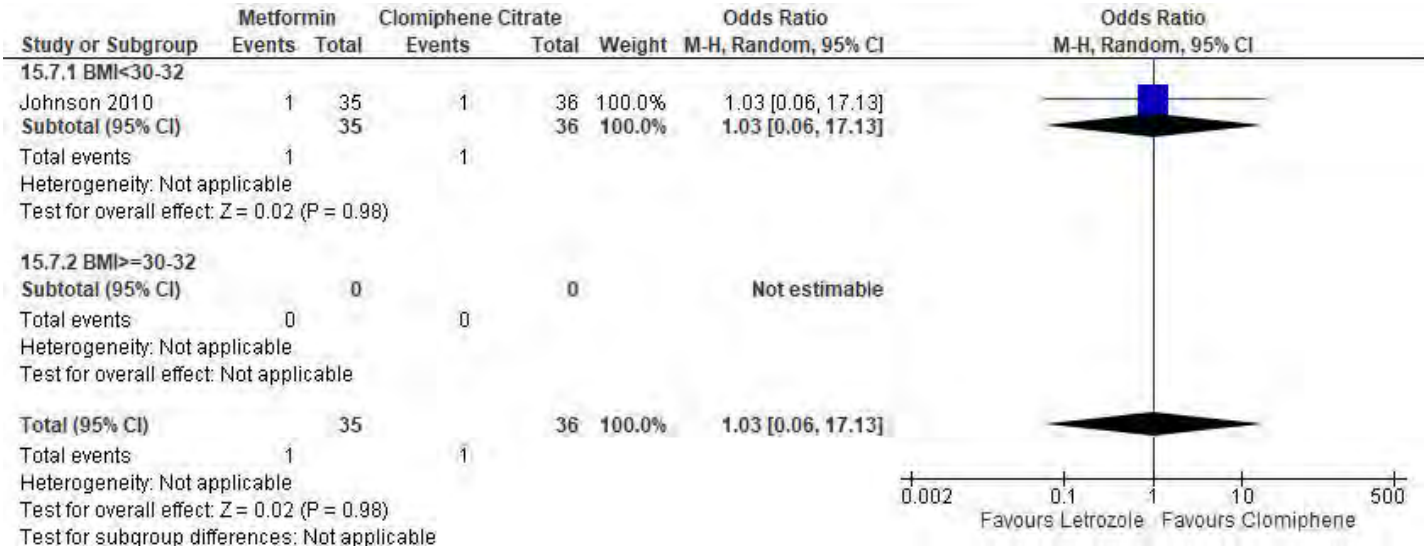
OUTCOME 2.5. Multiple pregnancy rate - per patient

2.5.1. Individual Study Data Table

OUTCOME: Multiple pregnancy rate per patient						**OUTCOME TYPE:** Dichotomous			
COMPARISON: Metformin vs Clomiphene Citrate									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in control / comparison group (MET)**	**N total in control/ comparison group (MET)**	**N events in intervention/ exposure group (CC)**	**N total in intervention/ exposure group (CC)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Johnson 2010 (MRB)	Mixed	Count	Investigator	1	35	1	36	Crude	NA

Mixed, includes clomiphene citrate resistant/failure and therapy naïve and/or not reported; **OI**, ovulation induction

2.5.2. Forest Plot of all included RCTs comparing Metformin and Clomiphene Citrate for multiple pregnancy rate- per patient, sub-grouped by BMI



OUTCOME 2.6. Miscarriage rate - per patient

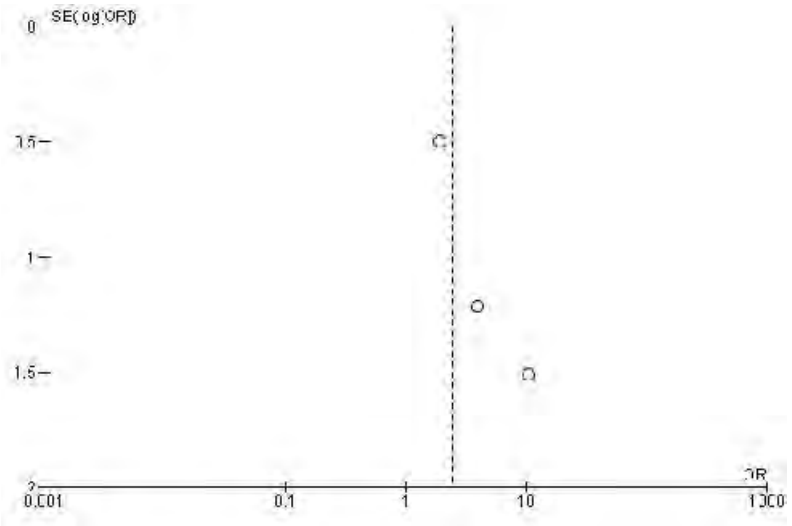
2.6.1. Individual Study Data Table

OUTCOME: Miscarriage rate - per patient				**OUTCOME TYPE:** Dichotomous					
COMPARISON: Metformin vs Clomiphene Citrate									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in control / comparison group (MET)**	**N total in control/ comparison group (MET)**	**N events in intervention/ exposure group (CC)**	**N total in intervention/ exposure group (CC)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Johnson 2010 (MRB)	Mixed	Count	Investigator	4	35	0	36	Crude	NA
Kar 2015 (MRB)	TN	Count	Investigator	4	13	1	10	Crude	NA
Legro 2007 (LRB)	Mixed	Count	Investigator	10	25	16	62	Crude	Na

TN, therapy naïve**; Mixed**, includes clomiphene citrate resistant/failure and therapy naïve and/or not reported; **OI**, ovulation induction

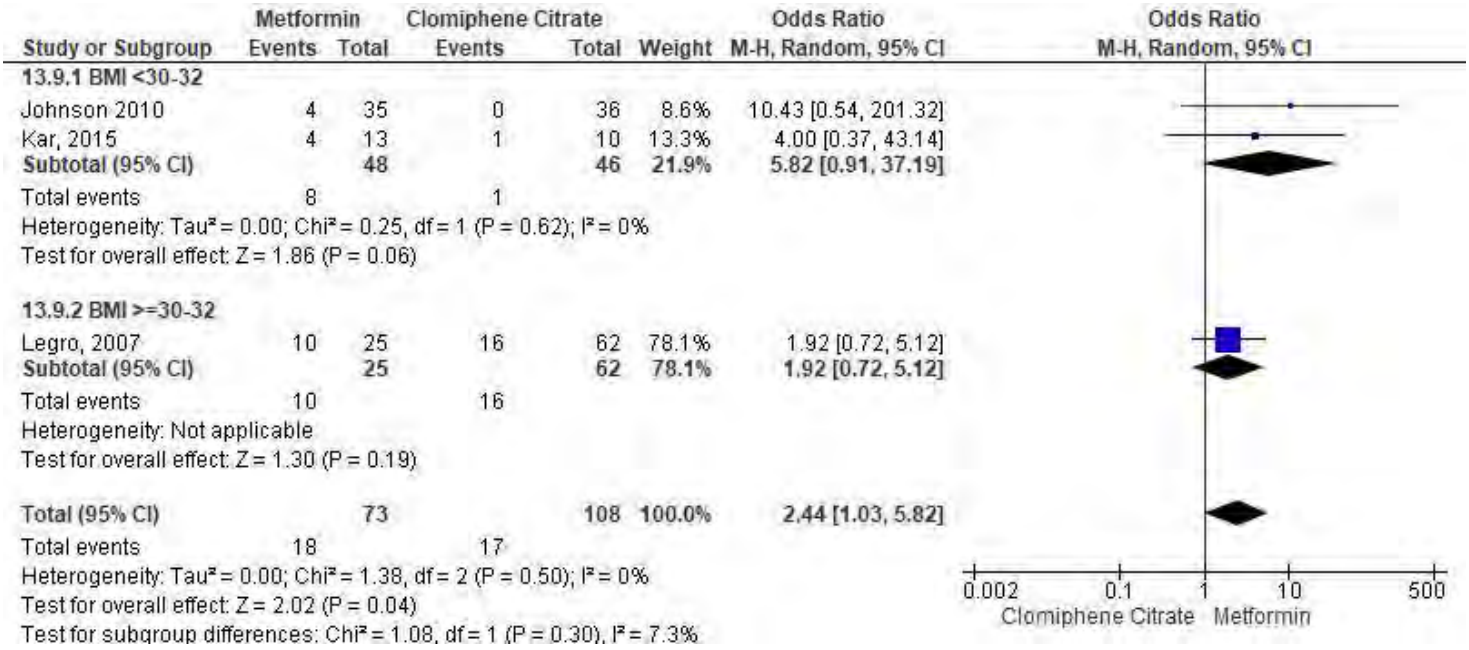
2.6.2. Forest plot of all included RCTs comparing Metformin and Clomiphene Citrate for miscarriage rate- per patient

2.6.3. Funnel plot for assessment of publication bias



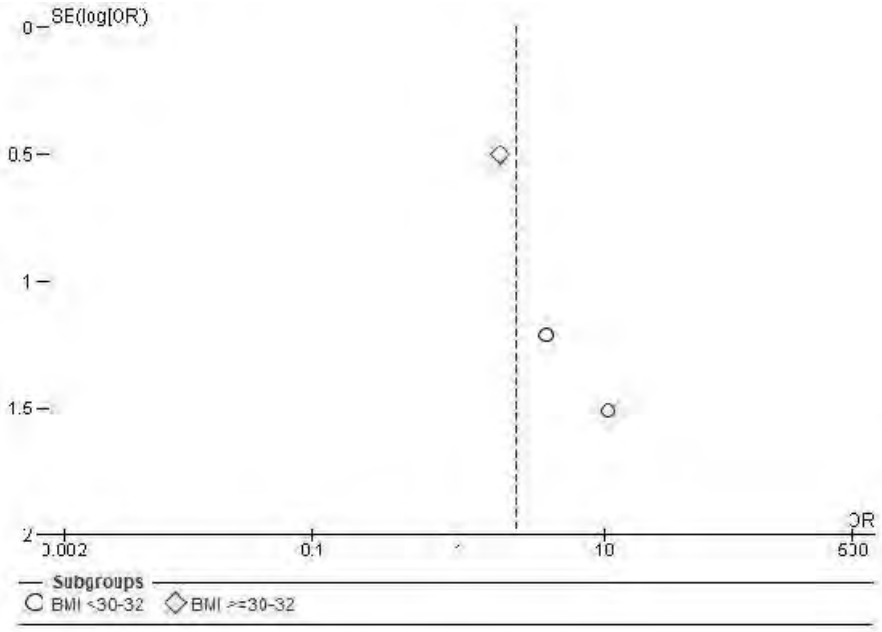
2.6.4.SUBGROUP ANALYSIS: Miscarriage rate – per patient

2.6.4.1. Forest Plot of all included RCTs comparing Metformin and Clomiphene Citrate for miscarriage rate- per patient, sub-grouped by BMI



Note: The above can also be considered subgrouped by risk of bias since Johnson and Kar were moderate risk and Legro was low risk

2.6.4.2. Funnel plot for assessment of publication bias: subgroup analysis: miscarriage rate - per patient



COMPARISON 3. Metformin + Clomiphene Citrate versus Metformin

- **EVIDENCE SUMMARY:**

Three studies examined metformin + clomiphene citrate compared with metformin alone in women with PCOS. Of these, one had a moderate risk of bias (Kar et al. 2015) in therapy naïve women with PCOS in India. The remaining two were moderate (Johnson et al. 2010) and low risk (Legro et al. 2007) studies in New Zealand and the US, respectively, with mixed ovulation induction medication use history.

- **META-ANALYSIS SUMMARY:**

In meta-analysis of the three RCTs, metformin combined with clomiphene citrate had a favourable effect on live birth rate and ovulation rate per patient, with odds ratios of 2.44 and 3.72, respectively. These outcomes were both of moderate certainty; live birth rate was downgraded for indirectness resulting from diverse populations since the studies included treatment naïve patients and those with clomiphene-citrate resistance or failure; and ovulation rate was downgraded due to being derived from a single study (despite its relatively large sample size, the result requires replication to increase certainty in the evidence). Subgroup analysis by BMI showed that the beneficial effect of metformin + clomiphene citrate on live birth rate was most pronounced in women with a BMI ≥30-32 kg/m^2, however only one study was included in this subgroup.

Summary Table for meta-analysis results:

Outcome or Subgroup	Studies	n	Effect Estimate; OR [95% CI], M-H, random	P	Favours	Certainty
Live birth rate- per patient	3	535	2.44 [1.03, 5.76]	0.04	**MET + CC** (live birth is higher with MET + CC)	⊕⊕⊕◯ MODERATE
Clinical pregnancy rate- per patient†	3	535	2.11 [0.75, 5.93]	0.16	None	⊕⊕◯◯ LOW
Ovulation Rate- per patient	1	48	3.00 [0.77, 11.63]	0.11	None	⊕⊕◯◯ LOW
Ovulation Rate- per cycle	1	1983	3.72 [3.09, 4.49]	<0.00001	**MET + CC** (ovulation per cycle is higher with MET + CC)	⊕⊕⊕◯ MODERATE
Multiple pregnancy rate- per patient	1	70	1.00 [0.06, 16.65]	1.0	None	⊕⊕⊕◯ MODERATE
Miscarriage rate- per patient	3	200	0.63 [0.30, 1.31]	0.22	None	⊕⊕⊕◯ MODERATE

†clinical pregnancy rate is confirmed by ultrasound detection of gestational sac/ fetal heart activity

OUTCOME 3.1. Live birth rate- per patient

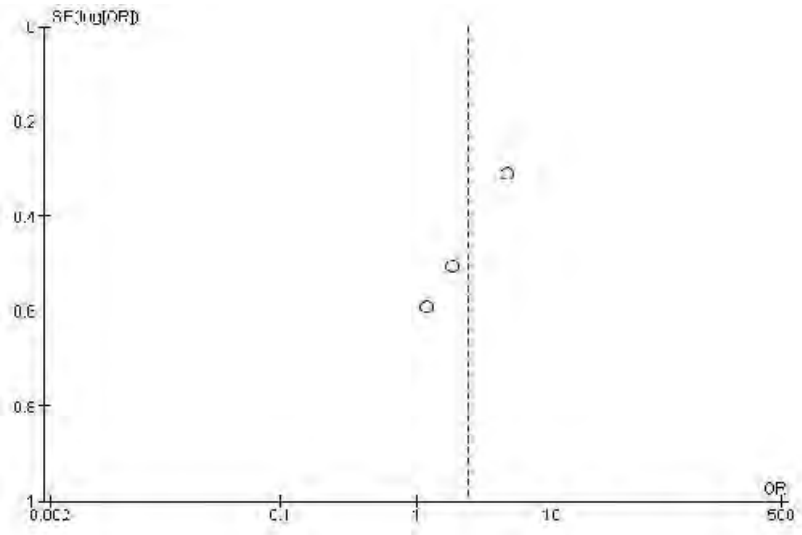
3.1.1. Individual Study Data Table

OUTCOME: Live birth rate per patient						**OUTCOME TYPE:** Dichotomous			
COMPARISON: Metformin + Clomiphene Citrate vs Metformin									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in control / comparison group (MET+CC)**	**N total in control/ comparison group (MET+CC)**	**N events in intervention/ exposure group (MET)**	**N total in intervention/ exposure group (MET)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Johnson 2010 (MRB)	Mixed	Count	Investigator	15	35	10	35	Crude	NA
Kar 2015 (MRB)	TN	Count	Investigator	10	24	9	24	Crude	NA
Legro 2007 (LRB)	Mixed	Count	Investigator	56	209	15	208	Crude	Na

TN, therapy naïve; **Mixed**, includes clomiphene citrate resistant/failure and therapy naïve and/or not reported; **OI**, ovulation induction

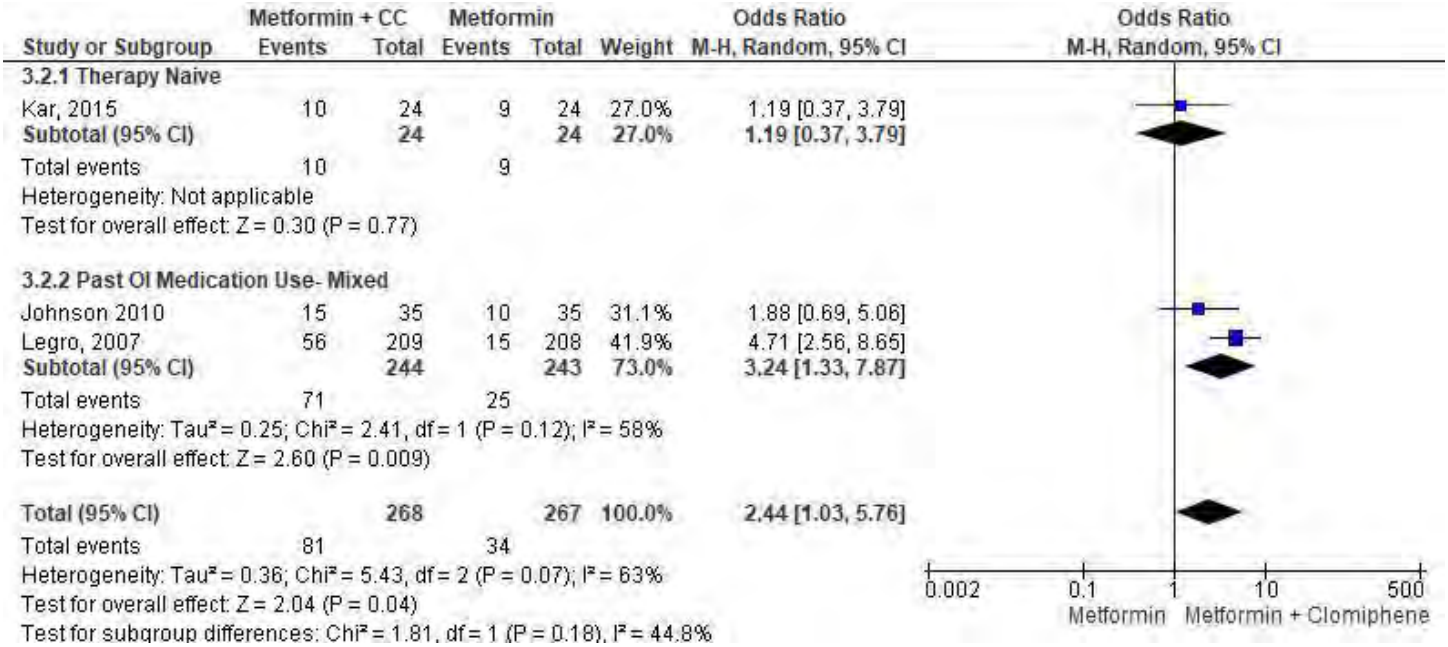
3.1.2. Forest Plot of all included RCTs comparing Metformin + Clomiphene Citrate vs Metformin for live birth rate- per patient

3.1.3. Funnel plot for assessment of publication bias

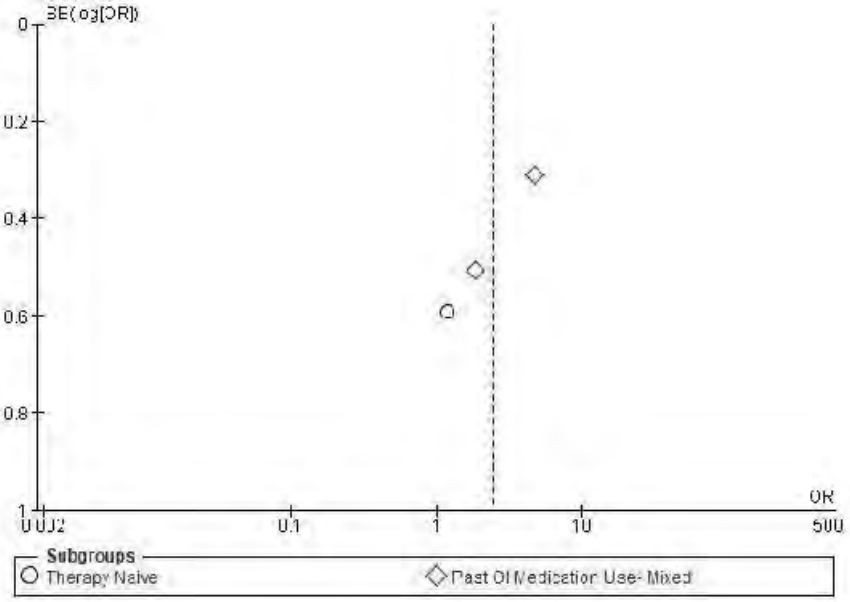


3.1.4. SUBGROUP ANALYSIS: Live birth rate – per patient

3.1.4.1. Forest Plot of all included RCTs comparing Metformin + Clomiphene Citrate vs Metformin for live birth rate- per patient, sub-grouped by past ovulation induction (OI) medication use

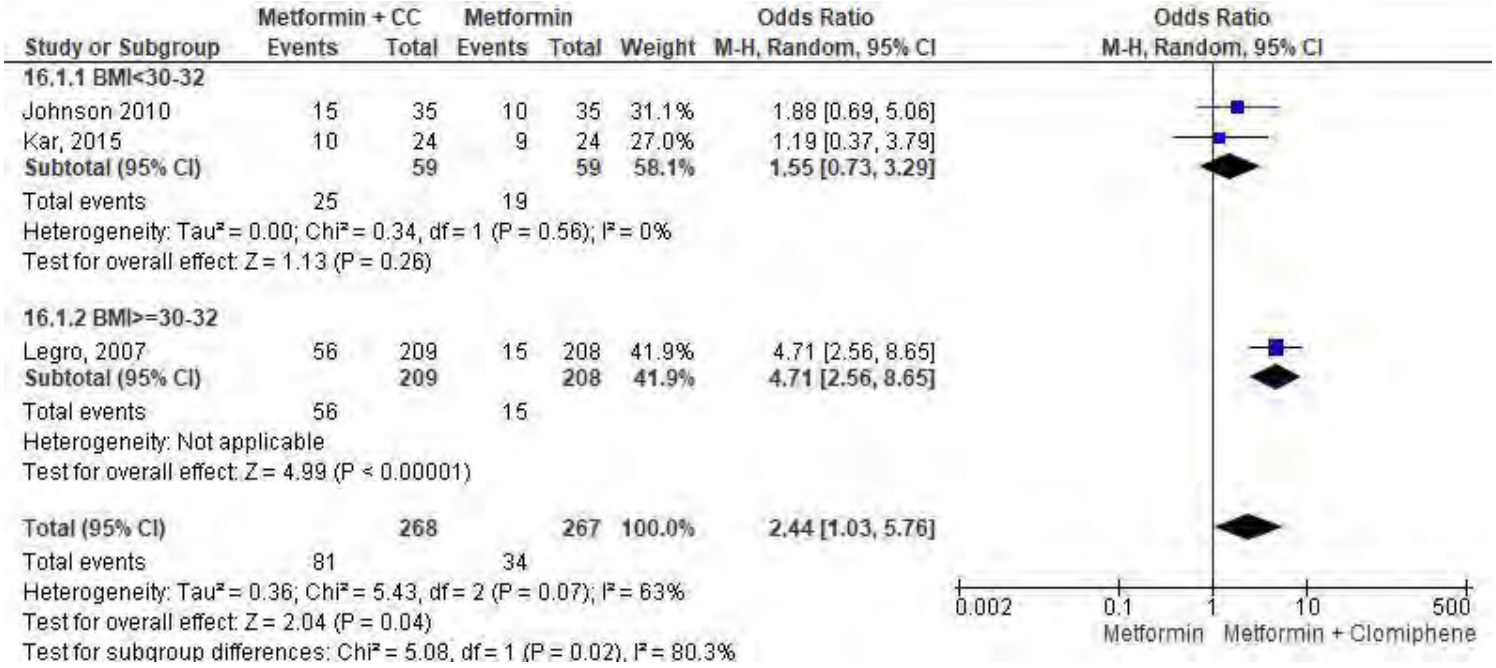


3.1.4.2. Funnel plot for assessment of publication bias: subgroup analysis: live birth rate - per patient



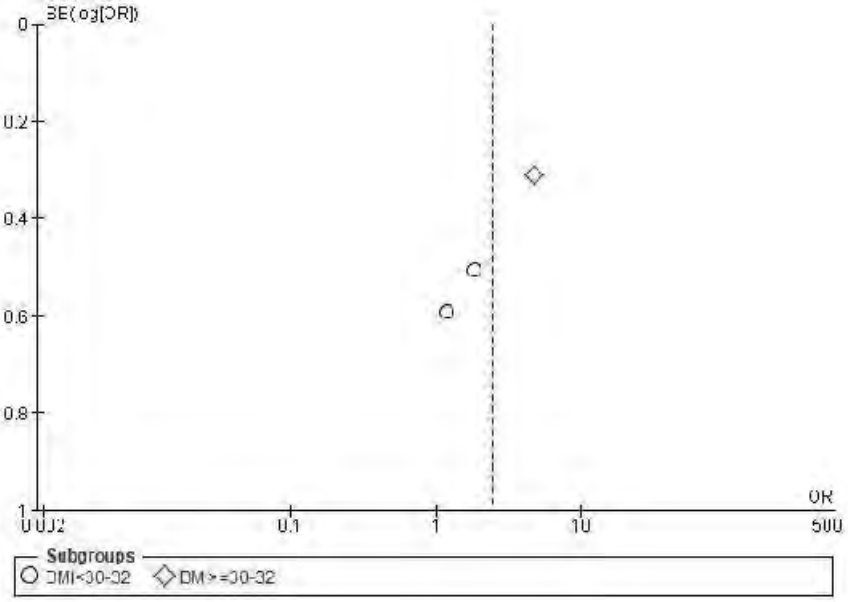
3.1.5.SUBGROUP ANALYSIS: Live birth rate – per patient

3.1.5.1. Forest Plot of all included RCTs comparing Metformin + Clomiphene Citrate vs Metformin for live birth rate- per patient, sub-grouped by BMI



Note: The above can also be considered subgrouped by risk of bias since Johnson and Kar were moderate risk and Legro was low risk

3.1.5.2. Funnel plot for assessment of publication bias: subgroup analysis: live birth rate - per patient



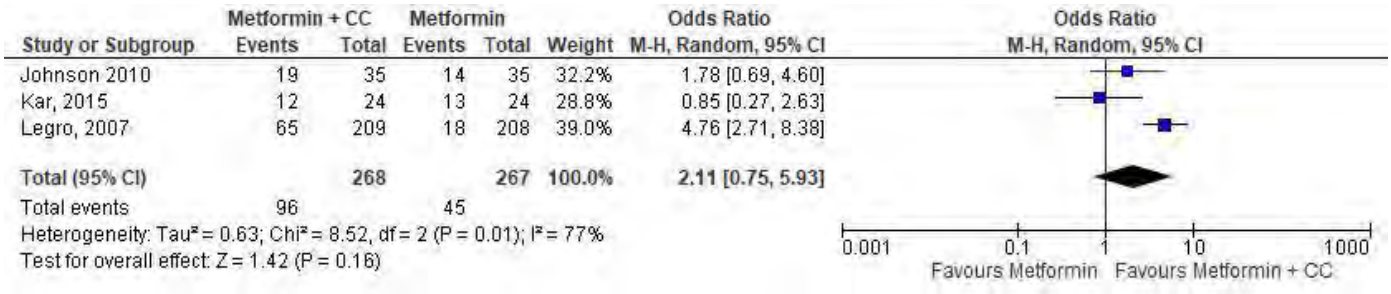
OUTCOME 3.2. Clinical pregnancy rate- per patient

3.2.1. Individual Study Data Table

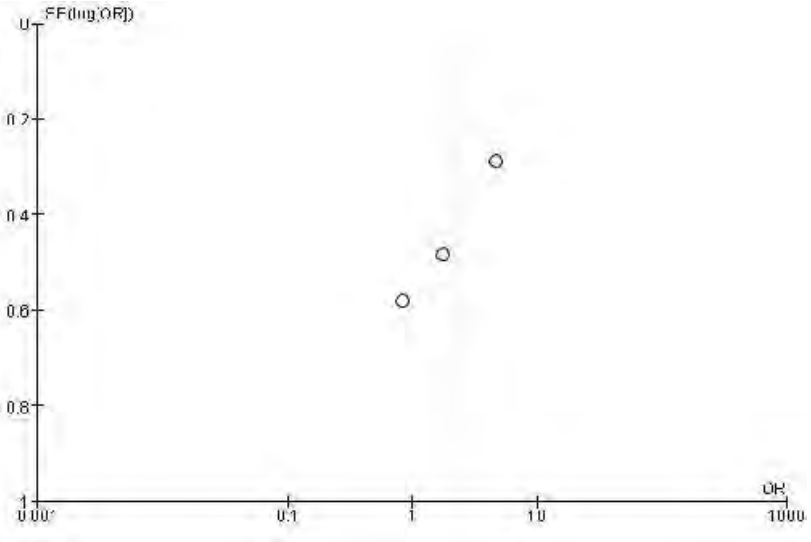
OUTCOME: Clinical pregnancy rate per patient				**OUTCOME TYPE:** Dichotomous					
COMPARISON: Metformin + Clomiphene Citrate vs Metformin									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in control / comparison group (MET+CC)**	**N total in control/ comparison group (MET+CC)**	**N events in intervention/ exposure group (MET)**	**N total in intervention/ exposure group (MET)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Johnson 2010 (MRB)	Mixed	Count	Investigator	19	35	14	35	Crude	NA
Kar 2015 (MRB)	TN	Count	Investigator	12	24	13	24	Crude	NA
Legro 2007 (LRB)	Mixed	Count	Investigator	65	209	18	208	Crude	Na

TN, therapy naïve; **Mixed**, includes clomiphene citrate resistant/failure and therapy naïve and/or not reported; **OI**, ovulation induction

3.2.2 Forest Plot of all included RCTs comparing Metformin + Clomiphene Citrate vs Metformin for clinical pregnancy rate- per patient

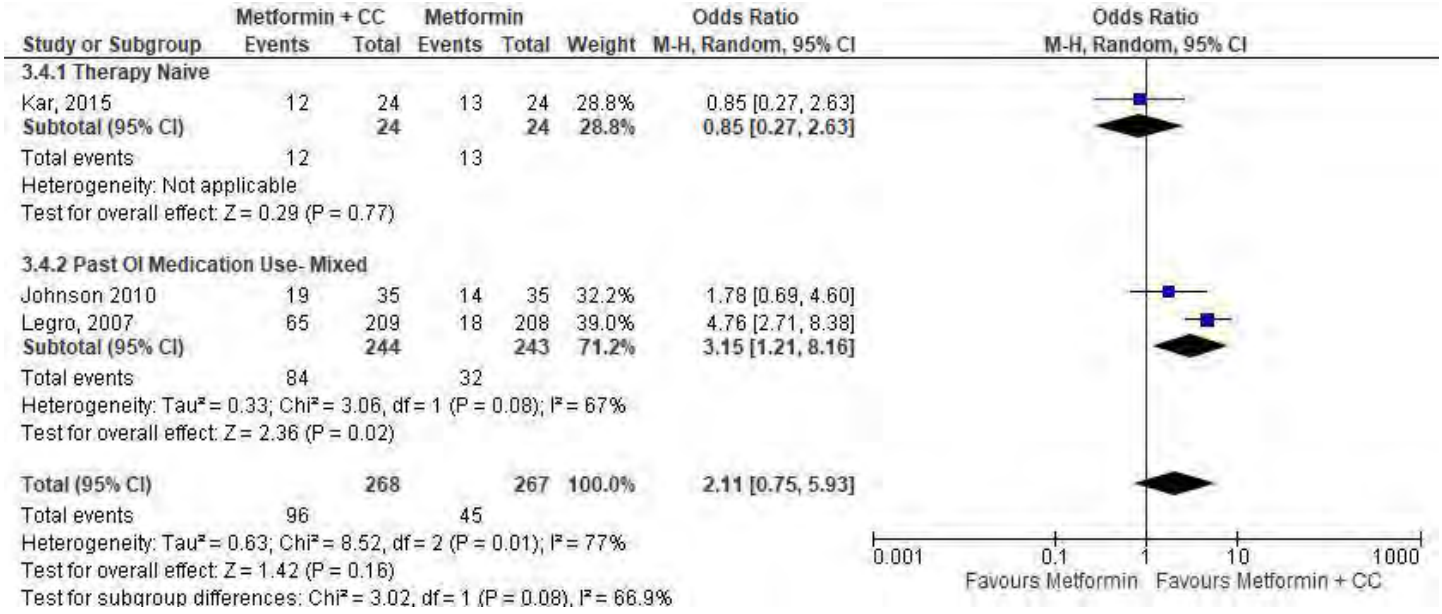


3.2.3. Funnel plot for assessment of publication bias

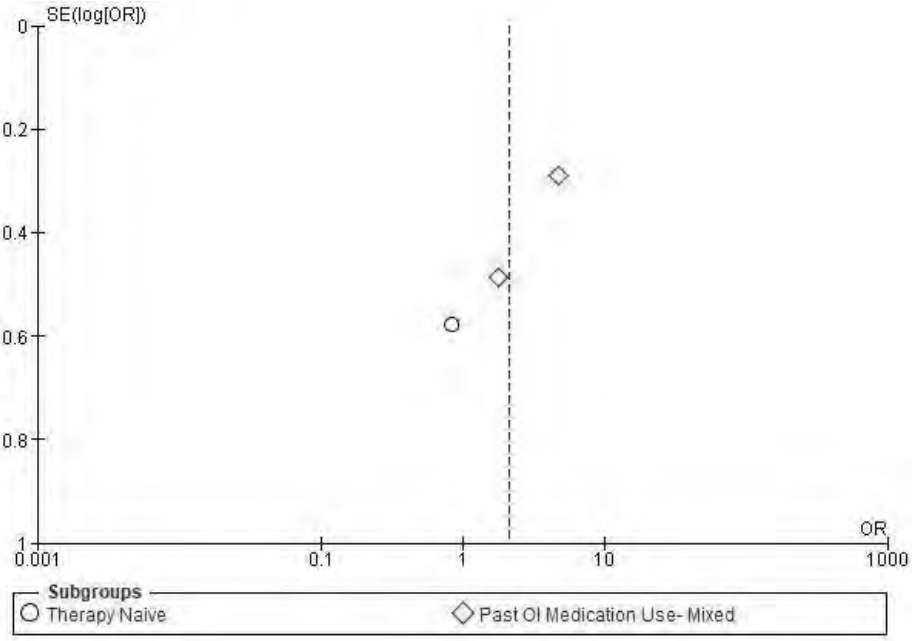


3.2.4. SUBGROUP ANALYSIS: Clinical pregnancy rate – per patient

3.2.4.1. Forest Plot of all included RCTs comparing Metformin + Clomiphene Citrate versus Clomiphene Citrate for clinical pregnancy rate- per patient, sub-grouped by past ovulation induction (OI) medication use

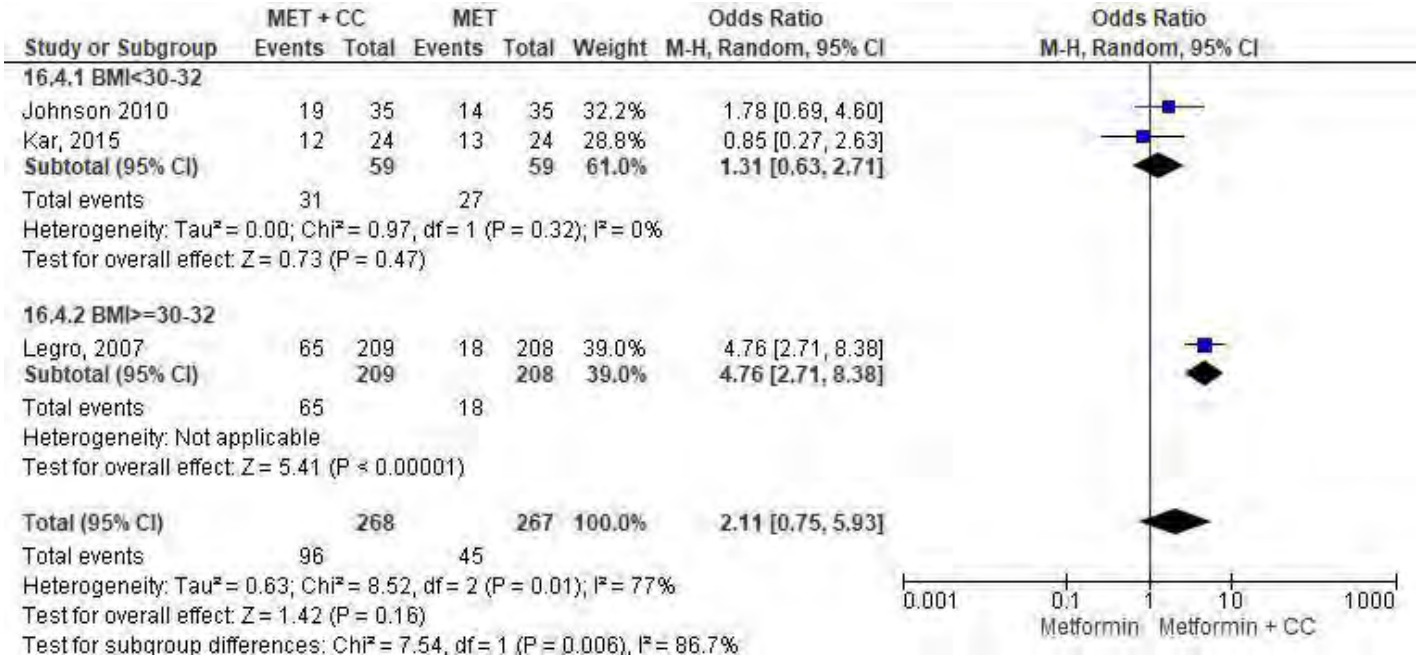


3.2.4.2. Funnel plot for assessment of publication bias: subgroup analysis: clinical pregnancy rate - per patient



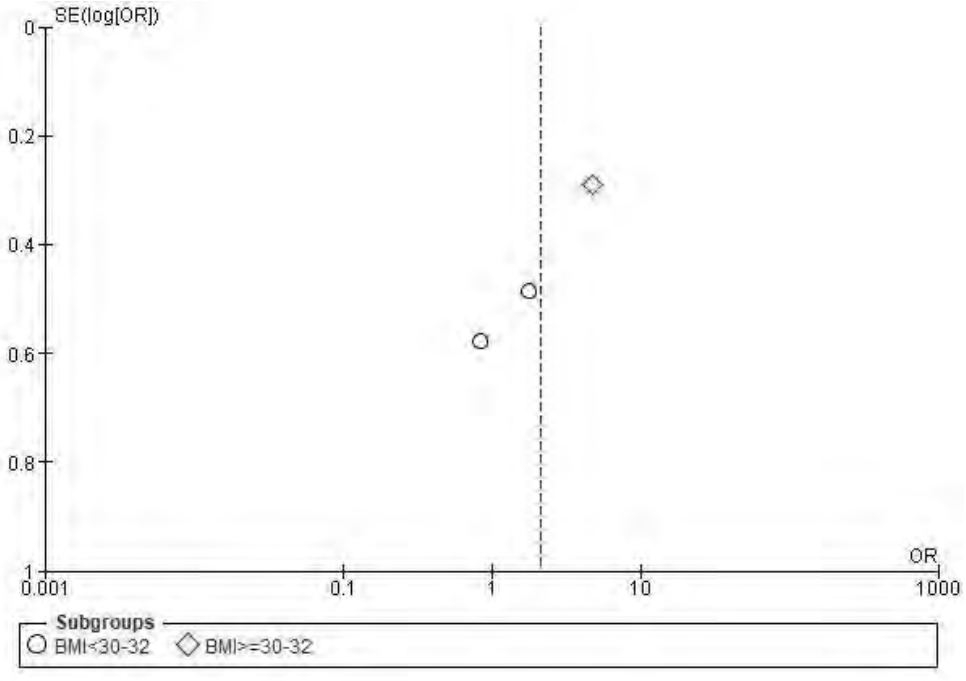
3.2.5.SUBGROUP ANALYSIS: Clinical pregnancy rate – per patient

3.2.5.1. Forest Plot of all included RCTs comparing Metformin + Clomiphene Citrate vs Metformin for clinical pregnancy rate- per patient, sub-grouped by BMI



Note: The above can also be considered subgrouped by risk of bias since Johnson and Kar were moderate risk and Legro was low risk

3.2.5.2. Funnel plot for assessment of publication bias: subgroup analysis: clinical pregnancy rate - per patient



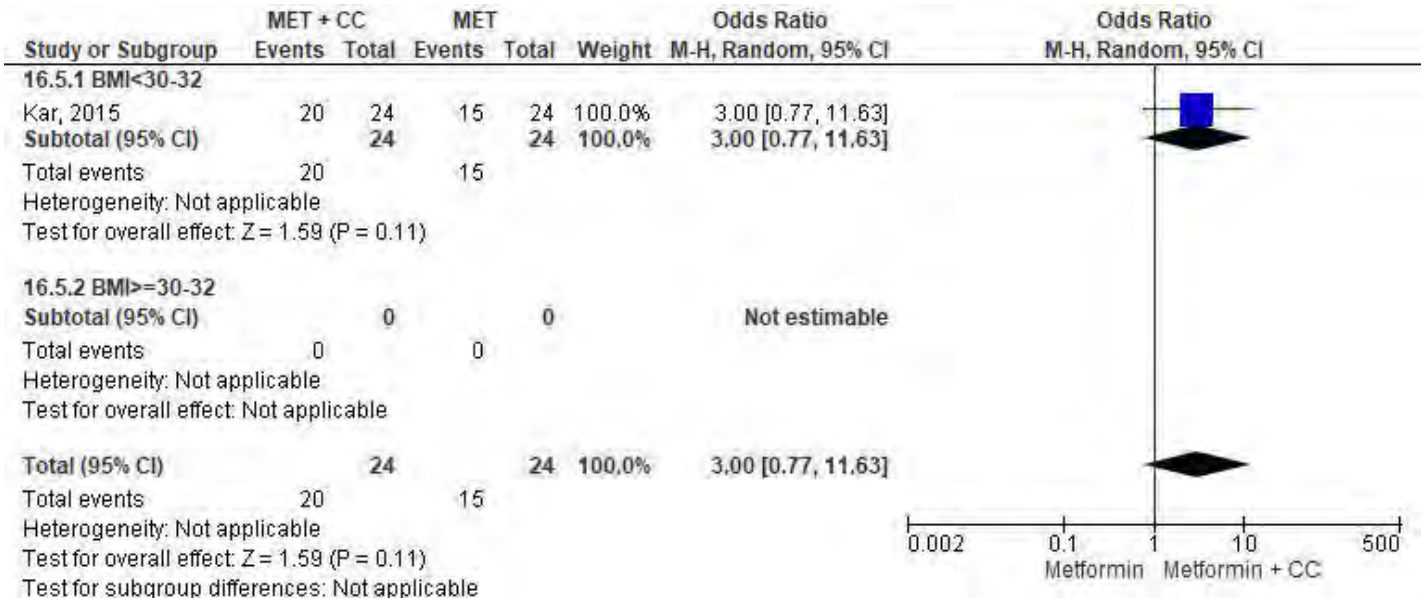
OUTCOME 3.3. Ovulation rate- per patient

3.3.1. Individual Study Data Table

OUTCOME: Ovulation rate per patient					**OUTCOME TYPE:** Dichotomous				
COMPARISON: Metformin + Clomiphene Citrate vs Metformin									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in control / comparison group (MET+CC)**	**N total in control/ comparison group (MET+CC)**	**N events in intervention/ exposure group (MET)**	**N total in intervention/ exposure group (MET)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Kar 2015 (MRB)	TN	Count	Investigator	10	24	9	24	Crude	NA

TN, therapy naïve

3.3.2. Forest Plot of all included RCTs comparing Metformin + Clomiphene Citrate vs Metformin for ovulation rate- per patient, sub-grouped by BMI



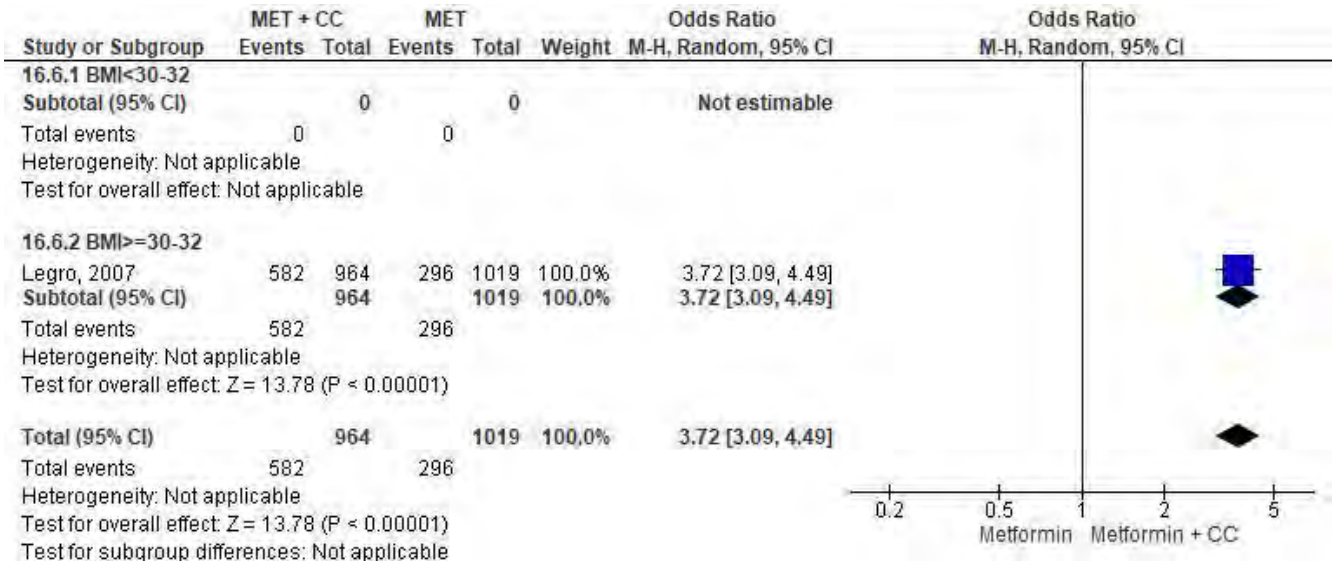
OUTCOME 3.4. Ovulation rate- per cycle

3.4.1. Individual Study Data Table

OUTCOME: Ovulation rate per cycle					**OUTCOME TYPE:** Dichotomous				
COMPARISON: Metformin + Clomiphene Citrate vs Metformin									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in control / comparison group (MET+CC)**	**N total in control/ comparison group (MET+CC)**	**N events in intervention/ exposure group (MET)**	**N total in intervention/ exposure group (MET)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Legro 2007 (LRB)	Mixed	Count	Investigator	582	964	296	1019	Crude	Na

Mixed, includes clomiphene citrate resistant/failure and therapy naïve and/or not reported; **OI**, ovulation induction

3.4.2. Forest Plot of all included RCTs comparing Metformin + Clomiphene Citrate vs Metformin for ovulation rate- per cycle, sub-grouped by BMI



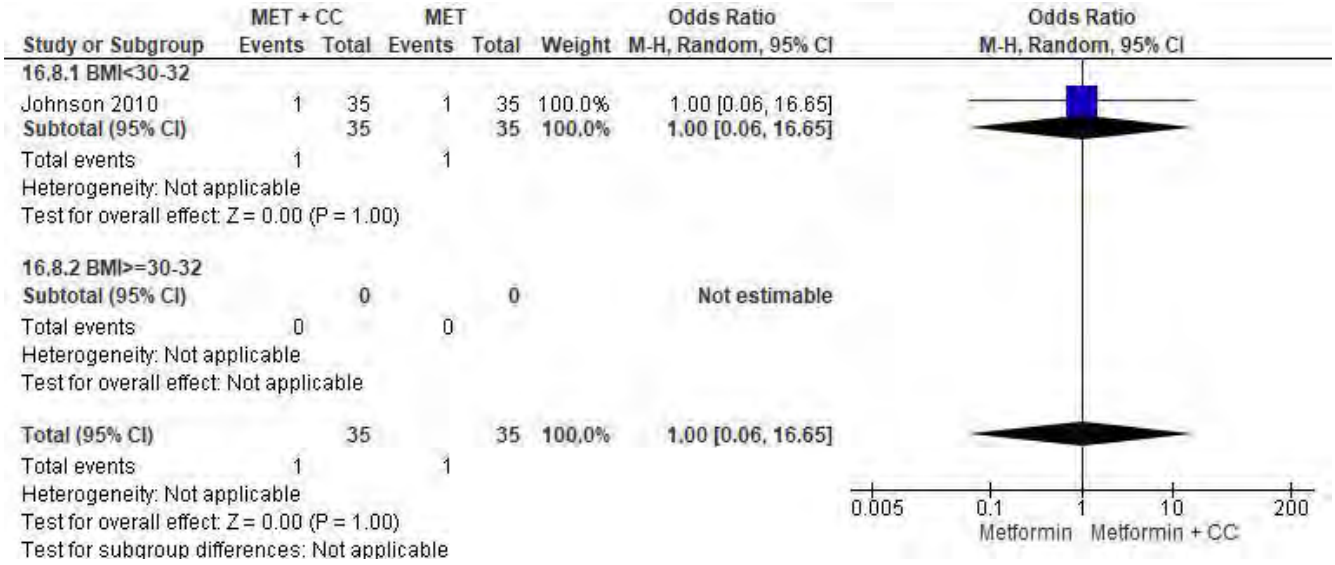
OUTCOME 3.5. Multiple pregnancy rate- per patient

3.5.1. Individual Study Data Table

OUTCOME: Multiple pregnancy rate- per patient					**OUTCOME TYPE:** Dichotomous				
COMPARISON: Metformin + Clomiphene Citrate vs Metformin									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in control / comparison group (MET+CC)**	**N total in control/ comparison group (MET+CC)**	**N events in intervention/ exposure group (MET)**	**N total in intervention/ exposure group (MET)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Johnson 2010 (MRB)	Mixed	Count	Investigator	1	35	1	35	Crude	NA

Mixed, includes clomiphene citrate resistant/failure and therapy naïve and/or not reported; **OI**, ovulation induction

3.5.2. Forest Plot of all included RCTs comparing Metformin + Clomiphene Citrate vs Metformin for multiple pregnancy rate- per patient, sub-grouped by BMI

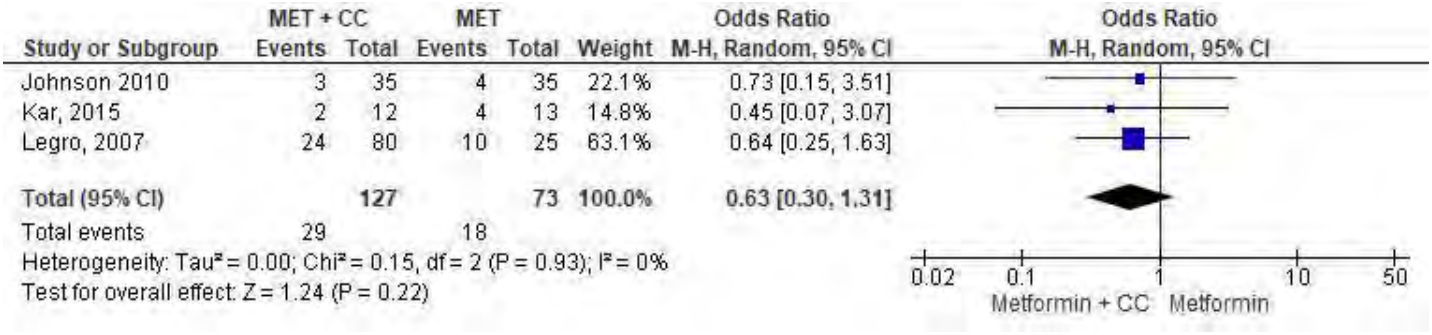


3.6.1. Individual Study Data Table

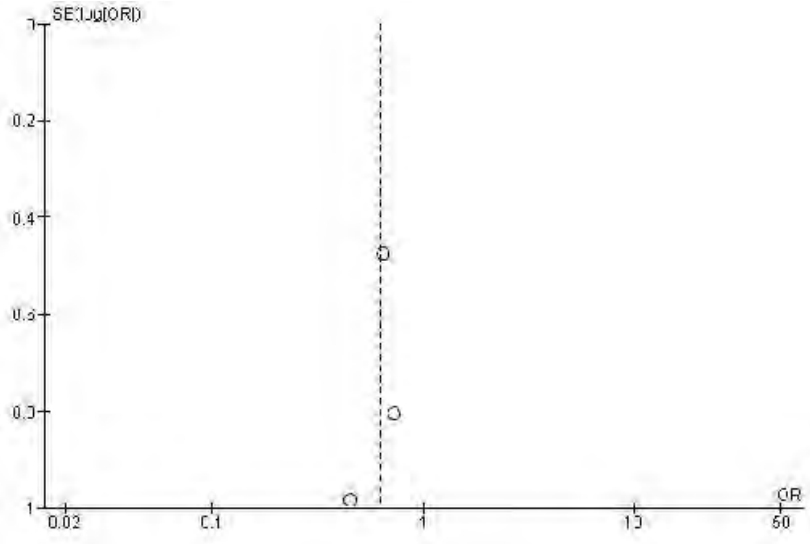
OUTCOME: Miscarriage rate- per patient						**OUTCOME TYPE:** Dichotomous			
COMPARISON: Metformin + Clomiphene Citrate vs Metformin									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in control / comparison group (MET+CC)**	**N total in control/ comparison group (MET+CC)**	**N events in intervention/ exposure group (MET)**	**N total in intervention/ exposure group (MET)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Johnson 2010 (MRB)	Mixed	Count	Investigator	3	35	4	35	Crude	NA
Kar 2015 (MRB)	TN	Count	Investigator	2	12	4	13	Crude	NA
Legro 2007 (LRB)	Mixed	Count	Investigator	24	80	10	25	Crude	Na

TN, therapy naïve; **Mixed**, includes clomiphene citrate resistant/failure and therapy naïve and/or not reported; **OI**, ovulation induction

3.6.2. Forest Plot of all included RCTs comparing Metformin + Clomiphene Citrate versus Metformin for miscarriage rate- per patient

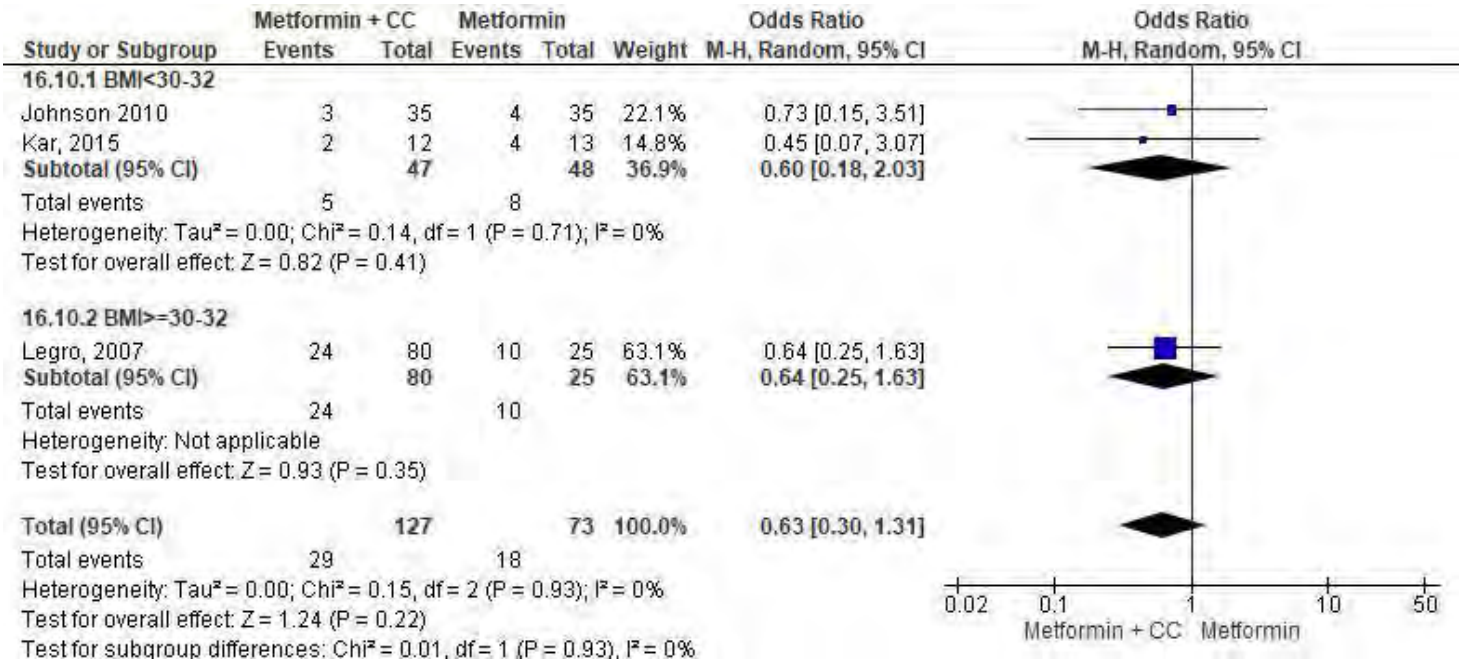


3.6.3. Funnel plot for assessment of publication bias



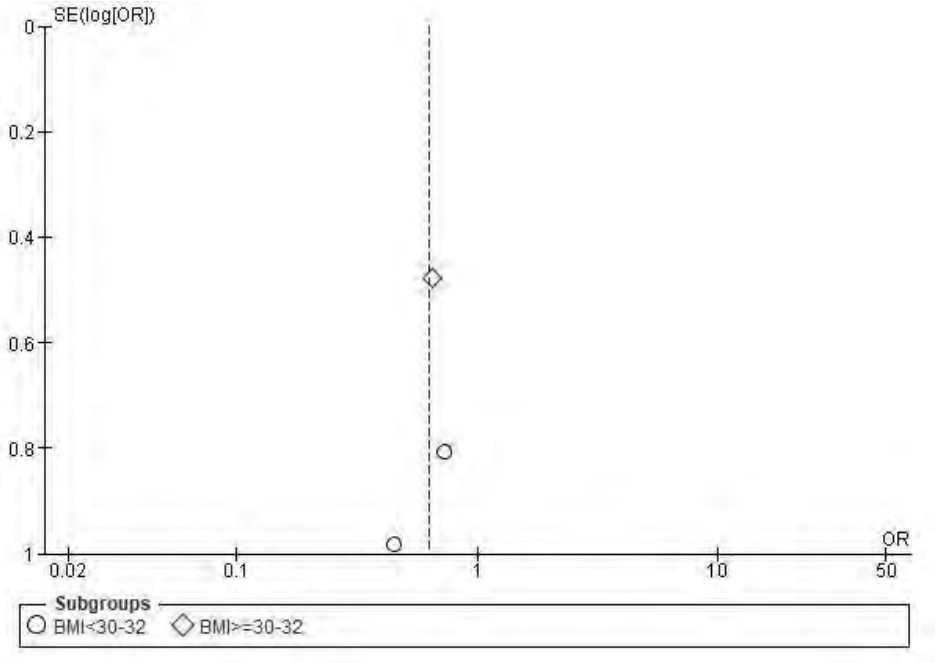
3.6.4. SUBGROUP ANALYSIS: miscarriage rate – per patient

3.6.4.1. Forest Plot of all included RCTs comparing Metformin + Clomiphene Citrate vs Metformin for miscarriage rate- per patient, sub-grouped by BMI



Note: The above can also be considered subgrouped by risk of bias since Johnson and Kar were moderate risk and Legro was low risk

3.6.4.2. Funnel plot for assessment of publication bias: subgroup analysis: miscarriage rate - per patient



COMPARISON 4. Metformin + Letrozole versus Letrozole

- **EVIDENCE SUMMARY:**

Only two studies compared metformin + letrozole with letrozole alone. One of the studies performed in Iran (Pourghasem, et al. 2019) in letrozole-resistant women (no ovulation at 7.5 mg letrozole), provided folic acid 200 µg daily (as a placebo) to both the letrozole + metformin and letrozole groups; whilst the other did not. The second study by Liu et al. (2017) was conducted in China in 119 women with PCOS (for this comparison) aged 20-35, with a BMI ≤35 kg/m^2. Reported outcomes of relevance were clinical pregnancy rate, live birth rate and miscarriage rate per patient and ovulation rate per cycle. Both studies had a high risk of bias due to issues around lack of blinding and insufficient information about randomisation or allocation concealment. The study by Liu et al. (2017) also had a high dropout rate of 15% in the letrozole + metformin group, with 7.5% drop outs in the letrozole group.

- **META-ANALYSIS SUMMARY:**

Meta-analysis was only possible for the outcome of clinical pregnancy rate per person, with two studies pooled for this analysis (Liu, et al. 2017; Pourghasem, et al. 2019), showing no difference between metformin + letrozole versus letrozole alone for this outcome. There is very low certainty in this result due to very serious risk of bias, with serious imprecision and serious indirectness. There were no differences in live birth rate between metformin + letrozole vs letrozole alone (33.9% vs 36.8%). Clinical pregnancy rate per patient (48.6% vs 40.2%) and ovulation rate per cycle (89/118 cycles vs 93/130 cycles) were higher in the letrozole + metformin group than letrozole alone, but these were not statistically significant. Similarly, miscarriage/ abortion rate per patient was slightly higher with metformin + letrozole than letrozole alone, but the difference was not statistically significant (21.1% vs 12.9%, p > .05). These results are of very low certainty given that they are derived from a single study with a high risk of bias.

Summary Table for meta-analysis results:

Outcome or Subgroup	Studies	n	Effect Estimate; OR [95% CI], M-H, random	P-value	Favours	Certainty
Live birth rate- per patient	1	119	1.14 [0.54, 2.42]	0.7	None	⊕◯◯◯ Very low
Clinical pregnancy rate- per patient†	2	219	1.44 [0.84, 2.49]	0.2	None	⊕◯◯◯ Very low
Ovulation Rate- per cycle	1	248	1.22 [0.69, 2.15]	0.5	None	⊕◯◯◯ Very low
Miscarriage rate- per patient	1	119	1.80 [0.68, 4.79]	0.2	None	⊕◯◯◯ Very low

†clinical pregnancy rate is confirmed by ultrasound detection of gestational sac/ fetal heart activity

OUTCOME 4.1. Live birth rate- per patient

4.1.1. Individual Study Data Table

OUTCOME: Live birth rate - per patient				OUTCOME TYPE: Dichotomous					
COMPARISON: Metformin + Letrozole vs Letrozole									
Author, year	Past OI Med Use	Unit of outcome (e.g. g, mg, µg)	Method of measurement	N events in control / comparison group (MET+LET)	N total in control/ comparison group (MET+LET)	N events in intervention/ exposure group (LET)	N total in intervention/ exposure group (LET)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Liu 2017 (HRB)	Mixed	Count	Investigator	21	57	21	62	Crude	NA

Mixed, includes clomiphene citrate resistant/failure and therapy naïve and/or not reported; **OI**, ovulation induction

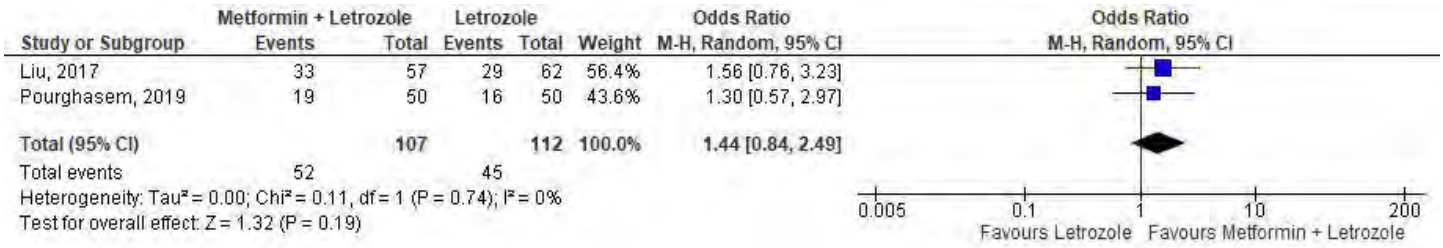
OUTCOME 4.2. Clinical pregnancy rate- per patient

4.2.1. Individual Study Data Table

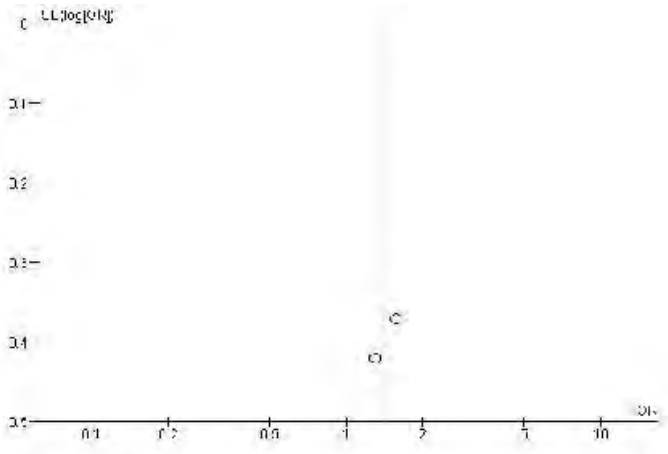
OUTCOME: Clinical pregnancy rate - per patient				OUTCOME TYPE: Dichotomous					
COMPARISON: Metformin + Letrozole vs Letrozole									
Author, year	Past OI Med Use	Unit of outcome (e.g. g, mg, µg)	Method of measurement	N events in control / comparison group (MET+LET)	N total in control/ comparison group (MET+LET)	N events in intervention/ exposure group (LET)	N total in intervention/ exposure group (LET)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Liu 2017 (HRB)	Mixed	Count	Investigator	33	57	29	62	Crude	NA
Pourghasem 2019 (HRB)	LR	Count	Investigator	19	50	16	50	Crude	NA

LR, letrozole resistant; **Mixed**, includes clomiphene citrate resistant/failure and therapy naïve and/or not reported; **OI**, ovulation induction

4.2.2. Forest Plot of all included RCTs comparing Metformin + Letrozole vs Letrozole for clinical pregnancy rate- per patient



4.2.3. Funnel plot for assessment of publication bias



OUTCOME 4.3. Ovulation rate- per cycle

4.3.1. Individual Study Data Table

OUTCOME: Ovulation rate - per cycle					**OUTCOME TYPE:** Dichotomous				
COMPARISON: Metformin + Letrozole vs Letrozole									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in control / comparison group (MET+LET)**	**N total in control/ comparison group (MET+LET)**	**N events in intervention/ exposure group (LET)**	**N total in intervention/ exposure group (LET)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Liu 2017 (HRB)	Mixed	Count	Investigator	89	118	93	130	Crude	NA

Mixed, includes clomiphene citrate resistant/failure and therapy naïve and/or not reported; **OI**, ovulation induction

OUTCOME 4.4. Miscarriage rate- per patient

4.4.1. Individual Study Data Table

OUTCOME: Miscarriage rate - per patient					**OUTCOME TYPE:** Dichotomous				
COMPARISON: Metformin + Letrozole vs Letrozole									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in control / comparison group (MET+LET)**	**N total in control/ comparison group (MET+LET)**	**N events in intervention/ exposure group (LET)**	**N total in intervention/ exposure group (LET)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Liu 2017 (HRB)	Mixed	Count	Investigator	12	57	8	62	Crude	NA

Mixed, includes clomiphene citrate resistant/failure and therapy naïve and/or not reported; **OI**, ovulation induction

COMPARISON 5. Metformin + Letrozole versus Metformin + Clomiphene Citrate

▪ EVIDENCE SUMMARY:

Two studies compared metformin + letrozole with metformin + clomiphene citrate (Liu, et al. 2017; Sohrabvand, et al. 2006), with relevant outcomes including ovulation rate per cycle and pregnancy and miscarriage rate per patient. Liu et al. (2017) additionally assessed live birth rate per patient, whereas Sohrabvand et al. (2006) reported full term pregnancy per patient. Both studies were moderate (Sohrabvand, et al. 2006) or high (Liu, et al. 2017) risk of bias due to lack of blinding of participants and insufficient information around allocation concealment.

▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

Meta-analysis of these two studies was performed for ovulation rate per cycle and pregnancy and miscarriage rate per patient, with results in the table below. Clinical pregnancy and ovulation rates were greater with metformin + letrozole compared with metformin + clomiphene citrate with odds ratios of 1.90 and 2.02, respectively. Miscarriage rates per patient did not differ between groups. Certainty of the evidence for these three outcomes was low, downgraded once due to high/ moderate risk of bias and once for serious imprecision (small n and wide confidence intervals).

The study by Liu et al. (2017) additionally assessed live birth rate per patient, showing no difference between metformin + letrozole versus metformin + clomiphene citrate groups. Sohrabvand et al. (2006) assessed full term pregnancy per patient and found that metformin + letrozole was more effective than metformin + clomiphene citrate for this outcome (10 versus 3 full term pregnancies per group, respectively, p=0.03).The results for both these outcomes are of very low certainty given that they are derived from only single studies with moderate to high risk of bias.

Summary Table for meta-analysis results:

Outcome or Subgroup	Studies	n	Effect Estimate; OR [95% CI], M-H, random	P	Favours	Certainty
Live birth rate- per patient	1	115	1.30 [0.60, 2.81]	0.5	None	⊕○○○ VERY LOW
Clinical pregnancy rate- per patient†	2	174	1.90 [1.01, 3.58]	0.0486	**MET + LET** (clinical pregnancy is higher with MET + LET)	⊕⊕○○ LOW
Ovulation rate- per cycle	2	369	2.02 [1.24, 3.30]	0.005	**MET + LET** (ovulation per cycle is higher with MET + LET)	⊕⊕○○ LOW
Miscarriage rate- per patient	2	174	0.98 [0.12, 7.89]	0.98	None	⊕⊕○○ LOW
Full term pregnancy- per patient	1	59	4.74 [1.15, 19.55]	0.03	**MET + LET** (full term pregnancy is higher with MET + CC)	⊕○○○ VERY LOW

†clinical pregnancy rate is confirmed by ultrasound detection of gestational sac/ fetal heart activity

OUTCOME 5.1. Live birth rate – per patient

5.1.1. Individual Study Data Table

OUTCOME: Live birth rate – per patient						**OUTCOME TYPE:** Dichotomous			
COMPARISON: Metformin + Letrozole vs. **Metformin + Clomiphene Citrate**									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in intervention/ exposure group (MET + LET)**	**N total in intervention/ exposure group (MET + LET)**	**N events in control / comparison group (MET +CC)**	**N total in control/ comparison group (MET+ CC)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Liu 2017 (HRB)	Mixed	Count	Investigator	21	57	18	58	Crude	NA

Mixed, includes some clomiphene citrate resistant/failure and/or therapy naïve and/or not reported.

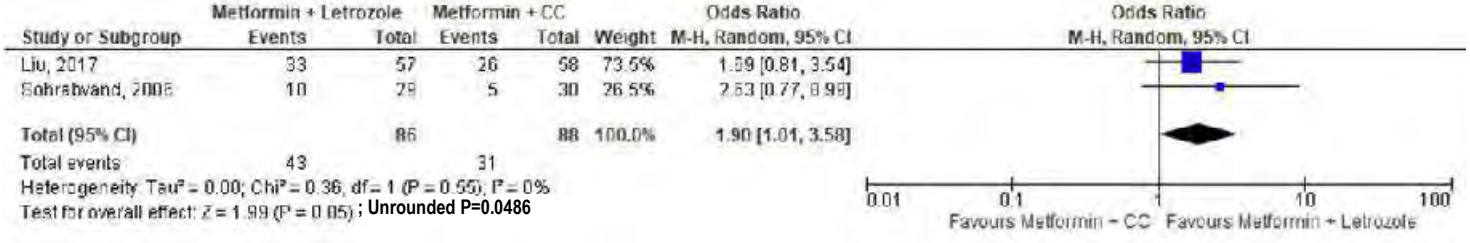
OUTCOME 5.2. Clinical pregnancy rate- per patient

5.2.1. Individual Study Data Table

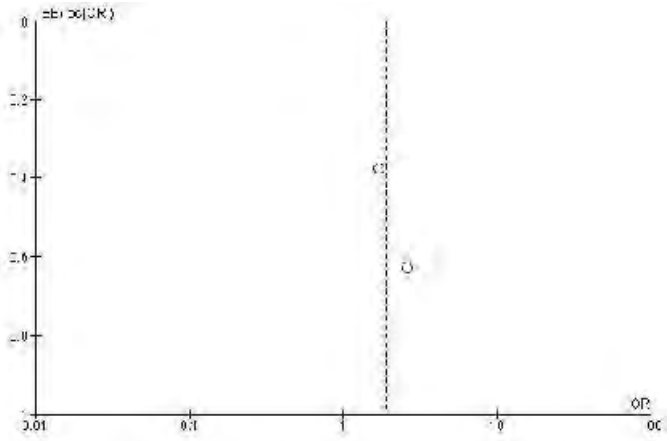
OUTCOME: Clinical pregnancy rate - per patient						**OUTCOME TYPE:** Dichotomous			
COMPARISON: Metformin + Letrozole vs. **Metformin + Clomiphene Citrate**									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (MET + LET)**	**N total in intervention/ exposure group (MET + LET)**	**N events in control / comparison group (MET +CC)**	**N total in control/ comparison group (MET+ CC)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Liu 2017 (HRB)	Mixed	Count	Investigator	33	57	26	58	Crude	NA
Sohrabvand 2006 (MRB)	CCF	Count	Investigator	10	29	5	30	Crude	NA

CCF, Clomiphene citrate failure; **Mixed**, includes some clomiphene citrate resistant/failure and/or therapy naïve and/or not reported.

5.2.2. Forest Plot of all included RCTs comparing Metformin + Letrozole vs Metformin + Clomiphene Citrate for clinical pregnancy rate- per patient



5.2.3. Funnel plot for assessment of publication bias



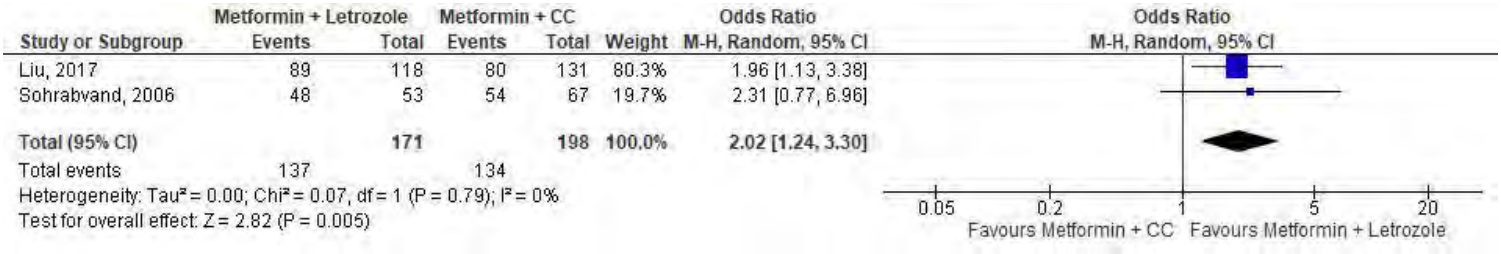
OUTCOME 5.3. Ovulation rate- per cycle

5.3.1. Individual Study Data Table

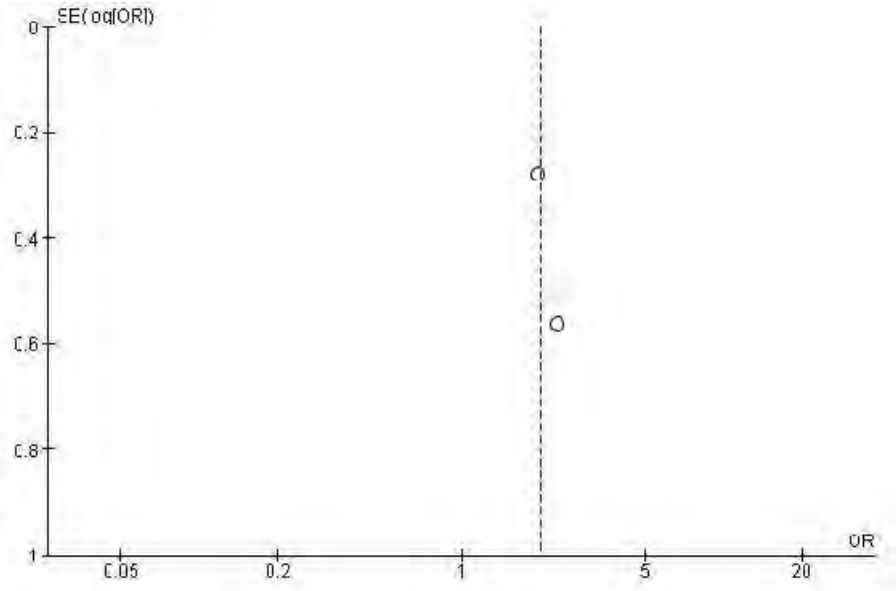
OUTCOME: Ovulation rate - per cycle						**OUTCOME TYPE:** Dichotomous			
COMPARISON: Metformin + Letrozole vs. **Metformin + Clomiphene Citrate**									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (MET + LET)**	**N total in intervention/ exposure group (MET + LET)**	**N events in control / comparison group (MET +CC)**	**N total in control/ comparison group (MET+ CC)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Liu 2017 (HRB)	Mixed	Count	Investigator	89	118	80	131	Crude	NA
Sohrabvand 2006 (MRB)	CCF	Count	Investigator	48	53	54	67	Crude	NA

CCF, Clomiphene citrate failure; **Mixed**, includes clomiphene citrate resistant/failure and therapy naïve and/or not reported; **OI**, ovulation induction

5.3.2. Forest Plot of all included RCTs comparing Metformin + Letrozole versus Metformin + Clomiphene Citrate for ovulation rate – per cycle



5.3.3. Funnel plot for assessment of publication bias



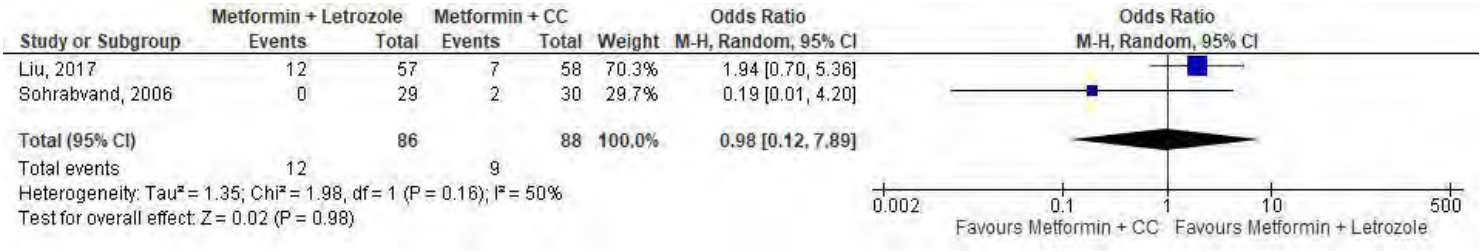
OUTCOME 5.4. Miscarriage rate – per patient

5.4.1. Individual Study Data Table

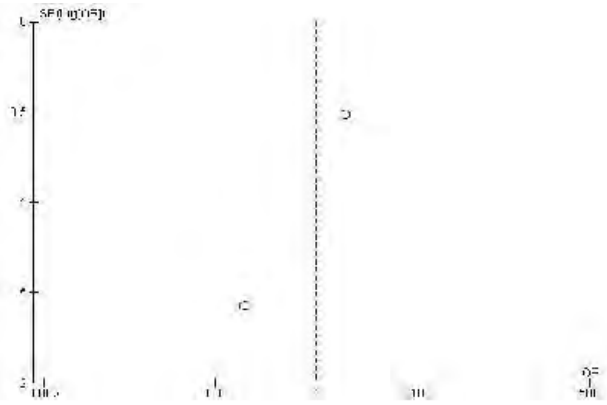
OUTCOME: Miscarriage rate - per patient					**OUTCOME TYPE:** Dichotomous				
COMPARISON: Metformin + Letrozole vs. **Metformin + Clomiphene Citrate**									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (MET + LET)**	**N total in intervention/ exposure group (MET + LET)**	**N events in control / comparison group (MET +CC)**	**N total in control/ comparison group (MET+ CC)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Liu 2017 (HRB)	Mixed	Count	Investigator	12	57	7	58	Crude	NA
Sohrabvand 2006 (MRB)	CCF	Count	Investigator	0	29	2	30	Crude	NA

CCF, Clomiphene citrate failure; **NR**, not reported; **Mixed**, includes clomiphene citrate resistant/failure and therapy naïve and/or not reported; **OI**, ovulation induction

5.4.2. Forest Plot of all included RCTs comparing Metformin + Letrozole and Metformin + Clomiphene Citrate for miscarriage rate – per patient



5.4.3. Funnel plot for assessment of publication bias



OUTCOME 5.5. Full term pregnancy – per patient

5.4.1. Individual Study Data Table

OUTCOME: Full term pregnancy – per patient						**OUTCOME TYPE:** Dichotomous			
Metformin + Letrozole vs. **Metformin + Clomiphene Citrate**									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in intervention / exposure group (MET + LET)**	**N total in intervention / exposure group (MET + LET)**	**N events in control / comparison group (MET +CC)**	**N total in control/ comparison group (MET+ CC)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Sohrabvand 2006	CCF	Count	Investigator	10	29	3	30	Crude	NA

CCF, Clomiphene citrate failure

COMPARISON 6. Metformin vs gonadotropins (hMG)

▪ EVIDENCE SUMMARY:

A single study by George et al. 2003 compared metformin with human menopausal gonadotropin (hMG) in 60 clomiphene citrate-resistant women with PCOS. Outcomes assessed included pregnancy rate per patient and ovulation rate per cycle. The study was judged as being of moderate risk of bias due to lack of blinding.

▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

There were no differences between metformin versus hMG in pregnancy or ovulation rates. Certainty was ranked as low due to being reliant on a single small study of moderate risk of bias.

Outcome or Subgroup	Studies	n	Effect Estimate; OR [95% CI], M-H, random	P-value	Favours	Certainty
Pregnancy rate- per patient*	1	60	0.66 [0.18, 2.36]	0.5	None	⊕⊕◯◯ LOW
Ovulation rate- per patient	1	60	1.31 [0.47, 3.65]	0.6	None	⊕⊕◯◯ LOW

*includes clinical, biochemical (or undefined pregnancy rate) as reported in each study

OUTCOME 6.1. Pregnancy rate – per patient
6.1.1. Individual Study Data Table

OUTCOME: Pregnancy rate – per patient						**OUTCOME TYPE:** Dichotomous			
COMPARISON: Metformin vs. **hMG**									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in intervention group (MET)**	**N total in intervention group (MET)**	**N events in control / comparison group (hMG)**	**N total in control/ comparison group (hMG)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
George 2003	CCR	Count	Investigator	5	30	7	30	Crude	NA

CCR, Clomiphene citrate-resistant

OUTCOME 6.2. Ovulation rate – per patient
6.2.1. Individual Study Data Table

OUTCOME: Ovulation rate – per patient						**OUTCOME TYPE: Dichotomous**			
COMPARISON: Metformin vs. hMG									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in intervention group (MET)**	**N total in intervention group (MET)**	**N events in control / comparison group (hMG)**	**N total in control/ comparison group (hMG)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
George 2003	**CCR**	**Count**	**Investigator**	**14**	**30**	**12**	**30**	**Crude**	**NA**

CCR, Clomiphene citrate-resistant

COMPARISON 7. Metformin + gonadotropins (FSH) versus gonadotropins (FSH)

▪ EVIDENCE SUMMARY:

Three studies compared metformin combined with FSH versus FSH alone in women with PCOS. A study by De Leo (1999) in Italy was conducted in 20 women with PCOS and clomiphene failure or resistance (i.e. failed to ovulate or conceive after clomiphene citrate treatment up to a daily dose of 50 mg from cycle days 3–7 during at least three consecutive cycles). This study has a high risk of bias due to its small sample size and likely lack of power as well as lack of blinding and allocation concealment information.

The remaining two studies by Tasdemir et al. (2004) and Yarali (2002) were conducted in Turkey, also in women with clomiphene-citrate resistance and PCOS. One study (Tasdemir et al. 2004) was judged as being at high risk of bias due to lack of reporting on key elements such as blinding and randomisation, while Yarali et al. (2002) had a moderate risk of bias as it was likely underpowered (small sample size with no sample size calculation) but was reported to be double-blinded.

▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

There were no differences between metformin + FSH versus FSH alone in pregnancy rate, ovulation rate, multiple pregnancy rate or miscarriage rate per patient. There was very low certainty for multiple pregnancy rate per patient due to the evidence being derived from a single, small study with a high risk of bias. For the remaining outcomes, the evidence was of low certainty, downgraded for risk of bias (all moderate or high risk studies) and for inconsistency (varied effect estimates, including different directions and wide CIs).

Outcome or Subgroup	Studies	n	Effect Estimate; OR [95% CI], M-H, random	P-value	Favours	Certainty
Pregnancy rate- per patient*	3	77	0.96 [0.18, 5.10]	0.9	None	⊕⊕◯◯ LOW
Ovulation rate- per patient	1	25	3.27 [0.31, 34.72]	0.3	None	⊕⊕◯◯ LOW
Multiple pregnancy rate -per patient	1	32	0.31 [0.01, 8.28]	0.5	None	⊕◯◯◯ VERY LOW
Miscarriage rate- per patient	1	25	4.89 [0.18, 132.83]	0.4	None	⊕⊕◯◯ LOW

*includes clinical, biochemical (or undefined pregnancy rate) as reported in each study

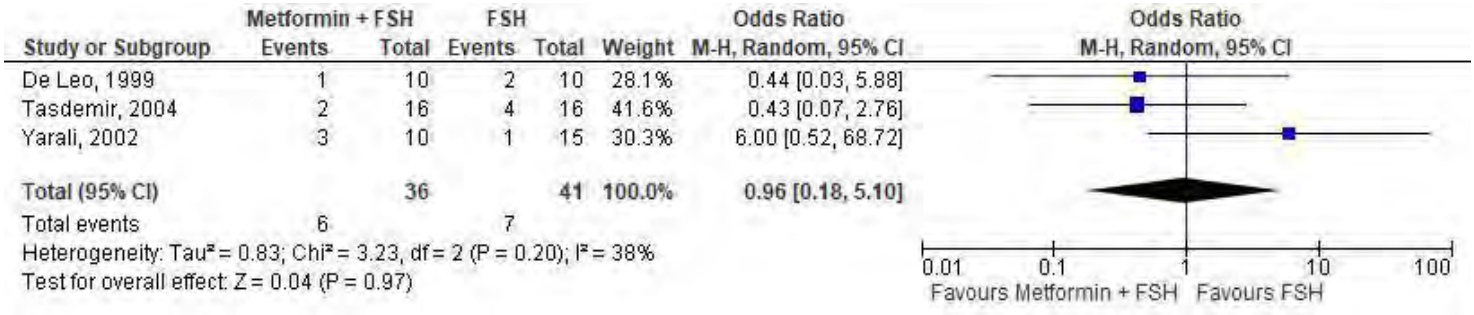
OUTCOME 7.1. Pregnancy rate – per patient

7.1.1. Individual Study Data Table

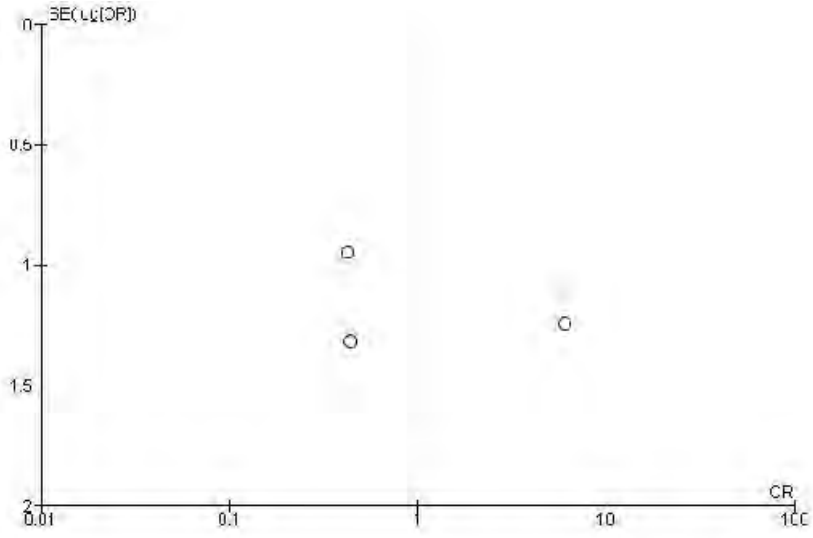
OUTCOME: Pregnancy rate – per patient						**OUTCOME TYPE:** Dichotomous			
COMPARISON: Metformin + FSH vs FSH (+/- placebo)									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in intervention group (MET +FSH)**	**N total in intervention group (MET +FSH)**	**N events in control / comparison group (FSH)**	**N total in control/ comparison group (FSH)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
De Leo 1999 (HRB)	CCR/ CCF	Count	Investigator	1	10	2	10	Crude	NA
Tasdemir 2004 (HRB)	CCR	Count	Investigator	2	16	4	16	Crude	NA
Yarali 2002 (MRB)	CCR	Count	Investigator	3	10	1	15	Crude	NA

CCR/CCF, Clomiphene citrate-resistant/ failure.

7.1.2. Forest Plot of all included RCTs comparing Metformin + FSH with FSH for pregnancy rate – per patient



7.1.3. Funnel plot for assessment of publication bias



OUTCOME 7.2. Ovulation rate – per patient

7.2.1. Individual Study Data Table

OUTCOME: Ovulation rate – per patient						OUTCOME TYPE: Dichotomous			
COMPARISON: Metformin + FSH vs FSH (+/- placebo)									
Author, year	Past OI Med Use	Unit of outcome (e.g. g, mg, µg)	Method of measurement	N events in intervention group (MET +FSH)	N total in intervention group (MET +FSH)	N events in control / comparison group (FSH)	N total in control/ comparison group (FSH)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Yarali 2002 (MRB)	CCR	Count	Investigator	9	10	11	15	Crude	NA

CCR, Clomiphene citrate-resistant.

OUTCOME 7.3. Multiple pregnancy rate – per patient

7.3.1. Individual Study Data Table

OUTCOME: Multiple pregnancy rate – per patient						OUTCOME TYPE: Dichotomous			
COMPARISON: Metformin + FSH vs FSH (+/- placebo)									
Author, year	Past OI Med Use	Unit of outcome (e.g. g, mg, µg)	Method of measurement	N events in intervention group (MET +FSH)	N total in intervention group (MET +FSH)	N events in control / comparison group (FSH)	N total in control/ comparison group (FSH)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Tasdemir 2004 (HRB)	CCR	Count	Investigator	0	16	1	16	Crude	NA

CCR, Clomiphene citrate-resistant.

OUTCOME 7.4. Miscarriage rate – per patient

7.4.1. Individual Study Data Table

OUTCOME: Miscarriage rate – per patient						OUTCOME TYPE: Dichotomous			
COMPARISON: Metformin + FSH vs FSH (+/- placebo)									
Author, year	Past OI Med Use	Unit of outcome (e.g. g, mg, µg)	Method of measurement	N events in intervention group (MET +FSH)	N total in intervention group (MET +FSH)	N events in control / comparison group (FSH)	N total in control/ comparison group (FSH)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Yarali 2002 (MRB)	CCR	Count	Investigator	1	10	0	15	Crude	NA

CCR, Clomiphene citrate-resistant.

COMPARISON 8. Clomiphene Citrate versus Metformin + Clomiphene Citrate

▪ EVIDENCE SUMMARY:

Eight studies compared clomiphene citrate with metformin + clomiphene citrate, with several relevant outcomes. Studies were conducted across China, New Zealand, South Africa, Turkey, USA and India. One study had a low risk of bias, three moderate and four high risk. Two studies were specifically in women with clomiphene citrate-resistant, three had mixed populations and one was in therapy naïve PCOS (the remaining two did not report ovulation induction medication use in their populations).

▪ META-ANALYSIS SUMMARY:

Meta-analysis was possible for five outcomes as per the table below. Clomiphene citrate alone was less effective than the combination of clomiphene and metformin for clinical pregnancy rates and ovulations rates per patient and per cycle. In subgroup analysis by BMI, metformin + clomiphene citrate was more effective for clinical pregnancy rate in the BMI<30-32 kg/m^2 subgroup, and more effective for ovulation rate per patient in the BMI ≥30-32 kg/m^2 subgroup. Ovulation rate per cycle was better with metformin + clomiphene than clomiphene alone across both BMI subgroups. There were no significant differences in live birth rates, multiple pregnancy rates or miscarriage rates per patient or per pregnancy, including after subgrouping by BMI. There is low to moderate certainty in the evidence for these outcomes, which were downgraded due to risk of bias since most of the studies were of moderate to high risk of bias. Evidence was also downgraded for indirectness since some analyses included diverse populations with and without clomiphene citrate- resistance.

Summary Table for meta-analysis results:

Outcome or Subgroup	Studies	n	Effect Estimate; OR [95% CI], M-H, random	P	Favours	Certainty
Live birth rate- per patient	5	687	0.73 [0.52, 1.03]	0.07	None	⊕⊕◯◯ LOW
Clinical pregnancy rate- per patient†	7	767	0.60 [0.44, 0.83]	0.002	**MET + CC** (clinical pregnancy is lower with CC)	⊕⊕◯◯ LOW
Ovulation rate- per patient	3	138	0.12 [0.04, 0.33]	<0.0001	**MET + CC** (ovulation per patient is lower with CC)	⊕⊕◯◯ LOW
Ovulation rate - per cycle	4	2383	0.64 [0.54, 0.75]	<0.0001	**MET + CC** (ovulation per cycle is lower with CC)	⊕⊕⊕◯ MODERATE
Multiple pregnancy rate- per patient	1	71	0.97 [0.06, 16.16]	0.9	None	⊕⊕⊕◯ MODERATE
Miscarriage rate- per patient	5	377	0.75 [0.42, 1.33]	0.3	None	⊕⊕◯◯ LOW
Miscarriage rate- per pregnancy	1	8	0.43 [0.01, 14.08]	0.6	None	⊕◯◯◯ VERY LOW

†clinical pregnancy rate is confirmed by ultrasound detection of gestational sac/ fetal heart activity

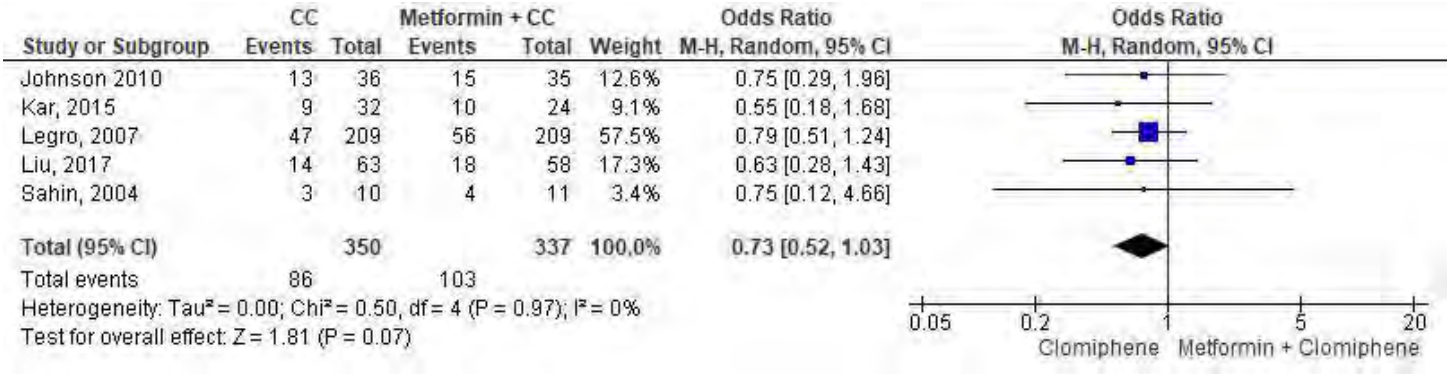
OUTCOME 8.1. Live birth rate- per patient

8.1.1. Individual Study Data Table

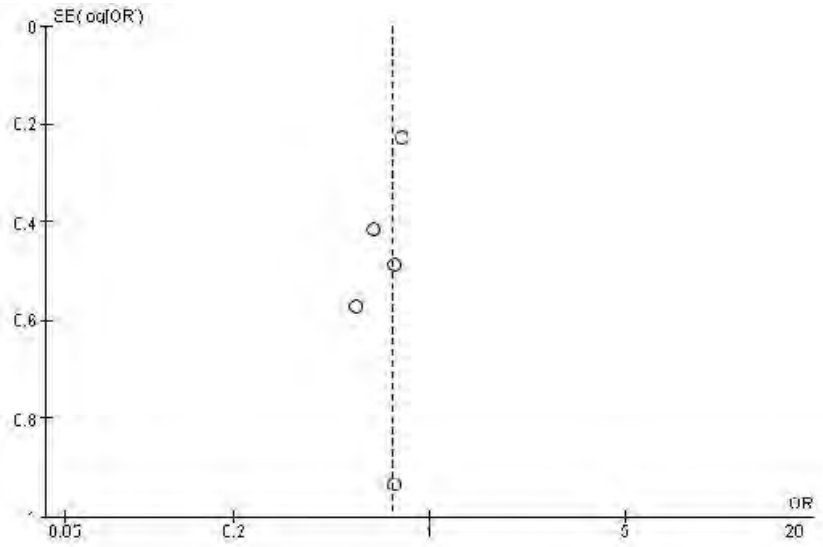
OUTCOME: Live birth rate – per patient						**OUTCOME TYPE:** Dichotomous			
COMPARISON: Clomiphene Citrate vs Metformin + Clomiphene Citrate									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in intervention group (CC)**	**N total in intervention group (CC)**	**N events in control / comparison group (MET+CC)**	**N total in control/ comparison group (MET+CC)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Johnson 2010 (MRB)	Mixed	Count	Investigator	13	36	15	35	Crude	NA
Kar 2015 (MRB)	TN	Count	Investigator	9	32	10	24	Crude	NA
Legro 2007 (LRB)	Mixed	Count	Investigator	47	209	56	209	Crude	NA
Liu 2017 (HRB)	Mixed	Count	Investigator	14	63	18	58	Crude	NA
Sahin 2004 (HRB)	NR	Count	Investigator	3	10	4	11	Crude	NA

TN, therapy naïve; **NR**, not reported; **Mixed**, includes clomiphene citrate resistant/failure and therapy naïve and/or not reported; **OI**, ovulation induction

8.1.2. Forest Plot of all included RCTs comparing Clomiphene Citrate vs Metformin + Clomiphene Citrate for live birth rate – per patient

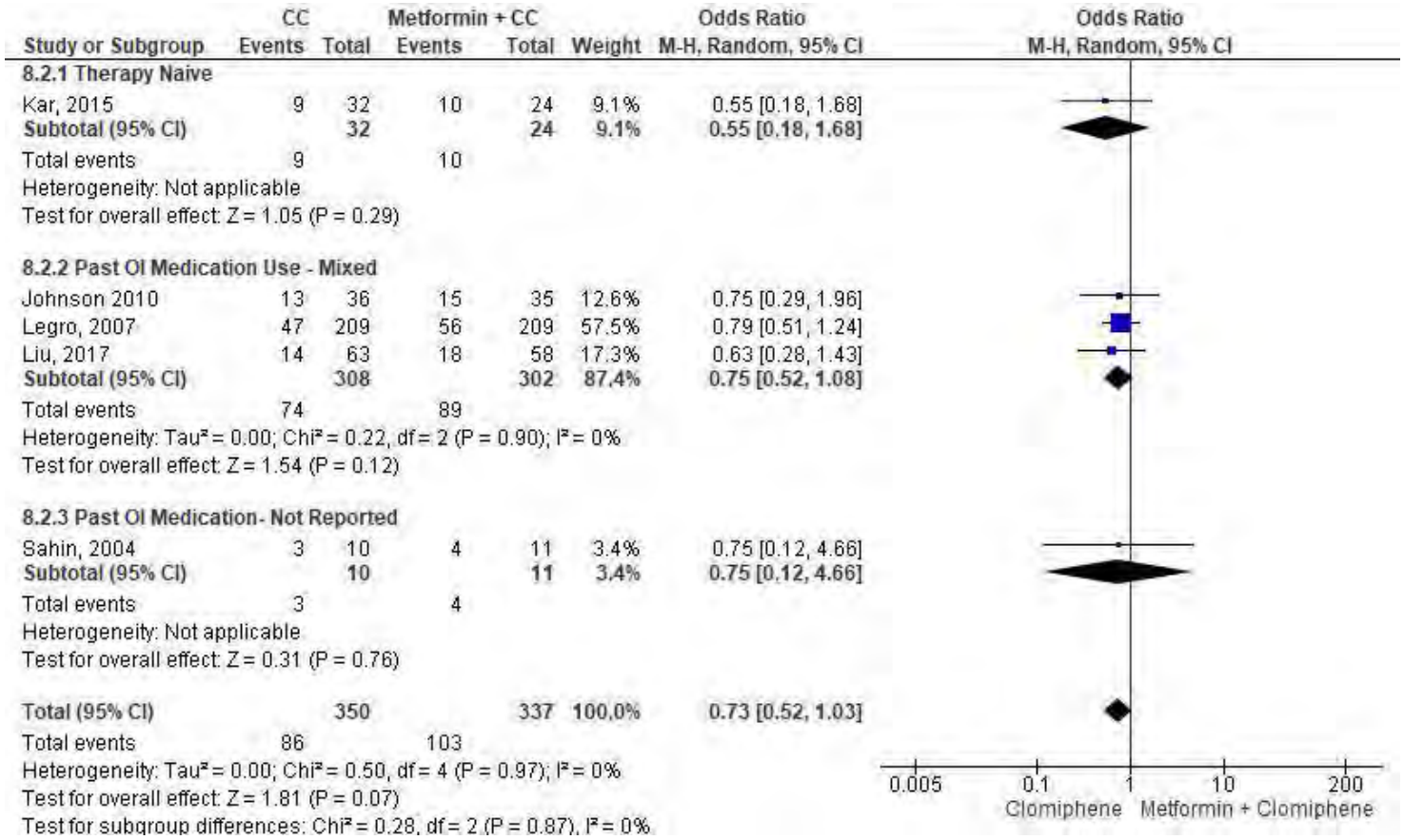


8.1.3. Funnel plot for assessment of publication bias

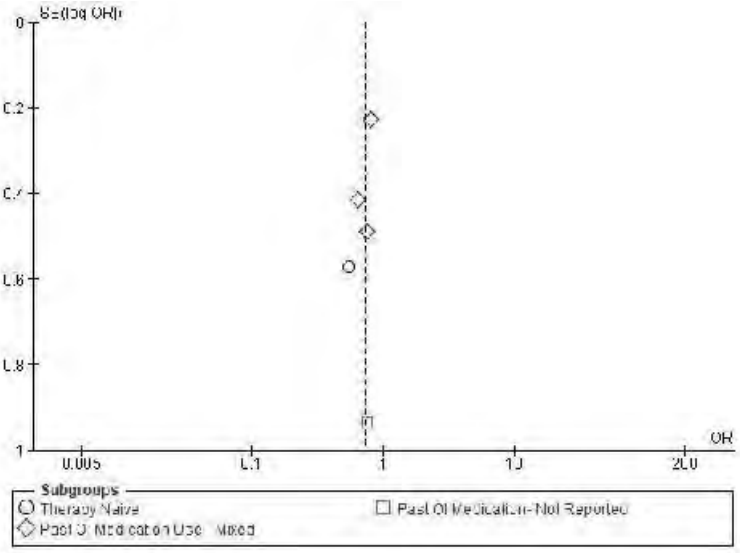


8.1.4.SUBGROUP ANALYSIS: Live birth rate – per patient

8.1.4.1. Forest Plot of all included RCTs comparing Clomiphene Citrate vs Metformin + Clomiphene Citrate for live birth rate- per patient, sub-grouped by past ovulation induction (OI) medication use

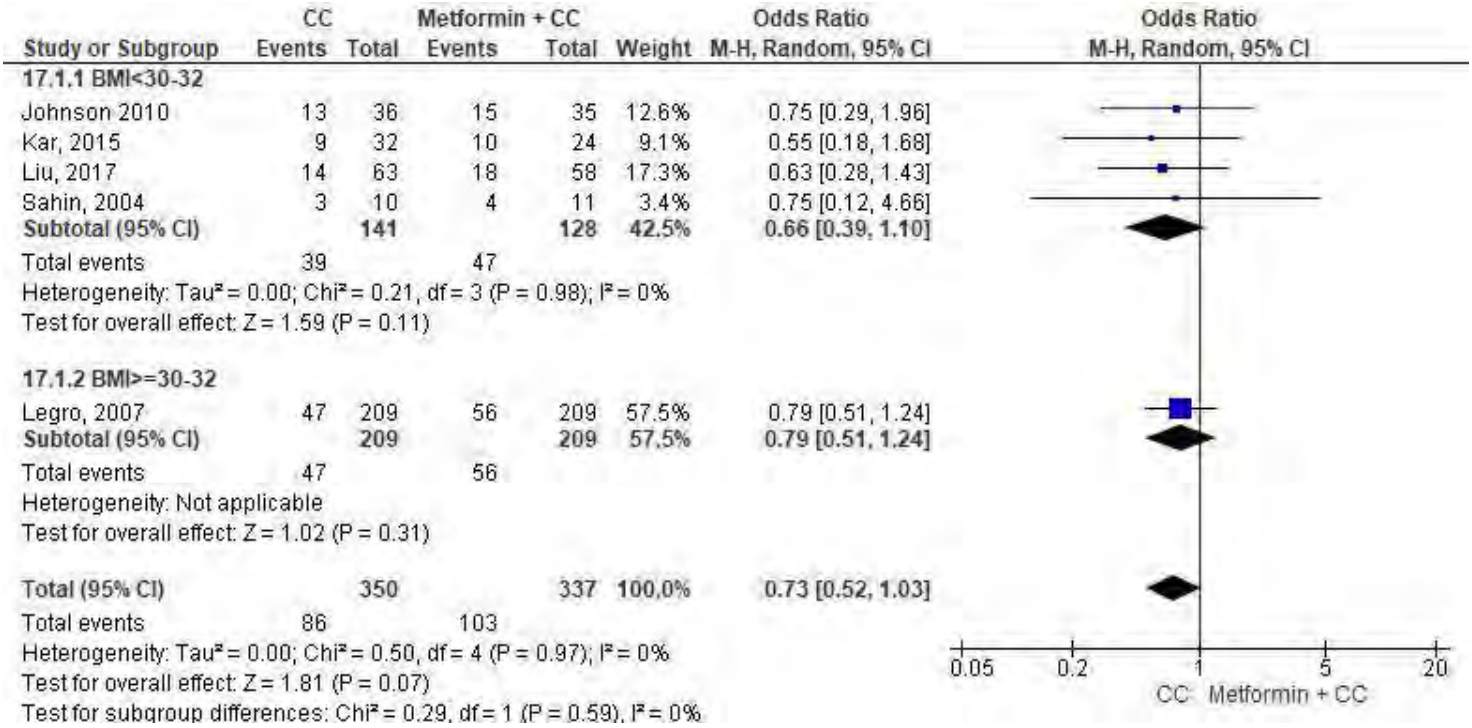


8.1.4.2. Funnel plot for assessment of publication bias: subgroup analysis: live birth rate - per patient

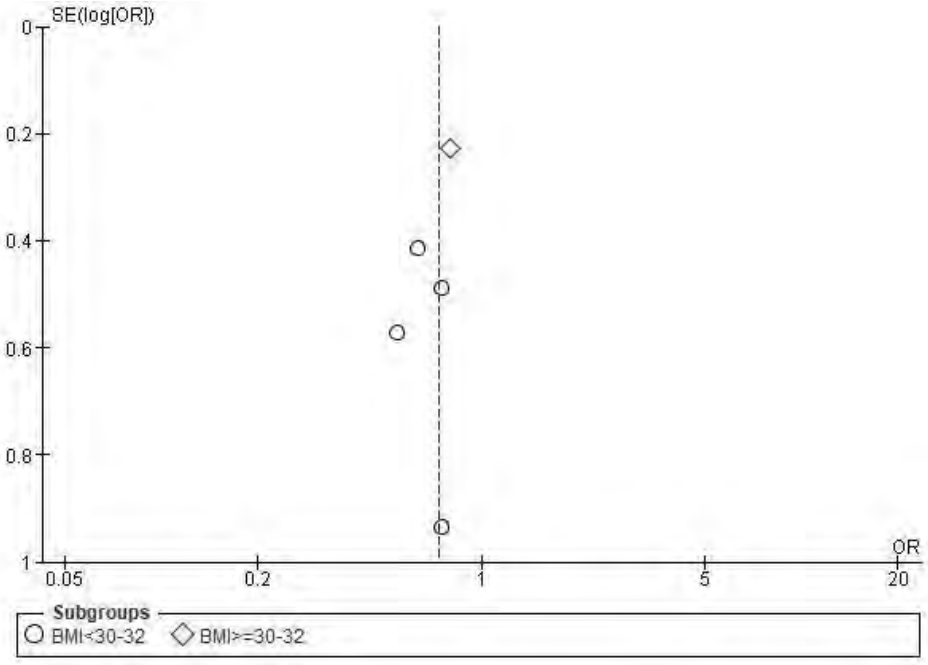


8.1.5.SUBGROUP ANALYSIS: Live birth rate – per patient

8.1.5.1. Forest Plot of all included RCTs comparing Clomiphene Citrate vs Metformin + Clomiphene Citrate for live birth rate- per patient, sub-grouped by BMI



8.1.5.2. Funnel plot for assessment of publication bias: subgroup analysis: live birth rate - per patient



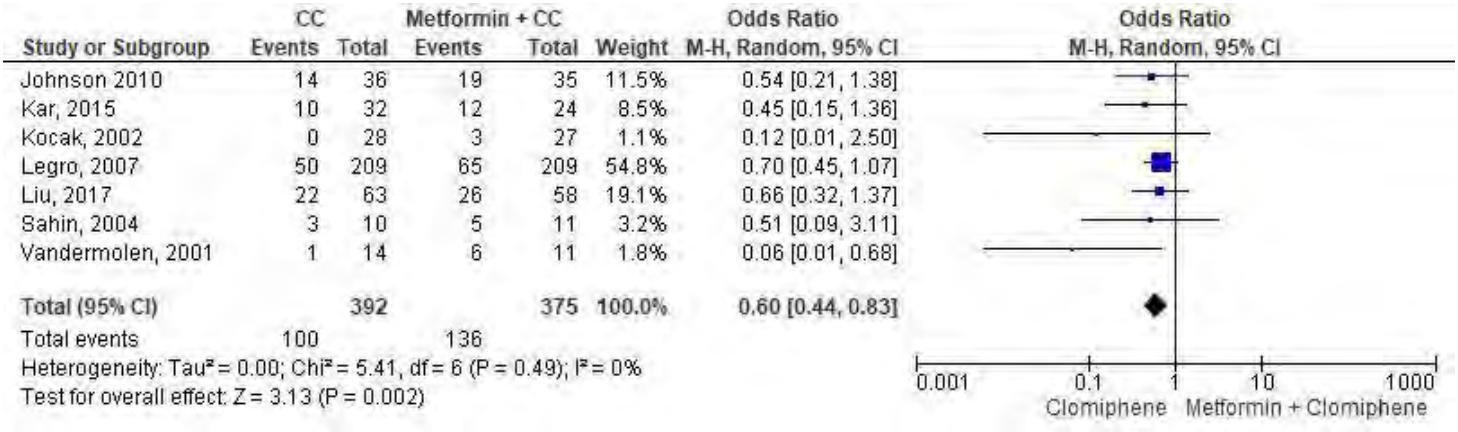
OUTCOME 8.2. Clinical pregnancy rate- per patient

8.2.1. Individual Study Data Table

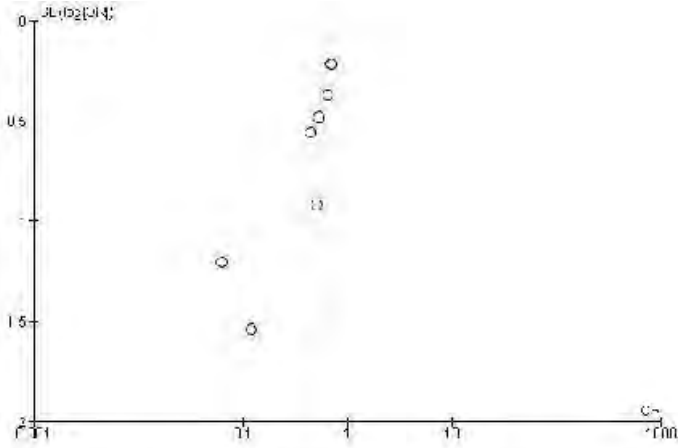
OUTCOME: Clinical pregnancy rate – per patient						**OUTCOME TYPE:** Dichotomous			
COMPARISON: Clomiphene Citrate vs Metformin + Clomiphene Citrate									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in intervention group (CC)**	**N total in intervention group (CC)**	**N events in control / comparison group (MET+CC)**	**N total in control/ comparison group (MET+CC)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Johnson 2010 (MRB)	Mixed	Count	Investigator	14	36	19	35	Crude	NA
Kar, 2015 (MRB)	TN	Count	Investigator	10	32	12	24	Crude	NA
Kocak, 2002 (MRB)	CCR	Count	Investigator	0	28	3	27	Crude	NA
Legro, 2007 (LRB)	Mixed	Count	Investigator	50	209	65	209	Crude	NA
Liu, 2017 (HRB)	Mixed	Count	Investigator	22	63	26	58	Crude	NA
Sahin, 2004 (HRB)	NR	Count	Investigator	3	10	5	11	Crude	NA
Vandermolen 2001 (HRB)	CCR	Count	Investigator	1	14	6	11	Crude	NA

TN, therapy naïve; **CCR**, Clomiphene citrate resistant; **NR**, not reported; **Mixed**, includes clomiphene citrate resistant/failure and therapy naïve and/or not reported; **OI**, ovulation induction

8.2.2. Forest Plot of all included RCTs comparing Clomiphene Citrate vs Metformin + Clomiphene Citrate for clinical pregnancy rate – per patient

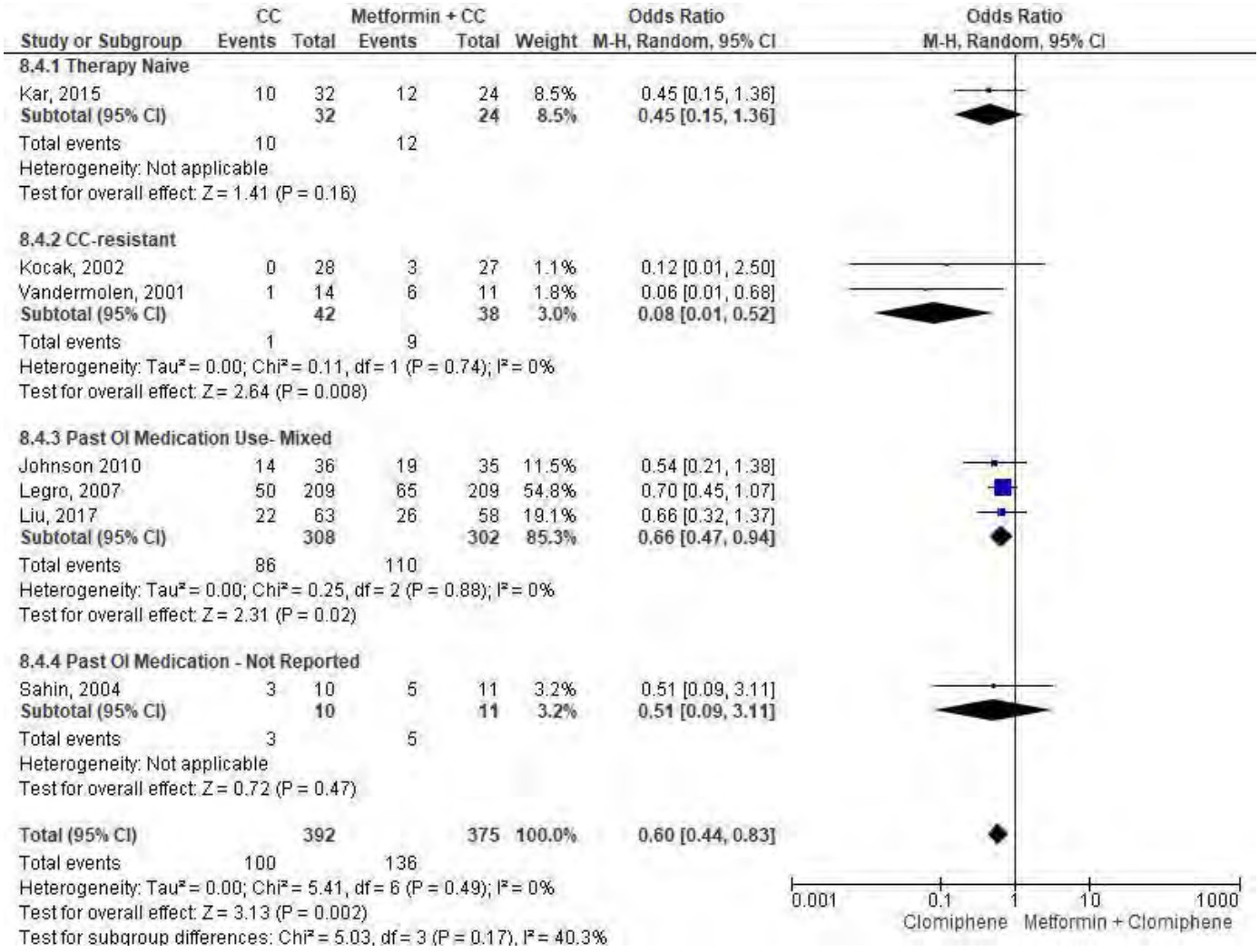


8.2.3. Funnel plot for assessment of publication bias

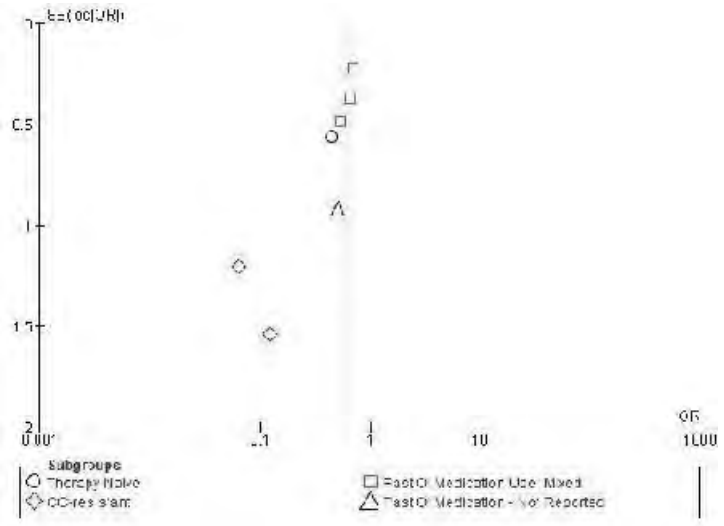


8.2.4.SUBGROUP ANALYSIS: Clinical pregnancy rate – per patient

8.2.4.1. Forest Plot of all included RCTs comparing Clomiphene Citrate vs Metformin + Clomiphene Citrate for clinical pregnancy rate – per patient, sub-grouped by past ovulation induction (OI) medication use

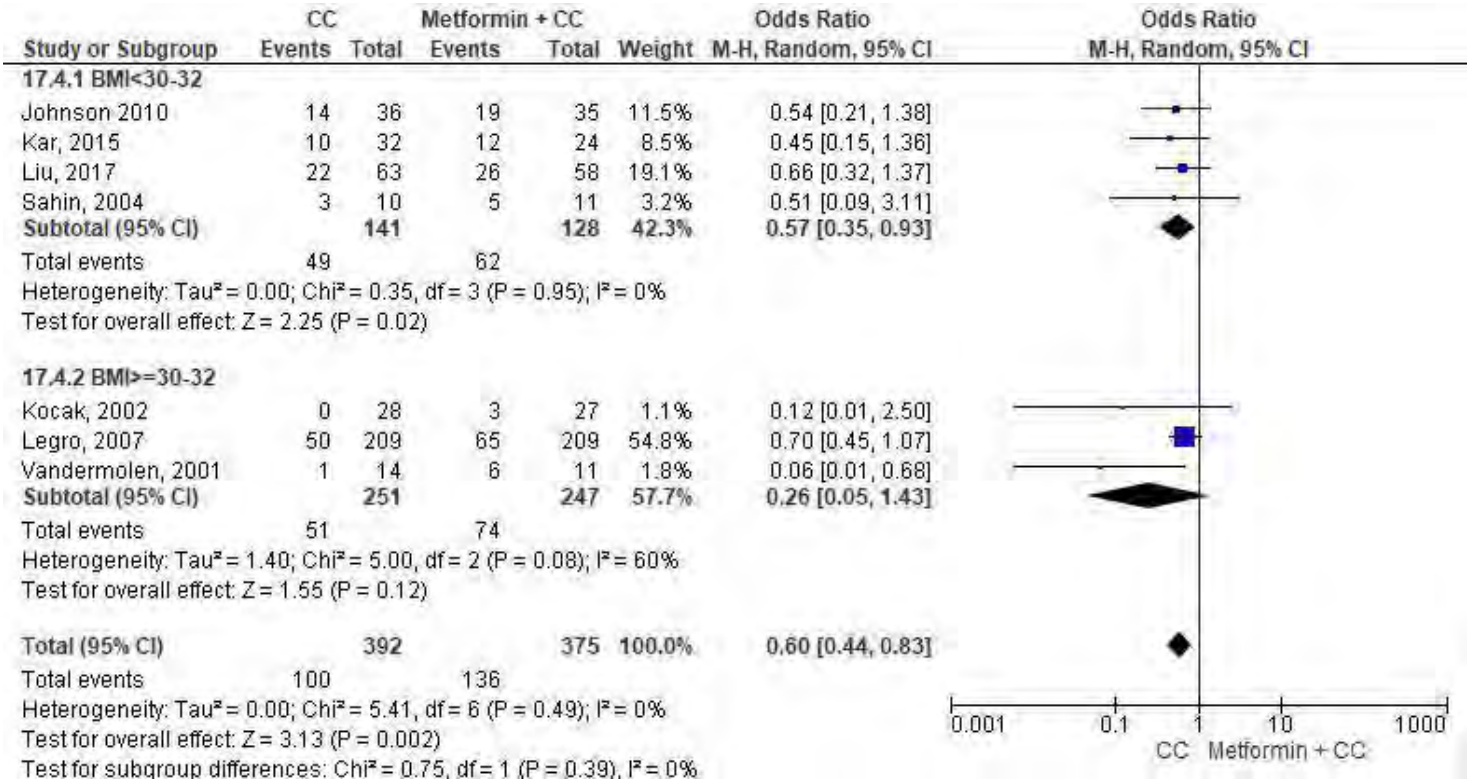


8.2.4.2. Funnel plot for assessment of publication bias: subgroup analysis: clinical pregnancy rate - per patient

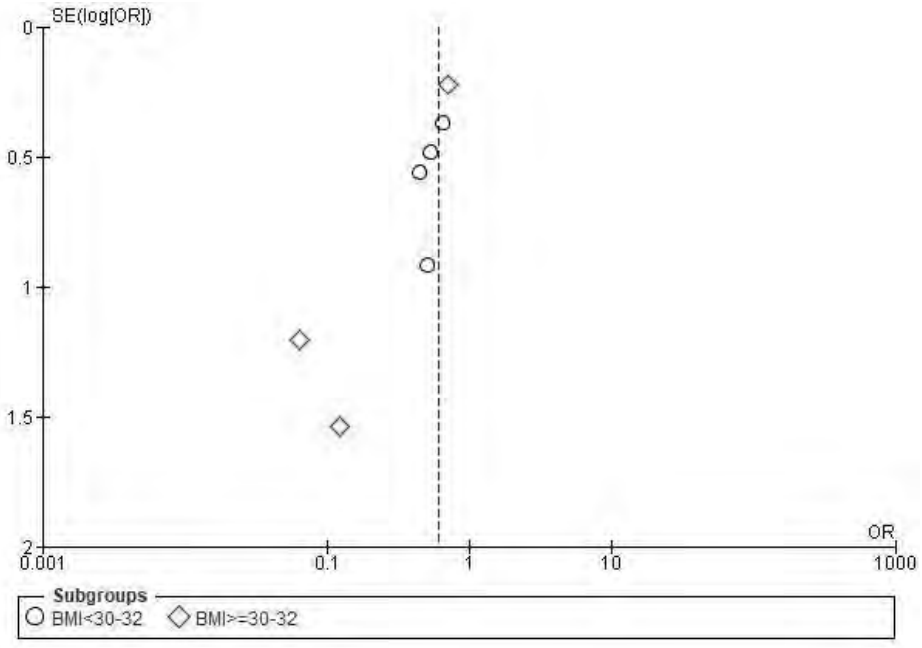


8.2.5.SUBGROUP ANALYSIS: Clinical pregnancy rate – per patient

8.2.5.1. Forest Plot of all included RCTs comparing Clomiphene Citrate vs Metformin + Clomiphene Citrate for clinical pregnancy rate – per patient, sub-grouped by BMI



8.2.5.2. Funnel plot for assessment of publication bias: subgroup analysis: clinical pregnancy rate - per patient



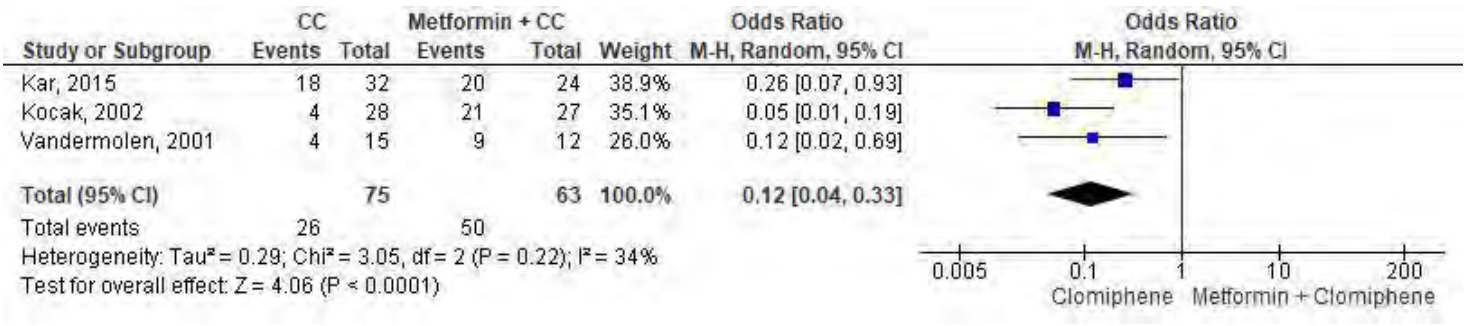
OUTCOME 8.3. Ovulation rate- per patient

8.3.1. Individual Study Data Table

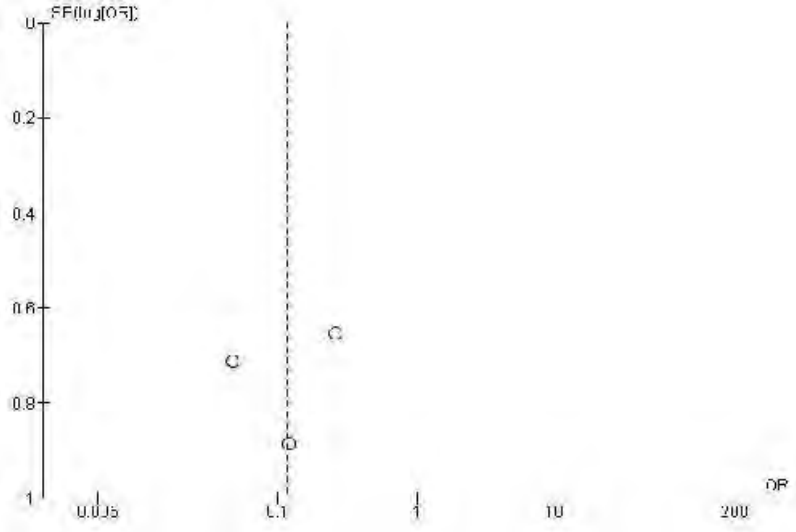
OUTCOME: Ovulation rate – per patient						**OUTCOME TYPE:** Dichotomous			
COMPARISON: Clomiphene Citrate vs Metformin + Clomiphene Citrate									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in intervention group (CC)**	**N total in intervention group (CC)**	**N events in control / comparison group (MET+CC)**	**N total in control/ comparison group (MET+CC)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Kar 2015 (MRB)	TN	Count	Investigator	18	32	20	24	Crude	NA
Kocak 2002 (MRB)	CCR	Count	Investigator	4	28	21	27	Crude	NA
Vandermolen 2001(HRB)	CCR	Count	Investigator	4	15	9	12	Crude	NA

TN, therapy naïve; **CCR**, Clomiphene citrate resistant; **OI**, ovulation induction

8.3.2. Forest Plot of all included RCTs comparing Clomiphene Citrate vs Metformin + Clomiphene Citrate for ovulation rate – per patient

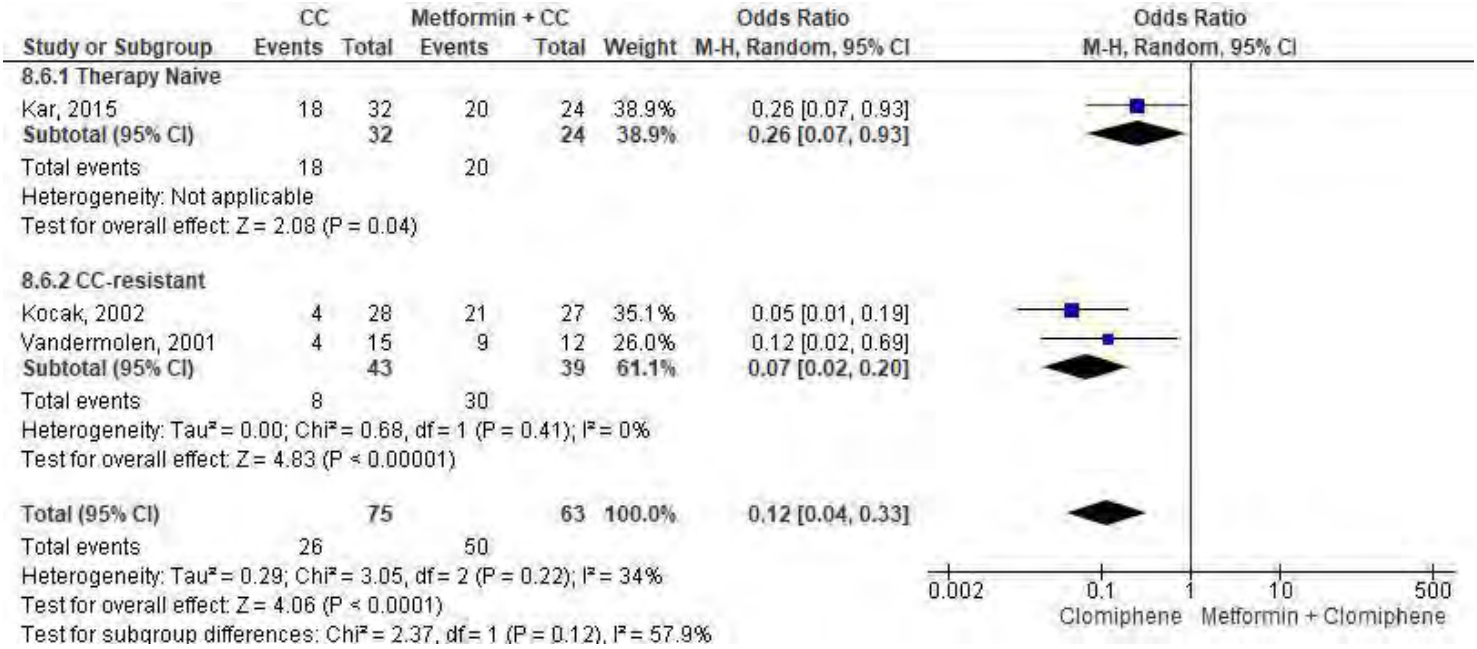


8.3.3. Funnel plot for assessment of publication bias

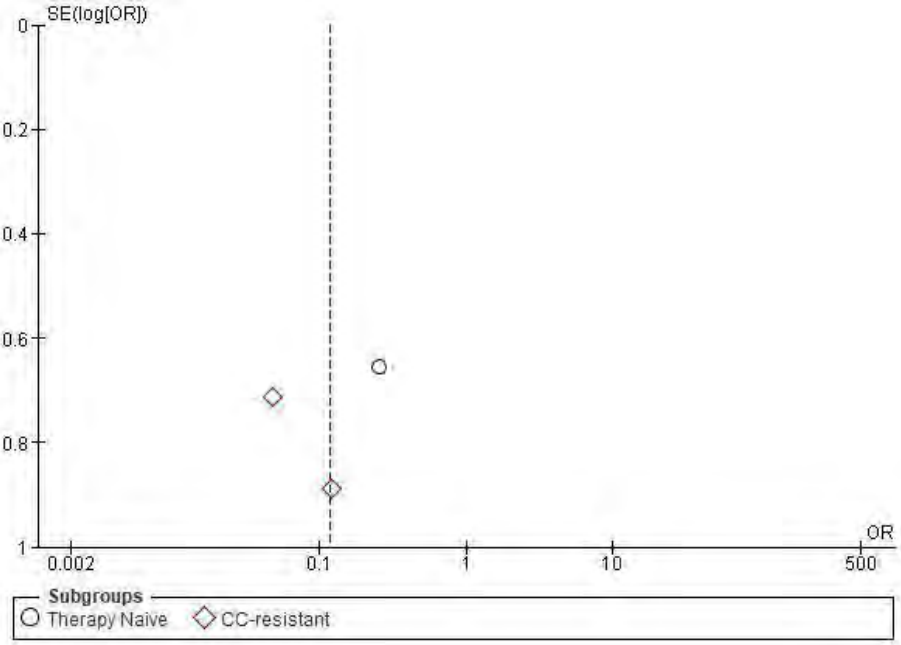


8.3.4.SUBGROUP ANALYSIS: Ovulation rate – per patient

8.3.4.1. Forest Plot of all included RCTs comparing Clomiphene Citrate vs Metformin + Clomiphene Citrate for ovulation rate – per patient, sub-grouped by past ovulation induction (OI) medication use

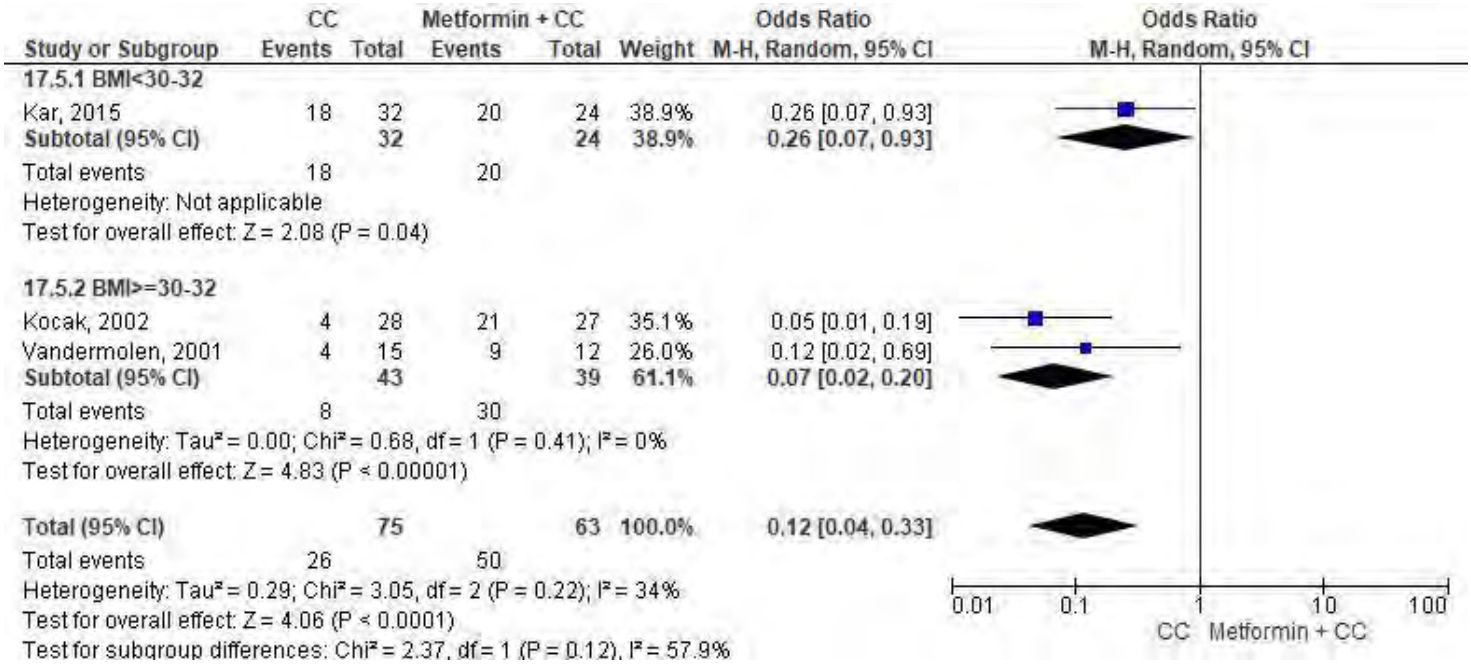


8.3.4.2. Funnel plot for assessment of publication bias: subgroup analysis: ovulation rate- per patient

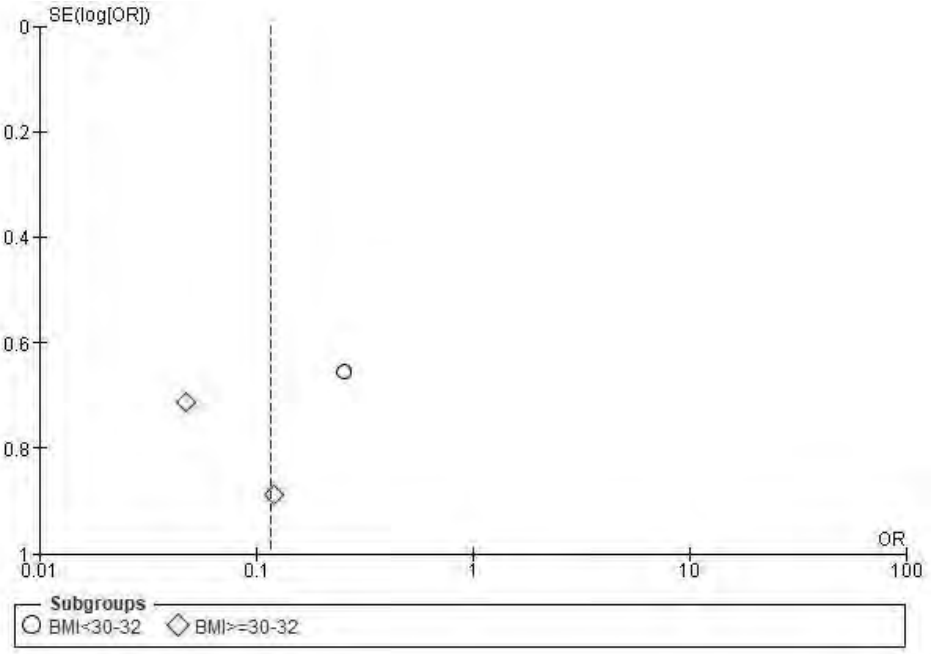


8.3.5.SUBGROUP ANALYSIS: Ovulation rate – per patient

8.3.5.1. Forest Plot of all included RCTs comparing Clomiphene Citrate vs Metformin + Clomiphene Citrate for ovulation rate – per patient, sub-grouped by BMI



8.3.5.2. Funnel plot for assessment of publication bias: subgroup analysis: ovulation rate- per patient



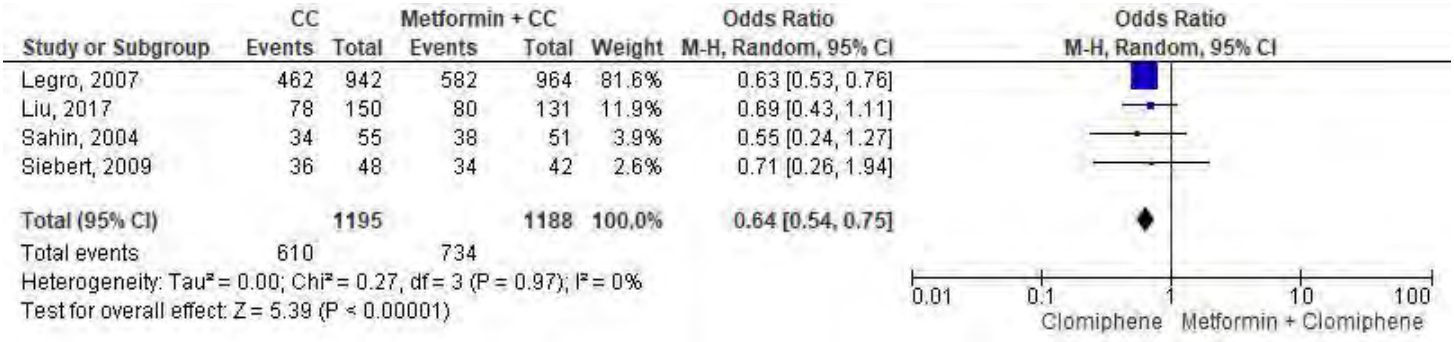
OUTCOME 8.4. Ovulation rate- per cycle

8.4.1. Individual Study Data Table

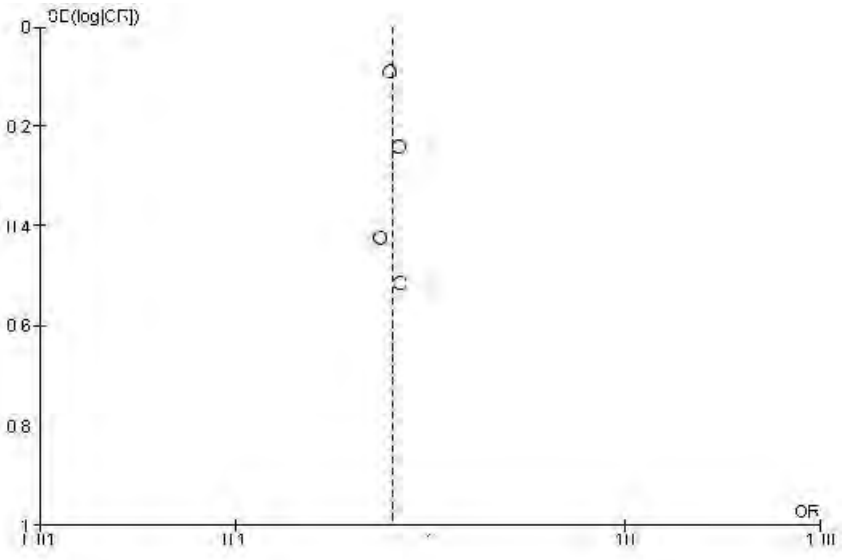
OUTCOME: Ovulation rate – per cycle						**OUTCOME TYPE:** Dichotomous			
COMPARISON: Clomiphene Citrate vs Metformin + Clomiphene Citrate									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in intervention group (CC)**	**N total in intervention group (CC)**	**N events in control / comparison group (MET+CC)**	**N total in control/ comparison group (MET+CC)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Legro 2007 (LRB)	Mixed	Count	Investigator	462	942	582	964	Crude	NA
Liu 2017 (HRB)	Mixed	Count	Investigator	78	150	80	131	Crude	NA
Sahin 2004 (HRB)	NR	Count	Investigator	34	55	38	51	Crude	NA
Siebert 2009 (HRB)	NR	Count	Investigator	36	48	34	42	Crude	NA

NR, not reported; **Mixed**, includes clomiphene citrate resistant/failure and therapy naïve and/or not reported; **OI**, ovulation induction

8.4.2. Forest Plot of all included RCTs comparing Clomiphene Citrate vs Metformin + Clomiphene Citrate for ovulation rate – per cycle

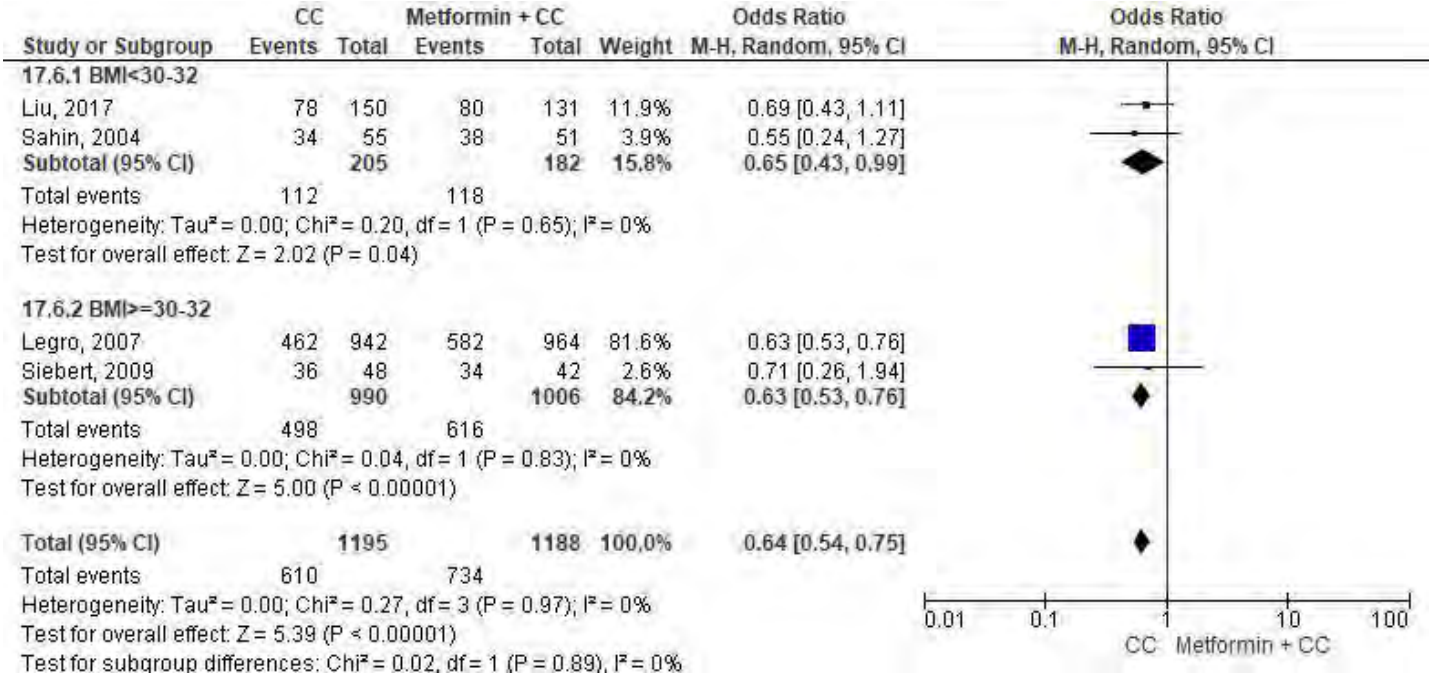


8.4.3. Funnel plot for assessment of publication bias

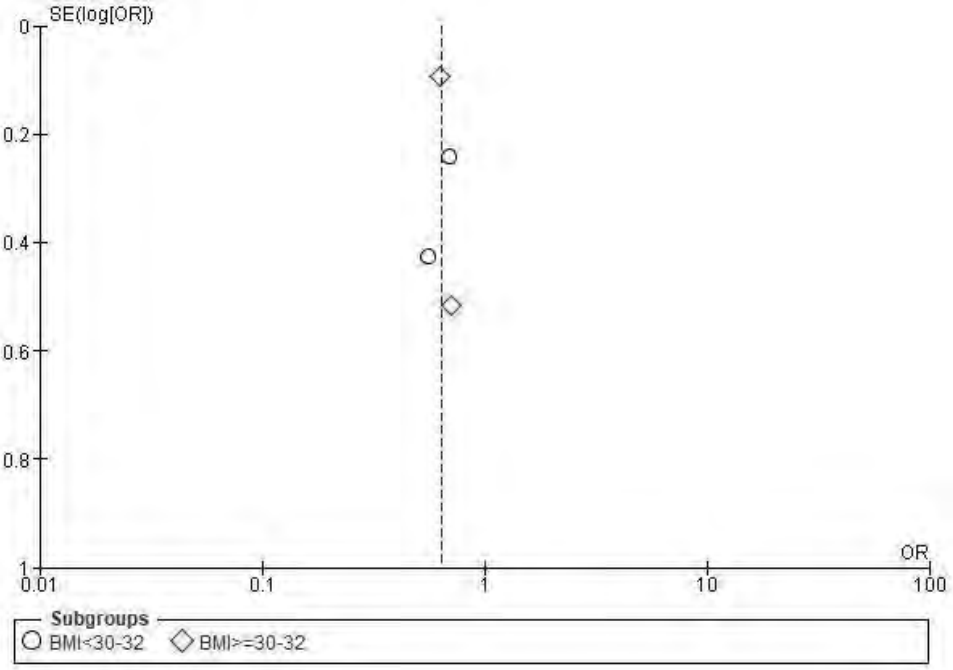


8.4.4.SUBGROUP ANALYSIS: Ovulation rate – per cycle

8.4.4.1. Forest Plot of all included RCTs comparing Clomiphene Citrate vs Metformin + Clomiphene Citrate for ovulation rate – per cycle, sub-grouped by BMI



8.4.4.2. Funnel plot for assessment of publication bias: subgroup analysis: ovulation rate- per cycle



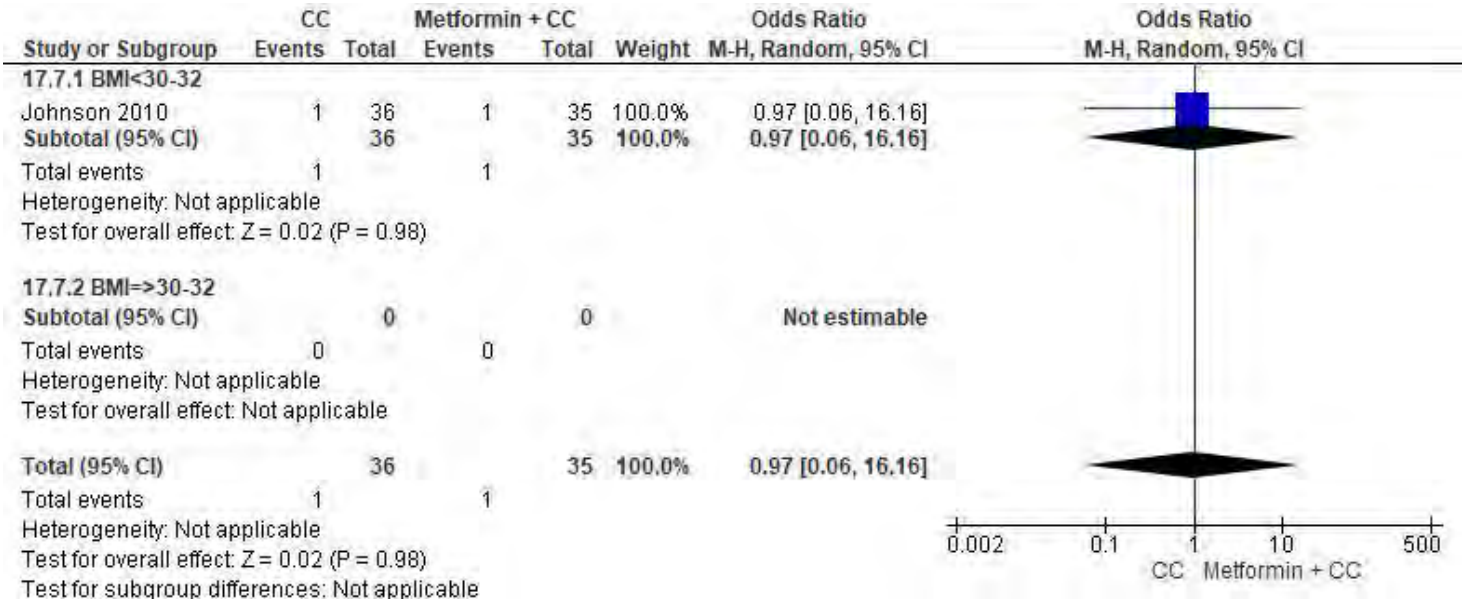
OUTCOME 8.5. Multiple pregnancy rate- per patient

8.5.1. Individual Study Data Table

OUTCOME: Multiple pregnancy rate – per patient						OUTCOME TYPE: Dichotomous			
COMPARISON: Clomiphene Citrate vs Metformin + Clomiphene Citrate									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in intervention group (CC)**	**N total in intervention group (CC)**	**N events in control / comparison group (MET+CC)**	**N total in control/ comparison group (MET+CC)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Johnson 2010 (MRB)	Mixed	Count	Investigator	1	36	1	35	Crude	NA

Mixed, includes clomiphene citrate resistant/failure and therapy naïve and/or not reported; **OI**, ovulation induction

8.5.2.SUBGROUP ANALYSIS: Forest Plot of all included RCTs comparing Clomiphene Citrate vs Metformin + Clomiphene Citrate for multiple pregnancy rate – per patient, sub-grouped by BMI



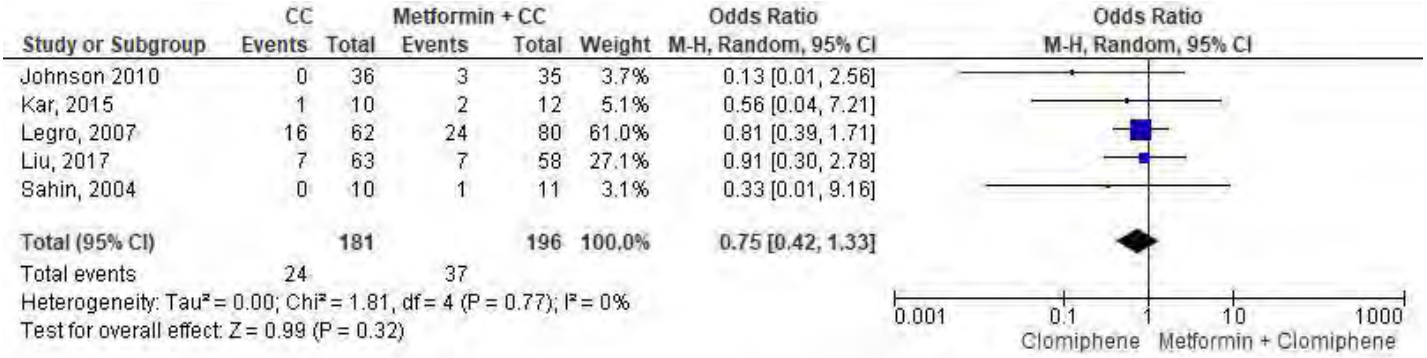
OUTCOME 8.6. Miscarriage rate- per patient

8.6.1. Individual Study Data Table

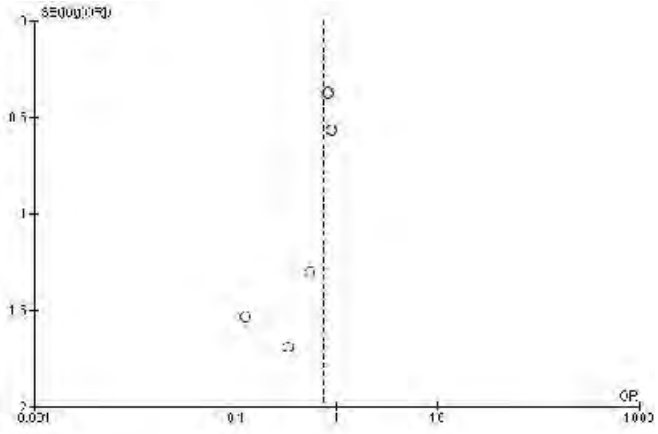
OUTCOME: Miscarriage rate – per patient						OUTCOME TYPE: Dichotomous			
COMPARISON: Clomiphene Citrate vs Metformin + Clomiphene Citrate									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in intervention group (CC)**	**N total in intervention group (CC)**	**N events in comparison group (MET+CC)**	**N total in comparison group (MET+CC)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Johnson 2010 (MRB)	Mixed	Count	Investigator	0	36	3	35	Crude	NA
Kar 2015 (MRB)	TN	Count	Investigator	1	10	2	12	Crude	NA
Legro 2007 (LRB)	Mixed	Count	Investigator	16	62	24	80	Crude	NA
Liu 2017 (HRB)	Mixed	Count	Investigator	7	63	7	58	Crude	NA
Sahin 2004 (HRB)	NR	Count	Investigator	0	10	1	11	Crude	NA

TN, therapy naïve; **NR**, not reported; **Mixed**, includes clomiphene citrate resistant/failure and therapy naïve and/or not reported; **OI**, ovulation induction

8.6.2. Forest Plot of all included RCTs comparing Clomiphene Citrate vs Metformin + Clomiphene Citrate for miscarriage rate – per patient

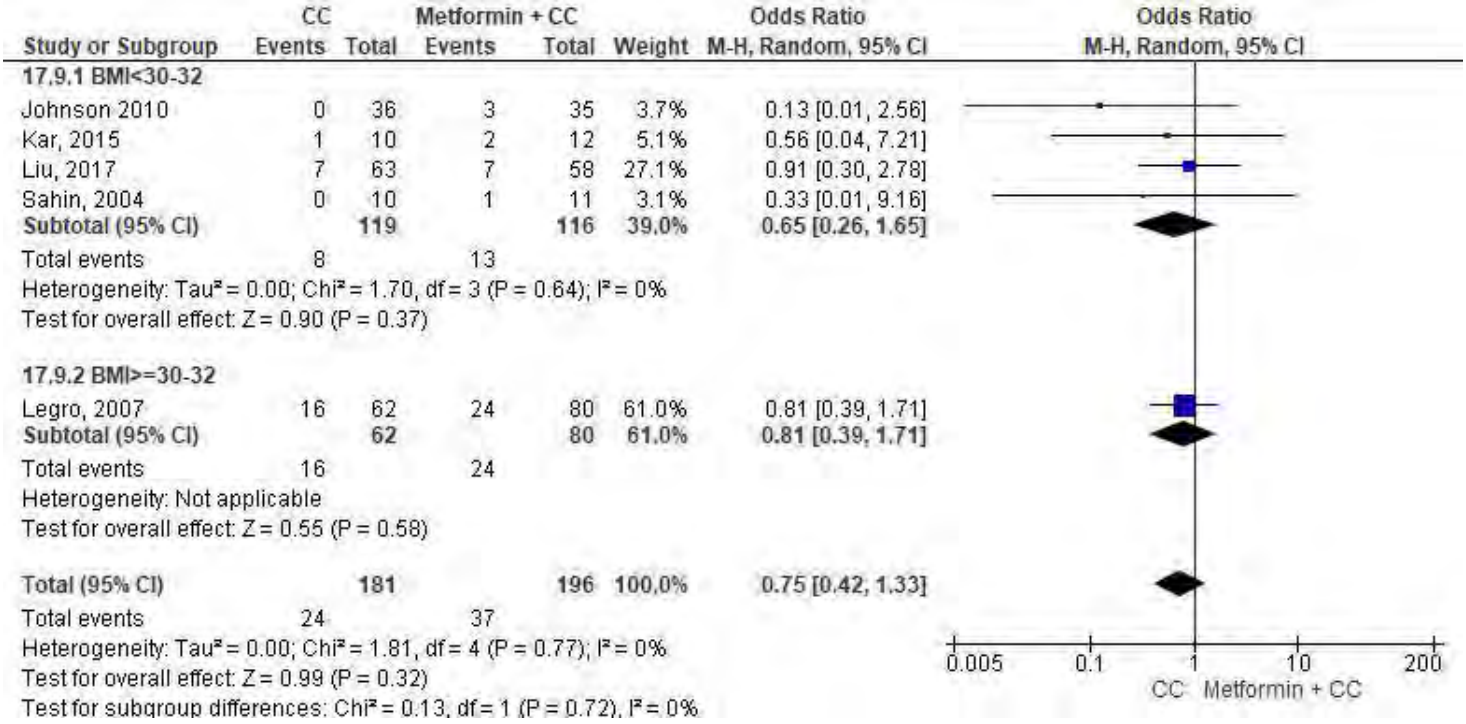


8.6.3. Funnel plot for assessment of publication bias

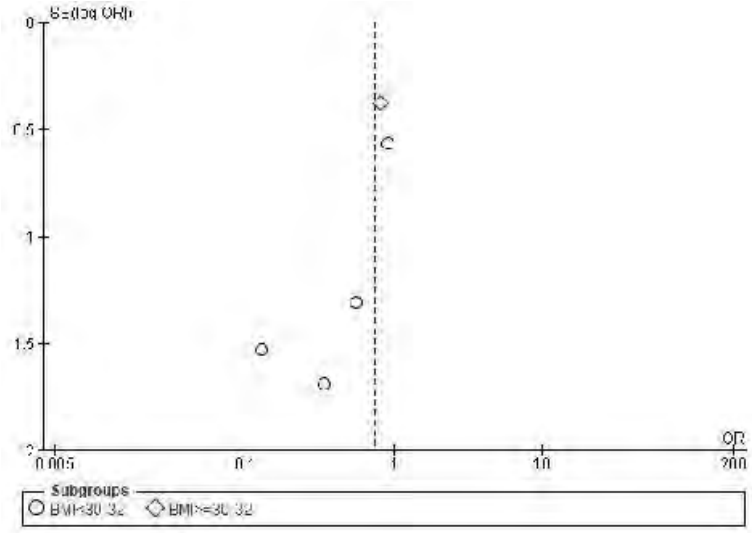


8.6.4.SUBGROUP ANALYSIS: Miscarriage rate – per patient

8.6.4.1. Forest Plot of all included RCTs comparing Clomiphene Citrate vs Metformin + Clomiphene Citrate for miscarriage rate – per patient, sub-grouped by BMI



8.6.4.2. Funnel plot for assessment of publication bias: subgroup analysis: miscarriage rate- per patient

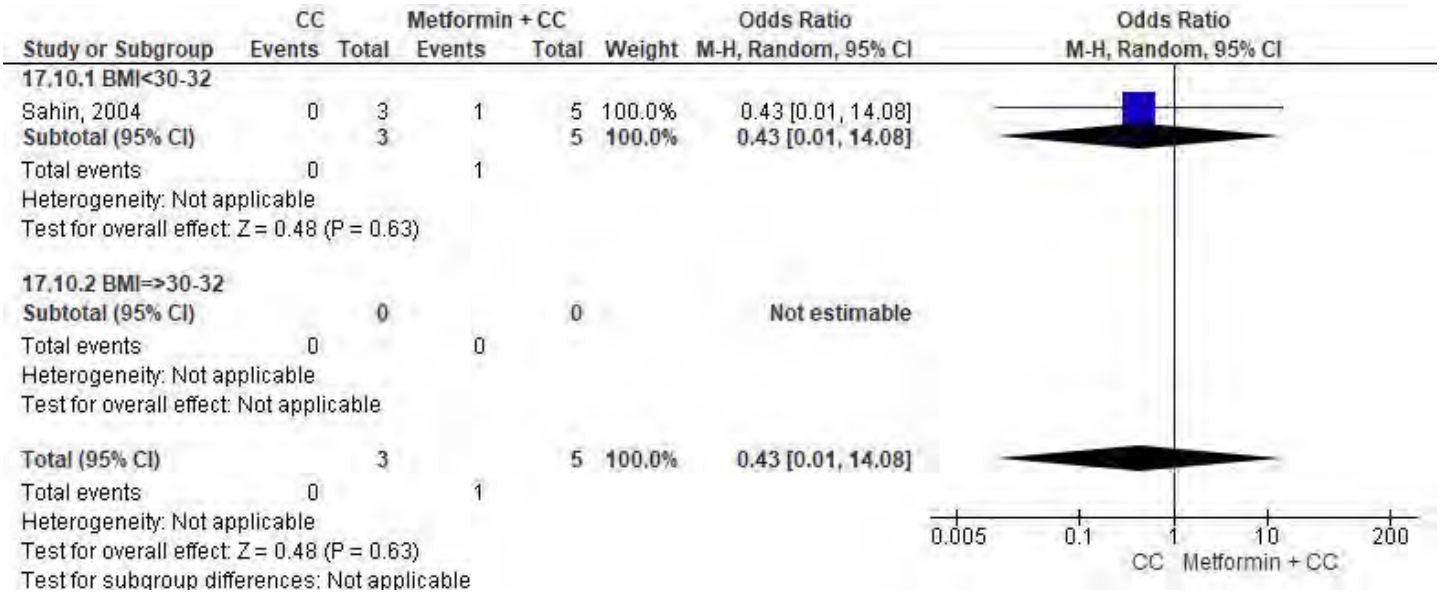


OUTCOME 8.7. Miscarriage rate- per pregnancy

OUTCOME: Miscarriage rate – per pregnancy						OUTCOME TYPE: Dichotomous			
COMPARISON: Clomiphene Citrate vs Metformin + Clomiphene Citrate									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in intervention group (CC)**	**N total in intervention group (CC)**	**N events in control / comparison group (MET+CC)**	**N total in control/ comparison group (MET+CC)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Sahin 2004 (HRB)	NR	Count	Investigator	0	3	1	5	Crude	NA

8.7.1. Individual Study Data Table

8.7.2. SUBGROUP ANALYSIS: Forest Plot of all included RCTs comparing Clomiphene Citrate vs Metformin + Clomiphene Citrate for miscarriage rate – per pregnancy, sub-grouped by BMI



COMPARISON 9. Clomiphene Citrate vs Letrozole

- **EVIDENCE SUMMARY:**

Eleven RCTs compared clomiphene citrate with letrozole, of which six had a high risk of bias (Atay, 2006; Nazik, 2012; Ray, 2012; Zeinalzadeh, 2010; Bansal, 2021; Liu, 2017), one had a moderate risk of bias (Begum, 2009), and four had a low risk of bias (Legro, 2014; Roy, 2012; Amer, 2017; Bayar, 2006). Studies were conducted in the UK, USA, Iran, India, Bangladesh and China.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

In meta-analysis, letrozole was superior to clomiphene citrate for ovulation rate per patient; pregnancy rate and clinical pregnancy rate per patient; and live birth rate per patient. Certainty in the evidence is high for live birth rate, and moderate for pregnancy rate, clinical pregnancy rate and ovulation rate, downgraded once for serious risk of bias since the majority of studies included had high to moderate risk of bias.

There were no differences between clomiphene citrate and letrozole for other outcomes including live birth rate per pregnancy, multiple pregnancy rate (per patient or pregnancy); and miscarriage rate (per patient or pregnancy). Certainty in these findings ranged from low to very low due to risk of bias, serious imprecision and serious inconsistency, except for multiple pregnancy rate per patient which was moderate due to 3 of the 5 studies having a high risk of bias. There was no evidence of statistical heterogeneity or publication bias for any of the outcomes.

Summary Table for meta-analysis results:

Outcome or Subgroup	Studies	n	Effect Estimate; OR [95% CI], M-H, random	P	Favours	Certainty
Live birth rate- per patient	6	1449	0.56 [0.44, 0.71]	<0.00001	**LET** (live birth rate is lower with CC)	⊕⊕⊕⊕ HIGH
Live birth rate- per pregnancy	4	319	0.70 [0.30, 1.61]	0.4	None	⊕⊕◯◯ LOW
Clinical pregnancy rate- per patient†	8	1668	0.53 [0.43, 0.66]	<0.00001	**LET** (clinical pregnancy is lower with CC)	⊕⊕⊕◯ MODERATE
Pregnancy rate- per patient*	11	1870	0.55 [0.44, 0.67]	<0.00001	**LET** (pregnancy rate is lower with CC)	⊕⊕⊕◯ MODERATE
Ovulation Rate- per patient	8	1697	0.52 [0.36, 0.74]	0.0003	**LET** (ovulation per patient is lower with CC)	⊕⊕⊕◯ MODERATE
Ovulation Rate- per cycle	1	280	0.43 [0.26, 0.71]	0.0009	**LET** (ovulation per cycle is lower with CC)	⊕◯◯◯ VERY LOW
Multiple Pregnancy Rate- per patient	7	1394	0.83 [0.33, 2.08]	0.7	None	⊕◯◯◯ VERY LOW
Multiple pregnancy rate- per pregnancy	5	318	2.65 [0.96, 7.31]	0.06	None	⊕⊕◯◯ LOW
Miscarriage rate- per patient	8	1511	1.09 [0.52, 2.26]	0.8	None	⊕◯◯◯ VERY LOW
Miscarriage rate- per pregnancy	6	353	1.00 [0.60, 1.67]	0.9	None	⊕⊕◯◯ LOW

*includes biochemical (or undefined pregnancy rate) as reported in each study; †clinical pregnancy rate is confirmed by ultrasound detection of gestational sac/ fetal heart activity

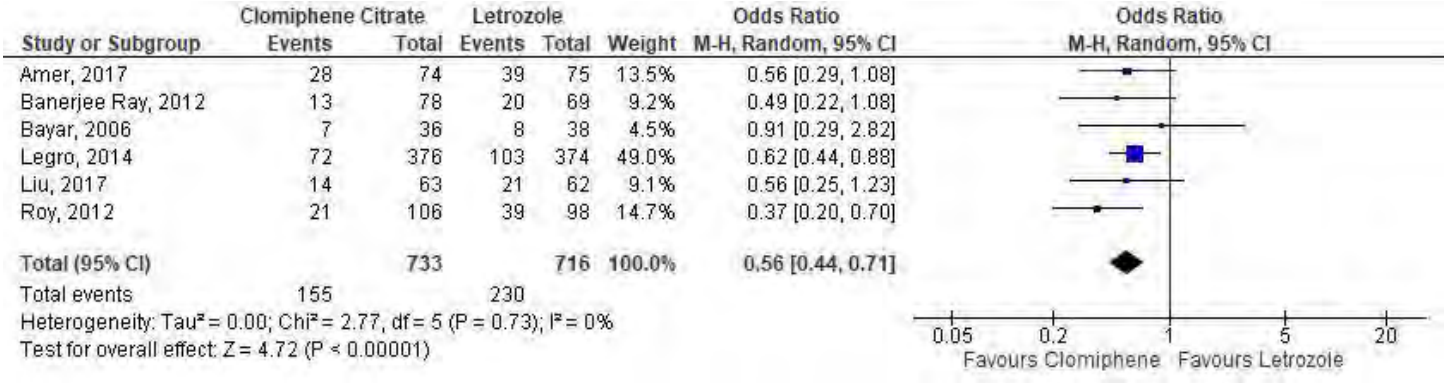
OUTCOME 9.1. Live birth rate – per patient

OUTCOME: Live birth rate - per patient						**OUTCOME TYPE:** Dichotomous			
COMPARISON: Clomiphene Citrate vs Letrozole									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (CC)**	**N total in intervention/ exposure group (CC)**	**N events in control / comparison group (LET)**	**N total in control/ comparison group (LET)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Amer 2017 (LRB)	NR	Count	Investigator	28	74	39	75	Crude	NA
Banerjee Ray 2012 (HRB)	NR	Count	Investigator	13	78	20	69	Crude	NA
Bayar 2006 (LRB)	TN	Count	Investigator	7	36	8	38	Crude	NA
Legro 2014 (LRB)	NR	Count	Investigator	72	376	103	374	Crude	NA
Liu 2017 (HRB)	Mixed	Count	Investigator	14	63	21	62	Crude	NA
Roy 2012 (LRB)	NR	Count	Investigator	21	106	39	98	Crude	NA

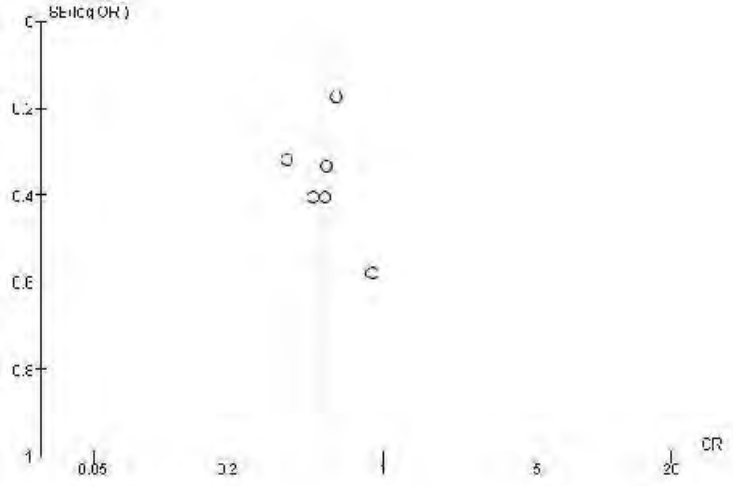
9.1.1. Individual Study Data Table

CCR, Clomiphene citrate resistant; **TN**, therapy naïve; **NR**, not reported; **Mixed**, includes some clomiphene citrate resistant/failure and/or therapy naïve and/or not reported.

9.1.2. Forest Plot of all included RCTs comparing Clomiphene Citrate versus Letrozole for live birth rate – per patient

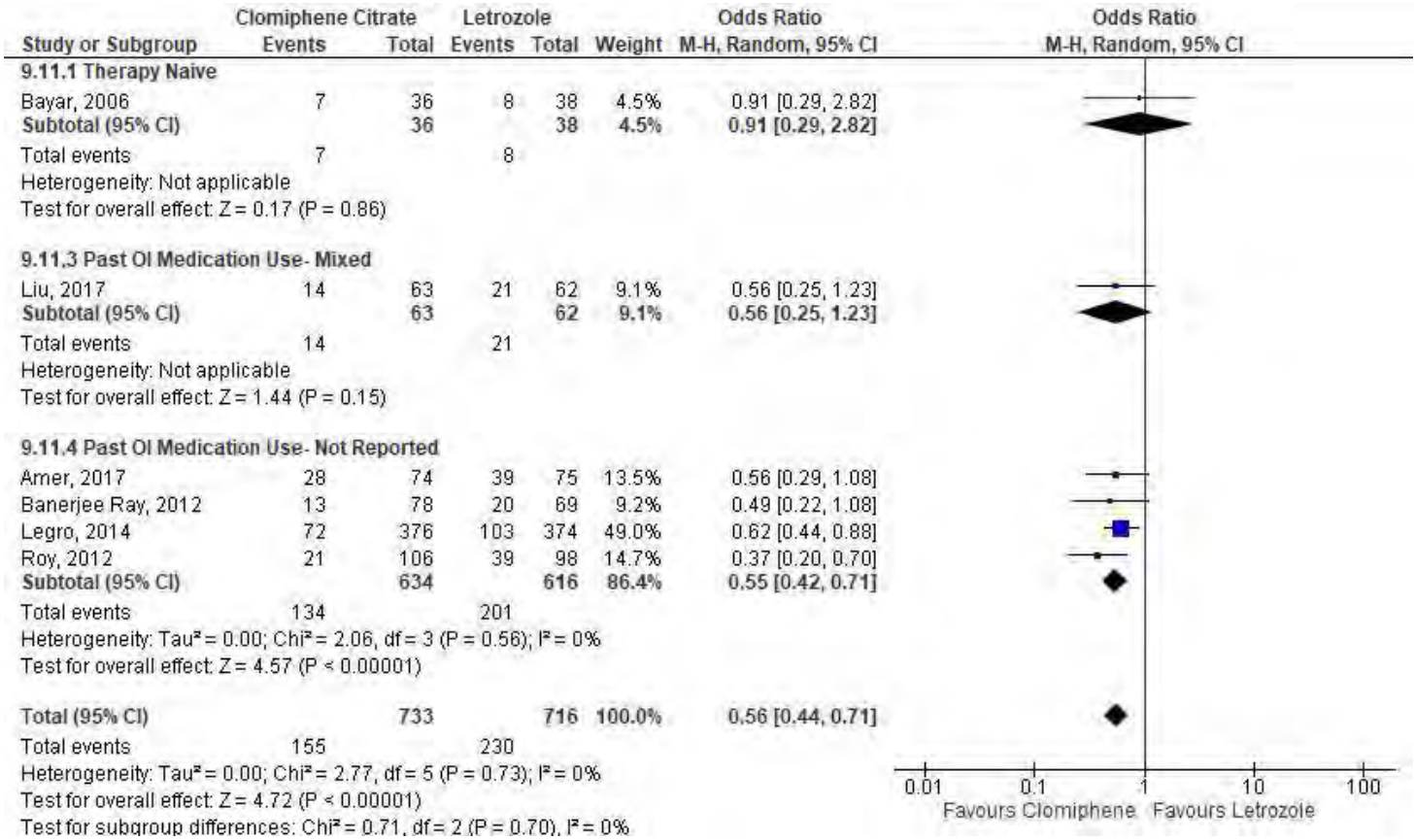


9.1.3. Funnel plot for assessment of publication bias

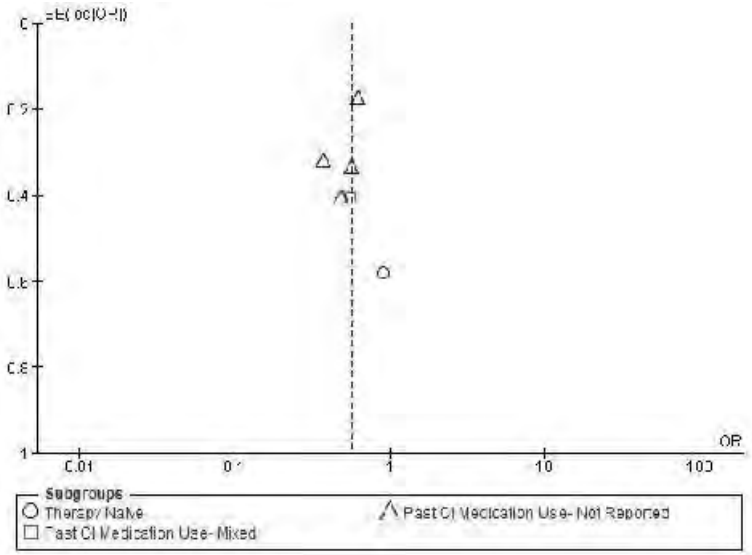


9.1.4. Subgroup analysis: Live birth rate- per patient

9.1.4.1. Forest Plot of all included RCTs comparing Clomiphene Citrate versus Letrozole for live birth rate- per patient, sub-grouped by past ovulation induction (OI) medication use



9.1.4.2. Funnel plot for assessment of publication bias for subgroup analysis



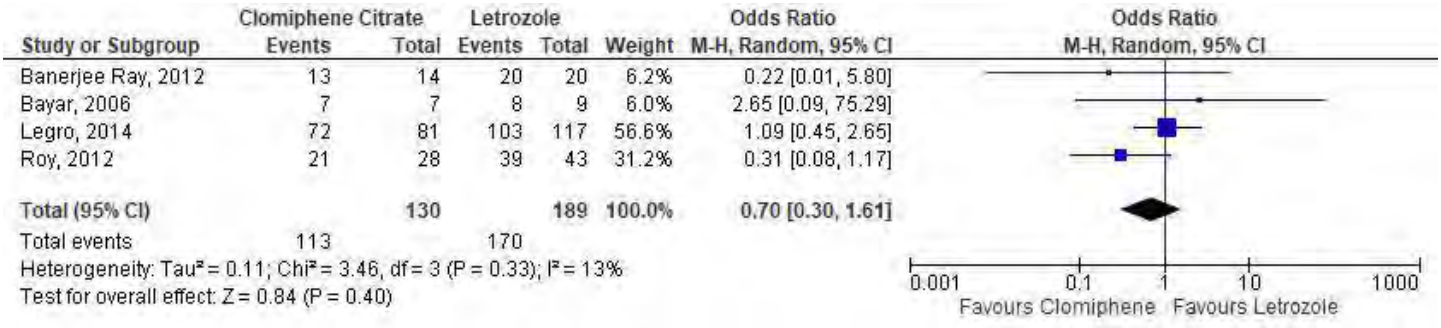
OUTCOME 9.2. Live birth rate – per pregnancy

9.2.1. Individual Study Data Table

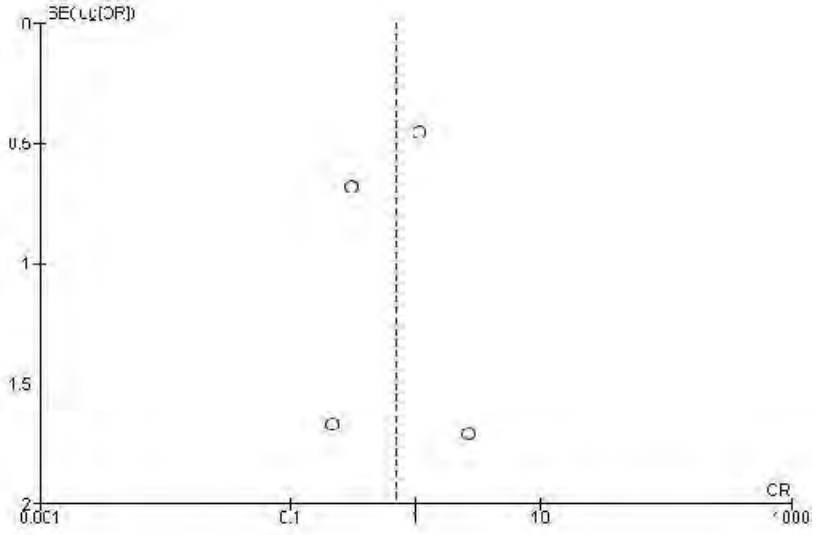
OUTCOME: Live birth rate - per pregnancy						**OUTCOME TYPE:** Dichotomous			
COMPARISON: Clomiphene Citrate vs Letrozole									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (CC)**	**N total in intervention/ exposure group (CC)**	**N events in control / comparison group (LET)**	**N total in control/ comparison group (LET)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Banerjee Ray 2012 (HRB)	NR	Count	Investigator	13	14	20	20	Crude	NA
Bayar 2006 (LRB)	TN	Count	Investigator	7	7	8	9	Crude	NA
Legro 2014 (LRB)	NR	Count	Investigator	72	81	103	117	Crude	NA
Roy 2012 (LRB)	NR	Count	Investigator	21	28	39	43	Crude	NA

CCR, Clomiphene citrate resistant; **TN**, therapy naïve; **NR**, not reported; **Mixed**, includes some clomiphene citrate resistant/failure and/or therapy naïve and/or not reported.

9.2.2. Forest Plot of all included RCTs comparing Clomiphene Citrate versus Letrozole for live birth rate – per pregnancy



9.2.3. Funnel plot for assessment of publication bias



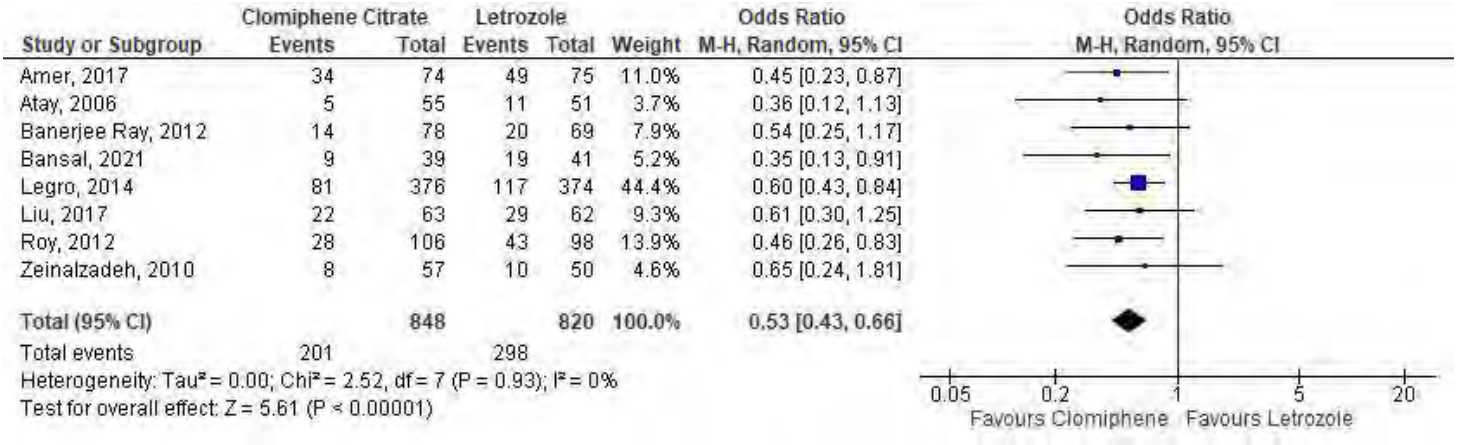
OUTCOME 9.3. Clinical pregnancy rate – per patient

9.3.1. Individual Study Data Table

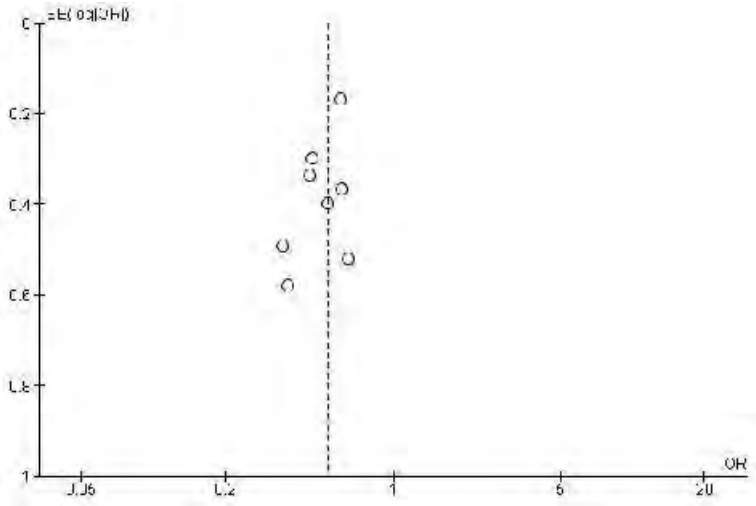
OUTCOME: Pregnancy rate - per patient				**OUTCOME TYPE:** Dichotomous					
COMPARISON: Clomiphene Citrate vs Letrozole									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (CC)**	**N total in intervention/ exposure group (CC)**	**N events in control / comparison group (LET)**	**N total in control/ comparison group (LET)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Amer 2017 (LRB)	NR	Count	Investigator	34	74	49	75	Crude	NA
Atay 2006 (HRB)	NR	Count	Investigator	5	55	11	51	Crude	NA
Banerjee Ray 2012 (HRB)	NR	Count	Investigator	14	78	20	69	Crude	NA
Bansal 2021 (HRB)	NR	Count	Investigator	9	39	19	41	Crude	NA
Legro 2014 (LRB)	NR	Count	Investigator	81	376	117	374	Crude	NA
Liu 2017 (HRB)	Mixed	Count	Investigator	22	63	29	62	Crude	NA
Roy 2012 (LRB)	NR	Count	Investigator	28	106	43	98	Crude	NA
Zeinalzadeh 2010 (HRB)	NR	Count	Investigator	8	57	10	50	Crude	NA

NR, not reported; **Mixed**, includes clomiphene citrate resistant/failure and therapy naïve and/or not reported; **OI**, ovulation induction

9.3.2. Forest Plot of all included RCTs comparing Clomiphene Citrate versus Letrozole for clinical pregnancy rate- per patient

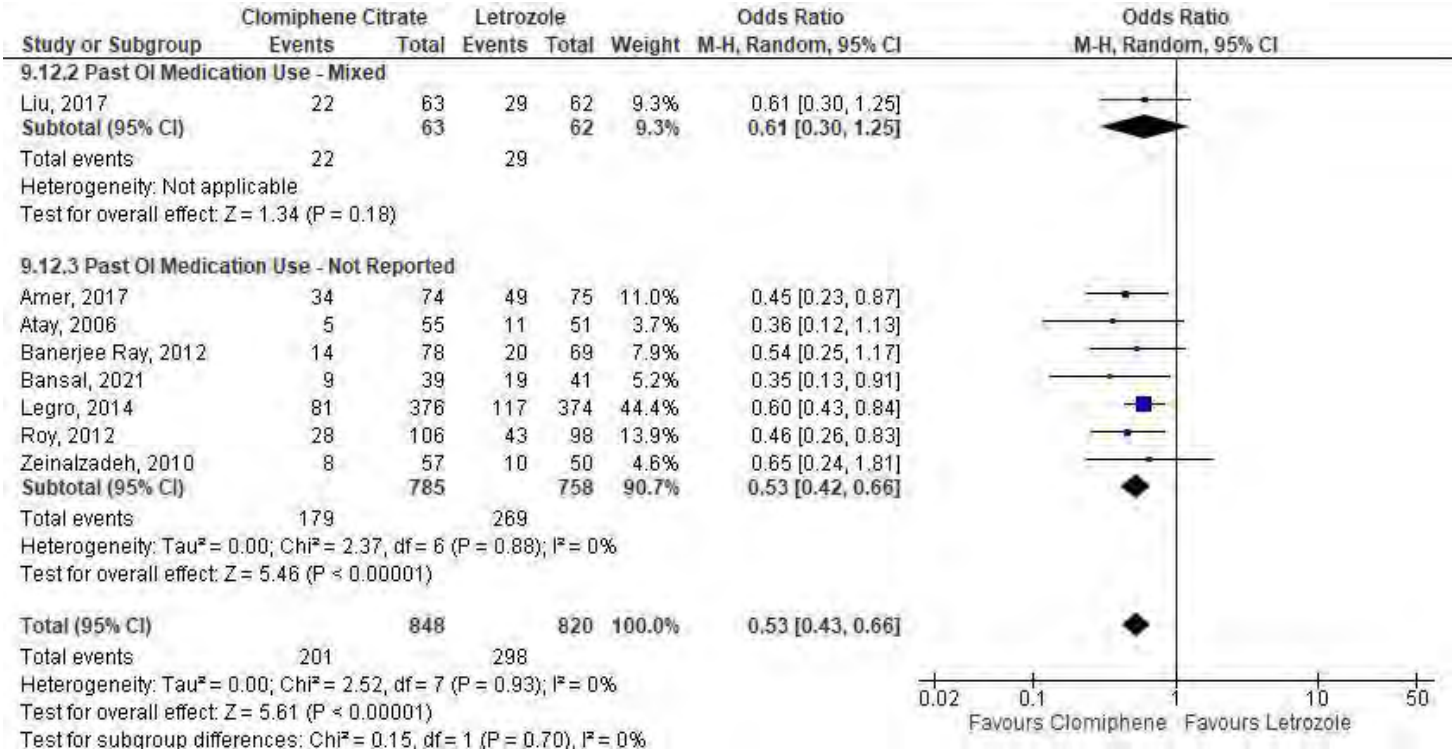


9.3.3. Funnel plot for assessment of publication bias

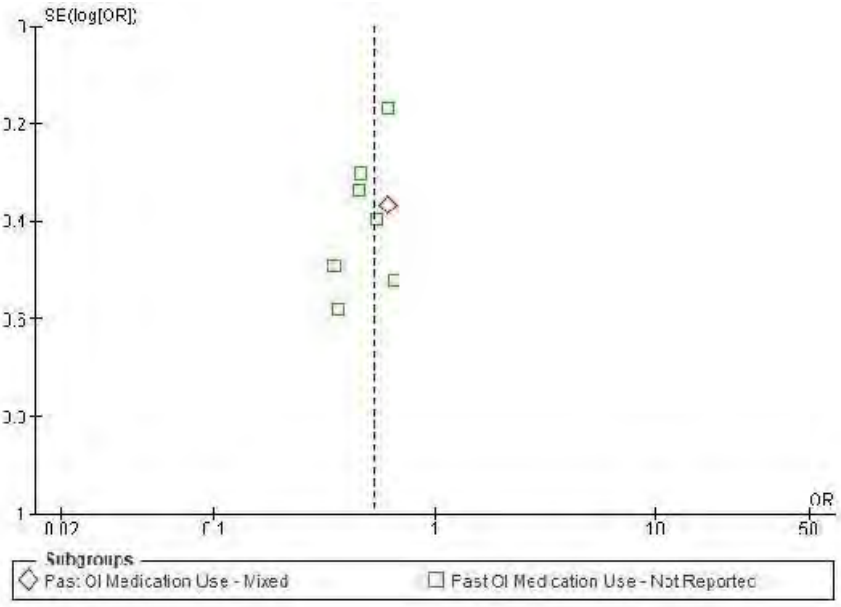


9.3.4. SUBGROUP ANALYSIS: Clinical pregnancy rate-per patient

9.3.4.1. Forest Plot of all included RCTs comparing Clomiphene Citrate and Letrozole for clinical pregnancy rate- per patient, sub-grouped by past ovulation induction (OI) medication use



9.3.4.2. Funnel plot for assessment of publication bias for subgroup analysis



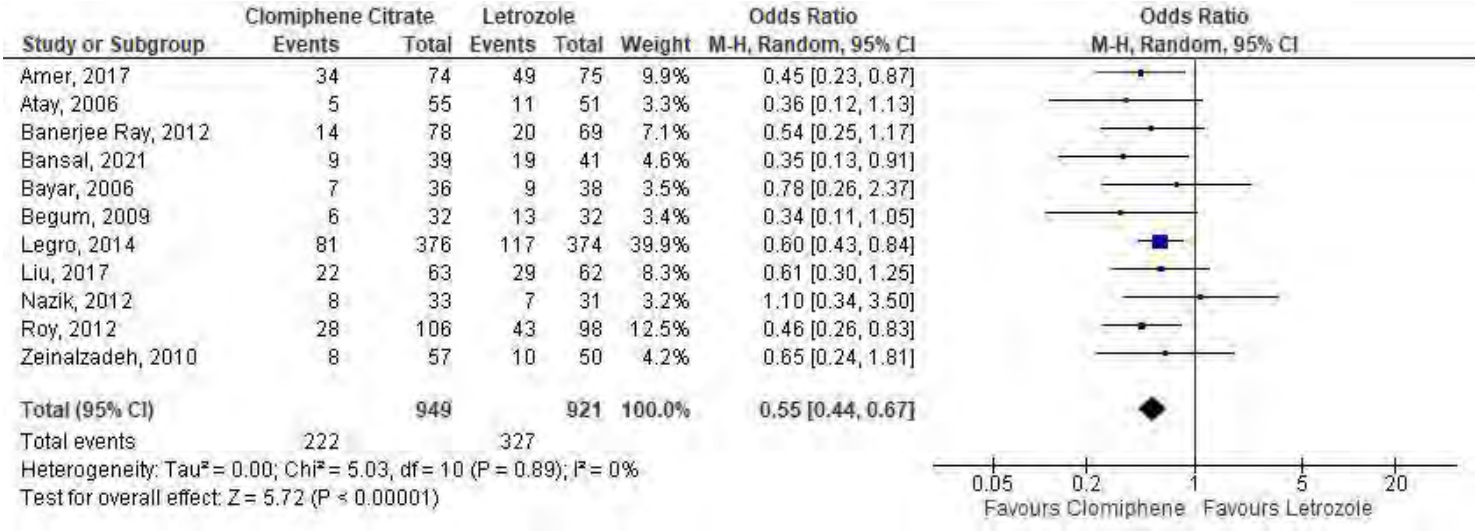
OUTCOME 9.4. Pregnancy rate – per patient

9.4.1. Individual Study Data Table

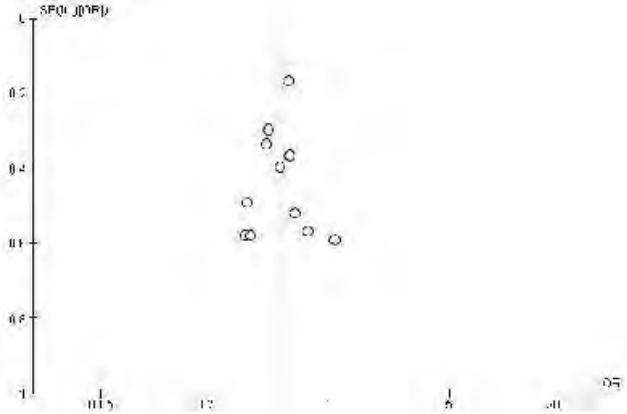
OUTCOME: Pregnancy rate - per patient				**OUTCOME TYPE:** Dichotomous					
COMPARISON: Clomiphene Citrate vs Letrozole									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (CC)**	**N total in intervention/ exposure group (CC)**	**N events in control / comparison group (LET)**	**N total in control/ comparison group (LET)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Amer 2017 (LRB)	NR	Count	Investigator	34	74	49	75	Crude	NA
Atay 2006 (HRB)	NR	Count	Investigator	5	55	11	51	Crude	NA
Banerjee Ray 2012 (HRB)	NR	Count	Investigator	14	78	20	69	Crude	NA
Bansal 2021 (HRB)	NR	Count	Investigator	9	39	19	41	Crude	NA
Bayar 2006 (LRB)	TN	Count	Investigator	7	36	9	38	Crude	NA
Begum 2009 (MRB)	CCR	Count	Investigator	6	32	13	32	Crude	NA
Legro 2014 (LRB)	NR	Count	Investigator	81	376	117	374	Crude	NA
Liu 2017 (HRB)	Mixed	Count	Investigator	22	63	29	62	Crude	NA
Nazik 2012 (HRB)	Mixed	Count	Investigator	8	33	7	31	Crude	NA
Roy 2012 (LRB)	NR	Count	Investigator	28	106	43	98	Crude	NA
Zeinalzadeh 2010 (HRB)	NR	Count	Investigator	8	57	10	50	Crude	NA

CCR, Clomiphene citrate resistant; **TN**, therapy naïve; **NR**, not reported; **Mixed**, includes some clomiphene citrate resistant/failure and/or therapy naïve and/or not reported.

9.4.2. Forest Plot of all included RCTs comparing Clomiphene Citrate and Letrozole for pregnancy rate- per patient

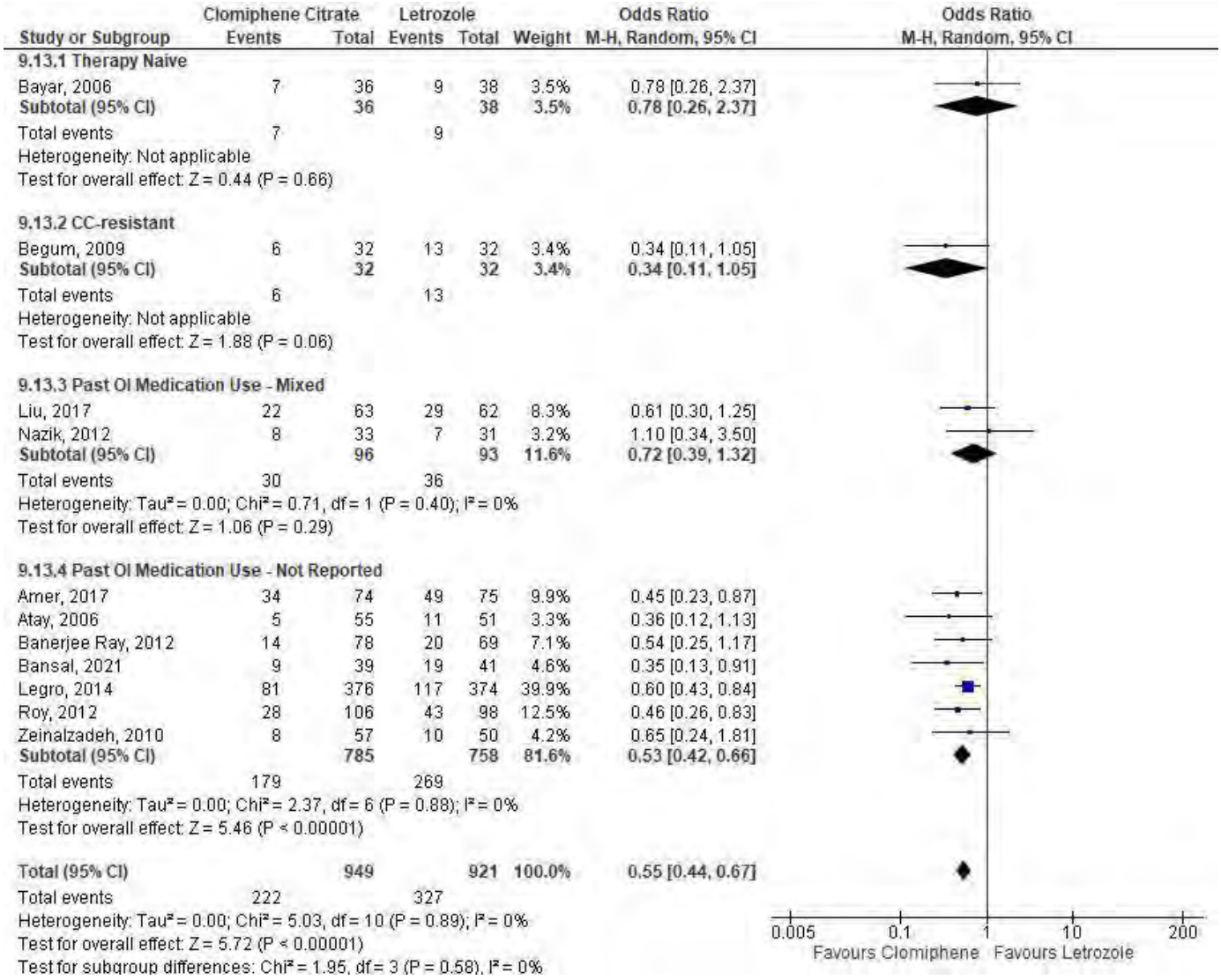


9.4.3. Funnel plot for assessment of publication bias for subgroup analysis

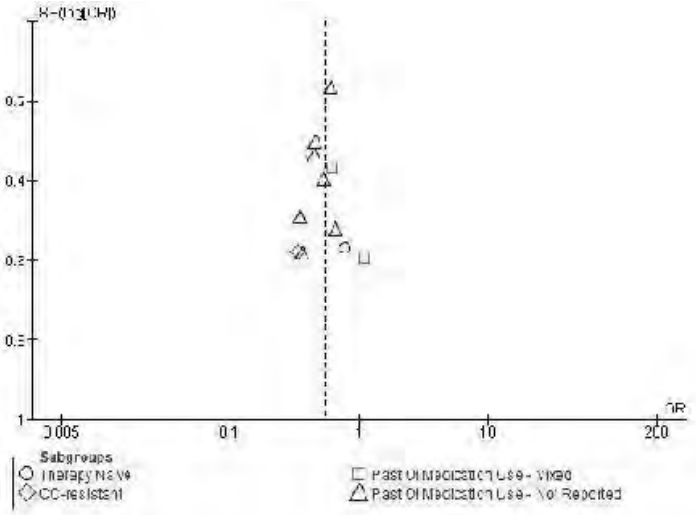


9.4.4. SUBGROUP ANALYSIS: Pregnancy rate-per patient

9.4.4.1. Forest Plot of all included RCTs comparing Clomiphene Citrate and Letrozole for pregnancy rate- per patient, sub-grouped by past ovulation induction (OI) medication use



9.4.4.2. Funnel plot for assessment of publication bias- subgroup analysis: pregnancy rate-per patient



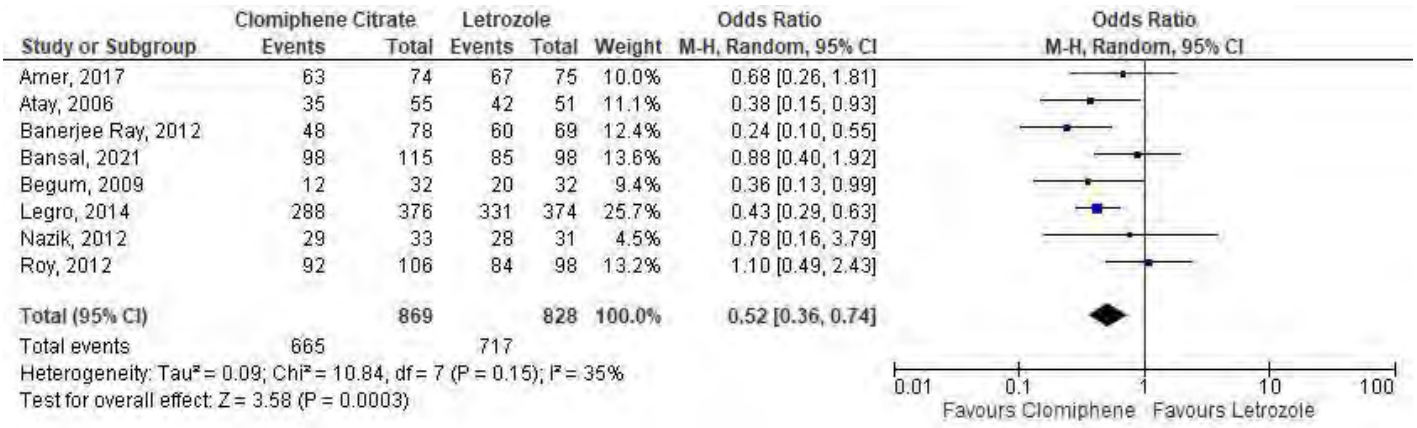
OUTCOME 9.5. Ovulation rate- per patient

OUTCOME: Ovulation rate - per patient					OUTCOME TYPE: Dichotomous				
COMPARISON (if applicable): Clomiphene Citrate vs Letrozole									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (CC)**	**N total in intervention/ exposure group (CC)**	**N events in control / comparison group (LET)**	**N total in control/ comparison group (LET)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Amer 2017 (LRB)	NR	Count	Investigator	63	74	67	75	Crude	NA
Atay 2006 (HRB)	NR	Count	Investigator	35	55	42	51	Crude	NA
Banerjee Ray 2012 (HRB)	NR	Count	Investigator	48	78	60	69	Crude	NA
Bansal 2021 (LRB)	NR	Count	Investigator	98	115	85	98	Crude	NA
Begum 2009 (MRB)	CCR	Count	Investigator	12	32	20	32	crude	NA
Legro 2014 (LRB)	NR	Count	Investigator	288	376	331	374	Crude	NA
Nazik 2012 (HRB)	Mixed	Count	Investigator	29	33	28	31	Crude	NA
Roy 2012 (LRB)	NR	Count	Investigator	92	106	84	98	Crude	NA

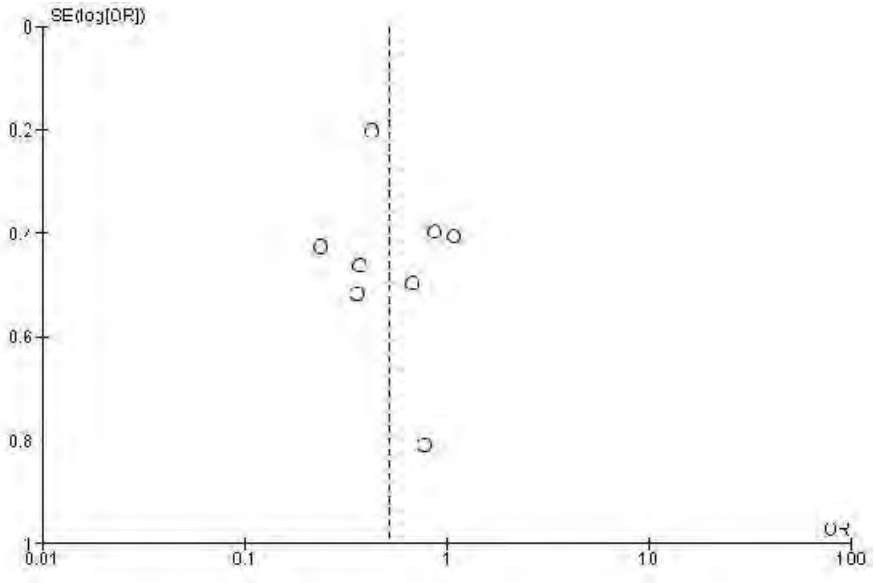
9.5.1. Individual Study Data Table

CCR, Clomiphene citrate resistant; **TN**, therapy naïve; **NR**, not reported; **Mixed**, includes clomiphene citrate resistant/failure and therapy naïve and/or not reported; **OI**, ovulation induction

9.5.2. Forest Plot of all included RCTs comparing Clomiphene Citrate versus Letrozole for ovulation rate- per patient

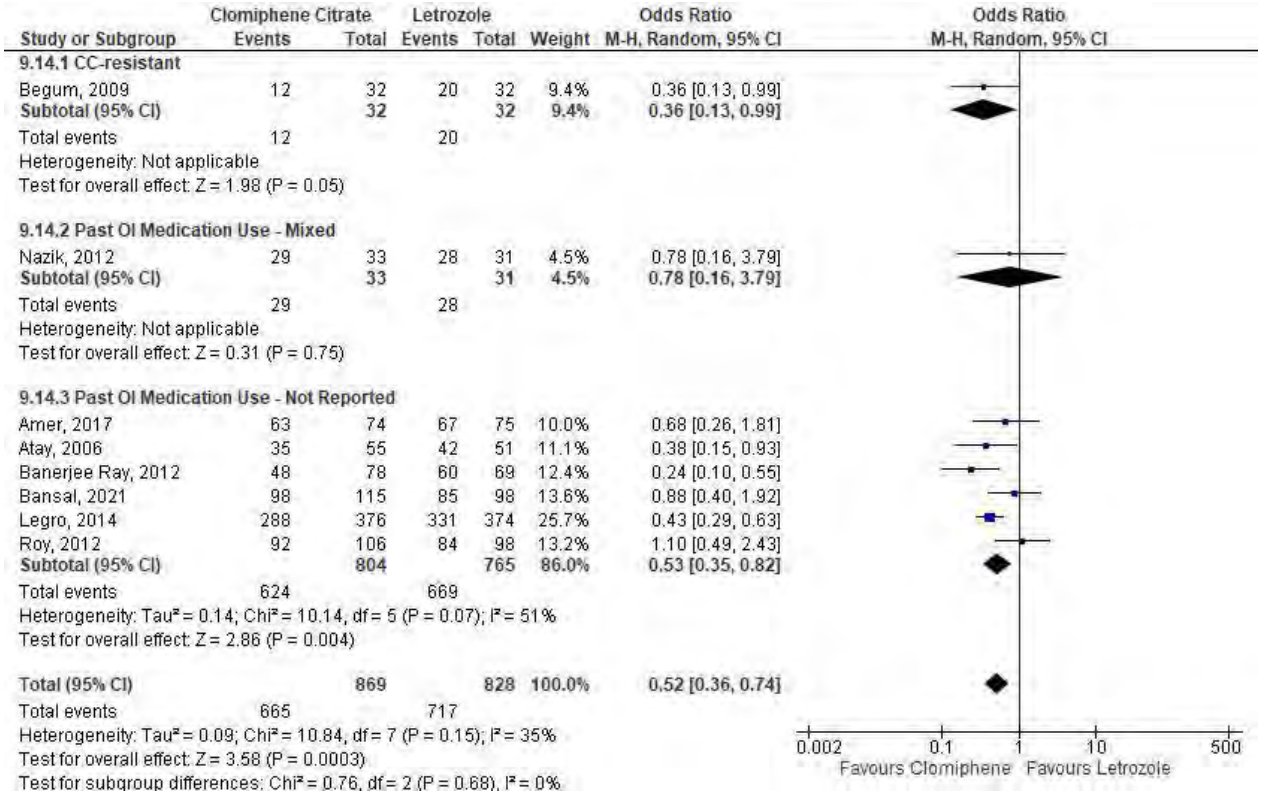


9.5.3. Funnel plot for assessment of publication bias

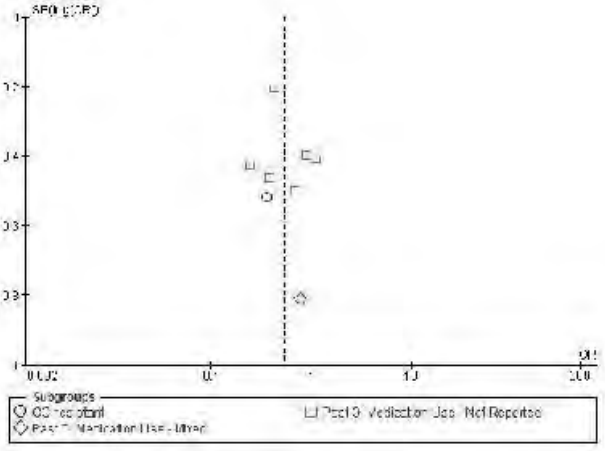


9.5.4. SUBGROUP ANALYSIS: Ovulation rate- per patient

9.5.4.1. Forest Plot of all included RCTs comparing Clomiphene Citrate versus Letrozole for ovulation rate- per patient, sub-grouped by past ovulation induction (OI) medication use



9.5.4.2. Funnel plot for assessment of publication bias- subgroup analysis: ovulation rate - per patient



OUTCOME 9.6. Ovulation rate- per cycle

9.6.1. Individual Study Data Table

OUTCOME: Ovulation rate per cycle					OUTCOME TYPE: Dichotomous				
COMPARISON: Clomiphene Citrate vs Letrozole									
Author, year	Past OI Med Use	Unit of outcome (e.g. g, mg)	Method of measurement	N events in intervention/ exposure group (CC)	N total in intervention/ exposure group (CC)	N events in control / comparison group (LET)	N total in control/ comparison group (LET)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Liu 2017 (HRB)	Mixed	Count	Investigator	78	150	93	130	Crude	NA

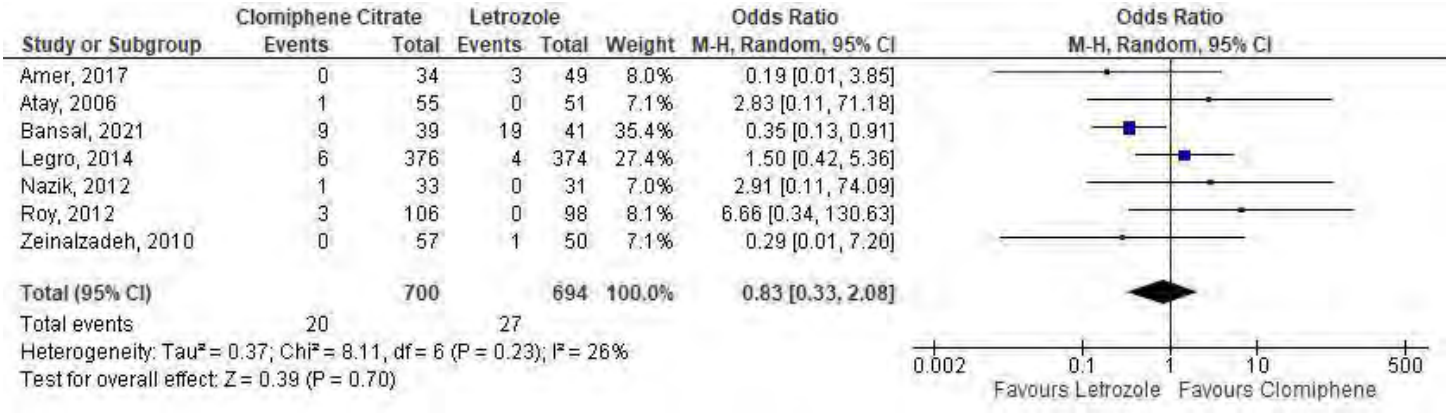
OUTCOME 9.7. Multiple pregnancy rate – per patient

OUTCOME: Multiple pregnancy rate per patient					OUTCOME TYPE: Dichotomous				
COMPARISON: Clomiphene Citrate vs Letrozole									
Author, year	Past OI Med Use	Unit of outcome (e.g. g, mg)	Method of measurement	N events in intervention/ exposure group (CC)	N total in intervention/ exposure group (CC)	N events in control / comparison group (LET)	N total in control/ comparison group (LET)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Amer 2017 (LRB)	NR	Count	Investigator	0	34	3	49	Crude	NA
Atay 2006 (HRB)	NR	Count	Investigator	1	55	0	51	Crude	NA
Bansal 2021 (HRB)	NR	Count	Investigator	9	39	19	41	Crude	NA
Legro 2014 (LRB)	NR	Count	Investigator	6	376	4	374	Crude	NA
Nazik 2012 (HRB)	Mixed	Count	Investigator	1	33	0	31	Crude	NA
Roy 2012 (LRB)	NR	Count	Investigator	3	106	0	98	Crude	NA
Zeinalzadeh 2010 (HRB)	NR	Count	Investigator	0	57	1	50	Crude	NA

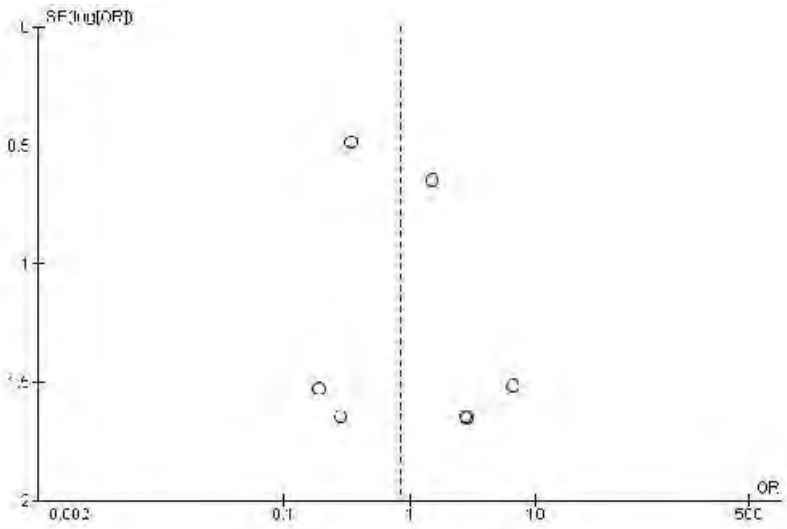
9.7.1. Individual Study Data Table

CCR, Clomiphene citrate resistant; **TN**, therapy naïve; **NR**, not reported; **Mixed**, includes some clomiphene citrate resistant/failure and/or therapy naïve and/or not reported.

9.7.2. Forest Plot of all included RCTs comparing Clomiphene Citrate versus Letrozole for multiple pregnancy rate – per patient



9.7.3. Funnel plot for assessment of publication bias



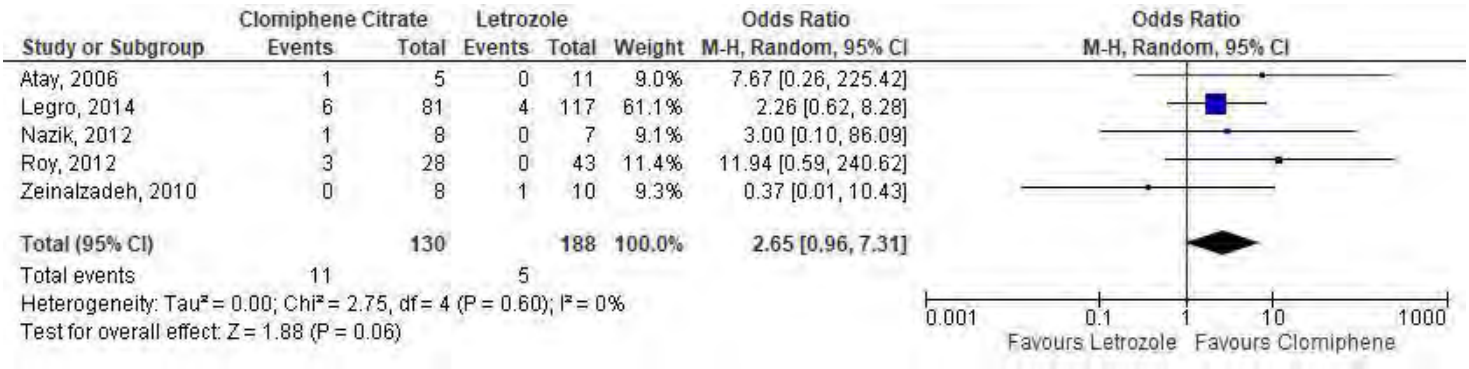
OUTCOME 9.8. Multiple pregnancy rate – per pregnancy

9.8.1. Individual Study Data Table

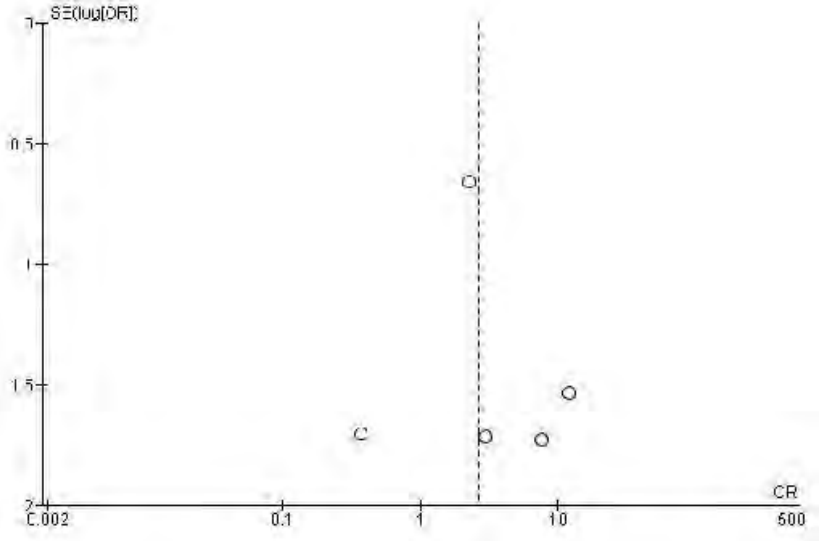
OUTCOME: Multiple pregnancy rate per pregnancy						**OUTCOME TYPE:** Dichotomous			
COMPARISON: Clomiphene Citrate vs Letrozole									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (CC)**	**N total in intervention/ exposure group (CC)**	**N events in control / comparison group (LET)**	**N total in control/ comparison group (LET)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Atay 2006 (HRB)	NR	Count	Investigator	1	5	0	11	Crude	NA
Legro 2014 (LRB)	NR	Count	Investigator	6	81	4	117	Crude	NA
Nazik 2012 (HRB)	Mixed	Count	Investigator	1	8	0	7	Crude	NA
Roy 2012 (LRB)	NR	Count	Investigator	3	28	0	43	Crude	NA
Zeinalzadeh 2010 (HRB)	NR	Count	Investigator	0	8	1	10	Crude	NA

CCR, Clomiphene citrate resistant; **TN**, therapy naïve; **NR**, not reported; **Mixed**, includes some clomiphene citrate resistant/failure and/or therapy naïve and/or not reported.

9.8.2. Forest Plot of all included RCTs comparing Clomiphene Citrate versus Letrozole for multiple pregnancy rate – per pregnancy



9.8.3. Funnel plot for assessment of publication bias



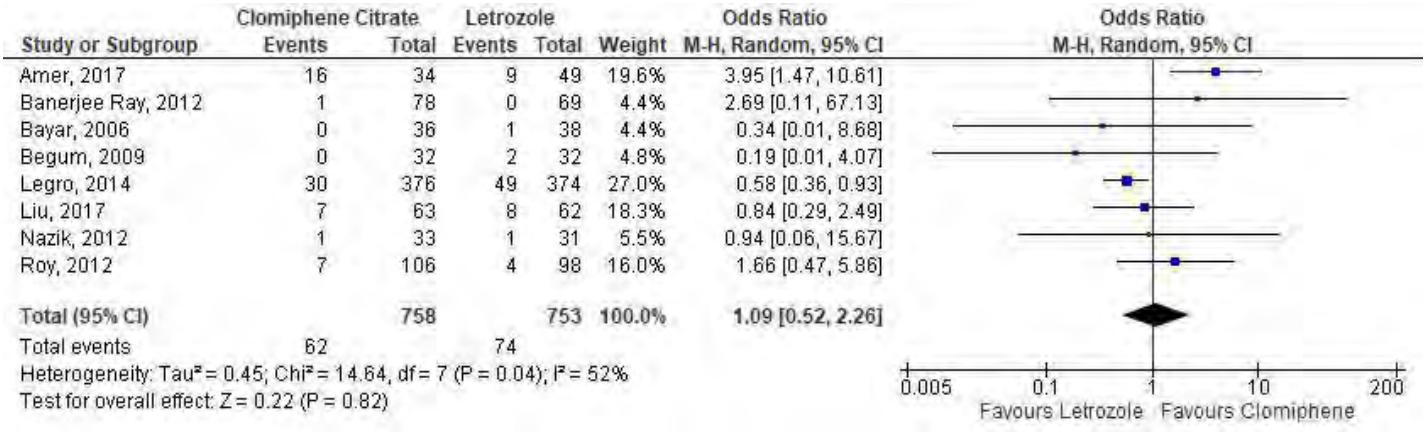
OUTCOME 9.9. Miscarriage rate – per patient

9.9.1. Individual Study Data Table

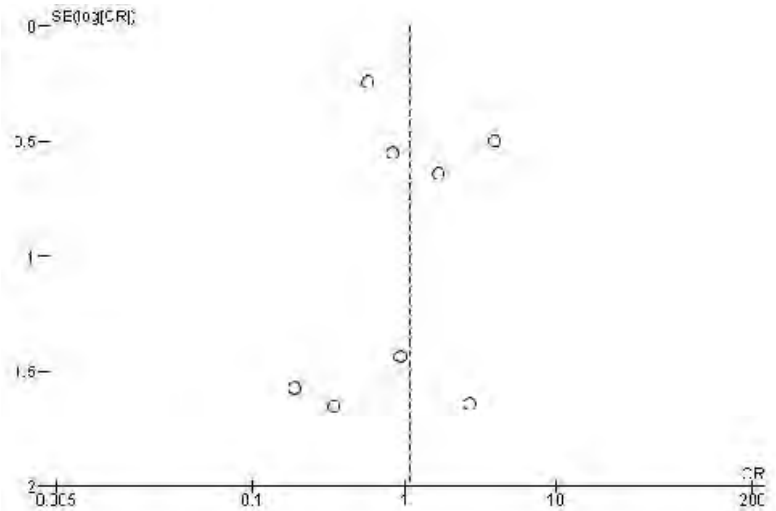
OUTCOME: Miscarriage rate per patient					**OUTCOME TYPE:** Dichotomous				
COMPARISON: Clomiphene Citrate vs Letrozole									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (CC)**	**N total in intervention/ exposure group (CC)**	**N events in control / comparison group (LET)**	**N total in control/ comparison group (LET)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Amer 2017 (LRB)	NR	Count	Investigator	16	34	9	49	Crude	NA
Banerjee Ray 2012 (HRB)	NR	Count	Investigator	1	78	0	69	Crude	NA
Bayar 2006 (LRB)	TN	Count	Investigator	0	36	1	38	Crude	NA
Begum 2009 (MRB)	CCR	Count	Investigator	0	32	2	32	Crude	NA
Legro 2014 (LRB)	NR	Count	Investigator	30	376	49	374	Crude	NA
Liu 2017 (HRB)	Mixed	Count	Investigator	7	63	8	62	Crude	NA
Nazik 2012 (HRB)	Mixed	Count	Investigator	1	33	1	31	Crude	NA
Roy 2012 (LRB)	NR	Count	Investigator	7	106	4	98	Crude	NA

CCR, Clomiphene citrate resistant; **TN**, therapy naïve; **NR**, not reported; **Mixed**, includes some clomiphene citrate resistant/failure and/or therapy naïve and/or not reported.

9.9.2. Forest Plot of all included RCTs comparing Clomiphene Citrate versus Letrozole for miscarriage rate – per patient



9.9.3. Funnel plot for assessment of publication bias



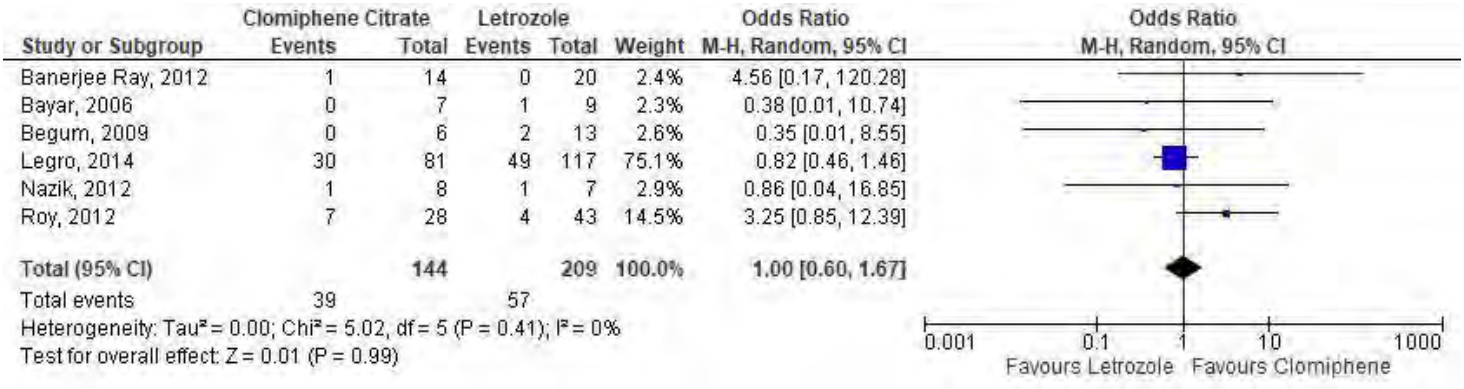
OUTCOME 9.10. Miscarriage rate – per pregnancy

9.10.1. Individual Study Data Table

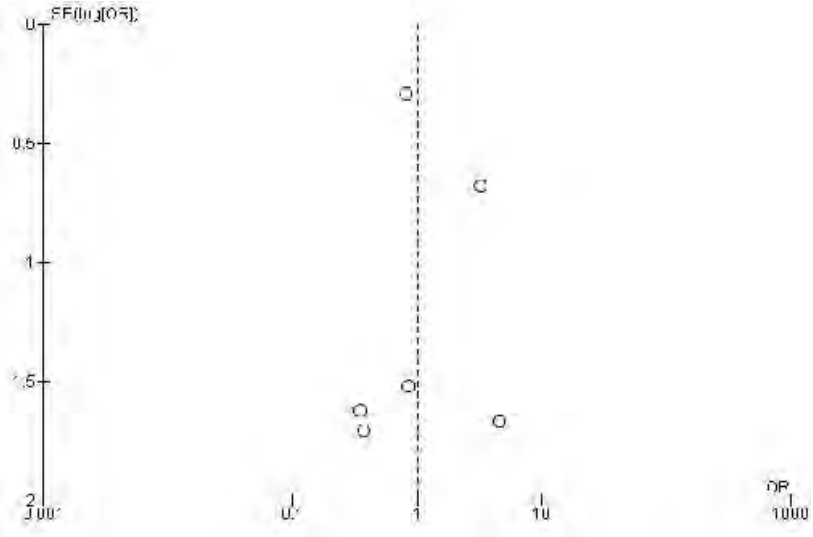
OUTCOME: Miscarriage rate - per pregnancy						**OUTCOME TYPE:** Dichotomous			
COMPARISON: Clomiphene Citrate vs Letrozole									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (CC)**	**N total in intervention/ exposure group (CC)**	**N events in control / comparison group (LET)**	**N total in control/ comparison group (LET)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Banerjee Ray 2012 (HRB)	NR	count	Investigator	1	14	0	20	Crude	NA
Bayar 2006 (LRB)	TN	Count	Investigator	0	7	1	9	Crude	NA
Begum 2009 (MRB)	CCR	Count	Investigator	0	6	2	13	Crude	NA
Legro 2014 (LRB)	NR	Count	Investigator	30	81	49	117	Crude	NA
Nazik 2012 (HRB)	Mixed	count	Investigator	1	8	1	7	Crude	NA
Roy 2012 (LRB)	NR	Count	Investigator	7	28	4	43	Crude	NA

CCR, Clomiphene citrate resistant; **TN**, therapy naïve; **NR**, not reported; **Mixed**, includes some clomiphene citrate resistant/failure and/or therapy naïve and/or not reported.

9.10.2. Forest Plot of all included RCTs comparing Clomiphene Citrate versus Letrozole for miscarriage rate – per pregnancy



9.10.3. Funnel plot for assessment of publication bias



COMPARISON 10: Clomiphene Citrate versus Metformin + Letrozole

▪ EVIDENCE SUMMARY:

One study compared clomiphene citrate with metformin + letrozole (Liu, et al. 2017), with relevant outcomes including live birth, clinical pregnancy and miscarriage rate per patient, and ovulation rate per cycle. This study, by Liu et al. (2017) was conducted in China with 120 participants and had a high risk of bias due to lack of blinding of participants and insufficient information around allocation concealment.

▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

Clomiphene citrate alone was less effective than metformin + letrozole for clinical pregnancy rate and ovulation rate per cycle. There were no differences between clomiphene citrate and combine metformin + letrozole for the outcomes of live birth or miscarriage rate per patient. Given that these results are from a single, relatively small, high-risk of bias study, certainty in the evidence is very low for all outcomes.

Outcome or Subgroup	Studies	n	Effect Estimate; OR [95% CI], M-H, random	P	Favours	Certainty
Live birth rate- per patient	1	120	0.49 [0.22, 1.09]	0.08	None	⊕◯◯◯ Very low
Clinical pregnancy rate- per patient†	1	120	0.39 [0.19, 0.82]	0.01	**MET + LET** (clinical pregnancy is lower with CC)	⊕◯◯◯ Very low
Ovulation rate - per cycle	1	268	0.35 [0.21, 0.60]	0.0001	**MET + LET** (ovulation per cycle is lower with CC)	⊕◯◯◯ Very low
Miscarriage rate- per patient	1	120	0.47 [0.17, 1.29]	0.1	None	⊕◯◯◯ Very low

OUTCOME 10.1 – 10.4: Live birth rate- per patient, clinical pregnancy rate-per patient; ovulation rate- per cycle, miscarriage rate-per patient

10.1.1 - 10.4.1. Individual Study Data Tables

OUTCOME: LISTED BELOW						**OUTCOME TYPE: Dichotomous**			
COMPARISON: Clomiphene Citrate versus Metformin + Letrozole									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in intervention / exposure group (CC)**	**N total in intervention / exposure group (CC)**	**N events in control / comparison group (MET+ LET)**	**N total in control/ comparison group (MET + LET)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
OUTCOME: Live birth rate – per patient									
Liu 2017 (HRB)	**Mixed**	**Count**	Investigator	14	63	21	57	Crude	NA
OUTCOME: Clinical pregnancy rate – per patient						OUTCOME TYPE: Dichotomous			
Liu 2017 (HRB)	Mixed	Count	Investigator	22	63	33	57	Crude	NA
OUTCOME: Ovulation rate – per cycle						OUTCOME TYPE: Dichotomous			
Liu 2017 (HRB)	Mixed	Count	Investigator	78	150	89	118	Crude	NA
OUTCOME: Miscarriage rate – per patient						OUTCOME TYPE: Dichotomous			
Liu 2017 (HRB)	Mixed	Count	Investigator	7	63	12	57	Crude	NA

COMPARISON 11: Clomiphene Citrate + Metformin versus Letrozole

▪ EVIDENCE SUMMARY:

One study compared clomiphene citrate combined with metformin versus letrozole (Liu, et al. 2017), with relevant outcomes including live birth, clinical pregnancy and miscarriage rate per patient, and ovulation rate per cycle. This study, by Liu et al. (2017) was conducted in China with 120 participants and had a high risk of bias due to lack of blinding of participants and insufficient information around allocation concealment.

▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

There were no differences between clomiphene citrate + metformin compared with letrozole for any of the outcomes. Certainty in these results is very low due to being derived from a single, relatively small, high-risk of bias study.

Outcome or Subgroup	Studies	n	Effect Estimate; OR [95% CI], M-H, random	P	Favours	Certainty
Live birth rate- per patient	1	120	0.88 [0.41, 1.89]	0.7	None	⊕◯◯◯ Very low
Clinical pregnancy rate- per patient†	1	120	0.92 [0.45, 1.90]	0.8	None	⊕◯◯◯ Very low
Ovulation rate - per cycle	1	261	0.62 [0.37, 1.05]	0.07	None	⊕◯◯◯ Very low
Miscarriage rate- per patient	1	120	0.93 [0.31, 2.74]	0.9	None	⊕◯◯◯ Very low

†clinical pregnancy rate is confirmed by ultrasound detection of gestational sac/ fetal heart activity

OUTCOME 11.1 – 11.4: Live birth rate- per patient, clinical pregnancy rate-per patient; ovulation rate- per cycle, miscarriage rate-per patient

11.1.1 - 11.4.1. Individual Study Data Tables

OUTCOME: LISTED BELOW						**OUTCOME TYPE:** Dichotomous			
COMPARISON: Clomiphene Citrate + Metformin versus Letrozole									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in intervention / exposure group (CC +MET)**	**N total in intervention / exposure group (CC +MET)**	**N events in control / comparison group (LET)**	**N total in control/ comparison group (LET)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
OUTCOME: Live birth rate – per patient									
Liu 2017 (HRB)	Mixed	Count	Investigator	18	58	21	62	Crude	NA
OUTCOME: Clinical pregnancy rate – per patient					**OUTCOME TYPE:** Dichotomous				
Liu 2017 (HRB)	Mixed	Count	Investigator	26	58	29	62	Crude	NA
OUTCOME: Ovulation rate – per cycle					**OUTCOME TYPE:** Dichotomous				
Liu 2017 (HRB)	Mixed	Count	Investigator	80	131	93	130	Crude	NA
OUTCOME: Miscarriage rate – per patient					**OUTCOME TYPE:** Dichotomous				
Liu 2017 (HRB)	Mixed	Count	Investigator	7	58	8	62	Crude	NA

COMPARISON 12: Clomiphene Citrate versus gonadotropins (FSH)

▪ EVIDENCE SUMMARY:

Two studies compared clomiphene citrate versus gonadotropins (FSH) (Homburg et al. 2012 and Lopez et al. 2004), both in therapy naïve women with PCOS. Relevant outcomes included live birth rate, clinical pregnancy rate, ovulation rate, multiple pregnancy rate and miscarriage rate per patient, as well as ovulation rate per cycle. The studies were judged as moderate (Homburg et al. 2014) or high (Lopez et al. 2004) risk of bias.

▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

There were no differences in ovulation rate, multiple pregnancy rate or miscarriage rate per patient; however, FSH was superior to clomiphene citrate for live birth rate and clinical pregnancy rate per patient, as well as ovulation rate per cycle. Evidence for these outcomes was moderate, with the exception of ovulation rate per cycle which was of very low quality due to being derived from a single small study with a high risk of bias.

Outcome or Subgroup	Studies	n	Effect Estimate; OR [95% CI], M-H, random	P	Favours	Certainty
Live birth rate – per patient	2	331	0.58 [0.37, 0.91]	0.02	FSH (live birth rate is lower with CC)	⊕⊕⊕◯ MODERATE
Clinical pregnancy rate – per patient	2	331	0.54 [0.35, 0.85]	0.007	FSH (clinical pregnancy is lower with CC)	⊕⊕⊕◯ MODERATE
Ovulation rate – per patient	1	76	0.32 [0.08, 1.32]	0.1	None	⊕◯◯◯ VERY LOW
Ovulation rate – per cycle	1	195	0.40 [0.22, 0.74]	0.003	FSH (ovulation per cycle is lower with CC)	⊕◯◯◯ VERY LOW
Multiple pregnancy rate – per pregnancy	2	155	0.42 [0.06, 2.78]	0.4	None	⊕⊕◯◯ LOW
Miscarriage rate- per pregnancy	2	155	1.04 [0.38, 2.79]	0.9	None	⊕⊕⊕◯ MODERATE

†clinical pregnancy rate is confirmed by ultrasound detection of gestational sac/ fetal heart activity

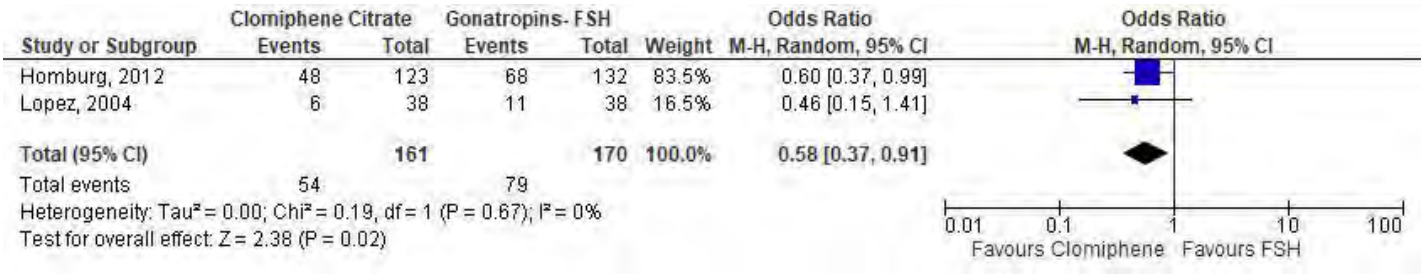
OUTCOME 12.1. Live birth rate– per patient

12.1.1. Individual Study Data Tables

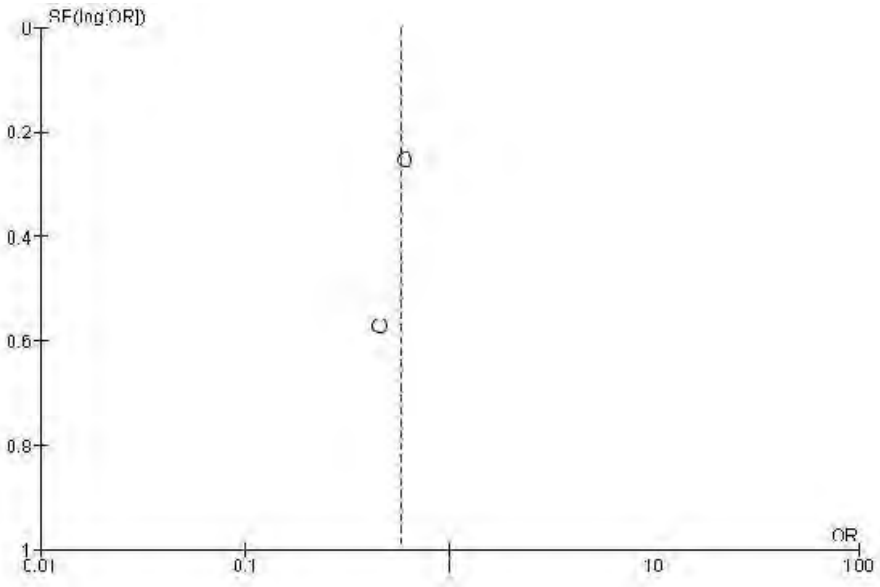
OUTCOME: Live birth rate per patient						**OUTCOME TYPE:** Dichotomous			
COMPARISON: Clomiphene Citrate vs FSH									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (CC)**	**N total in intervention/ exposure group (CC)**	**N events in control / comparison group (FSH)**	**N total in control/ comparison group (FSH)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Homburg 2012 (MRB)	TN	Count	Investigator	48	123	68	132	Crude	NA
Lopez 2004 (HRB)	TN	Count	Investigator	6	38	11	38	Crude	NA

TN, therapy naïve; **OI**, ovulation induction

12.1.2. Forest Plot of all included RCTs comparing Clomiphene Citrate versus FSH for live birth rate – per patient



12.1.3. Funnel plot for assessment of publication bias



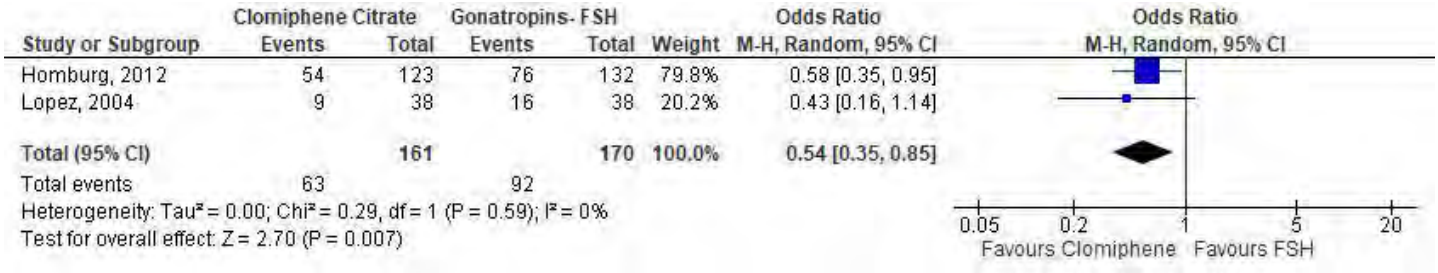
OUTCOME 12.2. Clinical pregnancy rate– per patient

12.2.1. Individual Study Data Tables

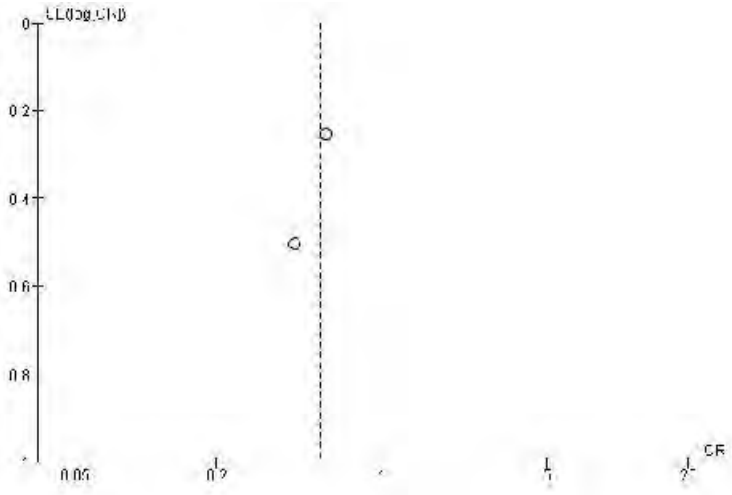
OUTCOME: Clinical pregnancy rate per patient						**OUTCOME TYPE:** Dichotomous			
COMPARISON: Clomiphene Citrate vs FSH									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (CC)**	**N total in intervention/ exposure group (CC)**	**N events in control / comparison group (FSH)**	**N total in control/ comparison group (FSH)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Homburg 2012 (MRB)	TN	Count	Investigator	54	123	76	132	Crude	NA
Lopez 2004 (HRB)	TN	Count	Investigator	9	38	16	38	Crude	NA

TN, therapy naïve; **OI**, ovulation induction

12.2.2. Forest Plot of all included RCTs comparing Clomiphene Citrate versus FSH for clinical pregnancy rate – per patient



12.2.3. Funnel plot for assessment of publication bias



OUTCOME 12.3. Ovulation rate– per patient

12.5.1. Individual Study Data Tables

OUTCOME: Ovulation rate per patient						OUTCOME TYPE: Dichotomous			
COMPARISON: Clomiphene Citrate vs FSH									
Author, year	Past OI Med Use	Unit of outcome (e.g. g, mg)	Method of measurement	N events in intervention/ exposure group (CC)	N total in intervention/ exposure group (CC)	N events in control / comparison group (FSH)	N total in control/ comparison group (FSH)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Lopez 2004 (HRB)	TN	Count	Investigator	30	38	35	38	Crude	NA

TN, therapy naïve; **OI**, ovulation induction

OUTCOME 12.4. Ovulation rate– per cycle

12.5.1. Individual Study Data Tables

OUTCOME: Ovulation rate per cycle						OUTCOME TYPE: Dichotomous			
COMPARISON: Clomiphene Citrate vs FSH									
Author, year	Past OI Med Use	Unit of outcome (e.g. g, mg)	Method of measurement	N events in intervention/ exposure group (CC)	N total in intervention/ exposure group (CC)	N events in control / comparison group (FSH)	N total in control/ comparison group (FSH)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Lopez 2004 (HRB)	TN	Count	Investigator	55	104	67	91	Crude	NA

TN, therapy naïve; **OI**, ovulation induction

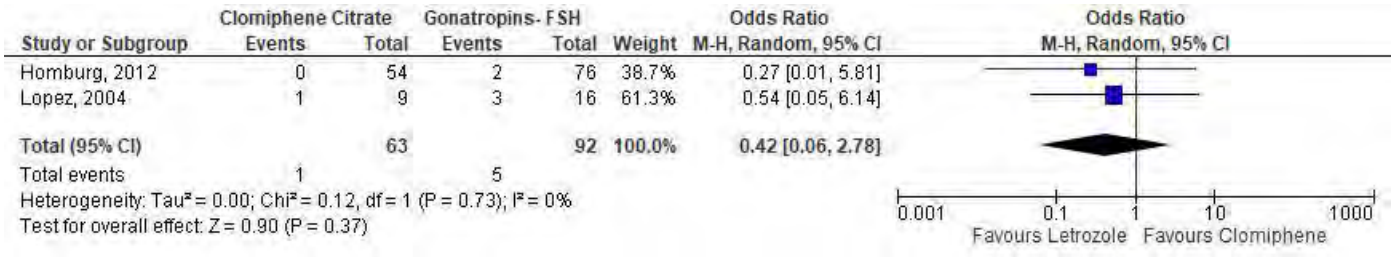
OUTCOME 12.5. Multiple pregnancy rate – per pregnancy

12.5.1. Individual Study Data Tables

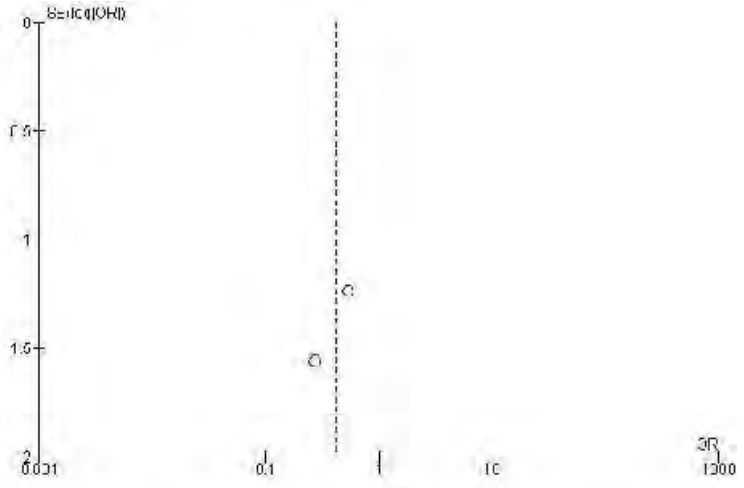
OUTCOME: Multiple pregnancy rate- per pregnancy						OUTCOME TYPE: Dichotomous			
COMPARISON: Clomiphene Citrate vs FSH									
Author, year	Past OI Med Use	Unit of outcome (e.g. g, mg)	Method of measurement	N events in intervention/ exposure group (CC)	N total in intervention/ exposure group (CC)	N events in control / comparison group (FSH)	N total in control/ comparison group (FSH)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Homburg 2012 (MRB)	TN	Count	Investigator	0	54	2	76	Crude	NA
Lopez 2004 (HRB)	TN	Count	Investigator	1	9	3	16	Crude	NA

TN, therapy naïve; **OI**, ovulation induction

12.5.2. Forest Plot of all included RCTs comparing Clomiphene Citrate versus FSH for multiple pregnancy rate – per pregnancy



12.5.3. Funnel plot for assessment of publication bias



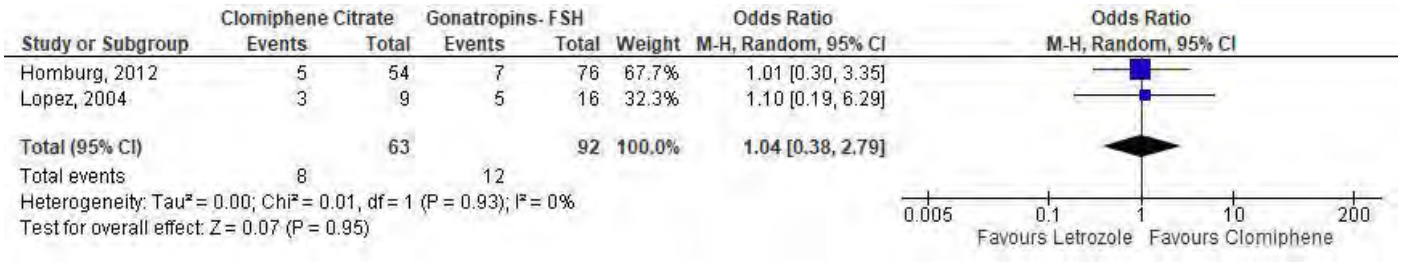
OUTCOME 12.6. Miscarriage rate – per pregnancy

12.6.1. Individual Study Data Tables

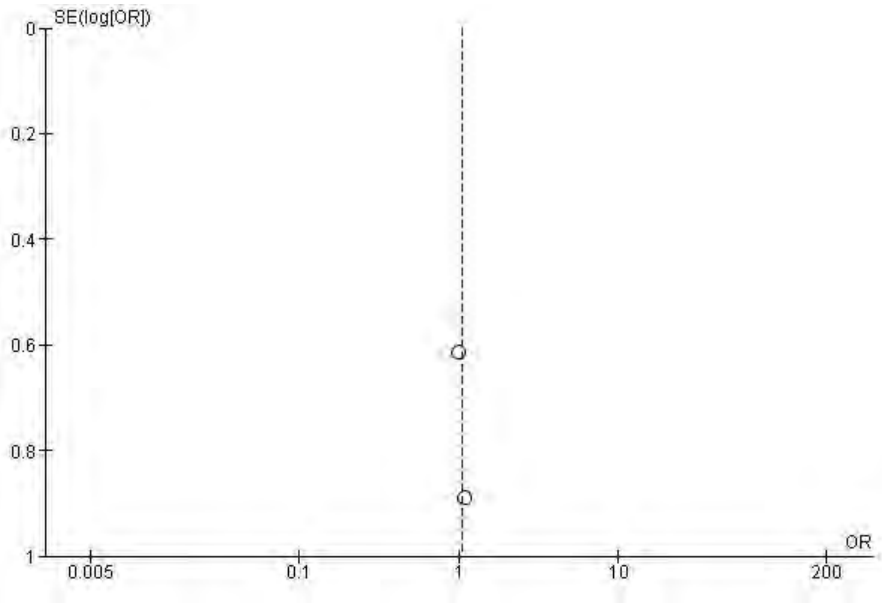
OUTCOME: Miscarriage rate- per pregnancy									**OUTCOME TYPE:** Dichotomous
COMPARISON: Clomiphene Citrate vs FSH									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (CC)**	**N total in intervention/ exposure group (CC)**	**N events in control / comparison group (FSH)**	**N total in control/ comparison group (FSH)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Homburg 2012 (MRB)	TN	Count	Investigator	5	54	7	76	Crude	NA
Lopez 2004 (HRB)	TN	Count	Investigator	3	9	5	16	Crude	NA

TN, therapy naïve; **OI**, ovulation induction

12.6.2. Forest Plot of all included RCTs comparing Clomiphene Citrate versus FSH for miscarriage rate – per pregnancy



12.6.3. Funnel plot for assessment of publication bias



COMPARISON 13: Clomiphene Citrate + gonadotropins (FSH) versus gonadotropins (FSH)

▪ EVIDENCE SUMMARY:

Two studies compared clomiphene citrate + rFSH versus rFSH alone, one in India (Ganesh et al. 2009) and one in Egypt (Ghanem et al. 2012), with outcomes assessed including live birth rate, clinical pregnancy rate and ovulation rate per patient, and miscarriage rate per pregnancy. The study in India involved 1387 women with PCOS who had previously failed to conceive or ovulate with CC and were undergoing IUI. Three groups were included: Group A received letrozole, Group B received clomiphene citrate with two doses rFSH from cycle days 3-8 and Group C received continuous rFSH from day 2 onwards until hCG injection. The second study by Ghanem et al. (2012) included 174 women with clomiphene-citrate resistant PCOS, who received highly purified urinary FSH from days 3 to 13, with or without 100 mg of clomiphene citrate. Both studies were judged as having a moderate risk of bias due to their single-blind design.

▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

There were no differences in any outcomes between clomiphene citrate + FSH versus urinary or recombinant FSH alone. Certainty in the evidence for these comparisons ranges from very low to moderate as shown below; downgraded for risk of bias (both studies moderate risk), as well as varied effect estimates (including differing directions of effect), and high statistical heterogeneity.

Outcome or Subgroup	Studies	n	Effect Estimate; OR [95% CI], M-H, random	P	Favours	Certainty
Live birth rate -per patient	1	174	1.21 [0.60, 2.44]	0.6	None	⊕⊕◯◯ LOW
Clinical pregnancy rate- per patient†	2	1189	0.83 [0.61, 1.14]	0.3	None	⊕⊕◯◯ LOW
Ovulation rate - per patient	2	1189	0.79 [0.03, 21.36]	0.9	None	⊕◯◯◯ VERY LOW
Miscarriage rate- per pregnancy	1	158	1.18 [0.48, 2.86]	0.7	None	⊕⊕⊕◯ MODERATE

†clinical pregnancy rate is confirmed by ultrasound detection of gestational sac/ fetal heart activity

OUTCOME 13.1. Live birth rate- per patient

13.1.1. Individual Study Data Tables

OUTCOME: Live birth rate- per patient						OUTCOME TYPE: Dichotomous			
COMPARISON: Clomiphene Citrate + FSH versus FSH									
Author, year	Past OI Med Use	Unit of outcome (e.g. g, mg, µg)	Method of measurement	N events in intervention / exposure group (CC +FSH)	N total in intervention / exposure group (CC +FSH)	N events in control / comparison group (FSH)	N total in control/ comparison group (FSH)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
OUTCOME: Live birth rate – per patient					OUTCOME TYPE: Dichotomous				
Ghanem 2013 (MRB)	CCR	Count	Investigator	22	87	19	87	Crude	NA

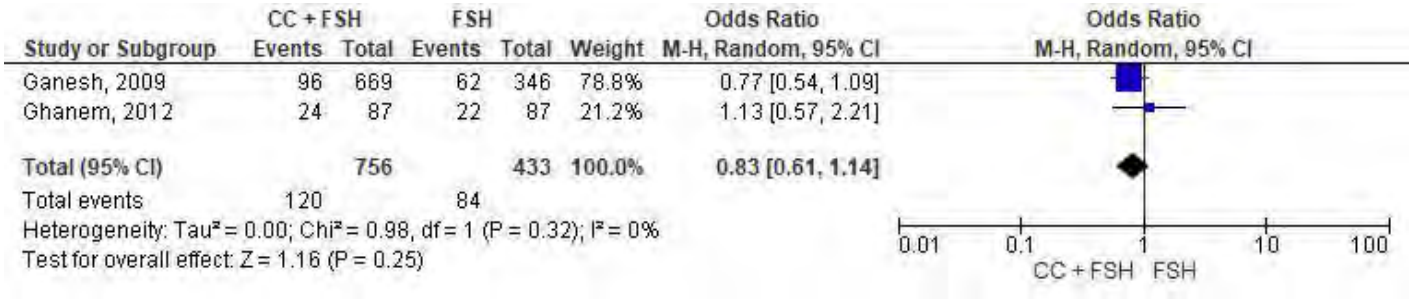
CCR/CCF, clomiphene citrate-resistant or failure

OUTCOME 13.2. Clinical pregnancy rate – per patient

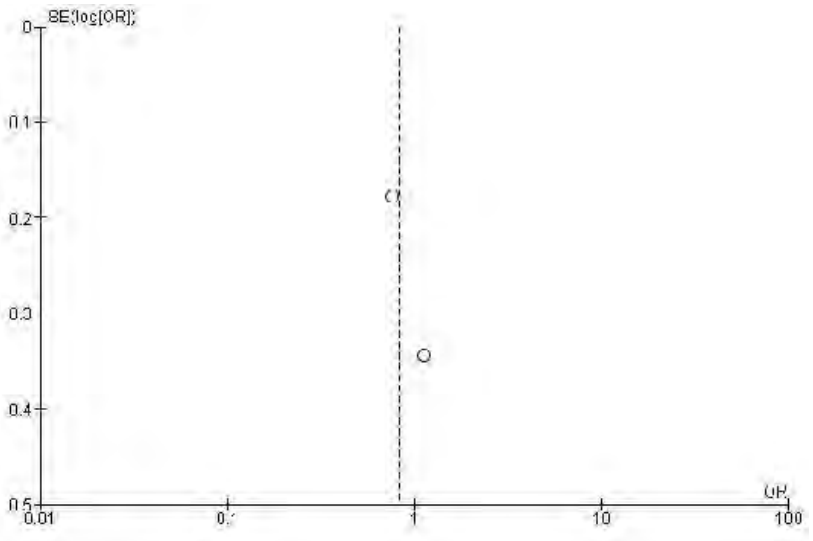
13.2.1. Individual Study Data Tables

OUTCOME: Clinical pregnancy rate per patient						OUTCOME TYPE: Dichotomous			
COMPARISON: FSH + Clomiphene Citrate vs FSH									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (FSH + CC)**	**N total in intervention/ exposure group (FSH + CC)**	**N events in control / comparison group (FSH)**	**N total in control/ comparison group (FSH)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Ganesh 2009 (MRB)	CCR/ CCF	Count	Investigator	96	669	62	346	Crude	NA
Ghanem 2013 (MRB)	CCR	Count	Investigator	24	87	22	87	Crude	NA

13.2.2. Forest Plot of all included RCTs comparing Clomiphene Citrate + FSH versus FSH for clinical pregnancy rate – per patient



13.2.3. Funnel plot for assessment of publication bias



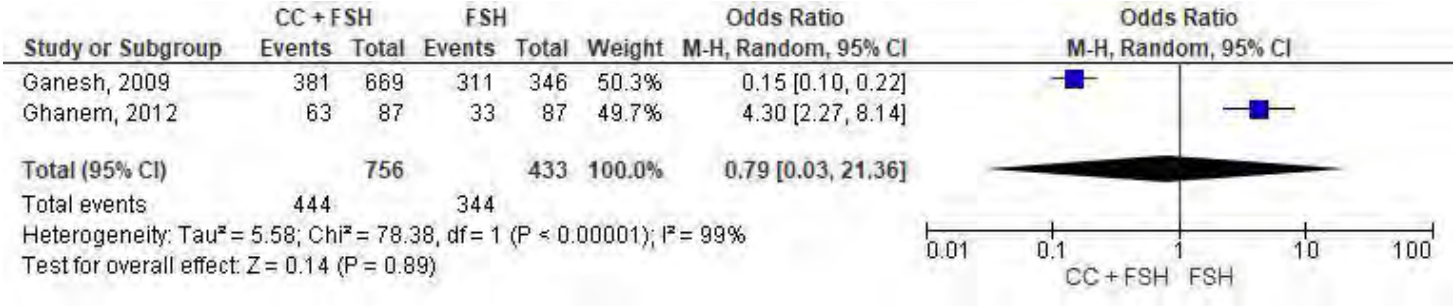
OUTCOME 13.3. Ovulation rate – per patient

13.3.1. Individual Study Data Tables

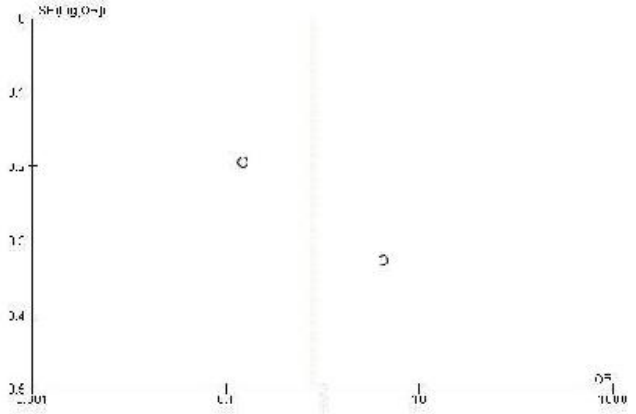
OUTCOME: Ovulation rate per patient						OUTCOME TYPE: Dichotomous			
COMPARISON: FSH + Clomiphene Citrate vs FSH									
Author, year	Past OI Med Use	Unit of outcome (e.g. g, mg)	Method of measurement	N events in intervention/ exposure group (FSH+ CC)	N total in intervention/ exposure group (FSH + CC)	N events in control / comparison group (FSH)	N total in control/ comparison group (FSH)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Ganesh 2009 (MRB)	CCR/ CCF	Count	Investigator	381	669	311	346	Crude	NA
Ghanem 2013 (MRB)	CCR	Count	Investigator	63	87	33	87	Crude	NA

CCR/CCF, clomiphene citrate-resistant or failure

13.3.2. Forest Plot of all included RCTs comparing Clomiphene Citrate + FSH versus FSH for ovulation rate – per patient



13.3.3. Funnel plot for assessment of publication bias



OUTCOME 13.4. Miscarriage rate – per pregnancy

13.4.1. Individual Study Data Tables

OUTCOME: Miscarriage rate- per pregnancy						OUTCOME TYPE: Dichotomous			
COMPARISON: Clomiphene Citrate + FSH versus FSH									
Author, year	Past OI Med Use	Unit of outcome (e.g. g, mg, µg)	Method of measurement	N events in intervention / exposure group (FSH + CC)	N total in intervention / exposure group (FSH + CC)	N events in control / comparison group (FSH)	N total in control/ comparison group (FSH)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Ganesh 2009 (MRB)	CCR/ CCF	Count	Investigator	16	96	9	62	Crude	NA

CCR/CCF, clomiphene citrate-resistant or failure

COMPARISON 14: Clomiphene Citrate + gonadotropins (FSH) versus letrozole

▪ EVIDENCE SUMMARY:

The same study in India compared clomiphene citrate + gonadotropins (rFSH) versus letrozole (Ganesh et al. 2009). Outcomes assessed included clinical pregnancy, ovulation rate, and miscarriage rate per patient. The study was judged as having a moderate risk of bias due to the single-blind design.

▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

Combined clomiphene citrate and FSH was less effective than letrozole in achieving clinical pregnancy or ovulation per patient in this study, with odds ratios of 0.55 and 0.35, respectively. There were no differences between clomiphene citrate + FSH compared with letrozole for miscarriage rates per patient. Certainty in these results is moderate given the narrow confidence intervals and large sample size, downgraded once due to risk of bias given its single-blind design.

OUTCOME 14.1 – 14.3: Clinical pregnancy rate-per patient; ovulation rate- per patient, miscarriage rate-per pregnancy

Outcome or Subgroup	Studies	n	Effect Estimate; OR [95% CI], M-H, random	P	Favours	Certainty
Clinical pregnancy rate- per patient†	1	1041	0.55 [0.40, 0.76]	0.0003	LET (clinical pregnancy is lower with CC+ FSH)	⊕⊕⊕◯ Moderate
Ovulation rate - per patient	1	1041	0.35 [0.26, 0.46]	<0.00001	LET (ovulation rate is lower with CC + FSH)	⊕⊕⊕◯ Moderate
Miscarriage rate- per pregnancy	1	183	1.25 [0.55, 2.82]	0.6	None	⊕⊕⊕◯ Moderate

†clinical pregnancy rate is confirmed by ultrasound detection of gestational sac/ fetal heart activity

14.1.1 - 14.4.3. Individual Study Data Tables

OUTCOME: LISTED BELOW						OUTCOME TYPE: Dichotomous			
COMPARISON: Clomiphene Citrate + FSH versus Letrozole									
Author, year	Past OI Med Use	Unit of outcome (e.g. g, mg, µg)	Method of measurement	N events in intervention / exposure group (CC +FSH)	N total in intervention / exposure group (CC +FSH)	N events in control / comparison group (LET)	N total in control/ comparison group (LET)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
OUTCOME: Clinical pregnancy rate – per patient						OUTCOME TYPE: Dichotomous			
Ganesh 2009 (MRB)	CCR/ CCF	Count	Investigator	96	669	87	372	Crude	NA
OUTCOME: Ovulation rate – per patient						OUTCOME TYPE: Dichotomous			
Ganesh 2009 (MRB)	CCR/ CCF	Count	Investigator	381	669	295	372	Crude	NA
OUTCOME: Miscarriage rate – per pregnancy						OUTCOME TYPE: Dichotomous			
Ganesh 2009 (MRB)	CCR/ CCF	Count	Investigator	16	96	12	87	Crude	NA

CCR/CCF, clomiphene citrate-resistant or failure

COMPARISON 15: Clomiphene Citrate + Metformin vs Gonadotropins (rFSH)

▪ EVIDENCE SUMMARY:

A single study in Bangladesh compared clomiphene citrate + metformin versus gonadotropins (rFSH) in clomiphene citrate-resistant women with PCOS (Begum et al. 2013). Outcomes assessed included clinical pregnancy and miscarriage rate per patient. The study was judged as having a high risk of bias due to being unblinded (presumably, as this was not described), and lack of information regarding randomisation and attrition.

▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

Meta-analysis was not possible due to having a single eligible study with this comparison. Using this study alone, however, clinical pregnancy rate was higher with FSH compared to clomiphene citrate + Metformin, with an OR of 2.81 favouring FSH. Certainty in these results is very low given the reliance on a single study, with a high risk of bias and relatively small sample size.

Outcome or Subgroup	Studies	n	Effect Estimate; OR [95% CI], M-H, random	P	Favours	Certainty
Clinical pregnancy rate- per patient†	1	110	2.81 [1.05, 7.52]	0.04	FSH (clinical pregnancy is higher with FSH)	⨁◯◯◯ VERY LOW
Miscarriage rate- per pregnancy	1	23	1.38 [0.12, 16.23]	0.8	None	⨁◯◯◯ VERY LOW

†clinical pregnancy rate is confirmed by ultrasound detection of gestational sac/ fetal heart activity

OUTCOME 15.1 – 15.2: Clinical pregnancy rate-per patient and miscarriage rate-per pregnancy

15.1.1 - 15.1.2. Individual Study Data Tables

OUTCOME: LISTED BELOW						OUTCOME TYPE: Dichotomous			
COMPARISON: Clomiphene Citrate + Metformin versus rFSH									
Author, year	Past OI Med Use	Unit of outcome (e.g. g, mg, µg)	Method of measurement	N events in intervention / exposure group (CC +MET)	N total in intervention / exposure group (CC +MET)	N events in control / comparison group (FSH)	N total in control/ comparison group (FSH)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
OUTCOME: Clinical pregnancy rate – per patient					OUTCOME TYPE: Dichotomous				
Begum 2013 (HRB)	CCR	Count	Investigator	7	55	16	55	Crude	NA
OUTCOME: Miscarriage rate – per pregnancy					OUTCOME TYPE: Dichotomous				
Begum 2013 (HRB)	CCR	Count	Investigator	1	7	3	16	Crude	NA

CCR, clomiphene citrate-resistant

COMPARISON 16: Clomiphene Citrate versus LOD

▪ EVIDENCE SUMMARY:

A single UK-based study by Amer et al. (2009) examined the efficacy of clomiphene citrate versus LOD in 76 women with anovulatory PCOS and clomiphene citrate resistance. Women treated with clomiphene citrate unsuccessfully for 6 cycles were then also offered LOD. There was no blinding in this study; once randomised, the allocation was revealed to the investigators and patients. Hence, the study was judged as moderate risk of bias.

▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

There were no differences between CC versus LOD in live birth rate or clinical pregnancy rate per patient or miscarriage rate per pregnancy. There was low certainty for all outcomes due to the evidence being derived from a single, small study (downgraded once for imprecision) with a moderate risk of bias (downgraded once for risk of bias).

Outcome or Subgroup	Studies	n	Effect Estimate; OR [95% CI], M-H, random	P	Favours	Certainty
Live birth rate- per patient	1	65	1.54 [0.58, 4.10]	0.4	None	⊕⊕◯◯ LOW
Clinical pregnancy rate- per patient†	1	65	1.66 [0.59, 4.70]	0.3	None	⊕⊕◯◯ LOW
Miscarriage rate- per pregnancy	1	43	0.86 [0.11, 6.72]	0.9	None	⊕⊕◯◯ LOW

† clinical pregnancy rate is confirmed by ultrasound detection of gestational sac/ fetal heart activity

OUTCOME 2.1. Live birth rate – per patient

2.1.1. Individual Study Data Table

OUTCOME: Live birth rate – per patient						**OUTCOME TYPE:** Dichotomous			
COMPARISON: LOD vs CC									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in intervention group (CC)**	**N total in intervention group (CC)**	**N events in control / comparison group (LOD)**	**N total in control/ comparison group (LOD)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Amer 2009 (MRB)	CCR	Count	Investigator	18	32	15	33	Crude	NA

CCR, Clomiphene citrate-resistant

OUTCOME 2.2. Clinical pregnancy rate – per patient

2.2.1. Individual Study Data Table

OUTCOME: Clinical pregnancy rate – per patient						OUTCOME TYPE: Dichotomous			
COMPARISON: LOD vs CC									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in intervention group (CC)**	**N total in intervention group (CC)**	**N events in control / comparison group (LOD)**	**N total in control/ comparison group (LOD)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Amer 2009 (MRB)	CCR	Count	Investigator	23	32	20	33	Crude	NA

CCR, Clomiphene citrate-resistant.

OUTCOME 2.3. Miscarriage rate – per pregnancy

2.3.1. Individual Study Data Table

OUTCOME: Miscarriage rate – per pregnancy						OUTCOME TYPE: Dichotomous			
COMPARISON: LOD vs CC									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in intervention group (CC)**	**N total in intervention group (CC)**	**N events in control / comparison group (LOD)**	**N total in control/ comparison group (LOD)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Amer 2009 (MRB)	CCR	Count	Investigator	2	23	2	20	Crude	NA

CCR, Clomiphene citrate-resistant.

5. GRADE ASSESSMENTS AND EVIDENCE PROFILE

COMPARISON 1: Metformin versus Placebo												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	MET	Placebo	Effect, random [95% CI]	Favours	Certainty	Importance
Outcome: Live birth rate- per patient												
4	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	109/ 275 (39.6%)	74/ 277 (26.7%)	1.84 [1.27, 2.66]	MET (live birth rate is higher with metformin)	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Clinical pregnancy rate- per patient												
5	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	66/ 219 (30.1%)	43/ 224 (19.2%)	1.93 [1.19, 3.10]	MET (clinical pregnancy is higher with metformin)	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Multiple pregnancy rate- per patient												
1	RCT	serious[1]	not applicable	not applicable	serious[2]	none	4/34 (11.8%)	9/ 32 (28.1%)	0.34 [0.09, 1.25]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Pregnancy rate- per patient												
7	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	149/ 402 (37.1%)	100/ 403 (24.8%)	1.89 [1.37, 2.61]	MET (pregnancy rate is higher with metformin)	⊕⊕⊕◯ MODERATE	IMPORTANT
Outcome: Ovulation rate- per patient												
2	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	41/ 55 (74.6%)	33/ 57 (57.8%)	2.34 [0.99, 5.53]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Multiple pregnancy rate per pregnancy												
3	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	4/62 (6.5%)	4/50 (8.0%)	0.61 [0.13, 2.91]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Miscarriage rate per pregnancy												
5	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	14/142 (9.9%)	16/108 (14.8%)	0.48 [0.14, 1.62]	No difference	⊕⊕◯◯ LOW	IMPORTANT

[1] Downgraded once as the majority of evidence (half or more) is at moderate or high risk of bias
[2] Downgraded once due to small sample size and/or wide CIs

COMPARISON 2: Metformin versus Clomiphene Citrate												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	MET	CC	Effect, random [95% CI]	Favours	Certainty	Importance
Outcome: Live birth rate- per patient												
3	RCT	no serious risk of bias	very serious[2]	no serious indirectness	no serious imprecision	none	34/ 267 (12.7%)	69/ 277 (24.9%)	0.61 [0.21, 1.73]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Clinical pregnancy rate- per patient												
3	RCT	no serious risk of bias	very serious[2]	no serious indirectness	no serious imprecision	none	45/ 267 (16.9%)	74/ 277 (26.7%)	0.88 [0.24, 3.21]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Multiple pregnancy rate- per patient												
1	RCT	no serious risk of bias	not applicable	not applicable	serious[3]	none	1/35 (2.9%)	1/36 (2.8%)	1.03 [0.06, 17.13]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Ovulation rate- per patient												
1	RCT	serious[1]	not applicable	not applicable	serious[3]	none	15/ 24 (62.5%)	18/ 32 (56.3%)	1.30 [0.44, 3.82]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Ovulation rate- per cycle												
1	RCT	no serious risk of bias	not applicable	not applicable	serious[4]	none	296/ 1019 (29.1%)	462/ 942 (49.1%)	0.43 [0.35, 0.51]	CC (ovulation is lower with metformin)	⊕⊕⊕◯ MODERATE	IMPORTANT
Outcome: Miscarriage rate- per patient												
3	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	18/73 (24.7%)	17/108 (15.7%)	2.44 [1.03, 5.82]	CC (miscarriage is higher with metformin)	⊕⊕⊕◯ MODERATE	IMPORTANT

[1] Downgraded once as the majority of evidence (half or more) is at moderate or high risk of bias
[2] Downgraded twice due to high statistical heterogeneity ($p<0.05$ for I^2) and variations (including in the direction) of effect estimates
[3] Downgraded once for imprecision due to small sample size from single RCT
[4] Downgraded once as evidence was derived from a single study (despite its relatively large sample size, the result requires replication to increase certainty in the evidence)

COMPARISON 3: Metformin + Clomiphene Citrate versus Metformin												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	MET + CC	MET	Effect, random [95% CI]	Favours	Certainty	Importance
Outcome: Live birth rate- per patient												
3	RCT	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	81/ 268 (30.2%)	34/ 267 (12.7%)	2.44 [1.03, 5.76]	MET + CC (live birth rate is higher with MET + CC)	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Clinical pregnancy rate- per patient												
3	RCT	no serious risk of bias	serious[2]	serious[1]	no serious imprecision	none	96/ 268 (35.8%)	45/ 267 (16.9%	2.11 [0.75, 5.93]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Multiple pregnancy rate- per patient												
1	RCT	no serious risk of bias	not applicable	not applicable	serious[3]	none	1/ 35 (2.9%)	1/ 35 (2.9%)	1.00 [0.06, 16.65]	No difference	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Ovulation rate- per patient												
1	RCT	serious[1]	not applicable	not applicable	serious[3]	none	10/ 24 (41.7%)	9/ 24 (37.5%)	3.00 [0.77, 11.63]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Ovulation rate- per cycle												
1	RCT	no serious risk of bias	not applicable	not applicable	serious[4]	none	582/ 964 (60.4%)	296/ 1019 (29.1%)	3.72 [3.09, 4.49]	MET + CC (ovulation per cycle is higher with MET + CC)	⊕⊕⊕◯ MODERATE	IMPORTANT
Outcome: Miscarriage rate- per patient												
3	RCT	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	29/ 127 (22.8%)	18/ 73 (24.7%)	0.63 [0.30, 1.31]	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT

[1] Downgraded once due to indirectness resulting from diverse populations including treatment naïve patients and those with clomiphene-citrate resistance or failure.
[2] Downgraded once due to variations (including in the direction) of effect estimates
[3] Downgraded once for imprecision due to small sample size from single RCT
[4] Downgraded once as evidence was derived from a single study (despite its relatively large sample size, the result requires replication to increase certainty in the evidence)

COMPARISON 4: Metformin + Letrozole vs. Letrozole												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	MET + LET	LET	Effect, random OR, [95% CI]	Favours	Certainty	Importance
Outcome: Live birth rate - per patient												
1	RCT	very serious[1]	not applicable	not applicable	serious[3]	none	21/57 (33.9%)	21/62 (36.8%)	1.14 [0.54, 2.42]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Clinical Pregnancy rate - per patient												
2	RCT	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	52/107 (48.6%)	45/112 (40.2%)	1.44 [0.84, 2.49]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Ovulation rate - per cycle												
1	RCT	very serious[1]	not applicable	not applicable	serious[3]	none	89/118 (75.4%)	93/130 (71.5%)	1.22 [0.69, 2.15]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Miscarriage rate – per patient												
1	RCT	very serious[1]	not applicable	not applicable	serious[3]	none	12/57 (21.1%)	8/62 (12.9%)	1.80 [0.68, 4.79]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT

[1] Downgraded twice due to both studies having high risk of bias or the single study reporting a given outcome having high risk of bias
[2] Downgraded once due to indirectness since one study included adolescents and provided folic acid whereas the other was in adults and did not provide folic acid
[3] Downgraded once due to imprecision given the small number of studies and/or participants

COMPARISON 5: Metformin + Letrozole vs. Metformin + Clomiphene Citrate												
	Quality assessment						No. participants					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**MET + LET**	**MET + CC**	**Effect, random, OR [95% CI]**	**Favours**	**Certainty**	**Importance**
Outcome: Live birth rate- per patient												
1	RCT	very serious[5]	Not applicable	Not applicable	serious imprecision[6]	none	21 / 57 (36.8%)	18 / 58 (31.0%)	1.30 [0.60, 2.81]	No difference	⨁◯◯◯ VERY LOW	CRITICAL
Outcome: Clinical Pregnancy rate- per patient												
2	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious imprecision[4]	none	43 / 86 (50.0%)	31 / 88 (35.2%)	1.90 [1.01, 3.58]	**MET + LET** (clinical pregnancy is higher with MET + LET)	⨁⨁◯◯ LOW	CRITICAL
Outcome: Ovulation rate- per cycle												
2	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious imprecision[4]	none	137 / 171 (80.1%)	134 / 198 (67.7%)	2.02 [1.24, 3.30]	**MET + LET** (ovulation per cycle is higher with MET + LET)	⨁⨁◯◯ LOW	IMPORTANT
Outcome: Miscarriage rate- per patient												
2	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious imprecision[4]	none	12 / 86 (14.0%)	9 / 88 (10.2%)	0.98 [0.12, 7.89]	No difference	⨁⨁◯◯ LOW	IMPORTANT
Outcome: Full term pregnancy- per patient												
1	RCT	serious[1]	Not applicable	Not applicable	very serious imprecision[6]	none	10 / 29 (34.5%)	3 / 30 (10.0%)	4.74 [1.15, 19.55]	**MET + LET** (full term pregnancy is higher with MET + LET)	⨁◯◯◯ VERY LOW	IMPORTANT

[1] Downgraded once as the majority of evidence (half or more) is at moderate or high risk of bias
[2] Downgraded once due to varied confidence intervals
[3] Downgraded once due to varied effect estimates and inconsistent direction of effect
[4] Downgraded once due to imprecision as confidence intervals (CIs) were wide
[5] Downgraded twice due to having a single high risk of bias study
[6] Downgraded once due to having a small number of studies/ participants or twice for having a very small number of participants

COMPARISON 6: Metformin vs Gonadotropins (hMG)												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	MET	hMG	Effect, random, OR [95% CI]	Favours	Certainty	Importance
Outcome: Pregnancy rate- per patient												
1	RCT	serious[1]	not applicable	not applicable	serious[2]	none	5/30 (16.7%)	7/30 (23.3%)	0.66 [0.18, 2.36]	No difference	⨁⨁◯◯ LOW	IMPORTANT
Outcome: Ovulation rate- per patient												
1	RCT	serious[1]	not applicable	not applicable	serious[2]	none	14/30 (46.7%)	12/30 (40.0%)	1.31 [0.47, 3.65]	No difference	⨁⨁◯◯ LOW	IMPORTANT

[1] Downgraded once due to the evidence being derived from a single moderate risk of bias study
[2] Downgraded once due to having a small number of participants

COMPARISON 7: Metformin + Gonadotrophins (FSH) versus gonadotrophins (FSH) (+/- placebo)												
	Quality assessment						**No. participants**					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**MET + FSH**	**FSH**	**Effect, random , OR [95% CI]**	**Favours**	**Certainty**	**Importance**
Outcome: Pregnancy rate- per patient												
3	RCT	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	6/36	7/41	0.96 [0.18, 5.10]	No difference	⨁⨁◯◯ LOW	CRITICAL
Outcome: Multiple pregnancy rate- per patient												
1	RCT	very serious[1]	not applicable	not applicable	serious[3]	none	0/16	1/16	0.31 [0.01, 8.28]	No difference	⨁◯◯◯ VERY LOW	CRITICAL
Outcome: Ovulation rate- per patient												
1	RCT	serious[1]	not applicable	not applicable	serious[3]	none	9/10	11/15	3.27 [0.31, 34.72]	No difference	⨁⨁◯◯ LOW	IMPORTANT
Outcome: Miscarriage rate - per patient												
1	RCT	serious[1]	not applicable	not applicable	serious[3]	none	1/10	0/15	4.89 [0.18, 132.83]	No difference	⨁⨁◯◯ LOW	IMPORTANT

[1] Downgraded once if the majority of included studies have mod/high risk of bias or twice if all included studies are at high risk of bias
[2] Downgraded once due to varying effect estimates (different directions) and wide confidence intervals
[3] Downgraded once due to the evidence being derived from a single study with a very small sample size

COMPARISON 8: Clomiphene Citrate versus Metformin + Clomiphene Citrate												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	CC	MET + CC	Effect, random, OR [95% CI]	Favours	Certainty	Importance
Outcome: Live birth rate- per patient												
5	RCT	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	86/ 350 (24.6%)	103/ 337 (30.6%)	0.73 [0.52, 1.03]	No difference	⨁⨁◯◯ LOW	CRITICAL
Outcome: Clinical Pregnancy rate- per patient												
7	RCT	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	100/ 392 (25.5%)	136/ 375 (32.3%)	0.60 [0.44, 0.83]	MET + CC (clinical pregnancy is lower with CC)	⨁⨁◯◯ LOW	CRITICAL
Outcome: Multiple pregnancy rate- per patient												
1	RCT	no serious risk of bias	not applicable	not applicable	serious[3]	none	1/36 (2.8%)	1/35 (2.9%)	0.97 [0.06, 16.16]	No difference	⨁⨁⨁◯ MODERATE	CRITICAL
Outcome: Ovulation rate- per patient												
3	RCT	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	26/ 75 (34.6%)	50/ 63 (79.4%)	0.12 [0.04, 0.33]	MET + CC (ovulation per patient is lower with CC)	⨁⨁◯◯ LOW	IMPORTANT
Outcome: Ovulation rate- per cycle												
4	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	610/ 1195 (51.0%)	734/ 1188 (61.8%)	0.64 [0.54, 0.75]	MET + CC (ovulation per cycle is lower with CC)	⨁⨁⨁◯ MODERATE	IMPORTANT
Outcome: Miscarriage rate- per patient												
5	RCT	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	24/ 181 (13.3%)	37/ 196 (18.9%)	0.75 [0.42, 1.33]	No difference	⨁⨁◯◯ LOW	IMPORTANT
Outcome: Miscarriage rate- per pregnancy												
1	RCT	very serious[4]	not applicable	not applicable	very serious[5]	none	0/3 (0%)	1/5 (20%)	0.43 [0.01, 14.08]	No difference	⨁◯◯◯ VERY LOW	IMPORTANT

[1] Downgraded once as the majority of evidence (half or more) is at moderate or high risk of bias
[2] Downgraded once due to including diverse populations (clomiphene-resistance/ failure; therapy naïve and mixed groups)
[3] Downgraded once due to imprecision as derived from a single small study (this outcome was still ranked as moderate as the single study was of low risk of bias)
[4] Downgraded twice due to the evidence being derived from a single high risk of bias study
[5] Downgraded twice due to having a very small number of participants and wide CI

COMPARISON 9: Clomiphene Citrate vs Letrozole												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	CC	LET	Effect, random, OR [95% CI]	Favours	Certainty	Importance
Outcome: Live birth rate - per patient												
6	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	155/ 733 (21.1%)	230/ 716 (32.1%)	0.56 [0.44, 0.71]	LET (live birth rate is lower with CC)	⊕⊕⊕⊕ HIGH	CRITICAL
Outcome: Clinical pregnancy rate- per patient												
8	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	201/ 848 (23.7%)	298/ 820 (36.3%)	0.53 [0.43, 0.66]	LET (clinical pregnancy is lower with CC)	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Multiple pregnancy rate - per patient												
7	RCT	serious[1]	serious[2]	no serious indirectness	serious[3]	none	20/ 700 (2.9%)	27/ 694 (3.9%)	0.83 [0.33, 2.08]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Live birth rate - per pregnancy												
4	RCT	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	113/ 130 (86.9%)	170/ 189 (89.9%)	0.70 [0.30, 1.61]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Pregnancy rate- per patient												
11	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	222/ 949 (23.4%)	327/ 921 (35.5%)	0.55 [0.44, 0.67]	LET (pregnancy rate is lower with CC)	⊕⊕⊕◯ MODERATE	IMPORTANT
Outcome: Ovulation rate - per patient												
8	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	605/ 869 (69.6%)	717/ 828 (86.6%)	0.52 [0.36, 0.74]	LET (ovulation per patient is lower with CC)	⊕⊕⊕◯ MODERATE	IMPORTANT
Outcome: Ovulation rate - per cycle												
1	RCT	serious[1]	not applicable	not applicable	very serious[4]	none	78/150 (52%)	93/130 (71.5%)	0.43 [0.26, 0.71]	LET (ovulation per cycle is lower with CC)	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Multiple pregnancy rate - per pregnancy												
5	RCT	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	11/ 130 (8.5%)	5/ 188 (2.7%)	2.65 [0.96, 7.31]	No difference	⊕⊕◯◯ LOW	IMPORTANT
Outcome: Miscarriage rate - per patient												
8	RCT	serious[1]	serious[2]	no serious indirectness	serious[3]	none	62/ 758 (8.2%)	74/ 753 (9.8%)	1.09 [0.52, 2.26]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Miscarriage rate - per pregnancy												
6	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	39/ 144 (27.1%)	57/ 209 (27.3%)	1.00 [0.60, 1.67]	No difference	⊕⊕◯◯ LOW	IMPORTANT

[1] Downgraded once due to the majority of studies (half or more) having high or moderate risk of bias
[2] Downgraded once due to inconsistency of direction of effect and/ or variations in effect estimates/ CIs
[3] Downgraded once for imprecision due to wide CIs in more than one study
[4] Downgraded twice due to the evidence being derived from a single small high risk of bias study

COMPARISON 10: Clomiphene Citrate vs Metformin + Letrozole												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	CC	MET + LET	Effect, random, OR [95% CI]	Favours	Certainty	Importance
Outcome: Live birth rate - per patient												
1	RCT	very serious[1]	not applicable	not applicable	serious[2]	none	14/63 (22.2%)	21/57 (36.8%)	0.49 [0.22, 1.09]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Clinical pregnancy rate- per patient												
1	RCT	very serious[1]	not applicable	not applicable	serious[2]	none	22/63 (34.9%)	33/57 (57.9%)	0.39 [0.19, 0.82]	MET + LET (clinical pregnancy is lower with CC)	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Ovulation rate - per cycle												
1	RCT	very serious[1]	not applicable	not applicable	serious[2]	none	78/150 (52.0%)	89/118 (75.4%)	0.35 [0.21, 0.60]	MET + LET (ovulation per cycle is lower with CC)	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Miscarriage rate - per patient												
1	RCT	very serious[1]	not applicable	not applicable	serious[2]	none	7/63 (11.1%)	12/57 (21.1%)	0.47 [0.17, 1.29]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT

[1] Downgraded twice due to the evidence being derived from a single high risk of bias study
[2] Downgraded once due to having a small number of studies/ participants

COMPARISON 11: Clomiphene Citrate + Metformin vs Letrozole												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	CC + MET	LET	Effect, random, OR [95% CI]	Favours	Certainty	Importance
Outcome: Live birth rate - per patient												
1	RCT	very serious[1]	not applicable	not applicable	serious[2]	none	18/58 (31.0%)	21/62 (33.9%)	0.88 [0.41, 1.89]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Clinical pregnancy rate- per patient												
1	RCT	very serious[1]	not applicable	not applicable	serious[2]	none	26/58 (44.8%)	29/62 (46.8%)	0.92 [0.45, 1.90]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Ovulation rate - per cycle												
1	RCT	very serious[1]	Not applicable	not applicable	serious[2]	none	80/131 (61.1%)	93/130 (71.5%)	0.62 [0.37, 1.05]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Miscarriage rate - per patient												
1	RCT	very serious[1]	not applicable	not applicable	serious[2]	none	7/58 (12.1%)	8/62 (12.9%)	0.93 [0.31, 2.74]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT

[1] Downgraded twice due to the evidence being derived from a single high risk of bias study
[2] Downgraded once due to having a small number of studies/ participants

COMPARISON 12: Clomiphene Citrate vs Gonadotropins (FSH)

	Quality assessment						No. participants					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**CC**	**FSH**	**Effect, random , OR [95% CI]**	**Favours**	**Certainty**	**Importance**
Outcome: Live birth rate - per patient												
2	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	54/ 161 (33.5%)	79/ 170 (46.5%)	0.58 [0.37, 0.91]	**FSH** (live birth rate is lower with CC)	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Clinical pregnancy rate- per patient												
2	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	63/ 161 (39.1%)	92/ 170 (54.1%)	0.54 [0.35, 0.85]	**FSH** (clinical pregnancy is lower with CC)	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Multiple pregnancy rate - per pregnancy												
2	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	1/ 63 (1.6%)	5/ 92 (5.4%)	0.42 [0.06, 2.78]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Ovulation rate - per patient												
1	RCT	very serious[3]	not applicable	not applicable	very serious[4]	none	30/ 38 (78.9%)	35/ 38 (92.1%)	0.32 [0.08, 1.32]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Ovulation rate - per cycle												
1	RCT	very serious[3]	not applicable	not applicable	very serious[4]	none	55/ 104 (52.9%)	67/ 91 (73.6%)	0.40 [0.22, 0.74]	**FSH** (ovulation per patient is lower with CC)	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Miscarriage rate - per pregnancy												
2	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	8/ 63 (12.7%)	12/ 92 (13.0%)	1.04 [0.38, 2.79]	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT

[1] Downgraded once due to the majority of studies (half or more) having high or moderate risk of bias

[2] Downgraded once for imprecision due to wide CIs

[3] Downgraded twice due to the evidence being derived from a single high risk of bias study

[4] Downgraded twice due to the very small sample size (n=17) and single study used for evidence on this outcome

COMPARISON 13: Gonadotrophins (FSH) + Clomiphene Citrate versus Gonadotrophins (FSH)												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	FSH + CC	FSH	Effect, random , OR [95% CI]	Favours	Certainty	Importance
Outcome: Live birth rate- per patient												
1	RCT	serious[1]	not applicable	not applicable	serious[2]	none	22/87 (25.3%)	19/87 (21.8%)	1.21 [0.60, 2.44]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Clinical pregnancy rate- per patient												
2	RCT	serious[1]	serious[3]	no serious indirectness	no serious imprecision	none	120/ 756 (15.9%)	84/433 (19.4%)	0.83 [0.61, 1.14]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Ovulation rate - per patient												
2	RCT	serious[1]	very serious[4]	no serious indirectness	no serious imprecision	none	444/ 756 (58.7%)	344/ 433 (79.4%)	0.79 [0.03, 21.36]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Miscarriage rate - per pregnancy												
1	RCT	serious[1]	not applicable	not applicable	no serious imprecision[5]	none	16/ 96 (16.7%)	9/ 62 (14.5%)	1.18 [0.48, 2.86]	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT

[1] Downgraded once for risk of bias due to one or both studies being of moderate risk of bias
[2] Downgraded once for imprecision since the evidence is derived from a single, relatively small study
[3] Downgraded once because effects estimates vary (including having different directions)
[4] Downgraded twice because effect estimates vary (different directions) and due to high statistical heterogeneity (I^2 = 99%, with a p<0.00001)
[5] Not downgraded for imprecision despite being a single study, due to its relatively large sample size (n=1387 of which there were 158 pregnancies)

COMPARISON 14: Clomiphene Citrate + gonadotropins (FSH) versus letrozole												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	CC + FSH	LET	Effect, random , OR [95% CI]	Favours	Certainty	Importance
Outcome: Clinical pregnancy rate- per patient												
1	RCT	serious[1]	not applicable	not applicable	no serious imprecision	none	96/ 669 (14.3%)	87/ 372 (23.4%)	0.55 [0.40, 0.76]	LET (clinical pregnancy is lower with CC + FSH)	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Ovulation rate - per patient												
1	RCT	serious[1]	not applicable	not applicable	no serious imprecision	none	381/ 669 (57.0%)	295/ 372 (79.3%)	0.35 [0.26, 0.46]	LET (ovulation rate is lower with CC + FSH)	⊕⊕⊕◯ MODERATE	IMPORTANT
Outcome: Miscarriage rate - per pregnancy												
1	RCT	serious[1]	not applicable	not applicable	no serious imprecision	none	16/ 96 (16.7%)	12/ 87 (13.8%)	1.25 [0.55, 2.82]	No difference	⊕⊕⊕◯ MODERATE	IMPORTANT

[1]Downgraded once for risk of bias (despite being a single study, imprecision was not downgraded given the large sample size)

COMPARISON 15: Clomiphene Citrate + metformin versus gonadotropins (FSH)												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	FSH	CC + MET	Effect, random , OR [95% CI]	Favours	Certainty	Importance
Outcome: Clinical pregnancy rate- per patient												
1	RCT	very serious[1]	not applicable	not applicable	serious[2]	none	16/55 (29.1%)	7/55 (12.7%)	2.81 [1.05, 7.52]	FSH (clinical pregnancy is higher with FSH)	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Miscarriage rate - per pregnancy												
1	RCT	very serious[1]	not applicable	not applicable	serious[2]	none	3/16 (18.6%)	1/7 (14.3%)	1.38 [0.12, 16.23]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT

[1] Downgraded twice due to all studies (or the single study) included having a high risk of bias

[2] Downgraded once due to the small sample size from a single study

COMPARISON 16: Clomiphene citrate (CC) versus Laparoscopic ovarian drilling (LOD)												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	CC	LOD	Effect, random , OR [95% CI]	Favours	Certainty	Importance
Outcome: Live birth rate- per patient												
1	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	18/32 (56.3%)	15/33 (45.5%)	1.54 [0.58, 4.10]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Clinical pregnancy rate- per patient												
1	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	23/32 (71.9%)	20/33 (60.6%)	1.66 [0.59, 4.70]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Miscarriage rate - per pregnancy												
1	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	2/23 (8.7%)	2/20 (10.0%)	0.86 [0.11, 6.72]	No difference	⊕⊕◯◯ LOW	IMPORTANT

[1] Downgraded once for risk of bias due to high or moderate risk for the majority of included studies (half or more)

[2] Downgraded once for imprecision due to the evidence being derived from a single small study

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 5

Question 5.4.

In women with PCOS, is clomiphene citrate effective for improving fertility outcomes? In women with PCOS, is metformin effective for improving fertility outcomes? In women with PCOS and a BMI<30-32, what is the effectiveness of metformin compared to clomiphene citrate for improving fertility outcomes?

BACKGROUND

Clomiphene citrate

Clomiphene citrate is a selective oestrogen receptor modulator with both oestrogenic and anti-oestrogenic properties (1). It was first approved for use in women with anovulation in 1967 and has been used as a first line ovulation induction agent for over 40 years (2). Acting as an anti-oestrogen, clomiphene citrate competitively inhibits the binding of oestradiol to its receptors in the hypothalamus and pituitary which in turn blocks the negative feedback effect of endogenous oestrogens including oestradiol. This release of the hypothalamus from negative inhibition results in an increased secretion of pulsatile gonadotrophin-releasing hormone secretion from the hypothalamus leading to an increase in FSH and luteinizing hormone production and secretion from the pituitary gland. This increase in FSH secretion stimulates follicular growth and oestradiol production with the aim of inducing a midcycle luteinizing hormone surge and ovulation (3).

Clomiphene citrate is usually given for 5 days, commencing on menstrual cycle day 2 to 5, starting with 50mg/day and increasing to a maximum of 150 mg/day. If ovulation cannot be achieved with clomiphene citrate administration at maximum doses, clomiphene citrate resistance is defined. If pregnancy cannot be achieved after six ovulatory cycles with clomiphene citrate, then the patient is described as having clomiphene citrate failure (4).

Studies with clomiphene citrate have shown an ovulation rate of 60–85% and a pregnancy rate of 30–50% after 6 ovulatory cycles. This apparent discrepancy between good ovulation rates and lower pregnancy rates has been partially attributed to the anti-oestrogenic effects of clomiphene citrate on the endometrium and cervical mucus. The rates of twin pregnancy and triplets with clomiphene citrate are 5–7% and 0.3%, respectively depending on the closeness of monitoring of the cycle. The incidence of ovarian hyperstimulation syndrome is less than 1% (5). A patient’s lifetime exposure to clomiphene citrate without pregnancy is often limited to 12 treatment cycles, as additional cycles have been alleged (without adequate evidence) to be at increased risk of borderline ovarian tumours (6). There is insufficient evidence to suspect clomiphene citrate in causing congenital abnormalities in children born from the treatment.

Metformin

Hyperinsulinaemia with insulin resistance is a prominent feature of PCOS (7) affecting approximately 65 to 80% of women with PCOS (8). This results in increased ovarian androgen biosynthesis *in vivo* and *in vitro* and decreased SHBG synthesis from the liver, leading to increased bioavailability of free androgens. This excess in local ovarian androgen production augmented by hyperinsulinaemia causes premature follicular atresia and anovulation (9).

This contribution to anovulation in PCOS has led to the introduction of insulin-sensitizing drugs in an attempt to restore ovulation and enhance pregnancy. Metformin has been the one studied most widely in PCOS and has the most reassuring safety profile (4). It is a biguanide which is used as an oral antihyperglycaemic agent in the treatment of DM2 (10). The first published report on the use of metformin as a treatment for PCOS was in 1994 and early studies examining the reproductive system effects of metformin in women with PCOS showed promising results.

Metformin is available in two formulations: immediate and extended-release. Therapeutic regimens of metformin administration in PCOS are not well standardized in clinical practice, and various protocols have been used in the studies available in literature with an extremely variable target dose of 1500 to 2550 mg per day having been proposed (11). Some studies have continued use of metformin into pregnancy while others have ceased its use once a positive pregnancy test has been achieved.

Metformin for fertility purposes has been used on its own or with other drugs such as clomiphene citrate, letrozole or gonadotrophins.

Methodological quality/risk of bias
Risk of bias for the included studies were rated as low to high risk of bias. Studies of moderate to high risk of bias should be interpreted with caution. The most common reasons for the ratings assigned include: unclear whether randomization had been performed appropriately; unclear whether allocation to the intervention group was concealed; unclear whether participants, investigators and outcome assessors were blinded to the intervention group; unclear if all participants were analysed in the groups to which they were randomly allocated; power calculations were not reported; lack of direct comparisons between the two groups; insufficient number of patients in the trials; unclear whether selective outcome reporting had occurred; and a lack of conflict of interest statements. These methodological issues are likely to have an impact on the direction of bias and reliability of the findings.

Research Integrity check was applied (see general Integrity guideline section).

Generalisability
Studies were conducted in university departments, outpatient clinics in hospitals and laboratories covering countries across Australia, Europe, South America, USA and Asia.

Comparisons

1. **Metformin vs. placebo**

Seven studies compared metformin with placebo for fertility outcomes in PCOS. Studies were conducted in the UK, Europe (Norway, Finland, Sweden, Denmark), China, New Zealand and Jordan. Five of the studies had a moderate risk of bias and two had a low risk. Two studies were specifically in women with clomiphene citrate-resistant PCOS, and three had a mixed population (the remaining two did not report ovulation induction medication use in their populations).

All outcomes assessed were amenable to meta-analysis except for multiple pregnancy rate per patient which was only reported in a single study. Metformin was superior to placebo for improving live birth, clinical pregnancy and overall pregnancy rates, with ORs >1.8 and moderate certainty in the evidence for all. Downgrading was due to risk of bias since most of the studies (half or more) in these three analyses were of moderate risk of bias. No differences between metformin and placebo were identified for ovulation rate per patient, miscarriage rate or multiple pregnancy rates per patient or pregnancy. Evidence for these outcomes was of low certainty due to small sample sizes, wide confidence intervals and risk of bias.

2. **Metformin vs. clomiphene citrate**

Only three included studies compared metformin with clomiphene citrate, two of which included women with a BMI<30-32 kg/m2 (12, 13), while the remaining study included women with a mean BMI ≥30-32 kg/m2 (14).

One of the studies (12) had a moderate risk of bias and the other (14) had a low risk of bias. Both studies included participants with a mixed history of past ovulation induction medication use, with the study by Legro et al. 2007 (14) being of a relatively large sample size (n>400). The third study (13) had a moderate risk of bias and included therapy naïve women with PCOS.

In meta-analysis, there were no differences between metformin and clomiphene citrate for live birth, clinical pregnancy, multiple pregnancy or ovulation rates per patient. In a single study, ovulation rate per cycle was significantly lower with metformin compared with clomiphene citrate (OR= 0.43) and miscarriage rate per patient was significantly higher with metformin in meta-analysis of three studies (OR= 2.44). In subgroup analysis by BMI, clomiphene citrate was more effective than metformin for achieving live birth rate and clinical pregnancy rates among women with a BMI ≥30-32 kg/m2. This result was derived from a single study, however, and should be interpreted with caution. Certainty in the evidence was low for live birth, clinical pregnancy, and ovulation rate per cycle while the remaining outcomes were of moderate certainty (refer table below), with main reasons for downgrading the evidence including risk of bias and imprecision due to small sample sizes or single studies for some outcomes.

3. Metformin and clomiphene citrate vs. metformin

Three studies examined metformin + clomiphene citrate compared with metformin alone in women with PCOS. Of these, one was moderate risk of bias (13) in therapy naïve women with PCOS in India. The remaining two were low risk studies (12, 14) in New Zealand and the US, with mixed ovulation induction medication use history.

In meta-analysis of the three RCTs, metformin combined with clomiphene citrate had a favourable effect on live birth rate and ovulation rate per patient, with odds ratios of 2.44 and 3.72, respectively. These outcomes were both of moderate certainty; live birth rate was downgraded for indirectness resulting from diverse populations since the studies included treatment naïve patients and those with clomiphene-citrate resistance or failure; and ovulation rate was downgraded due to being derived from a single study (despite its relatively large sample size, the result requires replication to increase certainty in the evidence). Subgroup analysis by BMI showed that the beneficial effect of metformin + clomiphene citrate on live birth rate was most pronounced in women with a BMI ≥30-32 kg/m2, however only one study was included in this subgroup.

4. Clomiphene citrate vs. metformin and clomiphene citrate

Eight studies compared clomiphene citrate with metformin + clomiphene citrate, with several relevant outcomes. Studies were conducted across China, New Zealand, South Africa, Turkey, USA and India. Two studies had low risk of bias, two moderate and four high risk. Two studies were specifically in women with clomiphene citrate-resistant, three had mixed populations and one was in therapy naïve PCOS (the remaining two did not report ovulation induction medication use in their populations).

Meta-analysis was performed for 5 possible outcomes. Clomiphene citrate alone was less effective than the combination of clomiphene citrate and metformin for clinical pregnancy rates and ovulations rates per patient and per cycle. In subgroup analysis by BMI, metformin + clomiphene citrate was more effective for clinical pregnancy rate in the BMI<30-32 kg/m2 subgroup, and more effective for ovulation rate per patient in the BMI ≥30-32 kg/m2 subgroup. Ovulation rate per cycle was better with metformin + clomiphene citrate than clomiphene citrate alone across both BMI subgroups. There were no significant differences in live birth rates, multiple pregnancy rates or miscarriage rates per patient or per pregnancy, including after subgrouping by BMI. There is low to moderate certainty in the evidence for these outcomes, which were downgraded due to risk of bias since most of the studies were of moderate to high risk of bias. Evidence was also downgraded for indirectness since some analyses included diverse populations with and without clomiphene citrate- resistance.

5. Clomiphene citrate vs. letrozole

Eleven RCTs compared clomiphene citrate with letrozole, of which six had a high risk of bias (15-20), one had a moderate risk of bias (21), and four had a low risk of bias (22-25). Studies were conducted in the UK, USA, Iran, India, Bangladesh and China.

In meta-analysis, letrozole was superior to clomiphene citrate for ovulation rate per patient; pregnancy rate and clinical pregnancy rate per patient; and live birth rate per patient. Certainty in the evidence is high for live birth rate, and moderate for pregnancy rate, clinical pregnancy rate and ovulation rate, downgraded once for serious risk of bias since the majority of studies included had high to moderate risk of bias.

There were no differences between clomiphene citrate and letrozole for other outcomes including live birth rate per pregnancy, multiple pregnancy rate (per patient or pregnancy); and miscarriage rate (per patient or pregnancy). Certainty in these findings ranged from low to very low due to risk of bias, serious imprecision and serious inconsistency, except for multiple pregnancy rate per patient which was moderate due to 3 of the 5 studies having a high risk of bias. There was no evidence of statistical heterogeneity or publication bias for any of the outcomes.

6. Clomiphene citrate and metformin vs letrozole

One study compared clomiphene citrate combined with metformin versus letrozole, (20) with relevant outcomes including live birth, clinical pregnancy and miscarriage rate per patient, and ovulation rate per cycle. This study, by Liu et al. (2017) (20) was conducted in China with 120 participants and had a high risk of bias due to lack of blinding of participants and insufficient information around allocation concealment. There were no differences between clomiphene citrate + metformin compared with letrozole for any of the outcomes. Certainty in these results is very low due to being derived from a single, relatively small, high-risk of bias study.

7. Metformin and letrozole vs. letrozole

Only two studies compared metformin + letrozole with letrozole alone. One of the studies performed in Iran (26) in letrozole-resistant women (no ovulation at 7.5 mg letrozole), provided folic acid 200 µg daily (as a placebo) to both the letrozole + metformin and letrozole groups; whilst the other did not. The second study by Liu et al. (2017) (20) was conducted in China in 119 women with PCOS (for this comparison) aged 20-35, with a BMI ≤35 kg/m2. Reported outcomes of relevance were clinical pregnancy rate, live birth rate and miscarriage rate per patient and ovulation rate per cycle. Both studies had a high risk of bias due to issues around lack of blinding and insufficient information about randomisation or allocation concealment. The study by Liu et al. (2017) (20) also had a high dropout rate of 15% in the letrozole + metformin group, with 7.5% drop outs in the letrozole group.

Meta-analysis was only possible for the outcome of clinical pregnancy rate per person, with two studies pooled for this analysis (20, 26) , showing no difference between metformin + letrozole versus letrozole alone for this outcome. There is very low certainty in this result due to very serious risk of bias, with serious imprecision and serious indirectness. There were no differences in live birth rate between metformin + letrozole vs letrozole alone (33.9% vs 36.8%). Clinical pregnancy rate per patient (48.6% vs 40.2%) and ovulation rate per cycle (89/118 cycles vs 93/130 cycles) were higher in the letrozole + metformin group than letrozole alone, but these were not statistically significant. Similarly, miscarriage/ abortion rate per patient was slightly higher with metformin + letrozole than letrozole alone, but the difference was not statistically significant (21.1% vs 12.9%, $p > .05$). These results are of very low certainty given that they are derived from a single study with a high risk of bias.

8. Metformin and letrozole vs. metformin and clomiphene citrate

Two studies compared metformin + letrozole with metformin + clomiphene citrate (20, 27) with relevant outcomes including ovulation rate per cycle and pregnancy and miscarriage rate per patient. Liu et al. (20) additionally assessed live birth rate per patient, whereas Sohrabvand et al. (27) reported full term pregnancy per patient. Both studies were moderate (27) or high (20) risk of bias due to lack of blinding of participants and insufficient information around allocation concealment.

Meta-analysis of these two studies was performed for ovulation rate per cycle and pregnancy and miscarriage rate per patient, with results in the table below. Clinical pregnancy and ovulation rates were greater with metformin + letrozole compared with metformin + clomiphene citrate with odds ratios of 1.90 and 2.02, respectively. Miscarriage rates per patient did not differ between groups.

Certainty of the evidence for these three outcomes was low, downgraded once due to high/ moderate risk of bias and once for serious imprecision (small n and wide confidence intervals). The study by Liu et al. (20) additionally assessed live birth rate per patient, showing no difference between metformin + letrozole versus metformin + clomiphene citrate groups. Sohrabvand et al. (27) assessed full term pregnancy per patient and found that metformin + letrozole was more effective than metformin + clomiphene citrate for this outcome (10 versus 3 full term pregnancies per group, respectively, p=0.03). The results for both these outcomes are of very low certainty given that they are derived from only single studies with moderate to high risk of bias.

9. Clomiphene citrate vs metformin and letrozole

One study compared clomiphene citrate with metformin + letrozole, (20) with relevant outcomes including live birth, clinical pregnancy and miscarriage rate per patient, and ovulation rate per cycle. This study, by Liu et al. (2017) (20) was conducted in China with 120 participants and had a high risk of bias due to lack of blinding of participants and insufficient information around allocation concealment.
Clomiphene citrate alone was less effective than metformin + letrozole for clinical pregnancy rate and ovulation rate per cycle. There were no differences between clomiphene citrate and combined metformin + letrozole for the outcomes of live birth or miscarriage rate per patient. Given that these results are from a single, relatively small, high-risk of bias study, certainty in the evidence is very low for all outcomes.

EVIDENCE-BASED RECOMMENDATIONS	
Metformin could be used alone, in women with PCOS with anovulatory infertility and no other infertility factors, to improve clinical pregnancy and live birth rates, whilst informing women should be informed that there are more effective ovulation agents.	Low
Clomiphene citrate could be used in preference to metformin in women with PCOS with anovulatory infertility and no other infertility factors, to improve ovulation, clinical pregnancy and live birth rates.	Low
Clomiphene citrate combined with metformin could be used rather than clomiphene citrate alone in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation and clinical pregnancy rates.	Low

Clomiphene citrate combined with metformin could be used rather than metformin alone in women with PCOS with anovulatory infertility and no other infertility factors to improve live birth rates.	Low
Letrozole should be used rather than clomiphene citrate in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation, clinical pregnancy, and live birth rates.	Low

PRACTICE POINTS
● Women should be counselled as to potential mild gastrointestinal side-effects of metformin ● Healthcare and resource burden including monitoring, travel and costs are lower with metformin ● Consideration of age and screening for other fertility factors needs to be discussed before prescribing metformin
The risk of multiple pregnancy is increased with clomiphene citrate use (alone or in combination with metformin) and therefore clomiphene cycles will require ultrasound monitoring.
Monitoring of combined cycles will need to be equivalent to clomiphene citrate alone
There is evidence of no harm in terms of foetal abnormality rates in women exposed to clomiphene compared with letrozole.

GRADE EVIDENCE CERTAINTY	
Comparison	**GRADE for critical outcomes**
Comparison 1. Metformin vs Placebo	⊕⊕◯◯ LOW
Comparison 2. Metformin vs Clomiphene citrate	⊕⊕◯◯ LOW
Comparison 3. Metformin + Clomiphene citrate vs Metformin	⊕⊕◯◯ LOW
Comparison 4. Clomiphene citrate vs Metformin + Clomiphene citrate	⊕⊕◯◯ LOW
Comparison 5. Clomiphene citrate vs Letrozole	⊕◯◯◯ VERY LOW
Comparison 6. Clomiphene citrate + Metformin vs Letrozole	⊕◯◯◯ VERY LOW

Comparison 7. Metformin + Letrozole vs Letrozole	⊕◯◯◯ VERY LOW
Comparison 8. Metformin + Letrozole vs Metformin + Clomiphene citrate	⊕◯◯◯ VERY LOW
Comparison 9. Clomiphene citrate vs Metformin + Letrozole	⊕◯◯◯ VERY LOW

COMPARISONS (option versus other option)

1. Metformin vs placebo

EVIDENCE-BASED RECOMMENDATION(S)

EBR: Metformin could be used alone, in women with PCOS with anovulatory infertility and no other infertility factors, to improve clinical pregnancy and live birth rates, whilst informing women that there are more effective ovulation agent.

LOW

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

PRACTICE POINT(S)

- Women should be counselled as to potential mild gastrointestinal side-effects
- Healthcare and resource burden including monitoring, travel and costs are lower with metformin
- Consideration of age and screening for other fertility factors needs to be discussed before prescribing metformin

GRADE CONSIDERATIONS

Justifications:

Two critical criteria (live birth and clinical pregnancy rate) and one important criterion (pregnancy rate per patient) had moderate certainty

Subgroup considerations:

Implementation considerations:

Potential side-effects of the drug should be considered

Low cost, limited expertise and resource, monitoring limited and should be balanced in terms of efficacy versus health resource

Monitoring and evaluation considerations:

As there is no increase in multiple pregnancy rates, monitoring may not be required

Research priorities:

- Degree of side-effects and attempts to reduce these
- When the drug should be stopped if pregnant

A definitive trial to assess magnitude of efficacy on the critically important outcome of live birth is recommended

GRADE framework

GRADE DECIDE Interactive Evidence to Decision Framework

- **DESIRABLE EFFECTS**

How substantial are the desirable anticipated effects?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Is cheap and seemingly effective with side-effects in up to 20% of patients which can be mitigated by advice and drug timing

- **UNDESIRABLE EFFECTS**

How substantial are the undesirable anticipated effects?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

GIT side-effects are potentially increased which may lead to cessation by the patient

- **CERTAINTY OF THE EVIDENCE**

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☐ Very low	☒ Low	☐ Moderate	☐ High

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Limited numbers in trials to date

Moderate evidence for efficacy and low evidence for effects on multiple pregnancy

- **VALUES**

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☐ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☒ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Research evidence:

No research evidence was identified

Panel discussion:

Unlikely

-

- **BALANCE OF EFFECTS**

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:

The ease of use and cost must be balanced by potential GIT effects. May be better with slow release tablets but efficacy of these are uncertain in terms of fertility outcomes

- **COSTS**

How large are the resource requirements (costs)?

Judgement:

☐ Don't know	☐ Varies	☐ Large costs	☐ Moderate costs	☐ Negligible costs or savings	☐ Moderate savings	☒ Large savings

Research evidence:

No research evidence was identified

Panel discussion:

Much cheaper than all other examined medical options

- **CERTAINTY OF COST EVIDENCE**

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

No research evidence was identified

Panel discussion:

Despite this the widespread availability for other medical reasons suggests cheaper costs

- **COST-EFFECTIVENESS**

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☒ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

No research evidence was identified

Panel discussion:

Compared to other outcomes cost effectiveness would be expected but there are no published studies

- **EQUITY**

What would be the impact on health equity?

Judgement:

☐ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☒ Probably increased	☐ Increased

Research evidence:

No research evidence was identified

Panel discussion:

Widely available around the world and no monitoring required, lower cost burden and can be used in primary care

Need access to fertility factor screening if used in primary care

- **ACCEPTABILITY**

Is the option acceptable to key stakeholders?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Patients probably prefer oral drugs that are cheap, do not need monitoring and are easy to remember. Patient autonomy is maximised by regular oral use without intermittent health care centre attendance for results and investigations

- **FEASIBILITY**

Is the option feasible to implement?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☐ Probably Yes	☒ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Yes, as the drug is freely available all over the world.

COMPARISONS (option versus other option)

2. Clomiphene citrate vs. metformin

EVIDENCE-BASED RECOMMENDATION(S)

EBR: Clomiphene citrate could be used in preference to metformin in women with PCOS with anovulatory infertility and no other infertility factors, to improve ovulation, clinical pregnancy and live birth rates.

(Note: Low evidence rating as clinical pregnancy rate and multiple pregnancy rate had lower certainty than live birth rate)

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

PRACTICE POINT(S)

The risk of multiple pregnancy is increased with clomiphene citrate use (alone or in combination with metformin) and therefore clomiphene cycles will require ultrasound monitoring.

GRADE CONSIDERATIONS

Justifications:

Clomiphene citrate vs. metformin all data:

There is evidence from high quality studies with low risk of bias for improvement of live birth rate

For clinical pregnancy rate overall, there were wide odds ratios but twice the chance of pregnancy with the combination suggesting the lower number of subjects contributes to non-significance.

Multiple pregnancy rate had an odds ratio of 1.00 indicating the same risk as clomiphene citrate alone

Ovulation rate per cycle was strongly associated with the combination with an odds ratio of 3.72 and confidence limits well away from 1.00.

Subgroup considerations:

Additional discussion BMI subgroups, apparent better success CC in BMI < 30kgm2 in Legro et al, (14, 22) yet evidence was inconclusive.

Recognition on the challenges of heterogeneous data, sensitivity analysis on high quality studies.

Implementation considerations: Monitoring and burden of clomiphene citrate is higher
Monitoring and evaluation considerations: Usual ultrasound monitoring of clomiphene citrate should apply
Research priorities: Impact by BMI subgroups

GRADE framework

GRADE DECIDE **Interactive Evidence to Decision Framework**

- **DESIRABLE EFFECTS**

How substantial are the desirable anticipated effects?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Confidence around effects relies on 3 studies heavily dominated in numbers by one study (22) as the only high-quality study.

- **UNDESIRABLE EFFECTS**

How substantial are the undesirable anticipated effects?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

The addition of clomiphene citrate may increase side-effects but not documented

- **CERTAINTY OF THE EVIDENCE**

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☐ Very low	☒ Low	☐ Moderate	☐ High

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Reduced by no difference in clinical pregnancy rate and multiple pregnancy rate where there are few studies

- **VALUES**

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☐ Important uncertainty or variability	☒ Possibly important uncertainty or variability	☐ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Research evidence:

No research evidence was identified

Panel discussion:

Little to inform decisions in this area.

Women should be informed on the balance of risks and benefits compared to other agents

- **BALANCE OF EFFECTS**

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:

- **COSTS**

How large are the resource requirements (costs)?

Judgement:

☐ Don't know	☐ Varies	☐ Large costs	☒ Moderate costs	☐ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:

No research evidence was identified

Panel discussion:

Monitoring adds costs

- **CERTAINTY OF COST EVIDENCE**

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☐ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

Systematic review on costs in PCOS – see HEA section

Panel discussion:

Monitoring adds costs

- **COST-EFFECTIVENESS**

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

Systematic review on costs in PCOS – see HEA section

Panel discussion:

The drug is relatively inexpensive but monitoring costs are potentially greater for clomiphene citrate

- **EQUITY**

What would be the impact on health equity?

Judgement:

☐ Don't know	☒ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☐ Probably increased	☐ Increased

Research evidence:

No research evidence was identified

Panel discussion:

Complex considerations to be discussed based on shared decision making

- **ACCEPTABILITY**

Is the option acceptable to key stakeholders?

Judgement:

☐ Don't know	☒ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Depends on the health system and prescribing costs. Clomiphene citrate may be less accessible and needs more monitoring.

Practitioners may need more skill in monitoring and patients may need to attend for monitoring more often.

Complex considerations to be discussed based on shared decision making

- **FEASIBILITY**

Is the option feasible to implement?

Judgement:

☐ Don't know	☒ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Dependent on the health care system in which this operates and access to monitoring

COMPARISONS (option versus other option)

3. Clomiphene citrate and metformin vs. clomiphene citrate alone

EVIDENCE-BASED RECOMMENDATION(S)

EBR: Clomiphene citrate combined with metformin could be used rather than clomiphene citrate alone in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation and clinical pregnancy rates.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

GRADE CONSIDERATIONS

Justifications:

5 studies contributed to this outcome for clinical pregnancy was 0.60 rates and although numbers were small, the OR was 0.60 (CI 0.44-0.83).

This was minimal heterogeneity implying these results were generally applicable.

There were no significant subgroup differences

Subgroup considerations:

No subgroups

Implementation considerations:

If clomiphene citrate is being used, addition of metformin could improve ovulation and clinical pregnancy rates

Monitoring and evaluation considerations:

Standard monitoring of oral agents needed

Research priorities:

Definitive trial of live birth rates could be prioritised

GRADE framework

GRADE DECIDE Interactive Evidence to Decision Framework

- **DESIRABLE EFFECTS**

How substantial are the desirable anticipated effects?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Small numbers but several studies contributed to this finding

- **UNDESIRABLE EFFECTS**

How substantial are the undesirable anticipated effects?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

The combination of Metformin and CC may have added side-effects

- **CERTAINTY OF THE EVIDENCE**

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☐ Very low	☒ Low	☐ Moderate	☐ High

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

- **VALUES**

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☐ Important uncertainty or variability	☒ Possibly important uncertainty or variability	☐ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Research evidence:

No research evidence was identified

Panel discussion:

Women may value extra benefit

- **BALANCE OF EFFECTS**

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:

COSTS

How large are the resource requirements (costs)?

Judgement:

☐ Don't know	☐ Varies	☐ Large costs	☐ Moderate costs	☒ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:

Cost effectiveness systematic review is done across PCOS. Please reference the overarching section on cost

Panel discussion:

Metformin is an inexpensive drug and adding this will not increase cost drug or monitoring

- **CERTAINTY OF COST EVIDENCE**

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☐ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

Cost effectiveness systematic review is done across PCOS. Please reference the overarching section on cost

Panel discussion:

- **COST-EFFECTIVENESS**

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

Cost effectiveness systematic review is done across PCOS. Please reference the overarching section on cost

Panel discussion:

Aligns to recommendations

- **EQUITY**

What would be the impact on health equity?

Judgement:

☐ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☒ Probably increased	☐ Increased

Research evidence:

No research evidence was identified

Panel discussion:

Oral more accessible

No increased cost for better efficacy

- **ACCEPTABILITY**

Is the option acceptable to key stakeholders?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Minimal cost

- **FEASIBILITY**

Is the option feasible to implement?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

COMPARISONS (option versus other option)

4. Metformin and clomiphene citrate vs metformin alone

EVIDENCE-BASED RECOMMENDATION(S)

EBR: Clomiphene citrate combined with metformin could be used rather than metformin alone in women with PCOS with anovulatory infertility and no other infertility factors to improve live birth rates

(Low as clinical pregnancy rate and multiple pregnancy rate had lower certainty than live birth rate)

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

PRACTICE POINT(S)

Monitoring of combined cycles will need to be equivalent to clomiphene citrate alone.

GRADE CONSIDERATIONS

Justifications:

There is moderate evidence for improvement of live birth rate overall with nonsignificant effect on clinical pregnancy rate.

For clinical pregnancy rate there were wide odds ratios but twice the chance of pregnancy with the combination suggesting the lower number of subjects contributes to non-significance.

Multiple pregnancy rate had an odds ratio of 1.00 indicating the same risk as clomiphene citrate alone

Ovulation rate per cycle was strongly associated with the combination with an odds ratio of 3.72 and confidence limits well away from 1.00.

Subgroup considerations:

Previous unsuccessful use of medication led to higher results in the combined group while the numbers in therapy naïve groups was low.

Patients with a BMI >30-32 had a higher difference than those with a lower BMI where the difference was not obvious. The former group OR was 4.71 (2.56-8.65) compared with the latter 1.55 (0.73-3.29) although numbers were lower in this group.

Implementation considerations:

Two medications need to be dispensed with differing instructions for both (clomiphene citrate for 5 days, metformin continuous).

Monitoring and evaluation considerations:

Usual monitoring should apply.

Research priorities:

The impact of BMI needs more investigation as there is only one good quality study that examines this (14) .

GRADE framework

GRADE DECIDE **Interactive Evidence to Decision Framework**

- **DESIRABLE EFFECTS**

How substantial are the desirable anticipated effects?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Confidence around effects relies on 3 studies heavily dominated in numbers by one study (22) .

- **UNDESIRABLE EFFECTS**

How substantial are the undesirable anticipated effects?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

The addition of clomiphene citrate may increase side-effects but not documented.

- **CERTAINTY OF THE EVIDENCE**

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☐ Very low	☒ Low	☐ Moderate	☐ High

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Reduced by no difference in clinical pregnancy rate and multiple pregnancy rate where there are few studies

Studies on BMI and previous therapy dominated by one study

- **VALUES**

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☐ Important uncertainty or variability	☒ Possibly important uncertainty or variability	☐ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Research evidence:

No research evidence was identified

Panel discussion:

Little to inform decisions in this area.

More monitoring and doctor interface may mean an intrusion in regular living.

- **BALANCE OF EFFECTS**

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:

- Insufficient information to decide.

- **COSTS**

How large are the resource requirements (costs)?

Judgement:

☐ Don't know	☐ Varies	☐ Large costs	☒ Moderate costs	☐ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:

Cost effectiveness systematic review is done across PCOS. Please reference the overarching section on cost

Panel discussion:

Addition of a second drug and monitoring adds costs.

- **CERTAINTY OF COST EVIDENCE**

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☐ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

Cost effectiveness systematic review is done across PCOS. Please reference the overarching section on cost.

Panel discussion:

Addition of a second drug and monitoring adds costs.

- **COST-EFFECTIVENESS**

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

Cost effectiveness systematic review is done across PCOS. Please reference the overarching section on cost.

Panel discussion:

The extra drug is relatively inexpensive but monitoring costs are potentially greater by adding in clomiphene citrate.

- **EQUITY**

What would be the impact on health equity?

Judgement:

☒ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☐ Probably increased	☐ Increased

Research evidence:

No research evidence was identified.

Panel discussion:

Unable to tell.

- **ACCEPTABILITY**

Is the option acceptable to key stakeholders?

Judgement:

☐ Don't know	☒ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified.

Panel discussion:

Depends on the health system and prescribing costs. Clomiphene citrate may be less accessible and needs more monitoring.

- Practitioners may need more skill in monitoring and patients may need to attend for monitoring more often.

- **FEASIBILITY**

Is the option feasible to implement?

Judgement:

☐ Don't know	☒ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified.

Panel discussion:

Very dependent on the health care system in which this operates.

COMPARISONS (option versus other option)
5. Clomiphene citrate vs letrozole
EVIDENCE-BASED RECOMMENDATION(S)

EBR: Letrozole should be used rather than clomiphene citrate in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation, clinical pregnancy, and live birth rates.

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☒ Strong recommendation for the option

PRACTICE POINT

There is evidence of no harm in terms of foetal abnormality rates in women exposed to clomiphene citrate compared with letrozole.

GRADE CONSIDERATIONS

Justifications:

Evidence is high for live birth, moderate for pregnancy and low for multiple pregnancy. There are wide confidence limits for multiple pregnancy rates but strong evidence for the other parameters.

Subgroup considerations:

Numbers of patients in documented therapy naïve and previous medication patients are too low to make a recommendation on subgroup analysis for live birth rates. The majority of patients contributing to the overall result did not have any prior medication reported. This was also true for clinical pregnancy rates.

With regard to ovulation rates per cycle, only one study reported prior clomiphene-resistance and the majority did not report any prior medication use. The same was true for ovulation rate per cycle.

Implementation considerations:

Letrozole is used similarly to clomiphene citrate and needs the same monitoring regimen.

It should not prove any more difficult to use this agent compared with clomiphene

Monitoring and evaluation considerations:

The same monitoring regimen as for clomiphene citrate is required

Research priorities:

What is the impact of additional metformin?

GRADE framework

GRADE DECIDE Interactive Evidence to Decision Framework

- **DESIRABLE EFFECTS**

How substantial are the desirable anticipated effects?

Judgement:

☒ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Evidence for livebirth rates being superior is high while clinical pregnancy rates are moderate.

There is no evidence for better or worse multiple pregnancy rates.

Last guideline:

Patients are significantly more likely both to ovulate and to have a live birth after use of letrozole compared to clomiphene, the previous first line agent. The likelihood of live birth is increased 40-60% with letrozole compared to clomiphene. Similarly, the failure to ovulate at all (letrozole resistance) is reduced 2-3 fold with letrozole versus clomiphene citrate (absolute chance ~10%).

- **UNDESIRABLE EFFECTS**

How substantial are the undesirable anticipated effects?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

No evidence is presented in either direction.

Last guideline:

Multiple pregnancy rate appears lower than clomiphene. Hot flushes, generally the least desired side effect of any anti-oestrogen, is less common with letrozole than clomiphene, but still present. Fatigue and dizziness are more common. While current data do not support the association of letrozole use with increased anomaly rates, anomalies still occur without a specific pattern to suggest a potential interaction or mechanism.

CERTAINTY OF THE EVIDENCE

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☐ Very low	☐ Low	☒ Moderate	☐ High

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

A good number of high-quality studies and relatively tight confidence limits contribute to this conclusion.

Last guideline:

The body of evidence included here is of very low to moderate certainty with serious to very serious risk of bias, serious inconsistency, imprecision, indirectness, and publication bias.

- **VALUES**

  Is there important uncertainty about, or variability in, how much people value the main outcomes?

  Judgement:

☐ Important uncertainty or variability	☒ Possibly important uncertainty or variability	☐ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Research evidence:

No research evidence was identified

Panel discussion:

Higher chance of pregnancy would lead to better valuation although no data available

Last guideline*:*

Generally, a live birth, as opposed to restoration of ovulation or a clinical pregnancy remains the desired infertility treatment outcome of both patient and clinician. Further research should focus on healthy perinatal outcomes of infant and mother, and eventual long-term development of the infant.

- **BALANCE OF EFFECTS**

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:

No side-effects are presented but expected to be low

Last guideline:

The balance of benefits in terms of improved live births with letrozole and less hot flushes currently outweighs the adverse effects of relatively increased fatigue and dizziness, multiple pregnancy, and concerns about congenital anomalies (given limited evidence for these effects)

- **COSTS**

How large are the resource requirements (costs)?

Judgement:

☐ Don't know	☐ Varies	☐ Large costs	☐ Moderate costs	☒ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:

Cost effectiveness systematic review is done across PCOS. Please reference the overarching section on cost

Panel discussion:

Expected similar costs of the drug and monitoring

Last guideline

Proscription of prescribing by national agencies may limit use of letrozole is specific countries or regions. These may change with time. For instance, letrozole, previously proscribed in India, may now be used for ovulation induction. Because letrozole is a newer drug than clomiphene citrate and may enjoy ongoing patent protection in specific countries or regions, the associated increased expense of the drug may favour cheaper generic forms of clomiphene. However as patent exclusivity expires, the price of letrozole and clomiphene citrate may be comparable.

- **CERTAINTY OF COST EVIDENCE**

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

Cost effectiveness systematic review is done across PCOS. Please reference the overarching section on cost.

Panel discussion:

Likely to be more cost-effective due to higher pregnancy and live birth rates.

- **COST-EFFECTIVENESS**

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

Cost effectiveness systematic review is done across PCOS. Please reference the overarching section on cost.

Panel discussion:

Likely to be more cost-effective due to higher pregnancy and live birth rates.

- **EQUITY**

What would be the impact on health equity?

Judgement:

☐ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☒ Probably no impact	☐ Probably increased	☐ Increased

Research evidence:

No research evidence was identified

Panel discussion:

Last guideline:

There are currently no known disadvantaged group or different baseline conditions that may selectively favour use of any ovulation induction agent. Varies by availability in different countries. Willingness of HPs to prescribe.

- **ACCEPTABILITY**

Is the option acceptable to key stakeholders?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Health delivery personnel will favour the better clinical outcomes as will patients.

Better results for the same clinical intervention as clomiphene citrate incorporating similar monitoring will be acceptable for those who accept oral ovulation induction

Last guideline

Perception of the risks of letrozole, including multiple pregnancy or congenital anomalies, may lead to the choice of other treatment modalities with greater control over these outcomes.

- **FEASIBILITY**

Is the option feasible to implement?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Different attitudes by health authorities and staff to letrozole may delay implementation although there is no evidence of increased congenital abnormalities with this drug

Last guideline:

- The major barriers to implementation of the recommendation are regulatory agencies forbidding the off-label use of letrozole for ovulation induction and the perceptions of patients and clinicians to stick with established treatment options.

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PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by the Evidence Team: Aya Mousa, Jillian Tay
Other team members: Loyal Pattuwage

GDG 5

Question 5.5.

In women with PCOS, are gonadotrophins effective for improving fertility outcomes?

1. STUDY SELECTION

Table 1. PICO Criteria for Inclusion	
Question	**In women with PCOS, are gonadotrophins effective for improving fertility outcomes?**
Clinical leads (key contacts)	**Adam Balen**
Allocation ranking	**Level 2- updated systematic review (with update of integrity check for all studies)**

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(language, year)*
Inclusion	Women of any age, ethnicity and weight with PCOS diagnosed by Rotterdam, NIH or AIS and 1) at least one patent tube 2) normal sperm AND 3) have never been treated or been exposed to treatment for infertility (therapy naïve) OR 4) have been treated or exposed to treatment OR 5) have been treated or exposed to clomiphene citrate and ovulate but don't conceive (clomid failure) OR 6) have been treated or exposed to clomid and don't ovulate (clomid resistant). Also specifically identifying the 4 phenotypes where possible.	Any type, dose and frequency of gonadotrophins	Placebo, no intervention, other infertility treatment interventions (ie. aromatase inhibitor, metformin, clomiphene citrate, ovarian surgery) including gonadotrophins in combination with other infertility treatment intervention(s).	Live birth rate, pregnancy rate (biochemical or clinical ultrasound), ovulation, single and multiple pregnancies, miscarriage rate, other adverse events, quality of life, cost effectiveness.	Evidence based guidelines, systematic reviews, health technology assessments, randomised controlled trials (RCTs).	None
Exclusion	Women without diagnosis of PCOS.	Placebo, no intervention or any intervention other than an gonadotrophins.	Any intervention other than those listed in the inclusion criteria.	None	Nonevidence based guidelines, non-systematic reviews, any study lower than a RCT.	None

2. SEARCH STRATEGY

The search and screening for all GDG 5 questions were done together. Details can be found in the GDG 5 Methodology Appendix, including for:

- Databases
- Search Dates
- Search String(s)
- PRISMA flowchart
- Full list of included studies
- Full list of excluded studies with reasons for exclusion

Evidence processing: The literature search and screening were performed together in one Endnote library and Covidence project for all non-IVF, IVF and IVM fertility treatments in PCOS. Studies were selected by one reviewer/s in consultation with the evidence team/ key contact(s) using study selection and appraisal criteria (PICOs) established a priori. The articles were screened by title and abstract by one reviewer. When a decision could not be made based on title and abstract alone, full text was retrieved. Study appraisal was conducted by two reviewers independently with discussion to resolve any discrepancy. In total, 102 unique studies met inclusion criteria across all non-IVF, IVF and IVF questions, of which 57 were included in the guideline update following the integrity check (refer to methodology appendix for details).

Of these eligible 102 studies, 12 studies met the inclusion criteria for this particular question (Q.5.5) on gonadotrophins, as detailed below.

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3. STUDY CHARACTERISTICS TABLE FOR INCLUDED STUDIES

Author, year, country	Population/ PCOS criteria/ Setting/ CC sensitivity	Study Design	Intervention N	Intervention description	Comparison N	Comparison description	Follow Up	Outcomes	Pooled in MA?	RoB
Baryam 2004 The Netherlands	Chronic anovulation (World Health Organization type II) and polycystic ovaries, diagnosed by transvaginal Ultrasonography, 29 Dutch hospitals; **CCR**	RCT	**Laparoscopic surgery**: 83 Age: 28.5±3.7 BMI: 27.9±6.3	**Laparoscopic electrocautery of the ovaries.** If ovulated, no further treatment. Each ovary was randomly punctured 5-10 times, depending on its size using 15mm long 0.9mm diameter needle. If anovulation persisted, 50mg clomiphene citrate (CC) increased to max 150mg.	**FSH**: 85 Age: 28.7±4.1 BMI: 27.3±8.8	10 mg medroxy-progesterone for 10 days, followed by daily 75 IU **rFSH**. If the diameter of the follicles remained < 10 mm, the dose was increased by half an ampoule (37.5 IU) on each of cycle days 16 and 23.	12 months	Pregnancy, miscarriages, multiple pregnancies, premature deliveries Unclear on how pregnancy was tested: " The primary end point was ongoing pregnancy within 12 months, defined as a viable pregnancy of at least 12 weeks."	Yes	High – drop outs in controls and non-blinded
Begum 2013, Bangladesh	PCOS patients diagnosed with Rotterdam criteria; Outpatient department of a teaching hospital; **CCR**	RCT (3 groups)	**MET + CC**: 55 Age: 26.96±4.05 BMI: 27.71±3.61 **MET + rFSH**: 55 Age: 26.84±5.13 BMI: 28.36±4.54	**MET + CC** 500 mg metformin 3x daily (1500 mg) for 4 weeks then the same dose was continued for another 6 months along with scheduled CC 150 mg daily for 5 days (D3–D7 of the cycle). **MET + rFSH** 500 mg metformin 3x daily (1500 mg) for 4 weeks, then same dose was continued for 6 months with 75 IU rFSH every alternate day from D3 of the cycle (then daily if needed after first monitoring on D12) till maturity of follicles or maximum 15 doses of rFSH.	**rFSH**: 55 Age: 27.15±4.20 BMI: 28.98±3.19	75 IU **rFSH** every alternate day starting from D3 of the cycle (then daily if necessary after first monitoring on D12) till maturity of follicles or maximum 15 doses of rFSH.	6 cycles	Primary: Clinical pregnancy, live-birth rate Secondary: ovulation, spontaneous abortion, ectopic pregnancy, multiple pregnancies, congenital anomaly and other adverse perinatal or obstetric complications. Unclear on how pregnancy was tested: "Treatment was terminated:…(iv) after positive pregnancy test."	No	High Unblinded Missing details on randomisation, dropouts, blinding etc.
De Leo 1999, Italy	Women with **CCR/CCF** and PCOS (chronic oligomenorrhoea or amenorrhoea and	RCT	10 Age: 28.0 ± 4.0	Started with FSH (75 IU then increased to 5 ampoules/day) alone for two cycles and then for a month with metformin, then	10 Age: 29.5±2.9	Metformin (1500 mg) for a month before undergoing ovarian stimulation with combined metformin and FSH for one cycle	2-4 cycles	Primary: number of FSH ampoules, days of treatment, E2 level on the day of hCG, number of follicles > 15mm, number of hyperstimulation, number of cycles with hCG withheld	Yes	High

	hyperandrogenemia); University department		BMI: 27.7±3.1	underwent a third cycle of combined metformin and FSH stimulation	BMI: 26.9±4.8			Secondary: Number of pregnancies (NR if clinical or biochemical)		
Farquhar 2002 New Zealand	PCOS diagnosed based on criteria by Adams et al. (1985)[redacted]; publicly funded and private tertiary level fertility clinics; all patients had infertility and treatment before; **CCR**	RCT (N per group dissimilar due to unblocked randomization)	**Laparoscopic ovarian diathermy**: 29 Age: 29.6±4.7 BMI: 28.3±3.9	**Laparoscopic ovarian diathermy:** A monopolar electrocautery needle of 1 cm in length was used to drill 10 holes in each ovary. The diathermy was done with cutting power at 30 units and was continued for 10 seconds	**Urinary or recombinant FSH** (3 cycles): 21 Age: 29.6±4.2 BMI: 27.8±4.8	**Urinary or rFSH**: 75 IU/day (one ampoule) was given for 2 weeks, adjusted accordingly depending on the serum E2	6 months (for surgery) 3 cycles (FSH)	Ovulation rates, pregnancy outcomes, birth after 20 weeks of gestation Pregnancy detection: serum β-hCG of >50 IU/l and foetal heart activity on ultrasound scan	Yes	High – small and non-blinded
Ganesh 2009, India	Women with PCOS by Rotterdam who had previously failed to conceive or ovulate with CC and undergoing IUI (**CCR and CCF**); tertiary infertility care unit	Single blind RCT	**LET:** 372 analysed Age: 30.3 ± 4.9 BMI: 24.5 ± 3.8	**LET**: letrozole, 5 mg/day orally given for 5 days from cycle days 3 - 7	**CC + FSH:** 669 analysed Age: 30.4 ± 5.2 BMI: 24.8 ± 4.1 **FSH**: 346 analysed Age: 30.8 ± 4.6 BMI: 24.1 ± 3.4	**CC + FSH:** clomiphene citrate, 100 mg/day orally given for 5 days from cycle days 3 - 7 + 75 or 100 IU rFSH during cycle days 3 and 8 **FSH**: rFSH 75IU/100IU from day 2 until the day of hCG administration	NR	**Primary**: ovulation rate, cancellation rate, miscarriage rate and clinical pregnancy rate **Secondary**: OHSS rate and multiple pregnancy rate. Clinical pregnancy: defined as the presence of a gestational sac with cardiac activity as detected by transvaginal ultrasound at 7 weeks of gestation	Yes	Mod*
George 2003 India	Diagnosis of PCOS based on oligomenorrhoea and hyperandrogenism + biochemical abnormalities of a raised LH/FSH ratio or LH or ultrasound features of polycystic ovary; Medical clinical at a medical school; **CCR** patients	RCT	**MET**: 30 Age: 25.1±3 BMI: 25.5 ± 3.7	**MET**: 1500 mg/day in three divided doses for 6 months	**hMG**: 30 Age: 26. ± 2.9 BMI: 24.6 ± 2.6	**hMG**: starting at 75 units 5 days after a spontaneous or induced cycle increased by increments of 75 units every 7±10 days	NR	Pregnancy rate How conception was ascertained is not reported	No	Mod – high drop-out rate, small n, blinding not possible
Ghanem 2012, Egypt	PCOS women aged 18-38; Diagnosis of PCOS based on Rotterdam criteria; The women	RCT	**CC-HP uFSH**: 87	**CC** 100 mg daily doses for 5 days plus intramuscular (IM) injection	**HP uFSH**: 87 Age:	Highly purified (**HP uFSH**) only in the same daily doses and for the	NR	Primary: ovulation rate	Yes	Mod-single blind

Based on clinical registry entry: Egypt	had not undergone a similar treatment protocol before; **CCR**		Age: 24.8±4.7 BMI: 33.3±5.4	of 37.5 IU/day highly purified (HP) urinary FSH (uFSH) from the 3rd to the 13th cycle day. Subsequent increments of uFSH by 37.5 IU/day were made according to response	24.7±4.3 BMI: 33.2±5.7	same duration. Subsequent increments of uFSH by 37.5 IU/day were made according to response	(? 1 cycle)	Secondary: clinical pregnancy rates, number of follicles, endometrial thickness, and gonadotropins consumption. Clinical pregnancy was defined by intrauterine gestational sac observed by an ultrasound scan 2 weeks after a positive pregnancy test in urine or blood		
Homburg 2012, Europe and South America	PCOS by Rotterdam; **Therapy naïve**	Multi-centre RCT	**CC**: Assigned: 143 Received CC= 123 Age: 29.4±4 BMI: 25.7±6.0	Starting dose of **CC** was 50 mg/day (oral) for 5 days from Day 4 of a spontaneous or progestin-induced menstruation, rising by 50 mg/day up to 150 mg in subsequent cycles if ovulation was not achieved	**FSH**=Assigned 159 Received FSH=132 Age:29.8±3.8 BMI: 25.1±5.2	**rFSH** was given s.c. in a low-dose protocol starting with 50 IU on cycle day 4, with weekly increments of 25 IU as necessary to induce a follicular response	NR	**Primary**: clinical pregnancy rate (as a pregnancy diagnosed by ultrasonographic visualization of one or more gestational sacs with at least one foetus at 6–7 weeks gestation)	Yes	Mod
Lopez 2004, Spain	PCOS by Rotterdam; single centre; **Therapy naïve;**	RCT Cross-over (if un-successful)	**CC**= 38 (104 cycles) Age: 29 (23-38) Median (range) BMI: 22.3±1.9	**CC** daily dose of 50 mg for 5 days, starting on day 5 following spontaneous or induced uterine bleeding, increased by 50mg from next cycle if ovulation not achieved until 150mg max.	**FSH**= 38 (91 cycles) Age: 30 (22-39) Median (range) BMI: 21.9±1.9	**rFSH** commencing at 75 IU daily on day 3 following spontaneous or induced menses with dose increments of 37.5 IU daily every 7 days if there was no evidence of ovarian response	Up to 3-6 cycles	**Primary**: cumulative pregnancy (before crossover) **Secondary**: cycle cancellation rate, ovulation rate per cycle, cumulative ovulation rate, clinical pregnancy rate per cycle, incidence of OHSS, cumulative live birth rate, and multiple birth rate Pregnancy was initially diagnosed by increasing serum concentrations of β-HCG after missed menses	Yes	High Blindiing NR, underpowered
Tasdemir 2003 Turkey	PCOS diagnosed based on oligomenorrhea (<6 periods in a year), hyperandrogenism (hirsutism, acne, increased free and total testosterone, androstenedione, DHEASO4, and FAI), and FSH/LH level >2; hospital IVF centre; **CCR**	RCT	**MET+FSH**: 16 Age: 31.8±2.7 BMI: 28.5±3.5	**MET+FSH** 850mg metformin twice daily for 8 weeks in advance followed by rFSH 75IU given first 7 days (1 ampoule/day) adjusted based on ultrasonography findings of follicle development	**FSH**: 16 Age: 30.6±3.2 BMI: 29.0±2.1	**FSH** rFSH 75IU given first 7 days (1 ampoule/day) adjusted based on ultrasonography findings of follicle development	NR ≥8 weeks	Total gonadotropin dosage, duration of gonadotropin therapy, estradiol level on HCG-day, number of follicles with ≥16 mm diameter, number of cases with hyperstimulation development, number of cancelled cycles, endometrial thickness on HCG-day, pregnancy outcome (NR if clinical or biochemical), multiple pregnancy rate.	Yes	High-small n and unblinded
Yadav 2017 India	Chronic anovulation and polycystic ovaries diagnosed by transvaginal ultrasonography-Any standard criteria not reported. Hospital-based setting; **CCR**	RCT	**rFSH**: 44 Age: 26.23±2.9 BMI: 24.94±2.8	**rFSH** subcutaneous injection of 37.5/75 IU/daily started on cycle day 3-If the diameter of the follicle remained <10 mm, dose was increased by half an ampoule (37.5 IU)	**LOD**: 45 Age: 26.11±2.7 BMI: 25.0±2.35	**LOD:** An insulated monopolar needle was introduced at 90° angle to the ovarian cortex and 4-5 puncture sites were created. Those who failed to ovulate on LOD	12 months	Primary: ongoing pregnancy within 12 months (defined: a viable pregnancy of at least 12 weeks) Secondary: ovulation, miscarriage, ectopic pregnancy, multiple pregnancies, and live birth	Yes	High – lacking critical info

				on days 16 and 23. If no follicle development was seen on day 30, the cycle was terminated because of poor response.		spontaneously at 8 wk, were then added with CC for 1 cycle followed by gonadotrophin.		Pregnancy was ascertained based on positive urine pregnancy test		
Yarali 2002 Turkey	Peripubertal onset of oligo-amenorrhoea, elevated serum testosterone levels (>80 ng/dl; conversion factor=0.03467; >2.4 nmol/l) and U/S evidence of polycystic ovaries (PCO); setting NR; **CCR**	RCT Double blind	**MET + FSH**: 16 Age: 29.7±5.6 BMI: 28.6±4.0	**Metformin**, 850 mg, 2 times daily for 6 weeks + FSH (later) starting with 75 IU for 14 days and increased as required based on ovarian response	**Placebo + FSH**: 16 Age: 28.4±5.1 BMI:29.6±4.8	**Placebo** for 6 weeks + FSH (later) starting with 75 IU for 14 days and increased as required based on ovarian response	NR (≥ 6 weeks)	Duration of stimulation, total dose, number of vials used, follicle development, ovulation, pregnancy per cycle "A serum pregnancy test was performed 13-15 days after administration of HCG."	Yes	Mod – small and lacking info on blinding

CC, clomiphene citrate; CCR, clomiphene citrate resistant (to ovulate); CCF, clomiphene citrate failure (to become pregnant); LET, letrozole; MET, metformin; NR; not reported; OHSS, ovarian hyperstimulation syndrome; IUI, intrauterine insemination; hCG, human chorionic gonadotrophin; LH, luteinizing hormone; FSH, follicle stimulating hormone; MA, meta-analysis; RoB, risk of bias. All age data is in years and BMI is in kg/m^2. *Risk of bias assessment derived from reliable systematic review (e.g. Cochrane or previous review from the guideline evidence team). ⧖Ref: Adams J, et al. *Lancet* 1985;1375–9.

4. FINDINGS

Comparisons Included:

- **Comparison 1.** FSH vs CC
- **Comparison 2.** FSH + CC vs FSH
- **Comparison 3.** FSH + CC vs LET
- **Comparison 4.** FSH vs LOD
- **Comparison 5.** FSH + Metformin vs FSH +/- Placebo
- **Comparison 6.** FSH vs Clomiphene Citrate + Metformin
- **Comparison 7.** hMG vs Metformin

COMPARISON 1: Gonadotropins (FSH) versus Clomiphene Citrate

▪ EVIDENCE SUMMARY:

Two studies compared gonadotropins (FSH) versus clomiphene citrate (Homburg et al. 2012 and Lopez et al. 2004), both in therapy naïve women with PCOS. Relevant outcomes included live birth rate, clinical pregnancy rate, ovulation rate, multiple pregnancy rate and miscarriage rate per patient, as well as ovulation rate per cycle. The studies were judged as moderate (Homburg et al. 2014) or high (Lopez et al. 2004) risk of bias.

▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

There were no differences ovulation rate, multiple pregnancy rate or miscarriage rate per patient; however, FSH was superior to clomiphene citrate for live birth rate, clinical pregnancy rate per patient and ovulation rate per cycle. Evidence for these outcomes was moderate, with the exception of ovulation rate per patient and per cycle which was of very low quality due to being derived from a single small study with a high risk of bias.

Outcome or Subgroup	Studies	n	Effect Estimate; OR [95% CI], M-H, random	P	Favours	Certainty
Live birth rate – per patient	2	331	1.74 [1.10, 2.74]	0.02	**FSH** (live birth rate is higher with FSH)	⊕⊕⊕◯ MODERATE
Clinical pregnancy rate – per patient†	2	331	1.84 [1.18, 2.87]	0.007	**FSH** (clinical pregnancy is higher with FSH)	⊕⊕⊕◯ MODERATE
Ovulation rate – per patient	1	76	3.11 [0.76, 12.79]	0.1	None	⊕◯◯◯ VERY LOW
Ovulation rate – per cycle	1	195	2.49 [1.36, 4.55]	0.003	**FSH** (ovulation per cycle is higher with FSH)	⊕◯◯◯ VERY LOW
Multiple pregnancy rate – per pregnancy	2	155	2.41 [0.36, 16.10]	0.4	None	⊕⊕◯◯ LOW
Miscarriage rate- per pregnancy	2	155	0.97 [0.36, 2.60]	0.9	None	⊕⊕⊕◯ MODERATE

† clinical pregnancy rate is confirmed by ultrasound detection of gestational sac/ fetal heart activity.

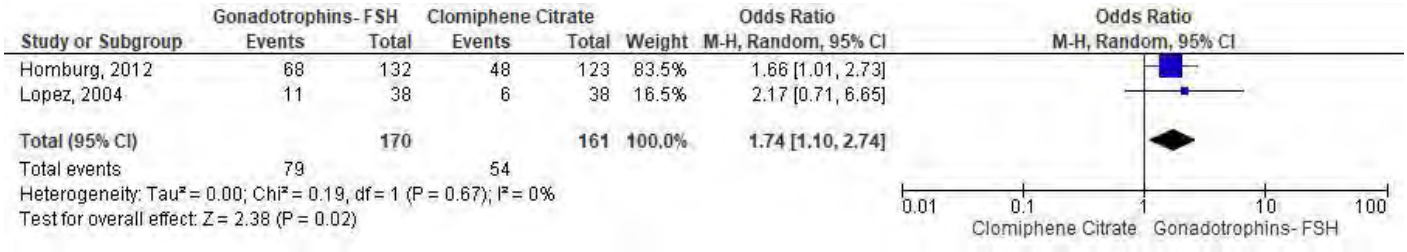
OUTCOME 1.1. Live birth rate– per patient

1.1.1. Individual Study Data Tables

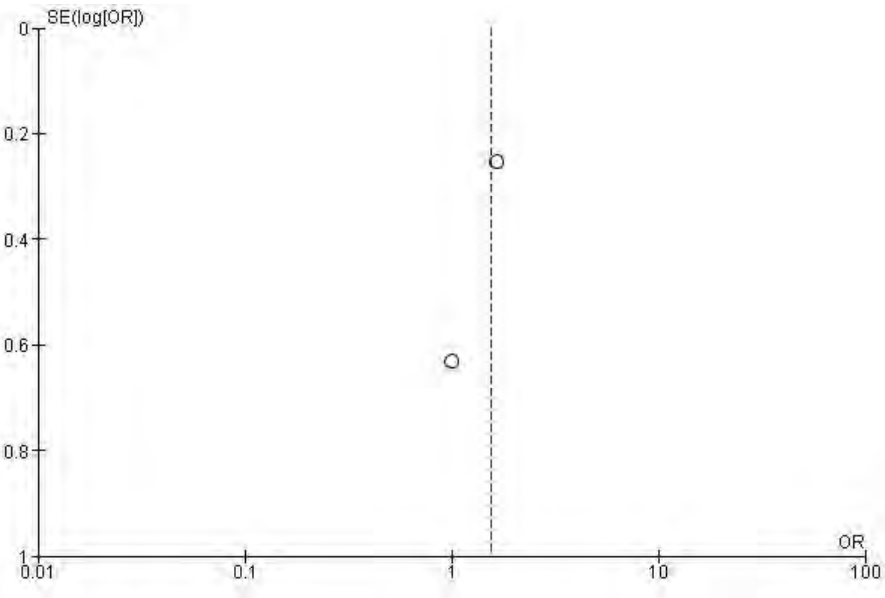
OUTCOME: Live birth rate per patient						OUTCOME TYPE: Dichotomous			
COMPARISON: FSH vs Clomiphene Citrate									
Author, year	Past OI Med Use	Unit of outcome (e.g. g, mg)	Method of measurement	N events in intervention/ exposure group (FSH)	N total in intervention/ exposure group (FSH)	N events in control / comparison group (CC)	N total in control/ comparison group (CC)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Homburg 2012 (MRB)	TN	Count	Investigator	68	132	48	123	Crude	NA
Lopez 2004 (HRB)	TN	Count	Investigator	11	38	6	38	Crude	NA

TN, therapy naïve; **OI**, ovulation induction

1.1.2. Forest Plot of all included RCTs comparing FSH versus Clomiphene Citrate for live birth rate – per patient



1.1.3. Funnel plot for assessment of publication bias



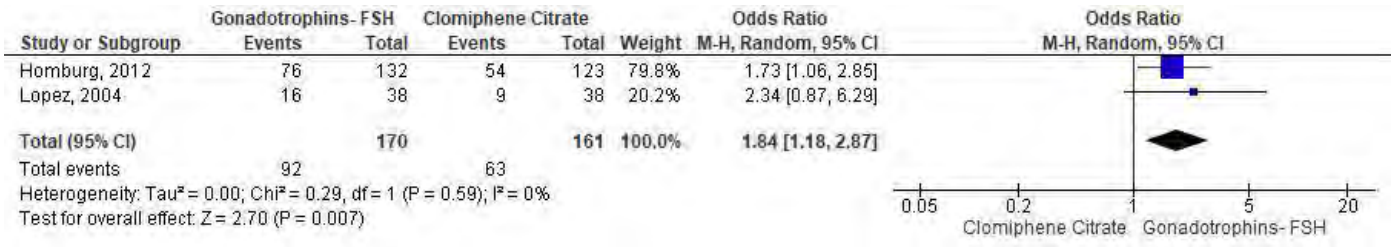
OUTCOME 1.2. Clinical pregnancy rate– per patient

1.2.1. Individual Study Data Tables

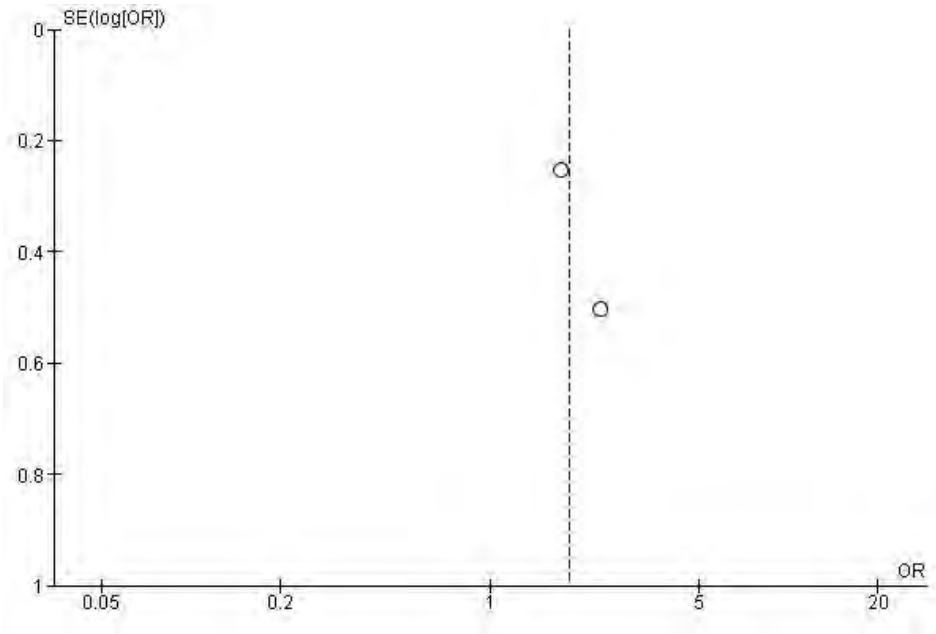
OUTCOME: Clinical pregnancy rate per patient						OUTCOME TYPE: Dichotomous			
COMPARISON: FSH vs Clomiphene Citrate									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (FSH)**	**N total in intervention/ exposure group (FSH)**	**N events in control / comparison group (CC)**	**N total in control/ comparison group (CC)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Homburg 2012 (MRB)	TN	Count	Investigator	76	132	54	123	Crude	NA
Lopez 2004 (HRB)	TN	Count	Investigator	16	38	9	38	Crude	NA

TN, therapy naïve; **OI**, ovulation induction

1.2.2. Forest Plot of all included RCTs comparing FSH versus Clomiphene Citrate for clinical pregnancy rate – per patient



1.2.3. Funnel plot for assessment of publication bias



OUTCOME 1.3. Ovulation rate– per patient

1.3.1. Individual Study Data Tables

OUTCOME: Ovulation rate per patient						OUTCOME TYPE: Dichotomous			
COMPARISON: FSH vs Clomiphene Citrate									
Author, year	Past OI Med Use	Unit of outcome (e.g. g, mg)	Method of measurement	N events in intervention/ exposure group (FSH)	N total in intervention/ exposure group (FSH)	N events in control / comparison group (CC)	N total in control/ comparison group (CC)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Lopez 2004 (HRB)	TN	Count	Investigator	35	38	30	38	Crude	NA

TN, therapy naïve; **OI**, ovulation induction

OUTCOME 1.4. Ovulation rate– per cycle

1.4.1. Individual Study Data Tables

OUTCOME: Ovulation rate per cycle						OUTCOME TYPE: Dichotomous			
COMPARISON: FSH vs Clomiphene Citrate									
Author, year	Past OI Med Use	Unit of outcome (e.g. g, mg)	Method of measurement	N events in intervention/ exposure group (FSH)	N total in intervention/ exposure group (FSH)	N events in control / comparison group (CC)	N total in control/ comparison group (CC)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Lopez 2004 (HRB)	TN	Count	Investigator	67	91	55	104	Crude	NA

TN, therapy naïve; **OI**, ovulation induction

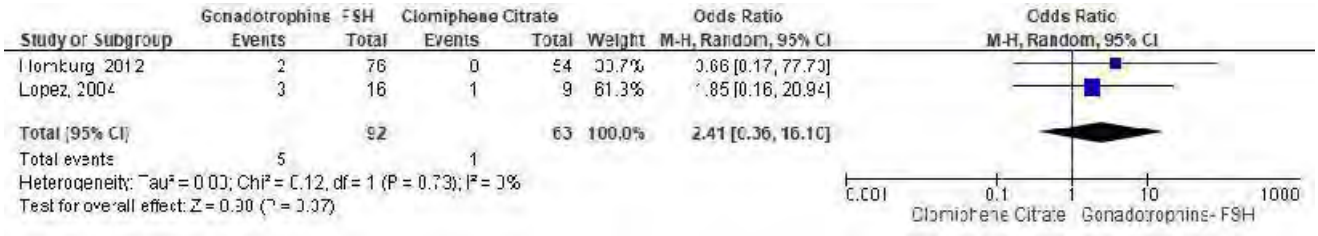
OUTCOME 1.5. Multiple pregnancy rate – per pregnancy

1.5.1. Individual Study Data Tables

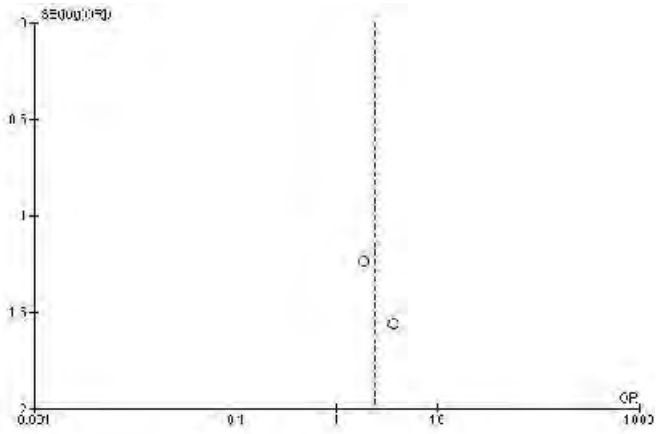
OUTCOME: Multiple pregnancy rate per pregnancy						OUTCOME TYPE: Dichotomous			
COMPARISON: FSH vs Clomiphene Citrate									
Author, year	Past OI Med Use	Unit of outcome (e.g. g, mg)	Method of measurement	N events in intervention/ exposure group (CC)	N total in intervention/ exposure group (CC)	N events in control / comparison group (FSH)	N total in control/ comparison group (FSH)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Homburg 2012 (MRB)	TN	Count	Investigator	2	76	0	54	Crude	NA
Lopez 2004 (HRB)	TN	Count	Investigator	3	16	1	9	Crude	NA

TN, therapy naïve; **OI**, ovulation induction

1.5.2. Forest Plot of all included RCTs comparing Clomiphene Citrate versus FSH for multiple pregnancy rate – per pregnancy



1.5.3. Funnel plot for assessment of publication bias



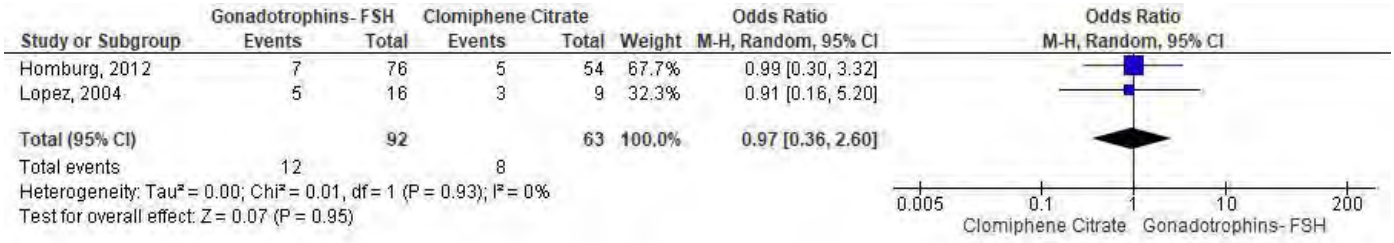
OUTCOME 1.6. Miscarriage rate – per pregnancy

1.6.1. Individual Study Data Tables

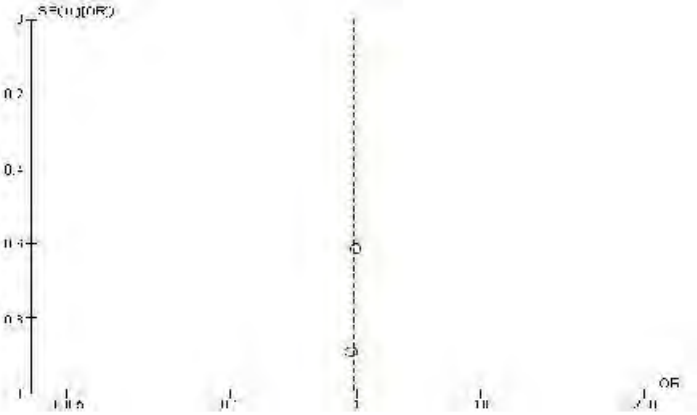
OUTCOME: Miscarriage rate per pregnancy								**OUTCOME TYPE:** Dichotomous	
COMPARISON: Clomiphene Citrate vs FSH									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (CC)**	**N total in intervention/ exposure group (CC)**	**N events in control / comparison group (FSH)**	**N total in control/ comparison group (FSH)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Homburg 2012 (MRB)	TN	Count	Investigator	7	76	5	54	Crude	NA
Lopez 2004 (HRB)	TN	Count	Investigator	5	16	3	9	Crude	NA

TN, therapy naïve; **OI**, ovulation induction

1.6.2. Forest Plot of all included RCTs comparing Clomiphene Citrate versus FSH for miscarriage rate – per pregnancy



1.6.3. Funnel plot for assessment of publication bias



COMPARISON 2: Gonadotropins (FSH) + clomiphene citrate versus gonadotropins (FSH)

▪ EVIDENCE SUMMARY:

Two studies compared rFSH alone versus clomiphene citrate + rFSH, one in India (Ganesh et al. 2009) and one in Egypt (Ghanem et al. 2012), with outcomes assessed including live birth rate, clinical pregnancy rate and ovulation rate per patient, and miscarriage rate per pregnancy. The study in India involved 1387 women with PCOS who had previously failed to conceive or ovulate with CC and were undergoing IUI. Three groups were included: Group A received letrozole, Group B received clomiphene citrate with two doses rFSH from cycle days 3-8 and Group C received continuous rFSH from day 2 onwards until hCG injection. The second study by Ghanem et al. (2012) included 174 women with clomiphene-citrate resistant PCOS, who received highly purified urinary FSH from days 3 to 13, with or without 100 mg of clomiphene citrate. Both studies were judged as having a moderate risk of bias due to their single-blind design.

▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

There were no differences in any outcomes between FSH + clomiphene citrate versus urinary or recombinant FSH alone. Certainty in the evidence for these comparisons ranges from very low to moderate as shown below; downgraded for risk of bias (both studies moderate risk), as well as varied effect estimates (including differing directions of effect), and high statistical heterogeneity.

Outcome or Subgroup	Studies	n	Effect Estimate; OR [95% CI], M-H, random	P	Favours	Certainty
Live birth rate- per patient	1	174	1.21 [0.60, 2.44]	0.6	None	⊕○○○ LOW
Clinical pregnancy rate- per patient†	2	1189	0.83 [0.61, 1.14]	0.3	None	⊕⊕○○ LOW
Ovulation rate - per patient	2	1189	0.79 [0.03, 21.36]	0.9	None	⊕⊕○○ VERY LOW
Miscarriage rate- per pregnancy	1	158	1.18 [0.48, 2.86]	0.7	None	⊕⊕⊕○ MODERATE

† clinical pregnancy rate is confirmed by ultrasound detection of gestational sac/ fetal heart activity

OUTCOME 2.1: Live birth rate- per patient

2.1.1. Individual Study Data Tables

OUTCOME: Live birth rate- per patient						**OUTCOME TYPE:** Dichotomous			
COMPARISON: Clomiphene Citrate + FSH versus FSH									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in intervention / exposure group (CC +FSH)**	**N total in intervention / exposure group (CC +FSH)**	**N events in control / comparison group (FSH)**	**N total in control/ comparison group (FSH)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
OUTCOME: Live birth rate – per patient					**OUTCOME TYPE:** Dichotomous				
Ghanem 2013 (MRB)	CCR	Count	Investigator	22	87	19	87	Crude	NA

CCR/CCF, clomiphene citrate-resistant or failure

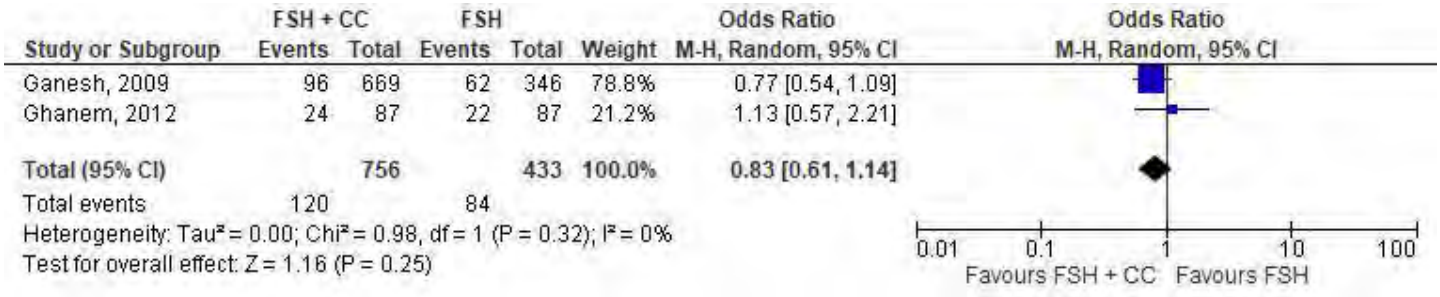
OUTCOME 2.2. Clinical pregnancy rate – per patient

2.2.1. Individual Study Data Tables

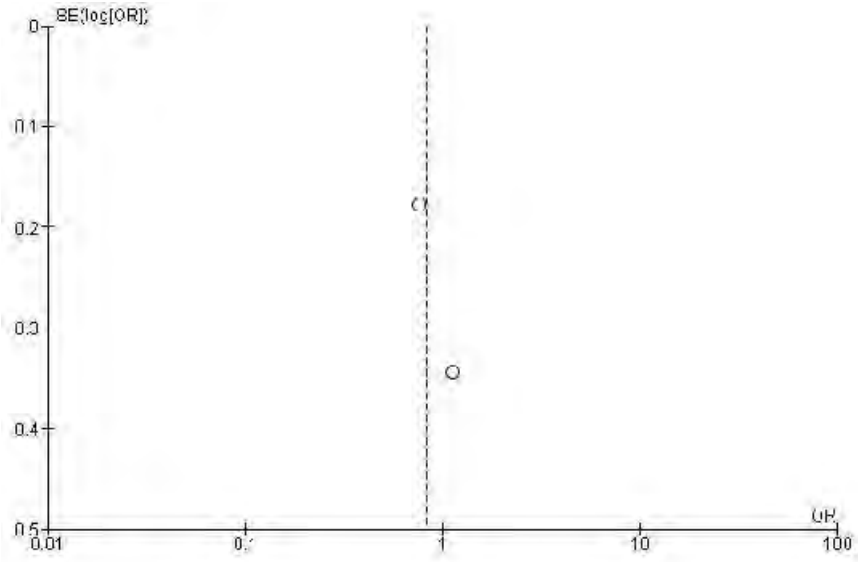
OUTCOME: Clinical pregnancy rate per patient						OUTCOME TYPE: Dichotomous			
COMPARISON: FSH + Clomiphene Citrate vs FSH									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (FSH + CC)**	**N total in intervention/ exposure group (FSH + CC)**	**N events in control / comparison group (FSH)**	**N total in control/ comparison group (FSH)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Ganesh 2009 (MRB)	CCR/ CCF	Count	Investigator	96	669	62	346	Crude	NA
Ghanem 2013 (MRB)	CCR	Count	Investigator	24	87	22	87	Crude	NA

CCR/CCF, clomiphene citrate-resistant or failure

2.2.2. Forest Plot of all included RCTs comparing Clomiphene Citrate + FSH versus FSH for clinical pregnancy rate – per patient



2.2.3. Funnel plot for assessment of publication bias



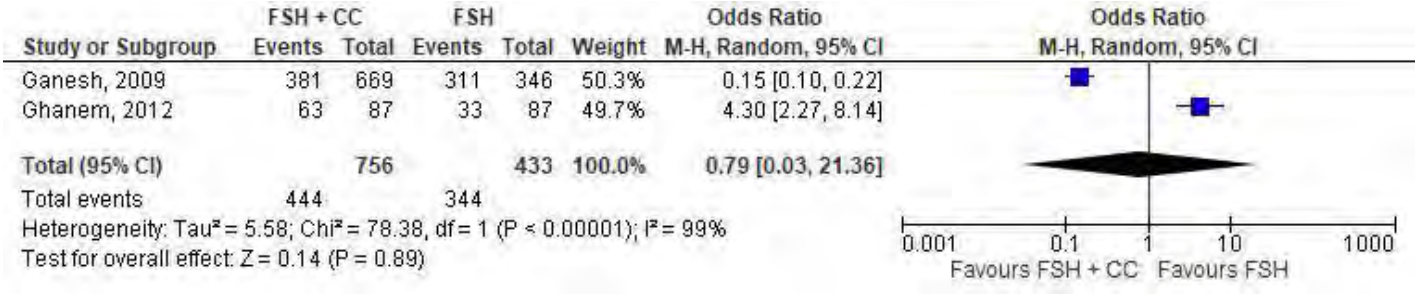
OUTCOME 2.3. Ovulation rate – per patient

2.3.1. Individual Study Data Tables

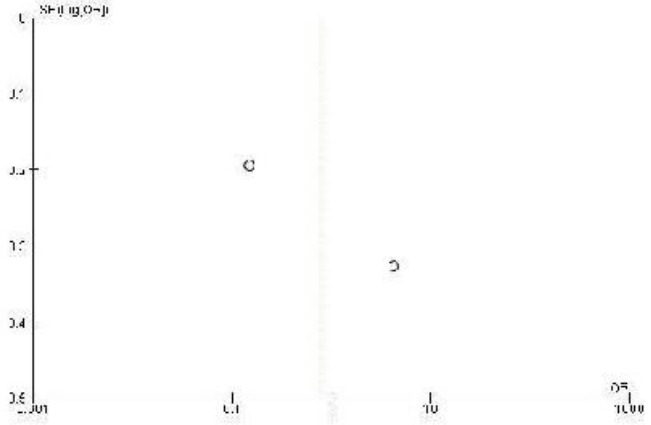
OUTCOME: Ovulation rate per patient						**OUTCOME TYPE:** Dichotomous			
COMPARISON: FSH + Clomiphene Citrate vs FSH									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (FSH+ CC)**	**N total in intervention/ exposure group (FSH + CC)**	**N events in control / comparison group (FSH)**	**N total in control/ comparison group (FSH)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Ganesh 2009 (MRB)	CCR/ CCF	Count	Investigator	381	669	311	346	Crude	NA
Ghanem 2013 (MRB)	CCR	Count	Investigator	63	87	33	87	Crude	NA

CCR/CCF, clomiphene citrate-resistant or failure

2.3.2. Forest Plot of all included RCTs comparing Clomiphene Citrate + FSH versus FSH for ovulation rate – per patient



2.3.3. Funnel plot for assessment of publication bias



OUTCOME 2.4. Miscarriage rate – per pregnancy

2.4.1. Individual Study Data Tables

OUTCOME: Miscarriage rate- per pregnancy						**OUTCOME TYPE:** Dichotomous			
COMPARISON: Clomiphene Citrate + FSH versus FSH									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in intervention / exposure group (FSH + CC)**	**N total in intervention / exposure group (FSH + CC)**	**N events in control / comparison group (FSH)**	**N total in control/ comparison group (FSH)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Ganesh 2009 (MRB)	CCR/ CCF	Count	Investigator	16	96	9	62	Crude	NA

CCR/CCF, clomiphene citrate-resistant or failure

COMPARISON 3: Gonadotrophins (FSH) + Clomiphene Citrate versus Letrozole

▪ EVIDENCE SUMMARY:

The same study by Ganesh et al. (2009) compared gonadotrophins (rFSH) + clomiphene citrate versus letrozole. Outcomes assessed included clinical pregnancy, ovulation rate, and miscarriage rate per patient. The study was judged as having a moderate risk of bias due to the single-blind design.

▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

Combined FSH and clomiphene citrate were less effective than letrozole in achieving clinical pregnancy or ovulation per patient in this study, with odds ratios of 0.55 and 0.35, respectively. There were no differences between FSH + clomiphene citrate compared with letrozole for miscarriage rates per patient. Certainty in these results is moderate given the narrow confidence intervals and large sample size, downgraded once due to risk of bias given its single-blind design.

Outcome or Subgroup	Studies	n	Effect Estimate; OR [95% CI], M-H, random	P	Favours	Certainty
Clinical pregnancy rate- per patient†	1	1041	0.55 [0.40, 0.76]	0.0003	**LET** (clinical pregnancy is lower with CC+ FSH)	⊕⊕⊕◯ MODERATE
Ovulation rate - per patient	1	1041	0.35 [0.26, 0.46]	<0.00001	**LET** (ovulation rate is lower with CC + FSH)	⊕⊕⊕◯ MODERATE
Miscarriage rate- per pregnancy	1	183	1.25 [0.55, 2.82]	0.6	None	⊕⊕⊕◯ MODERATE

† clinical pregnancy rate is confirmed by ultrasound detection of gestational sac/ fetal heart activity

OUTCOME 3.1 – 3.3: Clinical pregnancy rate-per patient; ovulation rate- per patient, miscarriage rate-per patient

3.1.1 - 3.3.1. Individual Study Data Tables

OUTCOME: LISTED BELOW						**OUTCOME TYPE:** Dichotomous			
COMPARISON: Clomiphene Citrate + FSH versus Letrozole									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in intervention / exposure group (FSH + CC)**	**N total in intervention / exposure group (FSH + CC)**	**N events in control / comparison group (LET)**	**N total in control/ comparison group (LET)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
OUTCOME: Clinical pregnancy rate – per patient						**OUTCOME TYPE:** Dichotomous			
Ganesh 2009 (MRB)	CCR/ CCF	Count	Investigator	96	669	87	372	Crude	NA
OUTCOME: Ovulation rate – per patient						**OUTCOME TYPE:** Dichotomous			
Ganesh 2009 (MRB)	CCR/ CCF	Count	Investigator	381	669	295	372	Crude	NA
OUTCOME: Miscarriage rate – per pregnancy						**OUTCOME TYPE:** Dichotomous			
Ganesh 2009 (MRB)	CCR/ CCF	Count	Investigator	16	96	12	87	Crude	NA

CCR/CCF, clomiphene citrate-resistant or failure

COMPARISON 4: FSH vs LOD

- **EVIDENCE SUMMARY:**

Three studies (Baryam et al. 2004; Farquhar et al. 2002; Yadav et al. 2017) compared FSH with laparoscopic ovarian drilling (LOD), conducted in the Netherlands, New Zealand and India. All three studies were in women with clomiphene-citrate resistant PCOS and all were judged as having a high risk of bias due to lack of blinding (or insufficient information to ascertain blinding), as well as small sample sizes and high dropout rates.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

FSH was superior to LOD for live birth rates; however, FSH also resulted in a much higher rate of multiple pregnancies, with an OR of 5.10. While certainty in the evidence for live birth rates per patient was moderate (downgraded once due to risk of bias), certainty in the evidence for all other outcomes was low or very low due to risk of bias, varied effect estimates and varied and/or wide CIs. Given that all studies for this comparison had a high risk of bias, findings should be interpreted with caution.

Outcome or Subgroup	Studies	n	Effect Estimate; OR [95% CI], M-H, random	P	Favours	Certainty
Live birth rate- per patient	3	307	2.21 [1.32, 3.71	0.003	**FSH** (live birth rate is higher with FSH)	⊕⊕◯◯ MODERATE
Clinical pregnancy rate- per patient†	3	307	2.27 [0.82, 6.34]	0.1	None	⊕⊕◯◯ LOW
Ovulation rate - per patient	1	50	1.52 [0.48, 4.76]	0.5	None	⊕◯◯◯ VERY LOW
Multiple pregnancy rate – per patient	3	307	5.10 [1.39, 18.68]	0.01	**LOD** (multiple pregnancy rate is higher with FSH)	⊕⊕◯◯ LOW
Miscarriage rate- per patient	3	307	1.37 [0.60, 3.11]	0.5	None	⊕⊕◯◯ LOW

† clinical pregnancy rate is confirmed by ultrasound detection of gestational sac/ fetal heart activity

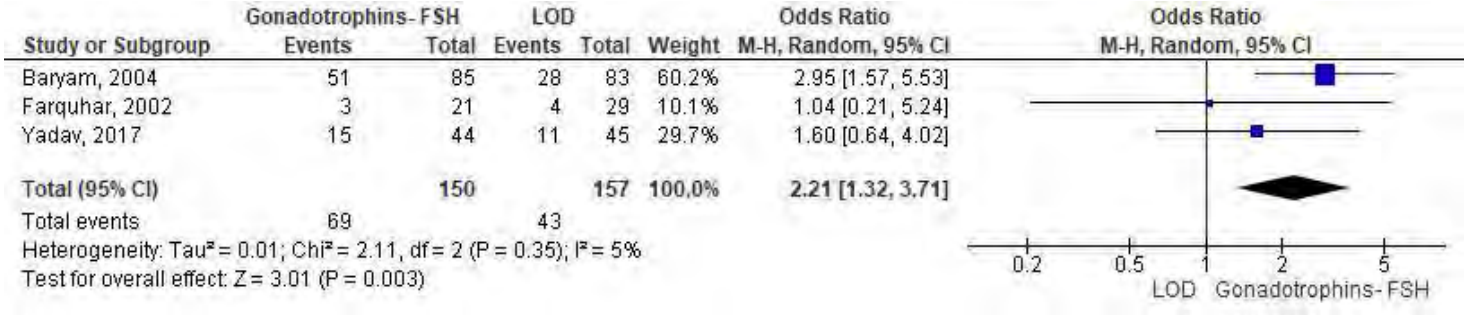
OUTCOME 4.1. Live birth rate – per patient

4.1.1. Individual Study Data Tables

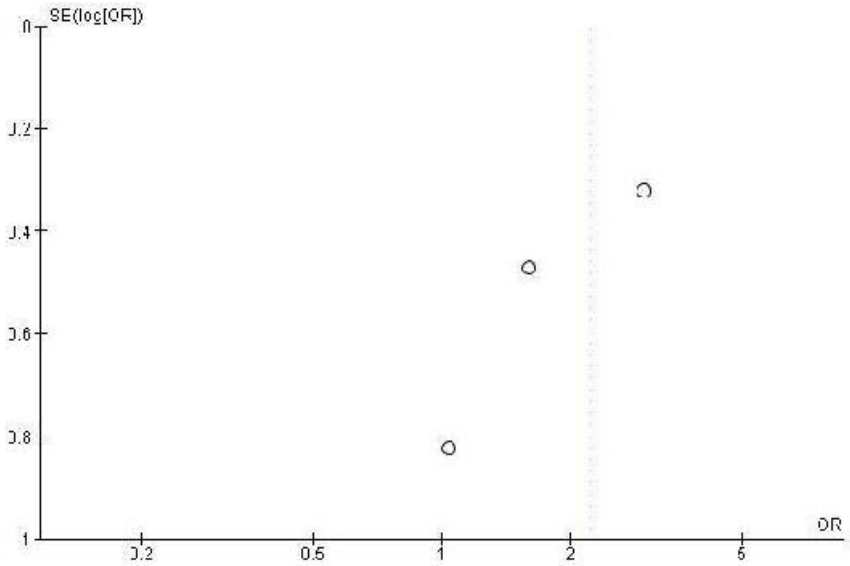
OUTCOME: Live birth rate per patient									
OUTCOME TYPE: Dichotomous									
COMPARISON: FSH + LOD									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (FSH)**	**N total in intervention/ exposure group (FSH)**	**N events in control / comparison group (LOD)**	**N total in control/ comparison group (LOD)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Baryam 2004 (HRB)	CCR	Count	Investigator	51	85	28	83	Crude	NA
Farquhar 2002 (HRB)	CCR	Count	Investigator	3	21	4	29	Crude	NA
Yadav 2017 (HRB)	CCR	Count	Investigator	15	44	11	45	Crude	NA

CCR, clomiphene citrate-resistant

4.1.2. Forest Plot of all included RCTs comparing FSH versus LOD for live birth rate – per patient



4.1.3. Funnel plot for assessment of publication bias



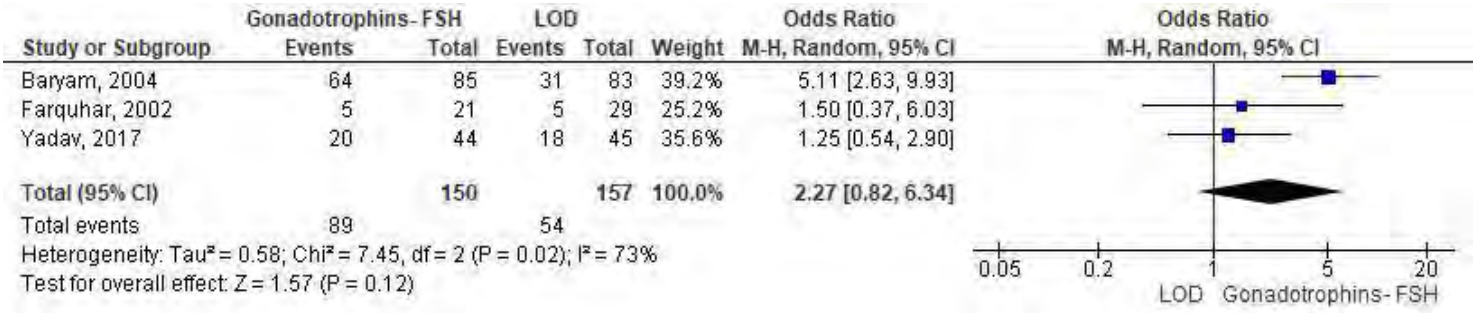
OUTCOME 4.2. Clinical pregnancy rate – per patient

4.2.1. Individual Study Data Tables

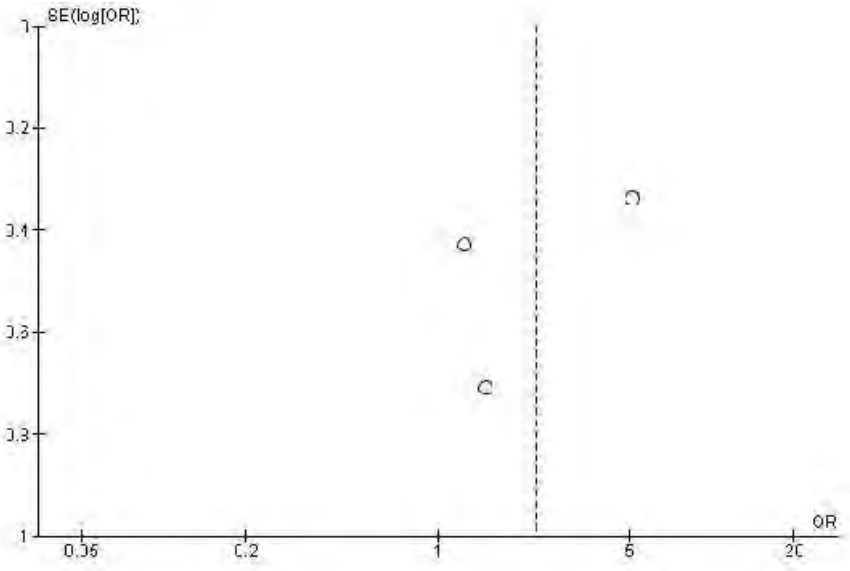
OUTCOME: Clinical pregnancy rate per patient									
OUTCOME TYPE: Dichotomous									
COMPARISON: FSH + LOD									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (FSH)**	**N total in intervention/ exposure group (FSH)**	**N events in control / comparison group (LOD)**	**N total in control/ comparison group (LOD)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Baryam 2004 (HRB)	CCR	Count	Investigator	64	85	31	83	Crude	NA
Farquhar 2002 (HRB)	CCR	Count	Investigator	5	21	5	29	Crude	NA
Yadav 2017 (HRB)	CCR	Count	Investigator	20	44	18	45	Crude	NA

CCR, clomiphene citrate-resistant

4.2.2. Forest plot of all included RCTs comparing FSH versus LOD for clinical pregnancy rate – per patient



4.2.3. Funnel plot for assessment of publication bias



OUTCOME 4.3. Ovulation rate – per patient

4.3.1. Individual Study Data Tables

OUTCOME: Ovulation rate per patient						OUTCOME TYPE: Dichotomous			
COMPARISON: FSH + LOD									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (FSH)**	**N total in intervention/ exposure group (FSH)**	**N events in control / comparison group (LOD)**	**N total in control/ comparison group (LOD)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Farquhar 2002 (HRB)	CCR	Count	Investigator	13	21	15	29	Crude	NA

CCR, clomiphene citrate-resistant

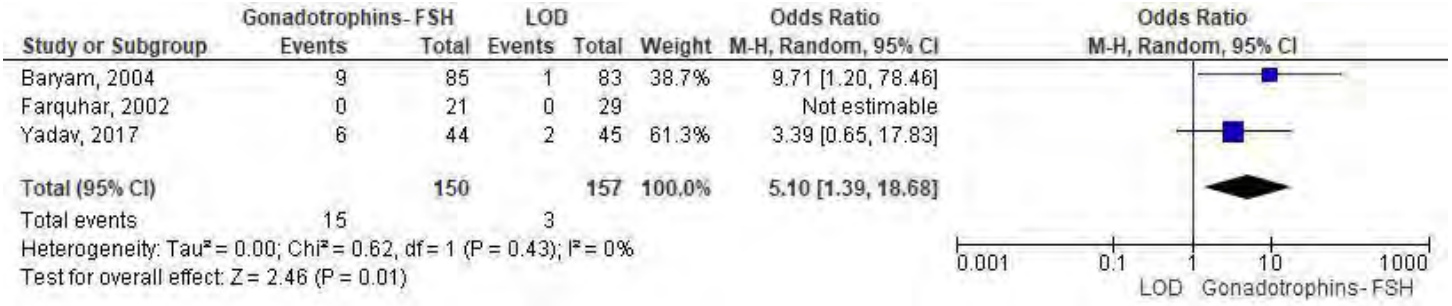
OUTCOME 4.4. Multiple pregnancy rate – per patient

4.4.1. Individual Study Data Tables

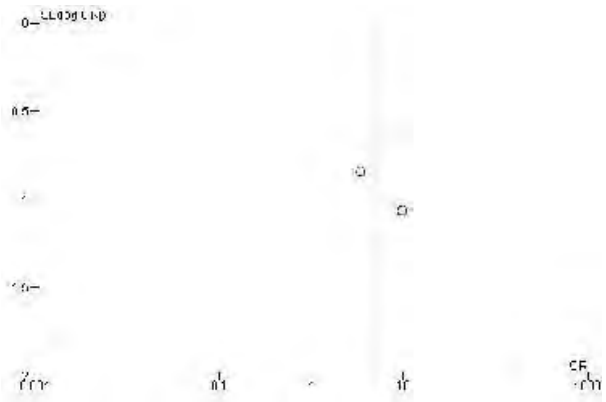
OUTCOME: Multiple pregnancy rate per patient						OUTCOME TYPE: Dichotomous			
COMPARISON: FSH + LOD									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (FSH)**	**N total in intervention/ exposure group (FSH)**	**N events in control / comparison group (LOD)**	**N total in control/ comparison group (LOD)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Baryam 2004 (HRB)	CCR	Count	Investigator	9	85	1	83	Crude	NA
Farquhar 2002 (HRB)	CCR	Count	Investigator	0	21	0	29	Crude	NA
Yadav 2017 (HRB)	CCR	Count	Investigator	6	44	2	45	Crude	NA

CCR, clomiphene citrate-resistant

4.4.2. Forest Plot of all included RCTs comparing FSH versus LOD for multiple pregnancy rate – per patient



4.4.3. Funnel plot for assessment of publication bias



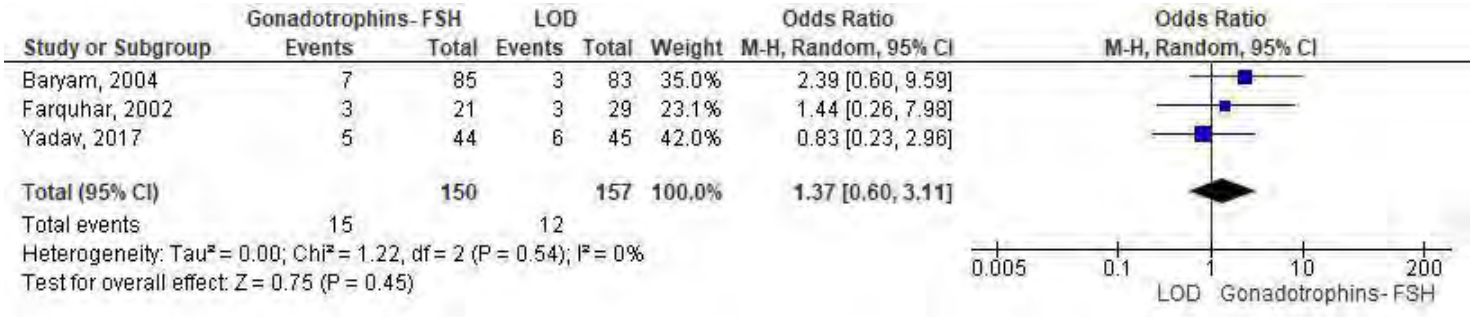
OUTCOME 4.5. Miscarriage rate – per patient

4.5.1. Individual Study Data Tables

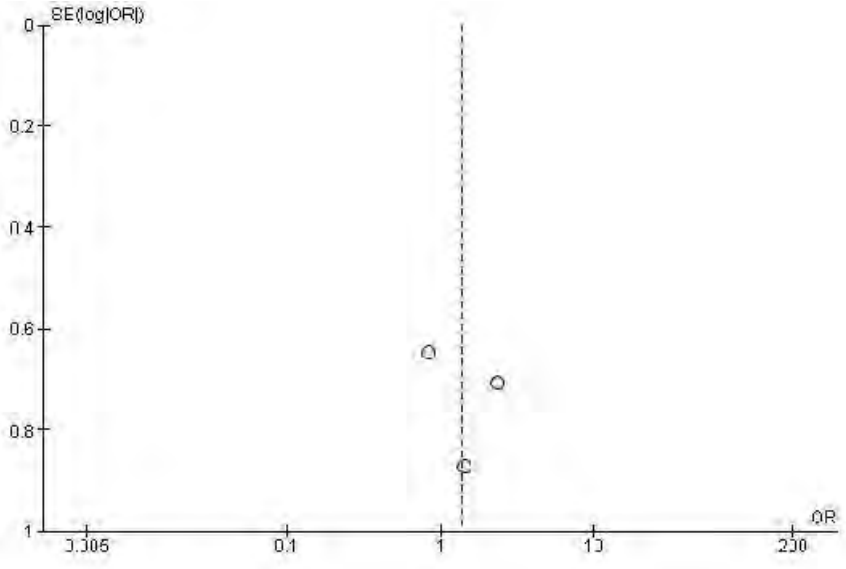
OUTCOME: Miscarriage rate per patient									
OUTCOME TYPE: Dichotomous									
COMPARISON: FSH + LOD									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (FSH)**	**N total in intervention/ exposure group (FSH)**	**N events in control / comparison group (LOD)**	**N total in control/ comparison group (LOD)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Baryam 2004 (HRB)	CCR	Count	Investigator	7	85	3	83	Crude	NA
Farquhar 2002 (HRB)	CCR	Count	Investigator	3	21	3	29	Crude	NA
Yadav 2017 (HRB)	CCR	Count	Investigator	5	44	6	45	Crude	NA

CCR, clomiphene citrate-resistant

4.5.2. Forest Plot of all included RCTs comparing FSH versus LOD for miscarriage rate – per patient



4.5.3. Funnel plot for assessment of publication bias



COMPARISON 5: FSH + Metformin versus FSH (+/- Placebo)

▪ EVIDENCE SUMMARY:

Three studies compared FSH + metformin versus FSH alone in women with PCOS. A study by De Leo et al. (1999) in Italy, examined 20 women with PCOS and clomiphene failure or resistance (i.e. failed to ovulate or conceive after clomiphene citrate treatment up to a daily dose of 50 mg from cycle days 3–7 during at least three consecutive cycles). This study has a high risk of bias due to its small sample size and likely lack of power as well as lack of blinding and allocation concealment information.

The remaining two studies by Tasdemir et al. (2004) and Yarali (2002) were conducted in Turkey, also in women with clomiphene-citrate resistance and PCOS. One study (Tasdemir et al. 2004) was judged as being at high risk of bias due to lack of reporting on key elements such as blinding and randomisation, while Yarali et al. (2002) had a moderate risk of bias as it was likely underpowered (small sample size with no sample size calculation) but was reported to be double-blinded.

▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

There were no differences between FSH + metformin versus FSH in pregnancy rate, ovulation rate, multiple pregnancy rate or miscarriage rate per patient. There was very low certainty for multiple pregnancy rate per patient due to the evidence being derived from a single, small study with a high risk of bias. For the remaining outcomes, the evidence was of low certainty, downgraded for risk of bias (all moderate or high risk studies) and for inconsistency (varied effect estimates, including different directions and wide CIs).

Outcome or Subgroup	Studies	n	Effect Estimate; OR [95% CI], M-H, random	P	Favours	Certainty
Pregnancy rate- per patient*	3	77	0.96 [0.18, 5.10]	0.9	None	⊕⊕◯◯ LOW
Ovulation rate- per patient	1	25	3.27 [0.31, 34.72]	0.3	None	⊕⊕◯◯ LOW
Multiple pregnancy rate -per patient	1	32	0.31 [0.01, 8.28]	0.5	None	⊕◯◯◯ VERY LOW
Miscarriage rate- per patient	1	25	4.89 [0.18, 132.83]	0.4	None	⊕⊕◯◯ LOW

*includes clinical, biochemical (or undefined pregnancy rate) as reported in each study

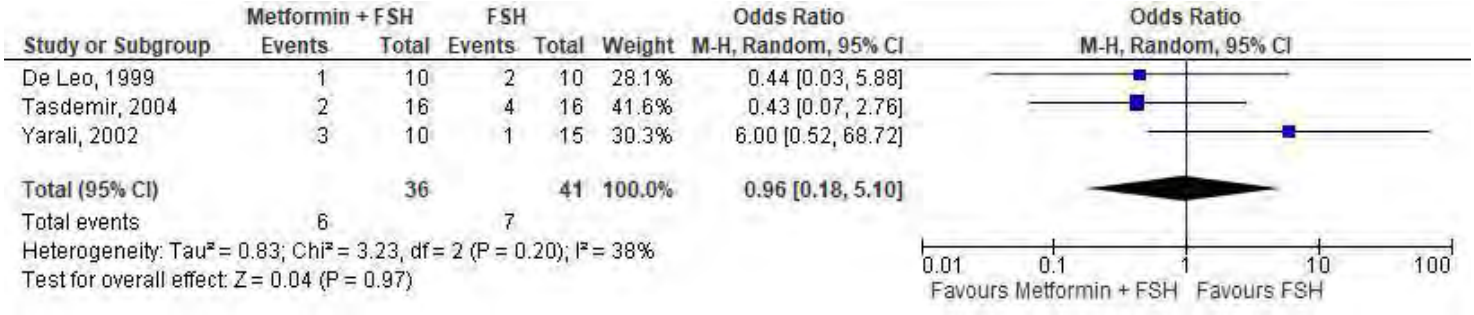
OUTCOME 5.1. Pregnancy rate – per patient

5.1.1. Individual Study Data Table

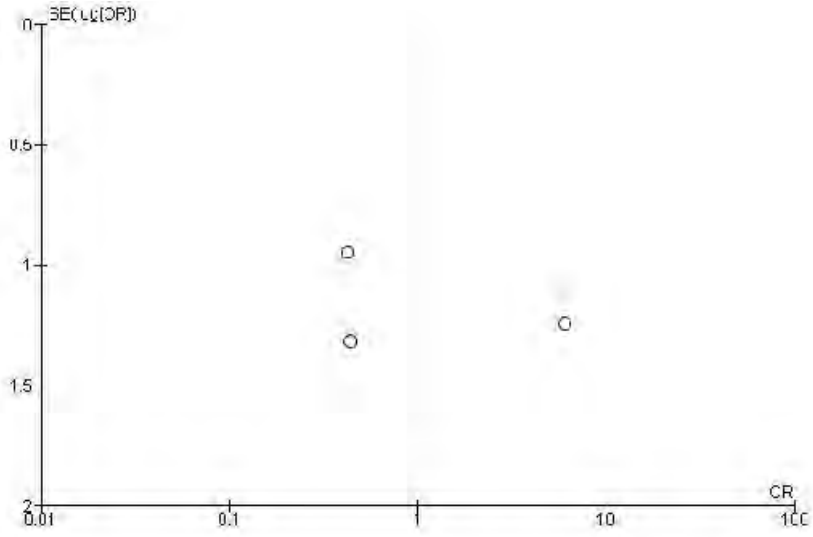
OUTCOME: Pregnancy rate – per patient						**OUTCOME TYPE:** Dichotomous			
COMPARISON: Metformin + FSH vs FSH (+/- placebo)									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in intervention group (MET +FSH)**	**N total in intervention group (MET +FSH)**	**N events in control / comparison group (FSH)**	**N total in control/ comparison group (FSH)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
De Leo 1999 (HRB)	CCR/ CCF	Count	Investigator	1	10	2	10	Crude	NA
Tasdemir 2004 (HRB)	CCR	Count	Investigator	2	16	4	16	Crude	NA
Yarali 2002 (MRB)	CCR	Count	Investigator	3	10	1	15	Crude	NA

CCR/CCF, Clomiphene citrate-resistant/ failure.

5.1.2. Forest Plot of all included RCTs comparing Metformin + Letrozole and Metformin + Clomiphene Citrate for miscarriage rate – per patient



5.1.3. Funnel plot for assessment of publication bias



OUTCOME 5.2. Ovulation rate – per patient

5.2.1. Individual Study Data Table

OUTCOME: Ovulation rate – per patient						**OUTCOME TYPE:** Dichotomous			
COMPARISON: Metformin + FSH vs FSH (+/- placebo)									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in intervention group (MET +FSH)**	**N total in intervention group (MET +FSH)**	**N events in control / comparison group (FSH)**	**N total in control/ comparison group (FSH)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Yarali 2002 (MRB)	CCR	Count	Investigator	9	10	11	15	Crude	NA

CCR, Clomiphene citrate-resistant.

OUTCOME 5.3. Multiple pregnancy rate – per patient

5.3.1. Individual Study Data Table

OUTCOME: Multiple pregnancy rate – per patient						**OUTCOME TYPE:** Dichotomous			
COMPARISON: Metformin + FSH vs FSH (+/- placebo)									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in intervention group (MET +FSH)**	**N total in intervention group (MET +FSH)**	**N events in control / comparison group (FSH)**	**N total in control/ comparison group (FSH)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Tasdemir 2004 (HRB)	CCR	Count	Investigator	0	16	1	16	Crude	NA

CCR, Clomiphene citrate-resistant.

OUTCOME 5.4. Miscarriage rate – per patient

5.4.1. Individual Study Data Table

OUTCOME: Miscarriage rate – per patient						**OUTCOME TYPE:** Dichotomous			
COMPARISON: Metformin + FSH vs FSH (+/- placebo)									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in intervention group (MET +FSH)**	**N total in intervention group (MET +FSH)**	**N events in control / comparison group (FSH)**	**N total in control/ comparison group (FSH)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Yarali 2002 (MRB)	CCR	Count	Investigator	1	10	0	15	Crude	NA

CCR, Clomiphene citrate-resistant.

COMPARISON 6: FSH vs Clomiphene Citrate + Metformin

▪ EVIDENCE SUMMARY:

A single study in Bangladesh compared gonadotropins (rFSH) versus clomiphene citrate + metformin in clomiphene citrate-resistant women with PCOS (Begum et al. 2013). Outcomes assessed included clinical pregnancy and miscarriage rate per patient. The study was judged as having a high risk of bias due to being unblinded (presumably, as this was not described), and lack of information regarding randomisation and attrition.

▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

Meta-analysis was not possible due to having a single eligible study with this comparison. Using this study alone, however, clinical pregnancy rate was higher with FSH compared to clomiphene citrate + metformin, with an OR of 2.81 favouring FSH. Certainty in these results is very low given the reliance on a single study, with a high risk of bias and relatively small sample size.

Outcome or Subgroup	Studies	n	Effect Estimate; OR [95% CI], M-H, random	P	Favours	Certainty
Clinical pregnancy rate- per patient†	1	110	2.81 [1.05, 7.52]	0.04	**FSH** (clinical pregnancy is higher with FSH)	⊕○○○ VERY LOW
Miscarriage rate- per pregnancy	1	23	1.38 [0.12, 16.23]	0.8	None	⊕○○○ VERY LOW

† clinical pregnancy rate is confirmed by ultrasound detection of gestational sac/ fetal heart activity

OUTCOME 6.1 – 6.2: Clinical pregnancy rate-per patient and miscarriage rate-per pregnancy

6.1.1 - 6.1.2. Individual Study Data Tables

OUTCOME: LISTED BELOW						**OUTCOME TYPE:** Dichotomous			
COMPARISON: Clomiphene Citrate + Metformin versus rFSH									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in intervention/ exposure group (FSH)**	**N total in intervention/ exposure group (FSH)**	**N events in control / comparison group (CC +MET)**	**N total in control/ comparison group (CC +MET)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
OUTCOME: Clinical pregnancy rate – per patient						**OUTCOME TYPE:** Dichotomous			
Begum 2013 (HRB)	CCR	Count	Investigator	16	55	7	55	Crude	NA
OUTCOME: Miscarriage rate – per pregnancy						**OUTCOME TYPE:** Dichotomous			
Begum 2013 (HRB)	CCR	Count	Investigator	3	16	1	7	Crude	NA

CCR, clomiphene citrate-resistant

COMPARISON 7. Gonadotropins (hMG) versus Metformin

- **EVIDENCE SUMMARY:**

A single study by George et al. 2003 compared human menopausal gonadotropin (hMG) with metformin 60 clomiphene citrate-resistant women with PCOS. Outcomes assessed included pregnancy rate per patient and ovulation rate per cycle. The study was judged as being of moderate risk of bias due to lack of blinding.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

There were no differences between hMG and metformin in pregnancy or ovulation rates.
Certainty was ranked as low due to being reliant on a single small study of moderate risk of bias.

Outcome or Subgroup	Studies	n	Effect Estimate; OR [95% CI], M-H, random	P-value	Favours	Certainty
Pregnancy rate- per patient*	1	60	1.52 [0.42, 5.47]	0.5	None	⊕⊕◯◯ LOW
Ovulation rate- per patient	1	60	0.76 [0.27, 2.12]	0.6	None	⊕⊕◯◯ LOW

*includes clinical, biochemical (or undefined pregnancy rate) as reported in each study

OUTCOME 7.1. Pregnancy rate – per patient

7.1.1. Individual Study Data Table

OUTCOME: Pregnancy rate – per patient						**OUTCOME TYPE:** Dichotomous			
COMPARISON: hMG vs Metformin									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in intervention group (hMG)**	**N total in intervention group (hMG)**	**N events in control / comparison group (MET)**	**N total in control/ comparison group (MET)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
George 2003	CCR	Count	Investigator	7	30	5	30	Crude	NA

CCR, Clomiphene citrate-resistant

OUTCOME 7.2. Ovulation rate – per patient

7.2.1. Individual Study Data Table

OUTCOME: Ovulation rate – per patient						**OUTCOME TYPE:** Dichotomous			
COMPARISON: hMG vs Metformin									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in intervention group (hMG)**	**N total in intervention group (hMG)**	**N events in control / comparison group (MET)**	**N total in control/ comparison group (MET)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
George 2003	CCR	Count	Investigator	12	30	14	30	Crude	NA

CCR, Clomiphene citrate-resistant

5. GRADE ASSESSMENTS AND EVIDENCE PROFILE

COMPARISON 1: Gonadotrophins (FSH) versus Clomiphene Citrate												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	FSH	CC	Effect, random , OR [95% CI]	Favours	Certainty	Importance
Outcome: Live birth rate - per patient												
2	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	79/ 170 (46.5%)	54/ 161 (33.5%)	1.74 [1.10, 2.74]	**FSH** (live birth rate is higher with FSH)	⨁⨁⨁◯ MODERATE	CRITICAL
Outcome: Clinical pregnancy rate- per patient												
2	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	92/ 170 (54.1%)	63/ 161 (39.1%)	1.84 [1.18, 2.87]	**FSH** (clinical pregnancy is higher with FSH)	⨁⨁⨁◯ MODERATE	CRITICAL
Outcome: Multiple pregnancy rate - per pregnancy												
2	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	5/ 92 (5.4%)	1/ 63 (1.6%)	2.41 [0.36, 16.10]	No difference	⨁⨁◯◯ LOW	CRITICAL
Outcome: Ovulation rate - per patient												
1	RCT	very serious[3]	not applicable	not applicable	very serious[4]	none	35/ 38 (92.1%)	30/ 38 (78.9%)	3.11 [0.76, 12.79]	No difference	⨁◯◯◯ VERY LOW	IMPORTANT
Outcome: Ovulation rate - per cycle												
1	RCT	very serious[3]	not applicable	not applicable	very serious[4]	none	67/ 91 (73.6%)	55/ 104 (52.9%)	2.49 [1.36, 4.55]	**FSH** (ovulation per cycle is higher with FSH)	⨁◯◯◯ VERY LOW	IMPORTANT
Outcome: Miscarriage rate - per pregnancy												
2	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/ 92 (13.0%)	8/ 63 (12.7%)	0.97 [0.36, 2.60]	No difference	⨁⨁⨁◯ MODERATE	IMPORTANT

[1] Downgraded once due to the majority of studies (half or more) having high or moderate risk of bias
[2] Downgraded once for imprecision due to wide CIs
[3] Downgraded twice due to the evidence being derived from a single high risk of bias study
[4] Downgraded twice due to the very small sample size (n=17) and single study used for evidence on this outcome

COMPARISON 2: Gonadotrophins (FSH) + Clomiphene Citrate versus Gonadotrophins (FSH)												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	FSH + CC	FSH	Effect, random , OR [95% CI]	Favours	Certainty	Importance
Outcome: Live birth rate- per patient												
1	RCT	serious[1]	not applicable	not applicable	serious[2]	none	22/87 (25.3%)	19/87 (21.8%)	1.21 [0.60, 2.44]	No difference	⨁⨁◯◯ LOW	CRITICAL
Outcome: Clinical pregnancy rate- per patient												
2	RCT	serious[1]	serious[3]	no serious indirectness	no serious imprecision	none	120/ 756 (15.9%)	84/433 (19.4%)	0.83 [0.61, 1.14]	No difference	⨁⨁◯◯ LOW	CRITICAL
Outcome: Ovulation rate - per patient												
2	RCT	serious[1]	very serious[4]	no serious indirectness	no serious imprecision	none	444/ 756 (58.7%)	344/ 433 (79.4%)	0.79 [0.03, 21.36]	No difference	⨁◯◯◯ VERY LOW	IMPORTANT
Outcome: Miscarriage rate - per pregnancy												
1	RCT	serious[1]	not applicable	not applicable	no serious imprecision[5]	none	16/ 96 (16.7%)	9/ 62 (14.5%)	1.18 [0.48, 2.86]	No difference	⨁⨁⨁◯ MODERATE	IMPORTANT

[1] Downgraded once for risk of bias due to one or both studies being of moderate risk of bias
[2] Downgraded once for imprecision since the evidence is derived from a single, relatively small study
[3] Downgraded once because effects estimates vary (including having different directions)
[4] Downgraded twice because effect estimates vary (different directions) and due to high statistical heterogeneity (I^2 = 99%, with a p<0.00001)
[5] Not downgraded for imprecision despite being a single study, due to its relatively large sample size

COMPARISON 3: Gonadotrophins (FSH) + Clomiphene Citrate versus Letrozole												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	FSH + CC	LET	Effect, random , OR [95% CI]	Favours	Certainty	Importance
Outcome: Clinical pregnancy rate- per patient												
1	RCT	serious[1]	not applicable	not applicable	no serious imprecision	none	96/ 669 (14.3%)	87/ 372 (23.4%)	0.55 [0.40, 0.76]	LET (clinical pregnancy is lower with CC + FSH)	⨁⨁⨁◯ MODERATE	CRITICAL
Outcome: Ovulation rate - per patient												
1	RCT	serious[1]	not applicable	not applicable	no serious imprecision	none	381/ 669 (57.0%)	295/ 372 (79.3%)	0.35 [0.26, 0.46]	LET (ovulation per patient is lower with CC + FSH)	⨁⨁⨁◯ MODERATE	IMPORTANT
Outcome: Miscarriage rate - per pregnancy												
1	RCT	serious[1]	not applicable	not applicable	no serious imprecision	none	16/ 96 (16.7%)	12/ 87 (13.8%)	1.25 [0.55, 2.82]	No difference	⨁⨁⨁◯ MODERATE	IMPORTANT

[1]Downgraded once for risk of bias (despite being a single study, imprecision was not downgraded given the large sample size)

COMPARISON 4: Gonadotrophins (FSH) versus Laparoscopic Ovarian Drilling (LOD)												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	FSH	LOD	Effect, random , OR [95% CI]	Favours	Certainty	Importance
Outcome: Live birth rate- per patient												
3	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	69/150 (46.0%)	43/157 (27.4%)	2.21 [1.32, 3.71]	**FSH** (live birth rate is higher with FSH)	⊕⊕◯◯ MODERATE	CRITICAL
Outcome: Clinical pregnancy rate- per patient												
3	RCT	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	86/150 (57.3%)	54/157 (34.4%)	2.27 [0.82, 6.34]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Multiple pregnancy rate- per patient												
3	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	15/150 (10.0%)	3/157 (1.92%)	5.10 [1.39, 18.68]	**LOD** (multiple pregnancy rate is higher with FSH)	⊕⊕◯◯ LOW	CRITICAL
Outcome: Ovulation rate - per patient												
1	RCT	very serious[2]	not applicable	not applicable	serious[4]	none	13/21 (61.9%)	15/29 (51.7%)	1.52 [0.48, 4.76]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Miscarriage rate - per patient												
3	RCT	serious[1]	serious[5]	no serious indirectness	no serious imprecision	none	15/150 (10.0%)	12/157 (7.64%)	1.37 [0.60, 3.11]	No difference	⊕⊕◯◯ LOW	IMPORTANT

[1] Downgraded once for risk of bias due to high or moderate risk for the majority of included studies (half or more) or twice if all included studies are at high risk of bias
[2] Downgraded once for inconsistency due to varying confidence intervals and effects estimates
[3] Downgraded once for imprecision due to wide confidence intervals
[4] Downgraded once for imprecision due to the evidence being derived from a single study with a small sample size
[5] Downgraded once for inconsistency due to varying effect estimates (different directions) and wide confidence intervals

COMPARISON 5: Gonadotrophins (FSH) + Metformin versus gonadotrophins (FSH) (+/- placebo)												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	FSH + MET	FSH	Effect, random , OR [95% CI]	Favours	Certainty	Importance
Outcome: Pregnancy rate- per patient												
3	RCT	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	6/36	7/41	0.96 [0.18, 5.10]	No difference	⨁⨁◯◯ LOW	CRITICAL
Outcome: Multiple pregnancy rate- per patient												
1	RCT	very serious[1]	not applicable	not applicable	serious[3]	none	0/16	1/16	0.31 [0.01, 8.28]	No difference	⨁◯◯◯ VERY LOW	CRITICAL
Outcome: Ovulation rate- per patient												
1	RCT	serious[1]	not applicable	not applicable	serious[3]	none	9/10	11/15	3.27 [0.31, 34.72]	No difference	⨁⨁◯◯ LOW	IMPORTANT
Outcome: Miscarriage rate - per patient												
1	RCT	serious[1]	not applicable	not applicable	serious[3]	none	1/10	0/15	4.89 [0.18, 132.83]	No difference	⨁⨁◯◯ LOW	IMPORTANT

[1] Downgraded once if the majority of included studies have mod/high risk of bias or twice if all included studies are at high risk of bias
[2] Downgraded once due to varying effect estimates (different directions) and wide confidence intervals
[3] Downgraded once due to the evidence being derived from a single study with a very small sample size

COMPARISON 6: Gonadotrophins (FSH) versus Clomiphene Citrate + metformin												
	Quality assessment						**No. participants**					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**FSH**	**CC + MET**	**Effect, random , OR [95% CI]**	**Favours**	**Certainty**	**Importance**
Outcome: Clinical pregnancy rate- per patient												
1	RCT	very serious[1]	not applicable	not applicable	serious[2]	none	16/55 (29.1%)	7/55 (12.7%)	2.81 [1.05, 7.52]	**FSH** (clinical pregnancy is higher with FSH)	⨁◯◯◯ VERY LOW	CRITICAL
Outcome: Miscarriage rate - per pregnancy												
1	RCT	very serious[1]	not applicable	not applicable	serious[2]	none	3/16 (18.6%)	1/7 (14.3%)	1.38 [0.12, 16.23]	No difference	⨁◯◯◯ VERY LOW	IMPORTANT

[1] Downgraded twice due to all studies (or the single study) included having a high risk of bias
[2] Downgraded once due to the small sample size from a single study

COMPARISON 7: Gonadotrophins (hMG) versus Metformin												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	hMG	MET	Effect, random, OR [95% CI]	Favours	Certainty	Importance
Outcome: Pregnancy rate- per patient												
1	RCT	serious[1]	not applicable	not applicable	serious[2]	none	7/30 (23.3%)	5/30 (16.7%)	1.52 [0.42, 5.47]	No difference	⨁⨁◯◯ LOW	IMPORTANT
Outcome: Ovulation rate- per patient												
1	RCT	serious[1]	not applicable	not applicable	serious[2]	none	12/30 (40.0 %)	14/30 (46.7%)	0.76 [0.27, 2.12]	No difference	⨁⨁◯◯ LOW	IMPORTANT

[1] Downgraded once due to the evidence being derived from a single moderate risk of bias study
[2] Downgraded once due to having a small number of participants

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 5

Question 5.5.

In women with PCOS, are gonadotrophins effective for improving fertility outcomes?

BACKGROUND

Gonadotrophin therapy is usually second- or third-line therapy for women with PCOS and may be indicated for women with anovulatory PCOS who have been treated with anti-estrogens (clomiphene citrate, CC) or aromatase inhibitors (letrozole, LET) if they have failed to ovulate or if they have a response that is likely to reduce their chance of conception (e.g., with CC the persistent hypersecretion of LH, or an antiestrogenic effect on the endometrium). In order to prevent overstimulation and multiple pregnancy, the traditional standard step-up regimens, when 75–150i.u. were increased by 75i.u. every 3–5 days (1) have been replaced by either low-dose step-up regimens (2, 3) or step-down regimens (4). The low-dose step-up regimen employs a starting dose of 50-75 i.u., which is only increased after 14 days if there is no response and then by only 25-37.5 i.u. every 7 days. Treatment cycles using this approach can be quite long – up to 28–35 days – but the risk of multiple follicular growth is lower than with conventional step-up regimens. With the step-down protocol, follicular recruitment is achieved using 150 i.u. daily for 3 or 4 days before decreasing the dose to 50–75 i.u. to maintain follicular development. In all the above-mentioned ovulation induction regimens, gonadotrophins are used alone, without a background of pituitary desensitization, which does not confer any advantage.

Gonadotrophin preparations are derived from either purified menopausal urine (hMG) or recombinantly-derived (recFSH). There appears to be no difference in efficacy between the different preparations in the context of anovulatory PCOS (5). All gonadotrophin preparations are significantly more expensive than oral agents (CC and LET) and require parenteral administration and close monitoring with regular ultrasound scan.

It can be extremely difficult to predict the response to stimulation of a woman with polycystic ovaries and achieve the development of a single dominant follicle in order to reduce the risks of multiple pregnancy and ovarian hyperstimulation syndrome (OHSS). Treatment with gonadotrophins should be commenced within the first 3 days of a natural or induced menstrual bleed, when a pelvic USS indicates that the endometrium is thin (less than 5mm) and that there are no ovarian cysts. It is essential to carefully monitor follicular development by ultrasound scan (USS). Ovulation is usually triggered with a single injection of human chorionic gonadotrophin (hCG) 5000 units (s.c.), when at least one follicle of at least 17 mm in its largest diameter has developed. To reduce the risks of multiple pregnancy, hCG should not be administered if a total of two or more follicles larger than 14 mm in diameter have developed. In overstimulated cycles hCG is withheld, the patient counselled about risks and advised to refrain from unprotected intercourse.

If conception has failed to occur after six ovulatory cycles in a woman younger than 35 years or after 12 ovulatory cycles in women older than 35, then it can be assumed that anovulation is unlikely to be the cause of the couple's infertility. The couple should have been comprehensively investigated by this stage with a test of tubal patency and sperm function tests. If no other explanation has been found for their infertility assisted conception (usually IVF) is now indicated.

Comparisons:

1. Gonadotrophins (FSH) vs. Clomiphene Citrate (CC)

Two RCTs were identified by the search to address this comparison. One RCT was low quality with high risk of bias (6) compared recombinant FSH with CC in women with PCOS who were therapy naïve and found that there was no difference between the two interventions for all fertility outcomes. The second was a multi-centre RCT with moderate risk of bias (7) comparing CC with low dose gonadotrophins, as the first line therapy for ovulation induction in anovulatory women with PCOS who were also therapy naïve. They reported with per protocol analysis that the clinical pregnancy rate was significantly higher in the gonadotrophin treated group. Furthermore, the chance of pregnancy was almost double in the first treatment cycle when compared to clomiphene citrate.

Meta-analysis of the two studies has demonstrated no differences ovulation rate, multiple pregnancy rate or miscarriage rate per patient; however, FSH was superior to clomiphene citrate for live birth rate OR 1.74 [95% CI 1.10, 2.74], clinical pregnancy rate per patient OR 1.84 [95% 1.18, 2.87] and ovulation rate per cycle OR 3.11 [95% CI 0.76, 12.79]. Evidence for these outcomes was moderate, with the exception of ovulation rate per patient and per cycle which was of very low quality due to being derived from a single small study with a high risk of bias. There was no difference in risk of multiple pregnancy or miscarriage.

2. **Gonadotrophins (FSH) + clomiphene citrate vs. gonadotrophins (FSH)**

Two studies compared rFSH alone with clomiphene citrate + rFSH (8) and one in Egypt (9), and a meta-analysis has shown no differences in any outcomes with very low to moderate certainty.

3. Gonadotrophins (FSH) vs. Laparoscopic Ovarian Diathermy/Drilling (LOD)

Three studies (10-12) compared FSH with laparoscopic ovarian diathermy/drilling (LOD), all in women who were CC resistant. Meta-analysis shows that FSH was superior to LOD for live birth rates OR 2.21 [95% CI 1.32, 3.71] (moderate certainty) it also resulted in a much higher rate of multiple pregnancy OR 5.10 [95% CI 1.39, 18.68], with no difference in the other outcomes.

4. Gonadotrophins (FSH) vs Clomiphene citrate + Metformin

.

A single study compared gonadotrophins (rFSH) with clomiphene citrate + metformin in clomiphene citrate-resistant women with PCOS. (13) Clinical pregnancy rate was higher with FSH compared with clomiphene citrate + Metformin (OR 2.81 [95% CI 1.05, 7.52]) with very low certainty.

5. Gonadotrophins (hMG) vs. Metformin

A single study (14) compared human menopausal gonadotrophin (hMG) with metformin in clomiphene citrate-resistant women. There was no difference in pregnancy or ovulation rates with low certainty.

GRADE EVIDENCE CERTAINTY	
Comparison	**GRADE for critical outcomes**

Comparison 1. FSH vs. Clomiphene citrate	⊕⊕◯◯ LOW
Comparison 2. FSH + Clomiphene citrate vs. FSH	⊕⊕◯◯ LOW
Comparison 3. FSH vs LOS	⊕⊕◯◯ LOW
Comparison 4. FSH vs. Clomiphene citrate + Metformin	⊕◯◯◯ VERY LOW
Comparison 5. hMG vs. Metformin	⊕⊕◯◯ LOW

Evidence to Recommendations Framework

COMPARISONS (option versus other option)

1. Gonadotrophins (FSH) versus Clomiphene Citrate (CC)
2. FSH + CC vs. FSH
3. FSH vs. Laparoscopic ovarian surgery (LOS)
4. FSH vs. CC + Metformin
5. hMG vs. Metformin

EVIDENCE-BASED RECOMMENDATION(S)

This first recommendation was included in the last set of recommendations and was not updated here, given that gonadotrophin preparations stimulate ovulation yet are significantly more expensive than oral agents (CC and LET) and require parenteral administration and close monitoring with regular ultrasound scan.

EBR 1: Gonadotrophins alone could be considered rather than clomiphene citrate in therapy naïve women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation, clinical pregnancy and live birth rates.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

EBR 2: Gonadotrophins alone could be used over gonadotrophins combined with clomiphene citrate in women with PCOS who are anovulatory and infertile with clomiphene citrate resistance or failure, and no other infertility factors.

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GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☒ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

EBR 3: Either gonadotrophins or Laparoscopic Ovarian Surgery (LOS) could be used in women with PCOS who are anovulatory and infertile, with clomiphene citrate-resistance with no other infertility factors, following counselling on higher live birth rate and higher multiple pregnancy rates with gonadotrophins.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☒ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

EBR 4: Gonadotrophins could be considered rather than the combination of clomiphene citrate and metformin in women with PCOS who are anovulatory and infertile, with clomiphene citrate-resistance and no other infertility factors.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

EBR 5: Gonadotrophins could be second line pharmacological therapy for women with PCOS who are anovulatory and infertile, with no other infertility factors and who have failed first line oral ovulation induction.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

PRACTICE POINT(S)

Where gonadotrophins are to be prescribed, the following should be considered:

- Cost of the ovulation induction intervention
- Expertise required for the use of the intervention for ovulation induction.
- The degree of intensive ultrasound monitoring that is required.
- A low dose step up gonadotrophin protocol should be used to optimize the chance of monofollicular development.
- Implications of potential multiple pregnancy.

There appears to be no difference in the clinical efficacy of the available gonadotrophin preparations.

When using gonadotrophins, best clinical practice is to avoid multiple pregnancy. Considerations here include cancelling cycles when there is more than a total of two follicles greater than 14mm in diameter and advise avoiding unprotected intercourse.

Live birth rate, clinical pregnancy rate per patient and ovulation rate per cycle are higher with gonadotrophins than with clomiphene citrate.

A low dose step up gonadotrophin protocol should be used to optimise the chance of monofollicular growth and minimize multiple pregnancy.

Cycle monitoring and drug costs coupled with multiple injection will influence choice in gonadotrophin use.

GRADE CONSIDERATIONS

Justifications:

Gonadotrophin therapy is an effective treatment for anovulatory women with PCOS and no other fertility factors, but requires adequate resource (trained medical/nursing personnel and ultrasound machinery). All gonadotrophin preparations are significantly more expensive than oral agents (CC and LET) and require parenteral administration and close monitoring with regular ultrasound scans. They generally require increased travel for regular appointments.

Subgroup considerations:

The subjects studied were heterogeneous, with respect to baseline characteristics and prognostic factors (e.g. age, BMI, ethnicity and numerous other confounding factors that have not been described). Some were treatment naïve and some clomiphene-resistant and in some studies, it is unclear.

Implementation considerations:

Key considerations include cost of medication, training of staff, parenteral administration and clinic visits for scans and risk of multiple pregnancy.

Monitoring and evaluation considerations:

Indicators that should be monitored:

- Singleton live birth rates
- Multiple pregnancy rates
- Routine safety monitoring for long term risks including pregnancy outcomes, congenital anomalies, childhood development
- Quality of life
- Cost effectiveness

Research priorities:

Compare letrozole versus gonadotrophins in women with anovulatory PCOS who are therapy naïve in terms of clinical and cost effectiveness and quality of life.

GRADE framework

GRADE DECIDE Interactive Evidence to Decision Framework

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1. **Evidence-based recommendation (EBR 1):**

Gonadotrophins alone could be considered rather than clomiphene citrate in therapy naïve women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation, clinical pregnancy and live birth rates.

- **DESIRABLE EFFECTS**

How substantial are the desirable anticipated effects?

☒ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

- Gonadotrophin therapy provides better per cycle and cumulative pregnancy and livebirth rates compared with the use of oral anti-oestrogens in anovulatory women with PCOS

There is no evidence of teratogenicity.

● UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

- Daily injections
- The need for intensive monitoring with ultrasound, including travel times to clinic
- The potential risk of multiple pregnancy
- Increased cost of medication compared with oral agents in treatment naïve patients

● CERTAINTY OF THE EVIDENCE

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☐ Very low	Low	☒ Moderate	☐ High

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Direct quote from 2018:

The body of evidence included here is of very low to moderate certainty with serious to very serious risk of bias, serious inconsistency, very serious to serious imprecision, and serious indirectness; with no publication bias.

● VALUES

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☐ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☒ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Research evidence:

No research evidence was identified.

Panel discussion:

The prime outcome is livebirth and main risk multiple pregnancy.

● BALANCE OF EFFECTS

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:

Desirable effects outweigh undesirable effects.

● COSTS

How large are the resource requirements (costs)?

Judgement:

☐ Don't know	☐ Varies	☐ Large costs	☒ Moderate costs	☐ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:

No research evidence was identified

Panel discussion:

- Clinical and nursing skill to assess appropriate starting dose and monitor treatment
- Ultrasound skills
- Ultrasound equipment
- Drug costs
- Travelling cost to clinic

● CERTAINTY OF COST EVIDENCE

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

No research evidence was identified.

Panel discussion:

No (or possibly limited) evidence on cost-effectiveness.

● COST-EFFECTIVENESS

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

No research evidence was identified.

Panel discussion:

No (or possibly limited) evidence on cost-effectiveness.

● EQUITY

What would be the impact on health equity?

Judgement:

☐ Don't know	☒ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☐ Probably increased	☐ Increased

Research evidence:

No research evidence was identified.

Panel discussion:

Regional contact/health systems and resources will influence.

● ACCEPTABILITY

Is the option acceptable to key stakeholders?

Judgement:

☐ Don't know	☒ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified.

Panel discussion:

Are key stakeholders likely to find the recommendation acceptable, given the relative importance they attach to the desirable and undesirable consequences of implementing the recommendation; the timing of the benefits, harms and costs; and their moral values? This includes considering patients values and preferences.

Stakeholders are likely to accept the balance of benefits over harms and costs.

● FEASIBILITY

Is the option feasible to implement?

Judgement:

☐ Don't know	☒ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

- Regional contact/health systems and resources will influence.
- The need for:
- Clinical and nursing skill to assess appropriate starting dose and monitor treatment
- Ultrasound skills
- Ultrasound equipment

GRADE framework

GRADE DECIDE **Interactive Evidence to Decision Framework**

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2. Evidence-based recommendation (EBR 2):

Gonadotrophins use combined with clomiphene citrate is not recommended over gonadotrophins alone in women with PCOS who are anovulatory and infertile with clomiphene citrate resistance or failure, and no other infertility factors.

- **DESIRABLE EFFECTS**

How substantial are the desirable anticipated effects?

Judgement:

☐ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☒ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

- Gonadotrophin therapy provides better per cycle and cumulative pregnancy and livebirth rates compared with the use of oral anti-oestrogens in anovulatory women with PCOS
- There is no evidence of teratogenicity

- **UNDESIRABLE EFFECTS**

How substantial are the undesirable anticipated effects?

Judgement:

☒ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

- Daily injections
- The need for intensive monitoring with ultrasound, including travel times to clinic
- The potential risk of multiple pregnancy

● CERTAINTY OF THE EVIDENCE

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☒ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Direct quote from 2018:

The body of evidence included here is of very low to moderate certainty with serious to very serious risk of bias, serious inconsistency, very serious to serious imprecision, and serious indirectness; with no publication bias.

● VALUES

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☒ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☐ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Research evidence:

No research evidence was identified

Panel discussion:

The prime outcome is livebirth and main risk multiple pregnancy.

● BALANCE OF EFFECTS

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☐ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☒ Probably favours other options	☐ Favours other options

Panel discussion:

Desirable effects outweigh undesirable effects

● COSTS

How large are the resource requirements (costs)?

Judgement:

☐ Don't know	☐ Varies	☐ Large costs	☒ Moderate costs	☐ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:

No research evidence was identified

Panel discussion:

- Clinical and nursing skill to assess appropriate starting dose and monitor treatment
- Ultrasound skills
- Ultrasound equipment
- Drug costs
- Travelling cost to clinic

● CERTAINTY OF COST EVIDENCE

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

No research evidence was identified.

Panel discussion:

No (or possibly limited) evidence on cost-effectiveness.

● COST-EFFECTIVENESS

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☒ Probably favours other options	☐ Favours other options

Research evidence:

No research evidence was identified.

Panel discussion:

No (or possibly limited) evidence on cost-effectiveness.

● EQUITY

What would be the impact on health equity?

Judgement:

☒ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☐ Probably increased	☐ Increased

Research evidence:

No research evidence was identified.

Panel discussion:

Regional contact/health systems and resources will influence.

- **ACCEPTABILITY**

Is the option acceptable to key stakeholders?

Judgement:

☒ Don't know	☐ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Are key stakeholders likely to find the recommendation acceptable, given the relative importance they attach to the desirable and undesirable consequences of implementing the recommendation; the timing of the benefits, harms and costs; and their moral values? This includes considering patients values and preferences.

Stakeholders are likely to accept the balance of benefits over harms and costs.

- **FEASIBILITY**

Is the option feasible to implement?

Judgement:

☐ Don't know	☐ Varies	☒ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

- Regional contact/health systems and resources will influence.
- The need for:
- Clinical and nursing skill to assess appropriate starting dose and monitor treatment
- Ultrasound skills
- Ultrasound equipment

GRADE framework

GRADE DECIDE **Interactive Evidence to Decision Framework**

3. Evidence-based recommendation (EBR 3):

Either gonadotrophins or Laparoscopic Ovarian Surgery (LOS) could be used in women with PCOS who are anovulatory and infertile, with clomiphene citrate-resistance with no other infertility factors, following counselling on higher live birth rate and higher multiple pregnancy rates with gonadotrophins.

● DESIRABLE EFFECTS

How substantial are the desirable anticipated effects?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

- Gonadotrophin therapy provides better livebirth rates compared with the use of LOD in anovulatory women with PCOS.
- There is no evidence of teratogenicity.

● UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

- Daily injections
- The need for intensive monitoring with ultrasound, including travel times to clinic
- The potential risk of multiple pregnancy
- Increased cost of medication
- Risk of surgery

● CERTAINTY OF THE EVIDENCE

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☐ Very low	☐ Low	☒ Moderate	☐ High

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

● VALUES

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☐ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☒ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Research evidence:

No research evidence was identified.

Panel discussion:

The prime outcome is livebirth and main risk multiple pregnancy.

● BALANCE OF EFFECTS

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:

Desirable effects outweigh undesirable effects

- **COSTS**

How large are the resource requirements (costs)?

Judgement:

☐ Don't know	☐ Varies	☐ Large costs	☒ Moderate costs	☐ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:

No research evidence was identified.

Panel discussion:

- Clinical and nursing skill to assess appropriate starting dose and monitor treatment
- Ultrasound skills
- Ultrasound equipment
- Drug costs
- Travelling cost to clinic
- Risk of surgery

- **CERTAINTY OF COST EVIDENCE**

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

No research evidence was identified - there has been a cost effectiveness analysis in the Netherlands (15).

Panel discussion:

No (or possibly limited) evidence on cost-effectiveness.

- **COST-EFFECTIVENESS**

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

No research evidence was identified

Panel discussion:

No (or possibly limited) evidence on cost-effectiveness.

● EQUITY

What would be the impact on health equity?

Judgement:

☐ Don't know	☒ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☐ Probably increased	☐ Increased

Research evidence:

No research evidence was identified.

Panel discussion:

Regional contact/health systems and resources will influence.

● ACCEPTABILITY

Is the option acceptable to key stakeholders?

Judgement:

☐ Don't know	☒ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified.

Panel discussion:

Are key stakeholders likely to find the recommendation acceptable, given the relative importance they attach to the desirable and undesirable consequences of implementing the recommendation; the timing of the benefits, harms and costs; and their moral values? This includes considering patients values and preferences.

Stakeholders are likely to accept the balance of benefits over harms and costs.

- **FEASIBILITY**

Is the option feasible to implement?

Judgement:

☐ Don't know	☒ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

- Regional contact/health systems and resources will influence.
- The need for:
- Clinical and nursing skill to assess appropriate starting dose and monitor treatment
- Ultrasound skills
- Ultrasound equipment
- Surgical skills and equipment

GRADE framework

GRADE DECIDE **Interactive Evidence to Decision Framework**

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4. Evidence-based recommendation (EBR 4):

Gonadotrophins could be considered rather than the combination of clomiphene citrate and metformin in women with PCOS who are anovulatory and infertile, with clomiphene citrate resistance or failure, and no other infertility factors.

- **DESIRABLE EFFECTS**

How substantial are the desirable anticipated effects?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

● UNDESIRABLE EFFECTS

How substantial are the undesirable anticipated effects?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

- Daily injections
- The need for intensive monitoring with ultrasound, including travel times to clinic
- The potential risk of multiple pregnancy

● CERTAINTY OF THE EVIDENCE

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☒ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

● VALUES

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☐ Important uncertainty or variability	☒ Possibly important uncertainty or variability	☐ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Research evidence:

No research evidence was identified

Panel discussion:

The prime outcome is livebirth and main risk multiple pregnancy.

● BALANCE OF EFFECTS

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:

Desirable effects outweigh undesirable effects.

● COSTS

How large are the resource requirements (costs)?

Judgement:

☐ Don't know	☐ Varies	☐ Large costs	☒ Moderate costs	☐ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:

No research evidence was identified.

Panel discussion:

- Clinical and nursing skill to assess appropriate starting dose and monitor treatment
- Ultrasound skills
- Ultrasound equipment
- Drug costs
- Travelling cost to clinic

● CERTAINTY OF COST EVIDENCE

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

No research evidence was identified.

Panel discussion:

No (or possibly limited) evidence on cost-effectiveness.

● COST-EFFECTIVENESS

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

No research evidence was identified.

Panel discussion:

No (or possibly limited) evidence on cost-effectiveness.

● EQUITY

What would be the impact on health equity?

Judgement:

☐ Don't know	☒ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☐ Probably increased	☐ Increased

Research evidence:

No research evidence was identified.

Panel discussion:

Regional contact/health systems and resources will influence.

● ACCEPTABILITY

Is the option acceptable to key stakeholders?

Judgement:

☐ Don't know	☒ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified.

Panel discussion:

Are key stakeholders likely to find the recommendation acceptable, given the relative importance they attach to the desirable and undesirable consequences of implementing the recommendation; the timing of the benefits, harms and costs; and their moral values? This includes considering patients values and preferences.

Stakeholders are likely to accept the balance of benefits over harms and costs.

● FEASIBILITY

Is the option feasible to implement?

Judgement:

☐ Don't know	☒ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

Regional contact/health systems and resources will influence.

The need for:

Clinical and nursing skill to assess appropriate starting dose and monitor treatment

Ultrasound skills

Ultrasound equipment.

GRADE framework

GRADE DECIDE **Interactive Evidence to Decision Framework**

5. Evidence based recommendation (EBR 5):
Gonadotrophins could be second line pharmacological therapy for women with PCOS who are anovulatory and infertile, with no other infertility factors and who have failed first line oral ovulation induction.

- **DESIRABLE EFFECTS**

How substantial are the desirable anticipated effects?

Judgement:

☒ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

- Single intervention that leads to the preferred outcome (singleton birth) in a significant proportion of women in the target group in a sustained way (but not permanent).
- No need for ongoing cycle monitoring (because of mono-ovulation).
- Normal risk of multiple pregnancy.

- **UNDESIRABLE EFFECTS**

How substantial are the undesirable anticipated effects?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

- LOD requires an invasive surgical intervention.
- Small risk it could lead to reduced ovarian reserve or loss of ovarian function.
- Adhesion formation.

- **CERTAINTY OF THE EVIDENCE**

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☐ Very low	☒ Low	☐ Moderate	☐ High

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

- The body of evidence included here remains of very low to moderate certainty with very serious risk of bias and imprecision, and serious risk of inconsistency, imprecision and indirectness; with no publication bias.

- **VALUES**

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☐ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☒ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Research evidence:

No research evidence was identified.

Panel discussion:

People are likely to value this determination.

- **BALANCE OF EFFECTS**

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:

Balance of effects is positive toward recommendations.

- **COSTS**

How large are the resource requirements (costs)?

Judgement:

☐ Don't know	☐ Varies	☒ Large costs	☐ Moderate costs	☐ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:

No research evidence was identified.

Panel discussion:

- Access to a day surgery centre with endoscopic equipment.

Access to skilled surgeons.

- **CERTAINTY OF COST EVIDENCE**

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☐ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

Refer to overarching Cost effectiveness analysis.

Panel discussion:

No evidence for resource requirements.

- **COST-EFFECTIVENESS**

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

Refer to overarching Cost effectiveness analysis.

Panel discussion:

- Single costly procedure but without need for further medications and monitoring and high probability of singleton pregnancies.

- **EQUITY**

What would be the impact on health equity?

Judgement:

☐ Don't know	☒ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☐ Probably increased	☐ Increased

Research evidence:

No research evidence was identified.

Panel discussion:

In certain healthcare systems access to surgery may be restricted or unaffordable

- **FEASIBILITY**

Is the option feasible to implement?

Judgement:

☐ Don't know	☒ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified.

Panel discussion:

- Other than local health care resources, no potential barriers identified to interfere with feasibility.

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PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by the Evidence Team: Aya Mousa, Jillian Tay
Other team members: Loyal Pattuwage

GDG 5

Question 5.6.

In women with PCOS, is ovarian surgery effective for improving fertility outcomes?

1. STUDY SELECTION

Table 1. PICO Criteria for Inclusion	
Question	**In women with PCOS, is ovarian surgery effective for improving fertility outcomes?**
Clinical leads (key contacts)	**Luk Rombauts**
Allocation ranking	**Level 2- updated systematic review (with update of integrity check for all studies)**

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(language, year)*
Inclusion	Women of any age, ethnicity and weight with PCOS diagnosed by Rotterdam, NIH or AIS and 1) at least one patent tube 2) normal sperm AND 3) have never been treated or been exposed to treatment for infertility (therapy naïve) OR 4) have been treated or exposed to treatment OR 5) have been treated or exposed to clomiphene citrate and ovulate but don't conceive (clomid failure) OR 6) have been treated or exposed to clomid and don't ovulate (clomid resistant). Also specifically identifying the 4 phenotypes where possible.	Any type of ovarian surgery alone, including: laser or diathermy laparoscopy, laparotomy, transvaginal hydrolaparoscopy. Unilateral or bilateral	Placebo, no intervention, other infertility treatment interventions including metformin, clomiphene citrate, aromatase inhibitors, gonadotrophin, or ovarian surgery in combination with other infertility treatment intervention(s). Compare uni v bi	Live birth rate, pregnancy rate (biochemical or clinical ultrasound), ovulation, single and multiple pregnancies, miscarriage rate, other adverse events, quality of life, cost effectiveness.	Evidence based guidelines, systematic reviews, health technology assessments, randomised controlled trials (RCTs).	None
Exclusion	Women without diagnosis of PCOS.	Placebo, no intervention or any intervention other than a type of ovarian surgery	Any intervention other than those listed in the inclusion criteria.	None	Non-evidence based guidelines, non-systematic reviews, any study lower than a RCT.	None

2. SEARCH STRATEGY

The search and screening for all GDG 5 questions were done together. Details can be found in the GDG 5 Methodology Appendix, including for:

- Databases
- Search Dates
- Search String(s)
- PRISMA flowchart
- Full list of included studies
- Full list of excluded studies with reasons for exclusion

Evidence processing: The literature search and screening were performed together in one Endnote library and Covidence project for all non-IVF, IVF and IVM fertility treatments in PCOS. Studies were selected by one reviewer/s in consultation with the evidence team/ key contact(s) using study selection and appraisal criteria (PICOs) established a priori. The articles were screened by title and abstract by one reviewer. When a decision could not be made based on title and abstract alone, full text was retrieved. Study appraisal was conducted by two reviewers independently with discussion to resolve any discrepancy. In total, 102 unique studies met inclusion criteria across all non-IVF, IVF and IVF questions, of which 57 were included in the guideline update following the integrity check (refer to methodology appendix for details).

Integrity Assessment: Of these eligible 102 studies, 6 studies met the inclusion criteria for this particular question (Q.5.6) on ovarian surgery, as detailed below.

Table of Included Studies
Amer SA, Li TC, Metwally M, Emarh M, Ledger WL. Randomized controlled trial comparing laparoscopic ovarian diathermy with clomiphene citrate as a first-line method of ovulation induction in women with polycystic ovary syndrome. Hum Reprod. 2009 Jan;24(1):219-25. doi: 10.1093/humrep/den325. Epub 2008 Sep 14.
Baryam N, van Wely M, Kaaijk EM, Bossuyt PM, van der Veen F. Using an electrocautery strategy or recombinant follicle stimulating hormone to induce ovulation in polycystic ovary syndrome: randomised controlled trial. BMJ. 2004 Jan 24;328(7433):192. doi: 10.1136/bmj.328.7433.192.
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Roy KK, Baruah J, Moda N, Kumar S. Evaluation of unilateral versus bilateral ovarian drilling in clomiphene citrate resistant cases of polycystic ovarian syndrome. Arch Gynecol Obstet. 2009 Oct;280(4):573-8. doi: 10.1007/s00404-009-0961-z. Epub 2009 Feb 13. PMID: 19214545.
Sharma, M., Kriplani, A., & Agarwal, N. (2006). Laparoscopic bipolar versus unipolar ovarian drilling in infertile women with resistant polycystic ovarian syndrome: a pilot study. Journal of gynecologic surgery, 22(3), 105-111.
Yadav P, Singh S, Singh R, Jain M, Awasthi S, Raj P. To study the effect on fertility outcome by gonadotropins vs laparoscopic ovarian drilling in clomiphene-resistant cases of polycystic ovarian syndrome. Journal of SAFOG 2017; 9(4): 336-340.

3. STUDY CHARACTERISTICS TABLE FOR INCLUDED STUDIES

Author, year, country	Population/ PCOS criteria/ Setting/ CC sensitivity	Study Design	Intervention N	Intervention description	Comparison N	Comparison description	Follow Up	Outcomes	Pooled in MA?	RoB
Amer 2009 UK	Women with BMI ≤32 kg/m² anovulatory infertility ≥1 year associated with PCOS (PCOS diagnosed by; at least two of: clinical (oligo/ amenorrhoea and/or hyperandrogenaemia), biochemical [LH ≥ 10 IU/l, LH/FSH ratio ≥2, T >2.6 nmol/l or FAI >5] and/or polycystic ovaries on U/S; Reproductive Medicine Centre; **CCR**	RCT	**LOD: 36** Age: 28.1 ± 4.3 BMI: 26.2 ± 3.9	Monopolar electrocautery probe was used to penetrate the ovarian capsule making four punctures per ovary at a power setting of 30 W applied for 5 s per puncture If the patient did not ovulate as evidenced by the low progesterone levels or lack of menstruation, CC would be started 6–8 weeks after surgery	**CC: 36** Age: 29.1 ± 4.8 BMI: 26.1 ± 3.5	Incremental doses starting with a daily dose of 50 up to 150 mg on Days 2–6 of a menstrual period or after a progestogen withdrawal bleed using medroxy-progesterone acetate. Continued for 6 cycles and if still anovulatory after the maximum dose of CC or failed to conceive after six ovulatory cycles, surgery was offered.	Up to 12 months after surgery	Primary: cumulative pregnancy rate at 12 months Secondary: ovulation, miscarriage, multiple pregnancy and live birth rates Conception was diagnosed with a positive urinary pregnancy test taken 1 week after a missed period, then transvaginal ultrasound scan at 7 weeks of gestation	No	Mod – no blinding
Baryam 2004 The Netherlands	Chronic anovulation (World Health Organization type II) and polycystic ovaries, diagnosed by transvaginal Ultrasonography, 29 Dutch hospitals; **CCR**	RCT	**Laparoscopic surgery**: 83 Age: 28.5±3.7 BMI: 27.9±6.3	**Laparoscopic electrocautery of the ovaries.** If ovulated, no further treatment. Each ovary was randomly punctured 5-10 times, depending on its size using 15mm long 0.9mm diameter needle. If anovulation persisted, 50mg clomiphene citrate (CC) increased to max 150mg.	**FSH**: 85 Age: 28.7±4.1 BMI: 27.3±8.8	10 mg medroxy-progesterone for 10 days, followed by daily 75 IU **rFSH**. If the diameter of the follicles remained < 10 mm, the dose was increased by half an ampoule (37.5 IU) on each of cycle days 16 and 23.	12 months	Pregnancy, miscarriages, multiple pregnancies, premature deliveries Clinical pregnancy: The primary end point was ongoing pregnancy within 12 months, defined as a viable pregnancy of at least 12 weeks.	Yes	High – high drop outs in controls and non-blinded
Farquhar 2002 New Zealand	PCOS diagnosed based on criteria by Adams et al. (1985)✶; publicly funded and private tertiary level fertility clinics; all patients had infertility and treatment before; **CCR**	RCT (N per group dissimilar due to unblocked random-ization)	**Laparoscopic ovarian diathermy**: 29 Age: 29.6±4.7 BMI: 28.3±3.9	**Laparoscopic ovarian diathermy:** A monopolar electrocautery needle of 1 cm in length was used to drill 10 holes in each ovary. The diathermy was done with cutting power at 30 units and was continued for 10 seconds	**Urinary or recombinant FSH** (3 cycles): 21 Age: 29.6±4.2 BMI: 27.8±4.8	**Urinary or rFSH**: 75 IU/day (one ampoule) was given for 2 weeks, adjusted accordingly depending on the serum E2	6 months (for surgery) 3 cycles (FSH)	Ovulation rates, pregnancy outcomes, birth after 20 weeks of gestation Pregnancy detection: serum β-hCG of >50 IU/l and foetal heart activity on ultrasound scan	Yes	High – small and non-blinded
Roy 2009 India	PCOS patients based on Rotterdam criteria; No other infertility factor; National centre; **CCR**	RCT	Unipolar diathermy: 22 Age: 28.2±1.7	Unilateral ovarian drilling A unipolar diathermy drilling needle was used to penetrate the ovarian capsule at right angle to a standard depth of 8 mm at points with 60 W cutting current to make 5	Bipolar diathermy: 22 Age: 28.8±2.9	Bilateral ovarian drilling. A unipolar diathermy drilling needle was used to penetrate the ovarian capsule at right angle to a standard depth of 8 mm at points with 60 W cutting current	1 year	Clinical and biochemical response, ovulation rate and pregnancy rate How pregnancy was ascertained not reported		High- no randomisation or concealment details, no blinding

			BMI ≤30: 63.6%	punctures in the ovary; If no ovulation within 3 months, the patients were started on CC 50 mg daily for 5 days increasing up to maximum of 150 mg daily for 5 days for maximum of 6 cycles.	BMI ≤30: 5 4.5%	to make 5 punctures each in both ovaries If no ovulation within 3 months, the patients were started on CC 50 mg daily for 5 days increasing up to maximum of 150 mg daily for 5 days for maximum of 6 cycles.				
Sharma 2006 India	Criteria used to identify PCOS women - National Institute of Health Consensus Conference on PCOS-no citation available; setting: a national centre; **CCR**	RCT	Unipolar electocautery: 10 Age: 27.3 BMI: 26.68	Unipolar electocautery Carried out with unipolar diathermy needle at power settings of 30–40 watts (average number of punctures 14.8)	Bipolar electocautery: 10 Age: 25.5 BMI: 24.13	Bipolar electocautery bipolar diathermy needle at power settings of 40–50 watts (average number of punctures 14.9)	1 and 3 months at onset of period, up to conception, if ovulation and conception had not occurred by 3 months	pregnancy rate, changes in luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone levels, and alteration of glucose tolerance and insulin levels How pregnancy was ascertained not reported	Yes	High- no randomisation or concealment details, no blinding, small n
Yadav 2017 India	Chronic anovulation and polycystic ovaries diagnosed by transvaginal ultrasonography-Any standard criteria not reported. Hospital-based setting; **CCR**	RCT	**rFSH**: 44 Age: 26.23±2.9 BMI: 24.94±2.8	**rFSH** subcutaneous injection of 37.5/75 IU/daily started on cycle day 3-If the diameter of the follicle remained <10 mm, dose was increased by half an ampoule (37.5 IU) on days 16 and 23. If no follicle development was seen on day 30, the cycle was terminated because of poor response.	**LOD**: 45 Age: 26.11±2.7 BMI: 25.0±2.35	**LOD:** An insulated monopolar needle was introduced at 90° angle to the ovarian cortex and 4-5 puncture sites were created. Those who failed to ovulate on LOD spontaneously at 8 wk, were then added with CC for 1 cycle followed by gonadotrophin.	12 months	Primary: Pregnancy was ascertained based on positive urine pregnancy test but defined as a viable pregnancy of at least 12 weeks Secondary: ovulation, miscarriage, ectopic pregnancy, multiple pregnancies, and live birth	Yes	High – lacking critical info

CC, clomiphene citrate; CCR, clomiphene citrate resistant (to ovulate); CCF, clomiphene citrate failure (to become pregnant); LET, letrozole; MET, metformin; NR; not reported; OHSS, ovarian hyperstimulation syndrome; IUI, intrauterine insemination; hCG, human chorionic gonadotrophin; LH, luteinizing hormone; FSH, follicle stimulating hormone; MA, meta-analysis; RoB, risk of bias. All age data is in years and BMI is in kg/m^2. *Risk of bias assessment derived from reliable systematic review (e.g. Cochrane or previous review from the guideline evidence team). ⧖Ref: Adams J, et al. *Lancet* 1985;1375–9.

4. FINDINGS

Comparisons Included:

- **Comparison 1.** LOD vs gonadotrophins (FSH)
- **Comparison 2.** LOD vs CC
- **Comparison 3.** Unilateral LOD vs Bilateral LOD

COMPARISON 1: LOD versus Gonadotrophins (FSH)

▪ EVIDENCE SUMMARY:

Three studies (Baryam et al. 2004; Farquhar et al. 2002; Yadav et al. 2017) compared laparoscopic ovarian drilling (LOD) with FSH, conducted in the Netherlands, New Zealand and India. All three studies were in women with clomiphene-citrate resistant PCOS and all were judged as having a high risk of bias due to lack of blinding (or insufficient information to ascertain blinding), as well as small sample sizes and high dropout rates.

▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

FSH was superior to LOD for live birth rates; however, FSH also resulted in a higher rate of multiple pregnancies per patient, with an OR of 0.20 favouring LOD (i.e. 80% lower odds with LOD). While certainty in the evidence for live birth rates per patient was moderate (downgraded once due to risk of bias), certainty in the evidence for all other outcomes was low or very low due to risk of bias, varied effect estimates and varied and/or wide CIs. Given that all studies for this comparison had a high risk of bias, findings should be interpreted with caution.

Outcome or Subgroup	Studies	n	Effect Estimate; OR [95% CI], M-H, random	P	Favours	Certainty
Live birth rate- per patient	3	307	0.45 [0.27, 0.76]	0.003	**FSH** (live birth rate is higher with FSH)	⊕⊕◯◯ MODERATE
Clinical pregnancy rate- per patient†	3	307	0.44 [0.16, 1.23]	0.1	None	⊕⊕◯◯ LOW
Ovulation rate - per patient	1	50	0.66 [0.21, 2.07]	0.5	None	⊕◯◯◯ VERY LOW
Multiple pregnancy rate – per patient	3	307	0.20 [0.05, 0.72]	0.01	**LOD** (multiple pregnancy rate is higher with FSH)	⊕⊕◯◯ LOW
Miscarriage rate- per patient	3	307	0.73 [0.32, 1.66]	0.5	None	⊕⊕◯◯ LOW

† clinical pregnancy rate is confirmed by ultrasound detection of gestational sac/ fetal heart activity.

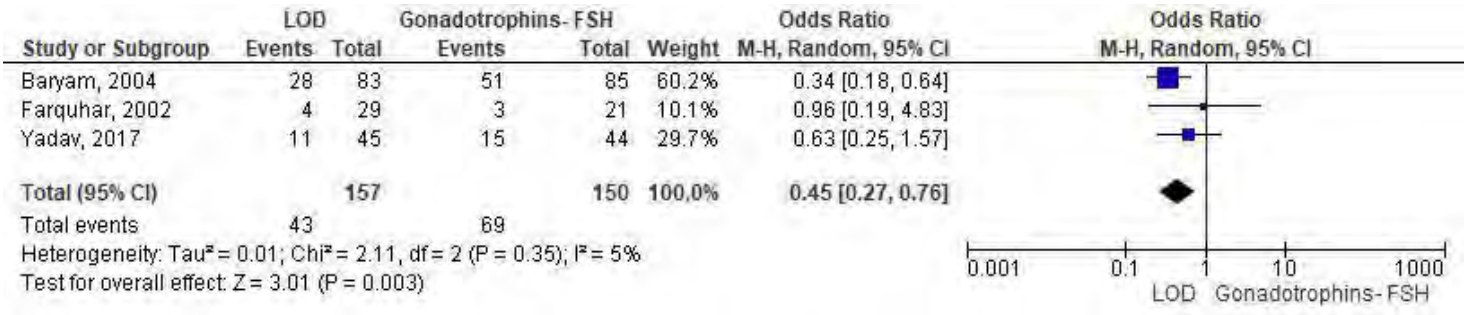
OUTCOME 1.1. Live birth rate – per patient

1.1.1. Individual Study Data Tables

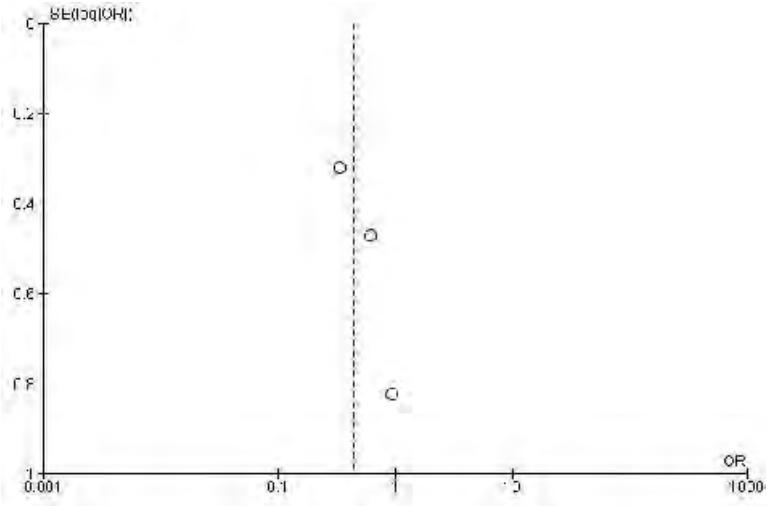
OUTCOME: Live birth rate per patient				**OUTCOME TYPE:** Dichotomous					
COMPARISON: LOD vs FSH									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in control / comparison group (LOD)**	**N total in control/ comparison group (LOD)**	**N events in intervention/ exposure group (FSH)**	**N total in intervention/ exposure group (FSH)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Baryam 2004 (HRB)	CCR	Count	Investigator	28	83	51	85	Crude	NA
Farquhar 2002 (HRB)	CCR	Count	Investigator	4	29	3	21	Crude	NA
Yadav 2017 (HRB)	CCR	Count	Investigator	11	45	15	44	Crude	NA

CCR, clomiphene citrate-resistant

1.1.2. Forest Plot of all included RCTs comparing LOD versus FSH for live birth rate – per patient



1.1.3. Funnel plot for assessment of publication bias



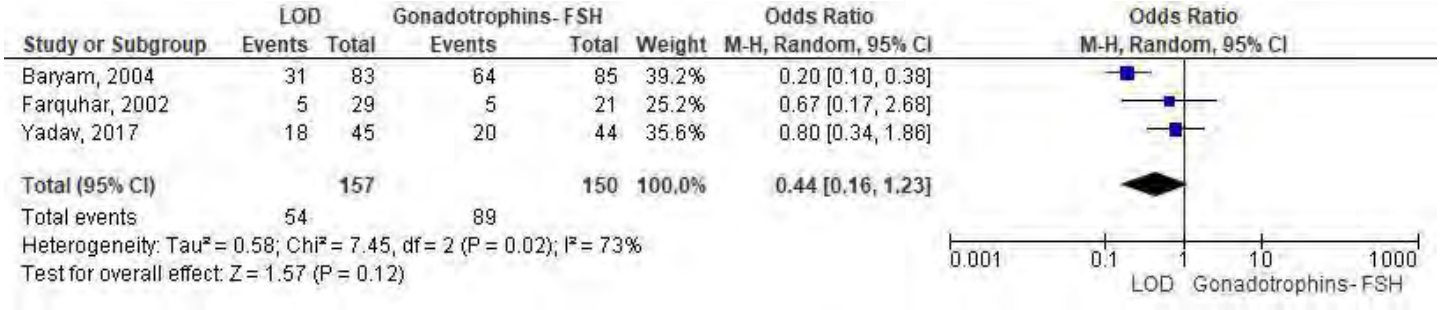
OUTCOME 1.2. Clinical pregnancy rate – per patient

1.2.1. Individual Study Data Tables

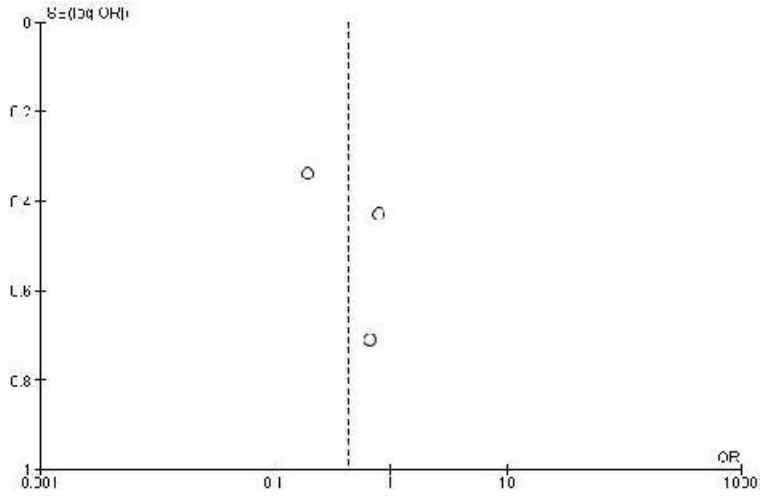
OUTCOME: Clinical pregnancy rate per patient						**OUTCOME TYPE:** Dichotomous			
COMPARISON: LOD vs FSH									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (LOD)**	**N total in intervention/ exposure group (LOD)**	**N events in control / comparison group (FSH)**	**N total in control/ comparison group (FSH)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Baryam 2004 (HRB)	CCR	Count	Investigator	31	83	64	85	Crude	NA
Farquhar 2002 (HRB)	CCR	Count	Investigator	5	29	5	21	Crude	NA
Yadav 2017 (HRB)	CCR	Count	Investigator	18	45	20	44	Crude	NA

CCR, clomiphene citrate-resistant

1.2.2. Forest plot of all included RCTs comparing LOD versus FSH for clinical pregnancy rate – per patient



1.2.3. Funnel plot for assessment of publication bias



OUTCOME 1.3. Ovulation rate – per patient

1.3.1. Individual Study Data Tables

OUTCOME: Ovulation rate per patient						OUTCOME TYPE: Dichotomous			
COMPARISON: LOD vs FSH									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (LOD)**	**N total in intervention/ exposure group (LOD)**	**N events in control / comparison group (FSH)**	**N total in control/ comparison group (FSH)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Farquhar 2002 (HRB)	**CCR**	**Count**	**Investigator**	**15**	**29**	**13**	**21**	**Crude**	**NA**

CCR, clomiphene citrate-resistant

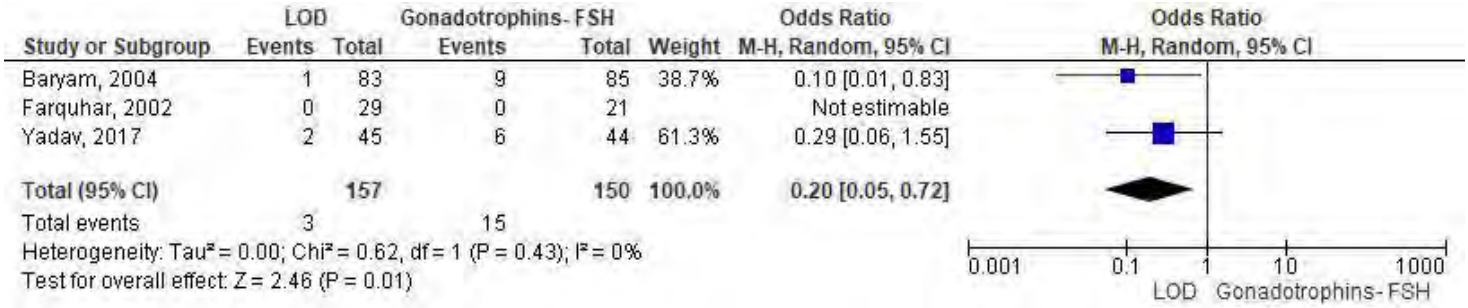
OUTCOME 1.4. Multiple pregnancy rate – per patient

1.4.1. Individual Study Data Tables

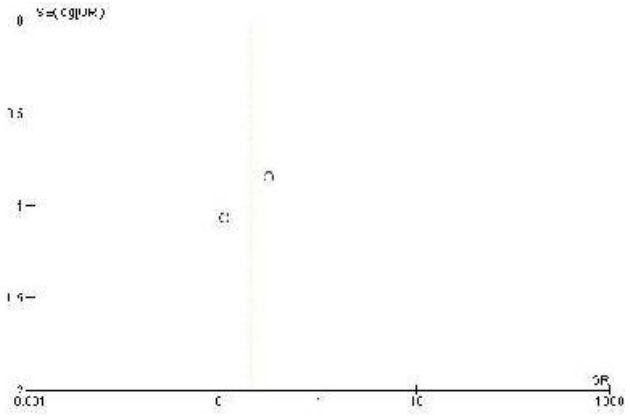
OUTCOME: Multiple pregnancy rate per patient						OUTCOME TYPE: Dichotomous			
COMPARISON: LOD vs FSH									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (LOD)**	**N total in intervention/ exposure group (LOD)**	**N events in control / comparison group (FSH)**	**N total in control/ comparison group (FSH)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Baryam 2004 (HRB)	CCR	Count	Investigator	1	83	9	85	Crude	NA
Farquhar 2002 (HRB)	CCR	Count	Investigator	0	29	0	21	Crude	NA
Yadav 2017 (HRB)	CCR	Count	Investigator	2	45	6	44	Crude	NA

CCR, clomiphene citrate-resistant

1.4.2. Forest Plot of all included RCTs comparing LOD versus FSH for multiple pregnancy rate – per patient



1.4.3. Funnel plot for assessment of publication bias



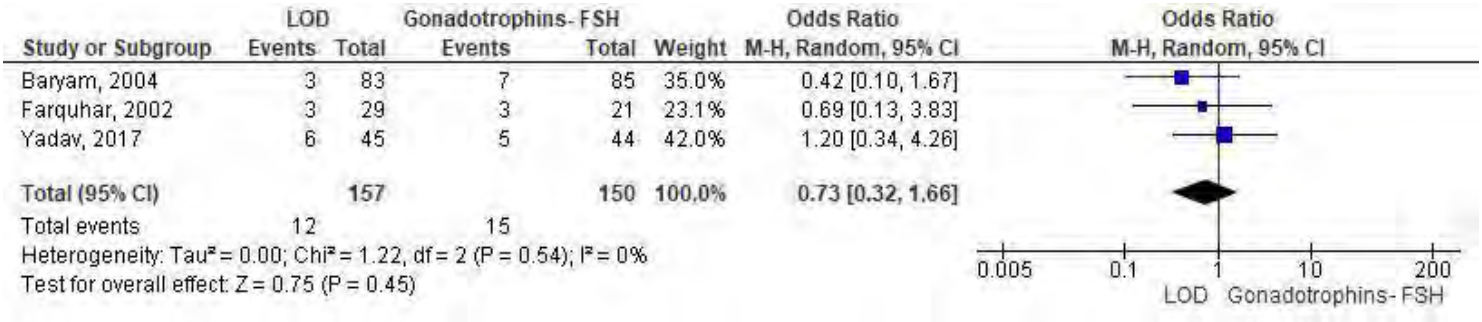
OUTCOME 1.5. Miscarriage rate – per patient

1.5.1. Individual Study Data Tables

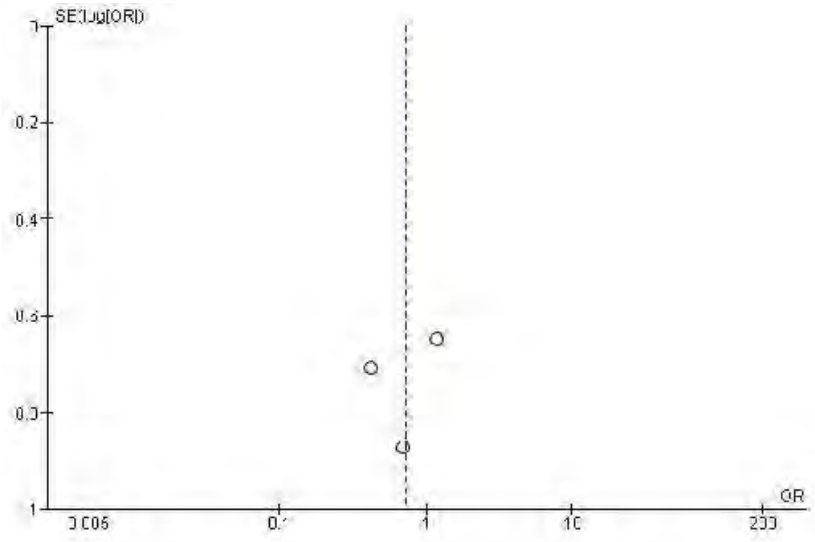
OUTCOME: Miscarriage rate per patient						**OUTCOME TYPE:** Dichotomous			
COMPARISON: LOD vs FSH									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (LOD)**	**N total in intervention/ exposure group (LOD)**	**N events in control / comparison group (FSH)**	**N total in control/ comparison group (FSH)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Baryam 2004 (HRB)	CCR	Count	Investigator	3	83	7	85	Crude	NA
Farquhar 2002 (HRB)	CCR	Count	Investigator	3	29	3	21	Crude	NA
Yadav 2017 (HRB)	CCR	Count	Investigator	6	45	5	44	Crude	NA

CCR, clomiphene citrate-resistant

1.5.2. Forest Plot of all included RCTs comparing FSH versus LOD for miscarriage rate – per patient



1.5.3. Funnel plot for assessment of publication bias



COMPARISON 2: LOD versus Clomiphene Citrate

- **EVIDENCE SUMMARY:**

A single UK-based study by Amer et al. (2009) examined the efficacy of LOD compared with clomiphene citrate in 76 women with anovulatory PCOS and clomiphene citrate resistance. Women treated with clomiphene citrate unsuccessfully for 6 cycles were then also offered LOD. There was no blinding in this study; once randomised, the allocation was revealed to the investigators and patients. Hence, the study was judged as moderate risk of bias.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

There were no differences between LOD versus CC in live birth rate or clinical pregnancy rate per patient or miscarriage rate per pregnancy. There was low certainty for all outcomes due to the evidence being derived from a single, small study (downgraded once for imprecision) with a moderate risk of bias (downgraded once for risk of bias).

Outcome or Subgroup	Studies	n	Effect Estimate; OR [95% CI], M-H, random	P	Favours	Certainty
Live birth rate- per patient	1	65	0.65 [0.24, 1.72]	0.4	None	⊕⊕◯◯ LOW
Clinical pregnancy rate- per patient†	1	65	0.60 [0.21, 1.70]	0.3	None	⊕⊕◯◯ LOW
Miscarriage rate- per pregnancy	1	43	1.17 [0.15, 9.14]	0.9	None	⊕⊕◯◯ LOW

† clinical pregnancy rate is confirmed by ultrasound detection of gestational sac/ fetal heart activity

OUTCOME 2.1. Live birth rate – per patient

2.1.1. Individual Study Data Table

OUTCOME: Live birth rate – per patient						**OUTCOME TYPE:** Dichotomous			
COMPARISON: LOD vs CC									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in intervention group (LOD)**	**N total in intervention group (LOD)**	**N events in control / comparison group (CC)**	**N total in control/ comparison group (CC)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Amer 2009 (MRB)	CCR	Count	Investigator	15	33	18	32	Crude	NA

CCR, Clomiphene citrate-resistant

OUTCOME 2.2. Clinical pregnancy rate – per patient

2.2.1. Individual Study Data Table

OUTCOME: Clinical pregnancy rate – per patient						**OUTCOME TYPE:** Dichotomous			
COMPARISON: LOD vs CC									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in intervention group (LOD)**	**N total in intervention group (LOD)**	**N events in control / comparison group (CC)**	**N total in control/ comparison group (CC)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Amer 2009 (MRB)	CCR	Count	Investigator	20	33	23	32	Crude	NA

CCR, Clomiphene citrate-resistant.

OUTCOME 2.3. Miscarriage rate – per pregnancy

2.3.1. Individual Study Data Table

OUTCOME: Miscarriage rate – per pregnancy						**OUTCOME TYPE:** Dichotomous			
COMPARISON: LOD vs CC									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg, µg)**	**Method of measurement**	**N events in intervention group (LOD)**	**N total in intervention group (LOD)**	**N events in control / comparison group (CC)**	**N total in control/ comparison group (CC)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Amer 2009 (MRB)	CCR	Count	Investigator	2	20	2	23	Crude	NA

CCR, Clomiphene citrate-resistant.

COMPARISON 3: Unilateral LOD vs Bilateral LOD

- **EVIDENCE SUMMARY:**

Two studies in India examined unilateral versus bilateral LOD in women with PCOS and clomiphene citrate resistance (Roy et al. 2009; Sharma et al. 2006). Both studies were judged as high risk of bias due to lacking information on blinding and allocation concealment and having small sample sizes.

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

There were no differences between bilateral versus unilateral LOD for any of the assessed outcomes, including live birth rate, pregnancy rate, ovulation rate and multiple pregnancy rate per patient or miscarriage rate per patient or per pregnancy. Certainty in the evidence was low for live birth rate, but very low for the remaining outcomes due to risk of bias (high for all), imprecision (being derived from a single small study) or inconsistency (having varied effect estimates or wide CIs).

Outcome or Subgroup	Studies	n	Effect Estimate; OR [95% CI], M-H, random	P	Favours	Certainty
Live birth rate- per patient	2	64	0.60 [0.22, 1.66]	0.3	None	⊕⊕◯◯ LOW
Pregnancy rate- per patient*	1	20	0.43 [0.07, 2.68]	0.4	None	⊕◯◯◯ VERY LOW
Ovulation rate- per patient	1	20	1.00 [0.05, 18.57]	1.0	None	⊕◯◯◯ VERY LOW
Multiple pregnancy rate- per patient	1	44	0.32 [0.01, 8.25]	0.5	None	⊕◯◯◯ VERY LOW
Miscarriage rate- per patient	2	64	1.39 [0.24, 8.00]	0.7	None	⊕◯◯◯ VERY LOW
Miscarriage rate- per pregnancy	2	32	1.60 [0.25, 10.11]	0.6	None	⊕◯◯◯ VERY LOW

*includes clinical, biochemical (or undefined pregnancy rate) as reported in each study

OUTCOME 3.1. Live birth rate – per patient

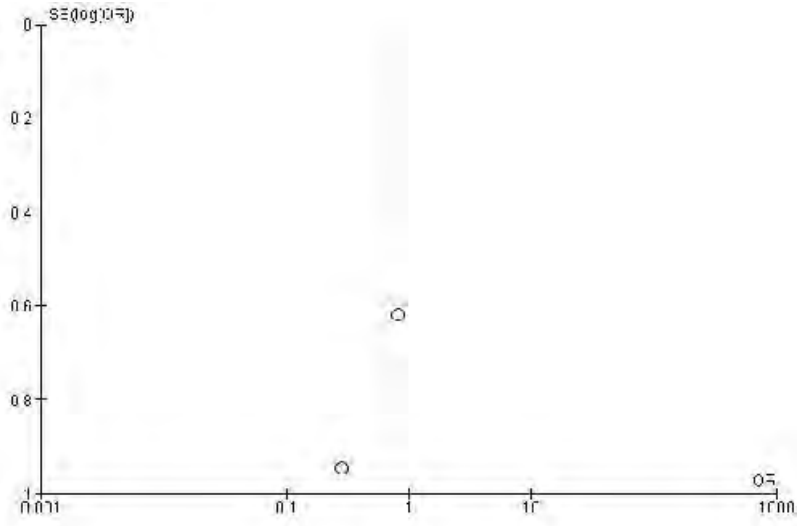
3.1.1. Individual Study Data Table

OUTCOME: Live birth rate per patient									**OUTCOME TYPE:** Dichotomous
COMPARISON: Unilateral vs Bilateral LOD									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (uni-LOD)**	**N total in intervention/ exposure group (uni-LOD)**	**N events in control / comparison group (bi-LOD)**	**N total in control/ comparison group (bi-LOD)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Roy 2009 (HRB)	CCR	Count	Investigator	8	22	9	22	Crude	NA
Sharma 2006 (HRB)	CCR	Count	Investigator	4	10	7	10	Crude	NA

CCR, Clomiphene citrate-resistant

3.1.2. Forest plot of all included RCTs comparing bilateral LOD versus unilateral LOD for live birth rate – per patient

3.1.3. Funnel plot for assessment of publication bias



OUTCOME 3.2. Pregnancy rate – per patient

3.2.1. Individual Study Data Table

OUTCOME: Pregnancy rate per patient						**OUTCOME TYPE:** Dichotomous			
COMPARISON: Unilateral vs Bilateral LOD									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (uni-LOD)**	**N total in intervention/ exposure group (uni-LOD)**	**N events in control / comparison group (bi-LOD)**	**N total in control/ comparison group (bi-LOD)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Sharma 2006 (HRB)	CCR	Count	Investigator	5	10	7	10	Crude	NA

CCR, Clomiphene citrate-resistant

OUTCOME 3.3. Ovulation rate – per patient

3.3.1. Individual Study Data Table

OUTCOME: Pregnancy rate per patient						**OUTCOME TYPE:** Dichotomous			
COMPARISON: Unilateral vs Bilateral LOD									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (uni-LOD)**	**N total in intervention/ exposure group (uni-LOD)**	**N events in control / comparison group (bi-LOD)**	**N total in control/ comparison group (bi-LOD)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Sharma 2006 (HRB)	CCR	Count	Investigator	9	10	9	10	Crude	NA

CCR, Clomiphene citrate-resistant

OUTCOME 3.4. Multiple pregnancy rate – per patient

3.4.1. Individual Study Data Table

OUTCOME: Pregnancy rate per patient						**OUTCOME TYPE:** Dichotomous			
COMPARISON: Unilateral vs Bilateral LOD									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (uni-LOD)**	**N total in intervention/ exposure group (uni-LOD)**	**N events in control / comparison group (bi-LOD)**	**N total in control/ comparison group (bi-LOD)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Roy 2009 (HRB)	CCR	Count	Investigator	0	22	1	22	Crude	NA

CCR, Clomiphene citrate-resistant

OUTCOME 3.5. Miscarriage rate – per patient

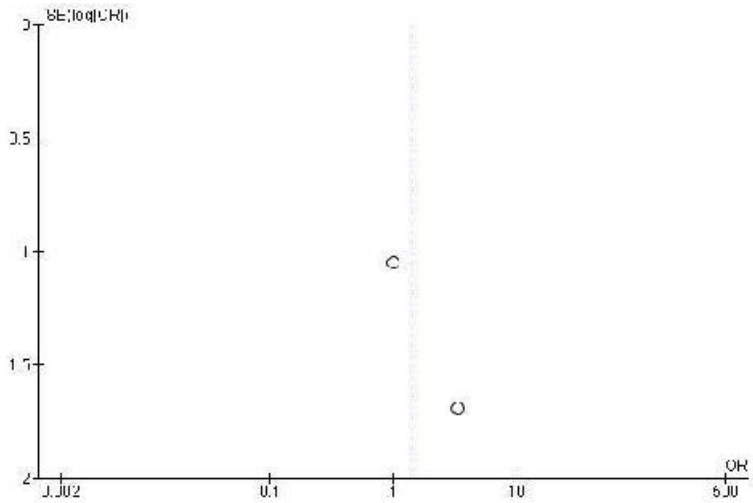
3.5.1. Individual Study Data Table

OUTCOME: Miscarriage rate per patient									
OUTCOME TYPE: Dichotomous									
COMPARISON: Unilateral vs Bilateral LOD									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (uni-LOD)**	**N total in intervention/ exposure group (uni-LOD)**	**N events in control / comparison group (bi-LOD)**	**N total in control/ comparison group (bi-LOD)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Roy 2009 (HRB)	CCR	Count	Investigator	2	22	2	22	Crude	NA
Sharma 2006 (HRB)	CCR	Count	Investigator	1	10	0	10	Crude	NA

CCR, Clomiphene citrate-resistant

3.5.2. Forest plot of all included RCTs comparing bilateral LOD versus unilateral LOD for miscarriage rate – per patient

3.5.3. Funnel plot for assessment of publication bias



OUTCOME 3.6. Miscarriage rate – per pregnancy

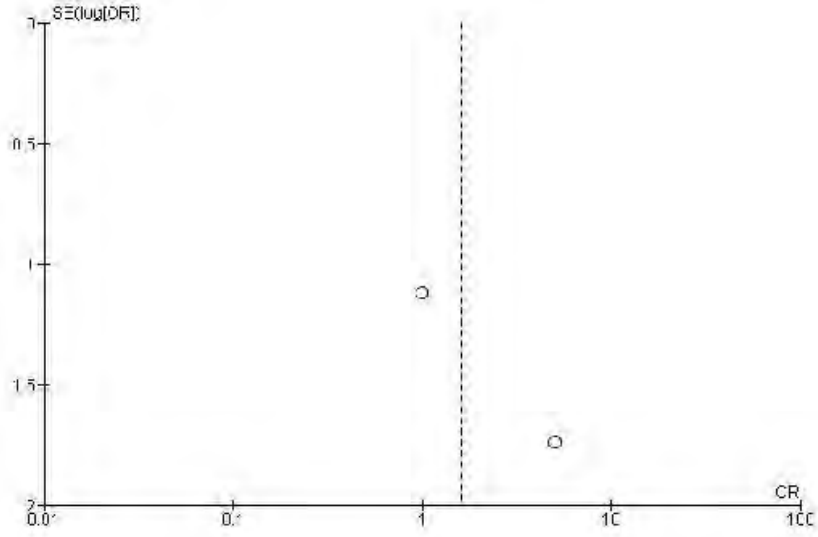
3.6.1. Individual Study Data Table

OUTCOME: Miscarriage rate per pregnancy									
OUTCOME TYPE: Dichotomous									
COMPARISON: Unilateral vs Bilateral LOD									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (uni-LOD)**	**N total in intervention/ exposure group (uni-LOD)**	**N events in control / comparison group (bi-LOD)**	**N total in control/ comparison group (bi-LOD)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Roy 2009 (HRB)	CCR	Count	Investigator	2	10	2	10	Crude	NA
Sharma 2006 (HRB)	CCR	Count	Investigator	1	5	0	7	Crude	NA

CCR, Clomiphene citrate-resistant

3.6.2. Forest plot of all included RCTs comparing bilateral LOD versus unilateral LOD for miscarriage rate – per pregnancy

3.6.3. Funnel plot for assessment of publication bias



5. GRADE ASSESSMENTS AND EVIDENCE PROFILE

COMPARISON 1: Laparoscopic Ovarian Drilling (LOD) versus Gonadotrophins (FSH)												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	LOD	FSH	Effect, random , OR [95% CI]	Favours	Certainty	Importance
Outcome: Live birth rate- per patient												
3	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	43/157 (27.4%)	69/150 (46.0%)	0.45 [0.27, 0.76]	**FSH** (live birth rate is lower with LOD)	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome: Clinical pregnancy rate- per patient												
3	RCT	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	54/157 (34.4%)	86/150 (57.3%)	0.44 [0.16, 1.23]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Multiple pregnancy rate- per patient												
3	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	3/157 (1.92%)	15/150 (10.0%)	0.20 [0.05, 0.72]	**LOD** (multiple pregnancy rate is lower with LOD)	⊕⊕◯◯ LOW	CRITICAL
Outcome: Ovulation rate - per patient												
1	RCT	very serious[2]	not applicable	not applicable	serious[4]	none	15/29 (51.7%)	13/21 (61.9%)	0.66 [0.21, 2.07]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Miscarriage rate - per patient												
3	RCT	serious[1]	serious[5]	no serious indirectness	no serious imprecision	none	12/157 (7.64%)	15/150 (10.0%)	0.73 [0.32, 1.66]	No difference	⊕⊕◯◯ LOW	IMPORTANT

[1] Downgraded once for risk of bias due to high or moderate risk for the majority of included studies (half or more) or twice if all included studies are at high risk of bias
[2] Downgraded once for inconsistency due to varying confidence intervals and effects estimates
[3] Downgraded once for imprecision due to wide confidence intervals
[4] Downgraded once for imprecision due to the evidence being derived from a single study with a small sample size
[5] Downgraded once for inconsistency due to varying effect estimates (different directions) and wide confidence intervals

COMPARISON 2: Laparoscopic ovarian drilling (LOD) versus Clomiphene citrate (CC)												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	LOD	CC	Effect, random , OR [95% CI]	Favours	Certainty	Importance
Outcome: Live birth rate- per patient												
1	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	15/33 (45.5%)	18/32 (56.3%)	0.65 [0.24, 1.72]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Clinical pregnancy rate- per patient												

1	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20/33 (60.6%)	23/32 (71.9%)	0.60 [0.21, 1.70]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Miscarriage rate - per pregnancy												
1	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	2/20 (10.0%)	2/23 (8.7%)	1.17 [0.15, 9.14]	No difference	⊕⊕◯◯ LOW	IMPORTANT

[1] Downgraded once for risk of bias due to high or moderate risk for the majority of included studies (half or more)
[2] Downgraded once for imprecision due to the evidence being derived from a single small study

COMPARISON 3: Unilateral versus Bilateral Laparoscopic Ovarian Drilling (LOD)												
	Quality assessment						**No. participants**					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Uni-LOD**	**Bi-LOD**	**Effect, random , OR [95% CI]**	**Favours**	**Certainty**	**Importance**
Outcome: Live birth rate- per patient												
2	RCT	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/32 (37.5%)	16/32 (50.0%)	0.60 [0.22, 1.66]	No difference	⊕⊕◯◯ LOW	CRITICAL
Outcome: Pregnancy rate- per patient												
1	RCT	very serious[1]	not applicable	not applicable	serious[2]	none	5/10 (50.0%)	7/10 (70.0%)	0.43 [0.07, 2.68]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Multiple pregnancy rate- per patient												
1	RCT	very serious[1]	not applicable	not applicable	serious[2]	none	0/22 (0.0%)	1/22 (4.5%)	0.32 [0.01, 8.25]	No difference	⊕◯◯◯ VERY LOW	CRITICAL
Outcome: Ovulation rate - per patient												
1	RCT	very serious[1]	not applicable	not applicable	serious[2]	none	9/10 (90.0%)	9/10 (90.0%)	1.00 [0.05, 18.57]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Miscarriage rate - per patient												
2	RCT	very serious[1]	serious[3]	no serious indirectness	no serious imprecision	none	3/32 (9.4%)	2/32 (6.3%)	1.39 [0.24, 8.00]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT
Outcome: Miscarriage rate- per pregnancy												
2	RCT	very serious[1]	serious[3]	no serious indirectness	no serious imprecision	none	3/15 (20.0%)	2/17 (11.8%)	1.60 [0.25, 10.11]	No difference	⊕◯◯◯ VERY LOW	IMPORTANT

[1] Downgraded twice because all included studies are at high risk of bias
[2] Downgraded once for imprecision due to the evidence being derived from a single small study
[3] Downgraded once for inconsistency due to varied effect estimates and/or wide confidence intervals

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 5

Question 5.6.

In women with PCOS, is ovarian surgery effective for improving fertility outcomes?

BACKGROUND

In 1935 Stein and Leventhal were the first to describe an association between the presence of polycystic ovaries, oligo/anovulation and hirsutism, later known as PCOS (1). The observation that women with PCOS resumed regular ovulations following ovarian biopsies led to the belief that the condition was primarily ovarian in origin. This also resulted in the development of a surgical treatment for the condition involving a wedge resection of both ovaries via laparotomy (2). A 15-25 year follow-up of nearly 150 women after ovarian wedge resection shows that regular menstrual patterns lasting up to 25 years after surgery were restored in 88% of patients with a cumulative pregnancy/live birth rate of 78% (3).

No alternative treatment was available until the arrival of hormonal preparations such as clomiphene citrate and gonadotrophins. Ovarian wedge resection was then soon abandoned because of the relative cost of the surgical treatment and the risk of post-operative adhesions.

It was not until the introduction of minimally invasive techniques that surgical approaches were revisited. The laparoscopic ovarian drilling procedure was first described by Gjønæss in 1984 (4). Minor variations of the technique have been reported (electrocautery, laser vaporization, multiple ovarian biopsies and others) but all are characterised by an altered endocrine profile following surgery. Some studies have also examined the relative effectiveness of unilateral versus bilateral laparoscopic ovarian drilling. It remains poorly understood, however, which mechanisms bring about the hormonal changes and the resumption of ovulation.

The main reason laparoscopic ovarian surgery has found support for the treatment of women with CCR PCOS is the fact that the endoscopic approach is thought 1) to cause fewer adhesions, 2) to be more cost-effective as an outpatient-procedure and 3) to restore regular mono-ovulations, albeit for a limited time in the majority of cases. In contrast, ovulation induction with gonadotrophins is expensive, requires regular monitoring and often results in the development of multiple mature follicles with a potential risk of multiple pregnancies and ovarian hyperstimulation syndrome. It is important to establish the effectiveness of laparoscopic ovarian surgery, particularly in comparison to other treatments, in infertile women with PCOS in light of the potential risks.

This review focuses on the clinical effectiveness of laparoscopic ovarian surgery compared to non-surgical treatments for PCOS. It also compares the clinical effectiveness of unilateral versus bilateral laparoscopic ovarian surgery.
For the purpose of this review, laparoscopic ovarian drilling (LOD), sometimes also referred to as laparoscopic ovarian diathermy or laparoscopic ovarian surgery (LOS) is a keyhole surgical procedure in which a diathermy instrument (usually a monopolar needle) is used to puncture the ovarian cortex followed by the delivery an electrical current to the ovarian stroma.

GRADE EVIDENCE CERTAINTY	
Comparison	**GRADE for critical outcomes**
Comparison 1. Laparoscopic Ovarian Surgery (LOS) vs gonadotrophins (FSH)	⊕⊕◯◯ LOW
Comparison 2. LOS vs Clomiphene citrate	⊕⊕◯◯ LOW
Comparison 3. Unilateral LOS vs Bilateral LOS	⊕◯◯◯ VERY LOW

Evidence to Recommendations Framework

COMPARISONS (option versus other option)

Comparison 1. LOS vs gonadotrophins (FSH)

Comparison 2. LOS vs Clomiphene citrate

Comparison 3. Unilateral LOS vs Bilateral LOS

EVIDENCE-BASED RECOMMENDATION(S)

EBR: Laparoscopic ovarian surgery could be second line therapy for women with PCOS who are anovulatory and infertile, with clomiphene citrate resistance and no other infertility factors

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

PRACTICE POINT(S)

When using laparoscopic ovarian surgery, the following should be considered:

- Cost of either intervention for ovulation induction
- Expertise required for the safe use of either intervention for ovulation induction
- Both intra-operative and post-operative risks should be considered which are higher in women who are above healthy weight

GRADE CONSIDERATIONS

Justifications:

- FSH was superior to LOD for live birth rates; however, FSH also resulted in a higher rate of multiple pregnancies per patient, with an OR of 0.20 favouring LOD (i.e. 80% lower odds with LOD). While certainty in the evidence for live birth rates per patient was moderate (downgraded once due to risk of bias), certainty in the evidence for all other outcomes was low or very low due to risk of bias, varied effect estimates and varied and/or wide CIs. Given that all studies for this comparison had a high risk of bias, findings should be interpreted with caution.
- A single UK-based study by Amer et al. (2009) (5) examined the efficacy of LOD compared with clomiphene citrate in 76 women with anovulatory PCOS and clomiphene citrate resistance. Women treated with clomiphene citrate unsuccessfully for 6 cycles were then also offered LOD. There was no blinding in this study; once randomised, the allocation was revealed to the investigators and patients. Hence, the study was judged as moderate risk of bias.
- Two studies in India examined unilateral versus bilateral LOD in women with PCOS and clomiphene citrate resistance (6, 7) . Both studies were judged as high risk of bias due to lacking information on blinding and allocation concealment and having small sample sizes.

Subgroup considerations

N/A

Implementation considerations:

- Adequate surgical skill training of surgeons and facilities. Access to effective first line ovulation induction treatments prior to LOS.

Monitoring and evaluation considerations:

Standard monitoring for long term outcomes

Research priorities:

Further research is required to understand how LOS restores ovulatory function.

Further adequately powered, well designed, conducted and reported RCTs are required to compare LOS with other ovulation induction agents in women with PCOS.

Further research is required in identifying profiles of women with PCOS who may respond to LOS.

Further research is required to determine the minimal effective intervention of LOS (i.e. how many drillings, at which energy level and modality and unilateral or bilateral)

GRADE framework

GRADE DECIDE Interactive Evidence to Decision Framework

- **DESIRABLE EFFECTS**

How substantial are the desirable anticipated effects?

Judgement:

☒ Favours this option	☐ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

- Single intervention that leads to the preferred outcome (singleton birth) in a significant proportion of women in the target group in a sustained way (but not permanent).
- No need for ongoing cycle monitoring (because of mono-ovulation).
- Normal risk of multiple pregnancy.

- **CERTAINTY OF THE EVIDENCE**

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☐ Very low	☒ Low	☐ Moderate	☐ High

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

The body of evidence included here remains of very low to moderate certainty with very serious risk of bias and imprecision, and serious risk of inconsistency, imprecision and indirectness; with no publication bias.

- **COSTS**

How large are the resource requirements (costs)?

Judgement:

☐ Don't know	☐ Varies	☒ Large costs	☐ Moderate costs	☐ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:

No research evidence was identified.

Panel discussion:

- Access to a day surgery centre with endoscopic equipment.
  Access to skilled surgeons.

- **CERTAINTY OF COST EVIDENCE**

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☐ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

Refer to overarching Cost effectiveness analysis.

Panel discussion:

No evidence for resource requirements.

- **COST-EFFECTIVENESS**

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

Refer to overarching Cost effectiveness analysis.

Panel discussion:

Single costly procedure but without need for further medications and monitoring and high probability of singleton pregnancies.

- **EQUITY**

What would be the impact on health equity?

Judgement:

☐ Don't know	☒ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☐ Probably increased	☐ Increased

Research evidence:

No research evidence was identified.

Panel discussion:

In certain healthcare systems access to surgery may be restricted or unaffordable.

- ## FEASIBILITY

Is the option feasible to implement?

Judgement:

☐ Don't know	☒ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified.

Panel discussion:

Other than local health care resources, no potential barriers identified to interfere with feasibility.

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PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by the Evidence Team: Aya Mousa, Jillian Tay
Other team members: Loyal Pattuwage

GDG 5

Question 5.7.

In women with PCOS, is stimulated IVF/ICSI effective for improving fertility outcomes?

1. STUDY SELECTION

Table 1. PICO Criteria for Inclusion	
Question	In women with PCOS, is stimulated IVF/ICSI effective for improving fertility outcomes?
Clinical leads (key contacts)	Edgar Mocanu
Allocation ranking	Level 2- updated systematic review (with update of integrity check for all pre-2017 studies)

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(language, year)*
Inclusion	Women of any age, ethnicity and weight with PCOS diagnosed by Rotterdam, NIH or AEPCOS AND with or without co-existing infertility factors (other than anovulation) Also specifically identifying the 4 phenotypes where possible.	IVF/ICSI treatment using the following (controlled) ovarian (hyper) stimulation protocols: □ GnRH antagonist protocol □ GnRH agonist long protocol	Placebo, no intervention, other infertility treatment interventions (ie. aromatase inhibitor, metformin, clomiphene citrate, gonadotrophins, ovarian surgery) including IUI or IVM	Live birth rate, pregnancy rate (biochemical or clinical ultrasound), ovulation, amount of gonadotrophins used, duration of ovarian stimulation, maximum serum estradiol level (or serum estradiol level on the day of trigger), number of oocytes collected, single and multiple pregnancies, miscarriage rate, OHSS rate, other adverse events, quality of life, cost effectiveness.	Evidence based guidelines, systematic reviews, health technology assessments, randomised controlled trials (RCTs).	None
Exclusion	Women without diagnosis of PCOS.	Placebo, no intervention or any intervention other than IVF.	Any intervention other than those listed in the inclusion criteria.	None	Non-evidence based guidelines, nonsystematic reviews, any study lower than a RCT.	None

2. SEARCH STRATEGY

The search and screening for all GDG 5 questions were done together. Details can be found in the GDG 5 Methodology Appendix, including for:

- Databases
- Search Dates
- Search String(s)
- PRISMA flowchart
- Full list of included studies
- Full list of excluded studies with reasons for exclusion

Evidence processing: The literature search and screening were performed together in one Endnote library and Covidence project for all non-IVF, IVF and IVM fertility treatments in PCOS. Studies were selected by one reviewer/s in consultation with the evidence team/ key contact(s) using study selection and appraisal criteria (PICOs) established a priori. The articles were screened by title and abstract by one reviewer. When a decision could not be made based on title and abstract alone, full text was retrieved. Study appraisal was conducted by two reviewers independently with discussion to resolve any discrepancy. In total, 102 unique studies met inclusion criteria across all non-IVF, IVF and IVF questions, of which 57 were included in the guideline update following the integrity check (refer to methodology appendix for details).

Of these eligible 102 studies, **1 study met the inclusion criteria for this particular question** (Q.5.7) on stimulated IVF/ICSI, as detailed below.

Table of Included Studies
Zheng X, Guo W, Zeng L, Zheng D, Yang S, Xu Y, Wang L, Wang R, Mol BW, Li R, Qiao J. In vitro maturation without gonadotropins versus in vitro fertilization with hyperstimulation in women with polycystic ovary syndrome: a non-inferiority randomized controlled trial. Hum Reprod. 2022 Jan 28;37(2):242-253. doi: 10.1093/humrep/deab243. PMID: 34849920; PMCID: PMC9115328.

3. STUDY CHARACTERISTICS TABLE FOR INCLUDED STUDIES

Author, year, country	Population/ PCOS criteria/ Setting/ CC sensitivity	Study Design	Intervention N	Intervention description	Comparison N	Comparison description	Follow Up	Outcomes	Pooled in MA?	RoB
Zheng 2022 China	Infertile women aged 20–38 years with PCOS and infertility scheduled for their first IVF attempt / academic infertility centre; **CC sensitivity NR**	RCT	IVF: 176	Unstimulated IVM	IVM: 175	Standard IVF with a flexible GnRH antagonist protocol (n=176)	1 cycle	Primary: ongoing pregnancy (leading to live birth, defined as a baby born live at ≥ 22 weeks of gestation within 6months of the first oocyte retrieval cycle after randomization) Secondary: implantation, **clinical pregnancy**, and time to ongoing pregnancy leading to live birth. Safety outcomes included OHSS (classified as mild, moderate, miscarriage, ectopic pregnancy and obstetric and perinatal complications Initial pregnancy diagnosis: positive pregnancy test (not specified) Confirmed by: gestational sac	No	Low

CC, clomiphene citrate; CCR, clomiphene citrate resistant (to ovulate); CCF, clomiphene citrate failure (to become pregnant); LET, letrozole; MET, metformin; NR; not reported; OHSS, ovarian hyperstimulation syndrome; IUI, intrauterine insemination; hCG, human chorionic gonadotrophin; LH, luteinizing hormone; FSH, follicle stimulating hormone; MA, meta-analysis; RoB, risk of bias. All age data is in years and BMI is in kg/m^2. *Risk of bias assessment derived from reliable systematic review (e.g. Cochrane or previous review from the guideline evidence team).

4. FINDINGS

Comparisons Included:

- **Comparison 1.** IVF vs IVM

COMPARISON 1. IVF vs. IVM

▪ EVIDENCE SUMMARY:

A single study by Zheng et al. (2022) compared standard IVF with stimulated IVM in infertile women aged 20–38 years with PCOS and infertility scheduled for their first IVF attempt at an academic infertility centre. Relevant outcomes included live birth rate per patient and per pregnancy, clinical pregnancy rate per patient, and miscarriage rate per pregnancy. This study had a low risk of bias, with high-quality methodology despite being unblinded due to the nature of the intervention/s.

▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

Pooled meta-analysis was not possible due to having a single study. However, in comparing the differences between groups, IVF resulted in higher rates of live births per patient and clinical pregnancy rates per patient compared with IVM. There were no differences in live birth rates or miscarriage rates per pregnancy. Certainty in the evidence is moderate for all outcomes, downgraded once due to being derived from a single study with a modest sample size.

Outcome or Subgroup	Studies	n	Effect Estimate; OR [95% CI], M-H, random	P-value	Favours	Certainty
Live birth rate per patient	1	351	3.57 [2.25, 5.67]	<0.00001	**IVF** (live birth per patient is higher with IVF)	⊕⊕⊕◯ MODERATE
Live birth rate per pregnancy	1	351	1.55 [0.75, 3.19]	0.2	None	⊕⊕⊕◯ MODERATE
Clinical pregnancy rate- per patient†	1	170	3.91 [2.51, 6.09]	<0.00001	**IVF** (clinical pregnancy is higher with IVF)	⊕⊕⊕◯ MODERATE
Miscarriage rate- per pregnancy	1	170	0.53 [0.26, 1.07]	0.08	None	⊕⊕⊕◯ MODERATE

†clinical pregnancy rate is confirmed by ultrasound detection of gestational sac/ fetal heart activity

OUTCOME 1.1. Live birth rate – per patient

1.1.1. Individual Study Data Table

OUTCOME: Live birth rate - per patient					**OUTCOME TYPE:** Dichotomous				
COMPARISON: Standard in vitro fertilization (IVF) vs. in vitro maturation (IVM)									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (IVF)**	**N total in intervention/ exposure group (IVF)**	**N events in control / comparison group (IVM)**	**N total in control/ comparison group (IVM)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Zheng 2022 (LRB)	NR	Count	Investigator	89	176	39	175	Crude	NA

NR, not reported; **OI**, ovulation induction

OUTCOME 1.2. Live birth rate – per pregnancy

1.2.1. Individual Study Data Table

OUTCOME: Live birth rate - per pregnancy					**OUTCOME TYPE:** Dichotomous				
COMPARISON: Standard in vitro fertilization (IVF) vs. in vitro maturation (IVM)									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (IVF)**	**N total in intervention/ exposure group (IVF)**	**N events in control / comparison group (IVM)**	**N total in control/ comparison group (IVM)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Zheng 2022 (LRB)	NR	Count	Investigator	89	114	39	56	Crude	NA

NR, not reported; **OI**, ovulation induction

OUTCOME 1.3. Clinical pregnancy rate – per patient

1.3.1. Individual Study Data Table

OUTCOME: Clinical pregnancy rate - per patient					**OUTCOME TYPE:** Dichotomous				
COMPARISON: Standard in vitro fertilization (IVF) vs. in vitro maturation (IVM)									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (IVF)**	**N total in intervention/ exposure group (IVF)**	**N events in control / comparison group (IVM)**	**N total in control/ comparison group (IVM)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Zheng 2022 (LRB)	NR	Count	Investigator	114	176	56	175	Crude	NA

NR, not reported; **OI**, ovulation induction

OUTCOME 1.4. Miscarriage rate – per pregnancy

1.4.1 Individual Study Data Table

OUTCOME: Miscarriage rate – per pregnancy					**OUTCOME TYPE: Dichotomous**				
COMPARISON: Standard in vitro fertilization (IVF) vs. in vitro maturation (IVM)									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events intervention group (IVF)**	**N total in intervention group (IVF)**	**N events in control / comparison group (IVM)**	**N total in control/ comparison group (IVM)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Zheng 2022 (LRB)	**Mixed**	**Count**	**Investigator**	**26**	**114**	**20**	**56**	**Crude**	**NA**

NR, not reported; **OI**, ovulation induction

5. GRADE ASSESSMENTS AND EVIDENCE PROFILE

COMPARISON 1: Standard in vitro fertilization (IVF) vs. in vitro maturation (IVM)												
	Quality assessment						No. participants					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**IVF**	**IVM**	**Effect, random , OR [95% CI]**	**Favours**	**Certainty**	**Importance**
Outcome: Live birth rate - per patient												
1	RCT	no serious risk of bias	not applicable	not applicable	serious[1]	none	89/176 (50.6%)	39/175 (22.3%)	3.57 [2.25, 5.67]	IVF (live birth rate per patient is higher with IVF)	⨁⨁⨁◯ MODERATE	CRITICAL
Outcome: Clinical pregnancy rate- per patient												
1	RCT	no serious risk of bias	not applicable	not applicable	serious[1]	none	114/176 (64.8%)	56/175 (32.0%)	3.91 [2.51, 6.09]	IVF (clinical pregnancy per patient is higher with IVF)	⨁⨁⨁◯ MODERATE	CRITICAL
Outcome: Live birth rate - per pregnancy												
1	RCT	no serious risk of bias	not applicable	not applicable	serious[1]	none	89/114 (78.1%)	39/56 (69.6%)	1.55 [0.75, 3.19]	None	⨁⨁⨁◯ MODERATE	IMPORTANT
Outcome: Miscarriage rate- per pregnancy												
1	RCT	no serious risk of bias	not applicable	not applicable	serious[1]	none	26/114 (22.8%)	20/56 (35.7%)	0.53 [0.26, 1.07]	None	⨁⨁⨁◯ MODERATE	IMPORTANT

[1] Downgraded once due to the evidence being derived from a single study

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 5

Question 5.7.

In women with PCOS, is stimulated IVF/ICSI effective for improving fertility outcomes?

BACKGROUND:

Prevalence and problem

The prevalence of polycystic ovarian syndrome (PCOS), a heterogenic condition is high at 20% (1). The diagnosis can be a challenging one, the most accepted criteria for the diagnosis of PCOS being published in 2004 by the Rotterdam Consensus Group (2). Women desiring a pregnancy and presenting with PCOS and anovulation receive ovulation induction therapy: first line with antioestrogens and second line therapy with gonadotrophins. This low intervention therapeutic step has its challenges: side effects of and resistance to antioestrogen therapy, poor compliance, need for ultrasound monitoring, multiple pregnancy and OHSS, the last two occurring mainly with gonadotrophin use. Assisted Reproductive Technology (ART) therapies like IVF and ICSI are offered to patients after investigation of infertility and usually when other therapies have failed. While IVF is offered where the semen quality is within normal parameters, ICSI is usually reserved for situations where a male factor is present. In the PCOS context, women that do not achieve pregnancy after ovulation induction therapy are advised to proceed with IVF/ ICSI. The challenges of performing IVF for PCOS patients are significant namely, over-response to stimulation, high oestradiol levels, accelerated endometrial maturation and the need for a “freeze all” intervention due to the risk of OHSS, particularly if the long, GnRH analogue protocol, is used. One alternative to full IVF is in vitro maturation (IVM) of oocytes followed by in vitro fertilisation using intracytoplasmic sperm injection (ICSI). The IVM protocol, particularly in the circumstances where no gonadotrophins are used, eliminates the risk of OHSS, reduces patient burden and offers a potential treatment alternative prior to stimulated IVF/ICSI.

Clinical practice gap: need for guidance

Among reproductive age females, PCOS is the most common cause of anovulatory infertility (3). For PCOS patients presenting with infertility, reported as high as 40% in some studies, (4) ovulation induction is the first line therapy. While ovulation rates are satisfactory, long-term cumulative pregnancy rates are below 50%. Gonadotrophin stimulation, as second line therapy, is used when no response to first line therapy is present and has risks similar to IVF. Alternative therapies like IVF offer, in one cycle of treatment pregnancy rates that can reach 50%, particularly in women younger than 37 years old. A recent publication (5) offers a potentially viable alternative between ovulation induction and stimulated IVF, namely unstimulated IVM and ICSI. The clinical practice questions are if women with anovulatory PCOS should pursue IVF/ICSI sooner rather than after failed ovulation induction, if IVF is effective in improving outcomes when compared to pre-IVF interventions and if unstimulated IVM with ICSI outcomes are comparable to stimulated IVF/ICSI? There are no randomised trials comparing pre-IVF therapies with IVF in anovulatory PCOS women. The ability to advise such patients as to what is the preferred choice of intervention is very limited. Although patient relevant aspects like quality of life has been extensively studied in the general population with infertility issues and in PCOS (6, 7), few comparative studies of PCOS versus other infertile populations exist. The work that exists suggests patients with PCOS and Infertility are more distressed in emotional, social and mind/body life domains than patients with unexplained infertility. Support for fertility problems is readily available through online resources (e.g., peer support groups, mobile applications) and through clinics which patients find useful and may help some patients cope during treatment (8-10).

There is a single RCT comparing live birth rates after unstimulated IVM (ICSI) treatments with stimulated IVF/ ICSI treatments after freeze all and embryo transfers in frozen cycles.

Summary of key information

There are no randomised controlled trails comparing stimulated IVF/ ICSI therapy with alternative therapies like aromatase inhibitors, metformin, clomiphene citrate, gonadotrophins, ovarian surgery, IUI or no intervention, in women diagnosed with PCOS. The risks associated with gonadotrophin use in this group of patients are better controlled in an IVF or in an unstimulated IVM (ICSI) treatment. In stimulated IVF/ ICSI the exclusive use of a GnRH antagonist protocol (11) coupled with a GnRH agonist trigger significantly lowers the major risk of OHSS and elective single embryo transfer policies significantly reduce the risk of multiple pregnancy. There is a single RCT (5) comparing live birth rates after unstimulated IVM (ICSI) treatments with stimulated IVF/ ICSI treatments after freeze all and embryo transfers in frozen cycles.
Control of multiple pregnancy rates is not possible outside the unstimulated IVM (ICSI) or stimulated IVF/ ICSI therapy. Access related to cost of therapy remains a major limiting factor for stimulated IVF compared to unstimulated IVM (ICSI) and all non-IVF related therapies.

The patient and societal benefits of pre-IVF therapies compared with unstimulated IVM (ICSI) and stimulated IVF/ ICSI treatments in anovulatory PCOS women require systematic analysis in randomised controlled studies. Outcomes as time to conception, cost of therapy, quality of life, risk of OHSS, multiple pregnancy, miscarriage and cumulative livebirth rates should be investigated (6, 7).

GRADE EVIDENCE CERTAINTY	
Comparison	**GRADE for critical outcomes**
Comparison 1. IVF versus IVM	⊕⊕⊕◯ MODERATE

Evidence to Recommendations Framework

COMPARISONS (option versus other option)
● Standard stimulated in vitro fertilization (IVF) [option] vs. unstimulated in vitro maturation of oocytes and ICSI [other option]
CONSENSUS RECOMMENDATION(S)

CR: In the absence of an absolute indication for IVF / intracytoplasmic sperm injection (ICSI), IVF could be offered in women with PCOS and anovulatory infertility, if first- or second-line ovulation induction therapies have failed.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☒ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

PRACTICE POINT(S)

1. In women with anovulatory PCOS, the use of IVF is effective and when elective single embryo transfer is used multiple pregnancies can be minimised.
2. Women with PCOS undergoing IVF/ICSI treatment should be counselled prior to starting treatment about the increased risk of ovarian hyperstimulation syndrome (OHSS) and options to reduce the risk should be offered.

GRADE CONSIDERATIONS

Justifications:

Stimulated IVF (option) when compared with IVM+ IVF (other option) results in a significantly higher:

Life birth rate per patient – MODERATE

Clinical pregnancy rate per patient – MODERATE

The following outcomes are similar in stimulated IVF (option) when compared with IVM+ IVF (other option)

Life birth rate per pregnancy - MODERATE

Miscarriage per pregnancy - MODERATE

Subgroup considerations:

None

Implementation considerations:

While IVM is no longer considered experimental, potential limitations in offering IVM are the costs of implementation and the expertise related to both the surgical procedure and the laboratory consumables and processes.

Monitoring and evaluation considerations:

If IVM+ICSI is to be implemented, services should consider:

1. Identification of an ideal cohort of patients (high risk of OHHS (AMH), affordability, access (distance)
2. Monitoring and benchmarking laboratory parameters (oocytes maturation, blastocyst and embryo utilisation rates)

Research priorities:

Exploring benefits of stimulated IUI vs IVF in PCOS

Comparing IVM-ICSI to Stimulated-ICSI only

Comparing cumulative outcomes after the use of all embryos from a performed cycle in IVM.

Exploring the optimal day of freezing and embryo transfers for efficacy in IVM

Long term follow-up of children.

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PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by the Evidence Team (Aya Mousa, Jillian Tay)

Other team members: Loyal Pattuwage

GDG 5

Question 5.7.1

In women with PCOS undergoing IVF/ICSI treatment, is the GnRH antagonist protocol or GnRH agonist long protocol the most effective for improving fertility outcomes?

1. STUDY SELECTION

Table 1. PICO Criteria for Inclusion	
Question	**In women with PCOS undergoing IVF/ICSI treatment, is the GnRH antagonist protocol or GnRH agonist long protocol the most effective for improving fertility outcomes?**
Clinical leads (key contacts)	**Roger Hart**
Allocation ranking	**Level 2- updated systematic review (with update of integrity check for all studies)**

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(language, year)*
Inclusion	Women of any age, ethnicity and weight with PCOS diagnosed by Rotterdam, NIH or AEPCOS AND with or without co-existing infertility factors (other than anovulation) Also specifically identifying the 4 phenotypes where possible.	"IVF/ICSI treatment with GnRH antagonist protocol"	IVF/ICSI treatment with GnRH agonist long protocol	Live birth rate, pregnancy rate (biochemical or clinical ultrasound), ovulation, amount of gonadotrophins used, duration of ovarian stimulation, maximum serum estradiol level (or serum estradiol level on the day of trigger), number of oocytes collected, single and multiple pregnancies, miscarriage rate, OHSS rate, other adverse events, quality of life, cost effectiveness.	Evidence based guidelines, systematic reviews, health technology assessments, randomised controlled trials (RCTs).	None
Exclusion	Women without diagnosis of PCOS.				Non-evidence based guidelines, non-systematic reviews, any study lower than a RCT.	None

2. SEARCH STRATEGY

The search and screening for all GDG 5 questions were done together. Details can be found in the GDG 5 Methodology Appendix, including for:

- Databases
- Search Dates
- Search String(s)
- PRISMA flowchart
- Full list of included studies
- Full list of excluded studies with reasons for exclusion

Evidence processing: The literature search and screening were performed together in one Endnote library and Covidence project for all non-IVF, IVF and IVM fertility treatments in PCOS. Studies were

selected by one reviewer/s in consultation with the evidence team/ key contact(s) using study selection and appraisal criteria (PICOs) established a priori. The articles were screened by title and abstract by one reviewer. When a decision could not be made based on title and abstract alone, full text was retrieved. Study appraisal was conducted by two reviewers independently with discussion to resolve any discrepancy. In total, 102 unique studies met inclusion criteria across all non-IVF, IVF and IVF questions, of which 57 were included in the guideline update following the integrity check (refer to methodology appendix for details).

Of these eligible 102 studies, **7 studies met the inclusion criteria for this particular question** (Q.5.7.1) on GnRH antagonist protocol versus agonist long protocols, as detailed below.

Table of Included Studies
Ashrafi, Mahnaz & Moini, Ashraf & Mohammadzadeh, Afsaneh & Ezabadi, Zahra & Zafarani, Fatemeh & Baghestani, Ahmad. (2005). A comparative study of GnRH antagonist and GnRH agonist in PCO patients undergoing IVF/ICSI cycles. Iranian Journal of Reproductive Medicine (ISSN: 1680-6433) Vol 3 Num 1. 3.
Bahceci, M.; Ulug, U.; Ben-Shlomo, I.; Erden, H. F.; Akman, M. A. Use of a GnRH antagonist in controlled ovarian hyperstimulation for assisted conception in women with polycystic ovary disease: a randomized, prospective, pilot study. Journal of Reproductive Medicine 2005, 50, 84-90
Engmann L, DiLuigi A, Schmidt D, Nulsen J, Maier D, Benadiva C. The use of gonadotropin-releasing hormone (GnRH) agonist to induce oocyte maturation after cotreatment with GnRH antagonist in high-risk patients undergoing in vitro fertilization prevents the risk of ovarian hyperstimulation syndrome: a prospective randomized controlled study. Fertil Steril. 2008 Jan;89(1):84-91. doi: 10.1016/j.fertnstert.2007.02.002. Epub 2007 Apr 26. PMID: 17462639.
Haydardedeoglu, B., Kilicdag, E. B., Parlakgumus, A. H., & Zeyneloglu, H. B. (2012). IVF/ICSI outcomes of the OCP plus GnRH agonist protocol versus the OCP plus GnRH antagonist fixed protocol in women with PCOS: a randomized trial. *Archives of Gynecology & Obstetrics, 286*(3), 763-769
Kurzawa, R.; Ciepiela, P.; Baczkowski, T.; Safranow, K.; Brelik, P. Comparison of embryological and clinical outcome in GnRH antagonist vs. GnRH agonist protocols for in vitro fertilization in PCOS non-obese patients. A prospective randomized study. J Assist Reprod Genet 2008, 25, 365-74
Lainas, T. G.; Petsas, G. K.; Zorzovilis, I. Z.; Iliadis, G. S.; Lainas, G. T.; Cazlaris, H. E.; Kolibianakis, E. M. Initiation of GnRH antagonist on Day 1 of stimulation as compared to the long agonist protocol in PCOS patients. A randomized controlled trial: effect on hormonal levels and follicular development. *Hum Reprod* **2007**, 22, 1540-6
Lainas, T. G., Sfontouris, I. A., Zorzovilis, I. Z., Petsas, G. K., Lainas, G. T., Alexopoulou, E., & Kolibianakis, E. M. (2010). Flexible GnRH antagonist protocol versus GnRH agonist long protocol in patients with polycystic ovary syndrome treated for IVF: a prospective randomised controlled trial (RCT). *Human Reproduction, 25*(3), 683-689.

3. STUDY CHARACTERISTICS TABLE FOR INCLUDED STUDIES

Author, year, country	Population/ PCOS criteria/ Setting/ CC sensitivity	Study Design	Intervention N	Intervention description	Comparison N	Comparison description	Follow Up	Outcomes	Pooled in MA?	RoB
Ashrafi 2005 Iran	Patients <35 years old with oligomenorrhea, hyperandrogenism, LH/FSH>2.5 and ultrasonographic features of PCOS (Adams criteria); medical institute; CC status: **NR**	RCT	GnRH agonist n=30 Age (years) GnRH agonist 28.3 ± 4 BMI (kg/m2) GnRH agonist 30.45 ± 6.09	Standard long GnRH analogue protocol 21 day of cycle GnRH agonist Suprefact 500µg/day When pituitary suppression was achieved, Buserline was reduced to 200µg/day and gonadotrophin (Pregonal) 150IU/day was started	GnRH antagonist n=30 Age (years) GnRH antagonist 29.2 ± 4.6 BMI (kg/m2) GnRH antagonist 27.97 ± 6.71	HMG (150 IU/day) was started from third day of cycle. Then GnRH antagonist (0.25mg) was administered from 6th day after HMG initiation (LH≤5 IU/ml) to the day of HCG injection	1 cycle	Duration of treatment, Duration of HMG stimulation, Serum LH and E2, follicle development, risk of OHSS, number of embryos, fertilisation 10 to 12 days after embryonic transfer**, βHCG was tested**.		High
Bahceci 2005 Turkey	PCOD patients admitted to hospital to undergo ART; PCOS defined as defined as primary infertility, oligomenorrhea, clinical hyperandrogenism (hirsutism Ferriman-Galway score >7), reversed FSH /LH ratio and polycystic appearance of ovaries on ultrasound; a tertiary hospital; CC sensitivity: **NR**	RCT	GnRH agonist n=73 (Cetrorelix) Age (years) 29.43 ± 4.3 BMI 26.03 ± 4.2	Pituitary desensitization with daily LA, 0.5mg, on day 14 of the cycle. Daily administration of gonadotropins, 2 or 3 ampules was initiated on the 3rd day of the anteceding menstrual period. All patients received OC for 21 days from the preceding menstrual period	GnRH antagonist n=75 (Leuprolide) Age (years) 30.06 ± 4.8 BMI 26.1 ± 3.8	Gonadotropins were administered in 2-3 ampoules on the 3rd day of the antecedent bleeding after OC usage. After 4 days, the starting regimen was adjusted based on the individual response. Cetrorelix 0.25 mg/d sc was starte when the leading follicle reached 14 mm All patients received OC for 21 days from the preceding menstrual period	? 1 cycle	Primary outcomes NR Stimulation duration Ampoules consumed E2 level on hCG day (pg/ml) Number of retrieved oocytes Fertilization rate Number of pregnancies Pregnancy rate Multiple pregnancy rate **Clinical pregnancy** was confirmed by ultrasonography.		High
Engmann 2007 US	Patients under 40 years of age with polycystic ovarian syndrome, polycystic ovarian morphology, or previous high response undergoing IVF; diagnosis based on Rotterdam criteria; University-based tertiary fertility centre CC sensitivity: NR	RCT	GnRH antagonist n=34 Age (yrs) 32.0 ± 3.7 BMI (kg/m2) 28.3 ± 7.1	Pre-treatment with OCPs for 21 days. If the ovaries were quiescent on ultrasound, COH was commenced on day 2 of withdrawal bleeding, and was achieved using a step-down protocol of recombinant FSH in a starting dose of 112–225 IU Both groups received luteal phase and early pregnancy supplementation with IM progesterone	GnRH agonist n=32 Age (yrs) 33.1 ± 3.6 BMI (kg/m2) 30.7 ± 6.4	Pre-treatment with OCP for 25 days overlapping with 1 mg leuprolide acetate commencing on day 21 of the OCP. Ganirelix acetate was commenced once the leading follicle was R14 mm and continued every morning until and including the day of trigger. Both groups received luteal phase and early pregnancy supplementation with IM progesterone	1 cycle	Primary: incidence of OHSS, Secondary: implantation rate. Others: number of oocytes retrieved, proportion of mature oocytes retrieved, fertilization rate, midluteal phase mean ovarian volume (MOV), clinical and ongoing pregnancy rates, and luteal phase serum E2 and P levels. **Clinical pregnancy**: "…until a negative pregnancy test or a viable fetus was documented by transvaginal sonography."		Mod

Haydardedeoglu 2012 Turkey	PCOS patients in the first IVF/ICSI cycles; diagnosis by Rotterdam criteria; University Department; CC sensitivity: NR	RCT	GnRH agonist n=150 Age 27.70±3.59 BMI 24.97 ± 4.36	GnRH agonist long protocol (Leuprolide acetate) 1 mg/d from day 21 of the preceding menstruation (last 3 tablets of OCP). If there were no cysts ≥2 cm and the E2 was <50 pg/ml, gonadotropin stimulation with 150 IU of gonadotropins rFSH was performed. All patients received oral contraceptive pills (OCPs) for 21 days	GnRH antagonist n=150 Age 27.57±3.54 BMI 25.74 ± 4.37	150 IU rFSH was initiated on day 3 of menstruation after discontinuation of OCPs, then GnRH antagonist protocol (Ganirelix) 0.25 mg/d was initiated on day 6 of gonadotropin stimulation, until day of hCG. All patients received oral contraceptive pills (OCPs) for 21 days	NR	Primary: Ongoing pregnancy rates (defined as a pregnancy proceeding beyond 12 weeks of gestation) Secondary: E2 and progesterone levels on the day of hCG administration, duration of rFSH stimulation, total dose of rFSH administered, cost of COH, cycle cancellation rate, number of metaphase II oocytes, fertilization rates, cryopreservation rates, hospitalized OHSS rates. Hospitalized OHSS was diagnosed when the hematocrit level rose > 45 % and abdominal discomfort, and/or progressive oliguria and/or respiratory difficulties were found together with moderate ascites and/or thrombocytosis, and leucocytosis. **Clinical pregnancy** was detected by identifying an embryo with cardiac activity using transvaginal ultrasound		High
Kurzawa 2008 Poland	Non-obese PCOS patients were considered eligible if they were scheduled for controlled ovarian stimulation and intracytoplasmic sperm injection (ICSI); diagnosis of PCOS by Rotterdam criteria; University department; CC sensitivity: NR	RCT	Agonist protocol n=37 Age (years) 30.36 ± 3.40 BMI 22.3 ± 1.6	During OCP use on day 16-18 of the preceding cycle, GnRH agonist (Triptorelin) was given, then rFSH 150 IU/d* after confirmation of pituitary desensitization, continued until β-hCG trigger (10000 IU when 3 follicles reached mean diameter ≥17mm)	Antagonist protocol n=33 Age (years) 31.33 ± 3.91 BMI 23.1 ± 1.3	rFSH 150 IU/d* from 2nd day of cycle. GnRH antagonist (Cetrorelix) 0.25mg when at least 2 follicles reached 14mm in diameter (average 4 injections per day), then 10000 IU hCG administered when dominant follicle reached diameter ≥18mm	NR	Primary endpoints: Embryological: •Matured oocytes (M2) rate, defined as proportion of metaphase II to total number of retrieved oocytes •Fertilization rate, defined as proportion of two pronuclei oocytes to number of injected oocytes •Quality of zygotes on the first day of culture •Quality of embryos on the third day of culture Secondary endpoints: Clinical: •Delivery per attempt, defined as a live birth after 32 weeks of gestation •**Clinical pregnancy** per attempt, defined as an ongoing pregnancy at 12 weeks of gestation •Implantation rate; defined as gestational sacs per number of transferred embryos •Multiple pregnancy per viable pregnancy •Miscarriage per intrauterine pregnancy, defined as a miscarriage of an ongoing pregnancy after 12 weeks of gestation •Occurrence of severe OHSS •Number of days of gonadotropin treatment •Gonadotropin consumption		Low

								•Correlation between serum LH level and IVF outcome **Ultrasound Pregnancy** was checked by pregnancy test in serum 14 days after ET and confirmed by vaginal ultrasound scan at 12 weeks of gestation.		
Lainas 2007 Greece	Patients were diagnosed based on oligoovulation/ anovulation (Ehrmann et al., 2006) and polycystic ovaries; single IVF clinic CC sensitivity: NR	RCT	GnRH agonist n=52 Age: 30.5 (16) BMI: 23.6 (18.9) Median (IQR)	GnRH agonist (Triptorelin) 0.1mg/d, commenced 3 days before discontinuation of OCP. rFSH* 150 IU/d when desensitization achieved (GnRH agonist reduced to 0.05mg/d that day), continued until β-hCG trigger (10000 IU when 3 follicles reached mean diameter ≥17mm) *dose adjusted after day 5 of stimulation	GnRH antagonist n=26 Age: 32.0 (14) BMI: 23.2 (20.9) Median (IQR)	rFSH* daily (Puregon) + GnRH antagonist protocol (Ganirelix) 0.25mg/d from day 2 of menses, until and including day of β-hCG trigger (10000 IU when 3 follicles reached mean diameter ≥17mm)	1 cycle	Primary outcome measure: E2 levels on Day 5 of stimulation, Secondary outcome measures: Follicular development, LH and progesterone levels **Clinical pregnancy** was determined by sac with foetal heart at 7 weeks and ongoing pregnancy rates by sac with foetal heart at 12 weeks		Mod
Lainas 2010 Greece	Patients could enter the study only once after being diagnosed as PCOS [presence of oligoovulation/anovulation (Ehrmann et al., 2006) and polycystic ovaries]; single centre; CC sensitivity: NR	RCT	GnRH agonist long protocol n=110 Age: 32 (29-35) BMI: 23.2 (20.9-25.8) Media (IQR)	GnRH agonist long protocol (Triptorelin) 0.1 mg, commenced 3 days before the discontinuation of the OCP. Once desensitization was achieved (~10-15 days after Triptorelin commenced), 150 IU/d* rFSH (Puregon) was commenced (GnRH agonist was decreased on that day to 0.05 mg/d and continued until and including the day of hCG trigger)* *5000 IU hCG when three follicles reached a mean diameter of ≥17 mm	GnRH antagonist protocol n=110 Age: 31 (28-35) BMI: 24.6 (20.9-29.3) Median (IQR)	rFSH from Day 2 of cycle that followed discontinuation of the OCP, then GnRH antagonist (Ganirelix) commenced at 0.25mg/d when at least one of the following criteria were fulfilled: (i) the presence of at least one follicle measuring >14 mm; (ii) (ii) serum E2 levels >600 pg/ml; (iii) (iii) serum LH levels>10 IU/l. Both continued until and including the day of hCG trigger*	1 cycle	The primary outcome measure: •ongoing **clinical pregnancy rate** per patient randomized (defined as the presence of gestational sac with fetal heart beat detection at 12 weeks and at 6–7 weeks of gestation, respectively). Secondary outcome measures: •incidence of OHSS; duration of rFSH stimulation; total dose of rFSH, E2 and progesterone concentration on the day of hCG administration; cycle cancellation rate; number of cumulus-oocyte complexes (COCs) retrieved, number of metaphase II oocytes and fertilization rates.		Mod

NR; not reported; OHSS, ovarian hyperstimulation syndrome; IUI, intrauterine insemination; MA, meta-analysis; RoB, risk of bias. All age data is in years and BMI is in kg/m^2.

4. FINDINGS

Comparisons Included:

- **Comparison 1.** GnRH antagonist protocol vs GnRH agonist long protocol

COMPARISON 1: Gonadotrophin-releasing hormone (GnRH) antagonist protocol versus GnRH agonist long protocol

▪ EVIDENCE SUMMARY:

Seven studies compared gonadotropin-releasing hormone antagonist protocol with the GnRH agonist long protocol in women with PCOS undergoing IVF. Relevant outcomes included clinical pregnancy rate, OHSS rate, multiple pregnancy rate, miscarriage rate and cancellation rate per patient, as well as miscarriage rate per pregnancy, number of oocytes collected, amount of gonadotropins used, duration of ovulation stimulation and serum E2 concentration on the day of trigger. Most studies were judged as moderate risk of bias (Bahceci et al. 2005; Engmann et al. 2008; Lainas et al. 2007 and 2010) while two had a high risk of bias (Ashrafi et al. 2005; Haydardedeoglu et al. 2012) and only one study by Kurzawa et al. (2008) had a low risk.

▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

There were no differences in any of the measured outcomes between the GnRH antagonist protocol compared with the GnRH agonist long protocol, with the exception of days of ovarian stimulation, which were lower with the GnRH antagonist protocol with a mean difference of -3.07 days. Certainty for most outcomes was low to moderate, mainly due to risk of bias and some inconsistencies in effect estimates or CIs; however, certainty was very low for days of ovarian stimulation due to serious risk of bias and very serious inconsistency (high heterogeneity and wide variation in effect estimates and CIs).

Outcome or Subgroup	Studies	n	Effect Estimate; OR [95% CI], M-H, random	P	Favours	Certainty
Clinical pregnancy rate- per patient†	6	827	0.89 [0.65, 1.23]	0.5	None	⊕⊕⊕◯ MODERATE
OHSS rate- per patient	7	903	0.50 [0.23, 1.10]	0.09	None	⊕⊕◯◯ LOW
Multiple pregnancy rate- per patient	3	470	1.04 [0.62, 1.76]	0.9	None	⊕⊕⊕◯ MODERATE
Miscarriage rate- per patient	7	874	0.92 [0.55, 1.52]	0.7	None	⊕⊕◯◯ LOW
Miscarriage rate- per pregnancy	5	321	0.80 [0.41, 1.56]	0.5	None	⊕⊕◯◯ LOW
Cancellation rate - per patient	4	727	1.10 [0.41, 2.96]	0.9	None	⊕⊕⊕◯ MODERATE
Number of oocytes collected	6	604	0.44 [-1.67, 2.56]	0.7	None	⊕⊕◯◯ LOW
Amount of gonadotropins used (IU)	3	488	-77.68 [-205.96, 50.61]	0.2	None	⊕⊕◯◯ LOW
Duration of ovarian stimulation (days)	7	903	-3.07 [-4.68, -1.46]	0.0002	**GnRH antagonist** (lower with GnRH antagonist)	⊕◯◯◯ VERY LOW
Serum E2 on day of trigger (pg/ml)	4	535	-34.61 [-354.92, 285.71]	0.8	None	⊕⊕◯◯ LOW

† clinical pregnancy rate is confirmed by ultrasound detection of gestational sac/ fetal heart activity.

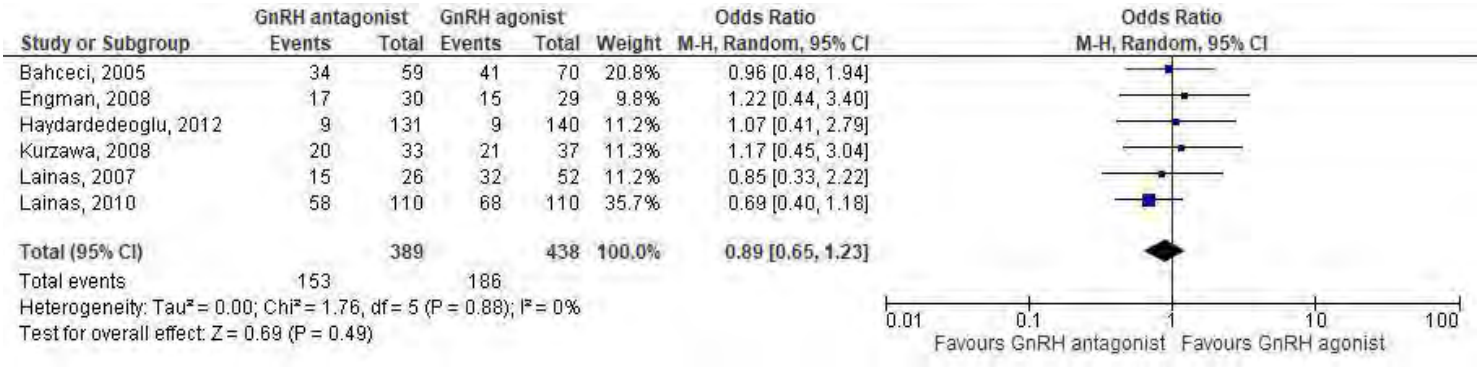
OUTCOME 1.1. Clinical pregnancy rate– per patient

1.1.1. Individual Study Data Tables

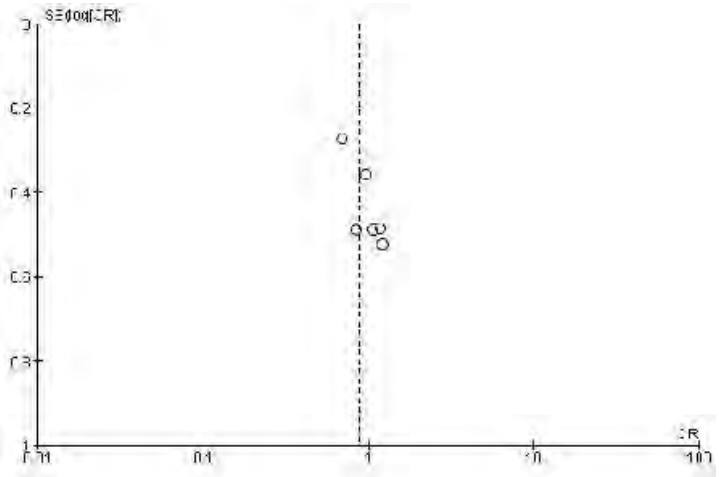
OUTCOME: Clinical pregnancy rate per patient						**OUTCOME TYPE:** Dichotomous			
COMPARISON: GnRH antagonist versus agonist									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention group (GnRH antagonist)**	**N total in intervention group (GnRH antagonist)**	**N events in comparison group (GnRH agonist)**	**N total in comparison group (GnRH agonist)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Bahceci 2005 (MRB)	NR	Count	Investigator	34	59	41	70	Crude	NA
Engmann 2008 (MRB)	NR	Count	Investigator	17	30	15	29	Crude	NA
Haydardedeoglu 2012 (HRB)	NR	Count	Investigator	9	131	9	140	Crude	NA
Kurzawa 2008 (LRB)	NR	Count	Investigator	20	33	21	37	Crude	NA
Lainas 2007 (MRB)	NR	Count	Investigator	15	26	32	52	Crude	NA
Lainas 2010 (MRB)	NR	Count	Investigator	58	110	68	110	Crude	NA

OI, ovulation induction; **NR**, not reported; **NA**, not applicable.

1.1.2. Forest Plot of all included RCTs comparing GnRH antagonist versus GnRH agonist long protocol for clinical pregnancy rate – per patient



1.1.3. Funnel plot for assessment of publication bias



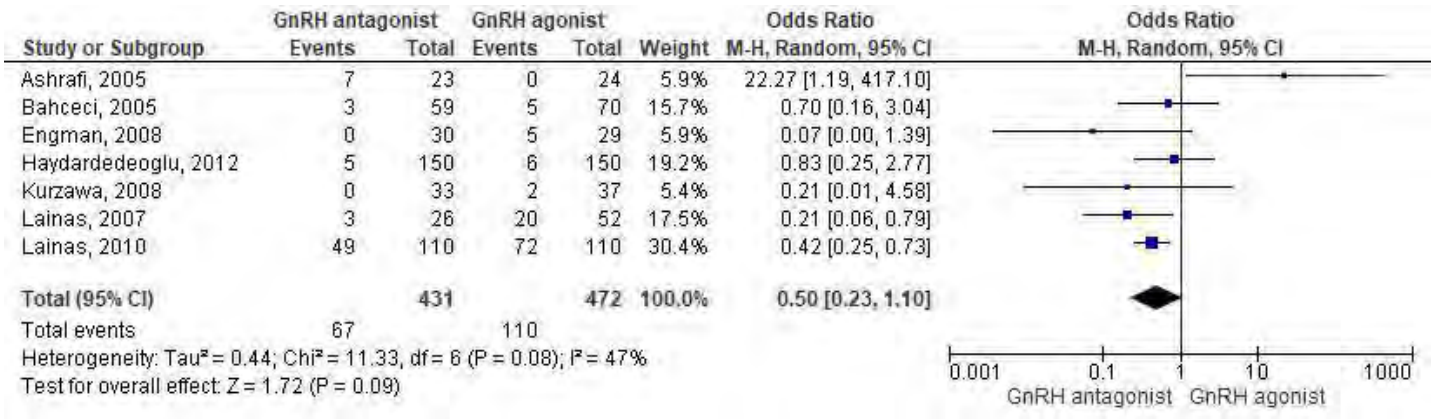
OUTCOME 1.2. OHSS rate– per patient

1.2.1. Individual Study Data Tables

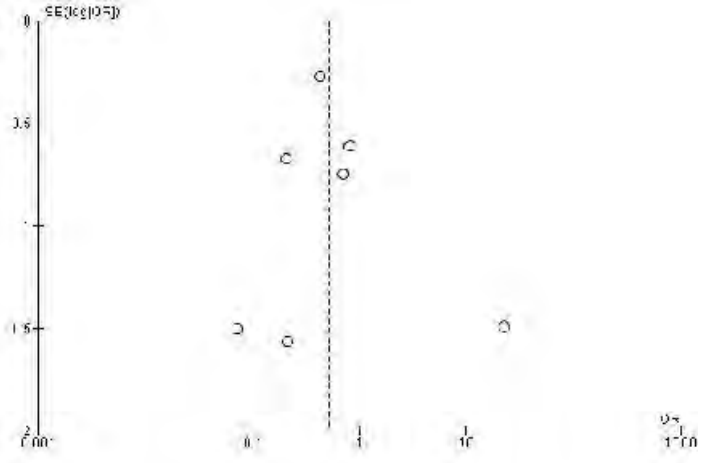
OUTCOME: OHSS rate per patient						OUTCOME TYPE: Dichotomous			
COMPARISON: GnRH antagonist versus agonist									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention group (GnRH antagonist)**	**N total in intervention group (GnRH antagonist)**	**N events in comparison group (GnRH agonist)**	**N total in comparison group (GnRH agonist)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Ashrafi 2005 (HRB)	NR	Count	Investigator	7	23	0	24	Crude	NA
Bahceci 2005 (MRB)	NR	Count	Investigator	3	59	5	70	Crude	NA
Engmann 2008 (MRB)	NR	Count	Investigator	0	30	5	29	Crude	NA
Haydardedeoglu 2012 (HRB)	NR	Count	Investigator	5	150	6	150	Crude	NA
Kurzawa 2008 (LRB)	NR	Count	Investigator	0	33	2	37	Crude	NA
Lainas 2007 (MRB)	NR	Count	Investigator	3	26	20	52	Crude	NA
Lainas 2010 (MRB)	NR	Count	Investigator	49	110	72	110	Crude	NA

OI, ovulation induction; **NR**, not reported; **NA**, not applicable.

1.2.2. Forest Plot of all included RCTs comparing GnRH antagonist versus GnRH agonist long protocol for OHSS rate – per patient



1.2.3. Funnel plot for assessment of publication bias



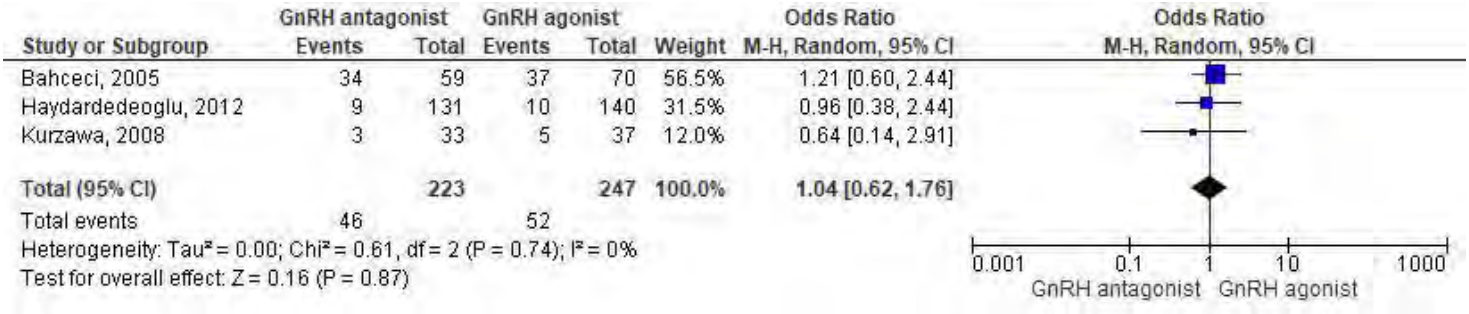
OUTCOME 1.3. Multiple pregnancy rate– per patient

1.3.1. Individual Study Data Tables

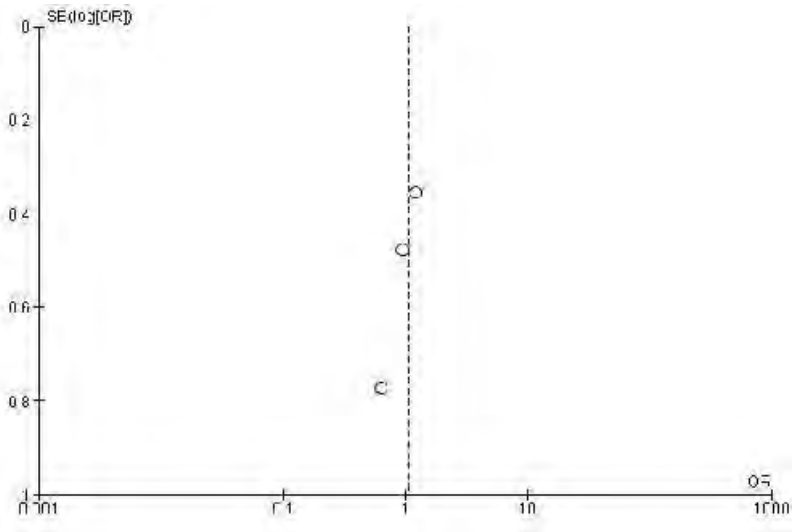
OUTCOME: Multiple pregnancy rate per patient						OUTCOME TYPE: Dichotomous			
COMPARISON: GnRH antagonist versus agonist									
Author, year	Past OI Med Use	Unit of outcome (e.g. g, mg)	Method of measurement	N events in intervention group (GnRH antagonist)	N total in intervention group (GnRH antagonist)	N events in comparison group (GnRH agonist)	N total in comparison group (GnRH agonist)	Are these values adjusted or crude?	If adjusted, what variables were in the model?
Bahceci 2005 (MRB)	NR	Count	Investigator	34	59	37	70	Crude	NA
Haydardedeoglu 2012 (HRB)	NR	Count	Investigator	9	131	10	140	Crude	NA
Kurzawa 2008 (LRB)	NR	Count	Investigator	3	33	5	37	Crude	NA

OI, ovulation induction; **NR**, not reported; **NA**, not applicable.

1.3.2. Forest Plot of all included RCTs comparing GnRH antagonist versus GnRH agonist long protocol for multiple pregnancy rate – per patient



1.3.3. Funnel plot for assessment of publication bias



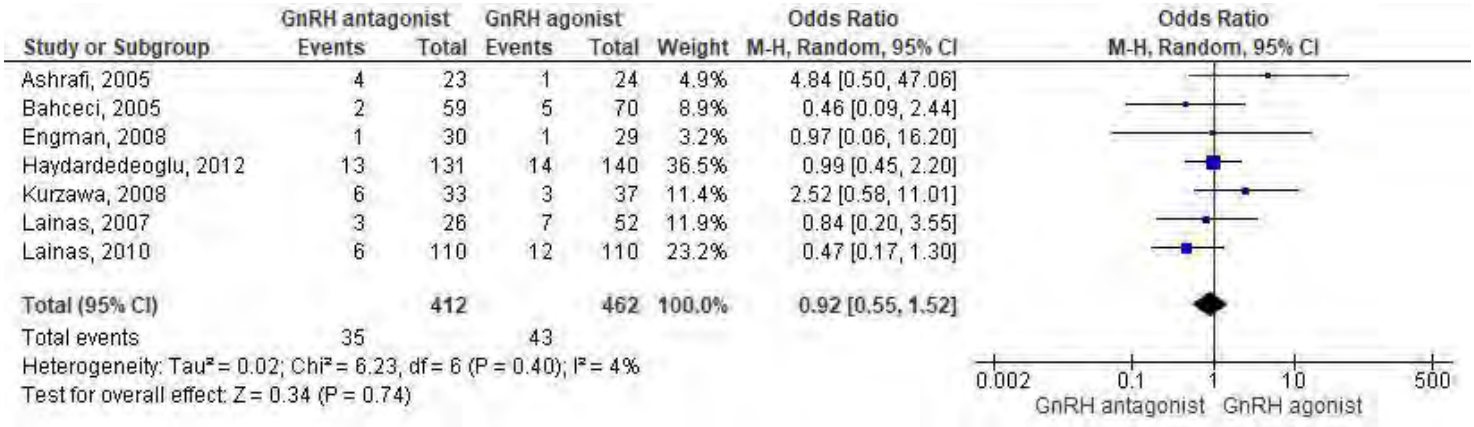
OUTCOME 1.4. Miscarriage rate per patient

OUTCOME: Miscarriage rate per patient									
OUTCOME TYPE: Dichotomous									
COMPARISON: GnRH antagonist versus agonist									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention group (GnRH antagonist)**	**N total in intervention group (GnRH antagonist)**	**N events in comparison group (GnRH agonist)**	**N total in comparison group (GnRH agonist)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Ashrafi 2005 (HRB)	NR	Count	Investigator	4	23	1	24	Crude	NA
Bahceci 2005 (MRB)	NR	Count	Investigator	2	59	5	70	Crude	NA
Engmann 2008 (MRB)	NR	Count	Investigator	1	30	1	29	Crude	NA
Haydardedeoglu 2012 (HRB)	NR	Count	Investigator	13	131	14	140	Crude	NA
Kurzawa 2008 (LRB)	NR	Count	Investigator	6	33	3	37	Crude	NA
Lainas 2007 (MRB)	NR	Count	Investigator	3	26	7	52	Crude	NA
Lainas 2010 (MRB)	NR	Count	Investigator	6	110	12	110	Crude	NA

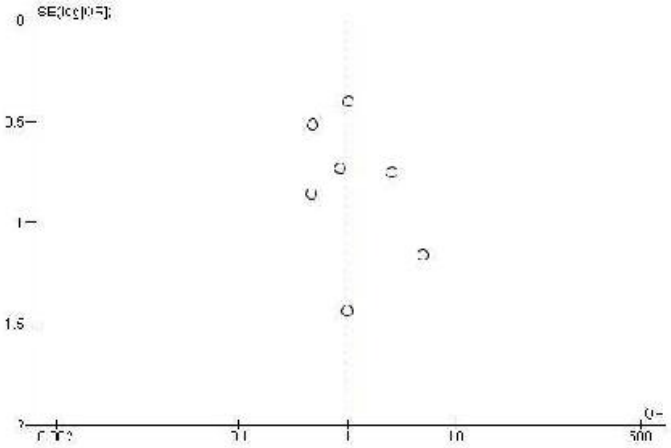
1.4.1. Individual Study Data Tables

OI, ovulation induction; **NR**, not reported; **NA**, not applicable.

1.4.2. Forest Plot of all included RCTs comparing GnRH antagonist versus GnRH agonist long protocol for miscarriage rate per patient



1.4.3. Funnel plot for assessment of publication bias



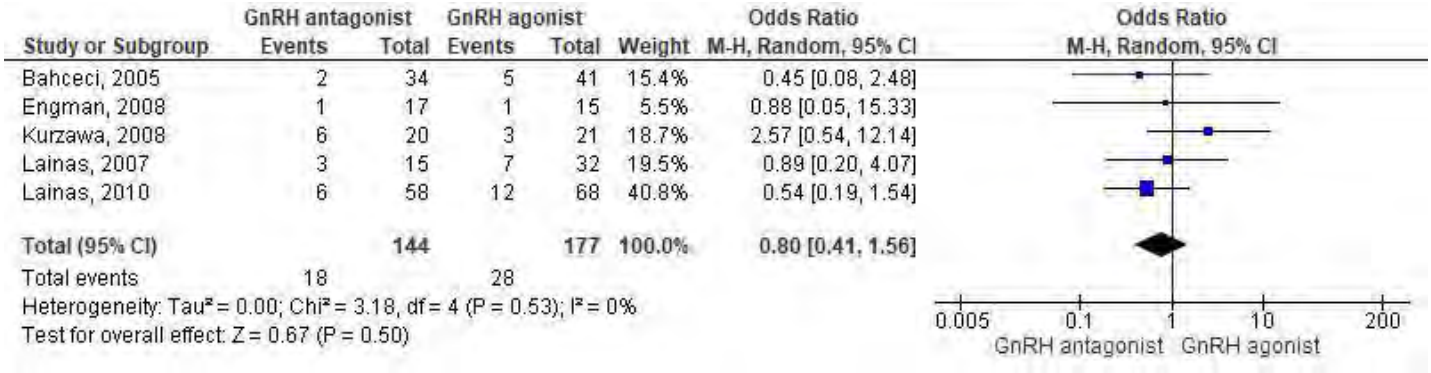
OUTCOME 1.5. Miscarriage rate- per pregnancy

1.5.1. Individual Study Data Tables

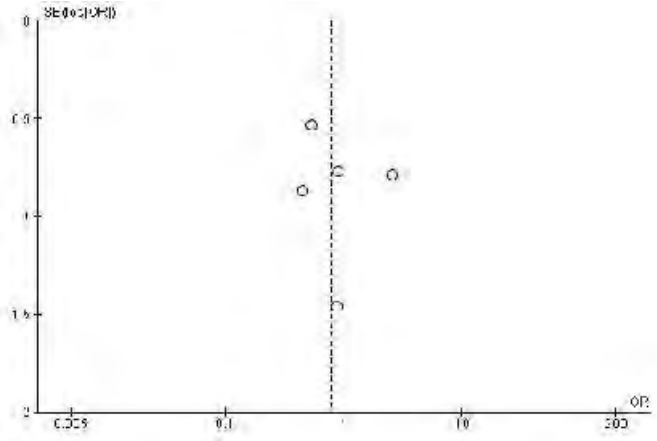
OUTCOME: Miscarriage rate per pregnancy									
OUTCOME TYPE: Dichotomous									
COMPARISON: GnRH antagonist versus agonist									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention group (GnRH antagonist)**	**N total in intervention group (GnRH antagonist)**	**N events in comparison group (GnRH agonist)**	**N total in comparison group (GnRH agonist)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Bahceci 2005 (MRB)	NR	Count	Investigator	2	34	5	41	Crude	NA
Engmann 2008 (MRB)	NR	Count	Investigator	1	17	1	15	Crude	NA
Haydardedeoglu 2012 (HRB)*	NR	Count	Investigator	13	9	14	9	Crude	NA
Kurzawa 2008 (LRB)	NR	Count	Investigator	6	20	3	21	Crude	NA
Lainas 2007 (MRB)	NR	Count	Investigator	3	15	7	32	Crude	NA
Lainas 2010 (MRB)	NR	Count	Investigator	6	58	12	68	Crude	NA

OI, ovulation induction; **NR**, not reported; **NA**, not applicable.*not included in meta-analysis due to differing units or varied estimates suggesting incorrect units or unit mismatch; and/or due to reporting only medians and ranges/ IQR

1.5.2. Forest Plot of all included RCTs comparing GnRH antagonist versus GnRH agonist long protocol for miscarriage rate per pregnancy



1.5.3. Funnel plot for assessment of publication bias



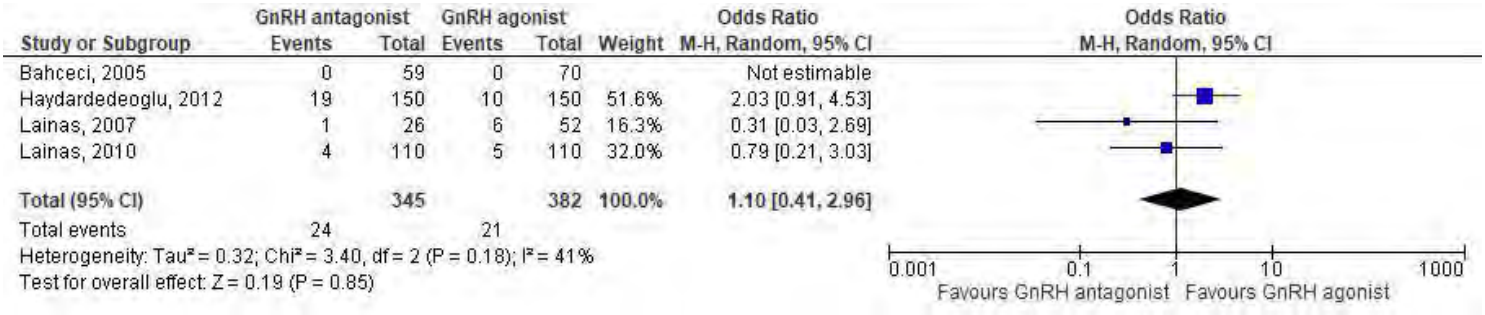
OUTCOME 1.6. Cancellation rate– per patient

1.6.1. Individual Study Data Tables

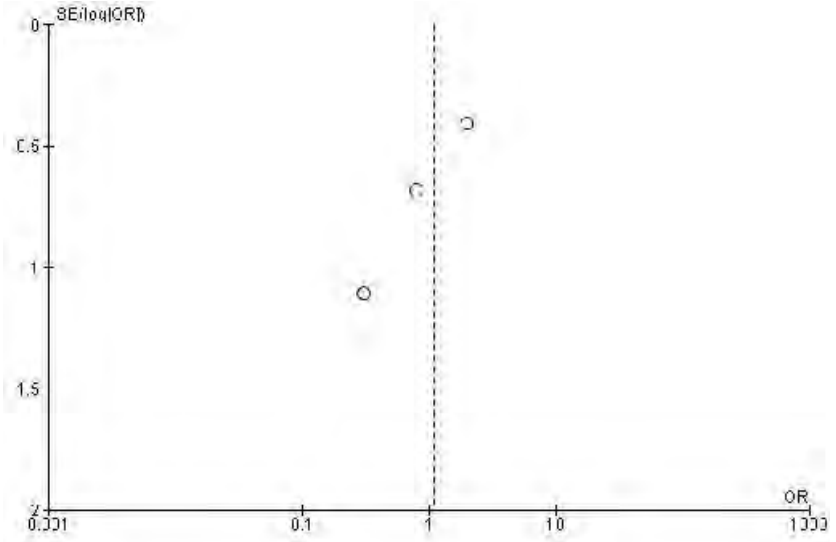
OUTCOME: Cancellation rate- per patient						**OUTCOME TYPE:** Dichotomous			
COMPARISON: GnRH antagonist versus agonist									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention group (GnRH antagonist)**	**N total in intervention group (GnRH antagonist)**	**N events in comparison group (GnRH agonist)**	**N total in comparison group (GnRH agonist)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Bahceci 2005 (MRB)	NR	Count	Investigator	0	59	0	70	Crude	NA
Haydardedeoglu 2012 (HRB)	NR	Count	Investigator	19	150	10	150	Crude	NA
Lainas 2007 (MRB)	NR	Count	Investigator	1	26	6	52	Crude	NA
Lainas 2010 (MRB)	NR	Count	Investigator	4	110	5	110	Crude	NA

OI, ovulation induction; **NR**, not reported; **NA**, not applicable.

1.6.2. Forest Plot of all included RCTs comparing GnRH antagonist versus GnRH agonist long protocol for cancellation rate– per patient



1.6.3. Funnel plot for assessment of publication bias



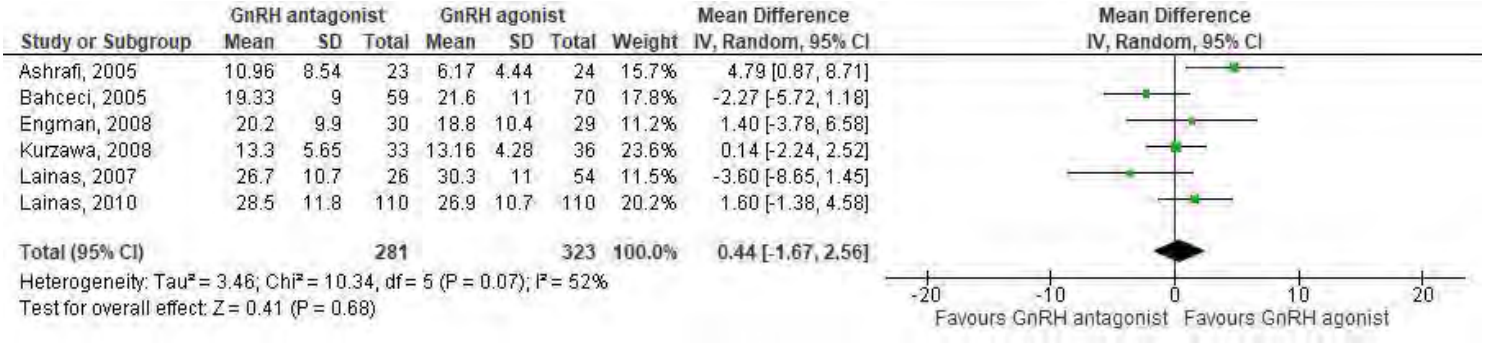
OUTCOME 1.7. Number of oocytes collected

1.7.1. Individual Study Data Tables

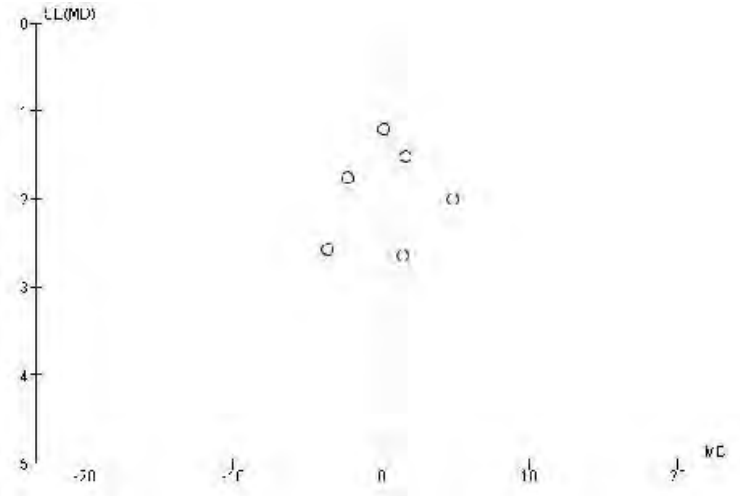
OUTCOME: Number of oocytes collected							OUTCOME TYPE: Continuous				
COMPARISON: GnRH antagonist versus agonist											
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method**	**Mean in intervention group (GnRH antagonist)**	**SD in intervention group (GnRH antagonist)**	**N total in intervention group (GnRH antagonist)**	**Mean in comparison group (GnRH agonist)**	**SD in comparison group (GnRH agonist)**	**N total in comparison group (GnRH agonist)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Ashrafi 2005 (HRB)	NR	Count	Investigator	10.96	8.54	23	6.17	4.44	24	Crude	NA
Bahceci 2005 (MRB)	NR	Count	Investigator	19.33	9.0	59	21.6	11.0	70	Crude	NA
Engmann 2008 (MRB)	NR	Count	Investigator	20.2	9.9	30	18.8	10.4	29	Crude	NA
Haydardedeoglu 2012 (HRB)	NR	Count	Investigator	13.3	5.65	33	13.16	4.28	36	Crude	NA
Kurzawa 2008 (LRB)	NR	Count	Investigator	26.7	10.7	26	30.3	11.0	54	Crude	NA
Lainas 2007 (MRB)	NR	Count	Investigator	28.5	11.8	110	26.9	10.7	110	Crude	NA
Lainas 2010 (MRB)	NR	Count	Investigator	10.96	8.54	23	6.17	4.44	24	Crude	NA

OI, ovulation induction; **NR**, not reported; **NA**, not applicable.

1.7.2. Forest Plot of all included RCTs comparing GnRH antagonist versus GnRH agonist long protocol for number of oocytes collected



1.7.3. Funnel plot for assessment of publication bias



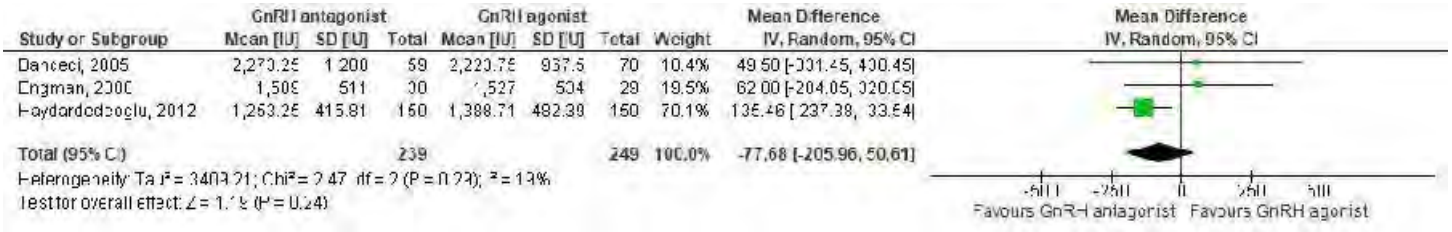
OUTCOME 1.8. Amount of gonadotropins used (IU)

1.8.1. Individual Study Data Tables

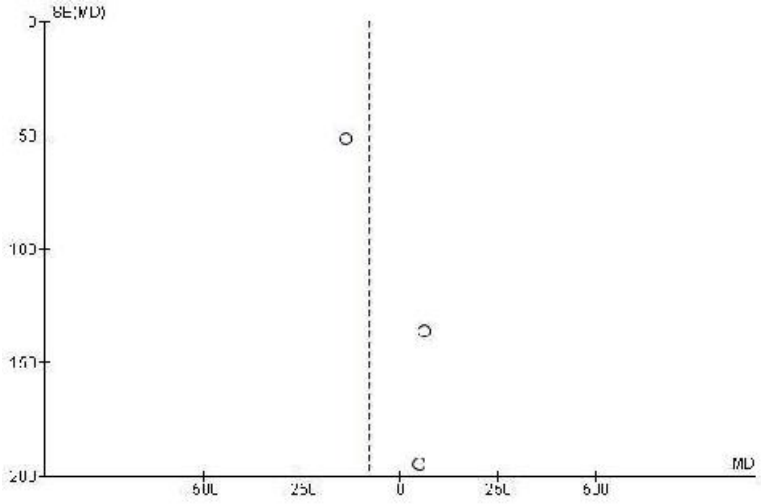
OUTCOME: Amount of gonadotropins used (IU)											**OUTCOME TYPE:** Continuous
COMPARISON: GnRH antagonist versus agonist											
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method**	**Mean in intervention group (GnRH antagonist)**	**SD in intervention group (GnRH antagonist)**	**N total in intervention group (GnRH antagonist)**	**Mean in comparison group (GnRH agonist)**	**SD in comparison group (GnRH agonist)**	**N total in comparison group (GnRH agonist)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Ashrafi 2005 (HRB)*	NR	Number of hMG ampoules (IU NR)*	Investigator	24.5	9.6	23	30	11.3	24	Crude	NA
Bahceci 2005 (MRB)	NR	(n ampoules x 75 IU each)	Investigator	2273.25	1200.0	59	2223.75	967.5	70	Crude	NA
Engmann 2008 (MRB)	NR	IU	Investigator	1589.0	511.0	30	1527.0	534.0	29	Crude	NA
Haydardedeoglu 2012 (HRB)	NR	IU	Investigator	1253.25	415.81	150	1388.71	482.39	150	Crude	NA
Kurzawa 2008 (LRB)*	NR	IU	Investigator	21.7	9.55	33	27.22	9.93	37	Crude	NA
Lainas 2007 (MRB)*	NR	IU	Investigator	26.25	6.58	26	28.66	10.98	52	Crude	NA
Lainas 2010 (MRB)*	NR	Total FSH IU	Investigator	Median 1575	1306-2212	110	Median 1850	1370–2480	110	Crude	NA

OI, ovulation induction; **NR**, not reported; **NA**, not applicable.*not included in meta-analysis due to differing units or varied estimates suggesting incorrect units or unit mismatch and/or due to reporting only medians and ranges/ IQR

1.8.2. Forest Plot of all included RCTs comparing GnRH antagonist versus GnRH agonist long protocol for amount of gonadotropins used (IU)



1.8.3. Funnel plot for assessment of publication bias



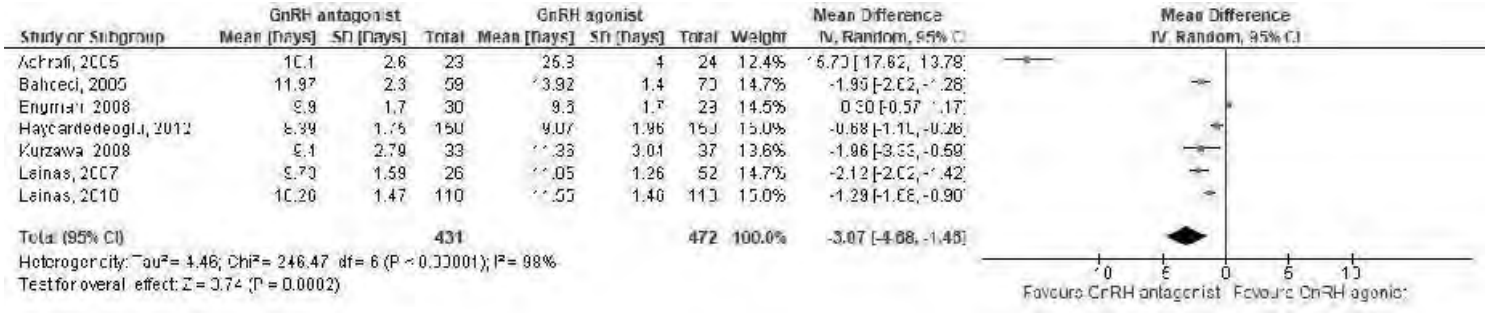
OUTCOME 1.9. Duration of ovarian stimulation (IU)

1.9.1. Individual Study Data Tables

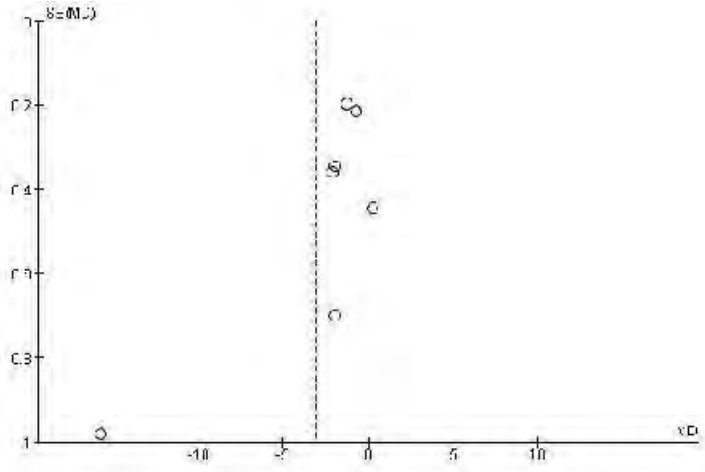
OUTCOME: Duration of ovarian stimulation (days)				**OUTCOME TYPE:** Continuous							
COMPARISON: GnRH antagonist versus agonist											
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method**	**Mean in intervention group (GnRH antagonist)**	**SD in intervention group (GnRH antagonist)**	**N total in intervention group (GnRH antagonist)**	**Mean in comparison group (GnRH agonist)**	**SD in comparison group (GnRH agonist)**	**N total in comparison group (GnRH agonist)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Ashrafi 2005 (HRB)	NR	Days	Investigator	10.1	2.6	23	25.8	4.0	24	Crude	NA
Bahceci 2005 (MRB)	NR	Days	Investigator	11.97	2.3	59	13.92	1.4	70	Crude	NA
Engmann 2008 (MRB)	NR	Days	Investigator	9.9	1.7	30	9.6	1.7	29	Crude	NA
Haydardedeoglu 2012 (HRB)	NR	Days	Investigator	8.39	1.75	150	9.07	1.96	150	Crude	NA
Kurzawa 2008 (LRB)	NR	Days	Investigator	9.4	2.79	33	11.36	3.04	37	Crude	NA
Lainas 2007 (MRB)	NR	Days	Investigator	9.73	1.59	26	11.85	1.26	52	Crude	NA
Lainas 2010 (MRB)	NR	Days	Investigator	10.26	1.47	110	11.55	1.46	110	Crude	NA

OI, ovulation induction; **NR**, not reported; **NA**, not applicable.

1.9.2. Forest Plot of all included RCTs comparing GnRH antagonist versus GnRH agonist long protocol for duration of ovarian stimulation (days)



1.9.3. Funnel plot for assessment of publication bias



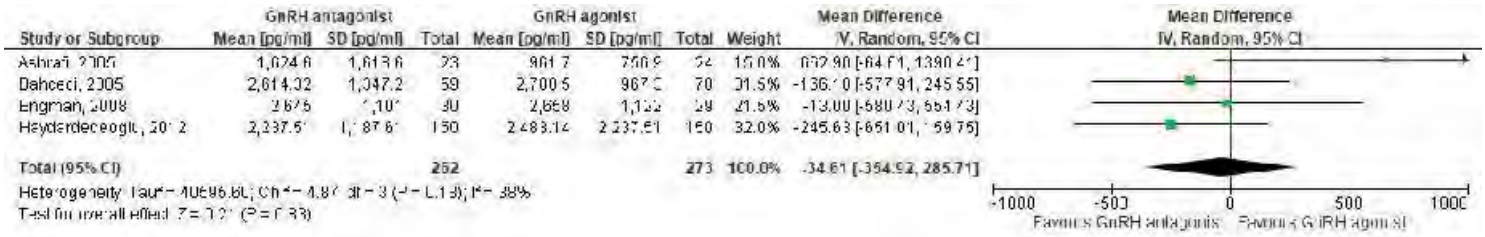
OUTCOME 1.10. Serum E2 on day of trigger

1.10.1. Individual Study Data Tables

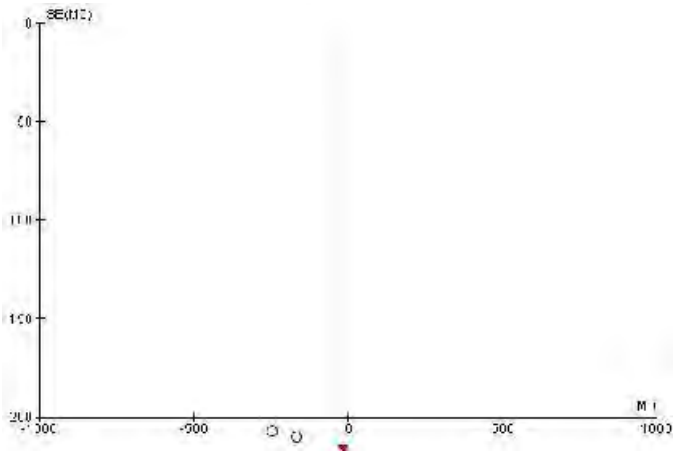
OUTCOME: Serum E2 on day of trigger (pg/ml)				**OUTCOME TYPE:** Continuous							
COMPARISON: GnRH antagonist versus agonist											
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method**	**Mean in intervention group (GnRH antagonist)**	**SD in intervention group (GnRH antagonist)**	**N total in intervention group (GnRH antagonist)**	**Mean in comparison group (GnRH agonist)**	**SD in comparison group (GnRH agonist)**	**N total in comparison group (GnRH agonist)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Ashrafi 2005 (HRB)	NR	pg/ml	Commercial assay	1624.6	1618.6	23	961.7	756.9	24	Crude	NA
Bahceci 2005 (MRB)	NR	pg/ml	Commercial assay	2614.32	1347.2	59	2780.5	967.3	70	Crude	NA
Engmann 2008 (MRB)	NR	pg/ml	Commercial assay	2645.0	1101.0	30	2658.0	1122.0	29	Crude	NA
Haydardedeoglu 2012 (HRB)	NR	pg/ml	Commercial assay	2237.51	1187.61	150	2483.14	2237.51	150	Crude	NA
Kurzawa 2008 (LRB)*	NR	pg/ml	Commercial assay	2200 median	752-8930 min-max	33	2037 median	426-7000 min-max	37	Crude	NA
Lainas 2007 (MRB)*	NR	pg/ml	Commercial assay	2333 median	1505 IQR	26	2858 median	1449 IQR	52	Crude	NA
Lainas 2010 (MRB)*	NR	pg/ml	Commercial assay	2144 median	1533–2977 lower-upper quartiles	110	2850 Median	1994–3585 lower-upper quartiles	110	Crude	NA

OI, ovulation induction; **NR**, not reported; **NA**, not applicable. *not included in meta-analysis due to differing units or varied estimates suggesting incorrect units or unit mismatch; and/or due to reporting only medians and ranges/ IQR

1.10.2. Forest Plot of all included RCTs comparing GnRH antagonist versus GnRH agonist long protocol for duration of serum E2 on day of trigger (pg/ml)



1.10.3. Funnel plot for assessment of publication bias



5. GRADE ASSESSMENTS AND EVIDENCE PROFILE

COMPARISON 1: GnRH antagonist protocol versus GnRH agonist long protocol												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	GnRH antagonist	GnRH agonist	Effect, random , OR [95% CI]	Favours	Certainty	Importance
Outcome: Clinical pregnancy rate- per patient												
6	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	153/389 (39.3%)	186/438 (42.5%)	0.89 [0.65, 1.23]	No difference	⨁⨁⨁◯ MODERATE	CRITICAL
Outcome: OHSS rate - per patient												
7	RCT	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	67/431 (15.5%)	110/472 (23.3%)	0.50 [0.23, 1.10]	No difference	⨁⨁◯◯ LOW	CRITICAL
Outcome: Multiple pregnancy rate - per patient												
3	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	46/223 (20.6%)	52/247 (21.1%)	1.04 [0.62, 1.76]	No difference	⨁⨁⨁◯ MODERATE	IMPORTANT
Outcome: Miscarriage rate - per patient												
7	RCT	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	35/412 (8.5%)	43/462 (9.3%)	0.92 [0.55, 1.52]	No difference	⨁⨁◯◯ LOW	IMPORTANT
Outcome: Miscarriage rate - per pregnancy												
5	RCT	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	18/144 (12.5%)	28/177 (15.8%)	0.80 [0.41, 1.56]	No difference	⨁⨁◯◯ LOW	IMPORTANT
Outcome: Cancellation rate - per patient												
4	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	24/345 (7.0%)	21/382 (5.5%)	1.10 [0.41, 2.96]	No difference	⨁⨁⨁◯ MODERATE	IMPORTANT
Outcome: Number of oocytes collected												
6	RCT	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	281	323	0.44 [-1.67, 2.56]	No difference	⨁⨁◯◯ LOW	IMPORTANT
Outcome: Amount of gonadotropins used (IU)												
3	RCT	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	239	249	-77.68 [-205.96, 50.61]	No difference	⨁⨁◯◯ LOW	IMPORTANT
Outcome: Duration of ovarian stimulation (days)												
7	RCT	serious[1]	very serious[3]	no serious indirectness	no serious imprecision	none	431	472	-3.07 [-4.68, -1.46]	**GnRH antagonist** (ovulation stimulation days lower with GnRH antagonist)	⨁◯◯◯ VERY LOW	IMPORTANT
Outcome: Serum E2 on day of trigger (pg/ml)												
4	RCT	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	262	273	-34.61 [-354.92, 285.71]	No difference	⨁⨁◯◯ LOW	IMPORTANT

[1] Downgraded once due to the majority of studies (half or more) having high or moderate risk of bias or twice if all studies have a high risk of bias
[2] Downgraded once for inconsistency due to variation in effect estimates and their directions and/or wide CIs
[3] Downgraded twice due to inconsistency due to variation in effect estimates and their directions, wide CIs and high heterogeneity (I^2>90%)

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 5

Question 5.7.1

In women with PCOS undergoing IVF/ICSI treatment, is the GnRH antagonist protocol or GnRH agonist long protocol the most effective for improving fertility outcomes?

BACKGROUND:

Women with PCOS are particularly vulnerable to a significant complication of IVF/ICSI treatment, whereby they have a florid response to stimulation with gonadotrophins (as they have multiple follicles within the ovary), and this can be associated with fluid extravasation from the vascular system- a condition called ovarian hyperstimulation syndrome (OHSS) (1). A woman with this condition experiences; abdominal distension (due to the development of ascites) which causes significant discomfort, and she will also experience shortness of breath, nausea and constipation. Consequently, fertility doctors should endeavour to avoid undertaking IVF treatment for women with PCOS, unless it is absolutely essential, or consider in-vitro maturation of oocytes, to completely avoid the risk of OHSS (2). Hence, approaches to minimise the risk of OHSS are important to consider for a patient with PCOS undertaking an IVF cycle (3, 4). One of the proposed methods to reduce the risk of OHSS is to use a GnRH antagonist (as opposed to an agonist) to suppress pituitary LH secretion to prevent an endogenous LH surge and precipitate ovulation, as it believed the pituitary suppression leads to a lower serum oestradiol concentration (5-7). A high serum oestradiol concentration is one of the potential warning signs of incipient OHSS. Although not the subject of this review the use of an GnRH antagonist enables the final trigger injection for oocyte maturation, prior to oocyte retrieval, to be a GnRH agonist, triggering an endogenous LH surge, which has a shorter half-life than the traditional hCG trigger reducing the duration of the OHSS symptoms (4). Hence in a patient at risk of OHSS, where all embryos generated will be frozen and no fresh embryo transfer performed to let incipient OHSS settle (4), the use of an GnRH agonist trigger after down-regulation with a GnRH antagonist offers an approach to reduce the duration of the OHSS symptoms. Further, if the GnRH antagonist approach offered a favourable risk of OHSS compared to the traditional ‘long-down regulation’ with a GnRH agonist, this would further endorse this approach.

Understandably the most important endpoint for any woman embarking on fertility treatment is the live-birth rate from her IVF cycle. Paradoxically, despite this being an apparently obvious endpoint, it is increasingly difficult to provide easily interpretable data. The main reason for this is confusion is that for many young women with PCOS, the IVF cycle commenced may be a planned ‘freeze-all’- to minimise the risk and duration of OHSS, and to completely avoid the discomfort of ‘secondary’ OHSS which occurs when a woman conceives, and the hCG now continues to stimulate follicular development, perpetuating the OHSS. Hence the live-birth rate from that cycle is zero; however, particularly if she is young with PCOS, she will generally generate many oocytes and indeed, ultimately, may have her entire family resulting from that single oocyte retrieval. Hence, IVF specialists may quote cumulative pregnancy rates per cycle commenced to a patient, generating significant confusion for the patient interpreting the data. Consequently, an outcome of live-birth rate should be interpreted with a degree of caution; perhaps a more useful endpoint is the cumulative pregnancy rate per cycle started, and the IVF cycle cancellation rate. Women with PCOS have multiple follicles, and hence many oocytes will be collected, and multiple embryos generated, and there potentially could be a difference between the two groups for these endpoints, and hence ultimately to a potential difference in the rate of miscarriage.

Additional endpoints that may be of interest are the duration of stimulation, as potentially a patient may have to self-inject for fewer days with one preparation in comparison to the other,

and further there may be cost benefits to the patient and health care providers if one treatment regime was cheaper than another if they were equally efficacious on clinical grounds.

GRADE EVIDENCE CERTAINTY	
Comparison	**GRADE for critical outcomes**
Comparison 1. GnRH antagonist versus agonist	⊕◯◯◯ VERY LOW

Evidence to Recommendations Framework

COMPARISON (option versus other option)
GnRH antagonist versus agonist
RESEARCH RECOMMENDATION
Adequately powered, well designed, conducted and reported RCTs are required to compare the effectiveness of GnRH antagonist protocol versus GnRH long protocol to improve reproductive outcomes.
PRACTICE POINT(S)
GnRH antagonist protocol cannot be recommended over GnRH agonist long protocol for women with PCOS undergoing IVF/ICSI to improve clinical pregnancy or live birth rate. The use of an antagonist protocol for women with PCOS undergoing IVF/ICSI is recommended as it enables the use of an agonist trigger, with the freezing of all embryos generated if required, without compromising the cumulative live birth rate, to reduce the risk of significant ovarian hyperstimulation syndrome.

REFERENCES

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3. Boothroyd, C., et al., Consensus statement on prevention and detection of ovarian hyperstimulation syndrome. Aust N Z J Obstet Gynaecol, 2015. 55(6): p. 523-34.
4. Practice Committee of the American Society for Reproductive Medicine, Prevention and treatment of moderate and severe ovarian hyperstimulation syndrome: a guideline. Fertil Steril, 2016. 106(7): p. 1634-1647.

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6. Lin, H., et al., Is a GnRH antagonist protocol better in PCOS patients? A meta-analysis of RCTs. PLoS One, 2014. 9(3): p. e91796.

7. Mancini, F., et al., Gonadotrophin-releasing hormone-antagonists vs long agonist in in-vitro fertilization patients with polycystic ovary syndrome: a meta-analysis. Gynecol Endocrinol, 2011. 27(3): p. 150-5.

PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by the Evidence Team: Aya Mousa, Jillian Tay
Other team members: Loyal Pattuwage

GDG 5

Question 5.7.2

In women with PCOS undergoing GnRH antagonist IVF/ICSI treatment, is the use of hCG trigger or GnRH agonist trigger the most effective for improving fertility outcomes?

1. STUDY SELECTION

Table 1. PICO Criteria for Inclusion	
Question	In women with PCOS undergoing GnRH antagonist IVF/ICSI treatment, is the use of hCG trigger or GnRH agonist trigger the most effective for improving fertility outcomes?
Clinical leads (key contacts)	Lan Vuong
Allocation ranking	Systematic review Level 2 (updated)

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(language, year)*
Inclusion	Women of any age, ethnicity and weight with PCOS diagnosed by Rotterdam, NIH or AEPCOS AND with or without coexisting infertility factors (other than anovulation). Also specifically identifying the 4 phenotypes where possible.	IVF/ICSI treatment with GnRH antagonist protocol and use of hCG trigger to induce final oocyte maturation. Note: It is important to clarify doses of HCG in GnRH antagonist trigger ovulation. HCG alone in traditional doses to trigger ovulation it is at risk of ovarian hyperstimulation.	IVF/ICSI treatment with GnRH antagonist protocol and use of GnRH agonist trigger to induce final oocyte maturation.	Live birth rate, pregnancy rate (biochemical or clinical ultrasound), ovulation, amount of gonadotrophins used, duration of ovarian stimulation, maximum serum estradiol level (or serum estradiol level on the day of trigger), number of oocytes collected, single and multiple pregnancies, miscarriage rate, OHSS rate, other adverse events, quality of life, cost effectiveness.	Evidence based guidelines, systematic reviews, health technology assessments, randomised controlled trials (RCTs).	
Exclusion	Women without diagnosis of PCOS.	Placebo, no intervention or any intervention other than IVF.	Any intervention other than those listed in the inclusion criteria.	None	Non-evidence based guidelines, nonsystematic reviews, any study lower than a RCT.	

2. SEARCH STRATEGY

The search and screening for all GDG 5 questions were done together. Details can be found in the GDG 5 Methodology Appendix, including for:

- Databases
- Search Dates
- Search String(s)
- PRISMA flowchart
- Full list of included studies
- Full list of excluded studies with reasons for exclusion

Evidence processing: The literature search and screening were performed together in one Endnote library and Covidence project for all non-IVF, IVF and IVM fertility treatments in PCOS. Studies were selected by one reviewer/s in consultation with the evidence team/ key contact(s) using study selection and appraisal criteria (PICOs) established a priori. The articles were screened by title and abstract by one reviewer. When a decision could not be made based on title and abstract alone, full text was retrieved. Study appraisal was conducted by two reviewers independently with

discussion to resolve any discrepancy. In total, 102 unique studies met inclusion criteria across all non-IVF, IVF and IVM questions, of which 57 were included in the guideline update following the integrity check (refer to methodology appendix for details).

3. FINDINGS

Of the eligible 57 studies (after integrity assessment) across all non-IVF, IVF and IVM, **none met the inclusion criteria for this particular question (Q 5.7.2) on hCG or GnRH trigger**. Therefore, the available evidence has been reviewed narratively.

See PART 2 for this question.

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 5

Question 5.7.2

In women with PCOS undergoing GnRH antagonist IVF/ICSI treatment, is the use of hCG trigger or GnRH agonist trigger the most effective for improving fertility outcomes?

BACKGROUND

Gonadotrophin releasing hormone agonists (GnRHa) are highly effective in inducing an LH surge, with levels comparable to those observed during the spontaneous surge during normal menstrual cycles so that it has been exploited clinically in women at risk of ovarian hyperstimulation syndrome (OHSS) such as PCOS women. GnRH-a trigger has become the trigger mode of choice in women at risk of OHSS because several previous trials showed a complete elimination of OHSS as well as reproductive outcomes similar to those seen with hCG trigger (1). Although a GnRHa induced LH surge is capable of inducing oocyte maturation, it is significantly shorter than that observed during a natural cycle, leading to a compromised corpus luteal function (2).

Evidence for defective luteal function included the observation that GnRHa cycles have a shorter luteal phase and that the luteal steroid profile is reduced in both non-supplemented and supplemented in-vitro fertilisation (IVF) cycles, as compared to an hCG trigger (3). The clinical impact of this defective corpus luteal function after a GnRHa trigger, is that when combined with standard luteal phase support, pregnancy rates are lower and miscarriage rates higher in fresh embryo transfer (4, 5). Segmentation of the cycle and freezing of all embryos is an appropriate alternative to avoid OHSS in women at risk of OHSS and is increasingly used in most IVF centers (6).

GRADE EVIDENCE CERTAINTY	
Comparison	**GRADE for critical outcomes**
No studies identified	

Recommendations Framework

CONSENSUS RECOMMENDATION(S)

CR: Triggering final oocyte maturation with a GnRH agonist and freezing all suitable embryos is recommended, in an IVF/ICSI cycle with a GnRH antagonist protocol, where a fresh embryo transfer is not intended or where there is an increased risk of Ovarian Hyperstimulation Syndrome.

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	X Strong recommendation for the option

PRACTICE POINT

See PP Q.5.7.1

CONSIDERATIONS

Justifications:

The choice to trigger final oocyte maturation with GnRH-agonist instead of hCG is important in prevention of OHSS as hCG alone induces oocyte maturation but is associated with OHSS. GnRH- agonist triggers are associated with lower pregnancy rates, primarily in fresh embryo transfers, which can be overcome in frozen cycles.

Subgroup considerations:

- Different regimes for luteal support in GnRH agonist trigger and fresh transfers.

Implementation considerations:

- Cost-effectiveness of GnRH agonist triggering + Freeze-all

Monitoring and evaluation considerations:

Cost-effectiveness of the strategies.

Research priorities:

Additional trials should ascertain whether the combination of GnRHa trigger and the intensive luteal steroid support package in the OHSS high-risk patient is associated with better clinical outcomes than the use of GnRHa trigger and subsequent frozen embryo transfer.

Equity:

May be less due to the cost issue related to GnRH agonist triggering and Freeze-all.

Acceptability

Yes.

FEASIBILITY

Only feasible in centres having good freezing program.

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maturation in in vitro fertilization patients after ovarian stimulation with recombinant follicle-stimulating hormone and GnRH antagonist cotreatment. J Clin Endocrinol Metab, 2003. **88**(9): p. 4186-92.
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PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by the Evidence Team: Aya Mousa, Jillian Tay
Other team members: Loyal Pattuwage

GDG 5

Question 5.7.3

In women with PCOS undergoing (controlled) ovarian (hyper) stimulation for IVF/ICSI, does the choice of FSH effect fertility outcomes?

1. STUDY SELECTION

Table 1. PICO Criteria for Inclusion	
Question	**In women with PCOS undergoing (controlled) ovarian (hyper) stimulation for IVF/ICSI, does the choice of FSH effect fertility outcomes?**
Clinical leads (key contacts)	**Luk Rombauts**
Allocation ranking	**Systematic review Level 2 (updated)**

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(language, year)*
Inclusion	Women of any age, ethnicity and weight with PCOS diagnosed by Rotterdam, NIH or AEPCOS AND with or without co-existing infertility factors (other than anovulation) AND Undergoing IVF/ICSI Treatment using a GnRH antagonist protocol or GnRH agonist long protocol (need to analyse separately as subgroups and also combined in any meta-analysis) Also specifically identifying the 4 phenotypes where possible.	Any type, dose and frequency of recombinant FSH (rFSH) or any of: HMG, HP-HMG (highly purified HMG), uFSH-P (purified urinary FSH) or uFSH-HP (highly purified urinary FSH)	Any other intervention out of: HMG, HP-HMG (highly purified HMG), uFSH-P (purified urinary FSH) or uFSH-HP (highly purified urinary FSH)	Live birth rate, pregnancy rate (biochemical or clinical ultrasound), ovulation, amount of gonadotrophins used, duration of ovarian stimulation, maximum serum estradiol level (or serum estradiol level on the day of trigger), number of oocytes collected, single and multiple pregnancies, miscarriage rate, OHSS rate, other adverse events, quality of life, cost effectiveness.	Evidence based guidelines, systematic reviews, health technology assessments, randomised controlled trials (RCTs).	English Human
Exclusion	Women without diagnosis of PCOS.	Placebo, no intervention or any intervention other than recombinant FSH.	Any intervention other than those listed in the inclusion criteria.	None	Non-evidence based guidelines, non-systematic reviews, any study lower than a RCT.	Women without diagnosis of PCOS.

2. SEARCH STRATEGY

The search and screening for all GDG 5 questions were done together. Details can be found in the GDG 5 Methodology Appendix, including for:

- Databases
- Search Dates
- Search String(s)
- PRISMA flowchart
- Full list of included studies
- Full list of excluded studies with reasons for exclusion

Evidence processing: The literature search and screening were performed together in one Endnote library and Covidence project for all non-IVF, IVF and IVM fertility treatments in PCOS. Studies were selected by one reviewer/s in consultation with the evidence team/ key contact(s) using study selection and appraisal criteria (PICOs) established a priori. The articles were screened by title and abstract by one reviewer. When a decision could not be made based on title and abstract alone, full text was retrieved. Study appraisal was conducted by two reviewers independently with discussion to resolve any discrepancy. In total, 102 unique studies met inclusion criteria across all non-IVF, IVF and IVM questions, of which 57 were included in the guideline update following the integrity check (refer to methodology appendix for details).

3. FINDINGS

Of the eligible 57 studies (after integrity assessment) across all non-IVF, IVF and IVM, **none met the inclusion criteria for this particular question (Q 5.7.3.) on choice of FSH**. Therefore, the available evidence has been reviewed narratively.

See PART 2 for this question.

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 5

Question 5.7.3

In women with PCOS undergoing (controlled) ovarian (hyper) stimulation for IVF/ICSI, does the choice of FSH effect fertility outcomes?

BACKGROUND:

Different preparations of FSH exist. FSH can be extracted from human urine (uFSH) or it can be synthesised by animal cell lines using recombinant DNA techniques (rFSH) (1). rFSH preparations are manufactured using both animal and human cell lines and can also be distinguished by their originator or biosimilar status.

Urinary FSH preparations have varying levels of LH activity and other impurities. The LH activity in urinary gonadotrophin preparations is known to stimulate androgen production in theca cells and it plays an important role in completing maturation of the follicle. However, it is assumed that less than 1% of follicular LH receptors needs to be occupied in order to elicit maximal steroidogenesis (2) and it is therefore possible that enough endogenous LH is present during controlled ovarian stimulation to promote androgen synthesis and oocyte maturation without the need for extra LH activity in FSH preparations.

The perceived clinical benefits of the different FSH preparations are the subject of ongoing debate (3), with evidence pointing at a lower risk of OHSS with human menopausal gonadotrophin (hMG) in a general population (4). All types of preparations remain commonly used.

GRADE EVIDENCE CERTAINTY	
Comparison	**GRADE for critical outcomes**
No studies identified	

Recommendations Framework

CONSENSUS RECOMMENDATION

CR: Either urinary or recombinant FSH could be used in women with PCOS undergoing (controlled) ovarian (hyper) stimulation for IVF/ICSI, with insufficient evidence to recommend a particular type of FSH preparation.

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☒ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

CONSIDERATIONS

Justifications:

Of the eligible 57 studies (after integrity assessment) across all non-IVF, IVF and IVM, none met the inclusion criteria for this particular question (Q 5.09d.) on choice of FSH. Therefore, the available evidence has been reviewed narratively.

Subgroup considerations:

N/A

Implementation considerations:

Availability, convenience and cost considerations may be an important factor in the decision.

Monitoring and evaluation considerations:

N/A

Research priorities

High quality studies are required comparing different types of FSH preparations in women with PCOS undergoing (controlled) ovarian (hyper) stimulation for IVF/ICSI using GnRH antagonist or GnRH agonist long protocol on live birth rate per cycles started, cumulative live birth rate from one egg retrieval, OHSS and cost effectiveness.

Equity:

Evidence was not sought to address this criterion.

Acceptability:

There are no foreseeable concerns stakeholders might have with the recommendation of no preference.

Feasibility:

Yes. No option was favoured.

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4. Witz, C.A., et al., Randomized, assessor-blinded trial comparing highly purified human menotropin and recombinant follicle-stimulating hormone in high responders undergoing intracytoplasmic sperm injection. Fertil Steril, 2020. 114(2): p. 321-330.

PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by the Evidence Team: Aya Mousa, Jillian Tay
Other team members: Loyal Pattuwage

GDG 5

Question 5.7.4

In women with PCOS undergoing (controlled) ovarian (hyper) stimulation for IVF/ICSI, is exogenous LH treatment during IVF/ICSI effective for improving fertility outcomes?

1. STUDY SELECTION

Table 1. PICO Criteria for Inclusion	
Question	In women with PCOS undergoing (controlled) ovarian (hyper) stimulation for IVF/ICSI, is exogenous LH treatment during IVF/ICSI effective for improving fertility outcomes?
Clinical leads (key contacts)	Dongzi Yang
Allocation ranking	Systematic review Level 2 (updated)

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(language, year)*
Inclusion	Women of any age, ethnicity and weight with PCOS diagnosed by Rotterdam, NIH or AIS and with or without co-existing infertility factors (other than anovulation) AND Treatment using a GnRH antagonist protocol or GnRH agonist long protocol or GnRH agonist short (flare) protocol (need to analyse separately as subgroups and also combined in any meta-analysis). Also specifically identifying the 4 phenotypes where possible.	Any type, dose and frequency of exogenous LH (rLH, rhCG, uhCG, HP-HMG, HMG)	Placebo, no exogenous LH (no intervention)	Live birth rate, pregnancy rate (biochemical or clinical ultrasound), ovulation, amount of gonadotrophins used, duration of ovarian stimulation, maximum serum estradiol level (or serum estradiol level on the day of trigger), number of oocytes collected, single and multiple pregnancies, miscarriage rate, OHSS rate, other adverse events, quality of life, cost effectiveness.	Evidence based guidelines, systematic reviews, health technology assessments, randomised controlled trials (RCTs).	
Exclusion	Women without diagnosis of PCOS.	Placebo, no intervention or any intervention other than the above.	Any intervention other than those listed in the inclusion criteria.	None	Non-evidence based guidelines, non-systematic reviews, any study lower than a RCT.	

2. SEARCH STRATEGY

The search and screening for all GDG 5 questions were done together. Details can be found in the GDG 5 Methodology Appendix, including for:

- Databases
- Search Dates
- Search String(s)
- PRISMA flowchart
- Full list of included studies
- Full list of excluded studies with reasons for exclusion

Evidence processing: The literature search and screening were performed together in one Endnote library and Covidence project for all non-IVF, IVF and IVM fertility treatments in PCOS. Studies were selected by one reviewer/s in consultation with the evidence team/ key contact(s) using study selection and appraisal criteria (PICOs) established a priori. The articles were screened by title and abstract by one reviewer. When a decision could not be made based on

title and abstract alone, full text was retrieved. Study appraisal was conducted by two reviewers independently with discussion to resolve any discrepancy. In total, 102 unique studies met inclusion criteria across all non-IVF, IVF and IVM questions, of which 57 were included in the guideline update following the integrity check (refer to methodology appendix for details).

3. FINDINGS

Of the eligible 57 studies (after integrity assessment) across all non-IVF, IVF and IVM, **none met the inclusion criteria for this particular question (Q 5.7.4.) on exogenous LH treatment**. Therefore, the available evidence has been reviewed narratively below and in PART 2 for this question.

▪ CLINICAL NEED FOR THE QUESTION

Options have been explored to reduce OHSS risk in IVF/ICSI in PCOS. The chronic low dose step-up protocol with exogenous FSH in securing single (fewer) dominant follicle selection is an alternative method to avoid multi-follicular development. During late follicular development, LH is essential to achieve adequate ovarian steroidogenesis and develop the subsequent capacity of the follicle to ovulate and luteinize. Increased LH secretion or elevated LH/FSH ratio in PCOS may influence fertility, with inhibition of oocyte maturation, deleterious effects on granulosa cell steroidogenesis and endometrial receptivity and with potential increased early pregnancy loss. The lack of clarity around the role of exogenous LH in the setting of IVF/ICSI prompted this clinical question.

▪ NARRATIVE SUMMARY

Obesity adversely impacts on ovulation and on responses to ovulation induction in PCOS. In PCOS, granulosa cells respond to LH at a relatively earlier follicular stage and are significantly more responsive than for ovulatory women with PCOS or women without PCOS. Granulosa cell differentiation may be prematurely advanced. Controlled ovarian stimulation for multiple follicular development in ART can be performed in a variety of ways to increase efficacy and reduce risks.

Systematic reviews and meta-analysis have demonstrated that there is no significant difference between different ovarian stimulation protocols (hMG, purified FSH, recombinant FSH) regarding the fertility outcomes. Therefore, clinical gonadotropin choice depends on the availability of the product, the convenience of its use, and the associated costs. Individualised gonadotrophin dose selection using markers of ovarian reserve for women undergoing IVF/ICSI. There is no clear evidence that co-administration of rLH to recombinant follicle-stimulating hormone (rFSH) in GnRHa down-regulated women resulted in more live births or fewer cases of OHSS than COH with rFSH alone Nevertheless, pooled clinical and ongoing pregnancy estimates suggested a beneficial effect of co-treatment with rLH.

There may be little or no difference in live birth, incidence of multiple pregnancy, clinical pregnancy rate, or miscarriage rate between urinary-derived gonadotrophins and recombinant follicle stimulating hormone in women with polycystic ovary syndrome. It is uncertain whether human menopausal gonadotropin or highly purified human menopausal gonadotrophin improves or lowers live birth, incidence of multiple pregnancy, clinical pregnancy rate, or miscarriage rate when compared with urinary follicle stimulating hormone. No current study investigates efficacy of exogenous LH supplement for fertility outcomes in PCOS during IVF/ICSI. Careful monitoring of follicular development during ovarian stimulation is critical.

The systematic review by Datta et al., (2021) reviewed RCTs comparing a mild (<150 IU daily dose) versus conventional stimulation in terms of clinical outcomes and cost-effectiveness in patients described as poor, normal and non-polycystic ovary syndrome (PCOS) hyper-responders to IVF. The review found that live birth rates (LBRs) per randomisation were similar following use of MD-IVF in poor (relative risk (RR) 0.91 (CI 0.68, 1.22)), normal (RR 0.88 (CI 0.69, 1.12)) and hyper-responders (RR 0.98 (CI 0.79, 1.22)) when compared to CD-IVF. Risk of ovarian hyperstimulation syndrome was significantly less with MD-IVF than CD-IVF in both normal (RR 0.22 (CI 0.10, 0.50)) and hyper-responders (RR 0.47 (CI 0.31, 0.72)). The CCRs were comparable in poor (RR 1.33 (CI 0.96, 1.85)) and hyper-responders (RR 1.31 (CI 0.98, 1.77)) but increased with MD-IVF among normal responders (RR 2.08 (CI 1.38, 3.14)). Although fewer oocytes were retrieved and fewer embryos created with MD-IVF, the proportion of high-grade embryos was similar in all three population types. Compared to CD-IVF, MD-IVF was associated with less gonadotrophin use and lower cost.

This updated review provides reassurance on using MD-IVF not only for the LBR per cycle but also for the cumulative LBR, with moderate QoE. With risks identified with 'freeze-all' strategies, it may be time to recommend mild-dose ovarian stimulation for IVF for all categories of women i.e. hyper, poor and normal responders to IVF.

A Cochrane review by Farquhar et al., 2018 compared recombinant versus urinary gonadotrophin for ovarian stimulation in ART cycles. It appears that all available gonadotrophins were equally effective and safe. Review authors stated that the choice of one or the other product would depend upon the availability of the product, the convenience of its use, and the associated costs, and that any specific differences were likely to be too small to justify further research (moderate- to high-quality evidence) (van Wely 2011).

Individualised gonadotrophin dose selection using markers of ovarian reserve for women undergoing IVF/ICSI: a decreased dose of FSH in predicted high responders appeared to reduce the likelihood of moderate or severe OHSS (low-quality evidence). Furthermore, ovarian reserve test (ORT) algorithms reduced the incidence of OHSS compared to standard dosing of 150 IU, probably by facilitating dose reductions among women with a predicted high response (moderate-quality evidence) (Lensen 2018)

Recombinant luteinising hormone (rLH) for controlled ovarian hyperstimulation (COH) in assisted reproductive cycles: there is no clear evidence that co-administration of rLH to recombinant follicle-stimulating hormone (rFSH) in GnRHa down-regulated women resulted in more live births or fewer cases of OHSS than COH with rFSH alone (very low- or low quality evidence). Nevertheless, pooled clinical and ongoing pregnancy estimates suggested a beneficial effect of co-treatment with rLH (moderate-quality evidence) (Mochtar 2017)

(Mochtar 2017) found no clear evidence of a difference between recombinant luteinising hormone (rLH) combined with recombinant follicle-stimulating hormone (rFSH) and rFSH alone in rates of live birth (very low-quality evidence) or OHSS (low-quality evidence), but evidence suggested that use of rLH combined with rFSHmay lead tomore clinical pregnancies than use of rFSH alone (moderate-quality evidence). Results show little or no difference between groups in rates of miscarriage (moderate-quality evidence). The review authors concluded that the evidence was insufficient to encourage or discourage stimulation regimens that include rLH combined with rFSH in IVF/ICSI cycles.

Wang et al., 2017 compared the effectiveness of alternative first line treatment options for women with WHO group II anovulation wishing to conceive and concluded that in women with WHO group II anovulation, letrozole and the combination of clomiphene and metformin are superior to clomiphene alone in terms of ovulation and pregnancy. Compared with clomiphene alone, letrozole is the only treatment showing a significantly higher rate of live birth.

Weiss et al., 2109 in a systematic review, compared the effectiveness and safety of gonadotrophins as a second-line treatment for ovulation induction in women with clomiphene citrate-resistant polycystic ovary syndrome (PCOS), and women who do not ovulate or conceive after clomiphene citrate and noted there may be little or no difference in the birth rate between rFSH and urinary-derived gonadotrophins (RR 1.21, 95% confidence interval (CI) 0.83 to 1.78; five trials, N = 505; IO = 9%; low-quality evidence). This suggests that for the observed average live birth per woman who used urinary-derived FSH of 16%, the chance of live birth with rFSH is between 13% and 28%. There may also be little or no difference between groups in incidence of multiple pregnancy (RR 0.86, 95% CI 0.46 to 1.61; eight trials, N = 1368; IO = 0%; low-quality evidence), clinical pregnancy rate (RR 1.05, 95% CI 0.88 to 1.27; eight trials, N = 1330; IO = 0; low-quality evidence), or miscarriage rate (RR 1.20, 95% CI 0.71 to 2.04; seven trials, N = 970; IO = 0; low-quality evidence). We are uncertain whether rFSH reduces the incidence of OHSS (RR 1.48, 95% CI 0.82 to 2.65, ten trials, n=1565, IO = 0%, very low-quality evidence).

When compared to uFSH, t is not clear whether HMG or HP-HMG improves live birth rate (RR 1.28, 95% CI 0.65 to 2.52; three trials, N= 138; IO = 0%; very low quality evidence), or reduces multiple pregnancy rate (RR 2.13, 95% CI 0.51 to 8.91; four trials, N = 161; IO = 0%; very low quality evidence). It is also uncertain whether HMG or HP-HMG improves clinical pregnancy rate (RR 1.31, 95% CI 0.66 to 2.59; three trials, N = 102; IO = 0; very low quality evidence), reduces miscarriage rate (RR 0.33, 95% CI 0.06 to 1.97; two trials, N = 98; IO = 0%; very low quality evidence), or reduces the incidence of OHSS (RR 7.07, 95% CI 0.42 to 117.81; two trials, N = 53; very low quality evidence) when compared to uFSH..

There may be little or no difference in live birth, incidence of multiple pregnancy, clinical pregnancy rate, or miscarriage rate between urinary-derived gonadotrophins and recombinant follicle stimulating hormone in women with polycystic ovary syndrome. For human menopausal gonadotropin or highly purified human menopausal gonadotrophin versus urinary follicle stimulating hormone , it is not clear whether one or the other improves or lowers live birth, incidence of multiple pregnancy, clinical pregnancy rate, or miscarriage rate. Whether any of the interventions reduce the incidence of ovarian hyperstimulation syndrome is unclear.

We suggest weighing costs and convenience in the decision to use one or the other gonadotrophin. In women with clomiphene citrate failure, gonadotrophins resulted in more live births than continued clomiphene citrate without increasing multiple pregnancies.

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 5

Question 5.7.4

In women with PCOS undergoing (controlled) ovarian (hyper) stimulation for IVF/ICSI, is exogenous LH treatment during IVF/ICSI effective for improving fertility outcomes?

BACKGROUND:

Folliculogenesis and oocyte maturation are complex processes that require the action of both LH and FSH (1). However, systematic reviews and meta-analysis have demonstrated that there is no significant difference between different ovarian stimulation protocols (hMG, purified FSH, recombinant FSH) regarding fertility outcomes (2-4). It has been suggested that the benefits of LH supplementation may occur in subpopulations characterized by LH insufficiency, including hypo–responders and advanced age women (5).

PCOS is the most common cause of anovulatory infertility. Increased LH secretion or elevated LH/FSH ratio in women with PCOS has been suggested to be involved in the pathogenesis of decreased fertility. The proposed mechanisms include inhibition of oocyte maturation leading to premature oocyte maturation as well as its deleterious effects on granulosa cell steroidogenesis and endometrial receptivity and with potential increased early pregnancy loss.

Ovulation stimulation protocols for PCOS patients need to benefit effectiveness and safety. Ovarian stimulation for IVF/ICSI in patients with PCOS is characterized by a risk of multiple follicular development leading to a high incidence of OHSS and multiple pregnancies. Reducing the incidence of OHSS is an important goal in PCOS treatment.

Options have been explored to reduce OHSS risk in IVF/ICSI in PCOS. In women predicted hyper-responder who undergo IVF/ICSI, individualised selection of gonadotrophin doses is found to reduce the likelihood of moderate or severe OHSS, while increasing the likelihood of cycle cancellations. The impact of gonadotrophin choice (with or without LH preparation) on the incidence of OHSS remains uncertain.

Some studies indicated that HP-hMG treatment of potential high responders (non-PCOS), was associated with a lower median number of retrieved oocytes, significantly lower incidence of high response, fewer interventions for OHSS, and increased live birth rate compared with rFSH in GnRH agonist or antagonist protocols (6-8).

The lack of clarity around the role of exogenous LH in the setting of IVF/ICSI prompted this clinical question.

GRADE EVIDENCE CERTAINTY	
Comparison	**GRADE for critical outcomes**
No studies identified	

Recommendations Framework

CONSENSUS RECOMMENDATION(S)

CR: Exogenous recombinant luteinising hormone treatment should not be routinely used in combination with follicle stimulating hormone therapy in women with PCOS undergoing controlled ovarian hyperstimulation for IVF / ICSI.

☐ Strong recommendation against the option	☒ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

CONSIDERATIONS
Justifications: There is no anticipated effect or benefit to add exogenous LH supplement in women with PCOS undergoing ovarian stimulation for IVF /ICSI. There is insufficient evidence to determine the benefits of using or not using exogenous LH.
Subgroup considerations: No studies were available for any subgroup analysis.
Implementation considerations: Not applicable.
Monitoring and evaluation considerations: Implementation not recommended.
Research priorities: The dose of exogenous LH in addition to FSH appropriate for follicular development should be further investigated. Identify whether there is benefit in terms of improving live birth rate or reducing OHSS, and which groups will benefit from exogenous LH addition to FSH in IVF +/- ICSI.
Equity: No research evidence was identified. There are currently no known advantaged group or different baseline conditions that may selectively favour use of LH agent.
Acceptability Not applicable.
FEASIBILITY Not applicable.

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PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by the Evidence Team: Aya Mousa, Jillian Tay
Other team members: Loyal Pattuwage

GDG 5

Question 5.7.5

In women with PCOS undergoing (controlled) ovarian (hyper) stimulation for IVF/ICSI, is adjuvant metformin effective for improving fertility outcomes?

1. STUDY SELECTION

Table 1. PICO Criteria for Inclusion	
Question	In women with PCOS undergoing (controlled) ovarian (hyper) stimulation for IVF/ICSI, is adjuvant metformin effective for improving fertility outcomes?
Clinical leads (key contacts)	Michael Costello
Allocation ranking	Updated systematic review (Level 2)

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(language, year)*
Inclusion	Women of any age, ethnicity and weight with PCOS diagnosed by Rotterdam, NIH or AEPCOS AND with or without co-existing infertility factors (other than anovulation). Also, specifically identifying the 4 phenotypes where possible.	IVF/ICSI treatment with GnRH antagonist protocol or GnRH agonist long protocol	IVF/ICSI treatment with GnRH antagonist protocol or GnRH agonist long protocol and adjuvant metformin before and during IVF/ICSI treatment	Live birth rate, pregnancy rate (biochemical or clinical ultrasound), ovulation, amount of gonadotrophins used, duration of ovarian stimulation, maximum serum estradiol level (or serum estradiol level on the day of trigger), number of oocytes collected, single and multiple pregnancies, miscarriage rate, OHSS rate, other adverse events, quality of life, cost effectiveness.	Evidence based guidelines, systematic reviews, health technology assessments, randomised controlled trials (RCTs).	None
Exclusion	Women without diagnosis of PCOS.				Non-evidence based guidelines, non-systematic reviews, any study lower than a RCT.	None

2. SEARCH STRATEGY

The search and screening for all GDG 5 questions were done together. Details can be found in the GDG 5 Methodology Appendix, including for:

- Databases
- Search Dates
- Search String(s)
- PRISMA flowchart
- Full list of included studies
- Full list of excluded studies with reasons for exclusion

Evidence processing: The literature search and screening were performed together in one Endnote library and Covidence project for all non-IVF, IVF and IVM fertility treatments in PCOS. Studies were selected by one reviewer/s in consultation with the evidence team/ key contact(s) using study selection and appraisal criteria (PICOs) established a priori. The articles were screened by title and abstract by

one reviewer. When a decision could not be made based on title and abstract alone, full text was retrieved. Study appraisal was conducted by two reviewers independently with discussion to resolve any discrepancy. In total, 102 unique studies met inclusion criteria across all non-IVF, IVF and IVF questions, of which 57 were included in the guideline update following the integrity check (refer to methodology appendix for details).

Of these eligible 102 studies (57 after integrity assessment), **8 studies met the inclusion criteria for this particular question** (Q.5.7.5.) on adjuvant metformin use during IVF/ICSI, as detailed below.

Table of Included Studies
Doldi, N., Persico, P., Di Sebastiano, F., Marsiglio, E., & Ferrari, A. (2006). Gonadotropin-releasing hormone antagonist and metformin for treatment of polycystic ovary syndrome patients undergoing in vitro fertilization-embryo transfer. Gynecological Endocrinology, 22(5), 235-238.
Fedorcsak, P.; Dale, P. O.; Storeng, R.; Abyholm, T.; Tanbo, T. The effect of metformin on ovarian stimulation and in vitro fertilization in insulin-resistant women with polycystic ovary syndrome: an open-label randomized crossover trial. Gynecol Endocrinol 2003, 17, 207-14 DOI: 10.1080/gye.17.3.207.214
Jacob SL, Brewer C, Tang T, Picton HM, Barth JH, Balen AH. A short course of metformin does not reduce OHSS in a GnRH antagonist cycle for women with PCOS undergoing IVF: a randomised placebo-controlled trial. Hum Reprod. 2016 Dec;31(12):2756-2764. doi: 10.1093/humrep/dew268. Epub 2016 Nov 5. PMID: 27816925.
Onalan G, Pabuçcu R, Goktolga U, Ceyhan T, Bagis T, Cincik M. Metformin treatment in patients with polycystic ovary syndrome undergoing in vitro fertilization: a prospective randomized trial. Fertil Steril. 2005 Sep;84(3):798-801. doi: 10.1016/j.fertnstert.2005.03.043. PMID: 16169430.
Kjotrod, S. B.; von During, V.; Carlsen, S. M. Metformin treatment before IVF/ICSI in women with polycystic ovary syndrome; a prospective, randomized, double blind study. Hum Reprod 2004, 19, 1315-22
Kjotrod, S. B., S. M. Carlsen, et al. (2011). "Use of metformin before and during assisted reproductive technology in non-obese young infertile women with polycystic ovary syndrome: a prospective, randomized, double-blind, multi-centre study." Human Reproduction 26(8): 2045-2053.
Qublan HS, Al-Khaderei S, Abu-Salem AN, Al-Zpoon A, Al-Khateeb M, Al-Ibrahim N, Megdadi M, Al-Ahmad N. Metformin in the treatment of clomiphene citrate-resistant women with polycystic ovary syndrome undergoing in vitro fertilisation treatment: a randomised controlled trial. J Obstet Gynaecol. 2009 Oct;29(7):651-5. doi: 10.1080/01443610903147576. PMID: 19757275.
Tang, T.; Glanville, J.; Orsi, N.; Barth, J. H.; Balen, A. H. The use of metformin for women with PCOS undergoing IVF treatment. Hum Reprod 2006, 21, 1416-25

3. STUDY CHARACTERISTICS TABLE FOR INCLUDED STUDIES

Author, year, country	Population/ PCOS criteria/ Setting/ CC sensitivity	Study Design	Intervention N	Intervention description	Comparison N	Comparison description	Follow Up	Outcomes	Pooled in MA?	RoB
Doldi 2006 Italy	PCOS patients, diagnosis align with Rotterdam CC sensitivity NR	RCT	[MET + rFSH + GnRH] N=20 Age: NR BMI: NR	Pre-treated with MET 1.5g/day for 2 months and then stimulated with rFSH 150 IU/day starting on day 3 of menstrual cycle. GnRH antagonist, cetrorelix acetate 0.25 mg/day started at follicle maturity	[rFSH + GnRH] Age: NR BMI: NR	No pre-treatment with metformin and same management with rFSH and GnRH antagonist	2 months + 1 cycle	The number and quality of oocytes, fertilization rate, number of embryos and cases of OHSS How pregnancy was assessed **not reported**	Yes	High
Fedorcsak 2003 Norway	Infertile PCOS women with insulin resistance and about to receive ovarian stimulation and IVF or intracytoplasmic sperm injection Age (years) Median (range) 31 (23-35) BMI (kg/m2) 31.5 (27.1-40.7) Median (range) CC sensitivity NR	RCT **Cross Over** *(only pre-cross over data was used)*	MET + rFSH + GnRH n=9 Age: NR BMI: NR	500mg Metformin t.i.d (3-week pre-treatment and 1 cycle co-administration with IVF protocol*, until hCG injection)	rFSH + GnRH n=8 Age: NR BMI: NR	rFSH + GnRH No co-treatment, IVF protocol* * Long protocol GnRH-agonist suppression + rFSH (150IU starting dose, step-up protocol) + hCG (10,000IU in presence of at least 2 dominant follicles >18mm)	Two consecutive cycles	• Primary outcomes a) **clinical pregnancy** rate per woman b) incidence of OHSS • Secondary outcomes: a) total dose of FSH (IU) given during stimulation b) number of collected oocytes c) number of days of gonadotrophin d) fertilisation rate e) number of embryos transferred f) miscarriage rate g) incidence of adverse side effects Pregnancy was detected on day 14 after follicle puncture with plasma β-hCG >20 IU	Yes	High
Jacob 2016 UK	PCOS women recruited from IVF clinic waiting list between October 2009 and June 2014; diagnosis align with Rotterdam CC sensitivity: NR	RCT	MET + rFSH + GnRH n=77 Age: 29.9 ± 4.4 BMI: 25.3 ± 3.4	Metformin in the range 100-150 IU started 7 days prior to the patient's anticipated menstruation, daily rFSH from day 2 and GnRH antagonist 250 µg added on day 6	Placebo + rFSH + GnRH n=76 Age: 29.6 ± 3.9 BMI: 25.0 ± 3.3	Placebo + rFSH + GnRH See intervention for rFSH and GnRH	? 1 cycle	Primary: Severe OHSS within 6 weeks of completing an IVF cycle Secondary: ovarian stimulation characteristics, embryological measures (including fertilisation rate and good quality Day 3 embryos) and cycle outcome including **clinical pregnancy** rate (CPR) and live birth rate (LBR). Pregnancy was detected on day 14 by serum hCG>2 IU/l and confirmed by foetal heart on scan to be considered a clinical pregnancy	Yes	Low
Onalan 2005 Turkey	PCOS patients aged <40 years and having PCOS without concomitant causes of infertility and those undergoing first IVF/ICSI attempts; Diagnosis align with Rotterdam criteria; IVF clinic;	RCT	MET n=53 Age (y), mean ± SD: 29.3 ± 3.9	Metformin 850mg, 2-3 times daily according to BMI (8- week pre-treatment and throughout ICSI*, until a positive pregnancy test).	Placebo n=55 Age (y), mean ± SD: 29.76 ± 5.3	Placebo 2-3 times daily according to BMI (8- week pre-treatment and throughout ICSI*, until a positive pregnancy test). *long protocol GnRH-agonist suppression +	8 weeks + 1 cycle?	• Primary outcomes: a) **clinical pregnancy** rate per woman b) incidence of OHSS • Secondary outcomes: a) number of days of gonadotrophins b) number of ampoules of gonadotrophins c) number of follicles (> 16 mm)	Yes	High

	CC sensitivity: NR		BMI (kg/m2): 25 (19.41)		BMI (kg/m2): 23.5 (19-34)	rFSH (150-300IU starting dose, stepdown protocol) + hCG (10000IU, in presence of at least 3 dominant follicles >18mm and E2 levels <5500 pg/ml)		d) number of mature oocytes e) fertilisation rate f) number of embryos transferred g) pregnancy rate per woman h) miscarriage rate i) serum E2 levels j) glucose/insulin rate		
Kjotrod 2004 Norway	Infertile PCOS patients (of 60% had undergone a laparoscopy); diagnosis aligns with Rotterdam criteria; IVF clinic at a university hospital CC sensitivity: **NR**	RCT	MET n=35 Age (years) (n=31; started IVF) mean 28.9 (95% CO 27.6-30.2) BMI <28 (kg/m2) (n=14; started IVF) mean 29.0 (95% CI 27.3-30.7) BMI ≥28 (kg/m2) (n=17; started IVF) mean 28.9 (95% CI 26.7-31.0)	Metformin 500mg b.d (for at least 16 weeks until the day of hCG)* * long protocol GnRH-agonist + rFSH (100IU daily in normal weight women or 150 IU in obese women) + hCG (5000IU in presence of E² levels <10nmol/l)	Placebo n=34 Age n (years) (n=32 started IVF) mean 30.2 (95% CI 29.0-31.5) BMI <28 (kg/m2) (n=13; started IVF) mean 30.7 (95% CI 28.7-32.7) BMI ≥28 (kg/m2) (n=19; started IVF) mean 29.9 (95% CI 28.1-31.8)	Placebo b.d (for at least 16 weeks until the day of hCG)* * long protocol GnRH-agonist + rFSH (100IU daily in normal weight women or 150 IU in obese women) + hCG (5000IU in presence of E² levels <10nmol/l)	16 weeks of metformin Pre-treatment + 1 cycle	Primary: total number of days of FSH stimulation; serum oestradiol on the day of HCG injection Secondary: number of oocytes, total gonadotrophin dose used, fertilization rates, embryo quality, pregnancy rates, **clinical pregnancy rate** (defined as a verified intrauterine gestational sac by ultrasound performed in week 7) live birth rates	Yes	Low
Kjotrod 2011 Norway, Denmark, Finland, and Sweden	Women diagnosed with PCOS, aged <38 years and with a BMI of <28 kg/m2. Multicentre study mainly from Norway; Diagnosis aligns with Rotterdam criteria. The majority of patients had previously received unsuccessful clomiphene citrate (CC) treatment (n = 59 in each treatment group). **Mixed CCR**	RCT	MET Age (years) Mean (SD) 29.6 (3.4) BMI, kg/m2 Mean (SD) 24.0 (2.7) number of previous cycles of CC mean (SD) 3.7 (1.8)	500mg Metformin q.i.d (≥12 weeks pre-treatment and throughout IVF/ICSI*, until pregnancy test). * long protocol GnRH-agonist suppression + rFSH (112.5IU starting dose, step-down protocol) + rhCG (250 µg) or hCG (5000 or 10000IU) in presence of at least 1 dominant follicle >17mm	Placebo Age (years) Mean (SD) 29.5 (3.8) BMI, kg/m2 Mean (SD) 23.6 (2.8) number of previous cycles of CC mean (SD) 3.5 (1.9)	Placebo q.i.d (≥12 weeks pre-treatment and throughout IVF/ICSI*, until pregnancy test). * long protocol GnRH-agonist suppression + rFSH (112.5IU starting dose, step-down protocol) + rhCG (250 µg) or hCG (5000 or 10000IU) in presence of at least 1 dominant follicle >17mm	12 weeks + IVF cycle If pregnant, up to a year	Primary: clinical pregnancy rate; Secondary: biochemical pregnancy and live birth rate – these were not reported for SP population. Safety variables included the incidence of adverse events (AEs) and OHSS. Pregnancy was detected initially by a serum pregnancy test performed on Days 13–15 after embryo transfer and women with a positive test underwent an ultrasound in week 7 of pregnancy	Yes	Mod

Qublan 2009 Jordan	PCOS patients undergoing IVF treatment; PCOS diagnosis based on Rotterdam criteria; setting hospital; CC sensitivity: CCR	RCT Single blind	MET n=34 Age (years) Mean (SD) 34.6+4.3 BMI 32.2 (27–39)	Metformin 850 mg b.d. commencing 1 month before IVF Long GnRH agonist protocol starting on day 21 of the menstrual cycle starting at 150 IU	Placebo n=32 Age (years) Mean (SD) 33.8+3.9 BMI 31.9 (26–38)	Placebo Long GnRH agonist protocol starting on day 21 of the menstrual cycle starting at 150 IU	1 month before a cycle	**Clinical pregnancy rates**; implantation rates; hormones including FSH, LH, testosterone (T), androstenedione (A), 17-hydroxyprogesterone (17-OHP), oestradiol (E2) and dehydroepiandrosterone sulphate (DHEAS) Pregnancy detected with serum β-hCG at 2 weeks and confirmed by ultrasound scan at 6 weeks.	Yes	Mod
Tang 2006 UK	PCOS patients, if BMI above 30 kg/m2 advised to reduce weight using lifestyle Modification; single fertility unit; diagnosis align with Rotterdam criteria CCR- not reported	RCT double blind	MET Age (years) Mean (SD) 31.3 (4.0) BMI (kg/m2) Mean (SD) 27.9 (5.6)	850mg Metformin b.d (from the 1st day of down-regulation* until oocyte retrieval) *long protocol GnRH-agonist suppression + rFSH (100IU starting dose, low-dose stepdown protocol) + hCG (10000IU in presence of at least 3 dominant follicle >17mm)	Placebo Age (years) Mean (SD) 31.1 (4.0) BMI (kg/m2) Mean (SD) 26.9 (4.8)	Placebo b.d (from the 1st day of downregulation* until oocyte retrieval) *long protocol GnRH-agonist suppression + rFSH (100IU starting dose, low-dose stepdown protocol) + hCG (10000IU in presence of at least 3 dominant follicle >17mm)	1 cycle	• Primary outcome: a) fertilisation rate • Secondary outcomes: a) number of days of gonadotrophins b) total dose of FSH given during stimulation c) number of follicles (> 14 mm) d) number of oocytes e) number of embryos transferred f) implantation rate g) pregnancy rate per woman h) **clinical pregnancy rate** per woman i) pregnancy rate per transfer j) clinical pregnancy rate per transfer k) live birth rate l) incidence of OHSS that required hospitalisation m) side effects n) fasting insulin o) fasting glucose p) SHBG q) free androgen index r) testosterone	Yes	High

CC, clomiphene citrate; CCR, clomiphene citrate resistant (to ovulate); CCF, clomiphene citrate failure (to become pregnant); LET, letrozole; MET, metformin; NR; not reported; OHSS, ovarian hyperstimulation syndrome; IUI, intrauterine insemination; hCG, human chorionic gonadotrophin; LH, luteinizing hormone; FSH, follicle stimulating hormone; MA, meta-analysis; RoB, risk of bias. All age data is in years and BMI is in kg/m^2. *Risk of bias assessment derived from reliable systematic review (e.g. Cochrane or previous review from the guideline evidence team).

4. FINDINGS

Comparisons Included:

- **Comparison 1.** Metformin versus placebo or no treatment (with IVF/ ICSI)

COMPARISON 1: Metformin versus Placebo or No Treatment

- **EVIDENCE SUMMARY:**

Eight studies were identified for this clinical question, all of which compared adjuvant metformin to placebo or no treatment in women with PCOS undergoing IVF/ICSI using either a GnRH agonist protocol (Qublan et al. 2009, Kjotrod et al. 2004; Kjotrod et al. 2011; Onalan et al. 2005; Tang et al. 2006 and Fedorcsak et al. 2003) or a GnRH antagonist protocol (Doldi et al. 2006; Jacob et al. 2006). Only one study by Fedorcsak et al. (2003) compared adjuvant metformin with no treatment, while the remaining seven studies were placebo-controlled. The study by Fedorcsak et al. (2003) was also a cross-over trial, but only data from the pre-cross-over phase was used in this analysis. Two studies had a low risk of bias (Jacob et al. 2006 and Kjotrod et al. 2004) two were moderate (Qublan et al. 2009 and Kjotrod et al. 2011) while the remaining four studies had a high risk of bias Doldi et al. 2006; Onalan et al. 2005; Tang et al. 2006 and Fedorcsak et al. 2003).

- **META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:**

There were no differences in any of the measured outcomes, except for side effects which were higher with adjuvant metformin compared with placebo. Certainty of the evidence was moderate to low for most outcomes, largely downgraded for risk of bias and inconsistency (heterogeneity, varying estimates and CIs). Only multiple pregnancy rate had a high certainty of evidence, while E2 on the day of hCG trigger had very low certainty due to serious risk of bias, inconsistency and imprecision (a very wide CI in the pooled estimate).

Outcome or Subgroup	Studies	n	Effect Estimate; OR [95% CI], M-H, random	P	Favours	Certainty
Live birth rate – per patient	5	553	1.09 [0.48, 2.47]	0.8	None	⊕⊕◯◯ LOW
Clinical pregnancy rate* – per patient	7	667	1.26 [0.68, 2.32]	0.5	None	⊕⊕◯◯ LOW
OHSS rate -per patient	7	690	0.56 [0.30, 1.06]	0.07	None	⊕⊕⊕◯ MODERATE
Multiple pregnancy rate – per pregnancy	3	121	0.77 [0.27, 2.21]	0.6	None	⊕⊕⊕⊕ HIGH
Miscarriage rate- per patient	7	667	0.76 [0.43, 1.33]	0.3	None	⊕⊕◯◯ LOW
Miscarriage rate- per pregnancy	7	266	0.59 [0.23, 1.52]	0.3	None	⊕⊕◯◯ LOW
Side effects rate – per patient	5	584	4.87 [2.60, 9.13]	<0.00001	**Placebo** (side effects are higher with metformin)	⊕⊕◯◯ LOW
Mean dose of gonadotrophins (IU) used- per patient	7	593	0.33 [-117.38, 118.05]	1.0	None	⊕⊕◯◯ LOW
Mean days of gonadotrophins- per patient	7	593	0.12 [-0.24, 0.49]	0.5	None	⊕⊕⊕◯ MODERATE
Number of oocytes retrieved- per patient	6	432	0.02 [-1.25, 1.28]	0.2	None	⊕⊕◯◯ LOW
E2 on day of hCG trigger (pg/ml)	2	106	-520.62 [-1332.27, 291.04]	0.2	None	⊕◯◯◯ VERY LOW

*refers to clinical pregnancy, determined by ultrasound confirmation of gestational sac/ fetal heart activity

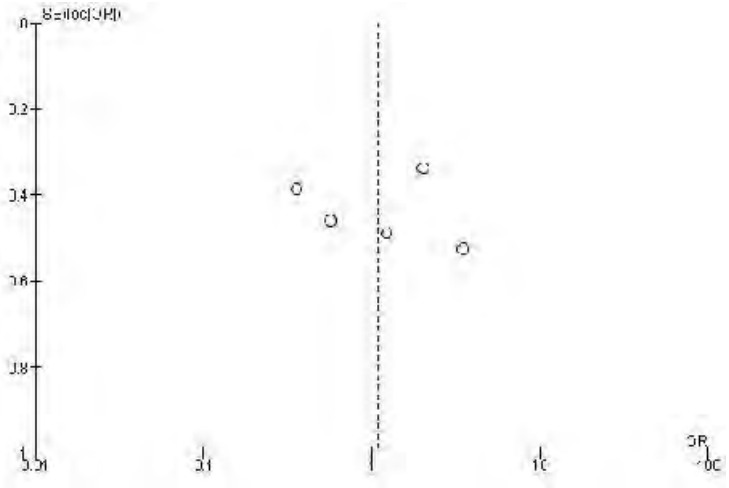
OUTCOME 1.1. Live birth rate– per patient

1.1.1. Individual Study Data Tables

OUTCOME: Live birth rate per patient						OUTCOME TYPE: Dichotomous			
COMPARISON: Metformin vs. placebo (with IVF/ICSI using a GnRH agonist or antagonist protocol)									
Author, year	**Protocol**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention / exposure group (MET)**	**N total in intervention / exposure group (MET)**	**N events in control / comparison group (Placebo)**	**N total in control/ comparison group (Placebo)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Jacob 2016 (LRB)	Antagonist	Count	Investigator	16	58	33	64	Crude	NA
Kjotrod 2004 (LRB)	Agonist	Count	Investigator	14	37	12	36	Crude	NA
Kjotrod 2011 (MRB)	Agonist	Count	Investigator	36	74	24	75	Crude	NA
Onalan 2005 (HRB)	Agonist	Count	Investigator	10	53	16	55	Crude	NA
Tang 2006 (HRB)	Agonist	Count	Investigator	17	52	6	49	Crude	NA

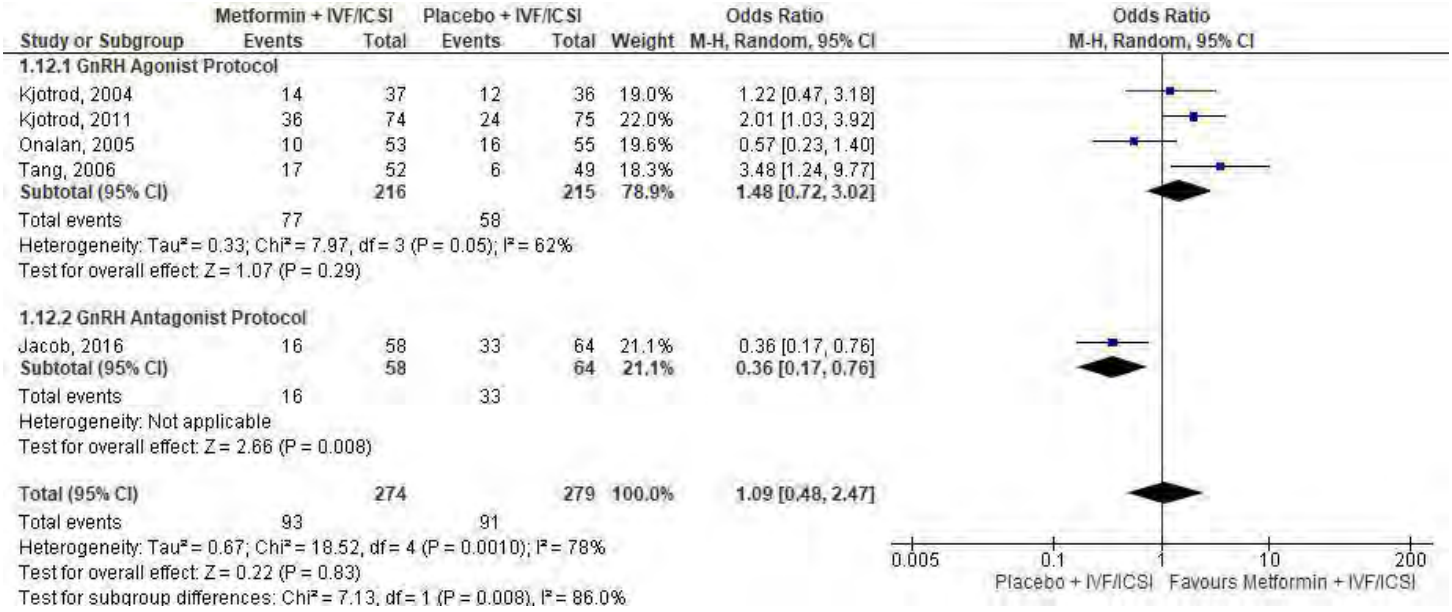
1.1.2. Forest Plot of all included RCTs comparing metformin versus placebo in women with PCOS undergoing IVF/ICSI for live birth rate- per patient

1.1.3. Funnel plot for assessment of publication bias

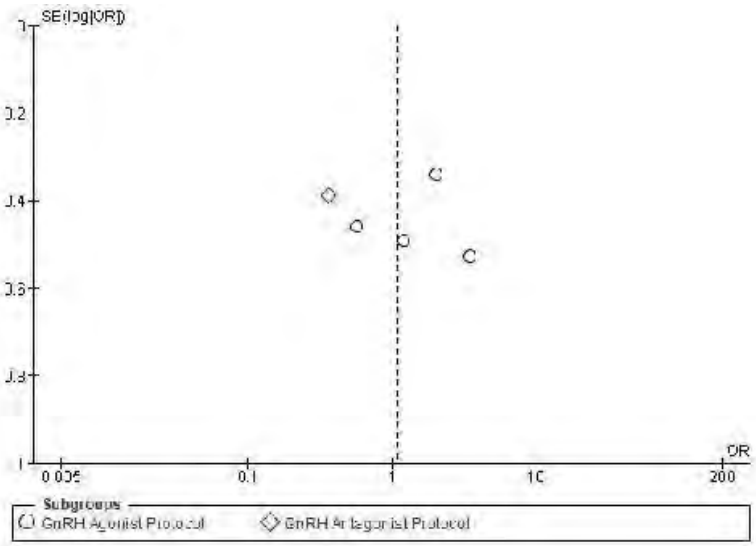


1.1.4. SUBGROUP ANALYSIS: Live birth rate- per patient

1.1.4.1. Forest plot comparing metformin versus placebo in women with PCOS undergoing IVF/ICSI for live birth rate- per patient, sub-grouped by GnRH protocol



1.1.4.2. Funnel plot for assessment of publication bias: subgroup analysis



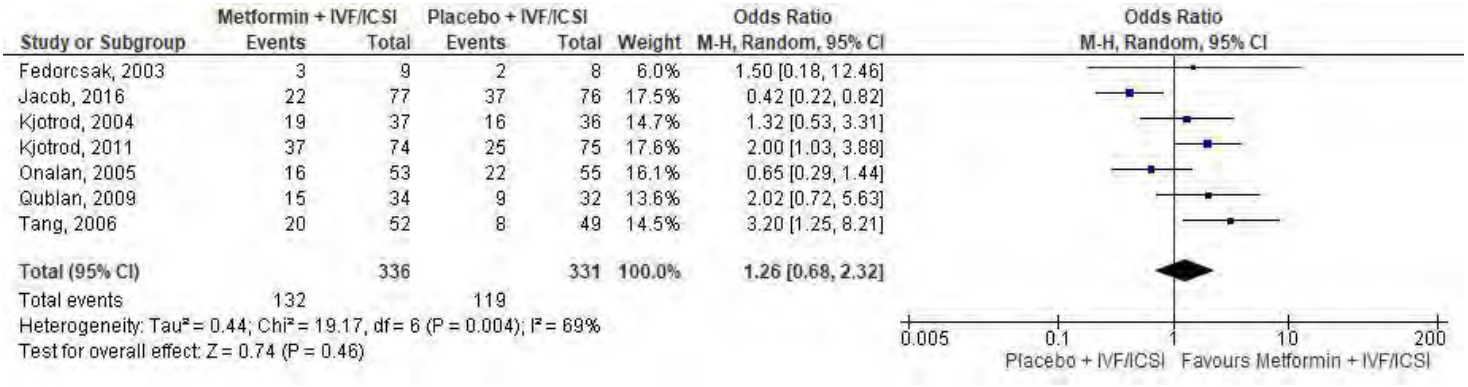
OUTCOME 1.2. Clinical pregnancy rate– per patient

1.2.1. Individual Study Data Tables

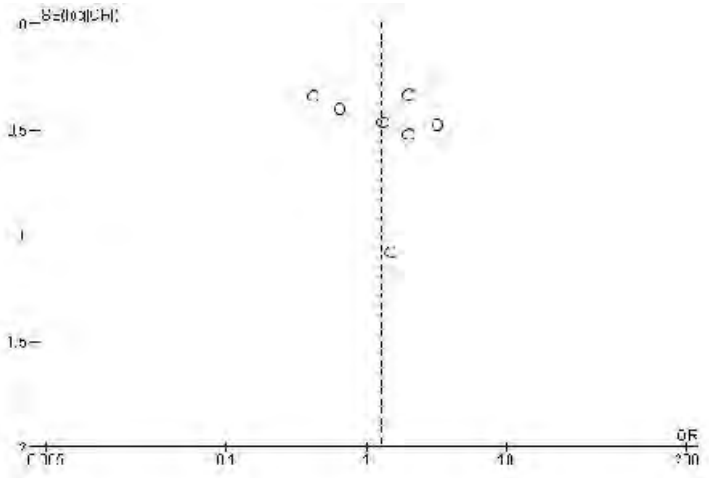
OUTCOME: Clinical pregnancy rate per patient				OUTCOME TYPE: Dichotomous					
COMPARISON: Metformin vs. placebo or no treatment (with IVF/ICSI using a GnRH agonist or antagonist protocol)									
Author, year	**Protocol**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (MET)**	**N total in intervention/ exposure group (MET)**	**N events in control / comparison group (Placebo)**	**N total in control/ comparison group (Placebo)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Fedorcsak 2003 (HRB)- Pre C/O†	Agonist	Count	Investigator	3	9	2	8	Crude	NA
Jacob 2016 (LRB)	Antagonist	Count	Investigator	22	77	37	76	Crude	NA
Kjotrod 2004 (LRB)	Agonist	Count	Investigator	19	37	16	36	Crude	NA
Kjotrod 2011 MRB)	Agonist	Majority	Investigator	37	74	25	75	Crude	NA
Onalan 2005 (HRB)	Agonist	Count	Investigator	16	53	22	55	Crude	NA
Qublan 2009 (MRB)	Agonist	Count	Investigator	15	34	9	32	Crude	NA
Tang 2006 (HRB)	Agonist	Count	Investigator	20	52	8	49	Crude	NA

†Pre C/O: only pre cross-over data was used in the analysis

1.2.2. Forest plot comparing metformin versus placebo or no treatment in women with PCOS undergoing IVF/ICSI for clinical pregnancy rate- per patient

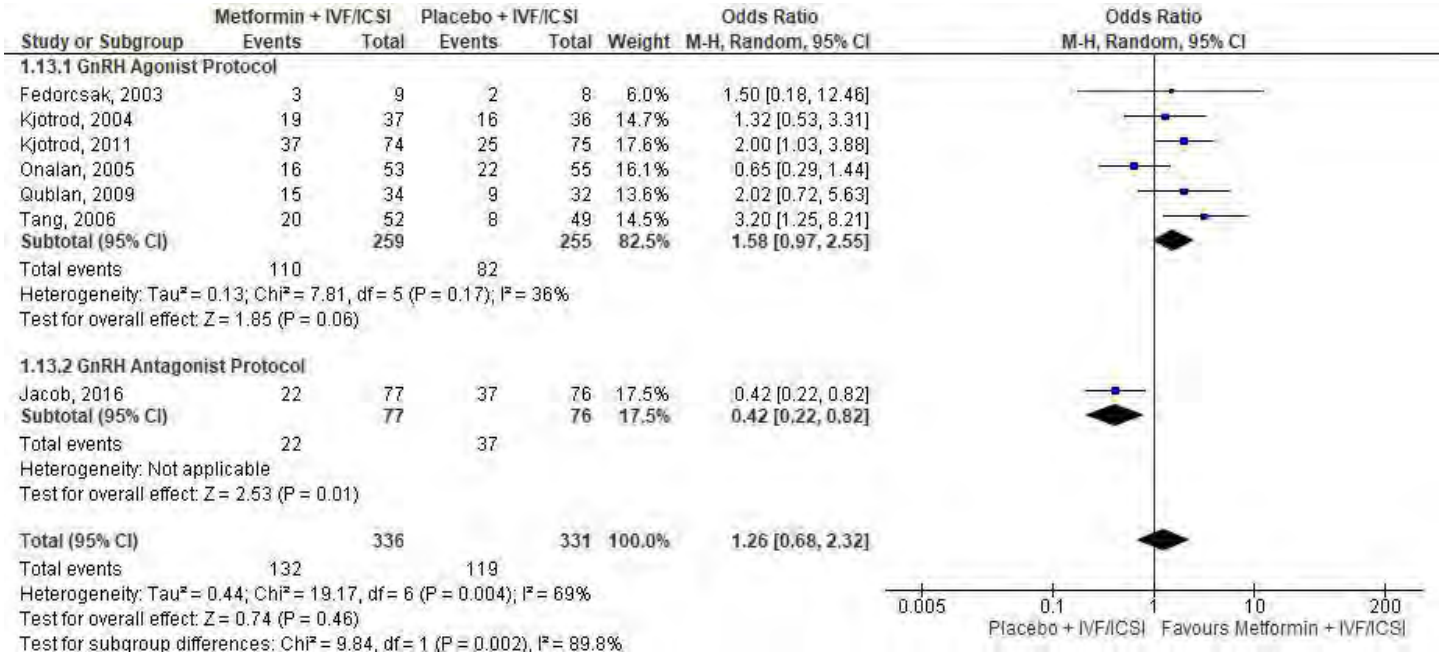


1.2.3. Funnel plot for assessment of publication bias

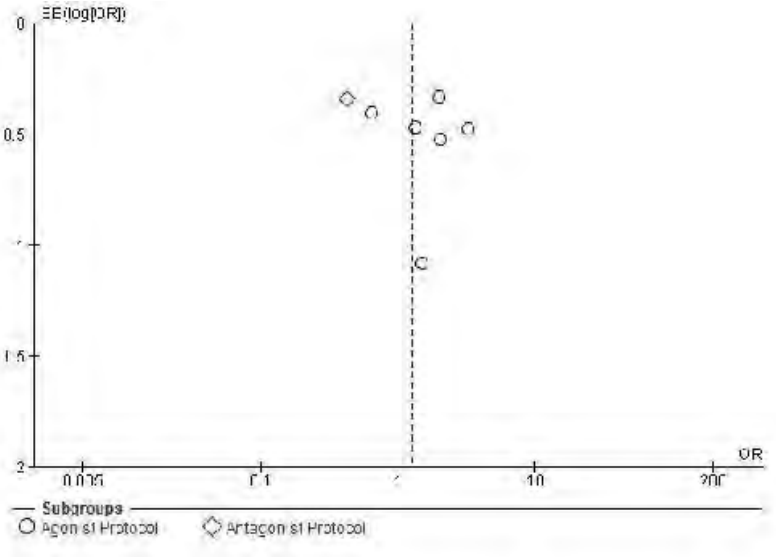


1.2.4. SUBGROUP ANALYSIS: Clinical pregnancy rate – per patient

1.2.4.1. Forest plot comparing metformin versus placebo or no treatment in women with PCOS undergoing IVF/ICSI for clinical pregnancy rate- per patient, sub-grouped by GnRH protocol



1.2.4.2. Funnel plot for assessment of publication bias: subgroup analysis

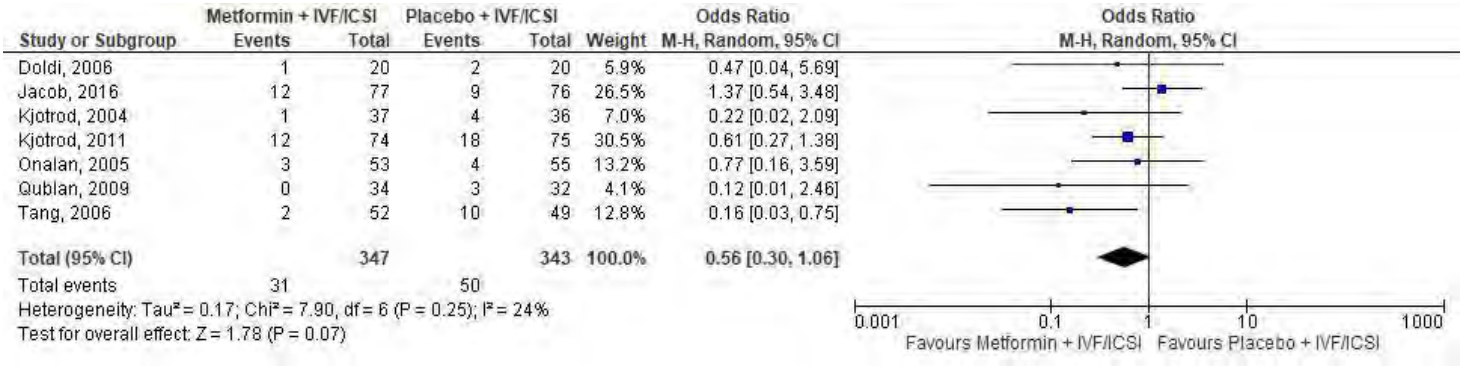


OUTCOME 1.3. OHSS rate - per patient

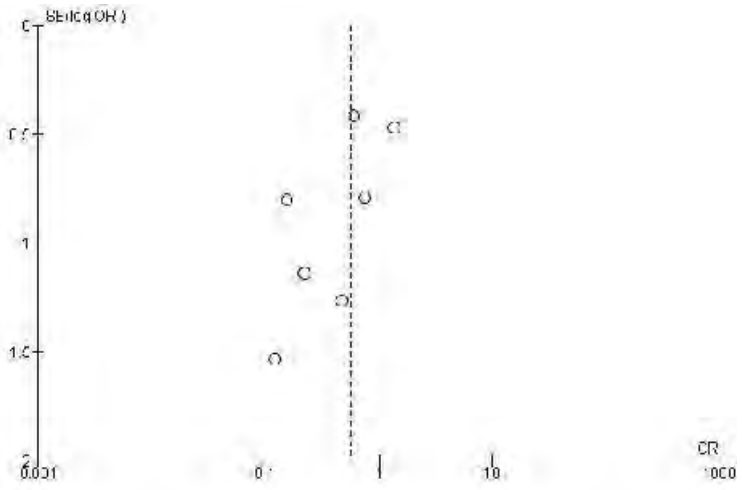
1.3.1. Individual Study Data Tables

OUTCOME: OHSS rate per patient						**OUTCOME TYPE:** Dichotomous			
COMPARISON: Metformin vs. placebo (with IVF/ICSI using GnRH agonist or antagonist protocol)									
Author, year	**Protocol**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (MET)**	**N total in intervention/ exposure group (MET)**	**N events in control / comparison group (Placebo)**	**N total in control/ comparison group (Placebo)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Doldi 2006 (HRB)	Antagonist	Count	Investigator	1	20	2	20	Crude	NA
Jacob 2016 (LRB)	Antagonist	Count (mod or severe)	Investigator	12	77	9	76	Crude	NA
Kjotrod 2004 (LRB)	Agonist	Count	Investigator	1	37	4	36	Crude	NA
Kjotrod 2011 (MRB)	Agonist	Count	Investigator	12	74	18	75	Crude	NA
Onalan 2005 (HRB)	Agonist	Count	Investigator	3	53	4	55	Crude	NA
Qublan 2009 (MRB)	Agonist	Count	Investigator	0	34	3	32	Crude	NA
Tang 2006 (HRB)	Agonist	Count	Investigator	2	52	10	49	Crude	NA

1.3.2. Forest plot comparing metformin versus placebo or no treatment in women with PCOS undergoing IVF/ICSI for OHSS rate - per patient

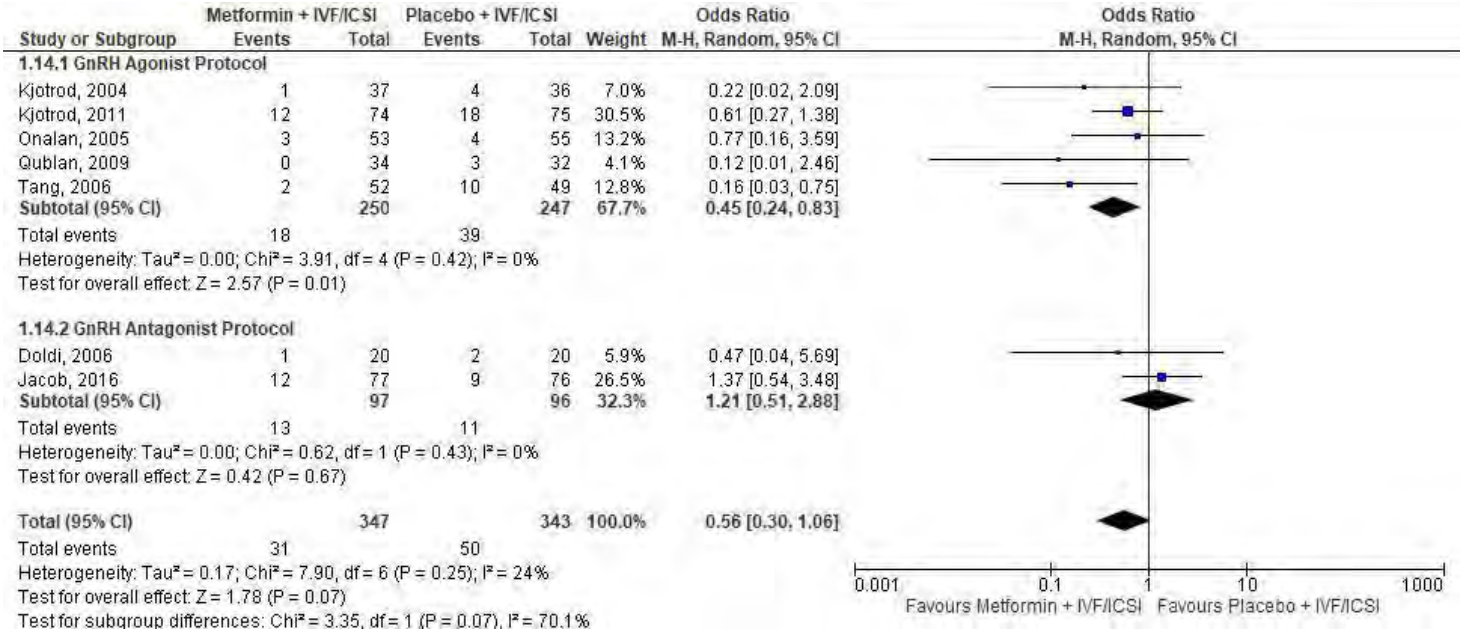


1.3.3. Funnel plot for assessment of publication bias

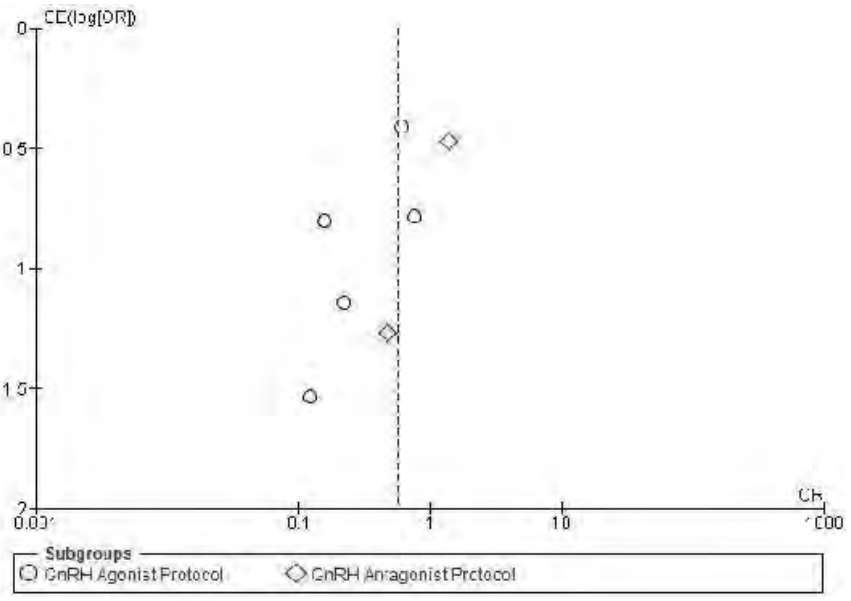


1.3.4. SUBGROUP ANALYSIS: OHSS rate – per patient

1.3.4.1. Forest plot comparing metformin versus placebo in women with PCOS undergoing IVF/ICSI for OHSS rate- per patient, sub-grouped by GnRH protocol



1.3.4.2. Funnel plot for assessment of publication bias: subgroup analysis

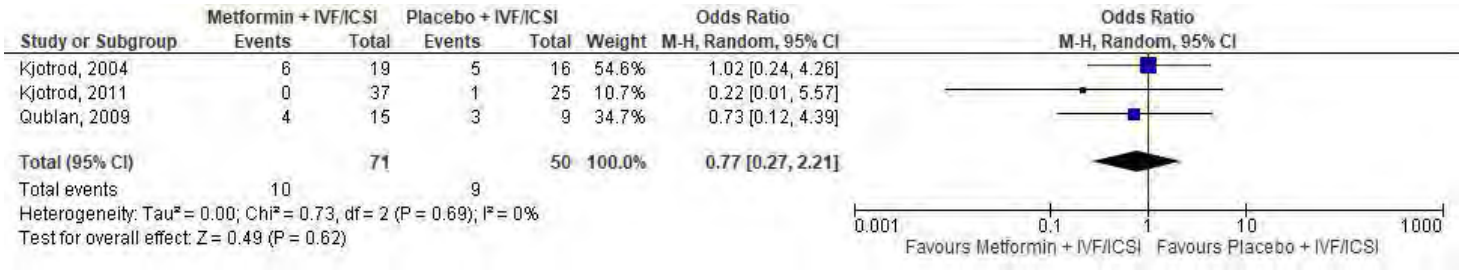


OUTCOME 1.4. Multiple pregnancy rate – per pregnancy

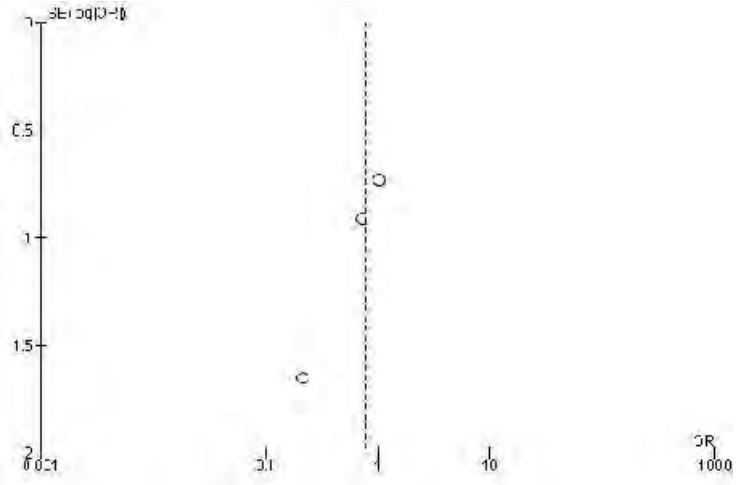
1.4.1. Individual Study Data Tables

OUTCOME: Multiple pregnancy rate per pregnancy						**OUTCOME TYPE:** Dichotomous			
COMPARISON: Metformin vs. placebo (with IVF/ICSI using GnRH agonist protocol)									
Author, year	**Protocol**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (MET)**	**N total in intervention/ exposure group (MET)**	**N events in control / comparison group (Placebo)**	**N total in control/ comparison group (Placebo)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Kjotrod 2004 (LRB)	Agonist	Count	Investigator	6	19	5	16	Crude	NA
Kjotrod 2011 (MRB)	Agonist	Count	Investigator	0	37	1	25	Crude	NA
Qublan 2009 (MRB)	Agonist	Count	Investigator	4	15	3	9	Crude	NA

1.4.2. Forest plot comparing metformin versus placebo in women with PCOS undergoing IVF/ICSI for multiple pregnancy rate- per pregnancy



1.4.3. Funnel plot for assessment of publication bias



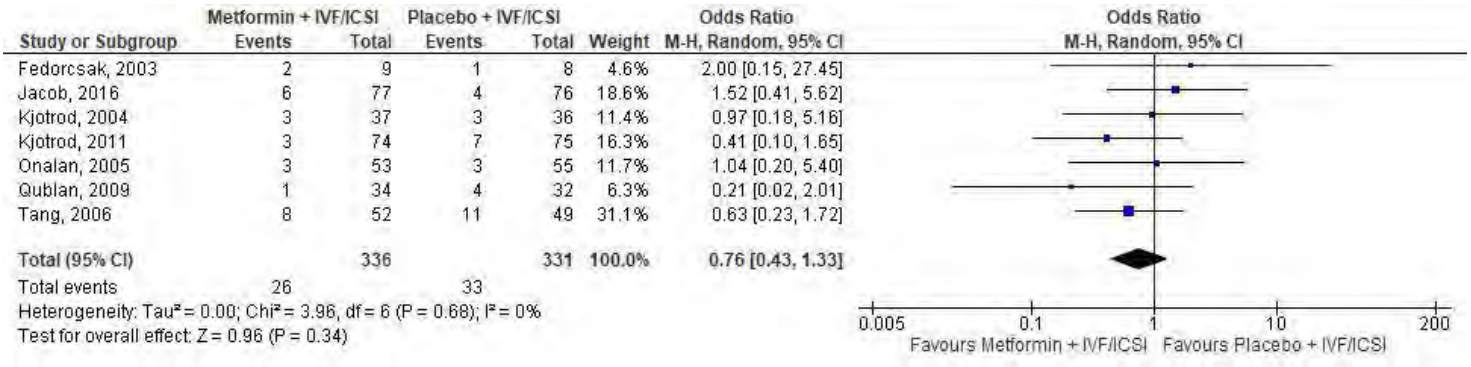
OUTCOME 1.5. Miscarriage rate – per patient

1.5.1. Individual Study Data Tables

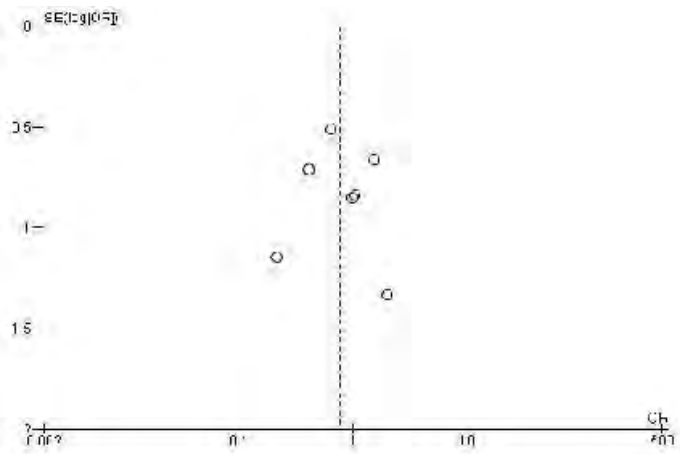
OUTCOME: Miscarriage rate per patient						**OUTCOME TYPE:** Dichotomous			
COMPARISON: Metformin vs. placebo or no treatment (with IVF/ICSI using GnRH agonist or antagonist protocol)									
Author, year	**Protocol**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (MET)**	**N total in intervention/ exposure group (MET)**	**N events in control / comparison group (Placebo)**	**N total in control/ comparison group (Placebo)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Fedorcsak 2003 (HRB) – Pre C/O†	Agonist	Count	Investigator	2	9	1	8	Crude	NA
Jacob 2016 (LRB)	Antagonist	Count	Investigator	6	77	4	76	Crude	NA
Kjotrod 2004 (LRB)	Agonist	Count	Investigator	3	37	3	36	Crude	NA
Kjotrod 2011 (MRB)	Agonist	Count	Investigator	3	74	7	75	Crude	NA
Onalan 2005 (HRB)	Agonist	Count	Investigator	3	53	3	55	Crude	NA
Qublan 2009 (MRB)	Agonist	Count	Investigator	1	34	4	32	Crude	NA
Tang 2006 (HRB)	Agonist	Count	Investigator	8	52	11	49	Crude	NA

†Pre C/O: only pre cross-over data was used in the analysis

1.5.2. Forest plot comparing metformin versus placebo or no treatment in women with PCOS undergoing IVF/ICSI for miscarriage rate- per patient

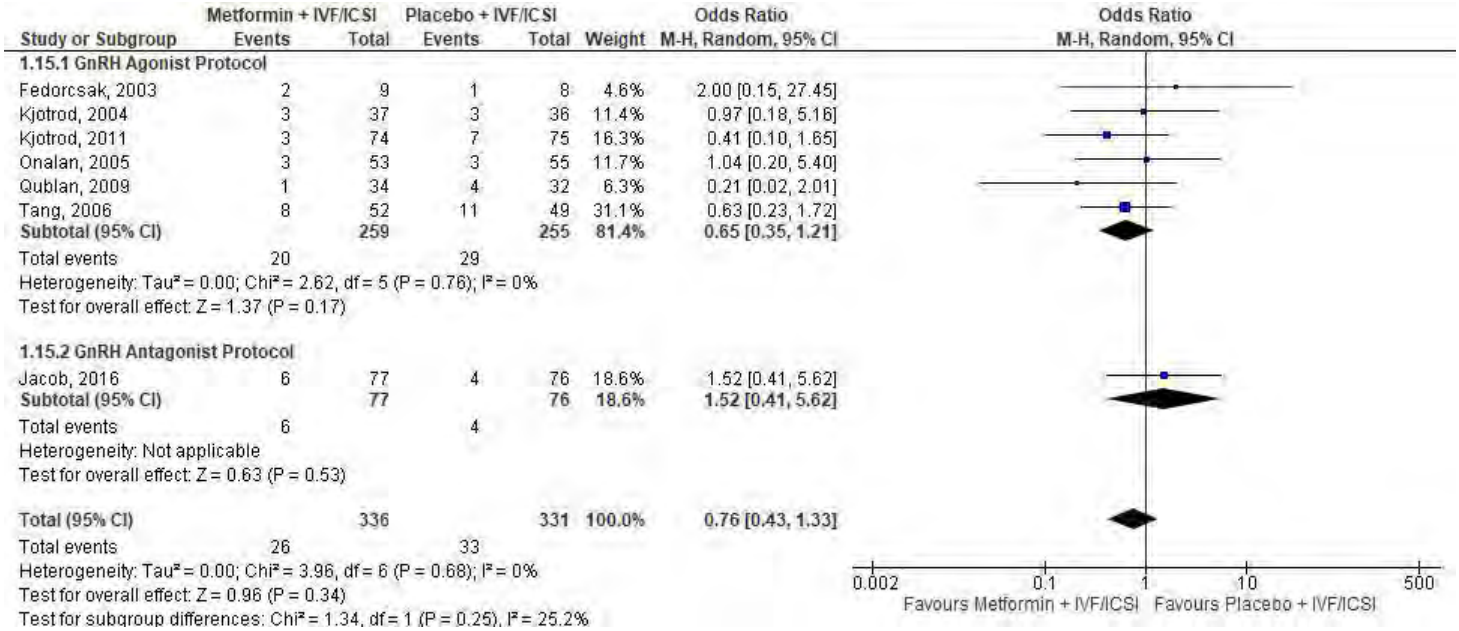


1.5.3. Funnel plot for assessment of publication bias

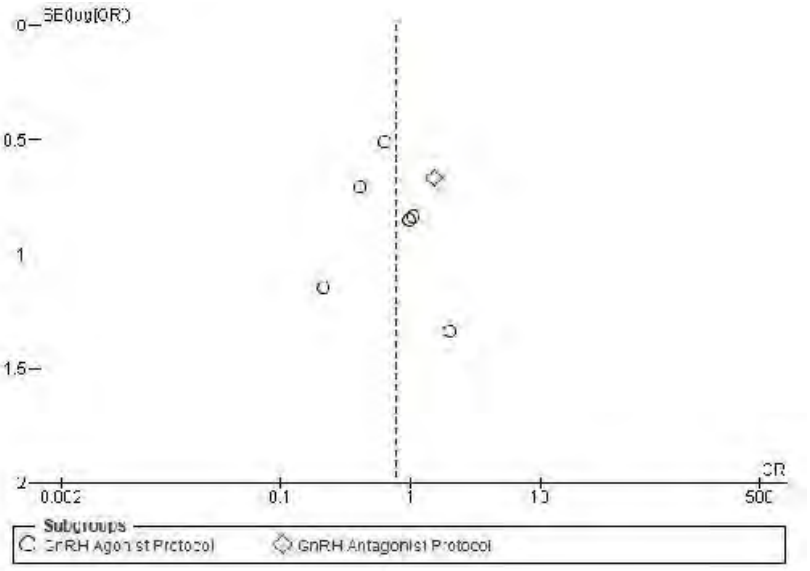


1.5.4. SUBGROUP ANALYSIS: Miscarriage rate – per patient

1.5.4.1. Forest plot comparing metformin versus placebo or no treatment in women with PCOS undergoing IVF/ICSI for miscarriage rate- per patient, sub-grouped by GnRH protocol



1.5.4.2. Funnel plot for assessment of publication bias: subgroup analysis



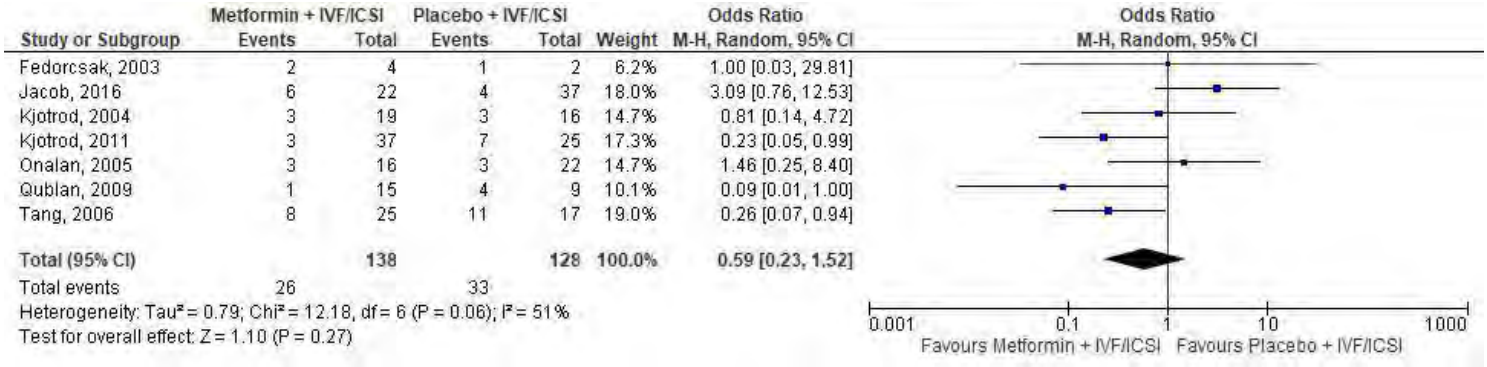
OUTCOME 1.6. Miscarriage rate – per pregnancy

1.6.1. Individual Study Data Table

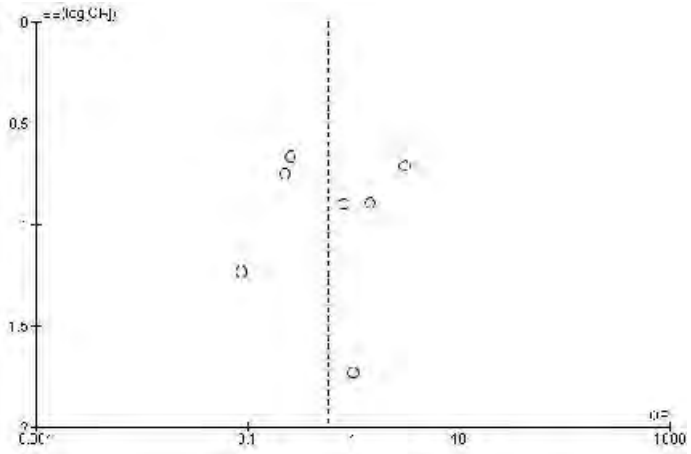
OUTCOME: Miscarriage rate per pregnancy						**OUTCOME TYPE:** Dichotomous			
COMPARISON: Metformin vs. placebo or no treatment (with IVF/ICSI using GnRH agonist or antagonist protocol)									
Author, year	**Protocol**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (MET)**	**N total in intervention/ exposure group (MET)**	**N events in control / comparison group (Placebo)**	**N total in control/ comparison group (Placebo)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Fedorcsak 2003 (HRB)- Pre C/O†	Agonist	Count	Investigator	2	4	1	2	Crude	NA
Jacob 2016 (LRB)	Antagonist	Count	Investigator	6	22	4	37	Crude	NA
Kjotrod 2004 (LRB)	Agonist	Count	Investigator	3	19	3	16	Crude	NA
Kjotrod 2011 (MRB)	Agonist	Count	Investigator	3	37	7	25	Crude	NA
Onalan 2005 (HRB)	Agonist	Count	Investigator	3	16	3	22	Crude	NA
Qublan 2009 (MRB)	Agonist	Count	Investigator	1	15	4	9	Crude	NA
Tang 2006 (HRB)	Agonist	Count	Investigator	8	25	11	17	Crude	NA

†Pre C/O: only pre cross-over data was used in the analysis

1.5.2. Forest plot comparing metformin versus placebo or no treatment in women with PCOS undergoing IVF/ICSI for miscarriage rate- per pregnancy

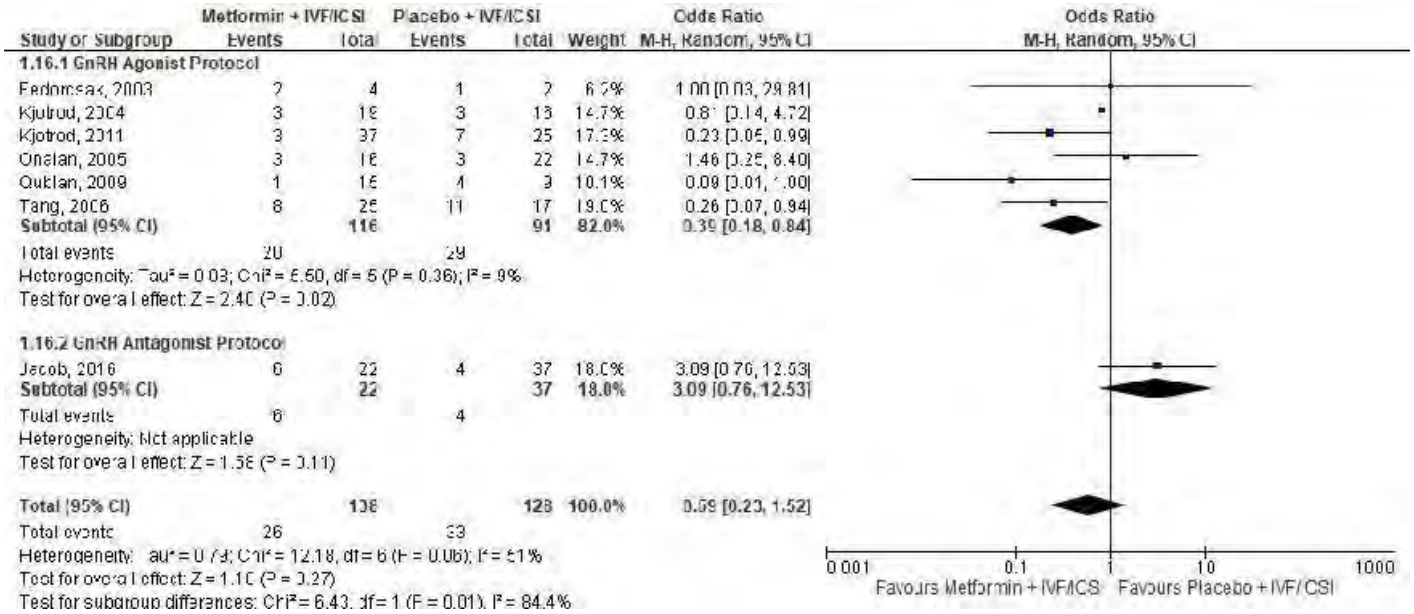


1.5.3. Funnel plot for assessment of publication bias

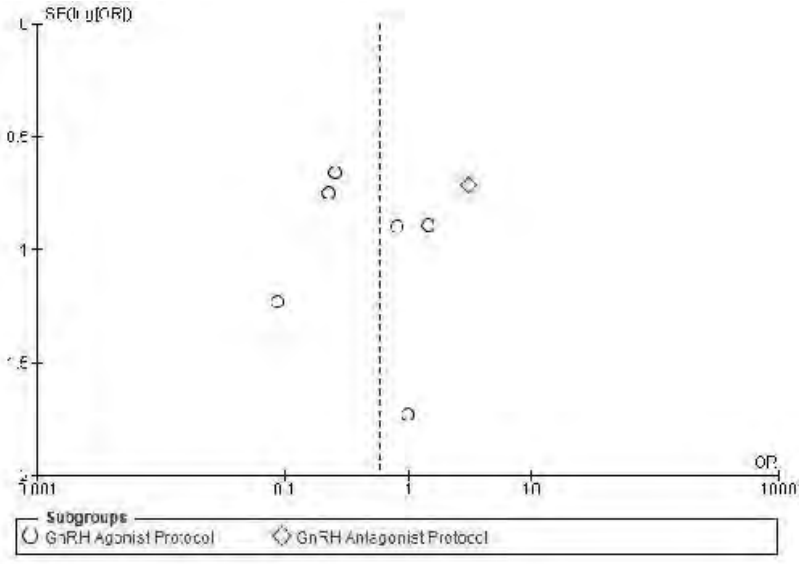


1.6.4. SUBGROUP ANALYSIS: Miscarriage rate – per pregnancy

1.6.4.1. Forest plot comparing metformin versus placebo or no treatment in women with PCOS undergoing IVF/ICSI for miscarriage rate- per pregnancy, sub-grouped by GnRH protocol



1.6.4.2. Funnel plot for assessment of publication bias: subgroup analysis

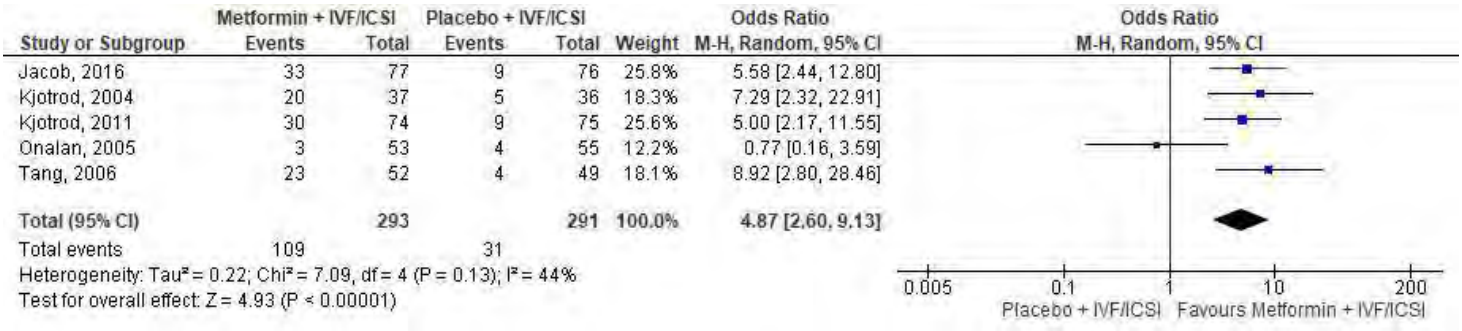


OUTCOME 1.7. Side effects - per patient

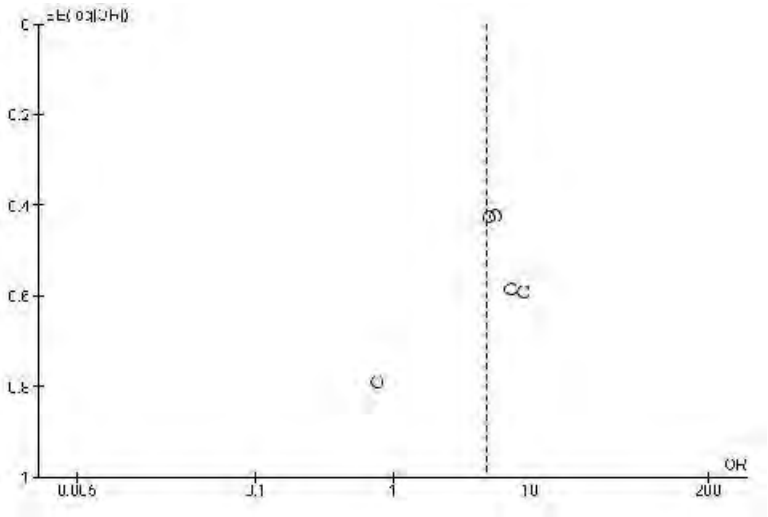
1.7.1. Individual Study Data Table

OUTCOME: Side-effects - per patient									
OUTCOME TYPE: Dichotomous									
COMPARISON: Metformin vs. placebo (with IVF/ICSI using GnRH agonist or antagonist protocol)									
Author, year	**Protocol**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (MET)**	**N total in intervention/ exposure group (MET)**	**N events in control / comparison group (Placebo)**	**N total in control/ comparison group (Placebo)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Jacob 2016 (LRB)	Antagonist	Count	Investigator	33	77	9	76	Crude	NA
Kjotrod 2004 (LRB)	Agonist	Count	Investigator	20	37	5	36	Crude	NA
Kjotrod 2011 (MRB)	Agonist	Count	Investigator	30	74	9	75	Crude	NA
Onalan 2005 (HRB)	Agonist	Count	Investigator	3	53	4	55	Crude	NA
Tang 2006 (HRB)	Agonist	Count	Investigator	23	52	4	49	Crude	NA

1.7.2. Forest plot comparing metformin versus placebo in women with PCOS undergoing IVF/ICSI for side effects- per patient

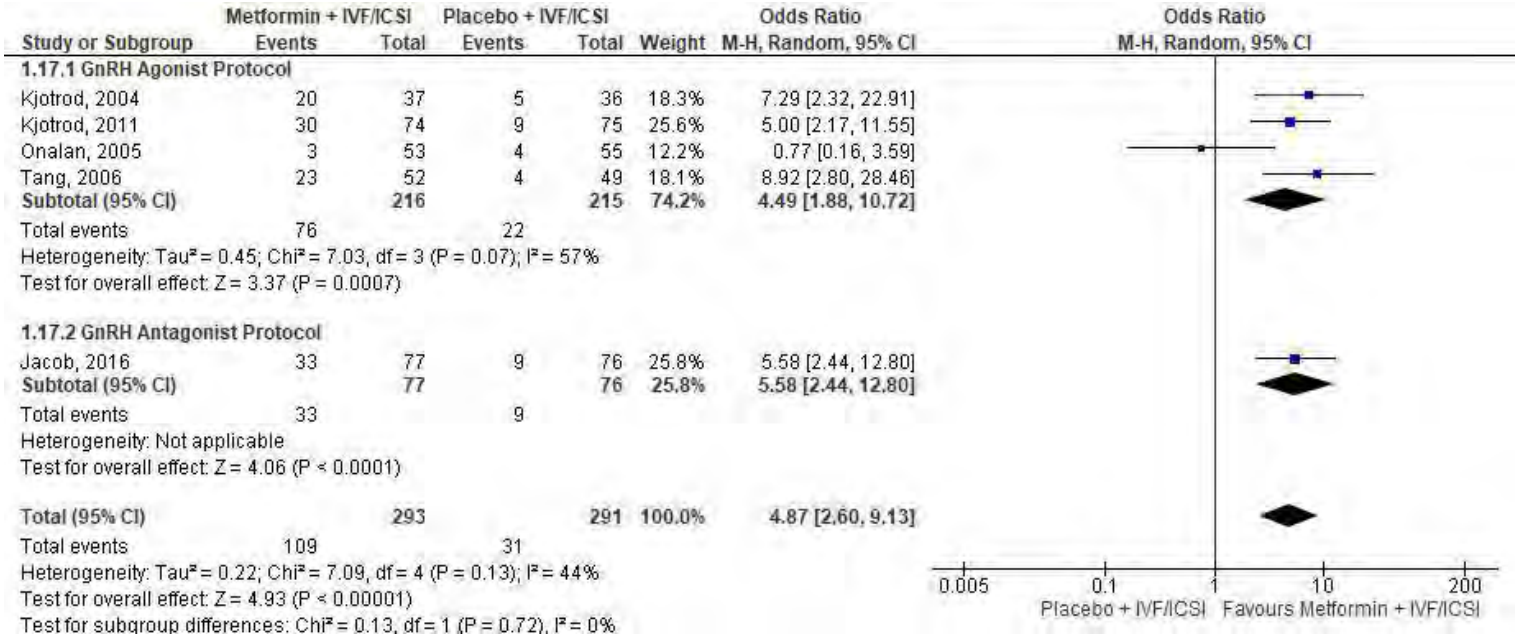


1.7.3. Funnel plot for assessment of publication bias

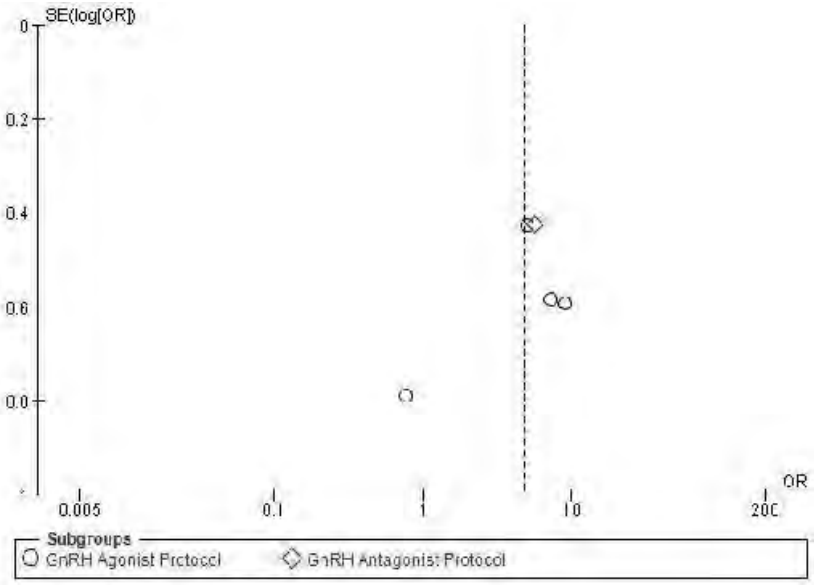


1.7.4. SUBGROUP ANALYSIS: Side effects – per patient

1.7.4.1. Forest plot comparing metformin versus placebo in women with PCOS undergoing IVF/ICSI for side effects – per patient, sub-grouped by GnRH protocol



1.7.4.2. Funnel plot for assessment of publication bias: subgroup analysis



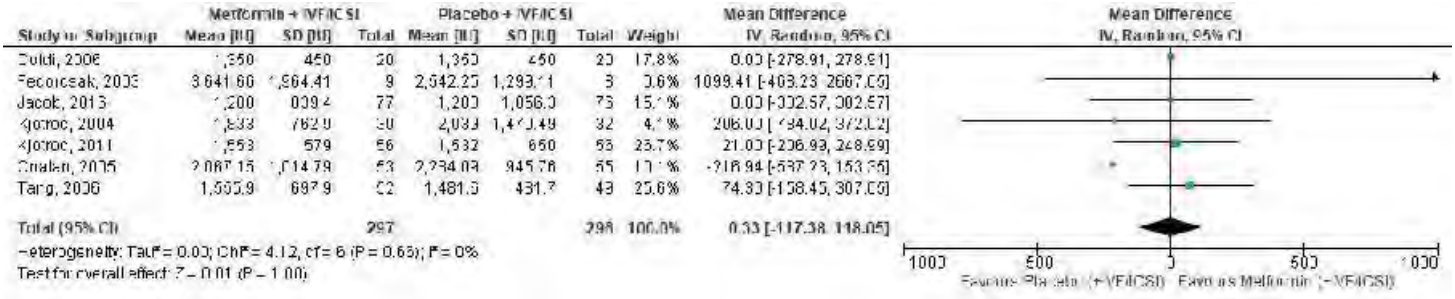
OUTCOME 1.8. Amount of gonadotrophins used- per patient

1.8.1. Individual Study Data Table

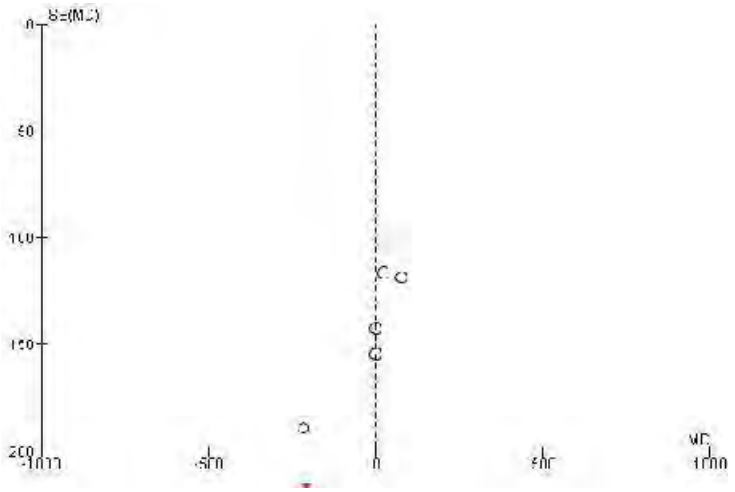
OUTCOME: Amount of gonadotrophins used (mean dose)											OUTCOME TYPE: Continuous
COMPARISON: Metformin vs. placebo or no treatment (with IVF/ICSI using GnRH agonist or antagonist protocol)											
Author, year	**Protocol**	**Unit**	**Method of measurement**	**Mean in intervention / exposure group MET**	**SD in intervention / exposure group MET**	**Sample size MET**	**Mean in control / comparison group Placebo**	**SD in control / comparison group Placebo**	**Sample size Placebo**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Doldi 2006 (HRB)	Antagonist	IU	Investigator	1350	450	20	1350	450	20	Crude	NA
Fedorcsak 2003 (HRB)-Pre C/O†	Agonist	IU	Investigator	3641.66	1964.41	9	2542.25	1299.11	8	Crude	NA
Jacob 2016 (LRB)	Antagonist	IU	Investigator	1200	839.4	77	1200	1056.3	76	Crude	NA
Kjotrod 2004 (LRB)	Agonist	IU	Investigator	1833	762.9	30	2039.0	1470.49	32	Crude	NA
Kjotrod 2011 (MRB)	Agonist	IU	Investigator	1553	579	56	1532.0	650.0	56	Crude	NA
Onalan 2005 (HRB)	Agonist	IU	Investigator	2067.15	1014.79	53	2284.09	945.76	55	Crude	NA
Tang 2006 (HRB)	Agonist	IU	Investigator	1555.9	697.9	52	1481.6	481.7	49	Crude	NA

†Pre C/O: only pre cross-over data was used in the analysis

1.8.2. Forest plot comparing metformin versus placebo or no treatment in women with PCOS undergoing IVF/ICSI for amount of gonadotrophin used- per patient

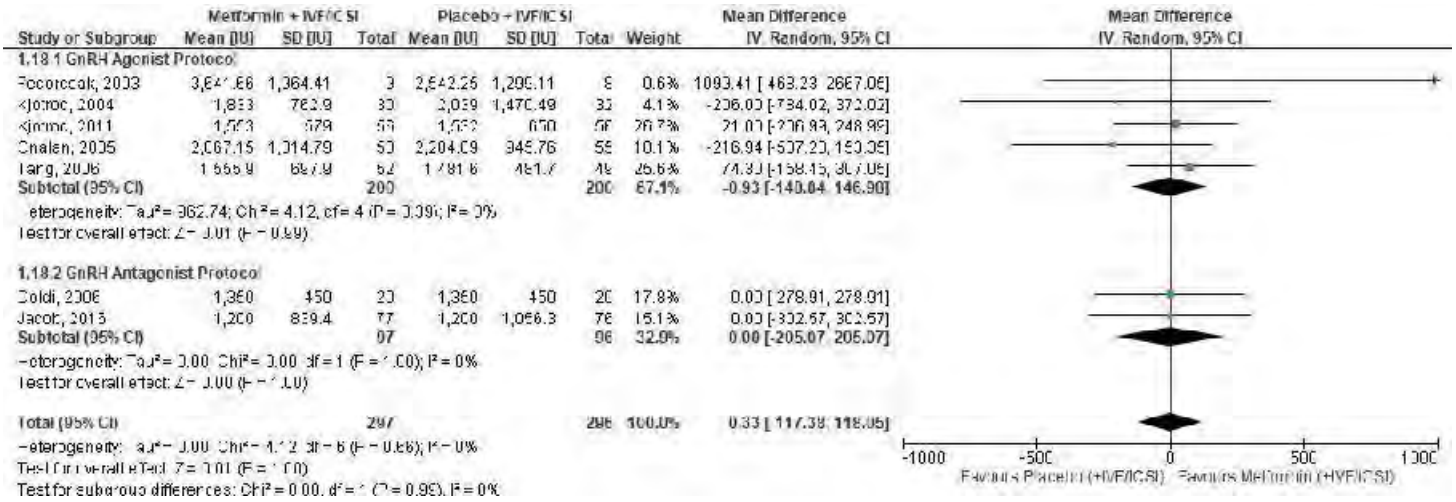


1.8.3. Funnel plot for assessment of publication bias

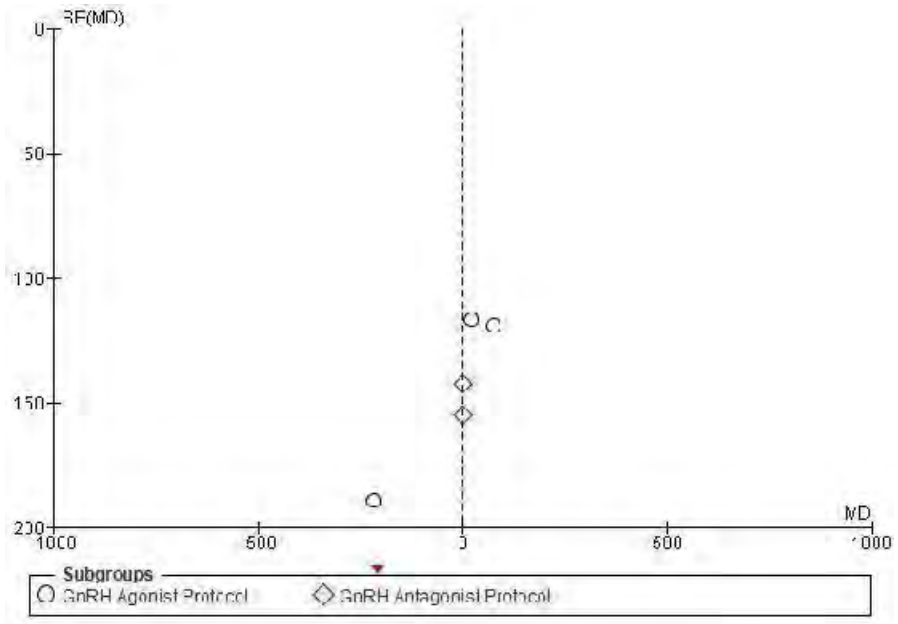


1.8.4. SUBGROUP ANALYSIS: Amount of gonadotrophin used- per patient

1.8.4.1. Forest plot comparing metformin versus placebo or no treatment in women with PCOS undergoing IVF/ICSI for amount of gonadotrophin used- per patient, sub-grouped by GnRH protocol



1.8.4.2. Funnel plot for assessment of publication bias: subgroup analysis



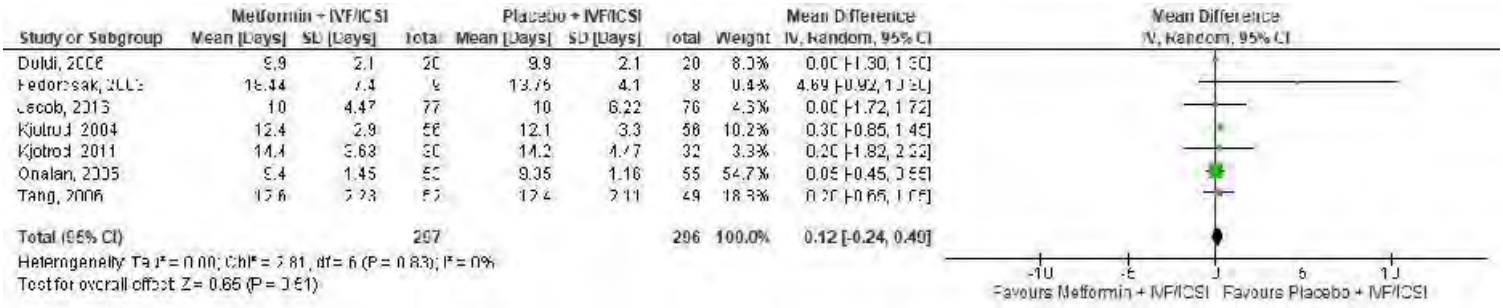
OUTCOME 1.9. Duration of ovarian stimulation (days)

1.9.1. Individual Study Data Table

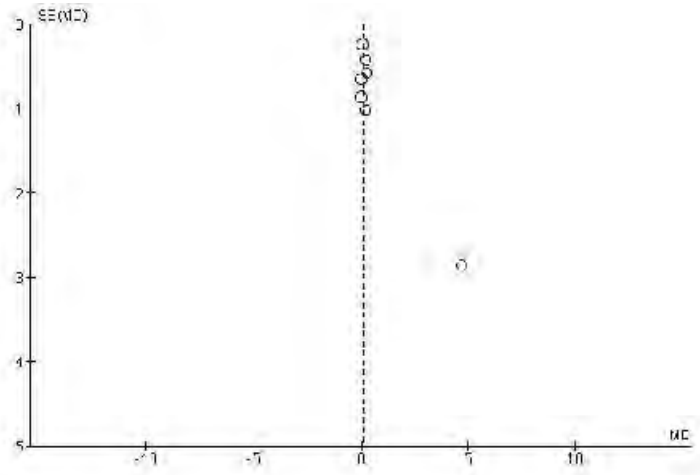
OUTCOME: Duration of ovarian stimulation							OUTCOME TYPE: Continuous				
COMPARISON: Metformin vs. placebo or no treatment (with IVF/ICSI using GnRH agonist or antagonist protocol)											
Author, year	**Protocol**	**Unit of outcome**	**Method of measurement**	**Mean in intervention / exposure group MET**	**SD in intervention / exposure group MET**	**Sample size MET**	**Mean in control / comparison group Placebo**	**SD in control / comparison group Placebo**	**Sample size Placebo**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Doldi 2006 (HRB)	Antagonist	Days	Investigator	9.9	2.1	20	9.9	2.1	20	Crude	NA
Fedorcsak 2003 (HRB)- Pre C/O†	Agonist	Days	Investigator	18.44	7.4	9	13.75	4.1	8	Crude	NA
Jacob 2016 (LRB)	Antagonist	Days	Investigator	10	4.47	77	10	6.22	76	Crude	NA
Kjotrod 2004 (LRB)	Agonist	Days	Investigator	12.4	2.9	56	12.1	3.3	56	Crude	NA
Kjotrod 2011 (MRB)	Agonist	Days	Investigator	14.4	3.63	30	14.2	4.47	32	Crude	NA
Onalan 2005 (HRB)	Agonist	Days	Investigator	9.4	1.45	53	9.35	1.16	55	Crude	NA
Tang 2006 (HRB)	Agonist	Days	Investigator	12.6	2.23	52	12.4	2.11	49	Crude	NA

†Pre C/O: only pre cross-over data was used in the analysis

1.9.2. Forest plot comparing metformin versus placebo or no treatment in women with PCOS undergoing IVF/ICSI for duration of ovarian stimulation

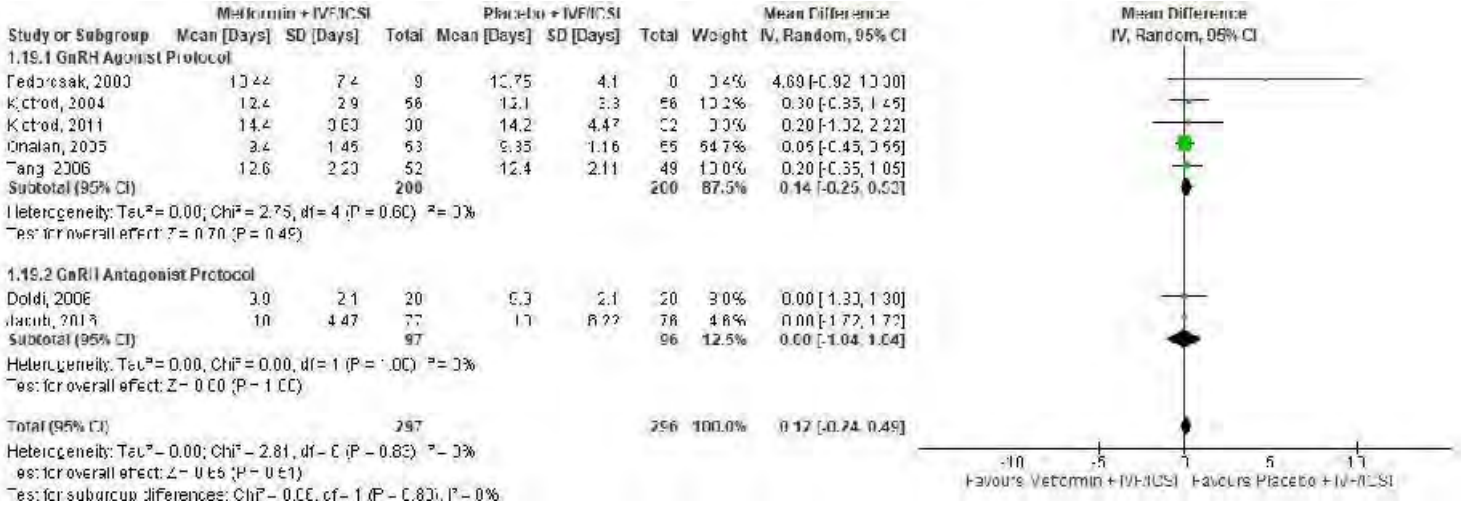


1.9.3. Funnel plot for assessment of publication bias

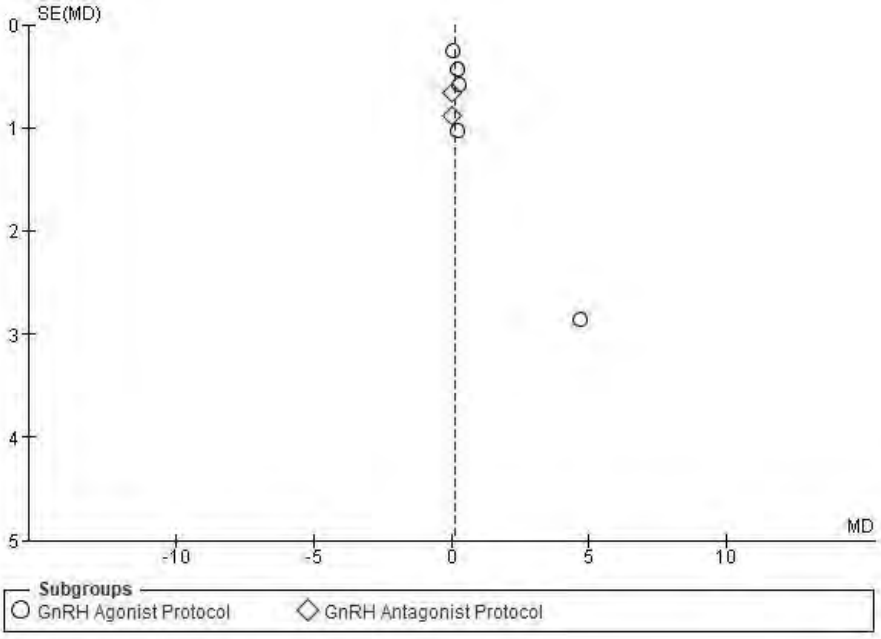


1.9.4. SUBGROUP ANALYSIS: Duration of ovarian stimulation (days)

1.9.4.1. Forest plot comparing metformin versus placebo or no treatment in women with PCOS undergoing IVF/ICSI for duration of ovarian stimulation, sub-grouped by GnRH protocol



1.9.4.2. Funnel plot for assessment of publication bias: subgroup analysis



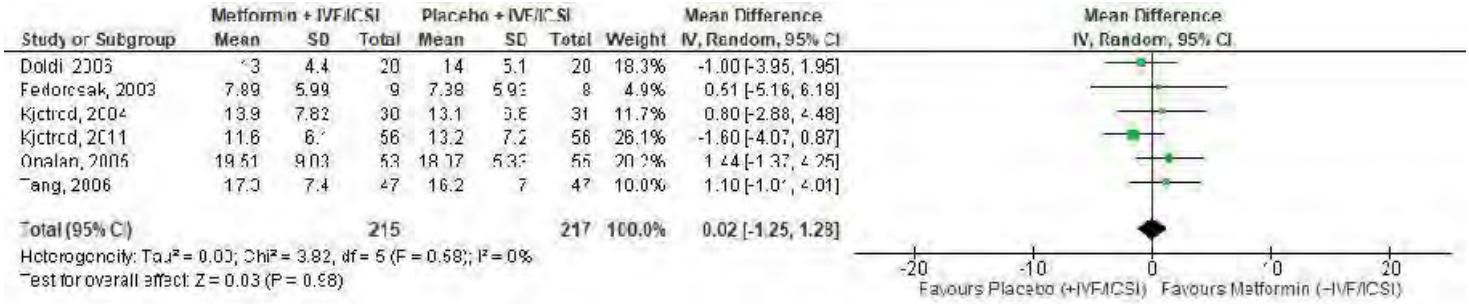
OUTCOME 1.10. Number of oocytes retrieved- per patient

1.10.1. Individual Study Data Table

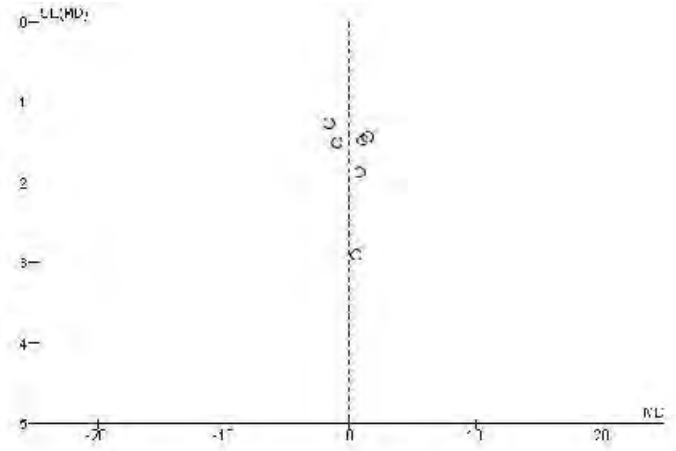
OUTCOME: Mean number of oocytes retrieved- per patient							OUTCOME TYPE: Continuous				
COMPARISON: Metformin vs. placebo or no treatment (with IVF/ICSI using GnRH agonist or antagonist protocol)											
Author, year	**Protocol**	**Unit of outcome**	**Method**	**Mean in intervention group MET**	**SD in intervention group MET**	**Sample size MET**	**Mean in control group Placebo**	**SD in control group Placebo**	**Sample size Placebo**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Doldi 2006 (HRB)	Antagonist	Count	Investigator	13	4.4	20	14	5.1	20	Crude	NA
Fedorcsak 2003 (HRB)-Pre C/O†	Agonist	Count	Investigator	7.89	5.99	9	7.38	5.93	8	Crude	NA
Jacob 2016 (LRB)*	Antagonist	Count	Investigator	Median 14	IQR 9-20	77	Median 15	IQR 9.8-21	76	Crude	NA
Kjotrod 2004 (LRB)	Agonist	Count	Investigator	13.9	7.82	30	13.1	6.8	31	Crude	NA
Kjotrod 2011 (MRB)	Agonist	Count	Investigator	11.6	6.1	56	13.2	7.2	56	Crude	NA
Onalan 2005 (HRB)	Agonist	Count	Investigator	19.51	9.03	53	18.07	5.33	55	Crude	NA
Tang 2007 (HRB)	Agonist	Count	Investigator	17.3	7.4	47	16.2	7	47	Crude	NA

*not included in meta-analysis due to reporting median (IQR); †Pre C/O: only pre cross-over data was used in the analysis

1.10.2. Forest plot comparing metformin versus placebo or no treatment in women with PCOS undergoing IVF/ICSI for number of oocytes retrieved- per patient

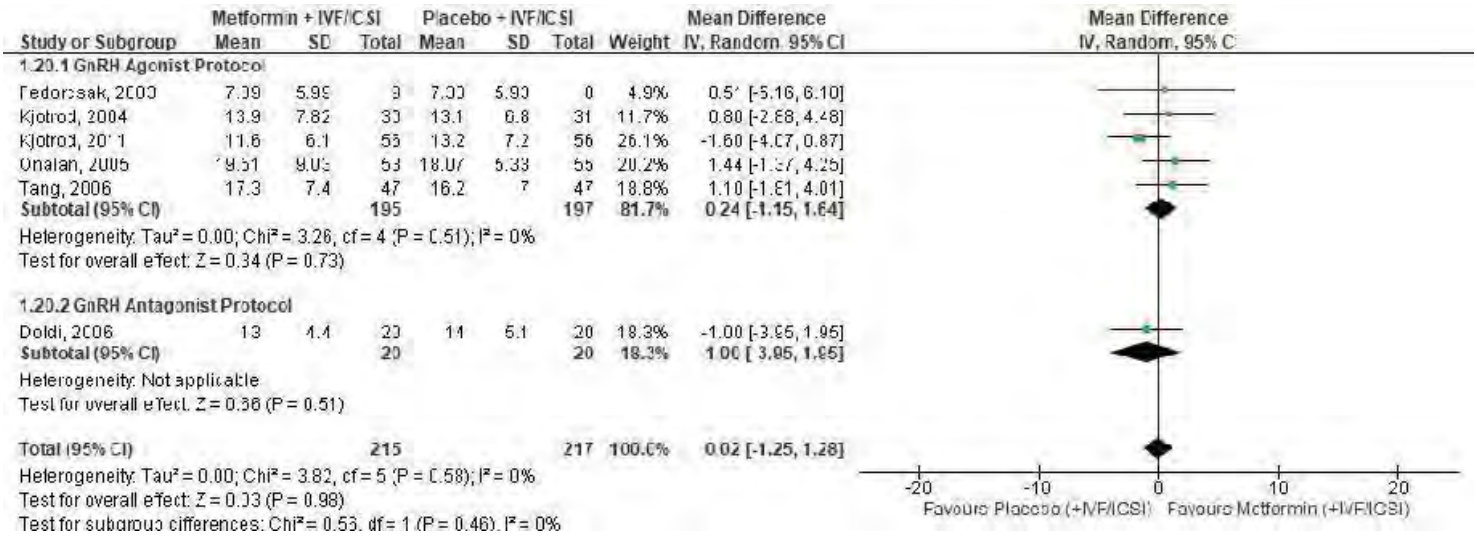


1.10.3. Funnel plot for assessment of publication bias

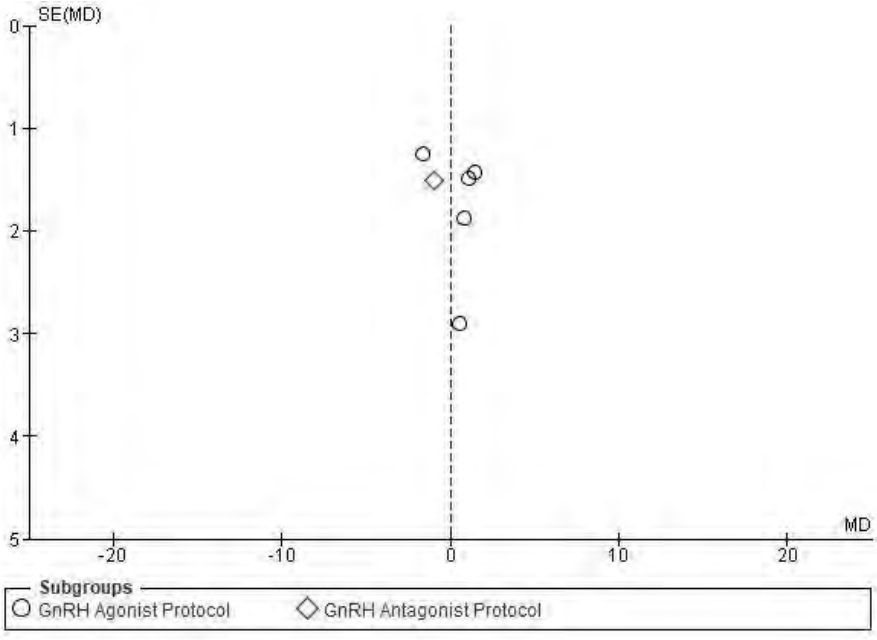


1.10.4. SUBGROUP ANALYSIS: Number of oocytes retrieved- per patient

1.10.4.1. Forest plot comparing metformin versus placebo or no treatment in women with PCOS undergoing IVF/ICSI for number of oocytes retrieved- per patient, sub-grouped by GnRH protocol



1.10.4.2. Funnel plot for assessment of publication bias: subgroup analysis



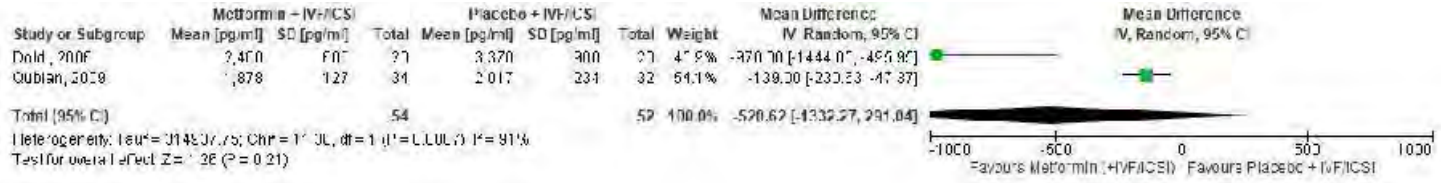
OUTCOME 1.11. E2 on day of hCG trigger

1.11.1. Individual Study Data Table

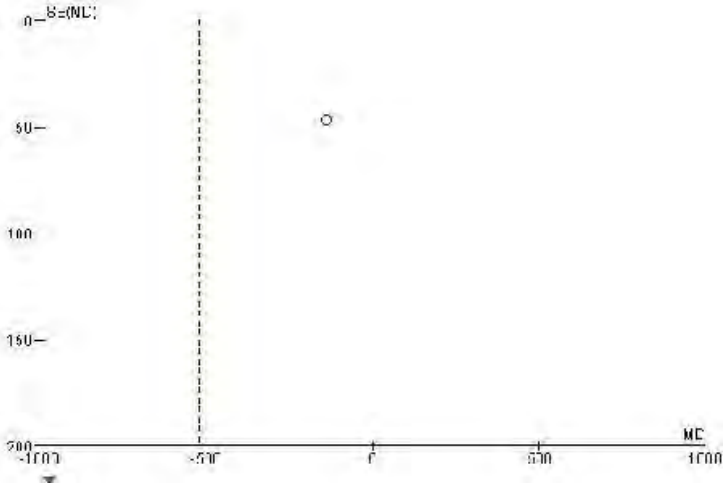
OUTCOME: E2 on day of hCG trigger											
OUTCOME TYPE: Continuous											
COMPARISON: Metformin vs. placebo (with IVF/ICSI using GnRH agonist or antagonist protocol)											
Author, year	**Protocol**	**Unit**	**Method of measurement**	**Mean in intervention group MET**	**SD in intervention group MET**	**Sample size MET**	**Mean in control group Placebo**	**SD in control group Placebo**	**Sample size Placebo**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Doldi 2006 (HRB)	Antagonist	pg/ml	Investigator	2400	600	20	3370	900	20	Crude	NA
Kjotrod 2004 (LRB)*	Agonist	nmol/l	Investigator	6.8	5.3-8.2	31	7.6	CI 5.6-9.6	30	Crude	NA
Onalan 2005 (HRB)*	Agonist	pg/mL	Investigator	3,946 (median)	1,069–5,592 Range	55	3,615 (median)	1,095–5,439 (range)	53	Crude	NA
Qublan 2009 (MRB)	Agonist	pg/ml	Investigator	1878	127	34	2017	234	32	Crude	NA

*not included in meta-analysis due to reporting median (IQR) or mean with 95% CI (not SD)

1.11.2. Forest plot comparing metformin versus placebo in women with PCOS undergoing IVF/ICSI for E2 on day of hCG trigger

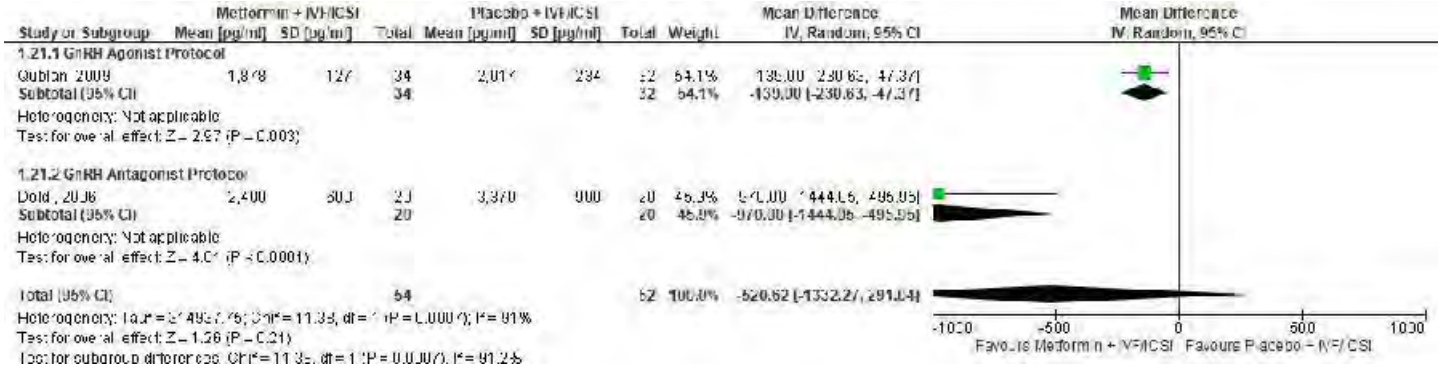


1.11.3. Funnel plot for assessment of publication bias

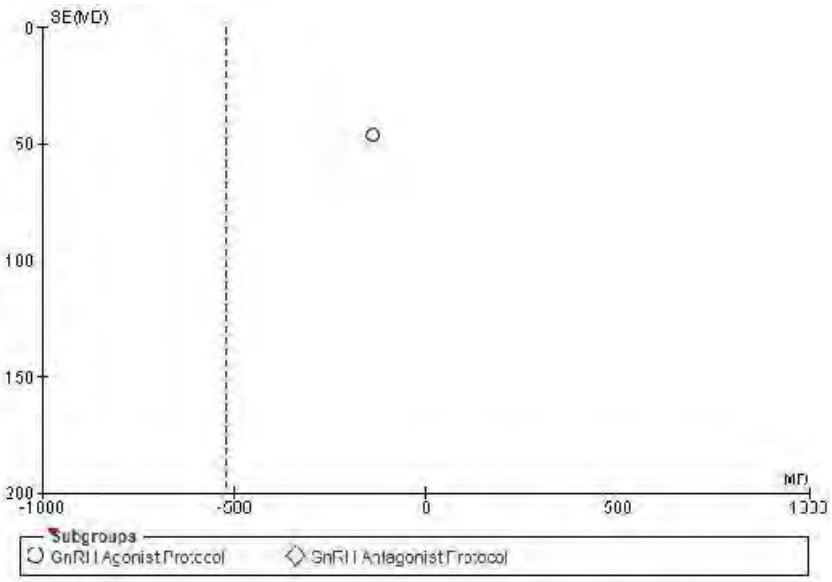


1.11.4. SUBGROUP ANALYSIS: E2 on day of hCG trigger

1.11.4.1. Forest plot comparing metformin versus placebo in women with PCOS undergoing IVF/ICSI for E2 on day of hCG trigger, sub-grouped by GnRH protocol



1.11.4.2. Funnel plot for assessment of publication bias: subgroup analysis



5. GRADE ASSESSMENTS AND EVIDENCE PROFILE

COMPARISON 1: Metformin vs. placebo or no treatment (undergoing IVF/ICSI using GnRH agonist or antagonist protocol)												
	Quality assessment						No. participants					
No. studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	MET	Placebo / no treatment	Effect, random, OR [95% CI]	Favours	Certainty	Importance
Outcome: Live birth rate - per patient												
5	RCT	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	93/ 274 (33.9%)	91/ 279 (32.6%)	1.09 [0.48, 2.47]	No difference	⨁⨁◯◯ LOW	CRITICAL
Outcome: Clinical pregnancy rate - per patient												
7	RCT	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	132/ 336 (39.3%)	119/ 331 (36.0%)	1.26 [0.68, 2.32]	No difference	⨁⨁◯◯ LOW	CRITICAL
Outcome: OHSS rate - per patient												
7	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	31/ 347 (8.9%)	50/ 343 (14.6%)	0.56 [0.30, 1.06]	No difference	⨁⨁⨁◯ MODERATE	CRITICAL
Outcome: Multiple pregnancy rate - per pregnancy												
3	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	10/ 71 (14.1%)	9/ 50 (18%)	0.77 [0.27, 2.21]	No difference	⨁⨁⨁⨁ HIGH	IMPORTANT
Outcome: Miscarriage rate - per patient												
7	RCT	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	26/ 336 (7.7%)	33/ 331 (9.7%)	0.76 [0.43, 1.33]	No difference	⨁⨁◯◯ LOW	IMPORTANT
Outcome: Miscarriage rate - per pregnancy												
7	RCT	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	26/138 (18.8%)	33/128 (25.8%)	0.59 [0.23, 1.52]	No difference	⨁⨁◯◯ LOW	IMPORTANT
Outcome: Side effects rate - per patient												
5	RCT	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	109/ 293 (37.2%)	31/ 291 (10.7%)	4.87 [2.60, 9.13]	**Placebo** (side effects higher with metformin)	⨁⨁◯◯ LOW	IMPORTANT
Outcome: Amount of gonadotrophin used, mean dose (IU) - per patient												
7	RCT	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	297	296	0.33 [-117.38, 118.05]	No difference	⨁⨁◯◯ LOW	IMPORTANT
Outcome: Mean days of gonadotrophins (days) - per patient												
7	RCT	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	297	296	0.12 [-0.24, 0.49]	No difference	⨁⨁⨁◯ MODERATE	IMPORTANT
Outcome: Number of oocytes retrieved - per patient												

6	RCT	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	215	217	0.02 [-1.25, 1.28]	No difference	⨁⨁◯◯ LOW	IMPORTANT
Outcome: E2 on day of hCG trigger (pg/ml)												
2	RCT	serious[1]	serious[2]	no serious indirectness	serious[3]	none	54	52	-520.62 [-1332.27, 291.04]	No difference	⨁◯◯◯ VERY LOW	IMPORTANT

[1] Downgraded once due to the majority of studies (half or more) having high/moderate risk of bias
[2] Downgraded once for inconsistency due to high statistical heterogeneity (I^2>60% with p<0.05) and/or variation in effect estimates (including direction) and CIs
[3] Downgraded once due to the very wide CI of the pooled estimate

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 5

Question 5.7.5

In women with PCOS undergoing (controlled) ovarian (hyper) stimulation for IVF/ICSI, is adjuvant metformin effective for improving fertility outcomes?

BACKGROUND:

IVF/ICSI treatment in women with PCOS is usually recommended either as a third-line treatment (after failed first- or second- line therapies including letrozole, clomiphene citrate, gonadotrophin or LOD ovulation induction) or in the presence of other infertility factors such as tubal damage, severe endometriosis or male factor infertility (1). IVF/ICSI treatment in women with PCOS poses a number of clinical challenges, in particular that of an increased risk of moderate to severe Ovarian Hyperstimulation Syndrome (OHSS) (2).

The aetiological hypotheses of PCOS are continually developing with the understanding and incorporation of the evolving evidence of the syndrome, which appears to be both multifactorial and polygenic and includes hypothalamic-pituitary-ovarian and adrenal axis contributions, ovarian thecal cell steroidogenesis dysfunction, and insulin resistance with compensatory hyperinsulinemia (3). Based on the association between insulin resistance and anovulation in both lean and obese PCOS women, insulin-sensitising drugs, such as metformin, have been added as a promising therapy to restore ovulation and enhance pregnancy in PCOS (4).

Metformin is a biguanide which reduces hepatic glucose production by reducing hepatic gluconeogenesis, improves insulin sensitivity by increasing insulin mediated glucose uptake by skeletal muscle / liver / adipose tissue, reduces intestinal absorption of glucose, reduces lipogenesis and increases fatty acid oxidation in skeletal muscle / liver / adipose tissue, and reduces ovarian androgen production both directly by a reduction in CYP17 enzyme activity and indirectly via a reduction in hyperinsulinemia. It is estimated that 10-15% of its efficacy in type 2 diabetes is due to peripheral improvement in insulin sensitivity, primarily in skeletal muscle. Thus, metformin is not primarily an insulin-sensitizing drug, although it is often labelled as such in the treatment of women with PCOS (5-7).

There is a good physiological rationale for believing that suppression of insulin levels, through the use of insulin sensitising agents such as metformin, may be useful in women with PCOS who are undergoing in vitro fertilisation (IVF) with or without intracytoplasmic sperm injection (ICSI). Suppression of insulin levels might ameliorate the adverse effects of ovarian stimulation and improve treatment outcomes in IVF/ICSI. It has also been suggested that metformin may reduce serum oestradiol levels during ovarian stimulation and it has also been hypothesized that metformin may reduce the production of vascular endothelial growth factor (VEGF), both of which are important factors involved in the pathophysiology of OHSS (8). Therefore, it is important to determine the effectiveness and safety of metformin as a co-treatment in achieving pregnancy or live birth and reducing OHSS in women with PCOS undergoing IVF or ICSI treatment.

GRADE EVIDENCE CERTAINTY	
Comparison	**GRADE for critical outcomes**
Comparison 1. Metformin versus placebo or no treatment	⊕⊕◯◯ LOW

Evidence to Recommendations Framework

COMPARISONS (option versus other option)

Metformin + IVF/ICSI (option) versus placebo or no treatment + IVF/ICSI (other option) (GnRH agonist long protocol)

EVIDENCE-BASED RECOMMENDATION(S)

EBR: Adjunct metformin therapy could be used before and/or during FSH ovarian stimulation in women with PCOS undergoing IVF/ICSI treatment with GnRH agonist long protocol, to reduce the risk of developing Ovarian Hyperstimulation Syndrome and miscarriage.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

PRACTICE POINT(S)

Practice Points

Good practice in PCOS and IVF is the use of an antagonist protocol as it gives the flexibility of using an agonist trigger, freeze all strategy to reduce the risk of ovarian hyperstimulation syndrome (OHSS). However, if using a GnRH agonist long protocol, then metformin could be considered.

If using metformin, the following could be considered:

- Commence metformin at the start of GnRH agonist treatment
- Gradually titrate metformin up to a dose of between 1000mg to 2500mg daily in order to minimise side effects
- Stopping metformin therapy at the time of the pregnancy test or period, unless the metformin therapy is otherwise indicated

GRADE CONSIDERATIONS

Justifications:

For GnRH agonist protocol: Adjuvant metformin may reduce the risk of OHSS rate per patient and miscarriage rate per pregnancy but may also increase the incidence of gastrointestinal side-effects

Subgroup considerations:

None

Implementation considerations:

Potential barriers (of limited impairment of implementation) to implementation of the recommendations relate to the availability of drug metformin and costs of the drugs which may vary depending on many factors including, but not limited to, the health care setting (IVF/ICSI funded, partly funded, or not funded) and socioeconomic status of the patient.

Monitoring and evaluation considerations:

It would be difficult to monitor and measure the success of implementing these recommendations as there are many individualized strategies to reduce the incidence of OHSS.

Research priorities:

Further adequately powered, well designed, conducted & reported RCTs are needed to assess the benefits and harms of adjunct metformin treatment before and/or during IVF/ICSI treatment in women with PCOS.

Further adequately powered, well designed, conducted & reported RCTs are needed to assess the benefits and harms of adjunct metformin treatment before and/or during IVF/ICSI treatment with GnRH antagonist protocol in women with PCOS.

Further adequately powered, well designed, conducted & reported RCTs are needed to determine the appropriate time to both start and cease metformin with regard to pregnancy rate, live birth rate and infant outcomes.

GRADE framework

GRADE DECIDE Interactive Evidence to Decision Framework

- **DESIRABLE EFFECTS**

How substantial are the desirable anticipated effects?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Summary of evidence for GnRH agonist protocol: There was no difference in all outcomes except

- a **reduction in E2 level on day of hCG trigger, OHSS rate per patient, miscarriage rate per pregnancy favouring metformin.**
- an increase in side-effects rate per patient if taking metformin.

With respect to the no difference in outcomes:

- The meta-analyses **did not exclude that metformin is superior to placebo/no Rx for clinical pregnancy rate per patient** as the 95% CI excluded an important reduction in clinical pregnancy rate per patient with metformin.
- There was equivalence (due to narrow 95% CI's excluding an important difference between metformin and placebo / no treatment) for duration of ovarian stimulation, number of eggs retrieved.
- There was uncertainty (inconclusive result due to wide 95% CI's) for live-birth rate per patient, amount of gonadotrophins used, multiple pregnancy rate per pregnancy, miscarriage rate per patient.

- **UNDESIRABLE EFFECTS**

How substantial are the undesirable anticipated effects?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Summary of evidence for GnRH agonist protocol: There was no difference in all outcomes except

- a reduction in E2 level on day of hCG trigger, OHSS rate per patient, miscarriage rate per pregnancy favouring metformin.
- **an increase in mild side-effects rate per patient if taking metformin**

With respect to the no difference in outcomes:

- the meta-analyses did not exclude that metformin is superior to placebo/no Rx for clinical pregnancy rate per patient as the 95% CI excluded an important reduction in clinical pregnancy rate per patient with metformin.
- there was equivalence (due to narrow 95% CI's excluding an important difference between metformin and placebo / no treatment) for duration of ovarian stimulation, number of eggs retrieved.
- there was uncertainty (inconclusive result due to wide 95% CI's) for live-birth rate per patient, amount of gonadotrophins used, multiple pregnancy rate per pregnancy, miscarriage rate per patient.

- **CERTAINTY OF THE EVIDENCE**

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☐ Very low	☒ Low	☐ Moderate	☐ High

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

The **overall certainty of the evidence** is determined by the critical (as opposed to important) outcome with the lowest certainty (quality) of the evidence.

- **VALUES**

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☐ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☒ Probably no important uncertainty or variability	☐ No important uncertainty or variability

Research evidence:

No research evidence was identified.

Panel discussion:

Patients (and clinicians) would generally strongly value (with probably no important uncertainty in or variability in) an

- a reduced risk for developing OHSS (with its associated morbidity and rarely mortality) .
- a reduced miscarriage rate per pregnancy

Patients (and clinicians) would generally mild to moderately value (with probably no important uncertainty in or variability in)

not having an increased incidence of side-effects.

- **BALANCE OF EFFECTS**

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:

Summary of evidence for GnRH agonist protocol: There was no difference in all outcomes except

- a **reduction in E2 level on day of hCG trigger, OHSS rate per patient, miscarriage rate per pregnancy favouring metformin.**
- **an increase in mild side-effects rate per patient if taking metformin.**

With respect to the no difference in outcomes:

- the meta-analyses **did not exclude that metformin is superior to placebo/no Rx for clinical pregnancy rate per patient** as the 95% CI excluded an important reduction in clinical pregnancy rate per patient with metformin.
- there was equivalence (due to narrow 95% CI's excluding an important difference between metformin and placebo / no treatment) for duration of ovarian stimulation, number of eggs retrieved.
- there was uncertainty (inconclusive result due to wide 95% CI's) for live-birth rate per patient, amount of gonadotrophins used, multiple pregnancy rate per pregnancy, miscarriage rate per patient.

For metformin, the balance of desirable effects in terms of a **reduction in E2 level on day of hCG trigger, OHSS rate per patient, & miscarriage rate per pregnancy** currently outweighs the undesirable effects of an **increase in mild side-effects rate per patient.**

- **COSTS**

How large are the resource requirements (costs)?

Judgement:

☐ Don't know	☐ Varies	☐ Large costs	☐ Moderate costs	☒ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:

No research evidence was identified.

Panel discussion:

Cost of oral metformin therapy small for up to 4 months.

Cost of managing OHSS moderate to large depending on severity and whether or not outpatient management or hospitalization required.

- **CERTAINTY OF COST EVIDENCE**

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

No research evidence was identified.

Panel discussion:

There is no certainty of evidence for this.

- **COST-EFFECTIVENESS**

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

No research evidence was identified.

Panel discussion:

Costs of oral metformin therapy are small for up to 4 months.

Costs of managing OHSS are moderate to large depending on severity and whether or not it involves outpatient management or hospitalization.

- **EQUITY**

What would be the impact on health equity?

Judgement:

☐ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☒ Probably no impact	☐ Probably increased	☐ Increased

Research evidence:

No research evidence was identified.

Panel discussion:

Limited impact.

- **ACCEPTABILITY**

Is the option acceptable to key stakeholders?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified.

Panel discussion:

Patients (and clinicians) probably likely to find the intervention (metformin) acceptable. However, some patients (and clinicians) may not find delaying IVF treatment for up to 4 months (if adjunct metformin treatment is started at such a time) acceptable despite the potential benefit of a reduction in the risk of developing OHSS.

- **FEASIBILITY**

Is the option feasible to implement?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☐ Probably Yes	☒ Yes

Research evidence:

No research evidence was identified.

Panel discussion:

Probably feasible to sustain the option recommended and probably no important potential barriers to implementation of the recommendation (apart from patients unable to tolerate oral metformin due to side-effects which affect approximately 5% of patients).

REFERENCES:

1. Teede, H.J., et al., Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome†‡. Human Reproduction, 2018. 33(9): p. 1602-1618.
2. Lin, K. and C. Coutifaris, In vitro fertilization in the polycystic ovary syndrome patient: an update. Clin Obstet Gynecol, 2007. 50(1): p. 268-76.
3. Baskind, N.E. and A.H. Balen, Hypothalamic-pituitary, ovarian and adrenal contributions to polycystic ovary syndrome. Best Pract Res Clin Obstet Gynaecol, 2016. 37: p. 80-97.

4. Costello, M.F., M. Chapman, and U. Conway, A systematic review and meta-analysis of randomized controlled trials on metformin co-administration during gonadotrophin ovulation induction or IVF in women with polycystic ovary syndrome. Hum Reprod, 2006. 21(6): p. 1387-99.

5. Legro, R.S., Ovulation induction in polycystic ovary syndrome: Current options. Best Pract Res Clin Obstet Gynaecol, 2016. 37: p. 152-159.

6. Naderpoor, N., et al., Metformin and lifestyle modification in polycystic ovary syndrome: systematic review and meta-analysis. Hum Reprod Update, 2015. 21(5): p. 560-74.

7. Sivalingam, V.N., et al., Metformin in reproductive health, pregnancy and gynaecological cancer: established and emerging indications. Hum Reprod Update, 2014. 20(6): p. 853-68.

8. Tso, L.O., et al., Metformin treatment before and during IVF or ICSI in women with polycystic ovary syndrome. Cochrane Database Syst Rev, 2020. 12(12): p. Cd006105.

PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by the Evidence Team: Aya Mousa, Jillian Tay
Other team members: Loyal Pattuwage

GDG 5

Question 5.7.6

In women with PCOS, is In Vitro Maturation (IVM) effective for improving fertility outcomes?

1. STUDY SELECTION

Table 1. PICO Criteria for Inclusion	
Question	In women with PCOS, is In Vitro Maturation (IVM) effective for improving fertility outcomes?
Clinical leads (key contacts)	Dr Ho Manh Tuong Reproductive endocrinologist My Duc Hospital, HOPE Research Centre, Vietnam tuongho.ivfmd@gmail.com Prof Roger Hart Reproductive endocrinologist The University of Western Australia, Australia roger.hart@uwa.edu.au
Allocation ranking	Systematic review Level 1- New systematic review (with integrity check for all studies)

	Participants (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Study type (S)	Limits *(language, year)*
Inclusion	Women of any age, ethnicity and weight with PCOS diagnosed by Rotterdam, NIH or AEPCOS AND with or without coexisting infertility factors (other than anovulation). Also specifically identifying the 4 phenotypes where possible.	IVM treatment using no or minimal ovarian stimulation	Placebo, no intervention, other infertility treatment interventions (ie. aromatase inhibitor, metformin, clomiphene citrate, gonadotrophins, ovarian surgery) including IUI or IVF.	Live birth rate, pregnancy rate (biochemical or clinical ultrasound), ovulation, amount of gonadotrophins used, duration of ovarian stimulation, maximum serum oestradiol level (or serum oestradiol level on the day of trigger), number of oocytes collected, single and multiple pregnancies, miscarriage rate, OHSS rate, other adverse events, quality of life, cost effectiveness. Number and/or percentage of metaphase II (mature) oocytes.	Evidence based guidelines, systematic reviews, health technology assessments, randomised controlled trials (RCTs).	English language. No date limit
Exclusion	Women without diagnosis of PCOS.	Placebo, no intervention or any intervention other than IVM.	Any intervention other than those listed in the inclusion criteria.	None	Non-evidence Based guidelines, non-systematic reviews, any study lower than a RCT.	

2. SEARCH STRATEGY

The search and screening for all GDG 5 questions were done together. Details can be found in the GDG 5 Methodology Appendix, including for:

- Databases
- Search Dates
- Search String(s)
- PRISMA flowchart
- Full list of included studies
- Full list of excluded studies with reasons for exclusion

Evidence processing: The literature search and screening were performed together in one Endnote library and Covidence project for all non-IVF, IVF and IVM fertility treatments in PCOS. Studies were selected by one reviewer/s in consultation with the evidence team/ key contact(s) using study selection and appraisal criteria (PICOs) established a priori. The articles were screened by title and abstract by one reviewer. When a decision could not be made based on title and abstract alone, full text was retrieved. Study appraisal was conducted by two reviewers independently with discussion to resolve any discrepancy. In total, 102 unique studies met inclusion criteria across all non-IVF, IVF and IVM questions, of which 57 were included in the guideline update following the integrity check (refer to methodology appendix for details).

Of these eligible 102 studies (57 after integrity assessment), **1 study met the inclusion criteria for this particular question** (Q.5.7.6.) on IVM, as detailed below.

Table of Included Studies

Zheng X, Guo W, Zeng L, Zheng D, Yang S, Xu Y, Wang L, Wang R, Mol BW, Li R, Qiao J. In vitro maturation without gonadotropins versus in vitro fertilization with hyperstimulation in women with polycystic ovary syndrome: a non-inferiority randomized controlled trial. Hum Reprod. 2022 Jan 28;37(2):242-253. doi: 10.1093/humrep/deab243. PMID: 34849920; PMCID: PMC9115328.

3. STUDY CHARACTERISTICS TABLE FOR INCLUDED STUDIES

Author, year, country	Population/ PCOS criteria/ Setting/ CC sensitivity	Study Design	Intervention N	Intervention description	Comparison N	Comparison description	Follow Up	Outcomes	Pooled in MA?	RoB
Zheng 2022 China	Infertile women aged 20–38 years with PCOS and infertility scheduled for their first IVF attempt / academic infertility centre; **CC sensitivity NR**	RCT	IVF: 176	Unstimulated IVM	IVM: 175	Standard IVF with a flexible GnRH antagonist protocol (n=176)	1 cycle	Primary: ongoing pregnancy (leading to live birth, defined as a baby born live at ≥ 22 weeks of gestation within 6months of the first oocyte retrieval cycle after randomization) Secondary: implantation, **clinical pregnancy**, and time to ongoing pregnancy leading to live birth. Initial pregnancy diagnosis: positive pregnancy test (not specified). Confirmed by: gestational sac	No	Low

CC, clomiphene citrate; NR; not reported; MA, meta-analysis; RoB, risk of bias.

4. FINDINGS

Comparisons Included:

- **Comparison 1.** In vitro maturation (IVM) vs. standard in vitro fertilization (IVF)

COMPARISON 1. IVM vs. IVF

▪ EVIDENCE SUMMARY:

A single study by Zheng et al. (2022) compared IVM with standard IVF in infertile women aged 20–38 years with PCOS and infertility scheduled for their first IVF attempt at an academic infertility centre. Relevant outcomes included live birth rate per patient and per pregnancy, clinical pregnancy rate per patient, and miscarriage rate per pregnancy. This study had a low risk of bias, with high-quality methodology despite being unblinded due to the nature of the intervention/s.

▪ META-ANALYSIS/ DESCRIPTIVE ANALYSIS SUMMARY:

Pooled meta-analysis was not possible due to having a single study. However, in comparing the differences between groups, IVM had a lower rate of live births and clinical pregnancies per patient compared with IVF. There were no differences in live birth rates or miscarriage rates per pregnancy. Certainty in the evidence is moderate for all outcomes, downgraded once for imprecision due to being derived from a single study with a modest sample size.

Outcome or Subgroup	Studies	n	Effect Estimate; OR [95% CI], M-H, random	P-value	Favours	Certainty
Live birth rate per patient	1	351	0.28 [0.18, 0.45]	<0.00001	**IVF** (live birth per patient is lower with IVM)	⊕⊕⊕◯ MODERATE
Live birth rate per pregnancy	1	351	0.64 [0.31, 1.33]	0.2	None	⊕⊕⊕◯ MODERATE
Clinical pregnancy rate- per patient†	1	170	0.26 [0.16, 0.40]]	<0.00001	**IVF** (clinical pregnancy is lower with IVM)	⊕⊕⊕◯ MODERATE
Miscarriage rate- per pregnancy	1	170	1.88 [0.93, 3.79]	0.08	None	⊕⊕⊕◯ MODERATE

†clinical pregnancy rate is confirmed by ultrasound detection of gestational sac/ fetal heart activity

OUTCOME 1.1. Live birth rate – per patient

1.1.1. Individual Study Data Table

OUTCOME: Live birth rate - per patient						**OUTCOME TYPE:** Dichotomous			
COMPARISON: In vitro maturation (IVM) vs. standard in vitro fertilization (IVF)									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (IVM)**	**N total in intervention/ exposure group (IVM)**	**N events in control / comparison group (IVF)**	**N total in control/ comparison group (IVF)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Zheng 2022 (LRB)	NR	Count	Investigator	39	175	89	176	Crude	NA

NR, not reported; **OI**, ovulation induction

OUTCOME 1.2. Live birth rate – per pregnancy

1.2.1. Individual Study Data Table

OUTCOME: Live birth rate - per pregnancy					**OUTCOME TYPE:** Dichotomous				
COMPARISON: In vitro maturation (IVM) vs. standard in vitro fertilization (IVF)									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (IVM)**	**N total in intervention/ exposure group (IVM)**	**N events in control / comparison group (IVF)**	**N total in control/ comparison group (IVF)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Zheng 2022 (LRB)	NR	Count	Investigator	39	56	89	114	Crude	NA

NR, not reported; **OI**, ovulation induction

OUTCOME 1.3. Clinical pregnancy rate – per patient

1.3.1. Individual Study Data Table

OUTCOME: Clinical pregnancy rate - per patient					**OUTCOME TYPE:** Dichotomous				
COMPARISON: In vitro maturation (IVM) vs. standard in vitro fertilization (IVF)									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (IVM)**	**N total in intervention/ exposure group (IVM)**	**N events in control / comparison group (IVF)**	**N total in control/ comparison group (IVF)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Zheng 2022 (LRB)	NR	Count	Investigator	56	175	114	176	Crude	NA

NR, not reported; **OI**, ovulation induction

OUTCOME 1.4. Miscarriage rate – per pregnancy

1.4.1 Individual Study Data Table

OUTCOME: Miscarriage rate – per pregnancy					**OUTCOME TYPE: Dichotomous**				
COMPARISON: In vitro maturation (IVM) vs. standard in vitro fertilization (IVF)									
Author, year	**Past OI Med Use**	**Unit of outcome (e.g. g, mg)**	**Method of measurement**	**N events in intervention/ exposure group (IVM)**	**N total in intervention/ exposure group (IVM)**	**N events in control / comparison group (IVF)**	**N total in control/ comparison group (IVF)**	**Are these values adjusted or crude?**	**If adjusted, what variables were in the model?**
Zheng 2022 (LRB)	Mixed	Count	Investigator	20	56	26	114	Crude	NA

NR, not reported; **OI**, ovulation induction

5. GRADE ASSESSMENTS AND EVIDENCE PROFILE

COMPARISON 1: In vitro maturation (IVM) vs. standard in vitro fertilization (IVF)												
	Quality assessment						No. participants					
No. studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**IVF**	**IVM**	**Effect, random, OR [95% CI]**	**Favours**	**Certainty**	**Importance**
Outcome: Live birth rate - per patient												
1	RCT	no serious risk of bias	not applicable	not applicable	serious[1]	none	39/175 (22.3%)	89/176 (50.6%)	0.28 [0.18, 0.45]	**IVF** (live birth rate per patient is lower with IVM)	⨁⨁⨁◯ MODERATE	CRITICAL
Outcome: Clinical pregnancy rate- per patient												
1	RCT	no serious risk of bias	not applicable	not applicable	serious[1]	none	56/175 (32.0%)	114/176 (64.8%)	0.26 [0.16, 0.40]	**IVF** (clinical pregnancy per patient is lower with IVM)	⨁⨁⨁◯ MODERATE	CRITICAL
Outcome: Live birth rate - per pregnancy												
1	RCT	no serious risk of bias	not applicable	not applicable	serious[1]	none	39/56 (69.6%)	89/114 (78.1%)	0.64 [0.31, 1.33]	None	⨁⨁⨁◯ MODERATE	IMPORTANT
Outcome: Miscarriage rate- per pregnancy												
1	RCT	no serious risk of bias	not applicable	not applicable	serious[1]	none	20/56 (35.7%)	26/114 (22.8%)	1.88 [0.93, 3.79]	None	⨁⨁⨁◯ MODERATE	IMPORTANT

[1] Downgraded once due to the evidence being derived from a single study

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 5

Question 5.7.6

In women with PCOS, is In Vitro Maturation (IVM) effective for improving fertility outcomes?

BACKGROUND:

Where IVF is indicated in PCOS women, OHSS risks are increased with gonadotropin stimulation. IVM of oocytes limits or omits ovarian stimulation prior to oocyte retrieval, with maturation of oocytes post retrieval, avoiding OHSS risk (1). The definition of an IVM cycle requires clarification (2), the term IVM treatment should include only the maturation of immature cumulus oocyte complexes from antral follicles, with or without HMG/FSH priming, but without hCG/GnRH trigger before oocyte retrieval.

Recently, there have been RCTs published relating to the efficacy of IVM versus IVF/ICSI in PCOS women.

Zheng et al., conducted (3) a large RCT (n=351), that compared IVM (without FSH priming) vs. conventional IVF/ICSI for PCOS women. The results showed that IVM procedure without additional gonadotropin resulted in a lower ongoing pregnancy (leading to live birth) within 6 months after randomization compared to standard IVF treatment (22.3% vs. 50.6%, p<0.001). Moderate-severe OHSS did not occur in the IVM group, while in the IVF group, ten women (5.7%) had moderate OHSS and one woman (0.6%) had severe OHSS.

Vuong et al., in 2020 (4) conducted a large RCT (N=546), IVM (with FSH priming) vs. conventional IVF/ICSI for high AFC women, in which majority of patients are PCOS women (more than 70%). The results showed that live birth rate per single transfer did not differ significantly between the IVM and IVF/ICSI groups, 35.2% vs. 43.2%, RR 0.81 (95% CI:0.66 - 1). There was no statistically significant difference in live birth rate after first transfer between the IVM and IVF/ICSI groups in patients with PCOS (35.7% vs. 41.1%; P=0.27). Cumulative ongoing pregnancy rates at 12 months after randomization were 44.0% in the IVM group and 62.6% in the IVF/ICSI group (absolute risk difference –18.7%; 95% CI –27.3%, –10.1%). Ovarian hyperstimulation syndrome did not occur in the IVM group, versus two cases in the IVF/ICSI group.

IVM could provide a comparable live birth rate per single transfer to conventional IVF for PCOS women, but a significantly lower cumulative live birth rate per started cycle. IVM could completely avoid OHSS in both studies (3, 4).

One small RCT, (N=36) (5), showed that FSH priming before oocyte retrieval might improve the maturational potential of the oocytes and the implantation rate of the cleaved embryos. Another small RCT, N=80 (6), showed that two-step IVM improved maturation and clinical pregnancy rates versus one-step standard IVM in PCOS women.

A RCT, that consisted of 40 participants (7) compared fresh embryo transfer versus freeze-only after IVM in women with high antral follicle count, in which, majority of patients are PCOS women. The live birth rate was significantly higher in the freeze-only than that in the fresh ET group (60% versus 20%; p = 0.02). The finding suggested that the effectiveness of IVM could be improved considerably by using a freeze-only strategy followed by frozen ET in subsequent cycles. Additional data from the author demonstrates that all women met PCOS criteria.
Observational data also suggests that fresh embryo transfers are inferior to frozen embryo transfers.
A recent study (8) followed-up of babies born to women who participated in a randomized controlled trial comparing IVM and IVF, in which developmental assessments were performed on 231 children over 24 months of follow-up. The study is still ongoing and once the final results are available, the evidence base for this question will be updated.

GRADE EVIDENCE CERTAINTY	
Comparison	**GRADE for critical outcomes**
Comparison 1. Comparison 1. IVM versus stimulated IVF	⊕⊕⊕◯ MODERATE
Comparison 2. Frozen embryo transfer versus Fresh embryo transfer after IVM	⊕◯◯◯ VERY LOW

Evidence to Recommendations Framework

COMPARISONS (option versus other option)

In vitro maturation (IVM) of oocytes versus standard stimulated in vitro fertilization (IVF).

EVIDENCE-BASED RECOMMENDATION(S)

EBR: The use of IVM and ICSI could be considered in women with PCOS, as an alternative to a stimulated IVF / ICSI cycle, where an embryo is frozen and replaced in a subsequent embryo transfer cycle, acknowledging there is no risk of Ovarian Hyperstimulation Syndrome, but a lower cumulative live birth rate.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☒ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

CONSENSUS RECOMMENDATION(S)

CR: The use of IVM and ICSI could be considered prior to stimulated IVF/ ICSI cycles acknowledging both benefits and limitations.

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☒ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

PRACTICE POINT(S)

1. IVM should only be considered in services with sufficient expertise, and advocacy is needed for regional centres of expertise.
2. IVM could be offered as an option in women with prior severe Ovarian Hyperstimulation Syndrome and where the risk of severe Ovarian Hyperstimulation Syndrome is deemed unacceptably high, provided expertise in the IVM technique exists.
3. Evidence suggests that IVM and ICSI is less effective than standard IVF/ICSI in terms of clinical pregnancy per patient and live birth rate per patient.

GRADE CONSIDERATIONS

Justifications:

IVM when compared with stimulated IVF in PCOS women, results in a significantly lower cumulative live birth rate per cycle and IVM completely avoids OHSS

Subgroup considerations:

None

Implementation considerations:

While IVM is no longer considered experimental, potential limitations in offering IVM are the costs of implementation and the expertise related to both the surgical procedure and the laboratory consumables and processes.

Monitoring and evaluation considerations:

If IVM is to be implemented, services should consider:

Identification of an ideal cohort of patients
IVM expertise
Monitoring and benchmarking laboratory parameters (oocytes maturation, blastocyst and embryo utilisation rates)

Research priorities:

The optimal IVM protocol for PCOS women.

Long term health of offspring with IVM

GRADE framework

GRADE DECIDE Interactive Evidence to Decision Framework

- **DESIRABLE EFFECTS**

How substantial are the desirable anticipated effects?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

Panel discussion:

IVM is a treatment option that could be considered for PCOS patient prior to stimulated IVF/ICSI, where available.

Safer, simpler, less costly with reasonable fertility outcomes.

- **UNDESIRABLE EFFECTS**

How substantial are the undesirable anticipated effects?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

The cumulative live birth rates are lower after IVM.

- **CERTAINTY OF THE EVIDENCE**

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☐ Very low	☐ Low	☒ Moderate	☐ High

Research evidence:

Panel discussion:

- **VALUES**

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☐ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☐ Probably no important uncertainty or variability	☒ No important uncertainty or variability

Research evidence:

Panel discussion:

Availability of IVM technique, facility and expertise

- **BALANCE OF EFFECTS**

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:

- **COSTS**

How large are the resource requirements (costs)?

Judgement:

☐ Don't know	☐ Varies	☐ Large costs	☐ Moderate costs	☐ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:

Panel discussion:

IVM might have lower cost compared to stimulated IVF.

- **CERTAINTY OF COST EVIDENCE**

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

No research evidence was identified

Panel discussion:

- **COST-EFFECTIVENESS**

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☒ Probably favours this option	☐ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

No evidence.

Panel discussion:

- **EQUITY**

What would be the impact on health equity?

Judgement:

☐ Don't know	☒ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☐ Probably increased	☐ Increased

Research evidence:

No research evidence was identified

Panel discussion:

Varies according to geographical location.

- **ACCEPTABILITY**

Is the option acceptable to key stakeholders?

Judgement:

☐ Don't know	☐ Varies	☐ No	☐ Probably No	☒ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified.

Panel discussion:

Are key stakeholders likely to find the recommendation acceptable, given the relative importance they attach to the desirable and undesirable consequences of implementing the recommendation; the timing of the benefits, harms and costs; and their moral values? This includes considering patients values and preferences.

Both patients and services could consider the IVM option if available, for safety, simplicity, less cost and reasonable result.

- **FEASIBILITY**

Is the option feasible to implement?

Judgement:

☐ Don't know	☒ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:

Panel discussion:

Varies according to facility and expertise.

REFERENCES:

1. Walls, M.L., et al., In vitro maturation as an alternative to standard in vitro fertilization for patients diagnosed with polycystic ovaries: a comparative analysis of fresh, frozen and cumulative cycle outcomes. Hum Reprod, 2015. 30(1): p. 88-96.
2. De Vos, M., et al., The definition of IVM is clear-variations need defining. Hum Reprod, 2016. 31(11): p. 2411-2415.
3. Zheng, X., et al., In vitro maturation without gonadotropins versus in vitro fertilization with hyperstimulation in women with polycystic ovary syndrome: a non-inferiority randomized controlled trial. Hum Reprod, 2022. 37(2): p. 242-253.
4. Vuong, L.N., et al., In-vitro maturation of oocytes versus conventional IVF in women with infertility and a high antral follicle count: a randomized non-inferiority controlled trial. Hum Reprod, 2020. 35(11): p. 2537-2547.
5. Mikkelsen, A.L. and S. Lindenberg, Benefit of FSH priming of women with PCOS to the in vitro maturation procedure and the outcome: a randomized prospective study. Reproduction, 2001. 122(4): p. 587-92.
6. Vuong, L.N., et al., Live births after oocyte in vitro maturation with a prematuration step in women with polycystic ovary syndrome. J Assist Reprod Genet, 2020. 37(2): p. 347-357.
7. Vuong, L.N., et al., Fresh embryo transfer versus freeze-only after in vitro maturation with a pre-maturation step in women with high antral follicle count: a randomized controlled pilot study. J Assist Reprod Genet, 2021. 38(6): p. 1293-1302.
8. Vuong, L.N., et al., Development of children born from IVM versus IVF: 2-year follow-up of a randomized controlled trial. Hum Reprod, 2022. 37(8): p. 1871-1879.

PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by ECR Lead: Victoria Fitz

Other team members: Carolyn Ee, Shruthi Mahalingaiah, Alison Maunder, Jing Liu, Sandro Graca, Lily Lai, Ali Butt, Vibhuti Rao, Dhevaksha Naidoo, Guoyan (Emily) Yang, Vaishnavi Vaddiparti, Mike Armour

Supervised, edited and supported by the Evidence Team (Aya Mousa, Jillian Tay)

GDG 5

Question 5.8.

In women with PCOS, is inositol alone or in combination with other therapies, effective for management of reproductive outcomes? (fertility outcomes only)

See Evidence Summary in GDG 4 technical report (Question 4.7.)

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 5

Question 5.8.

In women with PCOS, is inositol alone or in combination with other therapies, effective for management of reproductive outcomes? (fertility outcomes only)

BACKGROUND:

Women with PCOS are commonly treated with insulin sensitizing agents due to insulin resistance and hyperinsulinemia, common features of the syndrome both in obese and non-obese women. Due to gastrointestinal side effects related to metformin and more serious adverse effects related to glitazones other medical options are needed in treating insulin resistance in women with PCOS. Inositol (myo-inositol and di-chiro inositol) is a nutritional supplement that acts as a second messenger and has been shown to play a role in insulin signalling transduction. Previous studies have suggested improvement of insulin resistance and hormonal profile in women with PCOS during inositol treatment (1, 2). Furthermore, some data also suggests inositol may be effective in decreasing risk for gestational diabetes (3).

Please see the background section on Q 4.7 for more details.

GRADE EVIDENCE CERTAINTY	
Comparison	**GRADE for critical outcomes**
Comparison 1. Di-chiro inositol (DCI) vs. Placebo - single trial	⊕⊕◯◯ LOW
Comparison 2. Myo-inositol (MI) + FA vs. Folic Acid (FA)	⊕◯◯◯ VERY LOW
Comparison 3. MI vs. Metformin	⊕⊕◯◯ LOW
Comparison 4. MI + DCI (higher dose) vs. MI + DCI (lower dose)	⊕◯◯◯ VERY LOW

Evidence to Recommendations Framework

COMPARISONS (option versus other option)
Comparison 1: DCI vs placebo, Comparison 2: MI+FA vs FA Comparison 3: MI vs. Metformin Comparison 4: MI + DCI (higher dose) vs. MI + DCI (lower dose)
EVIDENCE-BASED RECOMMENDATION(S)

EBR: Inositol in any form alone, or in combination with other therapies, should be considered experimental therapy in women with PCOS, with benefits and risks currently too uncertain to recommend the use of these agents as fertility therapies.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☐ Conditional (weak) recommendation for either the option or the comparison	☒ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

PRACTICE POINT(S)

There is limited evidence with uncertain results, on the effect of inositol on ovulation, clinical pregnancy and live birth rates.

Side effects and safety are not fully documented for inositol

Women need to be aware that these agents have limited regulation with variable dose, quality, consistency and combination with other agents.

Women's personal goals and preferences should be considered when discussing complimentary therapies

GRADE CONSIDERATIONS

Justifications:

Most studies having a high to moderate risk of bias are small and heterogeneous with wide confidence intervals and evidence is uncertain.

Subgroup considerations:

Implementation considerations:

Monitoring and evaluation considerations:

Research priorities:
The effect, optimal formulations and dose of inositol on ovulation and critically important outcomes of clinical pregnancy and live birth needs to be established in large high quality trials.

The side effects and safety of inositol needs to be determined through large randomised trials,

GRADE framework

GRADE DECIDE **Interactive Evidence to Decision Framework**

- **DESIRABLE EFFECTS**

How substantial are the desirable anticipated effects?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

- **UNDESIRABLE EFFECTS**

How substantial are the undesirable anticipated effects?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

Side effects not reported

- **CERTAINTY OF THE EVIDENCE**

What is the overall certainty of the evidence of effects?

Judgement:

☐ No included studies	☐ Very low	☒ Low	☐ Moderate	☐ High

Research evidence:

See Part 1- Evidence Summary and GRADE document.

Panel discussion:

- **VALUES**

Is there important uncertainty about, or variability in, how much people value the main outcomes?

Judgement:

☐ Important uncertainty or variability	☐ Possibly important uncertainty or variability	☐ Probably no important uncertainty or variability	☒ No important uncertainty or variability

Research evidence:

No research evidence was identified.

Panel discussion:

- **BALANCE OF EFFECTS**

Does the balance between desirable and undesirable effects favour the option or the comparison?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Panel discussion:

- **COSTS**

How large are the resource requirements (costs)?

Judgement:

☐ Don't know	☐ Varies	☐ Large costs	☐ Moderate costs	☒ Negligible costs or savings	☐ Moderate savings	☐ Large savings

Research evidence:

No research evidence was identified.

Panel discussion:

Over the counter product with low to moderate cost.

- **CERTAINTY OF COST EVIDENCE**

What is the certainty of the evidence of resource requirements (costs)?

Judgement:

☒ No included studies	☐ Very low	☐ Low	☐ Moderate	☐ High

Research evidence:

No research evidence was identified

Panel discussion:

- **COST-EFFECTIVENESS**

Does the cost-effectiveness of the option favour the option or the comparison?

Judgement:

☐ Favours this option	☐ Probably favours this option	☒ Neither favours this option or other options	☐ Probably favours other options	☐ Favours other options

Research evidence:

No research evidence was identified.

Panel discussion:

- **EQUITY**

What would be the impact on health equity?

Judgement:

☒ Don't know	☐ Varies	☐ Reduced	☐ Probably reduced	☐ Probably no impact	☐ Probably increased	☐ Increased

Research evidence:

No research evidence was identified.

Panel discussion:

- **ACCEPTABILITY**

Is the option acceptable to key stakeholders?

Judgement:

☒ Don't know	☐ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified.

Panel discussion:

Are key stakeholders likely to find the recommendation acceptable, given the relative importance they attach to the desirable and undesirable consequences of implementing the recommendation; the timing of the benefits, harms and costs; and their moral values? This includes considering patients values and preferences.

- **FEASIBILITY**

Is the option feasible to implement?

Judgement:

☒ Don't know	☐ Varies	☐ No	☐ Probably No	☐ Probably Yes	☐ Yes

Research evidence:

No research evidence was identified

Panel discussion:

REFERENCES:

1. Balen, A., *The pathophysiology of polycystic ovary syndrome: trying to understand PCOS and its endocrinology.* Best Pract Res Clin Obstet Gynaecol, 2004. **18**(5): p. 685-706.
2. Balen, A.H., et al., *Polycystic ovary syndrome: the spectrum of the disorder in 1741 patients.* Hum Reprod, 1995. **10**(8): p. 2107-11.
3. Symonds, M.E., et al., *Nutritional programming of the metabolic syndrome.* Nat Rev Endocrinol, 2009. **5**(11): p. 604-10.

PART 1

EVIDENCE SUMMARY AND GRADE

Compiled by ECR Lead: Carolyn Ee

Other team members: Alyse Goldberg, Vibhuti Rao, Jing Liu, Sandro Graca

Supervised, edited and supported by the Evidence Team (Aya Mousa, Jillian Tay)

GDG 5

Question 5.9.

In women with PCOS, are anti-obesity pharmacological agents alone or in combination, effective for management of reproductive outcomes? (fertility outcomes only)

See Evidence Summary in GDG 4 technical report

(Question 4.5.)

PART 2

RECOMMENDATIONS

Compiled by the key contact(s)

GDG 5

Question 5.9.

In women with PCOS, are anti-obesity pharmacological agents alone or in combination, effective for management of reproductive outcomes? (fertility outcomes only)

BACKGROUND:

Obesity is a significant concern for many affected adolescents and women with PCOS. Whilst lifestyle change has a key role in the management of obesity, the role of anti-obesity pharmacological agents in achieving weight loss and potential associated health benefits is increasingly recognised with recent guidelines (1,2), and systematic reviews (3) in the area. However, the role of these agents in PCOS and in reproductive-aged women remains unclear.

Semaglutide, liraglutide, phentermine/topiramate, naltrexone/bupropion and orlistat are approved anti-obesity medications in adults, each of which has been compared to placebo in randomised controlled trials. These medications are increasingly being used in adults for assistance with weight loss. However, there is limited available data in women with PCOS. Consensus recommendation has been made by GDG to manage obesity independent of PCOS with these medications.

COMPARISONS (option versus other option)
Anti-obesity versus placebo Anti-obesity versus lifestyle
CONSENSUS RECOMMENDATION
We recommend using anti-obesity agents in PCOS for reproductive outcomes only in research settings to establish the efficacy and safety.

GRADE Direction and Strength of Recommendation:

☐ Strong recommendation against the option	☐ Conditional (weak) recommendation against the option	☒ Conditional (weak) recommendation for either the option or the comparison	☐ Conditional (weak) recommendation for the option	☐ Strong recommendation for the option

REFERENCES:

1. Apovian CM, Aronne LJ, Bessesen DH, McDonnell ME, Murad MH, Pagotto U, et al. Pharmacological Management of Obesity: An Endocrine Society Clinical Practice Guideline. The Journal of Clinical Endocrinology & Metabolism. 2015;100(2):342-62.
2. Grunvald E, Shah R, Hernaez R, Chandar AK, Pickett-Blakely O, Teigen LM, Harindhanavudhi T, Sultan S, Singh S, Davitkov P; AGA Clinical Guidelines Committee. AGA Clinical Practice Guideline on Pharmacological Interventions for Adults With Obesity. Gastroenterology. 2022 Nov;163(5):1198-1225
3. Mead E, Atkinson G, Richter B, Metzendorf M-I, Baur L, Finer N, et al. Drug interventions for the treatment of obesity in children and adolescents. Cochrane Database of Systematic Reviews. 2016(11).

PCOS Guideline Update 2023

Methodology Appendix
Guideline Development Group 5

Compiled by the Evidence Team

1. SEARCH AND SELECTION CRITERIA

Table 1.1. Search details	
Search strategy source: ***2018 PCOS Guideline Technical Report***	
Evidence source	**Date of search**
Medline (Ovid)	01/01/2017 until 08/07/2022
PsychInfo (Ovid)	01/01/2017 until 08/07/2022
EMBASE (Ovid)	01/01/2017 until 10/07/2022
All EBM (Ovid)	01/01/2017 until 10/07/2022
CINAHL	01/01/2017 until 10/07/2022
Any subsequent updates - enter database and date: Not applicable	

Table 1.2. Questions addressed by this search:	
Q 5.3	In women with PCOS, are aromatase inhibitors effective for improving fertility outcomes?
Q 5.4	In women with PCOS, is clomiphene citrate effective for improving fertility outcomes? In women with PCOS, is metformin effective for improving fertility outcomes? In women with PCOS and a BMI<30-32, what is the effectiveness of metformin compared to clomiphene citrate for improving fertility outcomes?
Q 5.5	In women with PCOS, are gonadotrophins effective for improving fertility outcomes?
Q 5.6	In women with PCOS, is ovarian surgery effective for improving fertility outcomes?
Q 5.7	In women with PCOS, is stimulated IVF/ICSI effective for improving fertility outcomes?
Q 5.7.1	In women with PCOS undergoing IVF/ICSI treatment, is the GnRH antagonist protocol or GnRH agonist long protocol the most effective for improving fertility outcomes?
Q 5.7.2	In women with PCOS undergoing GnRH antagonist IVF/ICSI treatment, is the use of hCG trigger or GnRH agonist trigger the most effective for improving fertility outcomes?
Q 5.7.3	In women with PCOS undergoing (controlled) ovarian (hyper) stimulation for IVF/ICSI, does the choice of FSH affect fertility outcomes?
Q 5.7.4	In women with PCOS undergoing (controlled) ovarian (hyper) stimulation for IVF/ICSI, is exogenous LH treatment during IVF/ICSI effective for improving fertility outcomes?
Q 5.7.5	In women with PCOS undergoing (controlled) ovarian (hyper) stimulation for IVF/ICSI, is adjuvant metformin effective for improving fertility outcomes?
Q 5.7.6	In women with PCOS, is In Vitro Maturation (IVM) effective for improving fertility outcomes?

OVID Medline, All EBM, PsychInfo, EMBASE		CINAHL	
1	exp polycystic ovary syndrome/	S1	SU polycystic ovary syndrome
2	polycystic ovar$.mp.	S2	polycystic ovar*
3	"poly cystic ovar$".mp.	S3	poly-cystic ovar*

4 PCO$.mp.	S4 PCO*
5 (stein?leventhal or leventhal).mp.	S5 stein-leventhal or Leventhal
6 anovulation/	S6 SU ovarian cysts
7 anovulat$.mp.	S7 SU anovulation
8 oligoovulat$.mp.	S8 oligo-ovulat*
9 "oligo ovulat$".mp.	S9 oligoovulat*
10 (ovar$ adj5 (sclerocystic or polycystic or "poly cystic" or degenerat$ or hyperandrogen$ or "hyper androgen$")).mp.	S10 ovar* N5 sclerocystic or ovar* N5 polycystic ovar* N5 hyperandrogen*or ovar* N5 poly-cystic or ovar* N5 degenerat* or ovar* N5 hyperandrogen* or over* N5 hyper-androgen*
11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	S11 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10
12 fertility/	S12 (("fertility") or (MH "Fertility") or (MH "Fertility Agents+")) or fertil*
13 fertility agents/	S13 (("infertility") or (MH "Infertility")) or infert*
14 fertility agents, female/	S14 (("pregnancy") or (MH "Pregnancy+") or (MH "Pregnancy Complications+") or (MH "Pregnancy Outcomes")) or pregnan*
15 fertil$.mp.	S15 S12 OR S13 OR S14
16 infertility/	S16 (MH "Fertilization in Vitro")
17 infertility, female/	S17 (MH "Reproduction Techniques+")
18 infert$.mp.	S18 ((in vitro or invitro) and (fertili?ation or maturation))
19 pregnancy complications/	S19 (intracytoplasm* sperm inject* or ICSI)
20 pregnancy/	S20 ((controlled or ovar*) and (hyper or stimulat*))
21 pregnancy outcome/	S21 (IVF or IVM)
22 pregnancy rate/	S22 (zygote intrafallopian transfer* or zygote intra fallopian transfer* or ZIFT)
23 pregnant women/	S23 (embryo transfer* or ET)
24 or/12-23	S24 S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23
25 exp Reproductive Techniques, Assisted/	S25 S15 OR S24
26 Ectogenesis/	S26 S11 AND S25
27 ((in vitro or invitro) adj (fertili?ation or maturation)).mp.	S27 S11 AND S25
28 (intracytoplasm* sperm inject* or ICSI).mp.	S28 MH randomized controlled trials OR MH double-blind studies OR MH single-blind studies OR MH random assignment OR (TI (randomised OR randomized)) OR AB (random*) OR TI (trial) OR PT (randomized controlled trial) OR AB (control* W5 group) OR (MH (crossover design)
29 ((controlled or ovar*) adj (hyper or stimulat*)).mp.	
30 (IVF or IVM).mp.	
31 (zygote intrafallopian transfer* or zygote intra fallopian transfer* or ZIFT).mp.	
32 (embryo transfer* or ET).mp.	
33 or/25-32	
34 clinical trial.mp. or random*.tw. or controlled trial.tw. or rct.tw. or single blind$.tw. or double blind$.tw.	

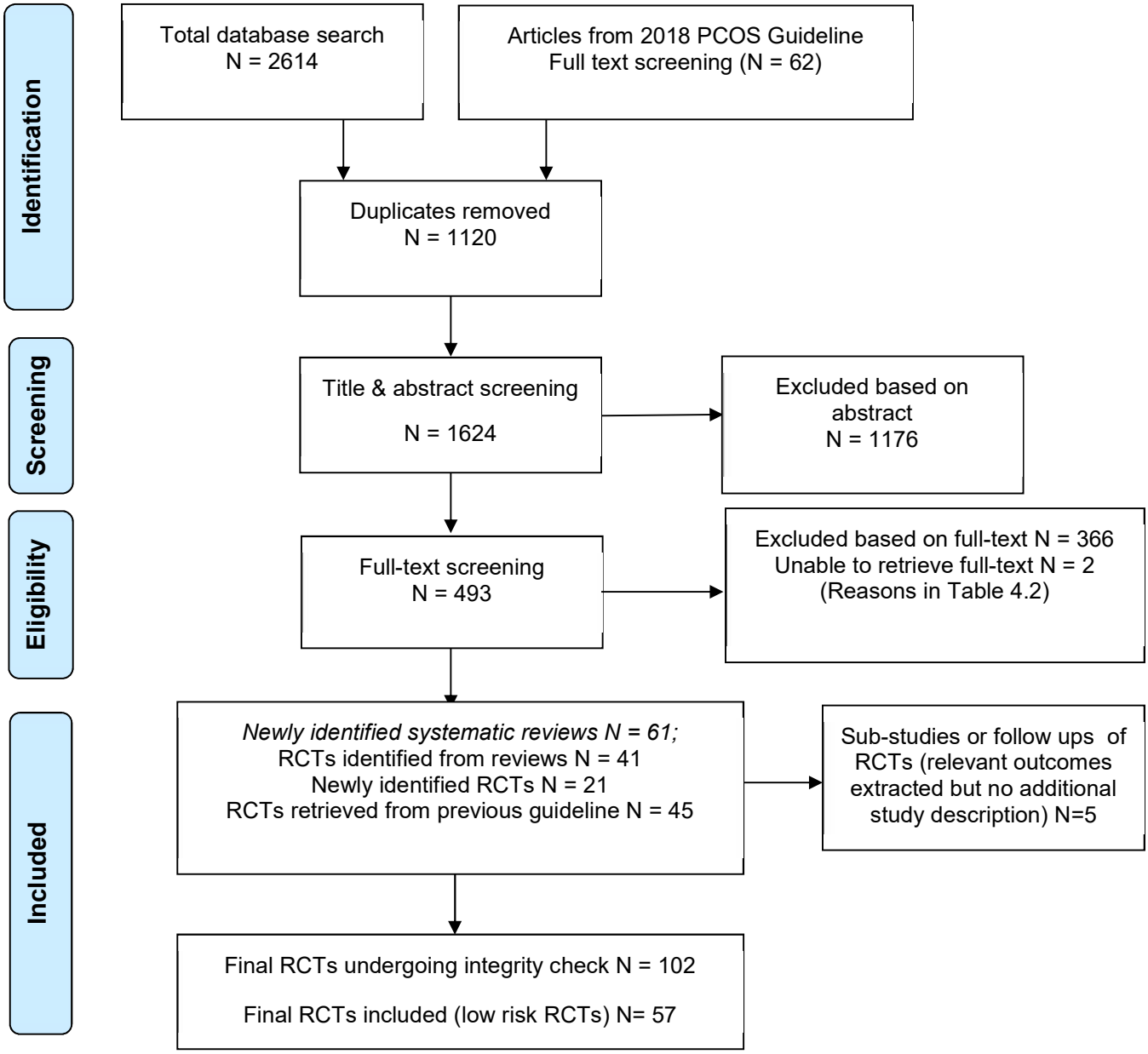
35 11 and 24 and 34 36 11 and 33 and 34 37 35 or 36 38 limit 37 to (human and english language and yr="2017 - 2022")	OR MH (comparative studies)) OR AB trial OR (TI (RCT) OR AB (RCT)) S29 S27 AND S28 S30 S27 AND S28 Limiters - Publication Year: 2017-2022; English Language; Human

Evidence processing: Literature search and screening were performed together in one Endnote library and Covidence project for all non-IVF, IVF and IVM fertility treatments in PCOS. Studies were screened and selected by title and abstract by one reviewer in consultation with the evidence team/ key contact(s) using study selection and appraisal criteria (PICOs) established a priori. When a decision could not be made based on title and abstract alone, full text was retrieved. Study appraisal was conducted by two reviewers independently with discussion to resolve any discrepancy.

In total, 107 studies met inclusion criteria for evidence review for all non-IVF fertility, IVF and IVM treatment in PCOS. Of these, five were sub-studies or follow-ups of published RCTs. Hence, a total of 102 unique studies were included across all of GDG 5.

Of the 102 eligible studies, 57 were included in the guideline update following the integrity check (refer to the methodology appendix of the guidelines for details).

2. SEARCH RESULTS - PRISMA flowchart for search of all non-IVF, IVF and IVM randomised controlled trials in PCOS



3. STUDY INCLUSION

Table 3.1. Included studies undergoing integrity check

RCTs retrieved from 2018 PCOS guideline

1. Abd Elgafor, I. (2013). Efficacy of combined metformin–letrozole in comparison with bilateral ovarian drilling in clomiphene-resistant infertile women with polycystic ovarian syndrome. Archives of gynecology and obstetrics, 288(1), 119-123.
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Table 3.2. Excluded Studies (on full text assessment)						
#	Title	Author/ Year	Journal	Vol	Pages	Reason
1	Pregnancy outcome and cost-effectiveness comparisons of artificial cycle-prepared frozen embryo transfer with or without GnRH agonist pretreatment for polycystic ovary syndrome: a randomised controlled trial	Luo 2021	BJOG: An International Journal of Obstetrics & Gynaecology	128	667-674	Wrong intervention
2	Predictive Values of Dheas, Tt and Igf1 in Successful Pregnancy Outcome of Patients Undergoing Ivf/Icsi-Et	Wadood 2019	Biochemical and Cellular Archives	19(2)	3979-3987	Wrong study design
3	Metformin and health outcomes: An umbrella review of systematic reviews with meta-analyses	Li 2021	European Journal of Clinical Investigation	51(7) (no pagination)		Wrong patient population
4	Does oral contraceptives pretreatment affect the pregnancy outcome in polycystic ovary syndrome women undergoing ART with GnRH agonist protocol?	Xu 2019	Gynecol Endocrinol	35	124-127	Wrong comparator
5	Cost Effective Protocol with Letrozole and 3 Doses of Gonadotropin Combination as an Alternative to Continuous Gonadotropin for Ovulation Induction for Iui in Clomiphene Citrate Resistant Pcos Patients - a Rct	Saha 2020	Fertility and Sterility	114(3 SUPPL)	e525	Wrong comparator
6	Short period-administration of myo-inositol and metformin on hormonal and glycolipid profiles in patients with polycystic ovary syndrome: a systematic review and updated meta-analysis of randomized controlled trials	Zhang 2022	European Review for Medical & Pharmacological Sciences	26	1792-1802	Wrong comparator
7	Operative transvaginal hydrolaparoscopy improve ovulation rate after clomiphene failure in polycystic ovary syndrome	Giampaolino 2018	Gynecol Endocrinol	34	32-35	Wrong study design
8	Ovarian drilling in polycystic ovary syndrome: Long term pregnancy rate	Debras 2019	European Journal of Obstetrics & Gynecology and Reproductive Biology	4	100093	Wrong study design
9	Unilateral ovarian drilling in polycystic ovarian syndrome: a prospective randomized study	H 2007	Reproductive biomedicine online	Vol.15	457-462p	Wrong patient population
10	[Therapeutic effects on ovulation and reproduction promotion with acupuncture and clomiphene in polycystic ovary syndrome]	Yu 2018	Zhongguo Zhen Jiu	38	263-8	Non English
11	A two-step protocol for oocyte In Vitro Maturation in PCO/PCOS patients increases the yield and quality of usable embryos and results in ongoing pregnancies	Sanchez 2018	Human reproduction. Conference: 34th annual meeting of ESHRE. Barcelona, spain	33		Conference abstract
12	Systematic review update and meta-analysis of randomized and non-randomized controlled trials of ovarian stimulation versus artificial cycle for endometrial preparation prior to frozen embryo transfer in women with polycystic ovary syndrome	Zhang 2022	Reprod Biol Endocrinol	20	62	Wrong intervention
13	Flexible GnRH Antagonist Protocol versus Progestin-primed Ovarian Stimulation (PPOS) Protocol in Patients with Polycystic Ovary Syndrome: Comparison of Clinical Outcomes and Ovarian Response	Xiao 2019	Curr Med Sci	39	431-436	Wrong comparator

14	Obstetric complications after frozen versus fresh embryo transfer in women with polycystic ovary syndrome: results from a randomized trial	B 2018	Fertility and Sterility	Vol.109	324-329p	Wrong comparator
15	Pretreatment with a GnRH agonist and hormone replacement treatment protocol could not improve live birth rate for PCOS women undergoing frozen-thawed embryo transfer cycles	Liu 2021	BMC Pregnancy & Childbirth	21	835	Wrong study design
16	Evaluation of pretreatment with Cetrotide in an antagonist protocol for patients with PCOS undergoing IVF/ICSI cycles: a randomized clinical trial	M 2018	JBRA assisted reproduction	Vol.22	238-243p	Wrong intervention
17	The role of Letrozole (LE) in controlled ovarian stimulation (COS) in patients at high risk to develop ovarian hyper stimulation syndrome (OHSS). A prospective randomized controlled pilot study	R 2020	Journal of gynecology obstetrics and human reproduction	Vol.49	101643p	Wrong intervention
18	The efficacy of gonadotropin-releasing hormone (GNRH) agonist before frozen embryo transfer in improving pregnancy outcome and decreasing miscarriage rate in hyperandrogenic polycystic ovary syndrome women: A randomized clinical trial	Aghahosei ni 2020	Minerva Ginecologica	72(4)	212-218	Wrong intervention
19	Evaluation of pretreatment with cetrotide in an antagonist protocol for patients with pcos undergoing IVF/ICSI cycles: A randomized clinical trial	Eftekhar 2018	Jornal Brasileiro de Reproducao Assistida	22(3)	238-243	Wrong comparator
20	The effect of letrozole versus artificial hormonal endometrial preparation on pregnancy outcome after frozen-thawed embryos transfer cycles: a randomized clinical trial	Hosseini-Najarkolae i 2020	Reproductive Biology and Endocrinology	18(1) (no pagination)		Wrong intervention
21	Endometrial preparation for vitrified-warmed embryo transfer with or without GnRH-agonist pre-treatment in patients with polycystic ovary syndrome: a randomized controlled trial	Salemi 2021	Reproductive BioMedicine Online	43(3)	446-452	Wrong comparator
22	Randomized, Controlled Pilot Study of Low-Dose Human Chorionic Gonadotropin Administration Beginning From the Early Follicular Phase for Women With Polycystic Ovarian Syndrome Undergoing Ovarian Stimulation Using the Progesterone Protocol	X 2019	Frontiers in endocrinology	10		Wrong intervention
23	Effects of clomiphene citrate for prevention of premature luteinizing hormone surge in those undergoing intrauterine insemination outcome: A randomized, double-blind, placebo-controlled trial	Zarei 2018	Journal of Advanced Pharmaceutical Technology and Research	9(3)	102-106	Wrong intervention
24	Pregnancy outcome and cost-effectiveness comparisons of artificial cycle-prepared frozen embryo transfer with or without GnRH agonist pretreatment for polycystic ovary syndrome: a randomised controlled trial	L 2021	Bjog	Vol.128	667-674p	Wrong intervention
25	Progesterone-primed ovarian stimulation in polycystic ovarian syndrome: an RCT	M 2019	International Journal of Reproductive BioMedicine	Vol.17	671-676p	Wrong comparator
26	The Effect of Supraphysiological Estradiol on Pregnancy Outcomes Differs Between Women With PCOS and Ovulatory Women	D 2018	Journal of Clinical Endocrinology and Metabolism	Vol.103	2735-2742p	Wrong intervention
27	Recombinant FSH as adjuvant in assisted reproduction: some data on the efficacy and efficiency of recombinant FSH urinary FSH (Structured abstract)	Centrefor Reviewsa ndDissemi nation 2015	Database of Abstracts of Reviews of Effects			Wrong patient population

28	The Impact of Bariatric Surgery Compared to Metformin Therapy on Pregnancy Outcomes in Patients with Polycystic Ovarian Syndrome: a Systematic Review and Meta-analysis	Chang 2021	Journal of Gastrointestinal Surgery	25	378-386	Wrong comparator
29	Evaluation of the effectiveness of transvaginal ovarian drilling under ultrasound guide in patients with resistant polycystic ovary syndrome to clomiphene citrate	Fadhil 2019	International Journal of Research in Pharmaceutical Sciences	10(2)	1556-1561	Wrong study design
30	Impact of Ultrasound-Guided Transvaginal Ovarian Needle Drilling Versus Laparoscopic Ovarian Drilling on Ovarian Reserve and Pregnancy Rate in Polycystic Ovary Syndrome: A Randomized Clinical Trial	Kandil 2018	J Minim Invasive Gynecol	25	1075-1079	Wrong comparator
31	Comparing the effect of sitagliptin and metformin on the oocyte and embryo quality in classic PCOS patients undergoing ICSI	Daneshjou 2021	Irish journal of medical science	Vol.190	685-692p	Wrong comparator
32	Highly purified hMG achieves better pregnancy rates in IVF cycles but not ICSI cycles compared with recombinant FSH: a meta-analysis (Structured abstract)	Centrefor ReviewsandDissemination 2015	Database of Abstracts of Reviews of Effects			Wrong patient population
33	Comparison of metformin plus myoinositol vs metformin alone in PCOS women undergoing ovulation induction cycles: randomized controlled trial	A 2019	Gynecological Endocrinology	Vol.35	511-514p	Wrong comparator
34	Endometrial scratch for infertile polycystic ovary syndrome (PCOS) women undergoing laparoscopic ovarian drilling: a randomized controlled trial	A 2020	Middle East Fertility Society Journal	24		Wrong comparator
35	Ovulation induction using clomiphene citrate using stair - Step regimen versus traditional regimen in polycystic ovary syndrome women - A randomized control trial	Agrawal 2017	Journal of Human Reproductive Sciences	10(4)	261-264	Wrong comparator
36	Fixed versus flexible antagonist protocol in women with predicted high ovarian response except PCOS: a randomized controlled trial	Luo 2021	BMC Pregnancy and Childbirth	21(1) (no pagination)		Wrong patient population
37	Does the repeat dose of gonadotropin-releasing hormone agonist trigger in polycystic ovarian syndrome improve in vitro fertilization cycles outcome? A clinical trial study	Aflatoonian 2020	International Journal of Reproductive BioMedicine	18(7)	485-490	Wrong comparator
38	Comparison of laparoscopic ovarian drilling success between two standard and dose-adjusted methods in polycystic ovary syndrome: a randomized clinical trial	L 2020	International Journal of Fertility and Sterility	Vol.13	282-288p	Wrong comparator
39	Individualized versus standard FSH dosing in women starting IVF/ICSI: an RCT. Part 2: The predicted hyper responder	Oudshoorn 2017	Human Reproduction	32	2506-2514	Wrong patient population
40	Effect of pretreatment with oral contraceptives and progestins on IVF outcomes in women with polycystic ovary syndrome	Daimin 2017	Human Reproduction	32	354-361	Wrong study design
41	Effect of estradiol valerate on the pregnancy rate in patients receiving letrozole for induction of ovulation	Alnemr 2018	Middle East Fertility Society Journal	23(2)	131-136	Wrong comparator
42	Time lapse selected elective single embryo transfer in hyaluronon enriched transfer medium in pcos improves live birth rates compared to use of conventional embryo transfer media. a possible alternative to freeze-all cycles in PCOS	Kandari 2019	Fertility and Sterility	112(3 Supplement)	e47-e48	Conference abstract

43	Stimulated cycle versus artificial cycle for frozen embryo transfer in patients with polycystic ovary syndrome: a Meta-analysis	Zeng 2021	Gynecological Endocrinology	37(4)	294-299	Wrong study design
44	A Randomized Cohort Study: Is It Worth the Time to Receive Antiandrogenic Pretreatment Before Ovulation Induction for Women With Polycystic Ovary Syndrome?	Chen 2022	Frontiers in Endocrinology	13 (no pagination)		Wrong intervention
45	Is there randomized controlled trial evidence to support the use of laparoscopic drilling by diathermy or laser for ovulation induction in women with clomifene-resistant polycystic ovary syndrome?	Opiyo 2019	Cochrane Clinical Answers			Wrong study design
46	Comparison of Clinical Outcomes Between IVM and Minimal Stimulation IVF in Patients With PCOS					trial register/protocol
47	Chromium in Patients With Polycystic Ovary Syndrome Undergoing Intracytoplasmatic Sperm Injection (ICSI)					trial register/protocol
48	A study to compare the efficacy of two drugs on the success of assisted reproductive therapy in women with polycystic ovarian syndrome and undergoing treatment with IVF					trial register/protocol
49	A prospective, interventional, randomized, controlled study to compare the clinical pregnancy rates in patients with type II Polycystic Ovary Syndrome (PCOS) receiving super-long GnRHa protocol versus long protocol with daily GnRHa in IVF					trial register/protocol
50	A Comparative Study on Therapeutic Effect of Metformin and Sitaformin in Infertile Women with polycystic ovary syndrome (PCOS) undergoing intra-cytoplasmic sperm injection (ICSI)					trial register/protocol
51	A comparative study of outcomes of pregnancy and delivery in overweight/obese patients with PCOS treated with exenatide or metformin					trial register/protocol
52	Does combination of metformin together with myoinositol and D-chiroinositol improve clinical, metabolic and hormonal parameters in women with polycystic ovaries					trial register/protocol
53	Evaluation of letrozole and letrozole combined with gonadotropin sequential treatment for ovulation induction in infertile patients with polycystic ovary syndrome: a randomized controlled trial					Non English
54	GnRHa preconditioning plus hormonal substitution protocol versus hormonal substitution protocol alone for frozen–thawed embryo transfer in patients with polycystic ovary syndrome: A prospective, randomized, controlled tial					trial register/protocol
55	IVM Versus Standard IVF in Infertile Patients Diagnosed With PCOS					trial register/protocol
56	Letrozole Step-up Protocol for Ovulation Induction in Infertile Women With PCOS					trial register/protocol
57	Letrozole Stimulation vs Artificial Hormone Cycles in Endometrial Preparation for Frozen Embryo Transfer in Women with Polycystic Ovary					trial register/protocol

	Syndrome Undergoing IVF: A Prospective Randomized Clinical Trial					
58	Myo-inositol as Pretreatment in Hyperandrogenic PCOS Patients					trial register/protocol
59	Pioglitazone Versus Metformin as First Treatment in Infertile Women With Polycystic Ovary Syndrome					trial register/protocol
60	Pulsatile Gonadotropin-releasing Hormone for Infertility in Non-obese Patients With Polycystic Ovary Syndrome					trial register/protocol
61	Reduction of cetrorelix dose in the antagonist multiple dose protocol and its impact on pregnancy rate and economic aspect. A randomized controlled study					trial register/protocol
62	Repeated gonadotropin-releasing hormone agonist (GnRH-a) versus low dose human chorionic gonadotropin (HCG)					Non English
63	Study to Assess the Effect of Metformin Supplementation on IVF Outcome in Patients With Polycystic Ovarian Syndrome					trial register/protocol
64	To compare effect of with or without pre-treatment of the combined oral contraceptive pills for PCOS patients undergoing COS- A single center, randomized, prospective, open-label study					trial register/protocol
65	Ultrasound-guided transvaginal ovarian needle drilling					trial register/protocol
66	Dose Adjusted vs. Fixed Dose Unilateral Laparoscopic Ovarian Drilling in PCOS Patients					trial register/protocol
67	Editor’s Note: badawy A, State O and Abdelgawad S. N-Acetyl cysteine and clomiphene citrate for induction of ovulation in polycystic ovary syndrome: a cross-over trial. Acta Obstetricia et Gynecologica Scandinavica, 2007;86: 218–222		Acta obstetricia et gynecologica Scandinavica	Vol.100	2126-p	Wrong study design
68	Effect of amlodipine on blood flow of preovulatory follicle in women with clomiphene resistant polycystic ovaries: a randomized controlled trial					trial register/protocol
69	Effect of Vitamin D Supplement in Induction of Ovulation in Overweight Women With Polycystic Ovary Syndrome					trial register/protocol
70	L-Carnitine and Clomiphene Citrate for Induction of Ovulation in Women With Polycystic Ovary Syndrome					trial register/protocol
71	LOD vs Gn in Anovulatory PCOs Resistant to First Line Agents					trial register/protocol
72	the Effect of Clomiphene Citrate Plus Estradiol Valerate Versus Letrozole on Endometrial Thickness and Pregnancy Rate in Infertile Women					trial register/protocol
73	IVM Versus IVF in High Antral Follicle Count Patients					trial register/protocol
74	Flexible progestin primed ovarian stimulation in patients with polycystic ovarian syndrome					trial register/protocol

75	HCG trigger versus GnRH agonist trigger in PCOS undergoing IVF cycles: frozen embryo transfer outcome	Krish 2019	Fertility and Sterility	112(3 Supplement)	e207	Conference abstract
76	Overview of systematic reviews of non-pharmacological interventions in women with polycystic ovary syndrome	Pundir 2019	Human Reproduction Update	25(2)	243-256	Wrong intervention
77	A comparative study between myo-inositol and metformin in the treatment of insulin-resistant women	Nas 2017	European Review for Medical & Pharmacological Sciences	21	77-82	Wrong intervention
78	Gestational weight gain, appetite regulating hormones, and metformin treatment in polycystic ovary syndrome: A longitudinal, placebo-controlled study	Molin 2022	BJOG: An International Journal of Obstetrics and Gynaecology	129(7)	1112-1121	Wrong outcome
79	Letrozole-human menopausal gonadotrophin for intracytoplasmic sperm injection in polycystic ovarian syndrome	Y 2017	Bjog	124		Conference abstract
80	Traditional clomiphene citrate with phytoestrogen vs traditional clomiphene citrate vs stair step protocol in patients with polycystic ovaries: a randomized controlled study					trial register/protocol
81	A randomized controlled study of PPOS protocol in IVF / ICSI treatment of polycystic ovary syndrome					trial register/protocol
82	Metformin Improves the fecundity of PCOS Infertile Patients with Insulin Resistance in IVF-ET: A Randomized Controlled Trial					trial register/protocol
83	The clinical pregant outcome of different doses of Letrozole used for endometrium preparation in non-PCOS women: a randomized controlled trial					trial register/protocol
84	LH based flexible GnRH antagonist protocol in PCOS patient undergoing in vitro fertilization and embryo transfer: a randomized controlled trial					trial register/protocol
85	IVF Outcome Following Progestogen Ovarian Stimulation					trial register/protocol
86	Clomiphene Citrate Stair-Step Protocol					trial register/protocol
87	Tamoxifen versus clomiphene citrate for ovulation induction in women with polycystic ovary syndrome: A prospective randomized trial	Topcu 2017	Journal of Reproductive Medicine	62(5)	507-512	Wrong comparator
88	Short-term intervention with liraglutide and metformin increased fertility potential in a subset of obese PCOS proceeding in vitro sterilisation	Janez 2017	Diabetes	66(Supplement 1)	A561	Wrong intervention
89	GLP-1 receptor agonist liraglutide increased IVF pregnancy rates in obese women with PCOS and previous poor response to first-line reproductive treatments	A 2018	Diabetes	67	A392-A393	Wrong intervention
90	A randomized, controlled clinical study of low molecular weight heparin improving pregnancy outcomes in patients with polycystic ovary syndrome					Wrong intervention
91	Growth hormone alleviates oxidative stress and improves oocyte quality in Chinese women with polycystic ovary syndrome: a randomized controlled trial	Gong 2020	Scientific reports	10(1)	18769	Wrong intervention
92	Phase III trial comparing the efficacy and safety of recombinant- or urine-derived human chorionic gonadotropin for ovulation triggering in Japanese	H 2017		16		Wrong patient population

	women diagnosed with anovulation or oligo-ovulation and undergoing ovulation induction with follitropin-alfa					
93	Effect of acupuncture and clomiphene in Chinese women with polycystic ovary syndrome: A randomized clinical trial	Wu 2017	JAMA - Journal of the American Medical Association	317(24)	2502-2514	Wrong intervention
94	Clinical efficacy of metformin combined with clomiphene in patients with polycystic ovary syndrome and their effect on serum sex hormones	Xiong 2018	International Journal of Clinical and Experimental Medicine	11(11)	12467-12473	Wrong patient population
95	Transfer of Fresh versus Frozen Embryos in Ovulatory Women	Y 2018	New England journal of medicine	Vol.378	126-136p	Wrong intervention
96	Predictive values of endometrial thickness for fecundity in women with polycystic ovary syndrome after ovulation induction	Y 2017	Journal of Obstetrics and Gynaecology Research	43	2017-06	Conference abstract
97	The use of metformin for ovulation induction in women with polycystic ovary syndrome	Sharpe 2020	BJOG: An International Journal of Obstetrics and Gynaecology	127(8)	e66-e67	Conference abstract
98	Obstetric complications after frozen versus fresh embryo transfer in women with polycystic ovary syndrome: results from a randomized trial	Zhang 2018	Fertility & Sterility	109	324-329	Wrong intervention
99	Pregnancy Outcome Difference between Fresh and Frozen Embryos in Women without Polycystic Ovary Syndrome: a Systematic Review and Meta-Analysis	Jin 2021	Reproductive Sciences	28(5)	1267-1276	Wrong comparator
100	Systematic review update and meta-analysis of randomized and non-randomized controlled trials of ovarian stimulation versus artificial cycle for endometrial preparation prior to frozen embryo transfer in women with polycystic ovary syndrome	Zhang 2022	Reproductive Biology and Endocrinology	20(1) (no pagination)		Wrong intervention
101	Effectiveness and safety of aspirin combined with letrozole in the treatment of polycystic ovary syndrome: a systematic review and meta-analysis	Yu 2021	Annals of palliative medicine	10(4)	4632-4641	Wrong comparator
102	Live birth after a freeze-only strategy versus fresh embryo transfer in three randomized trials considering progesterone concentration	Yu 2020	Reproductive BioMedicine Online	41(3)	395-401	Wrong comparator
103	Treatment strategies for women with WHO group II anovulation: systematic review and network meta-analysis	Wang 2017	BMJ	356	j138	Wrong patient population
104	Treatment strategies for women with WHO group II anovulation: Systematic review and network meta-analysis	Wang 2017	BMJ (Online)	356 (no pagination)		Wrong patient population
105	The effect of supraphysiological estradiol on pregnancy outcomes differs between women with PCOS and ovulatory women	Wei 2018	Journal of Clinical Endocrinology and Metabolism	103(7)	2735-2742	Wrong comparator
106	Effect of Preconception Impaired Glucose Tolerance on Pregnancy Outcomes in Women With Polycystic Ovary Syndrome	Wei 2017	Journal of Clinical Endocrinology & Metabolism		N.PAG-N.PAG	Wrong outcome
107	Comparison of Effect of Metformin Versus Combination of Folic Acid/Myo-inositol in Infertile Women with Poly Cystic Ovary Syndrome Undergoing in Vitro Fertilization: A Randomized Clinical Trial	F 2021	Biomedical Research and Therapy	Vol.8	4734-4739p	Wrong comparator
108	Therapeutic effects of metformin and clomiphene in combination with lifestyle intervention on infertility in women with obese polycystic ovary syndrome	Zhang 2017	Pakistan Journal of Medical Sciences	33(1)	8-12	Wrong patient population

109	The effects of di(2-ethylhexyl) phthalate exposure in women with polycystic ovary syndrome undergoing in vitro fertilization	Jin 2019	Journal of International Medical Research	47	6278-6293	Wrong intervention
110	Liraglutide increases IVF pregnancy rates in obese PCOS women with poor response to first-line reproductive treatments: a pilot randomized study	Salamun 2018	European Journal of Endocrinology	179(1)	1-11	Wrong intervention
111	Combination of alpha lipoic acid and metformin supplement improve assisted reproductive technologies outcomes in polycystic ovary syndrome patients	Jannatifar 2022	Anat Cell Biol	55	239-246	Wrong comparator
112	Inositol supplementation in women with polycystic ovary syndrome undergoing intracytoplasmic sperm injection: a systematic review and meta-analysis of randomized controlled trials	Mendoza 2017	Reprod Biomed Online	35	529-535	Wrong intervention
113	In vitro fertilization outcomes in women with polycystic ovary syndrome: A meta-analysis	Tang 2021	Eur J Obstet Gynecol Reprod Biol	259	146-152	Wrong patient population
114	Myoinositol versus metformin pretreatment in GnRH-antagonist cycle for women with PCOS undergoing IVF: a double-blinded randomized controlled study	K 2022	Gynecological endocrinology	Vol.38	140-147p	Wrong comparator
115	Repeat dose of gonadotropin-releasing hormone agonist trigger in polycystic ovarian syndrome undergoing in Vitro fertilization cycles provides a better cycle outcome - A proof-of-concept study	Deepika 2017	Journal of Human Reproductive Sciences	10(4)	271-280	Wrong comparator
116	Sitagliptin/metformin improves the fertilization rate and embryo quality in polycystic ovary syndrome patients through increasing the expression of GDF9 and BMP15: a new alternative to metformin (a randomized trial)	D 2022	Journal of reproductive immunology	150		Wrong comparator
117	Comparison of laparoscopic ovarian drilling success between two standard and dose-adjusted methods in polycystic ovary syndrome: A randomized clinical trial	Hafizi 2020	International Journal of Fertility and Sterility	13(4)	282-288	Wrong comparator
118	N-Acetylcysteine as an adjuvant to letrozole for induction of ovulation in infertile patients with polycystic ovary syndrome	F 2018	Advanced Biomedical Research	Vol.7	100p	Wrong comparator
119	Therapeutic effects of metformin and clomiphene in combination with lifestyle intervention on infertility in women with obese polycystic ovary syndrome	J 2017	Pakistan Journal of Medical Sciences	Vol.33	8-12p	Wrong patient population
120	Endometrial and follicular development following stair-step and traditional protocols in women with polycystic ovary syndrome: An rct	Shahgheibi 2021	International Journal of Reproductive BioMedicine	19(6)	537-544	Wrong patient population
121	Systematic review of black cohosh (cimicifuga racemosa) for management of polycystic ovary syndrome-related infertility	Fan 2020	JACCP Journal of the American College of Clinical Pharmacy	3(8)	1688-1689	Wrong intervention
122	[Efficacy of acupuncture as adjunctive treatment on infertility patients with polycystic ovary syndrome]	Xu 2018	Zhongguo Zhen Jiu	38	358-61	Wrong intervention
123	[Bushen Huoxue herbal medicine in subfertile women with polycystic ovary syndrome: a Meta-analysis]	Yuan 2019	Zhongguo Zhong Yao Za Zhi/Zhongguo Zhongyao Zazhi/China Journal of Chinese Materia Medica	44	1080-1086	Wrong intervention
124	Systematic Review of Black Cohosh (Cimicifuga racemosa) for Management of Polycystic Ovary Syndrome-Related Infertility	Fan 2021	J Pharm Pract		89719002 11012244	Wrong intervention

125	Vitamin D improves in-vitro fertilization outcomes in infertile women with polycystic ovary syndrome and insulin resistance	Zhao 2019	Minerva Medica	110	199-208	Wrong intervention
126	A randomized trial of endometrial scratching in women with PCOS undergoing ovulation induction cycles	Ej 2022	Reproductive biomedicine online	Vol.44	316-323p	Wrong intervention
127	Effect of amlodipine on blood flow of preovulatory follicle in women with clomiphene resistant polycystic ovaries: a randomized controlled trial	Ha 2020	Archives of Gynecology and Obstetrics	Vol.301	845-850p	Retracted
128	Effect of low-dose aspirin on the development of ovarian hyperstimulation syndrome and outcomes of assisted reproductive techniques in the women with PCOS, a randomized double-blinded clinical trial	B 2019	Taiwanese journal of obstetrics & gynecology	Vol.58	255-260p	Wrong intervention
129	Role of vitamin E and D₃ supplementation in Intra-Cytoplasmic Sperm Injection outcomes of women with polycystic ovarian syndrome: A double blinded randomized placebo-controlled trial	Fatemi 2017	Clinical Nutrition ESPEN	18	23-30	Wrong intervention
130	Myo-inositol administration positively effects ovulation induction and intrauterine insemination in patients with polycystic ovary syndrome: a prospective, controlled, randomized trial	Emek 2017	Gynecological endocrinology	Vol.33	524-528p	Wrong intervention
131	Influence of metabolic syndrome on female fertility and in vitro fertilization outcomes in PCOS women	He 2019	American Journal of Obstetrics and Gynecology	221(2)	138.e1-138.e12	Wrong intervention
132	l-Carnitine plus metformin in clomiphene-resistant obese PCOS women, reproductive and metabolic effects: a randomized clinical trial	ElSharkwy 2019	Gynecol Endocrinol	35	701-705	Wrong intervention
133	To compare the effect of metformin plus myoinositol vs metformin alone in terms of clinical pregnancy rate in infertile PCOS women	R 2018	Human reproduction. Conference: 34th annual meeting of the european society of human reproduction and embryology. ESHRE. Barcelona, spain	33	i433-i434	Wrong comparator
134	Unilateral Versus Bilateral Laparoscopic Ovarian Drilling Using Thermal Dose Adjusted According to Ovarian Volume in CC-Resistant PCOS, A Randomized Study	El-Sayed 2017	Journal of Obstetrics and Gynecology of India	67(5)	356-362	Wrong patient population
135	Emulating a target trial of the comparative effectiveness of clomiphene citrate and letrozole for ovulation induction	Yland 2022	Human Reproduction	37(4)	793-805	Wrong patient population
136	Clomiphene citrate versus letrozole with gonadotropins in intrauterine insemination cycles: A prospective randomized trial	Pourali 2017	International Journal of Reproductive BioMedicine	15(1)	49-54	Wrong patient population
137	A Randomized Controlled Trial of Combination of Letrozole and Clomiphene Citrate Versus Letrozole Alone for Ovulation Induction In women with Polycystic Ovary Syndrome	Mejia 2018	Fertility and Sterility	110(4 SUPPL)	e29-e30	Wrong patient population
138	A randomized controlled trial of combination letrozole and clomiphene citrate or letrozole alone for ovulation induction in women with polycystic ovary syndrome	Mejia 2019	Fertility and Sterility	111(3)	571-578.e1	Wrong patient population
139	Efficacy of letrozole versus clomiphene citrate on ovulation induction in patients with polycystic ovarian syndrome	M 2022	Pakistan Journal of Medical Sciences	Vol.38	1155-1158p	Wrong patient population

140	Ovulation induction and intrauterine insemination in infertile women with polycystic ovary syndrome: A comparison of drugs	Huang 2018	Eur J Obstet Gynecol Reprod Biol	231	117-121	Wrong study design
141	Tamoxifen versus clomiphene citrate for ovulation induction in women with polycystic ovary syndrome: a prospective randomized trial	Ho 2017	Journal of Reproductive Medicine	Vol.62	507-512p	Wrong comparator
142	Medical and surgical treatment of reproductive outcomes in polycystic ovary syndrome: An overview of systematic reviews	Gadalla 2020	International Journal of Fertility and Sterility	13(4)	257-270	Wrong study design
143	Effect of clomiphene citrate on endometrial thickness, ovulation, pregnancy and live birth in anovulatory women: systematic review and meta-analysis	Gadalla 2018	Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology	51(1)	64-76	Wrong patient population
144	Gonadotrophins or clomiphene citrate in women with normogonadotropic anovulation and CC failure: does the endometrium matter?	Em 2020	Human reproduction (Oxford, England)	Vol.35	1319-1324p	Wrong patient population
145	Long-term use of clomiphene citrate in induction of ovulation in PCO patients with clomiphene citrate resistance	Elkhateeb 2017	J Gynecol Obstet Hum Reprod	46	575-577	Wrong study design
146	A brief update on the evidence supporting the treatment of infertility in polycystic ovary syndrome	Costello 2019	Australian & New Zealand Journal of Obstetrics & Gynaecology	59	867-873	Wrong study design
147	[Effect of clomiphene citrate and Dingkun Dan on ovulation induction and clinical pregnancy of polycystic ovary syndrome]	Chen 2017	Zhongguo Zhong Yao Za Zhi	42	4035-4039	Wrong intervention
148	Comparison of tamoxifen and clomiphene citrate for ovulation induction: a meta-analysis (Structured abstract)	Centre for Reviews and Dissemination 2015	Database of Abstracts of Reviews of Effects			Wrong patient population
149	Systematic review of the treatment of ovulatory infertility with clomiphene citrate and intrauterine insemination (Structured abstract)	Centre for Reviews and Dissemination 2015	Database of Abstracts of Reviews of Effects			Wrong patient population
150	Comparison of the effects of bilateral and unilateral laparoscopic ovarian drilling on pregnancy rates in infertile patients with polycystic ovary syndrome	Turgut 2021	J Obstet Gynaecol Res	47	778-784	Wrong study design
151	Comparing the effect of sitagliptin and metformin on the oocyte and embryo quality in classic PCOS patients undergoing ICSI	Daneshjou 2021	Irish Journal of Medical Science	190(2)	685-692	Wrong comparator
152	Comparison of ovulation induction with letrozole plus dexamethasone and letrozole alone in infertile women with polycystic ovarian disease: an RCT	F 2020	International Journal of Reproductive BioMedicine	Vol.18	307-310p	Wrong comparator
153	Randomized controlled trial of N-acetylcysteine versus l-carnitine among women with clomiphene-citrate-resistant polycystic ovary syndrome	ElSharkwy 2019	International Journal of Gynecology and Obstetrics	147(1)	59-64	Wrong intervention
154	l-Carnitine plus metformin in clomiphene-resistant obese PCOS women, reproductive and metabolic effects: a randomized clinical trial	ElSharkwy 2019	Gynecological Endocrinology	35(8)	701-705	Wrong comparator

155	Mini review: The FDA-approved prescription drugs that induce ovulation in women with ovulatory problems	Sun 2020	Drug Development Research	81(7)	815-822	Wrong study design
156	The effect of inofolic supplementation on women with polycystic ovarian syndrome (Pcos): A randomized clinical trial study	Soufizadeh 2021	Italian Journal of Gynaecology and Obstetrics	33(4)	256-262	Wrong intervention
157	Treatment update for anovulation and subfertility in polycystic ovary syndrome	Mascarenhas 2020	Current Opinion in Endocrine and Metabolic Research	12	53-58	Wrong study design
158	The efficacy of vitamin D combined with clomiphene citrate in ovulation induction in overweight women with polycystic ovary syndrome: a double blind, randomized clinical trial	Rasheedy 2020	Endocrine	69(2)	393-401	Wrong comparator
159	Role of letrozole and metformin vs letrozole alone in ovulation induction in patients of polycystic ovarian syndrome	R 2019	Pakistan Journal of Medical and Health Sciences	Vol.13	350-352p	Wrong patient population
160	Innovations in infertility: a comprehensive analysis of the ClinicalTrials.gov database	Peipert 2021	Fertility and Sterility	116(5)	1381-1390	Wrong outcome
161	Comparative study between clomiphine citrate and letrozole for ovulation induction in women with polycystic ovarian syndrome	Hd 2020	Annals of Tropical Medicine and Public Health	23		Wrong patient population
162	Prediction of responsiveness to clomiphene citrate in infertile women with PCOS	Sachdeva 2019	Journal of Reproduction and Infertility	20(3)	143-150	Wrong study design
163	The Effects of Letrozole and Metformin Combined with Targeted Nursing Care on Ovarian Function, LH, and FSH in Infertile Patients with Polycystic Ovary Syndrome	Jiang 2022	Journal of Healthcare Engineering	2022	4E+06	Wrong patient population
164	Fixed versus flexible antagonist protocol in women with predicted high ovarian response except PCOS: a randomized controlled trial	X 2021	BMC Pregnancy and Childbirth	Vol.21	348p	Wrong patient population
165	Sildenafil citrate as an adjuvant to clomiphene citrate for ovulation induction in polycystic ovary syndrome: crossover randomized controlled trial	Mohammed 2022	Przeglad Menopauzalny	21(1)	20-26	Wrong intervention
166	Sildenafil citrate as an adjuvant to clomiphene citrate for ovulation induction in polycystic ovary syndrome: crossover randomized controlled trial	We 2022	Przeglad Menopauzalny	Vol.21	20-26p	Wrong intervention
167	Effect of bushen yangluan decoction combined with clomiphene citrate on ovulation and ovarian function in patients with infertility due to polycystic ovary syndrome	Zhang 2021	International Journal of Clinical and Experimental Medicine	14(2)	1095-1102	Wrong intervention
168	Ovarian stimulation with gonadotrophins in patients with polycystic ovary syndrome	Isnard 2019	Gynecologie Obstetrique Fertilite et Senologie	47(1)	44-53	Non English
169	The effect of clomiphene citrate versus letrozole on pregnancy rate in women with polycystic ovary syndrome: A randomized clinical trial	Behnoud 2019	Crescent Journal of Medical and Biological Sciences	6(3)	335-340	Wrong patient population
170	Comparison of clomiphene citrate plus n-Acetyl cysteine and clomiphene citrate alone for induction of ovulation in polycystic ovary syndrome	Waseem 2021	Pakistan Journal of Medical and Health Sciences	15(6)	1253-1255	Wrong comparator
171	Effectiveness of acupuncture in polycystic ovary syndrome: A systematic review and meta-analysis of randomized controlled trials	Jielei 2020	Medicine	99	1-10	Wrong intervention
172	The effect of modified erchen decoction on reproductive endocrine functions and glucose metabolism in patients with phlegm-dampness polycystic ovary syndrome complicated with insulin resistance	Gong 2020	International Journal of Clinical and Experimental Medicine	Vol.13	5932-5940p	Wrong intervention

173	Letrozole versus Clomiphene Citrate for induction of ovulation in PCOS Infertile patients for IUI : a comparative study	Jindal 2019	Human Reproduction	34(SUPPL 1)	i463-i464	Conference abstract
174	Effect of metformin and exenatide on pregnancy rate and pregnancy outcomes in overweight or obese infertility PCOS women: long-term follow-up of an RCT	Li 2022	Archives of Gynecology & Obstetrics	13	13	Wrong comparator
175	Unilateral ovarian diathermy is effective and longlasting in restoring spontaneous ovulation	E 2004	The 20th Annual Meeting of the European Society of Human Reproduction and Embryology. i64p.			Conference abstract
176	Comparison of the efficacy of letrozole stair-step protocol with clomiphene citrate stair-step protocol in the management of clomiphene citrate-resistant polycystic ovary syndrome patients	Sakar 2021	J Obstet Gynaecol Res	47	3875-3882	Wrong study design
177	Clomiphene citrate vs latrozole in PCO's patient's for ovulation induction	Ashfaq 2018	Pakistan Journal of Medical and Health Sciences	12(2)	781-783	Wrong patient population
178	Liraglutide increases IVF pregnancy rates in obese PCOS women with poor response to first-line reproductive treatments: a pilot randomized study	V 2018	European journal of endocrinology	Vol.179	1-11p	Wrong intervention
179	Efficacy of exenatide on weight loss, metabolic parameters and pregnancy in overweight/obese polycystic ovary syndrome	X 2017	Clinical endocrinology	Vol.87	767-774p	Wrong comparator
180	The effect of vitamin D and Co-enzyme Q10 replacement therapy on hormonal profile and ovulation statusin women with clomiphene citrate resistant polycystic ovary syndrome	Abdulameeryahya 2019	Journal of Pharmaceutical Sciences and Research	11(1)	208-215	Wrong comparator
181	Metabolic syndrome in obesity: treatment success and adverse pregnancy outcomes with ovulation induction in polycystic ovary syndrome	Arya 2021	American Journal of Obstetrics and Gynecology	225(3)	280.e1-280.e11	Wrong intervention
182	Combination of pioglitazone and clomiphene citrate versus clomiphene citrate alone for infertile women with the polycystic ovarian syndrome	Amirian 2021	BMC Women's Health	21(1) (no pagination)		Wrong intervention
183	Sildenafil citrate as an adjuvant to clomiphene citrate for ovulation induction in polycystic ovary syndrome: crossover randomized controlled trial	Mohammed 2022	Prz Menopauzalny	21	20-26	Wrong patient population
184	Clomiphene citrate plus cabergoline versus clomiphene citrate for induction of ovulation in infertile euprolactinemic patients with polycystic ovary syndrome: a randomized clinical trial	Km 2018	Middle East Fertility Society Journal			Wrong intervention
185	The bottom line of fresh versus frozen ART cycles in PCOS patients: Cost analysis of an RCT	Zolton 2017	Reproductive Sciences	24(1 Supplement 1)	296A	Conference abstract
186	Baseline AMH is associated with ovulation induction dose and ovulatory response and predicts ovulation rate in women with Polycystic Ovary Syndrome	Wu 2017	Human Reproduction	32(Supplement 1)	i473-i474	Conference abstract
187	Anovulatory women not conceiving after six ovulatory cycles with clomiphene citrate-should we switch to gonadotrophins and/or add IUI? A 2 by2 factorial RCT	Weiss 2017	Human Reproduction	32(Supplement 1)	i6	Conference abstract
188	Characteristics and obstetrics outcomes of different traditional Chinese medicine syndromes in women with polycystic ovary syndrome: A secondary analysis	Wang 2017	Journal of Obstetrics and Gynaecology Research	43(Supplement 1)	155	Conference abstract

189	Predictive values of endometrial thickness for fecundity in women with polycystic ovary syndrome after ovulation induction	Wang 2017	Journal of Obstetrics and Gynaecology Research	43(Supplement 1)	157	Conference abstract
190	Co-enzyme Q10-A mitochondrial antioxidant -a new hope for success in infertility in clomiphene-citrate-resistant polycystic ovary syndrome	SenSharma 2017	BJOG: An International Journal of Obstetrics and Gynaecology	124(Supplement 1)	9	Conference abstract
191	Comparison between adjuvant 1500I.U. hCG + GnRH agonist on trigger day or 1500 I.U. hCG 35-36h later, in OHSS high-risk patient with peak E2 level<4000pg/mL	PetanovskaKostova 2019	Human Reproduction	34(SUPPL 1)	i439-i440	Conference abstract
192	Short term effects of metformin, myo-inositol or combination on metabolic and endocrine profile of infertile women with polycystic ovarian syndrome (PCOS)	N 2019	Human reproduction (Oxford, England)	Vol.34	i421-i422p	Conference abstract
193	Correction of vitamin D deficiency on ovulation induction in women with PCOS	Mohamed 2021	BJOG: An International Journal of Obstetrics and Gynaecology	128(SUPP L 2)	236-237	Conference abstract
194	Metformin and pioglitazone comparison for ovulation induction in PCOS	Mahmood 2021	BJOG: An International Journal of Obstetrics and Gynaecology	128(SUPP L 2)	230	Conference abstract
195	To compare the effect of metformin plus myoinositol vs metformin alone in terms of clinical pregnancy rate in infertile PCOS women	Mahey 2018	Human Reproduction	33(Supplement 1)	i433	Conference abstract
196	Pregnancy outcome and cost-effectiveness comparisons of artificial cycle-prepared frozen embryo transfer with or without GnRH agonist pretreatment for polycystic ovary syndrome: a randomized controlled trial	Luo 2020	Human Reproduction	35(SUPPL 1)	i73-i74	Conference abstract
197	Induction of ovulation by low-dose gonadotropins is safe and effective treatment for both polycystic ovary syndrome (PCOS) and hypogonadotropic hypogonadism (HH): Results from 446 cases treated at a single centre	Lovelock 2017	Endocrine Reviews. Conference: 99th Annual Meeting of the Endocrine Society, ENDO	38		Conference abstract
198	Effect of N-acetylcysteine as an adjuvant to clomiphene citrate for induction of ovulation in patients with polycystic ovary syndrome	Hefny 2018	BJOG: An International Journal of Obstetrics and Gynaecology	125(Supplement 1)	38-39	Conference abstract
199	Genetic associations with outcomes after letrozole or clomiphene citrate treatment in women of european ancestry with pcos	Hayes 2017	Endocrine Reviews. Conference: 99th Annual Meeting of the Endocrine Society, ENDO	38		Conference abstract
200	Comparison of letrozole versus clomiphene citrate (CC) for ovulation induction in infertile women with polycystic ovary syndrome (PCOS) in Indian population: A prospective clinical trial	Gupta 2020	Human Reproduction	35(SUPPL 1)	i413	Conference abstract
201	Effect of Myo-Inositol and Alpha-Lipoic Acid on oocyte morphology and embryo morphokinetics: a prospective preliminary analysis of 40 overweight patients undergoing ICSI treatment	Gennarelli 2020	Human Reproduction	35(SUPPL 1)	i256	Conference abstract
202	Baseline characteristics and obstetric outcomes in polycystic ovary syndrome women with or without hyperandrogenemia	Gao 2017	Journal of Obstetrics and Gynaecology Research	43(Supplement 1)	155-156	Conference abstract
203	Predictive model of semen analysis for conception and live birth among WHO type II anovulatory women treated with ovulation induction	Gao 2017	Journal of Obstetrics and Gynaecology Research	43(Supplement 1)	145	Conference abstract

204	Efficacy of Interventions to Reduce Risk of Ovarian Hyperstimulation Syndrome	Gadson 2018	Fertility and Sterility	110(4 SUPPL)	e332	Conference abstract
205	Aromatase inhibitors (letrozole) for subfertile women with polycystic ovary syndrome-A Cochrane Systematic Review	Franik 2018	Human Reproduction	33(Supplement 1)	i131	Conference abstract
206	Letrozole-human menopausal gonadotrophin for intracytoplasmic sperm injection in polycystic ovarian syndrome	ElKassar 2017	BJOG: An International Journal of Obstetrics and Gynaecology	124(Supplement 1)	65	Conference abstract
207	Therapeutic Effect of Vitamin D3 Supplementation to Clomiphene Citrate Resistant PCOS Women: a Randomized Controlled Trial	El-DinHashaad 2020	QJM : monthly journal of the Association of Physicians	114	2020-11	Conference abstract
208	Prediction models for ovulation, conception, pregnancy and live birth in infertile women with polycystic ovary syndrome	Deng 2017	Human Reproduction	32(Supplement 1)	i454-i455	Conference abstract
209	66 the Impact of Bariatric Surgery Compared to Metformin Therapy on Pregnancy Outcomes in Patients with Polycystic Ovarian Syndrome	Chang 2020	Gastroenterology	158(6 Supplement 1)	S-1483	Conference abstract
210	Clomiphene citrate or gonadotrophins in women with WHO type II anovulation and CC failure; A role for EMT?	Bordewijk 2018	Human Reproduction	33(Supplement 1)	i130	Conference abstract
211	Laparoscopic ovarian drilling for ovulation induction in women with anovulatory polycystic ovary syndrome - a cochrane review	Bordewijk 2020	Human Reproduction	35(SUPPL 1)	i477-i478	Conference abstract
212	The selection of ovulation induction protocols in patients with PCO syndrome undergoing IVF procedures	Bila 2020	Human Reproduction	35(SUPPL 1)	i446-i447	Conference abstract
213	Association between letrozole dose and pregnancy rate in clomiphene-resistant women with polycystic ovary syndrome randomized controlled trial	As 2020	QJM : monthly journal of the Association of Physicians	Vol.113	i169-p	Conference abstract
214	Metabolic Syndrome (Mets): Fecundability and Adverse Pregnancy Outcomes with Ovulation Induction (Oi) in Polycystic Ovary Syndrome (Pcos)	Arya 2019	Fertility and Sterility	112(3 SUPPL)	e44-e45	Conference abstract
215	Sildenafil Citrate adjuvant Ovulation Induction Therapy with Clomiphen Citrate in Polycystic Ovarian Syndrome for Successful Ovulation; Cross-Over, Randomized Controlled Trial	Abbas 2021	QJM. Conference: 41st Annual International Ain Shams Medical Congress. Online.	114		Conference abstract
216	Randomized controlled open-label study of the effect of vitamin E supplementation on fertility in clomiphene citrate-resistant polycystic ovary syndrome	Aa 2020	Journal of Obstetrics and Gynaecology Research	Vol.46	2375-2382p	Wrong intervention
217	Comparison of letrozole versus clomiphene citrate on ovulation and achieving a successful pregnancy	A 2017	Pakistan Journal of Medical and Health Sciences	Vol.11	1143-1145p	Wrong patient population
218	Gonadotropin endocytosis as a biomarker of optimal FSH dosage-a randomised clinical trial	A 2017	Human reproduction	32		Conference abstract
219	The effect of letrozole versus artificial hormonal endometrial preparation on pregnancy outcome after frozen-thawed embryos transfer cycles: a randomized clinical trial	A 2020	Reproductive biology and endocrinology : RB&E	Vol.18	115p	Wrong patient population
220	Comparing a biosimilar follitropin alfa (Cinnal-f) with Gonal-f in women undergoing ovarian stimulation: An RCT	Rashidi 2021	International Journal of Reproductive BioMedicine	19(11)	1015-1024	Wrong intervention
221	Progestin-primed milder stimulation with clomiphene citrate yields fewer oocytes and suboptimal pregnancy outcomes compared with the standard progestin-primed ovarian stimulation	Ye 2018	Reprod Biol Endocrinol	16	53	Wrong study design

	in infertile women with polycystic ovarian syndrome					
222	Comparing the effect of clomiphene citrate and letrozole on ovulation induction in infertile women with polycystic ovary syndrome	Najafi 2020	JPMA - Journal of the Pakistan Medical Association	70	268-271	Wrong patient population
223	Does the repeat dose of gonadotropin-releasing hormone agonist trigger in polycystic ovarian syndrome improve in vitro fertilization cycles outcome? A clinical trial study	Aflatoonian 2020	International Journal of Reproductive BioMedicine	18	485-490	Wrong intervention
224	Erratum: editor's Note: abu Hashim, H., El Lakany, N. and Sherief, L. (2011), Combined metformin and clomiphene citrate versus laparoscopic ovarian diathermy for ovulation induction in clomiphene-resistant women with polycystic ovary syndrome: a randomized controlled trial. Journal of Obstetrics and Gynaecology Research, 37: 169-177. https: //doi.org/10.1111/j.1447-0756.2010.01383.x		Journal of Obstetrics and Gynaecology Research	Vol.47	2935p	Wrong study design
225	Clinical efficacy and safety of the Jinfeng pill in the adjuvant treatment of infertility in patients with polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trial	Xu 2022	Annals of Palliative Medicine	11	352-362	Wrong intervention
226	Effectiveness and safety of aspirin combined with letrozole in the treatment of polycystic ovary syndrome: a systematic review and meta-analysis	Yu 2021	Ann Palliat Med	10	4632-4641	Wrong intervention
227	Effects of Acupuncture Combined with Moxibustion on Reproductive and Metabolic Outcomes in Patients with Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis	Li 2022	Evid Based Complement Alternat Med	2022	4E+06	Wrong intervention
228	Metformin - a new approach	Cwynar-Zając 2021	Pediatr Endocrinol Diabetes Metab	27	134-140	Wrong study design
229	Comparison of efficacy of clomiphene citrate alone and with metformin for treatment of infertility in polycystic ovarian syndrome	A 2018	Rawal Medical Journal	Vol.43	285-288p	Wrong patient population
230	Letrozole is superior to clomiphene citrate in ovulation induction in patients with polycystic ovary syndrome	Sakar 2020	Pak J Med Sci	36	1460-1465	Wrong study design
231	A Predictive Model of Live Birth Based on Obesity and Metabolic Parameters in Patients With PCOS Undergoing Frozen-Thawed Embryo Transfer	Jiang 2021	Front Endocrinol (Lausanne)	12	799871	Exclusion reason: Wrong outcomes;
232	Chromium supplementation in women with polycystic ovary syndrome: Systematic review and meta-analysis	Tang 2018	Journal of Obstetrics & Gynaecology Research	44	134-143	Wrong intervention
233	Unilateral laparoscopic ovarian diathermy in infertile women with clomiphene citrate-resistant polycystic ovary syndrome	E 2007	Fertility and Sterility	Vol.88	1678-1680p	Wrong patient population
234	Pregnancy outcomes in PCOS patients undergoing IVF with long GnRH agonist protocol versus flexible GnRH antagonist	Ghaebi 2018	Iranian journal of obstetrics, gynecology and infertility	Vol.21	1-9p	Exclusion reason: Non-English;
235	Clomiphene citrate vs latrozole in PCO's patient's for ovulation induction	A 2018	Pakistan Journal of Medical and Health Sciences	Vol.12	781-783p	trial register/protocol
236	Letrozole versus clomiphene citrate for ovulation induction in patients with anovulatory cycles	Pakhale 2021	BJOG: An International Journal of Obstetrics and Gynaecology	128(SUPPL 2)	237	trial register/protocol

237	Effect of clomiphene citrate on endometrial thickness, ovulation, pregnancy and live birth in anovulatory women: systematic review and meta-analysis	Gadalla 2018	Ultrasound Obstet Gynecol	51	64-76	Wrong patient population
238	Notification			47	2935-2935	Wrong study design
239	Erratum to: combined metformin and clomiphene citrate versus laparoscopic ovarian diathermy for ovulation induction in clomiphene-resistant women with polycystic ovary syndrome: a randomized controlled trial: metformin-CC vs diathermy in PCOS (Journal of Obstetrics and Gynaecology Research, (2011), 37, 3, (169-177), 10.1111/j.1447-0756.2010.01383.x)		Journal of Obstetrics and Gynaecology Research	Vol.47	2935-p	Wrong study design
240	Effectiveness of Laser Acupoints on Women With Polycystic Ovarian Syndrome: A Randomized Controlled Trial	El-Shamy 2018	Journal of Lasers in Medical Sciences	9	113-120	Wrong intervention
241	Weight reduction intervention for obese infertile women prior to IVF: a randomized controlled trial	Einarsson 2017	Hum Reprod	32	1621-1630	Wrong intervention
242	Unilateral Versus Bilateral Laparoscopic Ovarian Drilling Using Thermal Dose Adjusted According to Ovarian Volume in CC-Resistant PCOS, A Randomized Study	El-Sayed 2017	J Obstet Gynaecol India	67	356-362	Wrong patient population
243	Ovulation induction in polycystic ovary syndrome	Tanbo 2018	Acta Obstet Gynecol Scand	97	1162-1167	Wrong study design
244	Inositol for subfertile women with polycystic ovary syndrome	Showell 2018	Cochrane Database Syst Rev	12	Cd012378	Wrong intervention
245	Efficacy of clomifene citrate combined Bushen Culuan Decoction for the treatment of infertility caused by polycystic ovary syndrome: A protocol of systematic review	Feng 2020	Medicine	99	e20969	Wrong comparator
246	The effect of myo-inositol/di-chiro-inositol on markers of ovarian reserve in women with PCOS undergoing IVF/ICSI: A systematic review and meta-analysis	Bhide 2019	Acta Obstetricia et Gynecologica Scandinavica	98	1235-1244	Wrong intervention
247	The use of metformin in women with polycystic ovary syndrome: an updated review	Notaro 2022	Journal of Assisted Reproduction and Genetics	39(3)	573-579	Conference abstract
248	Impact of myoinositol with metformin and myoinositol alone in infertile PCOS women undergoing ovulation induction cycles - randomized controlled trial	P 2021	Gynecological endocrinology	Vol.37	332-336p	Wrong intervention
249	A new look at low-dose aspirin: Co-administration with tamoxifen in ovulation induction in anovulatory PCOS women	Aref 2019	Journal of Gynecology Obstetrics and Human Reproduction	48(8)	673-675	Wrong intervention
250	Double-blind Randomized Controlled Trial of Letrozole Versus Clomiphenecitrate in Subfertile Women with Polycystic Ovarian Syndrome	Amer 2017	Obstetrical and Gynecological Survey	72(11)	657-658	Wrong study design
251	Pregnancy Outcomes within a Prospective Cohort of Women with Polycystic Ovary Syndrome (Pcos)	Ajjarapu 2019	Fertility and Sterility	112(3 SUPPL)	e393-e394	Conference abstract
252	The effect of vitamin D and Co-enzyme Q10 replacement therapy on hormonal profile and ovulation statusin women with clomiphene citrate resistant polycystic ovary syndrome	A 2019	Journal of Pharmaceutical Sciences and Research	Vol.11	208-215p	Wrong intervention
253	Comparison of metformin plus myoinositol vs metformin alone in PCOS women undergoing ovulation induction cycles: randomized controlled trial	Agrawal 2019	Gynecological Endocrinology	35(6)	511-514	Wrong comparator

254	Comparison between criteria and outcome of induction ovulation cycle with letrozole combined FSH and letrozole combined HMG in infertile polycystic ovarian syndrome patients	Afiat 2017	Journal of Reproduction and Infertility	18(2 Supplement 2)	169	Conference abstract
255	Impact of letrozole versus clomiphene citrate on endometrial receptivity in Iraqi women with polycystic ovarian syndrome	Al-Obaidi 2019	Journal of Clinical Pharmacy and Therapeutics	44(4)	618-622	Wrong patient population
256	Randomized controlled open-label study of the effect of vitamin E supplementation on fertility in clomiphene citrate-resistant polycystic ovary syndrome	Morsy 2020	Journal of Obstetrics and Gynaecology Research	46(11)	2375-2382	Wrong comparator
257	A Randomized Controlled Trial of Combination Letrozole and Clomiphene Citrate or Letrozole Alone for Ovulation Induction in Women with Polycystic Ovary Syndrome	Mejia 2019	Obstetrical and Gynecological Survey	74(6)	349-350	Wrong study design
258	A comparison of the effects of human chorionic gonadotropin and oxytocin on ovulation in PCOS patients from 2015 until 2018	Mj 2018	Acta Medica Mediterranea	Vol.34	1757-1763p	Wrong comparator
259	Methylprednisolone for prevention of ovarian hyperstimulation syndrome in patients with polycystic ovarian syndrome undergoing in-vitro fertilisation: a randomised controlled trial	L 2018	Journal of Obstetrics and Gynaecology	Vol.38	241-246p	Wrong comparator
260	Induction of ovulation with clomiphene citrate combined with bromocriptine in polycystic ovary syndrome patients with infertility: A prospective, randomized, and controlled clinical trial	Guan 2017	Reproductive and Developmental Medicine	1(4)	216-220	Wrong comparator
261	The Use of N-Acetyl Cysteine Versus Chromium Picolinate as an Adjuvant to Clomiphene Citrate and Metformin in PCOS Women to Improve Ovulation Induction and Insulin Resistance: A Pilot Randomized Controlled Trial	Alalfy 2022	Current Women's Health Reviews	18(2) (no pagination)		Wrong comparator
262	Effect of Clomiphene Citrate on Ovulation Induction and Hormones of Infertility with Inflammatory Effects on Gingiva	Arshad 2022	Pakistan Journal of Medical and Health Sciences	16(3)	847-849	Wrong patient population
263	Letrozole for patients with polycystic ovary syndrome: A retrospective study	Guang 2018	Medicine (Baltimore)	97	e13038	Wrong study design
264	HCG trigger versus GnRH agonist trigger in PCOS patients under-going IVF cycles: frozen embryo transfer outcomes	Deepika 2021	Jornal Brasileiro De Reproducao Assistida	25	48-58	Wrong study design
265	The effect of physical activity on reproductive health outcomes in young women: A systematic review and meta-analysis	Mena 2019	Human Reproduction Update	25(5)	542-564	Wrong intervention
266	The effect of physical activity on reproductive health outcomes in young women: a systematic review and meta-analysis	Mena 2019	Hum Reprod Update	25	541-563	Wrong intervention
267	Fertility and Pregnancy Outcomes in Women with Polycystic Ovary Syndrome Following Bariatric Surgery	Benito 2020	J Clin Endocrinol Metab	105		Wrong study design
268	Clomiphene citrate vs letrozole in the treatment of anovulatory infertility: a randomized controlled trial	Gihan 2019	Journal of Obstetrics and Gynaecology Research	Vol.46	52-p	Conference abstract
269	In-vitro maturation of oocytes versus conventional IVF in women with infertility and a high antral follicle count: A randomized non-inferiority controlled trial	Vuong 2020	Human Reproduction	35	2537-2547	Wrong patient population
270	Evaluation of pretreatment with Cetrotide in an antagonist protocol for patients with PCOS undergoing IVF/ICSI cycles: a randomized clinical trial	Eftekhar 2018	JBRA Assist Reprod	22	238-243	Wrong intervention

271	The freeze-all strategy versus agonist triggering with low-dose hCG for luteal phase support in IVF/ICSI for high responders: A randomized controlled trial	Santos-Ribeiro 2020	Human Reproduction	35	2808-2818	Wrong patient population
272	In vitro maturation (IVM) versus in vitro fertilization (IVF) in women with high antral follicle count (AFC): a randomized controlled trial (NCT03405701)	Vuong 2019	Fertility and Sterility	Vol.112	e435-e436p	Conference abstract
273	Gonadotrophins or clomiphene citrate in women with normogonadotropic anovulation and CC failure: does the endometrium matter?	Bordewijk 2020	Hum Reprod	35	1319-1324	Wrong patient population
274	Effect of non-pharmacological interventions for overweight/obese women with polycystic ovary syndrome on ovulation and pregnancy outcomes: a protocol for a systematic review and network meta-analysis	Yang 2022	BMJ Open	12	e059090	Wrong intervention
275	Effectiveness of spontaneous ovulation as monitored by urinary luteinising hormone versus induced ovulation by administration of human chorionic gonadotrophin in couples undergoing gonadotrophin-stimulated intrauterine insemination: a randomised controlled trial	Thomas 2019	BJOG: An International Journal of Obstetrics & Gynaecology	126 Suppl 4	58-65	Wrong patient population
276	Letrozole and Unexplained Infertility: A Contemporary Meta-analysis	Shao 2019	Journal of Obstetrics and Gynaecology Canada	41(6)	832-834	Wrong patient population
277	Efficacy and safety of moxibustion in the treatment of infertility with polycystic ovary syndrome: A protocol of systematic review and meta-analysis	Ye 2021	Medicine (Baltimore)	100	e24529	trial register/ protocol
278	Effectiveness and safety of in vitro maturation of oocytes versus in vitro fertilisation in women with high antral follicle count: Study protocol for a randomised controlled trial	Vuong 2018	BMJ Open	8(12) (no pagination)		trial register/ protocol
279	Editor's Note: Badawy A, State O and Abdelgawad S. N-Acetyl cysteine and clomiphene citrate for induction of ovulation in polycystic ovary syndrome: a cross-over trial. Acta Obstetricia et Gynecologica Scandinavica, 2007;86:218-222	Anonymous 2021	Acta Obstetricia et Gynecologica Scandinavica	100(11)	2126	Wrong study design
280	In vitro maturation of human oocytes: a systematic review and data analysis	Nikiforov 2021	Human Reproduction	36(SUPPL 1)	i243-i244	Conference abstract
281	Chinese herbal medicine for subfertile women with polycystic ovarian syndrome	Zhou 2021	Cochrane Database Syst Rev	6	Cd007535	Wrong comparator
282	Fresh versus freeze-all strategy in assisted reproductive technology - a cochrane review	Zaat 2019	Fertility and Sterility	112(3 Supplement)	e182	Conference abstract
283	A Review of First Line Infertility Treatments and Supporting Evidence in Women with Polycystic Ovary Syndrome	Costello 2019	Med Sci (Basel)	7		Wrong study design
284	Low-dose gonadotropin induction of ovulation in anovulatory women: still needed in the age of IVF	White 2018	Reproduction	156	F1-f10	Wrong study design
285	Effects of inositol and alpha lipoic acid combination for polycystic ovary syndrome: A protocol for systematic review and meta-analysis	Lei 2020	Medicine	99	e20696	trial register/protocol
286	The effects of Chinese herbal medicine on the pregnancy outcomes of infertile women with polycystic ovary syndrome undergoing in vitro fertilization-embryo transfer: A systematic review and meta-analysis	Liu 2021	Clinical and Experimental Obstetrics and Gynecology	48	1032-1043	Wrong comparator

287	Comparative Effectiveness of Three Ovarian Hyperstimulation Protocol in In Vitro Fertilization (IVF) Cycles for Women with Polycystic Ovary Syndrome	Chen 2018	Med Sci Monit	24	9424-9428	Wrong study design
288	In vitro maturation in subfertile women with polycystic ovarian syndrome undergoing assisted reproduction	Siristatidis 2018	Cochrane Database Syst Rev	11	Cd006606	Wrong intervention
289	Comparison of Tamoxifen and Clomiphene Citrate for Ovulation Induction in Women with Polycystic Ovarian Syndrome: A Prospective Study	Sharma 2021	J Reprod Infertil	22	274-281	Wrong study design
290	A prospective study comparing unilateral and bilateral laparoscopic ovarian diathermy in women with the polycystic ovary syndrome	Ah 1994	Fertility and Sterility	Vol.62	921-925p	Wrong patient population
291	Predictors of pregnancy after intrauterine insemination in women with polycystic ovary syndrome	Guan 2021	J Int Med Res	49	30006052 11018600	Wrong study design
292	The outcome of laparoscopic ovarian drilling in patients with clomiphene-resistant polycystic ovarian syndrome in ogbmoso, nigeria: A prospective evaluation	Fehintola 2020	World Journal of Laparoscopic Surgery	13(3)	101-107	Wrong study design
293	Association between letrozole dose and pregnancy rate in clomiphene-resistant women with polycystic ovary syndrome randomized controlled trial	Elhoussiny 2020	Qjm	113(SUPPL 1)	i169	Conference abstract
294	A modified GnRH antagonist method in combination with letrozole, cabergoline, and GnRH antagonist for PCOS: Safe and effective ovarian stimulation to treat PCOS and prevent OHSS	Yanagihara 2021	Reproductive Medicine and Biology.			Wrong study design
295	Erratum to: Combined metformin and clomiphene citrate versus laparoscopic ovarian diathermy for ovulation induction in clomiphene-resistant women with polycystic ovary syndrome: A randomized controlled trial: Metformin-CC vs diathermy in PCOS (Journal of Obstetrics and Gynaecology Research, (2011), 37, 3, (169-177), 10.1111/j.1447-0756.2010.01383.x)	Anonymous 2021	Journal of Obstetrics and Gynaecology Research	47(8)	2935	Wrong study design
296	Randomized controlled trial of astaxanthin impacts on antioxidant status and assisted reproductive technology outcomes in women with polycystic ovarian syndrome	Gharaei 2022	Journal of Assisted Reproduction and Genetics	39(4)	995-1008	Wrong intervention
297	Office hysteroscopy before first in vitro fertilization. A randomized controlled trial	H 2021	Journal of gynecology obstetrics and human reproduction	Vol.50	102109p	Wrong patient population
298	Induction of Ovulation Using Clomiphene Citrate Plus N-Acetyl Cysteine Versus Letrozole in Infertile Patients with Polycystic Ovarian Disease: A Randomized Clinical Trial	Farghaly 2018	Fertility and Sterility	110(4 SUPPL)	e102	Conference abstract
299	In vitro maturation versus in vitro fertilization in women with high antral follicle count: a cost-effectiveness analysis alongside a randomised clinical trial	H 2020	Human reproduction (Oxford, England)	Vol.35	i133-p	Conference abstract
300	Acupuncture and clomiphene citrate for anovulatory infertility: a systematic review and meta-analysis	Gao 2020	Acupuncture in medicine : journal of the British Medical Acupuncture Society	38(1)	25-36	Wrong patient population
301	Acupuncture for polycystic ovarian syndrome	Lim 2019	Cochrane Database of Systematic Reviews	2019(7) (no		Wrong comparator

				pagination)		
302	Myo-inositol supplementation reduces the amount of gonadotropins and length of ovarian stimulation in women undergoing IVF: a systematic review and meta-analysis of randomized controlled trials	Lagana 2018	Archives of Gynecology and Obstetrics	298(4)	675-684	Wrong patient population
303	A multicenter randomized trial of personalized acupuncture, fixed acupuncture, letrozole, and placebo letrozole on live birth in infertile women with polycystic ovary syndrome	Huang 2020	Trials	21(1) (no pagination)		Exclusion reason: trial register/protocol;
304	Therapeutic effects of dimethyldiguanide combined with clomifene citrate in the treatment of polycystic ovary syndrome	J 2019	Revista da Associacao Medica Brasileira (1992)	Vol.65	1144-1150p	Wrong patient population
305	Similar IVF birth rates for frozen and fresh embryos	Slomski 2018	JAMA - Journal of the American Medical Association	319(12)	1190	Wrong study design
306	Effect of pretreatment with combined oral contraceptives on outcomes of assisted reproductive technology for women with polycystic ovary syndrome: a meta-analysis	Song 2019	Archives of Gynecology and Obstetrics	300(3)	737-750	Wrong intervention
307	Comparative effectiveness of pioglitazone, raloxifene, and combined pioglitazone-raloxifene of ovulationinduction therapies in infertile patients with resistant polycystic ovary syndrome	Rh 2020	Systematic Reviews in Pharmacy	Vol.11	1876-1881p	Wrong intervention
308	Intracytoplasmic Sperm Injection in Non-male Factor Infertility in Advanced Maternal Age					Wrong study design
309	Weight reduction intervention for obese infertile women prior to In vitro fertilisation; a randomised controlled trial	S 2017	Human reproduction	32	2017-07	Wrong patient population
310	Cost Effective Protocol with Letrozole and 3 Doses of Gonadotropin Combination as an Alternative to Continuous Gonadotropin for Ovulation Induction for Iui in Clomiphene Citrate Resistant Pcos Patients - a Rct	S 2020	Fertility and Sterility	Vol.114	e520-p	Conference abstract
311	The effect of phytoestrogens (Cimicifuga racemosa) in combination with clomiphene in ovulation induction in women with polycystic ovarian syndrome: a clinical trial study	Sa 2022	Avicenna Journal of Phytomedicine	Vol.12	8-15p	Wrong comparator
312	Cost Effective Protocol with Letrozole and 3 Doses of Gonadotropin Combination as an Alternative to Continuous Gonadotropin for Ovulation Induction for Iui in Clomiphene Citrate Resistant Pcos Patients - a Rct	Saha 2020	Fertility and Sterility	114(3 Supplement)	e520	Conference abstract
313	Efficacy of follicle-stimulating hormone (FSH) alone, FSH + luteinizing hormone, human menopausal gonadotropin or FSH + human chorionic gonadotropin on assisted reproductive technology outcomes in the "personalized" medicine era: A meta-analysis	Santi 2017	Frontiers in Endocrinology	8(JUN) (no pagination)		Wrong patient population
314	Vitamin D, Early First Trimester Human Chorionic Gonadotropin Kinetics, and Birthweight: Evidence of Hormonal Regulation of Fetal Growth in Women with Vitamin D Deficiency	Senapati 2018	Fertility and Sterility	110(4 SUPPL)	e49-e50	Conference abstract
315	Comparison of myoinositol versus combination of metformin and myoinositol in ovulation induction in polycystic ovarian syndrome	T 2021	Pakistan Journal of Medical and Health Sciences	Vol.15	1494-1496p	Wrong patient population
316	INDUCTION OF OVULATION USING CLOMIPHENE CITRATE PLUS N-ACETYL CYSTEINE VERSUS LETROZOLE IN	T 2018	Fertility and Sterility	Vol.110	e102-p	Conference abstract

	INFERTILE PATIENTS WITH POLYCYSTIC OVARIAN DISEASE: a RANDOMIZED CLINICAL TRIAL					
317	Kuntai Capsule Combined With Letrozole on Gonadal Hormone Levels and Ovarian Function in Patients With PCOS: A Systematic Review and Meta-Analysis	Tang 2021	Frontiers in Endocrinology	12 (no pagination)		Wrong comparator
318	Short-term weight change and live birth among women with unexplained infertility and polycystic ovary syndrome undergoing ovulation induction	Vitek 2020	Fertility and Sterility	114(5)	1032-1039	Wrong patient population
319	Live births after oocyte in vitro maturation with a prematuration step in women with polycystic ovary syndrome	Vuong 2020	Journal of Assisted Reproduction and Genetics	37(2)	347-357	Wrong intervention
320	Effect of amlodipine on blood flow of preovulatory follicle in women with clomiphene resistant polycystic ovaries: a randomized controlled trial	Torky 2020	Archives of Gynecology and Obstetrics	301(3)	845-850	Retracted
321	A comparison of IVF outcomes transferring a single ideal blastocyst in women with polycystic ovary syndrome and normal ovulatory controls	Steiner 2020	Archives of Gynecology & Obstetrics	302	1479-1486	Wrong patient population
322	Comparison of efficacy of metformin versus Pioglitazone on ovulation in patients of polycystic ovarian syndrome	Syed 2018	Pakistan Journal of Medical and Health Sciences	12(3)	1240-1242	Wrong patient population
323	Myo-inositol may improve oocyte quality and fertilization rate in women with polycystic ovary syndrome undergoing assisted reproductive technology cycles	A 2019	Human reproduction (Oxford, England)	Vol.34	i457-i458p	Wrong intervention
324	Therapeutic Effect of Vitamin D3 Supplementation to Clomiphene Citrate Resistant PCOS Women: A Randomized Controlled Trial	El-DinHashaad 2021	QJM. Conference: 41st Annual International Ain Shams Medical Congress. Online.	114		Conference abstract
325	Association among depression, symptom experience, and quality of life in polycystic ovary syndrome	Greenwood 2018	American Journal of Obstetrics & Gynecology	219	279.e1-279.e7	Wrong outcome
326	Transvaginal ovarian drilling followed by controlled ovarian stimulation from the next day improves ovarian response for the poor responders with polycystic ovary syndrome during IVF treatment: A pilot study	Xu 2020	Reproductive Biology and Endocrinology	18(1) (no pagination)		Wrong study design
327	Evaluation of Laparoscopic Ovarian Drilling by Harmonic Scalpel versus Monopolar Drilling Needle in Cases of Clomiphene Citrate Resistant Polycystic Ovarian Response	Kk 2018	Journal of minimally invasive gynecology	Vol.25	S150-p	Conference abstract
328	Letrozole with or without gonadotropin as a first-line ovulation induction in anovulatory infertile women due to polycystic ovary syndrome	Alizzi 2018	Asian Journal of Pharmaceutical and Clinical Research	11(8)	129-133	Wrong study design
329	Polycystic Ovary Syndrome: A Contemporary Clinical Approach	Bjekić-Macut 2021	Curr Pharm Des	27	3812-3820	Wrong study design
330	Melatonin Application in Assisted Reproductive Technology: A Systematic Review and Meta-Analysis of Randomized Trials	Hu 2020	Frontiers in Endocrinology	11	160	Wrong intervention
331	Mild ovarian stimulation with letrozole plus fixed dose human menopausal gonadotropin prior to IVF/ICSI for infertile non-obese women with polycystic ovarian syndrome being pre-treated with metformin: a pilot study	D'Amato 2018	Reprod Biol Endocrinol	16	89	Wrong study design
332	Ovulation rates in a stair-step protocol with Letrozole vs clomiphene citrate in patients with polycystic ovarian syndrome	Thomas 2019	Contracept Reprod Med	4	20	Wrong study design

333	[Network meta-analysis on the effects of the acupuncture-related therapy on ovulation rate and pregnancy rate in patients with polycystic ovary syndrome]	Song 2019	Zhongguo Zhen Jiu	39	792-8	Non English
334	Vitamin D Supplementation and Improvement of PCOS Therapy and IVF Outcomes in Infertile Saudi Women					trial register/ protocol
335	The randomize control trial of clomiphene citrate plus letrozole versus clomiphene citrate alone for ovulation induction in infertile female with chronic anovulation					trial register/ protocol
336	N-acetylcysteine and metformin in induction of ovulation					trial register/ protocol
337	Letrozole Versus Gonadotropins in Clomiphene Citrate Resistance					trial register/ protocol
338	Gonadotropins- letrozole, gonadotropin-clomiphene citrate, and gonadotropins only for controlled ovarian super stimulation in women with polycystic ovary syndrome undergoing intracytoplasmic sperm injection					trial register/ protocol
339	Effect of Ubiquinol Supplementation on Ovulation Induction in Clomiphene Citrate Resistance					trial register/ protocol
340	The Effect of Pretreatment With Dydrogesterone Vs Combined Estradiol Valerate and Dydrogestrone on Clinical Pregnancy Outcome of ICSI in PCOS Patients"					trial register/ protocol
341	The effect of administering L-Carnitine to Clomiphene citrate stimulated cycles on conception rate and ovulation in infertile women with polycystic ovary syndrome					trial register/ protocol
342	The comparison of efficacy and outcomes of Triptorelin (Diphereline®) and hCG in ovulation trigger in infertile women with poly cystic ovarian syndrome					trial register/ protocol
343	Effect of Adding Isoflavonoids to Clomiphene Citrate for Ovulation Induction in Women With Polycystic Ovary Syndrome					trial register/ protocol
344	Different Induction Protocols in PCOS After Clomiphene Citrate Failed Pregnancy in Non-IVF Cycles					trial register/ protocol
345	Cost Effectiveness Analysis for Induction of Ovulation in the Polycystic Ovary Syndrome by Letrozole Versus Clomiphene Citrate					trial register/ protocol
346	Comparison of Two Ovarian Stimulation Protocols in Polycystic Ovarian Syndrome (PCOS) Patients Undergoing IVF/ICSI					trial register/protocol
347	Comparison of the effect of three drugs clomiphene, letrozole and gonadotropin on the dominant follicle and pregnancy in infertile women with polycystic ovaries					trial register/protocol
348	Comparison of Letrozole or clomifene for ovulation induction in women with polycystic ovarian syndrome					trial register/ protocol
349	Comparing the Effect of Sitagliptin/Metformin and Metformin in PCOS Patients					trial register/ protocol
350	Combined clomiphene and letrozole for ovulation induction in infertility patients with Polycystic ovarian syndrome					trial register/ protocol

351	Assessment of pregnancy rate by laparoscopic ovarian cautery in patients with poly cystic ovary syndrome and Previous failed IVF procedures					trial register/ protocol
352	Acupuncture and medicine of artificial cycle therapy in polycystic ovary syndrome: a randomized controlled trial					trial register/ protocol
353	A comparison between a combination of letrozole and clomiphene citrate versus gonadotropins for ovulation induction in infertile patients with clomiphene citrateresistant polycystic ovary syndrome - a retrospective study	Ege 2020	Ginekologia Polska	91	185-188	Wrong study design
354	The Risk of Subsequent Miscarriage in Pregnant Women with Prior Polycystic Ovarian Syndrome: A Nationwide Population-Based Study	Pan 2021	International Journal of Environmental Research & Public Health [Electronic Resource]	18	4	Wrong study design
355	Ovulation induction using clomiphene citrate using stair - Step regimen versus traditional regimen in polycystic ovary syndrome women - A randomized control trial	Agrawal 2017	Journal of Human Reproductive Sciences	10	261-264	Wrong population
356	Comparison of pregnancy rate in patients with polycystic ovary syndrome treated with clomiphene alone and in combination with n-acetyl cysteine: A randomized clinical trial	Ghomian 2019	International Journal of Women's Health and Reproduction Sciences	7	185-189	Wrong comparator
357	Endometrial scratch for infertile polycystic ovary syndrome (PCOS) women undergoing laparoscopic ovarian drilling: a randomized controlled trial	Gibreel 2020	Middle East Fertility Society Journal	21(1)	No pagination	Wrong intervention
358	Cost effectiveness of letrozole and purified urinary FSH in treating women with clomiphene citrate-resistant polycystic ovarian syndrome: a randomized controlled trial	Hassan 2017	Human Fertility	20(1)	37-42	Wrong patient population
359	Impact of laparoscopic ovarian drilling on the pregnancy rate in clomiphene-resistant polycystic ovarian syndrome patients undergoing in vitro fertilization: randomized controlled trial.	Nada 2020	Middle East Fertility Society Journal	25(1)	No pagination	Wrong comparator
360	The efficacy of vitamin D combined with clomiphene citrate in ovulation induction in overweight women with polycystic ovary syndrome: a double blind, randomized clinical trial	Rasheedy 2020	Endocrine	69(2)	393-401	Wrong comparator
361	A personalized medicine approach to ovulation induction/ovarian stimulation: development of a predictive model and online calculator from level-I evidence	Souter 2022	Fertility and Sterility	117	408-418	Wrong outcome
362	Ovulation induction in polycystic ovarian syndrome (pco) related subfertility: A comparison of clomiphene citrate and letrozole	Zaman 2021	Pakistan Journal of Medical and Health Sciences	15(4)	838-839	Wrong patient population
363	Clomiphene citrate or letrozole as first-line ovulation induction drug in infertile PCOS women: A prospective randomized trial	Kar 2012	Journal of Human Reproductive Sciences	5(3)	262-5	Wrong patient population
364	Aromatase inhibitors in women with clomiphene citrate resistance: a randomized, double-blind, placebo-controlled trial	Kamath 2010	Fertility and Sterility	94(7)	2857-9	Wrong patient population
365	PCOSMIC: a multi-centre randomized trial in women with PolyCystic Ovary Syndrome evaluating Metformin for Infertility with Clomiphene	Johnson 2009	Human Reproduction	25(7)	1675-83	Wrong patient population

366	An assessment of lifestyle modification versus medical treatment with clomiphene citrate, metformin, and clomiphene citrate–metformin in patients with polycystic ovary syndrome	Karimzadeh 2010	Fertility and Sterility	94(1)	216-20	Wrong patient population
367	RFSH versus transvaginal hydrolaparoscopic ovarian drilling in patients with polycystic ovary syndrome resistant to ovulation induction	Minareci 2021	Journal of Reproductive Medicine	66(1-2)	40-46	No full text
368	Effects of long-acting GnRH: a prolonged protocol in assisted pregnancy via IVF-ET in infertile patients with PCOS	Wang 2018	Minerva Chururgica	73(2)	251-253	No full text

4. Integrity Assessment of Eligible Studies

Table 4.1. Integrity assessment for the main search results for GDG 5 (applicable to all GDG 5 questions except Q5.1, Q5.2, Q5.8 and Q5.9), conducted using the TRACT checklist (Mol, et al. 2023)

Author, year	Governance			Author group			Plausibility of intervention		Timeframe			Drop outs		Baseline Characteristics		Outcomes		Total Score	Voting Record	Final Consensus Decision
	Absent or retrospective registration	Discrepant registration	Absent or vague ethics	Low # or ratio of authors	Retraction watch base	Large # RCTs	Implausible intervention	Illogical methods	Fast recruitment	Fast follow-up	No LTFU	Ideal numbers	No or few (<5) BL data	Implausible data	Perfectly balanced	Larger effect size than other RCTs	Conflicting outcomes			
Abdelgafor, 2013	Yes	No	No	Yes	No	No	No	No	No	No	Yes	No	No	Yes	No	No	No	4	Unanimous x6	Not Included
Abdellah, 2011	Yes	No	No	Yes	No	No	No	Yes	No	No	No	Yes	No	Yes	No	No	No	5	Unanimous x6	Not Included
Abdelmaged, 2009	No	No	No	No	Yes	Yes	No	Yes	No	No	Yes	No	Yes	Yes	No	No	No	6	Unanimous x6	Not Included
Abu Hashim, 2010a	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Unanimous x6	Retracted - Exclude
Abu Hashim, 2010b	No	No	No	No	Yes	Yes	No	Yes	No	No	Yes	No	No	No	No	No	No	4	Unanimous x6	Not Included
Abu Hashim, 2011a	No	No	No	No	Yes	Yes	No	Yes	No	No	Yes	No	No	No	No	No	No	4	Unanimous x6	Not Included
Abu Hashim, 2011b	No	No	No	No	Yes	Yes	No	Yes	No	No	No	No	No	Yes	No	No	No	4	Unanimous x6	Not Included
Abu Hashim, 2011c	No	No	No	Yes	Yes	Yes	No	No	No	No	Yes	No	No	Yes	No	No	No	5	Unanimous x6	Not Included
Abu Hashim, 2012	Yes	No	No	No	Yes	Yes	No	Yes	No	No	Yes	No	No	Yes	No	No	No	6	Unanimous x6	Not Included
Aflatoonian, 2020	Yes	No	No	No	Yes	Yes	No	No	No	Yes	No	No	No	No	No	No	No	4	Unanimous x6	Not Included
Alizzi, 2018	Yes	No	No	Yes	No	No	No	No	No	Yes	Yes	No	Yes	Yes	No	No	No	6	x2 mod (BM, MF); x4 high (HT, AM, JT, MC)	Awaiting Classification
Amer, 2009	Yes	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	2	Unanimous x6	Included
Amer, 2017	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	1	Unanimous x6	Included
Ashrafi, 2005	No	No	No	No	Yes	Yes	No	No	No	No	Yes	No	No	No	No	No	No	3	x4 low (AM, HT, JT, MC), x2 mod (BM, MF)	Included
Atay, 2006	No	No	No	No	No	No	No	No	No	No	Yes	No	Yes	Yes	No	No	No	3	Unanimous x6	Included

Atwa, 2021	Yes	No	No	No	Yes	Yes	No	No	No	No	Yes	No	No	Yes	No	No	No	5	Unanimous x6	Not Included
Ayaz, 2013 and 2013b	No	No	No	Yes	No	No	No	No	No	No	Yes	No	No	No	No	Yes	No	3	Duplicate studies; ENQUIRE; x1 high (JT); x5 mod (HT,AM, BM, MF, MC)	Not Included
Badawy, 2008	No	No	No	Yes	Yes	Yes	No	No	No	Yes	No	No	No	Yes	No	No	No	5	Unanimous x6	Not Included
Badawy, 2009	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Unanimous x6	Retracted - Exclude
Bahceci, 2005	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	Yes	No	No	2	Unanimous x6	Included
Banerjee Ray, 2012	Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	2	Unanimous x6	Included
Bansal, 2020	No	No	No	No	No	No	No	No	No	No	Yes	Yes	No	Yes	No	No	No	3	Unanimous x6	Included
Baryam, 2004	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	1	Unanimous x6	Included
Bayar, 2006	No	No	No	No	No	No	No	No	No	Yes	No	No	Yes	No	No	No	No	2	x2 mod (MF, BM); x4 low (HT, AM, JT, MC)	Included
Begum, 2009	No	No	No	No	No	No	No	No	No	No	Yes	No	No	Yes	No	No	No	2	x1 mod (AM), rest x5 low	Included
Begum, 2013	No	No	No	No	No	No	No	No	No	No	Yes	Yes	No	Yes	No	No	No	3	x1 mod (AM), rest x5 low	Included
De Leo, 199	No	No	No	No	No	Yes	No	No	No	No	Yes	Yes	No	No	No	No	No	3	Unanimous x6	Included
Dehbashi, 2009	No	No	No	No	No	Yes	No	No	No	No	Yes	Yes	No	No	No	No	No	3	Unanimous x6	Not Included
Doldi, 2006	No	No	Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	2	Unanimous x6	Included
Elgafor, 2013	Yes	No	No	Yes	No	No	No	No	No	No	Yes	No	No	No	Yes	No	No	4	Unanimous x6	Not Included
Elsedeek, 2011	No	No	No	Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	No	2	Unanimous x6	Not Included
Engman, 2008	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	1	Unanimous x6	Included
Farquar, 2002	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	1	Unanimous x6	Included
Fedorcsak, 2003	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	0	Unanimous x6	Included
Fleming, 2002	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	1	Unanimous x6	Included
Foroozanfard, 2011	No	No	No	No	No	Yes	No	No	No	No	Yes	Yes	No	Yes	No	No	No	4	Unanimous x6	Not Included
Ganesh, 2009	No	No	No	Yes	No	No	No	No	No	No	Yes	No	No	No	No	No	No	2	Unanimous x6	Included

George, 2003	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	0	Unanimous x6	Included
Ghanem, 2012	Yes	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	2	Unanimous x6	Included
Hamed, 2010	No	No	No	No	No	No	No	No	No	No	No	Yes	No	Yes	No	No	No	2	Unanimous x6	Not Included
Haydardedeoglu, 2012	Yes	No	No	No	No	No	No	No	No	No	Yes	Yes	No	No	No	No	No	3	Unanimous x6	Included
Hoeger, 2004	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	0	Unanimous x6	Included
Homburg, 2012	Yes	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	2	Unanimous x6	Included
Hwang, 2004	No	No	No	No	No	Yes	No	No	No	Yes	No	No	Yes	No	No	No	No	3	TIED VOTE 3/3: requires querying; kept as Moderate	Not Included
Ibrahim, 2017	Yes	No	No	No	No	No	No	No	Yes	Yes	Yes	Yes	No	No	No	No	No	5	Unanimous x6	Not Included
Jacob, 2016	No	No	No	No	No	Yes	No	No	No	No	Yes	No	No	No	No	No	No	2	Unanimous x6	Included
Jafarabadi, 2018	Yes	No	No	No	No	No	No	No	No	No	No	No	Yes	Yes	No	No	No	3	Unanimous x6	Not Included
Jiang, 2019	Yes	No	No	Yes	No	No	No	No	No	No	Yes	No	Yes	Yes	No	No	No	5	Unanimous x6	Not Included
Johnson, 2010	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	0	Unanimous x6	Included
Kandil, 2018	Yes	No	No	No	Yes	Yes	No	No	Yes	Yes	No	No	No	No	No	No	No	5	Unanimous x6	Not Included
Kar, 2015	Yes	No	No	Yes	No	Yes	No	No	No	No	No	No	No	No	No	No	No	2	Unanimous x6	Included
Kjotrod, 2004	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	1	Unanimous x6	Included
Kjotrod, 2011	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	1	Unanimous x6	Included
Kocak, 2002	No	No	No	No	No	Yes	No	No	No	No	Yes	No	No	No	No	No	No	2	x4 low (JT, HT, MC; AM) x2 mod (BM, MF)	Included
Kurzawa, 2008	No	Yes	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	2	Unanimous x6	Included
Lainas, 2007	No	No	No	No	No	Yes	No	No	No	No	Yes	No	No	No	No	No	No	2	Unanimous x6	Included
Lainas, 2010	No	Yes	No	No	No	Yes	No	No	No	No	No	Yes	No	No	No	No	No	3	Unanimous x6	Included
Legro, 2007	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	1	Unanimous x6	Included
Legro, 2014	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	1	Unanimous x6	Included
Liu, 2017	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	1	Unanimous x6	Included
Lopez, 2004	No	No	No	No	No	Yes	No	Yes	No	No	No	No	No	No	Yes	No	No	3	Unanimous x6	Included

Maged, 2015	Yes	No	No	No	No	Yes	No	No	No	No	Yes	Yes	No	Yes	No	No	No	5	x1 mod (JT), rest x5 high	Not Included
Mokhtar, 2015	Yes	No	No	No	No	No	No	No	No	Yes	Yes	Yes	No	No	No	No	No	4	Unanimous x6	Not Included
Morin-Papunen, 2012	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	1	Unanimous x6	Included
Mukherjee, 2010	No	No	No	Yes	No	No	No	No	Yes	No	Yes	No	No	Yes	No	No	No	4	Unanimous x6	Not Included
Najafi, 2020	Yes	No	No	No	No	No	No	No	Yes	No	Yes	Yes	Yes	No	Yes	No	No	6	Unanimous x6	Not Included
Nazik, 2012	No	No	No	Yes	No	No	No	No	No	No	Yes	No	No	No	No	No	No	2	Unanimous x6	Included
Ng, 2001	No	No	No	No	No	Yes	No	No	No	No	Yes	No	No	No	No	No	No	2	Unanimous x6	Included
Onalan, 2005	No	No	No	No	No	Yes	No	No	No	No	Yes	No	No	No	No	No	No	2	Unanimous x6	Included
Palomba, 2004	No	No	No	No	Yes	Yes	No	No	No	No	No	No	No	No	No	No	No	2	Unanimous x6	Awaiting Classification
Palomba, 2005	No	No	No	No	Yes	Yes	No	No	No	No	No	No	Yes	No	No	No	No	3	Unanimous x6	Awaiting Classification
Palomba, 2005b	No	No	No	No	Yes	Yes	No	No	No	No	Yes	No	No	No	No	No	No	3	Unanimous x6	Awaiting Classification
Palomba, 2005c	No	No	No	No	Yes	Yes	No	No	Yes	No	No	No	No	No	No	No	No	3	Unanimous x6	Awaiting Classification
Palomba, 2010	Yes	No	No	No	Yes	Yes	No	No	No	No	No	No	No	No	Yes	No	No	4	Unanimous x6	Awaiting Classification
Palomba, 2011	Yes	No	No	No	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	No	No	No	No	7	Unanimous x6	Awaiting Classification
Palomba, 2011b	Yes	No	Yes	No	Yes	Yes	No	Yes	No	No	Yes	No	No	No	No	No	No	6	Unanimous x6	Awaiting Classification
Pourghasm, 2019	Yes	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	2	Unanimous x6	Included
Qublan, 2009	No	No	No	No	No	No	No	No	No	Yes	Yes	No	No	No	No	No	No	1	Unanimous x6	Included
Rezk, 2017	Yes	No	No	Yes	Yes	Yes	No	No	Yes	Yes	No	No	Yes	No	No	No	No	7	Unanimous x6	Not Included
Roy, 2009	No	No	No	No	No	Yes	No	No	No	No	Yes	No	No	No	No	No	No	2	Unanimous x6	Included
Roy, 2012	No	No	No	No	No	Yes	No	Yes	No	No	No	No	No	No	No	No	No	2	Unanimous x6	Included
Sahin, 2004	No	No	No	No	No	Yes	No	No	No	No	Yes	No	No	No	No	No	No	2	Unanimous x6	Included
Selim, 2012	Yes	No	No	Yes	No	No	No	No	No	No	No	No	Yes	No	No	No	No	3	Unanimous x6	Not Included
Sharif, 2021	Yes	No	No	Yes	No	No	No	No	No	No	Yes	Yes	Yes	No	No	No	No	5	Unanimous x6	Not Included
Sharma, 2006	No	No	Yes	No	No	Yes	No	No	No	No	Yes	No	No	No	No	No	No	3	Unanimous x6	Included
Shi, 2020	Yes	No	No	No	No	No	No	No	No	Yes	Yes	No	No	Yes	No	No	No	4	Unanimous x6	Not Included
Siebert, 2009	No	No	No	Yes	No	Yes	No	No	No	No	No	No	No	No	No	No	No	2	Unanimous x6	Included

Sohrabvand, 2006	No	No	No	Yes	No	No	No	No	No	No	Yes	No	No	No	No	No	No	2	Unanimous x6	Included
Tang, 2006	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	0	Unanimous x6	Included
Tang, 2006b	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	0	Unanimous x6	Included
Tasdemir, 2004	No	No	Yes	No	No	Yes	No	No	No	No	Yes	No	No	No	No	No	No	3	Unanimous x6	Included
Tehraninejad, 2010	No	No	No	No	No	No	No	No	No	No	No	Yes	Yes	Yes	No	No	No	3	Unanimous x6	Awaiting Classification
Turkcapar, 2013	No	No	No	No	No	Yes	No	No	No	No	No	No	Yes	Yes	No	No	No	3	Unanimous x6	Not Included
Vandermolen, 2001	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	1	Unanimous x6	Included
Vrtacnik, 2009	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	1	Unanimous x6	Included
Wang, 2019	Yes	No	No	No	No	No	No	No	No	No	No	Yes	No	Yes	No	No	No	3	Unanimous x6	Not Included
Wang, 2020	Yes	Yes	No	No	No	No	No	No	Yes	No	Yes	Yes	No	No	No	No	No	5	Unanimous x6	Not Included
Yadav, 2017	Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	Yes	No	No	No	3	Unanimous x6	Included
Yarali, 2002	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	1	Unanimous x6	Included
Zafar, 2021	Yes	No	No	No	No	No	No	No	Yes	No	Yes	Yes	Yes	No	No	No	No	5	Unanimous x6	Not Included
Zeinalzadeh, 2010	No	No	No	Yes	No	No	No	No	No	No	Yes	No	No	No	Yes	No	No	3	Unanimous x6	Included
Zheng, 2022	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	1	Unanimous x6	Included

NB: Categories are not weighted equally; some studies may be ranked as Awaiting Classification or Not Included due to more critical concerns, despite achieving a low score on the checklist. Final decisions are made by the integrity committee on the basis of a majority vote.

Studies classified as 'Awaiting Classification' are where author(s) have responded indicating an intention to clarify the concerns raised. Studies classified as 'Not included' are those where the author(s) did not respond to emails requesting clarifications for concerns raised.

Table 4.2. Integrity assessment for the inositol search results (Q 5.8.), conducted using the TRACT checklist (Mol, et al. 2023)

Author, year	Governance			Author group			Plausibility of intervention		Timeframe			Drop outs		Baseline Characteristics		Outcomes		Total Score	Voting Record	Final Consensus Decision
	Absent or retrospective registration	Discrepant registration	Absent or vague ethics	Low # or ratio of authors	Retraction watch base	Large # RCTs	Implausible intervention	Illogical methods	Fast recruitment	Fast follow-up	No LTFU	Ideal numbers	No or few (<5) BL data	Implausible data	Perfectly balanced	Larger effect size than other RCTs	Conflicting outcomes			
Akbari, 2019	Yes	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	2	Unanimous x6	Included
Angik, 2015	Yes	No	No	No	No	No	No	Yes	No	No	Yes	Yes	No	No	No	No	No	4	x4 include; x2 AC	Included
Artini, 2013	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	1	Unanimous x6	Included
Ashraf, 2022	Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	2	Unanimous x6	Not Included
Bahadur, 2021	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	1	Unanimous x6	Included
Benelli, 2016	Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	2	Unanimous x6	Included
Brusco, 2013	Yes	No	Yes	Yes	No	No	No	No	Yes	No	Yes	No	Yes	No	No	No	No	6	Unanimous x6	Not Included
Chirania, 2017	Yes	No	No	Yes	No	No	No	No	No	No	Yes	No	No	No	No	No	No	3	Unanimous x6	Included
Ciotta, 2012	Yes	No	Yes	No	No	No	No	No	No	No	Yes	No	Yes	No	No	No	No	4	Unanimous x6	Not Included
Constantino, 2009	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	1	Unanimous x6	Included
Donna, 2012	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	1	Unanimous x6	Included
Donne, 2019	Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	2	Unanimous x6	Included
Gennazini, 2008	No	No	No	No	No	No	No	No	No	No	Yes	Yes	No	No	No	No	No	2	x4 include; x2 AC	Included
Gerli, 2003	No	No	No	Yes	Yes	Yes	No	No	No	No	No	No	No	No	No	No	No	3	Unanimous x6	Not Included
Gerli, 2007	No	No	No	No	Yes	Yes	No	No	No	No	No	No	No	No	No	No	No	2	Unanimous x6	Not Included
Iuorno, 2001	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	0	Unanimous x6	Included
Khan, 2022	Yes	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	Yes	No	3	Unanimous x6	Included
De Leo / Musacchio, 2013	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	1	Unanimous x6	Included
Mendoza, 2019	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes	No	2	Unanimous x6	Included

Mishra, 2022	Yes	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	Yes	No	3	Unanimous x6	Not Included
Nehra, 2017a	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	1	x4 include; x2 AC	Included
Nehra, 2017b	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	1	x4 include; x2 AC	Included
Nestler, 1999	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	0	Unanimous x6	Included
Nordio, 2012	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	1	Unanimous x6	Included
Nordio, 2014	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	1	Unanimous x6	Included
Özay, 2017	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	1	x4 include; x2 AC	Included
Pacchiarotti, 2015	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	0	Unanimous x6	Included
Papaleo, 2009	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	0	Unanimous x6	Included
Pizzo, 2014	Yes	No	Yes	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	3	Unanimous x6	Not Included
Pourghasem, 2018	Yes	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	2	Unanimous x6	Included
Rajasekaran, 2021	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	0	Unanimous x6	Included
Roy, 2020	Yes	No	Yes	Yes	No	No	No	No	Yes	No	No	Yes	Yes	No	No	Yes	No	7	Unanimous x6	Not Included
Tagliaferri*, 2017	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	1	Unanimous x6	Included
Unfer, 2011	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	0	Unanimous x6	Included
Akbari, 2019	Yes	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	2	Unanimous x6	Included

NB: Categories are not weighted equally; some studies may be ranked as Awaiting Classification due to more critical concerns, despite achieving a low score on the checklist. Final decisions are made by the integrity committee on the basis of a majority vote.

Studies classified as 'Awaiting Classification' are where author(s) have responded indicating an intention to clarify the concerns raised. Studies classified as 'Not included' are those where the author(s) did not respond to emails requesting clarifications for concerns raised.

Table 4.3. Integrity assessment for the anti-obesity search results (Q 5.9.); conducted using the TRACT checklist (Mol, et al. 2023)

Author, year	Governance			Author group			Plausibility of intervention		Timeframe			Drop outs		Baseline Characteristics		Outcomes		Total Score	Voting Record	Final Consensus Decision
	Absent or retrospective registration	Discrepant registration	Absent or vague ethics	Low # or ratio of authors	Retraction watch base	Large # RCTs	Implausible intervention	Illogical methods	Fast recruitment	Fast follow-up	No LTFU	Ideal numbers	No or few (<5) BL data	Implausible data	Perfectly balanced	Larger effect size than other RCTs	Conflicting outcomes			
Elkind-Hirsch, 2022	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	0	Unanimous x6	Included
Elkind-Hirsch, 2022	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	0	Unanimous x6	Included
Frossing, 2017	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	1	Unanimous x6	Included
Gu, 2022	Yes	No	No	No	No	Yes	No	No	No	Yes	Yes	No	No	No	No	No	No	3	x4 include; x2 AC	Included
Jensterle, 2014	Yes	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	2	Unanimous x6	Awaiting classification
Jensterele, 2015a	Yes	No	No	No	No	Yes	No	No	No	Yes	No	No	No	No	No	No	No	3	Unanimous x6	Awaiting classification
Jensterle, 2015b	Yes	No	No	No	No	Yes	No	No	Yes	No	No	No	Yes	No	No	No	No	4	Unanimous x6	Awaiting classification
Jensterle, 2021	Yes	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	2	x4 include; x2 AC	Included
Kumar, 2014	Yes	No	No	Yes	Yes	No	No	No	No	No	Yes	Yes	Yes	No	No	No	No	6	Unanimous x6	Not Included
Ma, 2021	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	1	Unanimous x6	Included
Moini, 2015	Yes	No	Yes	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	3	Unanimous x6	Included
Nylander, 2017	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	1	Unanimous x6	Included
Ruan , 2018	Yes	No	No	No	No	No	No	No	No	No	Yes	Yes	Yes	No	No	No	No	4	x4 include; x2 AC	Included
Salamun, 2018	Yes	Yes	No	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	3	Unanimous x6	Not Included
Tao, 2021	No	No	No	No	Yes	No	No	No	No	No	No	Yes	No	No	No	No	No	2	Unanimous x6	Included
Zheng, 2017	No	Yes	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	2	x4 include; x2 AC	Included
Liu, 2017	No	Yes	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	2	x4 include; x2 AC	Included

NB: Categories are not weighted equally; some studies may be ranked as Awaiting Classification due to more critical concerns, despite achieving a low score on the checklist. Final decisions are made by the integrity committee on the basis of a majority vote.

Studies classified as 'Awaiting Classification' are where author(s) have responded indicating an intention to clarify the concerns raised. Studies classified as 'Not included' are those where the author(s) did not respond to emails requesting clarifications for concerns raised.

QUALITY APPRAISALS – GDG 5

Study ID	*Amer 2017*
Study Citation	*Amer SA, Smith J, Mahran A, Fox P, Fakis A. Double-blind randomized controlled trial of letrozole versus clomiphene citrate in subfertile women with polycystic ovarian syndrome. Hum Reprod. 2017 Aug 1;32(8):1631-1638. doi: 10.1093/humrep/dex227. PMID: 28854590; PMCID: PMC5850470.*
Study Country	UK
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	*Age (y):* *letrozole: 28.3 (4.4) vs CC: 28.1 (4.2)* *BMI (kg/mO):* *letrozole: 27.5 (23.4 - 32.2) vs CC: 27.7 (23.0 - 31.0)* *"Eligible participants were women aged 18–39 years with BMI ≤35 kg/m2, anovulatory infertility, and a diagnosis of PCOS based on Rotterdam consensus (two of three criteria: oligo-/anovulation, hyperandrogenaemia and sonographic appearance of polycystic ovaries)"*
PCOS diagnostic criteria	*Rotterdam*
Presence of infertility	*Duration (y):* *1.5 (1.0 - 2.0) for both groups*
Presence of other condition/s	*"After the crossover, 45 women with CC-resistance/failure were allocated to letrozole and 31 with letrozole-resistance/failure were allocated to CC"*
Medication History	*"We excluded patients who have received OI within 6 months and those with uncontrolled thyroid disease or hyperprolactinaemia."*
N per group	*N=159 women randomised* *n= 79 (CC)* *n=80 (letrozole)*
Setting	*Fertility Unit, Teaching Hospital (single centre)*
Intervention	*letrozole was prescribed (by the senior investigator, SA) orally daily for 5 days starting on Days 2 – 4 of a menstrual period or a progestogen-induced bleed (medroxy-progesterone acetate 10 mg twice daily for 5 days).* *The starting dose was 1 tablet/day (letrozole 2.5 mg) and if ovulation was not achieved, the dose would be doubled in the second cycle.*

Comparison	*CC was prescribed daily for 5 days starting on days 2 – 4 of a menstrual period or a progestogen-induced bleed (medroxy-progesterone acetate 10mg twice daily for 5 days). The starting dose was 1 tablet/day (50 mg) and if ovulation was not achieved, the dose would be doubled in the second cycle.* *Participants who failed to ovulate on the maximum dose (2 tablets) or to conceive after 6 ovulatory cycles were crossed over to the other drug (after a 6-week wash-out period) following the same procedures as with the first drug.*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*clinical pregnancy (diagnosed by ultrasonographic visualisation of a gestational sac) rate per participant on primary treatment (before the cross-over).* *secondary outcomes included ovulation, live birth, pregnancy by ovulating participant, pregnancy by strata, mono-ovulation, endometrial development (thickness and grades), pregnancy outcome and pregnancy complications. Other outcomes included pregnancy and live birth rates on secondary and overall (primary and secondary) treatments.*	
Follow up Duration	*Six ovulatory cycles* *6-week break until crossover* *Duration of follow-up after crossover not reported*	
Summary Result/s	*"Amongst the 159 participants included in the intention-to-treat analysis, four women conceived before treatment and six were lost-to-follow-up. The remaining 149 participants (74 on CC and 75 on letrozole) completed at least the first treatment. Women receiving letrozole achieved a significantly (P = 0.022; absolute difference [95% confidence interval] 18% [3–33%]) higher pregnancy rate (61.%) than those on CC (43%). The median number of treatment cycles received until pregnancy was significantly (log rank P = 0.038) smaller with letrozole (4[3–5] cycles) compared to CC (6[4–7] cycles). LB rates were not statistically (P = 0.089) different between the two groups, although there was a trend towards higher rates on letrozole (48.8%) compared to CC (35.4%). After the crossover, pregnancy and LB rates on letrozole (n = 45; 28.9 and 24.4%, respectively) were not statistically (P = 0.539 and P = 0.601) different from CC (n = 31; 22.6 and 19.4%)."*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes	*"Would letrozole as a primary ovulation induction agent generate better pregnancy rates than clomiphene citrate (CC) in subfertile women with anovulatory polycystic ovarian syndrome (PCOS)?"*
Does the study have specified inclusion/exclusion criteria?	Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes	

Inclusion criteria		Yes	*"eligible participants were women aged 18 – 39 years with BMI e 35 kg/m2, anovulatory infertility, and a diagnosis of PCOS based on Rotterdam consensus (two of three criteria: oligo-/anovulation, hyperandrogaenemia and sonographic appearance of polycystic ovaries) (Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group, 2004). Diagnosis of oligo-/anovulation was based on a menstrual pattern of oligo-/amenorrhoea (cycle > 35 days) and/or a low mid-luteal serum progesterone concentration. Hyperandrogenaemia was diagnosed either clinically (acne/hirsutism) or biochemically (testosterone f 2.5 nmol/l or free androgen index [FAI] f 5). Ultrasound criteria included f 12 follicles (2 – 9 mm) and/or an ovarian volume of > 10 ml (Jonard et al., 2003). All participants had proven patency of at least one fallopian tube and normal semen analysis of their male partners (WHO, 1999)."*
Exclusion criteria		Yes	*"We excluded patients who have received OI within 6 months and those with uncontrolled thyroid disease or hyperprolactinaemia. Patients with marked hyperandrogaenemia were screened for adult onset congenital adrenal hyperplasia (by measuring serum 17- g -hydroxyl-progesterone concentration) and Cushing syndrome (by measuring urinary free cortisol)."*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes	*"An independent pharmacist randomly allocated participants to letrozole or CC, in 1:1 ratio according to a randomisation list created by the trial statistician using NQuery Advisor v6.0 software. Randomization was stratified by patients' BMI (non-obese < 30 kg/m2 and obese 30 – 35 kg/m2) using mixed block sizes."*
	Was allocation to intervention group concealed?	Yes	*"An independent pharmacist randomly allocated participants to letrozole or CC, in 1:1 ratio."*
PERFORMANC	**Were patients blind to intervention group?**	Yes	*"Investigators, patients, outcome assessors and the statistician were blinded to the allocation of participants."*

	Were investigators and care providers blind to intervention group?	Yes	*"Investigators, patients, outcome assessors and the statistician were blinded to the allocation of participants."*
	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes	*"Investigators, patients, outcome assessors and the statistician were blinded to the allocation of participants."*
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	*"3 women in the CC group discontinued treatment due to failing to attend; also 3 women discontinued treatment in the letrozole arm (1 due to social reasons, 1 failed to attend, 1 withdrew consent)."*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes	*all women randomised were also analysed in the ITT analysis.* *""Intention-to-treat (ITT) analysis included all randomised subjects, regardless of whether or not they received the study drug. Per protocol (PP) analysis included all randomised subjects who received the study drug and were not lost to follow-up. Participants who were lost to follow-up were assumed neither to be pregnant nor to have given LB in the ITT analysis."*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes	*All expected outcomes reported*

CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes	*“Baseline demographic, clinical and endocrine characteristics of the two trial groups were similar (Table I).”*
	If confounding was present, was it controlled for?	No	*No confounding was observed*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	No	*Sponsored by the University of Nottingham.* *“The authors have no conflicts of interest.”*
	Was the study sufficiently powered to detect any differences between the groups?	Partial	*“…"to detect a clinically significant difference of 20% between the previously reported pregnancy rate of CC (˜35%) and letrozole with a two-sided 5% significance level and power of 80%, a sample size of 212 participants (106 per arm) was required (Dickey and Holtkamp, 1996;Kousta et al., 1997; Imani et al., 2002)."* *“Although, the difference was statistically significant, the power of the study was only 65%. Based on these data, the sample size was recalculated as 75 participants per arm to achieve 80% power with a two-sided 5% significance level. We aimed to recruit 160 participants to allow for 5% drop-outs.”*
	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS			
What is the overall risk of bias?		Low	

Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	

Study ID	***Atay 2006***
Study Citation	Atay, V., Cam, C., Muhcu, M., Cam, M., & Karateke, A. (2006). Comparison of letrozole and clomiphene citrate in women with polycystic ovaries undergoing ovarian stimulation. *Journal of international medical research*, *34*(1), 73-76.
Study Country	Turkey
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	*Group 1 (CC) (n=55)* *Age (years) 26.2 ± 1.1* *BMI (kg / m^2) 25.8 ± 1.7* *Group 2 (Letrozole) (n=51)* *Age (years) 27.1 ± 0.9* *BMI (kg / m^2) 26.1 ± 1.91*
PCOS diagnostic criteria	Not reported. Apparently, all women had a prior diagnosis of PCOS
Presence of infertility	*All women had no known cause of infertility* *Group 1 (CC) (n=55)* *Mean fertility period (years) 2.4 ± 0.9* *Group 2 (Letrozole) (n=51)* *Mean fertility period (years) 2.2 ± 0.7*
Presence of other condition/s	*history of oligo- or amenorrhoea*
Medication History	*Not reported*
N per group	*N=106* *Letrozole (n=51)* *CC (n=55)*
Setting	*Probably a research/training hospital in Istanbul, Turkey*
Intervention	2.5 mg letrozole daily for 5 days beginning on day 3 of the menstrual cycle* * Data suggest each patient had one treatment cycle
Comparison	100 mg CC daily for 5 days beginning on day 3 of the menstrual cycle*

	* Data suggest each patient had one treatment cycle	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Follicular development (*transvaginal ultrasound from day 10 onwards) *Pregnancy (*diagnosed using □-hCG levels obtained 2 weeks after timed intercourse, and ultrasound was performed 2 –4 weeks after a positive pregnancy test to confirm clinical pregnancy by the presence of cardiac activity.)	
Follow up Duration	Follow-up time not reported.	
Summary Result/s	*The number of mature follicles was significantly lower, but endometrial thickness and ovulation and pregnancy rates were significantly higher in the letrozole group than in the CC group.*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes	*"*In this prospective, randomized study, the effect on ovulation induction of a standard dose of letrozole was compared with CC treatment in women with PCOs in order to investigate the role of letrozole as a first-line treatment."
Does the study have specified inclusion/exclusion criteria?	Partial	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Partial	
Inclusion criteria	Partial	*"*Women with primary infertility and PCOs with no other known cause of infertility were enrolled into the study. All patients had a history of oligo- or amenorrhoea and ovaries with at least 10 subcapsular cysts 2 – 10 mm in diameter and hyperechogenic stroma."
Exclusion criteria	No	."
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS **Did the study have an adequate method of randomisation?**	Not reported	
SELECTION BIAS **Was allocation to intervention group concealed?**	Not reported	

PERFORMANCE BIAS	**Were patients blind to intervention group?**	Not reported	
	Were investigators and care providers blind to intervention group?	Not reported	
	Aside from the experimental intervention, were the groups treated the same?	Not reported	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	Not reported	*The number randomised had been analysed and therefore likely not dropped off*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes	

CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes	*Only BMI, Fertility period and age have been reported and similar at baseline*
	If confounding was present, was it controlled for?	Not applicable	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Not reported	
	Was the study sufficiently powered to detect any differences between the groups?	Not reported	
	If statistical analysis was undertaken, was this appropriate?	Yes	The study intended to just compare the effect on ovulation induction of a standard dose of letrozole with CC treatment in women with PCOs
COMMENTS		*Lack of randomisation and blinding key reason for high RoB*	
What is the overall risk of bias?		High	*High*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	***Banerjee Ray 2012***
Study Citation	Comparison of efficacy of letrozole and clomiphene citrate in ovulation induction in Indian women with polycystic ovarian syndrome. Ray P, Ray A, Chakraborti PS. Archives Gynecology and Obstetrics (2012) 285:873–877
Study Country	India
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Infertile 18-35 year old Indian women • Age: CC=29 Median, 20-35 Range; letrozole=28 Median, 19-35 Range • BMI: CC=28.5 Median, 24.2-33.6 Range; letrozole=28.8 Median, 23.2-34.6 Range
PCOS diagnostic criteria	Rotterdam 2003 “The major criteria for the diagnosis of PCOS were oligo- and/or anovulation, clinical or biochemical signs of hyperandrogenism and polycystic ovaries, which is in accordance with the revised 2003 Rotterdam Criteria for the diagnosis of PCOS”
Presence of infertility	Duration of infertility in years (mean) 2.4 (CC) 2.2 (Letrozole)
Presence of other condition/s	*Not reported* patients with a history of liver and kidney failure, cardiovascular diseases, diabetes or patients who consumed metformin or drugs effecting insulin secretion or clomiphene citrate in the previous 2 month were not included in the study
Medication History	*Not reported*
N per group	N=147 Randomised: 69 in letrozole group, 78 in clomiphene citrate group Analysed: 147
Setting	Obstetrics and gynaecology hospital, India. Recruitment: Jan 2008 to Dec 2009 = 2 years
Intervention	Letrozole 2.5mg day 3-7 of menstrual cycle
Comparison	Clomiphene citrate 100mg
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Rate of ovulation (day 21 serum “progesterone >10ng/ml considered ovulatory”), average follicular diameter on day 16, number of mature follicles per cycle, oestradiol on day of hCG administration (≥100pg/ml satisfactory), endometrial thickness (>8mm), pregnancy rate. To evaluate physiological maturity, serum estradiol (E2) level was measured when the follicle was assumed to be anatomically mature.

		Follicular diameter/rupture was measured using ultrasonography	
Follow up Duration		*Unclear* "Overall, 288 ovarian cycles were studied in 147 patients (132 cycles in 69 patients in the letrozole group and 156 cycles in 78 patients in clomiphene group). Doesn't say how many cycles women received treatment for.	
Summary Result/s		"The pertinent results of the study are as follows: on the day of hCG injection, mean E2 level was significantly higher in the clomphene citrate group (817 ± 286.70 pg/ml) in comparison with letrozole group (444.03 ± 85.42 pg/ml). Mean endometrial development was 8.72 ± 1.41 mm in the letrozole and 8.78 ± 1.16 mm in the clomiphene group (P = 0.004)."	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT			
Does the study have a clearly focused question and/or PICO?		Yes	*"*The objective of this study was to compare the efficacy of letrozole versus clomiphene citrate as an ovulation induction drug in polycystic ovarian syndrome (PCOS) patients of Indian origin."
Does the study have specified inclusion/exclusion criteria?		Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes	
Inclusion criteria		Yes	*Infertile PCOS patients*
Exclusion criteria		Yes	Hyperprolactinaemia, thyroid disorder, male factor, tubal factor infertility (endometriosis, PID) Liver and kidney failure, cardiovascular disease, diabetes Consumption of metformin, drugs with effects on insulin secretion, clomiphene citrate in 2 months before study
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Not reported	*"*The patients were randomly assigned to receive either letrozole (2.5 mg) or clomiphene citrate (100 mg) from day 3 to day 7 of menstrual cycle."
	Was allocation to intervention group concealed?	No	*"*A comparative, prospective, phase III, open labelled trial Study….."
PER FOR	**Were patients blind to intervention group?**	No	*"*A comparative, prospective, phase III, open labelled trial Study….."

	Were investigators and care providers blind to intervention group?	No	*"*A comparative, prospective, phase III, open labelled trial Study….."
	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Not reported	*"*A comparative, prospective, phase III, open labelled trial Study….." No details given. In the acknowledgments, they thank the Department of Radiology "for their assistance in serial folliculometry". Unclear whether they were blind or independent, but the outcomes measured are fairly objective.
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Not reported	*No information available*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	*0%*	
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes	*Not relevant. No drop-outs*
REP ORT	**Is the paper free of selective outcome reporting?**	Yes	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Not reported	
	If confounding was present, was it controlled for?	Not reported	

OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	No	"Conflict of interest The authors hereby declare that they have not received any financial support for this studyand there is no conflict of interest."
	Was the study sufficiently powered to detect any differences between the groups?	Not reported	*Not much statistical information* "Statistical analysis, Chi square test and student's t test were performed using SPSS version 15. A P value of\0.05 was considered statistically significant."
	If statistical analysis was undertaken, was this appropriate?	Yes	Table 2 provides summary of outcome results with simple statistical analysis The study intended to just compare the two interventions
COMMENTS		Unclear how many cycles treatment was given for and unclear length of follow up. Less data in terms of baseline and outcomes compared with other, similar papers. No documentation of side effects or cost analysis.	
What is the overall risk of bias?		High	*High* No details of randomisation technique. Some lack of clarity as documented information
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	*Bansal 2020*
Study Citation	*Bansal S, Goyal M, Sharma C, Shekhar S. Letrozole versus clomiphene citrate for ovulation induction in anovulatory women with polycystic ovarian syndrome: A randomized controlled trial. Int J Gynaecol Obstet. 2021 Mar;152(3):345-350. doi: 10.1002/ijgo.13375. Epub 2020 Oct 14. PMID: 32920843.*
Study Country	India
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	*infertile women with PCOS* *Age (years)* *LET: 27.0.9±3.56* *CC: 26.0±3.97* *BMI (kg/m2)* *LET: 23.90±3.57* *CC: 23.10±3.64*

PCOS diagnostic criteria	Rotterdam
Presence of infertility	*Duration of infertility (years)* *LET: 3.9±2.3* *CC: 3.4±2.3*
Presence of other condition/s	*NR*
Medication History	*Those who had received ovulation induction in the previous 6 months were excluded*
N per group	*N=90* *Letrozole n=45* *Clomiphene citrate n=45*
Setting	*Tertiary care teaching institute*
Intervention	*Letrozole:* *Given as 2.5 mg once daily for 5 days (from day 2 to 6) after spontaneous or progesterone-induced bleeding and increased by 2.5 mg every cycle up to a maximum of 7.5 mg in each subsequent cycle if ovulation did not occur.* *When size of dominant follicle reached more than 18 mm, human chorionic gonadotropin (hCG) 5000 IU was given as a trigger intramuscularly for ovulation.*
Comparison	*Clomiphene citrate:* *Given as 50 mg once daily for 5 days in a similar fashion and increased by 50 mg every cycle up to a maximum of 150 mg in each subsequent cycle if ovulation did not occur.* *When size of dominant follicle reached more than 18 mm, human chorionic gonadotropin (hCG) 5000 IU was given as a trigger intramuscularly for ovulation.*
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Primary: endometrial thickness (ET)* *Secondary: ovulation rate, monofollicular development, pregnancy rate, and time to pregnancy assessment.* *Pregnancy defined by detection of urinary hCG after 7 days of missed period and or detection of gestational sac by ultrasound. Ovulation defined as the presence of free fluid in the pouch of Douglas and collapsed follicle on transvaginal ultrasound and/or day 21 serum progesterone value of at least 3 ng/mL.*
Follow up Duration	*Maximum of three cycles*
Summary Result/s	*“Mean endometrial thicknesses were 9.86 ± 2.32 mm and 9.39 ± 2.06 mm with letrozole and CC, respectively (P=0.751). Cumulative ovulation rates were 86.7% and 85.2% with letrozole and CC, respectively (P=0.751). Pregnancy was achieved in 42.2% of*

	women in the letrozole group and 20.0% of women in the CC group (P=0.04). *Monofollicular development was seen in 68.4% of ovulatory cycles in the letrozole group compared with 44.8% in the CC group (P=0.000). Mean time to achieve pregnancy was significantly shorter (log rank P=0.042) with letrozole (9.65 weeks) than with CC (11.07 weeks).”*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes	“To compare the efficacy of letrozole and clomiphene citrate (CC) for ovulation induction in infertile women with polycystic ovarian syndrome (PCOS).” *“Hence, we conducted this randomized controlled trial to compare the therapeutic efficacy of letrozole and CC among Indian women presenting with anovulatory infertility due to PCOS using the recommended incremental dosing of both drugs with clearly stated study end points.”*
Does the study have specified inclusion/exclusion criteria?	Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes	
Inclusion criteria	Yes	*“Eligible participants were women aged 18–35 years with anovulatory infertility due to PCOS diagnosed by Rotterdam criteria,16 which entails finding any two of the following* *(1) ovarian dysfunction, (2) androgen excess identified either by raised modified Ferryman-Gallwey score or raised serum testosterone, and (3) polycystic ovarian morphology on ultrasound.”*
Exclusion criteria	Yes	*“Additional workup included partner’s semen analysis, premenstrual endometrial biopsy, and tubal patency test. Women with an abnormality in any of the above tests were excluded from the study. Those with thyroid disorders and prolactin excess, with a major medical illness, and those who had received ovulation induction in the previous 6 months were also excluded.”*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes	*"Random sequence was generated online and was kept in sequentially numbered, opaque, sealed envelopes."*
	Was allocation to intervention group concealed?	Yes	*"Random sequence was generated online and was kept in sequentially numbered, opaque, sealed envelopes."*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	No	*"Another limitation of the index study is absence of blinding of the participants. However, this is unlikely to have affected the results as most of the outcomes studied are highly objective in nature."*
	Were investigators and care providers blind to intervention group?	Partial	*Patients not blinded, therefore most probably the care providers weren't* *If the investigator was the outcome assessor, he was blinded. Otherwise, not.*
	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes	*"This was a single center, double arm, assessor masked, randomized controlled trial."* *"The senior consultant who performed transvaginal ultrasound for outcome assessment and the statistician were blinded to treatment allocation."*
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Yes	

ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	*"In total, 205 women were approached for enrollment; 90 were randomized and 80 completed the study. A total of 213 cycles of ovulation induction were carried out in 90 women, out of which 98 cycles were in the letrozole group and 115 cycles were in the CC group"* *4 (8.8%) dropped out in intervention (LET)* *6 (13.3) dropped out in control (CC)*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes	*"Analysis was based upon intention-to-treat (ITT) as well as per protocol, and results of both analyses are presented."* *"Participants who were lost to follow up were assumed neither to have ovulated nor to have conceived in the ITT analysis."*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes	*"Baseline characteristics of both groups were comparable"*
	If confounding was present, was it controlled for?	No	*No confounding identified*
IER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	No	*"The authors have no conflicts of interest."*

	Was the study sufficiently powered to detect any differences between the groups?	Yes	*"Sample size calculation was based on the difference between the mean ET with CC and and that with letrozole on the day of hCG administration.17 A sample size of 90 (45 in each arm) was targeted to be able to detect a difference of 15% in ET between two groups, with 80% power and α (type 1 error) set at 0.05."*
	If statistical analysis was undertaken, was this appropriate?	Yes	*"Student's t test was used to analyze normally distributed data and Mann-Whitney U test was used for non-normally distributed data. For categorical variables, χ2 test was used at a two-sided significance level of 0.05 for testing the differences between two groups. The lengths of time (weeks) from commencing ovulation induction to pregnancy were compared using a Kaplan-Meier plot and significance used a log rank test."*
COMMENTS			
What is the overall risk of bias?		High	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*Some of the outcomes (e.g. pregnancy rate) may be low risk due to the objective nature of assessment.*	

Study ID	*Bayar 2006*
Study Citation	Bayar, U., S. Kiran, et al. (2006). "Use of an aromatase inhibitor in patients with polycystic ovary syndrome: a prospective randomized trial." Fertility and sterility 86(5): 1447-51.
Study Country	Turkey
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Anovulatory, infertile patients with PCOS who were therapy naïve. "In this study, we compared letrozole with CC as a first-line therapeutic agent for ovulation induction in patients with PCOS. In conclusion, in this study, we showed that letrozole is as effective as CC in PCOS patients who previously have not been treated with other ovulation-induction agents" Mean age: letrozole = 32.2 ± 3.9 CC = 30.6 ± 4.09, p=0.09 BMI not reported but women with a BMI > 25 were excluded.

PCOS diagnostic criteria	PCOS patients diagnosed by using the Rotterdam criteria.
Presence of infertility	Duration of infertility (years) Letrozole: 5 (1–10) CC: 3 (1–11) *Median (range)*
Presence of other condition/s	*Tubal, peritoneal, and uterine causes of infertility were excluded by hysterosalpingography, laparoscopy, or transvaginal ultrasonography (LOGIQ 7 Scanner, GE Medical Systems, Milwaukee, WI).*
Medication History	*Not reported*
N per group	Eligible and randomised – 80 Letrozole – 40, 2 lost to follow up (5%) CC - 40, 4 lost to follow up (10%)
Setting	Outpatient clinics of the Infertility and Reproductive Medicine Unit of the Zonguldak Karaelmas University Hospital (Zonguldak, Turkey) during the study period of 2004 through 2005.
Intervention	2.5 mg/d letrozole, administered on days 3 to 7 of the menstrual cycle. Treatment duration: was for a range of between 1 to 5 treatment cycles.
Comparison	100 mg/d CC, administered on days 3 to 7 of the menstrual cycle. Treatment duration: was for a range of between 1 to 5 treatment cycles.
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Ovulation rate per cycle, pregnancy rate per cycle and delivery rate per cycle. Primary outcomes were not specified, however other outcomes that are not relevant to this evidence review include: endometrial thickness (mm), number and size of follicles and E2.
Follow up Duration	Follow-up time not reported.
Summary Result/s	"Ovulation occurred in 65.7% (65/99) of letrozole cycles and in 74.7% (71/95) of CC cycles. The median (minimum-maximum) number of follicles sized >15 mm in diameter on the day of hCG administration were 1 (0-4) and 1 (0-5) in the letrozole and CC groups, respectively. On the day of hCG administration, median serum E(2) concentrations in the letrozole and CC groups were statistically significantly different: 189 pg/mL (18-1,581 pg/mL) and 386 pg/mL (27-6,190 pg/mL), respectively. The median serum E(2) concentrations per follicle sized >15 mm in diameter on the day of hCG also statistically significantly differed between the letrozole and CC groups: 160 pg/mL (18-808 pg/mL) and 281 pg/mL (27-2,615 pg/mL), respectively. The median endometrial thickness on the day of hCG did not significantly differ between the CC and letrozole groups; it was 8 mm. Pregnancy was achieved in nine cycles (9.1%) of the letrozole group and in seven cycles (7.4%) of the CC group, which also was not a statistically significant difference."
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT	

Does the study have a clearly focused question and/or PICO?		Yes	*"*In this study, we aimed to investigate the role of letrozole as a first-line ovulation-induction agent and to compare the clinical parameters with those of CC in PCOS patients."
Does the study have specified inclusion/exclusion criteria?		Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes	
Inclusion criteria		Yes	PCOS patients diagnosed by using the Rotterdam criteria.
Exclusion criteria		Yes	"Tubal, peritoneal, and uterine causes of infertility were excluded by hysterosalpingography, laparoscopy, or transvaginal ultrasonography (LOGIQ 7 Scanner, GE Medical Systems, Milwaukee, WI). Specific endocrine abnormalities (Cushing's disease, hypothyroidism, hyperthyroidism, congenital adrenal hyperplasia, and prolactinoma), male-factor infertility, and women with a body mass index of >25 kg/m2 were excluded from the study."
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes	*In this prospective double-blind study, each patient's treatment was determined by simple randomization, performed by a computer.*
	Was allocation to intervention group concealed?	Yes	*Allocation concealment was achieved by using central consultation for treatment of eligible patients.*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes	*Double-blind study.*
	Were investigators and care providers blind to intervention group?	Yes	*Double-blind study.*

	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	5% treatment 10% control/ comparison	*Intervention group: 2/40* *Comparison group: 4/40*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	No	*No ITT analysis*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Not reported	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes	*"The two groups were comparable regarding the baseline characteristics, including female age, basal FSH level, and duration of infertility (Table 1)."*

	If confounding was present, was it controlled for?	Not reported	*NA*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Not reported	
	Was the study sufficiently powered to detect any differences between the groups?	Yes	*Sample-size determination was based on the difference between the median number of follicles sized _15 mm and E2 concentration on hCG day.* *"A sample size of 60 patients (30 patients in each group) was targeted to be able to detect a difference of at least one follicle or of 200 pmol/L between the two groups, with _ (type I error) set at 0.05 and 80% power."*
	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS			
What is the overall risk of bias?		Low	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

- Begum 2009

Study ID	***Begum 2009***
Study Citation	Begum, M. R., J. Ferdous, et al. (2009). "Comparison of efficacy of aromatase inhibitor and clomiphene citrate in induction of ovulation in polycystic ovarian syndrome." Fertility & Sterility 92(3): 853-7.
Study Country	Bangladesh
BRIEF CHARACTERISTICS OF RCT	

Patient/population/ participants	Anovulatory patients with PCOS who failed to ovulate when taking 100 mg/day clomiphene citrate in previous cycles (and therefore are clomiphene citrate – resistant women with PCOS) Mean age: letrozole = 25.47 ± 3.98 CC = 26.09 ± 3.62, p=0.38 Mean BMI: letrozole = 22.72 ± 2.77 CC = 23.63 ± 3.23, p=0.12	
PCOS diagnostic criteria	Rotterdam	
Presence of infertility	*Duration of infertility (y)* *Letrozole 2.66 ± 1.11* *CC 2.58 ± 1.10* *Mean ± SD*	
Presence of other condition/s	*Not reported*	
Medication History	*Not reported*	
N per group	*64*	
Setting	Private infertility care setting between August 2004 and December 2005. Country: Bangladesh.	
Intervention	Letrozole group - 7.5 mg of letrozole daily for 5 days starting from day 3 of the cycle.	
Comparison	CC group - 150 mg of CC daily for 5 days starting from day 3 of the cycle.	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	The main outcome measure was rate of ovulation rate per patient and pregnancy rate per patient. “Two consecutive cycles were observed to declare ovulation failure. Six ovulatory cycles were observed for pregnancy.” *Follicular monitoring was done by transvaginal ultrasonography (TVS)* *“A level of R100 pg/mL of serum E2 was considered satisfactory”*	
Follow up Duration	2-6 cycles? *“Two consecutive cycles were observed to declare ovulation failure. Six ovulatory cycles were observed for pregnancy.”*	
Summary Result/s	*“Twenty (62.5%) patients from the letrozole group and 12 (37.50%) patients from the CC group ovulated during the observation period. Mean serum E2 level was 817.75 pg/mL and 448.03 pg/mL in the CC and letrozole groups, respectively, on the day of hCG administration. The mean endometrial thickness on the day of hCG administration was 9.03 mm and 10.37 mm in the CC and letrozole groups, respectively. The mean D21 serum P was 13.09 ng/mL and 19.09 ng/mL in the CC and letrozole groups, respectively. Thirteen patients from the letrozole group (40.63%) and six patients from the CC group (18.75%) became pregnant.”*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes	“the purpose of our study is to compare the efficacy of 7.5 mg of letrozole with that of 150 mg of CC in patients with PCOS who did not respond to 100 mg of CC.”

Does the study have specified inclusion/exclusion criteria?		Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes	
Inclusion criteria		Yes	"Anovulatory patients with PCOS, who failed to ovulate when taking 100 mg/day CC for 5 days in two consecutive cycles. Polycystic ovary syndrome was diagnosed by the Rotterdam criteria (19). Those patients who did not develop follicles of optimum size (>17 mm) by day 16 of the cycle were recruited for this study."
Exclusion criteria		Yes	."Patients who had hyperprolactinemia, thyroid disorder, male factor infertility, known or suspicious tubal factor infertility (endometriosis and pelvic inflammatory disease), and unexplained infertility were excluded from the study."
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Not enough information	*Patients were divided by lottery.*
	Was allocation to intervention group concealed?	Not reported	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Not reported	
	Were investigators and care providers blind to intervention group?	Not reported	
	Aside from the experimental intervention, were the groups treated the same?	Yes	

DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	0% Not reported	*Apparently no drop-outs*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Not reported	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Not reported	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes	*"Characteristics of age, duration of infertility, and basal hormone levels (Table 1) were similar in both groups of patients."*
	If confounding was present, was it controlled for?	Not reported	*N/A*

OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Not reported	
	Was the study sufficiently powered to detect any differences between the groups?	Not reported	
	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS		*Lack of randomisation and blinding key reason for high RoB*	
What is the overall risk of bias?		Moderate	*Few criteria fulfilled or the conclusions of the study are likely or very likely to be affected.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

Study ID	***Ganesh 2009***
Study Citation	*Ganesh A, Goswami SK, Chattopadhyay R, Chaudhury K, Chakravarty B. Comparison of letrozole with continuous gonadotropins and clomiphene-gonadotropin combination for ovulation induction in 1387 PCOS women after clomiphene citrate failure: a randomized prospective clinical trial. J Assist Reprod Genet. 2009 Jan;26(1):19-24. doi: 10.1007/s10815-008-9284-4. Epub 2009 Jan 7. PMID: 19127427; PMCID: PMC2649330.*
Study Country	India
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	*Women with PCOS, diagnosed by the Rotterdam criteria, who had previously failed to conceive or ovulate with CC treatment and undergoing IUI* *Mean Age (years)* *Group A: 30.25 ± 4.90* *Group B: 30.38 ± 5.18*

	Group C: 30.82 ± 4.56 *Mean BMI (kg/m2)* *Group A: 24.49 ± 3.83* *Group B: 24.75 ± 4.05* *Group C: 24.08 ± 3.43*
PCOS diagnostic criteria	*Rotterdam criteria*
Presence of infertility	*Only duration of marriage given*
Presence of other condition/s	*CC resistant* *(Patients who failed to ovulate or conceive despite 6 cycles of CC using 100 mg/day or showed poor endometrial development (endometrial thickness <0.7 cm on the day of hCG administration))*
Medication History	*NR*
N per group	*Group A; Letrozole (n=372)* *Group B; Clomiphene Citrate and rFSH (n=669)* *Group C: rFSH (n=346)*
Setting	*Tertiary infertility care unit, Institute of Reproductive Medicine, Kolkata, India*
Intervention	*Group A; Letrozole; 2.5 mg twice daily, starting from day 3 of the menstrual cycle for 5 days* *Group B: CC with two doses rFSH* *Clomiphene Citrate 100 mg daily from day 3 to day 7 of the menstrual cycle and two ampoules of rFSH subcutaneously (75 IU), one on day 3 and the other on day 8*
Comparison	*Group C: continuous rFSH* *continuously administered one ampoule (75 IU/100 IU rFSH daily) from day 2 onwards until the day of hCG administration, gonadotrophin dose subsequently adjusted based on the follicular response*
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Primary outcome measures: ovulation rate, cancellation rate, miscarriage rate and pregnancy rate* *Clinical pregnancy was defined as the presence of a gestational sac with cardiac activity as detected by transvaginal ultrasound at 7 weeks of gestation* *LH & FAH: immunoassay*
Follow up Duration	
Summary Result/s	*“Group A, B and C had an ovulation rate of 79.30%, 56.95% and 89.89% and cycle cancellation rate of 20.70%, 43.05% and 10.11%, respectively. Pregnancy rates in Group A, B and C were 23.39%, 14.35% and 17.92%,*

	while the miscarriage rates were 13.80%, 16.67% and 14.52%, respectively"	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	*Yes*	*"The purpose of this study is to compare the efficacy of letrozole with that of rFSH and clomiphene citrate(CC)/rFSH for ovarian stimulation in IUI cycles."*
Does the study have specified inclusion/exclusion criteria?	Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes	
Inclusion criteria	*Yes*	*PCOS* *normal TSH and prolactin levels* *Normozoospermic male partners as per WHO guidelines* *AT least one patent tube*
Exclusion criteria	*Yes*	*Patients with pre-existing ovarian cyst on day 3* *Previous history of ovarian drilling*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes	*"The method of simple randomization was used and the allocation was done using sealed envelopes where the person allocating was blinded to the type of protocol received by the patients"*
	Was allocation to intervention group concealed?	Yes	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	*Not reported*	*Only the allocating person appeared blind*
	Were investigators and care providers blind to intervention group?	Not reported	*"Randomized, prospective, single-blinded clinical trial."*

	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	*Not reported*	
	Were all outcomes measured in a standard, valid and reliable way?	*Yes*	
	Were outcomes assessed objectively and independently?	*Yes*	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	*Not reported*	*Apparently no drop outs? Not much information on patients who were treated with alternative protocols in the text*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	*Yes*	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	*Yes*	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	*Yes*	

	If confounding was present, was it controlled for?	NA	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	*Not reported*	*Only financial statement is available* *"*One of the authors, Dr. Ashalatha Ganesh sincerely acknowledges the Council of Scientific and Industrial Research (CSIR) for providing financial support."
	Was the study sufficiently powered to detect any differences between the groups?	*Not reported*	
	If statistical analysis was undertaken, was this appropriate?	*Yes*	*"Multiple comparison using one-way ANOVA and z-Test were performed, wherever appropriate, between the three groups A, B and C. Data are expressed as mean ± SD. Significance of the test was performed at the 5% level (P < 0.05)."*
COMMENTS			
What is the overall risk of bias?		*Moderate*	*Only the allocating person was blinded (not clear whether the treating clinicians and assessors were blinded-perhaps yes but not explicitly reported), no-dropouts is a concern but may be due to using alternative protocols which the information is not clearly available. This is a big study, but power calculation is not reported.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

Study ID	***Legro 2014***
Study Citation	Legro, R. S., R. G. Brzyski, et al. (2014). "Letrozole versus clomiphene for infertility in the polycystic ovary syndrome." New England Journal of Medicine 371(2): 119-129.
Study Country	US
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Infertile women 18 to 40 years of age with PCOS Age (yr): CC = 28.8±4.0; letrozole = 28.9±4.5 BMI: CC = 35.1±9.0; letrozole = 35.2±9.5
PCOS diagnostic criteria	modified Rotterdam criteria "…all participating women had ovulatory dysfunction combined with hyperandrogenism (on the basis of hirsutism or an elevated testosterone level), polycystic ovaries (defined by an increased number of small antral follicles [≥12 follicles that were <10 mm in diameter] or an increased individual ovarian volume [>10 cm3] in ≥1 ovary), or both."
Presence of infertility	Fertility history Duration of time attempting to conceive — months 42.5±37.6 (CC) 40.9±38.0 (Letrozole) Previous live birth — no. (%) 73 (19.4) (CC) 75 (20.1) (Letrozole)
Presence of other condition/s	Patients had no major medical disorders
Medication History	*Not reported*
N per group	3457 prescreened 1002 screened 750 randomized CC: 376; letrozole: 374 158 withdrawn CC: 85; letrozole: 73 750 analysed ITT
Setting	Academic Health Centers throughout the United States
Intervention	After spontaneous menses or withdrawal bleeding induced by progestin administration (medroxyprogesterone acetate [Provera], 5 mg per day for 10 days), ***clomiphene citrate (50 mg daily)*** was administered, beginning on cycle day 3 for 5 days and for up to five menstrual cycles. The dose was increased in subsequent cycles in cases of nonresponse (progesterone level during the midluteal phase, <3 ng per milliliter) or a poor ovulatory response (progesterone levels indicative of ovulation but with values clustering just above the cutoff point [see the Supplementary Appendix]), noted in 2% of 2777 treatment cycles.

	The maximum daily dose of clomiphene was 150 mg (three pills) given for 5 days. Investigators had the option to induce menstrual bleeding with medroxyprogesterone acetate after an anovulatory cycle; this option was exercised in 309 of 1255 anovulatory cycles (24.6%). Couples were instructed to have regular intercourse two to three times a week, and the women kept an intercourse diary. Ovulation predictor kits were not used.
Comparison	After spontaneous menses or withdrawal bleeding induced by progestin administration (medroxyprogesterone acetate [Provera], 5 mg per day for 10 days), ***letrozole (2.5 mg daily)*** was administered, beginning on cycle day 3 for 5 days and for up to five menstrual cycles. The maximum daily dose of letrozole was 7.5 mg (three pills) given for 5 days. Investigators had the option to induce menstrual bleeding with medroxyprogesterone acetate after an anovulatory cycle; this option was exercised in 309 of 1255 anovulatory cycles (24.6%). Couples were instructed to have regular intercourse two to three times a week, and the women kept an intercourse diary. Ovulation predictor kits were not used.
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Primary outcome: live birth; Secondary outcomes: ovulation, pregnancy loss, singleton birth, and congenital anomalies. Serious adverse events were defined as events that were fatal or immediately life-threatening, that were severely or permanently disabling, or that required or prolonged inpatient hospitalization; overdoses (intentional or accidental); congenital anomalies; pregnancy loss after 12 weeks of gestation; and any event deemed to be serious by the site principal investigator.
Follow up Duration	*Ongoing* *"Participants who conceived were followed until a viable intrauterine pregnancy was observed (fetal heart motion visualized on ultrasonography) and were then referred for prenatal care. Outcomes were tracked through review of maternal* *and infant medical records."* *An ongoing registry follows infants to 3 years of age for developmental delays*
Summary Result/s	*"Women who received letrozole had more cumulative live births than those who received clomiphene (103 of 374 [27.5%] vs. 72 of 376 [19.1%], P = 0.007; rate ratio for live birth, 1.44; 95% confidence interval, 1.10 to 1.87) without significant differences in overall congenital anomalies, though there were four major congenital anomalies in the letrozole group versus one in the clomiphene group (P = 0.65).*

	The cumulative ovulation rate was higher with letrozole than with clomiphene (834 of 1352 treatment cycles [61.7%] vs. 688 of 1425 treatment cycles [48.3%], P<0.001). There were no significant between-group differences in pregnancy loss (49 of 154 pregnancies in the letrozole group [31.8%] and 30 of 103 pregnancies in the clomiphene group [29.1%]) or twin pregnancy (3.4% and 7.4%, respectively). Clomiphene was associated with a higher incidence of hot flushes, and letrozole was associated with higher incidences of fatigue and dizziness."	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes	*"We designed a double-blind, multicenter, randomized trial to test the hypothesis that letrozole would be superior to clomiphene as an infertility treatment and would have a similar safety profile"*
Does the study have specified inclusion/exclusion criteria?	Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes	
Inclusion criteria	Yes	Infertile women 18 to 40 years of age with the polycystic ovary syndrome who had no major medical disorders and who were not taking confounding medications (primarily sex steroids, other infertility drugs, and insulin sensitizers, as described in the study protocol), their male partners, and their neonates participated in the study.9 We used modified Rotterdam criteria1 to diagnose the polycystic ovary syndrome. Additional eligibility criteria were at least one patent fallopian tube and a normal uterine cavity, as determined by sonohysterography (on the basis of the presence of free fluid in the pelvis), hysterosalpingography, a combined hysteroscopy and laparoscopy, or evidence of an intrauterine pregnancy within the previous 3 years; a male partner with a sperm concentration of at least 14 million per milliliter, according to World Health Organization cutoff points,11 with documented motility in at least one ejaculate during the previous year; and a commitment on the part of the women and their partners to have regular intercourse during the study with the intent of pregnancy.

Exclusion criteria		Yes	Described in detail in protocol and baseline paper.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes	Women were randomly assigned in a 1:1 ratio in permuted blocks of two, four or six. Stratified randomization with permuted blocking within each stratum was generated by the data coordination centre (DCC) statistician. The only stratification variable will be by site.
	Was allocation to intervention group concealed?	Yes	Once patient consent is received, the patient is entered into secure online system where the patient is randomised and the site is provided with a patient identifier and a study kit number. According to allocated kit number, the site coordinator dispenses the intervention.
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes	The purchased study drugs were overencapsulated to look the same, tested, and packaged by a commercial supply company (Almac Clinical Services). The two drugs were given for the same duration and with the same stepwise increase in dose.
	Were investigators and care providers blind to intervention group?	Yes	The randomization scheme (including block size) will not be disclosed to the investigators or staff, including the Protocol Lead Investigator. Unless otherwise specified, treatment group data will be presented in a blinded fashion within Data safety monitoring board (DSMB) reports.
	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Not reported	All reported laboratory values were determined by a central laboratory (Ligand Core Laboratory, University of Virginia) and all data entry and analysis was done by DCC but no mention of whether outcome assessors were blinded.
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Yes	

ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	22.6% CC 19.5% letrozole	CC: 85/376; letrozole 73/374 Reasons for drop out were described in detail.
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes	*ITT*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes	
	If confounding was present, was it controlled for?	Partial	*BMI*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes	*"*Dr. Legro reports receiving consulting fees from Ferring Pharmaceuticals, AstraZeneca, and Euroscreen. Dr. Diamond reports receiving consulting fees from EMD Serono and serving on the board of directors of and owning stock in Advanced Reproductive Care. Dr. Santoro reports receiving grant support from Bayer and holding stock options in MenoGeniX. No other potential conflict of interest relevant to this article was reported." Disclosure forms provided by the authors are available with the full text of this article at NEJM.org." *The interventions used in this study are made by Teva Pharmaceuticals USA and Novartis.*

	Was the study sufficiently powered to detect any differences between the groups?	Partial	"The study was designed to have 81% power to detect an absolute difference of 10 percentage points in cumulative live-birth proportions between treatment groups…We calculated that the analysis would require a sample of 300 patients per treatment group, which we increased to 375 to allow for a dropout rate of 20%." However drop out rate was a little bit more than 20% in the CC group and had less than 300 participants.
	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS			
What is the overall risk of bias?		Low	*Most of the criteria have been fulfilled or where criteria have not been fulfilled it is very unlikely the conclusions of the study would be affected.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

Study ID	*Liu 2017*
Study Citation	*Liu, C., G. Feng, W. Huang, Q. Wang, S. Yang, J. Tan, J. Fu and D. Liu (2017). "Comparison of clomiphene citrate and letrozole for ovulation induction in women with polycystic ovary syndrome: a prospective randomized trial." Gynecol Endocrinol 33(11): 872-876.*
Study Country	China
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	*Age (years)* *group A (CC) 26.8 ± 3.1;* *group B (CC + met) 27.2 ± 2.8;* *group C (letrozole) 27.0 ± 3.0;* *group D (letrozole + met) 27.2 ± 3.3* *BMI (kg/m^2)* *group A (CC) 21.1 (19.9, 22.8);* *Group B (CC + met) 21.4 (19.8, 23.6);* *group C (letrozole) 20.8 (19.1, 22.3);* *group D (letrozole + met) 21.6 (19.2, 23.6)*

PCOS diagnostic criteria	Rotterdam	
Presence of infertility	*Duration of infertility (years):* *group A (CC) 1 (0, 2);* *group B (CC + met) 1 (0, 3);* *group C (let) 1 (0, 2);* *group D (let + met) 1 (0, 3)*	
Presence of other condition/s	*NR*	
Medication History	*NR*	
N per group	*N=238*	
Setting	*Tertiary hospital*	
Intervention	*Group A: the oral administration of CC was started in the group CC or CC + met from day 3 to day 5 of the menstrual cycle at a daily dose of 50 mg for 5 days; and the daily dose gradually increased to 100 mg or 150 mg at maximum in the next cycle if the undeveloped follicle (< 16 mm) was present in the previous cycle.* *Group B: The oral administration of letrozole started in the group letrozole or letrozole + met from day 3 to day 5 of the menstrual cycle at a daily dose of 5 mg for 5 days.*	
Comparison	*Additional met (1000 – 1500 mg/d) was orally administered to participants in the groups CC + met and letrozole + met.*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Ovulation rate, pregnancy rate, live birth rate, miscarriage rate, premature delivery, OHSS, multiple pregnancy rate*	
Follow up Duration	*Three continuous cycles*	
Summary Result/s	*"The ovulation rate was significantly higher in the group LE than the group CC; however, no significant difference was noted between the groups LE and CC, CC, and CC + MET, or LE and LE + MET in the pregnancy rate, abortion rate, and live birth rate. No birth defect was found in the total of 63 newborns. CC regimen was still recommended to be the first-line therapy of ovulation induction for PCOS."*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes	*"To explore the optimal ovulation-induction therapy for PCOS patients, a perspective randomized controlled trial was conducted in the current study with PCOS patients who desired childbearing, to compare the therapeutic effect of CC, LE, and those in combination with MET."*

Does the study have specified inclusion/exclusion criteria?		Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes	
Inclusion criteria		Yes	*"PCOS patients attending the outpatient department of the hospital between April 2012 and March 2014, who had a desire for childbearing and fulfilled the Rotterdam diagnostic criteria as well, were recruited for this study. The inclusion criteria for this study were as follows: (1) patency of at least one side of the fallopian tube and (2) normal spouse's sperm."*
Exclusion criteria		Yes	*"The exclusion criteria were as follows: (1) patients with gynaecologic tumours or genital tract malformations, (2) patients with severe systemic disease or acute and chronic urogenital tract infections, (3) patients with other endocrine diseases such as thyroid disease and adrenal disease, (4) body mass index (BMI)>30, and (5) age over 35 years or below 20 years."*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes	*Randomisation with computer-generated blocks*
	Was allocation to intervention group concealed?	Not reported	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Not reported	*Probably not*
	Were investigators and care providers blind to intervention group?	Not reported	*Probably not*

	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Not reported	*Probably not*
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	*28 women left the study; 13 in the CC groups, 15 in the LE groups; 5 in the CC + met and 7 in the LE + met group left the study due to complications; 3 participants were excluded (no reasons reported), the rest were lost to follow-up*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Not reported	*Unknown if all 268 or only 240 were analysed* *28 of 268 women leN the study (> 10%)*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes	*All outcomes expected were reported*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes	*"No significant difference was noted among the four groups regarding to the baseline data of clinical manifestations, serum sex hormone levels, and serum insulin levels."*

	If confounding was present, was it controlled for?	No	*No confounding reported*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	No	*The study was self-supported by West China Women's and Children's Hospital S.C.U* *"The authors report no conflicts of interest."*
	Was the study sufficiently powered to detect any differences between the groups?	Partial	*The number required was not reported. However, the method used to derive a number is explicitly reported. Perhaps the authors missed to report this clearly even though they have actually done this. If so, this should be assessed as "Yes".* *"Ovulation rate as the main indictor, the sample size was calculated by introducing maximal and minimal ovulation rate retrieved in literatures into the formula (Figure 1) [8,11,12]. SPSS 21.0 software (IBM Inc., Armonk, NY) was used to create a random figure, and the participants were numbered and randomly divided into group CC, CCþMET, LE, and LEþMET according to the order of inclusion."* *"Figure 1. The formula of sample size calculation. The value of μ_a is 2.5758, value of μ_b is 1.2816, P1 (.604) is maximal ovulation rate, P_2 (.902) is minimal ovulation rate."*
	If statistical analysis was undertaken, was this appropriate?	Yes	*"The measurement data that fulfilled the normal distribution were presented as mean ± standard deviation (SD), and analysed by t-test and analysis of variance (ANOVA). The data that did not fulfill the normal distribution were presented as median (interquartile range) and analyzed by the rank sum test. The count data comparison was conducted by v2 test or Fisher exact test. p<.05 was considered as statistically significant."*
COMMENTS			
What is the overall risk of bias?		High	*Few or no criteria have been fulfilled and therefore likely to effect conclusion*

Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*No*

Study ID	***Nazik 2012***
Study Citation	Nazik, H., & Kumtepe, Y. (2012). Comparison of efficacy of letrozole and clomiphene citrate in ovulation induction for women with polycystic ovarian syndrome. *HealthMED*, *6*(3), 879-83.
Study Country	Turkey
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	*Group 1 (n=33) (CC)* *Age (years)* 27.80±6.18 *BMI (kg/m²)* 25.90±4.80 *Group 2 (n=31) (Letrozole)* *Age (years)* 25.55±4.45 *BMI (kg/m²)* 24.66±3.57
PCOS diagnostic criteria	"The diagnosis of PCOS was based on the 2003 Rotterdam criteria"
Presence of infertility	*3 arm study (only 2 arms used here). Group 3 letrozole 150mg/day of CC during successive cycles, added non-randomly was not discussed here.* *Group 1 (n=33) (CC)* *Duration of infertility (years)* 4.40±3.58 *Group 2 (n=31) (Letrozole)* *Duration of infertility (years* 3.40±3.04 "No male factor was detected in the two normal spermiograms conducted fortnightly."
Presence of other condition/s	*Not reported*
Medication History	Withdrawal bleeding was achieved using oral 10-mg medroxyprogesteron acetate for 6 days before stimulation for patients with oligomenore. 100 mg/day oral CC
N per group	(N=98, 120 cycles) Patients were divided into three groups. Patients receiving ovulation induction for the first time randomly established to the first two groups: Group 1: 100 mg/day clomiphene citrate (n=33, 40 cycles) Group 2: 2.5 mg/day letrozole (n=31, 40 cycles)

	The 3rd group consisted of patients who failed to ovulate after taking 50, 100, and 150 mg/day of CC treatment during successive cycles and therefore added non-randomly. Group 3: 2.5 mg/day of letrozole (n=34, 40 cycles) *[will not be included here]*	
Setting	Infertility Polyclinic of Atatürk University Medical Faculty (Erzurum, Turkey) between December 2005 and March 2007.	
Intervention	Letrozole 2.5mg/day (Femara, Novartis Pharma AG, Basel, Switzerland) to groups 2 and 3 from day 3 -7	
Comparison	All patients with oligomenorrhoea given 6 days of PO medroxyprogesterone acetate to achieve a withdrawal bleed. Clomiphene citrate 100mg/day (Gonaphene, Organon, Ilaclari AS, Turkey) to group 1 from day 3 to 7.	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Number of mature follicles, rate of ovulation (Follicles were measured with transvaginal ultrasound) pregnancy rate (serum hCG concentration) *miscarriage rate* multiple pregnancy adverse effects	
Follow up Duration	*Approximately 1 cycle*	
Summary Result/s	"There were no significant differences between the 1st and 2nd groups with respect to number of mature follicles (1.02±0.83 vs. 0.83±0.68), and in group 1 and 2 the number of mature follicles were significantly greater than group 3 (0.4±0.25). There were no significant differences between the 1st and 2nd groups with respect ovulation rate (72.5% vs. 70%), and in both groups ovulation rate were greater than group 3 (37.5%). The pregnancy rate was 20% in group 1 and 17.5% in group 2 without significant differences, while pregnancy was not detected in group 3."	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes	To compare the efficacy of letrozole and clomiphene citrate in ovulation induction for women with polycystic ovarian syndrome (PCOS).
Does the study have specified inclusion/exclusion criteria?	Partial	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes	
Inclusion criteria	Partial	Patients with PCOS applied to the Infertility Polyclinic of Atatürk University Medical Faculty

Exclusion criteria		Yes	." Patients who had ovarian or adnexial surgery, hypothyroidism, hyperprolactinemia, bilateral tubal occlusion diagnosed with hysterosalphingography and unexplained infertility were excluded from the study" Patients with follicles greater than 10 mm was excluded the study after the day 3 hormonal profile and transvaginal ultrasound
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes	*Computer random list*
	Was allocation to intervention group concealed?	Not reported	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Not reported	No evidence of blinding in this study
	Were investigators and care providers blind to intervention group?	Not reported	
	Aside from the experimental intervention, were the groups treated the same?	Yes	*Pertaining to groups 1 and 2 only. Group 3 is not considered for the PCOS evidence*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes	"Follicles were measured with USG daily or every other day until the diameter of the follicle reached ≥17 mm."
	Were outcomes assessed objectively and independently?	Yes	

ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	0% treatment 0% control/ comparison	
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes	*Apparently not drop-outs*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Not reported	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Partial	*"*The patients in group 2 were found to be significantly younger and have shorter duration of infertility the other two groups although the patients had been grouped randomly (Table 1). However, the BMI, the hormone values on 3rd day of menstruation were similar. This illustrates that the patients are homogeneously distributed among the three groups."
	If confounding was present, was it controlled for?	Yes	*"*CC-resistant patients who failed to ovulate when taking 50, 100, and 150 mg/day of CC during successive cycles, added non-randomly to the category of group three (34 patients, 40 cycles)."
ER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Not reported	

	Was the study sufficiently powered to detect any differences between the groups?	Not reported	No sample size calculation in paper. Likely Underpowered "The main outcome measures were the rate of ovulation and pregnancy. Statistical analysis was accomplished on a personal computer by using statistical program for social sciences version 12.0 (SPSS 12.0, demo, SPSS Inc. Chicago, Illinois). Normality of variables was analyzed and normally distributed variables in three groups were compared with One-Way ANOVA test. For post-hoc comparison Bonferroni test was used. Proportions were analyzed using the chi-square test. Results were expressed as mean and standard error of the mean. Statistical significance level was set at 5%."
	If statistical analysis was undertaken, was this appropriate?	Yes	This was just a comparison study ANOVA for 3 group analysis Bonferroni test, Chi-square Significance at 5%
COMMENTS		*Lack of randomisation and blinding key reason for high RoB*	
What is the overall risk of bias?		High	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

Study ID	*Pourghasem 2019*
Study Citation	*Pourghasem S, Bazarganipour F, Taghavi SA, Kutenaee MA. The effectiveness of inositol and metformin on infertile polycystic ovary syndrome women with resistant to letrozole. Arch Gynecol Obstet. 2019 Apr;299(4):1193-1199. doi: 10.1007/s00404-019-05064-5. Epub 2019 Feb 5. PMID: 30847561.*
Study Country	Iran
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	*Women with polycystic ovary syndrome (PCOS) resistant to letrozole.* *Age (years)* *Group I (LET + folic acid):* *30.42 ± 2.58* *Group II (LET + Metformin + folic acid):*

	31.06 ± 1.11 *Group lll (Letrozole + inositol + folic acid):* *31.08 ± 3.31* *BMI* *Group I (LET + folic acid):* *27.38 ± 4.02* *Group ll (LET + Metformin + folic acid):* *27.84 ± 3.68* *Group lll (Letrozole + inositol + folic acid):* *29.79 ± 3.58*
PCOS diagnostic criteria	Rotterdam
Presence of infertility	*Duration of infertility (years)* *Group I (LET + folic acid):* *4.36 ± 1.005* *Group ll (LET + Metformin + folic acid):* *5.10 ± 1.11* *Group lll (Letrozole + inositol + folic acid):* *6.36 ± 2.25*
Presence of other condition/s	*Resistant to letrozole (determined by not ovulating after 7.5 mg per day from the third day of menstruation for 5 days)*
Medication History	*NR*
N per group	*N=186 randomised, 162 underwent treatment* *Group I (LET + folic acid):* *n=62 randomised, 54 underwent treatment, 50 completed* *Group ll (LET + Metformin + folic acid):* *n=62 randomised, 53 underwent treatment, 50 completed* *Group lll (Letrozole + inositol + folic acid):* *n=62 randomised, 55 underwent treatment, 50 completed*
Setting	*Infertility clinic of Hormozgan University of Medical Sciences*
Intervention	*Group II, 1500 mg of metformin daily plus 200 µg of folic acid, Group III, inositol 2 g plus 200 µg of folic acid received twice daily for 3 months.* *In the last cycle, 7.5 mg letrozole was prescribed for the induction of ovulation*

Comparison	*Group I (control group), 200 µg of folic acid (as a placebo) received twice daily for 3 months.* *In the last cycle, 7.5 mg letrozole was prescribed for the induction of ovulation*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Primary: Ovarian function and pregnancy* *"The ovarian function was evaluated by the presence or absence of a mature follicle (≥17 mm seen by transvaginal ultrasound) during 12–16 menstrual cycles."* *"The clinical pregnancies were identified by the presence of a gestational sac on ultrasonography 5 weeks after HCG injection."*	
Follow up Duration	*3 cycles*	
Summary Result/s	*"The ovarian function was not significantly different in those groups, whereas the ovarian function of inositol + folic acid group in normal BMI found significantly higher than other BMI spectra. In addition, the ovarian function is significantly higher in the inositol + folic acid group by increasing the infertility duration. The incidence of pregnancy is lower in letrozole + folic acid + inositol group than the other groups; however, it is not significant."*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes	*To compare inositol and metformin on ovarian function and incidence of pregnancy in PCOS patients with letrozole resistance*
Does the study have specified inclusion/exclusion criteria?	Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes	
Inclusion criteria	Yes	*"Inclusion criteria were individuals of 15–38 years old with PCOS defined according to Rotterdam criteria as having at least two of the following three features: oligo and/or anovulation, hyperandrogenism (clinical and biochemical), and polycystic ovaries on ultrasound scan; inability to get pregnant despite having frequent, unprotected intercourse for at least a year; absence of tubal, anatomic and male factors; intact uterine cavity and normal level of thyroid hormones."*

Exclusion criteria		Yes	*"The study excluded patients diagnosed with the other endocrine disorders like hyperprolactinemia as well as the patients who have no desire for cooperation."*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes	*"…randomized single-blind controlled clinical trial…"* *"A table of random numbers was used for randomization."*
	Was allocation to intervention group concealed?	Not reported	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Not reported	*"…randomized single-blind controlled clinical trial…"* *Not sure who were blinded*
	Were investigators and care providers blind to intervention group?	Not reported	*"…randomized single-blind controlled clinical trial…"*
	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Not reported	*"…randomized single-blind controlled clinical trial…"*
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Yes	

ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	*Group I (LET + folic acid):* *19.35% lost after randomisation* *Group II (LET + Metformin + folic acid):* *19.35% lost after randomisation* *Group III (Letrozole + inositol + folic acid):* *19.35% lost after randomisation*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	No	*Only the participants who completed the study analysed*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes	*"There is no significant difference in appearance between study groups (P > 0.05)"*
	If confounding was present, was it controlled for?	No	
IER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Partial	*Not clear* *"Conflict of interest* *The authors have any conflict of interest to declare regarding the manuscript."*

	Was the study sufficiently powered to detect any differences between the groups?	Partial	*"The sample size was calculated; at least 45 people were estimated for each group."*
	If statistical analysis was undertaken, was this appropriate?	Yes	*"Data were analyzed by descriptive statistics (standard deviation, mean, percent, and frequency), followed by Chi-square, ANOVA, and Kruskal–Wallis tests. The Scheffe test was used for post hoc analysis. Data were analyzed using statistical software (version 21) (SPSS Inc., Chicago, IL, USA). The significance level for all tests P < 0.05 was considered.*
COMMENTS			
What is the overall risk of bias?		High	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*All high risk of bias*	

Study ID	***Roy 2012***
Study Citation	Roy KK, Baruah J, Singla S, Sharma JB, Singh N, Jain SK, Goyal M. A prospective randomized trial comparing the efficacy of Letrozole and Clomiphene citrate in induction of ovulation in polycystic ovarian syndrome. J Hum Reprod Sci. 2012 Jan;5(1):20-5. doi: 10.4103/0974-1208.97789. PMID: 22870010; PMCID: PMC3409915.
Study Country	India
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	PCOS patients 20–35 years having infertility for more than one year *Age* *Letrozole 26.1 ± 1.8* *CC 26.5 ± 1.3* *BMI* *Letrozole 25.8 ± 2.1* *CC 25.4 ± 1.56*

PCOS diagnostic criteria	Rotterdam's criteria
Presence of infertility	Mean infertility duration (in years) *Letrozole 6.4 ± 3.8* *CC 5.8 ± 3.1*
Presence of other condition/s	*Not reported*
Medication History	*Not reported*
N per group	*250 screened* *212 randomised* *Letrozole (n=104) (6 dropped out, 98 analysed)* *Clomiphene citrate (n=108) (2 dropped out, 106 analysed)*
Setting	tertiary care hospital from January 2005 to January 2010
Intervention	Letrozole: Starting dose of 2.5 mg letrozole, increasing up to 5 mg daily, administered from Day 3 to Day 7 (total of 5 days) of a spontaneous cycle or withdrawal bleeding after a 5-day course of 10 mg/ day medroxyprogester one acetate. 3 months
Comparison	Clomiphene Citrate: Starting dose of 50 mg, increasing up to 100 mg daily, administered from Day 3 to Day 7 (total of 5 days) of a spontaneous cycle or withdrawal bleeding after a 5- day course of 10 mg/ day medroxyprogester one acetate. 3 months
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Clinical pregnancy (*at least one gestational sac in USG) *Number of miscarriages* *Live birth* Other outcomes not relevant to this systematic review included: mean number of follicles and endometrial thickness.
Follow up Duration	*3 cycles*
Summary Result/s	"The mean number of dominant follicles in letrozole groups and CC groups was 1.86±0.26 and 1.92±0.17, respectively (*P*=0.126). Number of ovulatory cycle in letrozole group was 196 (66.6%) versus 216 (67.9%) in CC group (*P*=0.712). The mean mid-cycle endometrial thickness was 9.1±0.3 mm in letrozole group and 6.3±1.1 in CC group, which was statistically significant (*P*=0.014). The mean Estradiol [E2] level in clomiphene citrate group was significantly higher in CC group (364.2±71.4 pg/mL) than letrozole group (248.2±42.2 pg/mL). 43 patients from the letrozole group (43.8%) and 28 patients from the CC group (26.4%) became pregnant." "Letrozole and CC have comparable ovulation rate. The effect of letrozole showed a better endometrial response and pregnancy rate compared with CC."
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT	

Does the study have a clearly focused question and/or PICO?		Yes	"The aim of this present prospective randomized trial was to compare results of letrozole with CC in patients with PCOS."
Does the study have specified inclusion/exclusion criteria?		Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes	
Inclusion criteria		Yes	age group of 20–35 years having infertility for more than one year, body mass index (BMI) <28, patients of anovulatory PCOS oligomenorrhea (i.e., interval between periods were ≥35 days) or amenorrhea (i.e., absence of vaginal bleeding for 6 months), hirsutism, enlarged ovaries with multiple follicles (≥10 measuring 2–8 mm in diameter) as per Rotterdam's criteria on transvaginal ultrasonography (USG), and/or elevated serum testosterone.
Exclusion criteria		Yes	Patients having abnormality in any of the following tests: tubal patency test, pelvic ultrasonography, husband semen analysis, serum hormone measurements (FSH, LH, prolactin, estradiol, progesterone, and testosterone) on the 2nd to 5th day of the cycle Any abnormality found in laparoscopy that may be responsible for infertility
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes	Randomization of recruited women was carried out using online software (http://www.randomization.com) to generate a random number table
	Was allocation to intervention group concealed?	Yes	Randomization codes (A, B) were packed into sealed opaque envelopes by an individual not involved in enrollment, treatment and follow-up of subjects to ensure concealment of allocation

PERFORMANCE BIAS	**Were patients blind to intervention group?**	Not reported	
	Were investigators and care providers blind to intervention group?	Not reported	
	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes	Documentation of at least one gestational sac in USG was confirmed as clinical pregnancy.
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	6/104 in Letrozole (5.8%) *And* *2/106 in CC (1.9%)*	*8 patients dropped out*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	No	*ITT analysis not done*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Partial	*The outcomes to be assessed are not explicitly mentioned under methods but reported under results* Difficult to determine without a protocol.

CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes	There was no statistically significant difference in the mean age, BMI, and duration of infertility in both groups of patients.
	If confounding was present, was it controlled for?	Not reported	There was no statistically significant difference in the mean age, BMI, and duration of infertility in both groups of patients.
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	No	**Source of Support:** Nil, **Conflict of Interest:** None declared.
	Was the study sufficiently powered to detect any differences between the groups?	Yes	"Sample size was calculated using pregnancy rate as a primary outcome measure. On basis of previous studies,[3] to achieve a statistically valid comparison of pregnancy rates in the two groups, with a type I error of 0.05 and a power of 80%, a sample size of at least **40 women in each arm** was required"
	If statistical analysis was undertaken, was this appropriate?	Yes	Student's t-test, Chi-square and Fisher's exact testes were used when appropriate
COMMENTS			
What is the overall risk of bias?		Low	*Not clear whether the outcome assessors and the patients were blinded. The study does not identify itself as a double-blind study.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

Study ID	**Zeinalzadeh 2010**

Study Citation	Zeinalzadeh, M., Z. Basirat and M. Esmailpour (2010). "Efficacy of letrozole in ovulation induction compared to that of clomiphene citrate in patients with polycystic ovarian syndrome." J Reprod Med **55**(1-2): 36-40.
Study Country	Iran
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Infertile women with PCOS. Not reported whether these women were therapy naïve or clomiphene citrate-resistant. Mean age: letrozole = 23.8 ± 3.6 clomiphene citrate (CC) = 23.1 ± 3.6, p=0.34 BMI not reported.
PCOS diagnostic criteria	Patients had documented PCOS (defined on the basis of ultrasonography, oligo menorrhoea and increased LH / FSH ratio (>3)
Presence of infertility	*<5 years duration* *Duration of infertility (years)* *Letrozole 2.4 ± 1* *CC 2.6 ± 1.2* *(mean ± SD)*
Presence of other condition/s	*Not reported*
Medication History	*Not reported*
N per group	107 patients Letrozole group- 50 patients CC group - 57 patients
Setting	"Fatemeh Zahra Infertility Centre, Babol, Iran, in 2006 and 2007."
Intervention	Letrozole group- 5 mg of letrozole (Novartis, Basel, Switzerland) daily within days 3-7 of the menstrual cycle for 5 days.
Comparison	CC group - 100 mg of CC (Daroopakhsh Co., Tehran, Iran) daily within days 3-7 of the menstrual cycle for 5 days.
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Pregnancy rate (per patient), (diagnosed by hCG measurement and confirmed by TVS based on foetal heart activity) multiple pregnancy rate (per patient) ovulation rate (ovulation assessed by measuring progesterone 7 days after injection and level of >3ng/ml was considered the occurance)
Follow up Duration	Follow up time not reported
Summary Result/s	"The number and the size of mature follicles were similar between the 2 groups. The pregnancy rate in letrozole group was higher than that in the clomiphene group (20% vs. 14%), but the difference was not significant (p = 0.286). In letrozole group, 86% of patients developed mature follicles, all showing ovulation, whereas 72% of patients in clomiphene citrate group developed mature follicles (p = 0.07)."
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT	

Does the study have a clearly focused question and/or PICO?		Yes	*To evaluate the effects of clomiphene citrate and letrozole on inducing ovulation in infertile patients with PCOS*
Does the study have specified inclusion/exclusion criteria?		Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes	
Inclusion criteria		Yes	"Patients with primary infertility, documented PCOS, age >35 years, a history of <5 years of infertility and a body mass index (BMI) between 19 and 26kg/m2 were enrolled in the study." "PCOS was defined on the basis of ultrasonography findings, oligomenorrhea and an increased luteinizing hormone (LH)/follicle stimulating hormone (FSH) ratio (>3)."
Exclusion criteria		Yes	." "Subjects were excluded from the study if in the moderate or severe categories. Also, infertility resulting from male factors, tubular factors and endometriosis was considered an exclusion criterion."
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Partial	*"The subjects were assigned to 2 groups using systematic randomization method."*
	Was allocation to intervention group concealed?	Not reported	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Not reported	
	Were investigators and care providers blind to intervention group?	Not reported	

	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	*Not reported*	*Apparently, no drop-outs*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	No	*BMI and ovulation rate is listed as outcomes (data to be collected), however the results for these outcomes are not reported.*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes	

	If confounding was present, was it controlled for?	Not reported	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes	*"The authors have no connection to any companies or products mentioned in this article"*
	Was the study sufficiently powered to detect any differences between the groups?	Not reported	
	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS			
What is the overall risk of bias?		High	*Few criteria fulfilled and the conclusions of the study are likely to be affected.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

Study ID	***Amer 2009***
Study Citation	Amer, S. A., T. C. Li, et al. (2009). "Randomized controlled trial comparing laparoscopic ovarian diathermy with clomiphene citrate as a first-line method of ovulation induction in women with polycystic ovary syndrome." Human Reproduction 24(1): 219-225.
Study Country	UK
BRIEF CHARACTERISTICS OF RCT	

Patient/population/ participants	Women with anovulatory infertility associated with PCOS (therapy naïve). Mean age: group A = 28.1 ± 4.3 group B = 29.1 ± 4.8 Mean BMI: group A = 26.2 ± 3.9 group B = 26.1 ± 3.5
PCOS diagnostic criteria	At least two of the following three features: clinical (oligo/amenorrhoea and/or hyperandrogenaemia), biochemical [LH ≥10 IU/l, LH/FSH ratio _2, testosterone .2.6 nmol/l or free androgen index (FAI) and/or sonographic (polycystic ovaries) features "…all patients in the current study fulfilled the 2003 ESHRE/ASRM (Rotterdam) criteria of PCOS, but only 65 fulfilled the 1990 NIH criteria for PCOS."
Presence of infertility	Duration of infertility of ≥1 year
Presence of other condition/s	*Not reported*
Medication History	*Not reported*
N per group	72 women were randomized, 36 in each group. Of the 72 women randomized, 3 from group A and 3 from group B conceived before starting treatment and one patient from the CC group decided to postpone her treatment for personal reasons. The remaining 65 women (33 in the LOD group and 32 in the CC group) completed the study.
Setting	"This study was conducted in the Centre for Reproductive Medicine and Fertility, University of Sheffield."
Intervention	Laparoscopic monopolar ovarian diathermy (group A).
Comparison	"CC was given in incremental doses starting with a daily dose of 50 up to 150 mg on Days 2–6 of a menstrual period or after a progestogen withdrawal bleed using medroxyprogesterone acetate (Proveraw, Pharmacia, Kent, UK)." (Group B)). Once ovulation occurred on a certain dose, CC was continued at the same dose for six cycles.
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Cumulative pregnancy rate at 12 months, rates of ovulation (per patient and per cycle), miscarriage (per patient), multiple pregnancy (per patient) and live birth rates (per patient). "Conception was diagnosed with a positive urinary pregnancy test (Clearview, hCG II, Unipath Ltd, Bedford, UK) taken 1 week after a missed period." Powered for primary outcome – pregnancy rates at 12 months. "Ovulation was diagnosed when the progesterone level was _25 nmol/l."
Follow up Duration	*12 months*

Summary Result/s			"After the primary treatment, more pregnancies (44%) occurred in women receiving CC than in those undergoing LOD (27%), although the difference did not reach statistical significance [P = 0.13, OR 2.1 (0.7 – 5.8)]. After adding the second treatment, the pregnancy rate was still higher, but to a less extent, in the CC group [63% versus 52%, P = 0.2, OR 1.6 (0.6 – 4.2)]." "LOD is not superior to CC as a first-line method of OI in women with PCOS"
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT			
Does the study have a clearly focused question and/or PICO?		Yes	
Does the study have specified inclusion/exclusion criteria?		Yes	*See below*
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes	
Inclusion criteria		Yes	"Diagnostic criteria for PCOS included at least two of the following three features: clinical (oligo/amenorrhoea and/or hyperandrogenaemia), biochemical [LH ≥10 IU/l, LH/FSH ratio ≥2, testosterone >2.6 nmol/l or free androgen index (FAI) and/or sonographic (polycystic ovaries) features. The study included women aged 18–39, with body mass index (BMI) ≤32 kg/m2 and a duration of infertility of ≥1 year. Other inclusion criteria were at least one patent fallopian tube on hysterosalpingogram and normal semen analysis of the male partner."
Exclusion criteria		Yes	"Exclusion criteria were inability to give informed consent (eg. due to language barrier) and contraindication to CC or general anaesthetic. In addition, women who had received any OI therapy such as CC, metformin or gonadotrophin during the preceding 6 months were excluded."
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes	*"Suitable patients were randomized utilizing a block randomization method using a random number table generated by the pharmacist. This table was held centrally by a trial administrator."*
	Was allocation to intervention group concealed?	Yes	*"Randomization was carried out by telephone. The patient was assigned by the principal investigator to treatment Group A (LOD) or B (CC) according to the randomization. Allocation to*

			treatment was concealed, but once allocated, the treatment was revealed to both the investigator and the patient."
PERFORMANCE BIAS	**Were patients blind to intervention group?**	No	*"Allocation to treatment was concealed, but once allocated, the treatment was revealed to both the investigator and the patient."*
	Were investigators and care providers blind to intervention group?	No	
	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	No	
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	*No drop outs*	*3 patients each from intervention and control arms conceived after randomisation but before first treatment and one postponed the treatment for personal reasons Analysis was performed on an intention-to-treat basis*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes	
	If confounding was present, was it controlled for?	Not reported	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes	
	Was the study sufficiently powered to detect any differences between the groups?	Yes	*"From our review of the literature, we hypothesized pregnancy rates of 35% with CC and 70% with LOD. On the basis of this analysis, 36 patients were required in each arm to detect this difference with a 5% level of significance and 80% power."*
	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS			
What is the overall risk of bias?		Moderate	

Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	

Study ID	***Begum 2009***
Study Citation	Begum, M. R., J. Ferdous, et al. (2009). "Comparison of efficacy of aromatase inhibitor and clomiphene citrate in induction of ovulation in polycystic ovarian syndrome." Fertility & Sterility 92(3): 853-7.
Study Country	Bangladesh
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Anovulatory patients with PCOS who failed to ovulate when taking 100 mg/day clomiphene citrate in previous cycles (and therefore are clomiphene citrate – resistant women with PCOS) Mean age: letrozole = 25.47 ± 3.98 CC = 26.09 ± 3.62, p=0.38 Mean BMI: letrozole = 22.72 ± 2.77 CC = 23.63 ± 3.23, p=0.12
PCOS diagnostic criteria	Rotterdam
Presence of infertility	*Duration of infertility (y)* *Letrozole 2.66 ± 1.11* *CC 2.58 ± 1.10* *Mean ± SD*
Presence of other condition/s	*Not reported*
Medication History	*Not reported*
N per group	*64*
Setting	Private infertility care setting between August 2004 and December 2005. Country: Bangladesh.
Intervention	Letrozole group - 7.5 mg of letrozole daily for 5 days starting from day 3 of the cycle.
Comparison	CC group - 150 mg of CC daily for 5 days starting from day 3 of the cycle.
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	The main outcome measure was rate of ovulation rate per patient and pregnancy rate per patient. “Two consecutive cycles were observed to declare ovulation failure. Six ovulatory cycles were observed for pregnancy.” *Follicular monitoring was done by transvaginal ultrasonography (TVS)* *“A level of R100 pg/mL of serum E2 was considered satisfactory”*
Follow up Duration	2-6 cycles? *“Two consecutive cycles were observed to declare ovulation*

		failure. Six ovulatory cycles were observed for pregnancy."	
Summary Result/s		*"Twenty (62.5%) patients from the letrozole group and 12 (37.50%) patients from the CC group ovulated during the observation period. Mean serum E2 level was 817.75 pg/mL and 448.03 pg/mL in the CC and letrozole groups, respectively, on the day of hCG administration. The mean endometrial thickness on the day of hCG administration was 9.03 mm and 10.37 mm in the CC and letrozole groups, respectively. The mean D21 serum P was 13.09 ng/mL and 19.09 ng/mL in the CC and letrozole groups, respectively. Thirteen patients from the letrozole group (40.63%) and six patients from the CC group (18.75%) became pregnant."*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT			
Does the study have a clearly focused question and/or PICO?		Yes	"the purpose of our study is to compare the efficacy of 7.5 mg of letrozole with that of 150 mg of CC in patients with PCOS who did not respond to 100 mg of CC."
Does the study have specified inclusion/exclusion criteria?		Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes	
Inclusion criteria		Yes	"Anovulatory patients with PCOS, who failed to ovulate when taking 100 mg/day CC for 5 days in two consecutive cycles. Polycystic ovary syndrome was diagnosed by the Rotterdam criteria (19). Those patients who did not develop follicles of optimum size (>17 mm) by day 16 of the cycle were recruited for this study."
Exclusion criteria		Yes	."Patients who had hyperprolactinemia, thyroid disorder, male factor infertility, known or suspicious tubal factor infertility (endometriosis and pelvic inflammatory disease), and unexplained infertility were excluded from the study."
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Not enough information	*Patients were divided by lottery.*
	Was allocation to intervention group concealed?	Not reported	

PERFORMANCE BIAS	**Were patients blind to intervention group?**	Not reported	
	Were investigators and care providers blind to intervention group?	Not reported	
	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	0% Not reported	*Apparently no drop-outs*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Not reported	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Not reported	

CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes	*"Characteristics of age, duration of infertility, and basal hormone levels (Table 1) were similar in both groups of patients."*
	If confounding was present, was it controlled for?	Not reported	*N/A*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Not reported	
	Was the study sufficiently powered to detect any differences between the groups?	Not reported	
	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS		*Lack of randomisation and blinding key reason for high RoB*	
What is the overall risk of bias?		High	*High - Few or no criteria fulfilled or the conclusions of the study are likely or very likely to be affected.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

Study ID	*Begum 2013*

Study Citation	Begum, M. R., S. Akhter, et al. (2013). "Pretreatment and co-administration of oral anti-diabetic agent with clomiphene citrate or rFSH for ovulation induction in clomiphene-citrate-resistant polycystic ovary syndrome." Journal of Obstetrics & Gynaecology Research 39(5): 966-973.
Study Country	Bangladesh
BRIEF CHARACTERISTICS OF RCT	
	Infertile patients with CC-resistant PCOS. All patients were insulin resistant (by HOMA) Age (years) A: 26.96 ± 4.05 B: 26.84 ± 5.13 C: 27.15 ± 4.20 p=0.830 Body mass index (kg/m2) A: 27.71 ± 3.61 B: 28.36 ± 4.54 C: 28.98 ± 3.19 p=0.554
PCOS diagnostic criteria	"PCOS was diagnosed according to the revised Rotterdam criteria and included two of the following three findings: (i) oligo or anovulation; (ii) clinical and/or biochemical signs of hyperandrogenism; and (iii) polycystic ovaries according to ultrasonography"
Presence of infertility	*Duration of infertility (years)* *Group A (Mean ± SD) 6.13±2.38* *Group B 5.06±3.04* *Group C 4.72±2.78* *Type of infertility* *Primary:* *Group A: 94.55%* *Group B: 80%* *Group C: 74.55%*
Presence of other condition/s	*Not reported*
Medication History	*Not reported*
N per group	Randomised and analysed: 165 participants - 55 in each group (3 groups)
Setting	"Outpatient Department of Obstetrics and Gynecology of Dhaka Medical College and Hospital and the Infertility Care and Research Centre, Dhaka. The study was carried out from December 2004 until August 2009."
Intervention 1	Group A/M+CC: 500 mg metformin three times daily (1500 mg) for 4 weeks. After 4 weeks, the same dose was continued for another 6 months along with scheduled CC 150 mg daily for 5 days (D3–D7 of the cycle).
Intervention 2	Group B/M+rFSH: 500 mg metformin three times daily (1500 mg) for 4 weeks. After 4 weeks, the same dose was continued for another 6 months along with 75 IU rFSH every alternate day starting from D3 of the cycle (then daily if necessary after first monitoring on D12) till maturity of follicles or maximum 15 doses of rFSH.

Comparison/ control	Group C /rFSH alone: 75 IU rFSH every alternate day starting from D3 of the cycle (then daily if necessary after first monitoring on D12) till maturity of follicles or maximum 15 doses of rFSH.	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Primary: clinical pregnancy that occurred within six ovulatory cycles and resultant live birth. Secondary: ovulation, spontaneous abortion, ectopic pregnancy, multiple pregnancies, congenital anomaly and other adverse perinatal or obstetric complications. Serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid-stimulating hormone (TSH), prolactin, dehydroepiandrosterone sulfate and free testosterone were assayed by VIDAS. Oral glucose tolerance test was done to exclude diabetes mellitus. Fasting serum insulin level was measured to identify insulin resistance Insulin resistance was identified by calculating fasting glucose insulin ratio and homeostatic model assessment (HOMA).	
Follow up Duration	Six ovulatory cycles were assessed.	
Summary Result/s	*"*Ovulation (89.09%) and pregnancy (54.55%) rates were higher in group B. Ovulation (74.55%) and pregnancy (29.09%) rates were also satisfactory in group C but a dose of rFSH requirement was significantly higher (*P* = 0.000). In group A, both ovulation and pregnancy rate were much lower than the other two groups (27.27% and 12.73%, respectively)."	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes	*"*The objective of this study was to explore the result of pre-treatment and concomitant use of metformin with clomiphene citrate (CC) and rFSH for ovulation induction in clomiphene-citrate-resistant polycystic ovary syndrome (PCOS)."
Does the study have specified inclusion/exclusion criteria?	Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes	
Inclusion criteria	Yes	"PCOS was diagnosed according to the revised Rotterdam Criteria." "PCOS patients who did not produce any mature follicle with 150 mg clomiphene citrate daily for 5 days for two consecutive cycles were considered as CC-resistant8 and were recruited for the study." "All patients were included in the study irrespective of body mass index (BMI)."

Exclusion criteria		Yes	"Patients having hypothyroidism, hyperprolactinemia, altered glucose metabolism, associated endometriosis and pelvic inflammatory disease, suspected or proven tubal factor infertility and partners' abnormal semen parameters were excluded from the study."
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes	"Patients were divided into three treatment groups, group A, group B and group C by lottery." *Methodology not clear though*
	Was allocation to intervention group concealed?	Not reported	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Not reported	*However,* difficult to maintain blinding given the nature of the interventions ie. pill v pill + injection.
	Were investigators and care providers blind to intervention group?	Not reported	
	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes	"Ovulation was confirmed by: (i) transvaginal ultrasonography by observing collapse of the follicle, fluid in the Pouch of Douglas ortriple-lined endometrial development; and (ii) D21 serum progesterone level. A D21 serum progesterone level of ≥5 ng/mL was considered ovulatory."
	Were outcomes assessed objectively and independently?	Yes	

ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	0% treatment 0% control/ comparison	*None reported*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Not reported	*No dropouts*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Not reported	Difficult to determine without a protocol.
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes	"There was no significant difference between the groups regarding age, duration of marriage and duration of infertility (P > 0.05)…All were comparable between the groups and there were no significant differences in baseline parameters (P > 0.05)."
	If confounding was present, was it controlled for?	Not reported	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	No	The authors declare that: Nothing to be disclosed by any author.
	Was the study sufficiently powered to detect any differences between the groups?	Not reported	

	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS		*Unblinded Missing details on randomisation, dropouts, blinding etc*	
What is the overall risk of bias?		High	*Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.* lacks info on blinding, randomisation and dropouts
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

Study ID	De Leo 1999
Study Citation	De Leo V, la Marca A, Ditto A, Morgante G, Cianci A. Effects of metformin on gonadotropin-induced ovulation in women with polycystic ovary syndrome. Fertil Steril. 1999 Aug;72(2):282-5. doi: 10.1016/s0015-0282(99)00208-3. PMID: 10438996.
Study Country	Italy
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	N=20 FSH Age: 28.0 ± 4.0 BMI: 27.7 ± 3.1 FSH + metformin Age: 29.5 ± 2.9 BMI: 26.9 ± 4.8
PCOS diagnostic criteria	Chronic oligomenorrhea (fewer than six menstrual periods in the previous year) or amenorrhea and hyperandrogenemia (elevated serum free testosterone concentrations) Ultrasonographic diagnosis of PCOS was based on the presence of 10 or more follicles (2–10 mm in diameter) in one or both ovaries
Presence of infertility	n of infertility (y) 8 ±1 metformin 3.2 ± 0.8
Presence of other condition/s	hene Citrate–resistant PCOS (defined as failure to ovulate or conceive after clomiphene citrate treatment up to a daily dose of 150 mg from cycle days 3–7 during at least three consecutive cycles)

Medication History	"All women had pretreatment concentrations of FSH within normal limits and were normoprolactinemic, normotensive, and had no evidence of any other serious medical disorder. All had normal thyroid function. Their partners had adequate seminal parameters. **None of the women had taken medicines for at least 2 months before the study**."	
N per group	N=20 n=10 FSH n=10 FSH + metformin	
Setting	Department of Obstetrics and Gynaecology, University of Siena.	
Intervention	FSH (75 IU one ampoule per days for x5 days increasing by one ampule per day until an ultrasonically detectable ovarian response was obtained) for 2 cycles, then 1 month with metformin cycle, and then a cycle of combined metformin and FSH	
Comparison	Metformin for a month before undergoing ovarian stimulation with combined metformin and FSH for one cycle	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Not reported under methods. The following outcomes were extracted from results section. Number of cycles FSH (number of ampoules) Days of treatment Daily effective dose (no. of ampules) E2 level (ng/dL) Follicles >15 mm No. of pregnancies (%) No. of cycles with hCG withheld (%) No. with hyperstimulation after hCG (%) Plasma LH, FSH, E2, T, androstenedione (A) were measured by double-antibody RIA with use of Radim kits (Rome, Italy) for LH and FSH; Sorin kits (Saluggia, Italy) for A and T; and Biodata Kits (Rome, Italy) for E2.	
Follow up Duration	NR. AT least 4 cycles based on intervention	
Summary Result/s	"The number of follicles >15 mm in diameter on the day of hCG administration was significantly lower in cycles performed after metformin treatment. The percentage of cycles with hCG withheld because of excessive follicular development was significantly lower in cycles treated with metformin. Plasma levels of E2 were significantly higher in cycles treated with FSH alone than in those treated with FSH and metformin"	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes	"The aim of the present study was to evaluate whether metformin administration improves ovarian response to exogenous gonadotropin in women with clomiphene-resistant PCOS."
Does the study have specified inclusion/exclusion criteria?	Partial	

If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes	
Inclusion criteria		Partial	Normal pre-treatment FSH concentration Normoprolactinemic Normotensive No evidence of any other serious medical disorder Partners with adequate seminal parameters
Exclusion criteria		Partial	Congenital adrenal hyperplasia
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes	"The women were divided randomly, on the basis of a random number table, into two groups of 10 subjects…"
	Was allocation to intervention group concealed?	Not reported	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Not reported	
	Were investigators and care providers blind to intervention group?	Not reported	
	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Partial	

	Were outcomes assessed objectively and independently?	Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	Not reported	Apparently, no drop-outs
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Not reported	Outcomes of interest not reported in materials and methods, so difficult to assess because there is no protocol available (pre-2010 study)
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes	"As shown in Table 1, there were no statistically significant differences in age, duration of infertility, body mass index (BMI), and in hormonal data between the women divided according to treatments."
	If confounding was present, was it controlled for?	Not reported	N/A (see above)
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Not reported	
	Was the study sufficiently powered to detect any differences between the groups?	Not reported	

	If statistical analysis was undertaken, was this appropriate?	Yes	"The results are expressed as means 6 SD. Non–Gaussian-distributed variables were logarithmically transformed before analysis."
COMMENTS			
What is the overall risk of bias?		High	No information on concealment of allocation, blinding and pre-specified outcome data
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?			

Study ID	*Fleming, 2002*
Study Citation	*Fleming, R., Hopkinson, Z. E., Wallace, A. M., Greer, I. A., & Sattar, N. (2002). Ovarian function and metabolic factors in women with oligomenorrhea treated with metformin in a randomized double blind placebo-controlled trial. The Journal of Clinical Endocrinology & Metabolism, 87(2), 569-574.*
Study Country	UK
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	*who had previously failed to conceive or ovulate with CC treatment and undergoing IUI*
PCOS diagnostic criteria	Rotterdam
Presence of infertility	*Infertility in:* *No. of patients: placebo-treated, 47 (infertile, 19; hirsutism, 22); metformin-treated, 45 (infertile, 23; hirsutism, 13). P values are NS.*
Presence of other condition/s	*Blood samples were taken for assays of E2, T, androstenedione LH, FSH, triglycerides, cholesterol, lowdensity* *lipoprotein (LDL) cholesterol, and HDL cholesterol. Then, a standardized 75-g oral glucose tolerance test (GTT) was undertaken with blood samples collected at 0, 60, and 120 min for determination of serum glucose and insulin concentrations.*
Medication History	*NR*
N per group	*94 patients randomized, 2 withdrew before treatment commenced, 47 received placebo, and 45 received*

Setting	*University Departments of Obstetrics and Gynecology (R.F., Z.E.H., I.A.G.) and Pathological Biochemistry Royal Infirmary, Glasgow,*	
Intervention	*etrozole (Letroz, Sun Pharmaceuticals, Mumbai, India) 2.5 mg twice daily,*	
Comparison	*CC (Ovofar, Organon India Limited, Mumbai, India) 100 mg daily from day 3 to day 7 of the menstrual cycle and two ampoules of rFSH*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Biochemical pregnancy rate =Y*	
Follow up Duration	*16 Weeks*	
Summary Result/s	*using a comprehensive, detailed endocrinological assessment of ovarian function, we have shown that metformin treatment increases ovulation rates by a significant but modest degree in women with oligomenorrhea and PCOS. Continued treatment also resulted in significant weight loss (and leptin reduction) and an associated change in HDL cholesterol.*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes	*our study was to use a double-blind, placebo-controlled approach with detailed assessment of ovarian activity (two blood samples per week) to assess the validity of this therapeutic approach in this group of women.*
Does the study have specified inclusion/exclusion criteria?	Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes	
Inclusion criteria	Yes	*Women with oligomenorrhea (cycle length41d;8 cycles per year) or amenorrhea and PCOs, aged less than 35 yr,*
Exclusion criteria	Yes	*Patients with significant hyperprolactinemia, abnormal thyroid function tests, and congenital adrenal hyperplasia were excluded.*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes	
	Was allocation to intervention group concealed?	Yes	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes	
	Were investigators and care providers blind to intervention group?	Yes	
	Aside from the experimental intervention, were the groups treated the same?	Partial	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes	
	Were all outcomes measured in a standard, valid and reliable way?	Partial	
	Were outcomes assessed objectively and independently?	Partial	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**		*2 withdrew before treatment commenced, 47 received placebo, and 45 received metformin*

	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Partial	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Partial	
	If confounding was present, was it controlled for?	Not reported	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Not reported	
	Was the study sufficiently powered to detect any differences between the groups?	Yes	The study power was based upon predicted changes in the ovulation rate and circulating lipoprotein concentrations, using data derived from the literature and our own pilot study
	If statistical analysis was undertaken, was this appropriate?	Partial	

COMMENTS		
What is the overall risk of bias?	Moderate	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*No-all Moderate high risk of bias*	

Study ID	*Ghanem 2013*
Study Citation	Ghanem, M. E.; Elboghdady, L. A.; Hassan, M.; Helal, A. S.; Gibreel, A.; Houssen, M.; Shaker, M. E.; Bahlol, I.; Mesbah, Y. Clomiphene citrate cotreatment with low dose urinary FSH versus urinary FSH for clomiphene resistant PCOS: randomized controlled trial.[Erratum appears in J Assist Reprod Genet. 2014 Apr;31(4):505-6]. *J Assist Reprod Genet* **2013**, 30, 1477- 85
Study Country	? Egypt
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	FSH= 24.7±4.3 years FSH+CC= 24.8±4.7 years BMI: FSH= 33.2±5.7 kg/m² FSH + CC= 33.3±5.4 kg/m²
PCOS diagnostic criteria	Rotterdam
Presence of infertility	Mixture of primary and secondary infertility
Presence of other condition/s	Clomiphene citrate resistance. This was the first time these women were undergoing this particular protocol.
Medication History	'Use of medications known to alter insulin secretion or action either currently or within the previous 3 months was an exclusion criteria'.
N per group	The number of participants that were: □ Allocated/randomised: 87 per group □ Assessed at end of study: per protocol- FSH= 77, FSH + CC= 82
Setting	Not reported. Authors based in Egypt.

Intervention	‘37.5 IU/day HP uFSH from the 3rd to the 13th cycle day…if the follicle diameter was medium sized [12–15 mm] the starting dose was maintained. Should the growing follicle[s] was smaller; an increment of 37.5 IU was made. The lowest dose that achieved significant follicular increase was maintained until hCG ovulation trigger. Subsequent visits were scheduled according to ovarian response until the leading follicle mean diameter reached ≥18 mm. At this time ovulation was triggered by injection of hCG 10,000 IU [Choriomon, IBSA, Switzerland] and regular sexual relation advised’	
Comparison	‘CC in 100 mg daily doses for 5 days plus intramuscular injection of 37.5 IU/day HP uFSH from the 3rd to the 13th cycle day…if the follicle diameter was medium sized [12–15 mm] the starting dose was maintained. Should the growing follicle[s] was smaller; an increment of 37.5 IU was made. The lowest dose that achieved significant follicular increase was maintained until hCG ovulation trigger. Subsequent visits were scheduled according to ovarian response until the leading follicle mean diameter reached ≥18 mm. At this time ovulation was triggered by injection of hCG 10,000 IU [Choriomon, IBSA, Switzerland] and regular sexual relation advised’	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Primary outcome: ovulation rate Secondary outcome: clinical pregnancy rate per woman randomized	
Follow up Duration		
Summary Result/s	*“Our results have demonstrated that group I compared to group II had significantly higher ovulation rate per intention to treat [ITT] [72.4 % vs. 34.2 %,* p < *0.001]. Clinical pregnancy and live birth rates were comparable between the two groups. Group I consumed significantly lower total FSH dose and needed significantly shorter stimulation duration compared to group II.”*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes	*“The aim of this study was to examine the effect of clomiphene citrate [CC] co-administration during the use of exogenous low-dose urinary FSH [uFSH] for induction of ovulation in CC-resistant infertile PCOS women”*
Does the study have specified inclusion/exclusion criteria?	Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes	
Inclusion criteria	Yes	‘CC-resistant PCOS women, age between 18 and 38 years, fertile semen according to WHO standards as regard sperm concentration, motility and Kruger’s strict criteria for sperm morphology, patent fallopian tubes proved by hysterosalpingography and/or dye test with laparoscopy

			within the preceding 6 months, no history of previous genital surgery and no history of treatment by exogenous gonadotropin'
Exclusion criteria		Yes	'Exclusion criteria were: presence of any infertility factors other than anovulatory PCOS, use of medications known to alter insulin secretion or action either currently or within the previous 3 months, presence of other endocrinopathies'
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes	Computer generated random numbers
	Was allocation to intervention group concealed?	Partial	Sequentially numbered opaque and sealed envelopes can be subject to manipulation
PERFORMANCE BIAS	**Were patients blind to intervention group?**	No	
	Were investigators and care providers blind to intervention group?	No	
	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Not reported	Most outcomes are objective measures

ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**		FSH= 11.5% FSH + CC= 5.7%
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes	ITT and analysis per protocol data presented
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes	
	If confounding was present, was it controlled for?	N/A	No report of confounding
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	No	"The authors report no declarations of interest."
	Was the study sufficiently powered to detect any differences between the groups?	Partial	Required sample size for study to be powered was 160, 159 completed the study

	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS		Data used from erratum where required	
What is the overall risk of bias?		Moderate	*Moderate - Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

Study ID	George 2003
Study Citation	George SS, George K, Irwin C, Job V, Selvakumar R, Jeyaseelan V, Seshadri MS. Sequential treatment of metformin and clomiphene citrate in clomiphene-resistant women with polycystic ovary syndrome: a randomized, controlled trial. Hum Reprod. 2003 Feb;18(2):299-304. doi: 10.1093/humrep/deg105. PMID: 12571165.
Study Country	India
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Infertile CC-resistant women with PCOS (diagnosis of PCOS was based on clinical features of oligomenorrhoea and hyperandrogenism, along with either biochemical abnormalities of a raised LH/FSH ratio or LH or ultrasound features of polycystic ovary). Age Metformin: 25.1±3.0 hMG: 26.0± 2.9 BMI Metformin: 25.5±3.7 hMG: 24.6±2.6
PCOS diagnostic criteria	PCOS (diagnosis of PCOS was based on clinical features of oligomenorrhoea and hyperandrogenism, along with either biochemical abnormalities of a raised LH/FSH ratio or LH or ultrasound features of polycystic ovary)
Presence of infertility	women were included but no more information
Presence of other condition/s	hene resistant (defined as failure to ovulate to a dose schedule of 200 mg/day for 5 days)

	er medical conditions: “Laboratory investigations showed that all women had normal liver, renal and thyroid function, glucose tolerance and prolactin levels.”
Medication History	NR
N per group	N=60
Setting	Reproductive Medicine Unit of Christian Medical College in southern India between 1999 and 2001
Intervention	Group 1: (n=30) Metformin for 1500 mg/day in three divided doses for 6 months, followed by ovulation induction with clomiphene citrate 150mg/day (increased to 200mg if not ovulated) + metformin
Comparison	Group 2: (n=30) hMG 75 IU increased by increments of 75 units every 7-10 days if no ovarian response (n=30)
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Outcomes of interest not clearly specified under materials and methods. No protocol available Serum FSH, LH, glucose, insulin, testosterone, SHBG Follicular monitoring was carried out using ultrasound scan to study the ovulatory response FSH and LH were measured using a two-site sandwich immunoassay DHEAS and insulin were also estimated using solid-phase competitive radio-immunoassays
Follow up Duration	6 months + 3 cycles
Summary Result/s	“There was no significant difference in pregnancy rates between the two groups (16.7 versus 23.3%). In group I, there was a significant improvement in menstrual function and ovulation after treatment (40%, P < 0.001; and 46.7%, P < 0.001), with a significant decrease in fasting insulin levels (P <0.05). There were no changes in other biochemical parameters. The ovulation rate in group II was 43.3%, with a high drop-out rate. The cost-effective analysis for medications per pregnancy in group I was US$ 71 ± 3 versus US$ 277 ± 171 in group II.”

ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes	“A randomized, controlled trial was conducted to determine whether sequential treatment with metformin and clomiphene citrate would be as effective as hMG in improving ovulation and pregnancy rates in clomiphene-resistant PCOS women.”
Does the study have specified inclusion/exclusion criteria?	Partial	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes	

Inclusion criteria		Partial	PCOS
Exclusion criteria		Yes	Women with associated tubal or male factor infertility and those with a body mass index (BMI) >35 kg/m2
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes	"Block randomization was carried out using RALLOC software, with concealment of treatment allocation by use of opaque envelopes."
	Was allocation to intervention group concealed?	Yes	Opaque envelopes
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Not reported	
	Were investigators and care providers blind to intervention group?	Not reported	
	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes	The outcomes related to serum immune-assays were measured using standard methods
	Were outcomes assessed objectively and independently?	Yes	The outcomes related to serum immune-assays were measured using standard methods

ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	10% treatment 10% control/ comparison Not reported	3 dropped out in Metformin group (group 1) 3 dropped out in hMG group (group 2)
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes	ITT
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Not reported	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes	"The groups did not differ with respect to either anthropometric variables or biochemical values (Table I)."
	If confounding was present, was it controlled for?	Not reported	N/A
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Not reported	
	Was the study sufficiently powered to detect any differences between the groups?	Yes	"The accepted pregnancy rate with hMG is ~40%, and the expected pregnancy rate in the metformin group was 25%. However, it was decided to favour metformin even if the difference was 20%. By keeping alpha and beta errors at 5 and 20% respectively, the calculated sample size was 30 in each arm of the trial."

	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS			
What is the overall risk of bias?		Moderate	No information on blinding and pre-specified outcome data – blinding not possible with this comparison though so judged as moderate
Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?			

Study ID	*Hoeger, 2004*
Study Citation	*Hoeger, K. M., Kochman, L., Wixom, N., Craig, K., Miller, R. K., & Guzick, D. S. (2004). A randomized, 48-week, placebo-controlled trial of intensive lifestyle modification and/or metformin therapy in overweight women with polycystic ovary syndrome: a pilot study. Fertility and sterility, 82(2), 421-429.*
Study Country	USA
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	*All subjects were overweight or obese,* *with a minimum body mass index (BMI) of >25 mg/kg2*
PCOS diagnostic criteria	Rotterdam
Presence of infertility	*NR*
Presence of other condition/s	*All subjects were overweight or obese,* *with a minimum body mass index (BMI) of >25 mg/kg2.*
Medication History	*NR*
N per group	• *lifestyle modification plus metformin 850 mg two times per day (n=9)* • *lifestyle modification plus placebo (n=11)* • *lifestyle + metformin (n=9)* • *placebo alone (n=9)*
Setting	*Academic medical centre*
Intervention	*All subjects (n=38) were randomized to one of four 48-week interventions: metformin 850 mg two times per day,*

	• *lifestyle modification plus metformin 850 mg two times per day (n=9)* • *lifestyle modification plus placebo (n=11)* • *lifestyle + metformin (n=9)* • *placebo alone (n=9)*	
Comparison	*a lifestyle modification program with placebo by mouth two times per day*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Biochemical pregnancy rate*	
Follow up Duration	*48 weeks*	
Summary Result/s	*It was necessary to screen seven women to have one subject randomized. The dropout rate was >39%, with the majority of dropouts occurring within the first 24 weeks. Mean body mass index was >39 mg/kg2. Modest weight reduction was found in all treatment groups, with the most significant reduction occurring with the combination of metformin and lifestyle intervention. Significant androgen reduction occurred in the combination group only. Ovulation rates did not differ significantly between groups. However, when data were analyzed by presence or absence of weight reduction in subjects, independent of treatment group, the estimated odds ratio for weight loss was 9.0 (95% confidence interval 1.2-64.7) with respect to regular ovulation. If weight loss occurred during metformin therapy, the odds ratio for regular ovulation was 16.2 (95% confidence interval 4.4-60.2).*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes	
Does the study have specified inclusion/exclusion criteria?	Partial	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Partial	
Inclusion criteria	Partial	
Exclusion criteria	Partial	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes	*The randomization schedule was computer generated in blocks by an independent pharmacy representative, and the block schedule was blinded to the investigators.*
	Was allocation to intervention group concealed?	Partial	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes	
	Were investigators and care providers blind to intervention group?	Partial	
	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes	
	Were all outcomes measured in a standard, valid and reliable way?	Partial	
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**		*9 treatment 11 control* *"In this pilot study, overall dropout was 39%. The majority of subjects (34%) dropped out in the first 16 weeks "of the study.*

	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes	
	If confounding was present, was it controlled for?	Partial	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	No	
	Was the study sufficiently powered to detect any differences between the groups?	Yes	
	If statistical analysis was undertaken, was this appropriate?	Yes	

COMMENTS	*Lack of randomisation and blinding key reason for high RoB*	
What is the overall risk of bias?	Moderate	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*all outcomes Moderate risk of bias*	

Study ID	**Homburg 2012**
Study Citation	Homburg R, Hendriks ML, König TE, and Anderson RA, et al., Clomifene citrate or low-dose FSH for the first-line treatment of infertile women with anovulation associated with polycystic ovary syndrome: a prospective randomized multinational study. Hum Reprod. 2012 Feb;27(2):468-73. doi: 10.1093/humrep/der401. Epub 2011 Nov 28. PMID: 22128296.
Study Country	Europe and South America
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Infertile women (<40 years old) with PCOS-related anovulation, without prior ovulation induction treatment. Age (years) CC: 29.4 (SD 4.0) FSH: 29.8 (3.8) BMI (kg/m2) CC: 25.7 (6.0) FSH: 25.1 (5.2)
PCOS diagnostic criteria	Rotterdam
Presence of infertility	Infertility duration not reported and some might have had previous pregnancies "Treatment-naive women (n=302) with anovulatory or oligo-ovulatory infertility associated with PCOS…" "Tubo-peritoneal evaluation was performed only in subjects with a previous history of pregnancy resulting in a spontaneous abortion, a previous history of gynaecological or abdominal surgical intervention or pelvic inflammatory disease. Those admitted to the study all had a normal uterine cavity and tubal patency demonstrated by radiological (hysterosalpingogram), laparoscopic or ultrasonic means before entering the study. Male partners all had a normal semen analysis conforming to World Health Organization criteria (World Health Organization, 1999)."
Presence of other condition/s	*Not reported*
Medication History	*Not reported*
N per group	302 randomized – 143 participants to CC (340 cycles) and 159 participants to low-dose FSH (326 cycles).

	Analysed participants: 123 in CC (310 cycles) and 132 in FSH (288 cycles)	
Setting	10 centres throughout Europe and South America from August 2005 to March 2009.	
Intervention	CC: "The starting dose of CC was 50 mg/day (oral) for 5 days from Day 4 of a spontaneous or progestin-induced menstruation, rising by 50 mg/day up to 150 mg in subsequent cycles if ovulation was not achieved."	
Comparison	FDH: "Recombinant human FSH (Puregon, Schering-Plough, Houten, The Netherlands) was given s.c. in a low-dose protocol starting with 50 IU on cycle day 4, with weekly increments of 25 IU as necessary to induce a follicular response (Leader, 2006)."	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Primary: Clinical pregnancy rate; Secondary: Rates of miscarriage, multiple pregnancies, live births.	
Follow up Duration	*Three treatment cycles*	
Summary Result/s	"Per protocol analysis revealed that reproductive outcome was superior after OI with FSH than with CC with respect to PR per first cycle [30 versus 14.6%, respectively, 95% confidence interval (CI) 5.3–25.8, P ¼ 0.003], PR per woman, (58 versus 44% of women, 95% CI 1.5–25.8, P ¼ 0.03), LBR per woman (52 versus 39%, 95% CI 0.4–24.6, P ¼ 0.04), cumulative PR (52.1 versus 41.2%, P ¼ 0.021) and cumulative LBR (47.4 versus 36.9%, P ¼ 0.031), within three cycles of OI."	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes	
Does the study have specified inclusion/exclusion criteria?	Partial	*""Subjects were <40 years old. There were no weight or BMI restrictions…Those admitted to the study all had a normal uterine cavity and tubal patency demonstrated by radiological (hysterosalpingogram), laparoscopic or ultrasonic means before entering the study. Male partners all had a normal semen analysis conforming to World Health Organization criteria (World Health Organization, 1999)."* *Exclusion criteria not reported*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes	
Inclusion criteria	Partial	*"Subjects were <40 years old. There were no weight or BMI restrictions…Those admitted to the study all had a normal uterine cavity and tubal patency demonstrated by*

			radiological (hysterosalpingogram), laparoscopic or ultrasonic means before entering the study. Male partners all had a normal semen analysis conforming to World Health Organization criteria (World Health Organization, 1999).”
Exclusion criteria		Not reported	
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes	Computer-generated randomization. Randomization was stratified by centre in blocks of 20 inclusions per centre.
	Was allocation to intervention group concealed?	Partial	Sealed opaque envelopes
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Not reported	Difficult to maintain blinding given the nature of the interventions ie. pill v injection.
	Were investigators and care providers blind to intervention group?	Not reported	
	Aside from the experimental intervention, were the groups treated the same?	Yes	To be sure it’s the intervention which is responsible for the effect.
TECTION	**Were outcome assessors blind to intervention group?**	Not reported	

	Were all outcomes measured in a standard, valid and reliable way?	Yes	"Clinical pregnancy was defined as a pregnancy diagnosed by ultrasonographic visualization of one or more gestational sacs with at least one foetus at 6–7 weeks gestation and this pregnancy was deemed as ongoing pregnancy if it continued for more than 20 completed weeks of gestation. A miscarriage was defined as the spontaneous loss of a clinical pregnancy before 20 completed weeks of gestation and a multiple pregnancy as one in which there was more than one foetus. A live birth was defined as the birth of a viable infant, reported on a clinical research form transmitted to the co-ordinating centre."
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	14% CC 17% FSH	20 CC; 27 FSH "In the CC group, 20 patients did not complete the full study (5 inter-cycle and 1 chemical pregnancy and 14 for personal reasons) compared with 27 in the FSH group (4 inter-cycle and 3 chemical pregnancies, 19 for personal reasons and 1 following a cycle cancelled because of overstimulation).
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes	"Both per protocol analysis and intention-to-treat analysis were carried out."
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Not reported	Difficult to determine without a protocol. "This study was reported according to the CONSORT criteria for RCTs comparing medical treatment in two different arms."
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Partial	"The only demographic or clinical differences between the randomized groups, confirmed by multivariate analysis, were a higher prevalence of clinical hyperandrogenism ($P < 0.01$) and higher serum DHEAS concentrations ($P < 0.04$) in the CC group"

	If confounding was present, was it controlled for?	Not reported	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	No	The authors declared that there were no conflicts of interest. "This study was supported by an unrestricted educational grant from Organon, Oss, The Netherlands (now MSD/ Schering-Plough). The company played no part in study design, collection analysis, interpretation of data, writing of the report nor decision to submit the paper for publication. No medications were supplied"
	Was the study sufficiently powered to detect any differences between the groups?	Partial	"A power calculation, using Russ Lenth's power and sample size comparing two proportions (Lenth, 2006–2009) demonstrated that 150 subjects were required in each arm to achieve a relative increase in PR of 50% from 35 to 52.5% with 80% power, a significance level of 0.05 and allowing for a total of 50 drop outs from the study."
	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS			
What is the overall risk of bias?		Moderate	*Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

Study ID	*Johnson, 2010*
Study Citation	*Johnson, N. P., Stewart, A. W., Falkiner, J., Farquhar, C. M., Milsom, S., Singh, V. P., ... & REACT-NZ (REproduction And Collaborative Trials in New Zealand), a multi-centre fertility trials group. (2010). PCOSMIC: a multi-centre randomized trial in women with PolyCystic Ovary Syndrome*

	evaluating Metformin for Infertility with Clomiphene. Human reproduction, 25(7), 1675-1683.
Study Country	New Zealand
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	*Women with oligo- or anovulatory infertility owing to PCOS. 6 to 24% of patients had past treatment with metformin or clomiphenes citrate.* *Age:* *Metformin: 28.9 ± 4.4 years* *Clomiphene citrate: 28.2 ± 4.0 years* *BMI* *M=26.5±3.5* *CC+M=26.9+4.1*
PCOS diagnostic criteria	Rotterdam
Presence of infertility	
Presence of other condition/s	*14 to 20% of patients had past treatment with CC.* *Couples who had undergone previous fertility treatment involving > 5 months treatment with CC were excluded*
Medication History	*important medical disorders were assessed*
N per group	*Total with BMI ≤32 = 71* *Metformin = 35* *Clomiphene citrate = 36*
Setting	*Four recruiting centres in New Zealand*
Intervention **Comparison**	*Metformin 500 mg standard release tablets, CC 50 mg tablets with identical placebo tablets (to maintain blinding) for both metformin and CC. Each patient received up to two 3-month treatment packages. Drugs were commenced concurrently and standard monitoring as for a CC cycle was undertaken in each case, with any required dose modifications initiated as previously described (Johnson, 2006). Briefly, metformin 500 mg three times daily in a gradual increasing dose over 2 weeks was given; for CC 50 mg was the initial dose and 150 mg the highest dose used. All study drugs were stopped once pregnancy was diagnosed.*
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Primary outcome: clinical pregnancy that occurred within 6 months of randomization and resultant live birth* *Secondary outcomes: adverse events, ovulation, spontaneous abortion, ectopic pregnancy, multiple pregnancy and other adverse perinatal or obstetric complications.*
Follow up Duration	*Treatment duration: 6 months*
Summary Result/s	*For women with BMI . 32 kg/m2, clinical pregnancy and live birth rates were 22% (7/32) and 16% (5/32) with metformin, 15% (5/33) and 6% (2/33) with placebo. For women with BMI ≤ 32 kg/m2, clinical pregnancy and live birth rates were 40% (14/35) and 29% (10/35) with metformin, 39% (14/36) and 36% (13/36) with CC, 54% (19/35) and 43% (15/35) with combination metformin plus CC.*

ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT			
Does the study have a clearly focused question and/or PICO?		Yes	*to assess whether metformin provides benefit when added to standard treatment and to assess the best first line treatment for women with ovulation dysfunction related to PCOS*
Does the study have specified inclusion/exclusion criteria?		Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes	
Inclusion criteria		Yes	*However, women known to have stage 1 or 2 endometriosis and men with very mild oligospermia, with sperm count ≥15 million per ml, were included.*
Exclusion criteria		Yes	*Excluded couples who had undergone previous fertility treatment involving more than 5 months treatment with CC or metformin.*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Not reported	*Method of randomization was not reported in this paper. It may have been reported in Johnson 2006.*
	Was allocation to intervention group concealed?	Yes	*"Allocation concealment was strictly maintained by a telephone call from the recruiting research nurse to pharmacy, the research pharmacist then executing the assignment by dispensing pre-prepared drugs in a true third party randomization"*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes	*"Blinding (masking) of all parties was maintained in all cases by placebo control until the end of the course of treatment or, in the event of pregnancy, until after the pregnancy".*
	Were investigators and care providers blind to intervention group?	Yes	*"Blinding (masking) of all parties was maintained in all cases by placebo control until the end of the course of treatment or, in the event of pregnancy, until after the pregnancy".*

	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes	*"Blinding (masking) of all parties was maintained in all cases by placebo control until the end of the course of treatment or, in the event of pregnancy, until after the pregnancy".*
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**		*"Among 36 women with BMI ≤ 32 kg/m2 receiving CC, 32 completed treatment and follow-up (all of whom were fully adherent to treatment)—there was one loss to follow-up and three either stopped or failed to start treatment. Of 35 women with BMI ≤ 32 kg/m2 receiving metformin, 32 completed treatment and follow-up (all of whom were fully adherent)—three breached the protocol by stopping treatment early, one of whom failed to resume treatment after a pregnancy miscarried."* *CC = 4 drop outs (11%)* *Met = 3 drop outs (8.6%)*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes	*"This analysis was conducted on an intention-to-treat basis using 'worst case' assumptions that women lost to follow-up did not become pregnant, or that they did not have a live birth if pregnant at the time of loss to follow-up."*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Not reported	

CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes	
	If confounding was present, was it controlled for?	No	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes	*All conflicts of interest were noted and authors state that "The researchers maintained complete independence from the funders".*
	Was the study sufficiently powered to detect any differences between the groups?	Yes	*""Our power calculation (Johnson, 2006) suggested a sample size of 160 women distributed between the five treatment arms in the study would be required to show an increase in the pregnancy rate from 30 to 55% by adding metformin to standard therapy (to comfortably allow for attainment of at least 122 participants required to have adequate power for this primary comparison of 'standard care' versus 'standard care plus metformin')."* *"A sample size of 61 participants per group was required for 80% power to detect an increase in pregnancy rate from 30% in the 'standard care' group to 55% in the 'standard care plus metformin' group. Thus, 122 analysed participants were required."* *"The target number of 153 analysed participants (92 BMI ≤ 32 kg/m2; 61 BMI >32 kg/m2) was increased to 160 (97 BMI ≤ 32 kg/m2; 63 BMI ≤ 32 kg/m2) to allow for losses to follow-up and the possibility of preferential allocation to one treatment arm."*
	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS		*Lack of randomisation and blinding key reason for high RoB*	

What is the overall risk of bias?	Moderate	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*No – all outcomes Moderate of bias*	

Study ID	*Kar 2015*
Study Citation	*Kar, S., & Sanchita, S. (2015). Clomiphene citrate, metformin or a combination of both as the first line ovulation induction drug for Asian Indian women with polycystic ovarian syndrome: A randomized controlled trial. Journal of human reproductive sciences, 8(4), 197.*
Study Country	India
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	*Women with complaints of infertility and oligomenorrhea*
PCOS diagnostic criteria	Rotterdam
Presence of infertility	*Duration of infertility (years)* *Group I: 2.75 ± 1.56* *Group II: 1.7 ± 1.056* *Group III: 2.53 ± 2.15*
Presence of other condition/s	*"We noted CC resistance in 47.5% women (14/32) who failed to ovulate with 150mg of CC for 5 days."*
Medication History	*NR*
N per group	*Group I (CC 50-150 mg/day),* *Group II (metformin 1700 mg/day),* *Group III (CC + metformin in similar dosage to Groups I and II).* *Patients underwent follicular monitoring and advice on timed intercourse.*
Setting	*private hospital in Bhubaneswar, India*
Intervention	*CC 50-150 mg/day)*
Comparison	*metformin 1700 mg/day*
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Live birth rate; Clinical pregnancy rate; Ovulation rate*

Follow up Duration		*6 months*	
Summary Result/s		*There was no significant difference among the groups in baseline characteristics and biochemical parameters. LBR was 41.6%, 37.5%, and 28.1%, respectively in Groups III, II, and I. Group III (CC + metformin) had the highest ovulation (83.3%), pregnancy (50%), and LBRs (41.6%). Group II(metformin) was as good as Group I (CC) in all the outcomes. CC + metformin (Group III) had statistically significantly higher ovulation rate as compared to CC alone (Group I) (P= 0.03; odds ratio: 95% confidence interval: 3.888 [1.08-13.997]).*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT			
Does the study have a clearly focused question and/or PICO?		Yes	*To compare clomiphene citrate (CC), metformin or the combination of CC and metformin as the first line ovulation induction drug in Asian Indian women with polycystic ovary syndrome (PCOS)*
Does the study have specified inclusion/exclusion criteria?		Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes	
Inclusion criteria		Yes	*Women with PCOS* *"Only treatment naive patients with the 1 st time diagnosis and the evaluation of infertility were included."*
Exclusion criteria		Yes	*"Women with any major systemic illness such as diabetes, liver, heart, or kidney disease were excluded from the study."*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes	*"Eligible women were randomized by picking up envelopes to either one of the three groups, consisting of CC (Group I), metformin (Group II), or a combination of metformin and CC (Group III). Equal numbers of envelopes for the three groups labelled I, II, and III were prepared by a nurse, naive to this study. The patients picked up the envelope and returned to the investigator for further advice."*
	Was allocation to intervention group concealed?	Partial	*Allocation revealed in envelopes but not clear if opaque or sealed*

PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes	*Participants and personnel were blinded*
	Were investigators and care providers blind to intervention group?	Not reported	
	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	*"A total of 105 patients diagnosed as PCOS and found eligible for this study were randomized into thirty-five patients in each group. However, a total of eighty-one women completed the study, that is, 6 months of follow-up, or till pregnant, or CC resistant. Group I 32 patients (104 cycles), Group II 24 (70 cycles), and Group III 24 patients (84 cycles)."* *Dropouts: 25 (3 in the CC group, 11 in metformin group, 11 in combined group - 22.9% dropout rate, without reasons given)*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	No	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Partial	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Partial	
	If confounding was present, was it controlled for?	Partial	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	No	
	Was the study sufficiently powered to detect any differences between the groups?	Partial	
	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS		*Lack of randomisation and blinding key reason for high RoB*	
What is the overall risk of bias?		Moderate	

Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*No – all outcomes Moderate risk of bias*

Study ID	**Kjotrod 2011**
Study Citation	Kjotrod, S. B., S. M. Carlsen, et al. (2011). "Use of metformin before and during assisted reproductive technology in non-obese young infertile women with polycystic ovary syndrome: a prospective, randomized, double-blind, multi-centre study." Human Reproduction 26(8): 2045-2053.
Study Country	Denmark, Finland, Norway and Sweden
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women diagnosed with PCOS, aged <38 years and with a BMI of <28 kg/m2. The majority of patients had previously received unsuccessful clomiphene citrate (CC) treatment. Mean (SD) age, years M: 29.6 (3.4) P: 29.5 (3.8) Mean (SD) BMI, kg/m2 M: 24.0 (2.7) P: 23.6 (2.8)
PCOS diagnostic criteria	Rotterdam
Presence of infertility	*Duration of infertility (years) mean (SD)* *Metformin (n=74) : 2.6 (1.8)* *Placebo (n=75) : 2.8 (1.8)* *Cause of infertility, n* *PCOS only* *Metformin 45* *Placebo 44* *Additional male factor* *Metformin 21* *Placebo 26* *Additional tubal disease* *Metformin 6 (n=38)* *Placebo 6 (n=40)* *Additional endometriosis* *Metformin 4 (n=36)* *Placebo 2 (n=37)*
Presence of other condition/s	*Not reported*
Medication History	*Not reported*
N per group	□ Screened: 179 participants □ Allocated/randomised: 150 participants – M: 74, P:76 □ Assessed pre-ART: M: 74, P:75 □ Followed up – not relevant to this systematic review

Setting	"The study was planned as a multi-centre study (EUDRACTnr-2004-001124-20). Originally a centre in Leeds, UK was planned to be included; but we did not get the approval for study medications by the medical authorities in UK. One private IVF clinic in Helsinki, one in Oslo and one in Cophenhagen were also supposed to participate, but dropped out very early due to recruitment problems. To compensate for this, The Oslo University Hospital was recruited into the study during the last 1.5 years of the inclusion period." February 2005 - March 2010.	
Intervention	Metformin for ≥12 weeks prior to controlled ovarian stimulation (COS). "The dose of metformin was gradually increased from 500 to 2000 mg per day during the first 2 weeks of treatment." (spontaneous pregnancy (SP) group only) "Following a spontaneous menstrual period or a gestagen-induced shedding of the endometrium, pituitary down-regulation (nafarelin, 400 mg administered twice daily intranasally) was initiated (on cycle Day 20)" – assuming this to be post SP group data. The study continued throughout IVF/ICSI, and until the day of pregnancy testing, however we will only collect data relevant to pre-ART.	
Comparison	*Placebo*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Primary: clinical pregnancy rate; Secondary: biochemical pregnancy and live birth rate – these were not reported for SP population. Safety variables included the incidence of adverse events (AEs) and OHSS. *Pregnancy was detected initially by a serum pregnancy test performed on Days 13–15 after embryo transfer and women with a positive test underwent an ultrasound in week 7 of pregnancy*	
Follow up Duration	Haven't used entire study data, only pre ART data. The total study period was ~5 years.	
Summary Result/s	Among IVF treated women (n = 112), biochemical pregnancy rates were identical in both groups (42.9%), and there were no significant differences in the metformin versus the placebo group in CPR [39.3 versus 30.4%; 95% confidence interval (CI): 28.6 to 26.5]. The LBR was 37.5 versus 28.6% (95% CI: 28.4 to 26.3). However, prior to IVF there were 15 (20.3%) spontaneous pregnancies in the metformin group and eight (10.7%) in the placebo group (95% CI: 21.9 to 21.1; P = 0.1047). According to intention to treat analyses (n = 149); significantly higher overall CPR were observed in the metformin versus placebo group (50.0 versus 33.3%; 95% CI: 21.1 to 32.3; P = 0.0391). LBR was also significantly higher with use of metformin versus placebo (48.6 versus 32.0; 95% CI: 1.1 to 32.2; P = 0.0383). No major unexpected safety issues or multiple births were reported. More gastrointestinal side effects occurred in the metformin group (41 versus 12%; 95% CI: 0.15 to 0.42; P< 0.001).	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes	"To study the effect of metformin before and during assisted reproductive technology (ART) on the clinical pregnancy

			rate (CPR) in non-obese women with polycystic ovary syndrome (PCOS)."
	Does the study have specified inclusion/exclusion criteria?	Yes	
	If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes	
	Inclusion criteria	Yes	"The included patients had been trying, unsuccessfully, to conceive for at least 1 year and have a diagnosis of PCOS based on fulfilling at least two of the following three criteria: oligomenorrhoea/ amenorrhoea, clinical or biochemical hyperandrogenism and/or polycystic ovaries on ultrasound (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004)."
	Exclusion criteria	Yes	"Patients were excluded if they were contraindicated for a starting dose of 112.5 IU recombinant human follicle-stimulating hormone (r-hFSH), or had a basal serum FSH level of .10 IU/l. Patients with liver or kidney disease, diabetes mellitus (or fasting plasma glucose ≥7.0 mmol/l), alcoholism or drug abuse were excluded. Patients with hyperprolactinaemia (serum prolactin .700 mIE/l), abnormal thyroid function tests, congenital adrenal hyperplasia, androgen-secreting tumours or Cushing's syndrome were also excluded. Finally, patients who had received oral steroid hormones, cimetidine, anticoagulants, erythromycin or other macrolides were also excluded. A 1-month washout period was required for women who had previously received metformin."
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes	"Randomization was performed in blocks of four by the hospital pharmacy using a computer-generated list."
	Was allocation to intervention group concealed?	Yes	"The trial clinician and a study nurse at each site enrolled the patients." "Identical blister packs containing metformin or placebo tablets (of the same appearance, smell and taste) were made, and each centre was assigned 20 identical packs. The study medicine was delivered to the patients either by the hospital pharmacy or by a third, independent person who was not involved in the study. The patient screened and randomized as number one in the centre received package number one, randomization patient number two received package number two, etc. Randomization codes remained blinded until the database lock had taken

			place.”
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes	
	Were investigators and care providers blind to intervention group?	Yes	“All study site personnel, the sponsor and the monitor Operationally involved in the monitoring or conduct of the study were blinded to the study drug codes.”
	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Not reported	Unblinding was performed prior to serum analyses.
	Were all outcomes measured in a standard, valid and reliable way?	Yes	“The primary efficacy end-point was the CPR, defined by ultrasound evidence of an intrauterine gestational sac (with a beating heart) at Week 7 in the ITT population. Secondary efficacy endpoints included the SP rate during the pretreatment period (SP population); biochemical pregnancy (defined by a positive serum hCG test on Day 14 after embryo transfer) and CPRs following IVF/ICSI in the ART population and LBR (in the ITT, ART and SP populations). Safety variables included the incidence of adverse events (AEs), OHSS and coasting. According to prespecified criteria, OHSS and coasting were not considered AEs.”
	Were outcomes assessed objectively and independently?	Yes	
ATTRITIO N BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	0% M 1.3% P	This relates only to SP and not drops outs post ART.

	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes	However we have not used the ITT population, we have used the pre-ART population.
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Not reported	Difficult to determine without a protocol.
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes	Both groups were matched for age, cause and duration of infertility, weight, and BMI.
	If confounding was present, was it controlled for?		Both groups were matched for age, cause and duration of infertility, weight, and BMI.
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Partial	All were clearly declared.
	Was the study sufficiently powered to detect any differences between the groups?	Yes	"In our previous pilot study (Kjotrod et al., 2004) an increased pregnancy rate of almost 100% was observed among metformin-relative to placebo treated non-obese women with PCOS. A CPR of 0.35 was expected in the placebo group. With a study power of 0.80 and a significance level of 0.05, it was estimated that 120 patients were needed in each group to demonstrate a 50% increase in the CPR in the metformin group." However we will only use pre-ART data which which is in 74 participants and thus not adequately powered for that component of data.

	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS		*Lack of randomisation and blinding key reason for high RoB*	
What is the overall risk of bias?		Moderate	*Moderate - Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

Study ID	*Kocak 2002*
Study Citation	Kocak M, Caliskan E, Simsir C, Haberal A. Metformin therapy improves ovulatory rates, cervical scores, and pregnancy rates in clomiphene citrate-resistant women with polycystic ovary syndrome. Fertil Steril. 2002 Jan;77(1):101-6. doi: 10.1016/s00150282(01)02941-7.
Study Country	Turkey
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	*Fifty-six women with clomiphene citrate–resistant PCOS.* *Age years (mean ± SD)* *Group 1: 26.2 ± 3.7* *Group 2: 27.1 ± 4.5; p=0.3* *BMI* *Group 1: 31.91 ± 5.38* *Group 2: 30.8 ± 4.4*
PCOS diagnostic criteria	Align with Rotterdam “The diagnosis of PCOS was made according to following findings: oligomenorrhea (fewer than six menstrual periods in the preceding year) with hirsutism, hyperandrogenemia, or presence of multiple subcapsular follicles by vaginal ultrasound during the first 3 days of spontaneous menstrual bleeding. Adrenal, thyroid disorders, and hyperprolactinemia were specifically excluded by means of hormone assays.”

Presence of infertility	*Mean infertility period (3.2 ± 1.1 years) of group I (MET) women was not significantly different from the the mean infertility period (3.4 ± 0.9; P=.4) of group II (Placebo) women.*	
Presence of other condition/s	*Documented history of resistance to Clomiphene Citrate (CC) at doses ranging from 50 to 150 mg/day for 5 days (Clomiphene citrate resistance was defined as failure to have an ovarian response for three consecutive cycles on transvaginal ultrasonographic examination with concomitant failure of E2 levels to increase after treatment with CC, 150 mg daily for 5 days)*	
Medication History	*"None of the subjects had taken any medication that could influence carbohydrate metabolism for 2 months before the onset of the study, including oral contraceptives."*	
N per group	*N=56* *Met n=28* *Placebo n=28*	
Setting	*"Infertility clinic of a tertiary referral center"*	
Intervention	*MET (Group I): Two cycles of oral metformin therapy (850 mg, twice daily)* *Clomiphene citrate (100 mg/day) on cycle days 3–7 of the second cycle in both groups*	
Comparison	*Placebo (Group II): placebo therapy (twice daily)* *Clomiphene citrate (100 mg/day) on cycle days 3–7 of the second cycle in both groups*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Insulin, T, DHEAS, FSH, LH, body mass index (BMI), waist-to-hip ratio, endometrial thickness, cervical score, ovulation, and pregnancy rates*	
Follow up Duration	*Two cycles*	
Summary Result/s	*"Metformin therapy resulted in a significant decrease in total T, LH level, LH/FSH ratio, insulin resistance, and mean BMI. No difference in waist-to-hip ratio, DHEAS level, and fasting insulin level was observed. Clomiphene citrate induction resulted in higher ovulation rates and thicker endometrium in the metformin group than in the placebo group. There was higher cumulative pregnancy rate in the metformin group; however, there was no significant difference in the pregnancy rate between the two groups."*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes	*"To evaluate the effect of metformin therapy on hyperandrogenism, insulin resistance, cervical*

			scores, ovulation, and pregnancy rates in clomiphene citrate–resistant women with polycystic ovary syndrome (PCOS).”
Does the study have specified inclusion/exclusion criteria?		Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes	
Inclusion criteria		Yes	*PCOS* *Infertile* *CC resistant (failure to have an ovarian response for three consecutive cycles on transvaginal ultrasonographic examination with concomitant failure of E2 levels to increase after treatment with CC, 150 mg daily for 5 days)*
Exclusion criteria		Yes	*Diabetes* *Male factor infertility* *Tubal–uterine factor infertility* *Adrenal, thyroid disorders* *Hyperprolactinemia*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	No	*The admission was based on odd and even admission numbers.* *However, the study design mentions “Prospective, randomized, double-blind, placebo-controlled study”.* *“At the first presentation, each patient was given an individual admission number that was written in a sealed envelope and recorded by a nurse in the order of admission.”*
	Was allocation to intervention group concealed?	Partial	*“At the first presentation, each patient was given an individual admission number that was written in a sealed envelope and recorded by a nurse in the order of admission.”* *“After 75-g oral glucose challenge test, one of the authors opened the sealed envelope. Women having odd admission numbers were assigned to receive oral metformin”* *“Women having even admission numbers received oral placebo”*

PERFORMANCE BIAS	**Were patients blind to intervention group?**	Partial	*Whether placebo looked similar to metformin not reported*
	Were investigators and care providers blind to intervention group?	Partial	*"These measurements were taken by one of the authors who was blinded to the admission number of the patients."*
	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes	*"The authors obtaining these measurements were blinded to the medication received by the patient."*
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	*Apparently, only one (1/26= 3.8%) dropped off from the Metformin group and none dropped off from placebo group*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	No	*However, only one dropped out from the study and the effect may be negligible*

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes	*"There was no significant change between the two treatment groups in waist-to-hip ratio and FSH, compared to the baseline values (Table 1)."*
	If confounding was present, was it controlled for?	No	*No confounding identified*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Not reported	*No conflict of interest statement available.*
	Was the study sufficiently powered to detect any differences between the groups?	Not reported	
	If statistical analysis was undertaken, was this appropriate?	Yes	*"Comparisons of the data at baseline, after placebo administration or after metformin administration in the study group were performed using the distribution of continuous variables with the Shapiro-Wilk normality tests. Results within a group were compared using paired samples t-test or the Wilcoxon's signed rank test. Student's t-test or the Mann-Whitney rank sum test was used to compare results between the groups. Proportions were compared by using the X^2 test or Fisher's exact test whenever suitable. Differences were considered to be significant (P <.05), and data are reported as the mean ± SD."*
COMMENTS		Mod (randomisation method unclear, no SS calc, 1 drop out); no BL diff	

What is the overall risk of bias?	Moderate	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		

Study ID	**Lopez 2004**
Study Citation	Lopez, E., et al., Ovulation induction in women with polycystic ovary syndrome: randomized trial of clomiphene citrate versus low-dose recombinant FSH as first line therapy. Reproductive Biomedicine Online, 2004. 9(4): p. 382-90.
Study Country	Spain
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women aged <40 years with anovulatory infertility due to PCOS of at least 1 year duration who were therapy naïve. Median age (years), FSH = 30 (22-39) CC= 29 (23-38) Body mass index (kg/m2), FSH = 21.9 ± 1.9 CC= 22.3 ± 1.9
PCOS diagnostic criteria	Rotterdam
Presence of infertility	All women presented with oligomenorrhoea or amenorrhoea and primary infertility of a median duration of 3 years (range 1–8 years).
Presence of other condition/s	*Not reported*
Medication History	*Treatment naïve*
N per group	Assessed for eligibility = 76 patients Randomised total = 76 patients Randomised to FSH = 38 patients; all received allocated intervention; 1 patient refused to be treated for cycles 2 and 3; analysed 38 patients (ITT), 91 cycles Randomised to CC = 38; all received allocated intervention; analysed 38 patients, 104 cycles
Setting	Infertility clinic at the Hospital Virgen de la Arrixaca in Murcia in Spain over the period April 2000 to December 2001.
Intervention	Low-dose recombinant FSH for up to three cycles. “Treatment with recombinant FSH (Gonal-F; Serono S.A.) was commenced on day 3 following spontaneous or induced menses. The chronic low-dose, step-up regimen consisted of a starting dose of75 IU daily s.c., with dose increments of 37.5 IU daily every 7 days if there was

	no evidence of ovarian response by ultrasonography (i.e. no follicle >I0 mm in diameter). This stepwise increase was continued until ovarian activity was seen, at which time the dose was maintained. In successive treatment cvcles, the starting dose of FSH could be modified, based on the ovarian response in the previous cycle. Criteria for HCG injection (5000 1U i.m.) were the same as for clomiphene citrate treatment cycles. A treatment cycle was cancelled if there was no follicle growth after 21 days of gonadotrophin administration. The injection of HCG was withheld if four or more follicles >I4 mm in diameter were present, because of the increased risks of OHSS and multiple pregnancy." "Couples were advised to have sexual intercourse the evening of the HCG injection and the following day." "Women not conceiving after three cycles of treatment crossed over to the alternative treatment for a further three cycles, with an interval of at least 45 days between treatments." – wasn't required and only first arm data presented here.
Comparison	Clomiphene citrate for up to three cycles. It was "given at a daily dose of 50 mg for 5 days, starting on day 5 following spontaneous or induced uterine bleeding. If ovulation was documented but no pregnancy ensued, the same dose was used in the next cycle. However, if no ovulatory response occurred, the daily dose was increased by 50 mg for the subsequent cycle, up to a maximum daily dose of 150 mg in the third treatment cycle. Human chorionic gonadotrophin (HCG,Profasi; Serono S.A., Madrid, Spain), at a dose of 5000 IU i.m., was administered when the lead follicle was >I7 mm in diameter on transvaginal ultrasonography. The cycle was cancelled if no growing follicle was seen by day 18-20." "Couples were advised to have sexual intercourse the evening of the HCG injection and the following day." "Women not conceiving after three cycles of treatment crossed over to the alternative treatment for a further three cycles, with an interval of at least 45 days between treatments." – wasn't required and only first arm data presented here.
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	"The primary outcome measure was cumulative pregnancy after undergoing up to three treatment cycles. Secondary outcomes were cycle cancellation rate, ovulation rate per cycle, cumulative ovulation rate, pregnancy rate per cycle, incidence of OHSS, cumulative live birth rate, and multiple birth rate." "Ovarian response was monitored by transvaginal ultrasonography." "Pregnancy was diagnosed by increasing serum concentrations of β-HCG after missed menses, and the subsequent demonstration of an intrauterine gestational sac by transvaginal ultrasonography."
Follow up Duration	*Three cycles*
Summary Result/s	"The relative risk and its 95% confidence interval were 1.17 (0.97–1.46) for HCG cycles with ovulation, 1.78 (0.92–3.54) for the pregnancy rate per woman, and 1.83 (0.79–4.40) for live births per woman in favour of FSH.

	The cumulative pregnancy rate after three treatment cycles was 43% with FSH and 24% with clomiphene citrate (P = 0.06)."	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes	
Does the study have specified inclusion/exclusion criteria?	Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes	
Inclusion criteria	Yes	"A history of amenorrhoea (no menstrual periods for three or more months) or oligomenorrhoea (fewer than nine menstrual periods in a year), monophasic basal body temperature charting, proliferative endometrium on biopsy, or serum progesterone concentrations <l ng/ml were accepted as demonstration of anovulation. In addition, subjects were required to have the ultrasonographic appearance of polycystic ovaries (Adams et al., 1986), a positive response to the progestin challenge test (normal withdrawal bleeding after treatment with oral medroxyprogesterone acetate, 10 mg daily for 5 days), normal serum prolactin, dehydroepiandrosterone sulphate, and fasting glucose concentrations, a normal hysterosalpingogram (and laparoscopy when appropriate), and no history of pelvic surgery or pelvic inflammatory disease. When the study was started the criteria for PCOS that were used were as described and these are also in keeping with the ESHREIASRM guidelines for PCOS (Rotterdam ESHREIASRM sponsored PCOS consensus workshop group, 2003). Obesity was not an inclusion or exclusion criterion. The male partner had to have normal semen parameters according to World Health Organization criteria (Rowe et al., 2000)."
Exclusion criteria	Yes	"Women with a previous pregnancy or previous treatment with ovarian stimulation drugs were excluded."
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION **Did the study have an adequate method of randomisation?**	Yes	*"Women were allocated to the treatment groups according to a computer generated randomization table."*

	Was allocation to intervention group concealed?	Yes	*"Concealment of treatment allocation was achieved with the use of sealed opaque envelopes each containing a unique study number and prepared independently by a secretary."*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Not reported	
	Were investigators and care providers blind to intervention group?	Not reported	
	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	2.6% treatment 0% control/ comparison	*FSH = 2.6%* *CC = 0%*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Not reported	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes	*"there was no significant difference between groups for any characteristic."*
	If confounding was present, was it controlled for?	Not reported	*Not reported-probably not "there was no significant difference between groups for any characteristic."*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	No	
	Was the study sufficiently powered to detect any differences between the groups?	No	*"The sample size calculation was based on experience with ovulation induction in women with WHO group 11 anovulation, in whom cumulative pregnancy rates were obtained after three treatment cycles of 25% with clomiphene citrate and 40% with FSH, an absolute difference of 15% (Balasch, 1986; Balasch et al., 1996). The sample size required to provide power of 80% to detect this magnitude of treatment effect was calculated to be 152 women per treatment group, using a two-tailed analysis with a detection limit of 5% of avoiding a type I error in hypothesis testing. Recruitment was terminated after 21 months when it became evident that it would not be possible to recruit this number of subjects from a single centre in a reasonable time period."*
	If statistical analysis was undertaken, was this appropriate?	Yes	*Yes*
COMMENTS			

What is the overall risk of bias?	High	*lack of blinding info and small n*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		

Study ID	*Legro, 2007*
Study Citation	*Legro, R. S., Barnhart, H. X., Schlaff, W. D., Carr, B. R., Diamond, M. P., Carson, S. A., ... & Myers, E. R. (2007). Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. New England Journal of Medicine, 356(6), 551-566.*
Study Country	USA
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	*infertile women with the polycystic ovary syndrome* *metformin and CC vs CC vs metformin* *• Mean age (SD) 28.3 (4.0), 27.9 (4.0), 28.1 (4)* *• Mean BMI (SD) 34.2 (8.4), 36.0 (8.9), 35.6 (8.5)*
PCOS diagnostic criteria	Rotterdam
Presence of infertility	*Length of time subject had been attempting conception — months* *CC: 41.4±39.4* *MET: 39.0±31.9* *CC+MET: 40.7±36.0*
Presence of other condition/s	*Some had insulin resistance*
Medication History	*NR*
N per group	*626 into three groups* *CC: n=209,* *MET: n=208* *CC+MET: n=209*
Setting	*Multicentre study*
Intervention	*Main intervention: 2 extended-release metformin 500 mg or 2 placebo tablets twice daily*

Comparison	*CC 50 mg or second matching placebo tablet was commenced concurrently from day 3-7 of the cycle.* *When women had no or poor response, the dose was increased by 50 mg or 1 additional placebo tablet with the maximum dose of 150 mg or 3 placebo tablets*
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Primary: live birth rate, gastrointestinal side effects* *Secondary: clinical pregnancy, ovulation: progesterone > 5 ng/mL, BMI, fasting glucose, fasting insulin, serum testosterone, miscarriage, multiple pregnancy, other adverse events*
Follow up Duration	*6 months*
Summary Result/s	*The live-birth rate was 22.5% (47 of 209 subjects) in the clomiphene group, 7.2% (15 of 208) in the metformin group, and 26.8% (56 of 209) in the combination therapy group (P<0.001 for metformin vs. both clomiphene and combination therapy;* *P = 0.31 for clomiphene vs. combination therapy). Among pregnancies, the rate of multiple pregnancy was 6.0% in the clomiphene group, 0% in the metformin group, and 3.1% in the combination-therapy group. The rates of first-trimester pregnancy* *loss did not differ significantly among the groups. However, the conception rate among subjects who ovulated was significantly lower in the metformin group (21.7%) than in either the clomiphene group (39.5%, P = 0.002) or the combination therapy group (46.0%, P<0.001).*

ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes	
Does the study have specified inclusion/exclusion criteria?	Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes	
Inclusion criteria	Yes	*oligomenorrhoea (< 8 periods/year), biochemical hyperandrogenism (elevated* *testosterone level documented within the previous year on the basis of local laboratory results)* *Women should have at least 1 proven patent fallopian tube. Normal uterine cavity. Normal semen* *analysis (sperm concentration > 20 million/mL)*
Exclusion criteria	Yes	*hyperprolactinaemia, CSH, thyroid disease, Cushings's syndrome, androgen-secreting tumour*

INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes	*Computer-generated; participants were randomised by means of an interactive voice system and stratified based on study site and previous exposure to study drugs*
	Was allocation to intervention group concealed?	Yes	*Each participant received a medication package on a monthly basis that consisted of a bottle M (metformin or placebo) and a bottle C (CC or placebo). Data co-ordinating centre at the clinical research institute*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes	*Participants and personnel were blinded*
	Were investigators and care providers blind to intervention group?	Yes	*Participants and personnel were blinded*
	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes	*Investigators were blinded*
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**		*49 (23.7%) in the metformin and CC group, 55 (26.3%) in the placebo and CC group, 72 (34.6%) in the metformin group. The differences were not significant.*

	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes	All primary and secondary outcome measures reported. 3-arm study however outcome data presented for all 3 arms clearly.
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes	
	If confounding was present, was it controlled for?	No	*"There were no significant differences in baseline variables among the study groups".*
IER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	No	*Conflict of interest clearly documented*

	Was the study sufficiently powered to detect any differences between the groups?	Yes	*Based on the initial sample size calculation, 678 was needed to detect a 15% absolute difference in live birth rates with a power of 80% and a type I error of 0.05. Due to limitations in the supplying metformin and the matching placebo tablets, the number of required women was reduced to 626. This was approved after the assessment by the data safety and monitoring board. Because the observed live birth rate was lower than projected, the number of recruited participants (626) was sufficient to detect a 15% difference with the same magnitude of power and type I error.* *The original sample size was 678 to detect a 15% absolute difference in live birth rates. However, due to drug supply logistics, the sample size later reduced to 626 after the data safety and monitoring board review*
	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS			
What is the overall risk of bias?		Low	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*all outcomes Low risk of bias*	

Study ID	*Morin-Papunen, 2012*
Study Citation	*Morin-Papunen, L., Rantala, A. S., Unkila-Kallio, L., Tiitinen, A., Hippeläinen, M., Perheentupa, A., ... & Tapanainen, J. S. (2012). Metformin improves pregnancy and live-birth rates in women with polycystic ovary syndrome (PCOS): a multicenter, double-blind, placebo-controlled randomized trial. The Journal of Clinical Endocrinology, 97(5), 1492-1500.*
Study Country	Finland
BRIEF CHARACTERISTICS OF RCT	

Patient/population/ participants	*women aged 18–39 yr at entry, with a body mass index (BMI) greater than 19 kg/m2 and diagnosed with PCOS* *Metformin vs placebo* *• mean age (SD) 28.4 (3.9) vs 27.9 (4.1)* *• mean BMI (SD) 27.1 (6.3) vs 27.4 (6.2)* *• mean fasting insulin, microIU/mL (SD) 11.0 (11.2) vs 11.4 (11.8)* *• testosterone, ng/dL (SD) 43.2 (17.3) vs 45.8 (20.2)* *• mean fasting glucose, mg/dL (SD) 91.9 (7.2) vs 91.9 (9.0)*
PCOS diagnostic criteria	Rotterdam
Presence of infertility	*Duration of infertility (months)* *Met: 23.8 ± 18.8* *Placebo: 25.3 ± 22.3*
Presence of other condition/s	*Abnormal sperm (%)* *Met: 42 (26.2)* *Placebo: 39 (24.4)*
Medication History	*NR* *"Exclusion criteria were type 2 diabetes mellitus, active liver disease (alanine aminotransferase >100 IU/liter), history of cardiac or renal failure, hormone medication, alcohol use, and regular smoking."*
N per group	*N=320 (160 for each group)*
Setting	*Multicentre RCT (parallel-group study)*
Intervention	*Metformin 500 mg 1/d for 1 week, then increased weekly by 1 extra tablet/d to 1.5 g/d in non-obese and 2 g/d in obese women versus placebo)*
Comparison	*Placebo* *If pregnancy did not occur, ovulation induction was commenced: if the woman ovulated after clomiphene*
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Primary: live birth rate, gastrointestinal side effects* *Secondary: clinical pregnancy rate, BMI, miscarriage rate*
Follow up Duration	*3-9 months*
Summary Result/s	*Miscarriage rates were low and similar in the two groups (metformin 15.2% vs. placebo 17.9%, P=0.8). Intent-to-treat analysis showed that metformin significantly improved PR and LBR (vs. placebo) in the whole study population (PR: 53.6 vs. 40.4%, P = 0.006; LBR: 41.9 vs. 28.8%, P = 0.014) and PR in obese women (49.0 vs. 31.4%, P=0.04), and there was a similar trend in nonobese(PR:*

		58.6 vs. 47.6%, P=0.09; LBR: 46.7 vs. 34.5%, P=0.09) and in obese women with regard to LBR (35.7 vs. 21.9%, P = 0.07). Cox regression analysis showed that metformin plus standard infertility treatment increased the chance of pregnancy 1.6 times (hazard rate 1.6, 95% confidence interval 1.13–2.27).
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT			
Does the study have a clearly focused question and/or PICO?		Yes	*"We investigated whether metformin decreases the early miscarriage rate and improves the pregnancy rates (PR) and live-birth rates (LBR) in PCOS."*
Does the study have specified inclusion/exclusion criteria?		Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes	
Inclusion criteria		Yes	*aged 18–39 yr at entry, with a body mass index (BMI) greater than 19 kg/m2 and diagnosed with PCOS according to Rotterdam criteria*
Exclusion criteria		Yes	*type 1 diabetes mellitus, liver, cardiac or renal disease, hormone medication, alcohol use, regular smoking*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes	*Randomisation codes remained concealed. Metformin and placebo identically packaged and consecutively numbered.* *Performed by hospital pharmacy with 1:1 allocation in random blocks of 10 using computer-generated lists*
	Was allocation to intervention group concealed?	Yes	*Randomisation codes remained concealed. Metformin and placebo identically packaged and consecutively numbered.* *Metformin and placebo identically packaged and consecutively numbered. Randomisation codes remained blinded until database lock had taken place.*

PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes	*Participants and personnel were blinded*
	Were investigators and care providers blind to intervention group?	Partial	*Investigators were blinded*
	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes	
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	Varey per group (160 for each group)	*61 women were lost to follow-up or discontinued but their data were included in the ITT analysis*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes	*"Baseline characteristics of the women did not differ between the metformin and placebo groups"*
	If confounding was present, was it controlled for?	No	*"Baseline characteristics of the women did not differ between the metformin and placebo groups"*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	No	
	Was the study sufficiently powered to detect any differences between the groups?	Yes	*"Power analysis indicated that a total number of 120 pregnant women would be needed to reveal a possible decrease in risk of miscarriage from 45 to the 15% observed in the general population (4, 5) (α= 0.05 and power [1-β] = 0.9)."* *"To allow for dropouts, the planned sample size was at least 150 in each group."*
	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS			
What is the overall risk of bias?		Low	

Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	

Study ID	*Ng, 2001*
Study Citation	*Ng EH, Wat NM, Ho PC. Effects of metformin on ovulation rate, hormonal and metabolic profiles in women with clomiphene-resistant polycystic ovaries: a randomized, double-blinded placebo-controlled trial. Human Reproduction 2001;16(8):1625-31.*
Study Country	China (Hong Kong)
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	*Non-obese PCOS women, age of women <40, date-2 serum FSH <10IU/l, PCO diagnosed by transvaginal ultrasonography, irregular cycles and anovulation as shown mid luteal progesterone concentration <16* *MET vs. Placebo* *• mean age (± SD) 30.4 (2.1), 31.2 (2.6)* *• mean BMI (± SD) 25.5 (4.6), 23.5 (4.4)*
PCOS diagnostic criteria	Rotterdam
Presence of infertility	*Duration of infertility (years)* *Met: 3.3 (1.5-5.0)* *Placebo: 3.5 (1.5-7.0)*
Presence of other condition/s	*CC resistant*
Medication History	*NR*
N per group	*Met: n=10* *Placebo: n=10*
Setting	*University department*
Intervention	*Metformin 500mg three times a day*
Comparison	*Placebo*
Outcomes (primary and other) with definition (eg.	*Primary: live birth rate, gastrointestinal side effects*

self-reported, fasting etc.)		*Secondary: clinical pregnancy, ovulation: by serum progesterone (> 16 nmol/L) weekly, BMI, fasting blood glucose, fasting insulin, testosterone*	
Follow up Duration		*3 months. Continued for a further cycle if did not ovulate*	
Summary Result/s		*"The median ovulation rate in the placebo group was 0% (range: 0--50%) after placebo only and 6.9% (range: 0--50%) after placebo and CC, whereas the corresponding rates in the metformin group were 0% (range: 0--22%) and 0% (range: 0--22%) respectively. There was no improvement in the ovulation rate despite a significant reduction of body mass index, serum testosterone and fasting leptin concentrations in the metformin group."*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT			
Does the study have a clearly focused question and/or PICO?		Yes	
Does the study have specified inclusion/exclusion criteria?		Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes	
Inclusion criteria		Yes	*PCOS (irregular cycles of ≤ 21 days or ≥ 35 days and cycle-to-cycle variation of > 4 days, anovulation with mid-luteal progesterone < 16 nmol/L whilst taking CC 100 mg for 5 d over 3 cycles, exclusion of other endocrinopathy (raised prolactin, thyroid disorder*), US findings of PCO, age <40, day 2 FSH < 10, bilateral patent tubes demonstrated by laparoscopy, normal semen parameters*
Exclusion criteria		Yes	*Taking any sex hormones in previous 3 months, smokers, renal impairment*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes	*computer-generated list in sealed envelopes*

	Was allocation to intervention group concealed?	Yes	*In sealed envelopes however, does not state whether the envelopes were opaque. Double, identical appearance and packed by the hospital pharmacy. Code kept in the pharmacy department until the end of the trial*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes	*Participants and personnel were blinded*
	Were investigators and care providers blind to intervention group?	Yes	
	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes	*Investigators were blinded*
	Were all outcomes measured in a standard, valid and reliable way?	Yes	*In spite of the fact that anovulation and CC resistance was an inclusion criteria, 7 out of 9 women taking placebo ovulated (3 with placebo alone, and 4 out of the 6 remaining in the trial who had CC and placebo)*
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**		*5 (25%), 3 in placebo arm, 2 in metformin.*

	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes	*Analysis on ITT*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes	*All primary outcome measures reported*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes	*"Both groups were comparable with respect to age of women, duration of infertility, proportion of primary/secondary infertility, total ovarian volume, baseline body mass index (BMI)"*
	If confounding was present, was it controlled for?	No	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Partial	*Funding body is mentioned.* *No conflict of interest statement.*
	Was the study sufficiently powered to detect any differences between the groups?	Yes	*8 in each arm needed. 10 recruited.*
	If statistical analysis was undertaken, was this appropriate?	Yes	

COMMENTS		
What is the overall risk of bias?	Moderate	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*No – all outcomes* moderate *risk of bias*	

Study ID	Qublan 2009
Study Citation	H. S. Qublan, S. Al-Khaderei, A. N. Abu-Salem, A. Al-Zpoon, M. Al-Khateeb,N. Al-Ibrahim, M. Megdadi & N. Al-Ahmad (2009) Metformin in the treatment of clomiphene citrate-resistant women with polycystic ovary syndrome undergoing in vitro fertilisation treatment: A randomised controlled trial, Journal of Obstetrics and Gynaecology, 29:7, 651-655, DOI: 10.1080/01443610903147576
Study Country	Jordan
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women with PCOS
PCOS diagnostic criteria	Rotterdam ESHRE/ASRAM
Presence of infertility	Assumed due to anovulation/ CCR
Presence of other condition/s	CC-resistance (defined as failure to ovulate after CC treatment up to a daily dose of 150 mg from cycle day 5–9 for at least three consecutive cycles)
Medication History	Clomiphene citrate resistance: failure to ovulate after CC treatment up to a daily dose of 150 mg from cycle day 5–9 for at least three consecutive cycles.
N per group	Allocated/randomised: Not reported (NR drop outs, same numbers) Assessed: 34 metformin Assessed at end of study: 32 placebo
Setting	NR
Intervention	850 mg of metformin (n = 34) (Glucophage: Lipha Sante, Lyon, France)
Comparison	Placebo n=32

Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)		Clinical pregnancy rates; implantation rates; hormones including FSH, LH, testosterone (T), androstenedione (A), 17-hydroxyprogesterone (17-OHP), oestradiol (E2) and dehydroepiandrosterone sulphate (DHEAS)	
Follow up Duration		1 month before IVF until day of pregnancy test. If pregnant, continued metformin for 12 wks.	
Summary Result/s		Compared with the metformin-treated group, women who received a placebo had a significant increase in terms of days of stimulation with HMG, number of HMG ampoules, number of follicles 414 mm, number of oocytes retrieved, number of mature eggs, fertilisation rate and oestradiol level on the day of hCG administration	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT			
Does the study have a clearly focused question and/or PICO?		Partial	Determine the efficacy of metformin vs placebo in women with PCOS undergoing IVF treatment- primary outcomes not stated
Does the study have specified inclusion/exclusion criteria?		Yes	Yes
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes	Yes
Inclusion criteria		Yes	Congenital adrenal hyperplasia, Cushing's syndrome, hyperprolactinaemia and thyroid disease were excluded by appropriate tests. Liver and kidney function tests were assessed in all patients and all were normal. Clomiphene citrate resistance was defined as failure to ovulate after CC treatment up to a daily dose of 150 mg from cycle day 5–9 for at least three consecutive cycles. Progesterone level on day 21 and 28 410 ng/mL was indicative of ovulation. All patients were required to have normal uterine cavity and tubal patency on hysterosalpingography. All male partners had normal semen parameters according to World Health Organization criteria (WHO 1992).
Exclusion criteria		Yes	As above
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION	**Did the study have an adequate method of randomisation?**	Not reported	Not reported

	Was allocation to intervention group concealed?	No	Not reported
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes	Yes, single-blind
	Were investigators and care providers blind to intervention group?	No	No
	Aside from the experimental intervention, were the groups treated the same?	Yes	Yes
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Not reported	Not reported
	Were all outcomes measured in a standard, valid and reliable way?	Partial	Standard immunoassays but no QC info provided
	Were outcomes assessed objectively and independently?	Not reported	Unclear who assessed the outcomes eg. biochemical assays
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	Not reported	
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Not reported	Drop outs Not reported

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Partial	Appears to be but this is difficult to determine if there isn't a protocol and no primary outcomes stated
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes	No significant differences between the two groups in terms of age, BMI, type, cause and duration of infertility or biochemical measures
	If confounding was present, was it controlled for?	No	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	No	
	Was the study sufficiently powered to detect any differences between the groups?	Yes	The sample size was calculated at the design stage to detect an improvement rate in the treatment group of 20% with an alpha 0.05 in a one-sided test (Gordis 2000).
	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS		Lack of randomisation information and single-blinding main reasons behind mod RoB	
What is the overall risk of bias?			Moderate

Did risk of bias differ by outcome (eg. primary outcome was low risk but rest were high)?	No – all outcomes mod risk of bias

Study ID	***Roy 2012***
Study Citation	Roy KK, Baruah J, Singla S, Sharma JB, Singh N, Jain SK, Goyal M. A prospective randomized trial comparing the efficacy of Letrozole and Clomiphene citrate in induction of ovulation in polycystic ovarian syndrome. J Hum Reprod Sci. 2012 Jan;5(1):20-5. doi: 10.4103/0974-1208.97789. PMID: 22870010; PMCID: PMC3409915.
Study Country	India
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	PCOS patients 20–35 years having infertility for more than one year *Age* *Letrozole 26.1 ± 1.8* *CC 26.5 ± 1.3* *BMI* *Letrozole 25.8 ± 2.1* *CC 25.4 ± 1.56*
PCOS diagnostic criteria	Rotterdam's criteria
Presence of infertility	Mean infertility duration (in years) *Letrozole 6.4 ± 3.8* *CC 5.8 ± 3.1*
Presence of other condition/s	*Not reported*
Medication History	*Not reported*
N per group	*250 screened* *212 randomised* *Letrozole (n=104) (6 dropped out, 98 analysed)* *Clomiphene citrate (n=108) (2 dropped out, 106 analysed)*
Setting	tertiary care hospital from January 2005 to January 2010
Intervention	Letrozole: Starting dose of 2.5 mg letrozole, increasing up to 5 mg daily, administered from Day 3 to Day 7 (total of 5 days) of a spontaneous cycle or withdrawal bleeding after a 5-day course of 10 mg/ day medroxyprogester one acetate. 3 months
Comparison	Clomiphene Citrate:

	Starting dose of 50 mg, increasing up to 100 mg daily, administered from Day 3 to Day 7 (total of 5 days) of a spontaneous cycle or withdrawal bleeding after a 5- day course of 10 mg/ day medroxyprogester one acetate. 3 months	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Clinical pregnancy (*at least one gestational sac in USG) *Number of miscarriages* *Live birth* Other outcomes not relevant to this systematic review included: mean number of follicles and endometrial thickness.	
Follow up Duration	*3 cycles*	
Summary Result/s	"The mean number of dominant follicles in letrozole groups and CC groups was 1.86±0.26 and 1.92±0.17, respectively (*P*=0.126). Number of ovulatory cycle in letrozole group was 196 (66.6%) versus 216 (67.9%) in CC group (*P*=0.712). The mean mid-cycle endometrial thickness was 9.1±0.3 mm in letrozole group and 6.3±1.1 in CC group, which was statistically significant (*P*=0.014). The mean Estradiol [E2] level in clomiphene citrate group was significantly higher in CC group (364.2±71.4 pg/mL) than letrozole group (248.2±42.2 pg/mL). 43 patients from the letrozole group (43.8%) and 28 patients from the CC group (26.4%) became pregnant." *"*Letrozole and CC have comparable ovulation rate. The effect of letrozole showed a better endometrial response and pregnancy rate compared with CC."	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes	*"*The aim of this present prospective randomized trial was to compare results of letrozole with CC in patients with PCOS."
Does the study have specified inclusion/exclusion criteria?	Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes	
Inclusion criteria	Yes	age group of 20–35 years having infertility for more than one year, body mass index (BMI) <28, patients of anovulatory PCOS oligomenorrhea (i.e., interval between periods were ≥35 days) or amenorrhea (i.e., absence of vaginal bleeding for 6 months), hirsutism, enlarged ovaries with multiple follicles (≥10 measuring 2–8 mm in diameter) as per Rotterdam's criteria on transvaginal ultrasonography (USG), and/or elevated serum testosterone.

Exclusion criteria		Yes	Patients having abnormality in any of the following tests: tubal patency test, pelvic ultrasonography, husband semen analysis, serum hormone measurements (FSH, LH, prolactin, estradiol, progesterone, and testosterone) on the 2nd to 5th day of the cycle Any abnormality found in laparoscopy that may be responsible for infertility
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes	Randomization of recruited women was carried out using online software (http://www.randomization.com) to generate a random number table
	Was allocation to intervention group concealed?	Yes	Randomization codes (A, B) were packed into sealed opaque envelopes by an individual not involved in enrollment, treatment and follow-up of subjects to ensure concealment of allocation
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Not reported	
	Were investigators and care providers blind to intervention group?	Not reported	
	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes	Documentation of at least one gestational sac in USG was confirmed as clinical pregnancy.
	Were outcomes assessed objectively and independently?	Yes	

ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	6/104 in Letrozole (5.8%) *And* *2/106 in CC (1.9%)*	*8 patients dropped out*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	No	*ITT analysis not done*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Partial	*The outcomes to be assessed are not explicitly mentioned under methods but reported under results* Difficult to determine without a protocol.
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes	There was no statistically significant difference in the mean age, BMI, and duration of infertility in both groups of patients.
	If confounding was present, was it controlled for?	Not reported	There was no statistically significant difference in the mean age, BMI, and duration of infertility in both groups of patients.
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	No	**Source of Support:** Nil, **Conflict of Interest:** None declared.
	Was the study sufficiently powered to detect any differences between the groups?	Yes	"Sample size was calculated using pregnancy rate as a primary outcome measure. On basis of previous studies,[3] to achieve a statistically valid comparison of pregnancy rates in the two groups, with a type I error of 0.05 and a power of 80%, a sample size of at least **40 women in each arm** was required"

	If statistical analysis was undertaken, was this appropriate?	Yes	Student's t-test, Chi-square and Fisher's exact testes were used when appropriate
COMMENTS			
What is the overall risk of bias?		Low	*However, not clear whether the outcome assessors and the patients were blinded. The study does not identify itself as a double-blind study.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

Study ID	Sahin,2004
Study Citation	Sahin Y, Yirmibeş U, Keleştimur F, Aygen E. The effects of metformin on insulin resistance, clomiphene-induced ovulation and pregnancy rates in women with polycystic ovary syndrome. Eur J Obstet Gynecol Reprod Biol. 2004 Apr 15;113(2):214-20. doi: 10.1016/j.ejogrb.2003.09.036. PMID: 15063963.
Study Country	Turkey
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	No specific population but range across both arms: Age range : 19 - 31 years, with BMI range (23.1 - 35.7),
PCOS diagnostic criteria	3 or more of following criteria: Polycystic ovaries on pelvic ultrasound examination (presence of >=10 cysts, 2-10mm in diameter, arranged around a dense stroma or scattered), oligo/amenorrhoea, hirsutism, hyperandrogenaemia (total testosterone > 80 ng/dl and/or free testosterone > 3:18 pg/ml)) and elevated serum LH:FSH ratio (LH:FSH > 2).
Presence of infertility	Metformin + Clomiphene : 5 (2-10 years) Clomiphene: 3.5 (1-8 years)
Presence of other condition/s	NR
Medication History	For at least 12 weeks before the study, none of the subjects in both groups had received any medication known to affect pituitary–gonadal function or carbohydrate metabolism
N per group	Intervention – Metformin + Clomiphene (11), Control – Clomiphene (10)

Setting	No specifics on setting though authors are from ob/gyn & endocrinology at Ericyes University
Intervention	Metformin + Clomiphene Citrate
Comparison	Clomiphene Citrate
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Not reported Extracted from article: FGS, BMI, FSH, LH, Oestradiol, Total Test, Free Test, Androstenedione, SHBG, DHEAS, Prolactin, Fasting glucose, Fasting Insulin, AUC Glucose, AUC Insulin, Fasting glucose : insulin ratio, AUC glucose: AUC insulin ratio, HCG day, follicles >= 15 mm, cycles with ovulation, number of pregnancies, number of abortions, number of preterm deliveries, number of full term healthy babies
Follow up Duration	3 months
Summary Result/s	Serum androgens and insulin response to OGTT decreased significantly after metformin therapy. Midluteal serum P level was significantly higher in cycles treated with metformin plus CC (P < 0:05). The ovulation (38 of 51 cycles, 74.4% versus 34 of 55 cycles, 61.8%) and pregnancy rates (5 of 11 women, 45.5% versus 3 of 10 women, 30%) were higher, but not significantly, in the metformin plus CC group than in the CC alone group. All the patients who conceived had insulin resistance in group 1 whereas non-insulin resistance in group 2.

ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Partial	**Partial – no comparator** “The aim of the present study was to evaluate the effect of metformin on insulin resistance, ovarian androgen production, and clomiphene-induced ovulation and pregnancy rates in infertile women with PCOS for a relatively long treatment period.”.
Does the study have specified inclusion/exclusion criteria?	Not reported	**Not reported** (Not specifically signposted) – needed to be extracted
If there were specified inclusion/ exclusion criteria, were these appropriate?	Not reported	**Not reported**

Inclusion criteria		Partial	**Partial:** All patients had primary infertility
Exclusion criteria		Partial	**Partial:** Male factor & tubal-uterine factor infertility excluded with semen analyses and hysterosalpingogram and/or laparoscopy. "…A complete clinical and laboratory evaluation were performed to exclude the patients with androgen secreting tumors of ovarian or adrenal origin, Cushing's syndrome, thyroid dysfunctions, nonclassic adrenal hyperplasia and hyperprolactinemia.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	ot reported	**Not reported** (method not specified)
	Was allocation to intervention group concealed?	ot reported	**Not reported**
PERFORMANCE BIAS	**Were patients blind to intervention group?**	ot reported	Blinding was **not reported**
	Were investigators and care providers blind to intervention group?	Not reported	**Not reported**
	Aside from the experimental intervention, were the groups treated the same?	Yes	Yes
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	ot reported	**Not reported**

	Were all outcomes measured in a standard, valid and reliable way?	Yes	Yes
	Were outcomes assessed objectively and independently?	Partial	Partial
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	Not reported	**Not reported**
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Not reported	**Not reported**
REPORT BIAS	**Is the paper free of selective outcome reporting?**	ot reported	**Not reported**
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes	Yes
	If confounding was present, was it controlled for?	Not reported	**Not reported**

OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Not reported	**Not reported**
	Was the study sufficiently powered to detect any differences between the groups?	Not reported	**Not reported**
	If statistical analysis was undertaken, was this appropriate?	Yes	The results were reported as means +/- S:E:M: or median and range. Wilcoxon-signed rank test was used to evaluate the effect of metformin on hormones and glucose levels. Chi-square test was used to evaluate ordinal variables, and Mann–Whitney U-test and the unpaired Student's t-test were used to evaluate continuous numeric variables. **Yes**
COMMENTS		*Lack of specifics on randomisation and lack of blinding lead to high RoB*	
What is the overall risk of bias?		High	***High***
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No – all outcomes high risk of bias*	

Study ID	*Sohrabvand,2006*
Study Citation	Sohrabvand F, Ansari Sh, Bagheri M. Efficacy of combined metformin-letrozole in comparison with metformin-clomiphene citrate in clomiphene-resistant infertile women with polycystic ovarian disease. Hum Reprod. 2006 Jun;21(6):1432-5. doi: 10.1093/humrep/del020. Epub 2006 Feb 14. PMID: 16478764.
Study Country	Iran
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	*Mean BMI +/- SD : 29.98 +/- 4.83 in intervention group, 30.21 +/- 3.92 in comparison group, cc-resistant*

PCOS diagnostic criteria	Rotterdam	
Presence of infertility	*Yes – Mean in Met + Letrozole (Intervention) : Mean in Met + CC (Comparison) : 3.81*	
Presence of other condition/s	*Clomiphene Resistant*	
Medication History	*N/A*	
N per group	*Intervention : 29, Comparison : 30 (60 randomised – 1 drop out, per protocol analysis)*	
Setting	*Infertility clinic of Vali-e-Asr Hospital (Tehran, Iran)*	
Intervention	**Metformin** (500mg 3 times a day) for 6 - 8 weeks, in case of failure of pregnancy after the end of this period, 100 mg **clomiphene citrate** for 5 days starting from day 3 of their menstrual cycle,	
Comparison	**Metformin** (500mg 3 times a day) for 6 - 8 weeks, in case of failure of pregnancy after the end of this period, 2.5 mg **letrazole** for 5 days starting from day 3 of their menstrual cycle,	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Not specifically specified – extracted from paper: Regular menses after metformin Ovulation Adverse effects of metformin (not specified what adverse effects) Pregnancy Miscarriage Full term pregnancy Pregnancy per cycle	
Follow up Duration	*6 – 8 weeks*	
Summary Result/s	*Mean total E2 and E2 per mature follicle were significantly higher in clomiphene group without a difference in mean number of mature follicles >18 mm and ovulation rate. Endometrial thickness was significantly higher in letrozole group. The pregnancy rate in letrozole group (10 patients, 34.50%) as compared with clomiphene group (5 patients, 16.67%) did not show significant difference, whereas full-term pregnancies were higher in letrozole group [10 patients (34.50%) versus 3 patients (10%)].*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes	***Yes***
Does the study have specified inclusion/exclusion criteria?	Yes	***Yes***

If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes	***Yes***
Inclusion criteria		Yes	***Yes*** *Inclusion criteria were consisting of PCOS patients who had failed to become pregnant after three courses of 150 mg clomiphene citrate* *(considered as clomiphene resistant)*
Exclusion criteria		Yes	***Yes*** *Exclusion criteria included patients with a history of liver and kidney failure, cardiovascular disease, diabetes (based on criteria set by the American Diabetic Association) or patients who consumed metformin or drugs effecting insulin secretion* *or clomiphene citrate in the previous 2 months*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Partial	***Partial*** *– randomised by choosing envelopes* *"The patients were visited and examined by two gynaecologists. A series of blind envelopes numbered from 1 to 60 had been prepared. Each patient was invited to pull out an envelope and was placed by the clinic secretary in either the metformin–letrozole group (Group A: envelopes number 1–30) or metformin–clomiphene citrate group (Group B: envelopes number 31–60)"*
	Was allocation to intervention group concealed?	Yes	***Yes***
PERFORMANCE BIAS	**Were patients blind to intervention group?**	No	***No*** *Tablets had different shapes*

	Were investigators and care providers blind to intervention group?	No	***No***
	Aside from the experimental intervention, were the groups treated the same?	Yes	***Yes***
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Yes	***Yes***
	Were all outcomes measured in a standard, valid and reliable way?	Partial	***Partial -*** *Estrogen levels unsure how it was measured : Endometrial thickness, number of mature follicles, estradiol (E2) level and the ratio of E2 to number of mature follicle were determined on the day of HCG administration.*
	Were outcomes assessed objectively and independently?	Partial	***Partial –*** *Estrogen levels unsure how it was measured : Endometrial thickness, number of mature follicles, estradiol (E2) level and the ratio of E2 to number of mature follicle were determined on the day of HCG administration.*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	*1 drop out after therapy* *After metformin administration, one of the patients in the letrozole group became pregnant and was excluded from the study.*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	No	***No***

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Not reported	*Not reported – unsure of primary outcome*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes	*Yes*
	If confounding was present, was it controlled for?	Not reported	*Not reported*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Not reported	*Not reported*
	Was the study sufficiently powered to detect any differences between the groups?	Not reported	*Not reported*
	If statistical analysis was undertaken, was this appropriate?	Partial	*Partial – did not specify which test applied to which outcome* ***SPSS version 12.0 software was used for statistical analysis and the t-test i-square tests were used as appropriate. P-values less than 0.05 were considered as statistically significant***
COMMENTS		*Moderate due to partial outcome reporting and partial blinding, imperfect randomisation with envelopes*	

What is the overall risk of bias?	Moderate	*Moderate*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		

Study ID	*Vandermolen,2001*
Study Citation	Vandermolen DT, Ratts VS, Evans WS, Stovall DW, Kauma SW, Nestler JE. Metformin increases the ovulatory rate and pregnancy rate from clomiphene citrate in patients with polycystic ovary syndrome who are resistant to clomiphene citrate alone. Fertil Steril. 2001 Feb;75(2):310-5. doi: 10.1016/s0015-0282(00)01675-7. PMID: 11172832.
Study Country	USA
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Anovulatory women with the polycystic ovary syndrome (PCOS) who were resistant to CC, BMI - 37.6 +/- 4.3 in intervention group, 38.4 +/- 2.2 in placebo group, 18–35 years of age, cc-resistant
PCOS diagnostic criteria	Oligoovulation (< 6 menstrual periods annually); hyperandrogenism (by laboratory assay of androstenedione, free T, or total T or by clinical evidence of hirsutism); normal levels of TSH, PRL, and 17-hydroxyprogesterone (< 200 ng/dL); normal renal function (serum creatinine concentration < 1.4 mg/dL); and normal results on liver function tests.
Presence of infertility	*Not reported*
Presence of other condition/s	*N/A*
Medication History	*N/A*
N per group	*11 in intervention (metformin), 14 in placebo*
Setting	*Multicentre environment*
Intervention	metformin, 500 mg three times daily, for 7 weeks.
Comparison	*Placebo*
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Primary: Ovulation and pregnancy rates*

Follow up Duration		*6 cycles*	
Summary Result/s		In the metformin and placebo groups, 9 of 12 participants (75%) and 4 of 15 participants (27%) ovulated, and 6 of 11 participants (55%) and 1 of 14 participants (7%) conceived, respectively. Comparisons between the groups were significant.	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT			
Does the study have a clearly focused question and/or PICO?		Yes	"We therefore conducted a double-blind, randomized study of metformin versus placebo in CC-resistant women with PCOS and assessed ovulatory rates, pregnancy rates, and hormonal variables while attempting ovulation induction with CC."
Does the study have specified inclusion/exclusion criteria?		Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes	
Inclusion criteria		Yes	"Participants were also required to have oligoovulation (< 6 menstrual periods annually); hyperandrogenism (by laboratory assay of androstenedione, free T, or total T or by clinical evidence of hirsutism); normal levels of TSH, PRL, and 17-hydroxyprogesterone (, 200 ng/dL); normal renal function (serum creatinine concentration , 1.4 mg/dL); and normal results on liver function tests" "In addition, participants were required to have tubal patency on hysterosalpingography if they had a history of pelvic surgery or pelvic inflammatory disease, and they were required to have a partner with a normal semen analysis according to World Health Organization criteria."
Exclusion criteria		Yes	"Participants who had diabetes mellitus according to American Diabetic Association criteria (25) for oral glucose tolerance testing were excluded."
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes	*Yes - Randomization was done by computer generation in blocks of six.*

	Was allocation to intervention group concealed?	Partial	*Partial – mentions double blinded but no specifics on how this was done*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Partial	*Partial – mentions double blinded but no specifics on how this was done*
	Were investigators and care providers blind to intervention group?	Partial	*Partial – mentions double blinded but no specifics on how this was done*
	Aside from the experimental intervention, were the groups treated the same?	Yes	*Yes*
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Not reported	*Not reported*
	Were all outcomes measured in a standard, valid and reliable way?	Yes	*Yes*
	Were outcomes assessed objectively and independently?	Partial	*Partial – objective outcome measures, however unclear if assessed by independent clinician*
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	*1/12 in intervention group, 1/15 in comparison group*

	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Partial	*Partial - Occurrence of ovulation was analyzed by intention to treat. Because women who ovulated before addition of CC may not clinically need CC for ovulation induction, such women were excluded from the study and were not included in the analysis of pregnancy rates*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes	*Yes*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes	*Yes*
	If confounding was present, was it controlled for?	Not reported	*Not reported*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Not reported	Not reported
	Was the study sufficiently powered to detect any differences between the groups?	No	*No – "First, our strict entrance criterion (documented failure to ovulate with CC) limited the number of women available for enrollment and may have prevented us from having the power to detect a change in insulin or free T levels"*

	If statistical analysis was undertaken, was this appropriate?	Yes	*Yes*
COMMENTS			
What is the overall risk of bias?		High	*High*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		*No*	

Study ID	***Bayram 2004***
Study Citation	Bayram N, van Wely M, Kaaijk EM, Bossuyt PM, van der Veen F. Using an electrocautery strategy or recombinant follicle stimulating hormone to induce ovulation in polycystic ovary syndrome: randomised controlled trial. BMJ. 2004 Jan 24;328(7433):192. doi: 10.1136/bmj.328.7433.192. PMID: 14739186; PMCID: PMC318481.
Study Country	The Netherlands
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	*Women with PCOS resistant to CC* *Age years (SD)* *Electrocautery: 28.5 (3.7)* *rFSH: 28.7 (4.1)* *BMI* *Electrocautery: 27.9 (6.3)* *rFSH: 27.3 (8.8)*
PCOS diagnostic criteria	Women with chronic anovulation (World Health Organization type II) and polycystic ovaries diagnosed by transvaginal ultrasonography
Presence of infertility	*Type of infertility: Primary* *Electrocautery: 63/83 (76%)* *rFSH: 64/85 (75%)* *Duration of infertility (years) mean (SD)* *Electrocautery: 2.8 (2.2)* *rFSH: 2.8 (2.1)*

Presence of other condition/s	*clomiphene citrate resistant (persistent anovulation after taking 150 mg clomiphene citrate daily for five days)*	
Medication History	*NR*	
N per group	*Electrocautery n=83* *rFSH n=85*	
Setting	*29 Secondary and tertiary hospitals in the Netherlands between February 1998 and October 2001*	
Intervention	*Laparoscopic electrocautery of the ovaries followed by clomiphene citrate and recombinant follicle stimulating hormone if anovulation persisted* *"A bipolar insulated needle electrode (length 345 mm, shaft diameter 5 mm) was pressed at right angles to the surface of a follicle, and the needle (length 15 mm, diameter 0.9 mm) was inserted into the follicle and surrounding tissue. Each ovary was randomly punctured 5-10 times, depending on its size"* *If ovulated in 6 subsequent cycles: no further treatment* *If anovulation persisted after 8 weeks: 50 mg clomiphene citrate started* *Still no ovulation: CC increased to a maximum of 150 mg*	
Comparison	*Induction of ovulation with recombinant follicle stimulating hormone.* *10 mg medroxyprogesterone for 10 days after randomisation to induce a withdrawal bleed.* *Ovulation induction was started on cycle day 3 by subcutaneous injection of 75 IU recombinant follicle stimulating hormone daily according to the chronic low dose step up regimen and increased based on the size of the developing follicles*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Primary: Ongoing pregnancy within 12 months.* *Secondary: ovulation, miscarriage, ectopic pregnancy, multiple pregnancy, and live birth*	
Follow up Duration	*6 cycles or until pregnancy (if became pregnant)*	
Summary Result/s	*"The cumulative rate of ongoing pregnancy after recombinant follicle stimulating hormone was 67%. With only electrocautery it was 34%, which increased to 49% after clomiphene citrate was given. Subsequent recombinant follicle stimulating hormone increased the rate to 67% at 12 months (rate ratio 1.01, 95% confidence interval 0.81 to 1.24). No complications occurred from electrocautery with or without clomiphene citrate. Patients allocated to electrocautery had a significantly lower risk of multiple pregnancy (0.11, 0.01 to 0.86)."*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	*Yes*	*"To compare the effectiveness of an electrocautery strategy with ovulation induction using recombinant follicle stimulating hormone in patients with polycystic ovary syndrome."*

Does the study have specified inclusion/exclusion criteria?		Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes	
Inclusion criteria		*Yes*	*Women with PCOS and CC resistance*
Exclusion criteria		*Yes*	*Primary: other causes of infertility, including severe male factor subfertility, and age over 40 years* *Secondary: tubal obstruction, extensive adhesions of the ovaries or fallopian tubes, and endometriosis stages III or IV according to the classification of the American Fertility Society.*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes	*"…computer generated block randomisation during laparoscopy, stratified for centre."*
	Was allocation to intervention group concealed?	Not reported	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Not reported	*However, difficult to blind patients/ clinicians / outcome assessors due to the nature of the intervention*
	Were investigators and care providers blind to intervention group?	Not reported	*However, difficult to blind patients/ clinicians / outcome assessors due to the nature of the intervention*
	Aside from the experimental intervention, were the groups treated the same?	Yes	

DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Not reported	*However, difficult to blind patients/ clinicians / outcome assessors due to the nature of the intervention*
	Were all outcomes measured in a standard, valid and reliable way?	*Yes*	
	Were outcomes assessed objectively and independently?	*Yes*	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	*6/83 in Electrocautery group* *16/85 in rFSH group*	*7.2% in intervention* *18.8% in control*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	*Yes*	*ITT*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	*Yes*	*However, no protocol*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	*Yes*	*"Table 1 lists the characteristics of the patients at baseline. The treatment groups did not differ."*
	If confounding was present, was it controlled for?		*N/A*

OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	*Yes*	*Funding sources declared* *Funding: Serono Benelux provided financial support for recombinant follicle stimulating hormone during the first eight months of the study when this drug was not funded by the health services. FvdV was supported by a grant from the Health Insurance Funds Council (OG 97/007), Amstelveen, Netherlands.* *Competing interests: None declared.*
	Was the study sufficiently powered to detect any differences between the groups?	*Yes*	*"We designed our study as a non-inferiority trial for pregnancy rates because of the anticipated benefits of electrocautery. The electrocautery strategy started with a single procedure, leading to consecutive ovulations with minimal risks of multiple follicle growth and multiple pregnancy, and was expected to have fewer adverse events. We therefore considered the strategy sufficient to show a pregnancy rate within 12 months of no lower than 5% of that achieved by ovulation induction with recombinant follicle stimulating hormone. Assuming an ongoing pregnancy rate within 12 months of 38% after treatment with gonadotrophins, with an alpha of 5% and a β of 20%, and a pregnancy rate of 52% with the electrocautery strategy, we required 168 patients to exclude a difference of 5% or more to the detriment of electrocautery of the ovaries.20 21 All outcomes were analysed on an intention to treat basis"*
	If statistical analysis was undertaken, was this appropriate?	*Yes*	
COMMENTS			
What is the overall risk of bias?		*High*	*Due to non-blinding and drop outs in the control group* small n and unblinding- consistent with the others and high drop out rate
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

Study ID	***Farquhar 2002***

Study Citation	Farquhar CM, Williamson K, Gudex G, Johnson NP, Garland J, Sadler L. A randomized controlled trial of laparoscopic ovarian diathermy versus gonadotropin therapy for women with clomiphene citrate-resistant polycystic ovary syndrome. Fertil Steril. 2002 Aug;78(2):404-11. doi: 10.1016/s0015-0282(02)03225-9. PMID: 12137881.
Study Country	New Zealand
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	*Women with anovulatory infertility secondary to clomiphene-resistant polycystic ovary syndrome. 20 to 38 years of age, clomiphene citrate resistance, body mass index of <33 kg/m2 for women of European descent and of<35 kg/m2 for women of Pacific Island or NZ Maori descent*
PCOS diagnostic criteria	polycystic ovaries on ultrasound scan according to accepted criteria (10),, ref: Adams J, Franks S, Polson DW, Mason HD, Abdulwahid NA, Tucker M. Multifollicular ovaries: clinical and endocrine features and response to pulsatile gonadotrophin releasing hormone. Lancet 1985;1375–9.
Presence of infertility	*Infertility duration range from 11 months to >= 35 month.* *10%(n=3) of women had 11 month infertility in intervention group,* *38%(n= 11) women had infertility 12 – 35 months in intervention group, 81%(n=17) of women had infertility 12 – 35 months in comparison group* *proportion of women who had length of infertility of >= 36 months (52%(n=15) in group 1 compared with 19%(n=4) in group 2).*
Presence of other condition/s	*CC resistant*
Medication History	*NR*
N per group	*29 in intervention, 21 in comparison*
Setting	*A tertiary referral fertility clinic*
Intervention	*Laparoscopic ovarian diathermy (n=29)*
Comparison	*Urinary or recombinant gonadotropins (n=21)*
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Main: Cumulative pregnancy and miscarriage rates.* *Secondary: multiple pregnancy, live birth, birth weight, pregnancy with 6-12 mo follow-up period, number of women with >= 1 pregnancy during 0 – 12 month of follow up*
Follow up Duration	*6-12 months*
Summary Result/s	*Cumulative pregnancy rates were 28% at 6 months for laparoscopic ovarian diathermy and 33% for three cycles of ovulation induction with gonadotropins. There were three miscarriages in each group. Women in the laparoscopic ovarian diathermy arm of the study had four additional spontaneous pregnancies* *6 to 12 months after surgery.*

ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	*Yes*	*"The aim of this study was to compare laparoscopic ovarian diathermy with three cycles of FSH in women who had clomiphene citrate–resistant PCOS and who wished to conceive."*
Does the study have specified inclusion/exclusion criteria?	Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes	
Inclusion criteria	*Yes*	*"The inclusion criteria for the study were as follows: 20 to 38 years of age, clomiphene citrate resistance (no ovulation after one or more cycles of150 mg ofclomiphene citrate from day 2 to day 6 each month), infertility of ¬12 months duration, polycystic ovaries on ultrasound scan according to accepted criteria (10), a body mass index of ↕33 kg/m2 for women ofEuropean descent and of↕35 kg/m2 for women of Pacific Island or NZ Maori descent, and normal semen analysis (≏20 million per milliliter, ∉96% abnormal forms, and ¬50% motility). Elevations of LH and androgen levels were not inclusion criteria."*
Exclusion criteria	*Yes*	*"The exclusion criteria were other known causes of infertility, including male factor infertility or known tubal disease. The trial conditions were determined within the funding restrictions of a public fertility clinic. Tubal status in women with anovulatory infertility was only established after three ovulations had been induced with clomiphene citrate or gonadotropins. Therefore, not all women who were randomized had had tubal status established"*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS **Did the study have an adequate method of randomisation?**	Yes	*Randomization was performed using computer-generated sequences that were sealed in numbered opaque envelopes.* *Randomization was not blocked.*
SELECTION BIAS **Was allocation to intervention group concealed?**	Yes	*Opaque envelopes*

PERFORMANCE BIAS	**Were patients blind to intervention group?**	*No*	*Not possible due to the nature of intervention*
	Were investigators and care providers blind to intervention group?	*No*	*Not possible due to the nature of intervention*
	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	*No*	*Not possible due to the nature of intervention*
	Were all outcomes measured in a standard, valid and reliable way?	*Yes*	
	Were outcomes assessed objectively and independently?	*Yes*	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**		*1/29 in intervention group, 2/21 in comparison group*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	*Yes*	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	*Yes*	

CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	*Partial*	*The numbers are different in each group and the reason explained.* *"The baseline characteristics of women at the entry to the study are presented in Table 1. The numbers of women in each group are dissimilar because of unblocked randomization. There are no statistically significant differences between the two groups, with the exception of the proportion of women who had length of infertility of>36 months (52% in group 1 compared with 19% in group 2)."*
	If confounding was present, was it controlled for?	Not reported	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	*Not reported*	
	Was the study sufficiently powered to detect any differences between the groups?	*No*	*It was estimated that 55% of women, undergoing laparoscopic diathermy would conceive in the 6-month follow-up period (based on the results of a review by Donesky and Adashi [6]) and that only 30% of women having three cycles of gonadotropin therapy would conceive (8). Twenty-seven women were required in each arm of the study to detect a true difference at the 95% confidence level with 80% power. Taking dropouts into account, it was estimated that 30 women would be needed in each arm of the study to observe the difference described.* *"These difficulties, compounded by a failure to receive renewed funding, led to the study being closed after 50 patients were recruited, 10 short of the planned 60."*
	If statistical analysis was undertaken, was this appropriate?	*Yes*	
COMMENTS			
What is the overall risk of bias?		*High*	*small n and unblinded*

Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	

Study ID	***Yarali 2002***
Study Citation	*Yarali H, Yildiz BO, Demirol A, Zeyneloğlu HB, Yiğit N, Bükülmez O, Koray Z. Co-administration of metformin during rFSH treatment in patients with clomiphene citrate-resistant polycystic ovarian syndrome: a prospective randomized trial. Hum Reprod. 2002 Feb;17(2):289-94. doi: 10.1093/humrep/17.2.289. PMID: 11821265.*
Study Country	? Turkey
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	*PCOS patients with normal glucose tolerance* *Age* *Intervention: 29.7 ± 5.6 (years)* *Control: 28.4 ± 5.1 (years)* *BMI* *Intervention: 28.6 ± 4.0 (kh/m2)* *Control: 29.6 ± 4.8*
PCOS diagnostic criteria	Based on peripubertal onset of oligo-amenorrhoea, elevated serum testosterone levels (>80 ng/dl; conversion factor = 0.03467; >2.4 nmol/l) and ultrasonographic evidence of polycystic ovaries (PCO)
Presence of infertility	*Duration of infertility* *Intervention: 57.8 ± 37.9 (months)* *Control: 62.3 ± 41.9 (months) p>0.05*
Presence of other condition/s	*Clomiphene Citrate-resistant (defined as failure to ovulate with incremental doses of clomiphene citrate up to 250 mg/day for 5 days, if necessary, for 6 months)*
Medication History	*None of the patients had undergone any previous exogenous gonadotrophin treatment cycle.*
N per group	*N=32* *Intervention (metformin) n= 16* *Control (Oral placebo) n= 16* *"At the time of entry into the study, all the women were in the equivalent of the follicular phase of the menstrual cycle and they had either spontaneous or progesterone-induced menses during the preceding week."*
Setting	*?*
Intervention	*Metformin (850mg daily) for 6-12 weeks* *Followed by FSH 75 IU per days staring on the day 3 after menstrual bleeding, continued for 14 days or until follicles mature. Dose increased by*

	37.5 IU to 187.5 IU per day until dominant follicle emerged if follicles did not develop	
Comparison	*Oral placebo* *Followed by same FSH procedure as above*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*fasting glucose to insulin ratio* *insulin sensitivity index* *LH, FSH, E2, total testosterone and DHEAS were measured by chemiluminescent enzyme immunoassay* *Leptin was measured by using an immunoradiometric assay* *Free testosterone, androstenedione and insulin were measured by radioimmunoassay* *Plasma 17-OH progesterone was measured by radioimmunoassay* *How pregnancy was ascertained not reported*	
Follow up Duration	*12 weeks of pre-treatment + 1 cycle with FSH*	
Summary Result/s	*"There was no significant change in all insulin sensitivity indices in both groups. The only change noted was a decline in mean serum free testosterone concentration in the metformin group (P = 0.049). One patient on placebo and six patients on metformin ovulated spontaneously (P < 0.05). All parameters of ovarian response were comparable between the two groups during rFSH treatment. Combining the 6 week placebo or metformin-only period with a single rFSH treatment cycle, the overall ovulation rates were 75 and 94% in the placebo and metformin groups respectively (P > 0.05). The respective figures for pregnancy were 6.3 and 31.3% (P > 0.05)."*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	*Yes*	*"The aim of this prospective randomized, placebo-controlled study is to analyse the impact of metformin on ovarian response when co-administered during a low-dose step-up protocol using recombinant (r)FSH."*
Does the study have specified inclusion/exclusion criteria?	Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes	
Inclusion criteria	*Yes*	*PCOS* *Normal semen analysis according to World Health Organization criteria* *Normal hysterosalpingography and/or laparoscopy within the preceding 6 months* *No history of previous genital surgery.* *Normal glucose tolerance*

Exclusion criteria		*Yes*	*Presence of any infertility factor other than PCOS, The use of medications known to alter insulin secretion or action,* *Endocrinopathies, including non-classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency* *Cushing's syndrome* *Hyperprolactinaemia* *Thyroid dysfunction* *IGT*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes	*Divided into intervention and control groups using computer-generated numbers*
	Was allocation to intervention group concealed?	Not reported	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	*Yes*	*The study says it is 'double blind'. No further information is available*
	Were investigators and care providers blind to intervention group?	Yes	*The study says it is 'double blind'. No further information is available*
	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	*Not reported*	
	Were all outcomes measured in a standard, valid and reliable way?	*Yes*	
	Were outcomes assessed objectively and independently?	*Yes*	

ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	*0%*	*"There was no drug discontinuation due to side-effects."*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	*Yes*	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	*Yes*	*No protocol available. Difficult to determine.*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	*Yes*	*"On entry into the study, the metformin and placebo groups did not differ with respect to the anthropometric variables (Table I)"*
	If confounding was present, was it controlled for?	N/A	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	*Not reported*	
	Was the study sufficiently powered to detect any differences between the groups?	*Not reported*	

	If statistical analysis was undertaken, was this appropriate?	*Yes*	
COMMENTS			
What is the overall risk of bias?		*Moderate*	*Small study (n=32), it says consecutive PCOS patients were recruited, no information on allocation concealment and no information on blinding. Perhaps these were done but did not report in the study, but difficult to ascertain without contacting the authors.* small and lacks info on blinding
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

Study ID	*Sharma,2006*
Study Citation	Sharma M, Kriplani A, Agarwal N. Laparoscopic Bipolar Versus Unipolar Ovarian Drilling in Infertile Women with Resistant Polycystic Ovarian Syndrome: A Pilot Study. Journal of Gynecologic Surgery. 2006;22(3):105-11.
Study Country	India
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	CC Resistant, Average BMI: Intervention (26.68), Comparison (24.13) Average Age: Intervention (27.3 (21-32)), Comparison (25.5 (23.30)
PCOS diagnostic criteria	National Institute of Health Consensus Conference on PCOS
Presence of infertility	Yes (Avg: 4.5 years in intervention, 3.9 years in comparison)
Presence of other condition/s	1 patient developed gestational diabetes mellitus during the study, otherwise N/A Clomiphene Citrate resistant
Medication History	N/A

N per group	10 in intervention, 10 in comparison	
Setting	Department of Obstetrics and Gynaecology of the All India Institute of Medical Sciences	
Intervention	*Unipolar electrocautery (average number of punctures: 14.8)*	
Comparison	*Bipolar electrocautery ((average number of punctures: 14.9)*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Clinical outcomes: Oligomenorrhoea, secondary amenorrhoea, cycle length, duration of flow, ovulation (spontaneous), ovulation (induced), Pregnancy, live birth rate* *Biomarker changes: LH, FSH, Testo, Insulin, GI Ratio*	
Follow up Duration	*1 and 3 months*	
Summary Result/s	*After ovarian drilling, 6 patients (60%) in group I and 8 (80%) in group II ovulated spontaneously (p = 0.63), and 3 (30%) more patients ovulated after clomiphene citrate in group I and 1 (10%) in group II, with a total ovulation rate of 90% in both groups (p = 0.46). Six (6; 60%) pregnancies resulted in group I and 8 (80%) pregnancies resulted in group II (p = 0.63). LH levels fell significantly only in group II after 3 months (11.11 +/- 1.25 to 4.88 +/- 1.34 mIu/mL; p = 0.036), and there was no significant change in FSH and testosterone levels in either group. The fasting serum insulin levels increased nonsignificantly from 17.70 +/- 5.27 micoIU/mL to 21.90 +/- 7.43 microIU/mL (p = 0.71) in group I and from 7.73 +/- microIU/mL to 13.11 +/- 3.55 microIU/mL (p = 0.27) in group II 3 months after surgery. Area under curve (AUC) glucose and insulin values fell postoperatively in both the groups.*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes	***Yes*** *"to find the response of bipolar ovarian drilling in resistant PCOS on clinical outcome, endocrine profile, and insulin resistance in comparison of unipolar cautery"*
Does the study have specified inclusion/exclusion criteria?	Not reported	***Not reported***

If there were specified inclusion/ exclusion criteria, were these appropriate?		Not reported	***Not reported***
Inclusion criteria		Partial	**Partial** *Tubal patency, cc-resistance and normal semen analysis required and + PCOS diagnosis* However, no set inclusion criteria on age or bmi However, not explicitly signposted
Exclusion criteria		Not reported	***Not reported***
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes	***Yes*** *– computerised random table*
	Was allocation to intervention group concealed?	Not reported	***Not reported***
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Not reported	***Not reported***
	Were investigators and care providers blind to intervention group?	No	***No***
	Aside from the experimental intervention, were the groups treated the same?	Yes	***Yes***
DEDETECTION BIAS	**Were outcome assessors blind to**	Not reported	***Not reported***

	intervention group?		
	Were all outcomes measured in a standard, valid and reliable way?	Yes	***Yes*** *"Serum LH, FSH, and testosterone were measured by Elecsys 1010 by electrochemiluminiscence assay by Boehringer Mannheim (Mannheim, Germany). Serum insulin levels were measured by an Enzyme Immunoassay (EIA) kit from Mercodia (Uppsala, Sweden). Clinical outcome was assessed on the basis of achievement of regular cycles, ovulation, and conception. Endocrine parameters were assessed on the basis of changes in biochemical values. Hyperinsulinism was con-* *sidered when the glucose to insulin ratio (G/I) was more than 4.5."*
	Were outcomes assessed objectively and independently?	Partial	***Partial*** Biomarkers assessed via assay, however unclear whether clinical outcomes were assessed independently
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	X% treatment X% control/ comparison Not reported	***0% drop out***
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes	***Yes***
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Not reported	***Not reported –*** *Unregistered study, thus unsure of primary and secondary outcomes*

CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Partial	***Partial*** *(Insulin (F) significantly different between groups (p=0.001))*
	If confounding was present, was it controlled for?	Not reported	***Not reported***
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Not reported	***Not reported***
	Was the study sufficiently powered to detect any differences between the groups?	Not reported	***Not reported***
	If statistical analysis was undertaken, was this appropriate?	Yes	*The responses of ovarian drilling on clinical and biochemical parameters in each group were assessed by the Mann-Whitney test and chi-square test with Yate's correction factor. To see the trend within the group, Friedman two-way analysis of variance (ANNOVA) and the Wilcoxon signed test was applied separately for both groups and a p-value 0.05 was considered as one of statistical significance. The Kaplan-Meier test acturial survival analysis was done to see the probability of conception. The response to OGTT was analyzed as the area under curve (AUC) calculated by the trapezoidal method, and SPSS 7.5 (Chicago, IL) was used for calculation of the study.*

COMMENTS	*High due to lack of blinding*	
What is the overall risk of bias?	High	***High***
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*No – all outcomes were objective*	

Study ID	***Yadav 2017***
Study Citation	*Yadav, Poonam & Singh, Saroj & Singh, Richa & Jain, Meenal & Awasthi, Sarvesh & Raj, Pallavi. (2017). To Study the Effect on Fertility Outcome by Gonadotropins vs Laparoscopic Ovarian Drilling in Clomiphene-resistant Cases of Polycystic Ovarian Syndrome. Journal of SAFOG with DVD. 9. 336-340. 10.5005/jp-journals-10006-1525.*
Study Country	India
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	*CC resistant, aged 21-35 yrs-Hospital setting* *Age (years)* *Gonadotrophin: 26.23 ± 2.9* *LOD: 26.11 ± 2.7* *BMI* *Gonadotrophin: 24.94 ± 2.8* *LOD: 25.0 ± 2.35*
PCOS diagnostic criteria	Chronic anovulation and polycystic ovaries diagnosed by transvaginal ultrasonography-Any standard criteria not reported.
Presence of infertility	*Duration of infertility (years)* *Gonadotrophin: 4.5 ± 2.24* *LOD: 4.62 ± 2.36*
Presence of other condition/s	*NR*
Medication History	*NR*
N per group	*Group gonadotropin:44 randomised, 44 analysed;* *Group LOD 45 randomised, 45 analysed*
Setting	*Hospital setting*
Intervention	rFSH (subcutaneous injection of 37.5/75 IU daily started on cycle day 3)-If the diameter of the follicle remained <10 mm, the dose was increased by half an ampoule (37.5 IU) on days 16 and 23. If no follicle development was seen on day 30, the cycle was terminated because of poor response.

Comparison	*LOD* *If women underwent LOD failed to ovulate spontaneously at 8 weeks, were then subsequently added with clomiphene citrate for one cycle followed by gonadotropin.*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*The primary endpoint was ongoing pregnancy within 12 months, defined as a viable pregnancy of at least 12 weeks. Secondary endpoints were ovulation, miscarriage, ectopic pregnancy, multiple pregnancies, and live birth. The effectiveness of the ovarian drilling strategy was compared with recombinant FSH.*	
Follow up Duration	*3-6 months*	
Summary Result/s	*The ongoing pregnancy rate from ovulation induction with LOD alone was significantly less but if supplemented by clomiphene citrate and gonadotropin, it seems equivalent to ovulation induction with gonadotropin, but the former procedure carries a lower risk of multiple pregnancies.*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	*Yes*	*"To compare the effectiveness of laparoscopic ovarian drilling (LOD) for ovulation induction with gonadotropins in clomiphene-resistant PCOS in terms of ovulation, pregnancy, live birth, abortion, multiple pregnancies, and complication like ovarian hyperstimulation syndrome (OHSS)."*
Does the study have specified inclusion/exclusion criteria?	Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes	
Inclusion criteria	*Yes*	*Women were invited to participate if they had chronic anovulation and polycystic ovaries diagnosed by transvaginal ultrasonography. They had also to be resistant to clomiphene citrate, which is shown by persistent anovulation after taking 150 mg clomiphene citrate daily for 5 days for at least 3 cycles. Women aged between 21 and 35 years were included*
Exclusion criteria		*Exclusion criteria were severe male factor subfertility and other causes of infertility like tubal obstruction and extensive adhesion (endometriosis) stages III and IV according to the classification of the American Fertility Society.*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Not reported	
	Was allocation to intervention group concealed?	Not reported	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	*Not reported*	*However, difficult to blind this type of intervention / control*
	Were investigators and care providers blind to intervention group?	Not reported	
	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	*Not reported*	
	Were all outcomes measured in a standard, valid and reliable way?	*Yes*	
	Were outcomes assessed objectively and independently?	*Yes*	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	*0%*	
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	*Yes*	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	*Not reported*	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	*Yes*	
	If confounding was present, was it controlled for?	Yes	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	*No*	*"Source of support: Nil* *Conflict of interest: None"*
	Was the study sufficiently powered to detect any differences between the groups?	*Not reported*	
	If statistical analysis was undertaken, was this appropriate?	*Yes*	
COMMENTS			
What is the overall risk of bias?		*High*	*insufficient info on blinding, randomisation, drop outs etc.*

Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	*No*

Study ID	***Zheng 2022***
Study Citation	Zheng X, Guo W, Zeng L, Zheng D, Yang S, Xu Y, Wang L, Wang R, Mol BW, Li R, Qiao J. In vitro maturation without gonadotropins versus in vitro fertilization with hyperstimulation in women with polycystic ovary syndrome: a non-inferiority randomized controlled trial. Hum Reprod. 2022 Jan 28;37(2):242-253. doi: 10.1093/humrep/deab243. PMID: 34849920; PMCID: PMC9115328.
Study Country	China
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	*Infertile women aged 20–38 years with PCOS and infertility scheduled for their first IVF attempt.* *IVM* *Age: 28.9 ± 2,9* *BMI: 24.9 ±* *IVF* *Age: 29.5 ± 3.2* *BMI: 24.8 ± 4.0*
PCOS diagnostic criteria	Rotterdam
Presence of infertility	*A total of 231 were not eligible (43 women with a male partner diagnosed with azoospermia; 32 women or their male partner with a known abnormal chromosome karyotype)*
Presence of other condition/s	*NR*
Medication History	*"To initiate the IVM or IVF treatment cycle in anovulatory cases, patients were administered oral dydrogesterone (Duphaston, Abbott, OLST, Netherlands) 20mg daily for 10–14 days and oral contraceptives Diane-35 (cyproterone acetate 2mg, ethinylestradiol 35mg, Bayer and its generics) for 21 days."*
N per group	*IVM (n=175)* *IVF (n=176)*
Setting	*This single-centre, in an academic infertility centre in China was performed between March 2018 and July 2019.*
Intervention	*IVM (n=175)*

	"Transvaginal ultrasound-guided oocyte retrieval was conducted…All cumulus-oocyte complexes (COCs) were transferred into IVM medium …" "All MII oocytes were inseminated using intracytoplasmic sperm injection (ICSI)."	
Comparison	*IVF (n=176)* *Standard IVF with a flexible GnRH antagonist protocol (n=176)* *"Recombinant FSH with a starting dose ranging from 112.5 to 225 IU was administered on day 2/3 of the menstrual cycle. Transvaginal ultrasound, serum luteinizing hormone (LH), serum oestrogen, and progesterone were measured to monitor follicle growth. The doses of rFSH were adjusted according to the ovarian response. GnRH antagonist 0.25 mg daily was administered subcutaneously when at least one follicle reached a diameter of 12mm (usually between Day 5 and Day 8 of ovarian stimulation), until and including the ovulatory trigger day. When two or more follicles reached a diameter of at least 17mm, 250 mg of rhCG (Ovidrel; Serono, Aubonne, Germany) was administered for triggering. Oocyte retrieval was performed 36 (±2) hours after triggering with the use of intravenous sedation. IVF or ICSI was used for fertilization based on the semen analysis results.*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Primary: ongoing pregnancy (leading to live birth, defined as a baby born live at ≥ 22 weeks of gestation within 6months of the first oocyte retrieval cycle after randomization)* *Secondary: implantation, clinical pregnancy, and time to ongoing pregnancy leading to live birth.* *Safety outcomes included OHSS (classified as mild, moderate, miscarriage, ectopic pregnancy and obstetric and perinatal complications* *Initial pregnancy diagnosis: positive pregnancy test (not specified)* *Confirmed by: gestational sac*	
Follow up Duration	*1 cycle*	
Summary Result/s	*"The IVM procedure without additional gonadotropin resulted in a lower ongoing pregnancy (leading to live birth) within 6 months after randomization compared to standard IVF treatment (22.3% vs. 50.6%; rate difference 28.3%; 95% confidence interval [CI]: -37.9% to -18.7%). Moderate-severe OHSS did not occur in the IVM group, while in the IVF group, ten women (5.7%) had moderate OHSS and one woman (0.6%) had severe OHSS. There was no statistically significant difference in the occurrence of obstetric and perinatal complications"*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	*Yes*	*"Therefore, we performed an RCT to assess the effectiveness and safety of one cycle of IVM without the use of gonadotropins or hCG priming versus one cycle of standard IVF with ovarian stimulation and hCG as the ovulatory stimulus, both with a freeze-all and singleblastocyst transfer strategy, in women with PCOS."*

Does the study have specified inclusion/exclusion criteria?		Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes	
Inclusion criteria		*Yes*	*PCOS* *Awaiting first IVF attempt*
Exclusion criteria		*Yes*	*Couples scheduled for preimplantation genetic testing (PGT) with abnormal results on parental karyotyping* *Women who had undergone unilateral ovariectomy or had congenital/ acquired uterine malformations* *Male partner diagnosed with azoospermia*
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes	*"…computer-generated randomization list, with a variable block size of 4 or 6"*
	Was allocation to intervention group concealed?	Yes	*"Opaque sealed envelopes with randomized assigned groups printed inside were numbered consecutively……."*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	*No*	*"Due to the nature of the interventions, the study was not blinded."*
	Were investigators and care providers blind to intervention group?	No	*"Due to the nature of the interventions, the study was not blinded."*
	Aside from the experimental intervention, were the groups treated the same?	*Yes*	*"Due to the nature of the interventions, the study was not blinded."*

DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	*No*	*"Due to the nature of the interventions, the study was not blinded."*
	Were all outcomes measured in a standard, valid and reliable way?	*Yes*	
	Were outcomes assessed objectively and independently?	*Yes*	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	*3.4% IVM* *10.2% IVF*	
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	*Yes*	*ITT conducted*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	*Yes*	*Clinicaltrials.gov NCT03463772*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	*Yes*	*"The baseline characteristics of the women were comparable between the two groups (Table I)."*
	If confounding was present, was it controlled for?		*N/A*

OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	*Yes*	*"*B.W.M. was supported by a NHMRC Investigator (GNT1176437). All other authors declare no competing interests."
	Was the study sufficiently powered to detect any differences between the groups?	*Yes*	*"Assuming a live birth rate of 35% in the IVF group which was based on our clinical data, a sample size of at least 175 women per group was required to demonstrate non-inferiority with a power of 80%, and a non-inferiority margin of 15% for the lower limit of the two-sided 95% CI, including a dropout rate of 10%."*
	If statistical analysis was undertaken, was this appropriate?	*Yes*	
COMMENTS			
What is the overall risk of bias?		Low	*All of the criteria have been fulfilled or where criteria have not been fulfilled it is very unlikely the conclusions of the study would be affected.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

Study ID	***Ashrafi 2005***
Study Citation	Ashrafi, Mahnaz & Moini, Ashraf & Mohammadzadeh, Afsaneh & Ezabadi, Zahra & Zafarani, Fatemeh & Baghestani, Ahmad. (2005). A comparative study of GnRH antagonist and GnRH agonist in PCO patients undergoing IVF/ICSI cycles. Iranian Journal of Reproductive Medicine (ISSN: 1680-6433) Vol 3 Num 1. 3.
Study Country	Iran
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	*Patients under 35 years old patients with oligomenorrhea, hyperandrogenism, LH/FSH>2.5 and ultrasonographic features of PCOS (Adams criteria)* *Age (years)* *GnRH agonist 28.3 ± 4* *GnRH antagonist 29.2 ± 4.6* *BMI (kg/m2)*

	GnRH agonist 30.45 ± 6.09 *GnRH antagonist 27.97 ± 6.71*
PCOS diagnostic criteria	patients with oligomenorrhea, hyperandrogenism, LH/FSH>2.5 and ultrasonographic features of PCOS (Adams criteria) (Adams's criteria) [Ref: Adams J, Franks S, Polson DW, Mason HD, Abdulwahid N, Tucker M, et al . Multifollicular ovaries: clinical and endocrine features and response to pulsatile gonadotropin releasing hormone. Lancet 1985; 2: 1375-1379.]
Presence of infertility	*Duration of infertility (yr)* *GnRH agonist 9.2 ± 4.1* *GnRH antagonist 8.8 ± 4.7*
Presence of other condition/s	The patients have no history of thyroid disorder and hyperprolactinemia
Medication History	All patients received OCP (LD) before starting the treatment from 5th day of their previous menstrual cycle
N per group	*GnRH agonist randomised 30, analysed n=24* *GnRH antagonist randomised 30, analysed n=23*
Setting	Royan institute between 2001 and 2002.
Intervention	Agonist: underwent standard long GnRH analogue protocol 21st day of cycle with the GnRH agonist (Suprefact, Hoechst, Germany) 500µg/day When pituitary suppression was achieved (on second day of menstrual cycle FSH≤5IU/ml, LH≤5IU/ml, progesterone≤1ng/ml, and Estradiol≤50pg/ml), Buserline was reduced to 200µg/day and gonadotrophin (Pregonal, Organon, Netherland) 150IU/day was started based on the follicular growth When more than 3 follicles≥18mm were seen, HCG (Pregnyle, Organon, Germany) 10000 IU were injected
Comparison	*Antagonist:* HMG (150 IU/day) was started from third day of cycle. Then GnRH antagonist (0.25mg) was administered from 6th day after HMG initiation (LH≤5 IU/ml) to the day of HCG injection.
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Duration of treatment, Duration of HMG stimulation, Serum LH and E2, follicle development, risk of OHSS, number of embryos, fertilisation* *10 to 12 days after embryonic transfer, βHCG was tested.*
Follow up Duration	*1 cycle*
Summary Result/s	"There were no significant differences in age, duration of infertility, BMI, number of HMG ampules, number of follicles≥18mm, serum estradiol level on 6th day of HMG initiation and HCG injection time, fertilization and pregnancy rate between two groups. However there were significant

		differences regarding duration of treatment, duration of HMG usage, LH level at the initiation of HMG, OHSS rate and number of Metaphase II oocytes between two groups (p<0.05)."	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT			
Does the study have a clearly focused question and/or PICO?		Yes	The aim of this study was to compare the effects of GnRH agonists and antagonists in PCOS patients.
Does the study have specified inclusion/exclusion criteria?		Partial	
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes	
Inclusion criteria		Yes	*PCOS*
Exclusion criteria		Not reported	."
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Partial	*"Then they were randomly divided into two groups*
	Was allocation to intervention group concealed?	Not reported	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Not reported	
	Were investigators and care providers blind to intervention group?	Not reported	

	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	20% treatment 23.3% control/ comparison	*6 patients from GnRH agonist group and 7 from GnRH antagonist group were excluded due to either cycle discontinuation or failure in follicular development*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	No	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Not reported	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Partial	*"There were no statistically significant differences in mean age, mean duration of infertility, BMI, FSH, LH, and E2 between the two groups.* *This is however, after excluding the randomised patients*

	If confounding was present, was it controlled for?	Not reported	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Not reported	
	Was the study sufficiently powered to detect any differences between the groups?	Not reported	
	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS		*Lack of randomisation and blinding key reason for high RoB*	
What is the overall risk of bias?		High	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

- Bahceci 2005

Study ID	***Bahceci 2005***
Study Citation	Bahceci, M.; Ulug, U.; Ben-Shlomo, I.; Erden, H. F.; Akman, M. A. Use of a GnRH antagonist in controlled ovarian hyperstimulation for assisted conception in women with polycystic ovary disease: a randomized, prospective, pilot study. *Journal of Reproductive Medicine* **2005**, 50, 84-90
Study Country	Turkey
BRIEF CHARACTERISTICS OF RCT	

Patient/population/ participants	*PCOD patients admitted to hospital to undergo ART* GnRH agonist Number of patients n= 70 Age (years) (mean ± SD) 29.43 ± 4.3 Range (21-38) Median 29 BMI (kg / m^2) 26.03 ± 4.2 GnRH antagonist n= 59 30.06± 4.8 (21-38) 30 26.1 ± 3.8
PCOS diagnostic criteria	Patients with PCOD, defined as primary infertility, oligomenorrhea, clinical hyperandrogenism (hirsutism Ferriman-Galway score >7), reversed FSH /LH ratio and polycystic appearance of ovaries on ultrasound with no known history of previous ART or hyperprolactinemia or thyroid abnormalities.
Presence of infertility	*N=26 male partners of women (34.6%) in the antagonist arm and 35 (46.6%) in the agonist arm had oligoasthenoteratospermia as a coexisting infertility factor.* *Other n=87 couples had multiple unsuccessful attempts at ovulation induction with gonadotropins and intrauterine insemination attempts.* GnRH agonist Number of patients n= 70 Duration of infertility (years) (mean ± SD) 5.15 ± 2.2 Range (1-11) Median 5 GnRH antagonist n= 59 4.73 ± 2.6 (2-8) 5
Presence of other condition/s	*Not reported*
Medication History	*NR*
N per group	*N=148* *Antagonist protocol: n=73 (Cetrorelix)* *Agonist protocol: n=75 (Leuprolide acetate)*
Setting	*German Hospital, Istanbul, Turkey*
Intervention	All patients received OC for 21 days from the preceding menstrual period Agonist Protocol:

	The ovulation induction protocol in the agonist arm began with pituitary desensitization with daily LA, 0.5mg, on day 14 of the cycle. Daily administration of gonadotropins, 2 or 3 ampules was initiated on the 3rd day of the anteceding menstrual period. Pituitary desensitisation was confirmed by serum E_2 assay on the 3rd day (<50 pg/ml). Starting regimen was fixed for the first 4 days and then adjusted based on response on individual basis. When at least 2 follicles reached 18mm in diameter, 10,000IU of im hCG administered.	
Comparison	All patients received OCP for 21 days from the preceding menstrual period Antagonist protocol: Gonadotropins were administered in 2-3 ampoules on the 3rd day of the antecedent bleeding after OC usage. After 4 days, the starting regimen was adjusted based on the individual response. Cetrorelix 0.25 mg/d sc was starte when the leading follicle reached 14 mm. Cetrorelix was continued daily until hCG injection (10,000 IU) when at least 2 follicles reached 18 mm in diameter.	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Not specified* *Extracted from the paper: (table 2)* • *Stimulation duration* • *Ampoules consumed* • *E2 level on hCG day (pg/ml)* • *Number of retrieved oocytes* • *Fertilization rate* • *Number of pregnancies Pregnancy rate* • *Multiple pregnancy rate* *Clinical pregnancy was defined as a demonstrable gestational sac accompanied by foetal heart activity on ultrasonography.*	
Follow up Duration	*Not reported*	
Summary Result/s	*"* …in the antagonist arm a shorter duration of ovarian stimulation was recorded as compared to the agonist arm. Although similar numbers of oocytes was retrieved from both groups of patients, the quality of the oocytes, as measured by metaphase 2/total oocyte ratio, was lower in the antagonist arm as compared to the agonist arm. Pregnancy rates were 57.6% and 58.5% in the antagonist and agonist arms, respectively (p > 0.05). Implantation rates were not different (34.0% and 34.6%, respectively). The frequency of ovarian hyperstimulation syndrome also did not differ between the treatment groups (5% and 7.1%, respectively)."	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Partial	*"To examine the possible advantage of using GnRH antagonists in PCOD patients undergoing COH for ART, we designed a randomised, prospective, pilot study to compare the outcome of treatment with a GnRH agonist versus antagonist."*
Does the study have specified inclusion/exclusion criteria?	Partial	

If there were specified inclusion/ exclusion criteria, were these appropriate?		Partial	
Inclusion criteria		Not reported	
Exclusion criteria		Partial	Couples with co-existing male factor infertility due to nonobstructive azoospermia
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes	*Using a table of random numbers*
	Was allocation to intervention group concealed?	Not reported	however not possible to do so given differing protocol
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Not reported	
	Were investigators and care providers blind to intervention group?	Not reported	
	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes	

	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**		*5 (6.6%) from the agonist arm* *14 (19.1%) from the antagonist arm* *Dropped out after randomisation but before starting ovulation induction*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Partial	*Apparently, 148 patients were randomised but 19 dropped out before treatment. Only the participants who underwent treatment had been analysed.*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Not reported	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes	
	If confounding was present, was it controlled for?	Not reported	*Groups were similar at baseline (table 1)*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	No	*"Authors have no connection to any companies or products mentioned in this article"*
	Was the study sufficiently powered to detect any differences between the groups?	Not reported	*Not applicable* *Simple statistical analysis was used and a probability value of <0.05 was considered significant*

	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS		*Lack of randomisation and blinding key reason for high RoB*	
What is the overall risk of bias?		Moderate (technical report)	*Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.* *I would say the risk of bias is high: LP (16/09/2022)*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

- Engmann 2007

Study ID	***Engman 2007***
Study Citation	Engmann L, DiLuigi A, Schmidt D, Nulsen J, Maier D, Benadiva C. The use of gonadotropin-releasing hormone (GnRH) agonist to induce oocyte maturation after cotreatment with GnRH antagonist in high-risk patients undergoing in vitro fertilization prevents the risk of ovarian hyperstimulation syndrome: a prospective randomized controlled study. Fertil Steril. 2008 Jan;89(1):84-91. doi: 10.1016/j.fertnstert.2007.02.002. Epub 2007 Apr 26. PMID: 17462639.
Study Country	US
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	patients under 40 years of age with polycystic ovarian syndrome, polycystic ovarian morphology, or previous high response undergoing IVF *Age (yrs)* *Intervention: 32.0 ± 3.7 (GnRH antagonist)* *Control: 33.1 ± 3.6 (GnRH agonist)* *BMI (kg/m2)* *Intervention: 28.3 ± 7.1* *Control: 30.7 ± 6.4*
PCOS diagnostic criteria	Polycystic ovary syndrome was defined according to the Rotterdam consensus guidelines
Presence of infertility	*Duration of infertility (years)* *Intervention: 2.7 ± 1.8* *Control: 3.0 ± 2.1*
Presence of other condition/s	*NR*
Medication History	*NR*

N per group	*Intervention n=34 (Study group – GnRH antagonist)* *Control n=32 (control group; GnRH agonist)*
Setting	University-based tertiary fertility center.
Intervention	All of the women in the study group underwent pretreatment with OCPs for 21 days. If the ovaries were quiescent on ultrasound, COH was commenced on day 2 of withdrawal bleeding, as described in the following. Ganirelix acetate (Organon USA, Roseland, NJ) was commenced once the leading follicle was R14 mm and continued every morning until and including the day of trigger In both groups, COH was achieved using a step-down protocol of recombinant FSH (rFSH; Follistim; Organon USA) in a starting dose of 112–225 IU depending on the patient's age, body mass index, or previous ovarian response. Both groups received luteal phase and early pregnancy supplementation with IM progesterone (P), and patients in the study group also received E2 patches and their doses were adjusted according to the serum levels
Comparison	Pre-treatment with OCP for 25 days overlapping with 1 mg leuprolide acetate commencing on day 21 of the OCP. Once pituitary suppression was achieved, the dose of leuprolide was reduced to 0.5 mg daily and COH was commenced as follows; Ganirelix acetate was commenced once the leading follicle was R14 mm and continued every morning until and including the day of trigger. In both groups, COH was achieved using a step-down protocol of recombinant FSH (rFSH; Follistim; Organon USA) in a starting dose of 112–225 IU depending on the patient's age, body mass index, or previous ovarian response. Both groups received luteal phase and early pregnancy supplementation with IM progesterone (P), and patients in the study group also received E2 patches and their doses were adjusted according to the serum levels
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Primary: incidence of OHSS, Secondary: implantation rate. Others: number of oocytes retrieved, proportion of mature oocytes retrieved, fertilization rate, midluteal phase mean ovarian volume (MOV), clinical and ongoing pregnancy rates, and luteal phase serum E2 and P levels. *"…*until a negative pregnancy test or a viable fetus was documented by transvaginal sonography."
Follow up Duration	*1 cycle*
Summary Result/s	*"*None of the patients in the study group developed any form of OHSS compared with 31% (10/32) of the patients in the control group. There were no significant differences in the implantation (22/61 [36.0%] vs. 20/64 [31.0%]), clinical pregnancy (17/30 [56.7%] vs. 15/29 [51.7%]), and ongoing pregnancy rates (16/30 [53.3%] vs. 14/29 [48.3%]) between the study and control groups, respectively."

ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT			
Does the study have a clearly focused question and/or PICO?		Yes	"To determine whether there are any differences in the incidence of ovarian hyperstimulation syndrome (OHSS) and implantation rates in high-risk patients undergoing IVF using a protocol consisting of GnRH agonist trigger after cotreatment with GnRH antagonist or hCG trigger after dual pituitary suppression protocol"
Does the study have specified inclusion/exclusion criteria?		Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes	
Inclusion criteria		Yes	age 20–39 years at the time of screening, normal early follicular phase serum FSH concentration (%10.0 IU/L), and undergoing their first cycle of IVF with either PCOS or PCOM or undergoing a subsequent cycle with a history of high response in a previous IVF cycle.
Exclusion criteria		Yes	." Women with hypogonadotropic hypogonadism
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes	"Eligible women were recruited and randomly assigned to either group in a ratio of 1:1 by means of computer-generated random numbers."
	Was allocation to intervention group concealed?	Yes	"Selection into the groups and randomization into the appropriate treatment protocol were performed by a research nurse by using a series of consecutively numbered sealed opaque envelopes (one for each category of previous cycle), and therefore the sequence of allocation was concealed."
PERFORMANCE BIAS	**Were patients blind to intervention group?**	No	"The study was not blinded, because the patients as well as the clinicians were aware of the treatment group."
	Were investigators and care providers blind to intervention group?	No	"The study was not blinded, because the patients as well as the clinicians were aware of the treatment group."

	Aside from the experimental intervention, were the groups treated the same?	Yes	*"*patients in the study group also received E2 patches and their doses were adjusted according to the serum levels"
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	No	*"*The study was not blinded, because the patients as well as the clinicians were aware of the treatment group."
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	11% treatment 9% control/ comparison	*Four patients from the intervention and three from comparison group discontinued*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Partial	*"*All patients randomized and commencing ovarian stimulation were included in the analyses of the primary efficacy end point (intention-to-treat analysis" Other endpoints: per protocol
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes Partial	*"*No significant differences between the two groups."

	If confounding was present, was it controlled for?	N/A	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Partial	*"*Supported in part by an unrestricted educational grant from Organon USA, Roseland, New Jersey."
	Was the study sufficiently powered to detect any differences between the groups?	Yes	*"*…based on earlier publications (15) we hypothesized that GnRH agonist trigger should lead to a 95% relative decline in the incidence of OHSS. Further, the implantation rate after GnRH agonist trigger has been reported to be 3.4% compared with 34% after hCG trigger" *"*Based on a two-sided significance level of .05, we calculated that a sample size of 30 subjects in each group would provide 88% power to detect a significant difference in the incidence of OHSS between the control group proportion of 0.32 and a study group proportion of 0.016 (i.e., 95% decline). This sample size would also provide about 84% power to show a significant difference in implantation rate assuming the control group proportion of 0.34 and a study group proportion of 0.034. It was anticipated that with a fallout rate of about 10%, at least 66 patients would need to be recruited over an 18–24-month period."
	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS		*Lack of randomisation and blinding key reason for high RoB*	
What is the overall risk of bias?		Moderate	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

- Haydardedeoglu 2012

Study ID	***Haydardedeoglu 2012***
Study Citation	Haydardedeoglu, B., Kilicdag, E. B., Parlakgumus, A. H., & Zeyneloglu, H. B. (2012). IVF/ICSI outcomes of the OCP plus GnRH agonist protocol versus the OCP plus GnRH antagonist fixed protocol in women with PCOS: a randomized trial. *Archives of Gynecology & Obstetrics, 286*(3), 763-769
Study Country	Turkey
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	"All selected couples were in their first IVF/ICSI cycles" GnRH agonist group= 27.70±3.59 years GnRH antagonist group= 27.57±3.54 years *BMI:* *GnRH agonist: 24.97 ± 4.36* *GnRH antagonist: 25.74 ± 4.37*
PCOS diagnostic criteria	Rotterdam criteria
Presence of infertility	Duration of infertility: GnRH agonist group= 5.85±3.42 years GnRH antagonist group= 6.24±3.64 years
Presence of other condition/s	*None reported*
Medication History	"Patients treated with hormonal medications and other oral anti-diabetics within the previous 3 months were excluded from the study"
N per group	The number of participants that were: N=300 □ Allocated/randomised: 150 (GnRH agonist group), 150 (GnRH antagonist group) □ Assessed at end of study: Not reported
Setting	Baskent University Department of Obstetrics and Gynecology, Turkey
Intervention	GnRH agonist long protocol (Leuprolide acetate) 1 mg/d from day 21 of the preceding menstruation (last 3 tablets of OCP). After ovarian suppression was achieved, dose reduced to 0.5 mg until the day of hCG. If there were no cysts ≥2 cm and the E2 was <50 pg/ml, gonadotropin stimulation with 150 IU of gonadotropins rFSH was performed. When at least three follicles had a maximum diameter of >17 mm, 10000 IU hCG was administered. "In the GnRH agonist group, ovarian downregulation was initiated with daily

	leuprolide acetate 1 mg (Lucrin, Abbott, France), beginning on day 21 of the preceding menstruation (last 3 tablets of OCP). After ovarian suppression was achieved, the dose was reduced to 0.5 mg until the day of hCG. If there were no cysts ≥2 cm and the E2 was <50 pg/ml, gonadotropin stimulation with 150 IU of gonadotropins rFSH (Puregon, MSD, The Netherlands) was performed, with E2 monitoring commencing on the morning of stimulation day 5. Ultrasound and blood E2 monitoring continued until hCG administration criteria were met with at least three follicles having a maximum diameter of >17 mm…. The cycle was cancelled if there was monofollicular development (single dominant follicle over 17 mm) and/or serum progesterone level was >1.5 ng/ml on the day of hCG). Likewise, women deemed under high risk of OHSS based on the number of growing follicles or high serum E2 levels, and women who had abruptly decreasing E2 levels during coasting and couples with total fertilization failure had their cycles cancelled. 35–36 h after 10,000 IU hCG injection (Pregnyl, MSD, The Netherlands), transvaginal ultrasound-guided oocyte retrieval was performed under sedation with propofol (propofol 1 % Fresenius KabiR, Germany). The oocyte-corona complexes (OOC) were denuded, and ICSI was performed after 2 h of incubation and embryos were transferred on day 3. Our clinical policy is to use ICSI routinely in all patients. A maximum of three embryos were transferred to each participant before 6 March 2010. Thereafter, only a single embryo was transferred to all women under the age of 35 years due to the new national regulations” **Adjuvant hormonal treatment during study:** “All patients received oral contraceptive pills (OCPs) for 21 days containing 30 µg of ethinyl estradiol (E2) and 3 mg of drosprinone (Yasmin, Schering, Istanbul, Turkey) starting on day 3 of spontaneous menses of the cycle prior to the treatment cycle… All patients received luteal support with 90 mg/day progesterone administered intravaginally (Crinone 8 % gel, Serono, Turkey) starting after embryo transfer. Pregnant women continued luteal support until the 8th gestational week”
Comparison	150 IU rFSH was initiated on day 3 of menstruation after discontinuation of OCPs, then GnRH antagonist protocol (Ganirelix) 0.25 mg/d was initiated on day 6 of gonadotropin stimulation, until day of hCG. “In the GnRH antagonist group, gonadotropin stimulation with 150 IU of gonadotropins rFSH (Puregon, MSD, The Netherlands) was initiated on day 3 of menstruation after discontinuation of OCPs. In the fixed GnRH antagonist protocol (antagonist group) daily s.c administration of ganirelix 0.25 mg (Orgalutran, MSD, The Netherlands) was initiated on day 6 of gonadotropin stimulation. Ultrasound and blood E2 monitoring continued until hCG

	administration criteria were met with at least three follicles having a maximum diameter of >17 mm. The cycle was cancelled if there was monofollicular development (single dominant follicle over 17 mm) and/or serum progesterone level was >1.5 ng/ml on the day of hCG). Likewise, women deemed under high risk of OHSS based on the number of growing follicles or high serum E2 levels, and women who had abruptly decreasing E2 levels during coasting and couples with total fertilization failure had their cycles cancelled. 35–36 h after 10,000 IU hCG injection (Pregnyl, MSD, The Netherlands), transvaginal ultrasound-guided oocyte retrieval was performed under sedation with propofol (propofol 1 % Fresenius KabiR, Germany). The oocyte-corona complexes (OOC) were denuded, and ICSI was performed after 2 h of incubation and embryos were transferred on day 3. Our clinical policy is to use ICSI routinely in all patients. A maximum of three embryos were transferred to each participant before 6 March 2010. Thereafter, only a single embryo was transferred to all women under the age of 35 years due to the new national regulations"
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Primary outcomes: □ Ongoing pregnancy rates (defined as a pregnancy proceeding beyond 12 weeks of gestation) Secondary outcomes: *E2 and progesterone levels on the day of hCG administration, duration of rFSH stimulation,* *total dose of rFSH administered,* *cost of COH,* *cycle cancellation rate,* *number of metaphase II oocytes,* *fertilization rates,* *cryopreservation rates,* *hospitalized OHSS rates.* Ultrasound and blood E2 monitoring Hospitalized OHSS was diagnosed when the hematocrit level rose above 45 % and abdominal discomfort, and/or progressive oliguria and/or respiratory difficulties were found together with moderate ascites and/or thrombocytosis (platelet count greater than 400,000/_l), and leucocytosis (white blood cell count greater than 12,000/_l). *"Clinical pregnancy was defined as the presence of an embryo with cardiac activity detectable by transvaginal ultrasonography."*
Follow up Duration	*Not reported. Measured ongoing pregnancy rates. Interim analysis conducted when the sample size reached 300. The study recruitment was terminated due to futility.*
Summary Result/s	"Ongoing pregnancy rates were 36.4 % in the OCP + GnRH agonist group and 35.9 % in the OCP + GnRH antagonist group (p > 0.05). Progesterone levels on the day of hCG (0.76 ± 0.71 vs. 0.58 ± 0.50), endometrial thickness on the day of hCG (11.57 ± 2.50 vs. 10.50 ± 2.01), t`otal gonadotropin used (1388.71 ± 482.39 vs. 1253.25 ± 415.81), and duration of COH (9.07 ± 1.96 vs. 8.39 ± 1.75) were significantly lower in the OCP + GnRH antagonist group."

ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT			
Does the study have a clearly focused question and/or PICO?		Yes	
Does the study have specified inclusion/exclusion criteria?		Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes	
Inclusion criteria		Yes	"women with PCOS younger than 35 years old and older than 23 years old were recruited. All selected couples were in their first IVF/ICSI cycles. Women with PCOS whose body mass index was lower than 30 kg/m2 and higher than 20 kg/m2 were included in the study"
Exclusion criteria		Yes	. "We excluded women with PCOS whose ovaries did not appear polycystic… Patients treated with hormonal medications and other oral anti-diabetics within the previous 3 months were excluded from the study"
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes	Random numbers table. Study subjects were randomized in blocks of 30.
	Was allocation to intervention group concealed?	No	"Assigned using consecutively numbered opaque, sealed envelopes on the day of initiation of OCP… The envelopes were opened by the ART nurse coordinator who had no other involvement in the trial"
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Not reported	
	Were investigators and care providers blind to intervention group?	Not reported	

	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	*Apparently 0%*	No drop outs reported. Interim analysis conducted when the sample size reached 300.
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Not reported	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	No	Additional outcomes were reported to what was listed in the methods and the registered protocol.
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes	

	If confounding was present, was it controlled for?	Not reported	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	No	
	Was the study sufficiently powered to detect any differences between the groups?	No	"Based on our previous results we assumed an ongoing pregnancy rate of 35 % in women younger than 35 years who had PCOS. Testing for 5 % difference in favor of one protocol, which could be regarded as the minimum clinically significant difference would require approximately 1,500 patients in each arm to achieve 80 % power at 5% significance level. This was not deemed feasible for a single center trial, and we decided to conduct an interim analysis when 10 % of this sample size, i.e. 300 women, was reached. The trial would be continued if there was a difference of ≥3 % between trial arms. However, the difference between ongoing pregnancy rates was <1 % and we decided to terminate recruitment due to futility. We anticipate that our data can contribute to future meta-analysis on the issue" *"*Although this study consisting three hundred patients, seems to be large enough, we could not reach to the actual size of power analysis. We were able to recruit 300 patients through 27 months in a single center. This is the major weakness of this trial."
	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS		*Lack of randomisation and blinding key reason for high RoB*	
What is the overall risk of bias?		High	*Few criteria fulfilled and the conclusions of the study are likely to be affected.*

Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*	

- Kurzawa 2008

Study ID	***Kurzawa 2008***
Study Citation	Kurzawa, R.; Ciepiela, P.; Baczkowski, T.; Safranow, K.; Brelik, P. Comparison of embryological and clinical outcome in GnRH antagonist vs. GnRH agonist protocols for in vitro fertilization in PCOS non-obese patients. A prospective randomized study. J Assist Reprod Genet 2008, 25, 365-74
Study Country	Poland
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Non-obese PCOS patients were considered eligible if they were scheduled for controlled ovarian stimulation and intracytoplasmic sperm injection (ICSI). Age <35 years BMI<268kg/m^2 FSH <12IU/l Indications for ICSI included: male factor subfertility, several unsuccessful intrauterine inseminations, previous ineffective IVF (none or <30% of fertilizations). GnRH agonist GnRH antagonist Number of patients 33 37 Age (years) 31.33±3.91 30.36±3.40 BMI (kg/m2) 23.1±1.3 22.3±1.6
PCOS diagnostic criteria	Rotterdam
Presence of infertility	GnRH agonist GnRH antagonist Number of patients 33 37 Male cause of infertility (number of patients) Coexisting male factor 24 31 Mild OAT 10 13 Moderate OAT 8 11 Severe OAT 6 7

	[OAT oligoasthenoteratozoospermy]
Presence of other condition/s	*Not reported*
Medication History	All patients received oral contraceptives pills (Cilest; Janssen-Cilag, Belgium) for a month before starting COH. None of the patients used oral antidiabetic medications (biguanides or thiazolidinediones). GnRH agonist GnRH antagonist Number of patients 33 37 Previous treatment history (number of patients) Laparoscopy 19 31 IUI 17 21 IVF/ET 5 6 ICSI/ET 16 25
N per group	*Agonist protocol n=33* *Antagonist protocol n=37*
Setting	Department of Reproductive Medicine and Gynecology, Pomeranian University of Medicine in Szczecin – a single centre study
Intervention	GnRH agonist protocol During OCP use on day 16-18 of the preceding cycle, GnRH agonist (Triptorelin) was given, then rFSH 150 IU/d* after confirmation of pituitary desensitization, continued until β-hCG trigger (10000 IU when 3 follicles reached mean diameter ≥17mm) "During oral contraception (OC) on days 16–18 of the preceding cycle, after transvaginal ultrasonographic screening of ovaries, an intramuscular injection of GnRH agonist triptorelin (Diphereline SR 3.75; Boufor Ibsen Pharma, France) was given. After confirmation of pituitary desensitization (LH <2 mIU/mL and estradiol <40 pg/mL) the administration of FSH was commenced." "Women were given regular daily recombinant human FSH (Gonal F; Merck Serono, Switzerland) subcutaneous injections (usually between 1800 and 2000 hours). Also in this protocol starting dose was 150 IU/day, adjusted

	individually depending on ovarian response. Ultrasound and estradiol level monitoring started after five doses of rFSH and was continued every second day until the day of hCG administration." *dose adjusted according to individual ovarian response
Comparison	Antagonist protocols rFSH 150 IU/d* from 2nd day of cycle. GnRH antagonist (Cetrorelix) 0.25mg when at least 2 follicles reached 14mm in diameter (average 4 injections per day), then 10000 IU hCG administered when dominant follicle reached diameter ≥18mm "From the second day of the cycle women were given regular daily recombinant human FSH (Gonal F; Merck Serono, Switzerland) subcutaneous injections (usually between 1800 and 2000 hours). Starting dose of a 150 IU/day was adjusted individually depending on an ovarian response measured by transvaginal ultrasonography and the level of estradiol. Ultrasound and estradiol level monitoring started from the seventh day of the cycle (sixth day of COH) after five doses of rFSH and was continued every second day until the day of human chorionic gonadotropin (hCG) administration. A GnRH antagonist—cetrorelix (Cetrotide; Merck Serono, Germany) was administered subcutaneously between 900 and 1200 hours when at least two ovarian follicles reached 14 mm in diameter. The protocol consisted of daily Cetrotide 0.25 mg subcutaneous injections, average 4, until the criteria for recombinant hCG administration were met."
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Primary endpoints: Embryological: • Matured oocytes (M2) rate, defined as proportion of metaphase II to total number of retrieved oocytes • Fertilization rate, defined as proportion of two pronuclei oocytes to number of injected oocytes • Quality of zygotes on the first day of culture • Quality of embryos on the third day of culture Secondary endpoints: Clinical: • Delivery per attempt, defined as a live birth after 32 weeks of gestation • Clinical pregnancy per attempt, defined as an ongoing pregnancy at 12 weeks of gestation • Implantation rate; defined as gestational sacs per number of transferred embryos • Multiple pregnancy per viable pregnancy • Miscarriage per intrauterine pregnancy, defined as a miscarriage of an ongoing pregnancy after 12 weeks of gestation • Occurrence of severe OHSS • Number of days of gonadotropin treatment • Gonadotropin consumption • Correlation between serum LH level and IVF outcome Serum LH and estradiol levels were measured by an electrochemiluminescence immunoassay (ECLIA) Ultrasound Pregnancy was checked by pregnancy test in serum 14 days after ET and confirmed by vaginal ultrasound scan at 12 weeks of gestation.

Follow up Duration	*Not reported*	
Summary Result/s	Similar mature metaphase II oocyte rate (76% vs. 76%) was observed in both protocols. Optimal pronuclear morphology zygotes dominated in both groups (64% vs. 66%). Transferred embryo quality did not differ in both protocols. No significant differences between both protocols were found in delivery rate (p=0.481), pregnancy rate (p=0.810), multiple pregnancy rate (p=0.501), miscarriage rate (p=0.154), fertilization rate (p=0.388) and implantation rate (p=1.000). Duration of stimulation and total follicle-stimulating hormone (FSH) dose were significantly lower in GnRH antagonist protocol (p=0.0005).	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes	*To verify the embryological and clinical effectiveness of the GnRH antagonists protocols in comparison with GnRH agonist protocols in non-obese women with PCOS*
Does the study have specified inclusion/exclusion criteria?	Yes	*See below*
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes	*See below*
Inclusion criteria	Yes	(1) meeting of 2003 Rotterdam PCOS criteria (two of the following three manifestations: irregular or absent ovulation, elevated levels of androgenic hormones, and/or enlarged ovaries containing at least 12 follicles each; other conditions with similar signs, such as androgen-secreting tumors or Cushing's syndrome were ruled out); (2) age≤35 years; (3) body mass index<26 kg/m2; (4) FSH<12 mIU/ml on the third day of the cycle; (5) negative screening for hepatitis B and C virus infection and human immunodeficiency virus (HIV) infection.
Exclusion criteria	Yes	≥2 miscarriages, ≥3 unsuccessful IVF/ICSI cycles, anatomical abnormalities of the uterus on laparoscopy or hysteroscopy and existence of ovarian cysts.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes	computer generated random letters

	Was allocation to intervention group concealed?	Yes	concealed in opaque sealed envelopes,
PERFORMANCE BIAS	**Were patients blind to intervention group?**	No	However not possible to do so given differing protocol
	Were investigators and care providers blind to intervention group?	No	"In both protocols, only two clinicians and two embryologists, also not blinded to treatment group, were involved in the study."
	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	No	
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	*4/74 were lost after randomisation (5.4%)*	*"*4 women in the GnRH antagonist group were excluded after randomization, two of them because of insufficient compliance with medication as established by the respective protocol. Further two patients quit the preparations for the treatment without notice. " *"*All 70 women included in the study underwent embryo transfer and none was lost to follow-up."
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes	

REPORT BIAS	**Is the paper free of selective outcome reporting?**	No	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes	
	If confounding was present, was it controlled for?	N/A	"The clinical characteristics and the history of treatment of the patients in both examined groups are shown in Table 1. Baseline patient characteristics did not differ."
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Not reported	"Acknowledgement Financial support—grant number KBN 2 P05E 034 28 from State Committee for Scientific Research"
	Was the study sufficiently powered to detect any differences between the groups?	Yes	"The sample size analysis assuming comparison of two groups (with at least 40% patients in one of them) using Mann–Whitney test showed that 70 women in total will need to be recruited for a power of 80% and an alpha of 5% to detect the hypothetical true difference between the groups equal to 15% of mature oocyte (M2) when the estimated standard deviation of the parameter is 20% (M2% was approximately 75±20% according to our laboratory results), 66 women in total will need to be recruited for a power of 80% and an alpha of 5% to detect the hypothetical true difference between the groups equal to 2 of quality of zygotes on the first day of the culture when the estimated standard deviation of the parameter is 2.5 (optimal pronuclear morphology of all embryos (Z1+Z2) was approximately 5±2.5 according to our laboratory results), 42 women in total will need to be recruited for a power of 80% and an alpha of 5% to detect the hypothetical true difference between the groups equal to 0.5 of quality of zygotes on the 3rd day of the culture when the estimated standard deviation of the parameter is 0.5 (optimal pronuclear morphology of transferred on day 3 embryos (Z1+Z2) was approximately 2±0.5 according to our laboratory results)."

	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS			
What is the overall risk of bias?		Low	*All of the criteria have been fulfilled or where criteria have not been fulfilled it is very unlikely the conclusions of the study would be affected.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

- Lainas 2007

Study ID	***Lainas 2007***
Study Citation	Lainas, T. G.; Petsas, G. K.; Zorzovilis, I. Z.; Iliadis, G. S.; Lainas, G. T.; Cazlaris, H. E.; Kolibianakis, E. M. Initiation of GnRH antagonist on Day 1 of stimulation as compared to the long agonist protocol in PCOS patients. A randomized controlled trial: effect on hormonal levels and follicular development. *Hum Reprod* **2007**, 22, 1540-6
Study Country	Greece
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Antagonist group (n = 26) Agonist group (n = 52) P-value Baseline characteristics Age (years) 32.0 (14) 30.5 (16) 0.079 BMI (kg m22) 23.2 (20.9) 23.6 (18.9) 0.585 Duration of infertility (years) 4.0 (11) 3.5 (11) 0.905 Subjects with previous IVF attempts n (%) 10 (38.5) 16 (30.8) 0.497 Values are expressed as median (interquartile range) unless stated otherwise.
PCOS diagnostic criteria	Presence of oligoovulation/anovulation (Ehrmann et al., 2006) and polycystic ovaries
Presence of infertility	*Antagonist group 4.0 years (11)* *Agonist group 3.4 years (11)* median (interquartile range)
Presence of other condition/s	*Not reported*

Medication History	"All patients received oral contraceptive pill (OCP) starting on Day 2 of spontaneous menses of the cycle prior to the treatment cycle, after blood test confirmed the presence of a baseline hormone profile"	
N per group	Patients were treated either by GnRH antagonist starting from the first day of stimulation, (n = 26, antagonist group), or by a long GnRH agonist protocol (n = 52, agonist group)	
Setting	Single Centre - Eugonia-Iatriki Erevna IVF unit from January 2003 to January 2005 in Greece	
Intervention	rFSH* daily (Puregon) + GnRH antagonist protocol (Ganirelix) 0.25mg/d from day 2 of menses, until and including day of β-hCG trigger (10000 IU when 3 follicles reached mean diameter ≥17mm)	
Comparison	GnRH agonist (Triptorelin) 0.1mg/d, commenced 3 days before discontinuation of OCP. rFSH* 150 IU/d when desensitization achieved (GnRH agonist reduced to 0.05mg/d that day), continued until β-hCG trigger (10000 IU when 3 follicles reached mean diameter ≥17mm) *dose adjusted after day 5 of stimulation	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Primary outcome measure: E2 levels on Day 5 of stimulation, Secondary outcome measures: Follicular development, LH and progesterone levels *[*Ovarian stimulation was monitored by transvaginal ultrasound measurement of follicular growth, typically on days 1, 3, 5, 7 and 8 of stimulation and on the day of HCG administration. FSH, LH, E2 and progesterone levels were measured on an Immulite analyser using the corresponding commercially available kits]	
Follow up Duration	*Apparently 1 cycle*	
Summary Result/s	*"Significantly more follicles on days 5, 7 and 8 of stimulation, significantly higher estradiol (E2) levels on days 1, 3, 5, 7 and 8 and significantly higher progesterone levels on days 1, 5 and 8 of stimulation were observed in the antagonist when compared with the agonist group. E2 was approximately twice as high in the antagonist when compared with the agonist group on day 5 of stimulation (432 versus 204 pg ml21, P < 0.001). These differences were accompanied by significantly lower LH levels on days 3 and 5 and significantly higher LH levels on days 1, 7 and 8 of stimulation in the antagonist when compared with the agonist group."*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes	"The purpose of this RCT is to provide endocrine and follicular data during ovarian stimulation for IVF in patients with PCOS treated either with a long-GnRH agonist scheme or a fixed GnRH antagonist protocol in which GnRH antagonist is initiated on Day 1 of stimulation."

Does the study have specified inclusion/exclusion criteria?		Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes	
Inclusion criteria		Yes	• PCOS (as define above) • age 18–39 years • less than three previous IVF/ICSI attempts • no endometriotic cyst present as assessed by transvaginal ultrasound examination and basal hormonal levels of FSH in the early follicular phase of ≤10 IU l^{-1}
Exclusion criteria		Yes	." Patients with known previous poor ovarian response (Kolibianakis et al., 2004) were excluded"
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes	"Random allocation was performed by a study nurse on the basis of a computer-generated randomization list in a 1:2 ratio."
	Was allocation to intervention group concealed?	Not reported	however not possible to do so given differing protocol
PERFORMANCE BIAS	**Were patients blind to intervention group?**	No	"The responsible physicians (investigators) were not involved in the randomization process. Neither patients nor doctors were blinded to the treatment assigned."
	Were investigators and care providers blind to intervention group?	No	"The responsible physicians (investigators) were not involved in the randomization process. Neither patients nor doctors were blinded to the treatment assigned."
	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDE TECTI	**Were outcome assessors blind to intervention group?**	No	

	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	0%	*However, the analysis contains 78 patients so it is assumed that no one dropped out from the study even this was not explicitly mentioned*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes	"No significant differences were observed between the antagonist and the agonist group. All patients in this study reach the HCG criteria and all patients underwent oocyte retrieval."
	If confounding was present, was it controlled for?		*Not relevant (see above)*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Not reported	

	Was the study sufficiently powered to detect any differences between the groups?	Yes	"It was calculated that group sample sizes of 26 and 52 would achieve 81% power to detect a difference in E2 levels on Day 5 of stimulation of 225 pg ml21 between the null hypothesis that both group means are 450 pg ml^{-1} of E2 and the alternative hypothesis that the mean of E2 in the agonist group is 225 pg ml^{-1} with a significance level (alpha) of 0.05 using a two-sided Mann–Whitney U test"
	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS		*Lack of randomisation and blinding key reason for high RoB*	
What is the overall risk of bias?		Moderate	*Moderate - Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

- Lainas 2010

Study ID	***Lainas 2010***
Study Citation	Lainas, T. G., Sfontouris, I. A., Zorzovilis, I. Z., Petsas, G. K., Lainas, G. T., Alexopoulou, E., & Kolibianakis, E. M. (2010). Flexible GnRH antagonist protocol versus GnRH agonist long protocol in patients with polycystic ovary syndrome treated for IVF: a prospective randomised controlled trial (RCT). *Human Reproduction, 25*(3), 683-689.
Study Country	Greece
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Baseline characteristics Agonist group (n=110) Antagonist group (n=110) Age (years) 32 (29–35) 31 (28–35) BMI (kg/m2) 23.2 (20.9–25.8) 24.6 (20.9–29.3) Number of previous IVF attempts 1 (0–4) 1 (0–3) Subjects with previous IVF attempts, n (%) 69 (62.7, 53.7–71.7) 69 (62.7, 53.7–71.7) Values are expressed as medians (lower-upper quartiles) unless stated otherwise. Differences between groups are not statistically significant.
PCOS diagnostic criteria	Aligns with Rotterdam?

	"Patients could enter the study only once after being diagnosed as PCOS [presence of oligoovulation/anovulation (Ehrmann et al., 2006) and polycystic ovaries]."
Presence of infertility	*Duration:* *Agonist group (years) 3 (2-5)* *Antagonist group (years) 3 (2-5)* *median (lower-upper quartiles)* Indication for IVF, n (%, 95% CI) Agonist group (n=110) Antagonist group (n=110) PCOS only 22 (20.0, 12.5–27.5) 28 (25.5, 17.3–33.6) PCOS þ male factor 53 (48.2, 38.9–57.5) 52 (47.3, 38.0–56.6) PCOS þ tubal factor 27 (24.5, 16.5–32.5) 18 (16.4, 9.5–23.3) PCOS þ other 8 (7.3, 2.4–12.2) 12 (10.9, 5.1–6.7)
Presence of other condition/s	*See above for the reasons of infertility. Other conditions not reported*
Medication History	*Not reported*
N per group	*N=220* long GnRH agonist down-regulation protocol (n = 110) flexible GnRH antagonist protocol (n = 110)
Setting	"…single center RCT performed at the Eugonia-Iatriki Erevna IVF unit from November 2004 to February 2008"
Intervention	GnRH agonist long protocol (Triptorelin) 0.1 mg, commenced 3 days before the discontinuation of the OCP. Once desensitization was achieved (~10-15 days after Triptorelin commenced), 150 IU/d* rFSH (Puregon) was commenced (GnRH agonist was decreased on that day to 0.05 mg/d and continued until and including the day of hCG trigger)* *5000 IU hCG when three follicles reached a mean diameter of ≥17 mm
Comparison	rFSH from Day 2 of cycle that followed discontinuation of the OCP, then GnRH antagonist (Ganirelix) commenced at 0.25mg/d when at least one of the following criteria were fulfilled: (i) the presence of at least one follicle measuring >14 mm; (ii) (ii) serum E2 levels >600 pg/ml; (iii) (iii) serum LH levels>10 IU/l. Both continued until and including the day of hCG trigger*
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Used ultrasound and laboratory assays. The primary outcome measure:

	• ongoing pregnancy rate per patient randomized (defined as the presence of gestational sac with fetal heart beat detection at 12 weeks and at 6–7 weeks of gestation, respectively) Secondary outcome measures: • incidence of OHSS, • duration of rFSH stimulation, • total dose of rFSH, E2 and progesterone concentration on the day of hCG administration, • cycle cancellation rate, • number of cumulus-oocyte complexes (COCs) retrieved, • number of metaphase II oocytes and fertilization rates.	
Follow up Duration	*1 cycle*	
Summary Result/s	"No differences were observed in ongoing pregnancy rates [50.9 versus 47.3%, difference 3.6%, 95% confidence interval (CI): -9.6 to +16.8%] in the agonist and antagonist protocols, respectively. Incidence of OHSS Grade II was lower in the antagonist compared with agonist group (40.0 versus 60.0%, difference -20.0%, 95% CI: -7.1 to -32.9%, P < 0.01). Duration of stimulation (10 versus 12 days, difference 2 days, 95% CI: +1 to +2, p <0.001) and total gonadotrophin required (1575 versus 1850 IU, difference -275 IU, 95% CI: -25 to -400, P < 0.05) were also lower in the antagonist compared with agonist protocol."	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes	*"*The aim of the present RCT was to compare the flexible GnRH antagonist and the GnRH agonist long protocols in a large group of PCOS patients undergoing IVF treatment, with primary end-point being ongoing pregnancy rate per patient randomized."
Does the study have specified inclusion/exclusion criteria?	Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes	
Inclusion criteria	Yes	age 18–39 years, no endometriotic cyst present, as assessed by transvaginal ultrasound examination, basal hormonal levels of FSH in the early follicular phase of ≤10 IU/ml.
Exclusion criteria	Yes	." Patients with known previous poor ovarian response (Kolibianakis et al., 2004)….."
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?		

SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes	*"*Random allocation was performed by a study nurse at consultation, using a computer generated randomization list, in a 1:1 ratio."
	Was allocation to intervention group concealed?	No	Probably not possible to do so given differing protocol *"*Neither patients nor doctors were blinded to the treatment assigned."
PERFORMANCE BIAS	**Were patients blind to intervention group?**	No	May not be possible to do so given differing protocol *"*Neither patients nor doctors were blinded to the treatment assigned."
	Were investigators and care providers blind to intervention group?	No	*"*Neither patients nor doctors were blinded to the treatment assigned."
	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	No	*"*Neither patients nor doctors were blinded to the treatment assigned."
	Were all outcomes measured in a standard, valid and reliable way?	Yes	*Laboratory assays and ultrasound scans*
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	0%	*No drop outs reported*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes	*No drop-outs reported*

REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes	*"*No significant differences were observed between the agonist and the antagonist group regarding baseline characteristics and hormonal profile."
	If confounding was present, was it controlled for?		*Not applicable*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Not reported	

	Was the study sufficiently powered to detect any differences between the groups?	No	"We selected to set the baseline ongoing pregnancy rate for PCOS patients at 35%, and the detectable difference between groups at 5%, assuming an alpha level of 0.05. It was calculated that a sample size of 1471 patients was required in each group to achieve a 0.80 power. In confirmation of the values used for power analysis, Griesinger et al. (2006) reported 41.6 and 37.1% clinical pregnancy rates in PCOS patients treated by agonist and antagonist protocols respectively. In addition, Heijnen et al. (2006) showed that PCOS and control IVF patients achieve similar clinical pregnancy rates of approximately 35%, a percentage that was also accepted by The Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group (2008)." **"Obtaining such a sample size (1471 patients per group) is not easy to achieve in a single center, and is also extremely difficult for multicenter studies, especially when it refers to a small proportion of the population, such as PCOS patients, even during a 4-year period."** "Even for a 20% baseline pregnancy rate with 5% difference, more than 900 patients per group would be required. In addition, detecting a difference of 10% in pregnancy rates, which is not supported by the data published so far, would still require a considerable number of patients in each group (n = 376)."
	If statistical analysis was undertaken, was this appropriate?	Yes	*Also, see above* "Proportions were compared with the Fisher's exact test or the x2 test, where appropriate. Continuous variables (age, BMI), were compared with the Student's t-test for independent samples or the Mann–Whitney depending on the normality of their distribution. Statistical significance was accepted when P ≤ 0.05."
COMMENTS		*Lack of randomisation and blinding key reason for high RoB*	
What is the overall risk of bias?		Moderate	*Moderate - Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

- Vrtacnik-Bokal 2009

Study ID	***Vrtacnik-Bokal 2009***
Study Citation	Vrtacnik-Bokal E, Virant Klun I, Verdenik I. Follicular oestradiol and VEGF after GnRH antagonists or GnRH agonists in women with PCOS. Reprod Biomed Online. 2009 Jan;18(1):21-8. doi: 10.1016/s1472-6483(10)60420-8. PMID: 19146765.
Study Country	Slovenia
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	*Consecutive women with PCOS who were referred for intracytoplasmic sperm injection (ICSI) between January 2006 and February 2007 because of male factor infertility* *Age (years)* *GnRH GnRH antagonists: 29.8 ± 3.2* *GnRH agonists: 31.2 ± 3.4* *BMI (kg/m2)* *GnRH GnRH antagonists: 24.5 ± 4.3* *GnRH agonists: 25.3 ± 6.6*
PCOS diagnostic criteria	Rotterdam criteria
Presence of infertility	*male factor infertility*
Presence of other condition/s	*NR*
Medication History	*NR*
N per group	*Intervention n=10 (GnRH antagonist)* *Control n=10 (GnRH agonist)*
Setting	*NR*
Intervention	Antagonist: A daily dose of 225 IU recombinant FSH (follitropin alpha) (rFSH) was started on day 2 of the menstrual cycle. The GnRH antagonist cetrorelix acetate at a dose of 0.25 mg per day was administered from the day when the dominant follicle reached a mean diameter ≥14 mm until the day of HCG administration. In both treatment groups, ovarian stimulation was started with a fixed daily dose of 225 IU rFSH for the first 5 stimulation days. Thereafter, the dose of gonadotrophin was adjusted according to the ovarian response monitored via ultrasonography daily from day 5 of stimulation to the day of HCG administration. In both groups, HCG at a dose of 10,000 IU was administered when three or more follicles reached a diameter of 18 mm.
Comparison	*Agonist:* *Ovarian stimulation was performed using GnRH agonist buserelin*

	administered from day 22 of the cycle in a daily dose of 0.6 ml (600 pg) s.c. After 14 days, pituitary desensitization was checked by oestradiol determination and B-mode ultrasound scan. Once the criteria for desensitization were fulfilled (oestradiol ≤0.05 nmol/l, follicle diameter ≤5 mm and endometrial thickness ≤6 mm), ovarian stimulation with a daily dose of 225 IU rFSH was started. GnRH agonist administration was continued until HCG administration. *In both treatment groups, ovarian stimulation was started with a fixed daily dose of 225 IU rFSH for the first 5 stimulation days. Thereafter, the dose of gonadotrophin was adjusted according to the ovarian response monitored via ultrasonography daily from day 5 of stimulation to the day of HCG administration.* *In both groups, HCG at a dose of 10,000 IU was administered when three or more follicles reached a diameter of 18 mm.*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Not reported under method, extracted from outcomes:* *Oocyte quality, fertilization competence and embryo quality* *Vascular endothelial growth factor (VEGF) and oestradiol concentrations* *Oestradiol was measured using a commercial kit* *VEGF was measured using an enzyme-linked immunosorbent assay kit*	
Follow up Duration	*1 cycle*	
Summary Result/s	*"In the GnRH antagonist group 254 follicles and in the GnRH agonist group 245 follicles, were aspirated. Fewer metaphase II (MII) and more immature and degenerative oocytes were registered in the GnRH antagonist group. Follicular oestradiol and VEGF were lower in the GnRH antagonist group (P = 0.014 and P < 0.001, respectively). Moreover, higher oestradiol concentrations were related to embryos of higher quality (P = 0.037)."*	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes	"The aim of this study was to determine whether follicular oestradiol and VEGF concentrations differ according to the use of GnRH antagonists or GnRH agonists in women with PCOS."
Does the study have specified inclusion/exclusion criteria?	Partial	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes	

Inclusion criteria		Yes	*only women with PCOS with a favourable prognosis were included (≤35 years, undergoing first or second ICSI attempt).*
Exclusion criteria		Not reported	."
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	No	"The allocation was not randomized, the first 10 patients were allocated to the GnRH agonist group and the second group of 10 to the GnRH antagonist group."
	Was allocation to intervention group concealed?	No	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	No	
	Were investigators and care providers blind to intervention group?	No	
	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	No	
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Yes	

ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	0% treatment 0% control/ comparison	*No drop-outs*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Partial	*FSH (IU/ml)* *GnRH Antagonist 5.8 ± 1.07* *GnRH Agonist: 4.1 ± 1.55 0.016* *Significantly higher FSH level in antagonist group*
	If confounding was present, was it controlled for?	N/A	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes	*"Declaration: The authors report no financial or commercial* *conflicts of interest."*

	Was the study sufficiently powered to detect any differences between the groups?	Yes	"Sample size was calculated based on a review of the literature and the early results. It was assumed that a 10% difference in mean oestradiol concentrations with a 40% SD could be expected; after logarithmic normalization this changed to approximately a 1.6% difference and a 16% SD. This assumption yielded a required sample size of 214 in each group (using conventional values of 80% chance of rejecting the hypothesis of no difference at the 0.05 level). With 20–25 follicles per woman that meant that 10 women should be included in each group."
	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS		*Lack of randomisation and blinding key reason for high RoB*	
What is the overall risk of bias?		High	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

Study ID	*Doldi 2006*
Study Citation	Doldi, N., Persico, P., Di Sebastiano, F., Marsiglio, E., & Ferrari, A. (2006). Gonadotropin-releasing hormone antagonist and metformin for treatment of polycystic ovary syndrome patients undergoing in vitro fertilization-embryo transfer. Gynecological Endocrinology, 22(5), 235-238.
Study Country	Italy
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	PCOS No data on age or BMI available
PCOS diagnostic criteria	Two of the following criteria: chronic anovulation manifested by the symptoms of oligomenorrhea (>40 days per cycle), amenorrhea or irregular menstrual cycles; clinical or biochemical (serum testosterone concentration >0.8 ng/ml) signs of hyperandrogenism; and ultrasonographic evidence of polycystic ovaries.

Presence of infertility	*Not reported*
Presence of other condition/s	*Not reported*
Medication History	*The patients did not take any ovulation drugs or hormones for at least 3 months prior to the trial.*
N per group	*N=40* *(Group A n=20* *Group B n=20)*
Setting	*IVF Unit, Ob-Gyn Department, Vita-Salute University, Milan*
Intervention	*Group A **[MET + rFSH + GnRH]*** *Pre-treated with MET 1.5g/day for 2 months and then stimulated with rFSH 150 IU/day starting on day 3 of menstrual cycle.* *Then GnRH antagonist, cetrorelix acetate 0.25 mg/day was started when the leading follicle reached 14 mm diameter on ultrasound scan*
Comparison	*Group B **[rFSH + GnRH]*** *Stimulated with rFSH 150 IU/day starting on day 3 of menstrual cycle* *Then GnRH antagonist, cetrorelix acetate 0.25 mg/day was started when the leading follicle reached 14 mm diameter on ultrasound scan*
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*The number and quality of oocytes, fertilization rate, number of embryos and cases of OHSS* *How pregnancy was detected not reported* *"…oocyte retrieval and was continued until menstruation or a positive pregnancy test."* *The information on how the other outcomes were assessed not available*
Follow up Duration	*2 months + 1 cycle*
Summary Result/s	"In group A we found a statistically significant (p50.05) decrease in the number of ampoules of rFSH (A vs. B: 18+6 vs. 24+8) and estradiol levels (A vs. B: 2400+600 vs. 3370+900 pg/ml) (all values mean+standard deviation). Group A had significantly fewer cancelled cycles (A vs. B: 1 vs. 3; p50.05). The incidence of ovarian hyperstimulation syndrome was 5% in group A and 15% in group B (p50.05). In patients treated with metformin, the total number of follicles on the day of human chorionic gonadotropin treatment (23+1.2 vs. 33+2.6) was decreased with no change in the number of follicles _14 mm in diameter (A vs. B: 18+1.2 vs. 19+1.7). However, the mean number of mature oocytes (A vs. B: 8.4+1.5 vs. 5.0+1.5) was increased with metformin treatment (p50.05). No difference was found in the number of cleaved embryos (A vs. B: 2.5+0.5 vs. 2.2+0.3)."
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT	

Does the study have a clearly focused question and/or PICO?		Yes	*"The aim of the present study was to compare the stimulation characteristics and in vitro fertilization (IVF)–embryo transfer (ET) outcomes of the standard short GnRH antagonist protocol for ovarian stimulation with or without metformin."*
Does the study have specified inclusion/exclusion criteria?		Partial	
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes	
Inclusion criteria		Partial	*PCOS* *Attending the clinic*
Exclusion criteria		Yes	Congenital adrenal hyperplasia, Cushing's syndrome, androgen-producing tumour, hyperprolactinemia and thyroid dysfunction were all excluded. Exclusion criteria included patients age older than 40 years, serum FSH level >12 mIU/ml and the presence of other pathology.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Not reported	*"The population was randomly divided into two groups (A and B)."*
	Was allocation to intervention group concealed?	Not reported	
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Not reported	
	Were investigators and care providers blind to intervention group?	Not reported	

	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Not reported	
	Were outcomes assessed objectively and independently?	Not reported	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	Not reported	*Perhaps no drop-outs*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes	
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Not reported	

	If confounding was present, was it controlled for?	Not reported	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Not reported	
	Was the study sufficiently powered to detect any differences between the groups?	Not reported	
	If statistical analysis was undertaken, was this appropriate?	Yes	*"All data are expressed as mean+standard deviation. Data were analyzed by the Student t test. A value of p50.05 was considered statistically significant. Data were tabulated and analysed using Instat 3…"*
COMMENTS			
What is the overall risk of bias?		High	*Small study and important information missing. This should go either under insufficient information or high risk.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

- Fedorcsak 2003

Study ID	***Fedorcsak 2003***
Study Citation	Fedorcsak, P.; Dale, P. O.; Storeng, R.; Abyholm, T.; Tanbo, T. The effect of metformin on ovarian stimulation and in vitro fertilization in insulin-resistant women with polycystic ovary syndrome: an open-label randomized crossover trial. *Gynecol Endocrinol* **2003**, 17, 207-14 *DOI: 10.1080/gye.17.3.207.214*

Study Country	Norway
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	*Age (years) 31 (23-35)* *BMI (kg/m2) 31.5 (27.1-40.7)* *Median (range)*
PCOS diagnostic criteria	Aligns with Rotterdam PCOS was diagnosed when polycystic ovaries were seen on vaginal ultrasound scan according to the criteria of Adams *et al*. and two or more of the following conditions were present: oligo/amenorrhea, hirsutism and hyperandrogenism
Presence of infertility	The causes of infertility were not reported.
Presence of other condition/s	*Not reported*
Medication History	*Not reported*
N per group	*N=17* metformin–control (*n* = 9) control–metformin (*n* = 8)
Setting	University Hospital, Oslo, Norway
Intervention	500mg Metformin t.i.d (3-week pretreatment and 1 cycle co-administration with IVF protocol*, until hCG injection).
Comparison	No co-treatment, IVF protocol* * Long protocol GnRH-agonist suppression + rFSH (150IU starting dose, step-up protocol) + hCG (10,000IU in presence of at least 2 dominant follicles >18mm)
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	• **Primary outcomes** a) clinical pregnancy rate per woman b) incidence of OHSS • **Secondary outcomes:** a) total dose of FSH (IU) given during stimulation b) number of collected oocytes c) number of days of gonadotrophin d) fertilisation rate e) number of embryos transferred f) miscarriage rate g) incidence of adverse side effects
Follow up Duration	*two consecutive cycles*
Summary Result/s	*"Nine women completed both cycles, the results of eight women being excluded because of pregnancy after the first cycle (*n = *4) or because the protocol of the study was not followed (*n = *4). Mean total FSH dose was 2301 IU (range 1500–6563 IU) in metformin cycles and 2174 IU (range 1200–3900 IU) in parallel control cycles, while the mean number of*

		collected oocytes was 8.6 (range 2–28) and 4.6 (range 1–16), respectively. *Bayesian analysis showed probabilities of 0.05 that metformin reduces FSH requirement by at least 10%, and of 0.61 that at least 10% more oocytes are collected after metformin co-treatment."*
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT			
Does the study have a clearly focused question and/or PICO?		Yes	"the purpose of the present study was to examine whether metformin affects gonadotropin requirement and the number of collected oocytes during ovarian stimulation in insulin-resistant women with PCOS."
Does the study have specified inclusion/exclusion criteria?		Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes	
Inclusion criteria		Yes	Diagnosis of PCOS followed the Rotterdam criteria (ESHRE/ASRM). All women had insulin-resistance, based on an insulin resistance index.
Exclusion criteria		Yes	a) congenital adrenal hyperplasia b) Cushing's syndrome c) androgen-producing tumours d) hyperprolactinaemia Age: 23 to 35 years (median 31) The causes of infertility were not reported. Only the first arm was compared: 8 participants in the no-treatment group versus 9 participants in the metformin group.
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes	The randomization list was derived from a table of random numbers in blocks of 4, 6, or 8.
	Was allocation to intervention group concealed?	Yes	The list was concealed in a sequence of sealed envelopes from the single clinician who performed assignment and supervised treatment (T.T.).
PERFORMANCE	**Were patients blind to intervention group?**	No	This was an open-label trial as it was not placebo-controlled or blinded.

	Were investigators and care providers blind to intervention group?	No	This was an open-label trial as it was notplacebo-controlled or blinded.
	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	No	This was an open-label trial as it was not placebo-controlled or blinded.
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	0%	There were no withdrawals in the phase analysed (pre-cross-over phase).
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes	There were no withdrawals in the phase analysed (pre-cross-over phase).
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Partial	Live birth rate was not evaluated
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes	

	If confounding was present, was it controlled for?	Not reported	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Not reported	"This work was supported by grants from the Research Council of Norway, the Norwegian Women's Health Society, the Hungarian Eötvös fellowship, and the Gyermek-Áldás Foundation"
	Was the study sufficiently powered to detect any differences between the groups?	Not reported	In this study, prior and observed probabilities were expressed as normal distributions.
	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS		*Lack of randomisation and blinding key reason for high RoB*	
What is the overall risk of bias?		High	*High - Few or no criteria fulfilled or the conclusions of the study are likely or very likely to be affected.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

- Jacob 2016

Study ID	*Jacob 2016*
Study Citation	Jacob SL, Brewer C, Tang T, Picton HM, Barth JH, Balen AH. A short course of metformin does not reduce OHSS in a GnRH antagonist cycle for women with PCOS undergoing IVF: a randomised placebo-controlled trial. Hum Reprod. 2016 Dec;31(12):2756-2764. doi: 10.1093/humrep/dew268. Epub 2016 Nov 5. PMID: 27816925.
Study Country	UK

BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	*PCOS women recruited from IVF clinic waiting list between October 2009 and June 2014* *Age (years)* *MET: 29.9 ± 4.4* *Placebo: 29.6 ± 3.9* *BMI* *MET: 25.3 ± 3.4* *Placebo: 25.0 ± 3.3*
PCOS diagnostic criteria	Rotterdam criteria All women therefore had at least two of the following characteristics: evidence of hyperandrogenism (clinical or biochemical), oligo/anovulation (cycles longer than 35 days) polycystic ovarian morphology (PCOM) on ultrasound (one or more ovaries with ≥12 follicles and/ or volume ≥10 cm3)
Presence of infertility	*The patients' had on average entered their fourth year of subfertility (3.6 ± 2.3 years) with an average 94% undergoing their first IVF cycle.*
Presence of other condition/s	*NR*
Medication History	*No participant had received metformin within the 3 months prior to recruitment.*
N per group	*Of the 153 patients, 77 received metformin and 76 placebo.*
Setting	*tertiary infertility clinic.*
Intervention	***MET + rFSH + GnRH*** *(n=77)* *Metformin in the range 100-150 IU started 7 days prior to the patient's anticipated menstruation in those with a regular menstrual cycle (mid luteal) or Day 1 of the period if irregular and continued until the day before egg collection.* *Daily recombinant FSH (rFSH) was started from Day 2 of the menstrual cycle, at a dose adjusted for patient age, ovarian reserve and BMI.* *A GnRH antagonist (250 µg; Orgalutron, Organon or Cetrotide, Merck Serono) was added on Day 6 of the cycle.*
Comparison	***Placebo + rFSH + GnRH*** *(n=76)* *See intervention for rFSH and GnRH*
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Primary: Severe OHSS within 6 weeks of completing an IVF cycle* *Secondary: ovarian stimulation characteristics, embryological measures (including fertilisation rate and good quality Day 3 embryos) and cycle outcome including clinical pregnancy rate (CPR) and live birth rate (LBR).* *Detailed information provided in supplementary materials*

	"Demographic and baseline data were recorded at the start of the treatment cycle including a baseline transvaginal ultrasound scan (TVUSS) and hormone profile (including serum anti-Müllerian hormone (AMH), testosterone and sex hormone-binding globulin (SHBG))." *An embryo was referred to as good quality if graded ≥6.3.3 for Day 3 embryos or ≥2 Bb for blastocysts.* *A serum pregnancy test was taken on Day 14 or a urine test on Day 18 from oocyte collection. A serum hCG of >2 IU/l was deemed positive If a foetal heart was seen on this scan, it was deemed a clinical pregnancy.*	
Follow up Duration	*? 1 cycle*	
Summary Result/s	"There was no reduction in the incidence of moderate–severe OHSS (Placebo (PLA) 12.2%, metformin (MET) = 16%, 95% CI −0.08–0.16, P = 0.66). There was no difference in total gonadotrophin dose (PLA = 1200, MET = 1200, 95% CI −118.67–118.67, P = 0.75), oocytes retrieved (PLA = 15, MET = 14, 95% CI −2.37–4.37, P = 0.66) or fertilisation rate (PLA = 60.7%, MET = 53.3%, 95% CI −0.96–14.94, P = 0.07). However, using metformin resulted in a reduced clinical pregnancy rate (CPR) per cycle started (PLA = 48.7%, MET = 28.6%, 95% CI 0.04–0.35, P = 0.02) and live birth rate (PLA = 51.6%, MET = 27.6%, 95% CI 0.05–0.40, P = 0.02). Furthermore, when ethnicity was taken into account there was a significant reduction in pregnancy outcome for the South Asian population irrespective of metformin or placebo use (CPR per cycle started, White Caucasian = 44.4%, South Asian = 19.4%; 95% CI 0.06–0.39, P = 0.01)."	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes	*"Does 'metformin' reduce the incidence of ovarian hyperstimulation syndrome (OHSS) for women with polycystic ovary syndrome (PCOS) undergoing a GnRH antagonist assisted conception treatment cycle?"*
Does the study have specified inclusion/exclusion criteria?	Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes	
Inclusion criteria	Yes	*PCOS (see under diagnosis criteria)* *FSH <8.0 IU/l,* *age 20–39 years,* *BMI <35,* *serum testosterone <5.0 nmol/l,* *normal renal, liver and haematological indices.*
Exclusion criteria	Yes	*Concomitant use of medication that could interfere with the absorption, metabolism and excretion of metformin including anti-virals, cimetidine and other oral anti-diabetic medication*

			Patients with significant systemic disease or diabetes (Type 1 or 2)
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes	*"Randomisation was blinded to both patient and investigator, using a random permuted blocks method with a 50:50 allocation ratio."*
	Was allocation to intervention group concealed?	Yes	*"Randomisation was done by the hospital pharmacy, using a random permuted blocks method with a 50:50 allocation ratio. This process was blinded to both patient and investigator by using identical over-encapsulated tablets"* *"The allocation code was only broken when all women had been recruited and commenced treatment."*
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes	*"Randomisation was blinded to both patient and investigator…."* *"This process was blinded to both patient and investigator by using identical over-encapsulated tablets…"*
	Were investigators and care providers blind to intervention group?	Yes	*"Randomisation was blinded to both patient and investigator…."* *"This process was blinded to both patient and investigator by using identical over-encapsulated tablets…"*
	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Not reported	*Not sure whether the outcome assessor was the same investigator. If so, this should be "Yes"* *"Randomisation was blinded to both patient and investigator…."*
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Yes	

ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	0% treatment 0% control/	*2 from MET and 3 from placebo either discontinued or attained natural conception*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes	*ITT conducted*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes	*TRIAL REGISTRATION NUMBER:* *EudraCT number 2009-010952-81.*
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes	*"There were no significant differences in baseline characteristics between the two groups of women (Table II)."*
	If confounding was present, was it controlled for?	Yes	*N/A*
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Yes	*"STUDY FUNDING/COMPETING INTEREST(S): None."*
	Was the study sufficiently powered to detect any differences between the groups?	Yes	*"This study was powered to assess metformin's ability to reduce OHSS as an adjunct in an ART cycle."* *"The study was completed over 5 years (2009–2014) with 153 randomised patients. A sample size calculation based on the incidence of OHSS was completed prospectively suggesting a minimum of 146 recruits was required for the trial with a power of 80% and a type 1 error of 0.05."*

	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS			
What is the overall risk of bias?		Low	
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

- Onalan 2005

Study ID	**Onalan 2005**
Study Citation	Onalan G, Pabuçcu R, Goktolga U, Ceyhan T, Bagis T, Cincik M. Metformin treatment in patients with polycystic ovary syndrome undergoing in vitro fertilization: a prospective randomized trial. Fertil Steril. 2005 Sep;84(3):798-801. doi: 10.1016/j.fertnstert.2005.03.043. PMID: 16169430.
Study Country	Turkey
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Age (y), mean ± SD *Metformin 29.3 ± 3.9* *Placebo 29.76 ± 5.3* *BMI (kg/m^2)* *Metformin 25 (19.41)* *Placebo 23.5 (19-34)*
PCOS diagnostic criteria	Diagnosis of PCOS followed the Rotterdam criteria (ESHRE/ASRM).
Presence of infertility	*Duration of infertility* *Metformin (n=53) years 7 (2-15)* *Placebo (n=55) years 7 (2-22)* *Median (range)*
Presence of other condition/s	All patients had oligomenorrhea or amenorrhea since menarche as a surrogate for oligo-anovulaton All other causes of hyperandrogenism were ruled out before diagnosis of PCOS.
Medication History	*Not reported*
N per group	*N=110 (2 withdrew for personal reasons)* *108 randomised (53 in the metformin group and 55 in the placebo group).*
Setting	Centrum IVF Clinic, Turkey
Intervention	Metformin 850 mg twice or 3 times daily (according to BMI) for 8 weeks before their first ICSI cycle, through the luteal phase and until a positive pregnancy test
Comparison	*Placebo*
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	• **Primary outcomes:** a) clinical pregnancy rate per woman b) incidence of OHSS • **Secondary outcomes:** a) number of days of gonadotrophins b) number of ampoules of gonadotrophins c) number of follicles (> 16 mm) d) number of mature oocytes

	e) fertilisation rate f) number of embryos transferred g) pregnancy rate per woman h) miscarriage rate i) serum E2 levels j) glucose/insulin rate Insulin, LH, FSH, E2, and PRL levels were assessed with an autoanalyzer	
Follow up Duration	*2 months + One cycle?(or NR)*	
Summary Result/s	"In the metformin group, compared with the placebo group, patients with a glucose/insulin ratio <4.5 had lower day-3 serum levels of LH (4.8 IU/mL [range, 2.8–8.1 IU/mL] vs. 6.8 IU/mL [5–13.1 IU/mL], *P*=.04) and E2 (49 pg/mL [37–68 pg/mL] vs. 68.5 pg/mL [54–88 pg/mL], *P*_.002) and lower numbers of follicles ≥17 mm in diameter (5.5 [3– 8] vs. 8 [6–13], *P*=.01)." "Patients with a BMI <28 had similar measures of outcome in both placebo and metformin groups." "Patients with a BMI ≥28 in the metformin group had lower serum levels of LH (4.2 IU/mL [2.8–8.1 IU/mL] vs. 7.5 IU/mL [5.1–13.1 IU/mL], *P*=.006), increased numbers of antral follicles (12 [9 –15] vs. 8.5 [7–14], *P*=.015), and increased numbers of follicles ≥17 mm in diameter (9 [6 –13] vs. 5.5 [3–10], *P*=.046), compared with those in the placebo group." "…metformin had no effect on duration of stimulation, total dose of FSH, number of follicles 10 –16 mm and _17 mm in diameter, serum peak levels of E2 on the day of hCG injection, number of retrieved metaphase I and II oocytes, fertilization rate, number of transferred embryos, and total and clinical pregnancy rates."	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes	"we investigated the effects of metformin therapy on ICSI outcome in patients with PCOS."
Does the study have specified inclusion/exclusion criteria?	Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes	
Inclusion criteria	Yes	Infertile women <40 years old No concomitant causes of infertility Undergoing first IVF/ICSI attempts All patients had oligomenorrhea or amenorrhea since menarche as a surrogate for oligo-anovulaton At least one of the criteria of hyperandrogenism, including a hirsutism score of >7

Exclusion criteria		Yes	” previous treatments with hormonal medications and insulin-lowering agents in the last 3 months”
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes	computer randomisation system
	Was allocation to intervention group concealed?	Not reported	“… women were given an envelope containing either metformin (Glucophage Retard 850 mg; Ilsan-Iltas¸ Pharmaceuticals, Istanbul, Turkey) or placebo (identical to metformin capsules), according to the code provided by computer-generated randomization in blocks.”
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes	*“*…prospective, randomized, double-blind, placebo-controlled study,…” *“*Both patients and investigators were blinded to the content of tablets.”
	Were investigators and care providers blind to intervention group?	Yes	*“*…prospective, randomized, double-blind, placebo-controlled study,…” *“*Both patients and investigators were blinded to the content of tablets.”
	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	3.6% in metformin *0% in placebo*	

	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	No	ITT analysis was not performed.
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Partial	Live birth rate was not reported, however, the Cochrane authors have received them from the trail authors after contacting them However, which outcomes would be measured not reported in methods
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes	*"*There were no statistically significant differences between the two groups regarding baseline characteristics, duration of stimulation, total dose of FSH, number of follicles 10–16 mm and ≥17 mm in diameter, serum peak levels of E2 on the day of hCG injection, number of retrieved metaphase I and II oocytes, fertilization rate, number of transferred embryos, and total and clinical pregnancy rates (all *P*≥.05)"
	If confounding was present, was it controlled for?	N/A	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Not reported	
	Was the study sufficiently powered to detect any differences between the groups?	Not reported	*No power calculation*
	If statistical analysis was undertaken, was this appropriate?	Yes Partial No Not reported	Statistical analysis was performed with Student *t*,Mann-Whitney *U*, _2, and Fisher exact tests, as appropriate. Data are reported as mean _ SD or median (range). A *P* value of _.05 was considered significant.
COMMENTS		*Lack of randomisation and blinding key reason for high RoB*	

What is the overall risk of bias?	High	*High - Few or no criteria fulfilled or the conclusions of the study are likely or very likely to be affected.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*		

- Kjotrod 2004

Study ID	***Kjotrod 2004***
Study Citation	Kjotrod, S. B.; von During, V.; Carlsen, S. M. Metformin treatment before IVF/ICSI in women with polycystic ovary syndrome; a prospective, randomized, double blind study. *Hum Reprod* **2004**, 19, 1315-22
Study Country	Norway
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	*The data below are for patients who started IVF stimulation (i.e. drop outs and spontaneous pregnancies not included)* *Age (years)* *Placebo (n=32) mean 30.2 (95% CI 29.0-31.5)* *Metformin (n=31) mean 28.9 (95% CI 27.6-30.2)* *BMI <28 (kg/m2)* *Placebo (n=13) mean 30.7 (95% CI 28.7-32.7)* *Metformin (n=14) mean 29.0 (95% CI 27.3-30.7)* *BMI ≥28 (kg/m2)* *Placebo (n=19) mean 29.9 (95% CI 28.1-31.8)* *Metformin (n=17) mean 28.9 (95% CI 26.7-31.0)*
PCOS diagnostic criteria	Aligns with Rotterdam criteria “All the patients had oligo/amenorrhoea, defined as either menstruation periods between 32 and 42 days (30%), an interval of between 42 days and 6 months (47%), or >6 months between periods (23%). In addition, at least one of the following five criteria had to be fulfilled: testosterone >2.0 nmol/ l (65%), sex hormone-binding globulin (SHBG) <30 nmol/l (60%), LH/FSH ratio >2 (38%), fasting insulin C-peptide >1.0 nmol/l (41%) or hirsutism (37%).”
Presence of infertility	Duration of infertility (years) Placebo (n=32) 4.0 (3.3-4.6) Metformin (n=31) 4.2 (3.1-5.3)

Presence of other condition/s	"Of the 73 patients randomized, 41 patients (60%) had undergone a laparoscopy. Of these patients,12 (29 %) had tubal disease and three (7%) had endometriosis in addition to PCOS."
Medication History	*Not reported*
N per group	*73 randomised* *4 withdrew* *Metformin (n=35)* *Placebo (n=34)*
Setting	Seventy-three consecutive, infertile women with PCOS referred for treatment at the IVF-unit at Trondheim University Hospital between January 2001 and June 2002
Intervention	Metformin 500 mg (Metformin, Weifa, Oslo, Norway)
Comparison	Placebo
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	*Primary:* total number of days of FSH stimulation serum oestradiol on the day of HCG injection *Secondary:* number of oocytes, total gonadotrophin dose used, fertilization rates, embryo quality, pregnancy rates, clinical pregnancy rate (defined as a verified intrauterine gestational sac by ultrasound performed in week 7) live birth rates *Clinical pregnancy was defined as a verified intrauterine gestational sac by ultrasound performed in week 7*
Follow up Duration	*12 weeks + 1 cycle?* Pre-treatment with metformin for 16 weeks
Summary Result/s	"No differences were found in the primary end-points: duration of FSH stimulation 14.4 (13.1±15.7) versus 14.2 (12.6±15.7) days or estradiol on the day of HCG injection 6.8 (5.3±8.2) versus 7.6 (5.6±9.6) nmol/l in the metformin and placebo groups, respectively. The secondary end-points number of oocytes, fertilization rates, embryo quality, pregnancy rates and clinical pregnancy rates were equal. However, in the normal weight subgroup (BMI <28 kg/m2, n = 27), pregnancy rates following IVF were 0.71 (0.63±0.79) versus 0.23 (0.15±0.31) in the metformin and placebo groups, respectively (P = 0.04). Overall clinical pregnancy rates were equal: 0.51 (0.34±0.68) versus 0.44 (0.27±0.62) in the metformin and placebo groups, respectively. However, in the normal weight subgroup, clinical pregnancy rates were 0.67 (0.43±0.91) and 0.33 (0.06±0.60), respectively (P = 0.06)."

ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes	*"*to investigate the effect of pre-treatment with metformin in women with polycystic ovary syndrome (PCOS) scheduled for IVF stimulation"

Does the study have specified inclusion/exclusion criteria?		Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?		Yes	
Inclusion criteria		Yes	*"*All patients had polycystic ovaries (PCO) with at least 10 follicles 2±10 mm in diameter, and increased density and area of ovarian stroma determined by the use of ultrasound (Adams et al., 1986). All the patients had oligo/amenorrhoea, defined as either menstruation periods between 32 and 42 days (30%), an interval of between 42 days and 6 months (47%), or >6 months between periods (23%)." *"*In addition, at least one of the following five criteria had to be fulfilled: testosterone >2.0 nmol/ l (65%), sex hormone-binding globulin (SHBG) <30 nmol/l (60%), LH/FSH ratio >2 (38%), fasting insulin C-peptide >1.0 nmol/l (41%) or hirsutism (37%)."
Exclusion criteria		Yes	diabetes mellitus, renal insufficiency (creatinine >130 mmol/l), liver disease (alanine aminotransferase >80 U/l) or treatment with oral glucocorticoids. Patients with hyperprolactinaemia, abnormal thyroid function tests, congenital adrenal hyperplasia and androgen-secreting tumours were excluded
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes	Randomization codes were kept in the pharmacy until the last patient had finished the IVF procedure
	Was allocation to intervention group concealed?	Yes	Patients were treated with identical capsules of metformin or placebo.
PERFORMANCE	**Were patients blind to intervention group?**	Yes	Patients were treated with identical capsules of metformin or placebo.

	Were investigators and care providers blind to intervention group?	Yes	*Double-blind study*
	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	*22.22% in placebo and 21.6% in metformin*	*From the patients that were randomised, 22.22% of placebo and 21.6% in metformin did not undergo embryo transfer*
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes	*Intention to treat analysis conducted*
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes	
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Partial	"Except for testosterone levels and the free testosterone index (FTI) in the lean subgroup, there were no significant differences between the study groups regarding inclusion criteria and demographics"

	If confounding was present, was it controlled for?	Partial	
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Not reported	"We gratefully thank Weifa AS, Norway, for supplying the metformin used free of charge, and Organon AS, Norway, for supporting gonadotrophin for the last 15 cycles (after public financing of IVF changed in Norway on January 1, 2002)."
	Was the study sufficiently powered to detect any differences between the groups?	Partial	"A treatment effect of 63 days or D-estradiol 63.5 nmol/l was considered to be of clinical significance. **Thirty-two patients** would be needed in each group to detect such changes with a 80 percentage power and with a P-value of 0.05." *Around 20% of each arm have not had ET due to various reasons and this may affect the analysis*
	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS			
What is the overall risk of bias?		Low	*Low - Many of the criteria have been fulfilled or where criteria have not been fulfilled it is very unlikely the conclusions of the study would be affected.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

- Kjotrod 2011

Study ID	**Kjotrod 2011**
Study Citation	Kjotrod, S. B., S. M. Carlsen, et al. (2011). "Use of metformin before and during assisted reproductive technology in non-obese young infertile women with polycystic ovary syndrome: a prospective, randomized, double-blind, multi-centre study." Human Reproduction 26(8): 2045-2053.

Study Country	Denmark, Finland, Norway and Sweden
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	Women diagnosed with PCOS, aged <38 years and with a BMI of <28 kg/m2. The majority of patients had previously received unsuccessful clomiphene citrate (CC) treatment. Mean (SD) age, years M: 29.6 (3.4) P: 29.5 (3.8) Mean (SD) BMI, kg/m2 M: 24.0 (2.7) P: 23.6 (2.8)
PCOS diagnostic criteria	Rotterdam
Presence of infertility	*Duration of infertility (years) mean (SD)* *Metformin (n=74) : 2.6 (1.8)* *Placebo (n=75) : 2.8 (1.8)* *Cause of infertility, n* *PCOS only* *Metformin 45* *Placebo 44* *Additional male factor* *Metformin 21* *Placebo 26* *Additional tubal disease* *Metformin 6 (n=38)* *Placebo 6 (n=40)* *Additional endometriosis* *Metformin 4 (n=36)* *Placebo 2 (n=37)*
Presence of other condition/s	*Not reported*
Medication History	*Not reported*
N per group	□ Screened: 179 participants □ Allocated/randomised: 150 participants – M: 74, P:76 □ Assessed pre-ART: M: 74, P:75 □ Followed up – not relevant to this systematic review
Setting	"The study was planned as a multi-centre study (EUDRACTnr-2004-001124-20). Originally a centre in Leeds, UK was planned to be included; but we did not get the approval for study medications by the medical authorities in UK. One private IVF clinic in Helsinki, one in Oslo and one in Cophenhagen were also supposed to participate, but dropped out very early due to recruitment problems. To compensate for this, The Oslo University Hospital was recruited into the study during the last 1.5 years of the inclusion period." February 2005 - March 2010.
Intervention	Metformin for ≥12 weeks prior to controlled ovarian stimulation (COS). "The dose of metformin was gradually increased from 500 to 2000 mg per day during the first 2 weeks of treatment." (spontaneous pregnancy (SP) group only) "Following a spontaneous menstrual period or a gestagen-induced shedding of the endometrium, pituitary down-regulation (nafarelin, 400 mg administered twice daily intranasally) was initiated (on cycle Day 20)" – assuming this to be post SP group data.

	The study continued throughout IVF/ICSI, and until the day of pregnancy testing, however we will only collect data relevant to pre-ART.	
Comparison	*Placebo*	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	Primary: clinical pregnancy rate; Secondary: biochemical pregnancy and live birth rate – these were not reported for SP population. Safety variables included the incidence of adverse events (AEs) and OHSS. *Pregnancy was detected initially by a serum pregnancy test performed on Days 13–15 after embryo transfer and women with a positive test underwent an ultrasound in week 7 of pregnancy*	
Follow up Duration	Haven't used entire study data, only pre ART data. The total study period was ~5 years.	
Summary Result/s	Among IVF treated women (n = 112), biochemical pregnancy rates were identical in both groups (42.9%), and there were no significant differences in the metformin versus the placebo group in CPR [39.3 versus 30.4%; 95% confidence interval (CI): 28.6 to 26.5]. The LBR was 37.5 versus 28.6% (95% CI: 28.4 to 26.3). However, prior to IVF there were 15 (20.3%) spontaneous pregnancies in the metformin group and eight (10.7%) in the placebo group (95% CI: 21.9 to 21.1; P = 0.1047). According to intention to treat analyses (n = 149); significantly higher overall CPR were observed in the metformin versus placebo group (50.0 versus 33.3%; 95% CI: 21.1 to 32.3; P = 0.0391). LBR was also significantly higher with use of metformin versus placebo (48.6 versus 32.0; 95% CI: 1.1 to 32.2; P = 0.0383). No major unexpected safety issues or multiple births were reported. More gastrointestinal side effects occurred in the metformin group (41 versus 12%; 95% CI: 0.15 to 0.42; P< 0.001).	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes	"To study the effect of metformin before and during assisted reproductive technology (ART) on the clinical pregnancy rate (CPR) in non-obese women with polycystic ovary syndrome (PCOS)."
Does the study have specified inclusion/exclusion criteria?	Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes	
Inclusion criteria	Yes	"The included patients had been trying, unsuccessfully, to conceive for at least 1 year and have a diagnosis of PCOS based on fulfilling at least two of the following three criteria: oligomenorrhoea/ amenorrhoea, clinical or biochemical hyperandrogenism and/or polycystic ovaries on

			ultrasound (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004).“
Exclusion criteria		Yes	“Patients were excluded if they were contraindicated for a starting dose of 112.5 IU recombinant human follicle-stimulating hormone (r-hFSH), or had a basal serum FSH level of .10 IU/l. Patients with liver or kidney disease, diabetes mellitus (or fasting plasma glucose ≥7.0 mmol/l), alcoholism or drug abuse were excluded. Patients with hyperprolactinaemia (serum prolactin .700 mIE/l), abnormal thyroid function tests, congenital adrenal hyperplasia, androgen-secreting tumours or Cushing’s syndrome were also excluded. Finally, patients who had received oral steroid hormones, cimetidine, anticoagulants, erythromycin or other macrolides were also excluded. A 1-month washout period was required for women who had previously received metformin.”
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes	“Randomization was performed in blocks of four by the hospital pharmacy using a computer-generated list.”
	Was allocation to intervention group concealed?	Yes	“The trial clinician and a study nurse at each site enrolled the patients.” “Identical blister packs containing metformin or placebo tablets (of the same appearance, smell and taste) were made, and each centre was assigned 20 identical packs. The study medicine was delivered to the patients either by the hospital pharmacy or by a third, independent person who was not involved in the study. The patient screened and randomized as number one in the centre received package number one, randomization patient number two received package number two, etc. Randomization codes remained blinded until the database lock had taken place.”
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes	
	Were investigators and care providers blind to intervention group?	Yes	“All study site personnel, the sponsor and the monitor Operationally involved in the monitoring or conduct of the study were blinded to the study drug codes.”

	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Not reported	Unblinding was performed prior to serum analyses.
	Were all outcomes measured in a standard, valid and reliable way?	Yes	"The primary efficacy end-point was the CPR, defined by ultrasound evidence of an intrauterine gestational sac (with a beating heart) at Week 7 in the ITT population. Secondary efficacy endpoints included the SP rate during the pretreatment period (SP population); biochemical pregnancy (defined by a positive serum hCG test on Day 14 after embryo transfer) and CPRs following IVF/ICSI in the ART population and LBR (in the ITT, ART and SP populations). Safety variables included the incidence of adverse events (AEs), OHSS and coasting. According to prespecified criteria, OHSS and coasting were not considered AEs."
	Were outcomes assessed objectively and independently?	Yes	
ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	0% M 1.3% P	This relates only to SP and not drops outs post ART.
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes	However we have not used the ITT population, we have used the pre-ART population.
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Not reported	Difficult to determine without a protocol.

CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes	Both groups were matched for age, cause and duration of infertility, weight, and BMI.
	If confounding was present, was it controlled for?		Both groups were matched for age, cause and duration of infertility, weight, and BMI.
OTHER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Partial	All were clearly declared.
	Was the study sufficiently powered to detect any differences between the groups?	Yes	"In our previous pilot study (Kjotrod et al., 2004) an increased pregnancy rate of almost 100% was observed among metformin-relative to placebo treated non-obese women with PCOS. A CPR of 0.35 was expected in the placebo group. With a study power of 0.80 and a significance level of 0.05, it was estimated that 120 patients were needed in each group to demonstrate a 50% increase in the CPR in the metformin group." However we will only use pre-ART data which which is in 74 participants and thus not adequately powered for that component of data.
	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS		*Lack of randomisation and blinding key reason for high RoB*	
What is the overall risk of bias?		Moderate	*Moderate - Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

Study ID	***Tang 2006a***
Study Citation	Tang, T.; Glanville, J.; Orsi, N.; Barth, J. H.; Balen, A. H. The use of metformin for women with PCOS undergoing IVF treatment. *Hum Reprod* **2006**, 21, 1416-25
Study Country	UK
BRIEF CHARACTERISTICS OF RCT	
Patient/population/ participants	*Age (years)* *31.3 (4.0) Metformin* *31.1 (4.0) Placebo* *BMI (kg/m^2)* *27.9 (5.6) Metformin* *26.9 (4.8) Placebo* *Mean (SD)*
PCOS diagnostic criteria	Diagnosis of PCOS followed the Rotterdam criteria (ESHRE/ASRM) "…presence of polycystic ovaries on transvaginal ultrasound scan (TVUS), more than 10 cysts, 2–8 mm in diameter, usually combined with increased ovarian volume >10 cm3 (after the transabdominal ultrasound criteria of Adams *et al*., 1985), together with either oligomenorrhoea/amenorrhoea or clinical/ biochemical hyperandrogenism. Anovulation was defined as the presence of amenorrhoea or oligomenorrhoea (cycle length greater than 35 days) (Munster and Schmidt Lone Helm, 1993; Berek *et al*., 1996). This criterion would also meet the recent consensus (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004)."
Presence of infertility	Causes of infertility not reported *Duration of infertility (years)* *4.5 (Metformin)* *4.0 (Placebo)* *Median*
Presence of other condition/s	All women with BMI over 30 kg/m2 would have been advised to loose weight 6–12 months prior to the treatment through lifestyle modification
Medication History	No participant had received metformin treatment within the 3 months prior to recruitment.
N per group	101 PCOS participants were randomised (52 in the metformin group and 49 in the placebo group) 5 cycles in the metformin group and 2 in the placebo group were abandoned due to poor response. 47 cycles in each arm completed through to oocyte retrieval.
Setting	*Single fertility unit*

Intervention	Metformin 850 mg twice a day from the first day of downregulation GnRH-agonist to the day of oocyte retrieval	
Comparison	*Placebo (*were identical in appearance)	
Outcomes (primary and other) with definition (eg. self-reported, fasting etc.)	• **Primary outcome:** a) fertilisation rate • **Secondary outcomes:** a) number of days of gonadotrophins b) total dose of FSH given during stimulation c) number of follicles (> 14 mm) d) number of oocytes e) number of embryos transferred f) implantation rate g) pregnancy rate per woman h) clinical pregnancy rate per woman i) pregnancy rate per transfer j) clinical pregnancy rate per transfer k) live birth rate l) incidence of OHSS that required hospitalisation m) side effects n) fasting insulin o) fasting glucose p) SHBG q) free androgen index r) testosterone	
Follow up Duration	*1 cycle*	
Summary Result/s	*"*There was no difference in the total dose of rFSH required per cycle (median dose: MET = 1200 U, PLA = 1300 U; *P* = 0.937). The median number of oocytes retrieved per cycle (MET = 17.2, PLA = 16.2; *P* = 0.459) and the overall fertilization rates (MET = 52.9%, PLA = 54.9%; *P* = 0.641) did not differ. However, both the clinical pregnancy rates beyond 12 weeks gestation per cycle (MET = 38.5%, PLA = 16.3%; *P* = 0.023) and per embryo transfer (MET = 44.4%, PLA = 19.1%; *P* = 0.022) were significantly higher in those treated with metformin. Furthermore, a significant decrease in the incidence of severe ovarian hyperstimulation syndrome (OHSS) was observed (MET = 3.8%, PLA = 20.4%; *P* = 0.023), and this was still significant after adjustment for BMI, total rFSH dose and age (OR = 0.15; 95% CI: 0.03, 0.76; *P* = 0.022)."	
ISSUES TO CONSIDER TO ASSIST WITH RISK OF BIAS ASSESSMENT		
Does the study have a clearly focused question and/or PICO?	Yes	*"…*to perform a randomized, placebo-controlled, double-blind study (RCT) to explode the potential benefits of using metformin during IVF treatment."
Does the study have specified inclusion/exclusion criteria?	Yes	
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes	

Inclusion criteria		Yes	a) serum testosterone concentration < 5.0 nmol/L b) normal prolactin concentration, thyroid, renal, and haematological indices.
Exclusion criteria		Yes	a) concurrent hormone therapy within the previous 6 weeks b) any chronic disease that could interfere with the absorption, distribution, metabolism, or excretion of metformin c) renal or liver disease d) systemic disease or diabetes (types 1 and 2)
INTERNAL VALIDITY – HAS THIS STUDY BEEN CONDUCTED RIGOROUSLY IN ORDER TO REDUCE BIAS?			
SELECTION BIAS	**Did the study have an adequate method of randomisation?**	Yes	random numbers table
	Was allocation to intervention group concealed?	Yes	codes kept by a third party in the trial office
PERFORMANCE BIAS	**Were patients blind to intervention group?**	Yes	Double-blinded
	Were investigators and care providers blind to intervention group?	Yes	Double-blinded
	Aside from the experimental intervention, were the groups treated the same?	Yes	
DEDETECTION BIAS	**Were outcome assessors blind to intervention group?**	Not reported	
	Were all outcomes measured in a standard, valid and reliable way?	Yes	
	Were outcomes assessed objectively and independently?	Yes	

ATTRITION BIAS	**What percentage of the individuals recruited into each arm of the study dropped out?**	9.6% in treatment; 4% control/ comparison	Five cycles in the metformin group and two cycles in the placebo group were abandoned due to poor response. The difference was not significant (*P* = 0.487)
	Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes	Reasons for withdrawals were reported. ITT analysis was performed
REPORT BIAS	**Is the paper free of selective outcome reporting?**	Yes	All main outcomes were reported.
CONFOUNDING	**Were the groups similar at baseline with regard to key prognostic variables?**	Yes	
	If confounding was present, was it controlled for?		*Not applicable*
ER BIAS	**Were there any conflicts of interest in the writing or funding of this study?**	Not reported	

	Was the study sufficiently powered to detect any differences between the groups?	Partial	At the time when the study was planned, no RCT had been carried out to investigate the use of metformin during IVF treatment. Therefore, the power calculation was based on the data from retrospective studies. "…fertilization rate as our primary power calculation. The fertilization rates from the study by MacDougall *et al*. (1993) were 52.8 □□3.4% and 66.1 □□3.4% for patients with PCOS and non-PCOS, respectively. With an improvement of 20%, the calculated standardized difference (*d*) would be 0.67. The chosen power in the study was 90%, with a type I error of 0.05. From the power table (Machin and Campbell, 1987), when *d* = 0.67 and the power = 0.90, the projected sample size was 100 with 50 subjects in each arm." *1 subject in placebo arm (4%) but 5 (9.6%) in the intervention withdrew due to poor response*
	If statistical analysis was undertaken, was this appropriate?	Yes	
COMMENTS			
What is the overall risk of bias?		*Low*	*Low - All of the criteria have been fulfilled or where criteria have not been fulfilled it is very unlikely the conclusions of the study would be affected.*
Did risk of bias differ by outcome *(eg. primary outcome was low risk but rest were high)?*			

GUIDELINE DEVELOPMENT METHODS

This guideline was developed as outlined in National Health and Medical Research Council (NHMRC) standards and procedures for rigorously developed external guidelines and according to the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach. These methods were aligned with European Society of Human Reproduction and Embryology (ESHRE) guideline development methods.

The work builds on the original Australian guideline in PCOS, the update in 2014, the World Health Organisation (WHO) guideline evidence synthesis in infertility management, and the International Guideline in the assessment and management of PCOS.

The International evidence–based guideline for the assessment and management of PCOS underpins an international initiative to engage women affected by PCOS and their health professionals to improve health outcomes. The Centre for Research Excellence in PCOS and the CRE in Women's Health in Reproductive Life, funded by the National Health and Medical Research Council and led by Monash University, partnered with the American Society for Reproductive Medicine, the Endocrine Society, the European Society of Endocrinology and the European Society of Human Reproduction and Embryology. Extensive international health professional and consumer engagement informed the gaps, needs, priorities and core clinical outcomes for the guideline, through the CRE, partners and several organisations engaged in formal collaboration.

Guideline development groups (GDGs) included members nominated by the engaged international societies. Society-nominated panel members included women with PCOS, paediatricians, endocrinologists, gynaecologists, primary care physicians, reproductive endocrinologists, psychologists, dietitians, exercise physiologists, public health experts, researchers and other co-opted experts including in sleep and bariatric/ metabolic surgery. Other experts were engaged outside GDG meetings where specific individual questions required including dermatology and psychiatry. They were supported by an experienced project management, Evidence Synthesis Team and International Early Career Network and the translation team to develop the guideline. Here we provide a comprehensive review of the evidence and formulate recommendations using the GRADE Framework.

Governance and process

Governance included an international advisory board from across the continents, a project board, five GDGs, a paediatric advisory panel, and a translation and consumer committees (See Figure 1). The Australian Centre for Research Excellence in PCOS (CREPCOS) and the CRE in Women's Health in Reproductive Life, funded by the National Health and Medical Research Council and led by Monash University, partnered with the American Society for Reproductive Medicine, the Endocrine Society, the European Endocrine Society and the European Society of Human Reproduction and Embryology and collaborated with several organisations. The majority of the funding was provided by the Australian government, with contributions from partner organisations. Advisory, project board, GDG, translation and consumer committee meetings occurred online and face to face over 8 months across Europe, USA and Australia and enabled guideline training, development and informed translation. Feedback from the partner and collaborating societies and their convened special interest groups of experts and consumers as well as public consultation, have informed the final guideline.

Multidisciplinary international guideline development groups

GDGs were convened to address each of the five key clinical areas. Expertise was sought through partner and collaborator organisations aiming for multidisciplinary, consumer and geographical participation within each GDG. Each GDG comprised a chair, professional group members with specific expertise in PCOS and the clinical area of interest (i.e. psychologists in the emotional wellbeing GDG), consumer representatives, evidence officers and representative to consider cultural aspects (See Appendices). Co-opted experts were also included as needed.

Consumer participation

In the development of this guideline, we have sought not only to inform or consult with those affected by PCOS, but to partner with and empower them as the ultimate beneficiaries of this work. We have engaged with international consumer bodies in PCOS to this end. This included Polycystic Ovary Syndrome Association Australia (POSAA) (Australia), Verity (United Kingdom), PCOS Challenge (United States), and PCOS Vitality (Ireland), all of whom were actively partnered in the guideline process. Other groups including and PCOS consumer groups in India, were actively involved.

An international survey was completed by over 1500 women and focus groups were held with women with PCOS to inform priorities for the guideline update and we built here on the 2018 guideline process of priority setting and prioritised outcomes for each intervention. This work also informed guideline translation, education and support needs and preferred methods of delivery.

Consumer representatives participated in the development of the Centre for Research Excellence funding submission, in the guideline Project Board, International consumer advisory group and in all of the GDGs. Consumers have been involved in every stage, including development of the guideline scope, public consultation on the scope and developing and refining the clinical questions and recommendations as part of the GDGs. Consumer representatives are also extensively engaged and are partnering in the guideline translation activities.

Indigenous representation and CALD (culturally and linguistically diverse)

Ethnicity and culture were considered when making all recommendations. Indigenous representation was present on the PCOS Guideline Project Management Committee and the GDGs comprised clinicians with experience working with CALD and Indigenous communities. The translation of the guideline allows for adaptions on cultural and ethnicity grounds.

Declarations and conflicts of interest and confidentiality

Conflict of interest has been proactively managed throughout the guideline development process as outlined in

NHMRC Procedures and requirements for meeting the 2011 NHMRC standard for clinical practice guidelines. All members of the GDGs have provided signed declarations of interest and a confidentiality agreement. These conflicts are publicly available (refer to official guideline document). Additionally, declarations of interest were a standing agenda item at each meeting and at the GDG meeting where recommendations were endorsed and GRADE templates completed, all declarations of interest were presented. GDG members were requested to declare all interests.

The process for managing conflicts of interest and confidentiality and recorded declarations can be provided on request (cre-whirl@monash.edu).

Training of GDGs in evidence review and guideline development methods

All GDG members attended training sessions on both guideline development and on research integrity, where the methods of reviewing evidence and guideline development were described in detail. The purpose of these sessions was to familiarise the chairs and GDG members with:

- the process of guideline development overall
- the process of identifying, appraising and synthesising evidence in a format to facilitate the formulation of evidence-based recommendations
- the new research integrity process (Appendix III)
- grading the strength of evidence and its suitability to support evidence-based recommendations
- when to facilitate discussion and clinical judgement to formulate clinical consensus recommendations in the absence of evidence.

Clinical question development and prioritisation

An International survey and Delphi exercise was conducted to develop and prioritise clinical questions to be addressed in 2018 and informed work here, supplemented by extensive consultation with the development of the core outcome set in PCOS in 2020. For 2023, the prioritisation process involved a global survey of over 1500 women with PCOS to help determine the aspects of PCOS women prioritised, followed by all GDG members and consumer advisory groups to rank the importance of the 2018 guideline, considering clinical relevance and the evolution of evidence in the past five years. New questions were either put forward by chairs of each GDG group after discussion with panel members, or ranked as being high priority for inclusion by the consumer survey.

A scoping exercise was performed to identify published research since the 2018 PCOS guideline evidence review to assist expert GDGs and consumer advisory groups in deciding which clinical questions were to be addressed by a systematic review or by narrative review. Systematic reviews were performed for all questions where systematic evidence appraisal was suited. Narrative evidence reviews were completed where questions were less well suited to a PICO systematic review format.

Of the 55 questions, 52 were addressed by guideline systematic reviews, and three by narrative reviews of isolated PCOS studies supported by systematic reviews/guidelines in the general population. Of the 52 systematic reviews, some searches identified no evidence addressing the specific question and/or PICO (i.e. no eligible studies), in which case results were described narratively, drawing on clinical expertise and evidence from the general population.

The clinical questions addressed by each GDG are as follows:

GDG 1 – Screening, diagnostic assessment, risk assessment and life-stage

- In adolescents, at what time point after onset of menarche do irregular cycles indicate ongoing menstrual dysfunction?
- In women with suspected PCOS, what is the most effective measure to diagnose PCOS related hyperandrogenism (biochemical)?
- In women with suspected PCOS, what is the most effective measure to clinically diagnose PCOS related hyperandrogenism?
- What is the most effective ultrasound criteria to diagnose PCOS?
- When is ultrasound indicated to diagnose PCOS?
- Is anti-mullerian hormone (AMH) effective for diagnosis of PCOS?
- Is AMH effective for diagnosis of PCOM?
- In women with PCOS, is there evidence of ethnic variation in prevalence and presentation?
- What is the post-menopausal phenotype of PCOS and how elevated should androgens be to indicate PCOS? Are women with PCOS at increased risk for cardiovascular disease (CVD)?
- Are women with PCOS at increased risk for impaired glucose tolerance (IGT) and type 2 diabetes mellitus (T2DM)?
- In women with PCOS, what is the most effective tool/method to assess risk of T2DM?
- Are women with PCOS at increased risk for sleep apnoea?
- Are women with PCOS at increased risk of endometrial cancer?
- What is the risk of PCOS and cardiometabolic outcomes (CVD, T2DM) in relatives of women with PCOS?

GDG 2 - Prevalence, screening, diagnostic assessment and management of emotional wellbeing and models of care

- In women with PCOS, what is the prevalence and severity of reduced quality of life (QoL)? In women with PCOS, what dimensions of QoL are most affected?
- In women with PCOS, what is the prevalence and severity of depression and anxiety?
- In women with PCOS what is the prevalence and severity of psychosexual dysfunction?
- In women with PCOS, what is the prevalence and severity of body image distress?
- In women with PCOS what is the prevalence and severity of disordered eating?
- What are the information, resource and education needs of women, adolescents, CALD groups and healthcare providers regarding PCOS?
- What are the characteristics of available models of care implemented in PCOS clinic or service?
- How can we best support women to navigate the impact of PCOS on family and interpersonal relationships?
- What are the key challenges for those with PCOS when interacting with healthcare professionals about polycystic ovary syndrome and related features?
- Are anti-depressants and anxiolytics effective for management and support of depression and/or anxiety or disordered eating in women with PCOS?
- Is psychological therapy effective for management and support of depression and/or anxiety, disordered eating, body image distress, self-esteem, feminine identity or psychosexual dysfunction in women with PCOS?

GDG 3 – Lifestyle management

- In women with PCOS, are lifestyle interventions (compared to minimal or nothing) effective for

anthropometric, metabolic, reproductive, fertility, QoL and emotional wellbeing outcomes?
- In women with PCOS, are behavioural interventions (compared to different types of behavioural interventions) effective for improving anthropometric, metabolic, reproductive, fertility, QoL and emotional wellbeing outcomes?
- In women with PCOS, are diet interventions (compared to different diets) effective for improving anthropometric, metabolic, fertility, and emotional wellbeing outcomes?
- In women with PCOS, are exercise interventions (compared to different exercises) effective for improving anthropometric, metabolic, reproductive, fertility, QoL and emotional wellbeing outcomes?
- Why are women with PCOS at increased risk of weight gain?
- What is the burden of weight stigma in PCOS?

GDG 4 – Pharmacological treatment for non-fertility indications

- Is the oral contraceptive pill alone or in combination, effective for management of hormonal and clinical PCOS features in adolescents and adults with PCOS?
- Is metformin alone or in combination, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?
- Are anti-obesity pharmacological agents alone or in combination, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?
- Are anti-androgen pharmacological agents alone or in combination, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?
- In adults and adolescents with PCOS, is inositol alone or in combination with other therapies, effective for management of hormonal and clinical PCOS features, weight and reproductive outcomes?
- Is permanent hair reduction alone or in combination with other therapies, effective for management of hirsutism in adolescents and adults with PCOS?
- In adults and adolescents with PCOS, is bariatric surgery effective for management of hormonal and clinical PCOS features and weight?
- In women with PCOS in pregnancy, is metformin compared to placebo/standard care effective in reducing pregnancy complications and adverse neonatal outcomes?
- Are women with PCOS at increased risk of adverse pregnancy outcomes?

GDG 5 – Screening, diagnostic assessment and management of infertility

- In women with PCOS with infertility, what are the preconception risk factors associated with poor/negative fertility outcomes?
- Should women with PCOS and infertility due to anovulation alone with normal semen analysis undergo tubal patency testing prior to starting ovulation induction with timed intercourse or intrauterine insemination (IUI) treatment?
- In women with PCOS, are aromatase inhibitors (AIs) effective for improving fertility outcomes?
- In women with PCOS, is clomiphene citrate (CC) effective for improving fertility outcomes?
- In women with PCOS, is metformin effective for improving fertility outcomes?
- In women with PCOS and a BMI <30-32, what is the effectiveness of metformin compared to CC for improving fertility outcomes?
- In women with PCOS, are gonadotrophins effective for improving fertility outcomes?
- In women with PCOS, is ovarian surgery effective for improving fertility outcomes?
- In women with PCOS, is stimulated IVF/ICSI effective for improving fertility outcomes?
- In women with PCOS undergoing IVF/ICSI treatment, is the gonadotropin-releasing hormone (GnRH) antagonist protocol or GnRH agonist long protocol the most effective for improving fertility outcomes?
- In women with PCOS undergoing GnRH antagonist IVF/ICSI treatment, is the use of human chorionic

gonadotropin (hCG) trigger or GnRH agonist trigger the most effective for improving fertility outcomes?

- In women with PCOS undergoing (controlled) ovarian (hyper) stimulation for IVF/ICSI (In-vitro fertilisation/Intra- cytoplasmic sperm injection), does the choice of follicle-stimulating hormone (FSH) affect fertility outcomes?
- In women with PCOS undergoing (controlled) ovarian (hyper) stimulation for IVF/ICSI, is exogenous luteinizing hormone (LH) treatment during IVF/ICSI effective for improving fertility outcomes?
- In women with PCOS undergoing (controlled) ovarian (hyper) stimulation for IVF/ICSI, is adjuvant metformin effective for improving fertility outcomes?
- In women with PCOS, is In Vitro Maturation (IVM) effective for improving fertility outcomes?
- In women with PCOS, are anti-obesity pharmacological agents, alone or in combination with other therapies, effective for improving fertility outcomes in adolescents and adults with PCOS?
- Is inositol alone or in combination with other therapies, effective for management of fertility outcomes in adolescents and adults with PCOS?

* *Not all questions resulted in a recommendation. Where evidence was inadequate only research recommendations were made.*

Outcome prioritisation using the GRADE method

The most relevant outcomes were prioritised by ranking their importance by health professionals and consumers to help resolve or clarify disagreements and assist with grading the evidence. The importance of outcomes may vary across cultures and from different perspectives e.g. patients, public, health professionals or policy-makers. Table 1 outlines the considerations when deciding importance of outcomes. GDG members, including consumers also participated in this exercise.

Table 1: Steps for considering the relative importance of outcomes

What	Assessment and prioritisation of outcomes as critical, important but not critical, or low importance. Requires judgement of the balance between the desirable and undesirable health outcomes of an intervention.
Why	To focus attention on those outcomes that are considered most important when conducting evidence review and to resolve or clarify disagreements. To support making a recommendation and to determine the strength of the recommendation.
How	Scoping the relevant literature. By asking GDG members, including consumers to prioritise outcomes in light of the considerations for 'what' and 'why'.
Evidence	These judgments are ideally informed by a systematic review of the literature focusing on what the target population considers as critical or important outcomes for decision-making. Prior knowledge of the research evidence through systematic reviews; and information about values, preferences or utilities has been explored in the original guideline, that was systematic. Additionally, the collective experience of the GDG members, including consumers, will be used using transparent methods for documenting and considering them.

To facilitate ranking of outcomes according to their importance the following scale was used:

RATING SCALE:

1	2	3	4	5	6	7	8	9
of **least** importance							of **most** importance	
Of limited importance for making a decision (not included in evidence profile)			Important, but not critical for making a decision (included in evidence profile)			Critical for making a decision (included in evidence profile)		

Outcomes considered critical (rated 7-9) most greatly influenced a recommendation and the overall quality of evidence supporting the recommendation and the strength of the recommendation.

Adaptation of existing evidence-based guidelines

Given the time and resource-intensive nature of guideline development, existing high-quality evidence-based guidelines that address the clinical questions and PICO (Population, Intervention, Comparison, Outcome) of interest should be sought for adaptation before starting a new one. Apart from the International evidence-based guideline for the assessment and management of PCOS, completed by this group in 2018, no other international guideline covering all health aspects related to the syndrome was available. Professional society positions statements or clinical practice guidelines are more limited in scope, do not follow AGREE II (Appraisal of Guidelines for Research and Evaluation) process, involve more limited expertise and geographical representation and are often conflicting in recommendations. Here all partnering and collaborating organisations have agreed to adopt and if required adapt these guidelines and we have updated and expanded the scope and evidence from the 2018 guidelines. This process involved new questions and updated evidence review for all existing questions from 2018. It also included a new research integrity process aligned to the tools applied by Cochrane (Appendix III).

Evidence reviews to answer the clinical questions

Evidence reviews were conducted for each clinical question and from the evidence reviews, the GDGs developed guideline recommendations. The evidence reviews for each question can be found in the supplementary Technical report. The links between the body of evidence, the clinical need for the question and the clinical impact of the resulting recommendation(s), including potential changes in usual care and the way care is organised, acceptability, feasibility and resource implications are clearly explained in the accompanying GRADE evidence to decision framework supporting the recommendation.

Selection criteria

The PICO framework was used by the GDGs to explore the components of each clinical question and finalise the selection criteria for each question. These components were used to include and exclude studies in the evidence review. Details of the selection criteria for each question can be found in the supplementary Technical report.

The highest form of evidence, the most current (within 5 years), comprehensive (with the most outcomes relevant
to PICO) and highest quality systematic reviews that met our benchmark criteria (see Table 2) and met the selection criteria, was used as a starting point for the updated search and systematic review. For most questions, the systematic review and search results from the 2018 guideline were used as a starting point and updated as required. Additional randomised controlled trials (RCTs) that were not included in the previous systematic reviews, but met the current selection criteria were also used, with meta-analyses updated as needed. Where

applicable, risk of bias appraisals from previous systematic reviews were adopted.

Table 2. Benchmark criteria for a systematic review to be used as a starting point:

1. Must have met the PICO and completed a search in at least Medline and another relevant database;
2. Must have listed key search terms;
3. Must have listed selection criteria;
4. Must have used an appropriate framework to assess risk of bias/quality appraisal; and
5. Where the evidence is sought for an intervention question and a systematic review has included non-RCTs, the analysis must be sub-grouped by RCTs to be eligible for inclusion.

Systematic search for evidence

A broad-ranging systematic search for terms related to PCOS was developed by the Evidence Synthesis Team. This PCOS search string was then combined with specific searches tailored for each clinical question according to the PICO developed by the GDG. The search terms used to identify studies addressing the population of interest (i.e. women with PCOS) were only limited to PCOS terms. Therefore, studies addressing women with PCOS in all cultural, geographical and socioeconomic backgrounds and settings were identified by the search. Furthermore, whilst a systematic review of health economic analyses was performed in this guideline, very limited evidence curtailed consideration of costs. Costs were considered based on GDG expertise in the GRADE process. The search strategy was limited to English language articles and limits on year of publication are specified in the PICO for each clinical question.

The following electronic databases were employed to identify relevant literature:

- CINAHL (Cumulative Index to Nursing and Allied Health Literature)
- Medline (OVID)
- Medline in-process and other non-indexed citations (OVID)
- PsycINFO (OVID)
- EMBASE
- All EBM Reviews (OVID), which includes:
  - Cochrane Database of Systematic Reviews (Cochrane Reviews)
  - Database of Abstracts of Reviews of Effects (Other Reviews)
  - Cochrane Central Register of Controlled Trials (Clinical Trials)
  - Cochrane Database of Methodology Reviews (Methods Reviews)
  - The Cochrane Methodology Register (Methods Studies)
  - Health Technology Assessment Database (Technology Assessments)
  - NHS Economic Evaluation Database (Economic Evaluations)

GDG members were consulted, and the bibliographies of relevant reviews/meta-analysis studies identified by the search strategy were also searched for identification of additional studies. Details of the search strategies and search results for each evidence review can be found in the supplementary Technical report.

Inclusion of studies

To determine the literature to be assessed further, one to two reviewers scanned the titles, abstracts and keywords of every record retrieved by the search strategy. This process was supervised by the expert Evidence

Synthesis Team and GDG key contacts who also engaged in decisions on included studies. Full articles were retrieved for further assessment if the information given suggested that the study met the selection criteria. Studies were selected by one to two reviewers in consultation with an additional reviewer to resolve conflicts if required, using the PICO selection criteria established a priori. Where there was any doubt regarding these criteria from the information given in the title and abstract, the full article was retrieved for clarification.

Appraisal of the methodological quality/risk of bias of the evidence

Methodological quality of the included studies was assessed using criteria developed a priori according to study design (i.e. quality appraisal criteria used for an RCT is different to that used for a cohort study). Individual quality items were investigated using a descriptive component approach. Any disagreement or uncertainty was resolved by discussion among the Evidence Synthesis Team (or key contacts for content related queries) to reach consensus. Using this approach, each study was allocated a risk of bias rating (see Table 3). Quality appraisal tables for each evidence review can be found in the supporting document titled Technical report. This follows the NHMRC approved 2018 evidence synthesis process.

Table 3. Risk of bias ratings

RATING	DESCRIPTION
Low	All of the criteria have been fulfilled or where criteria have not been fulfilled it is very unlikely the conclusions of the study would be affected.
Moderate	Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.
High	Few or no criteria fulfilled or the conclusions of the study are likely or very likely to be affected.
Insufficient information	Not enough information provided on methodological quality to be able to determine risk of bias.

Data extraction

Data, according to the selection criteria, were extracted from included studies using a specially developed data extraction form developed by the Evidence Synthesis Team [604]. Information was collected on general details (title, authors, reference/source, country, year of publication, setting), participants (age, sex, inclusion/exclusion criteria, withdrawals/losses to follow-up, subgroups), results/ outcomes (point estimates and measures of variability, frequency counts for dichotomous variables, number of participants, intention-to-treat analysis) and validity results. Data extraction tables for each evidence review can be found in the supporting Technical report.

Data synthesis

In order to make a summary statement about the effect of the intervention and thus inform evidence-based recommendations, data were presented qualitatively by presenting the findings narratively in tables or discussion text; and where possible quantitatively, using statistical methods such as meta-analyses. A meta-analysis is a statistical technique for combining (pooling) the results of a number of studies, that report data for the same outcome for the same intervention, to produce a summary statistic to represent the effect of one intervention compared to another.

When high-quality trials were used, a meta-analysis summary statistic can be more powerful than an individual study to confirm or refute effectiveness of an intervention and thus to inform an evidence-based recommendation. Data were summarised statistically using meta-analysis if data were available, sufficiently

homogenous, and of sufficient quality. Clinical homogeneity was satisfied when participants, interventions, outcome measures and timing of outcome measurement were considered to be similar. Meta-analyses were performed using Review Manager 5.3. or 5.4. or STATA software. Where appropriate, subgroup analysis was conducted according to factors that may cause variations in outcomes, are likely to be a confounder, or may change the way the treatment works e.g. age, subtype, duration of treatment or study quality. These can be found in the supporting Technical report.

Research Integrity Process

Findings from systematic reviews are underpinned by the assumption that the included studies follow good clinical research practice to produce trustworthy results. However, the last decade has seen a rapid rise in the frequency of "problematic studies", the most visible of which are retracted studies (1, 2, 3), suggesting that these studies are increasing in number and/or that there is increased awareness of them among the scientific community. While there is no universally accepted definition of a "problematic study", the term generally refers to a study with questionable data or findings, irrespective of its retraction status. This could be a result of scientific misconduct, poor research practices, or naïve but honest error(s). Regardless of the cause, the resultant erroneous findings have significant and far-reaching consequences, jeopardising the validity of systematic reviews and undermining patient and public trust in scientific research. In response to this increasingly recognised issue, tools and policies have been introduced by several groups, including the Cochrane collaboration (4,5), the Committee on Publication Ethics (COPE) (6), and others (e.g. RIA (7) TRACT (8) to incorporate research integrity assessments as routine steps in systematic reviews and publishing processes. As yet, however, no process has been established to ensure the authenticity and accuracy of evidence in the context of guideline development. This is of critical importance since the evidence included in guidelines is used to formulate clinical practice recommendations which directly influence patient care, often on a global scale.

Here, we have developed the *Research Integrity for Guideline Development (RIGID)* framework - a transparent, unbiased, and rigorous process to identify and manage problematic studies encountered during the guideline development process. The RIGID framework, outlined in Appendix III, is a complementary but critical process to be integrated alongside risk of bias and GRADE assessments to ensure that recommendations are based on high-quality, authentic and accurate evidence. The framework was piloted across all clinical questions in GDG 5, with details provided in the supplementary Technical report and in our publication (9).

Briefly, the RIGID framework begins with the search and screening of studies for inclusion as per usual systematic review methodology. Once full text screening is complete and the final list of included studies is determined, the following integrity assessment steps are applied:

(1) Review team identifies and excludes studies on the Retraction Watch database (tabulated with reasons);

(2) Independent reviewer(s) assess(es) the remaining included studies using a research integrity tool/ checklist (e.g. Cochrane, RIA, TRACT, etc.), clearly documenting areas of concern;

(3) An integrity committee made up of guideline team members and external members independently reviews the checklist scores/ results. Each member places a vote on whether the study should be classified as low, moderate or high risk. Votes are tallied to reach a final classification and, if required, a meeting is convened to reach consensus;

(4) Studies considered *low risk* are included as part of the guideline evidence (and meta-analyses where applicable);

(5) Studies considered *moderate or high risk** are awaiting classification, and authors are contacted to clarify

the integrity issues identified. If authors respond with an acceptable explanation and/or supporting evidence to satisfy concerns, the study is reclassified as low risk and included as per step 4. If the authors provide an intention to submit (response indicating intention to supply the required information/ data within a specified timeframe) or if no response is provided, the study remains as moderate or high risk and is not included in the guideline until a satisfactory response is received as determined by the integrity committee;

(6) All moderate and high risk studies excluded from the guideline are tabulated with reasons/ integrity scores and/or contact log in technical documents or supplemental material for transparency.

*Classification as moderate or high risk does not imply fraudulent data or research misconduct. These classifications reflect a medium to high score on the integrity checklist, suggesting that issues were identified that require clarification (and may indeed be adequately justified) before guideline development groups can be confident in using these studies to inform recommendations with direct impact to patient care.

References:

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Quality (certainty) of the body of evidence using GRADE evidenceprofiles

As per the 2018 guideline, GRADE evidence profile was prepared for each comparison within each clinical question addressed by a systematic review. For each prioritised outcome, a certainty rating was documented with consideration of the following:

- information about the number and design of studies addressing the outcome; and
- judgments about the quality of the studies and/or synthesised evidence, such as risk of bias, inconsistency, indirectness, imprecision and any other considerations that may influence the quality of the evidence.

The definitions of these factors are described below:

- overall quality of evidence rating using the judgments made above (see ratings in Table 4);
- key statistical data; and
- classification of the importance of the outcome.

The certainty of evidence reflects the extent to which our confidence in an estimate of the effect is adequate to support a particular recommendation.

Although the quality of evidence represents a continuum, the GRADE approach results in an assessment of the quality of a body of evidence in one of four grades (adapted from GRADE).

Table 4. Quality of evidence

High	⊕⊕⊕⊕	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	⊕⊕⊕◯	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	⊕⊕◯◯	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low	⊕◯◯◯	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

GRADE notes that the quality of evidence is a continuum; any discrete categorisation involves some degree of arbitrariness. Nevertheless, advantages of simplicity, transparency, and vividness outweigh these limitations. Evidence profiles can be found in the Technical report.

Formulation of recommendations using the GRADE evidence to decision framework

As per the 2018 NHMRC approved guideline, the Evidence to Decision (EtD) framework was used to transparently document the judgments and decisions using the GRADE method for development of evidence-based recommendations. The framework prompts transparent documentation and discussion of decisions through assessment of the evidence, clinical expertise and patient preference capturing the strength of the recommendation and capturing factors including:

- desirable and undesirable effects of the intervention;
- certainty of the evidence;
- values associated with the recommended intervention;
- balance of effects;
- resource requirements;
- cost-effectiveness;
- equity; acceptability;
- feasibility;
- subgroup considerations;
- implementation considerations;
- monitoring and evaluation; and
- research priorities.

Using the framework, each of the evidence-based and consensus recommendations are given an overall grading of conditional or strong. Clinical practice points have also been included, where important issues

(such as safety, side effects or risks) arose from discussion of evidence-based or clinical consensus recommendations. Strong recommendations are reflected using the term “should” and conditional recommendations are reflected using the terms “could” or “should/could consider”.

Table 5. Recommendation types

EBR	Evidence based recommendations: Evidence sufficient to inform a recommendation made by the guideline development group.
CR	Clinical Consensus Recommendations: In the absence of adequate evidence, a clinical consensus recommendation has been made by the guideline development group, also informed by evidence from the general population.
PP	Clinical Practice Points: Evidence not sought. A practice point has been made by the guideline development group where important issues arose from discussion of evidence-based or clinical consensus recommendations.

The strength of the recommendations can be identified throughout the guideline by the following (adapted from ESHRE manual for guideline development and the GRADE approach).

Table 6: Strength of recommendations (adapted from GRADE and the ESHRE Manual)

TARGET GROUP	STRONG RECOMMENDATIONS*	CONDITIONAL (WEAK) RECOMMENDATIONS FOR THE OPTION (TEST OR TREATMENT)	CONDITIONAL (WEAK) RECOMMENDATION FOR EITHER THE OPTION OR THE COMPARISON	RESEARCH ONLY RECOMMENDATIONS	CLINICAL PRACTICE POINTS (CPP)**
CONSUMERS	Most people in your situation would want the recommended course of action and only a small proportion would not.	The majority of people in your situation would want the recommended course of action, but some would not.	There is considerable lack of clarity over whether the majority of people in your situation would want the recommended course of action or not.	The test or intervention should only be considered by patients and clinicians within the setting of a research trial with appropriate approvals and safety precautions have been established.	Clinicians, patients and policy makers are informed on the clinical implications relevant to implementation of recommendations.
HEALTH PROFESSIONALS	Most patients should receive the recommended course of action.	Recognise that different choices will be appropriate for different patients and that greater effort is needed with individuals to arrive at management decisions consistent with values and preferences. Decision aids and shared decision making are important here.		The test or intervention should only be considered by patients and clinicians within the setting of a research trial for which appropriate approvals and safety precautions have been established.	
POLICY MAKERS	The recommendation can be adopted as policy in most situations.	Policy making needs to consider perspectives and involvement of diverse stakeholders.	Policy decisions remain unclear.	Policy makers need to be aware of the need for evidence gaps and health professional and consumer prioritised research gaps.	

* Strong recommendations based on high quality evidence will apply to most patients for whom these recommendations are made, but they may not apply to all patients in all conditions; no recommendation can consider all of the often-compelling unique features of individual patients and clinical circumstances.

** A practice point (PP) is developed by the GDG to support recommendations. Advice can be provided to enhance shared decision making, and on factors to be considered in implementing a specific test or intervention

The words “should”, “could” and “should not” do not directly reflect the strength (strong or conditional) allocated to a recommendation and are independent descriptors intended to reflect the judgment of the multidisciplinary GDG on the practical application of the recommendation, balancing benefits and harms. Where the word “should” was used in the recommendations, the GDG judged that the benefits of the recommendation (whether evidence-based or clinical consensus) clearly exceed the harms, and that the recommendation can be trusted to guide practice. Where the word “could” was used, either the quality of evidence was underpowered, or the available studies demonstrated little clear advantage of one approach over another, or the balance of benefits to harm was unclear. Where the words “should not” are used, there is either a lack of appropriate evidence, or the harms outweigh the benefits.

Evidence to decision frameworks can be found in the supplementary document titled Technical report. Each recommendation is supported by a discussion (in the chapters of this document) about the clinical need for the question, the body of evidence identified to answer the question and a clinical justification for the recommendation(s).

The GDGs acknowledge that lack of evidence is not evidence of lack of effect and they have attempted to reflect this in the strength of the grading given to recommendations on interventions that are not directly supported by evidence in women with PCOS. In addition, some interventions were not supported by evidence in the recommendations due to lack of evidence of effect. The GDGs acknowledge that this refers to lack of evidence of effect over placebo; that is, patients may receive some beneficial outcomes from the intervention but these do not exceed the beneficial effects that can be expected from a placebo therapy.

Public consultation

Public and targeted consultation will be conducted for a period of thirty days commencing 6th February to 7th March 2023 in accordance with the legislative requirements set out in section 14A of the National Health and Medical Research Council Act 1992 as outlined in the NHMRC Procedures and requirements for meeting the 2011 NHMRC standard for clinical practice guidelines. The public consultation strategy is available upon request, email cre-whirl@monash.edu

External review

This guideline will be reviewed by the International Advisory Group, independently by relevant professional colleges and societies and consumer groups and through public consultation.

Scheduled review and update of the guideline

The GDGs will be re-convened to review relevant sections of this guideline if any of the following occur within five years:

- a change in the indications registered by regulatory bodies for any drug included in this guideline; or
- publication of any new major randomised controlled trials or systematic reviews that potentially have a bearing on the safety of the recommendations in this guideline

After five years the societies and organisations will be reengaged, the guideline panels revised and reconvened and the guideline updated as per NHMRC processes.

Appendix I:
INTERNATIONAL ADVISORYPANEL

ROLE	TITLE	NAME	DISCIPLINE	ORGANISATION	COUNTRY
Chair	Professor	Helena Teede	Endocrinologist	Centre for Research Excellence in Women's Health in Reproductive Life, Monash University	Australia
Member	Professor	Robert Norman	Obstetrician-Gynaecologist; Reproductive Endocrinologist; Chemical pathologist	University of Adelaide	Australia
Member	Professor	Cindy Farquhar	Obstetrician-Gynaecologist; Chairman of the NZ Guidelines Group	University of Auckland	New Zealand
Member American Society for Reproductive Medicine representative	Professor	Heather Huddelston	Obstetrician-Gynaecologist	University of California San Francisco	USA
Member Endocrine Society representative	Professor	Sabrina Gill	Endocrinologist	University of British Columbia	Canada
Member Endocrine Society representative	Associate Professor	Kristen Gill Hairston	Endocrinologist	Wake Forest University	USA
Member European Endocrine Society representative	Professor	Djuro Macut	Endocrinologist	University of Belgrade	Serbia
Member European Society of Human Reproduction and Embryology representative	Professor	Ying Cheong	Fertility Physician	University of South Hampton	UK
Member Patient representative		Rachel Morman	Chair of Verity	Verity – PCOS Charity	UK

Appendix II:

GUIDELINE DEVELOPMENT GROUPS

Terms of reference for each committee can be provided upon request (cre-whirl@monash.edu).

GDG1: Topic area – Screening, diagnostic assessment, risk assessment and life-stage

GDG ROLE	TITLE	NAME	DISCIPLINE	ORGANISATION	COUNTRY
Chair	Professor	Joop Laven	Obstetrician-Gynaecologist; Reproductive Endocrinologist	Erasmus MC Rotterdam	Netherlands
Deputy Chair	Doctor	Anju Joham	Endocrinologist	Monash University	Australia
Member	Professor	Wiebke Arlt	Endocrinologist	University of Birmingham	UK
Member	Professor	Ricardo Azziz	Reproductive Endocrinologist	University of Alabama at Birmingham	USA
Member	Ms	Lorna Berry	Consumer Representative	Polycystic Ovary Syndrome Association Australia	Australia
Member	Doctor	Caroline Ee	General Practitioner	Western Sydney University	Australia
Member	Associate Professor	Marla Lujan	Reproductive Sciences; Nutrition	Cornell University	USA
Member	Professor	Ronald Ma	Endocrinologist	Chinese University of Hong Kong	Hong Kong
Member	Doctor	Malika Patel	Obstetrician-Gynaecologist; Reproductive medicine sub-specialty	University of Cape Town; Groote Schuur Hospital	South Africa
Member	Doctor	Alexia Pena	Paediatric Endocrinologist	The Robinson Institute at the University of Adelaide	Australia
Member	Professor	Sharon Oberfield	Paediatric Endocrinologist	Columbia University Medical Center	USA
Member	Professor	Duru Shah	Obstetrician-Gynaecologist; Fertility Specialist	The PCOS Society of India; Gynaecworld: The Centre for Women's Health and Fertility	India
Member	Professor	Fahimeh Ramezani Tehrani	Obstetrician-Gynaecologist; Reproductive Endocrinologist	Shahid Beheshti University of Medical Sciences, Tehran	Iran

GDG2: Topic area – Prevalence, screening, and management of psychological features and models of care

GDG ROLE	TITLE	NAME	DISCIPLINE	ORGANISATION	COUNTRY
Chair	Professor	Anuja Dokras	Reproductive Endocrinologist and infertility	University of Pennsylvania	USA
Deputy Chair	Professor	Jacky Boivin	Psychologist	Cardiff University	UK
Member	Associate Professor	Leah Brennan	Psychologist	La Trobe University	Australia
Member	Associate Professor	Tania Burgert	Paediatric Endocrinologist	University Missouri – Kansas School of Medicine	USA
Member	Mrs	Maureen Busby	Consumer Representative	PCOS Vitality	Ireland
Member	Doctor	Rhonda Garad	Registered Nurse	Monash University	Australia
Member	Doctor	Melanie Gibson	Women's Public Health Researcher	Te Tātai Hauora o Hine --National Centre for Women's Health Research Aotearoa, Victoria University of Wellington; Monash University	New Zealand Australia
Member	Professor	Elisabet Stener-Victorin	Researcher in Reproductive Endocrinology and Metabolism	Karolinska Institutet	Sweden
Member	Doctor	Chau Thien Tay (Jillian)	Endocrinologist, Research Fellow	Monash University	Australia
Member	Doctor	Mala Thondan	General Practitioner	Harp Family Medical	Australia

GDG3: Topic area – Lifestyle management

GDG ROLE	TITLE	NAME	DISCIPLINE	ORGANISATION	COUNTRY
Chair	Associate Professor	Lisa Moran	Dietitian, Research Fellow	Monash University	Australia
Deputy Chair	Professor	Leanne Redman	Obesity; Lifestyle Interventions	Pennington Biomedical Research Centre	USA
Member	Ms	Lorna Berry	Consumer Representative	Polycystic Ovary Syndrome Australia	Australia
Member	Associate Professor	Leah Brennan	Psychologist	La Trobe University	Australia
Member	Doctor	Cheryce Harrison	Exercise Physiologist; Health Coach	Monash University	Australia
Member	Professor	Kathleen Hoeger	Reproductive Endocrinologist	University of Rochester	USA
Member	Professor	Angelica Lindén Hirschberg	Obstetrician-Gynaecologist	Karolinska Institutet and Karolinska University Hospital	Sweden
Member	Doctor	Kate Marsh	Dietitian; Diabetes Educator	Private Practice	Australia
Member	Doctor	Mala Thondan	General Practitioner	Harp Family Medical	Australia
Member	Professor	Chandrika Wijeyaratne	Endocrinologist	University of Colombo	Sri Lanka

GDG4: Topic area – Management of non-fertility features

GDG ROLE	TITLE	NAME	DISCIPLINE	ORGANISATION	COUNTRY
Chair	Professor	Terhi Piltonen	Obstetrician-Gynaecologist; Reproductive Endocrinologist	Oulu University Hospital, University of Oulu	Finland
Deputy Chair	Associate Professor	Jacqueline Boyle	Obstetrician-Gynaecologist	Monash University	Australia
Member	Doctor	Carolyn Ee	General Practitioner	Western Sydney University	Australia
Member	Professor	Rong Li	Obstetrician-Gynaecologist	Reproductive Medical Centre, Peking University Third Hospital	China
Member		Rachel Morman	Chair of Verity/ Patient Representative	Verity – PCOS Charity	UK
Member	Doctor	Aya Mousa	Academic Epidemiology	Monash University	Australia
Member	Doctor	Alexia Pena	Paediatric Endocrinologist	The Robinson Institute at the University of Adelaide	Australia
Member	Doctor	Daniela Romauldi	Obstetrician-Gynaecologist	Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome	Italy
Member	Professor	Poli Mara Spritzer	Endocrinologist	Universidade Federal do Rio Grande do Sul	Brazil
Member	Professor	Eszter Vanky	Obstetrician-Gynaecologist	Dept. of Clinical and Molecular Medicine, Norwegian University of Science and Technology; Dept. of Obstetrics and Gynecology, St.Olavs Hospital, University hospital of Trondheim	Norway
Member	Professor	Selma Witchel	Paediatric Endocrinologist	Children's Hospital of Pittsburgh of UPMC, University of Pittsburgh	USA
Member	Professor	Bulent Yildiz	Endocrinologist	Hacettepe University Turkey	Turkey
Co-opted Member	Professor	Wendy Brown	Bariatric Surgeon	Department of Surgery, Central Clinical School, Monash University; Alfred Health	Australia

GDG5: Topic area – Assessment and treatment of infertility

GDG ROLE	TITLE	NAME	DISCIPLINE	ORGANISATION	COUNTRY
Chair	Doctor	Michael Costello	Obstetrician-Gynaecologist; Reproductive Endocrinologist	University of NSW	Australia
Deputy Chair	Professor	Robert Norman	Obstetrician-Gynaecologist; Reproductive Endocrinologist; Chemical pathologist	University of Adelaide	Australia
Member	Professor	Adam Balen	Reproductive Medicine	Leeds Teaching Hospitals; British Fertility Society	UK
Member	Doctor	Lisa Bedson	General Practitioner; Fertility Clinician	Repromed	Australia
Member	Professor	Roger Hart	Obstetrician-Gynaecologist; Reproductive Endocrinologist	The University of Western Australia; City Fertility Clinics Australia	Australia
Member	Doctor	Tuong Ho	Fertility Specialist	HOPE Research Centre, My Duc Hospital	Vietnam
Member	Doctor	Kim Hopkins	Member, PCOS Challenge Patient Advisory Board	PCOS Challenge: The National Polycystic Ovary Syndrome Association	USA
Member		Cailin Jordan	Psychologist	Genea Hollywood Fertility	Australia
Member	Professor	Richard Legro	Obstetrician-Gynaecologist; Reproductive Endocrinologist	Penn State Clinical and Translational Institute	USA
Member	Doctor	Edgar Mocanu	Obstetrician-Gynaecologist	Rotunda Hospital	Ireland
Member	Professor	Luk Rombauts	Obstetrician-Gynaecologist; Infertility Specialist	Monash University	Australia
Member	Professor	Shakila Thangaratinam	Obstetrician-Gynaecologist; Clinical Academic	University of Birmingham	UK
Member	Professor	Dongzi Yang	Obstetrician-Gynaecologist; Reproductive Endocrinologist	Reproductive Medical Centre, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University	China

GUIDELINE DEVELOPMENT TECHNICAL TEAM MEMBERS

- Professor Helena Teede, Project Director, Monash Centre for Health Research and Implementation, Monash University
- Doctor Chau Thien Tay, Evidence synthesis co-lead and lead on the early career PCOS Network
- Doctor Aya Mousa, Evidence synthesis and integration co-lead, Monash University
- Ms Linda Downes, Project Manager – Monash University and CRE WHIRL
- Doctor Rhonda Garad, Senior Project Officer, Knowledge Translation in PCOS, Monash University
- Doctor Marie Misso, Evidence Synthesis expert advisor
- Loyal Pattuwage, Evidence synthesis co-ordinator

PAEDIATRIC GDG PANEL MEMBERSHIP

ROLE	TITLE	NAME	DISCIPLINE	ORGANISATION	COUNTRY
Chair	Professor	Helena Teede	Endocrinologist	Monash Centre for Health Research and Implementation	Australia
Member	Professor	Kathleen Hoeger	Reproductive Endocrinologist	University of Rochester	USA
Member	Professor	Sharon Oberfield	Paediatric endocrinologist	Columbia University Medical Center	USA
Member	Professor	Selma Witchel	Paediatric Endocrinologist	Children's Hospital of Pittsburgh of UPMC, University of Pittsburgh	USA
Member	Doctor	Alexia Peña	Paediatric Endocrinologist	The Robinson Research Institute at the University of Adelaide	

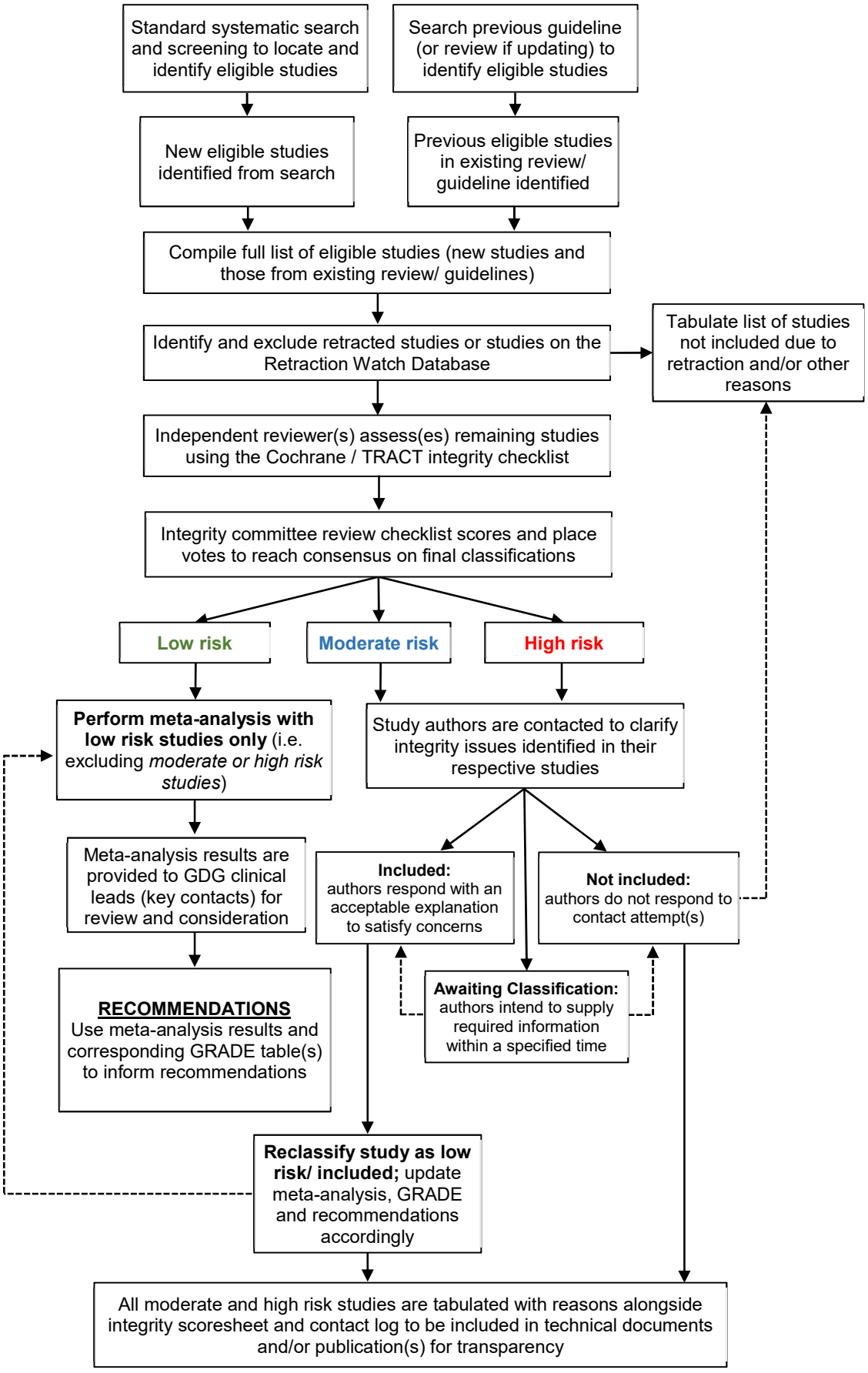
EVIDENCE INTEGRITY COMMITTEE

Role: The Evidence Integrity Committee is responsible for investigating and managing integrity issues in the identified literature, to ensure recommendations are based on sound evidence. Specifically, the Committee has developed and implemented the RIGID framework (Research Integrity in Guideline Development) to independently review and categorise all relevant studies and to contact authors, before evidence can be used to inform recommendations.

TITLE	NAME	ORGANISATION	COUNTRY
Professor	Ben Mol	Monash University	Australia
Doctor	Madeline Flanagan	Monash University	Australia
Doctor	Aya Mousa	Monash University	Australia
Doctor	Michael Costello	University of NSW	Australia
Professor	Robert Norman	University of Adelaide	Australia
Doctor	Chau Thien Tay	Monash University	Australia
Professor	Helena Teede	Monash University	Australia

Appendix III:
RESEARCH INTEGRITY PROCESS

Research Integrity in Guideline Development (RIGID) Framework



GDG, Guideline Development Group; **GRADE**, Grading of Recommendations, Assessment, Development and Evaluations; **TRACT**, Trustworthiness in RAndomised Controlled Trials.